A PHASE 1B STUDY OF THE 4-1BB AGONIST PF-05082566 IN COMBINATION WITH THE PD-1 INHIBITOR MK-3475 IN PATIENTS WITH ADVANCED SOLID TUMORS

Compound:	PF-05082566
	MK-3475
US IND Number:	109,154
Protocol Number:	B1641003
Phase:	1b

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 2	08-July-2014	**Protocol Summary: Study Treatments** • Deleted additional information concerning calculation of starting dose. **Section 5: Study Treatments** • **Section 5.2: Patient Compliance** This section was removed per FDA request to remove the language in this section, as the language in this section is redundant with language in revised Section 5.2.2 and there is no specific guidance for drugs administered intravenously.
Amendment 1	17 June 2014	**The following are changes that were requested by the FDA:** • **Protocol Summary: Study Treatments:** • Section was updated to reflect change in the dose range to be explored and in the starting dose (now 0.45 mk/kg). Deleted information concerning calculation of starting dose. • **Protocol Summary: Dose escalation Criteria:** • Table 1 was updated to reflect a starting dose (Dose Level 1, DL1) of 0.45 mg/kg and a -1 Dose Level (DL-1) of 0.20 mg/kg. The rest of the table was updated accordingly, deleting text concerning determination of starting dose. • **Starting Dose Selection Strategy**: • In Section 1.3, the starting dose was updated to reflect a starting dose of 0.45 mg/kg q3wks. • **Schedule of Activities:** • Additional information added to Footnote 24 (previously 25) stating that in addition to the timepoints specified,

		blood for cytokine assays may be drawn when clinically indicated. • Additional timepoint (Cycle 6 Day 1 pre-dose) for collection added to Footnote 22. • Additional column added to SOA for Cycle 6, Day 1. • Additional timepoints (End of infusion) for collection added to Footnotes 22, 23, and 24. • Additional information added to footnote 32 further defining parameters of when a patient is considered withdrawn from the study. • **Study Design:** • In Section 3.1 information was added on how drug/drug interactions in this study will be monitored. • In Section 3.1.1, the starting dose was updated to reflect a starting dose of 0.45 mg/kg q3wks. • Section 3.3 DLT Definition, Grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were added as dose-limiting toxicities. • **Patient Selection**: • In Section 4.1 Inclusion Criteria, Criterion 1 now reads as follows: Histological or cytological diagnosis of advanced/metastatic solid tumor malignancy **which has progressed on standard therapy or for which no standard therapy is available**. • **Study Treatments:** • In Section 5.3.4 (changed from Section 5.4.4) Treatment After Initial Evidence of Radiologic Progression, the text in the first paragraph and second paragraph was changed to provide consistency in the decision process to continue or

		discontinue therapy after disease progression is observed. • In Section 5.3.4 (changed from Section 5.4.4) Treatment After Initial Evidence of Radiologic Progression, text was added to last paragraph requiring re-consent of patients upon continuing treatment after confirmed progressive disease. • In Section 5.3.6 (changed from Section 5.4.6) Dose Delays, the platelet count was changed to **75,000/μL**; non-hematologic toxicity language was corrected to read **Grade ≤ 2** if not considered a safety risk for the patient. • In Sections 5.3.6, Tables 8, 9, and 10, and Section 5.3.7.3 (changed from 5.4.7.3) the period for resumption of treatment of study drugs was changed from 12 to **9 weeks**. • In Section 5.3.7 (changed from 5.4.7) Dose reductions, Table 7 was updated to reflect the -1 dose of 0.20 mg/kg. • In Section 5.3.7.2 (changed from 5.4.7.2) Supportive Care Guidelines, text was added to provide guidance on dose reductions of the study drugs after immune-related events. • **Assessments:** • In Section 7.2.1 PK for PF-05082566, an additional timepoint was added (End of infusion and Cycle 6 Day 1 pre-dose). • In Section 7.2.2 PK for MK-3475, two additional timepoints were added (End of infusion). • CCI [redacted] • Also added that for all patients: Cytokine analyses, in addition to the

		timepoints specified above, may be performed whenever clinically indicated.
		• **Data Analysis/Statistical Methods**:
		  • In Section 9.1. Analysis Sets: revised the definition of the DLT Evaluable Set. Added the ECG/QTc Analysis Set.
		  • In Section 9.2. Statistical Methods for Dose Allocation: TITE CRM, updated doses to reflect the 0.20 mg/kg dose and updated prior assumption.
		  • In Section 9.4. Efficacy Analysis: Added time to response description.
		  • In Section 9.5.1.1 additional information on how drug/drug interactions in this study will be monitored.
		• **Other Non-FDA Changes:**
		  • **IND #**
		  • Changed from 121, 729 to 109, 154.
		• **Schedule of Activities:**
		  • CCI [redacted]
		• **Study Design:**
		  • The protocol title was changed to Phase 1b from Phase 1 to be consistent with the Phase 1b designation on the title page and throughout the protocol
		• **Study Treatments**
		  • In Section 5.3 (changed from Section 5.4) Administration, the following text was added to the first paragraph: **Patients will be observed in the clinic for at least 2 hours after each infusion of study drug.**
		• **Administrative Changes:**
		  • Administrative changes were made to enhance the readability of the protocol

		and clarify inconsistencies. • **References:** • Added one additional reference for the use of TITE-CRM modeling.
Original protocol	17 April 2014	Not applicable (NA)

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, CD137, ILA
4-1BBL	4-1BB Ligand, TNFSF9
ACTH	Andrenocorticotropic hormone
ADA	Anti -drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse Event
ALT	Alanine amino transferase
ANOVA	Analysis of variance
APC	Antigen presenting cell
AST	Aspartate aminotransferase
AUC	Area under the concentration vs time curve
AUC0-168	area-under-the-curve from time zero to 168 hours
AUC0-672	area-under-the-curve from time zero to 672 hours
AUC0-last	area-under-the-curve from time zero to last measurable concentration
BUN	Blood urea nitrogen
CCR7	Chemokine (C-C motif) receptor 7; CD197
CD3	Cluster of differentiation 3
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CD16	Cluster of differentiation 16, FCγRIIIa and FCγRIIIb
CD20	Cluster of differentiation 20
CD25	Cluster of differentiation 25, alpha chain of the IL-2 receptor
CD40	Cluster of differentiation 40, TNFRSF5
CD45	Cluster of differentiation 45, Protein tyrosine phosphatase, receptor type C (PTPRC), leukocyte common antigen
CD45RA	CD45 (PTPRC) RA isoform
CD45RO	CD45 (PTPRC) RO isoform
CD56	Cluster of differentiation 56; neural cell adhesion molecule
CD134	Cluster of differentiation 134, TNFRSF4, OX-40
CD137	Cluster of differentiation 137, TNFRSF9, 4-1BB, ILA
Cave	Estimated average serum concentration
Cmax	Maximum observed serum concentration
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CRP	C reactive protein
CT	Computed Tomography
CTCAE	Common technical criteria for adverse events
CXCR6	Chemokine (C-X-C motif) receptor 6; CD186
DC	Dendritic cell
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
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
ELISA	Enzyme linked immunosorbent assay
ERK	Extracellular signal-regulated kinase
FACS	Fluorescent-activated cell sorting; flow cytometry
Fc	Fragment crystallizable
FL	Follicular lymphoma
GCP	Good clinical practice
GGT	Gamma-glutamyl traspeptidase
GTD	Greatest transverse diameter
Hb	Hemoglobin
HLA	Human leukocyte antigen
ICH	International conference on harmonization
ICOS	Inducible T-cell costimulator; CD278
IEC	Independent ethics committee
IFN-γ	interferon-gamma
IgG2	Immunoglobulin G subclass 2
IL-1β	Interleukin 1 beta
IL-2	Interleukin 2
IL-4	Interleukin 4
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-10	Interleukin 10
IL-12p70	Interleukin 12 (bioactive 75 kDa heterodimer of IL-12p40 and IL-12 p35)
IRB	Institutional Review Board
ITGB7	Integrin, beta 7
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
MABEL	Minimal anticipated biological effect level
MCL	Mantle cell lymphoma
MUGA	Multigated acquisition
MPK	Milligrams per kilogram, mg/kg
MTD	Maximum tolerated dose
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
OBD	Optimal biological dose
ORR	Overall response rate
OS	Overall survival

PBL	Peripheral blood leukocyte
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate Buffered Saline
CCI	[redacted]
PFS	Progression-free survival
PGRD	Pfizer Global Research & Development
PK	Pharmacokinetics
POM	Proof of mechanism
PR	Partial response
PT	Prothrombin time
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAMD	Single agent, multiple dose
SC	Subcutaneous
sCD25	Soluble CD25
sCD137	Soluble CD137 (soluble 4-1BB)
SCID	Severe combined immunodeficiency
SAE	Serious adverse event
SEM	Standard error of the mean
sFasL	Soluble Fas Ligand
SPR	Surface plasmon resonance
t1/2	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
VCAM1	Vascular cell adhesion protein 1
TSH	Thyroid Stimulating Hormone
Vss	Volume of distribution at steady state

PROTOCOL SUMMARY

Indication

Advanced solid tumors.

Study Rationale

PF-05082566 is a fully humanized IgG2 monoclonal antibody and promising new molecular entity that binds to human 4-1BB with high affinity and specificity. MK-3475 is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 (programmed death-1) and its ligands, PD-L1 and PD-L2. *In vitro* and *in vivo* data demonstrated immunomodulatory activity and anti-tumor activity of PF-05082566 when dosed as a single agent, in combination with antibody-dependent cellular cytotoxicity (ADCC) inducing antibodies, and significantly enhanced anti-tumor activity in combination with anti-PD1 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 (thus far up to 2.4 mg/kg) when administered every 4-weeks (q4wks), without adverse events (AEs) above Grade 1 severity attributed to PF-05082566, when administered as a single agent. 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.

MK-3475, previously known as SCH 900475, is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 has been studied in patients with advanced solid tumors. Anti-tumor activity has been noted in advanced melanoma, as well as advanced non-small cell lung cancer (NSCLC) patients. In addition, MK-3475 has been generally well tolerated in these patients.

While preclinical data demonstrated significant immunomodulatory activity and anti-tumor activity of PF-05082566 when dosed as a single agent, it is hypothesized that in some tumors upregulation of PD-1 on tumor-infiltrating lymphocytes, and its ligand PD-L1 on tumor cells, may down-modulate the activity of anti-tumor lymphocytes stimulated by an agonist anti-4-1BB antibody. PD-L1 may be expressed on tumor cells as a result of activated T cells within the tumor producing inflammatory cytokines, such as interferon gamma (IFN-γ). In accord with this, studies in mice suggest that activated tumor-infiltrating T lymphocytes (TILs) induce the expression of PD-L1, which in turn results in down modulation of the Tcells. This is thought to be one mechanism for tumor cell evasion of the immune system. Tumor cells expressing PD-L1 may be better candidates for anti-PD-1 therapies than tumors that do not express PD-L1. It is clear from the study of biopsies that many tumors do not contain detectable numbers of infiltrating T cells, which could account in part for lack of PD-L1 expression in many of these tumors. In theory, an agonist anti-4-1BB antibody may activate T cells, which can traffic to tumors that would not otherwise contain these activated cells, where they may induce the expression of PD-L1. Therefore, the local environment

within tumors that do not respond to anti-PD-1 therapies or anti-4-1BB single agent therapies may be converted to an immune responsive environment by combining an anti-PD-1 antagonist antibody with an anti-4-1BB agonist antibody. In support of this concept, an agonist anti-4-1BB antibody in combination with an anti-PD-1 antagonist antibody showed significantly improved anti-tumor activity compared with either single agent in multiple mouse models. In addition, safety data in mice indicated that the addition of an anti-PD-1 antibody did not add to the toxicity of an anti-4-1BB agonist antibody.

STUDY OBJECTIVES AND ENDPOINTS

Objectives

Primary Objectives

- To estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D) for the combination of PF-05082566 with MK-3475 in patients with advanced solid cancer.

Secondary Objectives

- To evaluate the overall safety profile;
- To characterize the pharmacokinetics of PF-05082566 and MK-3475 given in combination following IV administration;
- To evaluate the immunogenicity of PF-05082566 and MK-3475 when given in combination;
- To assess the anti-tumor effect of PF-05082466 in combination with MK-3475 (by RECIST criteria);
- **Expansion Cohorts Only:** To characterize the mechanism of sensitivity and/or resistance to PF-05082566 in combination with MK-3475 in tumor tissue.

CCI [redacted]

- CCI [redacted]
- CCI [redacted]

Endpoints

Primary Endpoint

- First 2 cycles Dose-Limiting Toxicity (DLT) of PF-05082566 in combination with MK-3475.

Secondary Endpoints

- Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566 in combination with MK-3475;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03);
- Vital signs, weight, Eastern Cooperative Oncology Group (ECOG) Performance Status;
- PK parameters of PF-05082566 and MK-3475, including but not limited to C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ CL and Vd (as data permits);
- Anti-Drug Antibody levels for PF-05082566 and MK-3475;
- Objective tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;
- Time-to-response (expansion cohorts only);
- Duration of response (expansion cohorts only);
- Progression–free survival (expansion cohorts only);
- **Expansion Cohorts Only**: Paired de-novo tumor biopsy collection at sequential time points for analysis of exploratory mechanistic biomarkers such as IHC assessment of tumor-infiltrating lymphocytes, quantitation of T cell receptor sequences, and gene expression.

CCI [redacted]

- CCI [redacted]
- CCI [redacted]

[redacted]

STUDY DESIGN

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, pharmacokinetic CCI study designed to estimate the maximum tolerated dose (MTD), and determine the Recommended Phase 2 Dose (RP2D) of PF-05082566 in combination with MK-3475 in patients with advanced solid tumors**.**

Once the MTD of PF-05082566 administered in combination with MK-3475 has been estimated with confidence, one or more expansion cohorts of patients with selected advanced solid tumors will be enrolled to further study the safety, tolerability, CCI and preliminary anti-tumor activity for PF-05082566 in combination with MK-3475 to support recommended Phase 2 dose (RP2D) selection, as well as to study tumor-associated biomarkers. The tumor types for further study could include NSCLC and potentially other tumor types based on emerging data from the dose escalation phase of this study.

Antitumor activity will be assessed by radiological tumor assessments conducted at baseline, at 9 weeks after the first dose of study drug, and every 6 weeks thereafter, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 6 weeks), using RECIST version 1.1. Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits. Pharmacokinetic CCI blood endpoints will also be monitored in all patients.

For all patients in dose-expansion cohorts, a de novo biopsy will be required at study entry followed by a second biopsy at the time of the week 9 scans (after 3 cycles of treatment). Optional de novo biopsies may be collected from patients in dose-escalation cohorts to support the assessment of disease progression. CCI

Study Treatments:

PF-05082566 will be administered as a 1 hour intravenous infusion q3wks in escalating doses and may include the following planned doses: 0.20 mg/kg, 0.45 mg/kg, 0.9 mg/kg, 1.8 mg/kg, 3.6 mg/kg, and 5 mg/kg. The starting dose of PF-05082566 will be set at 0.45 mg/kg.

MK-3475 will be administered as a 30 minutes IV infusion at a dose of 2 mg/kg q3wks. This MK-3475 dose was chosen based on PK, safety, and efficacy considerations (see Section 1.3 for more details).

After estimation of the MTD for the combination on the q3wk schedule, PF-05082566 may be co-administered along with MK-3475 to study safety and tolerability on an alternative

dosing schedule for both drugs. Other study drugs doses may also be tested based on emerging safety and tolerability data. The initiation of additional patient cohorts to explore additional dosing schedules or study drugs doses will be at the discretion of the Sponsor.

CCI [redacted] Therefore, patients with RECIST defined disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue treatment with PF-05082566 plus MK-3475 provided that the treating physician has determined that the benefit/risk for doing so is favorable. The duration of treatment will be up to 32 cycles (approximately 24 months) in all patients.

Dose escalation and MTD estimation for the PF-05082566 plus MK-3475 combination will be conducted according to the following algorithm:

a. Dose escalation and de-escalation of PF-05082566 follows the Time-to-Event Continual Reassessment Method (TITE-CRM) up to a maximum dose of 5.0 mg/kg q3wk.

b. The MTD is defined as the highest combination dose with a DLT rate <25% from the model estimate.

c. Dose escalation stops if:

- Maximum study sample size is reached; or
- 9 evaluable patients have been treated at the estimated MTD; or
- All doses appear to be overly toxic and the MTD cannot be determined in the current trial.

Treatment with study drugs will continue until completion of 32 cycles (approximately 24 months) of treatment, disease progression (RECIST v. 1.1), patient refusal, unacceptable toxicity occurs, or the study is prematurely terminated by the Sponsor; whichever comes first. Discontinuation from treatment may be considered at the investigator's discretion for patients who have attained a confirmed CR, have been treated for at least 24 weeks on study, and have at least two treatments with MK-3475 and PF-05082566 beyond the date the initial CR was declared. 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 complete a maximum number of 32 cycles (approximately 24 months) on study treatment and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study treatment will be given the opportunity to continue treatment upon agreement between investigator and sponsor.

Dose Escalation Criteria:

Based on the starting dose example above, dose escalation and de-escalation will be carried out according to Table 1.

Table 1. Dose Escalation Cohorts

Dose Escalation Cohort	PF-05082566	MK-3475
-1	0.20 mg/kg q3wks	2 mg/kg q3wks
1 (Starting Dose Level)	0.45 mg/kg q3wks	2 mg/kg q3wks
2	0.9 mg/kg q3wks	2 mg/kg q3wks
3	1.8 mg/kg q3wks	2 mg/kg q3wks
4	3.6 mg/kg q3wks	2 mg/kg q3wks
5	5 mg/kg q3wks	2 mg/kg q3wks

* q3wks: every 3 weeks

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 in the Schedule of Activities table, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Table 2. Schedule of Activities: (PF-05082566 Plus MK 3475: 21 Day Treatment Cycles)

	Screening[1]	CYCLES 1-2			CYCLES 3-8			CYCLES>8[35]	End of Treatment[31]	Follow up[32]
Protocol Activity	**Within 28 days of registration**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**		
Visit Window			**(±) 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	
ECOG Performance Status[6]	X	X			X			X	X	
Baseline signs and symptoms[7]	X									
Vital signs[8]	X	X	X	X	X			X	X	
Contraception Check	X	X	X	X	X	X	X	X	X	X
Safety Labs/Measurements										
12 lead ECG[9]	X	X			X				X	
Hematology[10]	X	X	X	X	X	X	X	X	X	
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	
Coagulation[12]	X	X	X	X	X			X	X	
Urinalysis[13]	X								X	
Pregnancy Test[14]	X	X			X			X	X	
Hepatitis B and C tests[37]	X									
T3, FT4 and TSH[36]	X	X			X			X	X	
Endocrine function assessment[15]	X	As clinically indicated								
Registration and Treatment										
Registration[16]		X								

Table 2. Schedule of Activities: (PF-05082566 Plus MK 3475: 21 Day Treatment Cycles)

	Screening[1]	CYCLES 1-2			CYCLES 3-8			CYCLES>8[35]	End of Treatment[31]	Follow up[32]
Protocol Activity	**Within 28 days of registration**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**		
Administration of PF-05082566[17]		X			X			X		
Administration of MK-3475[18]		X			X			X		
Tumor Assessments										
CT or MRI scan[19]	X					To be assessed at week 9 and then every 6 weeks			X	X
Other Clinical Assessments										
AEs[20]		Monitored and Recorded Continuously							X	X
Review Prior/Concomitant Medications[21]	X	Monitored and Recorded Continuously								

Table 3. Schedule of Activities: (PF-05082566 and MK 3475: Dose Escalation and Expansion): Pharmacokinetic, CCI and Pharmacogenomic Assessments

	Cycles 1-2	Cycles 3-4	Cycle 5			Cycle 6	Cycle 7		Cycles >7[35]	End of Treatment[31]	Follow up[32]
Assessments [(±) 2 days for Cycles 1-7 and (±) 7 days for Cycles >7]	**Day 1**	**Day 1**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 8**	**Day 1**		
Blood for PF-05082566 PK[22]	X	X	X	X	X	X	X	X	X	X	
Blood for MK-3475 PK[23]	X	X	X				X	X	X	X	X
CCI											
CCI											
Banked biospecimen (blood)[26]	X (Cycle 1)										
Blood for Pharmacogenomics (RNA)[27]	X										
Blood for T cell receptor quantitation[28]	X	X	X							X	
Blood for PF-05082566 Immunogenicity (ADA) testing[29]	X (Cycle 1)	X (Cycle 3)	X				X		X	X	
Blood for MK-3475 Immunogenicity (ADA) testing[30]	X (Cycle 1)	X (Cycle 3)	X				X		X	X	X
De novo tumor biopsy for biomarker assessment (Dose escalation)[33]	X (unscheduled, to be collected at discretion of investigator and sponsor)										
De novo tumor biopsy for biomarker assessment (Expansion cohorts only)[34]	X (taken prior to D1 dose)	X (taken at the time of Cycle 3 tumor assessment)									

Footnotes for Schedule of Activities:

1. **Screening:** To be performed within 28 days of treatment initiation.
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:** To be collected within 28 days prior to registration. Includes oncology history; information on prior regimens, including dosing and duration of administration plus description of best response observed.
4. **Medical History:** Include history of other diseases (active or resolved) and concomitant illnesses.
5. **Physical Examination:** Includes major body systems. Weight for the purposes of dose calculation must be recorded at Screening and within 7 days pre-dose Day 1 of each cycle. Height will be measured at baseline only.
6. **ECOG Performance Status:** ECOG performance scale is available in Appendix 2 of the protocol.
7. **Baseline signs and symptoms:** Patients will be asked about any signs and symptoms experienced within the past 14 days prior to starting treatment and record on the AE CRF page. During study treatment any new or worsened conditions since baseline should be reported on the AE CRF.
8. **Vital Signs:** Blood pressure, and pulse rate will be recorded in a supine or seated position.
9. **Triplicate 12 Lead ECG:** See Section 7.1.5 for details. 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. ECGs will be collected as follows: a) at Screening; b) On Cycles 1-8/Day 1, at pre PF-05082566 infusion and end of MK-3475 infusion; and c) at End of Treatment. If the mean QTc interval is prolonged (>500 msec), then the ECGs should be reevaluated by a qualified person at the center for confirmation. Additional triplicate ECGs may be performed as 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 escalation cohorts.
10. **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. To be performed weekly. 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 4 for the Required Laboratory Tests list.
11. **Blood Chemistry:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. To be performed weekly. See Table 4 for Laboratory Tests list.
12. **Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. To be performed weekly for Cycle 1 and on Day 1 for all remaining cycles and at the End of Treatment visit. See Table 4 for Laboratory Tests list.
13. **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 4). Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein.
14. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before study drug administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations. For Day 1 of each cycle, pregnancy testing is required immediately before study drug administration. See Section 7.1.1 for contraception guidelines.
15. **Endocrine function assessment (in addition to T3, FT4, and TSH):** During treatment, to be performed in cases of suspected hypoadrenalism or hypopituitarism. See Table 4 for Laboratory Tests list.
16. **Registration:** Patient number and dose level allocation operated by Pfizer Inc.
17. **Trial Treatment/PF-05082566 administration:** PF-05082566 will be administered once every 3 weeks (1 cycle = 21 days) as a 1 hour intravenous infusion.
18. **Trial Treatment/MK-3475 administration:** MK-3475 will be administered once every 3 weeks as a 30 minute infusion. MK-3475 infusion will start 30 minutes after completion of PF-05082566 infusion and after the post- PF-05082566 and pre-MK-3475 pharmacokinetic blood samples are drawn (See Section 5.3.6 for acceptable periods for dose delays due to infusion reactions).

19. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan, and bone scans (see Section 7.4.1). The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, at 9 weeks then every 6 weeks, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment (if not done in the previous 6 weeks). Timing should follow calendar days and should not be adjusted for delays in cycle starts. Follow-up bone scans are required every 15 weeks only if bone metastases are present at baseline. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of response for patients who have bone metastases. Assessment of response will be made using RECIST version 1.1.
20. **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 serious adverse events (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 90 calendar days after the last administration of the investigational products and before initiation of a new anti-cancer treatment. The prolonged follow up is due to the pharmacokinetic properties of the investigational product MK-3475. SAEs experienced by a patient after the active reporting period (see Section 8.2) 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. AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least one dose of study treatment through last patient visit (Day 28 after last dose). If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Pregnancy or breast feeding that occur during the trial, within 120 days of discontinuing treatment with MK-3475, or within 28 days after the cessation of study treatment if the patient begins a new anticancer therapy, whichever is earlier, should be reported as in Section 8.10 (Exposure During Pregnancy).
21. **Concomitant Medications:** All concomitant medications including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases should be recorded in the CRF.
22. **Blood for PF-05082566 Pharmacokinetics:** Blood samples will be collected during Cycle 1-4 on (a) Day 1 at pre-dose and end of infusion; (b) During Cycle 5 on Day 1 at pre-dose, end of infusion, and at 2, 6, and 24 hrs after the start of infusion; (c) on Days 8 (192 hours), and 15 (360 hours) after start of infusion (See Section 7.2 for guidelines on timing of blood draws); (d) During Cycle 6 on Day 1 at pre-dose; (e) During Cycle 7 on Day 1 at pre-dose, end of infusion, 24 hrs after the start of infusion and on Day 8; and (f) Beyond Cycle 7, PK samples will be collected at pre-dose, for every 2 cycles up to Cycle 12, every 4 cycles thereafter, and at the End of Treatment visit. **For patients in expansion cohorts**, same PK schedule will be followed for at least 10 patients in total from all expansion cohorts. For other patients (all expansion cohorts), predose samples on Day 1 will be collected for Cycles 1, 3, 5, 6 (Section 7.2.1) and 7. Beyond Cycle 7, PK samples will be collected at pre-dose, for every 2 cycles up to Cycle 12, and every 4 cycles thereafter. Timing of sampling may be modified based on emerging PK data. For patients discontinuing from the study, a PK sample should be collected at the End of Treatment assessment.
23. **Blood for MK-3475 Pharmacokinetics:** Blood samples will be collected (a) During Cycle 1- 4 on Day 1 at pre-dose and end of infusion; (b) During Cycle 5 on Day 1 at pre-dose; and end of infusion(c) During Cycle 7 on Day 1 at pre-dose, end of infusion, 24 hrs, and on Day 8 (192 hrs) after start of infusion (See Section 7.2 for guidelines on timing of blood draws). Beyond Cycle 7, PK samples will be collected at pre-dose every two cycles up to cycle 12, and every 4 cycles thereafter. Additionally, PK samples will be collected at 28 days, 3 months, and 6 months after the end of MK-3475 treatment. **For patients in an expansion cohort**, the same PK schedule will be followed for at least 10 patients in total from all expansion cohorts. For other patients (all expansion cohorts), predose samples on Day 1 will be collected for Cycles 1, 3, 5 and 7. Beyond Cycle 7, PK samples will be collected at pre-dose (Day 1), every 2 cycles up to Cycle 12, and every 4 cycles thereafter. Timing of sampling may be modified based on emerging PK data. For patients withdrawing from the study, a PK sample should be collected at the End of Treatment assessment.
24. CCI [redacted]

25. CCI [redacted]
26. **Banked Biospecimen (blood)**: A 4-mL blood biospecimen will be collected on Day 1 Cycle 1 **(pre-dose)** to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision.
27. **Blood for Pharmacogenomics (RNA):** Blood samples will be collected during Cycle 1 Day 1 (pre-dose) and Cycle 2 Day 1 (pre-dose).
28. **Blood for T cell Receptor Quantitation:** Blood sample taken pre-dose on Day 1 of Cycles 1 through 5, and at End of Treatment.
29. **Blood for PF-05082566 Immunogenicity (ADA) Testing:** Blood for PF-05082566 immunogenicity testing will be collected at pre-dose (Day 1), Cycles 1, 3, 5, 7, and subsequently pre-dose (Day 1) every 2 cycles up to Cycle 12, and every 4 cycles thereafter. For patients discontinuing study drug treatment, immunogenicity samples should be collected at the End of Treatment assessment day. If ADAs are detected, additional samples may be collected approximately every 3 months (coinciding with disease assessment visit) until ADA levels return to baseline.
30. **Blood for MK-3475 Immunogenicity (ADA) Testing:** Blood for MK-3475 immunogenicity testing will be collected at pre-dose in Cycles 1,3, 5, 7 and subsequently predose every 2 cycles up to Cycle 12 and every 4 cycles thereafter. Additionally, ADA samples will be collected at 28 days, and during Follow-Up (3 months and 6 months after the end of MK-3475 treatment).
31. **End of Treatment:** To be performed approximately 28 days after the last dose of study drug. Obtain these assessments if not completed during the previous week on study (during the previous 6 weeks on study for tumor assessments).
32. **Follow Up:** Patients should be evaluated up to 90 days after last dose of study treatment. Refer to the protocol for specific guidelines. Patients continuing to experience 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 Assessment section in Schedule of Activities (Table 3). 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 12 weeks ± 7-days. Once patients have exhibited disease progression or began a new anti-cancer therapy, or 6-month follow-up from the date of the first dose of the last enrolled patient, whichever occurs first, they will be withdrawn from the study. See Section 4.3.1 Contraception for guidelines on contraception checks during this period.
33. **De novo tumor biopsy for biomarker assessment (Dose escalation):** For patients in dose-escalation cohorts, unscheduled optional de novo tumor biopsies may be collected at the discretion of the investigator and sponsor to support the assessment of disease progression.
34. **De novo tumor biopsy for biomarker assessment (Expansion cohorts):** Mandatory for patients in expansion cohorts only. A de novo biopsy will be required at study entry followed by a second biopsy at the time of the Week 9 scans (after 3 cycles of treatment).
35. **Continued Treatment Beyond Cycle 8:** This will be on a reduced visit schedule (Day 1 of each cycle), or as clinically indicated.
36. **Thyroid Function Tests:** To be collected every 2 cycles for the first 8 cycles, and then every 4 cycles (Cycles 1, 3, 5, 7, 11, 15 etc.).
37. **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.

Table 4. Required Laboratory Tests

SAFETY LABORATORY REQUIREMENTS **Refer to the Schedule of Activities table for specific timepoints and instructions**	
Assessments	
Hematology Panel:	**Chemistry Panel:**
Absolute Neutrophil Count	Sodium
Hemoglobin	Potassium
	Total Calcium
Platelet Count	Creatinine
WBC with differential (5-part if available)	Albumin
	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
	Glucose
	Phosphorus
	Magnesium
	Total Bilirubin***
	Blood urea nitrogen (BUN)
	Alkaline phosphatase
	Lactate dehydrogenase (LDH)
	Immunoglobulin G
	Total protein
	Uric acid (or urate)
Coagulation Panel: international normalized ratio (INR) or prothrombin time (PT), Partial thromboplastin time (PTT)	**Thyroid function assessments:** T3, FT4 and TSH. In the presence of clinical suspicion of hypopituitarism or hypoadrenalism, laboratory testing should include one or more of the following: ACTH, and cortisol levels before and 30-60 minutes after corticotrophin stimulation.
Urinalysis: measurement of pH, specific gravity, protein/albumin, glucose, blood/hemoglobin, ketones/acetone. Urine dipstick for urine protein: if positive collect 24-hr and microscopic (Reflex Testing), Urine dipstick for urine blood: if positive collect a microscopic (Reflex Testing). **Pregnancy Test (serum or urine):** Conducted for women of childbearing potential only.	**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.
*** For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, and acetaminophen levels.	

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1. INTRODUCTION

This is a Phase 1b study of PF-05082566, a novel fully humanized IgG2 monoclonal anti-body (mAb) agonist of 4-1BB (CD137, TNFRSF9), in combination with MK-3475, a PD-1 inhibitor mAb. The study is designed to evaluate the safety, pharmacokinetics (PK) [redacted] of PF-05082566 administered intravenously in combination with MK-3475 to adults with advanced solid tumor malignancies.

1.1. Indication

Relapsed or refractory solid tumors.

1.2. Background and Rationale

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

4-1BB (CD137, TNFRSF9), first identified as an inducible costimulatory 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 NK and natural killer T (NKT) cells; regulatory T cells; dendritic cells (DC) including follicular DC; stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils (Wang et al. 2009),[21] and activated B cells (Zhang et al. 2011).[22] 4-1BB expression has also been demonstrated on tumor vasculature (Broll et al. 2001, Seaman et al. 2007)[1,19] and atherosclerotic endothelium (Olofsson et al. 2008).[16] The ligand that stimulates 4-1BB (4-1BBL) is expressed on activated antigen-presenting cells (APCs), myeloid progenitor cells and hematopoeitic stem cells.

4-1BB is undetectable on the surface of T cells but expression increases upon activation. Based on homology to other members of the TNFRSF, ligand binding is expected to induce receptor trimerization resulting in activation (Chan et al. 2007).[2] 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 (Furtner et al. 2005; Hentschel et al. 2006; Michel et al. 1998).[8,9,13]

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 NFkB and the Mitogen Activated Protein (MAP) Kinase cascade including Erk, Jnk, and p38 MAP kinases. NFkB 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 (Sabbagh et al. 2008).[18]

Numerous studies of murine and human T cells indicate that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production (Croft 2009).[4] Reports have shown that 4-1BB agonist mAbs increase costimulatory 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 (Lynch 2008).[12] 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models (Vinay et al. 2006).[20] 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 (Zhang et al. 2011).[22] 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 (Houot et al. 2011).[10] The addition of 4-1BB agonists to *in vitro* cultures of B lymphoma cells with rituximab and NK cells resulted in increased lymphoma killing (Kohrt et al.2010).[11]

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. Pre-clinical Development 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. Injection with PF-05082566 has been shown to correlate with tumor cell line growth inhibition in xenogenic tumor models as a single agent. 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 5.

Table 5. In Vitro Properties of PF 05082566

In vitro Assay	Activity (nM)
Affinity for 4-1BB	
Biacore Affinity (KD) On rate (Ka) Off rate (Kd)	 8.7±1.0 1.4±0.06 x10^6 M^{-1} s^{-1} 0.012±0.001s^{-1}
Saturation Binding	
4-1BB ECD binding ELISA (EC50; n=3) Human Cyno	 0.124±0.041 0.198±0.024
4-1BB expressing 300.19 cells (FACS EC50; n=2) Human Cyno	 1.8 4.2
PHA stimulated primary cells Human PBMC (FACS EC50; n=12) Cyno PBMC (FACS EC50; n=7) Dog, rat, mouse (FACS; n=2)	 48.9±24 149±68 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) Cyno (n=3)	 0.15±0.04 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
ECD = Extracellular Domain	
ELISA = Enzyme Linked Immunosorbent Assay	
FACS = Fluorescence Activated Cell Sorting	
PHA = Phytohemagglutinin	
PBMC = Peripheral Blood Mononuclear Cell	
NF-kB = Nuclear Factor kappa B	
IL-2 = Interleukin-2	

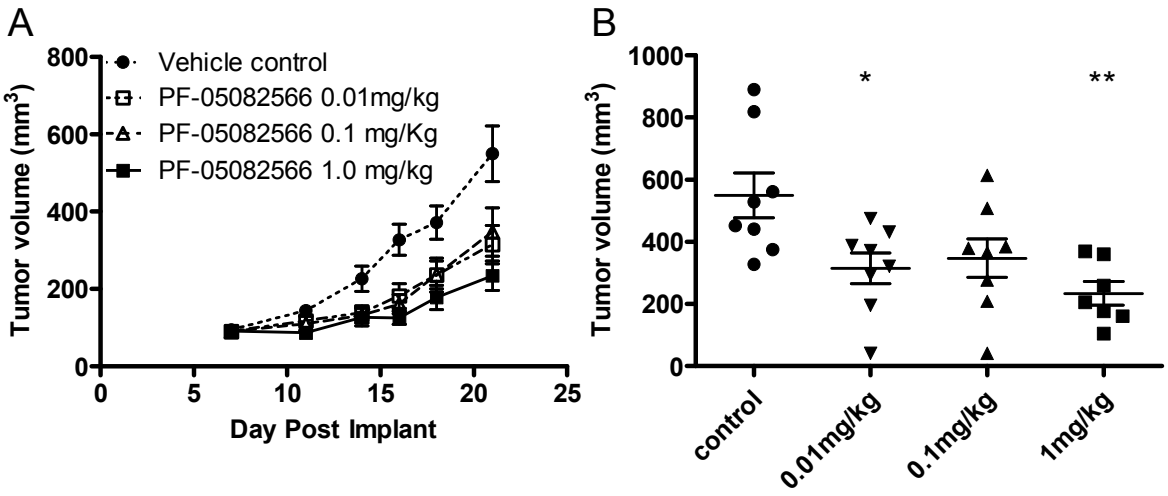
1.2.3. *In Vivo* Data: Functional Activity of PF-05082566

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 proliferation among cytotoxic central memory T cells (CD8 T_{CM}) in peripheral blood mononuclear cell (PBMC) samples. Taken together, these data demonstrate evidence of PF-05082566's ability to enhance lymphocyte response *in vivo*.

1.2.3.1. 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 xenogenic tumor model. None of the tumor lines expressed 4-1BB; therefore, tumor cells were mixed with primary human peripheral blood mononuclear cells (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



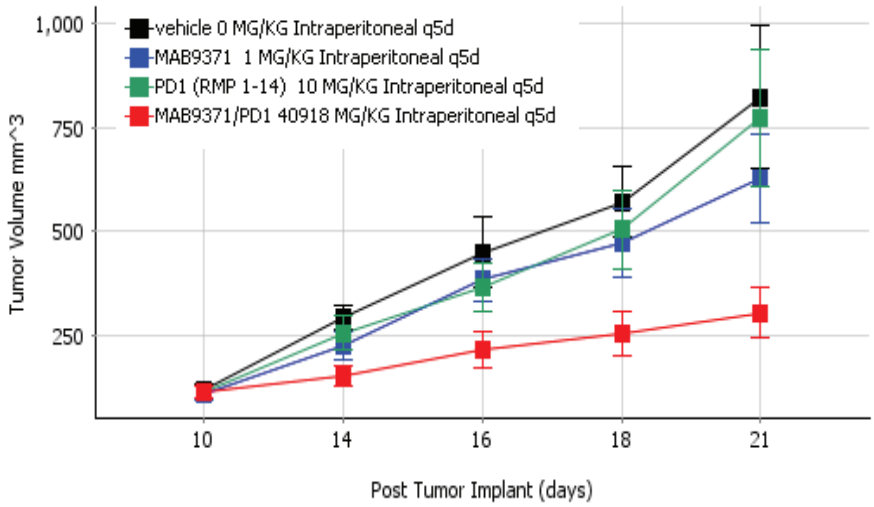
PF-05082566 inhibits the growth of the PC3 prostate carcinoma *in vivo* Panel A: mean tumor volume at each time point measured. Panel B: volume of each tumor on the final study day (Day 21). The mean and standard error of the mean (SEM) are indicated by bars. *p<0.05, ** p<0.005.

1.2.4. Combination Studies

As discussed in the Protocol Summary section, it is thought that tumor expression of PD-L1 can limit the ability of cytotoxic T cells to directly kill the tumor cells. Therefore, even if a 4-1BB agonist is used to stimulate cytotoxic T cells, capable of recognizing such tumors, PD-L1 expressed on the tumor cells may down-modulate the activity of these stimulated T cells. A 4-1BB agonist antibody resistant mouse MC38 colon cancer tumor model, that expresses PD-L1, was used to provide evidence for improved anti-tumor activity using the combination of a 4-1BB agonist antibody with PD-1 antagonist antibody compared with either single agent. Figure 2 shows the results of this experiment in a mouse model, in which statistically significant anti-tumor activity versus the vehicle control is observed in the cohort of mice that received a combination of a PD-1 antagonist antibody with a 4-1BB agonist antibody but not with either antibody administered as a single agent. Consistent with the proposed mechanism for the combination, significant increases in CD8+ effector memory

cells and tumor responsive IFN-γ producing cells were found in the spleens of mice treated with the combination (data not shown). In addition, preliminary toxicology data in mice suggest that the toxicity of an anti-4-1BB agonist is not increased by addition of an anti-PD-1 antagonist (data not shown).

Figure 2. Combinatorial Efficacy of Surrogate Anti-4-1BB combined with Surrogate Anti-PD-1 in a Colorectal Carcinoma Model



Combination of a 4-1BB agonist antibody with a PD-1 antagonist antibody shows significant inhibition tumor growth in a colon carcinoma model. C57BL6 mice were subcutaneously implanted with $1X10^6$ MC38 murine colon carcinoma cells. Tumor growth was monitored and animals randomized to four groups of 8 when the tumors reached an average size of 150 mm^3 and intraperitoneal dosed with vehicle (phosphate-buffered saline; PBS), 1 mg/kg anti-mouse 41BB agonist (MAB9371), 10 mg/kg anti-mouse PD-1 antagonist (RMP1-14), or the simultaneous combination of the two once every 5 days for a total of two doses. The study was terminated when tumor sizes of the controls reached 1000 mm^3. Combination treatment of animals with 41BB agonist plus PD-1 antagonist resulted in 63.2% reduction in tumor growth when compared to vehicle controls (unpaired t test *p = 0.0125). Significant tumor growth inhibition by either agent dosed individually was not observed.

1.2.5. Pre-Clinical Pharmacokinetics of PF-05082566

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

1.2.6. Pharmacokinetics CCI [redacted] 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 CCI [redacted] (PK CCI [redacted]) 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]

The sCD137 increased in a dose- and time-dependent manner following MAB9371 administration in mouse. Using the indirect-response model, the EC_{50} was estimated to be 11 nM (1650 ng/mL) and the derived EC_{10} was 4.2 nM (630 ng/mL). Administration of MAB9371 also resulted in a dose-dependent inhibition of tumor growth in the transplantable mouse lymphoma model. Based on the simulation from the PK CCI model of tumor growth inhibition, a 0.2 mg/kg dose corresponded to complete response of tumor inhibition during the study period. The estimated average serum concentration (C_{ave}) of MAB9371 at 0.2 mg/kg was 12 nM (1800 ng/mL), which was consistent with the EC_{50} of 11 nM estimated from the sCD137 data. The 0.02 mg/kg dose corresponded to 10% response in tumor growth inhibition (TGI). A mean drug serum concentration of 11.5 nM (1730 ng/mL) from the biomarker and TGI studies was used for human efficacious dose projection. The average circulating sCD137 of 5.25 ng/mL was correlated with complete TGI, and was assumed to be the desired drug-induced biomarker level for efficacy.

1.2.7. Preclinical Toxicology of PF-05082566

The nonclinical safety summaries for PF-05082566 and MK-3475 can be found in their respective investigators procures (IBs). No nonclinical toxicology studies have been conducted with the combination of PF-05082566 and MK-3475. However, in order to study the toxicology of the combination of an agonist anti-4-1BB with an antagonist anti-PD-1, a 2-week exploratory toxicology study was conducting in mice using subcutaneous injection of the surrogate anti-mouse 4-1BB (MAB9371) and the surrogate anti-mouse PD-1 (RMP-14). Male C57/Bl/6 mice were dosed once with vehicle, MAB9371, RMP 1-14, or a combination of RMP and MAB9371. Administration of MAB9371 at ≥0.1 mg/kg or RMP 1-14 at 20 mg/kg alone resulted in effects in white blood cell lineages. Platelet effects occurred at ≥1 mg/kg of MAB9371. Administration of MAB9371 at 1 or 5 mg/kg, or the combination of RMP 1-14/MAB9371 at 20/0.1, 20/1 or 20/5 mg/kg resulted in mild hepatic and/or splenic histologic changes. MAB9371 appeared to be the main contributor to the hepatic and splenic effects, as the effects were not significantly increased by the addition of RMP 1-14. Therefore, it did not appear that the anti-PD-1 mAb contributed significant additive toxicity when co-administered with the anti-4-1BB mAb.

1.2.8. Clinical Safety of PF-05082566

The safety of PF-05082566 is being assessed in an ongoing Phase 1, open-label, dose-escalation study (B1641001) aimed to evaluate the safety, pharmacokinetics CCI [redacted] and Maximum Tolerated Dose (MTD) 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-Hodgkins Lymphoma (NHL) (Portion B). As of the data cut-off date (16 July 2013) safety data were recorded in the study database for 23 patients treated with PF-0502566 in 6 sequential dose levels between 0.006 and 0.24 mg/kg in Portion A and for 13 patients treated in Portion B with PF-05082566 between 0.03 and 0.3 mg/kg in combination with rituximab. As with any ongoing study, the available data are preliminary in nature and are subject to change.

Adverse events (AEs) in Study B1641001 were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v 4.03). As of the data cutoff date, AEs possibly related to single agent PF-05082566 were all Grade 1 (see Table 6).

Table 6. PF-05082566 Treatment Emergent, Treatment Related Adverse Events reported in at least 1 Patient (Study B1641001 Portion A)

	NO.	(%)
EVALUABLE	**23**	
WITH ADVERSE EVENTS	**5**	**(21.7)**
GASTROINTESTINAL DISORDERS	4	(17.4)
Abdominal Pain	1	(4.3)
Diarrhoea	1	(4.3)
Dyspepsia	1	(4.3)
Vomiting	1	(4.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	(4.3)
Pain	1	(4.3)
INVESTIGATIONS	1	(4.3)
Weight decreased	1	(4.3)
PSYCHIATRIC DISORDERS	1	(4.3)
Insomnia	1	(4.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	(4.3)
Rash	1	(4.3)

Treatment-related adverse events are categorized by system organ class. MedDRA (v16.0) coding dictionary applied.

Currently, the dose escalation is at the 2.4 mg/kg level, with no DLTs observed to date, either for PF-05082566 as a single agent or in combination with rituximab.

The preliminary 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.

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.

1.2.9. MK-3475

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[23] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[24-28] In particular, the presence of CD8+ T-cells and the ratio of CD8+

effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The Programmed Death -1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[29,30] The structure of murine PD-1 has been resolved.[31] PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade.[32-35] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.[36,37] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [38; 39]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[40] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.[36,41,42,43] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[36] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with melanoma.[44] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

1.2.9.1. Clinical Safety and Efficacy of MK-3475

1.2.9.1.1. MK-3475 Safety Data

The safety of MK-3475 is being assessed in six ongoing clinical trials, PN001, PN002, PN006, PN010, PN011 and PN012. Safety data of single-agent MK-3475 are only available from Study PN001 at this time. Protocol 001 (PN001) is an open-label Phase I study, which includes a dose-escalation component in patients with solid tumors (Part A) and with subsequent expansion cohorts in patients with melanoma (Parts B and D) and NSCLC (Parts C and F). PN001 Part A evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered Q2W. All three dose levels were well tolerated and no dose-limiting toxicities were observed. Based on PK data showing a half-life of 21 days, the protocol was amended to include a dosing frequency of Q3W in the expansion cohorts (Parts B through F).

Preliminary data (as of 26 July 2013) are available from 479 patients enrolled in PN001: Part A (n=30) 1 mg/kg, 3 mg/kg, and 10 mg/kg MK-3475 dosed q2wks to q3wks, Part B (n=308) 2 mg/kg or 10 mg/kg MK-3475 dosed q2wks to q3wks, Part C (n=38) 10 mg/kg MK-3475 dosed q3wks, and Part D (n=103) 2 or 10 mg/kg MK-3475 dosed q3wks. Of the 479 patients who have received MK-3475 in Protocol 001, 466 (97.3%) experienced treatment emergent AEs of which 368 (76.8%) were considered drug-related. Significant adverse events (SAEs) were reported in 30.1% of patients, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by Investigators were reported in 6.7% of patients overall. Potentially immune-related AEs have been observed, including pneumonitis (Grade 1-2) in both melanoma and NSCLC cohorts. The most commonly reported treatment emergent AEs experienced are fatigue, nausea, cough, pruritus, diarrhea and rash. Most patients continued treatment in spite of adverse events, and only 4.2% of patients discontinued study treatment due to an AE that was considered related to study treatment by Investigators.

Of the 162 patients who received 2 mg/kg MK-3475 dosed q3wks (Parts B1, B2 and D) in PN001, 160 (98.8%) experienced treatment emergent AEs of which 128 (79.0%) were considered to be drug-related. SAEs were reported in 27.2% of patients, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by Investigators were reported in 9.3% of this subset of patients. The most commonly reported treatment emergent AEs experienced in this subset of patients are fatigue, nausea, cough, pruritus, rash and diarrhea.

Thus, the overall AE summary suggests that MK-3475 is generally tolerable and AEs are generally manageable in patients. Refer to the MK-3475 IB for specific details.

1.2.9.2. MK-3475 Clinical Efficacy

Study PN001 included a total of 135 patients with advanced melanoma who had initiated treatment by 06 September 2012.[45] Efficacy data that were available as of 01 February 2013 were included in the analyses of efficacy. The overall response rate (ORR) across all dose cohorts, evaluated by central radiologic review according to the RECIST v1.1, was 38% (95% CI, 25 to 44), with the highest confirmed response rate observed in the cohort that received 10 mg/kg q2wks (52%; 95% CI, 38 to 66). The response rate did not differ

significantly between patients who had received prior ipilimumab treatment and those who had not (confirmed response rate, 38% [95% CI, 23 to 55] and 37% [95% CI, 26 to 49], respectively). Responses were durable in the majority of patients (median follow-up, 11 months among patients who had a response); 81% of the patients who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median progression-free survival (PFS) among the 135 patients was longer than 7 months.

Study PN001 Part C enrolled 38 patients with NSCLC who experienced progression of cancer after initiation of their second line of systemic therapy to receive monotherapy MK-3475. The preliminary ORR was 24% by investigator assessment. Clinical responses have been observed in patients with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The median duration of treatment amongst responders is a minimum of 34 weeks.

Complete information for MK-3475 may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure (MK-3475 IB).

1.3. Starting Dose Selection Strategy

In the ongoing first in human Phase 1 Study B1641001, PF-05082566 has been well tolerated up to the current dose of 2.4 mg/kg, with no dose-limiting toxicities, and dose escalation continues. However, in order to minimize the theoretical risk of synergistic toxicity due to the combination, the PF-05082566 starting dose for this study will be set to 0.45 mg/kg.

The starting MK-3475 dose of 2 mg/kg (dosed q3wk) was well tolerated based on published single agent safety and tolerability data from the Phase 1 first-in-human study (PN001). In this study, MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg q2wks). PK data analysis of MK-3475 administered q2wks and q3wks showed slow systemic clearance, limited volume of distribution, and a long half-life of about 3 weeks (21 days), typical for therapeutic antibodies (refer to IB). CCI [redacted] This early PK CCI [redacted] data provides scientific rationale for testing q2wks or q3wks dosing schedules.

An interim analysis from the on-going MK-3475 protocol PN001 reported data from expansion cohorts with advanced melanoma that are naïve to or previously treated with ipilimumab who were treated on three different dosing regimens of MK-3475: 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks. One of the key clinical findings from this analysis suggests that there are not major differences in the AE profile or overall objective response rate (ORR) of MK-3475 when given on an every 3 week schedule at doses of 2 mg/kg or 10 mg/kg.

In the ongoing first-in-human Phase 1 Study B1641001, PF-05082566 is administered on a q4wk schedule. However, since in the present study MK-3475 will be administered on a q3wk dosing schedule, PF-05082566 will also be administered on a q3wk schedule.

Study Rationale

PF-05082566 is a fully humanized IgG2 mAb and promising new molecular entity that binds to human 4-1BB with high affinity and specificity. MK-3475 is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 (programmed death-1) and its ligands, PD-L1 and PD-L2. *In vitro* and *in vivo* data demonstrated immunomodulatory activity and anti-tumor activity of PF-05082566 when dosed as a single agent, in combination with ADCC inducing antibodies, and significantly enhanced anti-tumor activity in combination with anti-PD1 antibodies. The safety and tolerability of PF-05082566 is currently being evaluated in a Phase 1 study as a single agent and in combination with Rituximab (Study B1641001). PF-05082566 has been well tolerated (thus far up to 1.2 mg/kg, q4wk) with no adverse events above Grade 1 attributed to PF-05082566. The preliminary PK results from the ongoing first-in-human Phase 1 study suggest that exposure of PF-05082566 increases dose proportionally with a terminal half-life of approximately 10 days.

While preclinical data demonstrated significant immunomodulatory activity and anti-tumor activity of PF-05082566 when dosed as a single agent, it is hypothesized that in some tumors upregulation of programmed death-1 (PD-1) in tumor-infiltrating lymphocytes, and its ligand PD-L1 on tumor cells, may down-modulate the activity of anti-tumor lymphocytes stimulated by an agonist anti-4-1BB antibody. In multiple tumor models, an agonist anti-4-1BB antibody in combination with an anti-PD-1 antagonist antibody showed significantly improved anti-tumor activity compared with either single agent. In addition, safety data in mice indicated that the addition of an anti-PD-1 antibody did not add to the toxicity of an anti-4-1BB agonist antibody. Based upon the above considerations, 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 MK-3475 in patients with advanced solid tumors.

The Sponsor considers that the safety data in the ongoing Phase 1 first-in-human study B1641001 and the published safety data for MK-3475 support the development of the combination of PF-05082566 with MK-3475 for the treatment of advanced cancers and support the initiation of this Phase 1b clinical study B1641003. The available data support the benefit-risk for the conduct of the trial, and the study includes monitoring and measures that potentially mitigate risks to the patients enrolled.

The name, title, address and telephone number(s) of the sponsor's medical expert for the trial is located in the coordinator’s manual.

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) for the combination of PF-05082566 with MK-3475 in patients with advanced solid cancer.

Secondary Objectives

- To evaluate the overall safety profile;
- To characterize the single dose and multiple dose pharmacokinetics of PF-05082566 and MK-3475 given in combination following IV administration;
- To evaluate the immunogenicity of PF-05082566 and MK-3475 when given in combination;
- To assess the anti-tumor effect of PF-05082466 in combination with MK-3475 (by RECIST criteria);
- **Expansion Cohorts Only:** To characterize the mechanism of sensitivity and/or resistance to PF-05082566 in combination with MK-3475 in tumor tissue.

CCI [redacted]

- CCI [redacted]
- CCI [redacted]

2.2. Endpoints

Primary Endpoint

- First 2 cycles Dose-Limiting Toxicity (DLT) of PF-05082566 in combination with MK-3475.

Secondary Endpoints

- Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566 in combination with MK-3475;

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03);
- Vital signs, weight, ECOG Performance Status;
- PK parameters of PF-05082566 and MK-3475, including but not limited to C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ CL and Vd (as data permits);
- Anti-Drug Antibody levels for PF-05082566 and MK-3475;
- Objective tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;
- Time-to-response (expansion cohorts only);
- Duration of response (expansion cohorts only);
- Progression–free survival (expansion cohorts only);
- **Expansion Cohorts Only**: Paired de novo tumor biopsy collection at sequential time points for analysis of exploratory mechanistic biomarkers such as IHC assessment of tumor-infiltrating lymphocytes, quantitation of T cell receptor sequences, and gene expression.

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3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, pharmacokinetic CCI study designed to estimate the maximum tolerated dose (MTD), and determine the Recommended Phase 2 Dose (RP2D) of PF-05082566 in combination with MK-3475 in patients with advanced solid tumors**.**

PF-05082566 will be administered as a 1-hour intravenous infusion q3wks. On Day 1 of each dosing cycle, in which the drugs are co-administered, the MK-3475 infusion will start 30 minutes after completion of PF-05082566 infusion and after the post- PF-05082566 and pre-MK-3475 PK blood samples are drawn.

A maximum of 45 patients will be treated during the dose escalation phase of this study.

Treatment with study drugs will continue until completion of 32 cycles (approximately 24 months) of treatment, confirmed objective disease progression, patient refusal, patient lost to follow up, unacceptable toxicity occurs, or the study is terminated by the Sponsor, whichever occurs first.

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits.

Antitumor activity will be assessed by radiological tumor assessments conducted at baseline, at 9 weeks, and every 6 weeks thereafter, whenever disease progression is suspected (eg, symptomatic deterioration), at the time of End of Treatment (if not done in the previous 6 weeks), and during follow-up visits, using RECIST version 1.1.

Discontinuation from treatment may be considered at the investigator's discretion for patients who have attained a confirmed complete response (CR), that have been treated for at least 24 weeks on study, and have at least two treatments with MK-3475 and PF-05082566 beyond the date the initial CR was declared. Patients who then experience radiologic disease progression will be eligible for 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 open. Patients will resume therapy at the same dose and schedule at the time of initial discontinuation. Patients who complete a maximum number of 32 cycles (approximately 24 months) on study treatment and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study treatment will be given the opportunity to continue treatment upon agreement between investigator and sponsor.

CCI [redacted] In addition, patients with RECIST defined disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue treatment with PF-05082566 plus MK-3475 provided that the treating physician has determined that the benefit/risk for doing so is favorable. (Refer to Section 5.3.4 and Section 7.4.1 for details). Also in this case, the maximum period on-treatment will be 32 cycles (approximately 24 months).

After estimation of the MTD for the combination on the q3wk schedule, PF-05082566 may be co-administered along with MK-3475 to study safety and tolerability on an alternative dosing schedule for both drugs. Other study drug doses may also be tested based on emerging safety and tolerability data. The initiation of additional patient cohorts to explore

additional dosing schedules or study drug doses will be done at the discretion of the Sponsor, and can occur in parallel with enrollment of patients in expansion cohorts on the q3wk dosing schedule.

In addition, once the MTD of PF-05082566 administered in combination with MK-3475 has been estimated with confidence, one or more expansion cohorts of patients with selected advanced solid tumors will be enrolled to further study the safety, tolerability, PK[redacted] and preliminary anti-tumor activity for PF-05082566 in combination with MK-3475 to support RP2D selection, as well as to study tumor-associated biomarkers. The tumor types for further study could include NSCLC and potentially other tumor types based on emerging data from the dose escalation phase of this study.

PK/Anti-Drug Antibody (ADA) sampling will be required for all patients (See Table 3 and Section 7.2 for details). No drug interaction is anticipated between PF-05082566 and MK-3475. Since PF-05082566 and MK-3475 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 pharmacokinetics and the formation of anti-drug antibodies will be monitored for both the agents and compared with historical data.

For all patients in dose-expansion cohorts, a de-novo biopsy will be required at study entry followed by a second biopsy at the time of first follow up scans at 9 weeks (after 3 cycles of treatment). Optional de novo biopsies may be collected for patients in dose-escalation cohorts to support the assessment of disease progression. [redacted]

3.1.1. Starting Dose

The PF-05082566 starting dose is 0.45 mg/kg (see Section 1.3). The starting dose of MK-3475 will be 2 mg/kg (see Section 1.3). Both study drugs will be administered on a q3wk schedule. See Section 1.3 for more details.

3.2. Criteria for Dose Escalation

No dose escalation of MK-3475 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) (Cheung and Chappell, 2000)[3] up to 5.0 mg/kg. The first three patients (first cohort) 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 (25%). 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 <25% from the model estimate (explained in Section 9.2).

Dose escalation stops if:

- Maximum sample size (n=45, see Section 9.3) is reached; or
- 9 evaluable patients have been treated at the estimated MTD; 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 6-week (2 cycles of PF-05082566 and MK-3475) DLT observation period that the patients have completed (however, the weight function may be modified if accumulating safety data in 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.

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 or 1 cycle) 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 1. Intra-patient dose escalation will not be permitted.

Cumulative safety data will continue to be evaluated at the estimated MTD using the Bayesian statistical model. Should emerging data in the expansion cohort indicate the selected dose is more toxic than previously estimated (>25%), or in the case of an exposure plateau or biomarker saturation (eg, sCD137) the next lower dose or an intermediate dose level will be explored, and may be declared as the RP2D.

For the first cohort there will be a minimum 7-day window between the first dose of a patient and the first dose of the next patient. For the first 3 patients enrolled in additional dose escalation cohorts, a minimum 24-hour time window will apply between their first doses. There will be no required time window between first doses for patients enrolled in dose cohorts with at least 3 previously treated patients.

3.3. DLT Definition

Severity of AEs will be graded according to CTCAE v 4.03. For the purpose of dose escalation, any of the following adverse events occurring during the DLT observation period (first 2 Cycles, ie, 6 weeks) that are attributable to one or both study drugs will be classified as DLTs:

- Hematologic:
  - Grade 4 neutropenia;
  - 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 toxicities (non-laboratory);
  - Grade ≥3 nausea, vomiting or diarrhea despite maximal medical therapy;
  - Grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
- Other (non AST/ALT) non-hematologic Grade ≥3 laboratory value if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization.

- Inability to complete two infusions of MK-3475 and PF-05082566 during the DLT observation period.

3.4. MTD Definition

The MTD is defined as the highest combination dose with a DLT rate <25% from the TITE-CRM model estimate (explained in Section 9.2).

3.5. Dose Expansion Test Dose

The Expansion Test Dose will be either the estimated MTD or a lower dose if emerging data suggest the estimated MTD is more toxic than originally believed.

3.6. Dose Expansion Phase

The Dose Expansion Phase will test PF-05082566 in combination with MK-3475 in patients with selected advanced solid tumor type to be determined based on emerging safety and clinical activity data from this study.

All patients in the Dose Expansion Phase may be enrolled simultaneously. The total number of patients enrolled into one or more Dose Expansion Phase cohorts will be determined based on the tumor type, and patient population emerging data from this study. PK samples will be collected from all evaluable patients in the Dose Expansion Phase Cohort.

Further experience in the Dose Expansion Phase Cohort may result in the need to explore a lower Expansion Test Dose. Only doses declared safe in the Dose Escalation Phase will be considered.

3.7. Recommended Phase 2 Dose

The RP2D is the dose of PF-05082566 and MK-3475 in combination 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. 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 suggests 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.

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 appropriately qualified 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 which has progressed on standard therapy or for which no standard therapy is available.

2. Measurable disease per RECIST v1.1.

3. Expansion cohort patients must have tumor accessible for sequential biopsy (core needle biopsy or excision preferred).

4. Age 18 years or older.

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 2).

6. Adequate bone marrow function, defined as absolute neutrophil count (ANC) ≥1.5 x 109/L (≥1,500/μL), platelet count ≥100 x 109/L (≥100,000/μL), and hemoglobin >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 and ALT) ≤2.0 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 Grade ≤1 CTCAE 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 at the baseline visit (before the patient may receive the investigational product).

11. Male and female patients of childbearing potential must agree to use two (2) highly effective methods of contraception throughout the study and for 120 days after the last dose of assigned treatment.

    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.

12. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

13. 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. CNS 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 four weeks prior to registration and any neurologic symptoms have returned to baseline), have no evidence of new or progressing brain metastases, have not used steroids for at least 14 days prior to study entry. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

2. Chemotherapy, growth factors or investigational agents within 28 days before registration.

3. Systemic steroid therapy or any other form of immunosuppressive therapy within 14 days prior to registration.

4. Radiation therapy within 14 days of study entry. Therapeutic or experimental monoclonal antibodies in last 60 days prior to registration.

5. Therapeutic or experimental monoclonal antibodies in last 60 days prior to registration.

6. History of any of the following toxicities associated with a prior immunotherapy:

   - Grade ≥3 immune-mediated adverse event that was considered related to previous immunotherapy and required immune suppressive therapy;
   - Grade ≥2 hepatic function-related adverse event that persisted more than 1 week, was considered related to immunotherapy, or required treatment discontinuation or immunosuppressive therapy (previous immunotherapies include any anti-CD137, an anti-Programmed death-1 (anti-PD-1), anti-Programmed death

ligand 1 (anti-PD-L1), anti-Programmed death ligand 2 (anti-PD-L2), or anti-Cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways).

7. Major surgery within 28 days of registration.

8. History of active ethanol abuse, hepatitis (eg, alcohol or non-alcohol steatohepatitis [NASH], drug related, auto-immune, virally related), or liver lesions greater than 4 cm on the longest axis.

9. Has received a live vaccine within 30 days prior to registration.

10. 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.

11. Any of the following within the 12 months prior to registration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism.

12. 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.

13. Pregnant females; breastfeeding females; 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 120 days after last dose of investigational product.

14. Known prior or suspected hypersensitivity to study drugs or any component in their formulations.

15. Patients who previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody or who are known to be positive for anti-drug antibodies (ADA) to MK-3475 or PF-05082566.

16. 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.

17. History of or known presence of extensive, disseminated/bilateral or Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, or pulmonary fibrosis, but not including a history of prior radiation pneumonitis. Patients with clinically significant lung disease requiring oxygen therapy (eg, COPD).

18. Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception. Patients that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections and patients with hypothyroidism stable on hormone replacement will not be excluded from the study.

19. Participation in other 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 employees directly involved in the conduct of the study.

4.3. Life Style Guidelines

4.3.1. Contraception

In this study, patients of childbearing potential will receive PF-05082566 and MK-3475, agents for which the teratogenic risk is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 120 days after the last dose. The investigator or his/her designee, in consultation with the patient, will select the most appropriate methods of contraception for the individual patient from the permitted list of 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 Table 2 Schedule of Activities (SOA) and document such conversation in the patient chart. In addition, the investigator will instruct the patient to call immediately if the selected birth control 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 remains 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, suppository).

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).

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the study manual (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 number, 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 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 trial-related documentation or correspondence referencing that patient and (email) to the site.

For the purposes of this protocol, study drug refers to both PF-05082566 and MK-3475. 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;
- Permission to proceed with dosing the patient.

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 date.

5.2. Drug Supplies

PF-05082566 and MK-3475 will be supplied for the study by Pfizer Global Clinical Supply, 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.

5.2.1. Dosage Form and Packaging

5.2.1.1. PF-05082566

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

5.2.1.2. MK-3475

MK-3475 will be supplied in single-use vials containing 100 mg/4mL sterile solution for intravenous administration. Each vial is sealed with a coated stopper and oversealed and labeled according to local regulatory requirements.

5.2.2. Preparation and Dispensing

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.

See the Dosage and Administration Instructions (DAI) form for instructions on how to prepare the investigational product for administration. Investigational product 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.

5.3. Administration

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 3 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 each infusion of study drug.

All patients should be weighed within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of 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.

The study drug dose escalation levels are shown in Table 1. In addition, doses of PF-05082566 and MK-3475 available for dose modification according to guidelines in Section 5.3.7, are shown below in Table 7.

5.3.1. PF-05082566

PF-05082566 will be administered intravenously (IV), q3wks on Day 1 of each cycle.

PF-0508256 will be administered as a 1 hour infusion. 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.

5.3.2. MK-3475

MK-3475 will be administered IV, q3wks on Day 1 of each cycle, 30 minutes after completion of the PF-05082566 infusion and after the post-PF-05082566 and/or pre-MK-3475 pharmacokinetic blood samples are drawn.

MK-3475 will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. 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.

5.3.3. Treatment Duration

The study begins when the first patient signs the informed consent.

The treatment duration with both study drugs is 32 cycles (approximately 24 months) calculated from the date of the first combined doses of PF-05082566 and MK-3475. Patients may continue on treatment with both agents until disease progression (RECIST v. 1.1),

patient refusal, unacceptable toxicity occurs, or the study is prematurely terminated by the Sponsor; whichever comes first (see Section 6.3 for Patient Withdrawal).

Discontinuation from treatment may be considered at the investigator's discretion for patients who have attained a confirmed CR, that have been treated for at least 24 weeks on study, and have at least two treatments with MK-3475 and PF-05082566 beyond the date the initial CR was declared. 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 complete a maximum number of 32 cycles (approximately 24 months) on study treatment and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study treatment will be given the opportunity to continue treatment upon agreement between investigator and sponsor.

CCI [redacted]

CCI [redacted]

- CCI [redacted]

[redacted]

5.3.5. Recommended Dose Modifications

Every effort should be made to administer PF-05082566 and MK-3475 at the planned dose and on 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 5.3.7.1 and in consultation with the Sponsor.

Dose modifications may occur in two ways:

- 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.

5.3.6. Dose Delays

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

- ANC ≥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).

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

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.

After all toxicities have recovered within the limits described above, treatment with PF-05082566 and MK-3475 can be resumed. Both study drugs should be delayed simultaneously. If non-hematogic toxicity does not resolve to Grade 1 (or Grade ≤2 if not considered a safety risk for the patient) within 9 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 9 weeks may continue treatment in the trial only if asymptomatic and controlled. In addition, consider discontinuation for any severe or life-threatening event.

5.3.7. Dose Reductions

After the first two cycles (the DLT evaluation period), dose reductions in PF-05082566 and/or MK-3475 may be required based on the worst toxicity experienced in the previous cycle (see Table 8).

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 5.3.7.1, once recovery to ≤ Grade 1 or baseline is achieved. For guidance on dosing following immune related toxicities, see Section 5.3.7.2.

Patients requiring dose reductions in PF-05082566 may be decreased one dose level (see Table 7). Patients treated at 2 mg/kg MK-3475 may be dose reduced to 1mg/kg due to AEs possibly attributed to MK-3475 alone. Once a patient has a dose reduction in PF-05082566 or MK-3475 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.

5.3.7.1. Study Drug Dose Modification Guidelines

Table 7 below shows the PF-05082566 and MK-3475 doses available for this study. Suggested dose modification guidelines are presented in Table 8 below. Both study drugs should be held for the listed toxicities with dose modifications as suggested. For information

on the management of immune-related adverse events (see Section 5.3.7.2 below). Patients requiring dose reductions in PF-05082566 due to dose-limiting toxicities may have study drug doses decreased one dose level (see Table 7). MK-3475 may be dose-reduced to 1 mg/kg due to AEs which may be recurrent or intolerable (beyond the DLT evaluation period) and possibly related to MK-3475, rather than PF-05082566, based on emerging safety and tolerability data.

Table 7. Available Dose Levels

PF-05082566*	MK-3475
5 0. mg/kg 3.6 mg/kg 1.8 mg/kg 0.9 mg/kg 0.45 mg/kg	2 mg/kg 1 mg/kg
0.20 mg/kg	

Table 8. Dose Modification Guidelines for Treatment Related Adverse Events

Toxicity	Grade	Hold Treatment (Both Drugs)	Criteria for Treatment Restart (Both Drugs)	Dose Modification (Both Drugs*)	Discontinue Patient (after consultation with Sponsor) (Both Drugs)
Hematologic Toxicity meeting any of the DLT criteria in Section 3.3	3	Yes	Resolved to Grade 1 or better	Decrease dose by one dose level (based on Table 1).	If toxicity does not resolve within 9 weeks of last infusion, consider permanent discontinuation after consultation with the sponsor.
	4	Yes	Resolved to Grade 1 or better	Decrease dose by one dose level (based on Table 1).	If toxicity does not resolve within 9 weeks of last infusion, consider permanent discontinuation after consultation with the sponsor.
Non-Hematologic toxicity (other than immune-related toxicities described in Section 5.3.7.2, 5.3.7.3, 5.3.7.4)	1 and 2 (if not recurrent/ intolerable)	No	N/A	Continue at same dose level.	N/A
	2 (recurrent/ intolerable)	Consider withholding	Resolved to Grade 1 or better	Continue at same dose level. (reference Section 5.3.7.3 for recommendations regarding pneumonitis and Section 5.3.7.1 for guidance on reduction of the MK-3475 dose.	If toxicity does not resolve to Grade 1 or better within 9 weeks of last infusion, consider permanent discontinuation after consultation with the sponsor.

Toxicity	Grade	Hold Treatment (Both Drugs)	Criteria for Treatment Restart (Both Drugs)	Dose Modification (Both Drugs*)	Discontinue Patient (after consultation with Sponsor) (Both Drugs)
	3 (only of maximally treated)	Yes	Resolved to Grade 1 or baseline or, at the investigator discretion, to Grade ≤2 if not considered a safety risk for the patient. For laboratory AEs only: resolved to Grade 2 and asymptomatic. For LFTs: resolved to Grade 1 or baseline.	Decrease dose by one dose level (based on Table 1).	If toxicity does not resolve to Grade 1 or baseline (or, at the investigator discretion, to Grade ≤2 if not considered a safety risk for the patient) within 9 weeks of last infusion, consider permanent discontinuation after consultation with the sponsor (except as noted in Section 5.3.7.1 for laboratory AEs). *Permanent discontinuation should be considered for any severe or life-threatening event.*
	4	Yes	Hold treatment until toxicity resolves to Grade 1 or baseline. For laboratory AEs only: resolved to Grade 2 and asymptomatic. For LFTs: resolved to Grade 1 or baseline.	Decrease dose by one dose level (based on Table 1).	If toxicity does not resolve within 9 weeks of last infusion, consider permanent discontinuation after consultation with the sponsor. *Permanent discontinuation should be considered for any severe or life-threatening event.*
*PF-05082566 dose will be modified based on dose levels listed in Table 1. For AEs which are possibly related only to MK-3475, the dose may be reduced as described in Section 5.3.7.1. See Table 9 for dose modification guidelines and suggested supportive care for immune-related Adverse Events (irAEs)					
See Table 10 for dose modification guidelines and suggested supportive care in patients experiencing pneumonitis					
See Table 11 for dose modification guidelines and suggested supportive care in patients enterocolitis.					
See Table 12 for dose modification guidelines and suggested supportive care in patients experiencing infusion reactions.					

N/A: not applicable.

5.3.7.2. Supportive Care Guidelines for Immune-Related Events of Clinical Interest (irECI) and Immune-Related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the MK-3475 and/or PF-05082566 mAb, their mechanism of action, and reported experience with immunotherapies that have similar mechanisms of action. Specific irAEs for MK-3475 and associated AE reporting requirements are listed in Section 7.1.2.1. No irAEs have been observed with PF-05082566 to date. However, it is suggested that special attention should be paid to AEs that may be suggestive of potential irAEs related to both study drugs. An irAE can occur shortly after the first dose of either study drug or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document located in the Administrative Binder. Patients who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 9. If a decision is made to re-start treatment following irAEs, the PF-05082566 dose may be decreased one dose level (see Table 7). Patients treated at 2 mg/kg MK-3475 may be dose reduced to 1 mg/kg MK-3475 due to irAEs possibly attributed to MK-3475 alone. Once a patient has a dose reduction in PF-05082566 or MK-3475 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.

Table 9. General Approach to Handling irAEs

irAE	Management of Both Study Drugs	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3	Withhold Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 9 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.
Grade 4	Discontinue	

5.3.7.3. Supportive Care Guidelines for Pneumonitis

Patients with symptomatic pneumonitis should immediately stop receiving MK-3475 and PF-05082566 and have a clinical evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the patient is diagnosed with study drug-associated pneumonitis, the suggested treatment plan is described in Table 10.

Table 10. Recommended Approach to Handling Pneumonitis

Study Drug Associated Pneumonitis	Management of Both Study Drugs	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold both study drugs. May return to treatment if improves to Grade 1 or resolves within 9 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue study drugs	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to Section 5.3.7.3 for additional recommendations.

For Grade 2 pneumonitis that improves to Grade ≤1 within 9 weeks, the following rules should apply:

- First episode of pneumonitis - follow above recommended approach to handling pneumonitis.
- Second episode of pneumonitis – permanently discontinue MK-3475 and PF-05082566 if upon rechallenge patient develops pneumonitis Grade ≥2.

5.3.7.4. Recommended Study Drug Dose Modification and Supportive Care Guidelines for Enterocolits

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

Table 11. MK-3475 Recommended Dose Modifications and Supportive Care Guidelines for Enterocolits

Study Drug Associated Enterocolits	Management of Both Study Drugs	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	Both study drugs should be withheld	Anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade ≤1, corticosteroid taper should be started and continued over at least 1 month.
Grade 3 and 4	Both study drugs should be withheld	Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade ≤1, corticosteroid taper should be started and continued over at least 1 month

5.4. Drug Storage

PF-05082566 and MK-3475 will be shipped and stored at a temperature between 2°C and 8°C.

The storage conditions stated in the investigator brochures of both study drugs will be superseded by the label storage statement. The storage conditions and stability of the reconstituted product are detailed in the Dosing Administration Instructions. If a deviation to the storage condition occurs, contact Pfizer via the study team.

The Investigator or an approved representative (eg, pharmacist) will ensure that all investigational product is stored in a strictly controlled, secure area, at appropriate temperatures and in accordance with applicable regulatory requirements.

Site systems must be capable of measuring and documenting (for example, 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 (for example, 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.

The investigational product(s) must be stored as indicated. 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.

5.5. Drug Accountability

The Investigator or designated personnel must maintain adequate records documenting the receipt, use, loss or other disposition of the investigational product(s). 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, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by Pfizer. Destruction must be adequately documented.

5.6. Concomitant Treatments

Concomitant treatment considered necessary for the patient's well being may be given at discretion of the treating physician. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

Concomitant medications and treatments, including prescription, over-the-counter (OTC), herbal supplements, IV medications and fluids, antiemetic treatment and prophylaxis, and 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 and ECIs as defined in Section 8.14.1.

5.6.1. Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial, except in the case of hematopoietic growth factors and the use of steroids for symptomatic treatment. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director and/or Medical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient patient's primary physician. However, the decision to continue the patient on trial therapy or

vaccination schedule 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 trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy.
- Investigational agents other than MK-3475 or PF-05082566.
- Radiation therapy.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.

- Live vaccines.
- 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, IgG2 and IgG4), in patients where anti-drug antibodies are detected while on-study.

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

5.7. Rescue Medications and Supportive Care

5.7.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: 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. Patients may receive prophylaxis of treatment-induced diarrhea. Symptomatic care such as loperamide (Imodium®) is recommended.
- Nausea/Vomiting: 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.

- Anti-infectives: 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.]

- Anti-inflammatory or narcotic analgesics may be offered as needed. Acetaminophen/ paracetamol to a MAXIMUM total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

5.7.2. Supportive Care Guidelines For Infusion Reactions to Either Study Drug

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 (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); and Vomiting.

Table 12 below shows treatment guidelines for patients who experience an infusion reaction associated with administration of either study drug.

In the event that a site does not have established procedures for the treatment of study drug associated infusion reactions, the following guidelines are provided in Table 12.

Table 12. Infusion Reaction Treatment Guidelines for Either Study Drug

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAID, narcotics, IV fluids); prophylactic medications indicated for < = 24 hours	**Stop Infusion and monitor symptoms.** Additional 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 one 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). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patients may be premedicated 1.5 h (±30 minutes) prior to infusion of PF-05082566 and MK-3475) with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
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; pressor of ventilatory support indicated	**Stop infusion.** Additional 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
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration For further information, please refer to the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) at http://ctep.cancer.gov		

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.

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first two cycles of treatment but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines. (*J Clin Oncol, 2006.* ***24****(19): p. 3187-3205*).

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

5.8.1. Anti-inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatments section. Systemic anti-inflammatory therapies may be used to treat SAEs potentially related to the study drugs (see Section 5.3.7).

5.8.2. 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 5.3.7.

5.8.3. 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 MK-3475. As safety risks in this setting are unknown it is suggested that the study drugs be withheld for 21 days before performing major surgery. This will provide a margin of safety of one drug half-life (for MK-3475, which has the longer half-life of the two study drugs) before resuming therapy with the combination.

5.8.4. Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. 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 MK-3475 treatment be interrupted during palliative radiotherapy, in consultation with the Sponsor.

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:

- Pharmacokinetic blood specimens- obtain at the scheduled time.
- Electrocardiograms (ECGs) – obtain as close as possible to the scheduled time, but *prior to* blood specimen collection and within 30 minutes of the nominal time.
- Blood pressure/pulse rate – may be obtained prior to or after ECG collection but must be obtained *prior to* blood specimen collection and within 60 minutes of the nominal time.
- Clinical safety laboratory tests – obtain as close as possible to 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 the Schedule Of Activities and ASSESSMENTS sections. Screening is to be performed within 28 days of registration. For medical history, include history of other diseases (active or resolved) and concomitant illnesses.

6.2. Study Period

For treatment period procedures, see the Schedule Of Activities and ASSESSMENTS sections. The End of Treatment assessments are to be performed approximately 28 days after the last dose of study drug. Obtain these assessments if not completed during the previous week on study (during the previous 6 weeks on study for tumor assessments).

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 12 weeks ± 7-days. Once patients have exhibited disease progression or began a new anti-cancer therapy (not including radiotherapy to a non-target tumor), whichever occurs first, the date of progression will be recorded on the appropriate CRF page and they will be withdrawn from the study. No further data will be collected from these patients. 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.

For follow-up procedures see Schedule Of Activities.

6.3. 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:

- Confirmed objective disease progression according to RECIST version 1.1 (see the Study Design Section 3 for details and exceptions);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity (possibly associated with both study drugs);
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;
- 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 to 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 which he/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, SAEs, vital signs and physical examination, ECG (12-lead), laboratory assessments, including pregnancy tests and verification of concurrent medications.

7.1.1. Pregnancy Testing

MK-3475 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. See Section 8.10 for exposure during pregnancy. The current MK-3475 IB contains a full description of non-clinical reproductive toxicology. In the case of PF-05082566, reproductive toxicology has not been characterized.

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration, and at the End of Treatment visit . 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 during the active treatment period, at the end of study therapy and additionally whenever one 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 IRB/Ethics Committee (EC) 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) timing, seriousness, and relatedness.

AEs that occur during the study, including baseline signs and symptoms, will be recorded on the AEs CRF page.

7.1.2.1. MK-3475 Adverse Events of Special Interest

Selected non-serious and serious AEs are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms and reported within 24 hours to the Sponsor either by electronic media or paper.

ECIs for this trial include:

1. An overdose of Sponsor's product, as defined in Section 8.4 - Medication Errors, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

   Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. In the event a patient develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours of the event:

   a. Grade ≥3 diarrhea;

   b. Grade ≥2 colitis;

   c. Grade ≥2 pneumonitis;

   d. Grade ≥3 hypo- or hyperthyroidism.

A separate guidance document has been provided entitled “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document.” This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the SPONSOR within 24 hours of the event.

Patients should be assessed for possible ECIs prior to each dose. Laboratory results should be evaluated and patients should be asked for signs and symptoms suggestive of an immune related event. Patients who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If laboratory results or symptoms

indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur to any patient from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the administrative binder.

7.1.3. Laboratory Safety Assessment

Hematology, blood chemistry, coagulation and urinalysis will be carried out at the time points described in the Schedule of activities (see the Schedule Of Activities and Table 4) and analyzed at local laboratories. Thyroid function assessments will include T3, FT4, and thyroid stimulating hormone (TSH). In the presence of clinical suspicion of hypopituitarism or hypoadrenalism, laboratory testing should include one or both of the following: adrenocorticotropic hormone (ACTH) and cortisol levels before and 30-60 minutes after corticotrophin stimulation. Urinalysis will include measurement of pH, specific gravity, protein/albumin, glucose, blood/hemoglobin, ketones/acetone. Urine dipstick for urine protein: if positive collect 24-hr and microscopic (Reflex Testing). Urine dipstick for urine blood: if positive collect a microscopic (Reflex Testing).

7.1.4. Vital Signs and Physical Examination

Patients will have a physical exam that will include major body systems, weight, blood pressure, heart rate, assessment of ECOG status and height; height will be measured at baseline only. Physical exams will be performed at the time points described in the Schedule Of Activities.

7.1.5. ECG Assessments

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing in the supine or semi-recumbent position 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, three 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. If the mean QTc interval is prolonged (>500 msec), then the ECGs should be re-evaluated by a qualified person at the center for confirmation. 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 adverse events. ECG assessments beyond Screening will not be required for patients in dose expansion cohorts (see the Schedule Of Activities). Additional ECGs may be performed as 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 escalation cohorts.

Prior to concluding that an episode of prolongation of the QTcF interval is due to study drug, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

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

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. Pharmacokinetics Assessments (Dose Escalation and Dose Expansion Cohorts)

PK samples will be assayed for PF-05082566, and MK-3475 using a validated analytical method in compliance with Pfizer (PF-05082566) or Merck (MK-3475) standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

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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.

As part of understanding the pharmacokinetics 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.

7.2.1. PF-05082566

Blood samples will be collected for PK of PF-05082566 at the following time points:

- During Cycle 1-4 on (a) Day 1 at pre-dose and end of infusion;
- During Cycle 5 on (b) Day 1 at pre-dose, end of infusion, and at 2, 6 and 24 hr post start of infusion; (c) on Days 8 (192 hours) and 15 (360 hours) after start of infusion (See Section 7.2 above for guidelines on timing of blood draws);

- During Cycle 6 on (d) Day 1 at pre-dose only;
- During Cycle 7 on (e) Day 1 at pre-dose, end of infusion, 24 hrs post start of infusion and on Day 8.

Beyond Cycle 7, PK samples will be collected at pre-dose, every two cycles up Cycle 12, every 4 cycles thereafter, and at the End of Treatment visit.

For patients in expansion cohorts: The same PK schedule will be followed for at least 10 patients in total from all expansion cohorts. For other patients (in all expansion cohorts), predose samples on Day 1 will be collected for Cycles 1, 3, 5, 6 and 7. Beyond Cycle 7, PK samples will be collected at pre dose (Day 1), for every 2 cycles up to Cycle 12, and every 4 cycles thereafter. Timing of sampling may be modified based on emerging PK data. For patients discontinuing from the study, a PK sample should be collected at the End of Treatment assessment day.

7.2.2. MK-3475

Blood samples will be collected for PK of MK-3475 at the following time points:

- During Cycle 1- 4 on (a) Day 1 at pre-dose and end of infusion;
- During Cycle 5 on (b) Day 1 at pre-dose and end of infusion;
- During Cycle 7 on (c) Day 1 at pre-dose, end of infusion, 24 hrs, and on Day 8 (192 hours) post start of infusion (See Section 7.2 for guidelines on timing of blood draws).

Beyond Cycle 7, PK samples will be collected at pre-dose, every two cycles up to Cycle 12, and every 4 cycles thereafter. Additionally, PK samples will be collected at 28 days after end of MK-3475 treatment (during the End of Treatment visit) and during follow-up at 3 months and 6 months after the end of MK-3475 treatment.

For patients in expansion cohorts: The same PK schedule will be followed for at least 10 patients in total from all expansion cohorts. For other patients (in all expansion cohorts), predose samples on Day 1 will be collected for Cycles 1, 3, 5 and 7. Beyond Cycle 7, PK samples will be collected at pre dose (Day 1), for every 2 cycles up to Cycle 12, and every 4 cycles thereafter. Additionally, PK samples will be collected at 28 days after end of MK-3475 treatment (during the End of Treatment visit) and during follow-up at 3 months and 6 months after the end of MK-3475 treatment.

For patients ending from the study, PK samples should be collected at the End of Treatment assessment day. PK sampling schedule may be modified based on emerging PK data.

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7.4. Banked Biospecimen (Blood)

7.4.1. 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.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification (ID) number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which case any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical study.

A 4-mL blood biospecimen, Prep D1 (K_2 edetic acid (ethylenediaminetetraacetic acid)(EDTA)) whole blood collection optimized for DNA analysis), will be collected on Day 1 of Cycle 1 (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.

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.

7.4.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions;
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Markers of Drug Response Section will be used. Patients may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.5. Immunogenicity Assessments (ADA)

ADA (anti-drug antibodies) blood samples will be assayed for anti-PF-05082566, and anti-MK-3475 antibodies using a validated analytical method in compliance with Pfizer (anti-PF-05082566) or Merck (anti-MK-3475) standard operating procedures. All the samples that are positive for ADA may also undergo characterization for neutralizing antibodies.

As part of understanding the pharmacokinetics 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.

Blood samples (2 mL for PF-0508 2566 and 6 ml for MK-3475) for evaluation of immunogenicity of PF-05082566/MK-3475 will be collected at the following time points:

7.5.1. Immunogenicity to PF-05082566

- In Cycle 1, 3,5, 7 Day 1 at pre-dose;
- Cycles >7, Day 1 at predose for every two cycles up to Cycle 12, and every 4 cycles thereafter.

For patients discontinuing study drug treatment, immunogenicity samples should be collected at the End of Treatment assessment day. If ADAs are detected, additional samples may be collected approximately every 3 months (coinciding with disease assessment visits) until ADA levels return to baseline. Samples will be analyzed by a laboratory to be identified by Pfizer. See the Laboratory Manual for additional details.

7.5.2. Immunogenicity to MK-3475

- Cycle 1, 3, 5, and 7 Day 1 at pre-dose;
- Cycles >7, Day 1 at predose for every two cycles up to Cycle 12, and every 4 cycles thereafter;
- Additionally, ADA samples will be collected at 28 days, and during Follow-up (3 months and 6 months after end of MK-3475 treatment).

For patients ending from the study, immunogenicity samples should be collected at the End of Treatment assessment. MK-375 samples will be analyzed by a laboratory to be identified by Merck. See the Laboratory Manual for additional details.

7.6. Tumor Biopsies for Mechanistic Exploratory Biomarkers

Tumor growth inhibition following treatment with 4-1BB agonist monoclonal antibodies or with PD-1 antagonist monoclonal antibodies has been associated with increases in tumor-infiltrating lymphocytes. Paired de novo tumor biopsies are mandatory for the patients enrolled in the expansion cohorts in order to determine whether the combination of PF-05082566 and MK-3475 has this effect. A de novo biopsy will be required at study entry followed by a second biopsy at the time of the Cycle 3 tumor assessment. For patients in dose escalation cohorts, unscheduled optional de novo tumor biopsies may be collected at the discretion of the Sponsor and Investigator to support the assessment of disease progression. Biomarkers that will be assayed may include but will not be limited to IHC assessment of tumor-infiltrating lymphocytes, PD-L1 IHC, quantitation of T cell receptor sequences, and gene expression.

Please refer to the Study Manual for details pertaining to specific days of sample collection, and sample preparation and shipping

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7.8. Pharmacogenomic (RNA) Assessments

Blood samples for pharmacogenomic analysis will be required and will be collected on Day 1 of Cycles 1 and 2 (pre-dose). Samples will be used to explore gene expression signatures in PBMCs that would be predictive for or characteristic of responses to treatment. Candidate genes that might influence patient response, may include but will not be limited to CXCR3, IFNG, EOMES, CD28, ICOS, CD40LG, IL2RA, CD80, CCL5, FOXP3, CDC25A, GZMA, IL23A, SOCS1, IL10; PD-1, PD-L1.

7.9. Tumor Response 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; 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.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, at Week 9, and every 6 weeks thereafter. Timing should follow calendar days and should not be adjusted for treatment delays. Follow up bone scans is required every 16 weeks only if bone metastases are present at baseline. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of response for patients who have bone metastases. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment (if not done in the previous 6 weeks). Note that a post-treatment biopsied lesion or a lesion that is radiated during the study should no longer count as a target lesion.

Assessment of response will be made using RECIST version 1.1 (Appendix 1). CCI

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 a 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 non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an 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 90 calendar days after the last administration of study drug. 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 study drug are to be reported to the Sponsor.

AEs (serious and nonserious) should be recorded on the Case Report Form (CRF)from the time the subject has taken at least 1 dose of study treatment through the last subject visit.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious 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 120 days of discontinuing treatment with MK-3475, or within 28 days after the cessation of study treatment 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 adverse event (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 adverse event (AE) page and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page.

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-3475 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 (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event 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

A 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 a 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 a 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 adverse event and as a SAE with Common Terminology Criteria (CTC) Grade 5 (see Section 8.8).

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 for SAE Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (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 upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥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 a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up 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;
- Pre-planned 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 non-invasive 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

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 a 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 non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse 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 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 investigational 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 women (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male patient 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 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 safety within 24 hours of 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 study master file.

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

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

When a patient withdraws because of an 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 a SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If a SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event

information. This timeframe 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 a 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 timeframes 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 case report form. 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 Statistical Analysis Plan (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. Safety analysis set.

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

2. Full analysis set.

   The full analysis set includes all enrolled patients.

3. DLT evaluable set.

   All enrolled patients who are eligible, receive study treatment and who either experience a DLT during the first 2 cycles of PF-05082566, or complete the two cycles' DLT observation period. 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 two cycles' DLT observation period.

4. Response analysis set.

   All enrolled patients who are eligible, receive study treatment, have baseline tumor assessments and at least 1 on-study tumor assessment will be considered evaluable for response. Patients who are treated and removed from study prior to on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as failures. Response analysis will be performed for both the safety analysis set and the response analysis set.

5. PK analysis sets.

   The PK concentration population is defined as all enrolled patients treated who have at least one concentration of either PF-05082566 or MK-3475.

   The PK parameter analysis population is defined as all enrolled patients treated who have at least 1 of the PK parameters of interest.

6. Biomarker Analysis set.

   Treated patients who have baseline and at least 1 on study biomarker assessment will be considered evaluable.

7. ECG/QTc Analysis set

8. Treated patients who have baseline and at least 1 on study ECG/QTc measurement will be considered evaluable.

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),[17] and its variants.

Delayed-onset toxicities are a particular challenge for phase I trials of combination therapies.[14] 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.[3] and Normolle et al.[15] for the dose-escalation of PF-05082566. PF-05082566 may be administered intravenously at the following available dose levels of 0.20, 0.45, 0.9, 1.8, 3.6, and 5 mg/kg on an every 3 week schedule (q3wk). PF-05082566 will be co-administered with MK-3475 on Day 1 of each treatment Cycle. MK-3475 will be administered at 2 mg/kg, MK-3475 will be administered q3wk. Higher dose levels may be available based on the emerging safety data from single agent PF-05082566 dosed at 5 mg/kg in the Phase 1 first-in-human study. The MTD is defined as highest dose that is associated with a DLT rate ≤25%. A power function modeling DLT rate at each dose d_i (i=1, …, 6) expressed as Pr (DLT | d_i) = F_i (β) will be used:

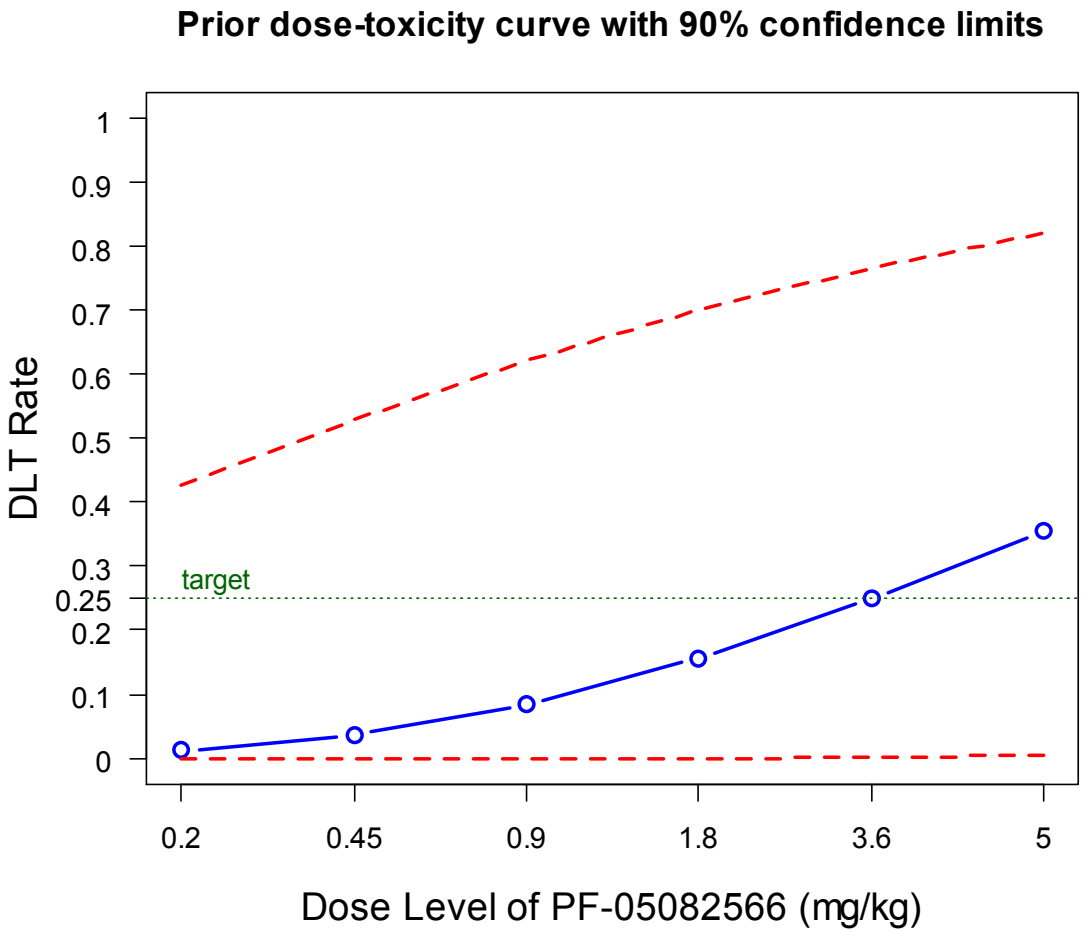
$$F_i(\beta) = p_i^{\exp(\beta)}$$

where p_i is the prior estimate of DLT rate at dose level d_i, and $p_1 \le p_2 \le \ldots \le p_6$. 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 (0.01, 0.04, 0.08, 0.16, 0.25, 0.35).

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 6-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. (2014) 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. (2014)[47].

Section 3.2 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 45 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 45 will ensure the estimates of any binary variable (eg, objective response rate) have a 95% confidence interval of width <0.30. A sample size of 45 also enables the detection of any unexpected toxicity that occurs at 5% rate (in a non-dose-dependent fashion) with a probability of 0.90, and that occurs at 10% rate with a probability of 0.99.

A stopping rule (see Section 3.2) 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

Assessment of 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 Duration of Response, and PFS for the expansion cohort. Kaplan-Meier plot will be created for TTR, DR and PFS in the expansion cohort. A bar plot for TTR and DR will also be created for confirmed responders defined by RECIST 1.1.

9.5. Analysis of Other Endpoints

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Pharmacokinetics Analysis of PF-05082566 and MK-3475

Standard plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma 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 plasma concentration (C_{min}), average plasma concentration (Cave), area under the plasma concentration versus time curve to infinity (AUC_{inf}), terminal elimination half-life ($t^{1/2}$), total systemic clearance (CL), volume of distribution (Vd), accumulation ratio (Rac) 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_{inf} (AUC_{τ} at steady state), AUC_{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 MK-3475, plasma pharmacokinetic parameters will be determined by Merck using a validated population pharmacokinetic model.

For PF-05082566 and MK-3475 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 MK-3475. Since PF-05082566 and MK-3475 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 pharmacokinetics 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 PK[redacted] Modeling

Pharmacokinetic [redacted] 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/ MK-3475 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.5.1.3. Analysis of Immunogenicity Data

ADA data will be listed and summarized for each dosing interval for PF-05082566 and MK-3475. The effect of ADA on PF-5082566 and MK-3475 concentration will be evaluated.

9.5.1.4. Statistical Analysis of Biomarker Endpoints

For tumor biopsy samples, the mean and standard deviation, median, and minimum/maximum levels of biomarker measures, including but not limited to percentage of CD3-positive T cells, will be determined at baseline and post-treatment. For each pair of

specimens, the percent change from baseline of these same parameters will also be calculated. The minimum percent change from baseline needed to declare proof of pharmacology will be based on assay precision and size of the expansion cohort.

CCI [redacted] The statistical approach will examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

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 dose level cohorts is used to estimate the MTD as described in Study Design Section 3. AEs constituting DLTs will be listed by 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 the Common Terminology Criteria for Adverse Events (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 and Cycles >2).

9.6.2.2. Laboratory Test 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 beyond 2).

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

9.6.3. ECG

The analysis of ECG results will be based on safety analysis set patients 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) 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 the first DESC meeting.

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 is 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 Case Report Form (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 is true. Any corrections to entries made in the CRFs, 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, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, 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)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In

that event, the investigator must notify the IRB/IEC 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 Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, 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 on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

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 document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements including applicable privacy laws.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his/her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult),

how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse) and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

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

13.1. End of Trial in a Member State

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 Study 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.

13.2. End of Trial in all other Participating Countries

End of Trial in all other participating countries is defined as Last Patient Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, 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 trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

The timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, Food and Drug Administration (FDA)-approved products, Pfizer posts results within 1 year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV);

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval or 1 year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within 1 year of discontinuation of the program (if there are no plans for outlicensing, or within 2 years if outlicensing plans have not completed).

Primary completion date is defined as the date that the final patient 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.

www.pfizer.com

Pfizer posts clinical trial results on www.pfizer.com for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an FDA-approved Pfizer product with a LSLV on or after 27-Sep-2007 for which Basic Results were posted on www.clinicaltrials.gov.

EudraCT

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01-May-2004, regardless of the marketing status of the compound.

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 multi-center 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. Determination of Efficacy

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 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 13. 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 14. 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

- Adapted from: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Appendix 2. 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.

CCI [redacted]

CCI [redacted]

Cancer Therapy: Clinical