A PHASE 1 DOSE ESCALATION AND EXPANSION STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND ANTI TUMOR ACTIVITY OF PF-07062119 IN PATIENTS WITH ADVANCED GASTROINTESTINAL TUMORS

Investigational Product Number:	PF-07062119
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	143416
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C3861001
Phase:	1
Short Title: A Phase 1, open-label, dose escalation and expansion study of PF-07062119 in patients with selected advanced or metastatic gastrointestinal tumors.	

Document History

Document	Version Date
Amendment 7	19 November 2021
Amendment 6	08 October 2021
Amendment 5	16 March 2021
Amendment 4	05 October 2020
Amendment 3	17 August 2020
Amendment 2	10 October 2019
Amendment 1	08 October 2019
Original protocol	20 August 2019

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ ECs and any protocol administrative clarification letter.

Protocol Amendments Summary of Changes Table

Amendment 7 (19 November 2021)

Overall Rationale for the Amendment: The primary purpose of the amendment is to incorporate feedback received from the United States (US) Food and Drug Administration (FDA). In addition, clarifications, administrative and typographical modifications were made.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Inclusion criterion #12 was adapted to **remove** the following language, "≤ULN if there is liver involvement secondary to tumor"	To require all participants (including those with liver metastases) to have AST and ALT ≤ 2.5 x ULN at study entry.
Section 6.7.3 Table 12	Dose modification guidelines for specific immune related toxicity attributed to investigational product were updated to provide additional detail around Liver (Hepatitis) and CRS events.	To provide specific dose interruption and modification guidelines based on grades for patients who experience liver and CRS events.
Section 10.11 Appendix 11	CRS management guidelines were added to accompany the CRS management algorithm	To provide suggested management guidelines for CRS
Section 10.13 Appendix 13	Dosing modifications and dose interruptions for Grade 2 hepatitis adverse events that last	To provide more detailed follow up instructions for Hepatitis

Section # and Name	Description of Change	Brief Rationale
	longer than 7 days have been provided in Table 12, management guidelines have been aligned in Table 20 and throughout the protocol.	(irAEs) management of Grade 2 events.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SCHEDULE OF ACTIVITIES (SOA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Appendix 18 presents alternative measures that may be used during the course of the study in light of the COVID-19 pandemic.

Table 1. Schedule of Activities for Part 1A, Part 1B, and Part 2 Without Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase- One Cycle = 28 days												End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
		Cycle 1							Cycles ≥2						
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 3	Day 5[23]	Day 8	Day 15	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window					±1 day	±1 day	±2 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days
Informed Consent[2]	X														
Medical/Oncological History	X														
Baseline Signs/Symptoms[3]		X													
Physical Examination[3]	X	(X)												X	
Brief Physical Examination[3]		X				X	X	X	X				X		X
Vital Signs[4]	X	X				X	X	X	X				X	X	X
ECOG Performance Status[5]	X	X							X					X	
Contraception Check	X	X							X					X	X
12-Lead ECG[6]	X	X	X	X[6]	X		X		X[6]	X(C4 only)	X(C4 only)	X(C4 only)	X (C4 only)	X	
Laboratory Studies															
Viral disease screening[7]	X														
Hematology[8]	X	X				X	X	X	X				X (C2 & C3 only)	X	(X)
Blood Chemistry[9]	X	X				X	X	X	X				X (C2 & C3 only)	X	(X)
Coagulation[10]	X	X												X	(X)

Table 1. Schedule of Activities for Part 1A, Part 1B, and Part 2 Without Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase- One Cycle = 28 days												End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
		Cycle 1							Cycles ≥2						
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 3	Day 5[23]	Day 8	Day 15	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window					±1 day	±1 day	±2 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days
Urinalysis[11]	X	X[11]					X[11]		X[11]				X[11]	X	(X)
Pregnancy test[12]	X	X							X[12]					X	X[12]
Cytokine evaluation (local lab)		Cytokines should be assessed with laboratory studies in the event of CRS.													
PK, PD, and Immunogenicity Assessments		Refer to Table 3 and Table 5													
Study Treatment															
Registration[13]	X														
Premedication[24]		X													
PF-07062119 administration[14]		X					X		X				X		
PF-06801591 administration[14]		X							X						
Bevacizumab- Pfizer administration[14]		X					X		X				X		
Injection Site Tolerability Assessment[15]		X	X(C1 only)				X		*As clinically indicated*						
Inpatient Monitoring[16]		◄--►					◄--►		X				X		
Other Clinical Assessments															
Adverse Event Reporting[17]	◄----------														----------►
Concomitant Medications/Treatments[18]	◄----------														----------►
Disease Assessments[21]															
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter.												X	
Carcinoembryonic Antigen (CEA) Assessment[22]	X	X							X					X	

Table 1. Schedule of Activities for Part 1A, Part 1B, and Part 2 Without Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase- One Cycle = 28 days												End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
		Cycle 1							Cycles ≥2						
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 3	Day 5[23]	Day 8	Day 15	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window					±1 day	±1 day	±2 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days

Notes: Visit windows are calculated from the first day of each cycle. Assessments that appear as (X) are optional.

1 **Screening**: to be obtained within 28 days prior to registration.

2 **Informed Consent:** must be obtained prior to undergoing any study specific procedures. May be obtained more than 28 days prior to registration. In Japan, after completion of Cycle 1, participants will be asked to sign an additional consent document in at least Part 1A for confirmation of the participant's willingness to continue participation in this study before starting Cycle 2.

3 **Complete Physical Examination:** No need to repeat on C1D1 if screening assessment is performed within 3 days of dosing, including assessment of weight. **Brief Physical Examination including** Baseline Signs and Symptoms: A symptom directed exam and assessment for emergent toxicities or changes from prior visits (See Section 8.1.1), does not need to be repeated if done within 24 hours of C1D1.

4 **Vital Signs:** Includes temperature (oral, tympanic, temporal or axillary), body weight, blood pressure (BP), and pulse rate to be recorded in a semisupine or seated position. On each dosing day, vitals should be measured prior to the PF-07062119 injection or infusion. In addition, pulse oximetry is to be recorded on dosing days prior to the PF-07062119 injection or infusion as part of the vital sign evaluation.

5 **Performance Status:** Use Eastern Cooperative Oncology Group (ECOG).

6 **Triplicate 12-Lead ECG:** Triplicate ECGs to be collected in Cycle 1 on Day 1, 2, 3 (participants in Part 1A and 1B only), 5, and 15 and on Day 1 of Cycles 2, 3, 4 and 5. Additionally, in Cycle 4 only, ECGs will be collected on Day 2, 5, 8, and 15, coinciding with the PK sample collection . Following Cycle 5, ECGs will be taken on Day 1 of every 3rd cycle only (ie, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc). Additional ECGs should be collected as clinically indicated, at the discretion of the investigator. At each time point 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF (QT using Fridericia's formula). When coinciding with blood sample collections for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation.

7 **Unique Screening/Viral Disease Laboratory Tests:** Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and HIV or AIDS as well as follicle stimulating hormone (FSH) for postmenopausal women who are amenorrhoeic for at least 12 consecutive months only. Samples will be analyzed locally.

8 **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 7 days of dosing. Assessments performed at all subsequent dosing visits should be obtained within 48 hours prior to dosing. Hematology assessment following cycle 1 (eg, C1D29 or C1D30) should be collected and reviewed prior to dosing on C2D1. Samples will be analyzed locally. A complete list of hematology labs can be found in Appendix 2.

9 **Blood Chemistry:** A complete list of blood chemistry labs can be found in Appendix 2. Measurement of C-reactive protein (CRP) not required after C2D1 if within normal range or similar to baseline levels; however, CRP should be measured anytime cytokine release syndrome is suspected and not already scheduled to be measured (eg, Cycle 2). No need to repeat on C1D1 if baseline assessment performed within 7 days prior to dosing. Assessments performed at all subsequent dosing visits should be obtained within 48 hours prior to dosing. Blood chemistry assessment following Cycle 1 (eg, C1D29 or C1D30) should be collected and reviewed prior to dosing on C2D1. Samples will be analyzed locally.

Table 1. Schedule of Activities for Part 1A, Part 1B, and Part 2 Without Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase- One Cycle = 28 days												End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
		Cycle 1							Cycles ≥2						
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 3	Day 5[23]	Day 8	Day 15	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window					±1 day	±1 day	±2 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days

10 **Coagulation:** A complete list of coagulation labs can be found in Appendix 2. No need to repeat on C1D1 if baseline assessment performed within 7 days of dosing. Samples will be analyzed locally.

11 **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days of dosing, with the exception of participants who are receiving bevacizumab-Pfizer who will require urinalysis (dipstick is acceptable) prior to every dose of bevacizumab-Pfizer. Samples will be analyzed locally. Urinalysis (dipstick is acceptable) assessment is required prior to every bevacizumab-Pfizer dose throughout the course of the study. If urinalysis demonstrates protein greater than or equal to 2+, then a 24-hour urine protein collection should follow. In participants with proteinuria greater than or equal to 2 grams per 24 hours, bevacizumab-Pfizer should be held until recovery (less than 2 grams per 24 hours). Discontinue bevacizumab-Pfizer in participants that develop nephrotic syndrome.

12 **Pregnancy Test:** For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on 2 occasions prior to starting study treatment – once at the start of screening and once on C1D1 immediately before administration of study intervention (within 24 hours prior to C1D1 dosing). Pregnancy tests will also be routinely repeated at every other cycle during the active treatment period following C1D1 and C2D1, at the end of study treatment and additional whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. During follow-up, a pregnancy test is only required 30, 90, and 180 days after EOT for participants who receive PF-06801591. Additional pregnancy tests may also be undertaken if requested by IRB or if required by local regulations.

13 **Registration:** Participant enrollment number and dose level allocation provided by Pfizer Inc. Registration should occur before any other Day 1 activities are performed.

14 **Study Treatment:** PF-07062119 will be administered once every 14 days as an SC injection.PF-06801591 will be administered once every 28-day cycle as an SC injection beginning on C1D1 of Part 1B. Bevacizumab-Pfizer or the biosimilar version of Avastin®, manufactured by Pfizer and hereafter referred to as bevacizumab-Pfizer will be used for this study and administered once every 14 days as IV infusion beginning on C1D1 of Part 1B. See Section 6.1.1 of the protocol for administration information. Participants planned to receive PF-07062119 in combination with bevacizumab-Pfizer should be weighed within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of bevacizumab-Pfizer required for dose preparation. Decision to recalculate bevacizumab-Pfizer dose based on the weight obtained at each cycle can be in accordance with institutional practice, however if the participant experienced either a weight loss or gain >10% compared to the weight used to calculate either the initial or previous dose, the amount of bevacizumab-Pfizer required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained. Participants in Part 2 will be observed for at least 24 hours after the first SC dose. Participants may only be released after the investigator has confirmed the participant has not exhibited signs of cytokine release syndrome.

15 **Injection Site Tolerability Assessment:** Assessment of each injection should be conducted for at least 1 hour following each treatment administration in Cycle 1. In addition, an assessment should be performed 24 hours (±1 hour) after the C1D1 dose. Injection site tolerability assessments should continue after each dosing visit in Cycle 2 and beyond, only if injection site pain or ISR characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve. All findings should be recorded on the injection site reaction CRF. See Section 8.1.7 for more details.

16 **Inpatient Monitoring:** Participants receiving PF-07062119 SC will be admitted for inpatient monitoring for at least 48 hours following the first administration of study treatment (C1D1) and for at least 8 hours following the second administration of study treatment (C1D15). Participants should remain in house for observation for at least 1-hour post dose for all visits after C1 for Parts 1A and 1B; inpatient monitoring after C1 for Part 2 is at the investigator's discretion. Participants may be released only after the investigator has confirmed the participant has not exhibited signs of a cytokine reaction. Participants should complete the required study specific laboratory assessments as detailed

Table 1. Schedule of Activities for Part 1A, Part 1B, and Part 2 Without Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase- One Cycle = 28 days												End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
		Cycle 1							Cycles ≥2						
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 3	Day 5[23]	Day 8	Day 15	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window					±1 day	±1 day	±2 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days

in the Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Parts 1A and 1B where PF-07062119 will be administered SC and should be monitored per local standard practice for inpatient monitoring.

17 **Adverse Event (AE) Assessments:** AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Participants must be followed for AEs for 28 days after the last study treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the participant commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study intervention, through and including 28 calendar days after the last study treatment administration. SAEs occurring to a participant after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study intervention are to be reported to the sponsor.

18 **Concomitant Treatments:** All concomitant medications should be recorded in the case report form (CRF) including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

19 **End of Treatment Visit/Withdrawal (EOT):** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).

20 **Follow-Up:** At least 28 days, and no more than 35 days, after discontinuation of treatment, all participants will return to obtain these assessments as well as an evaluate the resolution of any treatment-related toxicity. Participants who receive PF-06801591 will also return for follow-up assessments 30, 90, and 180 days after treatment discontinuation. Participants continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. Participants with an unresolved AE possibly related to anti-drug antibodies (ADA) will be asked to return to the clinic for ADA/neutralizing antibodies (NAb) and drug concentration assessments at approximately 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor up to a maximum of 9 months. Subsequent to the Follow-Up visit, participants should be contacted by telephone every 8 weeks (±7 days) to obtain information on subsequent anti-cancer treatment and overall survival for up to two years from the date of randomization.

21 **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans or equivalent. The same modality should be completed, if possible throughout the study. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic participants to rule out CNS metastases; participant ineligible if positive for new CNS metastases, previously treated CNS metastases are allowed as outlined exclusion criteria. CT or MRI scans to be done as outlined in the Schedule of Activities (SOA) until disease progression by irRECIST or death, or until permanent discontinuation of study treatment. Response (complete response (CR)/partial response (PR)) and disease progression will be confirmed with 2 consecutive timepoints at least 4 weeks apart (in the absence of rapid clinical deterioration for progression). Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.

22 **CEA Assessments**: Performed on Day 1 of each Cycle for up to 1 year. After 1 year, perform every 4 months thereafter.

23 The Day 5 visit window is expanded (±1 day) for participants in Part 2 only.

Table 1. Schedule of Activities for Part 1A, Part 1B, and Part 2 Without Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase- One Cycle = 28 days												End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
		Cycle 1							Cycles ≥2						
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 3	Day 5[23]	Day 8	Day 15	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window					±1 day	±1 day	±2 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days

24 **Premedication:** Approximately 1 hour prior to PF-07062119 dosing on C1D1 only, administer premedication as follows: acetaminophen 650 mg (or equivalent), oral; diphenhydramine 25 mg, oral or IV; dexamethasone 12 mg (or equivalent), oral or IV. In addition, premedication beyond the 1st full dose and modifications to the premedication regimen (eg, frequency of premedication, doses of individual agents, removal or addition of agents) may be implemented by the sponsor based on emerging data. Any exceptions to premedication require discussion and agreement between the sponsor and investigator.

Table 2. Schedule of Activities for Part 1A, Part 1B, and Part 2 With Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase (1 Cycle = 28 days)														
		Cycle 1							Cycles ≥2					End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 8	Day 15	Day 16	Day 19	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window				±1 day	±2 days		±1 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days
Informed Consent[2]	X														
Medical/Oncological History	X														
Baseline Signs/Symptoms[3]		X													
Physical Examination[3]	X	(X)			X									X	
Brief Physical Examination[3]		X		X				X	X				X		X
Vital Signs[4]	X	X		X	X			X	X				X	X	X
ECOG Performance Status[5]	X	X							X					X	
Contraception Check	X	X							X					X	X
12-Lead ECG[6]	X	X	X	X[6]	X				X[6]	X(C4 only)	X(C4 only)	X(C4 only)	X (C4 only)	X	
Laboratory Studies															
Viral disease screening[7]	X														
Hematology[8]	X	X		X	X			X	X				X (C2 & C3 only)	X	(X)
Blood Chemistry[9]	X	X		X	X			X	X				X (C2 & C3 only)	X	(X)
Coagulation[10]	X	X												X	(X)
Urinalysis[11]	X	X[11]			X[11]				X[11]				X[11]	X	(X)
Pregnancy test[12]	X	X							X[12]					X	X[12]
Cytokine evaluation (local lab)		Cytokines should be assessed with laboratory studies in the event of CRS.													
PK, PD, and Immunogenicity Assessments		See Table 4 and Table 6													
Study Treatment															
Registration[13]	X														
Premedication[23]		X			X										
PF-07062119 administration[14]		X			X				X				X		

Table 2. Schedule of Activities for Part 1A, Part 1B, and Part 2 With Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase (1 Cycle = 28 days)														
		Cycle 1							Cycles ≥2					End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 8	Day 15	Day 16	Day 19	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window				±1 day	±2 days		±1 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days
PF-06801591 administration[14]					X								X		
Bevacizumab- Pfizer administration[14]					X				X				X		
Injection Site Tolerability Assessment[15]		X	X(C1 only)		X				*As clinically indicated*						
Inpatient Monitoring[16]		◄--►			◄--►				X				X		
Other Clinical Assessments															
Adverse Event Reporting[17]	◄----------														----------►
Concomitant Medications/Treatments[18]	◄----------													----------►	
Disease Assessments[21]															
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease	X	Performed every 8 weeks from C1D1 (±7 days) for the first 6 months, every 12 weeks (±7 days) for the next 18 months, and every 4 months thereafter.													X	
CEA Assessment[22]	X	X							X						X	

Notes: Visit windows are calculated from the first day of each cycle. Assessments that appear as (X) are optional.

1 **Screening**: to be obtained within 28 days prior to registration.

2 **Informed Consent:** must be obtained prior to undergoing any study specific procedures. May be obtained more than 28 days prior to registration.

3 **Complete Physical Examination:** No need to repeat on C1D1 if screening assessment is performed within 3 days of dosing, including assessment of weight. **Brief Physical Examination including** Baseline Signs and Symptoms: A symptom directed exam and assessment for emergent toxicities or changes from prior visits (See Section 8.1.1), does not need to be repeated if done within 24 hours of C1D1.

4 **Vital Signs:** Includes temperature (oral, tympanic, temporal or axillary), body weight, BP, and pulse rate to be recorded in a semisupine or seated position. On each dosing day, vitals should be measured prior to the PF-07062119 injection or infusion. In addition, pulse oximetry is to be recorded on dosing days prior to the PF-07062119 injection or infusion as part of the vital sign evaluation.

5 **Performance Status:** Use ECOG.

6 **Triplicate 12-Lead ECG:** Triplicate ECGs to be collected in Cycle 1 on Day 1, 2 (participants in Part 1A and 1B only), 8, and 15 and on Day 1 of Cycles 2, 3, 4 and 5. Additionally, in Cycle 4 only, ECGs will be collected on Day 2, 5, 8, and 15, coinciding with the PK sample collection. Following Cycle 5, ECGs will be taken on Day 1 of every 3rd cycle only (ie, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc). Additional ECGs should be collected as clinically indicated, at the discretion of the investigator. At each time point 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF. When coinciding with blood sample collections for PK, ECG

Table 2. Schedule of Activities for Part 1A, Part 1B, and Part 2 With Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase (1 Cycle = 28 days)														
		Cycle 1							Cycles ≥2					End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 8	Day 15	Day 16	Day 19	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window				±1 day	±2 days		±1 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days

assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation.

7 **Unique Screening/Viral Disease Laboratory Tests:** Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and HIV or AIDS as well as FSH for postmenopausal women who are amenorrhoeic for at least 12 consecutive months only. Samples will be analyzed locally.

8 **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 7 days of dosing. Assessments performed at all subsequent dosing visits should be obtained within 48 hours prior to dosing. Hematology assessment following cycle 1 (eg, C1D29 or C1D30) should be collected and reviewed prior to dosing on C2D1. Samples will be analyzed locally. A complete list of hematology labs can be found in Appendix 2.

9 **Blood Chemistry:** A complete list of blood chemistry labs can be found in Appendix 2. Measurement of CRP not required after C2D1 if within normal range or similar to baseline levels; however, CRP should be measured anytime cytokine release syndrome is suspected and not already scheduled to be measured (eg, Cycle 2). No need to repeat on C1D1 if baseline assessment performed within 7 days prior to dosing. Assessments performed at all subsequent dosing visits should be obtained within 48 hours prior to dosing. Blood chemistry assessment following Cycle 1 (eg, C1D29 or C1D30) should be collected and reviewed prior to dosing on C2D1. Samples will be analyzed locally.

10 **Coagulation:** A complete list of coagulation labs can be found in Appendix 2. No need to repeat on C1D1 if baseline assessment performed within 7 days of dosing. Samples will be analyzed locally.

11 **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days of dosing, with the exception of participants who are receiving bevacizumab-Pfizer who will require urinalysis (dipstick is acceptable) prior to every dose of bevacizumab-Pfizer. Samples will be analyzed locally. Urinalysis (dipstick is acceptable) assessment is required prior to every bevacizumab-Pfizer dose throughout the course of the study. If urinalysis demonstrates protein greater than or equal to 2+, then a 24-hour urine protein collection should follow. In participants with proteinuria greater than or equal to 2 grams per 24 hours, bevacizumab-Pfizer should be held until recovery (less than 2 grams per 24 hours). Discontinue bevacizumab-Pfizer in participants that develop nephrotic syndrome.

12 **Pregnancy Test:** For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on 2 occasions prior to starting study treatment – once at the start of screening and once on C1D1 immediately before administration of study intervention (within 24 hours prior to C1D1 dosing). Pregnancy tests will also be routinely repeated at every other cycle during the active treatment period following C1D1 and C2D1, at the end of study treatment and additional whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. During follow-up, a pregnancy test is only required 30, 90 and 180 days after EOT for participants who receive PF-06801591. Additional pregnancy tests may also be undertaken if requested by IRB or if required by local regulations.

13 **Registration:** Participant enrollment number and dose level allocation provided by Pfizer Inc. Registration should occur before any other Day 1 activities are performed.

14 **Study Treatment:** PF-07062119 will be administered once every 14 days as an SC injection. A priming dose will be administered on C1D1 followed by a full dose on C1D15 and Q2W thereafter. See Section 4.1.1.2 for potential changes to the priming dose regimen (eg, step-up dosing strategy). PF-06801591 will be administered once every 28-day cycle as an SC injection beginning on C1D15 of Part 1B. Bevacizumab-Pfizer or the biosimilar version of Avastin®, manufactured by Pfizer and hereafter referred to as bevacizumab-Pfizer will be used for this study and administered once every 14 days as IV infusion beginning on C1D15 of Part 1B. See Section 6.1.1 of the protocol for administration information. Participants planned to receive PF-07062119 in combination with bevacizumab-Pfizer should be weighed within 72 hours prior to dosing for every

Table 2. Schedule of Activities for Part 1A, Part 1B, and Part 2 With Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase (1 Cycle = 28 days)														
		Cycle 1							Cycles ≥2					End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 8	Day 15	Day 16	Day 19	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window				±1 day	±2 days		±1 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days

cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of bevacizumab-Pfizer required for dose preparation. Decision to recalculate bevacizumab-Pfizer dose based on the weight obtained at each cycle can be in accordance with institutional practice, however if the participant experienced either a weight loss or gain >10% compared to the weight used to calculate either the initial or previous dose, the amount of bevacizumab-Pfizer required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained. Participants in Part 2 will be observed for at least 24 hours after the first SC dose. Participants may only be released after the investigator has confirmed the participant has not exhibited signs of cytokine release syndrome.

15 **Injection Site Tolerability Assessment:** Assessment of each injection should be conducted for at least 1 hour following each treatment administration in Cycle 1. In addition, an assessment should be performed 24 hours (±1 hour) after the C1D1 dose. Injection site tolerability assessments should continue after each dosing visit in Cycle 2 and beyond, only if injection site pain or ISR characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve. All findings should be recorded on the injection site reaction CRF. See Section 8.1.7 for more details.

16 **Inpatient Monitoring:** Participants receiving PF-07062119 SC will be admitted for inpatient monitoring for at least 24 hours following the first administration of study treatment (C1D1) and for at least 24 hours following the second administration of study treatment (C1D15). Participants should remain in house for observation for at least 1-hour post dose for all visits after C1D1 for Parts 1A and 1B; inpatient monitoring after C1 for Part 2 is at the investigator's discretion. Participants may be released only after the investigator has confirmed the participant has not exhibited signs of a cytokine reaction. Participants should complete the required study specific laboratory assessments as detailed in the Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Parts 1A and 1B where PF-07062119 will be administered SC and should be monitored per local standard practice for inpatient monitoring.

17 **AE Assessments:** AEs should be documented and recorded at each visit using the NCI CTCAE version 5.0. Participants must be followed for AEs for 28 days after the last study treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the participant commence another anticancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study intervention, through and including 28 calendar days after the last study treatment administration. SAEs occurring to a participant after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study intervention are to be reported to the sponsor.

18 **Concomitant Treatments:** All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

19 **EOT /Withdrawal:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).

20 **Follow-Up:** At least 28 days, and no more than 35 days, after discontinuation of treatment, all participants will return to obtain these assessments as well as an evaluate the resolution of any treatment-related toxicity. Participants who receive PF-06801591 will also return for follow-up assessments 30, 90 and 180 days after treatment discontinuation. Participants continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. Participants with an unresolved AE possibly related to ADA will be asked to

Table 2. Schedule of Activities for Part 1A, Part 1B, and Part 2 With Priming Dose

Protocol Activity	Screening[1]	Active Treatment Phase (1 Cycle = 28 days)														
		Cycle 1							Cycles ≥2					End of Treatment/ Withdrawal[19]	Post-Treatment Follow-Up[20]
Study Day	Within 28 days prior to registration	Day 1	Day 2	Day 8	Day 15	Day 16	Day 19	Day 22	Day 1	Day 2	Day 5	Day 8	Day 15		
Visit Window				±1 day	±2 days		±1 days	±2 days	±2 days		±1 day	±1 day	±2 days		±7 days

return to the clinic for ADA/ NAb and drug concentration assessments at approximately 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor up to a maximum of 9 months. Subsequent to the Follow-Up visit, participants should be contacted by telephone every 8 weeks (±7 days) to obtain information on subsequent anti-cancer treatment and overall survival for up to two years from the date of randomization.

21 **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans or equivalent. The same modality should be completed, if possible throughout the study. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline CNS imaging is not required with the exception of symptomatic participants to rule out CNS metastases; participant ineligible if positive for new CNS metastases, previously treated CNS metastases are allowed as outlined exclusion criteria. CT or MRI scans to be done as outlined in the Schedule of Activities (SOA) until disease progression by irRECIST or death, or until permanent discontinuation of study treatment. Response (CR, PR) and disease progression will be confirmed with 2 consecutive timepoints at least 4 weeks apart (in the absence of rapid clinical deterioration for progression). Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.

22 **CEA Assessments**: Performed on Day 1 of each Cycle for up to 1 year. After 1 year, perform every 4 months thereafter.

23 **Premedication**: Approximately 1 hour prior to PF-07062119 dosing during Cycle 1 only, administer premedication as follows: acetaminophen 650 mg (or equivalent), oral; diphenhydramine 25 mg, oral or IV; dexamethasone 12 mg (or equivalent), oral or IV. In addition, premedication beyond the 1st full dose and modifications to the premedication regimen (eg, frequency of premedication, doses of individual agents, removal or addition of agents) may be implemented by the sponsor based on emerging data. Any exceptions to premedication require discussion and agreement between the sponsor and investigator.

Table 3. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 1A and Part 1B Without Priming Dose

Visit Identifier	Screening	Cycle 1										Cycle ≥2					
Study Day	Within 28 days prior to registration	1			2	3	5	8	15		22	1	2	5	8	15	End of Treatment/ Withdrawal
Hours Pre-/Post-Dose[1]		0[2]	4	8	24	48	96	168	0	8 (Part 1B only)	168	0	24	96	168	0	
Visit window			±0.5 hr	±1 hr	±3 hrs	±6 hrs	±24 hrs	±24 hrs		±1hr	±48 hrs		±3 hrs	±24 hrs	±24 hrs		
Pharmacokinetic samples																	
Blood samples for PF-07062119 concentrations		X	X	X	X	X	X	X	X	X	X	X	X (C4 only)	X[1] (C4 only)	X (C4 only)	X	X
Blood samples for ADA/NAb against PF-07062119[3]		X							X			X[3]					X
Blood samples for PK/ADA/NAb against PF-06801591[3]		X							X			X[3]					X
Blood samples for PK/ADA/ NAb against bevacizumab-Pfizer[3]		X							X			X[3]					X
Pharmacodynamic samples																	
Pfizer Prep D1 banked sample[4]		X															
Archival Tumor Sample[5]	X																
Optional or Mandatory De Novo Pre-treatment biopsy[5,6]	X																
Optional or Mandatory On-Treatment Tumor Biopsy[6]												X C3 only (±7 days)					X (or 2nd on treatment)

Table 3. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 1A and Part 1B Without Priming Dose

Visit Identifier	Screening	Cycle 1										Cycle ≥2					
Study Day	Within 28 days prior to registration	1			2	3	5	8	15		22	1	2	5	8	15	End of Treatment/ Withdrawal
Hours Pre-/Post-Dose[1]		0[2]	4	8	24	48	96	168	0	8 (Part 1B only)	168	0	24	96	168	0	
Visit window			±0.5 hr	±1 hr	±3 hrs	±6 hrs	±24 hrs	±24 hrs		±1hr	±48 hrs		±3 hrs	±24 hrs	±24 hrs		
Blood sample for T cell Immunophenotyping[7]		X			X	X	X	X	X		X	X[7]				X (C2 and C3 only)	
Blood (serum) sample for Cytokines & Circulating Markers[8]		X	X	X	X	X	X	X	X	X	X	X[7]				X (C2 and C3 only)	

1 Sampling times indicated are related to the end of the SC injection. All efforts should be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the window specified will be considered acceptable. Starting Cycle 5, predose PK samples will be collected only on Day 1 of every 3rd cycle (Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.). **Additional PK/PD samples should also be taken if CRS is suspected, and PK/PD samples are not already scheduled to be taken.**

2 The 0-hour PK and ADA/NAb samples should be taken within 6 hours prior to PF-07062119 administration.

3 **Blood samples for PF-07062119, PF-06801591, and bevacizumab-Pfizer immunogenicity testing and PF-06801591, and bevacizumab-Pfizer PK:** Blood samples for PF-06801591 or bevacizumab-Pfizer will only be collected in participants receiving combination therapy (**ie, Part 1B**): Refer to Section 8.4 for details. A blood sample for PF-06801591 or bevacizumab-Pfizer PK analyses should be drawn with each immunogenicity sample for PF-06801591 or bevacizumab-Pfizer, respectively. All samples should be collected on Day 1 of a cycle (**also on Day 15, in Cycle 1 only**) and will be drawn predose - within 6 hours prior to any of the drugs being administered. Starting at Cycle 5, blood samples for PK and ADA/NAb against PF-07062119 (and PF-06801591 or bevacizumab-Pfizer in Part 1B) will be collected every 3rd cycle predose (ie, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.). Participants with an unresolved AE possibly related to ADA will be asked to return to the clinic for ADA and drug concentration assessments at approximately 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor up to a maximum of 9 months.

4 **Pfizer Prep D1 Banked Sample:** If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

5 **Tumor Tissue Samples:** Participants enrolled in Part 1A, and Part 1B of this study will provide either an archival formalin-fixed paraffin embedded material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or preferably a de novo pre-treatment biopsy. If the archival tumor is not available, participants must provide a de novo pre-treatment biopsy for evaluation of baseline tissue biomarkers (preferably collected within 28 days of study start). On-treatment biopsy samples collected preferably after the third dose and within 7 days of C3D1 are optional for participants enrolled in each cohort in Part 1A and Part 1B for evaluation of tissue biomarker modulations during treatment. **If on treatment tumor collection takes place greater than ±3 days from C3D1, additional unscheduled blood sample for cytokine and circulating markers and an unscheduled blood sample for T cell immunophenotyping sample should be collected to match the day of biopsy collection.** Specific tissue requirements and instructions are listed in Biomarker Section 8.8.

Table 3. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 1A and Part 1B Without Priming Dose

Visit Identifier	Screening	Cycle 1										Cycle ≥2					
Study Day	Within 28 days prior to registration	1			2	3	5	8	15		22	1	2	5	8	15	End of Treatment/ Withdrawal
Hours Pre-/Post-Dose[1]		0[2]	4	8	24	48	96	168	0	8 (Part 1B only)	168	0	24	96	168	0	
Visit window			±0.5 hr	±1 hr	±3 hrs	±6 hrs	±24 hrs	±24 hrs		±1hr	±48 hrs		±3 hrs	±24 hrs	±24 hrs		

6 **Paired Tumor Samples**: As the RP2D/MTD is approached or the RP2D/MTD of PF-07062119 has been determined, an optional subset of participants may be enrolled (approximately 6-12 participants) with the requirement of providing mandatory paired de novo pretreatment and on treatment biopsy samples in Parts 1A and 1B to enable evaluation of tissue biomarker PD activity. The option to enroll the subset of participants for mandatory paired tumor samples will be based on evaluation of emerging clinical data (including available safety/tolerability, PK, and PD findings) by the sponsor. De novo pre-treatment and on-treatment biopsies should be taken from the same lesion, not previously irradiated, if possible. De novo pre-treatment biopsies should be preferably collected within 28 days of study start after all eligibility criteria have been verified. On-treatment biopsy samples are to be collected preferably after the 3rd dose and within 7 days of C3D1. **If on treatment tumor collection takes place greater than ±3 days from C3D1, additional unscheduled blood sample for cytokine and circulating markers and an unscheduled blood sample for T cell immunophenotyping should be collected to match the day of biopsy collection.** Additional unscheduled on-treatment biopsies, after C4D15 (>6 weeks after initial on treatment biopsy) may be collected, if indicated to evaluate potential responses to treatment or suspected acquired resistance to therapy and agreed upon by the sponsor and investigator and agreed to by the participant. If the participant discontinues the study before the scheduled on-treatment biopsy (C3D1), the participant will be asked to provide a biopsy at the End of Treatment visit. Specific tissue requirements and instructions are listed in Biomarker Section 8.8.

7 **Blood sample for T cell Immunophenotyping:** One 5 mL blood sample will be collected for immunophenotype circulating lymphocytes at baseline (predose Cycle 1 Day 1), and during treatment as described above to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected. If Grade ≥2 diarrhea is observed or suspected and PD samples are not already scheduled for measurement this sample should be collected. Starting with Cycle 5, blood will be collected every 3rd cycle predose (ie., Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.) (Section 8.8.5).

8 **Blood Sample for Cytokines and Circulating Markers (central lab):** For central laboratory testing, one 5 mL blood sample will be collected to isolate serum for cytokine and circulating marker measurement. Baseline collection is required predose on Cycle 1 Day 1. On-treatment samples for cytokine and circulating marker measurement will be collected as described above. These samples will be used to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected to match clinically indicated safety cytokine samples. If Grade ≥2 diarrhea is observed or suspected and PD samples are not already scheduled for measurement this sample should be collected. Starting with Cycle 5, blood samples for cytokine and circulating markers will be collected every 3rd cycle predose (ie., Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.) (Section 8.8.4).

Table 4. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 1A and Part 1B With Priming Dose

Visit Identifier	Screening	Cycle 1										Cycle ≥2					
Study Day	Within 28 days prior to registration	1		2	8	15			16	19	22	1	2	5	8	15	EOT/ Withdrawal
Hours Pre-/Post-Dose[1]		0[2]	8	24	168	0	4	8	24	96	168	0	24	96	168	0	
Visit window			±1 hr	±3 hrs	±24 hrs		±0.5 hr	±1 hr	±3 hrs	±24 hrs	±48 hrs		±3 hrs	±24 hrs	±24 hrs		
Pharmacokinetic samples																	
Blood samples for PF-07062119 concentrations		X	X	X	X	X	X	X	X	X	X	X	X (C4 only)	X[1] (C4 only)	X (C4 only)	X	X
Blood samples for ADA/NAb against PF-07062119[3]		X				X						X[3]					X
Blood samples for PK/ADA/NAb against PF-06801591[3]						X										X[3]	X
Blood samples for PK/ADA/NAb against bevacizumab-Pfizer[3]						X						X[3]					X
Pharmacodynamic samples																	
Pfizer Prep D1 banked sample[4]		X															
Archival Tumor Sample[5]	X																
Optional or Mandatory De Novo Pre-treatment biopsy[5,6]	X																
Optional or Mandatory On-Treatment Tumor Biopsy[6]												X C3 only (±7 days)					X (or 2nd on treatment)
Blood sample for T cell Immunophenotyping[7]		X		X	X	X			X	X	X	X[7]				X (C2 and C3 only)	
Blood (serum) sample for Cytokines & Circulating Markers[8]		X	X	X	X	X	X	X	X	X	X	X[7]				X (C2 and C3 only)	

Table 4. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 1A and Part 1B With Priming Dose

Visit Identifier	Screening	Cycle 1										Cycle ≥2					
Study Day	Within 28 days prior to registration	1		2	8	15			16	19	22	1	2	5	8	15	EOT/ Withdrawal
Hours Pre-/Post-Dose[1]		0[2]	8	24	168	0	4	8	24	96	168	0	24	96	168	0	
Visit window			±1 hr	±3 hrs	±24 hrs		±0.5 hr	±1 hr	±3 hrs	±24 hrs	±48 hrs		±3 hrs	±24 hrs	±24 hrs		

1 Sampling times indicated are related to the end of the SC injection. All efforts should be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the window specified will be considered acceptable. Starting Cycle 5, predose PK samples will be collected only on Day 1 of every 3rd cycle (Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.). **Additional PK/PD samples should also be taken if CRS is suspected, and PK/PD samples are not already scheduled to be taken.**

2 The 0-hour PK and ADA/NAb samples should be taken within 6 hours prior to PF-07062119 administration.

3 **Blood samples for PF-07062119, PF-06801591, and bevacizumab-Pfizer immunogenicity testing and PF-06801591, and bevacizumab-Pfizer PK:** Blood samples for PF-07062119 will be collected in participants receiving monotherapy **(ie, Part 1A Dose Priming)**. Blood samples for PF-07062119, PF-06801591 or bevacizumab-Pfizer will be collected in participants receiving combination therapy **(ie, Part 1B Dose Priming)**: Refer to Section 8.4 for details. A blood sample for PF-06801591 or bevacizumab-Pfizer PK analyses should be drawn with each immunogenicity sample for PF-06801591 or bevacizumab-Pfizer, respectively. All samples for bevacizumab-Pfizer should be collected on Day 1 of a cycle (except on Day 15, in Cycle 1 only) and for PF-06801591 on Day 15 of each cycle. Samples will be drawn predose - within 6 hours prior to any of the drugs being administered. Starting at Cycle 5, blood samples for PK and ADA/NAb against PF-07062119 (and PF-06801591 or bevacizumab-Pfizer in Part 1B) will be collected every 3rd cycle predose (ie, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc. for PF-07062119/bevacizumab-Pfizer and Cycle 5 Day 15, Cycle 8 Day 15, Cycle 11 Day 15 for PF-06801591). Participants with an unresolved AE possibly related to ADA will be asked to return to the clinic for ADA and drug concentration assessments at approximately 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor up to a maximum of 9 months.

4 **Pfizer Prep D1 Banked Sample:** If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

5 **Tumor Tissue Samples:** Participants enrolled in Part 1A, and Part 1B of this study will provide either an archival formalin-fixed paraffin embedded material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or preferably a de novo pre-treatment biopsy. If the archival tumor is not available, participants must provide a de novo pre-treatment biopsy for evaluation of baseline tissue biomarkers (preferably collected within 28 days of study start). On-treatment biopsy samples collected preferably after the third dose and within 7 days of C3D1 are optional for participants enrolled in each cohort in Part 1A and Part 1B for evaluation of tissue biomarker modulations during treatment. **If on treatment tumor collection takes place greater than ±3 days from C3D1, additional unscheduled blood sample for cytokine and circulating markers and an unscheduled blood sample for T cell immunophenotyping sample should be collected to match the day of biopsy collection.** Specific tissue requirements and instructions are listed in Biomarker Section 8.8.

6 **Paired Tumor Samples**: As the RP2D/MTD is approached or the RP2D/MTD of PF-07062119 has been determined, an optional subset of participants may be enrolled (approximately 6-12 participants) with the requirement of providing mandatory paired de novo pretreatment and on treatment biopsy samples in Parts 1A and 1B to enable evaluation of tissue biomarker PD activity. The option to enroll the subset of participants for mandatory paired tumor samples will be based on evaluation of emerging clinical data (including available safety/tolerability, PK, and PD findings) by the sponsor. De novo pre-treatment and on-treatment biopsies should be taken from the same lesion, not previously irradiated, if possible. De novo pre-treatment biopsies should be preferably collected within 28 days of study start after all eligibility criteria have been verified. On-treatment biopsy samples are to be collected preferably after the 3rd dose and within 7 days of C3D1. **If on treatment tumor collection takes place greater than ±3 days from C3D1, additional unscheduled blood sample for cytokine and circulating markers and an unscheduled blood sample for T cell immunophenotyping should be collected to match the day of biopsy collection.** Additional unscheduled on-treatment biopsies, after C4D15 (>6 weeks after initial on treatment biopsy) may be collected, if indicated to evaluate potential

Table 4. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 1A and Part 1B With Priming Dose

Visit Identifier	Screening	Cycle 1										Cycle ≥2					
Study Day	Within 28 days prior to registration	1		2	8	15			16	19	22	1	2	5	8	15	EOT/ Withdrawal
Hours Pre-/Post-Dose[1]		0[2]	8	24	168	0	4	8	24	96	168	0	24	96	168	0	
Visit window			±1 hr	±3 hrs	±24 hrs		±0.5 hr	±1 hr	±3 hrs	±24 hrs	±48 hrs		±3 hrs	±24 hrs	±24 hrs		

responses to treatment or suspected acquired resistance to therapy and agreed upon by the sponsor and investigator and agreed to by the participant. If the participant discontinues the study before the scheduled on-treatment biopsy (C3D1), the participant will be asked to provide a biopsy at the End of Treatment visit. Specific tissue requirements and instructions are listed in Biomarker Section 8.8.

7 **Blood sample for T cell Immunophenotyping:** One 5 mL blood sample will be collected for immunophenotype circulating lymphocytes at baseline (predose Cycle 1 Day 1), and during treatment as described above to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected. If Grade ≥2 diarrhea is observed or suspected and PD samples are not already scheduled for measurement this sample should be collected. Starting with Cycle 5, blood will be collected every 3rd cycle predose (ie., Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.) (Section 8.8.5).

8 **Blood Sample for Cytokines and Circulating Markers (central lab):** For central laboratory testing, one 5 mL blood sample will be collected to isolate serum for cytokine and circulating marker measurement. Baseline collection is required predose on Cycle 1 Day 1. On-treatment samples for cytokine and circulating marker measurement will be collected as described above. These samples will be used to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected to match clinically indicated safety cytokine samples. If Grade ≥2 diarrhea is observed or suspected and PD samples are not already scheduled for measurement this sample should be collected. Starting with Cycle 5, blood samples for cytokine and circulating markers will be collected every 3rd cycle predose (ie., Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.) (Section 8.8.4).

Table 5. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 2 Without Priming Dose

Visit Identifier	Screening	Cycle 1						Cycle ≥2						
Study Day	Within 28 days prior to registration	1		5	8	15	22	1	2	5	8	15	EOT/ withdrawal	Post treatment follow up
Hours Pre-/Post-Dose[1]		0[2]	8	96	168	0	168	0	24	96	168	0		
Visit window			± 1 hr	±24 hrs	±24 hrs		±48 hrs		±3 hrs	±24 hrs	±24 hrs			±7 days
Pharmacokinetic samples														
Blood samples for PF-07062119 concentrations		X	X	X	X	X	X	X	X (C4 only)	X[1] (C4 only)	X (C4 only)	X	X	X
Blood samples for ADA/NAb against PF-07062119[3]		X				X		X[3]					X	X
Blood samples for PK/ADA/NAb against PF-06801591[3]		X				X		X[3]					X	
Blood samples for PK/ADA/NAb against bevacizumab-Pfizer[3]		X				X		X[3]					X	
Pharmacodynamic samples														
Pfizer Prep D1 banked sample[4]		X												
Archival Tumor sample[5]	X													
De Novo Pre-treatment Tumor Biopsy[5,6]	X													
Optional or Mandatory On-Treatment Tumor Biopsy[6]												X C2 only (±7 days)	X (or 2nd on treatment)	
Blood sample for Cytokines and Circulating Markers[7]		X	X	X	X	X	X	X[7]				X (C2 only)		
Blood sample for T cell Immunophenotyping[8]		X			X	X	X	X[7]				X (C2 only)		

1 Sampling times indicated are related to the end of the SC injection. All efforts should be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the window specified will be considered acceptable. Starting Cycle 5, predose PK samples will be collected only on Day 1 of every 3rd cycle (Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.). Additional PK/PD samples should also be taken if CRS is suspected, and PK/PD samples are not already scheduled to be taken.

2 The 0-hour PK and ADA/NAb samples should be taken within 6 hours prior to PF-07062119 administration.

3 **Blood samples for PF-07062119, PF-06801591, and bevacizumab-Pfizer immunogenicity testing and PF-06801591, and bevacizumab-Pfizer PK:** Blood samples for PF-06801591 or bevacizumab-Pfizer will only be collected in participants receiving combination therapy : Refer to Section 8.4 for details. A blood sample for PF-06801591 or

Table 5. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 2 Without Priming Dose

Visit Identifier	Screening	Cycle 1						Cycle ≥2						
Study Day	Within 28 days prior to registration	1		5	8	15	22	1	2	5	8	15	EOT/ withdrawal	Post treatment follow up
Hours Pre-/Post-Dose[1]		0[2]	8	96	168	0	168	0	24	96	168	0		
Visit window			± 1 hr	±24 hrs	±24 hrs		±48 hrs		±3 hrs	±24 hrs	±24 hrs			±7 days

bevacizumab-Pfizer PK analyses should be drawn with each immunogenicity sample for PF-06801591 or bevacizumab-Pfizer, respectively. All samples should be collected on Day 1 of a cycle (also on Day 15, in Cycle 1 only) and will be drawn predose within 6 hours prior to any of the drugs being administered. Starting Cycle 5, blood samples for PK and ADA/NAb against PF-07062119 (and PF-06801591 or bevacizumab-Pfizer in combination) will be collected every 3rd cycle predose (ie, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.). Participants with an unresolved AE possibly related to ADA will be asked to return to the clinic for ADA and drug concentration assessments at approximately 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor up to a maximum of 9 months.

4 **Pfizer Prep D1 Banked Sample:** If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

5 **Pretreatment Tumor Tissue Samples:** Participants should provide a de novo pre-treatment biopsy for evaluation of baseline tissue biomarkers, unless not medically feasible, for evaluation of baseline tissue biomarkers. De novo pretreatment biopsies are preferably collected within 28 days of study start after all eligibility criteria have been verified. In addition, submission of archival samples if available is also encouraged, but not mandatory, to compare possible changes in baseline tissue biomarkers due to prior therapies. Specific tissue requirements, instructions, and conditions for submitting archival samples when collection of de novo samples is not medically feasible are listed in Biomarker Section 8.8.

6 **Paired Tumor Samples**: Paired de novo pretreatment and on-treatment biopsy samples will be mandatory for approximately 10 participants in each of the dose expansion arms and optional but encouraged for all other participants to enable evaluation of tissue biomarker PD activity. On-treatment biopsies should be taken from the same lesion, not previously irradiated, if possible. On-treatment biopsy samples are to be collected preferably after the 3rd dose and within 7 days of C2D15. **If on treatment tumor collection takes place greater than ±3 days from C2D15, additional unscheduled blood sample for cytokine and circulating markers and an unscheduled blood sample for T cell immunophenotyping sample should be collected to match the day of biopsy collection.** Additional unscheduled on-treatment biopsies, after C4D15 (>6 weeks after initial on treatment biopsy) may be collected, if indicated to evaluate potential responses to treatment or suspected acquired resistance to therapy and agreed upon by the sponsor and investigator and agreed to by the participant. If the participant discontinues the study before the scheduled on-treatment biopsy (C2D15), the participant will be asked to provide a biopsy at the End of Treatment visit. Specific tissue requirements and instructions are listed in Biomarker Section 8.8.

7 **Blood Sample for Cytokines and Circulating Markers (central lab) :** For central laboratory testing, one 5 mL blood sample will be collected to isolate serum for cytokine and circulating marker measurement. Baseline collection is required predose on Cycle 1 Day 1. On-treatment samples for cytokine and circulating markers measurement will be collected as described above. These samples will be used to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected to match clinically indicated safety cytokine samples. If Grade ≥2 diarrhea is observed or suspected and PD samples are not already scheduled for measurement this sample should be collected. Starting with Cycle 5, blood samples for cytokine and circulating markers will be collected every 3rd cycle predose (i.e., Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.).

8 **Blood sample for T cell Immunophenotyping:** One 5 mL blood sample will be collected to immunophenotype circulating lymphocytes at baseline, predose Cycle 1 Day 1, and during treatment as described above to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected. If

Table 5. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 2 Without Priming Dose

Visit Identifier	Screening	Cycle 1						Cycle ≥2						
Study Day	Within 28 days prior to registration	1		5	8	15	22	1	2	5	8	15	EOT/ withdrawal	Post treatment follow up
Hours Pre-/Post-Dose[1]		0[2]	8	96	168	0	168	0	24	96	168	0		
Visit window			± 1 hr	±24 hrs	±24 hrs		±48 hrs		±3 hrs	±24 hrs	±24 hrs			±7 days

Grade ≥2 diarrhea is observed or suspected and PD samples are not already scheduled for measurement this sample should be collected. Starting with Cycle 5, blood samples for cytokine and circulating markers and blood sample will be collected every 3rd cycle predose (i.e., Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc).

Table 6. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 2 With Priming Dose

Visit Identifier	Screening	Cycle 1							Cycle ≥2						
Study Day	Within 28 days prior to registration	1		8	15		19	22	1	2	5	8	15	EOT/ Withdrawal	Post treatment follow up
Hours Pre-/Post-Dose[1]		0[2]	8	168	0	8	96	168	0	24	96	168	0		
Visit window			± 1 hr	±24 hrs		± 1 hr	±24 hrs	±48 hrs		±3 hrs	±24 hrs	±24 hrs			±7 days
Pharmacokinetic samples															
Blood samples for PF-07062119 concentrations		X	X	X	X	X	X	X	X	X (C4 only)	X[1] (C4 only)	X (C4 only)	X	X	X
Blood samples for ADA/NAb against PF-07062119[3]		X			X				X[3]					X	X
Blood samples for PK/ADA/NAb against PF-06801591[3]					X								X[3]	X	
Blood samples for PK/ADA/NAb against bevacizumab-Pfizer[3]					X				X[3]					X	

Table 6. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 2 With Priming Dose

Visit Identifier	Screening	Cycle 1							Cycle ≥2						
Study Day	Within 28 days prior to registration	1		8	15		19	22	1	2	5	8	15	EOT/ Withdrawal	Post treatment follow up
Hours Pre-/Post-Dose[1]		0[2]	8	168	0	8	96	168	0	24	96	168	0		
Visit window			± 1 hr	±24 hrs		± 1 hr	±24 hrs	±48 hrs		±3 hrs	±24 hrs	±24 hrs			±7 days
Pharmacodynamic samples															
Pfizer Prep D1 banked sample[4]		X													
Archival Tumor sample[5]	X														
De Novo Pre-treatment Tumor Biopsy[5,6]	X														
Optional or Mandatory On-Treatment Tumor Biopsy[6]													X C2 only (±7 days)	X (or 2nd on treatment)	
Blood sample for Cytokines and Circulating Markers[7]		X	X	X	X	X	X	X	X[7]				X (C2 only)		
Blood sample for T cell Immunophenotyping[8]		X		X	X		X	X	X[7]				X (C2 only)		

1 Sampling times indicated are related to the end of the SC injection. All efforts should be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the window specified will be considered acceptable. Starting Cycle 5, predose PK samples will be collected only on Day 1 of every 3rd cycle (Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.). Additional PK/PD samples should also be taken if CRS is suspected, and PK/PD samples are not already scheduled to be taken.

2 The 0-hour PK and ADA/NAb samples should be taken within 6 hours prior to PF-07062119 administration.

3 **Blood samples for PF-07062119, PF-06801591, and bevacizumab-Pfizer immunogenicity testing and PF-06801591, and bevacizumab-Pfizer PK:** Blood samples for PF-07062119 will be collected in participants receiving monotherapy. Blood samples for PF-07062119, PF-06801591 or bevacizumab-Pfizer will be collected in participants receiving combination therapy : Refer to Section 8.4 for details. A blood sample for PF-06801591 or bevacizumab-Pfizer PK analyses should be drawn with each immunogenicity sample for PF-06801591 or bevacizumab-Pfizer, respectively. All samples for bevacizumab-Pfizer should be collected on Day 1 of a cycle (except on Day 15, in Cycle 1 only) and for PF-06801591 on Day 15 of a cycle. Samples will be drawn predose within 6 hours prior to any of the drugs being administered. Starting Cycle 5, blood samples for PK and ADA/NAb against PF-07062119 (and PF-06801591 or bevacizumab-Pfizer in combination) will be collected every 3rd cycle predose (ie, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc. for PF-07062119/bevacizumab-Pfizer and Cycle 5 Day 15, Cycle 8 Day 15, Cycle 11 Day 15 for PF-06801591). Participants with an unresolved AE possibly related to ADA will be asked to return to the clinic for ADA and drug concentration assessments at approximately 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor up to a maximum of 9 months.

Table 6. Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Part 2 With Priming Dose

Visit Identifier	Screening	Cycle 1							Cycle ≥2						
Study Day	Within 28 days prior to registration	1		8	15		19	22	1	2	5	8	15	EOT/ Withdrawal	Post treatment follow up
Hours Pre-/Post-Dose[1]		0[2]	8	168	0	8	96	168	0	24	96	168	0		
Visit window			± 1 hr	±24 hrs		± 1 hr	±24 hrs	±48 hrs		±3 hrs	±24 hrs	±24 hrs			±7 days

4 **Pfizer Prep D1 Banked Sample:** If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

5 **Pretreatment Tumor Tissue Samples:** Participants should provide a de novo pre-treatment biopsy for evaluation of baseline tissue biomarkers, unless not medically feasible, for evaluation of baseline tissue biomarkers. De novo pretreatment biopsies are preferably collected within 28 days of study start after all eligibility criteria have been verified. In addition, submission of archival samples if available is also encouraged, but not mandatory, to compare possible changes in baseline tissue biomarkers due to prior therapies. Specific tissue requirements, instructions, and conditions for submitting archival samples when collection of de novo samples is not medically feasible are listed in Biomarker Section 8.8.

6 **Paired Tumor Samples**: Paired de novo pretreatment and on-treatment biopsy samples will be mandatory for approximately 10 participants in each of the dose expansion arms and optional but encouraged for all other participants to enable evaluation of tissue biomarker PD activity. On-treatment biopsies should be taken from the same lesion, not previously irradiated, if possible. On-treatment biopsy samples are to be collected preferably after the 3rd dose and within 7 days of C2D15. **If on treatment tumor collection takes place greater than ±3 days from C2D15, additional unscheduled blood sample for cytokine and circulating markers and an unscheduled blood sample for T cell immunophenotyping sample should be collected to match the day of biopsy collection.** Additional unscheduled on-treatment biopsies, after C4D15 (>6 weeks after initial on treatment biopsy) may be collected, if indicated to evaluate potential responses to treatment or suspected acquired resistance to therapy and agreed upon by the sponsor and investigator and agreed to by the participant. If the participant discontinues the study before the scheduled on-treatment biopsy (C2D15), the participant will be asked to provide a biopsy at the End of Treatment visit. Specific tissue requirements and instructions are listed in Biomarker Section 8.8.

7 **Blood Sample for Cytokines and Circulating Markers (central lab) :** For central laboratory testing, one 5 mL blood sample will be collected to isolate serum for cytokine and circulating marker measurement. Baseline collection is required predose on Cycle 1 Day 1. On-treatment samples for cytokine and circulating markers measurement will be collected as described above. These samples will be used to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected to match clinically indicated safety cytokine samples. If Grade ≥2 diarrhea is observed or suspected and PD samples are not already scheduled for measurement this sample should be collected. Starting with Cycle 5, blood samples for cytokine and circulating markers will be collected every 3rd cycle predose (ie, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc.).

8 **Blood sample for T-cell Immunophenotyping:** One 5 mL blood sample will be collected to immunophenotype circulating lymphocytes at baseline, predose Cycle 1 Day 1, and during treatment as described above to evaluate changes from baseline. If Grade ≥1 cytokine release syndrome is suspected, additional unscheduled samples should be collected. If Grade ≥2 diarrhea is observed or suspected and PD samples are not already scheduled for measurement this sample should be collected. Starting with Cycle 5, blood samples for cytokine and circulating markers and blood sample will be collected every 3rd cycle predose (ie, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, etc).

2. INTRODUCTION

PF-07062119 is an anti-Guanylyl Cyclase 2C (GUCY2c)/anti-CD3 bispecific Fc diabody targeting CD3 on T cells with one binding domain and GUCY2c with the other binding domain. PF-07062119 acts as a T cell redirecting bispecific for the treatment of gastrointestinal tumors including colorectal, gastric and esophageal adenocarcinomas.

2.1. Study Rationale

In the dose-escalation/finding phase (Part 1), PF-07062119 will be evaluated with or without a priming dose for the treatment of adult participants with advanced gastrointestinal adenocarcinomas (colorectal, gastric, and esophageal) known to express GUCY2c and for whom no standard therapy is available. The priming dose has been implemented to mitigate cytokine release syndrome (CRS) with the initial full dose. Based on available data from participants enrolled across dose escalation without priming, cytokine production and CRS occur primarily with the initial dose of PF-07062119, supporting the hypothesis that induction of immune activation with a lower priming dose may attenuate CRS associated with the initial full dose. The use of a priming approach to mitigate CRS is also supported by data from clinical studies with other T-cell engaging agents and will be evaluated in this clinical study.

In the dose-expansion phase (Part 2), PF-07062119 will be evaluated with or without a priming dose in separate dose-expansion arms as monotherapy and in combination with another agent (eg, immune checkpoint inhibitor and anti-VEGF, separately) in colorectal cancer (CRC) and then possibly be evaluated in other gastrointestinal adenocarcinomas, CRC subtypes, or combination options, as indicated.

A number of clinical trials have shown a correlation between certain tumor mutations (eg, KRAS or BRAF) and the lack of response to targeted therapy, such as anti-EGFR antibodies in participants with tumors that are KRAS positive (Allegra et al, 2009; Di Nicolantonio et al, 2008; Pratilas et al, 2008; Solit et al, 2006).[2,14,35,42] Pfizer's in vivo pharmacology studies demonstrated anti-tumor efficacy with PF-07062119 in cell line xenograft (CLX) and participant-derived xenograft (PDX) models of colorectal cancer, most of which are mutant for KRAS or BRAF oncogenes. Additionally, PF-07062119 has the potential to be used in the settings of either microsatellite stable (MSS) or high microsatellite instability (MSI-H) disease gastrointestinal adenocarcinomas as GUCY2C is expressed across both subtypes (Bashir et al, 2019).[5]

Additionally, immune checkpoint inhibition mechanisms (Salmaninejad, 2019),[39] such as upregulation of PD-L1 (Programmed death ligand 1) in response to treatment could lead to resistance to PF-07062119 activity, which is dependent on T-cell activation. To address this issue, PF-07062119 combinations with immune checkpoint inhibitors were evaluated and showed enhanced efficacy compared to single agents. Furthermore, combinations of PF-07062119 were evaluated with anti-angiogenesis agents, which have been reported to enhance T-cell infiltration into tumors (Allen et al 2017).[3] Accordingly, combinations of PF-07062119 with either an anti-VEGF-A antibody, or axitinib, a small molecule anti-angiogenic agent, showed complete tumor regressions compared to single agents, which

had minimal to moderate efficacy in the colorectal tumor model tested. These studies collectively suggest that single agent efficacy observed with PF-07062119 can be enhanced with immune checkpoint blockade agents, which prevent T-cell exhaustion, as well as with anti-angiogenesis agents which could increase tumor infiltrating lymphocytes (TILs).

2.2. Background

2.2.1. Advanced Gastrointestinal Adenocarcinomas

Certain gastrointestinal tumors, including colorectal cancer (CRC), gastric cancer, and gastroesophageal cancer, continue to be an area of unmet medical need despite advances in cytotoxic chemotherapies and newer targeted agents.

CRC globally ranks third in terms of incidence with over 1.8 million new CRC cases and 881,000 deaths are estimated to occur (Bray et al, 2018).[10] In the US, nearly 150,000 new cases of CRC are diagnosed each year, resulting in the deaths of nearly 50,000 people annually (Ahmedin et al, 2009).[1] Currently, treatment options include combinations of a fluoropyrimidine with either oxaliplatin or irinotecan as a backbone. Targeted agents have shown added benefit when added to these regimens, including monoclonal antibodies directed against the Epidermal Growth Factor Receptor (EGFR; cetuximab and panitumumab) and vascular endothelial growth factor (VEGF; bevacizumab, aflibercept) (Hurwitz HI et al, 2009; Saltz LB et al, 2008, Chau I and Cunningham D, 2009). [20,38,12] Also, though the clinical benefit is very limited, treatment for advanced refractory CRC has been developed, including regorafenib, an oral multikinase inhibitor, and trifluridine/tipiracil (Lonsurf®), a DNA synthesis modulator that inhibits cell proliferation (Grothey A et al, 2013, Lonsurf® USPI).[17] However, despite advances in the treatment of CRC, progression of disease will occur in a significant proportion of participants leading to morbidity and mortality.

Gastric cancer is also prevalent with an estimated 200,000 new cases in the US, EU5, and Japan and is the fifth most frequently diagnosed cancer worldwide (Bray F et al, 2018).[10] The diagnosis of gastric cancer occurs when already in advanced stage disease and may present in different areas of the stomach including the gastroesophageal junction. Systemic chemotherapy is the most common treatment approach for recurrent/metastatic disease that may include the use of FOLFOX and epirubicin-based platinum combination chemotherapy along with trastuzumab addition to those overexpressing HER2 as common frontline regimens. Ramucirumab (Cyramza®) with or without paclitaxel or paclitaxel with irinotecan and gemcitabine or other mono and combo chemotherapies are used in more advanced lines (Nagaich N and Sharma R, 2018).[33] Also, immuno-oncology compounds, such as pembrolizumab, have demonstrated limited clinical benefit and may be considered (Kiyozumi Y et al, 2018).[23]

Each year, over 500,000 new cases of esophageal cancer are diagnosed worldwide with over 17,000 cases diagnosed in the US, of which adenocarcinoma comprises an estimated 20% of cases (Bray et al, 2018).[10] Treatment options for esophageal adenocarcinoma are generally similar to those used in gastric adenocarcinoma. Chemotherapy, possibly along with targeted drug therapy has been used. Similar to CRC patients, outcomes for patients with recurrent

metastatic gastric and esophageal cancer disease are poor. Thus, effective therapies to address colon, gastric and esophageal adenocarcinomas are needed.

2.2.2. GUCY2c Expression in Human Cancers

GUCY2c is a candidate target for bispecific antibody-based immunotherapy due to its high expression across gastrointestinal tumors including colon cancer (expressed in >90% of cases across all stages), and gastric or gastroesophageal junction cancer (expressed in >50% of adenocarcinoma cases of the esophagus and stomach) (Birbe et al, 2005; Danaee et al, 2017).[9,13] Target expression in normal tissues is largely restricted to the apical side of intestinal epithelial tight junctions, which could allow for preferential uptake of GUCY2C targeted biologics by tumors that have disrupted tight junction architecture making it an appropriate antigen to targeted therapy approaches. These considerations highlight the potential of PF-07062119 as a treatment option for colon, gastric and esophageal adenocarcinomas.

2.2.3. Bispecific Redirected T-cell Engaging Therapies

The potential of redirected T-cell therapeutics in cancer treatment has been demonstrated by the United States Food and Drug Administration's approval of the bispecific T-cell engager, blinatumomab for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia.[42] Bispecifics with a redirected T-cell engaging modality have also shown promise for the treatment of solid tumors, including CRC, with several bispecific agents in early clinical studies (Tabernero et al, 2017; Moore PA et al, 2018).[45,27]

Cytotoxic T lymphocytes (CTLs) conventionally recognize cell protein antigens presented in complex with Major Histocompatibility Complex (MHC) Class I molecules on the cell surface via their T-cell receptors (TCRs).[38] CD3 bispecifics circumvent the need for TCR engagement through MHC Class I in complex with antigenic peptide, and instead recruit T cells to target cells expressing cell surface target protein (antigen). One arm of the bispecific binds to a tumor associated cell surface antigen, and the other arm binds to the CD3ε protein, which is a part of the TCR complex on T cells. Co-engagement of CD3ε on T cells and target antigen on tumor cells via a bispecific molecule leads to a cytotoxic response. Cytotoxicity is mediated by release and transfer of granzyme B and perforin from the T cell to the target cell. Using this CD3-bispecific mechanism of action, PF-07062119 redirects T cells to target GUCY2c expressing tumor cells through co-engagement of CD3ε on the T cell, and GUCY2c on the tumor cell surface, thereby broadening the repertoire of T cells that can recognize tumors and act as effector cells.

2.2.4. PF-07062119

PF-07062119 is a fully humanized and optimized anti-GUCY2c bispecific therapeutic drug candidate that is a heterodimeric diabody Fc fusion protein comprised of two recombinant scFv domains, one fully human domain directed against GUCY2c and the other against the CD3ε chain (humanized), fused to the human Fc domain of immunoglobulin 1 (IgG1). PF-07062119 binding of CD3ε on T cells and GUCY2c on tumor cells redirects T cells to target GUCY2c-expressing tumor cells which initiates killing of the GUCY2c expressing tumor cell. PF-07062119 allows the T-cell to circumvent the need for the interaction of the

TCR and MHC class I in complex with antigen, and instead redirects T-cells to target cells through direct co-engagement of CD3ε expressed on T-cells.

2.2.5. Nonclinical Pharmacology

Further details of the nonclinical pharmacology of PF-07062119 are provided in the IB.

2.2.5.1. In Vitro Pharmacodynamics

PF-07062119 demonstrated low-nM binding to human GUCY2c (K_D = 7.47 nM) and human CD3 (K_D = 23.97 nM) by surface plasmon resonance (SPR, 25°C), and low-nM binding to both targets simultaneously (EC_{50} = 8.78 nM) by recombinant protein enzyme linked immunosorbent assay (ELISA). PF-07062119 binding to cynomolgus monkey GUCY2c and mouse GUCY2c demonstrated K_D values of 3.01 nM and 17.27 nM, respectively.

2.2.5.1.1. Cell Surface Binding and Cytotoxicity of PF-07062119 in GUCY2c Expressing Tumor Cell Lines

PF-07062119 showed dose dependent binding by flow cytometry to cell line 300.19 engineered to express human GUCY2c, while no binding was observed in parental non-GUCY2c expressing 300.19 cells, thereby demonstrating specificity of PF-07062119 to GUCY2c. GUCY2c cell surface expression was quantified over a panel of cancer cell lines using a flow cytometry-based assay with an anti-human GUCY2c monoclonal antibody (mAb). HCT116 cells were verified as negative for GUCY2c expression and were used as the negative control cell line in subsequent CTL assays.

PF-07062119-mediated cell killing was assessed in these cell lines in a 48- hour CTL assay at a 5:1 or 1:1 effector (T cell) to target (tumor cell) ratio. The observed cytotoxicity was T cell dependent since no activity was observed with PF-07062119 in the absence of T cells. PF-07062119 demonstrated cell killing in all GUCY2c expressing cell lines but not in GUCY2c negative HCT116 cells. Cytokine release was also assessed in these in vitro CTL assays as a surrogate measure of PF-07062119 ability to activate human T cells. Following the addition of PF-07062119 and T cells, cytokines were detected in the supernatants of all GUCY2c-expressing cancer cell lines, but not in GUCY2c-negative HCT116 cells.

Additionally, PF-07062119 was assessed for its potential to agonize GUCY2c pathway activity by measuring the production of the downstream effector cyclic guanosine monophosphate (cGMP) in GUCY2c expressing T84 tumor cells. While the GUCY2c pathway agonist, bacterial enterotoxin STp, increased cGMP in a dose-dependent manner, cGMP production was not enhanced by the addition of increasing concentrations of PF-07062119. Additionally, PF-07062119 did not affect cGMP production induced by STp, indicating that PF-07062119 is neither a GUCY2c pathway agonist, nor does it neutralize GUCY2c pathway function in the presence of ligand.

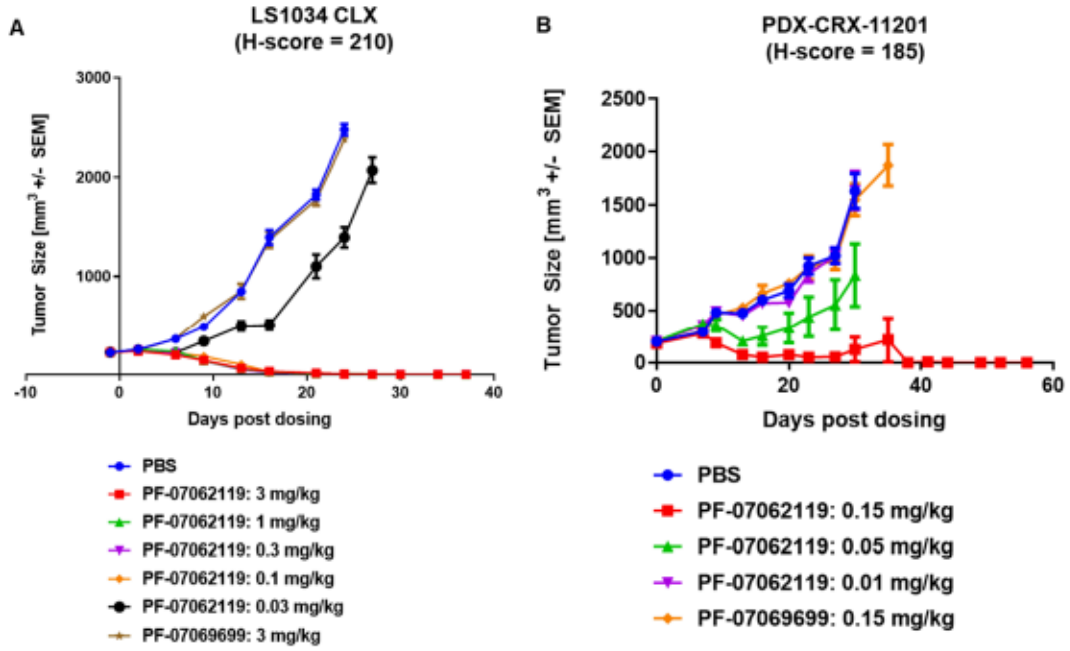
2.2.5.1.2. In Vivo Pharmacodynamics

Single Agent PF-07062119 Studies: Anti-tumor Efficacy of PF-07062119 in Colorectal Tumor Models with Varying GUCY2c Expression

In vivo studies with PF-07062119 were conducted in CLX and PDX models of colorectal cancer with varying levels of GUCY2c expression. Figure 1 highlights dose-dependent single agent anti-tumor activity observed in the LS1034 CLX model and the PDX-CRX-11201 PDX model, both of which had relatively high expression of GUCY2c and were mutant for BRAF and KRAS.

Female NOD-scid IL-2Rγγnull (NSG) mice were implanted subcutaneously with the LS1034 cell line or fragments of PDX-CRX-11201, using adoptive human T-cell transfer. In the LS1034 model, PF-07062119 treatment resulted in significant efficacy ($p < 0.0001$ versus vehicle) with complete tumor regressions in 10/10 mice dosed as low as 0.1 mg/kg (Figure 1-**A**). The anti-tumor activity was dose-dependent, since lower efficacy was observed at 0.03 mg/kg of PF-07062119. PDX-CRX-11201 tumor bearing mice treated with PF-07062119 also showed significant efficacy ($p < 0.0001$ versus vehicle) with 9/10 complete tumor regressions at 0.15 mg/kg (Figure 1-**B**). A lower dose of 0.05 mg/kg resulted in reduced efficacy ($p < 0.05$ versus vehicle), whereas 0.01 mg/kg did not show any tumor inhibition. Neither the PBS vehicle control, nor the negative control bispecific, PF-07069699, inhibited tumor growth in any model. All treatments were well tolerated with no overall effect on body weight.

Figure 1. Single Agent PF-07062119 Efficacy in Established Tumor Models with Adoptive Human T Cell Transfer



NSG mice bearing A.LS1034, B.PDX-CRX-11201 tumors were dosed IV with PF-07062119, PF-07069699 or PBS with weekly IV doses (3 doses for LS1034 and 4 doses for PDX-CRX-11201), and human T cells were administered one day after the first dose. Tumors were measured twice weekly. Data are reported as mean tumor volume ± SEM.

IV=intravenous; NSG=NOD-scid IL-2Rγ^{null}; PF-07062119=GUCY2c-CD3 bispecific; PF-07069699=negative control CD3 bispecific; SEM=standard error of the mean.

2.2.5.1.2.1. Evaluation of Intravenous versus Subcutaneous Dosing Following Single Agent PF-07062119 in a Colorectal Tumor Model

The route of administration of dosing PF-07062119 was compared in efficacy studies using the high GUCY2c-expressing LS1034 SC CLX model, where the bispecific was dosed Q7Dx3 IV or SC 0.1 mg/kg, 0.06 mg/kg and 0.03 mg/kg. There was no statistically significant difference in the efficacy observed with IV or SC administration of PF-07062119 at each dose level tested (p-values >0.05).

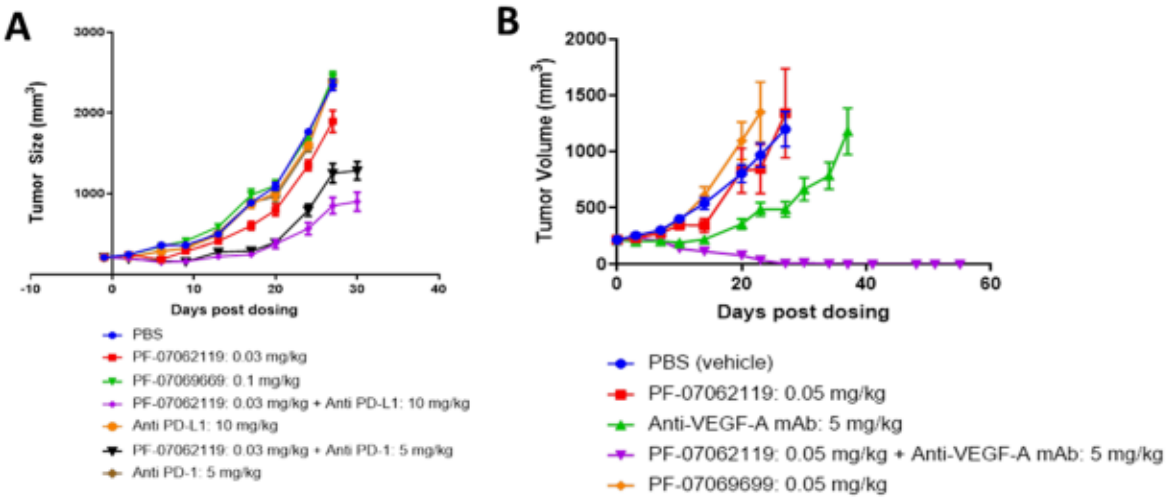
2.2.5.1.2.2. Combination Studies with PF-07062119 and Anti-PD-L1, Anti-PD-1, or Anti-VEGF-A

The LS1034 CLX model demonstrated PF-07062119 treatment dependent increase in TILs with expression of granzyme B that was polarized towards tumor cells, suggesting that these TILs were poised to form immune synapses and kill tumor cells. Additionally, tumors treated with PF-07062119 also showed upregulation of PD-L1 (avelumab mouse reverse chimeric antibody) at both 1 mg/kg and 0.03 mg/kg doses, indicating that checkpoint mechanisms that could dampen CTL activity were being induced with treatment. Therefore, PF-07062119

combinations with PD-1 (pembrolizumab antibody with human IgG2 Fc effector function mutant backbone [D265A hIgG2dA Fc effector function mutant])/PD-L1 checkpoint inhibitors were evaluated in this model. Tumor-bearing mice were treated with a minimally efficacious dose of 0.03 mg/kg of PF-07062119 as a single agent, in combination with either 10 mg/kg anti-PD-L1 or 5 mg/kg anti-PD-1. In both anti-PD-L1 and anti-PD-1 combinations with PF-07062119, a significant combination benefit was observed (p-values of <0.0001 and 0.0004 respectively), whereas minimal to no efficacy was observed with single agents (Figure 2).

In addition, anti-VEGF blockade, a mechanism known to increase T-cell infiltration in tumors was combined with PF-07062119. The PDX-CRX-11201 model, which is partially responsive to anti-VEGF-A mAb treatment, was used to evaluate the benefit of combining PF-07062119 with anti-VEGF-A therapy. The combination of the anti-VEGF-A treatment with a minimally efficacious single agent dose of PF-07062119 at 0.05 mg/kg led to complete tumor regressions in 10/10 mice. In all combination studies, all treatments were well tolerated and there was no overall effect on body weight.

Figure 2. Anti-tumor Efficacy following PF-07062119 in Combination with Anti PD-1, Anti-PD-L1, or Anti-VEGF-A in Colorectal Tumor Models



A. NSG mice bearing SC LS1034 tumors were dosed IV with PF-07062119 (as single agent or in combination with anti-PD-L1/ anti-PD-1 mAbs), PF-07069699 or PBS on Days -1, 6 and 13 (Q7Dx3) IV. Anti-PD-L1 mAb was administered IV on days -1, 2, 5, 8, 11 and 14 (Q3Dx6) either as a single agent or combination with PF-07062119. Anti-PD-1 mAb was dosed IV on days -1, 6 and 13 (Q7Dx13) either as single agent or in combination with PF-07062119. All mice were dosed IV with T cells on Day 0 to evaluate combination benefits of administering PF-07062119 with anti-PD-L1/anti-PD-1 vs single agent treatment.

B. NSG mice bearing SC PDX-CRX-11201 tumors were dosed IV with PF-07062119 (as single agent or in combination with anti-VEGF-A mAb), PF-07069699 or PBS on Days 0, 7 and 14 (Q7Dx3) IV. Anti-VEGF-A mAb was administered IV on days 0, 3, 6, 9 (Q3Dx4) either as a single agent or combination with PF-07062119. All mice were dosed IV with T cells on Day 1 to evaluate combination benefit of administering PF-07062119 **with** VEGF blockade. Tumor were measured twice weekly. Data are reported as mean tumor volume ± SEM.

IV=intravenous; NSG=NOD-scid IL-2Rγ^{null}; PF-07062119=GUCY2c-CD3 bispecific; PF-07069699=negative control CD3 bispecific; mAb=monoclonal antibody; Q7Dx3=dosing every 7 days for a total of 3 doses; Q3Dx6=dosing every 3 days for a total of 6 doses; Q3Dx4=dosing every 3 days for a total of 4 doses; SEM=standard error of the mean.

For additional details of the in vitro and in vivo activity of PF-07062119 refer to the IB.

2.2.6. Nonclinical Pharmacokinetics and Metabolism

PK of PF-07062119 was evaluated in cynomolgus monkeys following IV injections of PF-07062119 at doses from 1 µg/kg to 180 µg/kg and SC administration at 3 µg/kg to 60 µg/kg. PF-07062119 mean systemic exposure increased with dose in a generally dose-proportional manner suggesting no evidence of target-mediated drug disposition (TMDD) across the tested dose range. Based on population PK analysis, the mean drug clearance from the central compartment (CL) in cynomolgus monkeys was 0.22 mL/h/kg, the mean steady state volume of distribution (V_{ss}) was 73 mL/kg, and the mean terminal elimination half-life ($t_{½}$) was 10 days. Following subcutaneous (SC) administration, bioavailability was moderate (~60%) [as assessed by area under the curve within the first dosing interval (AUC_{tau})]. The mean PF-07062119 maximum observed concentration (C_{max}) after the first dose administration of

60 µg/kg SC was ~70% lower compared to 60 µg/kg IV administration. The incidence of ADA induction in the pivotal toxicity study was approximately 1/27 (3.7%), thus no formal assessment of the impact on ADA on PF-07062119 exposure was conducted. No apparent impact of gender on the systemic exposure of PF-07062119 was observed. Based on the PK observed in cynomolgus monkeys, the PK of PF-07062119 in humans is expected to be linear across the dose range to be tested with a $t_{½}$ of approximately 21 days.

2.2.7. Nonclinical Safety

In nonclinical IV or SC studies with PF-07062119 in cynomolgus monkeys of up to 1-month in duration, severely toxic findings were observed at the high non-tolerated dose of 60 µg/kg (once weekly IV or SC) in the 1-month GLP toxicity study. This dose was not tolerated due to declining condition related to extensive and persistent clinical observations of gastrointestinal distress (including diarrhea, dehydration, hypoactivity, reduced appetite, etc.) and body weight loss that resulted in unscheduled euthanasia of 4 animals (2 animals in the IV group and 2 animals in the SC group) and discontinuation of drug treatment for 3 additional animals at the high dose (1 and 2 animals in the IV and SC groups, respectively). Clinical signs of gastrointestinal distress, particularly diarrhea and dehydration, were also observed at a lower dose of 30 µg/kg IV during 10-day non-GLP toxicology studies but were tolerated with supportive care (oral and SC fluids). The dose of 3 µg/kg SC was tolerated in the 1-month GLP toxicity study with only minor occasional clinical observations of emesis or loose stool. Additionally, clinical observations of cytokine release syndrome (including emesis, hypoactivity, changes in body temperature, hunched posture, etc) were observed after the first dose of PF-07062119 and were associated with elevated serum cytokines and markers of T-cell activation. These observations were limited to 1/10 animals with transient emesis on Day 1 at 3 µg/kg SC. The incidence of clinical observations related to cytokine release as well as the magnitude of serum cytokine elevations were significantly lower and was associated with a decreased C_{max} of approximately 70% in animals dosed via the SC route compared with the IV route.

Test article-related, but nonadverse, target organs identified included the gastrointestinal tract (crypt cell hyperplasia, villous atrophy, mixed cell inflammation, gastric gland hypertrophy), hematolymphopoietic system (decreased cellularity of bone marrow, spleen and thymus), pancreas (mononuclear cell infiltrates of islet cells), testis (seminiferous tubular degeneration and reduced sperm), epididymis (cellular debris and epithelial vacuolation), and kidney (tubular dilatation of proximal and distal tubules and collecting duct) and all findings completely recovered or were only seen in animals euthanized early (kidney, testis, epididymis).

The No Adverse Effect Level (NOAEL)/Highest Non-Severely Toxic Dose (HNSTD) in the pivotal 1-month good laboratory practice (GLP) study was 3 µg/kg SC. The mean C_{max} and AUC_{168} after administration of one dose of 3 µg/kg SC were 24.7 ng/mL and 3710 ng·h/mL, respectively. The mean C_{max} and AUC_{168} after administration of 5 weekly doses of 3 µg/kg SC were 89.7 ng/mL and 13,600 ng·h/mL, respectively.

The starting dose of 45 µg Q2W is predicted to have a human C_{max} of 4.2 ng/mL and AUC_{168} of 566 ng•hr/mL. The margin of safety based on C_{max} and AUC_{168} was calculated as

approximately 21× and 24×, respectively based on the comparison of HNSTD exposure in the 1-month repeat-dose GLP toxicity study in monkeys to the predicted human exposure at the recommended starting dose.

Further details of the nonclinical safety program are provided in the current IB.

2.2.8. Summary of Current Clinical Data from Study C3861001

The current summary of clinical data is based on Part 1A, dose escalation of the PF-07062119 monotherapy without priming dose, of Study C3861001. As of 28 December 2020, 22 participants have been dosed across 5 dose levels (45 µg, 135 µg, 400 µg, 800 µg, and 1600 µg) of PF-07062119 administered SC Q2W.

2.2.8.1. Safety Data Update

The most common treatment-emergent adverse events occurring in ≥10% of participants and possibly related to PF-07062119 included fever, diarrhea, vomiting, CRS, nausea, pruritus, fatigue, injection site reaction, decreased appetite, hypotension, lipase increase, alanine aminotransferase increased, amylase increased, aspartate aminotransferase increased, chills, constipation, headache, and hypokalemia. A DLT of Grade 3 diarrhea (lasting >3 days) occurred in both participants treated at the highest dose level (1600 µg) without priming, and DLT of Grade 3 diarrhea (lasting >3 days) and Grade 3 CRS occurred respectively in 2 of 9 participants treated at the dose level (800 µg) established as the single-agent maximum tolerated dose (MTD) without priming.

2.2.8.2. Pharmacokinetics

Preliminary PK parameters for participants estimated using nominal collection times and quality-controlled, not quality-assured bioanalytical data are presented in Table 7. Data are summarized for all cohorts (45 µg, 135 µg, 400 µg, 800 µg, and 1600 µg) treated with a single SC dose of PF-07062119.

Following SC administration, PF-07062119 was absorbed slowly with a median T_{max} for most cohorts ranging from 4 to 7 days post single-dose administration. Overall, exposures increased in an approximately dose-proportional manner with increasing doses.

Following repeated dosing Q2W, the predose concentrations increased with each successive dose indicating potential accumulation of the drug. Limited data are available for multiple dose PK in Cycle 4, due to most participants coming off study prior to the assessment.

Table 7. Mean (% CV) PK Parameters Following Single SC Doses of PF-07062119 in Participants with Advanced GI Tumors (Study C3861001)

Dose (µg) SC/# of participants	Study Day	T_{max}[2] (hr)	C_{max}[1] (ng/mL)	AUC_{168}[1,3] (ng*hr/mL)	AUC_{336}[1,3] (ng*hr/mL)
45 (n=2)	C1D1	8-336	2.97	339	803
135 (n=3)	C1D1	168 (96-168)	9.03 (9.8)	1205 (4.4)	2600 (8.0)
400 (n=6)	C1D1	96 (96-336)	43.7 (40)	5582 (54)	12068 (42)
800 (n=9)	C1D1	96 (24-168)	66.8 (39)	9041 (39)	18943 (35)
1600 (n=2)[4]	C1D1	24	115	16451	--

1 C_{max}, AUC_{168} and AUC_{336}: mean (%CV). Only mean presented for N=2. Only individual value presented if N=1.
2 T_{max}: Median (Range). Only range presented for N=2. Only individual value presented if N=1.
3 800 µg: n=8 for AUC_{168} and AUC_{336}
4 1600 µg: n=1 for T_{max}, C_{max} and AUC_{168}. One of the 2 participants at this dose level provided PK only up to 48 hours.

2.3. Anti-Programmed Cell Death Protein-1 (Anti-PD-1)

Binding of the programmed cell death protein-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation, cytokine production, and its cytotoxic functions. Upregulation of PD-1 ligands occur in certain tumor types and signaling through this pathway can contribute to the inhibition of active T-cell immune surveillance of tumors. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Approval of nivolumab/Opdivo® (a fully human immunoglobulin G4 [IgG4] anti-PD-1 antibody [Ab]), pembrolizumab/Keytruda® (a humanized IgG4 anti-PD-1 Ab), Atezolizumab/Tecentriq® (a humanized IgG1 anti-PD-L1 Ab), durvalumab/Imfizi® (a humanize IgG1 anti-PD-1 Ab), and avelumab/Bavencio® (a fully human IgG1 anti-PD-L1 Ab) for the treatment of multiple tumor indications provide compelling evidence that blockage of the PD-1 pathway is a validated immunotherapeutic approach (Opdivo® United States Package Insert (USPI), 2019; Tecentriq® USPI, 2019; Keytruda® USPI, 2019; Imfinzi™ USPI, 2018; Bavencio® USPI, 2019).

2.3.1. PF-06801591, an Anti-PD-1 Antibody: Clinical Experience in Study B8011001 (NCT02573259)

B8011001 is an ongoing Phase 1, open-label, multi-center, multiple-dose, dose escalation and expansion, safety, PK, and PD study of PF-06801591. The primary purpose of this study is to evaluate safety and early signs of efficacy. This clinical study was divided into a dose escalation (Part 1) phase and a dose expansion (Part 2) phase. As of 10 February 2021, enrollment has been completed in this study and 146 participants have been dosed on the study ranging from 0.5 mg/kg IV up to 300 mg SC. Reference Section 10.9 for Preliminary Clinical Summary. More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06801591 may be found in the respective IB, which is the single reference safety document (SRSD).

2.4. Overview of Bevacizumab-Pfizer (Zirabev™)

Bevacizumab is a vascular endothelin growth factor (VEGF) inhibitor and approved for treatment of metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment and also in combination with fluoropyrimidine-, irinotecan- or fluoropyrimidine-oxaliplatin based chemotherapy for second-line treatment in participants who have progressed on a first-line bevacizumab product-containing regimen. Clinically significant adverse reactions include gastrointestinal perforations and fistulae, surgery and wound healing complications, hemorrhage, arterial and venous thromboembolic events, hypertension, posterior reversible encephalopathy syndrome, renal injury and proteinuria, infusion-related reactions, ovarian failure, and congestive heart failure (Pfizer, United States Package Insert (USPI), 2019). The biosimilar version of Avastin® will be used in this study, manufactured by Pfizer and hereafter referred to as bevacizumab-Pfizer. Bevacizumab-Pfizer is commercially available and will be used in accordance with its local label. The SRSD for bevacizumab-Pfizer is its core data sheet (CDS).

2.5. Benefit/Risk Assessment

There continues to be significant unmet medical need for more effective therapies for advanced or metastatic gastrointestinal adenocarcinomas that have relapsed or are refractory to current therapies. Currently available therapies for advanced or metastatic colorectal and gastric adenocarcinomas have very limited clinical benefit both in terms of response and duration of response. Although there is limited clinical experience with PF-07062119, which is an anti-GUCY2c/anti-CD3-bispecific being developed for advanced gastrointestinal malignancies including colorectal and gastric adenocarcinomas, significant tumor reduction was observed in preclinical pharmacology studies with PF-07062119 in a number of models with colorectal adenocarcinomas, including those that are especially resistant such as those with KRAS and BRAF positivity. Additionally, PF-07062119 has the potential to be used in the settings of either microsatellite stable (MSS) or high microsatellite instability high (MSI-H) disease gastrointestinal adenocarcinomas since GUCY2c is expressed across both subtypes (Bashir et al, 2019).[5]

The safety profile of PF-07062119 has been characterized in exploratory and pivotal toxicology studies and is described in Section 2.2.8. The primary toxicities associated with PF-07062119 in non-human primates include diarrhea and CRS at doses considered to not be tolerable. However, these toxicities were of limited frequency and grade and therefore considered non-adverse at tolerable doses. CRS and diarrhea have been observed in the clinical study. Close medical monitoring, including inpatient observation for at least 48 hours following the initial PF-07062119 SC dose and for at least 8 hours following the second PF-07062119 SC dose in the cohort without a priming dose and at least 24 hours after the first (priming) SC dose and 24 hours after the second (full) SC dose in the cohort with a priming dose, along with safety assessments will occur throughout the study. Supportive care measures as described in Section 6.6.2 are available that may be considered in the management of both CRS and diarrhea (Lee et al, 2014; Lee et al, 2019; Benson et al, 2004).[24,25,7]

At this stage of development, the benefit-risk for PF-07062119 is considered acceptable in participants with advanced gastrointestinal adenocarcinomas.

For this study, the study intervention is PF-07062119. PF-06801591 and bevacizumab-Pfizer will be used as combination agents with PF-07062119. More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07062119 and PF-06801591 may be found in their respective IBs, which are their SRSDs for this study. For the PET imaging study more detailed information about the known and expected benefits and risks and reasonably expected AEs of the PET tracer being used may be found in the ImaginAB IB which is the respective SRSD for this study. Bevacizumab-Pfizer is approved and will be commercially available in certain regions and will be used in accordance with its local label. The SRSD for bevacizumab-Pfizer is its CDS.

3. OBJECTIVES AND ENDPOINTS

Dose Escalation (Part 1):

Objectives	Endpoints
Primary:	**Primary:**
• To assess safety and tolerability of increasing dose levels of PF-07062119 with and without priming dose administered in participants with advanced gastrointestinal tumors, including colon, gastric, and esophageal adenocarcinomas, for whom no standard therapy is available in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D) as a monotherapy in Part 1A and in combination therapy in Part 1B with select tumor(s).	• First cycle Dose Limiting Toxicities (DLTs); • Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 5), timing, seriousness, and relationship to study therapy; • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version [version 5.0]), and timing.
Secondary:	**Secondary:**
• To characterize the single and multiple dose PK of PF-07062119; • To evaluate the immunogenicity of PF-07062119; • To evaluate the immunogenicity of PF-06801591 and bevacizumab-Pfizer given in combination with PF-07062119 (Part 1B); • To evaluate immune cells in archival tumor biopsies and/or pre and post treatment tumor biopsies (if available); • To evaluate preliminary anti-tumor activity.	PK parameters of PF-07062119: • Cycle 1 and Cycle 4 PK parameters maximum concentration (C_{max}), time to achieve C_{max} (T_{max}), area under the concentration versus time curve from time zero to the last quantifiable concentration (AUC_{last}). If data permits, other PK parameters will be derived such as apparent clearance (CL/F), terminal half-life ($t_{1/2}$), and the area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}); • Predose trough concentrations after multiple doses of PF-07062119; • Incidence and titers of ADA and NAb PF-07062119; • Incidence and titers of ADA and NAb against PF-06801591 and bevacizumab-Pfizer given in combination with PF-07062119 (Part 1B);

Objectives	Endpoints
	• Assessment of levels of intra-tumor T cells (eg, CD8 IHC); • Objective response, as assessed using RECIST version 1.1.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To explore preliminary anti-tumor activity by standard and immune-related response criteria and time to event endpoints; • To explore the relationship between target expression and biomarkers in archival tumor biopsies and/or pre and post treatment tumor biopsies (if available), whole blood, and serum samples in order to elucidate mechanism of action and response to therapy; • To explore additional biomarkers related to clinical response, in order to elucidate the mechanism of action of PF-07062119, predict response to therapy, and to understand resistance mechanisms that may predict escape from therapy; • To evaluate T, B, and Natural Killer (NK) subtypes for immunophenotyping in addition to T cell proliferation, activation, and exhaustion markers in whole blood; • To explore cytokines and chemokines as pharmacodynamic (PD) markers in pre and on treatment serum samples; • To explore the tumor biomarker carcinoembryonic antigen (CEA) levels; • To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision. • To evaluate the trough levels of PF-06801591 and bevacizumab-Pfizer given in combination with PF-07062119 (Part 1B;	• Progression free survival (PFS) and duration of response (DOR) by RECIST version 1.1; • Overall tumor assessment by the Immune Related Response Criteria in Solid Tumor (irRECIST) (criteria and immune-related progression free survival (irPFS); • GUCY2c expression levels in archival and/or pre and on/post treatment tumor biopsies; • Immunophenotyping of blood Immune cell subtypes frequency and activation; • Intra-tumor immune pathway modulation, gene expression profiles, DNA mutations and immune cell biomarkers in pre- and post-dose tumor biopsies; • Cytokine and chemokine PD markers in pre and on treatment serum samples; • CEA levels in serum; • Changes in CD8 PET tracer uptake pre and post treatment for participants involved in CD8 PET tracer substudy (Section 10.19.3) • Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study). • Trough levels of PF-06801591 and bevacizumab-Pfizer

Dose Expansion (Part 2):

Objectives	Endpoints
Primary:	**Primary:**
• To confirm safety and tolerability and evaluate preliminary evidence of anti-tumor activity of PF-07062119 at the RP2D in participants with advanced colorectal adenocarcinomas (as a monotherapy and in combination therapy).	• AEs as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version [version 5.0], timing, seriousness, and relationship to study therapy; • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 5.0]), and timing; • ORR as determined by the RECIST version 1.1 criteria.
Secondary:	**Secondary:**
• To evaluate the PK of PF-07062119 at the RP2D; • To evaluate the immunogenicity of PF-07062119; • To evaluate the immunogenicity of PF-06801591 and bevacizumab-Pfizer given in combination with PF-07062119; • To evaluate immune PD effects of PF-07062119 between pre-treatment and post treatment tumor biopsies; • To evaluate preliminary anti-tumor activity through time to event endpoints.	• PK concentrations of PF-07062119; • Predose trough concentrations after multiple doses of PF-07062119; • Incidence and titers of ADA and NAb PF-07062119; • Incidence and titers of ADA and NAb against PF-06801591 and bevacizumab-Pfizer given in combination with PF-07062119; • Assessment of increased intra-tumor T cells following PF-07062119 treatment (eg, CD8 IHC); • PFS and DOR by RECIST version 1.1.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To document any anti-tumor activity as assessed by immune related response criteria; • To explore the relationship between target expression and biomarkers in archival tumor biopsies and/or pre- and post-treatment tumor biopsies, whole blood, and serum samples in order to elucidate mechanism of action and response to therapy; • To explore additional biomarkers related to clinical response, in order to elucidate the mechanism of action of PF-07062119, predict response to therapy, and to understand resistance mechanisms that may predict escape from therapy; • To evaluate T, B, and NK subtypes for immunophenotyping in addition to T cell proliferation, activation, and exhaustion markers in whole blood;	• irRECIST and irPFS; • GUCY2c expression levels in archival and/or pre- and on/post-treatment tumor biopsies; • Immunophenotyping of blood Immune cell subtypes frequency and activation; • Intra-tumor immune pathway modulation, gene expression profiles, DNA mutations and immune cell biomarkers in pre- and post-dose tumor biopsies; • Cytokine and chemokine PD markers in pre- and on-treatment serum samples; • CEA levels in serum;

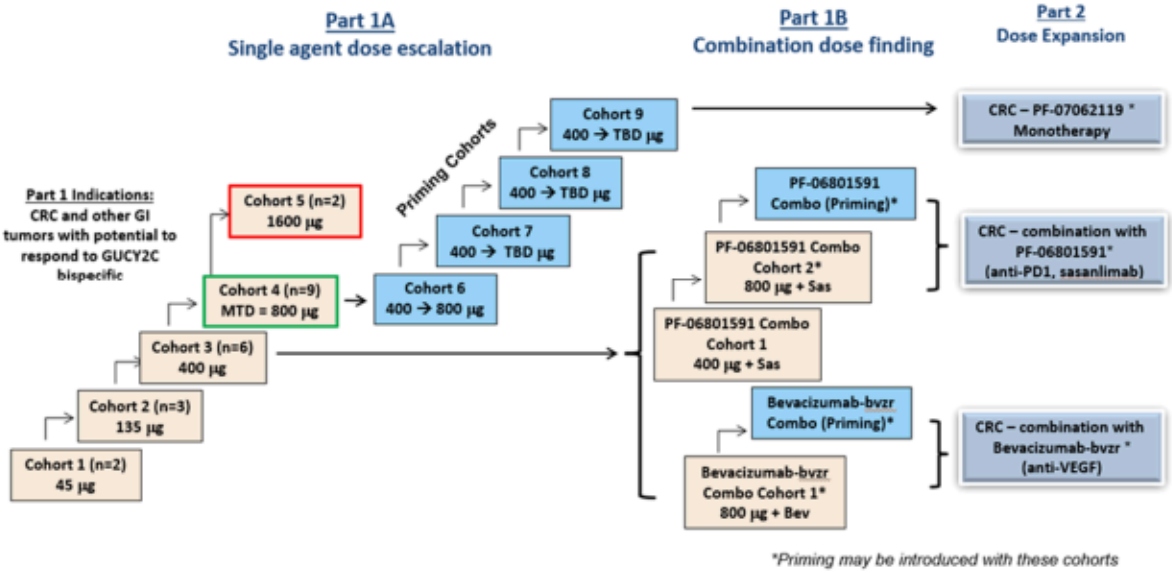
Objectives	Endpoints
• To explore cytokine and chemokine PD markers in pre and on treatment serum samples; • To explore the tumor biomarker CEA levels; • To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision. • To evaluate the trough levels of PF-06801591 and bevacizumab-Pfizer given in combination with PF-07062119;	• Changes in CD8 PET tracer uptake pre and post treatment for participants involved in CD8 PET tracer substudy (Section 10.19.3) • Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study). • Trough levels of PF-06801591 and bevacizumab-Pfizer

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, multi-center, multiple-dose, safety, PK and PD study of PF-07062119 in participants with selected advanced or metastatic gastrointestinal tumors. This study contains 2 parts: Part 1 dose escalation of PF-07062119, with and without a priming dose, as a monotherapy (Part 1A) and in combination with an anti-PD-1 or anti-VEGF agent (Part 1B) and Part 2 dose expansion (Figure 3). The PF-07062119 administration regimen for Parts 1A, 1B, and 2 may be guided by SC dose priming escalation cohorts and all available data will be used to make a decision on future dose regimens.

Figure 3. C3861001 Study Schema



As the RP2D/MTD of PF-07062119 is approached or has been determined in Parts 1A and 1B, an optional subset of participants may be enrolled (approximately 6 to 12 participants) with the requirement of providing mandatory paired de novo pre-treatment and on-treatment biopsy samples to enable evaluation of tissue biomarker PD activity. The option to enroll the subset of participants for mandatory paired tumor samples will be based on evaluation of emerging clinical data including available safety/tolerability, PK, and PD findings by the sponsor.

In the overall FIP study, approximately 130 participants are expected to be enrolled. Part 1 is estimated to enroll approximately 70 participants (35 participants in Part 1A and 35 participants in Part 1B). In Part 2, approximately 20 participants each will be enrolled in the monotherapy and both combination cohorts for a total of approximately 60 participants. If 15 participants have been enrolled in a cohort and <5 paired pre- and on-treatment biopsies have been collected, collections may be made mandatory for the remaining participants and/or the cohort may be expanded by up to 5 participants to obtain sufficient numbers of paired pre- and on-treatment biopsies.

A subset of participants enrolled in Part 1 and Part 2 will also be eligible for enrollment in the PET imaging substudy with the CD8 T-cell specific ^{89}Zr-deferoxamine (Df)-IAB22M2C PET tracer (CD8 PET Tracer). The CD8 PET tracer substudy is included to facilitate measurement of CD8 T-cell distribution across both tumor and normal tissues before and after therapy with PF-07062119. The CD8 PET tracer substudy will be opened initially at a subset of US sites that have been qualified for use with ^{89}Zr-Df-IAB22M2C. Additional details are provided in Section 10.19.

Participants in cohorts without a priming dose will be observed inpatient for at least 48 hours after the first SC dose on C1D1 and for at least 8 hours after the second SC dose on C1D15 and for at least 1 hour post dose for all subsequent visits. Participants in cohorts with a priming dose will be observed inpatient for at least 24 hours after the first (priming) SC dose on C1D1 and 24 hours after the second (full) SC dose on C1D15, and 1 hour postdose for all subsequent visits. Participants should be observed for at least 1 hour postdose for all visits starting with C2D11 in both cohorts, until the investigator has confirmed the participant has not exhibited signs of cytokine reaction.

In Part 2, all participants will be observed inpatient for at least 24 hours after the first SC dose, and if a priming dose approach is used, participants will be observed for up to 24 hours after the second (full) SC dose on C1D15. Participants may only be released after the investigator has confirmed the participant has not exhibited signs of CRS.

Table 8. Minimum Inpatient Observation Stays

Part	Cohort	C1D1	C1D15	All Other Visits
1	Without Priming	48 hours	8 hours	1 hour
	With Priming	24 hours	24 hours	1 hour
2		24 hours	24 hours if priming is used	At investigator's discretion

All inpatient observation stays may be extended at the discretion of the investigator and/or evolving clinical data.

Treatment with study intervention will continue until either disease progression, participant refusal, or unacceptable toxicity occurs, whichever is earliest, unless the investigator and medical monitor agree to treatment beyond disease progression based on individual benefit/risk assessments.

The biomarker studies will be used to help understand the in vivo mechanism of action of the agent(s) under study, as well as potential mechanisms of resistance. The studies may help in the future development of PF-07062119 as a single agent, or in combination with other compounds, and may provide information on tumor sub-types that may respond to the study intervention.

4.1.1. Part 1A

Part 1A will estimate the MTD and/or RP2D of PF-07062119 as a monotherapy with and without a priming dose. In Part 1A, sequential cohorts of participants with advanced gastrointestinal tumors, including colorectal, gastric and esophageal adenocarcinomas, who are not candidates for regimens known to provide clinical benefit, will receive escalating doses of PF-07062119 administered as an SC injection as guided by the Bayesian Logistic Regression Model (BLRM).

4.1.1.1. PF-07062119 Treatment Without a Priming Dose

With the determination that a dose level is safe following a DLT observation period of 28 days for the cohort without a priming dose and based on the discussion by the safety review team, dose escalation will proceed to the next dose level. The SC route has the potential to reduce the C_{max} which is believed to be associated with CRS and inflammatory responses, a common AE for bispecific antibodies. The starting SC dose is 45 µg Q2W. Maximum dose increases from the previous dose levels will be up to 200%, which is a consistent approach with biologic compounds including an anti-CD3 bispecific (Saber et al, 2017),[37] but will be adjusted to no more than 100% following the observation of a DLT or if there are two Grade 2 or higher clinically significant treatment related AEs. Cohort size will be approximately 3 participants. The first cohort of 45 µg Q2W in Part 1A will have at least 1 DLT-evaluable participant. All other cohorts in Part 1A will have at least 2 DLT evaluable participants. Part 1A is estimated to enroll approximately 35 participants, but the actual number of participants enrolled will depend on the tolerability of PF-07062119 and the number of dose levels required to identify the MTD, but will include at least 6 participants treated at the recommended RP2D/MTD (see Section 9.4.1).

4.1.1.2. PF-07062119 Treatment With a Priming Dose

An additional dose escalation cohort in Part 1A, which incorporates a lower priming dose on C1D1 followed by a full dose on C1D15 for all dose levels, will be initiated. Approximately 20 participants will be enrolled in the Part 1A cohort with a priming dose, with approximately 3 participants (minimum of 2 DLT evaluable participants) per dose level; additional participants will be treated at the RP2D/MTD for a total of 6 to 12 participants at

that dose level. The actual number of participants enrolled will depend on the tolerability of the priming strategy for PF-07062119 and the number of full dose levels required to identify the MTD (see Section 9.4.1).

Two weeks after the priming dose, participants will receive escalating full doses of PF-07062119 administered Q2W as an SC injection as guided by the BLRM. With the determination that a dose level is safe following a DLT observation period of 42 days (including both priming and 2 full doses) and based on the discussion by the safety review team, dose escalation will proceed to the next dose level. The priming dose will be 400 µg. The starting full dose will be 800 µg, which represents the MTD of the Part 1A cohort without a priming dose. The initial PF-07062119 regimen with a priming dose satisfies EWOC criteria (see Section 9.4.1 and Appendix 10, Section 10.10). The maximum allowable increase in the full dose, to be given after the priming dose, will be 100%. The priming dose may be modified based on emerging clinical data to a maximum of the highest dose previously determined to be safe. An alternate priming schedule (eg, using a step-up dosing strategy, with serially increasing doses to reach the full dose level), may be explored if evolving clinical data support the need and the DLT observation period will be adjusted accordingly (eg, to include the administrations of 2 full doses). If step-up dosing is investigated, participants will receive full doses of PF-07062119 2 weeks after the most recent priming dose.

4.1.2. Part 1B (Combination Cohorts)

Upon determining the single-agent PF-07062119 RP2D/MTD, Part 1B will be initiated to explore the safety, tolerability, and preliminary anti-tumor activity of PF-07062119 in combination with PF-06801591 (anti-PD-1) and bevacizumab-Pfizer (anti-VEGF) in participants with colorectal, gastric and esophageal adenocarcinomas.

The DLT period will be 28 days. BLRM will be used to guide the dose escalation/de-escalation process for each combination (PF-07062119/PF-06801591 and PF-07062119/bevacizumab-Pfizer) separately. The determination of safety for a given dose level for each combination will be based on the discussion by the safety review team.

In each combination treatment, there may be cohorts without a PF-07062119 priming dose and cohorts with a PF-07062119 priming dose; the decision to use a priming dose (on C1D1 followed by a full dose on C1D15) will be made following a review of all available clinical data from Part 1A and in consultation with the Study C3861001 Safety Review Team. In the event that the PF-07062119 dose priming strategy is employed with either combination therapy, the DLT period will be increased to 42 days to ensure a full 28 day cycle following the initiation of the full dose. Additionally, an alternative PF-07062119 dosing regimen (eg, Q4W) or a staggered dosing approach (eg, PF-07062119 to be initiated alone on C1D1 followed by the combination therapy 1 or 2 weeks later) may be initiated as guided by the clinical data. The starting dose of new regimen will satisfy EWOC criteria.

For the PF-07062119/PF-06801591 combination, the starting first dose of PF-07062119 in combination with PF-06801591 will be one dose level lower than the PF-07062119 monotherapy MTD to account for any potential increase in CRS that might be associated

with the PF-07062119/PF-06801591 combination. If the PF-07062119 RP2D from Part 1A is lower than the MTD, the RP2D will be used in combination with PF-06801591. Maximum increases of PF-07062119 from the previous level will be 100%. However, PF-07062119 in combination will not be dose-escalated beyond the corresponding single-agent MTD/RP2D as determined with or without priming for PF-07062119 in Part 1A. The dose of PF-06801591 will be 300 mg Q4W SC (Table 10). Study participants will be evaluated for safety and tolerability of the combination and the PF-07062119 dose used in the next cohort may remain the same, escalated, or de-escalated as guided by emerging clinical data and the BLRM design (see Section 4.3.6).

For the PF-07062119/bevacizumab-Pfizer combination, the starting dose of PF-07062119 will be the MTD or the RP2D determined in Part 1A with or without priming. Study participants will be evaluated for safety and tolerability of the combination and the PF-07062119 dose used in the next cohort may remain the same or de-escalated as guided by emerging clinical data and BLRM (See Section 4.3.6). However, PF-07062119 in combination will not be dose-escalated beyond the corresponding single-agent MTD/RP2D as determined with or without priming for PF-07062119 in Part 1A. The dose of bevacizumab-Pfizer will be 5 mg/kg Q2W IV infusion (Table 10).

The cohort size at each dose level of Part 1B for the PF-07062119/PF-06801591 and PF-07062119/bevacizumab-Pfizer combination will each be approximately 3 participants; all cohorts in Part 1B will each have at least 3 DLT evaluable participants. Part 1B is estimated to enroll approximately 35 participants (approximately 15 to 20 participants for each combination), but the actual number of participants enrolled will depend on the tolerability of PF-07062119 in combination with PF-06801591 and with bevacizumab-Pfizer and the number of dose levels required to identify the corresponding PF-07062119 MTDs in the combination setting with or without dose priming, but will include at least 6 participants treated at the corresponding recommended RP2D/MTDs (see Section 9.4.1).

Alternate priming strategies (e.g. step up priming strategy or prophylactic treatment) may be explored if evolving clinical data supports the need in Part 1B dose priming.

4.1.3. Part 2

In Part 2, the dose expansion phase will evaluate the RP2D (as determined either with or without a priming dose) of PF-07062119 as monotherapy and with a combination agent (anti-PD-1 [PF-06801591] and anti-VEGF [bevacizumab-Pfizer]) in participants with colorectal adenocarcinoma. Approximately 60 participants will be enrolled; 20 participants in each monotherapy and combination cohorts.. Responses in these initial dose expansion arms may lead to further evaluation of PF-07062119 in additional tumor indications and combination therapies.

In Part 2, de novo pre-treatment biopsies will be required from all participants, unless not medically feasible, in order to establish relationship between target expression and efficacy observations. If a de novo pre-treatment biopsy is not medically feasible, the sponsor should be contacted for approval before initiating screening activities. For a subset of participants in all cohorts (approximately 10 participants), mandatory on-treatment biopsy samples will also

be collected in order to confirm the mechanism of action and evaluate potential resistance mechanism during treatment. For all other participants, on-treatment biopsies are optional but encouraged.

4.2. Scientific Rationale for Study Design

In this clinical study, PF-07062119 with and without a priming dose will be evaluated for the treatment of adult participants with tumor types known to express GUCY2c, such as advanced colorectal, gastric, and esophageal adenocarcinomas, for which no standard therapy is available (Part 1). In the dose expansion phase (Part 2), PF-07062119 with and without a priming dose will be evaluated in separate dose expansion arms as monotherapy and in combination with another agent (eg, immune checkpoint inhibitor, anti-VEGF) in advanced CRC and then possibly be evaluated in other gastrointestinal adenocarcinomas, colorectal cancer subtypes, or combination options, as indicated. Key standard assessments in the study will include safety/tolerability, PK, PD and preliminary anti-tumor activity endpoints.

As part of the PD evaluation, the objective of the biomarker assessments is to provide insight into the pharmacological effects of PF-07062119 alone and potentially in combination with anti-PD-1 (PF-06801591) and in combination with anti-VEGF (bevacizumab-Pfizer) by characterizing the cellular and molecular profile of the participant prior to treatment, during treatment, and upon progression. The biomarker assessments, including the PET imaging substudy, may contribute to confirming target engagement, T cell activation, determining pharmacodynamic effects of PF-07062119 alone and potentially in combination with other agents, identifying those participants who are most likely to benefit from treatment, and identify potential resistance mechanisms to PF-07062119 alone and in combination with other agents. The collection of archival and/or de novo pre-treatment and on-treatment biopsies will be used to evaluate the association between target expression and response parameters to PF-07062119 as described in the Schedule of Activities) and the Study/Laboratory Manual.

Banked biospecimens will be collected for exploratory/pharmacogenomic/genomic/ biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the mechanism of action of the study intervention to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.3. Justification for Dose

4.3.1. Starting Dose for Monotherapy Dose Escalation Without a Priming Dose (Part 1A)

The initial clinical starting dose for PF-07062119 for this first-in-participant (FIP) study is 45 µg administered as a SC injection once every 2 weeks (Q2W). The selection of the starting dose for this study was based on the minimum anticipated biological effect level (MABEL) in accordance with the International Conference on Harmonization (ICH) S9 Guidance, given that PF-07062119 is a bispecific T cell-engaging agent with immune agonistic properties. The 45 µg Q2W SC starting dose is predicted to result in minimal biological effect considering a) in vitro cytokine release and cytotoxicity experiments, b)

receptor occupancy calculated based on in vitro binding affinities, and c) mouse PK/PD studies.

The in vitro biological activities for PF-07062119 were determined via cytokine release and cytotoxicity experiments and the most sensitive PF-07062119 concentration to achieve 50% maximal effect (EC50) across all in vitro assays was estimated as 13.6 ng/mL. With 45 µg Q2W as a starting dose, the predicted PF-07062119 C_{max} at steady-state assuming 50% bioavailability from the SC route is 8.9 ng/mL, which is ~34% lower than the EC50 of the most sensitive in vitro assay.

The receptor occupancy (RO) calculated based on in vitro binding affinities at a starting dose of 45 µg Q2W SC was ≤0.3% for both GUCY2c and CD3.

The predicted trough concentration (C_{trough}) after four doses achieved with 45 µg Q2W starting dose is 4.5 ng/mL which is less than the predicted clinical efficacious concentration (C_{eff}) estimated from mouse PK/PD studies.

Finally, PF-07062119 exposure at the recommended starting dose is expected to be lower (eg, 21-fold lower C_{max} and 24-fold lower AUC_{168}) compared to the HNSTD determined in the GLP one-month toxicology study (3 µg/kg SC).

Therefore, as stated above, the recommended MABEL starting dose of 45 µg Q2W via the SC route is expected to result in minimal biological effect and to provide an adequate safety margin. If the 45 µg Q2W dose is not tolerated, then a lower dose of 30 µg Q2W via SC route will be evaluated.

4.3.2. Starting Dose for Monotherapy Dose Escalation With a Priming Dose (Part 1A)

Available data from participants enrolled in Part 1A without priming shows that cytokine production and clinical CRS occur primarily with the initial dose of PF-07062119, supporting the hypothesis that induction of immune activation with a priming dose attenuates subsequent occurrence of CRS. The use of a priming approach to mitigate cytokine-mediated AEs is also supported by data from clinical studies of the bispecific T-cell engager, blinatumomab, which have demonstrated that use of a priming dose (ie, using a lower first dose) can be effective in dampening cytokine release-mediated AEs following administration of subsequent higher maintenance doses (Topp et al, 2014a; Topp et al, 2014b).

The first dose level for PF-07062119 in the Part 1A cohort with a priming dose will be a starting priming dose of 400 µg given as a SC injection on C1D1 followed by a full dose of 800 µg, which corresponds to the single agent MTD without priming administered as a SC injection, on C1D15 and Q2W thereafter.

The starting priming dose of 400 µg PF-07062119 was selected based on the following considerations from the available clinical data from the cohort without a priming dose: (1) PF-07062119 was observed to be safe and tolerable, with no DLTs after the first or second dose and no CRS events Grade ≥2 reported; (2) it was the lowest dose that demonstrated meaningful immune activation that is necessary to accomplish a priming effect,

as evidenced by increased measurable cytokine markers of T-cell activation and inflammation; and (3) 4/6 participants at this dose level also demonstrated reductions in CEA, a tumor marker.

The starting full dose of PF-07062119 will be 800 µg Q2W. This dose corresponds to the single agent MTD without priming and there is already available clinical data for 9 participants at this dose level. This dose would allow for objective assessment of the priming strategy based on comparison between the priming and non-priming settings at the same full dose (800 µg) of PF-07062119, in the context of safety events and level of cytokine activation. Additionally, the priming/full dose of 400 µg/800 µg Q2W satisfies EWOC criteria (see Section 9.4.1 and Appendix 10, Section 10.10).

4.3.3. Subcutaneous Route

The SC route will be employed in this study given the potential to reduce the C_{max}, which is believed to be associated with CRS and inflammatory responses. Depending on the available emerging clinical data (including safety/tolerability, PK, PD) from the dose escalation cohorts with SC administration, IV administration, including the use of an IV priming dose may be evaluated and would be accompanied with a protocol amendment.

In case of change of the dosing regimen, DLT data accumulated during the dose escalation with the previously explored regimen might be used to form a prior assumption for further BLRM analysis.

4.3.4. Fixed Dosing Approach

A fixed-dose approach will be applied for the FIP study of PF-07062119 given that fixed dosing approach was shown to provide similar PK variability compared to a body-weight adjusted dosing for monoclonal antibodies, therapeutic peptides, and proteins (Wang D et al; Zhang S et al).[49,51] In addition, fixed dosing offers ease of preparation and less chance of dosing errors. Alternatively, based on emerging PK data, body weight, or body surface area based dosing may be considered.

4.3.5. Dosing Interval (Q2W)

The Q2W dosing frequency of PF-07062119 in this study was selected based on (1) the projected $t_{1/2}$ of 21 days in humans and (2) the combination agents for PF-07062119 (PF-06801591 and bevacizumab-Pfizer) in this study will be administered Q2W or Q4W. A Q2W regimen was selected for this FIP study to reduce C_{max}, which is believed to be associated with CRS, compared to Q4W administration (comparing doses achieving matching overall exposure between Q2W and Q4W regimens). Based on emerging PK, PD, and safety data, regimens with alternative dosing frequencies (eg, weekly administration or Q4W) may also be considered.

4.3.6. Starting Dose for Combination Dose Finding (Part 1B)

The dose-finding evaluation of PF-07062119 in combination with PF-06801591 or bevacizumab-Pfizer will be initiated after determination of the MTD and/or RP2D for PF-07062119 as monotherapy with or without priming (Part 1A) and supported by emerging

clinical data including any available safety/tolerability, PK, PD, or preliminary evidence of efficacy.

For the PF-07062119/PF-06801591 combination, the starting dose of PF-07062119 will be one dose level lower than the PF-07062119 monotherapy MTD or the RP2D (or the highest dose level previously determined to be safe if the MTD or RP2D has not yet been identified) to account for any potential overlapping toxicities that might be associated with the PF-07062119/PF-06801591 combination. The starting dose for PF-07062119/PF-06801591 combination (Part 1B without priming) will be 400 µg. The dose of PF-06801591 will be 300 mg Q4W SC.

For the PF-07062119 combination with bevacizumab-Pfizer, the starting dose of PF-07062119 will be the MTD or RP2D determined without priming in Part 1A, and the dose of bevacizumab-Pfizer will be 5 mg/kg Q2W IV infusion (Table 10).

The starting dose of any new regimen, including combination with priming will satisfy EWOC criteria (see Technical Supplement to Appendix 10).

For the PF-07062119 combinations with PF-06801591 or bevacizumab-Pfizer with priming, PF-07062119 will be administered on C1D1 alone and will be administered on C1D15 in combination with either PF-06801591 or bevacizumab-Pfizer. For additional details, refer to Section 4.1.

4.3.7. Criteria for Dose Escalation

A BLRM, guided by the EWOC principle, will be used in dose escalation in Part 1A and dose finding in Part 1B. See Section 9.4 and Appendix 10 for more details on the model. Using DLT data at all tested dose levels and prespecified prior distribution of model parameters, posterior probabilities of the probability of having a DLT falling into 3 dosing intervals (under dosing, target dosing, and overdosing) will be calculated for all dose levels. A dose may only be used for newly enrolled participants if it satisfies EWOC principle (ie, the risk of over-dosing at this dose is predicted to be less than 25%).

Typically, participants will be enrolled in dose level cohorts of approximately 3 participants with at least 1 DLT evaluable participant in the first dose level in Part 1A without a priming dose and 2 DLT evaluable participants at all other dose levels in Part 1A with and without a priming dose. All dose levels in Part 1B with or without a priming dose will have at least 3 DLT evaluable participants.

The maximum dose increases from the previous dose levels for regimen will be up to 200% for cohorts without a priming dose but will be adjusted to no more than 100% following the observation of a DLT or if there are two Grade ≥2 clinically significant treatment-related AEs. The maximum allowable dose increment for dose escalation will be 100% for cohorts with a priming dose.

Table 9. SC Dose Escalation Levels for Administration Without Priming Dose

Dose Level*	Dose (µg)
DL 1 (Starting Dose**)	45
DL 2	135
DL 3 and higher	Escalation to continue to MTD or desired pharmacologic activity

* Intermediate doses may be evaluated based on clinical findings; DL = Dose Level; MTD = Maximum Tolerated Dose; SC = Subcutaneous.

** If the 45 µg SC Q2W dose is not tolerated, then a lower dose of 30 µg Q2W via SC route will be evaluated.

Dose escalation will stop when stopping criteria are met (see Section 4.3.8 and Appendix 10). According to the stopping criteria, at least 6 participants will be evaluated at the MTD.

Intraparticipant dose escalation to the next dose level may be considered in consultation with the sponsor for participants(s) who have completed the DLT period in the dose escalation phase if the next higher dose level has been cleared.

4.3.8. Dose Limiting Toxicity Definition

A participant is classified as DLT evaluable if he/she experiences a DLT (irrespective of whether they received all of the planned doses of each study intervention and scheduled safety assessments during the DLT window) or if he/she otherwise in the absence of a DLT receives all of the planned doses of each study intervention and has received scheduled safety assessments during the DLT window. If a participant fails to meet these criteria, he/she may be replaced.

DLTs will be assessed through Cycle 1 (28-day cycle with Day 29 [eg, C2D1]) for cohorts without priming and will be assessed through C2D15 (42-day cycle with Day 43 [eg, C2D15]) for cohorts with priming.

For the purpose of dose escalation, the DLT observation period for Q2W SC regimen will be 28 days for cohorts without a priming dose and 42 days for cohorts with a priming dose after the start of study treatment in each participant.

Significant AEs considered to be related to the study intervention or treatment under investigation that occur after the DLT observation period will be reviewed in context of all safety data available. That review may result in re-evaluation of the dosing level or regimen.

Severity of AEs will be graded according to CTCAE v5.0.

For the purpose of dose escalation, any of the following AEs with the associated parameters that occur during the DLT observation period that are attributable to one, the other, or both agents in the combination will be classified as DLTs:

Hematological DLTs:

- Grade 3 neutropenia lasting >5 days is a DLT.
- Febrile neutropenia is a DLT defined as an absolute neutrophil count (ANC) <1.0 x 109/L with a single temperature of >38.3°C, or 101°F, or a sustained temperature of ≥38°C, or 100.4°F, for more than one hour is a DLT.
- Grade ≥3 neutropenia with infection is a DLT.
- Grade 3 thrombocytopenia with Grade ≥2 (clinically significant) bleeding is a DLT.
- Any Grade 4 thrombocytopenia is a DLT.
- Anemia or thrombocytopenia requiring transfusion is a DLT.

Non-Hematological DLTs:

- Grade ≥3 fatigue lasting ≥7 days is a DLT.
- For participants with liver, bone, or lung metastasis, an AST or ALT increase >8 x ULN or alkaline phosphatase >10 x ULN is a DLT.
- Confirmed drug induced liver injury (DILI) meeting Hy's law criteria is a DLT.
- Grade 3 vomiting or diarrhea lasting ≥3 days despite adequate treatment (eg, antiemetic or antidiarrheal medications, respectively) and other supportive care is a DLT.
- Grade 4 vomiting or diarrhea is a DLT.
- Grade ≥3 CRS regardless of duration is a DLT.
- Grade ≥3 QTcF prolongation irrespective of duration is a DLT.
- Any death not clearly due to the underlying disease or extraneous causes is a DLT.

Clinically important or persistent toxicities (eg, toxicities responsible for significant dose delay) that are not included in the above criteria may also be considered a DLT following review by the investigators and the Sponsor. All DLTs need to represent a clinically significant shift from baseline.

Otherwise, AEs of CTCAE Grade greater than or equal to 3 will be considered to be DLTs, with the exception of the AEs listed below.

The following AEs will not be adjudicated as DLTs:

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

- Grade 3 amylase or lipase elevation not associated with clinical symptoms or clinical manifestations of pancreatitis.

4.3.9. Late Onset Toxicity

Significant AEs considered to be related to PF-07062119 as monotherapy or in combination treatment under investigation that occur after the DLT observation period will be reviewed in the context of all safety data available. This review may result in re-evaluation of the dosing level or regimen.

Pfizer will schedule a safety review meeting with the investigators to review the details of the potential late onset toxicity and determine if enrollment should be held, continued or if dose reduction should be implemented for ongoing participants. Late onset toxicities that meet the definition of DLT will be considered in the evaluation of the MTD.

4.3.10. Maximum Tolerated Dose Definition

MTD is defined as a dose with true DLT rate from the target toxicity interval. The target interval for the DLT rate is defined as (0.16, 0.33).

4.3.11. Recommended Phase 2 Dose Definition

The RP2D for PF-07062119 will be retrospectively determined as a monotherapy with and without priming, and in combination with PF-06801591 or in combination with bevacizumab-Pfizer for further study based on Phase 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of participants, the MTD with or without a priming dose could be selected as the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD. Alternatively, if data allows, the RP2D could be selected as the safe dose that demonstrates the desired pharmacological activity (optimal biological dose). PK data as well potential exposure-response relationships (safety and efficacy, as data permits) will be considered in identifying the RP2D. During escalation and prior to an MTD being reached, the sponsor may choose to advance a lower dose into expansion, particularly (but not exclusively) when considering combination cohorts. This decision must be made based on safety, PK, PD, and/or efficacy data.

4.3.12. Part 2 Respective Starting Doses for PF-07062119 as a Single Agent and Combination Dose Expansion Cohorts

Part 2 dose expansion is an open-label, multi-center, non-randomized study to assess the preliminary anti-tumor activity along with safety/tolerability, PK, and PD of PF-07062119. PF-07062119 will be evaluated at the RP2D in 28-day cycles in dose expansion arms as a single agent, in combination with PF-06801591, and in combination with bevacizumab-Pfizer. Following a review of all available data in Part 1 and in consultation

with the Study C3861001 Safety Review Team, a priming strategy for PF-07062119 may be initiated in Part 2.

The single-agent PF-07062119 RP2D from Part 1A will be used to initiate the Part 2 single-agent dose-expansion arm, which may be de-escalated based on emerging clinical data. Additionally, the PF-07062119 RP2D in combination with PF-06801591 and PF-07062119 RP2D in combination with bevacizumab-Pfizer from Part 1B will be used to initiate the Part 2 respective combination dose expansion arm studies, which may be de-escalated, if indicated from emerging clinical data.

4.3.13. Part 2 PF-07062119 as a Single Agent in Advanced or Metastatic Colorectal Adenocarcinoma

PF-07062119 will be evaluated as a single agent at the RP2D in advanced or metastatic colorectal adenocarcinoma that is resistant to standard therapy or for which no standard therapy is available. This expansion cohort will enroll approximately 20 participants.

4.3.14. Part 2 PF-07062119 in Combination with PF-06801591 in Advanced or Metastatic Colorectal Adenocarcinoma

PF-07062119 will be evaluated in combination with PF-06801591 at the RP2D in advanced or metastatic colorectal adenocarcinoma that is resistant to standard therapy or for which no standard therapy is available. This expansion cohort will enroll approximately 20 participants.

4.3.15. Part 2 PF-07062119 in Combination with Bevacizumab-Pfizer in Advanced or Metastatic Colorectal Adenocarcinoma

PF-07062119 will be evaluated in combination with bevacizumab-Pfizer at the RP2D in advanced or metastatic colorectal adenocarcinoma that is resistant to standard therapy or for which no standard therapy is available. This expansion cohort will enroll approximately 20 participants.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the end of treatment visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Female and/or male participants age ≥18 years and/or ≥20 years in Japan.

Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

2. For dose escalation/finding cohort(s) (Part 1A and 1B): Histological or cytological diagnosis of advanced/metastatic colorectal, gastric, or esophageal adenocarcinoma that is resistant to standard therapy or for which no local regulatory approved standard therapy is available that would confer significant clinical benefit in the medical judgement of the investigator.

3. For dose escalation/finding cohort(s) (Part 1A and 1B): Must have tumor tissue available for submission to the sponsor. Participants enrolled in Part 1 should have access to their archival formalin-fixed paraffin embedded material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or consent to undergo a biopsy during screening.

4. For dose expansion (Part 2): Histological or cytological diagnosis of previously treated colorectal adenocarcinoma that is resistant to standard therapy or for which no local regulatory approved standard therapy is available that would confer clinical benefit in the medical judgement of the investigator.

5. For dose expansion (Part 2): Must have tumor tissue available for submission to the sponsor. Participants enrolled in Part 2 should either have access to their archival FFPE material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or consent to undergo a biopsy during screening.

6. Participants entering the study in the expansion cohort(s) (Part 2) have at least 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 that has not been previously irradiated.

7. Participants entering the study in the subgroup(s) requiring mandatory pre- and on-treatment tumor biopsies in the dose escalation/finding cohort(s) (Part 1A and 1B) and dose expansion in Part 2 must have a tumor amenable to biopsy and consent to these planned biopsy procedures.

8. Body weight of >70 kg for Dose Level 1 only.

9. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) must be 0 or 1.

10. Adequate bone marrow function, including:

    - Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
    - Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
    - Hemoglobin ≥9 g/dL.

11. Adequate renal function, including:

    - Estimated creatinine clearance ≥60 mL/min for Part 1 and ≥50 mL/min for Part 2 as calculated using the method standard for the institution. In equivocal cases, a 24hour urine collection test can be used to estimate the creatinine clearance more accurately.

12. Adequate liver function, including:

    - Total serum bilirubin ≤1.5 x ULN unless the participant has documented Gilbert syndrome;
    - Aspartate and alanine transaminase (AST and ALT) ≤2.5 x ULN;
    - Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in case of bone, liver, or lung metastasis).

13. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for adverse events (AEs) not constituting a safety risk by investigator judgment.

14. Thyroid stimulating hormone (TSH) within normal limits (WNL) for institution; supplementation is acceptable to achieve a TSH WNL; in participants with abnormal TSH if Free T4 and Free Thyroxine are normal, and participant is clinically euthyroid, participant is eligible.

15. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

16. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participants with known symptomatic brain metastases requiring corticosteroids. Participants with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation

therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable for 3 months (requires magnetic resonance imaging [MRI] confirmation).

2. Participants with any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.

3. Major surgery within 3 weeks prior to study entry (except in participants receiving bevacizumab-Pfizer in which major surgery within 4 weeks prior to study entry would be exclusionary).

4. Radiation therapy within 3 weeks prior to study entry. Palliative radiotherapy to a limited field may be allowed after consultation with the sponsor's medical monitor unless it is clearly indicative of disease progression.

5. Systemic anti-cancer therapy within 4 weeks prior to study entry (6 weeks for mitomycin C or nitrosoureas) or 5 half-lives (whichever is shorter) of the agent(s) prior to receiving the study intervention/study treatment is required.

6. Participants with active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness. In equivocal cases, participants whose viral load is negative, may be eligible. HIV seropositive participants who are healthy and low-risk for AIDS-related outcomes could be considered eligible. Eligibility criteria for HIV-positive participants should be evaluated and discussed with sponsor's medical monitor and will be based on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions (eg, opportunistic infections), and status of HIV treatment. Also, the potential for drug- drug interactions will be taken into consideration.

7. COVID-19/SARS-CoV2: This protocol excludes participants with active infections, as noted above. While SARS-CoV2 testing is not mandated for entry into this protocol, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2, he/she will be excluded.

8. Baseline 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT [QTcF] interval >470 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate age myocardial infarction, ST segment or T wave interval changes suggestive of active myocardial ischemia, second or third degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >470 msec, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 470 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or

QRS values should be used to determine the participants eligibility. Computer interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants. Cases must be discussed in detail with sponsor's medical monitor to judge eligibility.

9. Any of the following in the previous 6 months: myocardial infarction, long QT syndrome, Torsade de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), serious conduction system abnormalities (eg, left anterior hemiblock, left bundle branch block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF, New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, symptomatic pulmonary embolism, and/or other clinical significant episode of thrombo-embolic disease, ongoing cardiac dysrhythmias of National Cancer Institute (NCI) CTCAE > Grade 2, atrial fibrillation of any grade (> Grade 2 in the case of asymptomatic lone atrial fibrillation). If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 msec, the participant can be considered eligible. Participants with cardiac rhythm device/pacemaker must be discussed in detail with sponsor's medical monitor to judge eligibility.

10. Anticoagulation with vitamin K antagonists or factor Xa inhibitors is not allowed. Anticoagulation with SC heparin is allowed.

11. Hypertension that cannot be controlled by medications (eg, >150/90 mmHg) despite optimal medical therapy.

12. Participation in other studies involving investigational drug(s) within 2 weeks of study entry except for participation in medical imaging studies, which is allowed.

13. Known or suspected hypersensitivity to PF-07062119, PF-06801591, or bevacizumab-Pfizer, or excipients associated with the preceding compounds for the respective planned investigational study treatments. History of Grade ≥3 immune mediated or related AE (including AST/ALT elevations that were considered drug related and cytokine release syndrome) that was considered related to prior immune modulatory therapy (eg, immune checkpoint inhibitors, co-stimulatory agents, etc) and required immunosuppressive therapy. An exception would be a participant with a history of vitiligo or thyroid dysfunction who has been off immunosuppressive therapy for at least 6 months.

14. Active or history of clinically significant autoimmune disease that required systemic immunosuppressive therapy or another medical condition that required immunosuppression within 2 years of treatment.

15. Requirement for systemic immune suppressive medication [eg, ≥10 mg of prednisone or equivalent (≥1.5 mg of dexamethasone)]. Inhaled, intranasal, intraocular, intraarticular, and topical corticosteroids are allowed.

16. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis or melena in the past 6 months.

17. Participants with the presence of any open, active wound.

18. Serum or urine pregnancy test (for females of childbearing potential) positive at screening or breast feeding female participants (including participants who intend to interrupt breastfeeding).

19. History of or active clinically significant gastrointestinal disease (including but not limited to inflammatory gastrointestinal disease [eg, ulcerative colitis, Crohn's disease], peptic ulcer disease, gastroesophageal reflux disease, gastrointestinal bleeding, chronic diarrhea) and other conditions that are unresolved and/or may increase the risk associated with study participation or study intervention/study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

20. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or study intervention/study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

21. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

Section 10.19.4 lists additional inclusion/exclusion criteria for the PET tracer substudy.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant [and his or her partner(s)] from the permitted list of contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. Screen failure data are collected as source and are reported to the clinical database.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a specific modifiable factor (eg, lab abnormality) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term study intervention may be used synonymously with study drug.

6.1. Study Intervention(s) Administered

See Table 10 for study interventions administered.

Table 10. Administered Study Interventions

Intervention Name	PF-07062119	PF-06801591	Bevacizumab-Pfizer
Type	Biologic	Biologic	Biologic
Dose Formulation	Lyophilized powder for solution for injection and diluent solution (histidine, sucrose, PS80, EDTA) for injection	Solution for injection	Solution for injection
Unit Dose Strength(s)	1.3 mL (5 mg/mL) PF-07062119 solution in vial following reconstitution with water for injection and diluent with 9.8 mL solution in 20 mL vial for dilution of reconstituted PF-07062119	50 mg/mL (2 mL vial)	100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) in a single dose vial
Dosage Level(s)	Dose amount and frequency – see the study schema and accompanying text in Section 4.1	300 mg Q4W	5 mg/kg Q2W
Route of Administration	SC after reconstitution with water for injection	SC	IV

Table 10. Administered Study Interventions

Investigational Medicinal Product (IMP) and Non Investigational Medicinal Product (NIMP)	IMP and NIMP - diluent	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in open label single use vials Each vial and diluent will be labeled as required per country requirement	Study intervention will be provided as 50 mg/mL (2 mL vial) in vials Each vial will be labeled as required per country requirement	Study intervention will be provided as single use vial as 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL). Each vial will be labeled as required per country requirement

6.1.1. Administration

6.1.1.1. PF-07062119

PF-07062119 will be administered via SC injection without adjustment for body size at every cycle.

Participants should have SC injections in the abdomen. For participants receiving 2 or more SC injections, study drug should be administered in 2 or more different quadrants of the abdomen (with preference given to the lower quadrant when possible); 1 or 2 injections per quadrant. The injection can be rotated with each administration for participant comfort. Additional guidance on subcutaneous injection site locations is provided in Section 10.20. Details for PF-07062119 preparation instructions are provided in the current PF-07062119 IP Manual.

Premedication with both the priming dose(s) and initial full dose of PF-07062119 for all participants has been implemented into this study to further improve tolerability and participant experience.

The following premedication should be administered approximately 1 hour prior to PF-07062119:

- Acetaminophen 650 mg (or equivalent), oral
- Diphenhydramine 25 mg, oral or IV
- Dexamethasone 12 mg (or equivalent), oral or IV

Premedication should be administered in Cycle 1 only on C1D1 in cohorts without a priming dose and should be administered on both C1D1 and C1D15 in cohorts with a priming dose. Premedication regimen beyond the first full dose and modifications to the premedication regimen (eg, frequency of premedication, doses of individual agents, removal or addition of agents) may be implemented by the sponsor based on emerging data. Any exceptions to premedication require discussion and agreement between the sponsor and investigator.

Participants will be required to remain in the clinic to observed for specific periods of time during the first cycle (see Section 4.1 for details).

Guidance is provided below (Section 8) for management of treatment related adverse events. Guidance for evaluation of Injection Site Tolerability is provided in Section Injection Site Tolerability Assessment (SC Only) (Section 8.1.7). Treatment-related AEs are all considered toxicities except those that are clearly not related to PF-07062119 (eg, disease progression, environmental, unrelated trauma, etc). Treatment related toxicities include any event considered related, probably related, or possibly related to PF-07062119.

6.1.1.2. PF-06801591

In the investigational combination therapy with PF-07062119, PF-06801591 300 mg (50 mg/mL), will be administered SC Q4W to the abdomen. PF-06801591 should be administered to 2 or more different quadrants of the abdomen (with preference given to the lower quadrants when possible); 1 or 2 injections per quadrant.

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs after discussion and agreement between investigator and the Sponsor. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

PF-06801591 SC injection will be administered at least 30 minutes after administration of PF-07062119. Additional guidance on subcutaneous injection site locations is provided in Section 10.20. For specific instructions on the handling and preparation instructions of study drug, refer to the Product Specific Investigational Product (IP) Manual.

6.1.1.3. Bevacizumab-Pfizer

For participants treated with the investigational therapy with PF-07062119, bevacizumab-Pfizer will be supplied as 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) in a single dose vial. The necessary amount of bevacizumab-Pfizer should be withdrawn, based on 5 mg/kg of body weight, and diluted in a total volume of 100 mL of 0.9% sodium chloride solution. The first infusion of the diluted solution should be administered with an infusion pump over 90 minutes. The second infusion should be administered over 60 minutes if the first infusion is well tolerated. All subsequent infusions should be administered over 30 minutes if the second infusion administered over 60 minutes is well tolerated. Bevacizumab-Pfizer IV infusion will be administered at least 30 minutes after administration of PF-07062119. For specific instructions on the handling and preparation instructions of study drug, refer to the Product Specific IP Manual. Participants planned to receive PF-07062119 in combination with bevacizumab-Pfizer should be weighed

within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of bevacizumab-Pfizer required for dose preparation. Decision to recalculate bevacizumab-Pfizer dose based on the weight obtained at each cycle can be in accordance with institutional practice, however if the participant experienced either a weight loss or gain >10% compared to the weight used to calculate either the initial or previous dose, the amount of bevacizumab-Pfizer required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

All participants receiving bevacizumab-Pfizer will require a proteinuria assessment (dipstick is acceptable) prior to each dose of bevacizumab-Pfizer for the duration of the study. If urinalysis demonstrates protein greater than or equal to 2+, then a 24-hour urine protein collection should follow. In participants with proteinuria greater than or equal to 2 grams per 24 hours, bevacizumab-Pfizer should be held until recovery (less than 2 grams per 24 hours). Discontinue bevacizumab-Pfizer in participants that develop nephrotic syndrome.

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using a study intervention accountability form/record.

Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Study interventions should be stored in their original containers and in accordance with the labels.

See the IP Manual, or equivalent for storage conditions of the study intervention once reconstituted and/or diluted.

Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described om the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation.

Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

6.3. Preparation and Dispensing

Detailed instructions for PF-07062119 on how to prepare the study intervention for administration are provided in the current IP Manual. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

See the IP manual for instructions on how to prepare PF-06801591 and bevacizumab-Pfizer for administration. PF-06801591 and bevacizumab-Pfizer should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

All active and diluent vials are for single use only.

6.4. Measures to Minimize Bias: Randomization and Blinding

6.4.1. Allocation to Investigational Product/Study Intervention

Dose level allocation will be performed by the sponsor after participants have given their written informed consent and have completed the necessary baseline assessments. The site staff will fax/email a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a participant identification number and supply this number to the site. The participant identification number will be used on all study-related documentation at the site.

No participant shall receive study intervention/study treatment until the investigator or designee has received the following information in writing from the Sponsor:

- Confirmation of the participant's enrollment;
- Specification of the dose level for that participant and;
- Permission to proceed with dosing the participant.

For Part 2 of the study:

Allocation of participants to treatment groups may proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to have an active or valid account and password with the IRT system, enter or select information including but not limited to the protocol number, specific protocol entrance criteria indicated in the system and the screening number. The site personnel will then be provided with, at a minimum, a treatment assignment, randomization number, and dispensable unit (DU) or container number when study intervention/study treatment is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files. Investigational product/study treatment will be dispensed at the study visits as summarized in the SoA. Returned study intervention/study treatment must not be re-dispensed to the participants.

The study -specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

All doses of study intervention/study treatment will be administered by the appropriately designated study staff at the investigator site.

The site will complete required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical sites documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.6. Concomitant Therapy

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions (eg, paracentesis) received by participants from screening until the end of study visit will be recorded on the CRF as outlined in the data entry guidelines.

All concomitant treatments must be approved by the sponsor at study entry.

Authorized or approved COVID-19 vaccines are considered allowed concomitant medications and standard AE collection and reporting processes should be followed. The timing of vaccine dosing relative to the dosing of study drug(s) is at the discretion of the investigator, although it may best to avoid the 7 days prior to C1D1 and the DLT observation period, to consider the potential for vaccine-related adverse events, and to administer the vaccine during scheduled dosing holidays, if applicable. Discussions between the investigator and the sponsor regarding individual cases may occur if further clarification is required.

PF-07062119 has been demonstrated to transiently increase cytokine levels (eg, IL-6) in vivo in monkeys (also demonstrated via in vitro assays) which is expected with CD3-targeted bispecifics. Cytokines have been shown to result in modest inhibition of some cytochrome P450 enzymes. Therefore, treatment with PF-07062119 has the potential to modestly increase the exposure of concomitant medications that are substrates for these enzymes. Caution should be used upon concomitant use of sensitive substrates of cytochrome P450 enzymes with narrow therapeutic index (eg, CYP3A4: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus; CYP2C9: phenytoin, warfarin) especially during the initial treatment cycle.

6.6.1. Other Anti-tumor/Anti-cancer Treatment

No additional anti-tumor treatment will be permitted while participants are receiving study treatment.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PF-07062119 with radiotherapy, PF-07062119 treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment after recovery to baseline.

6.6.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current American Society of Clinical Oncology (ASCO) guidelines.

6.6.2.1. Supportive Care for Cytokine Release Syndrome

Symptoms associated with cytokine release syndrome (CRS) vary greatly and may be difficult to distinguish from other conditions. The more common symptoms include fever, nausea, headache, tachycardia, hypotension, rash and shortness of breath. The severity of symptoms can be mild to life threatening and thus there should be a high suspicion for CRS if these symptoms occur. The grading of CRS and clinical management considerations are described by the ASTCT consensus working group and noted in Appendix 11 (Lee et al 2019).[25] However, if local standard of care for CRS management involves a different regimen then these guidelines should be considered and potentially utilized.

The decision to incorporate and/or change the premedication strategy (see Section 6.1.1) for CRS prophylaxis in all participants will be made following discussions between the sponsor and the investigators.

6.6.2.2. Supportive Care for Infusion-Related Reactions

An IRR is characterized by fever and chills, and less commonly hypotension, either experienced by a particular participant or if seen in other participants, pretreatment medication should be administered to reduce the incidence and severity. In the event of infusion related reactions, Investigators should institute treatment measures according to best medical and nursing practice. A local standard of care for the management of IRR should be utilized.

6.6.2.3. Supportive Care for Hypersensitivity Reactions Types 1 and 3

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of infusion and may include symptoms such as rash, urticaria, polyarthritis, myalgia, polysynovitis, fever, and, if severe, glomerulonephritis.

All participants should be closely observed while receiving study intervention/study treatment infusions and monitoring for clinical signs of a systemic reaction will continue thereafter for clinical signs of allergic reactions/hypersensitivity.

In the case of a hypersensitivity reaction, the participant will be treated symptomatically with supportive care, further monitoring, and treatment with anti-histamines and/or corticosteroids. Study infusions may be stopped, and the participant will be followed until the end of the study.

6.6.2.4. Supportive Care for Immune-Related Adverse Events

For immunotherapeutic agents, treatment of immune-related adverse events (irAEs) is mainly dependent upon severity (NCI CTCAE grade v5.0). In general, Grade 1 or 2 irAEs are treated symptomatically and persistent Grade 2, 3, or 4 irAEs are treated with moderate to high doses of corticosteroids.

Treatment of irAEs should follow guidelines as summarized in Appendix 13.

6.6.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first 28 days of Cycle 1 for cohorts without a priming dose and the first 42 days (C2D15) for cohorts with a priming dose, but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines or local regional guidelines. During screening window (28 days prior to Day 1), GCSF is not permitted to qualify a participant with low WBC counts.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia (Note: erythropoietin is not approved for anemia caused by chemotherapy in all local regions, nor is it currently approved in Japan).

6.6.4. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis beyond the recommended premedication for the first cycle (see Section 6.1.1) is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drug-drug interaction and the drug is not prohibited in the Concomitant Therapy section.

Diarrhea has been observed in participants receiving PF-07062119. (see Section 2.2.8.1). Early identification and intervention is critical for the optimal management of diarrhea. At the first sign of loose stools, participants should be instructed to start anti-diarrheal therapy (eg, loperamide 4 mg initial dose followed by 2 mg after every subsequent loose stool with no more than 16 mg daily), increase oral fluids, and notify the principal investigator for further instructions and appropriate follow up. Participants should be encouraged to increase oral fluids.

In general, management of cancer treatment-induced diarrhea has been described (Benson et al, 2004).[7] Initial management for mild to moderate diarrhea may include dietary modifications (eliminating lactose and other high-osmolar dietary supplements), loperamide or diphenoxylate/atropine, along with oral antibiotics if persistent with concern for infection. Management of higher severity or more complicated diarrhea may also include consideration of intravenous fluids for hydration, electrolyte replacement, octreotide, stool workup along with hospitalization for observation and treatment if indicated in the investigator's medical judgement.

In addition, management of diarrhea as described in supportive care for immune-related adverse events for diarrhea (Appendix 13) may also be considered if the clinical impression of the etiology of diarrhea is associated with immune dysfunction.

6.6.5. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in Section 6.6.

6.6.6. Corticosteroids

Chronic systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. However, systemic corticosteroid use at a low dose for a short duration (eg, 5 mg QD of prednisone, for 2 weeks) as symptomatic treatment on individual basis and upon discussion with the sponsor. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

6.6.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-07062119 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-07062119 and/or PF-06801591 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-07062119 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

In the setting of bevacizumab-Pfizer use as part of investigational combination therapy, bevacizumab-Pfizer should be discontinued for at least 28 days prior to elective surgery. Also, do not administer bevacizumab-Pfizer for at least 28 days following surgery and until the wound is fully healed.

6.6.8. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07062119; standard medical supportive care must be provided to manage the AEs.

6.7. Dose Modification

Every effort should be made to administer study intervention/study treatment on the planned dose and schedule. In the event of significant toxicity, which may include a DLT, dosing may be delayed, reduced and/or discontinued as described below and in Sections 6.7.1, 6.7.2 and 6.7.3. Participants experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved, and in the opinion of the investigator and sponsor, the participant is benefiting from therapy. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed (and attribution for the combination treatment in Part 1B and Part 2). Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

6.7.1. Dosing Interruptions

With respect to study intervention or investigational combination therapy, participants experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment interrupted.

Combination therapy with immune oncology compounds may augment irAEs, pneumonitis, colitis, creatinine, and liver function test (LFT) elevation should be monitored carefully with this class of agents. To facilitate the early recognition and prompt intervention of clinically relevant AEs related to study treatment, management algorithms have been developed for suspected pulmonary, gastrointestinal, liver, endocrine, skin, cardiac, renal, or other immune-related toxicities (see Appendix 13).

All participants receiving bevacizumab-Pfizer will require a proteinuria assessment (dipstick is acceptable) prior to each dose of bevacizumab-Pfizer for the duration of the study. If urinalysis demonstrates protein greater than or equal to 2+, then a 24-hour urine protein collection should follow. In participants with proteinuria greater than or equal to 2 grams per 24 hours, bevacizumab-Pfizer should be held until recovery (less than 2 grams per 24 hours). Discontinue bevacizumab-Pfizer in participants that develop nephrotic syndrome.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in the Dose Delays section.

Doses may be held up to 4 weeks until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the participant missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions section, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

6.7.1.1. Dose Interruption of Participants with Presumed or Active COVID-19/SARS-CoV2 Infection

Ongoing participants who have active (confirmed positive [by regulatory authority-approved test] or presumed test [pending/clinical suspicion]) SARS-CoV2 infection, should follow the treatment guidelines below:

- For symptomatic participants with active SARS-CoV2 infection, investigational treatment should be delayed for at least 14 days from start of symptoms. This delay is intended to allow resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours and SARS-CoV2-related symptoms should have recovered to Grade ≤ 1 for a minimum of 72 hours. The sponsor should be informed when restarting treatment.

- Continue to consider potential drug-drug interactions for any concomitant medication administered for treatment of SARS-CoV2 infection.

More information on COVID-19 is provided in Appendix 18.

6.7.2. Dose Delays

Re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC $\geq$1,000/mm^3.
- Platelets count $\geq$50,000/mm^3.
- Nonhematologic toxicities have returned to baseline or Grade $\leq$1 severity (or, at the investigator's discretion, Grade $\leq$2 if not considered a safety risk for the participant).

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 4 weeks of treatment interruption, PF-07062119 may be resumed. Refer to the Dose Reductions section for adverse events requiring dose reduction at the time of treatment resumption.

If participants require discontinuation of PF-07062119 for more than 4 weeks at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the Sponsor's medical monitor.

If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

6.7.3. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-07062119 dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their participants according to their medical judgment based on the particular clinical circumstances.

For non-immune-related toxicities, toxicities not otherwise specified in Table 11, and immune-related toxicities, dose reduction of PF-07062119 by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered and based on the discretion of the investigator and in communication with the sponsor. Participants requiring more than 2 dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor.

For investigational combination therapy, dose modifications, delays or interruptions should be assigned to each product based on attribution to each component (ie, when compound A and B are combined, and toxicity occurs and is attributed to compound A, a dose lowering, delay, or interruption of compound A may be applicable but not necessarily to compound B).

If in the investigator's medical judgement, a toxicity leading to dose interruption or delay is attributed to the combination agent (either PF-06801591 or bevacizumab-Pfizer), and treatment with PF-07062119 alone is expected to derive clinical benefit, then the treatment with PF-07062119 may be resumed at the same or reduced dose level (according the tables below) with discontinuation of the combination agent following discussion and agreement with the Sponsor.

For non-immune-related toxicities specified in Table 11: In the setting of investigational combination therapy with PF-07062119 and combination agent (either PF-06801591 or bevacizumab-Pfizer), discontinuation, but no dose reduction for the combination agent (either PF-06801591 or bevacizumab-Pfizer), is allowed. All dose discontinuations/modifications/adjustments must be clearly documented in the participant's source notes and CRF.

For immune-related toxicities specified in Table 12: In the setting of investigational combination therapy with PF-07062119 and combination agent (either PF-06801591 or bevacizumab-Pfizer), discontinuation, but no dose reduction for the combination agent (either PF-06801591 or bevacizumab-Pfizer), is allowed depending on the toxicity and severity. All dose discontinuations/modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intraparticipant dose re-escalation is not allowed.

Participants experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved, and in the opinion of the investigator and sponsor, the participant is benefiting from therapy.

In some cases, participants experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade $\leq$1 or baseline is achieved.

Study treatment for participants should include PF-07062119 and not be limited to a combination agent (PF-06801591 or bevacizumab-Pfizer) only.

Recommended dose reductions for non-immune related toxicities and toxicities not otherwise specified in Table 12 that are attributed to study intervention or investigational combination therapy are described in Table 11. Dose Modifications for Adverse Reactions related to Bevacizumab-Pfizer can be found below in Table 14.

Table 11. Dose Modifications for Toxicity Attributed to Investigational Product or Investigational Combination Therapy for Non-Immune-Related AEs[c]

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nonhematologic	Continue at the same dose level	Continue at the same dose level	• Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the PF-07062119 dose by 1 level and subsequently an additional 1 level at the discretion of the investigator.[a,b,d] • Additionally, in combination therapy (with PF-06801591), PF-06801591 may resume treatment at the same dose level or discontinue at the discretion of the investigator.[a, b] • Additionally, in combination therapy (with bevacizumab-Pfizer), bevacizumab-Pfizer may resume treatment at the same dose level or discontinue at the discretion of the investigator.[a, b]	• Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the PF-07062119 dose by 1 level and subsequently an additional 1 level or discontinue at the discretion of the investigator.[a,b,d] • Additionally, in combination therapy (with PF-06801591), discontinue PF-06801591.[a, b] • Additionally, in combination therapy (with bevacizumab-Pfizer), discontinue the bevacizumab-Pfizer dose.[a, b]

Table 11. Dose Modifications for Toxicity Attributed to Investigational Product or Investigational Combination Therapy for Non-Immune-Related AEs[c]

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic	Continue at the same dose level	Continue at the same dose level	• Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level at the discretion of the investigator.[a, b, d] • Additionally, in combination therapy (with PF-06801591), PF-06801591 may resume treatment at the same dose level or discontinue at the discretion of the investigator.[a, b] • Additionally, in combination therapy (with bevacizumab-Pfizer), bevacizumab-Pfizer may resume treatment at the same dose level or discontinue at the discretion of the investigator.[a, b]	• Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the PF-07062119 dose by 1 level and subsequently an additional 1 level at and resume treatment at the discretion of the investigator.[a, b, d] • Additionally, in combination therapy (with PF-06801591), discontinue the PF-06801591 dose.[a, b] • Additionally, in combination therapy (with bevacizumab-Pfizer), discontinue the bevacizumab-Pfizer dose.[a, b]

a Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification.
b Cycle will not be extended to cover for the missing doses.
c If toxicity is considered immune related then should follow Table 12 – Dose Modifications for Specific Immune Related Toxicity Attributed to Investigational Product or Combination Investigational Therapy (Table 12).
d Dose reduction of PF-07062119 may be reduced to the next lower dose level(s) that was previously determined to be safe/tolerable during the dose escalation phase of the study.

Recommended dose reductions for immune related toxicities that are attributed to study intervention or investigational combination therapy are described in Table 12.

Table 12. Dose Modifications for Specific Immune Related Toxicity Attributed to Investigational Product or Combination Investigational Therapy

Organ System	Grade 1	Grade 2	Grade 3	Grade 4
GI (diarrhea)	Continue investigational treatment.	Withhold investigational treatment. If diarrhea improves to Grade ≤1, resume treatment at the same dose level.	•Withhold investigational treatment. •If diarrhea improves to Grade ≤1, resume treatment at the same dose level or reduce PF-07062119 dose by 1 level at the discretion of the investigator. •Additionally, in combination therapy (with PF-06801591), PF-06801591 may resume treatment at the same dose level or discontinue at the discretion of the investigator.* •Additionally, in combination therapy (with bevacizumab-Pfizer), bevacizumab-Pfizer may resume treatment at the same dose level or discontinue at the discretion of the investigator.*	Discontinue investigational treatment.
Skin (Dermatitis)	Continue investigational treatment. If persists >1-2 weeks, withhold. If improves after treatment with corticosteroids, then resume investigational treatment.	Continue investigational treatment. If persists >1-2 weeks, withhold. If improves after treatment with corticosteroids, then resume investigational treatment.	Withhold or discontinue investigational treatment. If improves to Grade ≤1, resume investigational therapy at the discretion of the investigator.	Withhold or discontinue investigational treatment. If improves to Grade 1 after treatment, resume investigational therapy at the discretion of the investigator.
Lung (pneumonitis)	Consider delay of investigational treatment Monitor	Withhold investigational treatment; re-image. If symptoms return to baseline then resume	Discontinue	Discontinue

Table 12. Dose Modifications for Specific Immune Related Toxicity Attributed to Investigational Product or Combination Investigational Therapy

Organ System	Grade 1	Grade 2	Grade 3	Grade 4
		investigational treatment.		
Liver (hepatitis)	Continue investigational treatment	Withhold investigational treatment and increase monitoring of transaminases. If transaminases improve within ≤7 days to Grade ≤1, resume treatment at same dose level. If transaminases do not improve within ≤7 days to Grade ≤1, treat with corticosteroids and reduce dose of PF-07062119 by 1 level when transaminases improve to Grade ≤1.	Discontinue	Discontinue
Cytokine Release Syndrome	Hold investigational treatment; after resolution, continue investigational treatment, after resolves, continue investigational treatment	Hold investigational treatment; after resolution, continue investigational treatment, after resolves, continue investigational treatment	Hold investigational treatment; after resolution, continue investigational treatment, after resolves, reduce dose of PF-07062119 by 1 level	Discontinue
Endocrine: TSH abnormality	Continue investigational treatment			
Symptomatic endocrinopathy	If symptomatic, abnormal labs, abnormal pituitary scan- withhold investigational treatment. After treatment, and with normal labs and MRI, resume investigational treatment.			

Table 12. Dose Modifications for Specific Immune Related Toxicity Attributed to Investigational Product or Combination Investigational Therapy

Organ System	Grade 1	Grade 2	Grade 3	Grade 4
Suspicion of adrenal crisis	Withhold or discontinue investigational treatment. If adrenal crisis ruled out, treat as for symptomatic endocrinopathy.			

* Dose reduction of PF-07062119 may be reduced to the next lower dose level(s) that was previously determined to be safe/tolerable during the dose escalation phase of the study.

Table 13. Dosage Modifications for Adverse Reactions

	Severity	Dosage Modification
Gastrointestinal Perforations and Fistulae	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue BEVACIZUMAB-PFIZER
Wound Healing Complications	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue BEVACIZUMAB-PFIZER
Hemorrhage	• Grade 3 or 4	Discontinue BEVACIZUMAB-PFIZER
	• Recent history of hemoptysis of ½ teaspoon (2.5 mL) or more	Withhold BEVACIZUMAB-PFIZER
Thromboembolic Events	• Arterial thromboembolism, severe	Discontinue BEVACIZUMAB-PFIZER
	• Venous thromboembolism, Grade 4	Discontinue BEVACIZUMAB-PFIZER
Hypertension	• Hypertensive crisis Hypertensive encephalopathy	Discontinue BEVACIZUMAB-PFIZER
	• Hypertension, severe	Withhold BEVACIZUMAB-PFIZER if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES)	• Any	Discontinue BEVACIZUMAB-PFIZER

Table 13. Dosage Modifications for Adverse Reactions

	Severity	Dosage Modification
Renal Injury and Proteinuria	• Nephrotic syndrome	Discontinue BEVACIZUMAB-PFIZER
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold BEVACIZUMAB-PFIZER until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions	• Severe	Discontinue BEVACIZUMAB-PFIZER
	• Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure	• Any	Discontinue BEVACIZUMAB-PFIZER

6.8. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Request to Continue Treatment

If the investigator feels the participant is still deriving benefit from treatment, following discussion with the sponsor the participant may have an option to continue dosing at the same dose or one dose lower, as long as the criteria below are met, until such benefit no longer exists.

Criteria that must be met to ensure that participants are not exposed to unreasonable risks by continued use of the investigational agent in spite of progression of disease. Such criteria may include the following:

- Absence of symptoms and signs indicating clinically significant progression of disease.
- No decline in ECOG performance status.
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression).

At the time of radiographic progression of disease, obtain the re-consent of participants using a written informed consent document that details all FDA-approved therapy, and potential clinical benefit, that the participant may be foregoing in order to continue receiving the study intervention.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Reasons for withdrawal of study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;

- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Safety assessments will include collection of AEs, serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

8.1.1. Physical Examinations

Participants will have a physical examination to include weight, vital signs, assessment of ECOG performance status and height; height will be measured at baseline only.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.1.2. COVID-19: Use of Alternative Methods for In-Person Visits

In light of the COVID-19 pandemic, alternative methods for conducting safety assessments must be considered, when feasible and when safety can be assured. These may include:

- Conducting telehealth visits (eg, phone/video [using HIPAA-compliant video-conference tools or as permitted by local regulations])
- Moving participants to less crowded family health centers and local laboratories for blood draws, and imaging/radiographs.
- Refer to Appendix 18 for a more comprehensive list of acceptable alternative measures during the COVID-19 public emergency.

8.1.3. Vital Signs

Vital signs will be measured with the participant in a semi-supine position or seated position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse rate, pulse oximetry and weight.

8.1.4. Electrocardiograms

Standard 12-Lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected in triplicate at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads

(eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

At each time point (SoA), 3 consecutive ECGs will be performed at approximately (1 to 4) minutes apart to determine the mean QTcF interval. To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. In addition, if verified QTcF values continue to exceed the criteria above, immediate correction for reversible causes including electrolyte abnormalities, hypoxia, and concomitant medications for drugs with the potential to prolong the QTcF interval should be performed.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

If a participant experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

ECG values of potential clinical concern are listed in Appendix 7.

8.1.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 84 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.1.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in women of childbearing potential (WOCBP) at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the PF-07062119. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.1.7. Injection Site Tolerability Assessment

Assessments of the injection sites in the abdominal fat fold to monitor local tolerability to PF-07062119 and PF-06801591 SC injections will be performed for at least 1 hour following study drug administration in Cycle 1, as per the SoA. An assessment should also be performed 24 hours (±1 hour) after the C1D1 dose. Injection site tolerability assessments for at least 1 hour post the PF-07062119 injection should continue after each dosing day visit in Cycle 2 and beyond, only if injection site pain or ISR characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve. The injection sites will be assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after PF-07062119 and PF-06801591 administration. The diameter of the affected area will be measured, and the condition of the injection site will be recorded on the injection site reaction CRF. Any observed abnormality at the injection site will be judged by the investigator to determine if the event should also be reported as an AE. ISRs should be immediately photographed in color, with scaled ruler placed by the reaction, and these photographs should be included in the participant's source documentation. When appropriate, at the discretion of the investigator, a participant with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR.

8.2. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (Section 7.1).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.2.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.2.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study intervention must be reported to Pfizer Safety.

8.2.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.2.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.2.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.2.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.2.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 105 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.2.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.2.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.2.6. Medication Errors

Medication errors may result from the administration or consumption of the study intervention/study treatment by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately (within 24 hours).

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.3. Treatment of Overdose

For this study, any dose of PF-07062119 as a monotherapy or with a combination agent greater than the intended dose within a 24-hour time period will be considered an overdose, unless this dose level has been declared as safe in the dose escalation phase. Additionally any dose of PF-06801591 or bevacizumab-Pfizer greater than the intended dose within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study intervention (whichever is longer).

3. Obtain a blood sample for PK analysis within two weeks from the date of the last dose of the study intervention if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.4. Pharmacokinetics and Immunogenicity

8.4.1. Pharmacokinetic Assessments

Blood samples of approximately 4 mL, to provide a minimum of 2 mL serum, will be collected for measurement of serum concentrations of PF-07062119, PF-06801591 or bevacizumab-Pfizer as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual collection times may change, but the number of planned samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples that are obtained within the specified time window will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

Samples will be used to evaluate the PK of PF-07062119, PF-06801591 or bevacizumab-Pfizer. Samples collected for analyses of serum drug concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of serum concentrations of PF-07062119, PF-06801591 or bevacizumab-Pfizer as indicated will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping

conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.4.2. Analysis of Anti-Drug Antibodies and Neutralizing Anti-Antibodies (PF-07062119, PF-06801591, or bevacizumab-Pfizer)

Blood samples of approximately 4 mL, to provide a minimum of serum 2 mL, will be collected for determination of ADA and NAb against PF-07062119, PF-06801591 or bevacizumab-Pfizer, as indicated as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5. Pharmacodynamics

Pharmacodynamic (PD) parameters will be evaluated in this study. See Section 8.8 Biomarkers.

8.6. Biomarker and Pharmacodynamic Assessments

A key element of this study is the evaluation of potential cellular and molecular signatures that exist before treatment and could be modified in vivo by PF-07062119 used in this study to target GUCY2C and activate T cells. The biomarker studies will be used to help understand the in vivo mechanism of action of PF-07062119, to evaluate the monotherapy PF-07062119, and potential combinatorial effects of PF-07062119 with other agents, as well as evaluate potential mechanisms of resistance. Biomarker studies may help in the future development of this drug as a single agent, or in combination with other compounds.

Table 14 below summarizes the biomarker assays that include, but are not limited to, those which will be used and the source of the samples. Additional biospecimens collected over the course of participant disease management may be submitted for biomarker analyses. Refer to the SoA for details pertaining to specific days of sample collection and to the study manual for details of sample preparation.

Table 14. Biomarker Collections and Analyses

Assay	Sample Type
Measurement of GUCY2C Expression Levels	Archival and de novo pre-treatment tumor biopsies
Immunophenotyping of blood immune cell subtypes frequency and activation modulation	Whole blood
Measurement of peripheral cytokines and other circulating markers	Whole blood
Modulation of intra-tumoral target pathway modulation (ie, gene expression signature, cellular and protein changes)	De novo pre-, on-, post-treatment tumor biopsies

Pharmacodynamic parameters will be evaluated in this study. See Section 8.8 Biomarkers.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

A 4 mL whole blood sample optimized for DNA isolation (Prep D1/Prep D1.5) will be collected as local regulations and IRBs/ECs allow (refer to the SoA for collection timepoints).

Banked biospecimens may be used for research related to drug response and disease under study. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for participants. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the study manual.

Details on processes for collection and shipment of these samples can be found in Laboratory Manual.

8.8. Biomarkers

Biospecimens collected for pharmacodynamic and other biomarker assessments may include, but are not limited to peripheral blood, tumor tissues and may be used to analyze DNA, RNA, proteins, or metabolic biomarkers, for achieving planned biomarker objectives. Refer to the SoA for sample collection time points and Study/Laboratory Manual for sample processing and shipping. The following biospecimen types are planned to be collected in support of study objectives. Additional biospecimens collected over the course of participant disease management may be submitted for biomarker analyses.

Tumor biospecimens from archival and/de novo biopsies will be used to analyze candidate nucleic acid and protein and cellular biomarkers for their ability to inform those participants who are most likely to benefit from treatment with the study drugs. Biomarkers may include, but are not limited to target expression, nucleic acid analyses, as well as cell types and constituents of the tumor microenvironment (TME). Optional, and/or de novo tumor biopsies obtained during therapy and upon disease progression may be used to help confirm pharmacodynamic effects of treatment and investigate potential acquired mechanisms of resistance (ie, presence of but not limited to regulatory T-cells or myeloid-derived suppressor cells and other immune suppressive cells or proteins).

8.8.1. Archival Pre-treatment and Optional De Novo Pre- and On-Treatment Tumor Biopsies for Part 1A and Part 1B

All participants in Part 1A and Part 1B must provide an archived FFPE tumor tissue sample (block preferred). Samples provided should be taken from the most recently conducted available biopsy, preferably within 6 months of start of study treatment. Tissue blocks are preferable, but freshly cut paraffin sections are acceptable. Sites should contact sponsor for approval to submit slides and refer to Laboratory/Study manual for instructions on submitting slides. Cytological or fine-needle aspiration samples are not acceptable.

If the archived sample is older than 6 months, the investigator must contact the sponsor's Medical Monitor to discuss eligibility prior to enrollment.

If an appropriate archival FFPE tumor sample is not available, a de novo fresh FFPE tumor sample should be collected. Each de novo collections (pre-treatment and on-treatment) should attempt to obtain 6 core biopsies, with a minimum of preferably 3 cores. Samples should be obtained in accordance with local institutional practice for tumor biopsies.

In Part 1A and Part 1B, optional de novo pre- and on-treatment tumor biopsies are encouraged for all participants on the trial when participants have accessible lesions. Optional on-treatment tumor biopsies are preferentially collected after the third dose, within 7 days of C3D1 (C3D1 ±7 days). If on treatment tumor collection takes places greater than ±3 days from C3D1, additional unscheduled blood sample for cytokine and circulating markers and an unscheduled blood sample for T-cell immunophenotyping sample should be collected to match the day of biopsy collection.

Additional information on tissue collection procedures can be found in the Laboratory/Study Manual.

8.8.2. Mandatory De Novo Pre- and On-Treatment Tumor Biopsies at RP2D in Part 1A, Part 1B, and Part 2

As the RP2D/MTD is approached or the RP2D/MTD of PF-07062119 has been determined, an optional subset of participants may be enrolled (approximately 6 to 12 participants) based on emerging clinical data with the requirement of providing mandatory paired de novo pretreatment and on-treatment biopsy samples in Parts 1A and Part 1B within 7 days of C3D1 (±7 days) to enable evaluation of tissue biomarker PD activity. The option to enroll the subset of participants for mandatory paired tumor samples will be based on evaluation of emerging clinical data including available safety/tolerability, PK, and PD findings by the sponsor.

In Part 2, de novo pre-treatment biopsies will be required from all participants, unless not medically feasible, in order to establish relationship between target expression and efficacy observations. If a de novo pre-treatment biopsy is not medically feasible, the sponsor should be contacted for approval before initiating screening activities. For a subset of participants in all cohorts (approximately 10 participants), mandatory on-treatment biopsy samples will also be collected in order to confirm the mechanism of action and evaluate potential resistance mechanism during treatment. For all other participants, on-treatment biopsies are optional but encouraged. In Part 2, approximately 20 participants each will be enrolled in the monotherapy and both combination cohorts. If 15 participants have been enrolled in a cohort and <5 paired pre- and on-treatment biopsies have been collected, collections may be made mandatory for the remaining participants and the cohort may be expanded by up to 5 participants to obtain sufficient numbers of paired pre- and on-treatment biopsies.

From these participants with paired pre- and on-treatment biopsies, an optional second on treatment- biopsy is also encouraged after C4D15 or at disease progression to evaluate potential responses to treatment or suspected acquired resistance to therapy.

Mandatory de novo tumor collections (pre-treatment and on-treatment) should attempt to obtain 6 core biopsies, with a minimum of preferably 3 cores. Samples should be obtained in

accordance with local institutional practice for tumor biopsies. Additional information on tissue collection procedures can be found in the Laboratory/Study Manual.

Mandatory pre-treatment de novo tumor biopsies are to be collected within 28 days of first study treatment dose. On-treatment tumor biopsies are preferably collected after the third dose, within 7 days of C2D15 (C2D15 ±7 days).

If on-treatment tumor collection takes place greater than ±3 days from C2D15, unscheduled blood samples for cytokine and circulating markers and T-cell immunophenotyping sample should be collected to match the day of biopsy collection.

Optional biopsies are encouraged at disease progression and/or end of treatment (assuming available tumor to biopsy) and as clinically indicated throughout treatment for all participants. If biopsy is to be completed the same day as CT scan, it must be completed after the CT scan.

8.8.3. Peripheral Blood Sample Assessments

Peripheral blood and derivatives may be used to characterize cell phenotypes, measure soluble proteins and analyze nucleic acids to support study objectives. Examples may include but are not limited to tumor exosomes, cell free DNA, circulating tumor cells (CTC), cytokines. Additional analyses may be warranted based on emerging data. Instructions for sample collection, processing, storage and shipment will be provided in the Laboratory/Study manual.

8.8.4. Cytokine Assessments

Samples will be collected for central evaluation of cytokines at the timepoints specified in the SoA. The cytokines to be measured may include, but not limited to IFN-γ, TNF-α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL 12-p70 and soluble IL-2R (sCD25). Additional exploratory circulating measures will also be evaluated to measure changes in immune activation after therapy. Instructions for sample collection, processing, storage and shipment will be provided in the Laboratory/Study manual.

8.8.5. T Cell Immunophenotyping

Whole blood samples for evaluation of T-cell, B-cell, and NK immunophenotyping as well as characterization of T cells for markers such as but not limited to KI67, PD-1, HLA-DR and other proliferation, activation, and exhaustion markers to measure changes in immune activation after therapy. Samples will be collected at the times specified in the SoA. Instructions for sample collection, processing, storage and shipment will be provided in the Laboratory/Study manual.

Samples may be used for flow cytometry assay development. Samples used for this purpose will be retained in accordance with local regulations and if not used within this timeframe, will be destroyed.

8.9. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging will include contrast enhanced chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan for participants with known or suspected brain metastases; bone scan and/or bone x-rays for participants with known or suspected bone metastases. For participants with known CT contrast allergy, a non-contrast CT of the chest with contrast enhanced abdominal and pelvic MRI can be used. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the SoA, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks). Assessment of response will be made using RECIST version 1.1 (Appendix 14).

All participants' files and radiologic images and pathology must be available for source verification and for potential peer review.

Disease response assessments will be based upon disease-specific response criteria (Appendix 14).

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and biomarker measurements.

9.1. Statistical Hypotheses

There will be no formal hypothesis testing in this study.

9.2. Sample Size Determination

Total number of participants is estimated to be approximately 130 participants.

9.2.1. Part 1 Dose Escalation

Approximately 35 participants each will be enrolled in the Part 1A (monotherapy) and Part 1B (combination) dose escalation portions of the study. However, the total number of

participants will depend on the number of dose levels needed to determine the MTD and number of participants evaluable for DLT at each dose level.

9.2.2. Part 2 Dose Expansion

Each of expansion cohorts will enroll approximately 20 to 30 participants. Participants from Part 1A and Part 1B who were treated at the dose level selected for Part 2 and fulfilling Part 2 inclusion/exclusion criteria may be counted towards the sample size of Part 2 at the corresponding regimen (monotherapy and combinations).

Assuming a non-informative prior (ie, Jeffrey's prior) if 6 out of 20 participants have tumor response, this would predict a posterior probability (Beta Binomial) equal to 0.71 that the true response is not inferior to target response rate of 25% and a posterior probability close to 0 (equal to 4e-07) that the true response is inferior to benchmark rate of 2%.

9.3. Populations for Analysis

- Full analysis set.
  - The full analysis set includes all enrolled participants.
- Safety analysis set.
  - The safety analysis set includes all enrolled participants who receive at least one dose of study treatment. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses.
- Per protocol analysis set (evaluable for MTD).
  - The per protocol analysis set includes all enrolled participants who had at least one dose of study treatment and either experienced DLT or do not have major treatment deviations during the DLT observation period.
- Modified Intent to Treat (mITT) Population.
  - The mITT is the analysis population that will follow the ITT principle and include participants receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population may be used for interim analysis and conference presentations when the study is still ongoing.
- PK analysis sets.
  - The PK parameter analysis population is defined as all enrolled participants treated who do not have protocol deviations influencing PK assessment and have sufficient information to estimate at least 1 of the PK parameters of interest.

- The PK concentration population is defined as all enrolled participants who are treated and have at least 1 analyte concentration.

- Response Evaluable Set.
  - The response evaluable population will include all participants who received at least one dose of study treatment and had baseline disease and at least one post baseline disease assessment.

- PD/Biomarker analysis set(s).
  - The PD/Biomarker analysis population is defined as all enrolled participants with at least 1 of the PD/Biomarkers evaluated at pre and/or post dose.

- Immunogenicity analysis set.
  - The immunogenicity analysis set includes all enrolled participants who receive at least one dose of study treatment and have at least one sample tested for ADA.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Maximum Tolerated Dose Determination

Determination of MTD will be performed using Per-protocol analysis set (evaluable for MTD).

Bayesian adaptive approach:

The dose escalation in the Part 1A and Part 1B (with and without priming separately) of the study will be guided by a Bayesian analysis of DLT data for PF-07062119. Toxicity is modelled using two-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose for the monotherapy and using BLRM model specifically developed for combinations separately for regimens with and without priming.

Assessment of participant risk (the three dosing intervals boundaries can be modified):

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07062119 will be evaluated separately for cohorts with and without priming, taking into account the different DLT observation periods (28 days for the regimen without priming and 42 days for the regimen with priming). The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0, 0.16]
Targeted dosing:	[0.16, 0.33]
Overdosing:	[0.33, 1]

The EWOC principle:

Dosing decisions are guided by the escalation with overdose control principal. [31] A dose may only be used for newly enrolled participants if the risk of excessive toxicity at that dose is less than 25%.

Prior distributions:

Weakly informative prior distributions based on pre-clinical/expert opinion information will be chosen for the logistic parameters for prior distribution in Part 1A, see Appendix 10.

A meta-analytic-predictive (MAP) approach will be used to derive the prior distribution for model parameters used in Part 1B based on the data collected in Part 1A. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data. [40,27,31] MAP priors are derived from hierarchical models, which take into account possible differences between the studies. A full description of the application of the MAP approach to derive the prior distributions of the model parameters is provided in Appendix 10.

Starting dose:

The starting dose of Part 1A without priming is 45 µg. For this dose the prior risk of overdosing is 9.7%, which satisfies the EWOC criterion. A full assessment of the prior risk to participants is given in Appendix 10.

The starting dose of Part 1A with priming is 400 µg for the priming dose and 800 µg for the full dose. For this dose the prior risk of overdosing is 12.8%, which satisfies the EWOC criterion. A full assessment of the prior risk to participants is given in Appendix 10.

The maximum number of participants in dose escalation part of the study was set to 50. The trial will be stopped when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD/RP2D.

- The dose $\tilde{d}$ satisfies one of the following conditions:

The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$.

- A minimum of 15 participants have been treated in the trial.

9.4.2. Efficacy Analyses

Response Evaluable Set will be used for all response related analyses including ORR, DOR, and PFS.

Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, dose on Day 1, tumor response at each visit, and best overall response.

Part 1A and Part 1B: progression date, death date, date of first response and last tumor assessment date and date of last contact will be listed.

Part 2: The Kaplan-Meier methods will be used to analyze all time to event endpoints. Median PFS (if reached). Details of these endpoint analyses methods will be included in the SAP.

PFS is defined the time from start date to date of first documentation of progression, or death due to any cause. Progression is defined as the appearance of local, regional or distant disease of the same type after complete response or progression of pre-existing lesions. It does not include second primary malignancies of unrelated types.

The definition of each response category is provided in Appendix 14 (RECIST v1.1) and Appendix 15 (irRECIST).

9.4.3. Safety Analyses

All safety analyses will be performed on the safety population.

Summaries and analyses of safety parameters will include all participants in the safety analysis set.

AEs, ECGs, BP, PR, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4.3.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTc value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the clinical study report (CSR) in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTc value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as a C1D1 predose.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (HR) (QTc) using standard correction factors (ie, Fridericia's (QTcF; default correction), Bazett's (QTcB), and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT, HR, response rate (RR), partial response (PR), QRS, QTcF (and other correction factors, eg, QTcB as appropriate) by study arm and presented by time and dose. Individual QT (all evaluated corrections) intervals will be listed by study, time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point. Details of additional analysis (if any) will be specified in SAP.

9.4.3.2. Adverse Events

AEs will graded by the investigator according to the CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event data will be reported in tables and listings. Summaries of adverse event by mapped terms, appropriate thesaurus level, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of adverse events leading to death and premature withdrawal from study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Listings of DLTs and deaths will be provided.

9.4.3.3. Laboratory Test Abnormalities

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.4.4. Other Analyses

9.4.4.1. Pharmacokinetic Analyses

Single-Dose and Multiple-Dose PF-07062119 PK Analysis

The concentrations of PF-07062119 will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum maximum, and geometric mean) by dosing cohort, cycle, and nominal time. Median profiles of the concentration-time profiles after the C1D1 dose, C1D15 dose (priming approach), and dose will be plotted separately by dosing cohort and cycle using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

The individual concentration-time data of PF-07062119 following the C1D1 dose, C1D15 dose (priming approach), and C4D1 dose will be analyzed separately using non-compartmental analysis to estimate the PK parameters. The PK parameters estimated will include C_{max}, time to maximum concentration (T_{max}), and concentration versus time curve (AUC_{last}). If data permit or if considered appropriate, other PK parameters including terminal elimination half-life ($t_{1/2}$), clearance (CL/F), AUC_{inf}, and volume of distribution at steady state ($V_{ss/F}$) may be determined. Non-compartmental PK parameters will be summarized descriptively by dose and cycle. Actual sample collection times will be used for the parameter calculations.

The concentrations of PF-06801591 or bevacizumab-Pfizer from Part 1B and Part 2 will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum maximum, and geometric mean) by dosing cohort, cycle, and nominal time.

Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

PF-07062119 PK and PD data from this study may be analyzed using population modeling approaches and may also be pooled with data from other future studies to investigate any association between PF-07062119 exposure and biomarkers or selected safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately from the clinical study report.

9.4.4.2. Pharmacodynamic Analyses

Analysis of Biomarker Endpoints

For biopsy samples, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and post-treatment. Further analysis will be specified in SAP.

Clinically relevant and interpretable biomarker assessments generated for Primary and Secondary objectives will be summarized in the CSR. Other biomarker data might be summarized in a separate technical document.

Immunogenicity Analysis

For the immunogenicity data, the percentage of participants with positive ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and post-randomization will be generated. Samples may also be analyzed for the presence of NAb, and any data will be similarly summarized. For participants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit. The potential impact of immunogenicity on PK and clinical response including pharmacodynamic markers, safety/tolerability and efficacy will be explored, if warranted by the data.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose -escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC). For the purpose of this protocol, Pfizer procedures for periodic safety review by a safety review team, comprised of the investigators and the sponsor, will be applied in order to review individual and summary data collected in the safety and clinical databases. These individual and summary data would also include participants who are determined to be not evaluable for DLT assessment.

Discussions between the investigators and the sponsor regarding safety will occur in an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and determine if further participant enrollment is appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention/study treatment, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally acceptable representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICDs must be provided to the participant or the participant's legally acceptable representative.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified

between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study manual.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts and submits all manuscripts or abstracts to the sponsor

30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 15. Safety Laboratory Tests

Hematology	Chemistry	Serology	Coagulation	Urinalysis	Pregnancy Test	Ad hoc Local Lab Cytokine Analysis†
Hemoglobin	ALT	HBV	PT	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a] 24 hour urine (protein collection)[b]	For female participants of childbearing potential, serum.	IL-6, IL-1β, IL-10, IFNγ, TNF-α, other cytokines
Platelets	AST	HCV	PTT or APTT			
WBC	Bicarbonate					
Absolute Neutrophils	CRP					
Absolute Lymphocytes	Alk Phos					
Absolute Monocytes	Sodium					
Absolute Eosinophils	Potassium					
Absolute Basophils	Magnesium					
Reticulocytes	Chloride					
	Total calcium					
	Total bilirubin***					
	Total Protein					
	BUN or Urea					
	Creatinine					
	Uric Acid					
	Glucose (nonfasted)					
	LDH					
	Albumin					
	Phosphorus or Phosphate					
	Amylase					
	Lipase					
	Thyroid Panel§					

Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; HBV = hepatitis B; HCV = hepatitis C; IFNγ = interferon-gamma; IL = interleukin; INR = International Normalized; LDH = lactate dehydrogenase; PTT = partial

Table 15. Safety Laboratory Tests

Hematology	Chemistry	Serology	Coagulation	Urinalysis	Pregnancy Test	Ad hoc Local Lab Cytokine Analysis†

thromboplastin time; TNFα = Tumor necrosis factor- alpha; TSH = Thyroid-stimulating hormone; WBC = white blood cells.

*** For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

§ Thyroid panel should be obtained at screening only (TSH, free thyroxine [T4], free triiodothyronine [total or free T3]).

† Cytokines for local lab evaluation will be collected if CRS is suspected. Local lab evaluation of cytokine is only required if the site require this information for participant management.

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

b. If urinalysis (dipstick acceptable) demonstrates protein greater than or equal to 2+, then a 24-hour urine protein collection should follow. In participants with proteinuria greater than or equal to 2 grams per 24 hours, bevacizumab-Pfizer should be held until recovery (less than 2 grams per 24 hours). Discontinue bevacizumab-Pfizer in participants that develop nephrotic syndrome.

Investigators must document their review of each laboratory safety report, including determination of clinical significance.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drugdrug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/selfharming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day to day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term "life threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately lifethreatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Assessment of Intensity section).
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as

serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	**All AEs/SAEs associated with** exposure during pregnancy **(EDP) or breastfeeding** Occupational exposure is not recorded.	All instances of EDP and exposure during breastfeeding (whether or not there is an associated SAE). All SAEs associated with occupational exposure. Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology, when available.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 105 days after the last dose of study intervention of PF-07062119 and for at least 6 months after the last dose of PF-06801591 (sasanlimab) and bevacizumab-Pfizer, which corresponds to the time needed to eliminate study intervention(s):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a longterm and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 105 days after the last dose of PF-07062119 intervention and at least 6 months after the last dose of PF-06801591 (sasanlimab) and bevacizumab-Pfizer, which corresponds to the time needed to eliminate any study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

      For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

      Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

    - A postmenopausal state is defined as age 60 years or older or 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 postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).When there is a high FSH level, it should be confirmed that there is no other medical cause.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

    - Oral;
    - Intravaginal (not approved in Japan);
    - Transdermal (not approved in Japan);
    - Injectable (not approved in Japan).

7. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral (not approved in Japan);
    - Injectable (not approved in Japan).

8. Sexual abstinence.

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the study intervention; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study intervention;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the study intervention prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the study intervention, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case by case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study treatments of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

Samples for banking (see Section 8.7.2) will be stored indefinitely or other period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (Tbili) elevations (>2 × ULN) by several days or weeks. The increase in Tbili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and Tbili values will be elevated within the same laboratory sample). In rare instances, by the time Tbili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to Tbili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and Tbili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a Tbili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** Tbili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

Preexisting values of Tbili above the normal range: Tbili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and Tbili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and Tbili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and Tbili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New onset- atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second degree- (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events (SAEs)
• QTcF prolongation >500 msec. • New ST-T changes suggestive of myocardial ischemia. • New onset left bundle branch block (QRS >120 msec). • New onset right bundle branch block (QRS >120 msec). • Symptomatic bradycardia. • Asystole: In awake, symptom free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node. In awake, symptom free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer. Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm. • Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute). • Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Country-Specific Requirements

The investigator agrees to abide by the ethical principles set forth in the World Health Organization's *Guiding Principles for Human Cell, Tissue and Organ Transplantation* (WHA63.22) (http://www.who.int/transplantation/en/) with regard to the study.

10.9. Appendix 9: Preliminary Clinical Summary for Study B8011001 Phase 1 FIH (PF-06801591)

Data Cutoff Date: 29 August 2019

Study Design:

B8011001 is an ongoing Phase 1, open-label, dose escalation and expansion study of PF-06801591 in participants with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma or other solid tumors. The primary purpose of this study is to evaluate safety and early signs of efficacy of PF-06801591. This clinical study was divided into a dose escalation (Part 1) phase, and a dose expansion (Part 2) phase.

Part 1 Dose Escalation

Part 1 dose escalation evaluated 4 pre-specified IV dose levels (0.5, 1, 3, and 10 mg/kg administered every 3 weeks [Q3W]), and 1 subcutaneous (SC) dose level (300 mg administered every 4 weeks [Q4W]) in adult participants with locally advanced or metastatic melanoma, squamous cell cancer of head and neck (SCCHN), ovarian cancer, sarcoma, small cell lung cancer (SCLC), adenocarcinoma of salivary gland, endometrial adenocarcinoma, malignant peritoneal neoplasm, esophageal adenocarcinoma or renal cell carcinoma. Patients had progressive disease on ≥1 prior line of therapy for locally advanced or metastatic disease or refused standard of care therapy; were not previously treated with an anti-PD-1/PD-L1 agent; and had adequate renal, bone marrow, liver, and cardiac function, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Forty participants were enrolled into Part 1 with 25 participants total enrolled into the IV dose cohorts and 15 participants enrolled into the SC dose cohort.

Part 2 Dose Expansion

The 300 mg SC dose was evaluated in an expanded population of 106 participants. This included 68 participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) and 38 participants with locally advanced or metastatic urothelial carcinoma (UC) who were anti-PD-1 or anti-PD-L1 treatment-naïve and who had progressive disease on or were intolerant to systemic therapy or for whom standard of care systemic therapy was refused or unavailable. Patients with NSCLC could have received up to one line of prior systemic therapy for locally advanced or metastatic disease and if they had known epidermal growth factor receptor (EGFR) activating mutation or an anaplastic lymphoma kinase (ALK) rearrangement were required to have, in addition, at least one targeted therapy for their disease. Patients with UC could have received up to 2 lines of prior systemic therapies for locally advanced or metastatic disease. The selected participants had adequate renal, bone marrow, liver, and cardiac function, with ECOG performance status 0 or 1. All participants received 300 mg of PF-06801591 SC every 4 weeks.

Clinical Overview

Study B8011001 is an ongoing Phase 1, open-label, dose escalation and expansion study of sasanlimab in participants with locally advanced or metastatic melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, sarcoma, NSCLC, UC, or other solid tumors. The primary purpose of the study was to evaluate safety and early signs of efficacy of sasanlimab. The clinical study was divided into a dose escalation (Part 1) phase, and a dose expansion (Part 2) phase. One hundred forty-six (146) participants have been dosed on the study. Forty (40) participants were enrolled into Part 1 and 106 participants (68 with NSCLC and 38 with UC) were enrolled into Part 2. In Part 1, 4 pre-specified IV dose levels (0.5, 1, 3, and 10 mg/kg administered Q3W), and 1 SC dose level (300 mg administered Q4W) were evaluated for safety. No DLTs were observed and thus, there was no maximum tolerated dose identified. The 300 mg SC dose was selected based on benefit/risk assessment.

As of the data cutoff of 28 August 2019, 13 of 15 participants treated with sasanlimab 300 mg SC dose (Part 1) experienced at least 1 treatment-related AE. The most common treatment-related AEs reported were diarrhea, fatigue and decrease appetite (n = 4 participants each, 26.7%), and nausea, cough, and dyspnea (n = 3 participants each, 20.0%). One participant experienced a Grade 3 treatment-related AE (anemia). There were no Grade 4 or Grade 5 treatment-related AEs.

A total of 60 of 106 participants experienced at least 1 treatment-related AE in Part-2. Most commonly reported treatment-related AEs experienced by >5% of participants were hyperthyroidism (n = 11; 10.4%), lipase increased and pruritus (n = 7; 6.6%) each and amylase increased, hypothyroidism, and anemia (n = 6; 5.7%) each. Grade 3 treatment-related AEs included lipase increase, amylase increased (each n = 2, 1.9%), blood alkaline phosphatase increased, decreased appetite, hypermagnesemia, pneumonitis, ageusia, anosmia, and jaundice (each n = 1, 0.9%). Grade 4 treatment-related AEs included lipase increased, neutrophil count decreased, white blood cell count decreased (each n = 1, 0.9%). Grade 5 treatment-related AE included arrhythmia (n = 1, 0.9%). For treatment-related SAEs reported, refer to the sasanlimab (PF-06801591) IB.

No significant injection site reactions were reported, except for 1 case of Grade 1 injection site pain. Safety data including possible irAE are mostly consistent with the known safety profile of anti-PD-1 treatment.

Detailed safety information from clinical studies, as well as nonclinical information, can be found in the sasanlimab (PF-06801591) IB.

Conclusions:

Based on the available safety and efficacy data for PF-06801591, the benefit risk profile of PF-06801591 is expected to be favorable.

10.10. Appendix 10: Detailed Dose Escalation/Finding Scheme for BLRM

This appendix provides the details of the statistical model, the description of prior distribution. The results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model could be found in the separate Technical supplement to this appendix.

10.10.1. Statistical Model

Let π (d) be the risk of DLT for PF-07062119 given as a single agent at dose d. The dose-DLT model is logistic:

$$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*)$$

$d^* = 1800$ µg and used to scale the doses of PF-07062119. Hence, α (>0) are the PF-07062119 odds of a DLT at d^* µg; and β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

10.10.2. Prior Specifications for Monotherapy Without Priming

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the parameters α and β. A weakly informative prior was used as there were no relevant human historical DLT data available. It was assumed that model parameters will follow a bivariate normal (BVN) distribution

$$(\log(\alpha), \log(\beta)) \sim N_2(m, S)$$

with prior means $m = (m_1, m_2)$, and prior covariance matrix S composed of standard deviations s_1, s_2 and correlation ρ. It was assumed that

$$(m_1, m_2, s_1, s_2, \rho) = (\text{logit}(p^*), 0, 2, 1, 0)$$

Here, p^* is the anticipated DLT rate at the scaling dose d^*. It was assumed based on pre-clinical data that DLT rate at 1800 µg was 0.33.

This prior is considered to be weakly informative (Neuenschwander et al. 2014).[31]

The prior distributions of the model parameters are provided in Table 16. Table 17 illustrates the resulting prior distribution of DLT rate derived from the prior given in Table 16 and rounded to 3 decimal points. Based on the available information the starting dose of PF-07062119 of 45 µg satisfies the EWOC criteria.

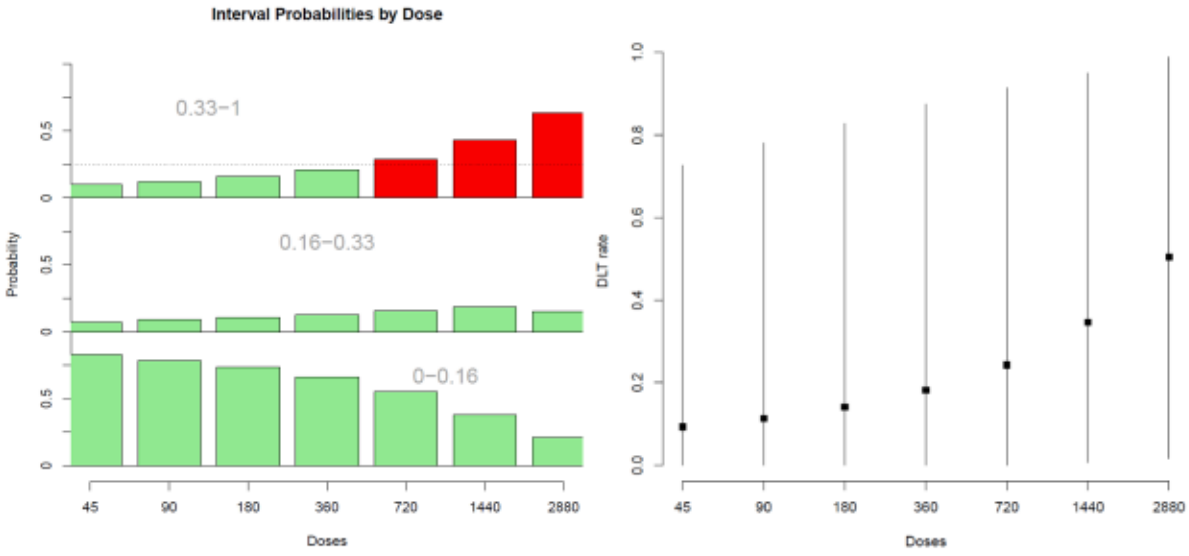
Table 16. Prior Distribution for the Model Parameters

PF-07062119 single agent parameters: BVN weakly informative prior			
Parameters	Means	Standard deviations	Correlation
$(\log(\alpha), \log(\beta))$	-0.708, 0	2, 1	0

Table 17. Summary of Prior Distribution of Dose Limiting Toxicity Rates for PF-07062119

$(d^* = 1800\ \mu g)$								
PF-07062119 Dose (µg)	Prior Probabilities that DLT Rate is in the Interval			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
45	0.829	0.074	0.097	0.093	0.186	0.000	0.008	0.727
90	0.788	0.091	0.121	0.113	0.203	0.000	0.016	0.780
180	0.736	0.107	0.157	0.141	0.223	0.000	0.030	0.828
360	0.664	0.127	0.209	0.181	0.247	0.000	0.060	0.874
720	0.553	0.158	0.288	0.242	0.273	0.000	0.122	0.914
1440	0.382	0.186	0.431	0.346	0.297	0.010	0.258	0.950
2880	0.214	0.153	0.633	0.504	0.324	0.016	0.500	0.989

Figure 4. Summary of DLT Rates for PF-07062119



10.10.3. Prior Specifications for Monotherapy with Priming

A weakly informative prior similar to one described in previous section was used. The scaling dose for the regimen with priming is 800 µg

As previously, it was assumed that (m1, m2, s1, s2, ρ) = (logit(p*), 0, 2, 1, 0)

Here, p* is the anticipated DLT rate at the scaling dose d*. It was assumed based on analysis of monotherapy dose escalation without priming that DLT rate at full dose 800 µg after priming with 400 µg was 0.048 via matching DLT rates at 400 µg monotherapy without priming with priming/full dose of 400 µg/ 800 µg.

The prior distributions of the model parameters are provided in Table 18. Table 19 illustrates the resulting prior distribution of DLT rate derived from the prior given in Table 18 and rounded to 3 decimal points. Based on the available information the starting dose of PF-07062119 of 400 µg/ 800 µg satisfies the EWOC criteria.

Table 18. Prior Distribution for the Model Parameters (With Priming)

PF-07062119 single agent parameters: BVN weakly informative prior			
Parameters	Means	Standard deviations	Correlation
(log(α), log(β))	-2.987, 0	2, 1	0

Table 19. Summary of Prior Distribution of Dose Limiting Toxicity Rates for PF-07062119 (With Priming Dose of 400 µg)

($d^* = 800\ \mu g$)								
PF-07062119 Dose (µg)	Prior Probabilities that DLT Rate is in the Interval			Mean	SD	Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33,1]			2.5%	50%	97.5%
800	0.747	0.125	0.128	0.131	0.188	0.001	0.047	0.716
1000	0.684	0.140	0.176	0.165	0.218	0.001	0.067	0.806
1200	0.631	0.149	0.220	0.198	0.246	0.002	0.085	0.890
1400	0.590	0.151	0.259	0.227	0.269	0.002	0.104	0.937
1600	0.558	0.152	0.290	0.252	0.287	0.002	0.120	0.964
1800	0.532	0.152	0.317	0.273	0.301	0.002	0.137	0.981
2000	0.509	0.150	0.341	0.292	0.312	0.002	0.153	0.989

10.11. Appendix 11: Suggested Cytokine Release Syndrome Management Algorithm and Revised CRS Grading System

Adapted from Lee DW, et al: ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells 2019.25: 625-638.

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

*Note – Hypoxia requiring low-flow simple facemask defined as oxygen delivered at ≤6 L/minute is Grade 2 CRS, whereas hypoxia requiring high-flow simple facemask defined as oxygen delivered at >6 L/minute is Grade 3 CRS.

CRS management guidelines

ASTCT Grade 1 CRS:

- Monitor vital signs for worsening of condition.

Fever

- Acetaminophen/paracetamol and hypothermia blanket for the treatment of fever.
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen can be used as second treatment option for fever if not contraindicated.
- Assess for infection using blood and urine cultures, and chest radiography.
- Empiric broad-spectrum antibiotics and filgrastim if neutropenic.
- Maintenance IV fluids for hydration.
- Symptomatic management of constitutional symptoms or organ toxicity.
- Consider tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever.

ASTCT Grade 2 CRS:

- Monitor vital signs every 4 hours for worsening of condition.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV fluid bolus of 500-1000 mL of normal saline. Can give second IV fluid bolus if systolic blood pressure remains <90 mmHg.

- Consider tocilizumab 8 mg/kg (maximum dose 800 mg) IV or siltuximab 11 mg/kg IV for treatment of hypotension refractory to fluid boluses; tocilizumab can be repeated after 6 h if needed.
- If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to intensive care unit (ICU), obtain echocardiogram (ECHO), and initiate other methods of hemodynamic monitoring.
- In patients at high-risk (bulky disease, older age or comorbidities) or if hypotension persists after 1-2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 hrs.

Hypoxia

- Supplemental oxygen.
- Tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension.

ASTCT Grade 3 CRS:

- Monitor patient (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, as needed, as recommended for Grade 2 CRS.
- Tocilizumab and siltuximab as recommended for Grade 2 CRS if not administered previously.
- Vasopressors as needed.
- Dexamethasone 10 mg IV every 6 hrs; if refractory, increase to 20 mg IV every 6 hrs.

Hypoxia

- Supplemental oxygen including high-flow oxygen delivery.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above.

ASTCT Grade 4 CRS:

- Monitor patient (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as recommended for grade 3 CRS.
- Methylprednisolone 1 g/day IV.

Hypoxia

- Supplemental oxygen via positive pressure/mechanical ventilation.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above.

10.12. Appendix 12: ECOG Performance Status

10.13. Appendix 13: Supportive Care for Immune-Related Adverse Events (irAEs)

Table 20. Management of Immune Related Adverse Events (irAEs)

	Grade	Management	Follow up
Gastrointestinal irAEs	**Grade 1** Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	Anti-diarrheal medication (eg, loperamide 4 mg initial dose followed by 2 mg after every subsequent loose stool with no more than 16 mg daily)	Continue study intervention therapy. If persists >48 hours, add second anti-diarrheal medication (eg, Lomotil 2 tablets 4 times daily).
	Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold study intervention therapy. Anti-diarrheal medication (eg, loperamide 4 mg initial dose followed by 2 mg after every subsequent loose stool with no more than 16 mg daily).	If improves to Grade 1: Resume study intervention therapy. If persists >48 hours, add second anti-diarrheal medication (eg, Lomotil 2 tablets 4 times daily). If persists >96 hours or recurs: Methylprednisolone 0.5 to 1.0 mg/kg/day or equivalent. When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study intervention therapy per protocol. If worsens or persists >3 days with steroids: Treat as Grade 3 to 4.
	Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs	Withhold study intervention therapy. Anti-diarrheal medication (eg, loperamide 4 mg initial dose followed by 2 mg after every subsequent loose stool with no more than 16 mg daily). Methylprednisolone 1.0 to 2.0 mg/kg/day IV or equivalent. Consider addition of prophylactic antibiotics for opportunistic infections. Consider endoscopy.	Investigational product therapy – See Table 12 – Dose Modifications for Specific Immune Related Toxicity. Continue steroids until Grade 1, then taper over at least 1 month. If persists >48 hours, add second anti-diarrheal medication (eg, Lomotil 2 tablets 4 times daily). If persists >96 hours or recurs: Consider addition of infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis.
Dermatitis irAE	**Grade 1 to 2** Covering ≤30% body surface area	Symptomatic therapy (eg, antihistamines, topical steroids) Continue study intervention therapy	If persists >1 to 2 weeks or recurs: Consider skin biopsy Withhold study intervention therapy.

Table 20. Management of Immune Related Adverse Events (irAEs)

	Grade	Management	Follow up
			Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study intervention therapy If worsens: Treat as Grade 3 to 4.
	Grade 3 to 4 Covering >30% body surface area; life threatening consequences	Withhold or discontinue study intervention therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. Resume study intervention therapy.
Pneumonitis irAEs	**Grade 1** Radiographic changes only	Consider delay of study intervention therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens, treat as Grade 2 or Grade 3 to 4
	Grade 2 Mild to moderate new symptoms	Withhold study intervention therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near baseline, taper steroids over at least 1 month and then resume study intervention therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
	Grade 3 to 4 Severe new symptoms; New/worsening hypoxia; life-threatening	Discontinue study intervention therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to baseline: Taper steroids over at least 6 weeks. If not improving after 48 hours or worsening: Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil).

Table 20. Management of Immune Related Adverse Events (irAEs)

	Grade	Management	Follow up
Hepatitis irAEs	**Grade 1** Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue study intervention 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 study intervention therapy Increase frequency of monitoring to every 3 days	If elevations return within ≤7 days to Grade ≤1: Resume routine monitoring and treatment at same dose level. If elevations do not improve within ≤7 days to Grade ≤1: Methylprednisolone 0.5 to 1 mg/kg/day (or oral/IV equivalent) and, when elevations improve to Grade ≤1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and reduce dose of PF-07062119 by 1 level.
	Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Discontinue study intervention therapy. Increase frequency of monitoring to every 1 to 2 days. 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade 2: 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. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Endocrine irAEs	Asymptomatic thyroid-stimulating hormone (TSH) abnormality	Continue study intervention therapy	If TSH <0.5 x lower limit of normal (LLN), or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements: include free thyroxine (T4) at subsequent cycles as clinically indicated; consider endocrinology consult.
	Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary MRI scan.	If improves (with or without hormone replacement):

Table 20. Management of Immune Related Adverse Events (irAEs)

	Grade	Management	Follow up
		If symptomatic with abnormal lab/pituitary scan: Withhold study intervention therapy: 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent. Initiate appropriate hormone replacement therapy. If normal lab/pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks/MRI in 1 month.	Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections. Resume study intervention therapy. Participants with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
	Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Withhold or discontinue study intervention therapy. Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids. Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy.	

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, irAE=immune-related adverse event, IV=intravenous, LFT=liver function test, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs, T4=thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

*Note – See Table 12 – Dose Modifications for Specific Immune Related Toxicity Attributed to Investigational Product or Combination Investigational Therapy for additional details on dose considerations with study intervention therapy.

10.14. Appendix 14: RECIST (Response Evaluation Criteria in Solid Tumors) Version 1.1 Guidelines

Adapted from E.A.Eisenhauer, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

Categorizing Lesions at Baseline

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable Disease

- Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.
- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion patientive to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If noncystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Note: For the participant population being evaluated in this protocol, the baseline assessment may be completed within 6 weeks prior to randomization.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

one or more target measurable lesions have not been assessed;

or assessment methods used were inconsistent with those used at baseline;

or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target Disease

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

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 21. Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 22. Objective Response Status at Each Evaluation for Patients with Non Target Disease Only

Non-target Disease	New Lesions	Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

10.15. Appendix 15: Immune-Related Response Criteria Derived from RECIST 1.1 (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics.

This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD-1/anti-PD-L1 antibodies which exert the antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects.[18,19] Clinical observations of participants with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.[46,29]

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of participants who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria.[49,29]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST v1.1 (irRECIST).[30]

For irRECIST, only target and measurable lesions are taken into account. In contrast to RECIST v1.1, irRECIST:

- Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and
- Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm longest diameter per non-nodal lesion and 15 mm shortest diameter per nodal lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial.

irRECIST is defined as follows:

1. Overall immune-related complete response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.

2. Overall immune-related partial response (irPR): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.

3. Overall immune-related stable disease (irSD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions is neither irCR, irPR, (compared to baseline) or immune-related progressive disease (irPD, compared to nadir).

4. Overall immune-related progressive disease (irPD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (ie, added to the target lesion measurements). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

New non-measurable lesions: Do not define progression but preclude irCR.

Overall responses derived from changes in index, non-index, and new lesions are outlines in Table 23.

Table 23. Overall Response Derived from Changes in Index, Non index and New Lesions

Measurable Response	Non-measurable Response		Overall Response Using irRECIST[b]
Index and New Measurable Lesions (Tumor Burden)[a]	Non-Index Lesions	New Non-Measurable Lesions	
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

a. Decrease assessed relative to baseline.
b. Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

10.16. Appendix 16: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Ab	antibody
ACRIN	American College of Radiology Imaging Network
ADA	antidrug antibodies
AE	adverse event(s)
AIDS	acquired immunodeficiency syndrome
ALL	Acute Lymphocytic Leukemia
ALT	alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	absolute neutrophil count
anti-PD-1	anti-programmed cell death protein-1
anti-EGFR	Anti-epidermal growth factor receptor pathway
anti-VEGF	Anti–vascular endothelial growth factor therapy
API	active pharmaceutical ingredient
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
AUC_{inf}	AUC from time zero extrapolated to infinite time
AUC_{last}	AUC from time zero to the last quantifiable concentration
AUC_{tau}	AUC within the first dosing interval
AV	atrioventricular
BA	bioavailability
BBS	Biospecimen Banking System
BID	twice daily
BLRM	Bayesian logistic regression model
BP	blood pressure
BRAF	serine/threonine-protein kinase B-Raf.
BSA	body surface area
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CEA	carcinoembryonic antigen
Ceff	clinical efficacious concentration
CDS	core data sheet
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	Clearance
CL/F	apparent clearance

Abbreviation	Term
Clx	Cell line xenograft
C_{max}	maximum observed concentration
CMC	Chemistry, Manufacturing, and Controls
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRA	clinical research associate
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRP	c- reactive protein
CRS	cytokine release syndrome
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTLs	Cytotoxic T lymphocytes
CTMS	clinical trial management system
C_{trough}	predicted trough concentration
CV	Cardiovascular
C#D#	cycle #, Day#
DCR	disease control rate
DCT	data collection tool
Df	deferoxamine
DILI	drug-induced liver injury
DLI	Donor Lymphocyte Infusion
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DRE	disease-related event
DU	dispensable unit
EC	ethics committee
EC50	concentration corresponding to 50% of the maximum effect
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EFS	Event-Free Survival

Abbreviation	Term
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	End of Trial
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	escalation with overdose control
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FIP	first-in-patient
FISH	Fluorescent in situ hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GUCY2c	anti-Guanylyl Cyclase 2C (GUCY2c)/anti-CD3 bispecific Fc diabody
GVHD	graft versus host disease
HbA1c	hemoglobin A1c
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HER	human epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICU	Intensive care unit
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon-gamma
IgG	immunoglobulin G
IgG1	immunoglobulin 1
IgG4	immunoglobulin 4
IHC	immunohistochemistry
IL	interleukin

Abbreviation	Term
IMP	Investigational Medicinal Product
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
irAE	immune-related adverse events
IRB	Institutional Review Board
IRC	internal review committee
irPFS	immune-related PFS
IRR	infusion related reaction
irRECIST	Immune Related Response Criteria in Solid Tumor
IRT	interactive response technology
ISR	injection site reaction
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWR	interactive Web-based response
KRAS	Kirsten Rat Sarcoma viral oncogene
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MAC	major histocompatibility complex
MAD	maximum administered dose
MAP	meta-analytic-predictive
Mb	minibody
MHC	major histocompatibility complex
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
mITT	modified intent to treat
MRI	magnetic resonance imaging
MSI-H	microsatellite instable – high
MSS	microsatellite stable
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition scan
N/A	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
NK	natural killer

Abbreviation	Term
NMCTG	Nuclear Medicine Clinical Trial Group, LLC
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NSG	Female NOD-scid IL-2Rγγnull
OR	objective response
ORR	overall response rate
OS	overall survival
PACL	Protocol Administrative Change Letter
PBMC	peripheral blood mononuclear cell
PCD	primary completion date
PD	pharmacodynamics(s)
PDL-1	programmed cell death protein -1
PDL-2	programmed cell death protein -2
PDX	participant derived xenograft
PET	positron emission tomography
PFS	Progression-Free Survival
PGx	pharmacogenomic(s)
PI	principal investigator
PIB	powder in bottle
PK	pharmacokinetic(s)
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PS	performance status
PT	prothrombin time
PVC	premature ventricular contraction/complex
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	every day
QTc	corrected QT
QTcB	corrected QT (Bazett method)
QTcF	corrected QT (Fridericia method)
R_{ac}	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-Free Survival
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	single dose

Abbreviation	Term
SoA	schedule of activities
SOP	standard operating procedure(s)
SRSD	single reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	standard uptake values
$t_{1/2}$	terminal half-life
Tbili	total bilirubin
TBR	tumor background ratio
TCRs	t-cell receptors
TIL	Tumor infiltrating lymphocytes
TME	tumor microenvironment
TNF	tumor necrosis factor
T_{max}	time to maximum concentration
TMDD	Target medication drug disposition
TME	tumor microenvironment
TSH	thyroid stimulating hormone
TTP	time to progression
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
UVB	ultraviolet B
VEGF-A	vascular endothelial growth factor
Vss	steady state volume distribution
WBC	white blood cell
WBS	whole body scan
WNL	within normal limits
WOCBP	woman/women of childbearing potential

10.17. Appendix 17: Japan Specific Matters

Japan participation

a) Suggested Cytokine Release Syndrome Management

Tocilizumab is not approved in Japan for the treatment of CRS other than the events associated with chimeric antigen receptor (CAR) T cell therapy.

b) Condition to be discharged:

When a participant is discharged from the hospital during the DLT evaluation period, the following conditions (tests, medical examinations, etc.) should be performed on the day of the scheduled discharge by the investigators, and the propriety of discharge should be determined. The tests/medical examinations which are needed to confirm the participant's status will be conducted per clinical practice in the study site as appropriate.

- There are no current clinically significant adverse or side effects, including CRS, or medical reasons that require monitoring in a hospital setting.
- If a clinically significant adverse or side effect has occurred or continues to be present, the investigator will determine that the event is manageable by appropriate treatment or prophylaxis in an out of the hospital setting.
- Overall physical condition is stable and acceptable.
- In case of emergency, the participant may return to the clinical study site or other medical institution. If participants go to a medical institution other than the clinical study site, the clinical study site asks that the participants contact the study site, study investigator and the doctor at the medical institution who will communicate to discuss appropriate treatments. A study site keeps framework to ready for emergency situations that is available even during nights and holidays, and the sponsor will ensure that the selected study site will thoroughly follow all participants according to study procedures.

c) Section 8.7 - Genetics and Section 8.8– Biomarkers:

Given the genetic testing is for exploratory purposes only and following Pfizer process, there is no expectation to disclose these genetic testing results to the study participants, at any time.

A study participant's participation in a clinical study shall not be conditioned on his or her informed consent for the use of biospecimens that is not related to a clinical endpoint, the drug being investigated in the trial, or the inclusion/exclusion criteria for the study.

10.18. Appendix 18: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

These planned changes are being implemented immediately in response to the COVID-19 pandemic and are planned for the duration of the COVID-19 pandemic. This applies to participants who are quarantined or wish to not attend scheduled visits or perform study procedures or tests on site due to safety concerns and/or local government health or health institute suggestions and/or guidelines issued in an effort to limit exposure of vulnerable populations to the virus.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per exclusion criterion #6: "Active and clinically significant bacterial, fungal, or viral infection, including HBV, HCV, known HIV or AIDS related illness. In equivocal cases, with positive serology, those participants with a negative viral load are potentially eligible provided the other entry criteria are met.

Telehealth Visits

Study participants who can attend scheduled study visits on site and complete all study procedures as described in the protocol per the Schedule of the Activities should do so; all other participants should make every effort to participate in study visits by telephone via a telehealth visit. Video contact can be used if available and permitted by local regulations.

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of the Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.1.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 of this appendix regarding pregnancy tests.
- Review of physical symptoms in place of mandated physical exams

Study participants must be reminded to promptly notify site staff about any change in their health status.

Alternative Facilities for Safety Assessments

If the study participant is unable to visit the study site, protocol specified safety laboratory tests and/or tumor assessments may alternatively be performed at an alternative local laboratory or facility, where allowable by law or local guidance. In these cases:

- Local laboratory reference ranges need to be documented and submitted to study team.
- Records of local laboratory tests, lab accreditation, and reports of tumor assessments should be retrieved and documented in site medical records.
- Relevant data from local laboratories and testing facilities are to be entered in the CRF.
- Visits must be conducted by staff who are appropriately qualified and trained on the study protocol
- Any results that are considered clinically significant must be reported in a timely manner and as directed in the protocol.

Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. At the discretion of the treating physician home blood draws may be permitted. All safety laboratory tests outlined in this protocol can be done at a local laboratory.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory

requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

Any results that are considered clinically significant must be reported in a timely manner and as directed in the protocol.

Imaging and Efficacy Assessments

If the participant is unable to visit the study site for planned or unplanned imaging assessments the participant may visit an alternative facility to have these assessments performed. Qualified study site personnel must order, receive, and review results and any abnormalities, including progression of disease must be reported to the Pfizer clinical time in a timely manner and as directed in the protocol.

Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

The following is recommended for the administration of PF-07062119, PF-06801591, and Bevacizumab-Pfizer, participants who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection:

For symptomatic participants with active SARS-CoV2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.

Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

Continue to consider potential drug-drug interactions as described in this protocol for any concomitant medication administered for treatment of SARS-CoV2 infection.

Home Health Visits

A home health care service maybe utilized to facilitate scheduled visits per the Schedule of Activities at the discretion of the treating physician and in consultation with the SPONSOR.

Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.2.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Adverse Events and Serious Adverse Events

Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.10.8 Patient Data Monitoring and Protocol Deviations

Every effort should be made to ensure that required protocol tests and procedures are completed as described with the protocol. However, the circumstances around the ongoing COVID-19 pandemic may make it unfeasible to perform some of the tests and procedures. In these cases, the investigator must take all of the necessary steps to ensure the safety and wellbeing of the study participant. When a required protocol test or procedure cannot be performed, the investigator will promptly document the reason for the missed test or procedure and any corrective and preventive actions they have taken to ensure that required processes will be adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If the study participant is unable to visit the study site, required protocol procedures that can be performed to the best of study site's ability via telephone contact or video (where allowed) should be considered, if in the opinion of the investigator it is the safest approach, eg, evaluation of physical symptoms in place of protocol mandated physical examinations, review of adverse events or serious adverse events, dosing compliance, contraception check, and concomitant medication checks, etc. Study participants should make every attempt to continue to maintain a dosing diary (where appropriate) and may send this to the site electronically or via mail.

Patient data monitoring will continue without interruption. Remote data monitoring will be permitted, wherever possible. The CRA will continue monitoring data in an ongoing manner via remote access following all institutional processes, if applicable.

Any other deviations to the protocol, except for these approved modifications, must be documented as protocol deviations, and if related to the pandemic, the reason should clearly state "COVID-19". These are not immediately required to be reported to health authorities or IRB/ECs unless requested locally.

The impact of COVID-19 on protocol visits and study tests or procedures and associated timeframes should be reported, preferably, on a case report form (CRF) if at all possible. For participant discontinuation reporting in the CRF: Please select the most appropriate status for discontinuation. If the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

10.19. PET Imaging Substudy with ^{89}Zr-Df-IAB22M2C

10.19.1. Overall design and Scientific Rational for Substudy

This substudy will evaluate CD8 PET tracer uptake, at baseline and on-treatment, in tumor lesions and reference tissues (including T-cell rich tissues and those expected to express GUCY2c) with the aim to measure potential change in CD8 PET tracer uptake in tumor lesions between baseline and on-treatment and in reference tissues.

The PET imaging substudy will be opened initially at a subset of US sites participating in Study C3861001, which have been qualified for use with ^{89}Zr-Df-IAB22M2C.

Sites qualified for use must have licenses which include handling of Zirconium-89 and appropriate procedures in place for handling of samples that are considered radioactive. This includes processing and analysis of blood samples that are collected within 30 days of CD8 PET tracer infusion.

Study population: Approximately 10 to 15 participants enrolled across the study (preferably those enrolled in the mandatory biopsy cohorts in Part 1 and Part 2) will also be eligible for enrollment in the PET imaging substudy with the CD8 T cell specific ^{89}Zr-Df-IAB22M2C PET tracer (CD8 PET tracer).

As part of its mechanism of action, PF-07062119 is expected to increase T-cell infiltration selectively into tumors expressing GUCY2c. CD8 PET tracer studies are intended to enable measurement of CD8+ T cells throughout the body, permitting the comparison of CD8+ T-cell levels in tumors (before and after administration of PF-07062119) with CD8 T cell distribution in reference tissues. Additionally, CD8 PET tracer methodology images multiple tumor lesions simultaneously in comparison to paired biopsy procedures which are usually limited to a single accessible lesion. CD8 PET tracer studies may therefore contribute toward a broader understanding of the PD effects of PF-07062119 alone and potentially in combination with other agents. This information is intended to characterize the mechanism of action PF-07062119, identify participants who are most likely to benefit from treatment, and identify potential resistance mechanisms to PF-07062119 alone and in combination with other agents.

The CD8 PET tracer is a ~80 kDa minibody (Mb) with high affinity (binding EC_{50} = 0.4 nM) for the CD8 glycoprotein that is conjugated with Df and radiolabeled with ^{89}Zr for imaging CD8+ T cells in humans. It binds to both CD8αα and CD8αβ and will therefore bind to mature T cells, developing thymocytes, TCR αβ-expressing gut intraepithelial T cells, some γδ T cells and some NK and dendritic cells. The Mb design of the CD8 PET tracer is intended to address the limitations of molecular imaging using intact monoclonal antibodies (prolonged blood circulation, significant background signal) and to prevent activation of immune cell Fc effector functions. The smaller size and inability of the Mb to interact with the FcγR and the neonatal Fc recycling receptor results in a relatively inert imaging agent with rapid clearance. IAB22M2C was engineered from the humanized heavy and light chain sequences of the murine OKT8 antibody that targets human CD8.

The CD8 PET tracer has completed a Phase 1 study (NCT03107663) and is currently being evaluated in a Phase 2, open-label study (NCT03802123) in participants with select advanced or metastatic solid tumors selected to receive standard of care immunotherapy only. This study is evaluating the safety of repeat doses of the CD8 PET tracer and aiming to assess and quantify any detectable changes in uptake between baseline and on-treatment. Interim results from this study have established the ability of the CD8 PET tracer to detect CD8+ T cells in tumors and confirmed the safety profile of the CD8 PET tracer after repeat doses. Additional information related to safety and imaging results is presented in the ^{89}Zr-Df-IAB22M2C investigator brochure. These data have established the potential utility of using the CD8 PET tracer for participants in Study C3861001.

10.19.2. Benefit/Risk Assessment

PET Scans with 89Zr-Df-IAB22M2C

Based on the available data, the principal risk is exposure to ionizing radiation released by ^{89}Zr. Additionally, there is low likelihood that the CD8 PET tracer may be associated with an adverse reaction or immunogenic response. The nonclinical data have demonstrated that IAB22M2C and Df-IAB22M2C had no measurable effects on T cell proliferation/activation or cytokine release. As of 04 August 2021, 88 patients have received the CD8 PET tracer. Monitoring of participants is recommended. The potential risks after infusion with the CD8 PET tracer include infusion site reactions of redness, itching and pain, allergic reaction (including anaphylaxis), kidney/liver/respiratory failure, thrombocytopenia, arthritis, and/or hypotension. Insertion of IV catheters for infusions and blood draws may cause minor pain, bruising, and/or infection at the infusion site.

10.19.3. PET Imaging Substudy Objectives

In addition to the core study objectives (Section 3), the PET imaging substudy (Section 10.19) will include the following exploratory objectives:

Objectives: Tertiary/Exploratory	Endpoints: Tertiary/Exploratory
•Measure potential change in CD8 PET tracer uptake and biodistribution in tumor lesions and reference tissues, including CD8+ T cell rich reference tissues between baseline and on-treatment with PF-07062119. •Measure potential changes in CD8 PET tracer uptake on baseline and on-treatment PET scans compared to change in CD8+ T cells in tumor lesions by IHC if the same lesion was biopsied at baseline and on-treatment visits. •Explore the qualitative and quantitative CD8 PET tracer measurements with clinical outcomes of PF-07062119 treatment. •Evaluate the association of CD8 PET tracer uptake with immune infiltrates and other molecular biomarkers (such as CD4, CD8, PD-1 and PD-L1).	Biopsy lesion: SUV measurement at baseline vs SUV measurement following treatment . Target lesion: SUV measurement at baseline vs SUV measurement following treatment. Nontarget lesions (if applicable): SUV measurement at baseline vs SUV measurement following treatment. Reference tissues (including but not limited to normal colon and other GUCY2c expressing tissues where applicable): SUV measurement at baseline vs SUV measurement following treatment Change in SUV measurement at baseline vs clinical biomarker or radiographic responses

SUV= standard uptake values

10.19.4. PET Imaging Substudy Design

Participants in this substudy will have 2 planned imaging sessions:

1. The first imaging session will take place prior to therapy ($PET_{Baseline}$). CD8 PET tracer will be administered with whole body PET/CT imaging acquired 24 hr (±3 hr) later and 7 to 9 days prior to the initiation of treatment with PF-07062119.

2. The second imaging session will take place after receiving the first 3 doses of PF-07062119, on C2D8, which will be approximately 5 to 6 weeks after initiation of treatment. CD8 PET tracer imaging agent will be administered on C2D8 and whole body PET/CT imaging acquired 24 hr (±3 hr) later.

3. An additional third optional imaging session is included in Cycle 3 or later. The optional third imaging session may only be performed after discussion and agreement between the investigator and sponsor.

Participants in the PET imaging substudy should be enrolled, if possible, in cohorts requiring mandatory pretreatment and on-treatment biopsies and will have 2 planned biopsy procedures to coincide with PET imaging sessions.

1. Baseline de novo biopsy collections will occur after the first infusion of the CD8 PET tracer and its associated PET scan.

2. On treatment biopsy collection will occur within 1 week after the second infusion of the CD8 PET tracer and its associated PET scan.

Inclusion Criteria

1. Participants must meet all eligibility criteria for enrollment in Study C3861001 prior to being enrolled in the PET imaging substudy and initiation of procedures.

2. Participants should have a tumor amenable to biopsy and consent to these planned biopsy procedures. Participants without a tumor amenable to biopsy must be approved by the sponsor.

Exclusion Criteria

1. Participants are excluded from the PET imaging substudy if any of the exclusion criteria are met for Study C3861001.

2. Participants for whom the only tumor amenable to biopsy is also a target lesion.

3. Participants who have previously received CD8 PET tracers or other ^{89}Zr labeled PET tracers in the prior 45 days.

10.19.5. CD8 PET Tracer Imaging Procedures:

Table 24. Overview of PET Imaging Substudy Visits

PET Imaging Procedures	Baseline Scan / Biopsy			Study Start	On-Treatment Scans / Biopsy		
	Visit 1	Visit 2	Visit 3	C1D1	Visit 4	Visit 5	Visit 6
	Day -7 to -9 from C1D1	24 hr (±3 hr) post infusion	Post CD8 Tracer CT/PET scan prior to C1D1		C2D8 (± 2 days)	24 hr (±3 hr) post infusion	C2D15 (±7 days) post CD8 Tracer CT/PET Scan
Vital Signs[1] (before and after infusion)	X				X		
CD8 PET Tracer infusion	X				X		
CD8 PET Tracer PET/CT scan[2]		X				X	
Tumor Biopsy[3]			X				X

1. Vital signs assessed 15 (±5) minutes prior to infusion and within 60 minutes after infusion of the CD8 PET tracer.
2. Tumor assessment scans scheduled per protocol for evaluation of response per RECIST criteria are to be collected separately from CD8 PET tracer substudy scans.
3. Tumor biopsies can be collected on the same day as imaging as long as they occur after the PET/CT scan

CD8 PET tracer infusion:

Dosing information:

The CD8 PET tracer is an ~80 kDa Mb with high affinity to CD8 glycoprotein (binding EC_{50} = 0.4 nM) that is conjugated with Df and radiolabeled with ^{89}Zr for imaging CD8+ T-cells in humans.

A dose of 1.0 (±20%) mCi of CD8 PET tracer as 1.5 mg of API will be administered IV over 5 to 10 minutes, within 1 week prior to the initiation of therapy with PF-07062119, and approximately 5 weeks after start of treatment with PF-07062119.

Dispensation of CD8 PET tracer

The CD8 PET tracer will be delivered from a central manufacturing facility to the investigational site's radiopharmacy or Nuclear Medicine Department. Upon receipt, qualified personnel will ensure that the study drug has been delivered in good condition, inventoried, stored properly, labeled and dispensed in compliance with the pharmacy manual, all regulatory agencies and per the investigator's prescription order.

The ^{89}Zr dose will be measured by the qualified personnel in a dose calibrator prior to dispensing. Then the syringe will be placed in a shielded carrier along with a designated IV

infusion pump for radioactive infusion and administration. After dose administration, the qualified personnel will return the syringe for residual measurement by the qualified personnel (such as the nuclear medicine technologist) at the site. Measured radioactivity values and times of measurement will be documented, as well as the total injected volume.

Regulatory agencies require accounting for the disposition of all investigational drugs received by each clinical site. Information on drug disposition required by law consists of the date received, date dispensed, quantity dispensed, and the participant identification number to whom the drug was dispensed. The Investigator is responsible for accounting for all unused study drug and destroying all used study drug containers in compliance with the Radiopharmacy Manual.

Infusion of CD8 PET tracer

The dispensed dose will be infused under the supervision of a qualified nuclear medicine personnel as an IV infusion with an infusion pump over no less than 5 minutes followed by a saline flush. The total infusion time should be between 5 and 10 minutes. Vital signs will be assessed 15 (±5) minutes prior to infusion and within 60 minutes after infusion of the CD8 PET tracer.

Premedication (for example, with acetaminophen and diphenhydramine) is not required but may be administered at the discretion of the investigator approximately 1 hour prior to infusion of the CD8 PET tracer.

^{89}Zr-Df-IAB22M2C PET/CT scan:

PET/CT scanner validation:

In an effort to generate the most accurate and consistent imaging data across all participating investigative sites, to support the data collection and analysis for this clinical study, the Sponsor is contracting with the Nuclear Medicine Clinical Trial Group, LLC (NMCTG) to conduct the validation of PET/CT scanners at each participating site that will be used in this study.

The NMCTG will provide a phantom along with detailed instructions of the PET/CT validation procedures on how to fill and scan the phantom and coordinate delivery of a dose of ^{89}Zr to the site. Each PET/CT scanner intended for use in this clinical study will be validated by the NMCTG. Once the validation is completed, the site will submit the data to the NMCTG for analysis. The site will store the phantom in a secure, dry area for 33 days (until the radioactivity has decayed to an undetectable level) before transporting back to the NMCTG.

Upon completion of the PET/CT scanner validation, the NMCTG will provide a validation certificate and the setting parameters specific to the validated scanner that should be saved into the site's scanner protocol for this clinical trial before imaging the first enrolled participant. It is required that sites only use NMCTG-validated PET/CT scanner(s), with the

setting parameters generated from the phantom-validation procedure, to image participants enrolled in this trial as per protocol.

Prior PET/CT scanner validation by NMCTG for use with the CD8 PET tracer is acceptable for use of a PET/CT scanner in this trial as long as PET/CT scans take place prior to expiration of scanner certification.

PET/CT Scans:

^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) PET/CT scan images must only be acquired on PET/CT scanners that have been approved by the sponsor. The Sponsor must be contacted for permission to use alternate scanners in case of equipment failure and/or major equipment upgrades or replacement. Acquisition and reconstruction parameters should be obtained according to the recommendation provided to each site based upon phantom validation of the scanner and should be obtained in List Mode, whenever possible, to allow for virtual radioactive dose reconstruction at a later date.

Scans are preferably whole body scans from the base of the skull through upper-thighs (encompassing the pelvis). Additional areas of known or suspected disease should be obtained (if they are outside of this area) at every scan visit using acquisition settings optimized for ^{89}Zr imaging. Please refer to the imaging manual regarding participant preparation, scanning times per bed position, ^{89}Zr-optimization, acquisition and reconstruction parameters, slice thickness, and other parameters as well as the instructions for how to submit images for central review.

PET/CT scans as part of the CD8 PET tracer study may be collected for central review. Additionally, baseline and tumor assessment scans scheduled per protocol for evaluation per RECIST criteria should be collected separately from CD8 PET tracer substudy scans and should be performed in accordance with institutional practices.

Tumor Biopsies:

Pretreatment and on-treatment de novo tumor biopsies should be collected as described in Biomarker Section 8.8.2 and the Laboratory Manual with the following additional requirements:

- Pretreatment de novo tumor biopsies must be collected at least 24 hr after CD8 PET tracer infusion and after the associated baseline PET/CT scan. Biopsies should not be collected before CD8 PET tracer infusion. Pretreatment tumor biopsies must also be collected prior to treatment with PF-07062119.

- On-treatment biopsies are scheduled for collection on C2D15 (±7 days). Ontreatment biopsies must be collected after C2D8 and at least after 24 hr post infusion, and within 2 weeks after infusion of CD8 PET tracer for the on-treatment PET/CT scan. All effort should be made to collect on-treatment biopsies from the same lesion that was biopsied before therapy. If biopsy of the same lesion is not possible, the biopsy should be preferably collected from a lesion at the same metastatic organ.

- After biopsy tissues (from both pretreatment and on-treatment samples) have been collected and undergone processing procedures as outlined in the Laboratory Manual, the biopsy must be stored on site at room temperature for 30 days (post infusion of CD8 PET tracer) before being shipped (to allow for decay of radioactivity).

Additional details can be found below in Table 25, and in the Laboratory Manual.

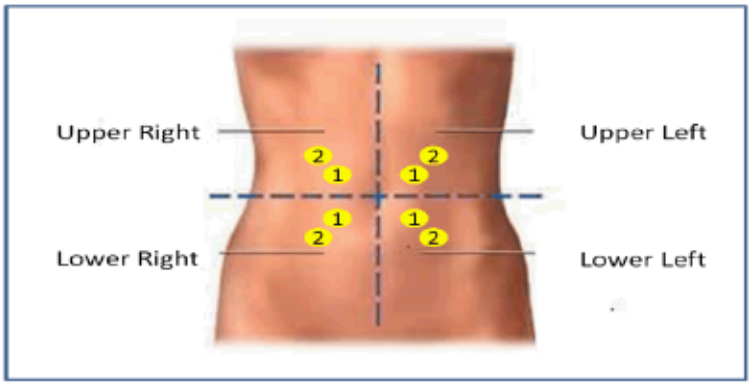
Table 25. Schedule of Assessments for ^{89}Zr-Df-IAB22M2C Immuno-PET CD8 Mini-body Imaging Substudy

Visit Identifier	Screening	Pre-Treatment PET Sub Study Assessments			Cycle 1		Cycle 2				Cycle ≥3			
		Tracer Infusion	PET Imaging	Pre-treatment Biopsy				Tracer Infusion	PET Imaging	On Treatment Biopsy	Tracer Infusion	PET Imaging	EOT/ Withdrawal	Post treatment follow up
Study Day	-28 to -9 days	-7-9	-6	-6 to -1	1	15	1	8	9	15	8	9		
Hours Pre-/Post-Dose[1]					0	0	0			0				
Visit window[2]		Tracer infusion starting -9 to -7 days pre treatment						±24 hrs						±7 days
Enrollment eligibility confirmation prior to entering PET Sub-Study	X													
PK and PD samples					*Patients should follow all scheduled assessment, including safety labs, based on the trial cohort that they are participating in*									
Mandatory Pre-treatment and on treatment Tumor Biopsy[3,]				X						X (±7 days)				
Optional Second On-Treatment Tumor Biopsy[3,4,]													X	
Vital Signs before and after infusion		X						X			X			
^{89}Zr-Df-IAB22M2C infusion[5]		X						X						
^{89}Zr-Df-IAB22M2C[6] PET/CT scan			X						X					
Optional Repeat PET Imaging Assessments[7]											X	X		

1 Sampling times indicated are related to the end of the SC injection. All efforts should be made to obtain scheduled PET assessments including biopsies prior to treatment if collection occurs on a day of a scheduled dose of PF-07062119.
2 Visit window is based on the initiation of PET tracer infusion.
3 Biopsies can be collected on the same day as PET imaging but must be collected after PET imaging has occurred.
4 Optional second on treatment biopsy may be collected either after optional repeat PET imaging or at EOT.
5 Pretreatment infusion must occur within 7-9 days before treatment (C1D1), and within 24 hrs of C2D8.
6 PET scan must take place 24 hours ±3 hrs after infusion of ^{89}Zr-Df-IAB22M2C, tumor assessment scans scheduled per protocol for evaluation of RECIST criteria should be collected separately from CD8 PET tracer substudy.
7 Optional repeat PET imaging may only be performed after discussion and agreement between the investigator and sponsor.

10.20. Subcutaneous Injection Site Locations

Injection site locations include a maximum of 8 unique administration sites distributed across 4 abdominal quadrants with a possibility of up to 2 injection locations per quadrant. For a given quadrant, Location 1 is proximal to the umbilicus and Location 2 is distal to the umbilicus.



Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs after discussion and agreement between investigator and the Sponsor. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

The following principles should guide selection of sites for SC injection:

Principle [1]: For participants receiving combination therapy involving >1 drug administered subcutaneously (for example, both PF-07062119 and PF-06801591), each drug should be administered in separate abdominal quadrant(s).

Principle [2]: If the total number of SC injections permits, then injection sites (even for the same drug) should be distributed among quadrants to the extent possible before utilizing 2 sites within the same quadrant, subject to constraint of principle [1].

Principle [3]: In the event of special circumstances (for example, an insufficient number of suitable injection sites on the abdomen), then the investigator should consult with the Sponsor for further guidance.

Track the participant's injection sites (s) sequentially on this diagram with a red pen and mark the injection sites on the participant's abdomen according to your clinic's standard practice.

Record the location and time of each injection and any ISR in the participant's source records and study CRF. See eCRF guidelines for more information.

10.21. Protocol Amendment Summary of Changes Table Through Amendment 6

Document History:
Protocol Amendment 6 (08-Oct-2021)

Rationale for Protocol Amendment 6: This amendment described a new CD8 PET tracer substudy intended to provide exploratory data to enable noninvasive visualization of the relevant CD8+ T-cell population of the immune system. In addition, this amendment provides modified guidance on (1) injection site locations and monitoring for ISRs; and (2) management of diarrhea.

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Table 2 in Section 1	Changed urinalysis collection day from C1D19 to C1D15	Change described in 06 April 2021 PACL
Schedule of Activities Table 2 in Section 1	Removed text from footnote number 2 pertaining to additional signing of consent document in Japan after at least Cycle 1 of Part 1A before continuing with Cycle 2.	Change described in 06 April 2021 PACL
Schedule of Activities Table 4 in Section 1	Blood samples for PK/ADA/NAb for PF-06801591 and bevacizumab-Pfizer will not be required on C1D1. On C2D1 (and all subsequent cycles with scheduled collections) "Blood samples for PK/ADA/NAb against PF-06801591" will not be required. Instead, "Blood samples for PK/ADA/NAb against PF-06801591" will be collected on Day 15 of all cycles	Change described in 06 April 2021 PACL
Schedule of Activities Table 4 in Section 1	Footnote #3 is clarified as follows: All pre-dose blood samples for PF-06801591 will be collected on Day 15 visit of	Change described in 06 April 2021 PACL

Document History:
Protocol Amendment 6 (08-Oct-2021)

Rationale for Protocol Amendment 6: This amendment described a new CD8 PET tracer substudy intended to provide exploratory data to enable noninvasive visualization of the relevant CD8+ T-cell population of the immune system. In addition, this amendment provides modified guidance on (1) injection site locations and monitoring for ISRs; and (2) management of diarrhea.

Section # and Name	Description of Change	Brief Rationale
	each scheduled collection Cycle. Pre-dose blood samples for bevacizumab-Pfizer will be collected on Day 15 visit in Cycle 1 and subsequently on Day 1 visit of each scheduled collection Cycle. The changes to Table 4 were made to better align with the dose priming strategy, where PF-06801591 or bevacizumab-Pfizer will be administered for the first time on C1D15, therefore collections from C1D1 were removed and/or moved to accommodate these changes	
Schedule of Activities Table 4 in Section 1	Footnote #3 was revised to clarify the collection schedules for PK/ADA/NAb for PF-07062119/bevacizumab-Pfizer and PF-06801591 in Cycles 5 and beyond.	Clarified blood collection schedule for PK/ADA/NAb for PF-07062119/bevacizumab-Pfizer and PF-06801591 in Cycles 5 and beyond.
Schedule of Activities Table 6 in Section 1	Blood samples for PK/ADA/NAb for PF-06801591 and bevacizumab-Pfizer will not be required on C1D1. On C2D1 (and all subsequent cycles with scheduled collections) "Blood samples for PK/ADA/NAb against PF-06801591" will not be	Change described in 06 April 2021 PACL

Document History:
Protocol Amendment 6 (08-Oct-2021)

Rationale for Protocol Amendment 6: This amendment described a new CD8 PET tracer substudy intended to provide exploratory data to enable noninvasive visualization of the relevant CD8+ T-cell population of the immune system. In addition, this amendment provides modified guidance on (1) injection site locations and monitoring for ISRs; and (2) management of diarrhea.

Section # and Name	Description of Change	Brief Rationale
	required. Instead, "Blood samples for PK/ADA/NAb against PF-06801591" will be collected on Day 15 of all cycles	
Schedule of Activities Table 6 in Section 1	Footnote #3 is clarified as follows: All pre-dose blood samples for PF-06801591 will be collected on Day 15 visit of each scheduled collection Cycle. Pre-dose blood samples for bevacizumab-Pfizer will be collected on Day 15 visit in Cycle 1 and subsequently on Day 1 visit of each scheduled collection Cycle. The changes to Table 6 were made to better align with the dose priming strategy, where PF-06801591 or bevacizumab-Pfizer will be administered for the first time on C1D15, therefore collections from C1D1 were removed and/or moved to accommodate these changes	Change described in 06 April 2021 PACL
Schedule of Activities Table 6 in Section 1	Footnote #3 was revised to clarify the collection schedules for PK/ADA/NAb for PF-07062119/bevacizumab-Pfizer and PF-06801591 in Cycles 5 and beyond.	Clarified blood collection schedule for PK/ADA/NAb for PF-07062119/bevacizumab-Pfizer and PF-06801591 in Cycles 5 and beyond.

Document History:
Protocol Amendment 6 (08-Oct-2021)

Rationale for Protocol Amendment 6: This amendment described a new CD8 PET tracer substudy intended to provide exploratory data to enable noninvasive visualization of the relevant CD8+ T-cell population of the immune system. In addition, this amendment provides modified guidance on (1) injection site locations and monitoring for ISRs; and (2) management of diarrhea.

Section # and Name	Description of Change	Brief Rationale
Section 2.5 Benefit/Risk Assessment	Paragraph 2 was revised to clarify that CRS and diarrhea has already been observed in the study. Furthermore, the qualifying text, "potentially at higher doses" has been removed.	To update the protocol that CRS and diarrhea are no longer expected AEs of PF-07062119. Rather they have been observed in the study. Furthermore, that as of the date of this protocol amendment, there is no clear dose-AE relationship.
Section 2.5 Benefit/Risk Assessment	In paragraph 4, new text was incorporated that refers the reader to the ImaginAB IB for detailed information on the expected benefits and risks and expected AEs of the PET tracer.	To direct reader to complete information on the benefits, risks and expected AEs of the PET tracer for the newly incorporated substudy.
Section 3, Objectives and Endpoints	Added new tertiary / exploratory endpoint of measuring changes in CD8 PET tracer uptake for both Part 1 (dose escalation) and Part 2 (dose expansion)	Documents the addition of new endpoints pertaining to CD8 PET tracer substudy.
Section 4.1, Overall Design	Added paragraph summarizing the CD8 PET tracer substudy, along with an intra-doc link to the complete description of the substudy in Section 10.19	Captures the new CD8 PET tracer substudy in the high-level study description.

Document History:
Protocol Amendment 6 (08-Oct-2021)

Rationale for Protocol Amendment 6: This amendment described a new CD8 PET tracer substudy intended to provide exploratory data to enable noninvasive visualization of the relevant CD8+ T-cell population of the immune system. In addition, this amendment provides modified guidance on (1) injection site locations and monitoring for ISRs; and (2) management of diarrhea.

Section # and Name	Description of Change	Brief Rationale
Section 4.2 Scientific Rationale for Study Design	Added italicized text to second paragraph. "The biomarker assessments, *including the PET imaging substudy,* may contribute to confirming target engagement…."	To provide a full description of the biomarker goals in the overview section.
Section 6.1.1.2 PF-06801591	Text was revised pertaining to situations where abdominal injection site locations are not possible.	Text was revised to align with the new Section 10.20 Appendix 20 Subcutaneous Injection Site Locations. This and the added Appendix 20, facilitate location of injection sites locations when investigational combination therapies are administered. This will facilitate monitoring for ISRs to either investigational therapy.
Section 6.6.4, Anti Diarrheal, Anti Emetic Therapy and Section 6.7.3 Dose Reductions – Table 12	Added text with additional guidance for managing diarrhea AEs (Section 6.6.4), revised Table 12 (Section 6.7.3)	Emphasizes importance of monitoring for diarrhea and prescribing immediate intervention towards early resolution.
Section 10.13 Appendix 13 Supportive Care for Immune-Related Adverse Events (irAEs)	To Table 20, added text with additional guidance for managing diarrhea AEs	Provides detailed instructions for treatment of diarrhea including dosing adjustments, and use of anti-diarrheal medications (loperamide, Lomotil, and methylprednisolone).

Document History:
Protocol Amendment 6 (08-Oct-2021)

Rationale for Protocol Amendment 6: This amendment described a new CD8 PET tracer substudy intended to provide exploratory data to enable noninvasive visualization of the relevant CD8+ T-cell population of the immune system. In addition, this amendment provides modified guidance on (1) injection site locations and monitoring for ISRs; and (2) management of diarrhea.

Section # and Name	Description of Change	Brief Rationale
Section 10.19 PET Imaging Substudy with ^{89}Zr-Df-IAB22M2C	Added complete description of the new CD8 PET tracer substudy including an SoA dedicated to the substudy procedures	Provide comprehensive information to the sites for conducting the CD8 PET tracer substudy
Section 10.20 Subcutaneous Injection Site Locations	Added clarifying instructions on abdominal subcutaneous injections in the combination studies (Parts 1B and 2)	The more detailed instructions will facilitate monitoring for and documenting ISRs following combination regimens with PF-070762119 that are injected Subcutaneous
Multiple Sections	Minor editorial changes and corrections	Minor revisions and corrections for improving understanding

Document History
Protocol Amendments -01 through -05

Document	Version Date	Summary of Changes and Rationale
Amendment 5	16 March 2021	The primary purpose of the amendment is to revise the study design to incorporate cohorts that receive a priming dose 2 weeks before receiving a full dose of PF-07062119. The priming dose is added to mitigate the occurrence of cytokine-mediated AEs following subsequent administrations of higher doses. **SOA for Part 1A, 1B, and Part 2 Without a Priming Dose (Table 1)**

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		A row for premedication was added with a corresponding footnote (also added to Section 6.1.1.1). Premedication has been implemented into this study to further improve tolerability and participant experience. For participants receiving PF-06801591, a pregnancy test is required 30 days after EOT and the follow-up visit will occur 30, 90, and 180 days after EOT. **PK, PD, and Immunogenicity Assessments for Part 2 Without a Priming Dose (Table 5)** The 4-hour time point on Day 1 was removed. **SOAs for Part 1A, Part 1B, and Part 2 With a Priming Dose (Table 2); PK, PD, and Immunogenicity Assessments for Part 1 and Part 1B With a Priming Dose SOA (Table 4); and PK, PD, and Immunogenicity Assessments for Part 2 With a Priming Dose (Table 6)** These tables were added for the cohort with a priming dose; schedules are similar to Table 1 except modified to accommodate the priming dose. **Section 2.2.8 Summary of Current Clinical Data from Study 3861001** Summary of data as of 28 December 2020 was added. **Section 2.3.1 PF-06801591, an Anti-PD-1 Antibody: Clinical Experience in Study B8011001**

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		(NCT02573259)/Appendix 9 Preliminary Clinical Summary for Study B8011001 Phase 1 FIH (PF 06801591) Data as of 10 February 2021 was included. **Section 2.5 Benefit/Risk Assessment** Expanded to include the benefit/risk assessment for cohorts with a priming dose. **Section 3 Objectives and Endpoints** Primary objective was modified to include the cohort with a priming dose. **Section 4 Study Design** Updated and reorganized to include details of the cohorts with the priming dose, including DLT observation period for Part 1 cohorts with a priming dose (42 days), justification for the starting dose (monotherapy, combination dose-finding, and dose expansion [Part 2]), criteria for dose escalation, and the total number of study participants. **Figure 3 C3861001 Study Schema** Updated to include the cohorts with a priming dose. **Section 5 Study Population** Inclusion criterion 5: tumor tissue is now required for Part 2 dose expansion.

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		Exclusion criterion 12: participation in medical imaging studies within 2 weeks of study entry is allowed. **Section 6.1.1.1 PF-07062119** Premedication to improve participant tolerability has been added. **Section 6.6 Concomitant Therapy** Guidelines around COVID-19 vaccines have been added. **Section 6.6.4 Anti-Diarrheal, Anti-Emetic Therapy** Additional details were provided regarding management of diarrhea. **Section 7.1.1 ECG Changes** This section was removed since it was unnecessary. Relevant ECG requirements are in the I/E criteria and DLT definitions. **Section 8.1.4 ECG** Text clarified to indicate that QTcF will be the correction factor for determining QTc. **Section 8.1.7 Injection Site Tolerability Assessment** To be performed after PF-06801591 injections as well. **Section 8.3 Treatment of Overdose**

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		Updated to include definition of overdose for PF-06801591 and bevacizumab-Pfizer. **Section 9 Statistical Considerations/Appendix 10** Updated to include statistical considerations for the cohorts with a priming dose. **Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information** Increased length of time that a highly effective contraceptive method must be used after the last dose of PF-06801591 and bevacizumab-Pfizer. **Appendix 9 Preliminary Clinical Summary for Study B8011001 Phase 1 FIH (PF-06801591)** Appendix 9 has been updated to include more recent safety information and to align with all other PF-068701591 protocols refers directly to the most recent PF-06801591 IB for other important information. Other minor clarifications, administrative, and typographical changes were made. The term 'patient' was replaced with 'participant throughout the protocol.
Amendment 4	05 October 2020	The primary purpose of the amendment is to incorporate feedback received from the United States (US) Food and Drug Administration (FDA). **<u>SOA for Part 1A, 1B, and Part 2</u>**

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		The following revisions were made: Mandatory proteinuria assessment (dipstick is acceptable) assessment is required prior to every bevacizumab-Pfizer dose throughout the course of the study. If urinalysis demonstrates protein ≥ 2+, then a 24-hour urine protein collection should follow. In patients with proteinuria greater than or equal to 2 grams per 24 hours, bevacizumab-Pfizer should be held until recovery (less than 2 grams per 24 hours). Patients who develop nephrotic syndrome should discontinue bevacizumab-Pfizer. In addition, this information was also added to: • Section 6.1.1.3 Bevacizumab-Pfizer. • Section 6.7.1 Dosing Interruptions • Appendix 2: Clinical Laboratory Tests **Section 6.7.3 Dose Reductions:** Table 5 Dose Modifications for Adverse Reactions related to Bevacizumab-Pfizer was added to the protocol for additional guidance. Other, minor clarifications, administrative and typographical changes were made.
Amendment 3	17 August 2020	The primary purpose of the amendment is to update the protocol to include operational details needed for the preplanned expansion of the study (Part 2). **SOA for Part 1A, 1B, and Part 2**

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		For participants in Part 2 the following revisions were made: • A ±1 day window was added to the Day 5 visit (footnote 23). • Subjects in Part 2 will not require a Day 3 visit, so for clarity, the footnote for the ECG assessment was modified (footnote 6). • The language detailing the frequency of CT/MRI scans was clarified in the table row. • The language in footnote 14 was clarified. • The CEA assessments were moved from the PK Assessments table to the standard assessments table. **SOA for PK, PD, and Immunogenicity for Part 1A and Part 1B** • Changed window of Day 5 (96 hour) PK collection to ±24 hours. • The optional or mandatory ontreatment biopsy sample collection schedule for within 28 days prior to registration was removed. • A Day 15, 8 hour sample collection for PF-07062199 concentration cytokines and circulating markers was added for participants in Part 1B. • Added collection of PK samples to the already scheduled ADA/NAb collections for Part 1B.

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		○ Footnote 3 updated to reflect the above change to PK sampling for Part 1B • Footnotes 5 and 6 updated to clarify tumor sample collection requirements. • **SOA and footnotes for PK, PD, and Immunogenicity Assessments for Part 2 added.** **Section 3 Objectives and Endpoints** • Tertiary/Exploratory Objective added for Part 1B and Part 2. The tertiary endpoint for Part 1B and Part 2 have been updated to reflect the output for these prespecified collections. **Section 4.1 Overall Design** • Tumor tissue sample language modified to incorporate Part 2 requirements. • Language was added to clarify inpatient observation period for Part 2. **Section 4.3.3 Fixed Dosing Approach** • Language was added to allow for body weight or BSA based dosing. **Section 5.1 Inclusion Criteria** • IC #5 was revised to incorporate tumor tissue sample requirements. **Section 5.2 – Exclusion Criteria**

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		Clarification was added to EC #6 to incorporate COVID-19 testing requirements. **Section 6.1.1.1 – PF-07062119** • Language was added to clarify inpatient observation period for Part 2. **Section 6.1.1.3 – Bevacizumab-Pfizer** • Administration instructions were updated. **Section 6.6.3 Hematopoietic Growth Factors** • Clarified that erythropoietin is not approved in Japan. **Added Section 6.7.1.1 – Dose Interruption of Participants with Presumed or Active COVID-19/SARS CoV2 Infection** **Added Section 8.1.2 COVID-19: Use of Alternative Methods for In-Person Visits** **Section 8.2.1.- Time Period and Frequency for Collecting AE and SAE Information** • Updated the text indicating how the investigator should notify Pfizer of an SAE, ie, using the CT SAE Report Form. **Section 8.2.6 Medication Errors**

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		• Clarified that medication dosing errors should be reported to the sponsor within 24 hours. **Section 8.3 Treatment of Overdose** • **Clarified that monitoring of any participant should continue for 5 half-lives or 28 calendar days after the overdose.** **Section 8.8, 8.8.1, 8.82** - Tumor tissue sample language revised to incorporate Part 2 requirements. **Section 10.3.2 Definition of SAE** • Text added to include the event of suspected transmission of an infectious agent, via a Pfizer product. **Section 10.3.3.– Recording/Reporting and Follow-up of AEs and/or SAEs** • Updated Exposure during pregnancy/breastfeeding AE/SAE reporting procedures. **Section 9.5.1 Data Monitoring Committee:** • Language added to clarify collected data which will be reviewed during the periodic safety review team. **Section 10.4.3 Woman of Childbearing Potential** • Language was added to clarify the procedure for participants with a high FSH.

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		Section 10.4.4 Contraception Method • Clarified contraception methods not approved in Japan. **Section 10.10.2 Prior Specifications** • The DLT rate was corrected. **Added Section 10.17 Japan Specific Matters** **Added Section 10.18: Alternative Measures During Public Emergencies** Other, minor clarifications, administrative and typographical changes were made.
Amendment 02	10 October 2019	The primary purpose of the amendment is to incorporate feedback received from the United States (US) Food and Drug Administration (FDA). In addition, clarifications, administrative and typographical modifications were made. 4.3.7 Criteria for Dose Escalation • Clarification, including typographical modifications around intra-participant dose escalation considerations were made. Section 4.3.8 Dose Limiting Toxicity Definition • Clarification made that all CRS events Grade 3 or higher, regardless of duration will be considered a DLT.

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		• Grade 3 infusion related reactions (IIR), allergic reactions or anaphylaxis will now be considered DLTs. Section 5.1 Inclusion Criteria • Typographical error was corrected splitting inclusion criteria #3 and #4 into two separate criterion. Section 6.7.3 Dose Reductions Typographical error was corrected properly link Table 3 in the text for the non-immune-related toxicities.
Amendment 01	08 October 2019	The primary purpose of the amendment is to incorporate feedback received from the United States (US) Food and Drug Administration (FDA). In addition, clarifications, administrative and typographical modifications were made.
		SCHEDULE OF ACTIVITIES (SOA) • Inpatient monitoring for Cycle 1 Day 15 (C1D15) has been extended to 8 hours post dose. Patients may be released only after the investigator has confirmed the participant has not exhibited signs and symptoms of a cytokine reaction. • C1D1 2-hour timepoint has been removed, which was relevant to Invtravenous (IV) dosing only, which has been removed from the protocol.

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		• In-house monitoring requirements and IV infusion instructions for IV dosing have been removed from the SOA, with removal of IV dosing from the protocol. • Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments for Parts 1A and 1B -footnote 7 "Blood Sample for Cytokines & Circulating Markers (central lab) and Blood sample for T cell Immunophenotyping" clarifies that: two (5 mL) blood samples will be collected to isolate serum for central laboratory tests for safety collected pre-dose on C1D1.
		Section 2.5 Benefit/Risk Assessment • Inpatient observation of IV dosing was removed from the protocol.
		Section 4.1 Overall Design • Clarification was added around the Bayesian logistic regression model (BLRM) and maximum dose increases in Part 1A and 1B. • Clarification was added around cohort size for dose level of Part 1B and Part 2. • Clarification that Part 1B will have at least 3 Dose Limiting Toxicity (DLT) evaluable participants, which was changed

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		from previous at least 2 DLT evaluable participant. • Figure 3: C3861001 Study Schema was updated to reflect number of participants in Part 1B. • Inpatient monitoring for C1D15 has been extended to 8 hours post dose. Patients may be released only after the investigator has confirmed the participant has not exhibited signs and symptoms of a cytokine reaction.
		Section 4.3.2 Subcutaneous Route • The protocol has been updated to clarify the use of subcutaneous dosing only at this time. If intravenous dose administration, including intravenous dose priming is going to be explored in this study, a future protocol amendment would occur prior to proceeding.
		Section 4.3.5 Starting Dose for Combination Dose Finding (Part 1B) • Clarification added around dose adjustments using BLRM with respect to PF-07062119.
		Section 4.3.7 Criteria for Dose Escalation • Clarification that Part 1B will have at least 3 DLT evaluable participants, which was changed from previous at least 2 DLT evaluable participant.

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		• Footnote was added to Table 1 for clarification, if the 45 µg subcutaneous (SC) Q2W dose is not tolerated, then a lower dose of 30 µg Q2W via SC route will be evaluated. • Intra-participant dose escalation guidelines have been revised so that at least 2 cycles beyond the DLT period for the next immediate higher dose level have passed prior to proceeding to a higher dose.
		Section 4.3.8 Dose Limiting Toxicity Definition • The definition of DLT evaluable participants have been revised to include any participant that has a DLT irrespective of whether they received all planned doses and received the scheduled safety assessments. • DLT criteria have been clarified for consistency. • Grade 4 vomiting or Grade 4 diarrhea has been added as a DLT. • Grade 3 Cytokine Release Syndrome (CRS) event criteria have been clarified.
		Section 5.1 Inclusion Criteria • Inclusion criteria # 2 and #3 have been updated to include that for Parts 1A and 1B participants must have exhausted all FDA or local

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		regulatory approved treatments that would confer significant clinically benefit for their disease.
		Section 5.2 Exclusion Criteria Exclusion criterion #13 has been added to include the exclusion of participants with active or history of clinically significant autoimmune disease that required systemic immunosuppressive therapy or another medical condition that required immunosuppression within 2 years of treatment.
		Section 6.1 Study Interventions Administered • Section has been updated to remove intravenous dose administration and intravenous dose priming.
		Section 6.1.1 Administration • Section has been updated to remove intravenous infusion administration and intravenous dose priming. • Guidance on where SC injections should be administered was added for clarification. • Inpatient monitoring for C1D15 has been extended to 8 hours post dose.
		Section 6.7 Dose Modification

Document History Protocol Amendments -01 through -05		
Document	**Version Date**	**Summary of Changes and Rationale**
		• Clarification of dose modifications and dosing options as a result of DLT have been included.
		Section 8.1.6 Injection Site Tolerability Assessment • Clarification made for SC dosing only.
		Section 9.2.1 Part 1 Dose Escalation • Clarification around total number of participants in the combination arms of Part 1B.
		Section 9.4.1 Maximum Tolerated Dose Determination • Clarification of the starting dose in Part 1A (45 µg).
		Section 9.4.4.1 Pharmacokinetic Analyses • Pharmacokinetic (PK) parameters involving IV dosing (eg, CL and Vss) have been removed.
Original Protocol	20 August 2019	n/a

11. REFERENCES

1. Ahmedin, J., et al., Cancer Statistics.CA A Cancer Journal for Clinicians. 2009;59(4):225-49.

2. Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in participants with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol. 2009;27(12):2091-6.

3. Allen E, Jabouille A, Rivera LB et al. Combined antiangiogenic and anti–PD-L1 therapy stimulates tumor immunity through HEV formation. Sci Transl Med. 2017;9(385):eaak9679.

4. Banholzer ML, Wandel C, Barrow P, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partner: update. Clin Transl Med/ 2016;5(1):23-37.

5. Bashir et al. Silencing the GUCA2A-GUCY2C tumor suppressor axis in CIN, serrated, and MSI colorectal neoplasia. Human Pathology. 2019;87:103-14.

6. EMD Serono, Inc (2019). Highlights of prescribing information. Bavencio® (avelumab) injection. Retrieved from https://www.emdserono.com/content/dam/web/corporate/non-images/country-specifics/us/pi/bavencio-pi.pdf.

7. Benson AB 3rd, Ajani JA, Catalano RB et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22(14):2918-26.

8. Amgen, Inc (2019).Blincyto™ (blinatumomab).Highlights of prescribing information. Retrieved from https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/blincyto/blincyto_pi_hcp_english.pdf.

9. Birbe R, Palazzo JP, Walters R et al. Hum Path. 2005;36(2):170-9.

10. Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin. 2018;68:394-24.

11. Bristol Myers Squibb (2019).Highlights of prescribing information. Opdivo® injection. Retrieved from https://packageinserts.bms.com/pi/pi_opdivo.pdf.

12. Chau, I. and Cunningham D, Treatment in advanced colorectal cancer: what, when and how [quest]. Br J Cancer. 2009;100(11):1704-19.

13. Danaee H, Kalebic T, Wyant T et al. Consistent expression of guanylyl cyclase-C in primary and metastatic gastrointestinal cancers. Plos One. 2017;12(12):e0189953.

14. Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26(35):5705-12.

15. Edler, Lutz and Burkholder, Iris. Overview of Phase I Trials. In: Handbook of Statistics in Clinical Oncology, 2nd Edition. Edited by John Crowley and Donna Pauler Ankerst. Boca Raton, FL, Chapman and Hall, 2006: 3-30.

16. Genentech, Inc (2019).Highlights of prescribing information. Tecentriq® (atezolizumab) injection. Retrieved from https://www.tecentriq.com/?_ga=2.222892123.1953547465.1563409718-375939400.1563409718&_gac=1.221828330.1563409718.Cj0KCQjwjrvpBRC0ARIsAFrFuV_UKK7L-U7wSl4SApMV6-3cTGH0kSM5UOcHv8nSbXNNl7FN__t0VF8aArdSEALw_wcB.

17. Grothey A, et al., Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. The Lancet. 2013;381(9863):303-12.

18. Hodi FS, Butler M, Oble DA, Seiden MV, Haluska FG et.al: Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer participants. Proc Natl Acad Sci U S A. 2008;105(8):3005-10.

19. Hoos A, Eggermont AM, Janetzki S, Hodi FS, Ibrahim R, et.al: Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst. 2010;102(18):1388-97.

20. Hurwitz, H.I., et al., The Clinical Benefit of Bevacizumab in Metastatic Colorectal Cancer Is Independent of K-ras Mutation Status: Analysis of a Phase III Study of Bevacizumab with Chemotherapy in Previously Untreated Metastatic Colorectal Cancer. Oncologist. 2009;14(1):22-8.

21. Genentech, Inc (2019).Highlights of prescribing information. Keytruda® (pembrolizumab) injection. Retrieved from http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

22. AstraZeneca (2018).Highlights of prescribing information. Imfinzi® (durvalumab) injection. Retrieved from https://www.imfinzihcp.com/non-small-cell-lung-cancer/stage-3/durvalumab-nsclc-clinical-trials.html?source=imz_n_h_9&umedium=cpc&uadpub=google&ucampaign=2019imfinzihcpnsclcbranded_general_hcp&ucreative=branded_alone_ph&uplace=imfinzi&outcome=hcp&cmpid=1.

23. Kiyozumi Y, Iwatsuki M, Yamashita K, et al. Update on targeted therapy and immune therapy for gastric cancer, 2018. J Cancer Metastasis Treat. 2018;4:31.

24. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124:188-195.

25. Lee DW, Santomasso BD, Locke FL, et al: ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells 2019;25:625-38.

26. "Metabolism and Transport, Drug Interaction Database", Department of Pharmaceutics, University of Washington.www.druginteractioninfo.org. Accessed May 2009.

27. Moore PA, Shah K, Yang Y, Alderson R et al. Development of MGD007, a gpA33 x CD3-Bispecific DART Protein for T-Cell Immunotherapy of Metastatic Colorectal Cancer. Mol Cancer Ther. 2018;17(8):1761-72.

28. Mullin JM, Laughlin KV, Ginanni N, et al. Increased tight junction permeability can result from protein kinase C activation/translocation and act as a tumor promotional event in epithelial cancers. Ann N Y Acad Sci. 2000;915:231-6.

29. Nishino, Mizuki M.D., Anita Giobbie-Hurder, M.S., Maria Gargano et.al: Developing a Common Language for Tumor Response to Immunotherapy: Immune-related Response Criteria using Unidimensional measurements. Clin Cancer Res. 2013;19(14):3936–43.

30. Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: Does reducing the number of lesions impact response assessment in melanoma participants treated with ipilimumab? J Immunother Cancer. 2014;2:17.

31. Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ, Summarizing historical information on controls in clinical trials. Clin Trials. 2010;7(1):5-18.

32. Neuenschwander B, Matano A, Tang Z, Roychoudhury S, Wandel S and Bailey S. A Bayesian Industry Approach to Phase I Combination Trials in Oncology. In *Statistical Methods in Drug Combination Studies*. Zhao W and Yang H (eds), Chapman & Hall/CRC, 2014.

33. Nagaich N and Sharma R. Gastric cancer – an update. J of Tumor Med Prev. 2018.2(5).

34. Pfizer, Inc.(2019).Highlights of prescribing information. Zirabev™ (bevacizumab) injection. Retrieved from: http://labeling.pfizer.com/ShowLabeling.aspx?id=11860.

35. Pratilas CA, Hanrahan AJ, Halilovic E, et al. Genetic predictors of MEK dependence in non-small cell lung cancer. Cancer Res 2008;68(22):9375-83.

36. Rogatko A1, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of innovative designs into phase I trials. J Clin Oncol. 2007;25(31):4982-6.

37. Saber H, Del Valle P, Ricks TK, Leighton JK. An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection. Regul Toxicol Pharmacol. 2017;90:144-52.

38. Saltz, L.B., et al., Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. J Clin Oncol. 2008;26(12):2013-9.

39. Salmaninejad A, Valilou SF, Shabgah AG, et al. PD-1/PD-L1 pathway: Basic biology and role in cancer immunotherapy. J Cell Physiol. 2019:1-14.

40. Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D., & Neuenschwander, B. Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics. 2014;70(4):1023-32.

41. Soler AP, Miller RD, Laughlin KV, et al. Increased tight junctional permeability is associated with the development of colon cancer. Carcinogenesis. 1999;20(8):1425-31.

42. Solit DB, Garraway LA, Pratilas CA et al. BRAF mutation predicts sensitivity to MEK inhibition. Nature. 2006;439(7074):358-62.

43. Smith-Garvin JE1, Koretzky GA, Jordan MS: T cell activation. Annu Rev Immunol. 2009;27:591-619.doi: 10.1146/annu rev. immunol. 021908.132706.

44. Spiegelhalter, D.J. Incorporating Bayesian Ideas into Health-Care Evaluation: Statist. Sci. 2014;19(1):156-174.

45. Tabernero J, Ignacio M, Willeke R, et al. Phase 1a and 1b studies of the novel carcinoembryonic antigen (CEA) T-cell bispecific (CEA CD3 TCB) antibody as a single agent and in combination with atezolizumab: Preliminary efficacy and safety in participants with metastatic colorectal cancer (mCRC). JCO. 2017;35(no.15 suppl):3002.

46. Taiho Oncology.(2019).Highlights of prescribing information. Lonsurf® (trifuridine/tipiracil).Retrieved from: https://www.taihooncology.com/us/prescribing-information.pdf.

47. Topp MS, Gökbuget N, Zugmaier G, et al: Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. J Clin Oncol. 2014;32(36):4134-40.

48. Topp MS, Gökbuget N, Stein AS, et al: Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukemia: a multicenter, single-arm, phase 2 study. Lancet Oncol. 2015;16:57-66.

49. Wang D.et al: Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials.

50. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, et.al: Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15(23):7412-20.

51. Zhang S, Shi R, Li C., et al: Fixed Dosing Versus Body Size–Based Dosing of Therapeutic Peptides and Proteins in Adults. J Clin Pharmacol. 2012;52(1):18-28.

52. Zimmerman, Maniar T, Nagorsen D: Unleashing the clinical power of T cells: CD19/CD3 bi-specific T cell engager (BiTE®) antibody construct blinatumomab as a potential therapy. Int Immunol. 2015;27(1):31-7.doi: 10.1093/intimm/dxu089.Epub.

53. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. JCO. 2006:3187-205.

54. Neelapu SS. Managing the toxicities of CAR T-cell therapy. Hematol Oncol. 2019;37 Suppl 1:48-52.

55. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62.