A PHASE 1B STUDY OF PF-05082566 IN COMBINATION WITH MOGAMULIZUMAB (KW-0761) IN PATIENTS WITH ADVANCED SOLID TUMORS

Compound:	PF-05082566
Compound Name:	Not Applicable
United States (US) Investigational New Drug (IND) Number:	109,154
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	B1641004
Phase:	1b

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	04 February 2016	**Protocol Summary: Secondary Endpoints** • Endpoint 4 changed V_d to V_{ss} and added AUC_{tau} and deleted AUC_{∞}. **Protocol Summary: Study Design: Dose Finding Portion:** • Changed the maximum tested dose from 10 mg/kg to 5 mg/kg. • Added the following in bold: Dose finding **may** stop if 9 DLT evaluable patients have been treated at the estimated MTD **(6 if no DLT observed at any dose).** • Added the 100 mg flat dose cohort to the dose finding portion of the trial which will only enroll SCCHN and/or squamous NSCLC patients. • Added that the 5.0 mg/kg cohort (if safe and tolerable) will enroll at least 6 squamous NSCLC patients. **Protocol Summary: Study Design: Dose Expansion Portion:** • Added that the expansion cohorts may include CRC, bladder, ovarian, squamous esophageal, SCCHN and squamous NSCLC. **Schedule of Activities:** • Removed the Baseline Signs and Symptoms CRF. • Updated, changed and clarified the timepoints for the PK, ADA and Cytokine blood draws. • Footnote #19: Changed time period for reporting of pregnancy/breast feeding from 28 days after last dose of PF-05082566 to 60 days.

Document	Version Date	Summary of Changes and Rationale
		• Footnotes # 29 and 30 added the following: "Upon progression in patients that showed initial response and /or stable disease, a biopsy may be taken unless in the opinion of the Investigator it poses an unacceptable safety risk to the patient". • Footnote #32:Changed the definition of the end of study from "6 months from the date of the first dose of the last patient enrolled" to "6 months from the date of the last dose of the last enrolled patient". • Administrative and formatting changes were made to enhance the readability of this section and reduce confusion and redundancy. **1.2.4.1 Pharmacokinetics of PF-05082566 In Humans:** • Added rationale for the addition of the 100 mg flat dose cohort in the dose finding portion of the trial. **2.2 Endpoints: Secondary Endpoints:** • Endpoint 4 changed V_d to V_{ss} and added AUC_{tau} and deleted AUC_{∞}. **3.1.1 Dose Finding Portion:** • Added the 100 mg flat dose cohort to the dose finding portion of the trial which will only enroll SCCHN and/or squamous NSCLC patients. • Added that the 5.0 mg/kg cohort (if safe and tolerable) will enroll at least 6 squamous NSCLC patients to determine RP2D. **3.1.2 Dose Expansion Portion:** • Added that the expansion cohorts may include CRC, bladder, ovarian, squamous esophageal, SCCHN and squamous NSCLC.

Document	Version Date	Summary of Changes and Rationale
		3.1.3 Study Treatment: • Updated timing of the mogamulizumab infusion from starting "30 minutes **(±30 min**) after completion of the PF-05082566 dose" **to** "30 minutes **(±10 min**) after completion of the PF-05082566 dose". **3.1.9 Criteria for Dose Escalation:** • Changed the maximum tested dose from 10 mg/kg to 5 mg/kg. • Added the 100 mg flat dose cohort to the dose finding portion of the trial which will only enroll SCCHN and/ or squamous NSCLC patients. • Added that the 5.0 mg/kg cohort (if safe and tolerable) will enroll at least 6 squamous NSCLC patients. • Added the following in bold: Dose escalation **may** stop if 9 DLT evaluable patients have been treated at the estimated MTD **(6 if no DLT observed at any dose).** • Updated Table 6 to include the 100 mg flat dose and the 50 mg flat dose. • Added the following: "A 24 hr time window between dosing is not necessary between cohorts dosed simultaneously". **3.5 Dose Expansion Portion:** • Added that the expansion cohorts may include CRC, bladder, ovarian, squamous esophageal, SCCHN and squamous NSCLC. **4.1 Inclusion Criteria:** • Criterion #1 Updated to specify that the dose finding cohort will enroll squamous NSCLC patients and that the expansion cohorts may include CRC, bladder, ovarian, squamous esophageal,SCCHN and squamous NSCLC.

Document	Version Date	Summary of Changes and Rationale
		• Criterion #6 updated to: Platelet count decreased from ≥100,000/μL to ≥75,000/μL. **4.2 Exclusion Criteria:** • Criterion #16 Updated to specify that except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix no other malignancy diagnosis within the 2 years prior to registration is permitted. **5.4 Administration:** • The following in bold was added for clarity: "Patients will be observed in the clinic for at least 2 hours after the **administration of study drug, throughout the duration of the study**." **5.4.2 Mogamulizumab:** • Updated timing of the mogamulizumab infusion from starting "30 minutes **(±30 min**) after completion of the PF-05082566 dose" **to** "30 minutes **(±10 min**) after completion of the PF-05082566 dose". **5.4.5 Treatment After Initial Evidence of Radiologic Disease Progression:** • Administrative and formatting changes were made to enhance the readability of this section and reduce confusion and redundancy. **5.4.9.1 Dose Modification Guidelines:** • Table 7 updated to add the 50 mg flat dose to be used for dose reductions for those on the 100 mg flat dose cohort. **7.1.2 Adverse Events:** • Deleted mention that the baseline signs and symptoms will be recorded on the AE CRF.

Document	Version Date	Summary of Changes and Rationale

		7.2 Tumor Assessments:
		• Administrative and formatting changes were made to enhance the readability of this section and reduce confusion and redundancy.
		7.3.1 Blood for PK Analyses of PF-05082566: Dose Finding Cohorts:
		• Timepoints updated/removed.
		7.3.1 Blood for PK Analyses of PF-05082566: Dose Expansion Cohorts:
		• Timepoints updated/removed.
		7.3.2 Blood for PK Analyses of Mogamulizumab: Dose Finding Cohorts:
		• Timepoints updated/removed.
		7.3.2 Blood for PK Analyses of Mogamulizumab: Dose Expansion Cohorts:
		• Timepoints updated/removed.
		7.4.1 Blood for Immunomodulation/Cytokine Release Biomarkers: Dose finding cohorts:
		• The following language in bold was added for clarity:
		  • Cycles 1-4 on Day 1 at pre dose **of the PF-05082566 infusion** and at the end of **the mogamulizumab** infusion;
		  • Cycle 5 on Day 1 at pre dose **of the PF-05082566 infusion**, at the end **of the PF-05082566** infusion, and at 2, and 6 hrs. after the start of **the PF-05082566** infusion.
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Document	Version Date	Summary of Changes and Rationale
		7.5.1: Immunogenicity Tests for PF-05082566: • Timepoints updated/removed. **7.5.2 Immunogenicity Tests for Mogamulizumab:** • Incorrect reference to PF-05082566 deleted. • Timepoints updated/removed. CCI [redacted] [redacted] **8.2 Reporting Period:** • Reporting period for breastfeeding/pregnancy changed from 28 days after last dose of PF-05082566 to 60 days. **8.8 Severity Assessment:** • Addition of CTCAE criteria information. **9.1 Analysis Sets:** • **Deletion of Response Analysis Set** **9.2 Statistical Methods for Dose Allocation: TITE-CRM:** • Addition of the 100 mg flat dose cohort and the deletion of the 10 mg/ kg cohort. • Figure 3 updated to reflect addition and deletion of cohorts. • Updates to power function modeling as a consequence of the 100 mg flat dose cohort update.

Document	Version Date	Summary of Changes and Rationale
		9.5.1.1 Pharmacokinetics Analyses of PF-05082566 and Mogamulizumab: • Updated plasma to serum. • AUC_{inf} deleted. • AUC_{tau} added. **References:** • Updated reference #27. • Added references # 34-37. **15.1 Communication of Results by Pfizer:** • Updated with latest template language. **Appendix 3:** • Incorrect reference deleted and current version of irRECIST added. **Administrative Changes:** • Updates made to Abbreviation Section. Administrative and formatting changes were made throughout the document to enhance the readability of the protocol and reduce redundancy.
Original protocol	19 December 2014	Not Applicable (N/A)

This amendment incorporates all revisions to date including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Abbreviations

4-1BB	TNFRSF9, [redacted], ILA
4-1BBL	4-1BB Ligand, TNFSF9
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APC	Antigen presenting cell
AST	Aspartate aminotransferase
AUC	Area under the concentration - time curve
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time zero to last measurable concentration
AUC_{tau}	Area under the concentration-time curve over dosing interval τ
BP	Blood pressure
BUN	Blood urea nitrogen
CCR4	Chemokine (C-C motif) receptor 4; CD194
CCR7	Chemokine (C-C motif) receptor 7; CD197
CD3	Cluster of differentiation 3
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CD20	Cluster of differentiation 20
CD40	Cluster of differentiation 40, TNFRSF5
CD45	Cluster of differentiation 45, Protein tyrosine phosphatase, receptor type C (PTPRC), leukocyte common antigen
CD134	Cluster of differentiation 134, TNFRSF4, OX-40
[redacted]	[redacted]
C_{ave}	Average serum concentration (estimated)
C_{max}	Maximum serum concentration
C_{trough}	Predose serum concentration during multiple dosing
CHF	Congestive heart failure
CL	Clearance
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRF	Case Report Form
CRM	Complete Reassessment Method
CT	Computed Tomography
CTCAE	Common terminology criteria for adverse events
DC	Dendritic cell
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DR	Duration of Response
EC	Ethic Committee
EC10	Concentration required to achieve 10% of the maximal response

ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ED50	Dose required to achieve 50% of the maximal response
EDP	Exposure during pregnancy
ELISA	Enzyme linked immunosorbent assay
ERK	Extracellular signal-regulated kinase
FACS	Fluorescent-activated cell sorting; flow cytometry
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FIP	First-In-Patient
FL	Follicular lymphoma
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
GTD	Greatest transverse diameter
Hb	Hemoglobin
HLA	Human leukocyte antigen
KHK	Kyowa Hakko Kirin Pharma, Inc.
ICH	International Conference on Harmonization
ICOS	Inducible T-cell costimulator; CD278
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
$IgG1_K$	Immunoglobulin G subclass 1 Kappa
IgG2	Immunoglobulin G subclass 2
IHC	Immunohistochemistry
IL-1β	Interleukin 1 beta
IL-2	Interleukin 2
IL-4	Interleukin 4
IL-6	Interleukin 6
IL-10	Interleukin 10
IL-12p70	Interleukin 12 (bioactive 75 kDa heterodimer of IL-12p40 and IL-12 p35)
IRB	Institutional Review Board
irRC	Immune-Related Response Criteria
IV	Intravenous
Ki-67	Antigen identified by mAb Ki-67
LDH	Lactate dehydrogenase
LFT	Liver function test
LOAEL	Lowest observed adverse effect level
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MPK	Milligrams per kilogram, mg/kg
MTD	Maximum tolerated dose
Nab	Neutralizing antibody
NCI	National Cancer Institute

NF-kB	Nuclear Factor kappa B
NHL	Non-Hodgkin's Lymphoma
NK	Natural killer cell
NKT	Natural killer T cell
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
OS	Overall survival
PBL	Peripheral blood leukocyte
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate Buffered Saline
PD	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SC	Subcutaneous
CCI	[redacted]
SCID	Severe combined immunodeficiency
SAE	Serious adverse event
SD	Stable disease
SEM	Standard error of mean
sFAsL	Soluble Fas Ligand
t1/2	Terminal elimination half-life
TGI	Tumor growth inhibition
TITE-CRM	Time-to-Event Continual Reassessment Method
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor alpha
TNFR	Tumor necrosis factor receptor
TNFRSF	Tumor necrosis factor receptor super family
TRAF	TNFR associated factor
TSH	Thyroid Stimulating Hormone
TTR	Time To Response
Vss	Volume of distribution at steady state

PROTOCOL SUMMARY

Indication

Advanced solid tumors.

Study Rationale

PF-05082566 is a fully human IgG2 monoclonal antibody (mAb) that binds to human 4-1BB with high affinity and specificity. PF-05082566 demonstrated *in vitro* and *in vivo* immunomodulatory activity along with anti-tumor activity when administered as a single agent, in combination with antibody-dependent cellular cytotoxicity (ADCC) inducing antibodies, and significantly enhanced anti-tumor activity in combination with anti-PD-1 antibodies.

The safety and tolerability of PF-05082566 is currently being evaluated in a First-in-Patient Phase 1 study as a single agent and in combination with rituximab (Study B1641001). PF-05082566 has been well tolerated up to a maximum tested dose of 10 mg/kg, when administered every 4-weeks (q4wks) as a single agent and in combination with rituximab without clinically significant adverse events (AEs) above Grade 1 severity attributed to PF-05082566. The preliminary pharmacokinetic (PK) results from the ongoing Phase 1 study suggest that exposure of PF-05082566 increases dose proportionally with a terminal half-life of approximately 10 days. Additionally, a Phase 1 combination study of PF-05082566 and MK-3475, an anti PD-1 mAb (Study B1641003) has been recently activated.

POTELIGEO® (mogamulizumab, KW-0761) is a humanized mAb of the IgG1/kappa isotype produced by applying POTELLIGENT®, a technology to produce antibodies with enhanced ADCC activity, which was developed exclusively by Kyowa Hakko Kirin Co., Ltd. (KHK). Mogamulizumab binds to chemokine [C-C motif] receptor 4 (CCR4) that is overexpressed or expressed at high frequency on the surface of cells in several T-cell malignancies including peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), and adult T-cell leukemia/lymphoma (ATL). This drug was approved in 2012 by the Ministry of Heath, Labor and Welfare in Japan for the treatment of relapsed or refractory CCR4 positive ATL, and subsequently $CCR4^+$ treatment-naïve ATL, and relapsed or refractory PTCL and CTCL, and it is currently under investigation as single agent in patients with advanced solid tumor. Mogamulizumab demonstrated an acceptable safety profile. The AEs reported have generally been mild to moderate in severity, with the most frequent mogamulizumab-related AEs being infusion related reactions, nausea, pyrexia, fatigue, and drug eruption, all manageable through the administration of appropriate treatment.

CCR4 has also been observed on the surface of regulatory T cells (Treg), a lymphocyte subpopulation that has been linked to suppression of anti-tumor immune responses. *In vitro* culture of mogamulizumab with peripheral blood mononuclear cells (PBMC) obtained from cancer patients, leads to depletion of CCR4+ Treg and expansion of anti-tumor T cells. *In vivo* experiments using a B16-F10 mouse melanoma model demonstrated that the antitumor activity of 4-1BB agonist can be significantly improved in combination with an anti-CD4 mAb, which depletes the CD4+ T cells, including Tregs. It has not been possible

to study the depletion of CCR4 positive (CCR4+) cells in mice, as no suitable anti-murine CCR4 mAbs are available. Therefore, *in vivo* experiments were conducted to study the effect of the co-administration of anti-4-1BB and anti-CD4 antibodies. These experiments showed that this combination therapy inhibited tumor growth along with an increased survival compared to the anti-4-1BB and anti-CD4 single agent treatment. Anti-4-1BB treatment resulted in the polyclonal expansion and differentiation of anti-tumor CD8+ T cells into, while the CD4+ T cell depletion, which is assumed to include Treg depletion, facilitated the infiltration of immune cells into the tumors.

These data support the hypothesis that depletion of CCR4+ Treg by mogamulizumab would enhance the efficacy of anti-tumor immune responses expanded by PF-05082566 and warrant confirmation in the clinical setting.

The Sponsor considers that the safety data from the ongoing Phase 1 First-In-Patient (FIP) study of PF-05082566 and the published safety data for mogamulizumab support the conduct of the proposed clinical trial, which will assess the safety and tolerability and establish the maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) of PF-05082566 in combination with mogamulizumab in patients with advanced solid tumors.

STUDY OBJECTIVES AND ENDPOINTS

Objectives

Primary Objective

- To estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D) of PF-05082566 in combination with mogamulizumab in patients with advanced solid tumors.

Secondary Objectives

- To evaluate the overall safety profile of the combination;
- To characterize the pharmacokinetics (PK) of PF-05082566 and mogamulizumab when given in combination;
- To evaluate the immunogenicity of PF-05082566 and mogamulizumab when given in combination;
- To document any anti-tumor activity.

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Endpoints

Primary Endpoint

- First 2 cycles Dose-Limiting Toxicities (DLTs).

Secondary Endpoints

- Adverse Events (AEs) as characterized by type, frequency, severity [(as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v. 4.03)], seriousness and relationship to study therapy;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03);
- Vital Signs (blood pressure and pulse rate), weight, Eastern Cooperative Oncology Group (ECOG) Performance Status;
- Pharmacokinetic parameters of PF-05082566 and mogamulizumab, including but not limited to C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last}$, AUC_{tau}, $t_{1/2}$, CL and V_{ss}, as data permits;
- Anti-drug Antibody (ADA)/neutralizing antibody (Nab) titers for PF-05082566 and mogamulizumab;
- Objective tumor response (see Appendix 2 and Appendix 3 for details);
- Duration of Response (DR) (expansion cohorts only);
- Time to Response (TTR) (expansion cohorts only);
- Progression-free Survival (PFS) (expansion cohorts only).

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- [redacted]
- [redacted]

STUDY DESIGN

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, pharmacokinetic and pharmacodynamic study designed to estimate the MTD, and determine the RP2D of PF-05082566 in combination with mogamulizumab in patients with advanced solid tumors.

This clinical study will include:

1. Dose-Finding portion

In the dose-finding portion, the MTD of the combination will be estimated in patients with advanced solid tumors.

PF-05082566 1.2 mg/kg and mogamulizumab 1 mg/kg will be the starting dose level. See Section 3.1.8 for further information on the Dose Escalation Strategy. The dose levels to be tested in the dose-finding portion are shown in Table 6 of Section 3.1.9.

Dose escalation and MTD estimation for the PF-05082566 plus mogamulizumab combination will be conducted according to the following algorithm:

a. Dose escalation and de-escalation of PF-05082566 will follow the Time-to-Event Continual Reassessment Method (TITE-CRM) up to a maximum dose of 5 mg/kg once every 4 weeks.

b. The MTD will be defined as the highest combination dose with a DLT rate <30% from the model estimate.

c. Dose escalation may stop if:

   - Maximum study sample size of 30 is reached; or
   - 9 DLT evaluable patients have been treated at the estimated MTD (6 if no DLT observed at any dose); or
   - All doses appear to be overly toxic and the MTD cannot be determined in the current trial.

A flat dosing of PF-05082566 100 mg will be studied to confirm the safety and PK at a dose that may be used for the expansion cohorts. This cohort will only enroll SCCHN and/or squamous NSCLC patients.

The 5.0 mg/kg cohort (if safe and tolerable) will enroll at least 6 squamous NSCLC patients.

It is estimated that approximately 30 patients would be required in the dose-finding portion to achieve the study objectives.

2. Dose Expansion portion

Once the MTD of PF-05082566 administered in combination with mogamulizumab has been estimated with confidence, one or more expansion cohorts of patients will be enrolled to further study the safety, tolerability, PK/PD, and preliminary anti-tumor activity for PF-05082566 in combination with mogamulizumab as well as to study CCI [redacted]. Tumor types for the expansion cohorts will be selected from CRC, bladder,

ovarian, squamous esophageal, SCCHN and/or squamous NSCLC patients. Dose, tumor types, CCI for these cohorts will be selected based on emerging data from the dose-finding portion of the study or data obtained from ongoing studies testing PF-05082566.

The total enrollment into all expansion cohorts will be up to 40 response-evaluable patients.

Study Treatment

In both portions, treatment will be administered in 4-week cycles.

PF-05082566 will be administered as a 1-hour intravenous (IV) infusion, every 4 weeks (q4wks), on Day 1 of each cycle. The starting dose of PF-05082566 will be 1.2 mg/kg.

Mogamulizumab will be given as a 1-hour IV infusion, every week (qwk), for 4 consecutive weeks (Days 1, 8, 15 and 22) followed by biweekly dosing (Days 1 and 15), at the dose of 1 mg/kg.

On Day 1 of a dosing cycle, in which the drugs are co-administered, and PK samples are collected, the mogamulizumab infusion will start 30 minutes (±10 min) after completion of PF-05082566 infusion and after the end of infusion PF-05082566 PK blood sample and pre-mogamulizumab PK blood sample are drawn. See Table 2.

Treatment with study drugs will continue until completion of 24 months of treatment (approximately 24 cycles), confirmed disease progression, patient refusal, unacceptable toxicity, whichever occurs first, or the study is prematurely terminated by the Sponsor, or for one of the other reasons for patient withdrawal as specified in Section 6.4.

Discontinuation from treatment may be considered at the investigator's discretion for patients who have attained a confirmed complete response (CR), and have received at least two cycles of mogamulizumab and PF-05082566 after the date the CR was confirmed. Patients who then experience radiologic disease progression will be eligible for re-treatment with both study drugs at the discretion of the investigator and by the approval of the Sponsor, if no anticancer treatment was administered since the last dose of study drugs, the patient meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is still open.

Patients will resume therapy at the same dose and schedule as at the time of initial discontinuation. Patients who completed the 24 months of treatment on-study and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study treatment will be given the opportunity to continue treatment off-study upon agreement between investigator and Sponsor.

Safety Assessments

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as reported in Schedule of Activities (Table 1) and in Section 7.1, Safety Assessments.

Efficacy Assessments

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, and on treatment every 8 weeks ±7 days starting from Cycle 1 Day 1 up to 1 year, then every 3 months (±7 days) as specified in the Schedule of Activity Table 1. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the End of Treatment (EOT) (if not done in the previous 8 weeks and during follow up visits (if applicable). Assessment of response will be made using RECIST version 1.1 (Appendix 2) and irRC (Appendix 3). Further details are provided in Section 7.2, Tumor Assessments.

Pharmacokinetic (PK)/Immunogenicity Assessments

PK/Immunogenicity sampling will be required for all patients (See Table 2 and Sections 7.3 and 7.5 for further details). The proposed PK timepoints may be reconsidered and amended during the study based on the emerging safety and pharmacokinetic data. No drug interaction is anticipated between PF-05082566 and mogamulizumab. Since PF-05082566 and mogamulizumab are eliminated via a non-specific catabolic degradation process, it is unlikely that concomitant medication can alter its clearance even if target expression is affected. To assess any potential interactions, steady state PK and the formation of anti-drug antibodies (ADA) will be monitored for both agents and compared with historical data.

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[redacted]

CCI [redacted]

[redacted]

Approximately 70 patients are expected to be enrolled in the study overall (including dose-finding and expansion cohorts).

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS Section of the protocol for detailed information on each assessment required for compliance with the protocol.

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

Table 1. Schedule of Activities: Safety and Efficacy Assessments (Dose-finding and Expansion Cohorts)

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)												Post Treatment	
	≤28 days of registration	CYCLE 1				CYCLE 2				CYCLES ≥3				End of Treatment /Withdrawal [31]	Follow Up[32]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Visit Window (days)	(-) 7		(+) 2	(+ 2)	(+) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(±) 2	(+) 7	
Informed Consent[2]	X														
Tumor History[3]	X														
Medical History[4]	X														
Physical Examination [5]	X	X	X	X	X	X	X	X	X	X	X up to C4	X	X up to C4	X	(X)
ECOG PS[6]	X	X				X				X				X	(X)
Vital signs[7]	X	X	X	X	X	X		X		X		X		X	(X)
Contraception check	X	X	X	X	X	X		X		X		X		X	X
Safety Labs/Measurements															
Hematology[8]	X	X	X	X	X	X		X		X		X		X	(X)
Blood Chemistry[9]	X	X	X	X	X	X	X	X	X	X	X up to C4	X	X up to C4	X	(X)
Coagulation[9]	X	X				X				X				X	(X)
Urinalysis[10]	X	X				X				X				X	(X)
Pregnancy Test[11]	X	X				X				X				X	(X)
12-Lead ECG [12]	X	X				X				X up to C4				X	(X)
Hepatitis B and C tests[13]	X														
Thyroid and other endocrine function tests[14]	X	X (As clinically indicated)													
Registration and Treatment															
Registration[15]		X													
PF-05082566 Administration[16]		X				X				X					
Mogamulizumab Administration[17]		X	X	X	X	X		X		X		X			
Tumor Assessments															
CT or MRI scan[18]	X	Every 8 weeks (±7 days) up to 1 year, then every 3 months (±7 days)												X	X
Other Clinical Assessments															
Adverse Events[19]		Monitored and Recorded Continuously												X	X
Concomitant Medication[20]	X	Monitored and Recorded Continuously												X	

Table 2. Schedule of Activities: Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments (Dose-finding and Expansion Cohorts)

Protocol Activities	Screening[1]	On Treatment (1 Cycle=28 days)									Post Treatment	
		Cycle 1				Cycles 2-4	Cycle 5			Cycles 8, 12, 16, 20, 24	EOT [31]	Follow Up [32]
Visit Window Cycle 1(+)2 days Cycles 2--5: (±) 2 days Cycles >5: (±) 7 days	**(≤28 days of registration**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**	**Day 8**	**Day 15**	**Day 1**		
Blood for PF-05082566 PK[21]		X				X	X	X	X	X	X	
Blood for Mogamulizumab PK[22]		X	X	X	X	X	X	X	X	X	X	
CCI [redacted]												
Banked Biospecimen (DNA)[25]		X										
Blood for Pharmacogenomics (RNA)[26]		X				X (C 2 & 3 only)	X				X	
Blood for PF-05082566 Immunogenicity testing[27]		X				X (C3 only)	X			X	X	X
Blood for Mogamulizumab Immunogenicity testing[28]		X				X (C3 only)	X			X	X	X
CCI [redacted]												

Footnotes for Schedules of Activities	
1.	**Screening:** To be obtained within 28 days prior to registration.
2.	**Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
3.	**Tumor History:** Includes oncology history; information on prior regimens (including dosing and duration of administration, description of best response observed, recurrence date), surgery and radiation therapy.
4.	**Medical History:** Includes history of other diseases (active or resolved) and concomitant illnesses.
5.	**Physical Examination:** Includes an examination of major body systems. Weight for the purposes of dose calculation will be recorded at screening and within 7 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment. Height will be measured at baseline only.
6.	**ECOG PS:** ECOG performance scale is available as Appendix 1.
7.	**Vital Signs:** blood pressure (BP) and pulse rate to be recorded in supine or sitting position.
8.	**Hematology:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study medications unless otherwise indicated. If during the first 2 cycles of treatment a Grade 4 hematologic event is evident, the hematology assessment should be repeated at least every other day to assess for events qualifying as DLT. See Table 10 in Section 7.1.3, Laboratory Safety Assessments, for the list of the required Laboratory Tests.
9.	**Blood Chemistry and Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. On treatment, to be performed prior to dosing with study medications unless otherwise indicated. See Table 10 in Section 7.1.3, Laboratory Safety Assessments, for the list of the required Laboratory Tests.
10.	**Urinalysis:** During the treatment period to be performed when clinically indicated. If protein ≥2+ by semiquantitative method (eg, urine dipstick), protein will be quantified by 24 hour urine collection (see Table 10). Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein.
11.	**Serum/Urine Pregnancy Test (serum/urine):** For female patients of childbearing potential, will be performed on 2 separate occasions prior to starting study treatment: once at the start of screening and once at the baseline visit, immediately before study drug administration.. Following a negative pregnancy result at screening, appropriate contraception must be commenced. Pregnancy tests to be routinely repeated on Day 1 every cycle. Additional pregnancy test to be done whenever one menstrual cycle is missed or when potential pregnancy is suspected. Additional pregnancy tests may also be done if requested by IRB/ECs or if required by local regulations. See Section 4.3 for contraception guidelines.
12.	**12-lead ECG**: At each time point, 3 consecutive 12 lead ECGs will be performed approximately 2 minutes apart to determine mean QTc. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. On treatment ECGs will be performed on Day 1 of Cycles 1-4, before and at the end of PF-05082566 infusion and at the end of mogamulizumab infusion. Cycle s>4, ECGs to be performed only if clinically indicated. While pre-dose ECG assessments will be required for all patients, post-dose ECG assessments will be required only for patients in dose-finding cohorts. See Section 7.1.5 for further details.
13.	**Hepatitis B and C Tests:** Conduct tests for hepatitis B surface antigen, core antibody, and anti-hepatitis C. Other tests may be conducted per standard practice to confirm an active hepatitis infection.
14.	**Thyroid and other Endocrine Function Tests :** On treatment, thyroid function tests will be performed in cases of clinical symptoms consistent with thyroiditis. On treatment, other endocrine function tests (in addition to T3, FT4, and TSH) will be performed in cases of suspected hypoadrenalism or hypopituitarism See Table 10, in Section 7.1.3, Laboratory Safety Assessments, for the list of the required Laboratory Tests.
15.	**Registration:** Patient number and dose level allocation operated by Pfizer Inc. Study treatments administration should begin within 7 days of registration.
16.	**PF-05082566 Administration:** Treatment will be administered in a 4-week cycle (ie, 28-day cycle). PF-05082566 will be administered as a 1-hour IV infusion on Day 1 of each cycle. When both PF-05082566-and mogamulizumab are administered, PF-05082566 will be administered first. Treatment will continue until completion of 24 months of treatment (approximately 24 cycles), or for one of the reasons listed for patient withdrawal as specified in Section 6.4.

17.	**Mogamulizumab Administration:** Treatment will be administered in a 4-week cycle (ie, 28-day cycle). In Cycle 1, Mogamulizumab will be administered as a 1-hour IV infusion every week (ie, on Days 1, 8, 15, 22). From Cycle 2 onwards, mogamulizumab will be administered every 2 weeks (ie, on Days 1 and 15 of every cycle). On Day 1, mogamulizumab infusion will start 30 minutes (±10 min) after completion of PF-05082566 infusion and after the post-PF-05082566 and pre-mogamulizumab pharmacokinetic blood samples are drawn. Treatment will continue until completion of 24 months of treatment (approximately 24 cycles), or for one of the reasons listed for patient withdrawal as specified in Section 6.4.
18.	**Tumor Assessments:** Assessment of response will be made using RECIST version 1.1 and irRC (see Appendix 2 and Appendix 3 for details). Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, on treatment every 8 weeks up to 1 year, then every 3 months and whenever disease progression is suspected (eg, symptomatic deterioration). To be repeated at EOT only if not done in the previous 8 weeks. Confirmation of response (CR/PR) should be done at least 4 weeks after the initial response. Timing should follow calendar days and should not be adjusted for delays in cycle starts. (See Section 7.2 for further details).
19.	**Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For SAEs, the active reporting period begins from the time that the patient provides informed consent, through and including 60 calendar days after the last administration of the investigational products and before initiation of a new anti-cancer treatment. SAEs experienced by a patient after the active reporting period has ended should be reported to the Sponsor if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. Pregnancy or breast feeding that occur during the trial, within 60 days of discontinuing treatment with mogamulizumab, or within 60 days after the cessation of PF-05082566 if the patient begins a new anticancer therapy, whichever is earlier, should be reported as stated in (see Section 8.10, Exposure During Pregnancy for details).
20.	**Concomitant Medications:** Concomitant medications will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment.
21.	**Blood for PF-05082566 Pharmacokinetics:** Blood samples (2 mL whole blood at each time point) will be collected as follows: Dose-finding cohorts**:** Cycles 1- 4 on Day 1 at pre-dose and at the end of PF-05082566 infusion; Cycle 5 on Day 1 at pre-dose, at the end of PF-05082566 infusion, and at 2, 6, 168 hrs. (Day 8) and 336 hrs. (Day 15) after the start of PF-05082566 infusion. Day 1 at pre-dose of Cycles 8, 12, 16, 20, 24 and at EOT. See Section 7.3.1 Expansion cohorts: the same PK schedule foreseen in the dose-finding portion will be followed **for at least 10 patients** in total from all expansion cohorts. **For all other patients in the expansion cohorts**, blood for PK will be taken on Cycle 1 Day 1 (at pre-dose and at the end of PF-05082566 infusion), Day 1 at pre-dose of Cycles 3, 5, 8, 12, 16, 20, 24 and at EOT. Timing of sampling may be modified based on emerging safety/PK data. See Section 7.3.1.
22.	**Blood for Mogamulizumab Pharmacokinetics:** Blood samples (3 mL whole blood at each time point) will be collected as follows: Dose-finding cohorts: Cycle 1: a) On Day 1, Day 8, Day 15 and Day 22 at pre-dose, at the end of mogamulizumab infusion, Cycles 2-4: at pre-dose; Cycle 5: a) on Day 1 at pre-dose, at the end of mogamulizumab infusion, and at 6 hrs., and 168 hrs. (Day 8) after the start of the mogamulizumab infusion; b): On Day 15 at pre-dose. Day 1 at pre-dose of Cycles 8, 12, 16, 20 , 24 and at EOT. Expansion cohorts: the same PK schedule foreseen in the dose-finding portion will be followed **for at least 10 patients** in total from all expansion cohorts. **For all other patients in the expansion cohorts,** blood for PK will be taken on Cycle 1 Day 1 (at pre-dose and end of mogamulizumab infusion), and Day 1 at pre-dose at of Cycles 3, 5, 8, 12, 16, 20, 24 and at EOT. Timing of sampling may be modified based on emerging safety/PK data. See Section 7.3.2 for further guidelines.
23.	CCI [redacted]

[redacted]

CCI CCI
26. Blood for Pharmacogenomics (RNA): Blood samples (2.5 mL whole blood at each time point) will be collected on Day 1 at pre-dose of Cycles 1, 2, 3, 5 and at the EOT. See Section 7.7 for details.
27. Blood for PF-05082566 Immunogenicity Testing: Blood samples (2 mL whole blood at each time point) for PF-05082566 immunogenicity testing will be collected on Day 1 at pre-dose of Cycles 1, 3, 5, 8, 12, 16, 20, 24 and EOT. If ADAs are detected, additional samples may be collected approximately every 8 weeks until ADA levels return to baseline. See Section 7.5.1 for details.
28. Blood for Mogamulizumab Immunogenicity Testing: Blood samples (3 mL whole blood at each time point) for mogamulizumab immunogenicity testing will be collected Day 1 at pre-dose of Cycles 1, 3, 5, 8, 12, 16, 20, 24 and EOT. If ADAs are detected, additional samples may be collected approximately every 8 weeks until ADA levels return to baseline. See Section 7.5.2 for details.
CCI
31. End of Treatment: To be performed no later than 28 days (+7 days) after the last dose of study drug. Obtain these assessments if not completed during the previous week on study, (during the previous 8 weeks on study, for tumor assessments).
32. Follow Up: Patients should be evaluated up to 60 days for safety (SAEs) after last dose of study treatment. Refer to the protocol for specific guidelines. Patients continuing to experience drug related toxicity following discontinuation of study 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. PK and immunogenicity samples should be collected as described in the PK and Immunogenicity ASSESSMENTS Section in SOA (Table 2). Patients whose disease has not progressed at the end of treatment will enter into disease follow up. During this follow up period, patients will have disease assessments performed every 8 weeks (±7 days). Once patients have exhibited disease progression or began a new anticancer therapy, or 6-month follow-up from the date of the last dose of the last enrolled patient, whichever occurs first, they will be withdrawn from the study. See Section 4.3 for guidelines on contraception during this period.

Legend (X) = optional activity to be executed only if applicable; ADA= anti-drug antibodies; AE= adverse event; C=cycle; CRF= case report form: ECG= electrocardiogram; D=day; irRC= Immune-Related Response Criteria; PK=Pharmacokinetics;

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-05082566 is a novel fully human IgG2 monoclonal anti-body (mAb) agonist of 4-1BB (CCI, TNFRSF9) that is being developed in combination with Poteligeo® (mogamulizumab), a recombinant humanized mAb targeting C-C chemokine receptor 4, (CCR4, CD194) registered in Japan for CCR4 expressing adult T-cell leukemia/lymphoma (ATL), peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL). The proposed combination is being studied for the treatment of adult patients with advanced solid malignancies that are unresponsive to currently available therapies, or for whom no standard therapy is available.

1.2. Background and Rationale

1.2.1. 4-1BB Target Biology and Mechanism of Action

4-1BB (CCI, TNFRSF9), first identified as an inducible co-stimulatory receptor expressed on activated T cells, is a membrane spanning glycoprotein of the Tumor Necrosis Factor (TNF) receptor superfamily. Current understanding of 4-1BB indicates that expression is generally activation dependent and encompasses a broad subset of immune cells including activated natural killer (NK) and natural killer T (NKT) cells, regulatory T cells (Treg), dendritic cells (DC) including follicular DC, stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils[1] and activated B cells.[2] 4-1BB expression has also been demonstrated on tumor vasculature[3,4] and atherosclerotic endothelium.[5] The ligand that stimulates 4-1BB (4-1BBL) is expressed on activated antigen-presenting cells (APCs), myeloid progenitor cells and hematopoietic stem cells.

4-1BB is undetectable on the surface of naïve T cells but expression increases upon activation. Based on homology to other members of the TNF receptor superfamily (TNFRSF), ligand binding is expected to induce receptor trimerization resulting in activation.[6] Some members of the TNFRSF can cleave the extracellular domain from the cell surface and exist in a soluble form. Soluble 4-1BB and soluble 4-1BBL have been demonstrated in the serum of some patients with autoimmune diseases and cancers.[7,8,9]

Upon 4-1BB activation, TRAF 1 and TRAF 2, pro-survival members of the TNFR-associated factor (TRAF) family are recruited to the 4-1BB cytoplasmic tail resulting in downstream activation of NF-kB and the Mitogen Activated Protein (MAP) Kinase cascade including Erk, Jnk, and p38 MAP kinases. NF-kB activation leads to upregulation of Bfl-1 and Bcl-XL, pro-survival members of the Bcl-2 family. The pro-apoptotic protein Bim is downregulated in a TRAF1 and Erk dependent manner.[10]

Numerous studies of murine and human T cells indicate that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production.[11] Reports have shown that 4-1BB agonist mAbs increase co-stimulatory molecule expression and markedly enhance cytolytic T lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings and both monotherapy and combination therapy tumor models and have established durable anti-tumor

protective T cell memory responses.[12] 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models.[13] This dual activity of 4-1BB offers the potential to provide anti-tumor activity while dampening autoimmune side effects that can be associated with immunotherapy approaches that break immune tolerance.

Interaction of 4-1BB on activated normal human B cells with its ligand at the time of B cell receptor engagement stimulates proliferation and enhances survival.[2] The potential impact of 4-1BB engagement in B cell lymphoma has been investigated in two published studies. Evaluation of several types of human primary non-Hodgkin's lymphoma (NHL) samples indicated that 4-1BB was expressed predominantly on infiltrating T cells rather than the lymphoma cells.[14] The addition of 4-1BB agonists to *in vitro* cultures of B lymphoma cells with rituximab and NK cells resulted in increased lymphoma killing.[15]

In addition, B cell immunophenotyping was performed in two experiments using PF-05082566 in cynomolgus monkeys with doses from 0.001-100 mg/kg; in these experiments peripheral blood B cell numbers were either unchanged or decreased.

1.2.2. Preclinical Profile of PF-05082566

PF-05082566, an intravenous (IV) fully human IgG2 monoclonal antibody (mAb), binds to the extracellular domain of human 4-1BB with high affinity and specificity and is capable of 4-1BB agonism. In a human xenograft tumor model, injection with PF-05082566 as a single agent has been shown to correlate with tumor cell line growth inhibition. In addition, 4-1BB agonist mAbs demonstrate significant combinatorial efficacy with antibody-dependent cellular cytotoxicity (ADCC) antibodies in lymphoma models. Preclinical studies support the use of this 4-1BB agonist mAb as a promising candidate for treatment of cancer, alone or in combination with ADCC-inducing mAbs.

1.2.2.1. *In Vitro* PF-05082566 Data

PF-05082566 has shown immunomodulatory activity in various *in vitro* assays. In concert with a signal through the T-cell receptor, PF-05082566 has been shown to mediate ligation of 4-1BB, which results in activation of NFkB culminating in T cell cytokine release and proliferation. The *in vitro* properties of PF-05082566 are summarized in Table 3.

Table 3. In Vitro Properties of PF 05082566

In vitro Assay	Activity (nM± SD)
Affinity for 4-1BB	
Biacore	
Affinity (KD)	8.7±1.0
On rate (Ka)	1.4±0.06 x10^6 M^{-1} s^{-1}
Off rate (Kd)	0.012±0.001s^{-1}
Saturation Binding	
4-1BB ECD binding ELISA (EC50; n=3)	
Human	0.124±0.041
Cyno	0.198±0.024
4-1BB expressing 300.19 cells (FACS EC50; n=2)	
Human	1.8
Cyno	4.2
PHA stimulated primary cells	
Human PBMC (FACS EC50; n=12)	48.9±24
Cynomolgus PBMC (FACS EC50; n=7)	149±68
Dog, rat, mouse PBMC (FACS; n=2)	No binding up to 100 nM
Inhibition of ligand binding	
Ligand competition ELISA (IC50; n=2)	0.200±0.003
***In vitro* stimulation**	
4-1BB transfected cells (NF-kB luciferase reporter) (EC50)	
Human (n=3)	0.15±0.04
Cyno (n=3)	0.4±0.039
Augmentation of primary human T cell activity	
CD3 induced IL-2 production (EC50{range max fold induction}; n=12)	22.6±7.63 {2-20}
Selectivity (FACS)	
CD40, CD134	No binding up to 1000 nM
4-1BB transfected cells (NF-kB luciferase reporter) (EC50)	
Human (n=3)	0.15±0.04
Cyno (n=3)	0.4±0.039

Abbreviations: ECD = Extracellular Domain; ELISA = Enzyme Linked Immunosorbent Assay; FACS = Fluorescence Activated Cell Sorting; IL 2 = Interleukin 2; NF-kB = Nuclear Factor kappa B; PBMC = Peripheral Blood Mononuclear Cell; PHA = Phytohemagglutinin

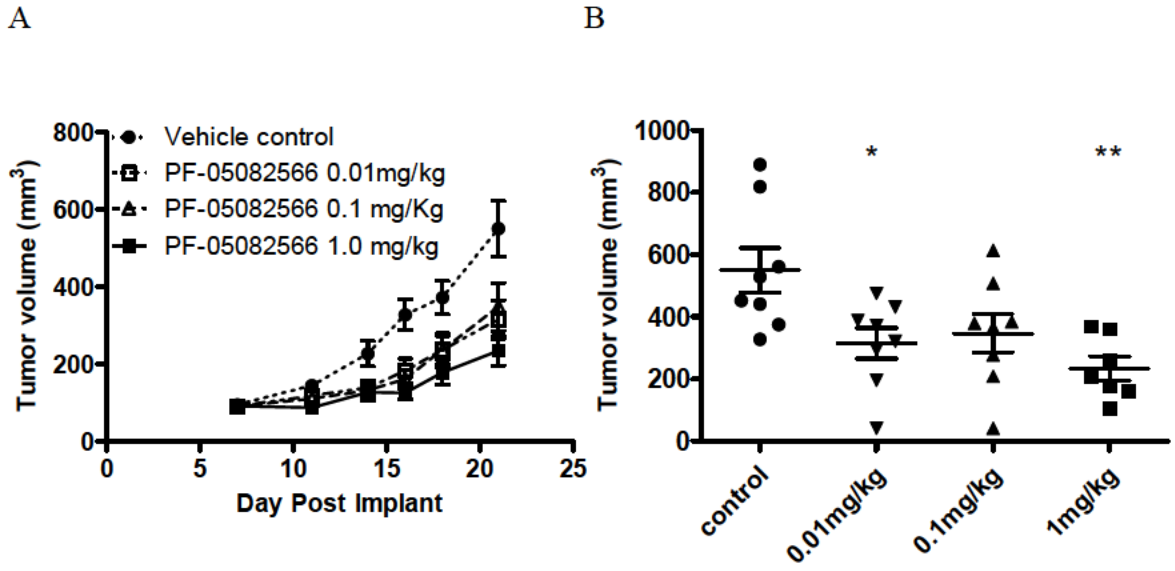
1.2.2.2. *In Vivo* Data: Functional Activity of PF-05082566

In pre-clinical studies, PF-05082566 has exhibited the ability to increase lymphocyte proliferation. In small animal models developed to test the *in vivo* function of PF-05082566, PF-05082566 was able to enhance expansion of human leukocytes in a dose dependent manner as evidenced by an increase in the proportion of human CD45+ cells in the peripheral blood of engrafted mice. Similarly, a dose dependent increase in the proportion of human leukocytes expressing the proliferation marker Ki-67 was noted. In addition, PF-05082566 treatment of cynomolgus monkeys in single or multiple dose studies increased cytotoxic central memory T cells (CD8 T_{CM}) proliferation in peripheral blood mononuclear cell (PBMC) samples. Taken together, these data demonstrate evidence of PF-05082566's ability to enhance lymphocyte response *in vivo*.

1.2.2.3. Preclinical Anti-Tumor Activity of PF-05082566

Single agent PF-05082566 has demonstrated anti-tumor activity in pre-clinical studies. Tumor cell lines representing melanoma, colon, and prostate tumor types were tested in a xenogeneic tumor model. None of the tumor lines expressed 4-1BB; therefore, tumor cells were mixed with primary human PBMC from a healthy volunteer donor prior to injection in all cases. Once tumors were established, animals were treated with PF-05082566. PF-05082566 was found to be efficacious against all 3 tumor types. An example growth curve demonstrating the response to a prostate carcinoma is shown in Figure 1.

Figure 1. Effect of PF-05082566 on the Growth of PC3 Prostate Carcinoma in a huPBL SCID Model



PF-05082566 inhibits the growth of the PC3 prostate carcinoma *in vivo* Panel A: mean tumor volume at each time point measured. Panel B: volume of each tumor on the final study day (Day 21). The mean and standard error of the mean (SEM) are indicated by bars. *p<0.05, ** p<0.005.

1.2.2.4. Preclinical Pharmacokinetics of PF-05082566

Complete information for PF-05082566 pre-clinical pharmacokinetic (PK) studies may be found in the PF-05082566 Investigator Brochure (IB).[16]

1.2.2.5. Pharmacokinetics and Pharmacodynamics Relationship of PF-05082566

PF-05082566 binds to recombinant human 4-1BB by Biacore analysis with an overall kinetic constant (K_D) of 8.7 nM. As noted above, PF-05082566, does not cross react with rodent 4-1BB. The pharmacokinetic/pharmacodynamic (PK/PD) relationship of PF-05082566 and its PD response to anti 4-1BB and tumor growth index (TGI) in a subcutaneous transplantable CT-26 model was evaluated using a surrogate antibody, a rat anti-mouse 4-1BB antibody (MAB9371). The surrogate antibody was administered as a single subcutaneous (SC) dose at 0.01, 0.1, 1 and 10 mg/kg to Balb/c mice 7 days after A20 murine lymphoma cells were implanted. The PK endpoints were represented by the serum

concentration-time profile over 3 weeks post dose. CCI

[redacted]

1.2.2.6. Preclinical Toxicology of PF-05082566

The nonclinical safety summaries for PF-05082566 can be found in the PF-05082566 IB.[16]

Nonclinical toxicology studies with the combination of PF-05082566 and mogamulizumab have not been performed.

1.2.3. Clinical Safety of PF-05082566

PF-05082566 is being developed for patients with relapsed or refractory solid tumor malignancies or B-cell lymphoma. The ongoing Phase 1, open-label, dose-escalation study (B1641001) is aimed to evaluate the safety, pharmacokinetics and pharmacodynamics, Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of PF-05082566 given as a single agent in patients with solid tumors or relapsed or refractory B-cell lymphoma (Portion A), and given in combination with rituximab in patients with relapsed or refractory CD20 positive non-Hodgkin's lymphoma (NHL) (Portion B).

In this study, as of data cut-off date of the current IB version, dated 27 June 2014, safety data are available for 40 patients treated IV every 4 weeks with PF-0502566 in sequential dose levels (ie, 0.006, 0.03, 0.06, 0.12, 0.18, 0.24, 0.6, 1.2, 2.4 and 5.0 mg/kg) in Portion A. In Portion B, 27 patients were treated with PF-05082566 at the doses of 0.03, 0.06, 0.12, 0.18, 0.24, 0.30, 0.60, 0.12 and 2.4 mg/kg in combination with rituximab at the fixed dose of 375 mg/m^2 IV every 4 weeks. As with any ongoing study, the available data are preliminary in nature and are subject to change. At the time of this document writing, the dose escalation of PF-05082566 has been completed and this drug continues to be well tolerated up to the maximum tested dose of 10.0 mg/kg as a single agent and in combination with rituximab.

In B1641001 Study, adverse events (AEs) were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v. 4.03).

AEs possibly related to single agent PF-05082566 reported for patients treated in Portion A are summarized in Table 4.

Table 4. Study B1641001- Portion A Treatment Emergent PF-05082566-Related Adverse Events Reported in at Least 1 Patient (Any CTC Grade)

	All Doses (N=40)			
AE Preferred Term by SOC	**Cycles 1-2**		**Cycles >2**	
	N	**%**	**N**	**%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Thrombocytopenia	1	2.5	-	-
EAR AND LABYRINTH DISORDERS				
Ear disorder	-	-	1	2.5
GASTROINTESTINAL DISORDERS				
Abdominal Pain	1	2.5	-	-
Diarrhea	1	2.5	-	-
Nausea	1	2.5	-	-
Paresthesia oral	-	-	1	2.5
Vomiting	2	5.0	-	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	1	2.5	-	-
Influenza like illness	-	-	1	2.5
Pain	1	2.5	-	-
Pyrexia	1	2.5	1	2.5
INVESTIGATIONS				
ALP increased	1	2.5	-	-
Weight decreased	1	2.5	-	-
MUSCULOSKELETAL DISORDERS				
Arthralgia	-	-	1	2.5
Back pain	1	2.5	-	-
Myalgia	-	-	1	2.5
NERVOUS SYSTEM DISORDERS				
Dizziness	-	-	1	2.5
Headache	-	-	1	2.5
Paraesthesia	-	-	1	2.5
PSYCHIATRIC DISORDERS				
Insomnia	1	2.5	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Dyspnoea	-	-	1	3.6
Oropharyngeal pain	-	-	1	3.6
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Papule	-	-	1	2.5
Pruritus	-	-	1	2.5
Rash	1	2.5	1	2.5
Abbreviations: AE=adverse event; ALP=alkaline phosphatase; CTC= common terminology criteria; SOC=system organ class;				

With exception of one case of treatment related Grade 3 alkaline phosphatase increase, only mild (Grade 1) toxicities were reported in Portion A.

No significant differences in terms of incidence and severity were observed between the AEs reported in the DLT observation period (ie, Cycles 1-2) and from Cycle 2 onwards.

A single case of dose-limiting toxicity (DLT) represented by elevated liver function tests (Grade 3 alkaline phosphatase associated with Grade 2 alanine and aspartate aminotransferase increase) was observed in a patient with pancreatic adenocarcinoma and large liver metastases treated at the 0.06 mg/kg dose. No severe liver function test abnormalities were observed at higher doses of PF-05082566.

The AEs possibly related to PF-05082566 administered in combination with rituximab (Portion B) are summarized in Table 5.

Table 5. Study B1641001 - Portion B Treatment Emergent Treatment Related Adverse Events Reported in at Least 1 Patient (Any CTC Grade)

	All Doses (N=27)			
AE Preferred Term by SOC	**Cycles 1-2**		**Cycles >2**	
	N	**%**	**N**	**%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Neutropenia	-	-	1	3.7
GASTROINTESTINAL DISORDERS				
Abdominal Pain	1	3.7	1	3.7
Diarrhea	1	3.7	1	3.7
Dyspepsia	1	3.7	-	-
Dry mouth	1	3.7	-	-
Gastro esophageal reflux	1	3.7	-	-
Mouth ulceration	1	3.7	-	-
Nausea	1	3.7	1	3.7
Vomiting	1	3.7	-	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	5	18.5	1	3.7
Influenza like illness	1	3.7	-	-
Mucosal dryness	1	3.7	-	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Contusion	1	3.7	-	-
Infusion related reactions	5	18.5	-	-
Procedural hypotension	1	3.7	-	-
INFECTIONS AND INFESTATIONS				
Respiratory tract infection	-	-	1	3.7
INVESTIGATIONS				
ECG QT prolonged	1	3.7	-	-
PLT count decreased	1	3.7	-	-
MUSCULOSKELETAL DISORDERS				
Arthralgia	1	3.7	-	-
Muscular weakness	1	3.7	-	-
Pain in extremity	1	3.7	-	-
Sensation of heaviness	1	3.7	-	-
NERVOUS SYSTEM DISORDERS				
Dizziness	1	3.7	-	-
Headache	2	7.4	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Nasal congestion	1	3.7	-	-

Table 5. Study B1641001 - Portion B Treatment Emergent Treatment Related Adverse Events Reported in at Least 1 Patient (Any CTC Grade)

	All Doses (N=27)			
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Alopecia	1	3.7	-	-
Hair texture abnormal	1	3.7	-	-
Rash*	1	3.7	3	11.1
VASCULAR DISORDERS				
Hypotension	1	3.7	-	-

* including rash maculo-papular and rash pruritic.
Abbreviations: AE=adverse event; CTC= common terminology criteria; ECG= electrocardiogram; PLT= platelet: SOC=system organ class;

In Portion B, all treatment-related AEs were mild to moderate in severity (Grade 1 or 2) and mostly observed during the first 2 cycles.

Overall 4 cases of Grade 3 treatment–related AEs were reported: 3 episodes occurred during the first 2 cycles and one from Cycle 2 onwards.

A Grade 3 procedural hypotension and Grade 3 infusion reaction occurred during the first 2 cycles at 0.18 mg/kg and 0.24 mg/kg doses of PF-05082566 respectively. Both AEs were considered related to rituximab infusion. A Grade 3 thrombocytopenia was observed at 1.2 mg/kg of PF-05082566 in a NHL patient which spontaneously recovered within 6 days.

One episode of Grade 3 neutropenia (at 0.03 mg/kg PF-05082566) was reported in Portion B after Cycle 2.

As reported in Table 5 the most frequent TE treatment–related AEs events are represented by fatigue and infusion related symptoms, which were mainly associated with rituximab administration.

Overall, PF-05082566 has been well tolerated across a broad dose range from 0.03 mg/kg to 10 mg/kg, based on the most recent safety data.

A new Phase 1b, open label, multi center, multiple dose, safety, pharmacokinetic and pharmacodynamic study designed to estimate the MTD and determine the RP2D of PF-05082566 in combination with MK 3475 (an anti PD-1 mAb) in patients with advanced solid tumors (B1641003 Study), has been recently activated. No safety data are available for this study at the time of writing this document.

1.2.4. Clinical Efficacy of PF-05082566

Preliminary evidence of anti-tumor activity was observed in both Portion A and B.

In Portion A, two patients with Merkel cell carcinoma (MCC) had prolonged and still ongoing partial responses (PR) (one at 0.24 mg/kg lasting >22 months and the other at 0.6 mg/kg lasting >12 months), while a mixed tumor response was observed in another patient with MCC (at 0.6 mg/kg). Moreover, long lasting stable disease (lasting >8 months) was reported in 2 patients with Merkel cell carcinoma (0.03 mg/kg, 0.12 mg/kg), as well as pancreatic cancer and colorectal carcinoma (both at 0.24 mg/kg), respectively.

In patients with B cell NHL treated with PF-05082566 in combination with rituximab (Portion B), there was evidence for anti-tumor activity in rituximab-refractory disease. Out of 11 patients with rituximab-refractory disease (defined by lack of response or progression within 6 months of rituximab-containing therapy) 2 patients with follicular B cell lymphoma (FL) achieved a complete response (CR), 1 patient each with FL and mantle cell lymphoma achieved a PR, and 1 patient achieved a mixed response with FL.

Two additional patients without a history of rituximab-refractory disease achieved PRs throughout the range of the PF-05082566 dose escalation, including a rituximab naïve patient with CD20 + nodular Hodgkin's lymphoma treated at 1.2 mg/kg.

No efficacy data are available for the Phase 1b study testing PF-05082566 in combination with MK-3475 (an anti PD-1 mAb) in patients with solid tumors at the time of writing this document (B1641003 Study).

1.2.4.1. Pharmacokinetics of PF-05082566 in Humans

As of September 1st, 2014, PK data have been analyzed from a total of 62 patients of study B1641001 (Portion A: 0.006-2.4 mg/kg doses and Portion B: 0.03-1.2 mg/kg doses). The preliminary PK results from the ongoing Phase 1 study suggest that exposure of PF-05082566 increases dose proportionally. In Cycle 1 of Portion A, following attainment of C_{max}, PF-05082566 serum concentrations showed a bi-exponential decline with a mean terminal elimination half-life of 135-280 hrs., a low systemic clearance (CL = 0.23- 0.34 mL/hr/kg) and a small volume of distribution (Vss = 68.7.-92.9 mL/kg). In Portion B, PF-05082566 also showed a bi-exponential decline with a mean terminal elimination half-life of 170-332 hrs., a low systemic clearance (CL = 0.13-0.288 mL/hr/kg) and a small volume of distribution (Vss = 55-94.4 mL/kg).

Preliminary population PK analysis showed that body weight accounts for only a small percentage (~7%) of the variability in PF-05082566 drug exposure. Simulations indicated that PF-05082566 exposure profiles are similar in both body weight and fixed PF-05082566 dosing regimens. Therefore, it is suggested a fixed dosing regimen be utilized for ease of use and to minimize potential medication errors.

1.2.4.2. Immunogenicity of PF-05082566

Based on the preliminary data obtained in Study B1641001, 26 out of 39 patients (66%) were positive for anti-drug antibodies (ADA) in Portion A, for at least one time point. The impact of ADA on PK and efficacy of PF-05082566 is being characterized. No immune mediated adverse events were reported and presence of ADA doesn't seem to preclude anti-tumor activity. No ADA's were detected in Portion B, when PF-05082566 was administered in combination with rituximab.

Complete pre-clinical and clinical information for PF-05082566, including PK data in patients, may be found in the single reference safety document (SRSD), which for this study is the PF-05082566 IB.[16]

1.2.5. Mogamulizumab

C-C chemokine receptor 4 (CCR4) is a cell surface receptor for the macrophage-derived chemokine (MDC), thymus and activation-regulated chemokine (TARC). Chemokines are considered to play a role both in the recruitment of immune and inflammatory cells for anti-tumor response and in the selective homing of neoplastic B and T cells. In normal tissue, CCR4 is known to be selectively expressed on a subset of activated T-helper (Th2) type CD4 positive (CD4+) T cells that produce inflammatory cytokines such as interleukin (IL)-4, IL-5, and IL-13, and has garnered attention as a molecular target for the treatment of allergic disorders such as asthma, atopic dermatitis or allergic rhinitis. CCR4 is also expressed on primed human T regulatory (Treg) cells, NK cells, basophils, monocytes, and platelets.

CCR4 is also overexpressed or expressed at high frequency on the surface of cells in several human T-cell malignancies including peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), and adult T-cell leukemia/lymphoma (ATL).

Preclinical studies conducted using the defucosylated chimeric (murine-human) anti- CCR4 mAb (KM2760), a precursor of the humanized mogamulizumab mAb, demonstrated a potent antibody-dependent cellular cytotoxicity (ADCC) activity against CCR4 positive human T-cell leukemia and lymphoma cell lines by using human peripheral blood mononuclear cells (PBMC) as effector cells *in vitro*. In addition, KM2760 showed significantly higher ADCC activity than the fucosylated antibody (KM3060) in *in vivo* T-cell leukemia mouse models.

The potent ADCC activity of mogamulizumab was further confirmed in *in vitro* and *in vivo* preclinical ATL and T-cell lymphoma models.

POTELIGEO® (Mogamulizumab, KW-0761) is a recombinant humanized monoclonal antibody (mAb) targeting CCR4-expressing cells. It is being developed by Kyowa Hakko Kirin Pharma, Inc. (KHK) for the treatment of T-cell malignancies, including PTCL, CTCL, and adult ATL.

Mogamulizumab was approved by the Ministry of Heath, Labor and Welfare in Japan in March 2012 for the treatment of relapsed or refractory CCR4 positive ATL and is the first POTELLIGENT® antibody to receive marketing approval anywhere in the world.

In March 2014, mogamulizumab received approval from Japan's Ministry of Health, Labour and Welfare for the additional indications relapsed or refractory CCR4-positive peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL).

As of 31 December 2013, globally approximately 340 subjects have received at least one dose of mogamulizumab in clinical studies, and an estimated 800 patients with ATL have received at least one dose of mogamulizumab.

1.2.5.1. Clinical Safety Data for Mogamulizumab

In the Phase 1 dose escalation study in patients with relapsed adult CCR4-positive T-cell leukemia/lymphoma (ATL), peripheral T-Cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL),[17] 16 patients received mogamulizumab once a week for 4 weeks by IV infusion at the doses of 0.01, 0.1, 0.5, and 1.0 mg/kg. Mogamulizumab was well tolerated at all tested doses. Neither the frequency nor the severity of toxicities increased with dose escalation. Only one patient, at the 1.0 mg/kg dose, developed dose-limiting toxicities namely Grade 3 skin rash and febrile neutropenia, and Grade 4 neutropenia. The total number of AEs was similar for all doses, demonstrating no dose relationship for AEs.

The most frequent treatment emergent AEs (TEAEs) considered to be at least possibly related to study drug were lymphocyte count decreased (94%), infusion related reaction (81%), pyrexia (69%), neutrophil count decreased (63%), white blood cell count decreased (63%), platelet count decreased (56%), and chills (50%). The MTD was not reached. Therefore, the RP2D was determined to be 1.0 mg/kg. The plasma maximum (C_{max}) and trough (C_{trough}), and the area under the curve of 0 to 7 days of mogamulizumab, tended to increase dose and frequency dependently.

The 1.0 mg/kg dose was used in all the following clinical studies Sponsored by Kyowa Hakko Kirin Co. Ltd. or Kyowa Hakko Kirin Pharma, Inc.

Clinical Studies Sponsored by Kyowa Hakko Kirin Co. Ltd. conducted in Japan

Mogamulizumab as monotherapy was administered weekly for 4 (Study 0761-0501) or 8 weeks (Studies 0761-002 and 0761-004). Sixteen patients with CCR4+ relapsed ATL, PTCL and CTCL were treated in Study 0761-0501, 27 patients with CCR4 relapsed ATL and 37 with CCR4+ relapsed PTCL and CTCL were treated in studies Study 0761-002 and Study 0761-004, respectively.

The most frequently observed TEAEs (≥10% of patients) that were considered to be at least possibly related to mogamulizumab were: lymphocyte count decreased (90.8%), white blood cell count decreased (63.3%), neutrophil count decreased (56.9%), platelet count decreased (55.1%), pyrexia (54.%), infusion related reaction (33.9%), alanine aminotransferase increased (ALT, 30.3%), aspartate aminotransferase increased (AST, 24.8%), chills (22.9%), anemia and rash (22.9% each), alkaline phosphatase increased and febrile neutropenia (21.1% each), nausea (20.2%), decreased appetite (19.3%), albumin decreased and lactate dehydrogenase (LDH) increased (18.4% each), weight decreased (17.4%), rash papular (16.5%), malaise (15.6%), constipation and stomatitis (14.7% each), headache (13.8%), phosphorus decreased (12.8%), vomiting (12.8%), blood pressure increased and sodium decreased (11.9% each), pruritus, rash erythematous and diarrhea (11.0% each), and potassium decreased and tachycardia (10.1% each).

The drug-related TEAEs that were ≥ Grade 3 in intensity and reported in at least 3 patients were: lymphocyte count decreased (78.0%), white blood cell count decreased (36.7%), neutrophil count decreased (35.8%), platelet count decreased (23.9%), febrile neutropenia (21.1%), anemia (20.2%), decreased appetite and popular rash (6.4% each), rash (5.5%),

ALT increased (4.6%), potassium decreased, sodium decreased, AST increased, gamma-glutamyltransferase increased, stomatitis and pneumonia (3.7% each), LDH increased, blood pressure increased, hypokalemia, hypophosphataemia, rash erythematous, hypoxia and interstitial lung disease (2.8% each), phosphorus decreased, hyperglycemia, toxic skin eruption and pneumonia cytomegaloviral (1.8% each).

Clinical Studies Sponsored by Kyowa Hakko Kirin Pharma, Inc. conducted outside of Japan

In addition to those conducted in Japan, clinical studies were also conducted in US, Europe and other countries. Mogamulizumab was administered weekly for 4 (Study KW-0761-001) or 5 weeks (Studies 0761-007, 0761-009, 0761-010) and then every other week until disease progression. Overall 152 patients with T cell lymphoma were treated as of the cut of date of the current mogamulizumab IB, version 31 December 2013.

The most frequently observed TEAEs (≥10% of patients) that were considered to be at least possibly related to mogamulizumab were: infusion related reaction (20.4%), nausea (13.8%), pyrexia (11.2%), fatigue (10.5%), and drug eruption (10.5%). The mogamulizumab-related TEAEs observed have been generally mild to moderate (Grade ≤2) in severity.

The drug-related TEAEs that were ≥ Grade 3 in intensity and reported in at least 2 patients were: infusion related reaction (4.6%), drug eruption (2.6%), thrombocytopenia (2.0%), neutropenia, acute myocardial infarction, hypertension, and hypotension (1.3% each).

Overall infusion reactions were the most common mogamulizumab-related non hematological TEAEs. Most infusion reactions were generally mild to moderate in severity and symptoms (chills, fever, headache, etc.) and were similar to what has been observed with other monoclonal antibodies. Grade 3 infusion reactions have been observed in a total of 10 (3.8%) patients on Day 1 of dosing. Infusion reactions led to discontinuation of mogamulizumab in 2 patients. Although no events were coded to the preferred term of infusion related reactions in Study 0761-003, the Sponsor considered 2 patients to have experienced symptoms of infusion reactions, ie, blood pressure increased (Grade 3) in one case, and oxygen saturation decreased (Grade 3) in the other case. No Grade 3 infusion reactions were observed in Study 0761-004. Infusion related reactions have been reported as serious adverse events (SAEs) in 3 patients.

Skin rashes, including drug eruptions, considered to be at least possibly related to mogamulizumab administration have been reported in all studies and occurred at an incidence >10% in oncology studies regardless of the Sponsor. In the completed US Study (KW-0761-001), mogamulizumab was administered to 42 patients with relapsed CTCL/PTCL as 4 weekly doses followed by one dose every other week. In this study, a total of 7 (17%) patients experienced study drug related drug eruptions, most of which were considered mild or moderate in severity; only one patient had a Grade 3 eruption.

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1.2.5.2. Pharmacokinetics of Mogamulizumab

Currently the PK of intravenously administered mogamulizumab has been assessed in 8 clinical studies. The PK results from 6 of the completed studies (0761-EU-001, 0761-0501, 0761-002, 0761-003, 0761-004 and KW-0761-001 are detailed in the mogamulizumab IB.

For the 1.0 mg/kg dose, administered IV (once a week for four weeks then every other week), mean ± standard deviation (SD) half-life values were 184±64 and 332±86 hrs. on Days 1 and 22, respectively.

1.2.5.3. Immunogenicity of Mogamulizumab

The presence of anti-mogamulizumab antibodies was monitored in studies performed on healthy adults (Study 0761-EU-001) as well as in patients with hematological malignancies (Studies 0761-0501, 0761-002, 0761-003 and 0761-004 and KW-0761-001).

No subjects in these studies had anti-mogamulizumab antibodies detected with the exception of study KW-076-001 in which the analysis, which are still ongoing, reported 4 patients who had positive responses in the pretreatment samples.

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[redacted]

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1.2.6. Study Rationale

Tumor metastasis represents the primary cause of mortality in neoplastic patients and remains the major challenge for cancer therapy.

The approach to cancer treatment for metastatic solid tumors, apart from rare exceptions, is mainly palliative and even in patients who present with remarkable responses to cytotoxic or targeted therapies, the disease eventually progresses.

Immuno-oncology therapies have the advantage of being able to mount an ongoing, dynamic immune response that can continue to seek out and kill tumor cells long after the therapy has been given. Thus this adaptive, long-lived response has the potential to completely eradicate tumor cells rather than just lead to a several-log kill.

However, despite recent developments in cancer immunotherapies, clinical benefit occurs in a minority of patients. Only a minority of patients respond to treatment with single agents such as IL-2 for melanoma and kidney cancer,[19] experimental cancer vaccines such as[20] Provenge® for prostate cancer,[21] anti–CTLA-4 monoclonal antibody (mAb) (ipilimumab) for melanoma,[22] and anti-PD-1 mAbs for multiple indications, with an objective response rate in immunoresponsive tumor types ranging between 16% and 37%.[23] Recent work has suggested that tumor resistance to immunotherapies might be due to an immunosuppressive status within the tumor microenvironment.

Preclinical experiments demonstrated that when compared with peripheral blood T cells, tumor-infiltrating T cells (TILs) contained a higher frequency of effector Tregs (eTregs), generally characterized by suppressive function. eTreg cells, but not naïve Treg cells, predominantly expressed CCR4 in both cancer tissues and peripheral blood. *In vitro* culture of mogamulizumab with PBMC obtained from cancer patients leads to depletion of CCR4+ Treg and expansion of anti-tumor T cells.[24] *In vivo* evaluation of the effect of CCR4 depletion on anti-tumor immune responses and tumor growth of mogamulizumab has not been performed since appropriate antibodies to murine CCR4 are not available.

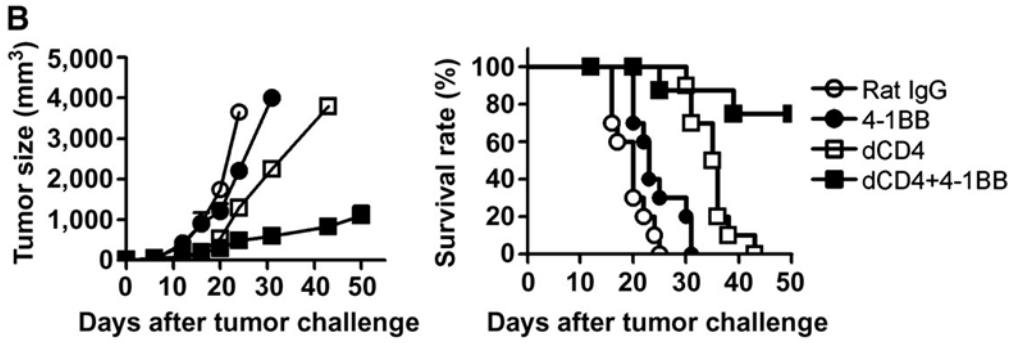
Of note, preclinical studies have demonstrated that Treg cells expressing the transcription factor FOXP3 play a critical role in suppressing antitumor immune responses.

In vitro or *in vivo* anti-CCR4 mAb treatment selectively depleted eTreg cells and efficiently induced tumor-antigen-specific CD4+ and CD8+ T cells and cytokine production. Thus, cell-depleting anti-CCR4 mAb therapy is instrumental for evoking and enhancing tumor immunity in humans via selectively removing eTreg cells.[25]

The efficacy of 4-1BB agonist as a cancer therapy has been documented. Its therapeutic effects are mediated by enhancing NK and CD8+ T-cell activation and IFN-γ production.

In vivo experiments on a B16-F10 mouse melanoma model demonstrated that the antitumor activity of an anti- 4-1BB can be significantly improved by the combination with an anti-CD4 mAb. When co-administered, anti-4-1BB and anti-CD4 mAbs were able to successfully inhibit tumor growth and induced increased survival (Figure 2). Anti-4-1BB treatment resulted in the polyclonal expansion and differentiation of CD8+ T cells into effective tumor killers while the CD4+ T-cell depletion facilitated the infiltration of immune cells into the tumors and removed regulatory barriers such as Tregs.[26]

Figure 2. Antitumor Effects of Combined Therapy with Anti-4-1BB and Anti-CD4 mAb in B16F10 Mouse Melanoma Model



Antitumor effects of combined therapy with anti-4-1BB and anti-CD4 mAb. B16F10 melanoma bearing mice 6 days after tumor cells sc injection (when the tumors were 3 to 5 mm in diameter) were injected i.p. with 100 μg anti-4-1BB (3E1) and/or 400 μg anti-CD4 (GK1.5), or 100 μg rat IgG as a control, five times every 5 d.

PF-05082566 is a fully human IgG2 agonist monoclonal antibody targeting 4-1BB. The safety and tolerability of PF-05082566 is currently being evaluated in a Phase 1 study as a single agent in patients with advanced solid tumors or B cell lymphoma and in combination with rituximab in patients with CD20+ NHL (Study B1641001). PF-05082566, administered every 4 weeks, has been well tolerated (up to 10 mg/kg dose as single agent and up to 2.4 mg/kg in combination with rituximab) with mostly Grade 1 TEAEs attributed to PF-05082566.

Mogamulizumab is a humanized mAb of the IgG1/kappa isotype targeting CCR4-expressing cells approved in Japan for the treatment of relapsed or refractory CCR4 positive ATL, PTCL and CTCL and currently under investigation as single agent in patients with advanced solid tumors. Mogamulizumab demonstrated an acceptable safety profile. The AEs reported have generally been mild to moderate in severity, with the most frequent mogamulizumab-related TEAEs being infusion related reactions, nausea, pyrexia, fatigue, and drug eruption, all easily manageable through the administration of appropriate treatment.

Based on the upon consideration that show a potential synergies of the two agents this Phase 1b study will assess the safety and tolerability, establish the maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) of PF-05082566 in combination with mogamulizumab in patients with advanced solid tumors.

The Sponsor considers that the safety data in the ongoing Phase 1 First-In-Patient (FIP) study B1641001 and the published safety data for mogamulizumab support the development of the combination for the treatment of advanced cancers and the initiation of this Phase 1b clinical study B1641004. Study B1641001 will assess the safety and tolerability, as well as establish the maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) of PF-05082566 in combination with mogamulizumab in patients with advanced solid tumors. The available data support the benefit risk for the conduct of the trial, and the study includes monitoring and measures that potentially mitigate risks associated with the treatment.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D) of PF-05082566 in combination with mogamulizumab in patients with advanced solid tumors.

Secondary Objectives

- To evaluate the overall safety profile;
- To characterize the pharmacokinetics (PK) of PF-05082566 and mogamulizumab when given in combination;
- To evaluate the immunogenicity of PF-05082566 and mogamulizumab when given in combination;
- To document any anti-tumor activity.

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- [redacted]

[redacted]

2.2. Endpoints

Primary Endpoint

- First 2 cycles Dose-Limiting Toxicities (DLTs).

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity [(as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v. 4.03)], seriousness and relationship to study therapy;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03);
- Vital Signs (blood pressure and pulse rate), weight, Eastern Cooperative Oncology Group (ECOG) Performance Status;
- PK parameters of PF-05082566 and mogamulizumab, including but not limited to C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last}$, AUC_{tau}, $t_{1/2}$, CL and V_{ss}, as data permits;
- Anti-drug Antibody (ADA)/neutralizing antibody (Nab) titers for PF-05082566 and mogamulizumab;
- Objective tumor response (see Appendix 2 and Appendix 3 for details);
- Duration of response (DR) (expansion cohorts only);
- Time to response (TTR) (expansion cohorts only);
- Progression-free Survival (PFS) (expansion cohorts only).

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3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, PK and PD study designed to estimate the maximum tolerated dose (MTD), and select the Recommended Phase 2 Dose (RP2D) of PF-05082566 in combination with mogamulizumab in patients with advanced solid tumors.

This clinical study will include:

3.1.1. Dose-Finding portion

In the dose-finding portion, MTD of the combination will be estimated in patients with advanced solid tumors (ie, locally advanced or metastatic disease based on the TITE-CRM design[[28] and [33]] and according to the algorithm detailed in Section 3.1.9.

PF-05082566 and mogamulizumab starting doses as well as the starting dose selection strategy are described in Section 3.1.8.

A flat dosing of PF-05082566 100 mg will be studied to confirm the safety and PK at a dose that may be used for the expansion cohorts. This cohort will only enroll SCCHN and/or squamous NSCLC patients.

The 5.0 mg/kg cohort (if safe and tolerable) will enroll at least 6 squamous NSCLC patients.

It is estimated that approximately 30 patients would be required in the dose-finding portion to achieve the study objectives.

3.1.2. Dose Expansion portion

Once the MTD of PF-05082566 administered in combination with mogamulizumab has been estimated with confidence, expansion cohorts of patients will be enrolled to further study the safety, tolerability, PK/PD, and preliminary anti-tumor activity for PF-05082566 in combination with mogamulizumab, as well as to study CCI [redacted]

Tumor types for the expansion cohorts will be selected from CRC, bladder, ovarian, squamous esophageal, SCCHN and/or squamous NSCLC. Dose, final tumor types, CCI [redacted] for these cohorts will be selected based on emerging data from the dose-finding portion of the study or obtained from ongoing studies testing PF-05082566.

The total enrollment into all expansion cohorts will be up to 40 response-evaluable patients.

3.1.3. Study Treatment

In both portions, treatment will be administered in a 4-week cycles.

PF-05082566 will be administered as a 1-hour intravenous infusion (IV), every 4 weeks (q4wks), on Day 1 of each cycle. The starting dose of PF-05082566 will be 1.2 mg/kg.

Mogamulizumab will be given as a 1-hour IV infusion every week (qwk) for 4 consecutive weeks (Days 1, 8, 15 and 22) followed by biweekly dosing (Days 1 and 15), at the dose of 1 mg/kg.

On Day 1 of a dosing cycle, in which the drugs are co-administered, and PK samples are collected the mogamulizumab infusion will start 30 minutes (±10 min) after completion of PF-05082566 infusion and after the end of infusion PF-05082566 PK blood sample and pre-mogamulizumab PK blood sample are drawn. See Table 2.

Treatment with study drugs will continue until completion of 24 months of treatment (approximately 24 cycles), confirmed disease progression, patient refusal, unacceptable toxicity, whichever occurs first or the study is prematurely terminated by the Sponsor or one of the reasons for patient withdrawal listed (for details see Section 6.4).

Discontinuation from treatment may be considered at the investigator's discretion for patients who have attained a confirmed complete response (CR), and have received at least two cycles with mogamulizumab and PF-05082566 after the date the CR was confirmed. Patients who then experience radiologic disease progression will be eligible for re-treatment with both study drugs at the discretion of the investigator and by the approval of the Sponsor, if no anticancer treatment was administered since the last dose of study drugs, the patient meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is still open. Patients will resume therapy at the same dose and schedule at the time of initial discontinuation.

Patients who completed the 24 months of treatment on-study and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study treatment will be given the opportunity to continue treatment off-study upon agreement between investigator and Sponsor.

3.1.4. Safety Assessments

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as reported in Schedule of Activities (SOA) (Table 1) and in Section 7.1, Safety Assessments.

3.1.5. Efficacy Assessments

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline and on treatment every 8 weeks ±7 days starting from Cycle 1 Day 1 up to 1 year, then every 3 months (±7 days) as specified in the SOA Table 1. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, Symptomatic deterioration), and at EOT (if not done in the previous 8 weeks) and during follow up visits (if applicable). Assessment of response will be made using RECIST version 1.1 (Appendix 2) and irRC (Appendix 3). Further details are provided in Section 7.2, Tumor Assessments.

3.1.6. Pharmacokinetic (PK)/Immunogenicity Assessments

PK/Immunogenicity sampling will be required for all patients (See Table 2) and Section 7.3 and 7.5 for further details). The proposed PK timepoints may be reconsidered and amended during the study based on the emerging safety and PK data. No drug interaction is anticipated between PF-05082566 and mogamulizumab. Since PF-05082566 and mogamulizumab are eliminated via a non-specific catabolic degradation process, it is unlikely that concomitant medication can alter its clearance even if target expression is affected. To assess any potential interactions, steady state PK and the formation of anti-drug antibodies (ADA) will be monitored for both agents and compared with historical data.

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Approximately 70 patients are expected to be enrolled in the study overall (including dose-finding and expansion cohorts).

3.1.8. Starting Dose Selection Strategy

In the ongoing First-In-Human Phase 1 Study B1641001, PF-05082566 as single agent has been well tolerated up to the dose of 10 mg/kg (the highest planned dose level), with only 1 DLT reported (Grade 3 alkaline phosphatase (ALP) increase at 0.06 mg/kg), which was not observed at higher dose levels and upon review was determined by two Pfizer safety review committees to be related to disease progression. No further DLTs have been reported.

However, in order to minimize the potential risk of synergistic toxicity due to the combination, the starting dose for PF-05082566 in this study will be set to 1.2 mg/kg. Exposure at 1.2 mg/kg is above the projected efficacious concentration and safety data supports this starting dose, as there were no severe PF-05082566 related AEs at this dose and at higher doses.

The starting dose of mogamulizumab will be 1 mg/kg. The dose selected for this study is the dose approved for the treatment of relapsed or refractory CCR4 positive ATL, PTCL and CTCL. This dose administered weekly for 4 weeks and then every other week (ie, biweekly) until disease progression, appeared to be safe in clinical trials conducted in more than 152 ex-Japan patients with T cell lymphoma and in more than 800 patients with ATL. The AEs reported have generally been mild to moderate in severity, with the most frequent mogamulizumab-related TEAEs being infusion related reaction, nausea, pyrexia, fatigue, and drug eruption, all easily manageable through the administration of specific treatment.

3.1.9. Criteria for Dose Escalation

No dose escalation of mogamulizumab is foreseen for the estimation of the combination MTD. Dose escalation and de-escalation of PF-05082566 will follow the Time-to-Event Continual Reassessment Method (TITE-CRM)[28,33] up to 5 mg/kg.

A flat dosing of PF-05082566 100 mg will be studied to confirm the safety and PK at a dose that may be used for the expansion cohorts. The safety data at 100 mg flat dose (equivalent to 1.2 mg/kg) will be pooled together with the data at 1.2 mg/kg in the TITE-CRM model.

The 5.0 mg/kg cohort (if safe and tolerable) will enroll at least 6 squamous NSCLC patients to determine RP2D.

In each cohort, 3 to 9 patients evaluable for MTD determination may be enrolled.

The first 3 patients (Dose Level 1) will be treated at the starting dose. For each subsequent patient, the probability of DLT is estimated for each level based on all the collected data from all treated patients up to that time and the prior expectations of toxicity, and the patient is assigned to the currently estimated target level (with escalation restrictions as indicated below), defined as the dose having an estimated probability of DLT closest to but not greater than the target rate (30%).

The probabilities of toxicity are estimated based on a Bayesian statistical model to learn about the overall dose-toxicity relationship.

Patients' DLT data will be reported to the study statistician who will update the dose-toxicity model before the next enrolled patient is treated.

The MTD is defined as the highest combination dose with a DLT rate <30% from the model estimate (see Section 9.2).

Dose escalation may stop if:

- Maximum sample size (n=30, see Section 9.2) is reached; or
- 9 DLT evaluable patients have been treated at the estimated MTD (6 if no DLT observed at any dose); or
- All doses appear to be overly toxic and the MTD cannot be determined in the current trial.

In the TITE-CRM paradigm, patients who have enrolled in the trial, but have not experienced DLT, will be included in the probability calculation with an initial weight equal to the proportion of the 8-week (2 cycles of PF-05082566 and mogamulizumab) DLT observation period that the patients have completed (however, the weight function may be modified if accumulating safety data suggest a different pattern).

Patients who experience DLT or complete the observation period without DLT will be assigned full weight (=1).

Details on the TITE-CRM method are provided in Section 9.2 and the Statistical Analysis Plan (SAP).

To avoid overly rapid escalation and to retain the efficiency of dose administration when enrollment is fast, the following restrictions and practical considerations will be followed.

- Dose skipping in escalation to untested doses is not allowed (k −> k+1). In particular, at least three patients should have been treated at dose level k before escalation to dose level k+1;
- At least three patients should have been on treatment (for a minimum of 3 weeks) and observed DLT rate <33% at dose level k before a patient is assigned to dose level k+1 (*Note that the waiting window depends on our knowledge in the time-to-event pattern of toxicity and accumulating safety data, and thereby the confidence in the associated weights. However, intentional delay in enrollment in the absence of DLT or serious AEs should be minimized and discouraged*);
- Dose escalation recommendation by the TITE-CRM algorithm may be overruled by the Sponsor if the nature of the existing data causes safety concern.

Dose escalation and de-escalation will be carried out according to Table 6.

Table 6. Dose Escalation and De-Escalation Cohorts

Dose Levels	PF-05082566 Doses* (mg/kg)	Mogamulizumab Doses (mg/kg)
Dose Level 3	5	1
Dose Level 2	2.4	1
Dose Level 1a**	100 mg flat dose	1
Dose Level 1 (starting dose)	1.2	1
Dose Level -1	1.2	0.5
Dose Level -1a***	50 mg flat dose	1

** Intermediate dose levels could be used for dose de-escalation based on DLTs observed.*
** This cohort can be dosed simultaneously with any other dose cohort..
*** To be used for dose reductions for those on the 100 mg flat dose cohort.

Occurrence of DLTs during the exploration of Dose Level (DL) 1 will require reduction of mogamulizumab to 0.5 mg/kg (ie, DL -1). If Dose Level -1 is tolerated with no DLTs, then dose escalation of PF-05082566 will continue according to the table above, maintaining mogamulizumab at 0.5 mg/kg until an MTD is reached and/or the PF-05082566 dose is escalated to the highest planned dose of 5 mg/kg.

Intra-patient dose escalation will not be permitted.

Cumulative safety data will continue to be evaluated at the estimated MTD in the expansion cohorts using the Bayesian statistical model. Should emerging data in the expansion cohorts indicate that the selected dose is more toxic than previously estimated (DLT rate >30%) or in case of exposure plateau CCI [redacted]

For the first dose-finding cohort, a minimum 7-day time window between the first doses of subsequent patients will be applied. For the following dose-finding cohorts, a minimum 24-hour time window between the first doses of the first 3 patients will apply. A 24 hr time window between dosing is not necessary between cohorts dosed simultaneously.

At a given dose level, a time window between first doses will not be required after the treatment of the first 3 patients.

3.2. DLT Definition

Severity of AEs will be graded according to CTCAE version 4.03. For the purpose of dose escalation, any of the following AEs occurring during the DLT observation period (first 2 Cycles, ie, 8 weeks) that are attributable to one or both study drugs will be classified as DLTs:

Hematologic

- Grade 4 neutropenia lasting >7 days;

- Febrile neutropenia, defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour;
- Grade ≥3 neutropenic infection;
- Grade ≥3 thrombocytopenia with bleeding;
- Grade 4 thrombocytopenia.

Non-Hematologic:

- Grade ≥3 non laboratory toxicities (excluding infusion reactions), except those that have not been maximally treated (eg, nausea, vomiting, diarrhea).
- Grade ≥3 laboratory abnormalities (other than AST/ALT) if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization.
- Grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increase.

3.3. MTD Definition

The MTD is defined as the highest combination dose with a DLT rate <30% from the TITE-CRM model estimate (see details in Section 9.2).

Once the MTD is estimated, additional patients may be enrolled at this dosing level. In the expansion cohort, patients' DLT data will be entered into the Bayesian statistical model of the TITE-CRM procedure. If the posterior distribution of the model incorporating the additional data from the expansion cohort suggest the estimated MTD is associated with a higher than expected DLT rate the next lower dose or an intermediate dose level will be expanded, and may be declared as the RP2D.

3.4. Dose for Expansion Cohorts

The expansion cohort(s) will be tested at either the estimated MTD or lower doses based on the emerging safety, efficacy and PK/PD data.

3.5. Dose Expansion Portion

Expansion cohort(s) will test PF-05082566 in combination with mogamulizumab in patients with select advanced solid tumors. Tumor types for the expansion cohorts will be selected from CRC, bladder, ovarian, squamous esophageal, SCCHN and/or squamous NSCLC. The PF-05082566 dose for expansion cohorts may be a flat dose of 100 mg. All patients in the expansion cohorts may be enrolled simultaneously. The total number of patients enrolled

into one or more expansion cohorts will be determined based on the tumor type, and patient population emerging data from this study. PK/ADA samples will be collected from all evaluable patients in the dose expansion cohorts.

3.6. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further study based on Phase 1 results. If the MTD proves to be clinically feasible for long term administration in a reasonable number of patients, such dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Histological or cytological diagnosis of advanced/metastatic solid tumor malignancy. Dose Finding Cohorts: Tumor types will be limited to CRC, SCCHN, squamous NSCLC, bladder, or ovarian carcinomas which have progressed on standard therapy, or for which no standard therapy is available. Expansion Cohorts: Tumor types may include: Histological or cytological diagnosis of either advanced/metastatic CRC, bladder, ovarian, squamous esophageal, SCCHN, or squamous NSCLC. **NOTE:** Final determination of tumor types for expansion will be made based on emerging data from the dose-finding portion of the study or obtained from ongoing studies testing PF-05082566.

2. Measurable disease by RECIST version 1.1.

3. For Expansion Cohorts only: patients must have tumor accessible for biopsies (core needle biopsy or excision preferred). See Section 3.1.7.

4. Age ≥18 years.

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

6. Adequate bone marrow function, defined as follows:

    - absolute neutrophil count (ANC) ≥1.5 x 10^9/L (≥1,500/μL);

- platelet (PLT) count ≥75 x 10^9/L (≥75,000/μL);
- hemoglobin (Hb) ≥9.0 g/dL (≥5.6 mmol/L).

Patients must be transfusion independent (ie, no blood product transfusions for a period of at least 14 days prior to study registration).

7. Adequate renal function, including:
   - serum creatinine ≤1.5 x upper limit of normal (ULN); **OR**
   - estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.
8. Adequate liver function, including:
   - Total serum bilirubin ≤1.5 x ULN (unless the patient has documented Gilbert syndrome);
   - Aspartate and Alanine aminotransferase (AST & ALT) ≤2.5 x ULN;
   - Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in case of bone metastasis).
9. 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.
10. Serum/urine pregnancy test (for females of childbearing potential) negative at screening and before the patient will receive the study treatment.
11. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two (2) highly effective methods of contraception throughout the study and for 60 days after the last dose of assigned study treatment.
12. Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):
    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; OR
    - Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.
13. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

14. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Central nervous system primary malignancies, active seizure disorder or spinal cord compression, or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to registration and any neurologic symptoms have returned to baseline), have no evidence of new or progressing brain metastases. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

2. Systemic anticancer therapy within 28 days prior to registration. In absence of persisting toxicity, 5 half-lives since completion of prior anti-cancer therapy is acceptable.

3. Therapeutic or experimental monoclonal antibodies within 60 days prior to registration.

4. Systemic corticosteroid therapy or any other form of immunosuppressive therapy within 14 days prior to registration. Patients that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded from the study.

5. Major surgery within 28 days prior to registration.

6. Radiation therapy within 14 days prior to registration.

7. History of, or active ethanol abuse or hepatitis (eg, alcohol or non-alcohol steatohepatitis [NASH], drug related, auto immune, virally related).

8. Live vaccine within 30 days prior to registration.

9. Active and clinically significant bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness (HIV testing is not required), including patients who have an active infection requiring systemic therapy. Active herpes simplex or herpes zoster. Patients on prophylaxis for herpes infection who started taking medication at least 30 days prior to study entry, and have no active signs of active infection, and whose last active infection was more than 6 months prior to registration, may enter the study, and should continue to take the prescribed medication for the duration of the study.

10. Known prior or suspected hypersensitivity to study drugs or any component in their formulations (including patients who are known to be positive for ADA to mogamulizumab or PF-05082566).

11. Patients who previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody.

12. Patients with a history of autoimmune disease (eg, rheumatoid arthritis, Addison's syndrome, multiple sclerosis, uveitis, systemic lupus erythematosus or Wegener's granulomatosis). Patients with vitiligo or alopecia are eligible. Patients with Graves disease or psoriasis not requiring systemic treatment within the past 3 years are eligible. Patients with hypothyroidism with stable hormone replacement are eligible.

13. Patients with known inflammatory bowel disease eg, ulcerative colitis, Crohn's disease, or celiac disease.

14. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

15. Any of the following within the 12 months prior to registration: myocardial infarction, congenital long QT syndrome, torsade de points, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism, ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, or QTcF interval >470 msec at screening.

16. Diagnosis of any other malignancy within 2 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix.

17. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant; male and female patients of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for 60 days after last dose of investigational product.

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

19. Participation in other therapeutic studies within 4 weeks before the current study begins and/or during study participation.

20. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer or KHK employees directly involved in the conduct of the study.

4.3. Lifestyle Guidelines

In this study, patients of childbearing potential will receive PF-05082566 and mogamulizumab, compounds for which the teratogenic risk in human is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 60 days after the last dose. The investigator or his/her designee, in consultation with the patient, will select two appropriate methods of contraception for the individual patient from the list of permitted contraception methods (see below) and instruct the patient in their consistent and correct use.

Patients need to affirm that they meet at least 2 of the selected methods of contraception. The investigator or his/her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity ultraviolet B light (UVB) sources such as tanning beds, tanning booths and sunlamps. Patients should be encouraged to apply sunscreen/sunblock daily.

4.4. 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 Study Manual (ie, coordinator's manual).

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study.

The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Dose level allocation will be performed by the Sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will fax or email a complete Registration Form to the designated Sponsor study team member. The Sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other study-related documentation or correspondence referencing that patient and fax or /email to the site.

For the purposes of this protocol, study drug or study treatment refers to both PF-05082566 and mogamulizumab. No patient shall receive study drug until the investigator or designee has received the following information in writing from the Sponsor:

- Confirmation of the patient's enrollment;
- Specification of the dose level for that patient; and

- The Sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment slot date.

5.2. Patient Compliance

There are no specific patient compliance guidelines for study drug administration, as the study drugs will be administered by designated study staff at the investigational site.

5.3. Drug Supplies

PF-05082566 and mogamulizumab will be supplied by Pfizer Global Clinical Supply Chain, Worldwide Research and Development. Drug supplies will be shipped to the study sites with a Drug Shipment & Proof of Receipt form. This form should be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment & Proof of Receipt form.

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. PF-05082566

PF-0508256 drug product will be supplied in clear glass vials at a 10 mg/mL concentration as sterile solution for intravenous administration and labeled as open supplies. Each vial is packed in an individual carton.

Each vial contains nominal 100 mg of PF-05082566 in a 10 mL solution. To ensure that the exact volume can be withdrawn by syringe, there is a small amount of overfill in the vial.

5.3.1.2. Mogamulizumab

Mogamulizumab drug product will be supplied as a 4 mg/mL, sterile solution for dilution for intravenous infusion. Each glass vial contains 20 mg of mogamulizumab.

5.3.2. Preparation and Dispensing

See the respective Dosage and Administration Instructions (DAI) for instructions on how to prepare the investigational products for administration. Investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

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

The site will complete required dosage Preparation Record located in the study 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 Pfizer monitor.

5.4. Administration

Study treatment administration should start no later than 7 days after registration.

A cycle is defined as the time from Day 1 dose to the next Day 1 dose of PF-05082566. If there are no treatment delays, a cycle will be 4 weeks in duration.

All trial treatments will be administered on an outpatient basis. After Cycle 1, study drugs may be administered up to 2 days before or after the scheduled treatment day of each cycle for administrative reasons. Patients will be observed in the clinic for at least 2 hours after the administration of study drug, throughout the duration of the study.

All patients should be weighed within 7 days prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of study drug required for dose preparation. Decision to recalculate the study drug dose based on the weight obtained at each cycle can be in accordance with institutional practice, however if the patient experienced either a weight loss or gain >10% compared to the weight used to calculate the initial dose, the amount of study drug required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat allergic or anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat allergic and anaphylactic reactions. Patients should be instructed to report any delayed reactions to the Investigator immediately. If a patient experiences an infusion related reaction at any time during the study, premedication is recommended prior to subsequent infusions (see Section 5.4.2 for details on premedication to be used).

For both drugs, the exact duration of infusion should be recorded in both sources document and CRFs. The infusion rate should be reduced or interrupted in the case of symptoms of infusion reaction, and symptomatic treatment administered. The infusion may be continued at one-half the previous rate upon improvement of symptoms. If symptoms persist or worsen, the infusion should be discontinued.

The study drug dose-escalation levels are shown in Table 6. In addition, doses of PF-05082566 and mogamulizumab available for dose modification according to guidelines in Section 5.4.9, are shown below in Table 7.

5.4.1. PF-05082566

PF-05082566 will be administered first, as a 1-hour IV infusion, q4wks, on Day 1 of each cycle. The starting dose of PF-05082566 will be 1.2 mg/kg.

5.4.2. Mogamulizumab

Mogamulizumab will be given after PF-05082566 administration, as a 1-hour IV infusion, at a dose of 1 mg/kg. Mogamulizumab will be administered weekly for 4 consecutive weeks in the first cycle (ie, on Days 1, 8, 15 and 22), followed by biweekly dosing in cycles ≥2 (ie, on Days 1 and 15).

The two study drugs are co-administered on Day 1 of each dosing cycle. In such case, the mogamulizumab infusion will start 30 minutes (±10 min) after completion of PF-05082566 infusion and after the end of infusion PF-05082566 PK blood sample and pre-mogamulizumab PK blood sample are drawn.

It is recommended that on Cycle 1 Day 1 administration of mogamulizumab, patients be premedicated according to the guidance below.

Premedication: Premedication with acetaminophen or paracetamol orally and diphenhydramine 50 mg IV (or equivalent antihistamine) to prevent hypersensitivity reactions is recommended before the first mogamulizumab infusion.

5.4.3. Food requirements

PF-05082566 and mogamulizumab may be administered without regard to meals.

5.4.4. Treatment Duration

The treatment duration with both study drugs is 24 months (approximately 24 cycles) calculated from Cycle 1 Day 1.

Patients may continue on treatment with both agents until disease progression (by RECIST v. 1.1 and/or irRC), patient refusal, unacceptable toxicity, whichever comes first, or the study is prematurely terminated by the Sponsor, or for one of the other reasons for patient withdrawal specified in Section 6.4.

Discontinuation from treatment may be considered at the investigator's discretion for patients who have attained a confirmed CR, and have had at least two cycles with mogamulizumab and PF-05082566 after the date the CR was confirmed. Patients who then experience radiologic disease progression will be eligible for re-treatment with both study drugs at the discretion of the investigator and by the approval of the Sponsor, if no cancer treatment was administered since the last dose of study drugs, the patient meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is still open. Patients will resume therapy at the same dose and schedule at the time of initial discontinuation.

Patients who completed the 24 months of treatment on-study and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study treatment will be given the opportunity to continue treatment off-study upon agreement between investigator and Sponsor.

5.4.5. Treatment After Initial Evidence of Radiologic Disease Progression

Immunotherapeutic agents such as mogamulizumab and PF-05082566 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Based on the proposed mechanism of action of PF-05082566, new lesions may appear as enlargements in regional tumor-draining lymph nodes, which might reflect anti-tumor immune responses.

Therefore, if radiologic imaging shows progressive disease, in the absence of clinical deterioration, tumor assessment must be repeated ≥4 weeks later in order to confirm progressive disease. There is the option of continuing treatment per below while awaiting radiologic confirmation of progression.

Note: Before continuation of treatment, the patient must be re-consented and informed that in order to continue receiving the investigational products on trial the patient may be foregoing Food and Drug Administration (FDA)-approved therapy with possible clinical benefit(s).

Patients may receive study treatment while waiting for confirmation of progressive disease if they are re-consented and are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If repeat imaging shows a reduction in the tumor burden demonstrating CR, partial response (PR) or stable disease (SD) compared to the previous scan, treatment may be continued.

If the repeat imaging confirms initially documented progressive disease, patients may be discontinued from the study. However, according to the investigator's judgment if a patient with evidence of disease progression is still experiencing clinical benefit, the patient will be eligible for continued treatment with PF-05082566 combined with mogamulizumab. The investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data.

Biopsies should be considered, when clinically indicated, to clarify disease involvement in such cases. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (please refer to the Site Imaging Manual).

5.4.6. Recommended Dose Modifications

Every effort should be made to administer study treatment (ie, PF-05082566 and mogamulizumab) at 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. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Patients who experience an AE meeting the definition of a DLT may be removed from treatment, based on the dose modification guidelines listed in Section 5.4.9 and in consultation with the Sponsor.

Dose modifications may occur in three ways:

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

Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Dose modifications will be reported in the CRF.

5.4.7. Dose Interruptions

Patients experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care, should have their treatment interrupted.

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Section 5.4.8, Dose Delays.

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

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 5.4.9, Dose Reductions, unless expressly agreed otherwise following discussion between the investigator and the Sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the Sponsor.

5.4.8. Dose Delays

Re-treatment at the start of any new cycle, intra cycle (when mogamulizumab only is administered), or following treatment interruption due to treatment related toxicity may not occur until all of the following parameters have been met:

- ANC ≥1,000/μL;
- Platelet count ≥75,000/μL;
- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator discretion, Grade ≤2 if not considered a safety risk for the patient).

After all toxicities have recovered within the limits described above, treatment with PF-05082566 and/or mogamulizumab can be resumed.

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

Intra cycle mogamulizumab dose delay due to treatment related toxicity is not allowed. If, within a cycle, retreatment with mogamulizumab is not possible due to persistent toxicity, the dose/s should be considered as omitted.

Withhold scheduled dose for liver function test (LFT) related AEs (including asymptomatic) Grade ≥3 until return to baseline or Grade ≤1 severity. In cases of potential liver injury, see Section 8.6.2. In such cases, consultation with a hepatologist should be considered in the decision to initiate treatment with anti-inflammatory medications.

If hematological toxicities do not recover to the above values and non-hematologic toxicity does not resolve to baseline or Grade ≤1 (Grade ≤2 if not considered a safety risk for the patient) within 4 weeks of last infusion, consider permanent discontinuation after consultation with the Sponsor. With investigator and Sponsor agreement, patients with a laboratory adverse event still at Grade 2 after 4 weeks may continue treatment in the trial only if asymptomatic and controlled.

Permanent discontinuation of study treatment should be considered for any life-threatening event.

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.

5.4.9. Dose Reductions

Dose reductions of PF-05082566 and/or mogamulizumab may be required based on the worst toxicity experienced in the previous administration or previous cycle (see Table 7).

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

Patients experiencing recurrent and intolerable Grade 2 non-hematologic toxicity may resume dosing, with specific dose modifications detailed in Section 5.4.9.1, once recovery to Grade ≤1 or baseline is achieved.

Once a patient has a dose reduction in PF-05082566 and/or mogamulizumab for a drug-related toxicity, the dose will not be re-escalated. Patients requiring more than one dose reduction will be withdrawn from treatment unless otherwise agreed between the investigator and the Sponsor.

5.4.9.1. Dose Modification Guidelines

Table 7 below shows the PF-05082566 and mogamulizumab doses available for dose reduction in this study. Suggested dose modification guidelines are presented in Table 8 below. Both study drugs or mogamulizumab only should be held for the listed toxicities with dose modifications as suggested.

Table 7. Available Doses for Dose Reduction

PF-05082566* (mg/kg)	Mogamulizumab (mg/kg)
2.4	0.5
1.2	
50 mg flat dose**	
0.6	

*Intermediate doses could be used for dose-reduction based of DLTs observed.
** To be used for the 100 mg flat dose cohort.

Patients experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved.

Recommended dose reductions are illustrated in Table 8. **The guidelines apply to both drugs when co-administered or to mogamulizumab alone (when applicable)**. These recommendations are applicable for all cycles.

Table 8. Dose Modification Guidelines for Treatment Related Adverse Events

Toxicity	Grade	Hold Treatment*	Criteria for Treatment Restart*	Dose Modification*	Discontinue Patient* (*after consultation with Sponsor*)
Hematologic Toxicity meeting any of the criteria in Section 3.2.	3	Yes	Hold treatment until toxicity resolved to Grade ≤1 (Grade 2 for ANC)	Decrease dose by one dose level (based on Table 7).	If toxicity does not resolve to Grade ≤1 or does not allow retreatment within 4 weeks of last infusion, consider permanent discontinuation after consultation with the Sponsor.
	4	Yes	Hold treatment until toxicity resolved to Grade ≤1 (Grade 2 for ANC)	Decrease dose by one dose level (based on Table 7).	If toxicity does not resolve to Grade ≤1 or does not allow retreatment within 4 weeks of last infusion, consider permanent discontinuation after consultation with the Sponsor.
Non-Hematologic Toxicity	1 and 2 (if Grade 2 is not recurrent/ intolerable)	No	N/A	Continue at same dose level.	N/A
	2 (only if recurrent/ intolerable)	Consider holding	Hold treatment until toxicity resolved to baseline or Grade ≤1	Continue at same dose level.	If toxicity does not resolve to baseline or Grade ≤1 within 4 weeks of last infusion, consider permanent discontinuation after consultation with the Sponsor.
	3 (if persisting when maximally treated)	Yes	Hold treatment until toxicity resolved to baseline or Grade ≤1 (or, at the investigator discretion, to Grade ≤2 if not considered a safety risk for the patient). For laboratory AEs other than LFTs only: resolved to Grade ≤2 and asymptomatic. For LFTs: resolved to baseline or Grade ≤1.	Decrease dose by one dose level.	If toxicity does not resolve to baseline or Grade ≤1 (or, at the investigator discretion, to Grade ≤2 if not considered a safety risk for the patient) within 4 weeks of last infusion, consider permanent discontinuation after consultation with the Sponsor (except as noted in Section 5.4.9.1 for laboratory AEs). *Permanent discontinuation should be considered for any life-threatening event.*

Table 8. Dose Modification Guidelines for Treatment Related Adverse Events

Toxicity	Grade	Hold Treatment*	Criteria for Treatment Restart*	Dose Modification*	Discontinue Patient* (*after consultation with Sponsor*)
	4	Yes	Hold treatment until toxicity resolves to baseline or Grade ≤1. For laboratory AEs other than LFTs only: resolved to Grade ≤2 and asymptomatic. For LFTs: resolved to baseline or Grade ≤1.	Decrease dose by one dose level	If toxicity does not resolve to baseline or Grade ≤1 within 4 weeks of last infusion, consider permanent discontinuation after consultation with the Sponsor. *Permanent discontinuation should be considered for any life-threatening event.*

*Both drugs (Day 1 of each cycle) or mogamulizumab only (when applicable);
PF-05082566 and mogamulizumab (if applicable) doses will be modified based on dose levels listed in Table 7.

5.5. Drug Storage

PF-05082566 will be stored at a temperature between 2°C and 8°C (36°F to 46°F).

Mogamulizumab will be stored at a temperature between 2 and 8°C (36 to 46°F), protected from light. The vials should not be vigorously shaken.

The investigator, or an approved representative (eg, pharmacist), will ensure that both PF-05082566 and mogamulizumab are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label. See the DAI for storage conditions and stability of the diluted products.

Storage conditions stated in the SRSDs (ie, IBs of PF-05082566 and mogamulizumab), will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (eg, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (eg, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

5.6. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies.

Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient by patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug and copies must be provided to Pfizer when directed.

At the end of the trial, the Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

5.7. Concomitant Treatment(s)

Concomitant treatment considered necessary for the patient's wellbeing may be given at discretion of the treating physician.

Medications intended solely for supportive care (ie, antiemetics, analgesics) are allowed.

All concomitant medications and treatments, including prescription, over-the-counter (OTC), herbal supplements, IV medications and fluids, supportive care (antiemetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, non-drug supportive interventions (transfusions) will be recorded in the CRF from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.

Concomitant medications administered after 28 days after the last dose of trial treatment should be recorded for SAEs only as defined in Section 8.14.1.

5.7.1. Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited at study entry as specified in the exclusion criteria are also not allowed during the study treatment period, except for hematopoietic growth factors and steroids for symptomatic treatment (for details see Section 5.8, Supportive Care).

If there is an important medical condition requiring any medication specifically prohibited during the trial, discontinuation from study treatment may be considered. The investigator should discuss the proposed course of action with the Sponsor Clinical Lead and/or Medical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study treatment requires the mutual agreement of the Investigator, the Sponsor, and the patient.

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this clinical protocol:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than mogamulizumab or PF-05082566.
- Live vaccines (flu vaccination allowed).
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology, except as agreed upon by the Sponsor.

Consider withholding or discontinuing concomitant therapy with monoclonal antibodies of the same subclass as the study drugs (ie, IgG_K and IgG2) in patients where anti-study drug antibodies are detected while on-study.

The concurrent use of vitamins or herbal supplements should be considered with caution.

5.7.2. Concomitant Surgery

No formal studies have been conducted to determine whether there is a risk to perform concomitant surgery in patients under treatment with either PF-05082566 or mogamulizumab. As safety risks in this setting are unknown, it is suggested that the study drugs be withheld for 12 days before performing major surgery. This will provide a margin of safety of one drug half-life (for mogamulizumab, which has the longer half-life of the two study drugs) before resuming therapy with the combination.

Postoperatively, the decision to reinitiate PF-05082566 and mogamulizumab treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.7.3. Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease (eg, to a symptomatic solitary lesion or to the brain) is permitted if considered medically necessary by the treating physician and after consultation with the sponsor. All attempts should be made to rule out disease progression in the event of increased localized pain. It is suggested that the smallest radiation doses and smallest fields possible be used for palliation to minimize the inflammatory effects of radiotherapy. It is suggested that PF-05082566 and mogamulizumab treatment be interrupted during palliative radiotherapy, in consultation with the Sponsor.

5.8. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the Investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined in the following Sections.

5.8.1. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first 2 cycles of treatment but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines.[27]

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

5.8.2. Anti-Emetic Therapy

Primary prophylaxis of nausea and vomiting is permitted. Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

5.8.3. Anti-Diarrheal Therapy

Patients may receive prophylaxis of treatment-induced diarrhea. Symptomatic care such as loperamide (Imodium®) is recommended. All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

5.8.4. Anti-Infective Therapy

Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

5.8.5. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming the drug is not included in Section 5.7.1, Prohibited Concomitant Treatment. There is no anticipated risk of drug-drug interaction between mogamulizumab and PF-0582566.

Acetaminophen/paracetamol to a MAXIMUM total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

5.8.6. Corticosteroids

Chronic, systemic corticosteroid use for palliative or supportive purpose is not permitted. Use of corticosteroids as symptomatic treatment may be allowed on individual basis and upon discussion with the Sponsor.

Acute emergency administration, topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed and guidelines are provided in Section 5.4.9.

5.8.7. Supportive Care Guidelines for Infusion Reactions to Either Study Drugs

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs.

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever), arthralgia, bronchospasm, cough, dizziness, dyspnea, fatigue/asthenia, lethargy, malaise, headache, hypertension, hypotension, myalgia, nausea, pruritus/itching, rash/desquamation, rigors/chills, sweating, tachycardia, tumor pain, urticaria (hives, welts, wheals) and vomiting.

In the event that a site does not have established procedures for the treatment of study drug associated infusion reactions, guidelines are provided in Table 9.

Table 9. Infusion Reaction Treatment Guidelines for Either Study Drug

NCI CTCAE Grade§	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated;	**Continue infusion as per protocol.** Increase monitoring of vital signs during the infusion as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	To be considered upon Investigator discretion.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids);	**Stop infusion and monitor symptoms.** Appropriate medical therapy may include but is not limited to: IV fluid Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the infusion rate (eg, from 100 mL/hr to 50 mL/hr). If symptoms last more than 1 hour after stopping infusion, dosing will be held. The patient should be monitored until symptoms resolve or is deemed medically stable in the opinion of investigator. **Patients who develop prolonged symptoms (>24 hrs.) despite premedication should be permanently discontinued from further trial treatment administration.**	Patients may be premedicated 1.5 h (±30 minutes) prior to infusion of mogamulizumab and/or PF-05082566) with: Diphenhydramine 50 mg PO or IV (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic eg, paracetamol).
Grades 3 or 4 Grade 3; Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; ventilator support indicated.	**Stop infusion.** Appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration §Classified per the Common Terminology Criteria for Adverse Events v. 4.03 (CTCAE) at http://ctep.cancer.gov		

6. STUDY PROCEDURES

For screening, treatment period and follow up procedures, see Schedule of Activities.

- Informed Consent must be obtained prior to undergoing any study specific procedure and may occur prior to the 28 day screening period.

For the treatment period discussed below, where multiple procedures are scheduled at the same nominal time point(s) relative to dosing, the following prioritization of events should be adhered to, where possible:

- Blood pressure/pulse rate – may be obtained prior to or after electrocardiogram (ECG) collection but must be obtained prior to blood specimen collection.
- ECGs – obtain as close as possible to the scheduled time, but prior to blood specimen collection and within 30 minutes of the nominal time.
- Clinical safety laboratory tests – obtain as close as possible to the scheduled time.
- Pharmacokinetic blood specimens obtain at the scheduled time.
- Other procedures – All other procedures should be obtained as close as possible to the scheduled time, but may be obtained before or after blood specimen collection, unless sampling is determined by the study personnel to potentially impact the results.

6.1. Screening

For screening procedures, see Schedule of Activities and ASSESSMENTS Sections.

Screening is to be performed within 28 days of registration. Tumor history includes information on prior regimens (including dosing and duration of administration, description of best response observed, recurrence date), surgery and radiation therapy. Medical history, includes history of other diseases (active or resolved) and concomitant illnesses.

6.2. Study Period

For treatment period procedures, see Schedule of Activities and ASSESSMENTS Sections.

The EOT assessments are to be performed 28 days (+7 days) after the last dose of study treatment. These assessments are to be performed if not completed during the previous week on study (during the previous 8 weeks on study for tumor assessments).

6.3. Follow-up Visit

For follow-up procedures, see Schedule of Activities and ASSESSMENTS Sections.

Patients continuing to experience treatment-related toxicity following discontinuation of study 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.

Only those patients whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 8 weeks ±7 days. Once patients have exhibited disease progression or began a new anti-cancer therapy (not including radiotherapy to a non-target tumor lesion), whichever occurs first, the date of progression or that of the new anticancer therapy initiation will be recorded on the appropriate CRF page, and the patients will be withdrawn from the study. No further data will be collected from these patients.

6.4. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator or Sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for discontinuation of study treatment may include:

- Disease progression according to RECIST v. 1.1 (Appendix 2) and/or irRC (Appendix 3) (see Section 5.4.5 for details and exceptions);
- Patients who have achieved a confirmed CR, and have had at least two additional cycles of mogamulizumab and PF-05082566 after the date the CR was confirmed;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment (follow up permitted by the patient);
- Consent withdrawal (cessation of follow up);
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;

- Start of another anticancer therapy;
- Refusal for further follow-up;
- Lost to follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, no further study specific 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.

7. ASSESSMENTS

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

7.1. Safety Assessment

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

7.1.1. Pregnancy Testing

PF-05082566 has not been characterized for reproductive toxicology.

Toxicological studies indicated that mogamulizumab has no potential for embryo-fetal lethality, teratogenicity, or fetal growth retardation in animals. However no data are available in humans. The current mogamulizumab IB version[18] contains a full description of non-clinical reproductive and developmental toxicology.

See Section 8.10 for exposure during pregnancy.

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy (ie, once at the start of screening and once at the baseline visit, immediately before investigational product administration). Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle (ie, on Day 1) during the active treatment period, at the End of Treatment visit, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from study medication but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards (IRBs)/Ethic Committee (ECs) or if required by local regulations.

7.1.2. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), seriousness, and relatedness.

7.1.3. Laboratory Safety Assessment

Hematology, blood chemistry, coagulation, urinalysis, thyroid and other endocrine function tests will be drawn at the time points described in the Schedule of Activities (Table 1) and analysed at local laboratories. There is no need to repeat these tests on Cycle 1 Day 1 if screening assessment was performed within 7 days prior to that date.

Laboratory certifications and normal ranges with units must be provided to the Sponsor. Laboratory tests may be repeated also as clinically indicated.

Required tests are indicated in Table 10.

Table 10. Laboratory Safety Assessments

Hematology	Hemoglobin (Hb) Platelets (PLTs) White Blood Cells (WBCs) Absolute Neutrophils Absolute Lymphocytes Absolute Monocytes Absolute Eosinophils Absolute Basophils

Table 10. Laboratory Safety Assessments

Chemistry	Alanine aminotransferase (ALT) Aspartate Aminotransferase (AST) Alkaline Phosphatase (ALP) Lactate Dehydrogenase (LDH) Sodium (Na) Potassium (K) Magnesium (Mg) Total Calcium (Ca) Phosphorus or Phosphate Total bilirubin*** Creatinine or creatinine clearance Albumin Total proteins Uric Acid BUN or Urea Immunoglobulin G Glucose (fasted)
Coagulation	Partial thromboplastin time (PTT) Prothrombin Time (PT) or International Normalized Ration (INR)
Urinalysis	Urine dipstick for urine protein. If positive collect 24-hrs and microscopic (Reflex Testing) Urine dipstick for urine blood. If positive collect a microscopic (Reflex Testing)
Hepatitis B and C Tests	Hepatitis B surface antigen, core antibody, and anti-hepatitis C. Other tests may be conducted per standard practice to confirm an active hepatitis infection.
Thyroid and other Endocrine Function Tests	Triiodothyronine (T3), Free-Thyroxine (FT4), Thyroid-Stimulating Hormone (TSH). In the presence of clinical suspicion of hypopituitarism or hypoadrenalism, laboratory testing should include one or more of the following: Adrenocorticotropic hormone (ACTH), and cortisol levels (before and 30- 60 minutes after corticotrophin stimulation).

*** *For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and ALP.*

7.1.4. Vital Signs and Physical Examination (PE)

Patients will have a physical exam (PE) that will include major body systems, weight, vital signs (blood pressure and heart rate), assessment of ECOG performance status, and height; height will be measured at baseline only. Each assessment will be performed at the time points described in the SOA Table 1.

7.1.5. Electrocardiogram (12-Lead)

ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see Table 1), three consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval.

If the mean QTcF is prolonged (>500 msec, ie, NCI CTC AE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, prior to concluding that an episode of prolongation of the QTcF interval is due to study drug and is considered clinically significant, immediate correction of potential precipitating factors (including change in patient clinical condition, electrolyte abnormalities, hypoxia and concomitant administration of drugs with the potential to prolong the QTcF interval) should be performed.

In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below ≤470 msec (ie, inclusion criteria) or is recovered to ≤480 msec (ie, NCI CTC AE Grade ≤1). If QTcF interval reverts to less than ≤480 msec, and in the judgment of the investigator(s) and Sponsor is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring at the same dose level.

If in this timeframe the QTcF intervals remains above 500 msec the study drug will be held until the QTcF interval decreases to ≤500 msec (NCI CTC AE Grade ≤2). Patients will then re-start the study drug at the next lowest dose level according to Investigator's judgment therefore excluding that the event is considered clinically significant.

If the QTcF interval has still not decreased to <500 msec after 2-weeks off treatment or if at any time a patient has a QTcF interval >515 msec (considered clinically significant) or becomes symptomatic, the study treatment will be permanently discontinued.

Additional triplicate ECGs may be performed as clinically indicated.

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

Pre-dose ECG assessments will be required for all patients, post-dose ECG assessments will be required only for patients in dose-finding cohorts (see Table 1).

Clinically significant abnormal findings in baseline ECGs will be recorded as medical history.

Clinically significant findings seen on the follow-up ECGs should be recorded as AEs.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.2. Tumor Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, and on treatment every 8 weeks ±7 days starting from Cycle 1 Day 1 up to 1 year, then every 3 months (±7 days) as specified in Table 1. Timing should follow calendar days starting from C1D1 and should not be adjusted for treatment delays.

Follow up bone scans are required every 16 weeks (±7 days) only if bone metastases are present at baseline and bone scan is used to follow bone lesions on treatment. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of complete response for patients who have bone metastases at baseline. The same imaging technique used at baseline for bone lesions assessments should be used to assess the on treatment response to bones.

In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of EOT (if not done in the previous 8 weeks).

Note that a lesion biopsied while on study, or a lesion that is irradiated during the study should no longer count as a target lesion.

Assessment of response will be made using RECIST version 1.1 (Appendix 2) and also by irRC (Appendix 3).

If radiologic imaging shows progressive disease, tumor assessment should be repeated ≥4 weeks later in order to confirm progressive disease with the option of continuing treatment per Section 5.4.5 while awaiting radiologic confirmation of progression.

In this trial, patients may be treated after initial progression by RECIST criteria and/or irRC, and patient's tumors will be subsequently assessed. A patient who has initial progression may be assigned PR or CR at a later time point as long as the patient meets all criteria for PR or CR compared to the pretreatment tumor assessment. If CR or PR is subsequently confirmed with respect to baseline, the patient's overall assessment will be CR or PR regardless of early assessment of progressive disease.

In addition to on-study tumor response assessments, the history of responses to previous therapy will be collected. This will include information on prior regimens, including dosing and duration of administration, plus a description of the best response observed for each prior regimen.

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

7.3. Pharmacokinetics Assessments

PK samples will be assayed for PF-05082566, and mogamulizumab using a validated analytical method in compliance with Pfizer (PF-05082566) or KHK (mogamulizumab) standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Laboratory Manual.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AE's and the date and time documented in the CRF.

CCI [redacted]

7.3.1. Blood for PK analysis of PF-05082566

Blood samples (2 mL whole blood at each time point) will be collected for PK analysis of PF-05082566 as outlined in the SOA Table 2 and reported herewith below:

- **Patients in <u>dose-finding cohorts</u>:**
  - Cycles 1- 4 on Day 1 at pre-dose and at the end of PF-05082566 infusion;
  - Cycle 5 on Day 1 at pre-dose, at the end of PF-05082566 infusion, at 2, 6, 168 hrs. (Day 8) and 336 hrs. (Day 15) after the start of PF-05082566 infusion;
  - Predose on Day 1 of Cycles 8, 12, 16, 20 and 24;
  - EOT.
- **Patients in <u>expansion cohorts</u>:** The same PK schedule foreseen in the dose-finding portion will be followed for at least 10 patients in total from all expansion cohorts.

  For all other patients (all expansion cohorts), blood for PK will be taken:
  - Cycle 1, on Day 1 at pre-dose and at the end of PF-05082566 infusion;
  - Predose on Day 1 of Cycles 3, 5, 8, 12, 16, 20, and 24;
  - EOT.

PK sampling schedule may be modified based on emerging safety/PK data.

7.3.2. Blood for PK analysis of Mogamulizumab

Blood samples (3 mL whole blood at each time point) will be collected for PK analysis of mogamulizumab as outlined in the SOA (Table 2) and reported herewith below:

- **Patients in dose-finding cohorts:**
  - Cycle 1:
    a. On Days 1, 8, 15 and 22 at pre-dose, at the end of mogamulizumab infusion,
  - Cycles 2, 3 and 4: at pre-dose;
  - Cycle 5:
    a. On Day 1 at pre dose, at the end of mogamulizumab infusion, and at 6 hrs., and 168 hrs. (Day 8) after the start of the mogamulizumab infusion;
    b. On Day 15 at pre-dose.
  - Pre-dose on Day 1 of Cycles 8, 12, 16, 20 and 24;
  - EOT.
- **Patients in expansion cohorts:** The same PK schedule foreseen in the dose-finding portion will be followed for at least 10 patients in total from all expansion cohorts.

  For all other patients in expansion cohorts, blood for PK will be taken:
  - Cycle 1 on Day 1 at pre-dose and at the end of mogamulizumab infusion;
  - Predose on Day 1 of Cycles 3, 5, 8, 12, 16, 20 and 24;
  - EOT.

PK sampling schedule may be modified based on emerging safety/PK data.

CCI [redacted]

CCI

7.5. Immunogenicity Assessments

Blood samples will be assayed for ADA including, anti PF-05082566, and anti mogamulizumab using a validated analytical method in compliance with Pfizer (anti-PF-05082566) or KHK (anti-mogamulizumab) standard operating procedures. All the samples that are positive for ADA may also undergo characterization for neutralizing antibodies.

As part of understanding the PK of the study drug, samples may be used for evaluation of the bioanalytical method. This additional characterization will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.5.1. Immunogenicity Tests for PF-05082566

Blood samples (2 mL whole blood at each time point) for evaluation of ADA of PF-05082566 will be collected at the following time points:

- Predose on Day 1 of Cycles 1, 3, 5, 8, 12, 16, 20 and 24;
- EOT.

If ADAs are detected, additional samples may be collected approximately every 8 weeks until ADA levels return to baseline. Samples will be analyzed by a laboratory identified by Pfizer. See the Laboratory Manual for additional details.

7.5.2. Immunogenicity Tests for Mogamulizumab

Blood samples (3 mL whole blood at each timepoint) for evaluation of ADA of mogamulizumab will be collected at the following time points:

- Predose on Day 1 of Cycles 1, 3, 5, 8, 12, 16, 20 and 24;
- EOT.

If ADAs are detected, additional samples may be collected approximately every 8 weeks until ADA levels return to baseline. Samples will be analyzed by a laboratory identified by KHK. See the Laboratory Manual for additional details.

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI

[redacted]

7.7. Banked Biospecimen

7.7.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

CCI

[redacted]

CCI [redacted]

A 4-mL blood biospecimen, CCI [redacted] will be collected on Cycle 1 Day 1 at pre-dose, to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

A 2.5 mL blood sample, CCI [redacted] will be collected on Day 1 at pre-dose of Cycles 1, 2, 3, 5 and at the EOT.

Detailed collection, processing, storage, and shipment instructions are provided in the central Laboratory Manual.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following Sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any nonserious AEs that are determined by the Sponsor to be serious will be reported by the Sponsor as a SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 60 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

AEs (serious and nonserious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

Pregnancy or breast feeding that occur during the trial, within 60 calendar days of discontinuing treatment with mogamulizumab, or within 60 days after the cessation of PF-05082566 if the patient begins a new anticancer therapy, whichever is earlier, should be reported as in Section 8.10 (Exposure During Pregnancy).

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;

Worsening of signs and symptoms of the malignancy under study should be reported 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.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the Sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error should be captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for mogamulizumab or PF-05082566 by 20% over the prescribed dose for the dosing cohort under study. No specific information is available on the treatment of overdose for either of the study drugs. In the event of overdose, both study drugs should be discontinued and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect;

- 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 safety reporting 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 safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with Common Terminology Criteria (CTC) Grade 5 (see Section 8.8, Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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. In addition, an overdose of study medication should only be captured as an SAE when it meets one of the criteria listed above.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous Sections and will be handled as SAEs in the safety database (see Section 8.14.1 on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller);

  Concurrent with

  - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥3 X ULN (whichever is smaller).

The patient should return to the investigational 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. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;

- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

AEs will be reported using concise medical terminology (verbatim) as well as the Common Terminology Criteria (CTC) term for Adverse Events (Version 4.03, Publish Date: June 14, 2010, http://ctep.cancer.gov/reporting/ctc.html) listed in the Cancer Therapy Evaluation Program.

The investigator may use the following definitions of Severity in accordance with CTCAE Version 4.03 to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 CTC document but may be used in certain circumstances.)
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 the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer 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 the 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).

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

- Additional information about pregnancy outcomes that are reported as SAEs follows;

- Spontaneous abortion includes miscarriage and missed abortion.

Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. 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 study patient with the Pregnant Partner Release of

Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

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

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE Report form is maintained in the investigative site file.

8.12. Withdrawal Due to Adverse Events (See also Section Patient Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of a SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP, which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis sets

1. Full analysis set.

   The full analysis set includes all enrolled patients.

2. Safety analysis set.

   The safety analysis set includes all enrolled patients who receive at least one dose of study medication.

3. DLT evaluable set.

   All enrolled patients who are eligible for the study and receive study treatment. Note that every patient will contribute to the determination of the MTD including patients who are lost to follow-up prior to completion of the 2 cycles' DLT observation period.

4. PK/Immunogenicity and PK parameter analysis sets.

   The PK/ADA concentration population is defined as all enrolled patients who have been treated and have at least one post dose concentration measurement of either PF-05082566 or mogamulizumab.

   The PK parameter analysis population is defined as all enrolled patients who have been treated and whose concentration-time data allows the estimation of at least 1 of the PK parameters of interest.

5. CCI [redacted]

   [redacted]

6. ECG/QTc Analysis set.

   Treated patients who have baseline and at least 1 on study ECG/QTc measurement.

9.2. Statistical Methods for Dose Allocation: TITE-CRM

A number of alternative designs have been proposed to the standard 3+3 design for Phase I dose escalation trials that improve its accuracy, efficiency and statistical validity, including the continual reassessment method (CRM)[30] and its variants.

Delayed-onset toxicities are a particular challenge for phase I trials of combination therapies.[31] Most of the available dose-escalation designs, including the 3+3 design, the up-and-down designs and the CRM design, require all patients to have completed a fixed observation period for toxicity (eg, 1-2 cycles of the experiment regimen, or 6-8 weeks after start of treatment) before additional cohorts of patients can be enrolled. Thus, trial accrual is patient to opening and closing which may pose logistical risk on the success and completion of the study. In addition, patients who are either lost to follow-up or die of events unrelated to treatment are usually required to be replaced. Due to these reasons, the trial duration could be unacceptably long in case of prolonged observation window and unexpected high rate of patient drop-out.

The time-to-event continual reassessment method (TITE-CRM), a variant of the original CRM method, is open to accrual continually, and maintains other advantages of the CRM relative to the 3+3 design. Like CRM, TITE-CRM seeks to determine the target MTD dose, defined as the dose most closely identified with the target rate, which is the largest acceptable DLT rate determined by the investigators based on the relative costs and benefits of the treatment.

TITE-CRM is to be implemented as described by Cheung et al.[28] and Huang et al.[33] for the dose-escalation and de-escalation of PF-05082566. PF-05082566 may be administered intravenously at the following available dose levels of 1.2, 2.4, 100 mg flat dose (equivalent to the 1.2 mg/kg) and 5.0 mg/kg on an every 4 week schedule (q4wk).

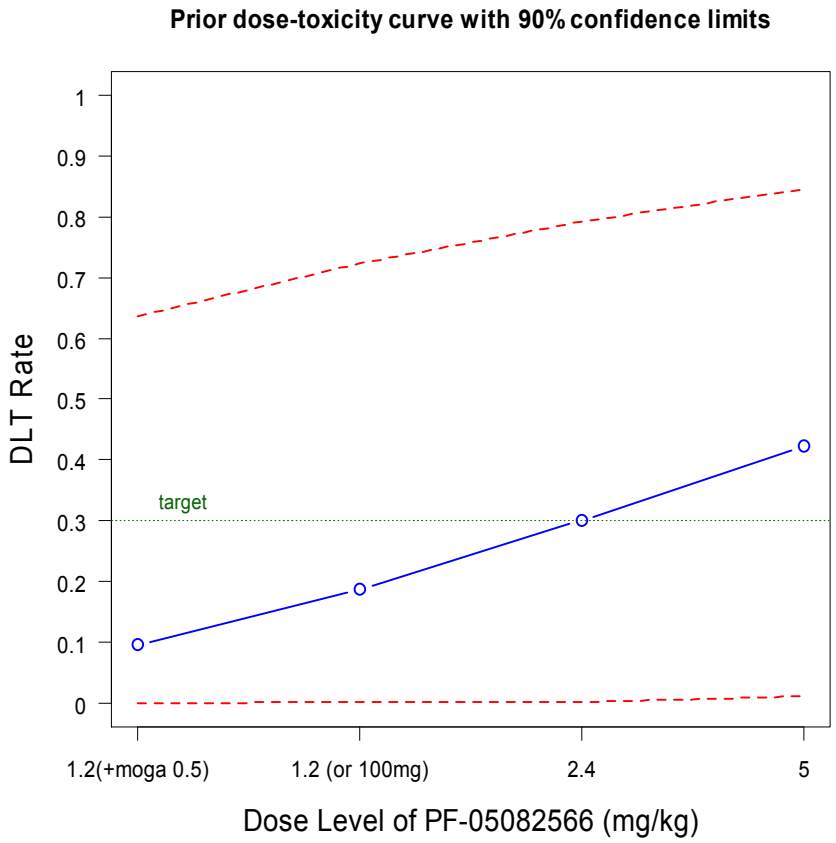
PF-05082566 will be co-administered with mogamulizumab on Day 1 of each treatment cycle. Mogamulizumab will be administered at 1 mg/kg, weekly on Cycle 1, biweekly from Cycle 2 onwards. A lower mogamulizumab dose of 0.5 mg/kg may be tested if the starting dose is not tolerable. Different doses and different dosing schedules of the combination may be investigated after the MTD is estimated. The MTD is defined as highest dose that is associated with a DLT rate <30%. A power function modeling DLT rate at each dose d_i (i=1, …, 4) expressed as Pr (DLT | d_i) = F_i (β) will be used:

$$F_i(\beta) = p_i^{\exp(\beta)}$$

where p_i is the prior estimate of DLT rate at dose level d_i, and $p_1 \le p_2 \le \ldots \le p_4$. These estimates will be projected based model sensitivity to DLTs, together with single agent safety data for both study drugs. β is an unknown single parameter modeling the dose-toxicity relationship, with prior distribution $N(0,\sigma_0^2)$, where σ_0 is the standard deviation of the normal prior distribution with mean=0. At the beginning of the trial, the initial prior value of β is set as 0, the prior mean, which gives a prior dose-toxicity model of $F_i(\beta) = p_i$ based on the power function.

In the Bayesian paradigm, the prior distribution $N(0,\sigma_0^2)$ expresses the researchers' belief in the quality of the initial estimates p_i. The smaller the standard deviation σ_0, the more confidence researchers have in the precision of p_i. and vice versa. As the trial progresses, this prior distribution is combined mathematically with the observed data to yield the posterior distribution of the parameter β (the posterior mean of β will be calculated to model the dose-toxicity relationship). The prior distribution determines how responsive TITE-CRM is to the accumulated data. With a small σ_0 upfront, the posterior toxicity probability estimates remain close to the prior estimates unless significantly discrepant data otherwise occur; with a large σ_0, the model will tend to be more immediately responsive to data. In this trial, σ_0=1, which provides a reasonably flat prior distribution of β, with 90% Bayesian credible interval of $\exp(\beta)$: [0.19, 5.21], sufficiently wide to cover a wide spectrum of dose-toxicity scenarios. Figure 3 illustrates the dose-toxicity curve (blue curve) with 90% upper and lower bounds (red curves) when the initial prior estimates p_i are (0.095, 0.186, 0.300, 0.422).

Figure 3. Example Plot of Prior Dose Toxicity Curve



In the TITE-CRM paradigm, patients who have enrolled in the trial but have not experienced a DLT will be included in the probability calculation with an initial weight equal to the proportion of the 8-week (2 cycles) DLT observation period the patients have completed. However the weight function will be modified if safety data suggest different weight (toxicity) patterns in Cycle 1 and Cycle 2 of PF-05082566. An adaptive cyclical weight function as proposed by Huang et al.[33] will be implemented.

Patients who experience a DLT or complete the observation period without a DLT will be assigned full weight (=1).

Extensive simulation results comparing the TITE-CRM using the adaptive cyclical weight function with the 3+3 design and other weight functions can be found in Huang et al.[33]

9.2.1. Statistical Methods for Dose Escalation/De-Escalation

Section 3.1.9 describes the dose escalation/de-escalation criteria, stopping rules and some restrictions and practical considerations on dose escalation.

9.3. Sample Size Determination

Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the TITE-CRM approach cannot be determined in advance. The maximum sample size is set as 30 for dose escalation cohorts in order to have a reliable and accurate estimate of the MTD based on simulation results. Based on probability theory, a sample size of 30 will ensure the estimates of any binary variable (eg, objective response rate) have a 95% confidence interval of width <0.36. A sample size of 30 also enables the detection of any unexpected toxicity that occurs at 5% rate (in a non-dose-dependent fashion) with a probability of 0.79, and that occurs at 10% rate with a probability of 0.96.

A stopping rule (see Section 3.1.9) will also be implemented for possible early stopping if there is strong confidence in the estimated MTD.

Additional patients will be required for expansion cohorts. The total number of patients in expansion cohorts will be determined based on emerging data from this study, cancer indication, and the patient population of interest.

9.4. Efficacy Analysis

In this Phase 1 study, anti-tumor activity is a secondary objective. Only descriptive efficacy summaries will be performed for this part of the study.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, received (maximum) dose, overall tumor response at each visit, and best overall response. In addition, disease progression date, death date, date of first response, and last tumor assessment date will be listed, together with DR and PFS for the expansion cohort. Kaplan-Meier plot will be created for DR, TTR and PFS in the expansion cohort. A bar plot for DR will also be created for confirmed responders defined by RECIST v 1.1 (Appendix 2) and Immune-Related Response Criteria (Appendix 3).

9.5. Analysis of Other Endpoints

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Pharmacokinetics Analysis of PF-05082566 and Mogamulizumab

Standard serum PK parameters including the maximum serum concentration (C_{max}), time to maximum serum concentration (T_{max}), and area under the serum concentration versus time curve (AUC) for PF-05082566 will be estimated using non-compartmental analysis, as data permits. If data permit or if considered appropriate, minimum serum concentration (C_{min}), average serum concentration (C_{ave}), terminal elimination half-life ($t_{1/2}$), clearance (CL), steady state volume of distribution (V_{ss}), will be estimated. Descriptive statistics will be provided for these PK parameters in tabular form (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle and day.

Dose normalized AUC_{tau} $AUC_{0\text{-last}}$, and C_{max} for PF-05082566 may be plotted against dose (using a logarithmic scale). These plots will include individual patient values and the geometric means for each dose. These plots will be used to help understand the dose proportionality for PF-05082566.

For mogamulizumab, serum PK parameters will be determined by KHK.

For PF-05082566 and mogamulizumab concentrations, individual values and descriptive statistics (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) will be presented by dose, cycle, day of assessment, and nominal time in tabular form. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

No drug interaction is anticipated between PF-05082566 and mogamulizumab. Since PF-05082566 and mogamulizumab are eliminated via a non-specific catabolic degradation process, it is unlikely that concomitant medication can alter their clearance even if target expression is affected. To assess any potential interactions, steady state PK and the formation of anti-drug antibodies will be monitored for both the agents and compared with historical data.

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

PK and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any causal relationship between PF-05082566/ mogamulizumab exposure and biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

9.5.2. Analysis of Immunogenicity Data

ADA/Nab data will be listed and summarized for PF-05082566 and mogamulizumab. The effect of ADA on PF-5082566 and mogamulizumab concentrations and PK parameters will be evaluated.

9.5.3. Statistical Analysis of Biomarker Endpoints

CCI [redacted]

CCI [redacted]

CCI [redacted]

9.6. Safety Analysis

Summaries and analyses of the primary safety endpoint will be based on the per protocol analysis set. Summaries and analyses of all other safety parameters will include all patients in the Safety Analysis Set.

9.6.1. Analysis of Primary Endpoint

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the Section 3, Study Design. AEs constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints

9.6.2.1. Adverse Events

AEs will be graded by the investigator according to CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients 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, Cycle 2 and Cycles >2).

9.6.2.2. Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1, Cycle 2 and Cycles >2). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTC grade definitions, results will be categorized as normal, abnormal or not done.

9.6.2.3. ECG

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. The most recent ECG collected prior to the first day of dosing will be considered the baseline ECG.

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 as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) 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, response rate (RR), PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate) by 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 value and changes from baseline in corrected QT after treatment, by dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT value.

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

Shift tables will be provided for baseline vs. worst on study QTc (one or more correction method will be used) using Maximum CTCAE Grade. As well as tables of ECG abnormality at baseline (yes, no, not done: (n, %)). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

9.7. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee will not be established for this study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an Internal Safety Review team consisting of physician, safety specialist, and statistician to review individual and summary data collected in the safety and clinical databases.

Procedures include:

- Surveillance for SAEs according to regulatory guidelines;
- Discussions between the Investigators and the Sponsor of AEs, laboratory test abnormalities, vital signs, and ECG findings observed at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and make a benefit/risk assessment and decide if further enrollment is appropriate;
- Findings having immediate implication for the management of patients on study will be communicated to all Principal Investigators in the timeframe associated with unexpected and drug-related SAEs.

During the dose escalation phase, a Dose Escalation Steering Committee (DESC) consisting of core clinical team members will be established to perform periodic review of the accumulating safety data, specifically, the DLTs. The guidance for dosing and enrollment decisions is based on the Bayesian statistical model of TITE-CRM. Other considerations may include lower grade AEs, nature and timing of the AEs, existing PK/PD data that may

cause safety concerns. Following each review, the DESC will inform the study team and participating investigators on dosing and enrollment decisions. A DESC Charter will be prepared and will be available before FSFV.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonization (ICH) 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study linking their numerical code to the patient's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the Sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. 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 competent 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 investigational product, 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 patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.1. End of Trial in All Participating Countries

End of Trial in all other participating countries is defined as last patient last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-05082566 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 5 business days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this Section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

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Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Grade	Description	*Karnofsky Score**
0	Fully active, able to carry on all predisease performance without restriction	*100*
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light house work, office work.	*80 or 90*
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	*60 or 70*
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	*40 or 50*
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	*20 or 30*

* Karnofsky Performance Score is provided for reference. Please record corresponding ECOG grade only.

Appendix 2. 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). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion 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 treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

  - One or more target measurable lesions have not been assessed;

    or

  - Assessment methods used were inconsistent with those used at baseline;

    or

  - One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

    or

  - One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

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

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

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Objective/Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 11. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table 12. Objective Response Status at each Evaluation for Patients with Non Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Appendix 3. Immune-related Response Criteria Derived from RECIST 1.1 (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics.

This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD1\anti PDL1 which exert the antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects.[34, 35] Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as RECIST and WHO criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.[36, 37]

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria.[36, 37]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST 1.1 criteria (irRECIST).[38]

For irRECIST, only target and new measurable lesions are taken into account. In contrast to the RECIST 1.1, the irRECIST criteria:

- Require confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and
- Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm longest diameter per non-nodal lesion and 15 mm shortest diameter per nodal lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial.

irRECIST criteria are defined as follows:

- Overall immune-related complete response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.
- Overall immune-related partial response (irPR): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.

- Overall immune-related stable disease (irSD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions is neither irCR, irPR, (compared to baseline) or immune-related progressive disease (irPD, compared to nadir).

- Overall immune-related progressive disease (irPD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (ie, added to the target lesion measurements). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

New non-measurable lesions: Do not define progression but preclude irCR.

Overall responses derived from changes in target, non-target, and new lesions are outlined in Table 13.

Table 13. Overall Response Derived from Changes in Target, Non-target and New Lesions

Measurable response	Non-measurable response		Overall response using irRECIST[b]
Target and New Measurable Lesions (Tumor Burden)[a]	Non-Target Lesions	New Non-Measurable Lesions	
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

a. Decrease assessed relative to baseline.
b. Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.