A PHASE 1 DOSE ESCALATION AND EXPANSION STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETIC, PHARMACODYNAMIC, AND ANTI-TUMOR ACTIVITY OF PF-07209960 IN PARTICIPANTS WITH ADVANCED OR METASTATIC SOLID TUMORS

Study Intervention Number:	PF-07209960
Study Intervention Name:	N/A
US IND Number:	CCI
EudraCT Number:	N/A
Protocol Number:	C4011001
Phase:	1

Short Title: Phase 1 Study of PF-07209960 in Advanced or Metastatic Solid Tumors

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original rotocol	15 September 2020	*N*/A
Amendment 1	30 October 2020	The prima1y purpose of the amendment is to incorporate feedback received from the United States (US) Food and Dmg Administration (FDA). In addition, clarifications, administrative and typographical modifications were made to improve upon the consistency of the protocol.
		Schedule of Activities (SOA) • C1D15 outpatient post-infusion PF-07209960 IV administration monitoring time has been extended from 1 hour to 8 hours. Paiiicipants may not be released until the investigator has confnmed the pa1iicipant has not exhibited signs and symptoms of a cytokine reaction. • Day 22 visit window is clai·ified to be ±24 hours for consistency. **Section 1.3.1 SOA for PK/PD:** • Clai·ification added to Notes column that if CRS is suspected, additional PK/PD and cytokine samples should be collected immediately. • Note added to clarify that if treatment is be_ond C_cle 3_the last blood sam_les CCI [redacted] **Section 1.3.2 SOA for EQT/Follow-Up:** • AE collection window extended to 90 days (from 28 days) after the last dose of study intervention due to possible late onset of AE. • Note added to clarify the collection of con-meds/interventions at EOT/Withdrawal Visit.
		Section 2.3.1 Risk Assessment • Additional language added to clai·ify that for C1D15 PF-07209960 IV administration,

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		participants should remain at the investigational sites for observation for at least 8-hours post dose.
		Section 5.1 Inclusion Criteria (IC): • IC #2 sub-criteria revised to clarify that anti-PD-1 wash-out period is required for all participants and not just for Part 2. • IC #2 sub-criterion (now sub-criterion "e") was revised to clarify that participants with OvCa or MSS CRC must not have received either anti-PD-1 or anti-PD-L1. • IC #7 – the method for estimating CrCl has been clarified to indicate the use of the Cockcroft-Gault method, as specified by the FDA. **Section 5.2 Exclusion Criteria (EC):** • EC #5 – Clarification that anti-PD-1 wash-out period is required for all participants and not just for Part 2.
		Section 4.3.3 Dose Limiting Toxicity Definition: • Updated definition to include "at least possible related to PF-07209960" as requested by the FDA. • All Grade ≥3 non-hematologic treatment-related AEs are DLTs with limited exceptions if they can be controlled with or without medical therapy and improve within 72 hours. The exceptions list was updated to include Grade 3 hypertension, hypotension, CRS, rash, and ISR as DLTs as specified by the FDA. • Sub-bullet #1 under Immune related AE (irAE) that meet the following criterion was updated to include the grade of toxicity for irAE regardless of duration.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Sub-bullet #7 under Immune related AE (irAE) that meet the following criterion was rewritten as a sub-bullet instead of a standalone exception. **Section 4.3.6 RP2D Definition**: • Added language to clarify that the occurrence of significant AEs that occur after the DLT observation period such as late-onset irAEs will be reviewed in context of all safety data available when determining the MTD/RP2D for Part 2 expansion phase.
		Section 8.3.5.1 Exposure During Preganancy • Details of EDP pregnancy report will be collected until 4 months after the last dose instead of 28 days.
		Section 10.4 Appendix 4: Contraceptive Guidance • Contraception period for males and females is extended from 28 days to a more conservative period of 4 months following last dose of study drug (>5 half-lives of the projected terminal half-life of study drug in humans) based on FDA recommendation.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: Phase 1 Study of PF-07209960 in Advanced or Metastatic Solid Tumors

Rationale

PF-07209960 is a fusion of a single, potency-reduced, IL-15 mutein and a bivalent high affinity anti-PD-1 full length IgG. This antibody-cytokine fusion molecule is designed to deliver PD-1-mediated avidity-driven IL-2/15 receptor stimulation preferentially to PD-1-positive CD8+ T cells, which are enriched in tumors and can mediate anti-tumor activity, while reducing the natural preference of IL-15 for majority PD-1-negative NK cells, which may mediate toxicity. The exposure of the IL-15 mutein is extended by fusing it to an antibody, which also reduces its potency to prevent systemic activation of PD-1 negative lymphocytes. Pre-clinical data suggest the stimulatory activity of PD-1 targeted IL-15 mutein is enhanced in tumor infiltrating lymphocytes preferentially over peripheral lymphocytes and can lead to anti-tumor activity greater than can be achieved with anti-PD-1 and IL-15 agonist either alone or in combination. The purpose of this FIH study is to evaluate the safety, tolerability, PK, PD and potential clinical benefits of PF-07209960 in participants with selected locally advanced or metastatic solid tumors in dose escalation/finding (Part 1) and selected solid tumors in dose expansion at the RP2D (Part 2). In order to explore the activity of PF-07209960 beyond tumor types which can be treated with anti-PD-1/PD-L1, these will include tumor types resistant to prior anti-PD-1/PD-L1 therapy (NSCLC, SCCHN, RCC, UC) and tumor types for which no anti-PD-1/PD-L1 standard of care therapy is available (OvCa, MSS CRC).

Objectives and Endpoints

PART 1 DOSE ESCALATION	
Objectives	**Endpoints**
Primary:	**Primary:**
• To assess safety and tolerability at increasing dose levels of PF-07209960 in participants with select locally advanced/metastatic solid tumors in order to estimate the MTD and select the RP2D/schedule.	• First cycle DLTs. • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0; for CRS as graded by ASTCT criteria), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.
Secondary:	**Secondary:**
• To characterize the single and multiple dose PK of PF-07209960.	• Single dose: C_{max}, T_{max}, AUC_{tau}. If data permits, AUC_{inf}, CL/F, $t_{1/2}$; • Multiple Dose: $C_{max,ss}$, $T_{max,ss}$, $AUC_{tau,ss}$. If data permits, CL_{ss}/F, $t_{1/2,ss}$, and R_{ac}; • C_{trough} at selected time points;
• To evaluate the immunogenicity of PF-07209960.	• Incidence, titers and endogenous IL-15 cross-reactivity of ADA and NAb against PF-07209960;
• To evaluate preliminary anti-tumor activity.	• ORR, DCR as assessed using the RECIST version 1.1. • Time-to-event endpoints: DOR, PFS, and TTP by RECIST version 1.1

PART 1 DOSE ESCALATION	
Objectives	**Endpoints**
Exploratory:	
[redacted]	[redacted]

PART 2 DOSE EXPANSION	
Objectives	**Endpoints**
Primary:	**Primary:**
• To confirm safety and tolerability of PF-07209960 at the RP2D in participants with selected tumor types. • To evaluate preliminary evidence of anti-tumor activity of PF-07209960 in participants with selected tumor types.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0; for CRS as graded by ASTCT criteria), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. • ORR as determined by RECIST version 1.1.
Secondary:	**Secondary:**
• To further evaluate the PK of PF-07209960 at the RP2D.	• Single dose: Cmax, Tmax, AUCtau, If data permits, AUCinf, CL/F, t½; • Multiple Dose: Cmax,ss, Tmax,ss, AUCtau,ss. If data permits, CLss/F, h/2,ss, and Rac; • Ctrough at selected time points.
• To evaluate the immunogenicity of PF-07209960.	• Incidence, titers and endogenous IL-15 cross-reactivity of ADA and NAb against PF-07209960.
• To evaluate the effect of PF-07209960 on immune cells in tumor biopsies.	• Intra-tumor T cells (such as by CDS IHC) in on-treatment versus baseline tumor biopsy samples.

PART 2 DOSE EXPANSION	
Ob"ectives	**End oints**
• To evaluate prelim.ina1y anti-tumor activity through time to event endpoints.	• DCR, DOR, PFS, and TIP by RECIST version 1.1
• To assess overall survival of participants treated with PF-07209960.	• Overall survival
Exploratory:	**Exploratory:**
[redacted] CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Overall Design

This is a Phase 1, open label, multicenter, multiple dose, dose escalation, safety, PK and PD study of PF-07209960 in paiticipants with selected locally advanced or metastatic solid tumors (anti-PD-1/PD-Ll resistant NSCLC, SCCHN, RCC, UC; or anti-PD-I nai:Ve OvCa and MSS CRC) for whom no standai·d therapy is available, or would not be an appropriate option in the opinion of the paiticipant and their treating physician, or paiticipants who have refused standai·d therapy.

The study contains 2 paits, single agent dose escalation (Pait 1) followed by a dose expansion at the RP2D (Pait 2). The overall study design is depicted in the schema (Section 1.2). Successive coho1ts of pa1ticipants in Pait 1 will receive escalating doses of PF-07209960 as a SC or IV administration eve1y 2 weeks. The first and second paiticipant in each dose level must be emolled >72 hours apait. BLRM guided by EWOC principle will be used to guide dose escalation process and detennine the MTD/RP2D. Part 1 will estimate the MTD/RP2D in sequential dose escalation coho1ts for PF-07209960 as single agent in paiticipants with selected solid tumors. After the MTD/RP2D for PF-07209960 single agent is detennined, Pait 2 expansion will be initiated in paiticipants with selected solid tumors as info1med by Pait 1.

Key Inclusion Criteria:

1. Locally advanced/metastatic NSCLC, SCCHN, RCC, UC, OvCa, or MSS CRC.
    a. At least 1 prior line of therapy for recurrent or metastatic disease, including either standards of care or investigational therapies. Participants must have progressed or relapsed after or be intolerant to standard therapy approved for the specific tumor type. Exception: participants who actively decline available standard of care therapies are eligible upon documentation of their refusal.
    b. Participants with NSCLC, SCCHN, RCC, or UC must have received prior anti-PD-1/PD-L1 either as monotherapy or in a combination regimen and had experienced radiographic progression.
    c. Participants with NSCLC must not have known ALK, ROS1, MET exon 14 skipping, RET rearrangement or EGFR mutation.
    d. Participants who had received prior anti-PD-1 must be ≥90 days from their last anti-PD-1 dose. Participants who received prior anti-PD-L1 are not subject to this restriction.
    e. Participants with OvCa or MSS CRC must not have received prior anti-PD-1/PD-L1 therapy.
    f. Demonstrated radiographic progression on most recent tumor assessment imaging.
    g. For Part 2, in addition:
        a) Participants with NSCLC must have received either ≥2 prior lines of therapy including at ≥1 prior regimen containing chemotherapy and ≥1 prior regimen containing anti-PD-1/PD-L1 or a prior regimen of anti-PD-1/PD-L1 in combination with chemotherapy (eg, atezolizumab with chemotherapy). In addition, NSCLC with a BRAF V600E mutation must have also received BRAF inhibitor with or without MEK inhibitor.
        b) Participants with RCC must have received either ≥2 prior lines of therapy including ≥1 prior regimen containing anti-PD-1/PD-L1 and ≥1 prior regimen containing a small molecule kinase inhibitor or a prior regimen of anti-PD-1/PD-L1 in combination with a small molecule kinase inhibitor (eg, avelumab with axitinib).
        c) Participants with UC must have received ≥2 prior linesof therapy including platinum-containing chemotherapy and anti-PD-1/PD-L1, or a single regimen of platinum-containing chemotherapy followed by anti-PD-1/PD-L1 maintenance therapy.
        d) Participants with MSS CRC must have received ≥2 prior lines of therapy including treatment regimens containing combinations of pyrimidine analog, oxaliplatin, irinotecan, anti-EGFR (RAS wild type), encorafenib (if BRAF V600E-positive) and anti-HER2 (if HER2 amplified and RAS and BRAF wild type).

e) Participants with OvCa must have received ≥2 prior lines of therapy including at least 1 regimen with platinum-based chemotherapy and progressed on last two consecutive regimens without evidence of clinical benefit.

2. Participants entering the study in the expansion cohort have ≥1 measurable lesion per RECIST version 1.1 that has not been previously irradiated.
3. Tumor tissue available or accessible for biopsy:
   a. Participants enrolled in Part 1 and Part 2 should consent to undergo biopsy during screening (pre-treatment) or be able to provide archival FFPE material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy taken ≤1 year prior to study start. If the archival sample is older than 1 year and a biopsy during screening cannot be performed, the investigator must contact the sponsor to discuss eligibility prior to enrollment.
   b. Participants enrolled in Part 2 dose expansion must have a tumor amenable to biopsy and consent to planned mandatory pre- and on-treatment biopsy procedures until the sponsor deems that an adequate number of participants (10-15 paired fresh biopsies per cohort) have been successfully biopsied, at which point participants will only be required to submit pre-treatment biopsies (either archival tissue or de novo biopsy as above). Special considerations will be made for participants with poorly-accessible tumors or deemed medically unsafe as determined by the investigator after discussion and agreement by the sponsor.
4. ECOG PS 0-2 for Part 1, 0-1 for Part 2.
5. Adequate hematologic function.
6. Adequate renal and liver function.
7. Adequate coagulation function.

Key Exclusion Criteria:

1. Symptomatic brain or leptomeningeal metastases requiring steroids.
2. 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 and/or radiation therapy within 4 weeks prior to planned first dose.
4. Systemic anti-cancer therapy within 4 weeks prior to planned first dose (6 weeks for mitomycin C or nitrosoureas). If the last immediate anti-cancer treatment contained an antibody based agent(s) (approved or investigational), then an interval of 28 days or 5 half-life (whichever is shorter) of the agent(s) prior to receiving the study intervention treatment is required. Participants who received anti-PD-1 (but not anti-PD-L1) therapy require an interval of 90 days prior to planned first dose.
5. Active and clinically significant bacterial, fungal, or viral infection, Hepatitis B or Hepatitis C infection at screening (positive HBsAg or positive HCV RNA if anti-HCV antibody test positive), known HIV or AIDS-related illness. HIV

seropositive participants, who are in good health and at low-risk for AIDS-related outcomes, may qualify for inclusion in the study after discussion with the sponsor, but AIDS is exclusionary.

6. Anticoagulation with vitamin K antagonists is not allowed. Anticoagulation with low molecular weight heparin and Factor Xa inhibitors or use of antiplatelet therapy is allowed but must be held per institutional requirements for biopsies and whenever platelet count is <50,000/mm^3. If participants are on antiplatelet therapy, they must be able to hold antiplatelet therapy for first week of study treatment without significantly increased risk of cardiovascular events.
7. AEs from prior therapy which have not recovered to Grade ≤1 or baseline.
8. History of Grade ≥3 immune-related AE considered related to prior immune modulatory therapy and required immunosuppressive therapy (except endocrine irAEs managed by hormone replacement therapy).
9. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
10. Current use of immunosuppressive medication at the time of randomization, EXCEPT for the following: a) intranasal, inhaled, topical steroids, or local steroid injection (eg, intra-articular injection); b) Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; c) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
11. Active bleeding disorder in the past 6 months prior to planned first dose.
12. History of interstitial lung disease or pneumonitis.
13. Pregnancy or breastfeeding.

Number of Participants

The total number of participants enrolled to study intervention is estimated to range from approximately 74 to 172.

Part 1 Dose Escalation:

Approximately 14-22 participants are expected to be enrolled in Part 1 dose escalation. The total number of participants will depend on the number of dose levels needed to determine the MTD/RP2D and the actual number of participants evaluable for DLT at each dose level. In general, each cohort in the dose escalation part will be approximately 2-4 participants. DLT observation period is 28 days after C1D1 for all participants. For the dose level that is estimated to be the MTD, a minimum of 6 DLT evaluable participants will be treated at this dose.

Part 2: Dose Expansion:

Each cohort in Part 2 will enroll 20-30 participants. Approximately 60-90 participants will be initially enrolled in the first three cohorts, with the option to further enroll approximately 40-

60 participants in an additional two cohorts. The Part 2 dose expansion phase will consist of approximately 5 cohorts, which will evaluate safety and anti-tumor activity of PF-07209960 at the RP2D determined in Part 1. Opening of cohorts in Part 2 will initially include tumor type(s) and setting(s) deemed more likely to demonstrate anti-tumor activity based on data from Part 1. At this time, Part 2 expansion cohorts in NSCLC, RCC and UC have been chosen as initial tumor types to study due to their responsiveness to immunotherapy agents. If preliminary anti-tumor activity is seen with OvCa and MSS CRC in Part 1 or if anti-tumor activity is observed in at least one tumor type out of NSCLC, RCC, and UC in Part 2, the optional OvCa and MSS CRC expansion cohorts would be considered for enrollment. Tumor indications for Part 2 could also be re-prioritized based on emerging data from Part 1. Sample size determination is presented in Section 9.2.

Intervention Groups and Duration

PF-07209960 will be administered as monotherapy, SC or IV infusion over 1 hours (±10 minutes) on Days 1 and 15 in 28 day cycles as described in Section 4.3.1. Treatment with study intervention will continue until either disease progression, unacceptable toxicity, participant refusal, or whichever is earliest, unless the investigator and medical monitor agree to treatment beyond disease progression based on individual benefit/risk assessments or agree to discontinue treatment or the study is terminated.

The starting dose for PF-07209960 for this FIH study has been determined to be [redacted]. The starting dose for IV infusion is described in Section 4.3.1.2. The SC route has the potential to reduce the C_{max} which is believed to be associated with CRS and inflammatory responses, common AEs for agents that stimulate T cells. If excessive ISR or unexpected low exposure is encountered with SC dosing, an alternative IV infusion Q2W administration may be explored. The IV dose escalation/finding would begin at a starting dose based on the available emerging clinical data (including safety/tolerability, PK, PD) from the dose escalation cohorts with SC Q2W administration. All participants will be monitored during and following their first dose (regardless of SC or IV dosing) with a 72-hour inpatient hospitalization period throughout dose escalation. Participants receiving IV dosing on C1D15 will remain at the investigational site for observation for at least 8 hours following IV infusion. Participants may not be released until the investigator has confirmed the participant has not exhibited signs and symptoms of a cytokine reaction. For additional information, refer to Section 4.3.1. Dose modification information is provided in Section 6.6.

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 will be the date of the last visit of the last participants or 2 years after the last participant receives their first dose (whichever occurs first). The study may also be terminated at any time at the discretion of the sponsor. Any additional treatment beyond 2 years shall be discussed and approved by the sponsor.

Statistical Methods

There is no formal hypothesis testing in this study.

Unless otherwise specified, summaries will be presented by dose group and overall. Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints. The rates of binary endpoints will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method. Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint will be provided.

The dose escalation in the Part 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07209960. Dose toxicity is modelled using two-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose.

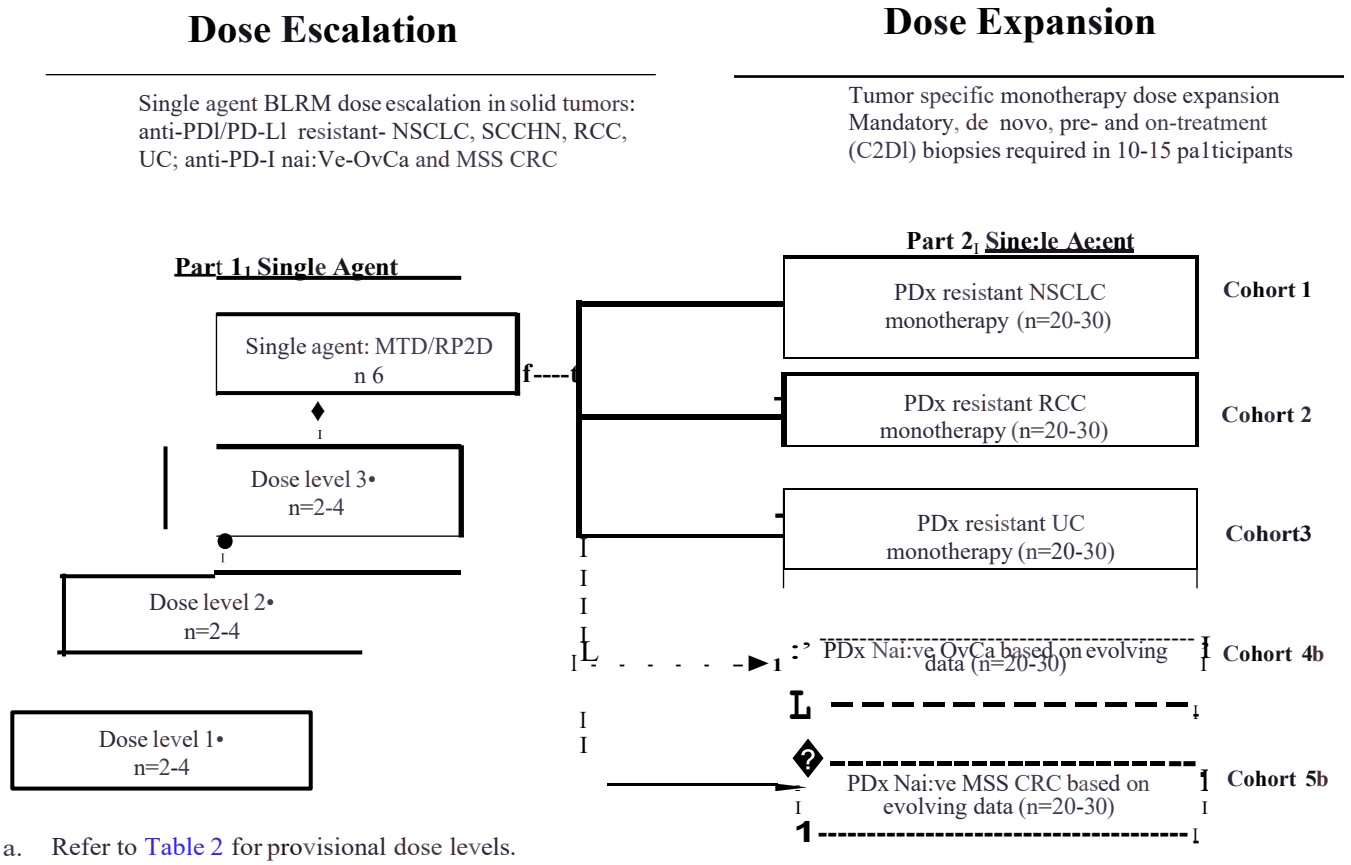
After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07209960 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

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

Dosing decisions are guided by the escalation with overdose control (Rogatko et al, 2007). A dose may only be used for newly enrolled participants if the probability of overdosing at that dose is CCI [redacted].

Recommendation from the BLRM, along with safety (AEs, SAEs), laboratory, PK, biomarker and other relevant data, will be used at the time of each dose escalation and for MTD/RP2D determination.

1.2. Schema



a. Refer to Table 2 for provisional dose levels.
b. Coho1ts 4 and *5* to be considered for activation only after early signs of efficacy are seen in Coho1ts 1, 2 and/or 3.

1.3. Schedule of Activities

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 infonnation 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 paiiicipant.

	Screening	Cycle 1 (28 days)-A Cycle 2 (28 days) - B Cvcle >3 (28 days) - C											Notes
Days	**Up to 28 days prior to ClDl**	**1 A**	**1 B/C**	2 **A**	3 **A**	4 **A**	**8 A**	**15 A/B/C**	**16 B**	**17 B**	**18 B**	**22 A/B**	
Visit Window		-72 **h1·s**	**±2 davs**	**±4 hrs**	**±4 h.-s**	**±4 hrs**	**±1 day**	**±2 davs**	**±4 h.-s**	**±4 h1·s**	**±24 h.-s**	**±24 hrs**	
Informed consent and registration	A	A											• Info,med consent must be obtained prior to undergoing any study-specific procedures. • Participant enrollment number and dose level allocation assigned by Pfizer Inc.
Medical History	A												• Includes tumor history and other medical history.
Phvsical Examination													
Complete Physical Exam	A	A											• Include height only at screen (not needed at ClDl). • Include weie.ht at screenine..
Brief Physical Exam			*B/C*	A	A	A	A	*AIB/C*				*AIB*	• Include weight D1 of each cycle only. • Height not needed. • Daily while hospitalized.
ECOG Pe,fonuance Status	A	A	*B/C*					*AIB/C*					
Vital Signs	A	A	*B/C*	A	A	A	A	*AIB/C*					• Meastu·e vitals prior to the PF-07209960 treatment.

	Screening	Cycle 1 (28 days)-A Cycle 2 (28 days) - B Cvcle >3 (28 days) - C											Notes
Days	**Up to 28 days prior to ClDl**	**1 A**	**1 B/C**	2 **A**	3 **A**	4 **A**	**8 A**	**15 A/B/C**	**16 B**	**17 B**	**18 B**	**22 A/B**	
Visit Window		-72 **h1·s**	**±2 davs**	**±4 hrs**	**±4 h.-s**	**±4 hrs**	**±1 day**	**±2 davs**	**±4 h.-s**	**±4 h1·s**	**±24 h.-s**	**±24 hrs**	
													• In addition, temperature (oral prefen-ed), HR, BP, will be collected eve,y 6 hotu·s and as needed dtuing initial 72-hom·inpatient monito,ine..
Electrocardiogram	A	A	*B/C*	A	A			*AIB*		B			• Pe1fo1m 3 consecutive 12-lead ECGs approximately 1-4 minutes apa,t to dete1mine mean QTcF interval. Additional triplicate ECGs may be pe1fo1med as clinically indicated. • Pe1fo1m ECGs before blood draw; plan the timing of ECG such that PK collection afte,wards can be around the intended time. • Additional ECG monito,ing if a) the mean value from the triplicate measm·ements for any postdose QTcF interval is increased by :C:::60 msec from the baseline **and** is >450 msec; orb) an absolute QTcF value is >500 msec for any scheduled ECG.) Consultation with a cardiologist will be performed if clinically waffanted or if the QTcF value is >500 msec for any scheduled ECG. • If treatment is :C::3 cycles, last electrocardiogram is done C3Dl.
Echocardiogram or MUGA	A	A											• MUGA preferred over echocardiogram; iniaging method must be consistent throughout the study for individual participants.

	Screening	Cycle 1 (28 days)-A Cycle 2 (28 days) - B Cvcle >3 (28 days) - C											Notes
Days	**Up to 28 days prior to ClDl**	**1 A**	1 B/C	2 **A**	3 **A**	4 **A**	**8** A	15 A/B/C	**16 B**	17 B	**18 B**	**22 A/B**	
Visit Window		-72 **h1·s**	**±2 davs**	**±4 hrs**	**±4 h.-s**	**±4 hrs**	**±1 day**	**±2 davs**	**±4 h.-s**	**±4 h1·s**	**±24 h.-s**	**±24 hrs**	
													• Assess at baseline. Additional testing as clinically indicated.
Blood Draw for Laboratory Assessments													• All blood draws for laboratory assessment can be done at the first draw for PK/ADA/immunogenicity as per Section 8.9. • No need to repeat on ClDl if baseline assessment performed within 72 hrs prior to ClDl. • ClDl onwards: perform assessments within 48 hours prior to dosing. • Samples will be analyzed locally. • Refer to Appendix 2 for additional information.
Hematology	A	A	B/C	A	A	A	A	*A/B/C*				A	
Blood Chemistry	A	A	B/C	A	A	A	A	*A/B/C*				A	• CRP and fen-itin measurement not required after C2Dl **if** within nonual range or similar to baseline levels; however, **CRP and fenitin should be measured anytime CRS** is **suspected and not already scheduled to be measured** (**eg,** Cycle 2).
Coagulation	A	A	B/C	A	A	A	A	*A/B/C*				A	• PT/INR and PTI/aPTI, • TT, fibrinogen, D-dimer for Cycle 1 and as clinically indicated.
Thyroid Test	A	A	C (Q12 W)										• TSH, free T4 • Assess eve1y 3 cycles after 3 cycles.

	Screening	Cycle 1 (28 days)-A Cycle 2 (28 days) - B C cle3 28 days - C											Notes
Days	**Up to 28 days prior to ClDl**	**1 A**	**1 B/C**	**2 A**	**3 A**	**4 A**	**8 A**	**15 A/B/C**	**16 B**	**17 B**	**18 B**	**22 A/B**	
Visit Window		-72	±2	±4	±4	±4	±1	±2	±4	±4	±24	±24	
		hrs	**days**	**hrs**	**hrs**	**hrs**	**day**	**days**	**hrs**	**hrs**	**hrs**	**hrs**	
CCI													
Hepatitis Serology	A	A											• Serology (HBsAg, anti-HCV antibody) • If anti-HCV antibody test is positive, HCV RNA test must be pe1fon11ed
Tumol' Mal'kel's													
CCI													
Pl'egnancy Testing	A	A	B/C										
Ul'inalysis	A	A	B/C					*AIBIC*					• No need to repeat on ClDl if baseline assessment pe1fo1med within 7 days prior to ClDl. • Dipstick is acceptable at minimum at screening and end of treatment visit. • Samples will be analyzed locally.
Pharmacokinetics Assessments													
PK Blood [semm] Sampling for PF-07209960		Schedule of Activities: Phanuacokinetic, Blood Phanuac,odynamic, Immunophenotyping, and Cytokine Activity											

	Screening	Cycle 1 (28 days)-A Cycle 2 (28 days) - B C cle3 28 days - C										Notes
Days	**Up to 28 days prior to ClDl**	**1 A**	**1 B/C**	**2 A**	**3 A**	**4 A**	**8 A**	**15 A/B/C**	**16 B**	**17 B**	**18 B**	**22 A/B**	
Visit Window		-72 hl·s	±2 da s	±4 hrs	±4 h.-s	±4 hrs	±1 day	±2 da s	±4 h.-s	±4 hl·s	±24 h.-s	±24 hrs	
Immunogenicity Assessments												
Anti-PF-07209960 Antibodies (ADA and NAb) Blood Samples (semm)		Schedule of Activities: Phannacokinetic, Blood Phannac,odynamic, Immunophenotyping, and Cytokine Activity										
Pharmacodynamic_A,s..s._e_ss_m_e_n_ts_												""T""
CCI [redacted]		Schedule of Activities: Phannacokinetic, Blood Phannac,odynamic, Immunophenotyping, and Cytokine Activity										
CCI [redacted]		Schedule of Activities: Phannacokinetic, Blood Phannac,odynamic, Immunophenotyping, and Cytokine Activity										
CCI [redacted]		Schedule of Activities: Phannacokinetic, Blood Phannac,odynamic, Immunophenotyping, and Cytokine Activity										
CCI [redacted]		Schedule of Activities: Phannacokinetic, Blood Phannac,odynamic, Immunophenotyping, and Cytokine Activity										
Treatment												
PF-07209960 Administration		A	*B/C*					*A!B/C*				• Participants should remain at the investigational site for observation for at least 1-hotu·post dose for all treatment visits after ClDl. For ClD15 PF-07209960 IV administration, participants should remain at the investigational site for observation for at least 8-hotu-spost dose. See requirements for ClDl under Inpatient Monitoring. Actual observation times for Cycle 2 and beyond may be adjusted per investigator's medical judgement, depending on clinical experience with revious doses.

	Screening	Cycle 1 (28 days)-A Cycle 2 (28 days) - B Cvcle >3 (28 days) - C											Notes
Days	**Up to 28 days prior to ClDl**	**1 A**	**1 B/C**	**2 A**	**3 A**	**4 A**	**8 A**	**15 A/B/C**	**16 B**	**17 B**	**18 B**	**22 A/B**	
Visit Window		-72 **h1·s**	**±2 davs**	**±4 hrs**	**±4 h.-s**	**±4 hrs**	**±1 day**	**±2 davs**	**±4 h.-s**	**±4 h1·s**	**±24 h.-s**	**±24 hrs**	
													• Observation periods will be re-evaluated prior to Patt 2 statt based on Patt **1** experience. • If CRS occurs, participants may be released only after the investigator has confomed the patticipant has sufficiently recovered from CRS. • Participants should complete the required study specific laboratory assessments as detailed in Aooendix 2.
Inpatient Monitoring (Hospitalization)		**A**		**A**	A	**A**							• Participants will be admitted for inpatient monitoring (per local standard of practice) dtuing and following their first dose for at least 72 hotu·s following the first administration of study treatment (ClDl). • Hospitalization period may be extended if the participant experiences abnonual laboratory findings or ongoing AEs that require further hospitalization.
Local Injection Site Tolerability Assessment (SC only)		**A**	*BIC*	**A**	A	**A**		*A!BIC*					• To be petfonued for SC injection only. • Assess injection site tolerability for at least **1** hotu·following treatment administration in Cycle 1. • Perform daily during hospitalization for first dose or until no skin changes are seen at injection site, whichever comes first.

	Screening	Cycle 1 (28 days)-A Cycle 2 (28 days) - B Cvcle >3 (28 days) - C											Notes
Days	**Up to 28 days prior to ClDl**	**1 A**	**1 B/C**	2 **A**	3 **A**	4 **A**	**8 A**	**15 A/B/C**	**16 B**	**17 B**	**18 B**	**22 A/B**	
Visit Window		-72 **h1·s**	**±2 davs**	**±4 hrs**	**±4 h.-s**	**±4 hrs**	**±1 day**	**±2 davs**	**±4 h.-s**	**±4 h1·s**	**±24 h.-s**	**±24 hrs**	
													• If injection site pain or ISR chara cteristics continue to persist after the first cycle, local site injection tolerability assessments should continue until the symptoms resolve.
Tumor Response Assessment													
CT or MRI scans of chest, abdomen, pelvis, any clinically indicated sites of disease, and of bone lesions; clinical evaluation of superficial disease	A	Pe1fon11ed eve1y 8 weeks from ClDl (±7 days) for the first 6 months, and then eveiy 12 weeks (±7 days) thereafter.											• Refer to Appendix 11 • If allergic to contrast agents for imaging, a non-contrast computed tomography of the chest with contrast enhanced abdominal and pelvic MRI can be used. • Brain scans and/or bone scans to be pe1formed at baseline if disease is suspected and during study as appropriate to follow disease.
Adverse Event Assessments		A	*B/C*	A	A	A	A	*A!B/C*	B	B	B	*AIB*	• Document AEs using the NCI CTCAE version *5* as described in Appendix 3. • If the participant begins a new anticancer therapy, refer to Section 8.3.1 for guidance on the recording of AEs on CRF.
Concomitant Treatment(s)		A	*B/C*	A	A	A	A	*A!B/C*	B	B	B	*AIB*	• All concomitant treatment and Non Dmg Supportive Interventions should be recorded on the CRF.
Tissue Sampling													

	Screening	**Cycle 1 (28 days)-A Cycle 2 (28 days) - B Cvcle >3 (28 days) - C**											**Notes**
Days	**Up to 28 days prior to ClDl**	**1 A**	**1 B/C**	**2 A**	**3 A**	**4 A**	**8 A**	**15 A/B/C**	**16 B**	**17 B**	**18 B**	**22 A/B**	
Visit Window		-72 **h1·s**	**±2 davs**	**±4 hrs**	**±4 h.-s**	**±4 hrs**	**±1 day**	**±2 davs**	**±4 h.-s**	**±4 h1·s**	**±24 h.-s**	**±24 hrs**	
Archival Tumor Tissue (Mandatory for both Part **1** Dose Escalation and Pait 2 Dose Expansion)	A												• An archival sample collected ::;l year prior to study stait should be submitted per laboratoiy manual. • If archival FFPE ::;l year is not available a fresh tumor sample must be collected at screening (see next row). • If the archival sample is older than 1 year and a biopsy dtuing screening cannot be peifoimed, the investigator must contact the sponsor to discuss elillibilitv orior to enrolhuent.
De Novo (Fresh) Tumor Biopsies (Optional for Part 1 Dose Escalation; Mandatory in Part 2 Dose Expansion with approxiniately10-15 Pre- and On-Treatment Paired Biopsies per Cohort)	A		B										• Optional (but highlyencom·aged) on-treatment fresh tumor biopsies at C2D1 in Part **1** dose escalation. • Paiticipants in Pait **1** who provide fresh on-treatment tumor biopsies should also provide fresh pre-treatment ttuuor biopsies as paired samples. • Part 2 dose expansion: mandatoiy fresh pre- and on-treatment tumor biopsy pairs must be collected from approximately 10-15 paiticipants at baseline and C2Dl (±5 days). • An archival sample collected prior to study stait may not be substituted for the mandatoiy pre-treatment paired biopsy in Part 2 dose expansion. • Paiticipants who provide fresh pre- and on-treatment tumor biopsy pairs could also orovide archival samples.

	Screening	Cycle 1 (28 days)-A Cycle 2 (28 days) - B Cvcle >3 (28 days) - C											Notes
Days	**Up to 28 days prior to ClDl**	**1 A**	**1 B/C**	**2 A**	**3 A**	**4 A**	**8 A**	**15 A/B/C**	**16 B**	**17 B**	**18 B**	**22 A/B**	
Visit Window		-72 h1·s	±2 davs	±4 hrs	±4 h.-s	±4 hrs	±1 day	±2 davs	±4 h.-s	±4 h1·s	±24 h.-s	±24 hrs	
													• For additional infonnation refer to Se.ction 8.8.1 and the laboratory manual.
Banked Biospecimen	A												• A blood sample (Prep D1) will be collected at the screening to be retained for potential pha1macogenomic/biomarker analyses related to dmg response and cancer, unless prohibited by local regulations or IRB or ethics committee decision. • If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in coniunction with a participant visit.

1.3.1. Schedule of Activities: Pharmacokinetic, Blood Pharmacodynamic, Immunophenotyping, and Cytokine Activity

	Cycle 1 (28 days)-A Cycle 2 (28 days)- B Cycle >3 (28 davs)- C																NOTES
Study Day	**1**				2	**3**	**4**	**8**	**15**				**16**	**17**	**18**	**22**	
Hom·s Pre/Post Dose	**Pre**	**EOI 1 hr**	**4 hrs**	**8 lu·s**	**24 hrs**	**48 lu·s**	72 **hrs**	**168 hrs**	**Pre**	**EOI llu·**	**4hrs**	**8** lu·s	**24** hrs	**48** lu·s	72 hrs	**168** lu·s	
Visit Window	<6 **hrs**	±6 **mins**	±30 **mins**	±1 ln·	±4 **hrs**	±8 **lu·s**	±24 **hrs**	±24 **hrs**	<6 **hrs**	±6 **mins**	±30 **mins**	±2 **lu·s**	±4 **hrs**	±4 **lu·s**	±24 **hrs**	±24 **lu·s**	
PK Blood [senun] Sampling for PF-07209960	*A/Bl* C*	A (IV only)	**A**	**A**	**A**	**A**	**A**	A	*AIB*	B (IV only)	B	B	B	B	B	B	• Predose **PK** should be collected before SC injection or IV infusion. • End of Infusion (EOI) sample timepoints is **only** applicable for IV infusion samples. End of infusion PK samples should be taken **+/-** 10% of the infusion duration length (ie within **+/-** 6 minutes of the stop time of a 60-minute infusion from the contra-lateral arm of IV infusion; the infusion duration includes the flush dm·ation if implemented). • SC injection: **PK** Sampling times indicated are related to the end of the SC injection. • IV infusion: PK sampling times indicated are related to the start of the IV infusion. • 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. • *Start.ing from Cycle 3, pre-dose PK samples will be collected on day 1 of eve1y cycle, from Cycle 9, on day 1 of eve1y 3rd cycle (C9Dl, C12Dl, ClSDl, etc). • Additional PK/PD and cytokine samples should also be taken inunediately if CRS is suspected, and PK/PD samples are not already scheduled to be taken.
Anti-PF-07209960 Antibodies (ADA and NAb) blood samples (senun)	*A/Bl* C*								**A**								• *Starting from Cycle 3, pre-dose anti-PF-07209960 samples will be collected on day 1 of eve1y cycle, and from Cycle 9, on day 1 of every 3rd cvcle (C9Dl, C12Dl, ClSDl, etc).

	Cycle 1 (28 days) -A Cycle 2 (28 days)- B Cycle 3 28 da's - C																NOTES
Study Day		**1**			2	3	4	8			15			**16**	**17**	**18**	**22**	
Hom·s Pre/Post Dose	**Pre**	**EOI 1 hr**	**4 hrs**	**8 lu·s**	**24 hrs**	**48 lu·s**	**72 hrs**	**168 hrs**	**Pre**	**EOI llu·**	**4 hrs**	**8 lu·s**	**24 hrs**	**48 lu·s**	72 **hrs**	**168 lu·s**	
Visit Window	**<6 hrs**	**±6 mins**	**±30 mins**	**±1 In·**	**±4 hrs**	**±8 lu·s**	**± 24 hrs**	**± 24 hrs**	**<6 hrs**	**± 6 mins**	**± 30 mins**	**±2 lu·s**	**±4 hrs**	**±4 lu·s**	**±24 hrs**	**±24 lu·s**	
																	• Predose Anti-PF-072009960 antibodies samples should be collected before SC injection or IV infusion.
CCI [redacted]																	
Blood for T Cell Immunophenotyping	*AIC*			**A**	**A**	**A**	A	A	*AIB*			B	B	B	B	B	• If treatment is c::3 cycles, last sample is collected at C3Dl • Refer to Se-ction 8.8.2 for additional infonuation. Detailed anel will be included in the lab manual.
Blood for Gemiline DNA Sequencing	A																
CCI [redacted]																	

1.3.2. Schedule of Activities: End of Treatment, Post-Treatment, and Survival Follow-up

	End of Treatment[1]/ Withdrawal	1-Month Follow-up[2]	Sunival Follow-up[3]	Notes Fo1· detailed notes refer· to main schedule of assessment
		28 days after last dose	**Every 2 months after 28 days Follow-u**	
Visit Window (days)		±7 **days**	±7 **days**	
Physical Exam				
Complete Physical Exam				
Brief Physical Examinatio				
ECOG Performance Stat[IS]				
Vital Signs				
Electrocardiogram Echocardiogram or MUGA	X			• Assessment ofLVEF using Echocardiogram or MUGA will be e1fo1med.
Blood draw for Laboratory A5sessment				
Hematology	X	X		
Blood chemistry	X	X		
Coagulation	X	X		• PT/INR, PTT/aPTT.
Thyroid Test	X	X		• TSH, free T4 testing.
CCI [redacted]				
Pregnancy Test	X			
Urinalysis	X	X		
Tumor Response Assessment				
CT or MRI scans of chest, abdomen, pelvis, any clinically indicated sites of disease, and ofbone lesions; clinical evaluation of superficial disease	X		X	• Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. • After EOT, continue to repo1t SOC imaging until sta1t of new therapy or EOS.

	End of Treatment[1]/ Withdrawal	1-Month Follow-up[2]	Sunival Follow-up[3]	Notes F01· detailed notes refer to main schedule of assessment
		28 days after· last dose	Every 2 months after· 28 days Follow-up	
Visit Window (davs)		±7 days	± 7 days	
Subsequent anti-cancer therapy		X	X	• Concomitant treatment(s) and non-drug suppo,tive interventions should be recorded on CRF through the End of Treatment/Withdrawal Visit should be recorded on the CRF for that visit. Only subsequent anti-cancer therapy initiated after End of Treatment/Withdrawal Visit will be repo,ted at the Follow-up visits.
Adverse Event Assessment	X	X	X	• All AEs and SAEs must be collected until a minimum of 90 days after the last administration of the study intervention due to possible late onset of AE/SAE. • The SAEs identified dtuing long-term follow-up will be reported to Pfizer Safety on the CT SAE Repo,t Form only if considered reasonablv related to the studv intervention.
PK Blood [sernm) Sampling for **PF-07209960**	X	X (if suspected ADA-relatedAE)	X (if suspected ADA-related AE)	• If unresolved AE is considered by the investigator as possibly related to or associated with ADA fonuation, the participant will be asked to rettun for drug concentration and ADA blood sampling at up to 3-month intervals (if feasible given the underlying disease), until the AE or its sequelae returns to baseline or stabilize at a level acceptable to the investigator and snonsor until the last follow-un of the AE.
Blood Samples for Anti-PF-07209960 antibodies (ADA and NAb)	X	X (if suspected ADA-relatedAE)	X (if suspected ADA-related AE)	• If unresolved AE is considered by the investigator as possibly related to or associated with ADA fonuation, the participant will be asked to rettun for drug concentration and ADA blood sampling at up to 3-month intervals (if feasible given the underlying disease), until the AE or its sequelae returns to baseline or stabilize at a level acceptable to the investigator and snonsor until the last follow-un of the AE.

	End of Treatment[1]/ Withdrawal	1-Month Follow-up[2]	Sunival Follow-up[3]	Notes F01· detailed notes refer to main schedule of assessment
		28 days after· last dose	Every 2 months after· 28 days Follow-up	
Visit Window (days)		±7 days	± 7 days	

I. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 28 days from the last dose of study intervention and prior to initiation of any new anticancer therapy. Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments). AEs/SAEs collected until a minimum of90 days after the last dose of study intervention due to possible late onset of AE/SAE.

2. **1-Month Follow-up:** At least 28 calendar days, and no more than 35 calendar days, after discontinuation of study intervention, participants will reb.un to tmdergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related AEs. AEs/SAEs collected tmtil a mininuu of 90 days after the last dose of study intervention due to possible late onset of AE/SAE.

3. **Survival Follow-up:** Subsequent to the 1-month follow-up visit, pa1ticipants survival status will be collected by telephone every 8 weeks (±7 days) to obtain information on subsequent anticancer treatment and overall survival tmtil the end of the study. If the participant is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit ma r lace the survival telephone call. Any standard of care (SOC) b.uuor response assessments including CT/MRI imaging and obtained between EOT and subsequent anti-cancer therapy w'ill also be collected.

2. INTRODUCTION

PF-07209960, a fusion of a single, potency-reduced, IL-15 mutein and a bivalent high affinity anti-PD-1 full length IgG. This antibody-cytokine fusion molecule is designed to deliver PD-1-mediated avidity-driven IL-2/15 receptor stimulation preferentially to PD-1-positive CD8+ T cells, which are enriched in tumors and can mediate anti-tumor activity, while reducing the natural preference of IL-15 for majority PD-1-negative NK cells, which may mediate toxicity. The exposure of the IL-15 mutein is extended by fusing it to an antibody, which also reduces its potency to prevent systemic activation of PD-1 negative lymphocytes.

2.1. Study Rationale

Pre-clinical data suggest the stimulatory activity of PD-1 targeted IL-15 mutein is enhanced in CD8+ TILs preferentially over peripheral lymphocytes and can lead to anti-tumor activity greater than can be achieved with anti-PD-1 and IL-15 agonist either alone or in combination, even in immunologically cold tumors that are not typically responsive to anti-PD-1 therapy. Moreover, PF-07209960 was shown to stimulate proliferation of CRC PD-1+ CD8+ TILs preferentially over other lymphocytes suggesting there may be a potential for activity even in a tumor type considered traditionally resistant to immune-based therapies.

The purpose of this FIH study is to evaluate the safety, tolerability, PK, PD and potential clinical benefits of PF-07209960 in participants with selected locally advanced or metastatic solid tumors for whom no standard therapy is available in dose escalation/finding (Part 1) and selected solid tumors in dose expansion at the RP2D (Part 2). In order to explore the activity of PF-07209960 beyond tumor types that can be treated with anti-PD-1/PD-L1, these will include tumor types resistant to prior anti-PD-1/PD-L1 therapy (NSCLC, SCCHN, RCC, UC) and tumor types for which no anti-PD-1/PD-L1 standard of care therapy is available (OvCa, MSS CRC).

2.2. Background

In order to optimally activate intra-tumoral CD8+ T cells that are enriched for the inhibitory marker PD-1, an anti-PD-1 antibody-IL-15 cytokine fusion approach was developed. This antibody-cytokine fusion molecule is designed to have decreased affinity for the IL-2/15 receptor in order to prevent systemic activation of NK cells and other PD-1-negative lymphocytes before reaching PD-1-expressing T cells. Differences in peripheral versus intratumoral activation of PD-1 expressing T cells could allow systemically administered PF-07209960 to reach levels required for tumor specific T cell proliferation and cytotoxicity in participants that may not necessarily lead to systemic toxicity.

PD-1, an immune checkpoint expressed primarily on T cells that inhibits their activation, has emerged as an attractive target for cancer therapy. PD-1 expression is enriched particularly in tumor-specific T cells (Gros et al, 2014; Topalian et al, 2015). Antibodies that block PD-1 or its ligand PD-L1 and activate these anti-tumor Tcells- are approved in multiple cancer indications as standard of care (BAVENCIO (avelumab), 2020; IMFINZI (durvalumab), 2020; KEYTRUDA (pembrolizumab), 2020; OPDIVO (nivolumab), 2020; TECENTRIQ

(atezolizumab), 2020). As the majority of patients with various tumor types treated with anti-PD-1/PD-L1 do not respond to treatment, there is a large unmet need to improve upon these therapies.

IL-15 and a related cytokine, IL-2, both bind to IL-15 receptors (IL-2Rβ/γ) to induce immune cell proliferation and survival, and enhance cytotoxic and cytokine-secreting effector functions of lymphocytes such as NK cells and CD8+, CD4+, gamma delta, and NK T cells (Waldmann, 1991; Marks-Konczalik et al, 2000; Fehniger & Caligiuri, 2001; Waldmann et al, 2001; Waldmann, 2006; Dubois et al, 2017). IL-15 and IL-2 differ in specifically binding to IL-15Rα or IL-2Rα, respectively (Waldmann, 2015). IL-15Rα and IL-2Rα are cytokine specific and stabilize binding but lack signaling activity (Giri et al, 1995; Liao et al, 2011; Ring et al, 2012). As the signal-initiating kinases Jak1 and Jak3 and transcription factor pSTAT5 are activated by the receptors for β and γ subunits, it is no surprise that the function of IL2 and IL-15 overlap (Waldmann, 2006; PROLEUKIN (aldesleukin), 2019). However, due to the differences in α subunit binding, IL-2 uniquely functions to maintain T reg cells and participates in activation induced cell death while IL-15 maintains NK cells and CD8+ memory T cells (Conlon et al, 2015; Waldmann, 2015).

IL-2 (aldesleukin) is approved for use in metastatic RCC and melanoma (PROLEUKIN (aldesleukin), 2019), but its use in the clinic at the prescribed dose required for anti-tumor activity has been limited due to short half-life and the primary toxicity of capillary leak syndrome associated with systemic immune activation, which requires intensive inpatient monitoring and management during administration and restricts treatment to only those with the best performance status. Recombinant human IL-15 has also been evaluated in a clinical trial, but dose limiting toxicities of grade 3 hypotension, thrombocytopenia and transaminase elevations stopped dose escalation without any objective responses observed (Conlon et al, 2015). Approaches to improve upon IL-2/15 efficacy, pharmacokinetics and toxicity through reduced binding to IL-2Rα are currently under evaluation in clinical trials ((Milla et al, 2019; Sharma et al, 2020) as are strategies to target IL-2 to tumors through fusion proteins ((Klein et al, 2017; Soerensen et al, 2018; Klein et al, 2019).

Combinations with anti-PD-1 antibodies and IL2/15-based molecules are currently under investigation in clinical trials and have shown promising anti-tumor activity beyond the efficacy observed with these therapies as monotherapies, and in some participants who were not expected to respond to anti-PD-1 or relapsed/refractory to it (Wrangle et al, 2018; Sharma et al, 2020). This suggests that resistance mechanisms to anti-PD-1/PD-L1 might be potentially overcome by cytokines.

The preferential stimulation and resulting uptake of IL-2/IL-15 therapeutic agents by the peripheral blood NK cells may limit ability to deliver sufficient exposure in the tumor required to activate intratumoral CD8+ T cells (Conlon et al, 2015; Miller et al, 2018). This is important as intratumoral CD8+ T cells have been associated with efficacy both in animal models and in the clinic (Eyles et al, 2010; Schiavoni et al, 2013). On the other hand, activation of NK cells was shown to mediate toxicity in animal models, and likely in humans, based on the similarities in toxicities observed in the clinic and in animals (Guo et al, 2015).

2.2.1. Nonclinical Pharmacology

In vitro, PF-07209960 exhibited similar affinity towards human and cynomolgus monkey PD-1 antigen and IL-15 c okine rece tors. PF-07209960 bound with hi h affini to human PD-1 with a CCI [redacted].

CCI [redacted]

Incubation of PF-07209960 with human PBMCs dose-dependently induced the production of CCI [redacted], was observed following incubation ofhepatocellular carcinoma patient-derived cells with PF-07209960.

In vivo, a mouse sunogate of PF-07209960 was utilized due to a lack of binding of PF-07209960 to mouse PD-1. CCI [redacted]. Dose-dependent tumor growth inhibition was observed following single SC administration of [redacted]. The highest response was observed at CCI [redacted] Comp ing SC versus IV administration of (a mouse tumor cell line with poor immunogenicity [dowmegulation of MHC-I, tumor antigens and T cell infiltration]), TGI was comparable (97% versus 104% TGI, respectively). In the B16-F10 model antitumor efficac followin amPD1-IL15ml treatment was de endent on CCI [redacted] had no impact on efficacy. In addition, administrntion of a T cell egress inhibitor, which inhibited T cell migration from lymph nodes to the tumor, did not affect amPD1-IL15mlinduced efficacy, suggesting T cell migration was not required for amPD1-IL15ml mediated anti-tumor immunity. Comparing amPD1-IL15ml to an IL-15 superagonist alone, amPD-1 mAb alone, or the combination of the IL-15 superagonist and amPD-1 in the B16-Fl 0 melanoma model, the PF-07209960 mouse smTogate was the most efficacious.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Details of the nonclinical ADME evaluation of PF-07209960 are provided in the IB. Briefly, the nonclinical PK and TK of PF-07209960 were characterized following SC and IV dosing in cynomolgus monkeys as part of a PK/PD study and in explorato1y and GLP repeat dose toxicity studies. After single IV dosing of PF-07209960, dose-de endent PK was observed consistent with TMDD. Following single SC dosing, the CCI [redacted]. In the GLP toxicity study, systemic exposure increased with increasing dose, with little to no accumulation observed after repeat SC dosing. In humans, the PK of PF-07209960 is redicted to be non-linear with clearance and volume of distribution ran ing from CCI [redacted] SC 10avai a 1 1ty 1s assume to be similar to that observed in cynomolgus monkey. The projected clinical dose of PF-07209960 that will provide PF-07209960 concentrations above the predicted CCI [redacted]

2.2.3. Nonclinical Safety

A 1-month repeat-dose GLP toxicity study in cynomolgus monkeys (CCI [redacted]) with integrated safety phannacology assessments was used to suppo1i FIH administration and ongoing clinical development of PF-07209960. In addition, the non • • • • ed in 2 non-GLP, QlW or Q2W repeat-dos dose finding toxicity studies in cynomolgus m • • ·ty studies, including activation and proliferation of CCI [redacted] levels, and enlarged spleen. Toxicities consistent with systemic inflammation and a dose-dependent cytokine-related response were observed from— . These toxicities including mo1iality, petechia and spontaneous b 1 mg/kg group, increased body temperature, reduced food consumption and activity, decreases in platelet counts and red blood cell mass parameters and increases in white blood cell counts (lymphocytes, monocytes, basophils and LUC), fibrinogen, CRP and coagulation parameters. Histopathological effects included increased cellulai·ity in lymphoid organs and minimal to marked infiltration of mononucleai·cells into vai·ious tissues, including the hea1i which was associated with mild cai·diomyocyte necrosis in two animals in the dose finding toxicity studies. Additional test article-related histopathological findings included tubular degeneration in kidneys and seminiferous tubular degeneration in the testes with severely reduced spe1m in animals administered PF-07209960 at— . The kidney-related findings conelated with increased blood urea nitrogen and creatinine concentrations. Findings in the toxicity studies ai·e consistent with the expected phannacology of PF-07209960 and were similai·between the SC and IV routes of administration.

2.2.4. Clinical Overview

This is a FIH study for PF-07209960, therefore, no clinical data is available. There ai·e cmTently no other PD-1-tai·geted IL-15 or IL-2 cytokines with available clinical data.

Anti-PD-1 therapy has become a standard of care in many different tumor types including NSCLC, RCC, SCCHN and UC, which will be evaluated in this study(KEYTRUDA (pembrolizumab), 2020; OPDIVO (nivolumab), 2020). However, treatment options following resistance to standard of care anti-PD-1 treatment remain an unmet need.

For patients with OvCa and MSS CRC no standard of care immune therapy exists. Anti-PD-1 therapy has been evaluated in OvCa with mixed results. Anti-PD-1 (ie, nivolumab, pembrolizumab, PF-06801591) antibodies have shown some single-agent, immunomodulatory and anti-tumor activity in participants with advanced OvCa (7%-22%), albeit to a much lower extent compared with other anti-PD-1 responsive tumor types (Hamanishi et al, 2015; Matulonis et al, 2018; Johnson et al, 2019; Varga et al, 2019). Intraperitoneal IL-2 administration in 31 patients with platinum resistant/refractory OvCa resulted in ORR 25% and CR rate of 17% (Vlad et al, 2010). Anti-PD-1 has been evaluated in CRC with 40% ORR in mismatch repair-deficient/microsatellite unstable disease but 0% ORR in mismatch repair-proficient/MSS disease, leading to approval for pembrolizumab only in mismatch repair-deficient disease (Le et al, 2015; KEYTRUDA (pembrolizumab), 2020). Despite the lack of activity with anti-PD-1 in MSS CRC, it is well established that PD-1 is expressed on CRC tumor infiltrating CD8+ T cells and in tumor draining lymph nodes (Wu et al, 2014), and these cells exhibit an exhausted phenotype. However, the expression of IL-15 within tumors correlates with better prognosis and CD8+ T cell expression levels (Mlecnik et al, 2014). Thus, targeting IL-15 to OvCa and CRC tumors through PD-1 may provide better activation and expansion of tumor infiltrating lymphocytes and potentially improve upon past results with immunotherapy in these tumor types.

High dose IL-2, which is approved for treatment of melanoma and RCC, is characterized by severe toxicities secondary to capillary leak syndrome, but these are not expected at lower doses (PROLEUKIN (aldesleukin), 2019). Second generation IL-2 therapies avoid binding to IL2-Rα. Bempegaldesleukin, a pegylated recombinant IL-2 is being studied in clinical trials with immune checkpoint inhibitors and has been well-tolerated. In a single-arm, Phase I dose-escalation trial of bempegaldesleukin in combination with nivolumab in advanced solid tumors, dose-limiting toxicities were reported in 2 of 17 patients during dose escalation and included the adverse events of hypotension (n=1), hyperglycemia (n=1), and metabolic acidosis (n=1). The most common treatment-related adverse events were flu-like symptoms (86.8%), rash (78.9%), fatigue (73.7%), and pruritus (52.6%). Grade 3 or 4 treatment-related adverse events were observed in 21.1% of patients and there were no treatment-related deaths (Diab et al, 2020). Response rates across tumor types (melanoma, RCC, and NSCLC) and dose cohorts was 59.5% (22 of 37) and 18.9% complete responses (7 of 37). Approaches to target a mutant IL-2 variant with reduced binding to IL2-Rα through antibodies to carcinoembryonic antigen in CRC and fibroblast activation protein expressed on cancer-associated fibroblasts have demonstrated a tolerable profile. In a biodistribution and tumor accumulation sub-study, 24 patients with advanced solid tumors were treated with cergutuzumab amunaleukin (CEA-IL2v). The most frequently observed adverse events related to treatment were infusion-related reactions (63%), pyrexia (54%), fatigue (46%), and nausea (46%). Four patients discontinued treatment due to AEs (pain, dyspnea, pulmonary hypertension and diarrhea) (van Brummelen & Huisman, 2018). RO6874281 (FAP-IL2v) was given in doses from 5 to 35 mg weekly IV to 35 patients with metastatic solid tumors

with most frequent adverse events (primarily Grade 1 or 2) of pyrexia, infusion related reactions, fatigue or asthenia, nausea, diarrhea, decreased appetite, and elevated alanine or aspartate transaminases in >30% of patients. Maximum tolerated dose was 20 mg. Objective response were observed in 3 patients with HNSCC, penile squamous cell carcinoma and checkpoint inhibitor-resistant melanoma (Soerensen et al, 2018).

Recombinant human IL-15 (rhIL-15) given intravenously daily over 12 days has been linked to severe toxicities including grade 3 fever and DLTs of grade 3 hypotension, thrombocytopenia, and ALT and AST elevations at 1 and 3 μg/kg per day resulting in an MTD of 0.3 μg/kg per day (Conlon et al, 2015). Continuous IV infusion of rhIL-15 over 10 days allowed for an increase in the MTD to 2 μg/kg/day (Conlon et al, 2019). In both studies with IV rhIL-15, no objective responses were seen. ALT-803, which is a variant of IL-15 with greater stability and potency than rhIL-15, has been tested intravenously and subcutaneously and appeared to be more tolerable as a subcutaneous monotherapy (Margolin et al, 2018). It has also been administered subcutaneously in combination with nivolumab safely (Wrangle et al, 2018).

In the FIH Phase I trial of ALT-803, 24 patients with advanced solid tumors received 0.3 to 6 μg/kg weekly IV (n=11) or 6 to 20 μg/kg weekly SC (n=13) for 4 consecutive weeks, every 6 weeks. Overall, ALT-803 was well tolerated, with IV toxicities being primarily of low grade (Grades 1–2) and consistent with cytokine administration: fatigue (55%), nausea (55%), vomiting (36%), chills (36%) and fever (27%). For the SC administration, the most common adverse event occurring in 85% of patients was injection site reaction, described as a large wheal around the prior injection site with onset at approximately 3 days, peak intensity at 5 days, and resolution by 7 days following the injection (Margolin et al, 2018). No clinical responses were observed in this study.

ALT-803 IV or SC once weekly for 4 doses (dose levels of 1, 3, 6, and 10 μg/kg) was also studied in 33 patients with hematologic malignancies who relapsed after allogeneic hematopoietic cell transplantation. There were no dose-limiting toxicities or treatment-emergent graft-versus-host disease requiring systemic therapy. Adverse events following the IV administration included constitutional symptoms (infusion-related fever and chills) temporally related to increased serum IL-6 and interferon-γ. Patients treated with the SC administration experienced injection site rashes (94%) without constitutional symptoms. All rashes resolved without systemic therapy by day 14. Hypertension was observed following both the IV and SC administration in 83% of patients but was transient and not clinically serious. None of the patients experienced severe cytokine release syndrome or capillary leak syndrome. A fatal intracranial hemorrhage (n = 1) was associated with disease-related thrombocytopenia (Romee et al, 2018). Out of 27 patients evaluable for response, 1 had complete response, 1 had partial response and 3 had stable disease.

ALT-803 in combination with nivolumab was evaluated in 21 patients with stage IIIB or IV NSCLC in a Phase 1b trial. Patients received nivolumab IV at 3 mg/kg or 240 mg flat dose every 14 days and ALT-803 SC at one of four escalating dose concentrations: 6, 10, 15, or 20 μg/kg once per week on weeks 1–5 of four 6-week cycles for 6 months. No DLTs were recorded, and the maximum tolerated dose was not reached. The most common adverse

events were injection-site reactions (90%) and flu-like symptoms (71%). The most common grade 3 adverse events, occurring in two patients each, were lymphocytopenia and fatigue. A grade 3 myocardial infarction occurred in one patient. No grade 4 or 5 adverse events were recorded (Wrangle et al, 2018). Of all patients treated, objective responses were seen in 29% (6 of 21) patients including 3 who were PD-1 relapsed and refractory and 3 who were PD-L1 negative.

As PF-07209960 is designed to preferentially target IL-15 to PD-1, which is preferentially expressed by tumor infiltrating T cells, it is expected to have more specific stimulation of tumor-specific T cells rather than a generalized stimulation of multiple non-specific lymphocytes. Although the stimulation of CD8+ TIL appears to be dose dependent, at higher doses, PF-07209960 may also stimulate more non- PD-1 expressing lymphocytes such as NK cells, thus causing more systemic toxicity. At the RP2D, it is expected that the dose will be tolerated with meaningful anti-tumor activity thus providing a positive benefit/risk ratio.

2.3. Benefit/Risk Assessment

No human studies have been conducted to date evaluating PF-07209960, as this is the FIH study. For selected disease indications where participants do not have access to curative treatment options, the benefit/risk relationship has been carefully considered in the planning of this trial based on pre-clinical, toxicology studies and safety profiles of PF-07209960.

Safety findings with PF-07209960 that were observed in the nonclinical studies include: fever, diarrhea, thrombocytopenia and immune cell infiltration of organs. During this Phase 1 study, clinical assessments will include frequent safety monitoring. The participants will be monitored during and following their first dose with a 72-hour inpatient hospitalization period. This will be implemented throughout dose escalation and length of inpatient hospitalization will be re-assessed based on safety data prior to starting dose expansion cohorts.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07209960 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07209960		
CRS	The potential risks are based on pre-clinical toxicology data for PF-07209960 and prior clinical experience with the IL-15 and anti-PD-1 drug classes.	CRS: Participants will be closely monitored with 72 hour inpatient hospitalization on first dose at least for all in dose escalation. Guidelines for the management of CRS (Appendix 9) and irAEs (Appendix 14) have been incorporated. If the IV route is evaluated, there will be a minimum 72-hour interval between the first dose administered to each of the initial 2 participants enrolled at a new dose level to allow the detection of CRS. For C1D15 PF-07209960 IV administration, participants should remain at the investigational site for observation for at least 8-hours post dose.
Thrombocytopenia including bleeding		Thrombocytopenia: Participants must have both adequate hematological functions (including platelet counts) and coagulation functions to be eligible to participate in this study. Hematological and coagulation functions will be performed throughout. Anti-coagulants must be held for low platelet counts, and anti-platelet medications must be held for at least the first week of treatment.
Abnormal liver function, abnormal kidney function		Abnormal liver and kidney functions: Participants must have adequate liver function and kidney functions to be eligible to participate in this study. Liver and kidney function tests will be performed throughout the study.

Potential Risk of Clinical Significance	Smnma1-y of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07209960		
irAEs including myocarditis		irAEs including myocarditis: Pa1ticipants must have a LVEF:?:50% by echocardiogram or MUGA to be eli◦ible. [redacted]
Male infertility due to low sperm count		Male pa1ticipants should be counseled on option of fe1tility preservation.
SC injection site reaction.	There is a risk associated with any SC injection.	ISRs will be monitored at each injection.
Study Procedures		
De novo (fresh) tumor biopsy • stinging pain from injection of local anesthetic; • pain or discomfo1t from the biopsy procedure; • disco1nfo1t from lying still for an extended time; • bleeding, swelling, scan-ing, soreness, or bruising at the biopsy site; • infection of wound contamination of cancer cells to unaffected tissue when removing biopsy needle.	There is a risk associated with any tumor biopsy.	Local anesthetic will be administered. Sterile techniques will be used. Procedures will be perfonned by qualified medical practitioners. Mandatory fresh biopsies will be limited to dose expansion (Pait 2). Participants should not be subjected to a significant risk procedure to obtain the biopsies (ie, the absolute risk of mortality or major morbidity in the pa1ticipant's clinical setting and at the institution completing the procedure should be<2%).

2.3.2. Benefit Assessment

There is a potential benefit of the pa1ticipant's tumors shrinking due to the study treatment, which could translate into an improvement in cancer-related symptoms or prolonged PFS or OS. The paiticipant would also be contributing to the development of a novel therapy in an ai·ea of unmet need. Medical evaluations and assessments on the study will allow for better monitoring of the pa1ticipants and recognition of AEs whether related to treatment or not.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measmes taken to minimize risk to paiticipants in this study, the potential risks identified in association with PF-07209960 ai·e justified by the anticipated benefits that may be afforded to participants with advanced or metastatic solid tumors.

3. OBJECTIVES AND ENDPOINTS

PART 1 DOSE ESCALATION	
Objectives	**Endpoints**
Primary:	**Primary:**
• To assess safety and tolerability at increasing dose levels of PF-07209960 in participants with select locally advanced/metastatic solid tumors in order to estimate the MTD and select the RP2D/schedule.	• First cycle DLTs. • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0; for CRS as graded by ASTCT criteria), timing, seriousness, and relationship to study therapy. • Laboratory abno1malities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.
• To chara cterize the single and multiple dose PK of PF-07209960.	• Single dose: Cmax, Tmax, AUCtau, If data permits, AUCinr, CL/F, t112; • Multiple Dose: Cma."<,Ss, Tmax,ss, AUCtau,ss, If data pe1mits, CLssfF, t112,ss,and Rae; Ctrou at selected time oints• Incidence, titers and endogenous IL-15 cross-reactivity of ADA and NAb aoainst PF-07209960·
• To evaluate the inimunogenicity of PF-07209960.	
• To evaluate prelimina1y anti-tumor activity.	ORR, DCR as assessed using the RECIST version 1.1. • Time-to-event endpoints: DOR, PFS, and TTP by RECIST version 1.1
Exploratory:	**Ex lorato1 :**
[redacted] CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

PART 1 DOSE ESCALATION	
Objectives	**Endpoints**
I CCI [redacted]	[redacted]
I [redacted]	[redacted]
I [redacted]	[redacted]

PART 2 DOSE EXPANSION	
Ob"ectives	**End oints**
Primary:	**Primai-:**
• To confinnsafety and tolerability of PF-07209960 at the RP2D in participants with selected tumor types. • To evaluate prelim.ina1y evidence of anti-tumor activity of PF-07209960 in pa1ticipants with selected tumor types.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0; for CRS as graded by ASTCT criteria), t.iniing, seriousness, and relationship to study therapy. • Laboratory abno1malities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and t.iniing. • ORR as detennined b RECIST version **1.1.**
Seconda1 :	**Seconda1 :**
• To fmther evaluate the PK of PF-07209960 at the RP2D.	• Single dose: Cmax, Tmu, AUC1au. If data pennits, AUCinf, CL/F, t½; • Multiple Dose: Cmax,ss, Tmax,ss, AUCtau,ss. If data pennits, CLssfF, t112,ss, and Rae; • Ctrough at selected time points.
• To evaluate the immunogenicity of PF-07209960.	• Incidence, titers and endogenous IL-15 cross-reactivity of ADA and NAb against PF-07209960.
• To evaluate the effect of PF-07209960 on immune cells in tumor biopsies.	• Intra-tumor T cells (such as by CDS IHC) in on-treatment versus baseline tumor biopsy samples.
• To evaluate prelim.ina1y anti-tumor activity through time to event endpoints.	• DCR, DOR, PFS, and TTP by RECIST version **1.1**
• To assess overall survival of participants treated with PF-07209960.	• Overall survival
Exploratory:	**Exploratory:**
I CCI [redacted]	[redacted]
I [redacted]	[redacted]
[redacted]	[redacted]

PART 2 DOSE EXPANSION	
Objectives	**Endpoints**
I CCI	[redacted]
I [redacted]	[redacted]
I [redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, multi-center, multiple-dose, dose escalation, safety, PK and PD study of PF-07209960 in cohoits of adult paiticipants with selected locally advanced or metastatic solid tumors (anti-PD-1/PD-Ll resistant- NSCLC, SCCHN, RCC, UC; or anti-PD-I nai:ve OvCa and MSS CRC) for whom no standard therapy is available or in the opinion of the paiticipant and their treating physician, that standai·d therapy would not be appropriate, or who have refused standai·d therapy.

The study contains 2 paits, single agent dose escalation (Pait 1) followed by a dose expansion at RP2D (Pait 2). Following the detennination of the RP2D based on sequential dose escalation coholis with single agent PF-07209960 in Pait 1, the respective expansion cohoits in Pait 2 will commence.

The Pait 2 dose expansion phase will consist of up to 5 cohoits, which will evaluate safety and anti-tumor activity of PF-07209960 at the RP2D determined in Pait 1. Opening of cohoits in Pait 2 will initially include tumor type(s) and setting(s) deemed more likely to demonstrate anti-tumor activity based on data from Pait 1. At this time, Pait 2 expansion cohoits in NSCLC, RCC and UC have been chosen due to their responsiveness to irmnunotherapy agents, and only if preliminaiy anti-tumor activity is seen with OvCa and MSS CRC in Pait 1 or in NSCLC, RCC, and UC in Pait 2, OvCa and MSS CRC expansion cohoits would be considered for emollment. TUillor indications for Pait 2 could be re-prioritized based on emerging data from Pait 1. Dose escalation and expansions combining PF-07209960 with anti-PD-LI or other agents may be added through protocol amendment based on emerging data. The overall study design is depicted in the schema (Section 1.2).

BLRM guided by EWOC principle will be used to guide dose escalation process and detennine the MTD/RP2D (Pait 1). Successive cohoits of paiticipants in Pait 1 will receive escalating doses of PF-07209960 as a SC injection eveiy 2 weeks in 28-day cycles; the SC route has the potential to reduce the Cmax which is believed to be associated with CRS and

inflammatory responses, a common AE for agents that stimulate T cells. If excessive ISR or unexpected low exposure is encountered with SC dosing, an alternative IV infusion Q2W administration may be explored. The IV dose escalation/finding would begin at a starting dose based on the available emerging clinical data (including safety/tolerability, PK, PD) from the dose escalation cohorts with SC Q2W administration. The first and second participant in each dose level must be enrolled >72 hours apart.

Approximately 14-22 participants are expected to be enrolled into Part 1 and approximately 60-90 participants will initially enroll into the first three cohorts in Part 2. Based on emerging data, with the option to further enroll approximately 40-60 participants in an additional two cohorts in Part 2. Clinical response will be continuously monitored in each expansion cohort and if no clinical benefit is observed enrollment may be stopped in the respective cohort.

All participants will complete up to 28 days of screening prior to enrollment.

Eligible participants will receive PF-07209960 as a SC injection or IV infusion on Days 1 and 15 as described in Section 4.3.1. A cycle will consist of 28 days and treatment with study intervention will continue until progression of disease, unacceptable toxicity, participant refusal, or whichever is earliest, unless the investigator and medical monitor agree to treatment beyond disease progression based on individual benefit/risk assessments or agree to discontinue treatment or the study is terminated. Participants will be allowed to stay on treatment despite initial radiological disease progression per RECIST version 1.1 (Eisenhauer et al, 2009) if all of the following criteria are met:

- The investigator feels that it is in the participant's best interest and has discussed with the medical monitor;
- There is absence of symptoms and signs indicating clinically significant progression of disease;
- There is no decline in performance status;
- There is absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression);
- It is documented that the participant consents to continued participation in the study even after being informed of all available approved therapies and their potential clinical benefit that they may be forgoing in order to continue the study intervention.

Participants experiencing toxicity including a DLT may be managed with dose modification or discontinuation from treatment. The proposed doses, schedule(s) and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data.

Assessment of late toxicities will also be completed after the DLT observation period of 28 days after C1D1 for all participants. Once a dose level has been declared safe following the post DLT observation window, participants at lower dose levels who have completed the DLT observation period may escalate to the next higher dose level, if criteria outlined in Section 4.3.2.1, Criteria for Intraparticipant Dose Escalation, have been met.

Participants continuing to experience AEs 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. Participant will continue a 1-month follow-up visit after the last dose for AE and SAE follow-up if necessary. After the 1-month follow-up, participants will be contacted by telephone every 8 weeks (±7 days) to obtain information on subsequent anticancer treatment, any AEs/SAEs experienced up to 90 days after the last dose, and survival status until the end of the study (Section 4.4). If the unresolved AE is considered by the investigator as possibly related to or associated with ADA formation, the participant will be asked to return to the clinic for ADA assessment at approximately 3 month intervals (if feasible given the underlying disease) until the AE or its sequelae return to baseline or stabilize at a level acceptable to the investigator and sponsor, until the last follow-up of the AE.

The biomarker studies will be used to help understand the in vivo mechanism of action of the agent(s) studied as well as potential mechanisms of resistance. The studies may help in the future development of PF-07209960 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.

4.2. Scientific Rationale for Study Design

In this study, all participants will receive PF-07209960. No reproductive or developmental toxicity studies have been performed. Based on the mechanism of action, the risk of teratogenicity is considered possible while there is no risk of clinically relevant genotoxicity or transmission of drug via ejaculate. Therefore, the use of a highly effective method of contraception is required (see Appendix 4, Section 10.4.2 and Section 10.4.3).

Participants may be asked to provide image-guided core needle biopsies at baseline and during treatment. When on-treatment biopsies are compared to baseline specimens, this information will enable the study of target engagement, optimal biologic dosing, and other genomic and translational markers of interest. Pre-treatment specimens to be collected from all patients as archival tissue and/or fresh tumor biopsies will enable study of baseline tumor markers that correlate with clinical outcomes.

Tumor imaging will be carried out at a rate that is within the standard frequency for Phase 1 oncology trials in solid tumors (every 8 weeks).

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

4.3.1. Starting Dose

4.3.1.1. Subcutaneous Dosing

The selection of the staiiing dose and regimen for this FIH study was based on the nonclinical toxicology and PK results, which are in accordance with the ICH S9 Guidance (ICH S9 Guideline, 2009) for the intended population. For biophaimaceuticals with immune agonist prope1iies such as PF-07209960, selection of the FIH staiiing dose using a MABEL should be considered. Saber et al., concluded that the FIH doses based on 20% to 80% phaimacology activity from the most sensitive assays had acceptable/manageable toxicities for immune activatin antibodies exce t CD3 bis ecific constructs Saber et al, 2016; Saber et al, 2017). A dosing was derived based on the a at the projected CCI [redacted] in in vitro pharmacology cell (hPBMC) assays. The projected C_{max} at this MABEL starting dose is also about CCI [redacted] in vitro pharmacology cell (hPBMC) assay. In addition, the projected C_{max} at this MABEL starting dose Is at CCI [redacted].

In addition to the MABEL approach, calculation of the staiiing dose based on 1/6 of the HNSTD from the definitive GLP toxici stud in monkeys was also considered. The dete1IDined 2W dosing schedule), which conesponds to a FIH interspecies scaling of the animal doses to an equivalent human dose based on nonnalization to body surface area) SC.

Therefore, the HNSTD derived dose for PF-07209960 would be lower com ai·ed to the MABEL derived dose. As a result, CCI [redacted] starting dose for PF-07209960.

The fixed-dose approach was chosen as it has been shown to provide similar PK vai·iability compai·ed to a body-weight adjusted dosing for monoclonal antibodies, therapeutic peptides, and proteins (Wang et al, 2009; Zhang et al, 2012). In addition, fixed dosing offers ease of prepai·ation and less chance of dosing enors.

4.3.1.2. Alternative IV Dosing

Based on the available emerging clinical data (including safety/tolerability, PK, PD) from the dose escalation coho1is with SC Q2W administi·ation, IV infusion Q2W administration may be explored in successive dose coho1is. If IV administration is inti·oduced, PF-07209960 will be administered over 1 hour (±10 minutes) without adjustment for body size at eve1y cycle as indicated in the IP manual. In case of change of the dosing regimen, DLT data accumulated during the dose escalation with the previously explored regimen may be used to fonn a prior disti·ibution for new BLRM paraineters.

If the IV route is evaluated, there will also be a minimum 72-hour interval between the first dose administered to each of the initial 2 paiiicipants (ie, paiiicipants contributing to initial DLT evaluation) emolled at a new dose level to allow the detection of possible infusion

reactions or possible CRS. The participants will be monitored during and following their first dose with at least a 72-hour inpatient hospitalization period. This will be implemented throughout dose escalation and length of inpatient hospitalization will be re-assessed based on safety data prior to starting dose expansion cohorts. Participants should remain at the investigational site for observation for at least 1-hour post dose for all treatment visits after C1D1. Additional inpatient observation for subsequent cycles beyond C1D1 may be considered based on the investigator's discretion and should be discussed with sponsor.

As described in Section 4.3.1.1, the SC starting dose is 1.1 mg SC (rounded to 1 mg). The corresponding IV CCI the projected exposure associated with the IV dose lower than the projected exposure associated with SC dosing (Table 1).

Table 1. Projected Exposure After SC and IV Dosing

Human Dose	Cmax (µg/ml)	AUC (µg*hr/mL)
CCI		

The C_{max} after IV dosing was calculated by the dose divided by the human plasma volume (2.8 L); the C_{max} and AUC in human after SC, and the AUC after IV dosing were derived from the projected human PK profile extrapolated from monkey PK.

The following scenarios would be used to determine the IV starting dose:

Scenario 1: during the course of the clinical study, if the observed exposure at the highest safe/tolerable tested SC dose is higher than that of the projected exposure of the FIH starting SC dose, the IV starting dose will be adjusted using the same principle as described above to ensure the exposure of the IV starting dose does not exceed the exposure of the highest observed clinical safe/tolerable SC dose.

Scenario 2: if the observed exposure at the highest safe/tolerable tested SC dose is lower than that of the projected exposure of the SC starting dose due to unexpectedly low bioavailability in human (bioavailability of 60% is assumed in the human PK projection), the IV starting dose will be the projected CCI to the SC starting dose described above, provided that any dose limiting safety events observed in the clinical study following SC dosing are related to local SC injection (eg, skin toxicity at the local SC injection site) but not due to systemic exposure.

4.3.2. Criteria for Dose Escalation

In part 1, a 2-parameter BLRM guided by the EWOC principle will be used to model the dose-DLT relationship of PF-07209960 and guide the dose escalation. Using DLT data at all tested dose levels and pre-specified prior distribution of model parameters, the posterior distribution for probability of having a DLT falling into three dosing intervals (underdosing, target dosing, overdosing) will be calculated for all dose levels. A dose may only be used for newly enrolled participants if the risk of overdosing, ie, toxicity higher than 0.33 at that dose is less than 25%.

Initially, dose escalation increases will be limited to no more than a half log increase from the previous dose level, which is a common approach for biologic compounds (Saber et al,

2016; Saber et al, 2017). Following the observation of a DLT in the current cohort, subsequent dose escalation increases will be limited to no more than 100%. A return to half log dose increases may be permitted at the discretion of the sponsor, in consultation with the participating investigators, if no DLT are seen at the following dose level.

The provisional dose levels to be evaluated are listed in Table 2.

Table 2. Provisional Dose Levels

Dose Level	SC	IV infusion
[redacted]	[redacted]	[redacted]

a. The IV infusion doses are tentative IV and will be based on emerging data.
b. To be determined by BLRM.

The starting dose in Part 1 will be [redacted] Q2W as described in Section 4.3.1. In a very unlikely case of observing DLT(s) at the starting dose level, lower dose level ([redacted]) might be considered for dose de-escalation (see Section 6.6.3). The dose level will be recommended by BLRM in such a way that EWOC criteria is fulfilled.

4.3.2.1. Criteria for Intraparticipant Dose Escalation

Intraparticipant dose escalation to the next dose-level will be permitted in this study for participants in dose escalation phase. Toxicity data observed after intraparticipant dose escalation will not be included in the BLRM but will be taken into account to assess the overall safety of the doses the participants was administered. Intraparticipant dose-escalation to the next dose level is permitted if all of the following conditions are met. Further intraparticipant dose escalations are permitted and will be based on the same criteria for each escalation.

1. The next dose level is deemed safe after at least the DLT evaluation period has been completed for all participants at that dose level.
2. The candidate for intraparticipant dose-escalation tolerated the current dose level well, with highest drug-related toxicity observed being Grade 2 or below.
3. Imaging for tumor response assessment can be performed within 1 week before start of treatment with the escalated dose if not done within the prior 28 days.
4. A discussion between the investigator and sponsor has been completed, and it is agreed that this will be in the participant's best interest.

4.3.3. Dose Limiting Toxicity Definition

For the purpose of dose escalation, any of the following AEs will be classified as DLTs:

- Occur in the first cycle of treatment, or within 28 days after the start of the study treatment; and
- Are at least possibly related to PF-07209960; A participant is classified as DLT evaluable if he/she experiences a DLT or if he/she otherwise in the absence of a DLT receives 2 doses of the study intervention during Cycle 1 and has received all scheduled safety assessments during the DLT window. If a participant fails to meet these criteria, he/she may be replaced. Monitoring for DLTs will occur during Part 1.

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.

Hematologic DLTs:

1. Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3) lasting >7 days;
2. Febrile neutropenia (defined as an ANC <1000/mm^3, with a single temperature of >38.3°C [101°F], or a sustained temperature of ≥38°C [100.4°F] for more than one hour);
3. Neutropenic infection (defined as an ANC <1000/mm^3 with Grade ≥3 infection);
4. Grade 3 thrombocytopenia (platelet count <50,000 mm^3) with any bleeding;
5. Grade 4 thrombocytopenia (platelet count <25,000/mm^3);
6. Grade 4 anemia (life-threatening consequences; urgent intervention indicated).

Non-Hematologic DLTs:

- Any Grade ≥3 non-hematologic treatment related AE is a DLT with the following exceptions:

  1. Grade 3 nausea, vomiting, diarrhea, or fatigue that can be controlled with or without medical therapy to Grade ≤2 within 72 hours;
  2. Grade ≥3 laboratory abnormalities without a clinical correlate and that do not require medical intervention, or are corrected to Grade ≤2 with supplementation/appropriate management within 72 hours;

Immune-related AE (irAE) that meet the following criteria:

1. Grade 4 irAE regardless of duration (for lab abnormalities without clinical correlate and do not require medical intervention please refer to criteria above);

2. Grade ≥3 colitis regardless of duration (diagnosis of colitis must be supported by diagnostic testing);

3. Grade ≥3 non-infectious pneumonitis regardless of duration;

4. Grade 2 non-infectious pneumonitis that does not resolve to ≤ Grade 1 within 72 hours of the initiation of maximal supportive care;

5. Any grade immune-mediated myocarditis;

6. Grade 3 irAE, excluding colitis and pneumonitis, that does not improve to ≤ Grade 2 within 72 hours after onset of the AE event despite maximal supportive care including systemic corticosteroids or downgrade to ≤ Grade 1 or baseline within 14 days;

7. Grade ≥3 immune-related endocrinopathies (eg, thyroid disorders, diabetes mellitus, adrenal insufficiency) that require treatment discontinuation or are not successfully managed with hormonal replacement therapy.

Other cases that meet the following DLT criteria:

1. Hy's Law cases defined as: ALT or AST >3 x ULN if normal at baseline OR >3 x ULN and doubling the baseline (if >ULN at baseline) associated with total bilirubin >2 x ULN and an alkaline phosphatase <2 x ULN.

2. A treatment related AE inducing a delay by ≥4 weeks in receiving the next scheduled cycle due to persisting toxicities attributable to PF-07209960 will be considered a DLT.

3. 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. While the rules for adjudicating DLTs are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT following assessment, based on the emerging safety profile.

4.3.4. 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).

4.3.5. Maximum Feasible Dose Definitions

Not applicable.

4.3.6. Recommended Phase 2 Dose Definition

The recommended dose for further study (which is normally the same as the RP2D) is the dose chosen for further investigation based on Phase 1 dose escalation study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of participants, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D lower than the MTD. During escalation and prior to an MTD being reached, the sponsor may choose to advance a lower dose into expansion. This decision must be made based on safety, PK, PD, and/or efficacy. Furthermore, after reaching the MTD, up to approximately 6-12 participants may be enrolled in the lower doses for the purpose of refining the RP2D based on emerging safety data.

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 MTD/RP2D for Part 2 expansion cohort.

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 last visit.

The end of the study will be the date of the last visit of the last participant or 2 years after the last participant receives their first dose (whichever occurs first) at which point all study participants will need to complete any protocol-specified post-treatment safety monitoring activities before final closure of the study. The study may also be terminated at any time at the discretion of the sponsor.

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.

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data.

5.1. Inclusion Criteria

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

1. Participants age ≥18 years.
   - Refer to Appendix 4 for contraceptive/reproductive criteria for male (Section 10.4.1) and female Section 10.4.2 participants.
2. Histological or cytological diagnosis of locally advanced/metastatic solid tumor (NSCLC, SCCHN, RCC, UC, OvCa, or MSS CRC).
   a. At least 1 prior line of therapy for recurrent or metastatic disease, including either standards of care or investigational therapies. Participants must have progressed or relapsed after or be intolerant to standard therapy approved for the specific tumor type. Exception: participants who actively decline available standard of care therapies are eligible upon documentation of their refusal.
   b. Participants with NSCLC, SCCHN, RCC, or UC must have received prior anti-PD-1/PD-L1 either as monotherapy or in a combination regimen and had experienced radiographic progression.
   c. Participants with NSCLC must not have known ALK, ROS1, MET exon 14 skipping, RET rearrangement or EGFR mutation.
   d. Participants who had received prior anti-PD-1 must be ≥90 days from their last anti-PD-1 dose. Participants who received prior anti-PD-L1 are not subject to this restriction.
   e. Participants with OvCa or MSS CRC must not have received prior anti-PD-1/PD-L1 therapy.
   f. Demonstrated radiographic progression on most recent tumor assessment imaging.
   g. For Part 2, in addition:
      a) Participants with NSCLC must have received either ≥2 prior lines of therapy including a ≥1 prior regimen containing chemotherapy and ≥1 prior regimen containing anti-PD-1/PD-L1 or a prior regimen of anti-PD-1/PD-L1 in combination with chemotherapy (eg, atezolizumab with chemotherapy). In addition, NSCLC with a BRAF V600E mutation must have also received BRAF inhibitor with or without MEK inhibitor
      b) Participants with RCC must have received either ≥2 prior lines of therapy including ≥1 prior regimen containing anti-PD-1/PD-L1 and ≥1 prior regimen containing a small molecule kinase inhibitor or a prior regimen of anti-PD-1/PD-L1 in combination with a small molecule kinase inhibitor (eg, pembrolizumab or avelumab with axitinib).
      c) Participants with UC must have received ≥2 prior lines of therapy including platinum-containing chemotherapy and anti-PD-1/PD-L1, or a single regimen

of platinum-containing chemotherapy followed by anti-PD-1/PD-L1 maintenance therapy.

d) Participants with MSS CRC must have received ≥2 prior lines of therapy including treatment regimens containing combinations of pyrimidine analog, oxaliplatin, irinotecan, anti-EGFR (RAS wild type), encorafenib (if BRAF V600E-positive) and anti-HER2 (if HER2-amplified and RAS and BRAF wild type).

e) Participants with OvCa must have received ≥2 prior lines of therapy including at least 1 regimen with platinum-based chemotherapy and progressed on last two consecutive regimens without evidence of clinical benefit.

3. Participants entering the study in ≥1 measurable lesion (at least 10 mm in the longest diameter by CT scan/MRI for non-lymph nodes and at least 15 mm in the short axis for lymph nodes) as defined by RECIST version 1.1 that has not been previously irradiated.
4. Must have tumor tissue available for submission to the sponsor:
   a. Participants enrolled in Part 1 and Part 2 should consent to undergo biopsy during screening (pre-treatment) or be able to provide archival FFPE material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy taken ≤1 year prior to study start. If the archival sample is older than 1 year and a biopsy during screening cannot be performed, the investigator must contact the sponsor to discuss eligibility prior to enrollment.
   b. Participants enrolled in Part 2 dose expansion must have a tumor amenable to biopsy and consent to planned mandatory pre- and on-treatment biopsy procedures until the sponsor deems that an adequate number of participants (10-15 paired fresh biopsies per cohort) have been successfully biopsied, at which point participants will only be required to submit pre-treatment biopsies (either archival tissue or de novo biopsy as above). Special considerations will be made for participants with poorly accessible tumors or deemed medically unsafe as determined by the investigator after discussion and agreement by the sponsor.
5. ECOG PS 0-2 for Part 1, 0-1 for Part 2.
6. Adequate hematologic function, including:
   a. ANC ≥1,500/mm^3 or ≥1.5 x 10^9/L;
   b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
   c. Hemoglobin ≥9 g/dL. Limited transfusions to reach this value are allowed, after discussion with the sponsor's medical monitor. There should not be chronic need for transfusions (>1 per month) in the recent (approximately 3 months) past.
7. Adequate renal function, including:
   d. Estimated creatinine clearance ≥50 mL/min as calculated by Cockcroft-Gault method. In equivocal cases, a 24-hour urine collection test can be used to estimate the creatinine clearance more accurately.

8. Adequate liver function, including:
    a. Total serum bilirubin ≤1.5 x ULN;
    b. AST and ALT ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor;
    c. Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).
9. Adequate coagulation function, including:
    a. INR or aPTT ≤1.5 x ULN.
10. LVEF ≥50% by echocardiogram or MUGA.
11. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment.
12. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
13. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

1. Known symptomatic brain or leptomeningeal metastases requiring steroids. Participants with previously diagnosed brain or leptomeningeal metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to planned first dose, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable for 3 months (requires MRI confirmation).
2. 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 4 weeks prior to planned first dose.
4. Radiation therapy within 4 weeks prior to planned first dose.
5. Systemic anti-cancer therapy within 4 weeks prior to planned first dose (6 weeks for mitomycin C or nitrosoureas). If the last immediate anti-cancer treatment contained an antibody-based agent(s) (approved or investigational), then an interval of 28 days or 5 half-life (whichever is shorter) of the agent(s) prior to receiving the study intervention treatment is required. Participants who received anti-PD-1 therapy (but not anti-PD-L1) require an interval of 90 days prior to planned first dose.
6. Active and clinically significant bacterial, fungal, or viral infection, Hepatitis B or Hepatitis C infection at screening (positive HBsAg or positive HCV RNA if anti-HCV antibody test positive), known HIV or AIDS-related illness. HIV seropositive participants, who are in good health and at low-risk for AIDS-related

outcomes, may qualify for inclusion in the study after discussion with the sponsor, but AIDS is exclusionary.

The following criteria for immune status and HIV ongoing therapy must be met for a HIV seropositive participant to be eligible for the study:

a) Immune status criteria:

   a. CD4+ T-cell counts ≥350 cells/μL at the study start;

   b. No history of AIDS-defining opportunistic infections;

   c. In general, patients should be eligible if they have not had an opportunistic infection within the past 12 months.

b) Ongoing HIV therapy criteria:

   d. Must be receiving recommended concurrent ART treatment according to the guidelines (AIDSinfo, 2020);

   e. Began ART treatment >4 weeks prior to study start (to ensure ART is tolerated and toxicities are not confused with study drug toxicities);

   f. HIV viral load <400 copies/mL for >4 weeks prior to study start (to ensure ART is tolerated and HIV controlled).

7. Active COVID-19/SARS-CoV2: Refer to Appendix 10 for further information.
8. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >470 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of active myocardial ischemia, second- or third-degree 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 QTc 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 participant's 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 abnormalities (e.g., bifascicular block [defined as right bundle branch and let anterior or posterior hemiblock], 3rd degree AV block), unstable angina, coronary/peripheral artery bypass graft, symptomatic 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 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. Abnormal cardiac valve morphology (≥grade 2) documented by echocardiogram (participants with grade 1 abnormalities [ie, mild regurgitation/stenosis] can be enrolled on study). Participants with valvular thickening should not be enrolled into the study.
11. Anticoagulation with vitamin K antagonists is not allowed. Anticoagulation with low molecular weight heparin and Factor Xa inhibitors or use of antiplatelet therapy is allowed but must be held per institutional requirements for biopsies and whenever platelet count is <50,000/mm^3. If participants are on antiplatelet therapy, they must be able to hold antiplatelet therapy for first week of study treatment without significantly increased risk of cardiovascular events.
12. AEs from prior therapy which have not recovered to Grade ≤1 or baseline.
13. Hypertension Grade 3 or higher (eg, ≥160/100 mmHg) that cannot be controlled by medications despite optimal medical therapy.
14. Participation in other studies involving investigational drug(s) within 4 weeks prior to first dose.
15. Known or suspected hypersensitivity to any PF-07209960 components, or to mAbs or other therapeutic proteins such as fresh frozen plasma, human serum albumin, cytokines, or interleukins.
16. History of clinically significant Grade ≥3 immune mediated AE that was considered related to prior immune modulatory therapy (eg, immune checkpoint inhibitors, co stimulatory agents, etc.) and required immunosuppressive therapy. Patients with immune-mediated endocrinopathies controlled with hormonal replacement therapy (eg, thyroid disorders, diabetes, adrenal insufficiency) are eligible.
17. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
18. Organ transplant requiring immunosuppressive treatment or prior allogeneic bone marrow or hematopoietic stem cell transplant.
19. Current use of immunosuppressive medication at the time of randomization, EXCEPT for the following: a) intranasal, inhaled, topical steroids, or local steroid injection (eg, intra-articular injection); b) Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; c) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
20. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis or melena in the past 6 months prior to first dose.
21. History of interstitial lung disease or pneumonitis.

22. Participants with the presence of any open, active wound.
23. Pregnancy or breastfeeding.
24. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
25. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

Not applicable, no restrictions are required.

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 schedule of activities (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 enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice after the initial screen fail.

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-07209960.

6.1. Study Intervention(s) Administered

Intervention Name	**PF-07209960**
ARM Name (group of participants receiving a specific treatment (or no treatment)	All
Type	Biologic
Dose Formulation	Lyophilized powder for solution for injection or infusion
Unit Dose Strength(s)	10 mg/vial
Dosage Level(s)	Dose amount and frequency – reference the study scheme/figure or text below as appropriate.
Route of Administration	SC (or IV if necessary)
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor. Specifics on ordering can be found in the IP manual.
Packaging and Labeling	Study intervention will be provided in single vials packaged in individual cartons. Each vial and carton will be labeled as required per country requirement. IP will be provided as open labeled material.
Current Name	PF-07209960, Targeted IL-15

PF-07209960 10 mg/vial is presented as a sterile lyophilized powder for solution for SC or IV administration. Each vial contains 10 mg of PF-07209960 as a white cake essentially free from visible particulates in a 6 mL type I clear glass vial, sealed with a 13 mm lyo stopper and 13 mm aluminum flip-off seal.

6.1.1. Administration

PF-07209960 will be administered once every 2 weeks as a flat dose SC injection or IV infusion over 1 hour (±10 minutes).

Each participant may receive PF-07209960 until disease progression, unacceptable toxicity, withdrawal of consent, or study termination. Treatment beyond disease progression may be discussed with sponsor if the investigator assesses that it is the participant's best interest to continue with treatment and would not derive as much benefit from alternative therapy and has met the criteria for treatment beyond progression as outlined in Section 4 .

Subcutaneous administration

Qualified and trained investigator site personnel will administer PF-07209960 to participants by SC injection. Ideally, each injection may be up to 2 mLs in volume. However, if the maximum volume allowed per institution's policy is lower, the number of injections may

increase to accommodate this difference in volume to ensure the correct final dose is delivered.

Study drug should be administered to the abdomen (with preference given to the lower quadrants when possible). Refer to Appendix 12, for details on administration of multiple injections to the abdomen. Study staff should refer to the IP Manual for specific instructions on the handling and preparation of study drug.

Cycle duration: A cycle is defined as 28 days, regardless of missed doses or dose delays.

Intravenous administration

Based on the available emerging clinical data (including safety/tolerability, PK, PD) from the dose escalation cohorts with SC Q2W administration, IV infusion Q2W administration may be explored in successive dose cohorts. If IV administration is introduced, PF-07209960 will be administered over 1 hour (±10 minutes) time period without adjustment for body size at every cycle as indicated in the IP manual.

6.2. Preparation/Handling/Storage/Accountability

1. 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.
2. 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 temperatures since previously documented for all site storage locations upon return to business.
3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in 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. 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.
4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
5. Study interventions should be stored in their original containers.
6. See the IP manual for storage conditions of the study intervention once reconstituted.

7. 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), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.
8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention 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. A second staff member will verify the dispensing. Vials are single-use.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of biologic agents.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Part 1: Dose Escalation

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/e-mail 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 will receive study intervention until the investigator or designee has received the following information in writing from the sponsor:

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

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participant.

Part 2: Dose Expansion

If IRT will be utilized for Dose Expansion, allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). If IRT will not be used, the Dose Expansion will follow the dose level allocation as indicated in the above Part 1, Dose Escalation section. 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 users' ID and password, protocol number, specific protocol entrance criteria indicated in the system and the participant number. The site personnel will then be provided with, at a minimum, a treatment assignment, randomization number, and DU or container number when study intervention 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.

Study intervention will be dispensed at the study visits as summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

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

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the 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 site's 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.

6.5. 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 received by participants from screening until the end of treatment visit will be recorded on the CRF.

PF-07209960 has been demonstrated to transiently increase cytokine levels (eg, IL-6) in vivo in monkeys (also demonstrated via in vitro assays). Cytokines have been shown to result in modulation of the expression of some cytochrome P450 enzymes. Therefore, treatment with PF-07209960 may potentially result in modest increase in 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.

6.5.1. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. Additionally, the concurrent use of vitamins beyond a daily multivitamin or supplementation for a documented vitamin deficiency or herbal supplements is not permitted.

6.5.2. Radiation Therapy

Palliative radiotherapy to a limited field but not to a target lesion(s) is allowed after consultation with sponsor's Medical Monitor at any time during study participation, including during screening, unless clearly indicative of disease progression. In view of the current lack of data about the interaction of PF-07209960 with radiotherapy, PF-07209960 treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment after 7 days. If the effects of palliative radiotherapy on overall anti-tumor efficacy cannot be clearly distinguished from those of PF-07209960 following radiotherapy, response assessments after radiotherapy should be considered as non-evaluable.

6.5.3. 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 ASCO guidelines (ASCO, 2020).

6.5.4. Hematopoietic Growth Factors

During the 14 days prior to Day 1, granulocyte colony stimulating factors are not permitted to qualify a participant with low WBC counts.

Primary prophylactic use of colony stimulating factors is not permitted during the first 28 days of Cycle 1 Part 1, but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines (ASCO, 2020).

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

6.5.5. Anticoagulation Therapy

Anticoagulation therapy with vitamin K antagonists is prohibited throughout the study and for at least 28 days post the last dose of study treatment. Anticoagulation with low molecular weight heparin and Factor Xa inhibitors or use of antiplatelet therapy is allowed but must be held per institutional requirements for biopsies and whenever platelet count is <50,000/mm^3 or when active bleeding occurs and resume only when platelet count is >50,000/mm^3 and there is no bleeding.

Antiplatelet therapy must be held during the first week of PF-07209960 and may resume if it is observed that the platelet count does not drop below 50,000/mm^3 the first week after receiving PF-07209960, and the platelet count has reached a nadir and shown a subsequent increase. If platelet count does drop below 50,000/mm^3 the first week after receiving PF-07209960, then antiplatelet agents should be held during the first week following every administration of PF-07209960. All antiplatelet therapy should be held per institutional requirements for biopsies and stopped when platelet count is <50,000/mm^3 or when active bleeding occurs and resume only when platelet count is >50,000/mm^3 and there is no bleeding. Platelet transfusions should be considered for active bleeding and platelet count <50,000/mm^3.

6.5.6. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis beyond the first dose is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator assuming there is no known or expected drug-drug interaction and assuming the drug is not listed in the Concomitant Therapy section. If irAE of diarrhea or colitis is suspected, please refer to Appendix 14 for guidance on the management of irAEs.

6.5.7. 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 the Concomitant Therapy section.

6.5.8. Corticosteroids

Chronic systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. Acute emergency administration (eg, for prophylaxis and/or management of CRS or other toxicities), topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

6.5.9. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-07209960 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-07209960 is recommended at least 7 days prior to surgery. Post-operatively, the decision to reinitiate PF-07209960 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6.5.10. Transfusion Support

Primary prophylactic use of transfusion support for anemia is allowed to treat anemia, as indicated by the current American Society of Clinical Oncology and American Association of Blood Banks guidelines (Carson et al, 2016). Primary prophylactic use of transfusion support for thrombocytopenia is allowed during screening if the transfusion is completed prior to planned study treatment start. Primary prophylactic use of transfusion support for thrombocytopenia is allowed to treat thrombocytopenia, as indicated by the current American Society of Clinical Oncology (Schiffer et al, 2018).

6.5.11. Management of Potential Study Intervention-Related Toxicities

6.5.11.1. Cytokine Release Syndrome

Symptoms associated with 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. If CRS is suspected, cytokines will be analyzed at central laboratories to determine if cytokine elevation consistent with CRS is observed (see Section 8.2.5). The severity of CRS will be assessed according to the modified grading described by ASTCT (Lee et al, 2019) and captured on the AE CRF and on the CRS CRF as described in Appendix 9.

CRS should be managed according to the CRS Mitigation and Management guidance in Appendix 9 or per local institutional guidelines.

6.5.11.2. Injection Site Reactions:

ISR may be immediate, although it usually appears within 24-48 hours after injection. ISR, by definition, includes the following: erythema, pruritus, pain, inflammation, rash, induration, itching and edema at the injection site. To evaluate ISRs, site tolerability assessments will be performed per SoA.

Topical corticosteroids and topical or systemic antihistamines may be applied to treat any rash or pruritis at the injection site.

6.5.11.3. 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 injection and may include symptoms such as rash, urticaria, polyarthritis, myalgia, polysynovitis, fever, and, if severe, glomerulonephritis.

All participants should be closely observed while receiving PF-07209960 injection and monitoring 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 intervention may be stopped, and the participant will be followed until the end of the study.

6.5.11.4. Infusion Related Reactions

IRRs are reactions that occur during or following an infusion of the study intervention. IRRs may present with different symptoms and are most commonly characterized by fever and chills, and less commonly hypotension or dyspnea. IRRs can typically be distinguished from CRS by their timing. IRRs usually occur during administration of the study intervention while CRS is delayed until several hours or days after administration of the study intervention. In the event of infusion related reactions, investigators should institute treatment measures according to best medical and nursing practice.

Premedication is not required but may be implemented at the investigator's discretion. If a participant experiences an IRR, premedication is recommended prior to subsequent infusions (eg, diphenhydramine and acetaminophen) approximately 0.5 to 2 hours before PF-07209960 administration. This regimen may be modified based on local standards; however, corticosteroids are not recommended. The pretreatment medications will not be supplied by Pfizer.

Detailed guidance on treatment, dose interruptions and potential retreatment of IRRs is provided in Appendix 15.

6.5.11.5. Immune-Related Adverse Events

irAEs are toxicities resulting from the non-specific activation of the immune system that can affect almost any organ system. Several irAEs have been described in association with the use of ICIs therapies including anti-PD-1, anti-PD-L1 and anti-CTLA-4. The most common irAEs described with ICIs are those involving the cutaneous, endocrine, gastrointestinal, pulmonary, hepatic and musculoskeletal systems. In addition, less frequent irAEs include those involving the cardiovascular, renal, pancreatic, neurological, ophthalmological, and hematological systems. In rare cases, irAEs may be life-threatening or lead to death. Treatment of irAEs is mainly dependent on severity. In general, Grade 1 or 2 irAEs are treated symptomatically with persistent Grade 2, Grade 3 or Grade 4 irAEs managed with moderate to high dose corticosteroids and/or hormonal therapy for immune-related

Guidelines for the treatment of irAEs are provided in Appendix 14.

6.6. Dose Modification

Every effort should be made to administer study intervention on the planned dose and schedule. In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom.

In addition to dose modifications, investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Toxicities potentially related to PF-07209960 should be managed according to the dose modifications described in Table 4.

Selected toxicities that do not resolve or worsen following supportive care and dose modifications and with a clinical presentation consistent with a potential irAE without a clear alternative explanation, may require treatment with corticosteroids or other immunosuppressants and should be managed according to the management of irAEs as described in Appendix 14.

CRS should be managed according to the CRS Mitigation and Management guidance as described in Appendix 9.

6.6.1. Dosing Interruptions

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Doses may be held up to 4 weeks until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the participant missing one or more of the subsequent planned doses.

Criteria required before treatment can resume are described in Dose Delays (Section 6.6.2), ISR Section 8.2.10), IRRs (Appendix 15) or in the specific toxicity management guidelines for CRS (Appendix 9), and irAEs (Appendix 14).

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 6.6.3, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

6.6.2. Dose Delays

Re-treatment following treatment interruption for treatment-related toxicity may not occur until all of the following parameters have been met:

- ANC ≥1,000/mm^3.
- Platelet count ≥50,000/mm^3
- Nonhematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator's discretion, Grade ≤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-07209960 may be resumed. Refer to the Section 6.6.3 for AEs requiring dose reduction at the time of treatment resumption.

If participants require discontinuation of PF-07209960 for more than 4 weeks from last dose (2 missed dose) 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.

6.6.3. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-07209960 dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, participants experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level based on investigator's medical judgment once recovery to Grade ≤1 or baseline is achieved.

Dose reduction of PF-07209960 by 1 dose level (with maximum reduction to dose level -1, 0.3 mg SC, 0.06 mg IV) (Table 2) will be allowed depending on the type and severity of toxicity encountered. Participants requiring more than 1 dose reduction will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose 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 reduced dose level, unless further dose reduction is required. Intraparticipant dose re-escalation may be allowed after discussion between the investigator and sponsor. Participant must not experience a Grade 2 or higher adverse event to be eligible for intraparticipant dose re-escalation.

Table 3. Available Dose Reduction Levels From Starting Dose

Dose Level[a]	SC	IV[b]
Starting	CCI	

a. PF-07209960 dose de-escalation below -1 dose level is not allowed.
b. IV infusion over 1 hour (±10 minutes)

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.

For management of immune-related adverse events, please refer to Appendix 14. For all other toxicities, recommended dose reductions for study intervention are described in Table 4.

Table 4. Treatment Dose Modifications for Study Intervention-Related Toxicity

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 dose by 1 level at the discretion of the investigator*.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator*.
Hematologic (except lymphopenia)	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**.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment**.

* Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification.
** Cycle will not be extended to cover for the missing doses.

6.7. Intervention After the End of the Study

No intervention will be provided per protocol to study participants beyond the end of the study. Availability of PF-07209960 following closure of the study through expanded access/compassionate/continued use mechanism if the investigator and participant desire to continue treatment would be at the discretion of the sponsor and subject to local conditions and regulations.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following:

- 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.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for long-term safety follow-up and survival. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include:

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

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.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) 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.

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.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention 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.

The following actions must be taken if a participant fails to return to the clinic for/attend 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.

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.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether 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.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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. Efficacy Assessments

8.1.1. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging will include contrast enhanced chest, abdomen and pelvis CT or for participants with known CT contrast allergy, a non-contrast CT of the chest with contrast enhanced abdominal and pelvic MRI; 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. CT/MRI imaging of other areas of tumor involvement not listed above should also be reported. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. It is important to use the same technique, especially if using non-contrast computed tomography of the chest and MRI of abdomen and pelvis for those with contrast allergy.

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 6 weeks). Assessment of response will be made using RECIST version 1.1 (Appendix 11). Tumor response assessment will be performed locally.

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

For Part 2 Dose Expansion, radiologic images will be submitted to an imaging laboratory for the purpose of holding for possible future central review if deemed necessary. In the event that central review is conducted, it would not be a complete medical review of participant and no incidental findings will be shared with the PI, site staff, or participant. All safety reviews will be the sole responsibility of the site staff.

Detailed information regarding the submission of images to the core laboratory is found in the Imaging Manual.

8.2. 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 issues.

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

8.2.1. Physical Examinations

Participants will have a physical examination to include weight, 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 eyes, ears, nose, throat, heart, lungs, abdomen, skin, and neurologic system.

A brief physical examination will include, at a minimum, assessments of the heart, lungs, and abdomen including skin at injection sites.

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

8.2.2. Vital Signs

Temperature (oral preferred), heart rate, and BP will be assessed.

Blood pressure and heart rate measurements will be assessed in the sitting or semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant.

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 heart rate and 3 blood pressure measurements (during screening). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected 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 QTcF 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 (see the schedule of activities), 3 consecutive ECGs will be performed at approximately 1-4 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. Consultation with a cardiologist will be performed if clinically warranted or if the QTcF value is >500 msec for any scheduled ECG.

If the QTcF interval reverts to less than the threshold criteria listed above, and in the judgment of the investigator(s) and sponsor, it is determined that the cause(s) of QTcF prolongation is something other than study intervention, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above the threshold values, the study intervention will be held until the QTcF interval decreases to below the threshold values. Participants will then restart the study intervention at the next lowest dose level. If the QTcF interval has still not decreased to 480 msec after 2 weeks, or if at any time a participant has a QTcF interval >515 msec attributed to study treatment or becomes symptomatic due to QTcF changes, the participant will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

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.

8.2.4. Echocardiogram or MUGA

Participants must be in supine position in a rested and calm state for at least 5 minutes before LVEF assessment is conducted. If the participant is unable to be in the supine position, the participant should be in the most recumbent position possible.

The investigator or designated site physician will review all echocardiograms. Once signed, the original echocardiogram will be retained with the participant's source documents. At the request of the sponsor, a copy of the original echocardiogram will be made available to Pfizer. Standard echocardiogram machines should be used for all study-related echocardiogram requirements.

Echocardiograms or MUGAs (preferred) will be measured at time points specified in the SoA or if clinically warranted. Imaging method must be consistent throughout the study for individual participants.

8.2.5. 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. All protocol required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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 28 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.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Safety Imaging Assessments

Not applicable. Refer to Section 8.1.1 for efficacy imaging.

8.2.7. 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 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 study intervention. 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.

8.2.8. Fertility Perservation

Male particpants planning to have children in the future should consider banking their sperm prior to starting the study. These discussions must take place prior to enrollment as sperm donations during or after the study are not recommended. Highly effective contraceptive precautions should be used to prevent pregnancy when either partner is receiving PF-07209960 as described in Appendix 4.

8.2.9. Inpatient Monitoring

Participants receiving PF-07209960 will be monitored (per local standard of practice) during and following their first dose with a 72-hour inpatient hospitalization period. This will be implemented throughout dose escalation, and length of inpatient hospitalization will be re-assessed based on safety data prior to starting dose expansion cohorts. Participants should remain at the investigational site for observation for at least 1-hour post dose for all treatment visits after C1D1. For C1D15 PF-07209960 IV administration, participants should remain at the investigational site for observation for at least 8-hours post dose. Participants may not be released until the investigator has confirmed the participant has not exhibited signs and symptoms of a cytokine reaction. Actual observation times for second and subsequent doses may be lengthened depending on clinical experience during hospitalization for previous doses. Participants may be released only after the investigator has confirmed the participant has sufficiently recovered from any CRS. Hospitalization period may be extended if the participant experiences abnormal laboratory findings or ongoing AEs that require further hospitalization. Participants should complete the required study specific laboratory assessments as detailed in the SoA and monitored per local standard practice for inpatient monitoring.

Record AEs (AEs consist of nonserious AEs and SAEs) as described in Appendix 3.

Refer to Appendix 9 for CRS Mitigation and Management guidance.

8.2.10. Local Site Injection Tolerability Assessment (SC Only)

Assessments of the injection sites in the abdominal fat fold to monitor local tolerability to PF-07209960 SC injections will be performed at least 1 hour following treatment administration in Cycle 1, and performed daily during hospitalization for first dose or until no skin changes are seen at injection site, whichever comes first as per the SoA. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted. Refer to Appendix 12 for more details.

Site tolerability assessments should continue at regularly scheduled visits if injection site pain or ISR characteristics continue to persist after the first cycle. The assessments should continue 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 study drug dosing. The diameter of the affected area will be measured, and the condition of the injection site will be recorded on the SC Injection Site Assessment CRF. Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported. 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. Deidentified photographs of the affected area may be requested by the sponsor to further understand the extent of skin toxicity. 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. The dermatology consultation is expected to take place at the dermatologist's practice location, or may occur within the same institution where this study is conducted.

Please refer to the laboratory manual.

Record AEs as described in Appendix 3.

8.2.11. One-Month Follow-up Visit

For follow-up procedures see SoA and Section 8.

At least 28 calendar days and no more than 35 calendar days, after discontinuation of study intervention, participants will return to undergo the assessments outlined in the SoA as well as a review of concomitant treatments, vital signs, and assessment for resolution of any treatment related AEs. Participants continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 28 days until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

In the event a participant is unable to return to the clinic for the follow-up visit, telephone contact with the participant to assess AEs and concomitant medications and treatment is expected. If laboratory assessments are needed to follow-up unresolved AEs, retrieval of assessments performed at an institution local to the participant is acceptable.

8.2.12. Survival Follow-up

Subsequent to the 1-month follow-up visit, participants survival status will be collected by telephone every 8 weeks (±7 days) to obtain information on subsequent anti-cancer treatment and overall survival until the end of the study. If the participant is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call. Any SOC tumor response assessments including CT/MRI imaging CCI [redacted] obtained between EOT and subsequent anti-cancer therapy will also be collected.

8.3. 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 the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner. In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. 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 90 calendar days, except as indicated below, after the last administration of the study intervention.

During the long-term follow-up period in this study for survival, only SAEs will be actively elicited and collected after completion of the active collection period described above. The SAEs identified during long-term follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study intervention.

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.

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.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

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, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness 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. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

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. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. 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.

8.3.3. 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.

8.3.4. 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 SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. 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.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by accidental injection or contact of study intervention with mucous membranes or open wounds.
    - A male family member or healthcare provider who has been exposed to the study intervention by accidental injection or contact of study intervention with mucous membranes or open wounds then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until 4 months after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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 preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. 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), 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 including 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.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so 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.

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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. 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.

8.3.6. Cardiovascular and Death Events

Not Applicable

8.3.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

CRS, thrombocytopenia (including bleeding), abnormal liver function, abnormal renal function, irAEs (including myocarditis) and ISRs will be monitored as AEs of special interest.

CRS and associated symptoms should be recorded within the CRF for CRS, and the overall CRS term should be recorded as an AE or SAE on the CRF as well using ASTCT grading scale. Any CRS-associated symptoms do not need to be duplicated within the AE or SAE CRFs.

Information regarding ISRs should be recorded within the injection site assessment CRF. If any ISRs are considered AEs or SAEs, they should also be graded by CTCAE v5.0 and reported within the AE CRF.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

Lack of efficacy (see Appendix 3, Section 10.3.1) is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention 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 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 the 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.

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the Sponsor that the study intervention under question is acceptable for use.

8.4. Treatment of Overdose

For this study, any dose of PF-07209960 greater than 50% of the assigned dose level for the participant 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.

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 PF-07209960 (whichever is longer).

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

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

5. Obtain a blood sample for PK analysis within 2 weeks from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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.

8.5. Pharmacokinetics

8.5.1. Analysis of PF-07209960

Blood samples will be collected for measurement of serum concentrations of PF-07209960 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.

For IV administration only, the EOI (the infusion duration includes the flush duration if implemented) samples should be collected from the contralateral arm of PF-07209960 infusion.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the sampling time window specified in the SoA will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

Samples collected for analyses of PF-07209960 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for evaluation of the bioanalytical method, or for other internal exploratory purposes. Any such data generated will not be included in the CSR.

Genetic analyses will not be performed on these 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-07209960 will be analyzed using a validated analytical method in compliance with applicable 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.

8.6. Pharmacodynamics

PD 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 blood sample optimized for DNA isolation (Prep D1) will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and cancer. Genes and other analytes (eg, proteins, RNA, nondrng metabolites) may be studied using the banked samples.

See Appendix 5 for info1mation regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laborato1y manual.

8.8. Biomarkers

Biospecimens collected for phaimacodynamic and other biomarker assessments will include peripheral blood, and tumor tissues which will be used to analyze DNA, RNA, and proteins, for achieving planned biomai·ker objectives. Refer to the SoA for sample collection time points and Study/Laborato1y Manual for sample processing and shipping. The following biospecimen types are planned to be collected in suppo1t of study objectives. Additional biospecimens collected over the course of pa1ticipant disease management may be submitted for biomai·ker analyses.

8.8.1. Archival/De Novo Tumor Biopsies

Tumor biospecimens from ai·chival FFPE or de novo biopsies will be used to analyze candidate nucleic acid and protein biomai·kers for their ability to identify those paiticipants who ai·e most likely to benefit from treatment with the study diugs. Biomai·kers may include, but ai·e not limited to tai·get expression, nucleic acid analyses, as well as cell types and constituents of the TME. De Novo tumor biopsies obtained upon disease progression may be used to investi ate hannacod amic activities mode of action and ac uired mechanisms of resistance, [redacted]. Additional info1mation on tissue collection procedures can be found in the Laborato1y/Study Manual.

Pre-treatment ai·chival FFPE material containing tumor that is of diagnostic quality and representative of the diagnosed malignancy collected :SI yeai· prior to study strut is required of all paiticipants, and if not available, a pre-treatment de novo (fresh) tumor biopsy will be required. If the ai·chived sample is older than 1 yeai·and a biopsy during screening cannot be perfo1med, the investigator must contact the sponsor to discuss eligibility prior to emollment.

For 10-15 aitici ants er cohort in Pait 2, a de novo tumor biopsy at pre-treatment [redacted] will be required. An ai·chival sample collected prior to study strut may not be substituted for the mandato1y pre-treatment paired biopsy in Pait 2 dose

expansion. For all other paiiicipants, [redacted] biopsy is optional but highly encouraged. However, if paiiicipants agree to provide fresh on-ti·eatment tumor biopsies then they will also need to provide fresh pre-ti·eatment tumor biopsies as paired samples. Tumor paired biopsies should preferably be taken from the same lesion and from a lesion that has not been previously inadiated. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) or bone specimen, is not adequate and should not be submitted.

Paiiicipants should not be subjected to a significant risk procedure to obtain the biopsies (ie, the absolute risk of mortality or major morbidity in the participant's clinical setting and at the institution completing the procedure should be <2%).

Additional infonnation on tissue collection procedures can be found in the Laborato1y Manual.

8.8.2. Whole Blood, Plasma, Serum

Peripheral blood and derivatives may be used to chai·acterize cell [redacted] enotypes, measure soluble proteins and analyze nucleic acids to support study objectives. [redacted]. We will also collect whole blood samples for DNA sequencing to detect gennline mutations to serve as a nonnal conti·ol for detecting somatic mutations. Additional analyses may be waiTanted based on emerging data. Should the site require cytokine info1mation for participant management such as in the case of suspected CRS, the site should collect an additional blood sample for local analysis.

[redacted].

[redacted] in the SoA. Instmctions for sample collection, processing, storage shipment and detailed panels of cytokine/chemokine and immunophenotyping markers will be provided in the laborato1y manual.

8.9. Immunogenicity Assessments

Blood samples will be collected for dete1mination of ADA and NAb as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laborato1y manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for detennination of ADA and NAb may also be used for additional chai·acterization of the immune response and/or evaluation of the bioanalytical method, or for other internal explorato1y pmposes. These data will be used for internal explorato1y pmposes and not repo1ied in CSR.

Genetic analyses will not be performed on these samples. 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 neutralization activity.

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.

8.10. 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 the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

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 is no formal hypothesis testing in this study.

9.2. Sample Size Determination

The total number of participants is estimated to be approximately 74-172 enrolled to study intervention.

9.2.1. Part 1: Dose Escalation

Approximately 14-22 participants are expected to be enrolled in Part 1 dose escalation. The total number of participants will depend on the number of dose levels needed to determine

the MTD/RP2D and the actual number of participants evaluable for DLT at each dose level. In general, each cohort in the dose escalation part will be approximately 2-4 participants. For the dose level that is estimated to be the MTD, a minimum of 6 evaluable participants will be treated at this dose.

9.2.2. Part 2: Dose Expansion

Each cohort in Part 2 will enroll 20-30 participants. Approximately 60-90 participants will be initially enrolled in the first three cohorts, with the option to further enroll approximately 40-60 participants in an additional two cohorts.

Clinical response will be continuously monitored in each expansion cohort and if no clinical benefit is observed enrollment may be stopped for the respective cohort.

A Beta-Binomial model, using a non-informative prior (ie, Jeffery's prior), was used to estimate the posterior probability that the true ORR is ≤10%, >20%, or >30% based on an observed ORR. Enrollment of participants into a given cohort may be discontinued if minimal or no anti-tumor activity (eg, 0 or 1 response) is observed in the first 10 evaluable participants. For example, if 1 out of 10 participants have tumor response, this would translate into a posterior probability equal to 0.77 that the true response is inferior to 20%. Alternatively, if 5 out of 20 participants have tumor response, this would translate into a posterior probability equal to 0.725 that the true response is not inferior to 20%. The results for observed response rates ranging from 20-40% with 20 or 30 participants per expansion cohort are provided in Table 5. Posterior probabilities may be calculated by using informative priors based on the anti-tumor activity that may be observed during dose escalation. These posterior probabilities will be assessed for each indication during Part 2 when at least 10 participants have been enrolled in a given indication/subgroup.

Table 5. Posterior Probability that the true ORR (θ) is above or below some threshold, for a given observed ORR.

Observed ORR	$P(\theta \leq 10\% \mid data)$	$P(\theta > 20\% \mid data)$	$P(\theta > 30\% \mid data)$
4/20 (20%)	0.078	0.523	0.165
5/20 (25%)	0.023	0.725	0.323
6/20 (30%)	0.005	0.866	0.513
7/20 (35%)	0.001	0.946	0.696
8/20 (40%)	0	0.982	0.836
6/30 (20%)	0.044	0.519	0.113
7/30 (23%)	0.014	0.689	0.216

Table 5. Posterior Probability that the true ORR (θ) is above or below some threshold, for a given observed ORR.

Observed ORR	P(θ ≤ 10%|data)	P(θ > 20%|data)	P(θ > 30%|data)
8/30 (27%)	0.004	0.822	0.354
9/30 (30%)	0.001	0.91	0.511
10/30 (33%)	0	0.96	0.663
11/30 (37%)	0	0.984	0.79
12/30 (40%)	0	0.994	0.882

9.3. Analysis Sets

1. Full analysis set.

   The full analysis set includes all enrolled participants.

   "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

2. Safety analysis set.

   The safety analysis set includes all enrolled participants who receive at least one dose of study intervention. Unless otherwise specified, the safety analysis set will be the default analysis set used for all analyses.

3. Per protocol analysis set (evaluable for MTD).

   The per protocol analysis set includes all enrolled and evaluable 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.

4. 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.

5. 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 postdose analyte concentration.

6. Response Evaluable Set.

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

7. 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.

8. 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 any analyses are performed and will describe 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.

Unless otherwise specified, summaries will be presented by dose group and overall. Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints. The rates of binary endpoints will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method. Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint will be provided.

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 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07209960. Dose toxicity is modelled using two-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose.

Assessment of Participant Risk:

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07209960 will be evaluated. 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 (Rogatko et al, 2007). A dose may only be used for newly enrolled participants if the probability of overdosing at that dose is CCI .

Recommendation from the BLRM, along with safety (AEs, SAEs), laboratory, PK, biomarker and other relevant data, will be used at the time of each dose escalation and for MTD/RP2D determination.

Prior distributions:

Weakly informative prior distributions based on pre-clinical/expert opinion information will be chosen for the logistic parameters, see Appendix 8.

Starting dose:

The starting dose is CCI in Part 1 Dose Escalation. For this dose the prior risk of overdosing satisfies the EWOC criterion.

9.4.1.1. Stopping Criteria

The dose escalation will be stopped when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD/RP2D.
- The dose $d^{\sim}$ satisfies 1 of the following conditions:
  - The probability (π) of target toxicity at dose $d^{\sim}$ exceeds 50%, ie, $Pr(0.16 \leq rr_{d^{\sim}} < 0.33) \geq 50\%$.
  - A minimum of 15 participants have been treated in the trial.

In case all doses explored appear to be overly toxic and the MTD cannot be determined, the dose escalation will stop.

In case of change of the dosing regimen, DLT data accumulated during the dose escalation with the original regimen might be used to form a MAP prior for further BLRM analysis. MAP priors are derived from hierarchical models, which take into account possible

differences between the studies. Details of priors and general description of MAP approach is presented in Appendix 8 and a statistical technical supplement.

To mitigate the risk of misclassifying DLTs, a sensitivity that uses weighted DLT/AE data (in equivocal cases) within the BLRM will be performed. If all investigators and the sponsor agree on the equivocal DLT/AE data, the DLT weighting approach could be the primary dose escalation method (see Appendix 8).

9.4.2. Efficacy Analysis

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

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. In addition, progression date, death date, date of first response and last assessment date, and date of last contact will be listed. A summary of tumor response based on RECIST 1.1 will also be presented.

Progression date, date of first response, last tumor assessment date, date of last contact, and death date will be listed.

The Kaplan-Meier methods will be used to analyze all time to event efficacy endpoints. The efficacy endpoints that will be analyzed in this study are defined as follows:

- ORR is defined as the percentage of participants with a BOR of CR or PR.
- DCR is defined as the percentage of participants with a BOR of CR, PR, non-CR/non PD or SD.
- DOR is defined as the time from first documentation of CR or PR to date of first documentation of PD or death due to any cause, whichever occurs first.
- PFS is defined as time from start date of treatment to the date of first documentation of PD or death due to any cause.
- TTP is defined as the time from start date of treatment to the date of the first documentation of PD.
- OS is defined as the time from start date of treatment to the date of death due to any cause.

The detailed analyses will be described in the SAP. The definition of each response category is provided in Appendix 11.

9.4.3. Pharmacokinetic Analysis

9.4.3.1. Single-Dose and Steady-State PF-07209960 Pharmacokinetic Analysis

Sernm concentrations of PF-07209960 will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose, cycle, day and nominal time. Median profiles of the concentrntion-time profiles after CIDI dose and C2D15 dose will be plotted separately by dosing coho1i and cycle using nominal times for Pa1i 1 only. Median profiles will be presented on both linear-linear and log-linear scales.

Individual participant semm concentration-time data within a dose interval after CIDI and C2D15 will be analyzed using noncompartmental methods to detennine single- and multiple- dose PK parameters. Single-dose PK parameters to be estimated will include the Cmax, Tmax, and AUC from time Oto AUC1ast, and if data pennit, AUC from time 0 extrapolated to AUCnr, t112, apparent oral *Cl.JF,* and VJF. Multiple-dose PK parameters to be estimated will include Cmax,ss, Tmax.ss, AUCtau.ss, sennn Ctrough.ss, CLsJF, and if data permit, Vz,ss!F, t112,ss, and Rae. The single dose and steady state PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose level, cycle and day.

Dose nonnalized AUCinf (AUCtau,ss), AUC1ast and Cmax will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual paiiicipant values and the geometric means for each dose.

9.4.4. Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of paiiicipants with positive ADA and NAb each will be smnmai·ized. Listings and summaiy tabulations of the ADA and NAb data at baseline and post-randomization will be generated. For paiticipants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data pennit. The potential impact of i1nmunogenicity on PK and clinical response including pha1macodynainic markers, safety/tolerability and efficacy will be explored, if waiTanted by the data.

9.4.5. Tertiary/Exploratory Endpoint(s)

CCI [redacted].

9.4.6. Other Safety Analyses

All safety analyses will be perfo1med on the safety population.

Smnmai·ies and analyses of safety pai·ameters will include all paiiicipants in the safety analysis set.

AEs, ECGs, BP, hea1t rate, and safety laborato1y data will be reviewed on an ongoing basis during the study to evaluate the safety of paiiicipants. Any clinical laborato1y, ECG, BP, and

PR 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, 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 examination conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Demographic data collected at screening will be reported.

9.4.6.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF 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 QTcF 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 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 QTcF 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 Cycle 1 Day 1 pre-dose.

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 HR (QTcF) using standard correction factors (ie, Fridericia's (default correction), Bazett's, and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate), and dose. Individual QT (all evaluated corrections) intervals will be listed by 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.

9.4.6.2. Adverse Events

AEs will graded by the investigator according to the CTCAE version 5.0 and coded using MedDRA, except CRS, which will be graded by ASTCT criteria (Lee et al, 2019). AE data will be reported in tables and listings. Summaries of AEs by mapped terms, appropriate thesaurus level, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of AEs 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.

9.4.6.3. 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.

9.4.7. Other Analyses

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4.7.1. Analysis of Biomarker Endpoints

For blood and 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 (if available). Further analysis will be specified in the SAP.

Clinically relevant and interpretable biomarker assessments generated for Primary and Secondary objectives will be summarized in the CSR. Results from exploratory endpoint analyses will be reported in the CSR or will be disclosed to the scientific community through publication(s) at scientific conferences and/or in peer-reviewed scientific journals. Given the exploratory nature of exploratory objectives and endpoints, the associated data analyses may not be complete at the time of CSR authoring.

9.4.7.2. Population Pharmacokinetic Analysis or PK/PD Modeling

PF-07209960 PK and pharmacodynamic 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-07209960 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.

9.5. 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 modeling, and/or supporting clinical development.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC. However, a DLRM will convene for dose escalation decisions. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the members of the DLRM after considering all safety information. The review team will composed of investigator(s), Pfizer GCL, Pfizer Study Clinician, and Pfizer study manager. Additional members may be added as needed (eg, Clinical Pharmacologist Lead, Translational Oncology, Safety Risk Lead or designee and Pfizer Biostatistics representative). A quorum, defined as >50% of the participating investigators or their qualified designee (ie, subinvestigator or research nurse or study coordinator possessing hard copy documentation [eg, email] of the investigator's vote regarding the dose level review), must be in attendance for the DLRM. The DLRM will be rescheduled if a quorum is not reached.

Voting members of the DLRM will include the Pfizer medical monitor, the Pfizer Safety Risk Lead or designee, and all participant investigators or their qualified medical doctor designee(s). The team may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion or a cohort, de-escalation at a lower dose, or termination of the study.

All available study day including demographics, medical history (including tumor history), concomitant medications, AEs, ECGs, vital signs, laboratory results, and emerging PK or PD data will be reviewed. Data to be reviewed may be unqueried.

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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), 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 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, 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 subinvestigators 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 authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

The investigator must ensure that each study participant or his or her legally authorized representative 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 or his or her legally authorized representative 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 ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

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 will 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 participants 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 and medical record identification. 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 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 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 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. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

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 corresponding study results are 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 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 patient-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes 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 Study Management 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 eCRF that are 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 Management Plan.

Description of the use of computerized system is documented in the CRF Guidelines.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

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 sponsor or designee/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.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory

requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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 the 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 supporting study documentation/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. 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 laborato1y tests will be perfo1med at times defined in the SoA section of this protocol. Additional laborato1y results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laborato1y, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laborato1y measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 6. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test	Other Labs
Hemoglobin Platelets WBC Differential • Absolute Neutrophils • Absolute Lymphocytes • Absolute Eosinophils • Absolute Basophils	ALT **AST** Bicarbonate CRP Fen-itin Alic Phos Sodium Potassium Magnesium Chloride Total Calcium Total bilirubinb Total Protein BUN Creatinine U1-ic Acid Glucose (nonfasted) LDH Albumin Phosphorus or Phosphate	PT/INR PTT/aPTT **TT** Fibrinogen D-dimer	**pH** Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrates Leukocyte esterase Urobilogen Bilimbin Microscopy"	WOCBP (semm /m-ine)	CCI **Serology:** HBsAg, Anti-HCV antibody! •HCVRNA (only if Anti-HCV is positive) CCI **Thyroid functio n Tests:** TSH, free T4 CCI

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For potential Hy's Law cases, in addition to repeating AST and ALT, laborato1y tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilimbin, ganuna-glutamyl transferase, PT/INR, alkaline phosphatase, total bile acids and acetaminophen dmg and/or protein adduct levels.
c. Cytok.ines for central labevaluation will be collected if CRS is suspected. Local labevaluation of cytokine is only required if the site requires this info,mation for participant management.
d. Polymerase chain reaction for HCV RNA if anti-HCV antibody is positive.

Investigators must document their review of each laborato1y safety report.

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 occunence in a patient or clinical study paiiicipant, 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 abnonnal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abno1mal laborato1y test results (hematology, clinical chemistiy, 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. Any abno1mal laborato1y test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms;
  - Requires additional diagnostic testing or medical/surgical intervention;
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drng tl'eatment, or other therapy.
- Exacerbation of a chronic or intennittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administl'ation even though it may have been present before the staii of the study.
- Signs, symptoms, or the clinical sequelae of a suspected diug-drng 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 repo1ied as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-haiming intent. Such overdoses should be repo1ied regai·dless of sequelae.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, "lack of efficacy" or "failure of expected pharmacological action" does not constitute an AE or SAE.

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).

An SAE is defined as any untoward medical occurrence that, at any dose:

g. Results in death

h. 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.

i. 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.

j. 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.

k. Is a congenital anomaly/birth defect

l. 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 life-threatening 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 CTCAE Grade 5 (see the Assessment of Intensity section).

- Suspected trnnsmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laborato1y findings indicating an infection in a patient exposed to a Pfizer product. The tenns "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by phannacovigilance personnel. Such cases are also considered for repo1iing 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 repo1iing serious adverse events on the CT SAE Repo1i Fonn 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 Repo1i Fo1m for repo1iing of SAE infonnation is not the same as the AE page of the CRF. When the same data are collected, the fonns must be completed in a consistent manner. AEs should be recorded using concise medical tenninology and the same AE te1m should be used on both the CRF and the CT SAE Repo1i Fo1m for repo1iing of SAE infonnation.

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 or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental fonn for EDP) Note: fuclude all SAEs associated with exposure during pregnancy or breastfeeding. fuclude 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 NCI CTCAE grading 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

Note: CRS will be assessed according to the modified grading described by ASTCT as described in Appendix 9.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study inte1vention and each occmTence 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 mled out.
- The investigator will use clinical judgment to detennine the relationship.
- Alternative causes, such as underlying disease(s), conc01nitant therapy, and other risk factors, as well as the temporal relationship of the event to study inte1vention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product infonnation, 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 occmTed and the investigator has minimal infonnation to include in the initial repo1i 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 infonnation and send an SAE follow-up repo1i with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulato1y reporting requirements.
- If the investigator does not know whether or not the study inte1vention caused the event, then the event will be handled as "related to study inte1vention" for repo1iing purposes, as defined by the sponsor. In addition, if the investigator detennines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and repo1i such an assessment in the dedicated section of the CT SAE Repo1i Fo1m and in accordance with the SAE repo1iing requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perfonn or anange 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 laborato1y tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated info1mation 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 infonnation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primaiy mechanism for repo1ting 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 repo1t 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 off-line to prevent the entiy of new data or changes to existing data. • If a site receives a report of a new SAE from a study paiticipant or receives updated data on a previously reported SAE after the electi·onic data collection tool has been taken off-line, then the site can repo1t this info1mation on a paper SAE fo1m (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile ti·ansmission of the CT SAE Repo1t Fo1m is the prefened method to ti·ansmit this info1mation to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Repo1t Fonn 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

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 4 months after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the 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 long-term 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.

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 Appendix 4, 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), preferably with low user dependency, as described below during the intervention period and for at least 4 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the 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

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 no menses for 12 months without an alternative medical cause. In addition, a

     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
     - Female 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

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibiton 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 WOCBP and the absence of spem has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

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

    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.

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

    - Oral;
    - Injectable.

3. 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.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07209960 or study interventions 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 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 will be stored indefinitely or for another 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 DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede 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, CK, direct and indirect bilirubin, GGT, PT/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/paracetamol (either by itself or as a coformulated 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 samples for acetaminophen/paracetamol 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 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 <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by60 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 PVCs, triplets, or sho1i intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as 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 paiiicipants in sinus rhythm, with documented periods of asystole3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free paiiicipants with atrial fibrillation and bradycai·dia 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 supraventriculai·tachycai·dia (rate>120 bpm) ("sustained"= sho1i duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventi·icular rhythm (heart rate <40 bpm), accelerated idioventi·icular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic venti·icular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) herui block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocru·dial infru·ction.
- Sustained venti·iculru·tachyruThythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Ati·ial flutter or fibrillation with rapid venti·iculru·response requiring cardioversion.
- Venti·icular fibrillation/flutter.
- At the discretion of the investigator, any ruThythmia classified as an adverse expenence.

The enllllllerated list of major events of potential clinical concem are recollllllended as "ale1ts" or notifications from the core ECG laborato1y to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be repo1ted as AEs/SAEs.

10.8. Appendix 8: Detailed Dose Escalation/De-escalation Scheme for BLRM Design

An adaptive Bayesian design using EWOC will guide the dose escalation for PF-07209960. The use of Bayesian response adaptive designs for Phase 1 studies has been advocated for and is one of the key elements of the FDA's Critical Path Initiative (Rogatko et al, 2007; Neuenschwander et al, 2015).

The BLRM will be set-up for the dose-toxicity relationship of PF-07209960 when administered as a single agent. This Bayesian analysis will be based on DLT data (absence or presence of DLT) during the first cycle (DLT observation period) accumulated throughout the dose escalation. This appendix provides details of the statistical models. The derivation of prior distributions, general description of MAP approach (in the event that alternative IV dosing is used), performance check of the model, some hypothetical dose escalation scenarios, and operating characteristics are presented in a technical supplement to this appendix.

10.8.1. Statistical Models

10.8.1.1. Prior Specifications for monotherapy BLRM

In the dose escalation Part 1, the DLT relationship will be described by a 2-parameter BLRM formulated as follows:

$$logit(\pi(d)) = log(a) + \beta \, log\left(\frac{d}{d^*}\right)$$

Where, π(d) is the probability that a participant has a DLT during the first cycle (28 days) when PF-07209960 is given as single agent. The parameter d* is the reference dose in the model and is used to scale the doses of PF-07209960. The α, β >0 are the parameters of the model such that a (>0) is the PF-07209960 odds of a DLT at d^*; and $f3$ (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

The Bayesian approach requires the specification of prior distributions for the model parameters log(a) and log$(f3)$. Available preclinical toxicology makes it difficult to predict toxicity profile of PF-07209960 single agent in humans. For this reason, the priors of the model parameter distribution are defined using a weakly informative prior. This approach allows for considerable uncertainty, so that the a-priori range for the parameters covers a wide range of plausible values.

Meta-Analytic-Predictive Priors Approach

A MAP prior may be used to define the prior for any or all of the treatment arms in the dose escalation in order to account for heterogeneity between the available DLT data and the actual study protocol population and treatment regimen/schedule. For example, if alternative IV dosing is used a MAP prior may be used to incorporate SC dosing data. Furthermore, a

MAP prior maybe used instead of, or in addition to a weakly informative prior to form a weighted mixture prior and account for uncertainty. A mixture prior can take the form

$$p \times BVN_{MAP} + (1 - p) \times BVN_{Weak}$$

The weights of the mixture prior are driven by clinical judgement. The aim of the MAP prior approach for treatment i is to derive a prior distribution for the logistic parameters $(log(a^*_i), log(f3^*_i))$ using prior DLT data, available from previously conducted trial, or from the same study but with another regimen.

Let r_i and n_i be the number of participants with a DLT, and the total number of participants at dose d_i in the DLT data available from the historical trial. The corresponding probability of a DLT is rr_{di}. The model specifications are as follows:

$$r_i/rr_{di} \sim Bin(rr_{di}, n_i)$$

$$ogit(rr_{di}) = log(a_i) + f3_i log(\frac{d_i}{d^*})$$

$$(log(a_i), log(f3_i))/\mu, 1/\sim BVN(\mu_i, 1/_i)$$

$$(log(a^*_i), log(f3^*_i))/\mu, 1/\sim BVN(\mu_i, 1/_i)$$

The parameter $\mu_i = (\mu_{i1}, \mu_{i2})$ is the mean for the logistic parameter, and $1/_i$ is the between-regimen/study covariance matrix. Covariance matric $1/_i$ is defined by the standard devations of (t_{i1}, t_{i2}), and correlation r_i.

The following priors will be used for these parameters:

- normal priors for μ_{i1} and μ_{i2};
- log-normal priors for t_{i1} and t_{i2};
- a uniform prior for r_i.

To further specify the details of these distributions the principles described in (Neuenschwander et al, 2015) will be followed. The MAP prior for model parameters of PF-07209960, is the predictive distribution.

$$(log(a^*_i), log(f3^*_i))/(r_i, n_i)$$

Since the predictive distribution is not available analytically, the MCMC method is used to simulate values from this distribution. This is implemented using JAGS version 4.10.

Sensitivity Analysis

Despite being prespecified in the protocol, some AEs that fall into the category of DLTs may need to be considered differently. Conversely, some AEs that are not defined as a DLT per protocol should be considered by the dose escalation BLRM. Accordingly, the new concept

of an "equivocal" DLT or AE is introduced: most AE/DLTs are considered "unequivocal," but certain types of AEs/DLTs are considered to be "equivocal." To mitigate the risk of dichotomizing and misclassifying DLTs, the sensitivity analysis that uses those weighted equivocal DLT/AE data into the BLRM model estimation will also be performed. The BLRM model uses all the equivocal and unequivocal AE/DLT data, but the variability associated with equivocal AEs/DLTs (less interpretable) is increased. So, the model recommendations are more heavily weighted towards unequivocal data. See below for the posterior distribution of the BLRM model parameters based on the theory of power prior.

Suppose n participants treated at dose d with m unequivocal DLTs and r equivocal DLTs/AEs, and the weight w for the equivocal data, then based on the power prior,

$$Posterior(a, f3|d, m, r, w) \propto L(m|a, f3, d, w) \times L(r|a, f3, d, w) \times prior(a, f3)$$
$$\propto p(a, f3, d)^m \times [1 - p(a, f3, d)]^{n-r-m} p(a, f3, d)^{rw} \times prior(a, f3),$$

Where L is the likelihood of the observed DLT data, and $p(a, f3, d)$ is the probability of DLT at dose d that is modeled by logistic regression in BLRM. To achieve the equality sign, approximate normalizing constant is required. The contribution of equivocal AEs/DLTs to the data (likelihood) and the Bayesian posterior estimation of the MTD are weighted; the weight parameter controls the influence and can be interpreted as a precision parameter for equivocal AE/DLT data, similar to the scale parameter in the power prior for the Bayesian historical borrowing. The weight for an equivocal DLT is decreased (eg, 1 decreased to 0.5) and the weight for an equivocal AE (non-DLT by protocol) is increased (eg, 0 increased to 0.5). To maintain the integrity of a trial, the weights pre-specified as 0.5 in the analysis. If all the investigators and the sponsor agree on the equivocal DLT/AE data, the DLT weighting approach could be the primary dose escalation method. This DLT weighting approach provides a flexible and powerful tool that may incorporate the clinician's valuable experience with some specific DLTs/AEs and improve MTD estimation in dose-escalation trials.

10.9. Appendix 9: CRS Mitigation and Management

CRS is a non-antigen-specific cytokine-associated toxicity that occurs as a result of high-level immune activation. CRS is a potentially life-threatening toxicity that has been observed following administration of immune-base therapies for cancer (antibodies and adoptive T cell therapies). CRS is likely to be a common toxicity that can be managed through supportive care and anti-cytokine interventions.

In cases of suspected CRS, a serum sample should be provided for cytokine release assay analysis by the local lab (see Section 8.2.5) so as long as the sampling does not interfere with the medical treatment of the participant.

Early intervention should be undertaken at the first sign of CRS; signs may include pyrexia, tachycardia, tachypnea and/or hypotension and are temporally related to PF-07209960 in the absence of alternative etiologies.

The ASTCT CRS criteria proposed by Lee et al. (Lee et al, 2019) as presented in Table 7 will be used for the assessment of the CRS severity grade which will be captured on the AE CRF and on the CRS CRF.

Table 7. ASTCT CRS Revised Grading System

CRS parameter:	Fever*	With Hypotension	And/or† Hypoxia
Grade 1	Temp. ≥38°C	None	None
Grade 2	Temp. ≥38°C	Not requiring vasopressors	Requiring low-flow‡ nasal cannula, low-flow‡ facemask or blow-by
Grade 3	Temp. ≥38°C	Requiring a vasopressor with or without vasopressin	Requiring high-flow‡ nasal cannula, high-flow‡ facemask, nonrebreather mask, or Venturi mask
Grade 4	Temp. ≥38°C	Requiring multiple vasopressors (excluding vasopressin)	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS should still be graded according to CTCAE v5.0 and do not influence CRS grading.
* Fever is defined as temperature ≥38°C and not attributable to any other cause. In participants 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 or facemask is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula or facemask is defined as oxygen delivered at >6 L/min. This is modified from original ASTCT criteria to differentiate between low-flow and high-flow facemask.

The definitions for high-dose vasopressors are shown in Table 8.

Table 8. Definition of High Dose Vasopressor

Pressor	High Dose (doses less than these would be considered low)
Norepinephrine monotherapy	≥20 µg/min
Dopamine monotherapy	≥10 µg/kg/min
Phenylephrine monotherapy	≥200 µg/min
Epinephrine monotherapy	≥10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 µg/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 µg/min*

* VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷10

CRS Management Guidelines (Neelapu et al, 2018; Neelapu, 2019):

These may be modified as needed by the responsible Investigator according to the best practices at their institute.

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 ICU, obtain ECHO, and initiate other methods of hemodynamic monitoring.
- In participants 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.

10.10. Appendix 10: 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 and will become effective for other public emergencies only upon written notification from Pfizer.

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).

10.10.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient 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 active SARS-CoV2. Patients with active infections are excluded from study participation.

10.10.2. Telehealth Visits

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 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 8.3.
- 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 and Appendix 10, Section 10.10.3.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.10.3. Alternative Facilities for Safety Assessments

An alternative facility to perform laboratory tests, imaging, or ECGs may be appropriate for study procedures that are standard safety assessments and are routinely performed by the alternative facility.

10.10.3.1. 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. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology
- Chemistry
- Coagulation: PT/INR, PTT/aPTT; TT, fibrinogen; D-dimer for Cycle 1
- Thyroid Test: TSH, free T4
- [redacted] CCI
- [redacted]
- Pregnancy test
- Urinalysis

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 mIU/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.

10.10.3.2. 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.

10.10.3.3. Echocardiogram or MUGA

If the participant is unable to visit the study site for echocardiogram or MUGA, the participant may visit an alternative facility to have the echocardiogram or MUGA performed. Qualified study site personnel must order, receive, and review results.

10.10.4. 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-07209960 for 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, PF-07209960 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 Section 6.5 for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.10.5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.11. Appendix 11: Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline version 1.1 (Eisenhauer et al, 2009).

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 subjected 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 non-cystic 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 randomization and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be non-evaluable.

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 CR, Non-CR/Non-PD, PD, Non-evaluable (NE). 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 might be non-evaluable.

Target Disease

1. 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.

2. 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.

3. 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.

4. 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.

5. Non-evaluable (NE): Progression has not been documented, and
   - One or more target measurable lesions have not been assessed; 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.

Non-Target Disease

1. 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).

2. Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

3. 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.

4. NE: 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

Participants 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 1. 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	NE or Missing	No	PR
PR	Non-CR/Non-PD, NE or Missing	No	PR
SD	Non-CR/Non-PD, NE or Missing	No	Stable
NE or Missing	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

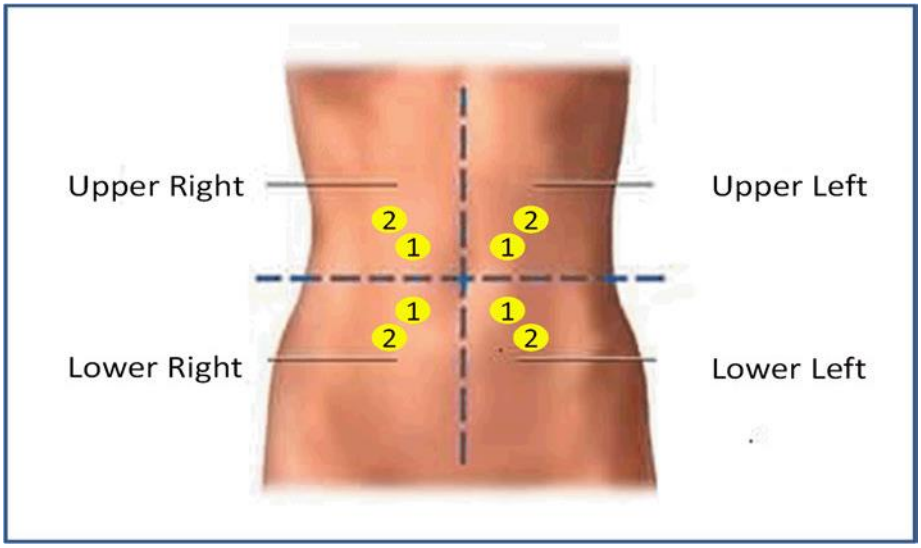
Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only		
Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
NE	No	NE
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Best Overall Response

The best overall response (BOR) is the best response recorded from the randomization until disease progression or death due to any cause. This is derived from the sequence of objective statuses. Objective statuses are not considered after objective progression is documented or after start of the first anticancer treatment post discontinuation of protocol treatment. BOR for each patient will be derived as one of the following categories:

- Complete response (CR): At least one objective status of CR documented before progression.
- Partial response (PR): At least one objective status of PR documented before progression.
- Stable disease (SD): At least one objective status of stable documented at least 8 weeks after randomization date and before progression but not qualifying as CR, PR.
- Progressive Disease (PD): Objective status of progression within 16 weeks of randomization, not qualifying as CR, PR or SD.
- Non-evaluable (NE): Progression not documented within 16 weeks after randomization and no other response category applies.

10.12. Appendix 12: 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. Location 1 is proximal to the umbilicus and Location 2 is distal to the umbilicus.

Administer the required number of injections in the following order:

1. Lower Left Quadrant Location 1;
2. Lower Right Quadrant Location 1;
3. Lower Left Quadrant Location 2;
4. Lower Right Quadrant Location 2;
5. Upper Right Quadrant Location 1;
6. Upper Left Quadrant Location 1;
7. Upper Right Quadrant Location 2;
8. Upper Left Quadrant Location 2.

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. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

Track the patient's injection site(s) sequentially on this diagram with a red pen and mark the injection sites on the patient's abdomen according to your clinic's standard practice.

Record the location, time of each injection and any ISRs in the patient's source records and study CRF. Complete one CRF per injection.

10.13. Appendix 13: ECOG Performance Status*

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

*As published in Am J Clin Oncol 5:649-655, 1982.

10.14. Appendix 14: Management for Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
K;rade 1 IDian-hea: <4 stools/day over baseline Colitis: asymptomatic	Continue study treatment Symptomatic treatment (eg [operarnide)	Close monitoring for worsening symptoms. Educate participant to report orsening illllllediately. If worsens: Treat as Grade 2, 3 or -
K;rade 2 IDian-hea: 4 to 6 stools per day over !Baseline; IV fluids indicated <24 hours; Mt interfering with ADL Colitis: abdominal pain; blood in stool	Withhold study treatment Symptomatic treatment	If improves to Gradel: Resume study treatment. If persists >5-7 days or recurs: rTreat as Grade 3 or 4.
K;rade 3 to 4 PiaIThea (Grade 3):?:.7 stools per day pver Baseline; incontinence; IV fluids 24 hours; interfering with ADL Colitis (Grade 3): severe abdominal ain, medical intervention indicated, peritoneal signs K}rade 4: life-threatening, perforation	Withhold for Grade 3 Permanently discontinue study eatment for Grade 4 or recuITent Kirade 3 1.0 to 2.0 mg/kg/day prednisone Irv or equivalent Add prophylactic antibiotics for ppportunistic infections Consider lower endoscopy	If improves: Continue steroids until Kn-adel, then taper over at least 1 month; resume study treatment !following steroids taper (for initial Kn-ade 3). If worsens, persists >3 to 5 days, or 1t·ecurs after improvement. Add infliximab 5 mg/kg (if no ontraindication). -Note: infliximab should not be ed in cases of perforation or sepsis.

Dermatoloidcal irAEs		
Grade of Rash (NCI-CTCAE vS.O)	**Initial Management**	**Follow-up Management**
rade 1 to2 Covering*90%* body swface area	Continue study treatment Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > I to 2 weeks or recurs: Withhold study treatment Consider skin biopsy Consider 0.5-1.0 mg/kg/day llrednisone or equivalent. Once !improving, taper steroids over at least I onth, consider prophylactic antibiotics Ifor oppo1tunistic infections, and reswne !study treatment following steroids aper. Ifworsens: Treat as Grade 3 to 4.
K;rade 3 to 4 K}rade 3: Covering >30% body isurface area; K}rade 4: Life threatening K:onsequences	Withhold study treatment for Grade 3 Pe1manently discontinue for Grade 4 or recwTent Grade 3 Consider skin biopsy Dennatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for oppo1tunistic infections	If improves to GradeI: Taper !steroids over at least I month; reswne istudy treatment following steroids aper (for initial Grade 3).

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up M.anagement**
rade 1 !Radiographic changes only	Consider withholding study treatment Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks. If worsens: Treat as Grade 2 or Grade 3 to 4.
rade2 Mild to moderate new symptoms	Withhold study treatment Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If 'mproves: When symptoms return to Grade :::;I, taper steroids over at least 1 month, and then resume study reatment following steroids taper. If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
rade 3 to 4 Kirade 3: Severe new symptoms; New/worsening hypoxia; Kirade 4: Life-threatening	Pe1manently discontinue study treatment. Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade :::;l: Taper steroids over at least 1 month. If not improving after 48 hours or worsening: Add additional 'mmunosuppression (for example, infliximab, cyclophosphamide, IV mmunoglobulin, or mycophenolate mofetil).

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
rade 1 KJrade I AST or ALT >ULN to .Ox ULN and/or Total bilimbin ULN to 1.5 x ULN	Continue study treatment	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 - 4.
K;rade 2 ST or ALT >3.0 to5 >ULN nd/or total bilimbin >1.5 to 3 x IULN	Withhold study treatment Increase frequency of monitoring o evely 3 days	If returns to GradeI: Resume routine monitoring; resume study treatment. If elevation persists >5 to 7 days or rsens: Treat as Grade 3 to 4.
rade 3 to 4 ST or ALT >5 x ULN and/or total IJilimbin >3 x ULN	Pennanently discontinue study reatment Increase frequency of monitoring o evely 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically wa1rnnted	If returns to GradeI: Taper steroids K>ver at least I month. If does not improve in >3 to 5 days, worsens or rebounds: Add niycophenolate mofetil I gram (g) tv.•ice klaily. If no response within an additional 3 to IS days, consider other immunosuppressants per local iguidelines.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE vS.0)	**Initial Management**	**Follow-up Manae:ement**
K;rade 1 K=:reatinine increased >ULN to 1.5 x IULN	Continue study treatment	Continue renal function nonitoring. If worsens: Treat as Grade 2 o 3 or 4.
rade 2 to3 t:reatinine increased >I.5 and :::;6 x IULN	Withhold study treatment Increase frequency of monitoring to eve1y 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If retums to Grade ::;I: Taper steroids over at least 1 month, and resume study treatment following steroids taper. If worsens: Treat as Grade 4.
K;rade 4 K=:reatinine increased >6 x ULN	Pe1manently discontinue study treatment Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If retums to Grade ::Sl: Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Mana ement**
New onset of cardiac signs or sym toms and / or new laboratory [redacted] or cardiac imaging abnormalities suggestive of nyocarditis	Withhold study treatment Hospitalize In the presence of life threatening cardiac ecompensation, consider transfer to a acility experienced in advanced heart failure nd an-hythmia management Consult cardiologist to establish etiology and ule-out immune-mediated myocarditis Guideline based suppo1tive treatment as per ardiology consult* Consider myocardial biopsy if recommende er cardiology consult	If symptoms improve and immune-mediated etiology is mled out, re-start study treatment. If symptoms do not improve/worsen, viral myocarditis is excluded, and irnmune-mediated etiology is suspected or confinned following cardiology consult, manage as illllllune-mediated yocarditis.
none-mediated myocarditis	Pemianently discontinue study treatment Guideline based suppo1tive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for oppo1tunistic infections	Once improving, taper teroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).

*Local guidelines, or eg, ESC or AHA guidelines
ESC guidelines website: https://wwv.r.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website:
http://professional.heait.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs		
Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Continue study treatment -Endocrinology consult if needed -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate -Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	-Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Withhold study treatment -Consider hospitalization - Endocrinology consult -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate -Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	-Resume study treatment once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). -Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/ Hypophysitis (secondaryendocrinopathies)	-If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): -Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) -Hormone replacement/suppressive therapy as appropriate -Perform pituitary MRI and visual field examination as indicated -If hypophysitis is confirmed: -Continue study treatment if mild symptoms with normal MRI. Repeat the MRI in 1 month -Withhold study treatment if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2	-Resume study treatment once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). -In addition, for hypophysitis with abnormal MRI, resume study treatment only once shrinkage of the pituitary gland on MRI/CT scan is documented. -Continue hormone replacement/suppression therapy as appropriate.

Endocrine irAEs		
!Endocrine Disorder	llnitial Management	IFollow-up Management
	rg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 montb Add prophylactic antibiotics for opportunistic !infections	

Other irAEs (not described above)		
Grade of other irAEs <NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	-Withhold study treatment pending clinical investigation	-If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-staiting study treatment -If irAE is confinned, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	-Withhold study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for oppo1tunistic infections -Specialty consult as aooropriate	-If improves to Grade ::Sl: -Taper steroids over at least 1 month and resume study treatment following steroids taper.
Recurrence of same Grade 3 irAEs	-Pe1manently discontinue study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for oppo1tunistic infections -Specialty consult as aooropriate	-If improves to Grade ::;1 : Taper steroids over at least 1 month.
Grade4	-Pe1manently discontinue study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other illllllunosuppressant as needed -Add prophylactic antibiotics for oppo1tunistic infections -Specialty consult	-If improves to Grade ::;1 : Taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than ho1·monal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	-Pe1manently discontinue study treatment -Specialty consult	

10.15. Appendix 15: Management of Infusion Related Reactions

NCI CTCAE Severity G1·ade	Treatment Modification
Grade 1 - mild Mild transient reaction; infusion intenuption not indicated; intervention not indicated.	Decrease the infusion rate by *50%* and monitor closely for any worsening.
Grade 2 - **moderate** Therapy or infusion intenuption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids; prophylactic medications indicated for 24 hours.	Temporarily discontinue infusion. Resume infusion at *50%* of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 - severe01·life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief intenuption of infusion); recwTence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the infusion immediately and disconnect infusion tubing from the patient. Treatment should be pennanently discontinued.

If infusion rate has been decreased by *50%* due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be retwned to baseline at subsequent infusions.

10.16. Appendix 16: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ACTH	adrenocorticotropic hormone
ADA	Anti-drug antibodies
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
am	anti-mouse
ANC	absolute neutrophil count
aPTT	activated partial prothrombin time
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time versus time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of last measurable concentration
$AUC_{tau,ss}$	area under the steady state dose concentration-time curve over dosing interval tau
AV	atrioventricular
BLRM	Bayesian Logistic Regression Model
BNP	Brain natriuretic peptide
BOR	best overall response
BP	blood pressure
Bpm	beats per minute
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
C1D15	Cycle 1 Day 15
C2D15	Cycle 2 Day 15
C3D1	Cycle 3 Day 1
CD4+	Cluster of differentiation 8 positive
CD8+	Cluster of differentiation 4 positive
CEA	cergutuzumab amunaleukin
CEA-IL2v	CEA-targeted IL-2 variant
cfDNA	cell free DNA
CFR	Code of Federal Regulations
CHF	congestive heart failure

Abbreviation	Term
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CK-MB	creatine kinase-muscle type, myocardial band
CL	total clearance of drug from eg, plasma
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography/clinical trial
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DCT	data collection tool
DILI	drug-induced liver injury
DLRM	Dose Level Review Meeting
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EC	exclusion criteria
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOI	end of infusion
EOS	end of study
EOT	end of treatment
EU	European Union
EWOC	escalation with overdose control
FAP	fibroblast activation protein
FAP-IL2v	FAP-targeted IL-2 variant

Abbreviation	Term
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed paraffin-embedded
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GH	Growth hormone
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
hPBMC	human peripheral blood monmuclear cells
hr	hour
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC	inclusion criteria
ICD	informed consent document
ICH	International Council for Harmonisation
ICIs	immune checkpoint inhibitors
ICU	intensive care unit
ID	identification
IF	immunofluorescence
IFN-γ	interferon gamma
IGF-1	insulin-like growth factor 1
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP-10	IFN-γ-inducible protein 10
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ISR	injection site reaction
IUD	intrauterine device
IUS	intrauterine hormone-releasing system

Abbreviation	Term
IV	intravenous
IWR	interactive Web-based response
JAGS	just another Gibbs sampler
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LUC	large unstained cells
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MAP	meta-analytic-predictive
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase kinase
MCMC	Markov Chain Monte Carlo Methods
mITT	Modified-intent-to-treat
MM	metastatic melanoma
MOA	mechanism of action
MRI	magnetic resonance imaging
msec	millisecond
MSS	microsatellite-stable
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N/A	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NE	non-evaluable
NIMP	non-investigational medicinal product
NK	natural killer
NOAEL	no observed adverse effect level
NSAIDS	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
OR	overall response
ORR	objective response rate
OS	overall survival
OvCa	ovarian cancer
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics(s)/progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)

Abbreviation	Term
PR	partial response
PRL	prolactin
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
Q1W	once every week
Q2W	once every two weeks
Q12W	once every twelve weeks
QTc	corrected QT
QTcB	QTc corrected QT (Bazett method)using Bazett's formula
QTcF	QTc corrected QT (Fridericia method)using Fridericia's formula
qual	qualitative
R_{ac}	accumulation ratio based on AUC (observed)
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
pSTAT5	signal transducer and activator of transcription 5 (protein)
rhIL-15	recombinant human Interleukin-15
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCCHN	squamous cell head and neck carcinoma
SD	stable disease
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	Single-reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal phase half-life
T4	thyroxine
TBili	total bilirubin
TGI	tumor growth inhibition
TIL	tumor infiltrating lymphocytes
TK	toxicokinetics
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-α
T_{max}	time to reach C_{max}
TME	tumor microenvironment
TSH	thyroid-stimulating hormone

Abbreviation	Term
TT	thrombin time
TTP	time to progression
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	woman of childbearing potential

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