A PHASE 1B STUDY OF CRIZOTINIB IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) IN PATIENTS WITH UNTREATED ADVANCED ALK-TRANSLOCATED NON-SMALL CELL LUNG CANCER

Compound:	PF-2341066/MK-3475
Compound Name:	Crizotinib/Pembrolizumab
United States (US) Investigational New Drug (IND) Number:	73,544
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Phase:	Phase 1b

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[redacted]

Document History

Document	Version Date	Summary of Changes
Original protocol	22 April 2015	Not Applicable (N/A)

Abbreviations

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

Abbreviation	Term
1L	first line
Ab	antibody
CCI [redacted]	[redacted]
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	Adenosine triphosphate
AUC_{0-8}	area under the plasma concentration-time curve from 0 to 8 hours post dose
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval
BAL	bronchoalveolar lavage
BCG	Bacillus Calmette–Guérin
BID	twice daily
BNP	B-type natriuretic peptide
BP	blood pressure
BUN	blood urea nitrogen
C	Cycle
CDR3	complementarity determining region 3
CHF	congestive heart failure
CI	confidence interval
CL	clearance
CL/F	apparent plasma clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CR	complete response
CSA	clinical study agreement
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Term
CTLA-4	cytotoxic T-lymphocyte antigen-4
CV	coefficient of variation
DAI	dosage and administration instructions
DCR	disease control rate
DL	dose level
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
Eg	for example
EGFR	epidermal growth factor receptor
EGFR MT	epidermal growth factor receptor mutant
EML4	echinoderm microtubule associated protein-like 4 gene
EORTC QLQ-LC-13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire– Lung Cancer 13
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
Etc	‘and other things’ or ‘and so forth’
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestina
GITR	glucocorticoid-induced tumor necrosis factor receptor
GnRH	gonadotropin-releasing hormone
GVHD	graft versus host disease
HBV	hepatitis B virus

[redacted]

Abbreviation	Term
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
Hgb	hemoglobin
HGFR	hepatocyte growth factor receptor
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
Ie	that is (id est)
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
irAEs	immune-related adverse events
IRB	institutional review board
IRC	internal review committee
irPFS	immune-related progression-free survival
irRC	immune-related response criteria
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
IUD	intrauterine device
IV	intravenous
KIR	killer cell immunoglobulin-like receptor
LAG3	lymphocyte activation gene-3
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
mTPI	modified toxicity probability interval
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
mPFS	median progression-free survival
$MRAUC_{tau}$	metabolite to parent ratio AUC_{tau}
MRC_{max}	metabolite to parent ratio C_{max}
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute

Abbreviation	Term
NHANES	National Health and Nutrition Examination Surveys
NONMEM	non-linear mixed effects modeling
NPM	nucleophosmin
NSCLC	non-small cell lung cancer
OBD	optimal biological dose
ORR	objective response rate
OS	overall survival
p_T	target probability
PCD	primary completion date
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death receptor-1 ligand-1
PD-L2	programmed death receptor-1 ligand-2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	oral (per os)
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
QD	every day
QOL	quality of life
QT	time between the start of the Q wave and the end of the T wave
QTc	QT interval corrected for heart rate
R	Ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RON	Recepteur d'Origine Nantais
RP2D	recommended phase 2 dose
RR	response rate
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SEER	(NCI) Surveillance, Epidemiology and End Results
SOA	Schedule of Activities
SRSD	Single Reference Safety Document
SST	serum separator tube

Abbreviation	Term
T	Time
$T_{1/2}$	terminal elimination half-life
TCR	T-cell receptor
TILs	tumor infiltrating lymphocytes
TIM3	T-cell immunoglobin- and mucin-domain-3-containing molecule 3
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum plasma concentration
TTP	time to progression
TTR	time to tumor response
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USPI	United States Package Insert
UTN	Universal Trial Number
V/F	apparent volume of distribution
VSAQ-ALK	Visual Symptom Assessment Questionnaire ALK
WBC	white blood cell

PROTOCOL SUMMARY

Background and Rationale

Non-small cell lung cancer (NSCLC) is the most common cause of fatal malignancy in the United States among both men and women, representing 28% and 26% of all cancer-related deaths, respectively. NSCLC represents the second most common cause of new cases of malignancies in men (14%) and women (13%) according to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program.[1] Similar results have been observed in Europe where NSCLC remains the most common cause of fatal malignancy.[2] There is also a growing burden of NSCLC in developing countries like India[3] and China[4] where the incidence in men is greater than women. ALK-positive NSCLC represents between 3 and 5% of all cases. These patients tend to be young (average age 50 years at diagnosis), light or never smokers, and with no difference in sex or ethnicity.[5]

The results from single-arm clinical Studies A8081005 and A8081001 supported accelerated regulatory approval of crizotinib in the US in August 2011 for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC. The results of randomized Phase 3 Study A8081007 demonstrated that crizotinib is superior to standard-of-care single-agent chemotherapy in patients with previously treated ALK-positive advanced NSCLC and confirmed the favorable benefit/risk profile of crizotinib in this population. Based upon substantially prolonged PFS (median 7.7 months for crizotinib and 3.0 months for chemotherapy; hazard ratio [HR] 0.487, 95% confidence interval [CI]: 0.37, 0.64; 1-sided p-value <0.001) and increased ORR (crizotinib 65% and chemotherapy 20%, 2-sided p-value ≤0.001), the results from this study supported conversion to full approval in the US. Validated questionnaires (EORTC QLQ-C30 and QLQ-LC13) showed a statistically significantly greater improvement in patient-reported lung cancer symptoms and global quality of life receiving crizotinib as compared with chemotherapy.[6,7] Recently, the results of randomized Phase 3 Study A8081014 demonstrated that crizotinib significantly prolonged PFS in the first-line treatment setting compared to standard platinum-based chemotherapy. The median PFS was 10.9 months for the 172 patients randomized to crizotinib and 7.0 months for the 171 patients randomized to chemotherapy. The HR comparing crizotinib with chemotherapy was 0.454 (95% CI: 0.346, 0.596) with a p-value of <0.0001.[8] Similarly in Study A8081007, crizotinib showed a statistically greater improvement in patient-reported lung cancer symptoms and global quality of life receiving crizotinib as compared with chemotherapy. Although crizotinib had impressive clinical activity in patients with previously untreated ALK-positive advanced NSCLC in each of these studies,[8] progression of disease generally occurs and is often related to the development of crizotinib-resistant ALK mutation or signal transduction bypass pathways. Therefore, newer agents with novel mechanisms of action are still desperately needed.

Evidence has demonstrated that tumors require interaction with the host immune system for continued growth and spread.[9] One way this occurs is by tumors interacting with the programmed death receptor-1 (PD-1) on the tumor infiltrating lymphocytes (TILs), causing the effector T cells to become regulatory T cells. The PD-1 receptor-ligand interaction is 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.[9-11] When PD-1 interacts with the ligand on the tumors, immune surveillance of the tumor ceases leading the body to consider the tumor a self-antigen and allowing tumor transit (spread) through the hematologic and lymphatic channels as well as increases in local vascular endothelial growth factor and correlates with a negative prognosis.[9] There are also reduced levels of IL-2 produced intratumorally when there is PD-1/PD-L1 interaction.

Pembrolizumab (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. In the NSCLC cohort of the KEYNOTE-001 study, the ORR was 21% based on an independent radiology review using RECIST v 1.1 among all patients with NSCLC who received 3 or more prior lines of therapy. The specific breakdown of the response rates were 16% for patients with advanced non-squamous NSCLC (4 of 26 patients) and 33% for patients with advanced squamous NSCLC (2 of 6 patients). The median PFS was 10.3 weeks for advanced non-squamous NSCLC patients and 15.2 weeks for advanced squamous NSCLC patients.[12]

Research on mouse models has been limited in the immune surveillance role and ALK-positive NSCLC, but one small study provided supporting rationale for a combination of crizotinib with an anti-PD-1 inhibiting antibody using an ALK vaccine. The tumors were noted to have lymphatic infiltration and these changed from regulatory to effector T cells, while the ALK-positive tumors were noted to have high levels of PD-L1. Using crizotinib in the place of ALK vaccine should not demonstrate a difference in response or changes to the lymphocytic infiltration noted. By adding pembrolizumab, there may be a potential to utilize immune stimulation and PD-L1 levels with the known signal transduction inhibition of crizotinib.

This study in previously untreated ALK-positive advanced NSCLC will consist of 2 phases, a Dose Finding Phase and a Dose Expansion Phase. The Dose Finding Phase will determine the maximum tolerated dose (MTD) of the combination of crizotinib and pembrolizumab using a dose de-escalation design through a modified Toxicity Probability Interval (mTPI)[13] design. The Dose Expansion Phase will explore the safety, tolerability, and anti-tumor activity of the combination at the MTD in order to determine the recommended Phase 2 dose (RP2D).

Study Objectives and Endpoints:

Primary Objective

- To assess safety and tolerability of crizotinib in combination with pembrolizumab in the first-line treatment of patients with ALK-positive advanced non-squamous NSCLC in order to identify the maximum tolerated dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

[redacted]

Secondary Objectives

- To evaluate the overall safety profile of crizotinib in combination with pembrolizumab.
- To document the anti-tumor activity of crizotinib in combination with pembrolizumab in previously untreated ALK-positive advanced NSCLC patients.
- To characterize the pharmacokinetics (PK) of crizotinib and pembrolizumab and to assess the effect of pembrolizumabon the PK of crizotinib.
- To evaluate tumor PD-L1 expression, as assessed by PD-L1 immunohistochemistry, as a predictor of anti-tumor activity.

CCI [redacted]

- [redacted]
- [redacted]
- To evaluate the impact of combination therapy of crizotinib and pembrolizumab on patient-reported lung cancer symptoms (such as dyspnea, cough and pain) and global Quality of Life (QOL) per the validated cancer specific EORTC QLQ-C30, and its lung cancer module, QLQ-LC-13, and visual symptoms per the Visual Symptom Assessment Questionnaire (VSAQ-ALK).

Primary Endpoint

- Dose-Limiting Toxicity (DLT).

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), timing, seriousness and relationship to study treatments.
- Objective response rate (ORR), as assessed using RECIST version 1.1, and also.
- Duration of Response (DR).
- Time to Tumor Response (TTR).

- PFS, 6-month, 12-month, and 18-month PFS probabilities, OS, 12-month and 18-month survival probabilities.

- Laboratory abnormalities as characterized by type, frequency, severity, and timing.

- The following PK parameters of crizotinib, its metabolite PF-06260182 and pembrolizumab PK (as data permits):

  Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), pre-dose concentration (C_{trough}), area under the plasma concentration time curve from 0 to 8 hours (AUC_{0-8}), area under the plasma concentration time curve over the dosing interval (AUC_{tau}), and apparent plasma clearance (CL/F) for crizotinib**;**

  C_{max}, T_{max}, C_{trough}, AUC_{tau}, metabolite to parent ratio for AUC_{tau} ($MRAUC_{tau}$), and metabolite–to-parent ratio for C_{max} (MRC_{max}) for PF-06260182;

  C_{trough} for pembrolizumab;

  Population-based PK parameters for pembrolizumab (if performed will be reported in a separate report).

- Association between tumor PD-L1 expression assessed by PD-L1 immunohistochemistry and endpoints of clinical outcome (response-related and time-to-event endpoints).

CCI [redacted]

- [redacted]
- [redacted] CCI

- Overall change from baseline in patient-reported lung cancer symptom, functioning, and global QOL scores.

- Frequency of occurrence and degree of bothersomeness of visual disturbances as reported by the patients on the VSAQ-ALK questionnaire.

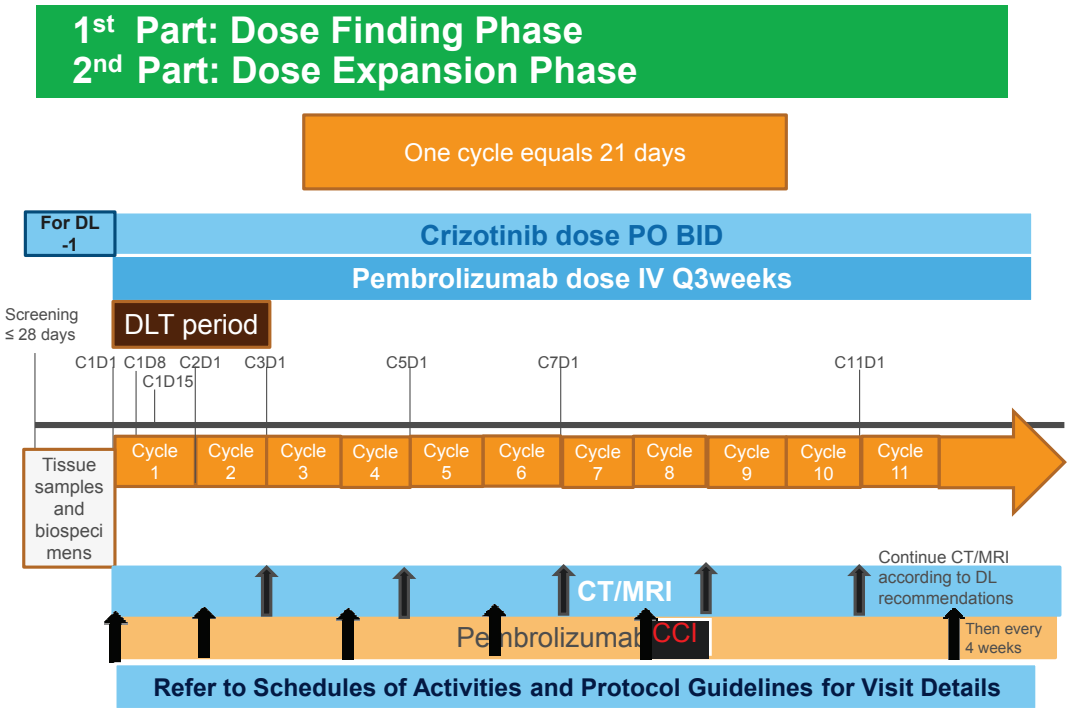
Study Design:

This is a Phase 1b, open-label, multi-center, multiple-dose, dose-finding, safety, and pharmacokinetic study of crizotinib in combination with pembrolizumab in sequential cohorts of adult patients with previously untreated ALK-positive advanced NSCLC. The study includes 2 phases (Dose Finding Phase and Dose Expansion Phase – See Study Schema in Figure 1).

[redacted]

Approximately 70 total patients are expected to be enrolled in this study. The first phase of the study, the Dose Finding Phase, will use a mTPI method to determine the MTD of the combination. The second study phase, the Dose Expansion Phase, will further evaluate the combination regimen at the MTD to determine whether the MTD will also be the RP2D.

Figure 1. STUDY DESIGN



Study Treatment Administration:

Crizotinib will be administered orally BID or QD at approximately the same time in the morning and evening (BID) or morning only (QD) on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Crizotinib capsules may be administered without regard to meals, and if administered on the BID schedule, the capsules should be taken approximately 12 hours apart. During the PK sampling days, the crizotinib dose should be taken in the clinic under supervision of the study site personnel.

Pembrolizumab will be administered intravenously on Day 1 of Q3week cycles. Treatment with pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (such as holidays).

The Dose Finding Phase will follow an "Up-and-Down" design (mTPI), using doses of crizotinib and pembrolizumab as shown in Table 6 (see Section 3.1.1). In this dosing algorithm there are up to 4 potential dose levels (DLs), with crizotinib doses ranging from 250 mg BID down to 250 mg QD, and pembrolizumab at a fixed dose of 200 mg Q3weeks.

Dosing will start at Dose Level 0 (DL0) which is the target dose; there are no plans to escalate dose above DL0. This study is designed to de-escalate doses as suggested by the safety profile. The detailed dose-finding rules based on the mTPI are illustrated in Table 6 (Section 3.1.1.1).

Rules for dose finding using the mTPI method include the following:

- The target enrollment cohort size is 3 patients. The first 3 patients treated at each dose level will initiate dosing sequentially, at least 2 days apart from each other.

- The next cohort will be enrolled when all patients at the current dose cohort have been evaluated for the first 2 cycles, ie, 6 weeks or experience a DLT, whichever comes first. The next cohort will receive the dose level as assigned by Table 5.

- If a patient does not receive at least 80% of the planned first 2 cycles dosing of crizotinib when combined with pembrolizumab, or both infusions of pembrolizumab within the DLT observation period for reasons other than study drug-related toxicity, another patient will be enrolled to current DL.

- The Dose Finding Phase of the trial is completed when 10 DLT-evaluable patients have been treated at the highest dose associated with a DLT rate <0.33. This will be considered the MTD of the combination. It is estimated that approximately 30 DLT-evaluable patients will need to be enrolled to estimate the MTD.

- The RP2D will be confirmed in the Dose Expansion Phase, taking into account the MTD determination from the Dose Finding Phase, and other factors related to safety, efficacy, and PK/PD involving all available data from test cohorts.

Patients will continue with combination crizotinib and pembrolizumab treatment until RECIST-defined progression of disease and investigator decision that the patient is no longer receiving clinical benefit, or unacceptable toxicity, death, or consent withdrawal, whichever comes first.

Tumor Assessments

Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline, then at Week 9, and every 6 weeks thereafter, using RECIST v 1.1 [See Schedule of Activities (SOA) – Table 1, and Table 3]. In addition, radiological tumor assessments will also be conducted to confirm a best response of CR or PR at ≥4 weeks after initial assessment of response, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not performed in the previous 6 weeks. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions and new lesions according to RECIST v1.1 (See Appendix 6).

SCHEDULE OF ACTIVITIES

The schedule of activities table provides details of the required protocol visits and procedures. Refer to the Assessments section (Section 7) of the protocol for detailed information on each assessment required for compliance with the protocol.

To allow for patient and investigator schedules, holidays, and weather or other emergencies requiring clinical facilities to be closed, all patient visits can be performed ±2 days of scheduled visit. The investigator may schedule visits (unplanned visits) in addition to those listed on the SOA, in order to conduct evaluations or assessments required to protect the well-being of the patient.

SCHEDULE OF ACTIVITIES FOR DOSE LEVELS 0, -2, and -3

Table 1. Schedule of Activities: Crizotinib + Pembrolizumab: 21-Day Treatment Cycles (Applicable to both the Dose Finding and Dose Expansion Phases of the Study)

		CYCLES 1-2			CYCLES 3-8	CYCLES >8		
Visit Identifier	**Screening**	**Day 1**	**Day 4-8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment[26]**	**Follow- up[27]**
Visit Time Window[a] (days)	**(≤28[1])**	**(±2)**		**(±2)**	**(±2)**	**(±2)**		
Informed consent[2]	X							
Tumor history	X							
Medical history	X							
Physical examination	X	X			X	X	X	
Baseline signs and symptoms[3]		X						
Height	X							
Weight	X	X			X	X	X	
Vital signs[4]	X	X			X	X	X	
ECOG Performance status[5]	X	X			X	X	X	
Laboratory								
Hematology[6]	X	X		X	X	X	X	
Blood Chemistry[7]	X	X		X	X	X	X	
Coagulation[8]	X	X			X	X	X	
T3, FT4, and TSH[9]	X	X			X[9]	X[9]	X	
Urinalysis[10]	X							
Pregnancy test[11]	X	X			X	X	X	
Contraception check[b]	X	X			X	X	X	X
12-Lead ECG[12]	X	X			X (Cycles 3 and 6 only)			

[redacted]

		CYCLES 1-2			CYCLES 3-8	CYCLES >8		
Visit Identifier	**Screening**	**Day 1**	**Day 4-8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment[26]**	**Follow- up[27]**
Visit Time Window[a] (days)	**(≤28[1])**	**(±2)**		**(±2)**	**(±2)**	**(±2)**		
Registration and Treatment								
Registration[13]		X						
Administration of crizotinib[14]		BID Continuously (QD Continuously at DL-3b only)						
Administration of pembrolizumab[14]		X			X	X		
Tumor assessments								
CT or MRI scan or equivalent[15]	X	To be assessed at Week 9 (+ 7 days) and every 6 weeks (+/- 7 days) thereafter					X	
Other clinical assessments								
AEs[16]		→	→	→	→	→	X	
Concomitant treatments[17]		→	→	→	→	→	X	
Other samplings								
Archival tumor tissue[18]	X							
De Novo Tumor Biospecimen[19]							X	
CCI [redacted]		[redacted]			[redacted]		[redacted]	
CCI [redacted]	[redacted]	[redacted]			[redacted]		[redacted]	
CCI [redacted]					[redacted]		[redacted]	

[redacted]

		CYCLES 1-2			CYCLES 3-8	CYCLES >8		
Visit Identifier	**Screening**	**Day 1**	**Day 4-8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment[26]**	**Follow- up[27]**
Visit Time Window[a] (days)	**(≤28[1])**	**(±2)**		**(±2)**	**(±2)**	**(±2)**		
CCI [redacted]	[redacted]							
Blood for crizotinib PK[24]		X [24]			X[24]		X[24]	
Blood for pembrolizumab PK[24]		X[24]	X[24]	X[24]	X[24]	X[24]	X[24]	X[24]
[redacted]		C CI			[redacted]	[redacted]	[redacted]	[redacted]
Patient Reported Outcomes (EORTC QLQ-C30, QLQ-LC-13, VSAQ)[25]		X			X	X	X	
Survival Follow-up[27]								X

Abbreviations: →= ongoing/continuous event; CCI [redacted]; AEs = adverse events; C = cycle; CT = computed tomography; MRI = magnetic resonance imaging; PK = pharmacokinetics

[redacted]

a. Day relative to start of study enrollment (Day 1).

b. **Contraception Check**: Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception throughout the study and continued for at least 90 days after the last dose of crizotinib and 120 days after the last dose ofr pembrolizumab. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

c. A cycle length is 3 weeks.

1. **Screening:** To be obtained within 28 days prior to study enrollment.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
3. **Baseline Signs and Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study enrollment. Baseline signs and symptoms will be recorded on the Adverse Events case report form (CRF) page.
4. **Vital Signs:** Blood pressure and pulse rate to be recorded in seated position.
5. **ECOG Performance Status: S**ee Appendix 2.
6. **Hematology:** No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
7. **Blood Chemistry:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
8. **Coagulation:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
9. **Thyroid Function Tests:** No need to repeat on C1D1 if screening assessment is performed within 7 days prior to study enrollment. Performed in odd-numbered cycles starting C1D1 or when clinically indicated. See ASSESSMENTS section for Laboratory Tests list. Thyroid function test are being performed due to the potential for immune-related hypo- or hyperthyroidism.
10. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
11. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.

[redacted]

12. **12-Lead ECG**: All patients require a single ECG measurement at screening. Triplicate ECGs measurements (approximately 2 minutes apart) will be measured at all other time points with all 3 measurements obtained within a 10-minute time window for each timepoint. ECGs should be performed immediately before PK blood draws at respective time points. ECGs should be obtained at 0 hour (pre-dose) on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 6 Day 1. ECGs should also be obtained between 2 and 6 hours following morning crizotinib dosing on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 6 Day 1. For all patients, if the QTc is prolonged (≥500 msec), then the ECG should be read by a cardiologist at the site for confirmation (to look for spurious QT effect). Additional ECGs will be performed as clinically indicated. See Section 7.1.4 for further details.
13. **Registration:** Patient number and dose level allocation operated by Pfizer Inc.
14. **Study Treatment Administration**: Crizotinib will be given orally BID (or QD at DL-3) on a continuous daily dosing schedule. Pembrolizumab will be given as a 30-minute infusion every 3 weeks. Patients will continue with combination crizotinib and pembrolizumab treatment until RECIST-defined progression of disease and investigator determination that the patient is no longer receiveing clinical benefit or, unacceptable toxicity, death or consent withdrawal, whichever occurs first.
15. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging will include chest, abdomen and pelvis CT or MRI scans. Baseline central nervous system (CNS) imaging is required to rule out asymptomatic brain metastases, and brain imaging scans will be performed at baseline and assessed along with the CT/MRI scans of the chest, abdomen and pelvis. CT or MRI scans are to be done starting at Week 9 (+1 week) after the start of pembrolizumab then repeated every 6 weeks (+/- 1 week). Bone scans will be performed at baseline if bony metastases are suspected. Patients with positive results on the bone scans will have these repeated every 12 weeks (± 1 week). Tumor assessments must continue until disease progression has been determined by the radiologist in consultation with the treating physician to determine whether the patient would benefit from treatment beyond RECIST v1.1 disease progression. Both target and non-target lesions are to be followed using the same modality used at baseline. Tumor assessment should be repeated to confirm response and disease progression and at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.
16. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Patients must be followed for AEs for 28 days after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the 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 28 calendar days after the administraton of crizotinib or 90 calendar days after the last administration of pembrolizumab, whichever is later, and before initiation of a new anti-cancer treatment. The prolonged follow-up is due to the pharmacokinetic properties of pembrolizumab. Serious adverse events 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 serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
17. **Concomitant Treatments:** All concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF.
18. **Archival Tumor Tissue:** A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be provided that is of sufficient size to allow, if possible, for sectioning of fifteen (15) 5-micron tissue sections. If an FFPE tumor tissue block cannot be provided, sites should try to obtain fifteen (15) unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. If archived FFPE tissue is not available, every effort should be made to collect a *de novo* (ie, fresh) tumor sample in accordance with local institutional practice for tumor biopsies. Archived or *de novo* tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Acquisition of the mandatory tumor tissue can be completed outside the 28-day screening window.

19. ***De Novo* Tumor Biospecimen:** An optional *de novo* (ie, fresh biopsy) tumor sample will be collected at End of Treatment if a patient discontinues due to disease progression. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted.
20. CCI [redacted]
21. CCI [redacted]
22. CCI [redacted]
23. CCI [redacted]
24. **PK Sampling:** Samples will be collected at the time points indicated in the Schedule for Pharmacokinetic CCI Sampling Schema Table 2. For crizotinib PK assessments, blood samples (3 mL) to obtain plasma will be collected prior to crizotinib morning dose (pre-dose) on Day 1 of Cycles 1, 2, 4, 6, and 8, and between 28-35 days after last pembrolizumab dose (at the End of Treatment Visit). For pembrolizumab PK assessments, blood samples (3 mL) to obtain serum will be collected: 1) prior to pembrolizumab (predose) and at end of pembrolizumab infusion (Day 1), between 72-168 hours (Days 4-8), and 336 hours (Day 15) of Cycle 1; 2) prior to pembrolizumab (predose) on Day 1 of Cycles 2, 4, 6, 8, and every 4 cycles thereafter and at the end of pembrolizumab infusion on Day 1 of Cycle 8; and 3) between 28-35 days (at the End of Treatment Visit) and at approximately 3 months (Follow-up) after last pembrolizumab dose (or until the patient starts new anti-cancer therapy). CCI [redacted] Also see Section 7.2.
25. **EORTC QLQ-C30, QLQ-LC13, and VSAQ-ALK:** Patients will complete the EORTC QLQ-C30, QLQ-LC13, and VSAQ-ALK questionnaires at the clinic prior to any study or medical procedure. If a person is illiterate and/or not able to read, they need not complete these questionnaires. Translation of the VSAQ-ALK is available in many different languages. However, if the VSAQ-ALK is not available in the patient's preferred language the patient does not need to complete this assessment.
26. **End of Treatment:** At least 28 days but no more that 35 days after the last dose of study treatment, patients will return to undergo review of AEs, and concomitant medications. Patients continuing to experience treatment-related toxicity at this point following discontinuation of treatment will continue to be followed every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
27. **Follow-up:**After discontinuation of study treatment, post-study survival status will be collected every 2 months until death or until 18 months after enrollment of the last patient, whichever occurs first. Includes collection of information on subsequent anticancer therapies. Telephone contact is acceptable.

[redacted]

Table 2. PK [redacted] Sampling Schema for Dose Levels 0, -2 and -3 (See Table 5)

Cycles 1, 2, 4, 6, 8				Cycle 12 and every 4 cycles thereafter		End of Treatment and Follow-up		
Day 1			Days 4-15(Cycle 1 only)	Day 1				
PK Samples for crizotinib[a]	**PK Samples for pembrolizumab**[b]	[redacted]	**PK Sample for pembrolizumab**[b]	**PK Sample for pembrolizumab**[b]	[redacted]	**PK Samples for crizotinib**[a]	**PK Sample for pembrolizumab**[b]	[redacted][c]
Prior to crizotinib morning dose[d]	Prior to pembrolizumab dose[e]	[redacted]	Between 72 and 168 hours (Day 4-8) and 336 hours (Day 15) after Cycle 1 dosing.	Prior to pembrolizumab dose[e]	[redacted]	Between 28-35 days after last pembrolizumab dose	Between 28-35 days after last pembrolizumab dose	[redacted]
	End of pembrolizumab infusion[f] (Only Cycles 1 and 8)						Approximately 3 months after last pembrolizumab dose (or until the patient starts new anti-cancer therapy)	[redacted]

PK= pharmacokinetics; [redacted]; note that PK samples for pembrolizumab [redacted] will be collected from all patients in the study. Crizotinib PK samples will be collected from all patients in the Dose Finding Phase and at least 8 patients in the Dose Expansion Phase.

a. One blood sample (3 mL) will be collected to obtain plasma at each time point for determining crizotinib and its metabolite PF-06260182 levels. Blood samples for crizotinib PK will be collected prior to crizotinib morning dose (pre-dose) on Day 1 of Cycles 1, 2, 4, 6, and 8, and between 28-35 days after last pembrolizumab dose (at the End of Treatment Visit). Also see Section 7.2.

b. One blood sample (3 mL) will be collected to obtain serum at each time point for determing pembrolizumab levels. Blood samples for pembrolizumab PK will be collected: 1) prior to pembrolizumab (predose) and at end of pembrolizumab infusion (Day 1), between 72-168 hours (Days 4-8), and 336 hours (Day 15) of Cycle 1; 2) prior to pembrolizumab (predose) on Day 1 of Cycles 2, 4, 6, 8, and every 4 cycles thereafter and at the end of pembrolizumab infusion on Day 1 of Cycle 8; and 3) between 28-35 days (at the End of Treatment Visit) and at approximately 3 months (Follow-up) after last pembrolizumab dose (or until the patient starts new anti-cancer therapy). Also see Section 7.2.

c. CCI [redacted]

d. Pre-dose trough crizotinib PK sample hould be drawn within 1 hour before crizotinb dosing.

e. Pre-dose trough pembrolizumab samples should be drawn within 24 hours before infusion of pembrolizumab.

f. Sample may be collected within 30 minutes after the end of pembrolizumab infusion.

[redacted]

SCHEDULE OF ACTIVITIES FOR PHASED-IN DOSE LEVEL -1 (See Table 5): Crizotinib monotherapy lead-in period for 21 days prior to start of pembrolizumab

Table 3. Schedule of Activities: Crizotinib + Pembrolizumab: 21-Day Treatment Cycles (Applicable to both the Dose Finding and Dose Expansion Phases of the Study)

		CYCLE -1 *Lead-in for DL-1 (21 days)*		CYCLES 1-2			CYCLES 3-8	CYCLES >8		
Visit Identifier	**Screen**	**Day 1**	**Day 15**	**Day 1**	**Day 4-8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment[26]**	**Follow-up[27]**
Visit Time Window[a] (days)	**(≤28[1])**	*Crizotinib 250 mg PO BID for 3 weeks*		**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**		
Informed consent[2]	X									
Tumor history	X									
Medical history	X									
Physical examination	X			X			X	X	X	
Baseline signs and symptoms[3]		X (prior to first dose of crizotinib only)		X						
Height	X									
Weight	X	X		X			X	X	X	
Vital signs[4]	X	X		X			X	X	X	
ECOG Performance status[5]	X	X		X			X	X	X	
Laboratory										
Hematology[6]	X	X	X	X		X	X	X	X	
Blood Chemistry[7]	X	X	X	X		X	X	X	X	
Coagulation[8]	X	X		X			X	X	X	
T3, FT4, and TSH[9]	X	X		X[9]			X[9]	X[9]	X	
Urinalysis[10]	X									
Pregnancy test[11]	X	X		X			X	X	X	
Contraception check[b]	X	X		X			X	X	X	X

[redacted]

		CYCLE -1 *Lead-in for DL-1 (21 days)*		CYCLES 1-2			CYCLES 3-8	CYCLES >8		
Visit Identifier	**Screen**	**Day 1**	**Day 15**	**Day 1**	**Day 4-8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment[26]**	**Follow-up[27]**
Visit Time Window[a] (days)	**(≤28[1])**	*Crizotinib 250 mg PO BID for 3 weeks*		**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**		
12-Lead ECG[12]	X	X		X			X (Cycles 3 and 6 only)			
Registration and Treatment										
Registration[13]	X			X						
Administration of crizotinib[14]		BID Continuously								
Administration of pembrolizumab[14]				X			X	X		
Tumor assessments										
CT or MRI scan or equivalent[15]	X	To be assessed at Week 9 after the start of pembrolizumab (+ 7 days) then every 6 weeks (+/- 7 days) thereafter							X	
Other clinical assessments										
AEs[16]		X		→	→	→	→	→	X	
Concomitant treatments[17]		X		→	→	→	→	→	X	
Other samplings										
Archival tumor tissue[18]	X									
De Novo Tumor Biospecimen[19]									X	
CCI [redacted]		[redacted]					[redacted]		[redacted]	
CCI [redacted]	[redacted]	[redacted]					[redacted]		[redacted]	

[redacted]

		CYCLE -1 *Lead-in for DL-1 (21 days)*		CYCLES 1-2			CYCLES 3-8	CYCLES >8		
Visit Identifier	**Screen**	**Day 1**	**Day 15**	**Day 1**	**Day 4-8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment[26]**	**Follow-up[27]**
Visit Time Window[a] (days)	**(≤28[1])**	*Crizotinib 250 mg PO BID for 3 weeks*		**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**		
CCI [redacted]		[redacted]		[redacted]			[redacted]		[redacted]	
CCI [redacted]	X									
Blood for crizotinib PK[24]			X[24]	X[24]			X[24]		X[24]	
Blood for pembrolizumab PK[24]				X[24]	X[24]	X[24]	X[24]	X[24]	X[24]	X[24]
Blood for pembrolizumab ADA (Immunogenicity) Testing[24]				X[24])			X[24]	X[24]	X[24]	X[24]
Patient-Reported Outcomes (EORTC QLQ-C30, QLQ-LC-13, VSAQ)[25]				X			X	X	X	
Survival Follow-up[27]										X

Abbreviations: → = ongoing/continuous event; CCI [redacted]; AEs = adverse events; C = cycle; CT = computed tomography; MRI = magnetic resonance imaging; PK = pharmacokinetics

a. Day relative to start of study enrollment (Day 1).

b. **Contraception Check**: Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception throughout the study and continued for at least 90 days after the last dose of crizotinib and 120 days after the last dose ofr pembrolizumab. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

c. A cycle length is 3 weeks.

[redacted]

1. **Screening**: To be obtained within 28 days prior to study enrollment.
2. **Informed Consent**: Must be obtained prior to undergoing any study-specific procedures.
3. **Baseline Signs and Symptoms**: Patients will be asked about any signs and symptoms experienced within the 14 days prior to study enrollment Baseline signs and symptoms will be recorded on the Adverse Events case report form (CRF) page.
4. **Vital Signs**: Blood pressure and pulse rate to be recorded in seated position.
5. **ECOG Performance Status**: See Appendix 2.
6. **Hematology**: No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
7. **Blood Chemistry**: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
8. **Coagulation**: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
9. **Thyroid Function Tests**: No need to repeat on C1D1 if screening assessment is performed within 7 days prior to study enrollment. Performed in odd-numbered cycles starting from C1D1 or when clinically indicated. See ASSESSMENTS section for Laboratory Tests list. Thyroid function test are being performed due to the potential for immune-related hypo- or hyperthyroidism.
10. **Urinalysis**: Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
11. **Serum/Urine Pregnancy Test**: For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
12. **12-Lead ECG**: All patients require a single ECG measurement at screening. Triplicate ECGs measurements (approximately 2 minutes apart) will be measured at all other time points with all 3 measurements obtained within a 10 minute time window for each timepoint. ECGs should be performed immediately before PK blood draws at respective time points. ECGs should be obtained at 0 hour (pre dose) on Lead-in Day 1, Cycles 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 6 Day 1, and during the lead-in period in DL-1. ECGs should also be obtained between 2 and 6 hours following morning crizotinib dosing on Lead-in Day 1, Cycles 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 6 Day 1. For all patients, if the QTc is prolonged (>500 msec), then the ECG should be read by a cardiologist at the site for confirmation (to look for spurious QT effect). Additional ECGs will be performed as clinically indicated. See Section 7.1.4 for further details.
13. **Registration**: Patient number and dose level allocation operated by Pfizer Inc.
14. **Study Treatment Administration**: Crizotinib will be given orally BID on a continuous daily dosing schedule. Crizotinib will be given for 3weeks as monotherapy (Cycle -1) prior to starting pembrolizumab. Pembrolizumab will be given as a 30-minute infusion every 3 weeks (as described in the STUDY TREATMENTS section). Patients will continue with combination crizotinib and pembrolizumab treatment until RECIST-defined progression of disease and investigator determination that the patient is no longer receiveing clinical benefit or, unacceptable toxicity, death or consent withdrawal, whichever comes first.

[redacted]

15. **Tumor Assessments**: Tumor assessments will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans. Baseline central nervous system (CNS) imaging is required to rule out asymptomatic brain metastases, and brain imaging scans will be performed at baseline and assessed along with the CT/MRI scan of the chest, abdomen, and pelvis. CT or MRI scans are to be done starting at Week 9 (+1 week) after the start of pembrolizumab then repeated every 6 weeks (+/- 1 week). Bone scans will be performed at baselinefor bony metastases are suspected. Patients with positive results on the bone scans will will have these repeated every 12 weeks (±1 week). Tumor assessments must continue until disease progression has been determined by the radiologist in consultation with the treating physician to determine whether the patient would benefit from treatment beyond RECIST v1.1 disease progression. Both target and non-target lesions are to be followed using the same modality used at baseline and interval unless clinically indictated. Tumor assessment should be repeated at to confirm response and disease progression and at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.
16. **Adverse Event (AE) Assessments**: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Patients must be followed for AEs for 28 days after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the mean time. 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 28 calendar days after the last administration of the investigational product. Serious adverse events 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 serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigtional product are to be reported to the sponsor.
17. **Concomitant Treatments**: All concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF.
18. **Archival Tumor Tissue**: A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be provided that is of sufficient size to allow, if possible, for sectioning of fifteen (15) 5-micron tissue sections. If an FFPE tumor tissue block cannot be provided, sites should try to obtain fifteen (15) unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. If archived FFPE tissue is not available, every effort should be made to collect a de novo (ie, fresh) tumor sample in accordance with local institutional practice for tumor biopsies. Archived or de novo tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Acquisition of the mandatory tumor tissue can be completed outside the 28-day screening window.
19. ***De Novo* Tumor Biospecimen**: An optional *de novo* (ie, fresh biopsy) tumor sample will be collected at End of Treatment if a patient discontinues due to disease progression. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted.
20. CCI [redacted]
21. CCI [redacted]
22. CCI [redacted]

23. CCI [redacted]

24. **PK Sampling**: Samples will be collected at the time points indicated in the Schedule for Pharmacokinetic CCI Samples Collection Table 4. For crizotinib PK assessments, blood samples (3 mL) to obtain plasma will be collected prior to crizotinib morning dose (pre-dose) on Day 1 of Cycles 1, 2, 4, and 8, and between 28-35 days after the last pembrolizumab dose (at the End of Treatment Visit). In addition, blood samples for full crizotinib PK profiles will be collected prior to (pre-dose) and at 1, 2, 4, 6, and 8 hours after crizotinib morning dose on Day 15 of the Lead in Period and on Day 1 of Cycle 6. For pembrolizumab PK assessments, blood samples (3 mL) to obtain serum will be collected: 1) prior to pembrolizumab (predose) and at end of pembrolizumab infusion (Day 1), between 72-168 hours (Days 4-8), and 336 hours (Day 15) of Cycle 1; 2) prior to pembrolizumab (predose) on Day 1 of Cycles 2, 4, 6, 8, and every 4 cycles thereafter and at the end of pembrolizumab infusion on Day 1 of Cycle 8; and 3) between 28-35 days (at the End of Treatment Visit) and at approximately 3 months (Follow-up) after last pembrolizumab dose (or until the patient starts new anti-cancer therapy). CCI [redacted] Also see Section 7.2.

25. **EORTC QLQ-C30, QLQ-LC13, and VSAQ-ALK**: Patients will complete the EORTC QLQ-C30, QLQ-LC13, and VSAQ-ALK questionnaires at the clinic prior to any study or medical procedure. If a person is illiterate and/or not able to read, they need not complete these questionnaires. Translation of the VSAQ-ALK is available in many different languages. However, if the VSAQ-ALK is not available in the patient's preferred language the patient does not need to complete this assessment.

26. **End of Treatment**: At least 28 days after the last dose of study treatment but no more than 35 days, patients will return to undergo review of AEs, or concomitant medications. Patients continuing to experience treatment-related toxicity at this point following discontinuation of treatment will continue to be followed every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

27. **Follow-up**:.After discontinuation of study treatment, post-study survival status will be collected every 2 months until death or until 18 months after enrollment of the last patient, whichever occurs first. Includes collection of information on subsequent anticancer therapies. Telephone contact is acceptable.

Table 4. PK [redacted] Sampling Schema for Dose Level -1 (See Table 5)

Crizotinib Lead-In (Cycle -1)	Cycles 1, 2, 4, 6, 8				Cycles 12 and every 4 Cycles thereafter		End of Treatment and Follow-up		
Day 15	Day 1			Days 4-15	Day 1				
PK Samples for Crizotinib[a]	**PK Samples for crizotinib[a]**	**PK Samples for pembrolizumab[b]**	CCI [redacted]	**PK Sample for pembrolizumab[b]**	**PK Sample for pembrolizumab[b]**	CCI [redacted]	**PK Samples for crizotinib[a]**	**PK Sample for pembrolizumab[b]**	CCI [redacted]
Prior to crizotinib morning dose	Prior to crizotinib morning dose[d]	Prior to pembrolizumab dose[e]	[redacted]	between 72 and 168 hours (Day 4-8) and 336 hours (Day 15) after Cycle 1 dosing.	Prior to pembrolizumab dose[e]	[redacted]	Between 28-35 days after Last pembrolizumab dose	Between 28-35 days after Last pembrolizumab dose	[redacted]
1 hr post crizotinib morning dose	1 hr post crizotinib morning dose (Cycle 6 only)	End of pembrolizumab infusion[f] (Cycles 1 and 8)						Approximately 3 months after last pembrolizumab dose (or until the patient starts new anti-cancer therapy)	[redacted]
2 hrs post crizotinib morning dose	2 hrs post crizotinib morning dose (Cycle 6 only)								
4 hrs post crizotinib morning dose	4 hrs post crizotinib morning dose (Cycle 6 only)								

Crizotinib Lead-In (Cycle -1)	Cycles 1, 2, 4, 6, 8				Cycles 12 and every 4 Cycles thereafter		End of Treatment and Follow-up		
Day 15	Day 1			Days 4-15	Day 1				
PK Samples for Crizotinib[a]	PK Samples for crizotinib[a]	PK Samples for pembrolizumab[b]	CCI	PK Sample for pembrolizumab[b]	PK Sample for pembrolizumab[b]	CCI	PK Samples for crizotinib[a]	PK Sample for pembrolizumab[b]	CCI
6 hrs post crizotinib morning dose	6 hrs post crizotinib morning dose (Cycle 6 only)								
8 hrs post crizotinib morning dose	8 hrs post crizotinib morning dose (Cycle 6 only)								

PK= pharmacokinetics; CCI ; note that PK samples for pembrolizumab CCI will be collected from all patients in the study. Crizotinib PK samples will be collected from all patients in the Dose Finding Phase and at least 8 patients in the Dose Expansion Phase.

a. One blood sample (3 mL) will be collected to obtain plasma at each time point for determining crizotinib and its metabolite PF-06260182 levels. Blood samples (3 mL) crizotinib PK to will be collected prior to crizotinib morning dose (pre-dose) on Day 1 of Cycles 1, 2, 4, and 8, and between 28-35 days after the last pembrolizumab dose (at the End of Treatment Visit). In addition, blood samples for full crizotinib PK profiles will be collected prior to (pre-dose) and at 1, 2, 4, 6, and 8 hours after crizotinib morning dose on Day 15 of the Lead in Period and on Day 1 of Cycle 6. Also see Section 7.2.

b. One blood sample (3 mL) will be collected to obtain serum at each time point for determining pembrolizumab levels. Blood samples for pembrolizumab PK will be collected: 1) prior to pembrolizumab (predose) and at end of pembrolizumab infusion (Day 1), between 72-168 hours (Days 4-8), and 336 hours (Day 15) of Cycle 1; 2) prior to pembrolizumab (predose) on Day 1 of Cycles 2, 4, 6, 8, and every 4 cycles thereafter and at the end of pembrolizumab infusion on Day 1 of Cycle 8; and 3) between 28-35 days (at the End of Treatment Visit) and at approximately 3 months (Follow-up) after last pembrolizumab dose (or until the patient starts new anti-cancer therapy). Also see Section 7.2.

c. CCI

d. Pre-dose trough sample for crizotinib should be drawn within 1 hour before crizotinb dosing.

e. Pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab.

f. Sample may be collected within 30 minutes after the end of pembrolizumab infusion.

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1. INTRODUCTION

This is a Phase Ib study of crizotinib (XALKORI®), an ATP-selective small-molecule oral inhibitor of the anaplastic lymphoma kinase (ALK), c-Met/hepatocyte growth factor receptor (HGFR), Recepteur d'Origine Nantais (RON), and ROS1 receptor tyrosine kinases and their oncogenic variants (eg, c-Met/HGFR mutations and ALK or ROS1 fusion proteins), in combination with pembrolizumab (KEYTRUDA®), a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype, which directly blocks the interaction between programmed death receptor-1 (PD-1) and its ligands, PD-L1 and PD-L2. The study is designed to determine the MTD and RP2D of this combination regimen in first-line (1L) treatment of patients with ALK-positive advanced non-small cell lung cancer (NSCLC).

1.1. NSCLC Background

Non-small cell lung cancer is the most common cause of fatal malignancy in the United States (US) among both men and women, representing 28% and 26% of all cancer-related deaths, respectively. NSCLC represents the second most common cause of new cases of malignancies in men (14%) and women (13%) according to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program.[1] Similar results have been described in Europe where NSCLC remains the most common cause of fatal malignancy.[2] There is also a growing burden of NSCLC in developing countries like India[3] and China[4] where the incidence in men is greater than women. The incidence of NSCLC has been decreasing in the US and Europe due to tobacco cessation programs.[1,2] The NSCLC rates have remained high in heavily polluted cities due to particulate matter, second-hand smoke exposure, and poor home ventilation systems where coal is used for cooking.[4,14] Another important issue with NSCLC is the low 5-year survival rate of 16.6%. This is usually due to the late stage of diagnosis but also due to the development of resistance to treatments.

1.1.1. Mutations/Fusions in NSCLC

Approximately 85% of all lung cancer cases are NSCLC. Of these cases, about 60% are considered non-squamous histologically with the remaining being squamous. Genetic aberrations have been noted to act as drivers for tumor growth in certain types of NSCLC. The presence of mutations and gene fusions, along with the development of targeted therapies, allowed for the improved treatment for patients with NSCLC. The first mutations that were targeted, *EGFR* mutations especially del exon 19 and L858R translocation in exon 21, showed improvement in objective response rate (ORR) and median progression-free survival (mPFS) using specific epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) but no improvement in overall survival (OS).[15,17-20]

Anaplastic lymphoma kinase (ALK) gene rearrangements are another molecularly defined subgroup of lung cancer patients. An inversion within chromosome 2p resulting in the formation of a fusion gene product comprising portions of the echinoderm microtubule associated protein-like 4 (EML4) gene and the ALK gene was discovered in 2007 in NSCLC cell lines and archived clinical specimens.[21] A subsequent series of studies have described 9 fusion variants of EML4-ALK plus additional but less common fusion partners with ALK.[22-29] Currently, there are at least 27 different ALK fusion variants reported in the

literature, the majority of isoforms involve EML4-ALK.[5] ALK-positive NSCLC patients, who represent between 3% and 5% of all non-squamous cases, tend to be young (average age 50 years at diagnosis), and light to never smokers.[5]

1.1.2. Immune System and NSCLC

Recent evidence has shown that tumors require interaction with the host immune system for continued growth and spread. Expression of antigens on the tumor cells are different from host cells due to genetic and epigenetic variations. In order for immune removal of tumor cells, there must be antigen recognition, followed by antigen presentation to T cells. The T cells will become activated and cell kill occurs. T cells are further modified by immune stimulatory and immune inhibitory signals; developed to prevent autoimmune diseases and inflammation. The immune co-stimulatory molecules include CD28, CD137, glucocorticoid-induced tumor necrosis factor receptor (GITR), and OX-40. Co-inhibitory or checkpoint molecules include cytotoxic T-lymphocyte antigen-4 (CTLA-4), PD-1, T-cell immunoglobulin- and mucin-domain-3-containing molecule 3 (TIM3), lymphocyte-activation gene-3 (LAG3), and killer cell immunoglobulin-like receptor (KIR). These immune checkpoint molecules lead to immune tolerance of the tumor, leading to increased tumor growth and vascularization.[30]

Until recently, attempts to modulate the immune system in NSCLC have met with limited benefit. Vaccine therapies have not shown benefits in NSCLC patients. The anti-CTLA-4 antibody ipilimumab was studied in combination with paclitaxel and carboplatin using 2 different dosing regimens. The phased regimen showed an improvement in median immune-related PFS (irPFS) of 5.7 vs. 4.6 months while the concurrent regimen showed an improvement in irPFS of 5.5 vs. 4.6 months. The phased regimen showed statistical significance while the concurrent did not.[31]

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[32] Accumulating evidence shows a correlation between TILs in cancer tissue and favorable prognosis in various malignancies.[33-37] 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 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).[9,11] 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.[9,38,40,41] 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.[42, 43] 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.[45, 45] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[46] 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.[42, 47-49] 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.[42] 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.[50] 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.

There have been a number of studies evaluating several different inhibitors of PD-1 or PD-L1 in NSCLC. Nivolumab (BMS-936558; a fully humanized anti-PD-1-antibody) showed an ORR of 18% in squamous and non-squamous NSCLC patients who were treated in the third-line and beyond.[51] Pembrolizumab (MK-3475; a fully humanized anti-PD-1 antibody) was studied in multiple tumor types. In patients with unselected advanced NSCLC, pembrolizumab was associated with an ORR of 36% by immune-related response criteria (irRC).[52] Studies using antibodies targeting the ligand on PD-1 (anti-PD-L1-antibodies), including MEDI4736 and MPDL3280A, are ongoing. The most mature data presented uses BMS-936559 (a fully humanized anti-PD-L1 antibody) that showed an objective response in 5 of 49 patients with NSCLC.[53]

1.2. Background and Rationale

Crizotinib (PF-02341066)Crizotinib (XALKORI®, PF-02341066) is indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) (actual indication varies according to region/country).[5]

Crizotinib is an oral inhibitor of ALK, HGFR, RON, and ROS1 receptor tyrosine kinases and their oncogenic variants (eg, c-Met/HGFR mutations and ALK or ROS1 fusion proteins). Consistent with this mechanism of action, crizotinib inhibited phosphorylation of c-Met/HGFR and selected ALK fusion or mutant variants in tumor cells both in vitro and in vivo, and RON and ROS1 in vitro. Crizotinib exhibited potent and selective growth inhibitory activity against tumor cells exhibiting translocation/inversion or selected mutations involving the ALK gene locus (echinoderm microtubule-associated protein-like-4 [EML4]-ALK or nucleophosmin [NPM]-ALK fusion variants).

1.2.1. Clinical Safety and Efficacy of Crizotinib

Clinical Safety

Overall, the AEs reported for crizotinib in clinical studies were considered generally tolerable and manageable. For single-agent crizotinib, the most common AEs (≥20% of patients) reported from 1511 patients with advanced NSCLC regardless of causality were vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue and decreased appetite. The majority of AEs were Grades 1 or 2 in severity, as treatment-related AEs of Grades 3, 4, or 5 in severity were observed among 547 (36.3%) advanced NSCLC patients who received at least 1 dose of single-agent crizotinib 250 mg BID. The most common Grade 3 treatment-related AEs were neutropenia, elevated transaminases, hypophosphatemia, fatigue, leukopenia, lymphopenia, nausea, vomiting, electrocardiogram QT prolonged, and edema. The most common Grade 4 treatment-related AEs were neutropenia, elevated transaminases, hepatotoxicity, interstitial lung disease, and abdominal pain. The Grade 5 treatment-related AEs that occurred most commonly were interstitial lung disease (5 patients; 0.3%), death (4 patients; 0.3%), pneumonia (2 patients; 0.1%), hepatotoxicity (2 patients; 0.1%), lung infection (2 patients; 0.1%), disseminated intravascular coagulation (1 patient; 0.1%), arrhythmia (1 patient; 0.1%), dyspnea (1 patient; 0.1%), and pulmonary embolism (1 patient; 0.1%).[7]

There are special warnings regarding crizotinib use that must be considered and are described in detail in the crizotinib Investigator's Brochure (IB). Drug-induced hepatotoxicity occurred in less than 1% of all patients treated with crizotinib and usually appeared within the first 2 months of therapy. Other warnings are pnerumonitis/interstitial lung disease and QTc prolongation which both occurred in fewer than 2% of patients and bradycardia which occurred in approximately 6% of patients.[7] Specific management for these events is noted in Table 8.

Clinical Efficacy

Clinical trials using crizotinib showed an impressive rate of objective tumor response that were were rapid and durable in Studies A8081001 and A8081005. In Study A8081007 (PROFILE 1007), treatment of advanced ALK-positive NSCLC patients in second-line (after initial platinum-based chemotherapy) with crizotinib demonstrated a statistically significant improvement in median PFS when compared to chemotherapy (pemetrexed or docetaxel monotherapy) of 3.0 months (median PFS: 7.7 months vs.of 3.0 months, respectively; HR 0.487; 95% CI: 0.371, 0.638; P <0.001). This study also showed an statistically significant improvement in ORR to 65% versus 20% for chemotherapy. Validated questionnaires (EORTC QLQ-C30 and QLQ-LC13) showed a significantly greater improvement in patient-reported lung cancer symptoms and global quality of life receiving crizotinib as compared with chemotherapy.[6, 7] In Study A8081014 (PROFILE 1014), treatment of ALK-positive NSCLC with crizotinib in the first-line showed statistically significant improvement in median PFS and ORR when compared with pemetrexed plus platinum-based chemotherapy (median PFS: 10.9 months vs. 7.0 months, respectively; HR 0.454; 95% CI: 0.346 -0.596; P <0.001; ORR: 74% vs. 45%, respectively; P <0.001).[8]

Complete information for crizotinib may be found in the crizotinib Single Reference Safety Document (SRSD) which for this study is the investigaor's brochure (IB).[7]

1.2.2. Pembrolizumab (MK-3475)

Pembrolizumab [Keytruda® (US); previously known as lambrolizumab, MK-3475, and SCH 9000475] 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.

Pembrolizumab [Keytruda(®) (US)], a humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co for the treatment of cancer. Pembrolizumab has received its first global approval for the treatment of advanced, unresectable or metastatic malignant melanoma in the US, for use in patients with disease progression after prior treatment with ipilimumab and, for BRAF V600 mutation-positive patients, a BRAF inhibitor. It is the first anti-PD-1 therapy to receive regulatory approval in the US, and is currently under regulatory review in the EU.[74] Clinical Safety and Efficacy of Pembrolizumab in Solid Tumors

The safety and efficacy data regarding the use of pembrolizumab comes from the multi-arm study PN001, also referred to as KEYNOTE-001, which studied patients with solid tumors, including melanoma, and NSCLC. This study is an open-label Phase 1 study, which includes a dose escalation component using 1, 3, and 10 mg/kg of pembrolizumab every 2 or 3 weeks in patients with solid tumors (Part A), subsequent expansion cohorts studying solid tumors at the MTD from Part A (Part B), at 2 different dose levels in patients with melanoma (Part D), expansion cohorts at the MTD from Part A in patients with melanoma (Part C), at 3 different dose levels in NSCLC (Part E), and at 2 different dose levels (1 mg/kg vs. 10 mg/kg only) in patients with NSCLC (Part F). KEYNOTE-001 Part A evaluated 3 dose levels and all 3 dose levels were well tolerated, as no DLTs were observed. Based on PK data showing a half-life of 21 days, the protocol was amended to include a dosing frequency of Q3weeks in the expansion cohorts (Parts B through F).

Clinical Safety

The safety of pembrolizumab is being assessed in 26 different studies as noted in http://www.clinicaltrials.gov. Currently, safety data of single agent pembrolizumab are only available from KEYNOTE-001.[122] [57,58] Preliminary data[59] are available from 479 patients enrolled in KEYNOTE-001: Part A (n=30) pembrolizumab 1 mg/kg, 3 mg/kg, and 10 mg/kg Q2weeks or Q3weeks, Part B (n=308) pembrolizumab 2 mg/kg or 10mg/kg Q2weeks or Q3weeks, Part C (n=38) pembrolizumab 10 mg/kg Q3weeks, and Part D (n=103) pembrolizumab 2 or 10 mg/kg Q3weeks. Of the 479 patients who have received pembrolizumab in KEYNOTE-001, 466 (97.3%) experienced all-causality AEs of which 368 were considered to be treatment-related. Serious adverse events (SAEs) were reported in 30.1% of patients. Potentially immune-related AEs (irAEs - also called immune-mediated adverse reactions) were observed, including pneumonitis (Grades 1-2) in patients with melanoma or NSCLC. The most commonly reported an all-causality AEs experienced were fatigue, nausea, cough, pruritus, diarrhea and rash. Most patients continued treatment, as only 4.2% of patients discontinued pembrolizumab due to treated-related AEs.

Of the 162 patients who received pembrolizumab 2 mg/kg Q3weeks in the treatment of melanoma in KEYNOTE-001, 160 experienced an treatment-related AEs of which 128 were considered to be treatment-related; 17 were Grades 3 or 4 in severity. SAEs were reported in 44 patients, but treatment-related SAEs were reported in 15 patients. This included 1 episode of hyperthyroidism and 1 episode of adrenal insufficiency. The most commonly reported all-causality AEs experienced in this subset of patients were fatigue (30%), pruritus (21%), rash (21%), diarrhea (20%), nausea (10%), and cough (8%). The most common treatment-related AEs included hypothyroidism (8%), vitiligo (9%), elevated AST (10%), elevated alanine aminotransferase (ALT) (8%), pneumonitis (4%), and immune-related renal failure (2%).[57] Additional safety signals that are seen with pembrolizumab related to its immune activity include hypophysitis, hypopituitarism, adrenal insufficiency, nephritis, uveitis, and diabetes mellitis. In order to manage any potential endocrine-related AE, thyroid function tests, renal function tests, and serum blood glucose tests are being performed.

Clinical Efficacy

Preliminary efficacy from KEYNOTE-001 is available for 135 patients with advanced melanoma.[57] The ORR across all dose cohorts, assessed by independent radiology review according to RECIST v1.1, was 38% (95% CI: 25, 44), with an ORR observed of 52% (95% CI: 38, 66) in the cohort that received 10 mg/kg Q2weeks. The ORR did not differ significantly between patients who had received prior ipilimumab (anti-CTLA-4 antibody) treatment and those who were ipilimumab-naïve (ORR= 38% [95% CI: 23, 55] and 37% [95% CI: 26, 49], respectively). Objective responses were durable in the majority of patients (median follow-up was 11 months); 81% (24/52) of the patients who had a response were still receiving treatment at the time of analysis. The overall median PFS among the 135 patients was estimated to be longer than 7 months (median PFS was not yet reached).[57]

1.2.2.1.1. Clinical Safety and Eficacy of Pembrolizumab in NSCLC

Clinical Safety

In KEYNOTE-001, Part C (n=38), 20 patients experienced ≥1 treatment-related AE of any grade across all dose levels (1mg/kg, 3 mg/kg, and 10 mg/kg Q3weeks). The most common treatment-related AEs were rash (21%), pruritis (18%), fatigue (16%), diarrhea (13%), arthralgia (11%), back pain (5%), cough (5%), and decreased appetite (5%). Grade 2 treatment-related AEs included hypothyroidism (1 patient), hyperthyroidism (1 patient), and pneumonitis (1 patient). There was 1 episode of a Grade 3 treatment-related AE (pulmonary edema). There were no Grade 4 and 5 treatment-related AEs.[12]

Clinical Efficacy

The preliminary ORR using RECIST v1.1 in KEYNOTE-001 Part C (n=38) across all dose levels among all patients who received 3 or more lines of prior therapy for NSCLC was 24% by investigator assessment using immune-related response criteria. The ORR was 21% as assessed by independent radiology review. The specific breakdown of responses by independent radiology review assessed by RECIST v1.1 was 16% (4/26) for patients with

non-squamous NSCLC and 33% (2/6) for patients with squamous NSCLC. The median PFS was 10.3 weeks for advanced non-squamous NSCLC patients and 15.2 weeks for advanced squamous NSCLC patients.[12]

The correlation of pembrolizumab activity with levels of tumoral PD-L1 was explored in a substudy using 146 NSCLC tumor samples across all KEYNOTE-001 NSCLC cohorts. Among the tumors that had ≥ 50% PD-L1 staining, the ORR was 37%. Among the tumors that had ≥1% PD-L1 staining, the ORR was 25%.[58]

Complete information for pembrolizumab may be found in the Single Reference Safety Document (SRSD), which for this study is the pembrolizumab IB.[59]

1.2.3. Rationale for Dose Selection/Regimen/Modification

The dosing of crizotinib was chosen to be 250 mg BID as this demonstrated robust antitumor activity in patients with ALK-positive advanced NSCLC. Similarly, pembrolizumab has shown dramatic antitumor activity at 2 mg/kg Q3weeks. There do not appear to be significant overlapping toxicities seen at these doses while there is a maximal antitumor activity. Because of these, this study will evaluate DL0 as the starting dose with crizotinib 250 mg BID combined with pembrolizumab at the equivalent dose of 200 mg Q3weeks.

In KEYNOTE-001, which treated a variety of tumor types, pembrolizumab 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 Q2weeks). Dose level 10 mg/kg Q3weeks was evaluated in previously treated patients with NSCLC in Part C.

PK data analysis of pembrolizumab administered Q2weeks showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to pembrolizumab IB).[59] Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing either a Q2weeks or Q3weeks dosing schedule. Previously treated patients with NSCLC in KEYNOTE-001 Part C have experienced durable objective responses with acceptable toxicity when treated with pembrolizumab at 10 mg/kg Q3weeks.

Preliminary data in patients with melanoma and NSCLC also demonstrated objective responses by pembrolizumab when administered at the 2 mg/kg Q3weeks dose and schedule. However, ongoing analysis of KEYNOTE-001 Parts B, C, and F may further define the activity of low vs. high doses included in this trial. In addition, given the lack of a dose response to date, modeling and simulation data indicate that a fixed dose of 200 mg provides adequate exposure for the largest patients based on body weight while not exceeding the exposure seen at 10 mg Q3weeks in the smallest patients based on body weight. A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, was within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Simulations were performed on the basis of the

population PK model, using a distribution of body weight reflective of the general population obtained from the National Health and Nutrition Examination Survey (NHANES) 2009-2010 database.

Differences in exposure for a 200 mg fixed dosing regimen relative to a 2 mg/kg Q3weeks body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. Thus, a fixed dose of 200 mg Q3weeks should result in adequate exposure to pembrolizumab across all body weights, similar to the exposures obtained with a 2 mg/kg Q3week regimen.

1.2.4. Rationale for the Combination of Crizotinib and Pembrolizumab

Patients with previously untreated ALK-positive advanced NSCLC treated with crizotinib have a median PFS of 10.9 months.[23] Progression of disease is often related to the development of crizotinib-resistant ALK mutation or signal transduction bypass pathways. Another potential cause of disease progression is related to tumoral growth and protection related to lack of immune surveillance, often due to overexpression of PD-L1 within the tumor. Although the incidence of changes in the tumor microenvironment are unknown, there remains the potential for improvement in ORR, DR, and PFS probability using a combination of targeted therapy (crizotinib) and immune therapy (pembrolizumab). The increase in regulatory T cells also allows for the metastatic spread of tumor both lymphatically and hematogeneously as well as increases in local vascular endothelial growth factor. These factors correlate with a negative prognosis for diseases like NSCLC.[12] The primary efficacy evaluation of this study is to show that combination therapy of crizotinib and pembrolizumab improves the ORR based on historical single-agent crizotinib data from Study A8081014 (>75% for crizotinib). Additional efficacy parameters evaluated will include PFS, duration of response (DR) and overall survival (OS).

Targeting of ALK has been noted because of the strong addiction for neoplastic cell growth and survival but also for the development of spontaneous immunogenicity. This was first noted in patients with NPM-ALK-positive anaplastic large cell lymphoma (ALCL) where circulating antibodies to NPM-ALK proteins were noted.[60, 61] CD8+ effector and memory T-cells were also found in these patients[62, 63] as were CD4+ helper T-cells.[64] The strongest immune response seen correlated with survival improvement in ALCL patients.[65] Experiments using ALK DNA vaccination in mice showed a cytotoxic immune response to the injected cells. Vaccination prevents lymphoma growth due to immune response and improved future immune protections as noted by increased interferon-gamma (IFN-γ) and CD8+ T-cells.[66]

Mice that were implanted with EML4-ALK- and TFG-ALK-expressing lung tumors developed lung masses with distant metastases. An additional experiment used 3 rounds of ALK vaccination to determine antitumor response. Cytotoxicity to the tumor occurred quickly. There were increases in effector T cells intratumorally as well as an increase in regulatory T cells over time. When the ALK vaccine was combined with an ALK TKI, tumors were noted to have increased PD-L1 expression by immunohistochemical (IHC) staining with delay in tumor relapse and extended survival.[67]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To assess safety and tolerability of crizotinib in combination with pembrolizumab in the first-line treatment of patients with ALK-positive advanced non-squamous NSCLC in order to identify the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile of crizotinib in combination with pembrolizumab;
- To document the anti-tumor activity of crizotinib in combination with pembrolizumab in previously untreated ALK-positive advanced NSCLC patients;
- To characterize the pharmacokinetics (PK) of crizotinib and pembrolizumab and to assess the effect of pembrolizumab on the PK of crizotinib;
- To evaluate tumor PD-L1 expression, as assessed by PD-L1 immunohistochemistry, as a predictor of anti-tumor activity.

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- [redacted]
- [redacted]
- To evaluate the impact of combination therapy of crizotinib and pembrolizumab on patient-reported lung cancer symptoms (such as dyspnea, cough and pain) and global Quality of Life (QOL) per the validated cancer specific EORTC QLQ-C30, and its lung cancer module, QLQ-LC-13, and visual symptoms per the Visual Symptom Assessment Questionnaire (VSAQ-ALK).

2.2. Endpoints

Primary Endpoint

- Dose-Limiting Toxicity (DLT).

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), timing, seriousness and relationship to study treatments.

- Objective response rate (ORR), as assessed using RECIST v1.1, and also:
- Duration of Response (DR).
- Time to Tumor Response (TTR).
- PFS, 6-month, 12-month, and 18-month PFS probabilities, OS, 12-month and 18-month survival probabilities.
- Laboratory abnormalities as characterized by type, frequency, severity, and timing.
- The following PK parameters of crizotinib, its metabolite PF-06260182 and pembrolizumab PK will be determined as data permits:
  - Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), pre-dose concentration (C_{trough}), area under the plasma concentration time curve from 0 to 8 hours (AUC_{0-8}), area under the plasma concentration time curve over the dosing interval (AUC_{tau}), and apparent plasma clearance (CL/F) for crizotinib;
  - C_{max}, T_{max}, C_{trough}, AUC_{tau}, metabolite to parent ratio for AUC_{tau} ($MRAUC_{tau}$), and metabolite to parent ratio for C_{max} (MRC_{max}) for PF-06260182;
  - C_{trough} for pembrolizumab;
  - Population-based PK parameters for pembrolizumab (if performed, will be reported in a separate report).
- Association between tumor PD-L1 expression assessed by PD-L1 immunohistochemistry and endpoints of clinical outcome (response-related and time-to-event endpoints).

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- [redacted]
- [redacted]
- Overall change from baseline patient-reported lung cancer symptom, functioning, and global QOL scores using the EORTC QLQ-C30 and QLQ-LC-13 questionnaires;
- Frequency of occurrence and degree of bothersomeness of visual disturbances as reported by the patients on the VSAQ-ALK questionnaire.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b, open-label, multicenter, multiple-dose, dose-finding, safety, and pharmacokinetic study of crizotinib in combination with pembrolizumab in sequential cohorts of adult patients with previously untreated ALK-positive advanced NSCLC with 2 phases (Dose Finding Phase and Dose Expansion Phase).

Approximately 70 total patients are expected to be enrolled in this study. The first phase of the study, the Dose Finding Phase, will utilize the mTPI method to determine the MTD of the combination regimen. The second phase, the Dose Expansion Phase, will further evaluate the combination regimen at the MTD to determine whether or not the MTD will also be the RP2D.

3.1.1. Study Treatment

Crizotinib will be given orally (PO) either BID or QD, with or without food on a continuous daily dosing schedule. Pembrolizumab will be given as a 30-minute intravenous (IV) infusion Q3 weeks. Patients will continue with combination crizotinib and pembrolizumab treatment until RECIST-defined progression of disease and investigator decision that the patient is no longer experiencing clinical benefit, or unacceptable toxicity, death, or consent withdrawal, whichever occurs first (see Section 7.4).

The initial starting dose for the Dose Finding Phase of the study will be crizotinib 250 mg given BID on a continuous schedule with pembrolizumab 200 mg given intravenously Q3weeks starting on Cycle 1 Day 1 as described in Table 5.

In the Dose Finding Phase, lower doses of crizotinib may or may not be administered in subsequent cohorts of patients according to Table 5 and Table 6 depending on the incidence of DLTs at DL0. However, if DL0 exceeds the MTD, then patients will be enrolled into the next lower dose level (DL-1) except as described in the Table 5 footnotes. DL-1 will use the same crizotinib and pembrolizumab dosing regimens in combination after assessing whether or not patients tolerate a 3-week lead-in period using crizotinib 250 mg BID as a monotherapy for 3 weeks, henceforth referred to as Cycle -1 in the SOA (see Table 3). During this lead-in period, additional laboratory studies and ECGs will be performed, as well as additional PK analyses (see Table 4). This will be followed by the addition of pembrolizumab 200 mg Q3weeks. This will allow both drugs to remain at their respective maximum effective doses before lowering the doses of crizotinib to a lower dose level. A lead-in period using pembrolizumab monotherapy will not be considered at this time due to the paucity of data in ALK-positive NSCLC patients in the 1L treatment setting.

If dose de-escalation is neccessary after evaluation is completed for DL-1, then the next dose level will be determined by the types of adverse events that occur. If the adverse events are immune-related and considered to be only related to pembrolizumab, such as thyroiditis or endocrinopathies, the next cohort of patients will be assigned to DL-2 to test a lower dose of crizotinib in combination with pembrolizumab. If the adverse events are considered to be only related to crizotinib, such as diarrhea, visual changes, or LFT abnormalities as described in the crizotinib IB, then the next cohort of patients will be assigned to DL-2 or DL-3.

Table 5. Crizotinib and Pembrolizumab Dose Level Cohorts

Dose Level	Crizotinib	Pembrolizumab
0*	250 mg BID	200 mg Q3weeks
-1	250 mg BID x 3 weeks as monotherapy, then if tolerated, in combination with pembrolizumab thereafter	200 mg Q3weeks after crizotinib monotherapy lead-in period
-2**	200 mg BID	200 mg Q3weeks
-3	250 mg QD	200 mg Q3weeks

*If the adverse events meeting DLT criteria in DL0 are considered related to one or both study drugs, then further dose levels of crizotinib may be explored.

**If the adverse events meeting DLT criteria in DL0 are considered to be only related to crizotinib, such as diarrhea, visual changes, or LFT abnormalities as described in the crizotinib IB, patients, then the next dose level will be DL-2 or DL-3 which decreases the crizotinib dose to 200 mg BID and 250 mg QD, respectively.

Patients will be monitored closely for toxicity, and, in the event of significant toxicity, dosing may be delayed (see Section 5.3.4 and Section 5.3.5). Further adjustment of crizotinib may be performed by dosing interruption with or without dose reduction after the DLT evaluation period (see Section 5.3.4.1). Pembrolizumab dose modification will be performed based upon treatment-related irAEs including nephritis, enterocolitis, or endocrine abnormalities (see Section 5.3.4.2). Refer to pembrolizumab Events of Clinical Interest (ECI) Guidance Document for supportive care guidance. The ECI Guidance Document is a separate document that is located in the study reference manual.

The Dose Finding Phase of the trial will be completed when 10 DLT-evaluable patients have been treated at the highest DL associated with a DLT rate of <0.33.

If a cohort has a lower starting dose of crizotinib than 250 mg BID, then after completion of the DLT observation period, the dose of crizotinib may be re-escalated up to a maximum dose of 250 mg BID on an individual basis if no DLTs are observed. This will be decided by the investigator in consultation with the Sponsor on a case-by-case basis.

The proposed doses, schedule(s), and PK timepoints may be reconsidered and amended during the study based on the emerging safety and PK data.

Patients will continue with combination crizotinib and pembrolizumab treatment until RECIST-defined progression of disease and investigator decision that the patient is no longer receiving clinical benefit, or unacceptable toxicity, death or consent withdrawal, whichever occurs first. If radiologic imaging shows PD and the patient is perceived to be experiencing clinical benefit (see Section 7.4), repeat tumor assessment is to be performed ≥4 weeks later in order to confirm tumor status; study treatment may be continued at the investigator's discretion while awaiting radiologic confirmation of disease progression.

3.1.1.1. Criteria for Dose De-Escalation

The Dose Finding Phase will follow the "Up-and-Down" design, using doses of crizotinib and pembrolizumab as shown in Table 5**.** Briefly, the mTPI method relies upon a statistical probability algorithm, calculated using all patients treated at the same dose level to determine where future cohorts should involve dose de-escalation, no change in dose, or dose re-escalation. The detailed dose-finding rules based on the mTPI are illustrated in Table 6.

In this dosing algorithm there are up to 4 potential dose levels as described in Table 5.

The specific sequence to be followed depends upon the number of overall patients enrolled in the study and the number of DLTs observed at each specific dose combination.

Dosing will begin at DL0. If no DLTs are observed, then the cohort will be expanded up to a total of 10 DLT-evaluable patients prior to opening this DL to the Dose Expansion Phase. If 1or more DLTs occur at DL0, then dosing will be continued with DL0 or will be de-escalated to DL-1 according to Table 6 see Section 3.1.1.1. Dose re-escalation from levels DL-1 (or lower dose levels as shown in Table 6) back to DL0 will be allowed as long as DL0 has not been determined to have exceeded the MTD.

Table 6. Detailed Dose Re-Escalation/De-Escalation Scheme

		Number of Patients Treated at Current Dose									
Number of tDLTs		1	2	3	4	5	6	7	8	9	10
	0	NA	NA	RE	RE	RE	RE	RE	RE	RE	RE
	1	NA	NA	S	S	S	RE	RE	RE	RE	RE
	2		NA	D	S	S	S	S	S	RE**	RE**
	3			DU	DU	D	D	S	S	S	RE**
	4*				DU	DU	DU	DU	DU	DU	DU
	5					DU	DU	DU	DU	DU	DU
	6						DU	DU	DU	DU	DU
	7							DU	DU	DU	DU
	8								DU	DU	DU
	9									DU	DU
	10										DU

*A modification has been applied to the original mTPI algorithm. Since this protocol specifies a DLT rate <33% in 10 patients, all entries on the row with 4 toxicities are fixed to DU since 4/10 would be ≥33%.

** This further modification will allow re-escalatation and exposure of up to 10 patients at the higher dose if ≤ 3 out of 10 patients with a DLT at the current dose and assuming the previous higher dose was not already a DU.

RE = Re-escalate to the next higher dose or if current dose level is DL0 stay on DL0

S = Stay at the current dose

D = De-escalate to the next lower dose

U = The current dose is unacceptably toxic

NA = Not applicable. The first three patients will have to be evaluable for DLT before assigning DL for the next patient

Targeted DLT rate at MTD <33%

As an example, if the total number of patients treated at DL0 is 3, then the following dosing rules are to be applied:

- 0 - 1 DLT → remain at the same dose (DL0);
- 2 DLTs → de-escalate to DL-1 and allow for possible escalation back to DL0;
- 3 DLTs → de-escalate to DL-1 as DL0 is intolerable.

If the dose is de-escalated to DL-1 and the total number of patients then treated at DL-1 is 3, the following dosing rules are to be applied:

- 0 DLTs → escalate back to DL0 if DL0 was not considered intolerable;
- 1 DLT → remain at the same dose (DL-1);
- 2 DLTs → de-escalate to DL-2 and allow for possible escalation back to DL-1;
- 3 DLTs → de-escalate to DL-2 as DL-1 is intolerable.

Rules for dose-finding, using the mTPI method, include the following:

- The target enrollment cohort size is 3 patients. The first 3 patients treated at each dose level will initiate dosing sequentially, at least 2 days apart from each other.
- The next cohort will be enrolled when all patients at the current dose cohort have been evaluated for 6 weeks (ie, the first 2 treatment cycles), or experience a DLT, whichever comes first. The next cohort will receive the dose level as assigned by Table 5.
- If a patient does not receive at least 80% of the planned first 2 cycles of crizotinib dosing or both infusions of pembrolizumab within the DLT observation period for reasons other than study drug-related toxicity, another patient will be enrolled to replace that patient at the current dose level.
- The Dose Finding Phase is completed when 10 DLT-evaluable patients (see Section 9.2) have been treated at the highest dose associated with DLT rate <0.33. This will be considered the MTD of the combination. It is estimated that approximately 30 DLT-evaluable patients will need to be enrolled to estimate the MTD.

The proposed doses and, schedules may be reconsidered and amended during the study based on the emerging safety and pharmacokinetic data.

The RP2D will be confirmed in the Dose Expansion Phase, taking into account the MTD determination from the Dose Finding Phase, and other factors related to safety, efficacy, and PK/PD involving all available data from test cohorts.

3.1.2. Tumor Assessments

Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline, then at Week 9, and every 6 weeks, thereafter, using RECIST v1.1 [See Schedule of Activities (SOA) – Table 1, and Table 3]. In addition, radiological tumor assessments will also be conducted to confirm a best response of CR or PR at ≥4 weeks after initial assessment of response, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not performed in the previous 6 weeks. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions and new lesions according to RECIST v1.1 (See Appendix 6).

Brain CT or MRI scans are required for all patients at baseline and subsequently while on treatment. These are to be repeated every 6 weeks along with the CT/MRI scan of the chest, abdomen, and pelvis. Bone scans will be performed at baseline. Patients with positive results on the bone scans will have these repeated every 12 weeks (±1 week). Bone imaging is also required at the time of confirmation of response for patients who have known bone metastases.

3.1.3. Pharmacokinetic Assessment

Crizotinib and pembrolizumab do not have competing elimination/metabolism pathways, hence an overt PK interaction between the 2 drugs is not anticipated. However, PK assessments (Section 7.2 and Table 2, and Table 4) will be performed in this study to confirm the absence of pembrolizumab effects on crizotinib metabolism. Crizotinib has a mean terminal half-life of 42 hours after single-dose administration. Pembrolizumab has a long plasma half-life (21 to 28 days) and trough concentrations increase with successive doses until steady state is reached (expected within 3.5-4.5 months of initial pembrolizumab dosing). The administration of pembrolizumab monotherapy has not been evaluated for this patient population. Except for DL-1, all doses of crizotinib and pembrolizumab will be given concurrently. With the exception of the lead-in period for DL-1, steady-state crizotinib PK data determined following concurrent administration of pembrolizumab will be compared to historical crizotinib data. In the event that DL-1 is evaluated, the crizotinib lead-in period will permit a within study comparison of steady state crizotinib PK given alone (Day 15 of lead-in period) versus crizotinib plus pembrolizumab (Cycle 2 Day 1). As this study does not include administration of pembrolizumab as a single agent, the effect of crizotinib on pembrolizumab can only be evaluated by comparing pembrolizumab PK at steady-state in the presence of crizotinib with those reported for pembrolizumab monotherapy in KEYNOTE-001. In order to obtain data that adequately characterizes PK at the potential RP2D, PK assessments will be done in at least 8 patients from the Dose Expansion Phase.

The schedule for pharmacokinetic collections is included in Table 2, and Table 4.

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3.1.5. Tumor Biopsy Requirements and Translational Studies

All patients will be required to provide archived or *de novo* FFPE tumor tissue (see Section 6.1.1). Acquisition of the mandatory tumor tissue sample may be completed outside the 28-day screening time window. This mandatory tumor tissue will be used for retrospective biomarker assessments including as a first priority evaluation of tumor PD-L1 expression by IHC [redacted] as described in Section 7.3.

3.2. Dose-Limiting Toxicity Definition

Severity of adverse events will be graded according to NCI CTCAE version 4.03. For the purpose of dose de-escalation, any of the following adverse events occurring in the first 2 cycles of treatment (6 weeks) which are attributable to crizotinib, pembrolizumab or both will be classified as DLTs:

Hematologic toxicities:

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

Non-hematologic toxicities:

- Grade ≥3 toxicities (non-laboratory);
- Grade ≥3 nausea, vomiting, or diarrhea despite maximal therapy;
- Non-hematologic Grade ≥3 laboratory value if medical intervention is required to treat the patient or the abnormality leads to hospitalization.

Other

- Inability to complete at least 80% of the first 2 cycles doses of crizotinib or both infusions of pembrolizumab within the DLT observation period due to treatment-related toxicity.

3.3. Maximum Tolerated Dose Definition

The MTD estimate is the highest DL of crizotinib in combination with pembrolizumab from Table 5 associated with the occurrence of DLTs in <33% of patients.

3.4. Recommended Phase 2 Dose Definition

The RP2D is the dose of crizotinib and pembrolizumab in combination for further clinical development. Additional safety experience in the Dose Expansion Phase may result in an RP2D at or below the MTD.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Histologically or cytologically proven diagnosis of locally advanced, recurrent, or metastatic non-squamous NSCLC that is not suitable for local treatment with curative intent.
2. ALK-positive NSCLC as determined by a test that is approved or validated for use as a companion diagnostic test in accordance with applicable local regulatory and practice guidelines.
3. Able to provide formalin-fixed, paraffin-embedded (FFPE) tumor tissue (see Section 6.1.1).
4. No prior systemic therapy for metastatic disease.
    a. Any prior adjuvant chemotherapy for Stage I to III disease or combined modality chemoradiotherapy for locally advanced disease must have been completed >12 months prior to study enrollment.
5. Tumors must have measurable disease as per RECIST (version 1.1); see Appendix 6.
6. Age ≥18 years (or ≥20 years for Japan).
7. ECOG PS must be:
    a. 0 or 1 for the Dose Finding Phase.

b. 0, 1, or 2 for the Dose Expansion Phase.

8. Adequate Bone Marrow Function, including:

   a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;

   b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;

   c. Hemoglobin ≥8 g/dL.

9. Adequate Renal Function, including:

   a. Serum creatinine <2x upper limit of normal (ULN).

10. Adequate Liver Function, including:

   a. Total serum bilirubin ≤1.5 x ULN;

   b. AST and ALT ≤2.5 x ULN (≤5.0 x ULN if there is liver involvement secondary to tumor);

   c. Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).

11. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.

   a. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective method(s) of contraception throughout the study and for 90 days after the last of crizotinib or 120 days after the last dose of pembrolizumab, whichever is later (see Section 4.3.1).

12. Evidence of a personally signed and dated informed consent document indicating that the patient or legally acceptable representative 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 with any of the following characteristics/conditions will not be included in the study:

1. Prior exposure to ALK receptor tyrosine kinase inhibitors, anti-PD-1, anti-PD-L1, anti-PD-L2, Anti-CD137, or anti-CTLA-4 monoclonal antibodies (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

2. Current treatment on another clinical trial.

3. Major surgery, adjuvant chemotherapy, radiotherapy, any investigational agents, or other anticancer therapy within 2 weeks prior to study enrollment or has not yet recovered (ie,Grade ≤1 or at baseline) from related acute adverse events more than 4 weeks earlier.

4. History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or any grade of interstitial lung disease, including a history of any of the following conditions: pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis and pulmonary fibrosis, but not history of prior radiation pneumonitis.

5. Active autoimmune disease that has required systemic treatment in the past 3 months (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or corticosteroids at physiologic doses for eg. thyroid, pancreatic or adrenal insufficiency is acceptable.

6. Known carcinomatous meningitis or leptomeningeal disease. Patients with brain metastases are only eligible if treated and neurologically stable with no ongoing requirement for corticosteroids, eg, dexamethasone, for at least 2 weeks and are not taking contraindicated medications.

7. History of malignancy within the past 3 years (with the exceptions of non-squamous NSCLC, in situ cervical cancer, colon polyps, prostate carcinoma in situ or status post-resection or radiotherapy, ductal carcinoma in situ of the breast, papillary thyroid cancer (resected and treated with curative intent), or resected/treated squamous cell or basal cell carcinoma of the skin).

8. Active infection requiring systemic therapy.

9. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

10. Known diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

11. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).

12. Administration of a live vaccine within 30 days prior to the first dose of trial treatment.

13. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, congestive heart failure, coronary/peripheral artery bypass graft, or cerebrovascular accident including transient ischemic attack. Appropriate treatment with anticoagulants is permitted.

14. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or machine-read ECG with QTc interval >470 msec.

15. Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease or previous gastric resection or lap-band. Gastroesophageal reflux disease under treatment with proton-pump inhibitors is allowed.

    a. For Japan only: patients who have following complications or symptoms:

        1. Serious wound such as chronic wound, or Grade ≥3 gastrointestinal ulcer.

        2. Serious gastrointestinal symptoms such as Grade ≥3 diarrhea.

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. 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.

18. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective method*(s)* of contraception as outlined in this protocol for the duration of the study and for at least 90 days after the last dose of crizotinib or 120 days after the last dose of pembrolizumab, or longer based upon the compound's half-life characteristics..

19. Use of drugs or foods that are known potent CYP3A4 inhibitors within 7 days prior to study enrollment, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconzole, and grapefruit or grapefruit juice. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed.

20. Use of drugs that are known potent CYP3A4 inducers within 12 days prior to study enrollment, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.

21. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market).

4.3. Lifestyle Guidelines

4.3.1. Contraception

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive crizotinib with is associated with teratogenic risk and pembrolizumab, a compounds for which the teratogenic risk is currently unknown. Those who, in the opinion of the investigator, are sexually active and at risk for pregnancy, must agree to use two (2) methods of highly effective contraception throughout the study and continue for at least 90 days after the last dose of crizotinib or 120 days after the last dose of pembrolizumab, whichever is later. The investigator or his/her designee, in consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his/her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the Schedule of Activities (SOA – Table 1 and Table 3) and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued or if pregnancy is known or suspected in the patient or the patient's partner.

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 the following:

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

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

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

4. Male sterilization with absence of sperm in the postvasectomy 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).

Female patients of non childbearing potential must meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or

- Achieved postmenopausal 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.

All other female patients (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 90 days after the last dose of crizotinib or 120 days after the last dose of pembrolizumab, whichever is later.

4.3.2. Sunlight Exposure

Patients treated with crizotinib should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study period. Sun exposure responses to pembrolizumab are unknown. Patients will be advised to report any reaction to sun exposed skin.

4.3.3. Food Limitations

Crizotinib is predominately metabolized by CYP3A4. Because grapefruit and grapefruit juice are strong CYP3A4 inhibitors, these should be avoided in this study.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list on the team's Sharepoint site. To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center 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 contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact 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

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Patient Compliance

Patients will be required to return all unused crizotinib at the beginning of each cycle. The number of crizotinib capsules returned by the patient at the end of the cycle will be counted, documented, and recorded.

The site will complete required dosage with preparation record located in the study manual for pembrolizumab. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Pfizer monitor.

5.2. Investigational Product Supplies

Crizotinib and pembrolizumab 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 will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment & Proof of Receipt form. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.2.1. Dosage Form(s) and Packaging

5.2.1.1. Crizotinib

Crizotinib will be supplied as 200 and 250 mg capsules for oral administration and will be packaged in HDPE bottles.

5.2.1.2. Pembrolizumab

Pembrolizumab will be supplied in single-use vials containing 100 mg/4 mL 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

Crizotinib should be dispensed at each visit per the schedule of treatment (Section 5.3). Dispensing will be by a qualified staff member in bottles provided, in quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

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

Pembrolizumab will be administered at the investigational site as indicated in Section 5.3.2.

Specific preparation and dispensing instructions are provided in the Dosage Administration Instructions located in the Study Manual.

5.3. Administration

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of the study drug may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, treatment interruption may be required for 1 or both study drugs in the combination. In the event treatment interruption is deemed necessary for just 1 of the study drugs in the combination, treatment with the other study drug will continue as planned.

The start of a cycle is defined as the day when crizotinib and pembrolizumab administration begins, starting with the first crizotinib dose at Cycle 1 Day 1, except for DL-1 where the start of Cycle 1 follows the 3-week lead-in period of crizotinib monotherapy. In case of crizotinib dosing interruptions, administration of prembrolizumab will continue according to the pre-planned schedule.

5.3.1. Crizotinib Administration

Crizotinib will be administered orally BID or QD (depending on the DL; see Table 5) at approximately the same time in the morning +/- evening on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Crizotinib should be taken in the morning prior to the pembrolizumab infusion. On the study day in which both crizotinib and pembrolizumab are administered, crizotinib capsules (on the BID schedule) are to be taken approximately 12 hours apart. Patients must swallow the investigational product whole and must not manipulate or chew the investigational product prior to swallowing. A dosing card will be provided to the patients to provide guidance for the correct use of crizotinib. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not “make it up” with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. If a patient inadvertently takes 1extra dose during a

day, the patient should not take the next dose. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

During the PK analysis evaluation period, the crizotinib dose should be taken in the clinic under the supervision of the study site personnel.

5.3.2. Pembrolizumab Administration

Pembrolizumab will be administered intravenously on Day 1 of every 3-week. Treatment with pembrolizumab may be administered up to 2 days before or after the scheduled Day 1 of each cycle due to administrative reasons (such as holidays).

Pembrolizumab 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. However, given the variability of infusion pumps from site to site, a window of (-) 5 minutes and (+) 10 minutes is permitted (ie, infusion time of 25 to 40 minutes are acceptable).

For purposes of this trial, an overdose will be defined as ≥1000 mg (5 times the standard dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Discontinuation from pembrolizumab 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 with pembrolizumab, and have received at least 2 pembrolizumab infusions beyond the date the initial CR was declared. Crizotinib treatment may continue in these patients. Patients who then experience radiologic disease progression will be eligible for re-treatment with pembrolizumab at the discretion of the investigator if 1) no cancer treatment was administered other than study drugs since the last dose of pembrolizumab, 2) the patient meets the safety parameters listed in the Inclusion /Exclusion criteria, and 3) the trial is still open. Patients will resume therapy at the same dose and schedule in use at the time of initial discontinuation. Pembrolizumab treatment will be administered for up to one additional year. Patients who continue to experience radiologic disease progression per RECIST 1.1 or have global deterioration of health status requiring discontinuation, will be discontinued from trial see Section 6.4.

5.3.3. Food Requirements

Both crizotinib and pembrolizumab may be administered without regard to meals.

5.3.4. Recommended Dose Modifications

Dose level assignments for the combination therapy will follow the recommendations in Table 5. Every effort should be made to administer both investigational products on the planned dose and schedule. Intra-patient dose modifications will be permitted with either drug individually, based upon any AEs as described in Table 8. In the event of significant toxicity, dosing may be interrupted, delayed, and/or reduced as described below. Patients are to be instructed to notify investigators at the first occurrence of any AE.

Dose modifications may occur in 2 ways:

- Within a cycle (for crizotinib only): dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles (for pembrolizumab only): next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.

Dose modifications will be reported in the CRF.

5.3.4.1. Intra-Patient Crizotinib Dose Modifications

In the Dose Finding Phase, crizotinib intra-patient dose reduction is permitted but the adverse event leading to the dose modification may be considered a DLT if this occurs during the first 2 cycles of the study during this phase, if the investigator grades the treatment-related AE as Grade ≥3 and in consultation with the Sponsor (see Table 8). In the Dose Expansion Phase, crizotinib intra-patient dose reduction or escalation is permitted and based upon treatment-related adverse events observed.

Patients in the Dose Expansion Phase who tolerate crizotinib below the 250 mg BID dose level and have no Grade >2 treatment-related adverse events for 3 consecutive weeks (1 treatment cycle) have the option to increase the dose of crizotinib 1 dose level according to Table 7. As long as crizotinib is tolerated, crizotinib may be increased up to 250 mg BID.

Table 7. Crizotinib Dose Modifications

Treatment Level	Crizotinib Dose
0	250 mg BID
-1	200 mg BID
-2	200 mg QD
Below -2	Discontinue crizotinib

5.3.4.1.1. Bradycardia

For a heart rate <40 beats per minute, the patient should be evaluated fully including an assessment of concomitant medications. The dosage of any medication known to be associated with bradycardia, eg, beta blockers, should be adjusted accordingly. If the bradycardia is symptomatic at any time or does not improve within 7 days of adjusting the concomitant medications, hold crizotinib dosing until recovery. Patient may continue treatment only with the agreement of both the sponsor and investigator. Concurrent use of crizotinib with other bradycardic agents (eg, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be avoided to the extent possible due to the increased risk of symptomatic bradycardia. Heart rate and blood pressure should be monitored regularly. Dose modification is not required in case of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia (see Table 8).

5.3.4.1.2. Pneumonitis

Investigators must evaluate thoroughly patients who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug-related lung injury, the following evaluations/procedures should be considered to support or exclude the diagnosis of pneumonitis during this period:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria;
- Blood culture should be performed in febrile patients;
- Thoracentesis if pleural fluid is present (examined for same pathogens as sputum);
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture and cytology (same pathogens as above);
- Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate;
- A plasma sample for BNP (B-type Natriuretic peptide) to evaluate for evidence of CHF;
- For Asian patients, a blood sample for β-D-glucan to evaluate for the presence of fungal pneumonia (eg, Pneumocystis *jirovecii*);
- If clinically appropriate, high-dose corticosteroid treatment should be initiated. Should the event be fatal, an autopsy is highly recommended to confirm/exclude the diagnosis.

For any case of drug-related pneumonitis, discontinue crizotinib (see Table 8).

5.3.4.1.3. Renal Cysts

The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from 2 to 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended.

Active surveillance with appropriate imaging (contrast-enhanced CT scanning or magnetic resonance imaging) should be performed at the time of the renal cysts diagnosis and as scheduled per protocol (as indicated in Table 1 and Table 3) Investigators should also review retrospectively all CT/MRIs for any prior occurrence of complex renal cysts.

In addition, dipstick urinalysis should be performed at the time of the renal cysts diagnosis and on Day 1 of each cycle thereafter; in Korea, dipstick urinalysis should be performed in all patients at screening and on Day 1 of each cycle thereafter.

Urine reflex microscopy is required whenever urine dipstick is positive for blood or protein.

Dose modifications based on specific treatment-related AEs are described in Table 8.

5.3.4.2. Intra-Patient Pembrolizumab Dose Modifications

Pembrolizumab is a humanized monoclonal antibody. Patients should be monitored for potential AEs during antibody infusion and throughout the study. In the event that a patient experiences an infusion reaction to pembrolizumab, , refer to Section 5.7.8 Pembrolizumab Infusion Reaction Treatment Guidelines and Table 9.

Intra-patient pembrolizumab dose modifications are not permitted. Permanently discontinue pembrolizumab for any severe or Grade ≥3 drug-related AE that recurs or any life-threatening treatment related adverse event. Rechallenge after delay due to pembrolizumab toxicities may be allowed once for some specific toxicity, but if it recurs, it will require permanent discontinuation. Refer to the ECI Guidance Document for supportive care guidance and Section 5.3.4.2.2 Supportive Care Guidance for irAEs Following Pembrolizumab Dosing. Management of treatment-related toxicity is described in Table 8.

Table 8. Crizotinib and Pembrolizumab Dose Modifications for Treatment-Related Toxicity

Toxicity	Severity Grade	Crizotinib Dose Modification	Pembrolizumab Dose Modification[a,]
Hematological Toxicity	1/2	Continue at the same treatment level	If considered related to pembrolizumab, refer to the ECI Guidance Document for supportive care guidance.
	3	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same treatment level or reduce the dose by 1 treatment level after discussion with the Sponsor. †	If considered related to pembrolizumab, refer to the ECI Guidance Document for supportive care guidance.
	4	Withhold until toxicity is Grade ≤2 or has returned to baseline, then reduce by 1 treatment level	If considered related to pembrolizumab, refer to the ECI Guidance Document for supportive care guidance.
Non-hematological toxicity and/or Other Drug Related Toxicities [b]	1/2	Continue at the same treatment level	Refer to the ECI Guidance Document for supportive care guidance.
	3	Continue at the same treatment level or reduce by 1 treatment level	Withhold until toxicity is Grade ≤1 or baseline. Discontinue pembrolizumab if the AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroids to ≤10 mg of prednisone or equivalent per day

Toxicity	Severity Grade	Crizotinib Dose Modification	Pembrolizumab Dose Modification[a,]
			within 12 weeks. Follow the ECI Guidance Document for supportive care guidance.
	4	Withhold until toxicity is Grade ≤1 or has returned to baseline, then reduce by 1 treatment level	Discontinue pembrolizumab. Follow the ECI Guidance Document for supportive care guidance.
ALT or AST elevation possibly related with total bilirubin <2x ULN	1	Continue crizotinib at the same treatment level.	Continue at the same dose level. If considered related to pembrolizumab, refer to the ECI Guidance Document for supportive care guidance.
	2	Continue crizotinib at the same treatment level Repeat ALT or AST and total bilirubin when patient is symptomatic or within 7 days if not symptomatic. Monitor weekly.	Withhold until resolution of ALT or AST to Grade ≤1 or baseline. Discontinue if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to ≤10 mg of prednisone or equivalent per day within 12 weeks. Refer to pembrolizumab ECI Guidance Document for supportive care guidance.
	3	Withhold dose until toxicity is Grade ≤ 1, or has returned to baseline, then resume treatment by reducing by one treatment level. If Grade 3 ALT or AST elevation recurs reduce further (at most by 2 treatment levels if starting dose is treatment level 0). If recurrence at dose level -2, then discuss with Sponsor whether or not to discontinue permanently. If ALT or AST elevation does not recur after at least 4 weeks, the dose may be escalated by single treatment level increments up to the initial dose level.	Discontinue pembrolizumab. For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued. Refer to pembrolizumab ECI Guidance Document for supportive care guidance.
	4	Discontinue crizotinib	Discontinue pembrolizumab. For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued. Refer to pembrolizumab ECI Guidance Document for supportive care guidance.
ALT or AST elevation and total bilirubin ≥ 2x ULN (in the absence of	1	Continue crizotinib at the same treatment level Repeat ALT or AST and total bilirubin within 48 hours and	Continue pembrolizumab. If considered related to pembrolizumab, refer to the ECI Guidance Document for supportive care guidance.

Toxicity	Severity Grade	Crizotinib Dose Modification	Pembrolizumab Dose Modification[a,]
cholestasis or hemolysis)		monitor every 48 hours until Grade <1.	
	2	Discontinue crizotinib	Withhold until resolution to Grade ≤1 or baseline. Discontinue if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to ≤10 mg of prednisone or equivalent per day within 12 weeks. Refer to pembrolizumab ECI Guidance Document for supportive care guidance.
	3/4	Discontinue crizotinib	Discontinue pembrolizumab. For patients with liver metastasis who begin treatment with Grade 2 AST or ALT. If AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued. Refer to pembrolizumab ECI Guidance Document for supportive care guidance.
Pneumonitis	1	Discontinue crizotinib	If considered related to pembrolizumab, refer to the ECI Guidance Document for supportive care guidance.
	2	Discontinue crizotinib	Withhold pembrolizumab until toxicity is Grade ≤1 or returns to baseline. Discontinue if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroids to ≤10 mg of prednisone or equivalent per day within 12 weeks. Refer to pembrolizumab ECI Guidance Document for supportive care guidance.
	3/4	Discontinue crizotinib	Discontinue pembrolizumab Refer to pembrolizumab ECI Guidance Document for supportive care guidance.
Diarrhea/Colitis	1	Continue crizotinib at the same treatment level Start supportive care with loperamide if clinically appropriate.	Continue pembrolizumab at the same treatment level Refer to the ECI Guidance Document for supportive care guidance.
	2	Continue crizotinib at the same level Start loperamide at 4 mg at onset then 2 mg every 2-4 hours until symptom free for 12 hours.	Withhold pembrolizumab until toxicity resolves to Grade ≤1 or baseline. Discontinue if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to ≤10 mg of prednisone or equivalent per

Toxicity	Severity Grade	Crizotinib Dose Modification	Pembrolizumab Dose Modification[a,]
			day within 12 weeks. Refer to pembrolizumab ECI Guidance Document for supportive care guidance.
	3	Grade 3: Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator (despite use of loperamide).	Withhold pembrolizumab until toxicity resolves to Grade ≤1 or baseline. Discontinue if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to ≤10 mg of prednisone or equivalent per day within 12 weeks. Refer to pembrolizumab ECI Guidance Document for supportive care.
	4	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator (despite use of loperamide).	Withhold pembrolizumab. Refer to pembrolizumab ECI Guidance Document for supportive care.
Bradycardia (Heart rate less than 60 bpm)	1	Continue crizotinib at the same treatment level	Continue pembrolizumab There are no specific recommendations – please consult the non-hematologic guidelines for recommendations and Refer to pembrolizumab ECI Guidance Document for supportive care.
	2/3	Withhold until toxicity is Grade ≤1 or heart rate ≥60 bpm, then reduce by 1 treatment level. Evaluate concurrent medications and serum electrolytes. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤1 or to heart rate ≥60 If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤1 or to heart rate ≥60	Continue pembrolizumab There are no specific recommendations – please consult the non-hematologic guidelines for recommendations and Refer to pembrolizumab ECI Guidance Document for supportive care.
	4	Discontinue crizotinib if no contributing concomitant	There are no specific recommendations – please consult the non-hematologic

Toxicity	Severity Grade	Crizotinib Dose Modification	Pembrolizumab Dose Modification[a,]
		medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤1 or to heart rate ≥60, with frequent monitoring or discuss with sponsor. Permanently discontinue for recurrence.	guidelines for recommendations and Refer to pembrolizumab ECI Guidance Document for supportive care.
Left ventricular systolic dysfunction	1 / 2	Continue crizotinib at the same treatment level	Continue pembrolizumab There are no specific recommendations – please consult the non-hematologic guidelines for recommendations and Refer to pembrolizumab ECI Guidance Document for supportive care.
	3 / 4	Discontinue crizotinib	There are no specific recommendations – please consult the non-hematologic guidelines for recommendations and Refer to pembrolizumab ECI Guidance Document for supportive care.

Toxicity	Severity Grade	Crizotinib Dose Modification	Pembrolizumab Dose Modification[a,]
Prolonged QTc interval	1 / 2	Continue crizotinib at the same treatment level For Grade 2 only: assess electrolytes and concomitant medications Correct any electrolyte or magnesium abnormalities.	Continue pembrolizumab There are no specific recommendations – please consult the non-hematologic guidelines for recommendations and Refer to pembrolizumab ECI Guidance Document for supportive care.
	3	Interrupt crizotinib until recovery to Grade ≤1, then resume at a lower dose level. Assess and correct electrolytes and concomitant medications. In case of recurrence, withhold until recovery to Grade ≤1, then resume at 250 mg once daily or discuss with sponsor. Permanently discontinue in case of further Grade ≥3 recurrence.	There are no specific recommendations – please consult the non-hematologic guidelines for recommendations and Refer to pembrolizumab ECI Guidance Document for supportive care.
	4	Discontinue crizotinib and do not retreat	There are no specific recommendations – please consult the non-hematologic guidelines for recommendations and Refer to pembrolizumab ECI Guidance Document for supportive care.
Visual disturbance	1 / 2	Continue crizotinib at the same treatment level Obtain an ophthalmology consultation	Refer to pembrolizumab ECI Guidance Document for supportive care.
	3	Interrupt crizotinib until recovery to Grade ≤1. Obtain an ophthalmologic consultation Resume treatment by reducing the dose by one dose level upon recovery to Grade ≤1.	Refer to pembrolizumab ECI Guidance Document for supportive care.
	4	Discontinue crizotinib and do not retreat Obtain an ophthalmology consultation	Refer to pembrolizumab ECI Guidance Document for supportive care.
Type 1 diabetes mellitus (if new onset) or hyperglycemia	1/2	Continue crizotinib at the same dose level	Continue pembrolizumab and refer to the ECI Guidance Document for supportive care guidance.
	3 / 4	Grade 3: Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure. Resume Pembrolizumab when patients are clinically and metabolically stable. Refer to pembrolizumab ECI Guidance

Toxicity	Severity Grade	Crizotinib Dose Modification	Pembrolizumab Dose Modification[a,]
		Grade 4: Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.	Document for supportive care.
Hypophysitis	1	Continue crizotinib at the same dose level	Continue pembrolizumab. Follow the ECI Guidance Document for supportive care guidance.
	2	Continue crizotinib at the same treatment level	Discontinue if toxicity does not resolves within 12 weeks of last dose or inability to reduce corticosteroids to ≤10 mg of prednisone or equivalent per day within 12 weeks. Hold treatment until toxicity resolves to Grade ≤1 or baseline. Therapy with pembrolizumab may continue while endocrine replacement therapy is instituted. Refer to the ECI Guidance Document for supportive care guidance.
	3 / 4	Grade 3: Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator. Grade 4: Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.	Discontinue if toxicity does not resolves within 12 weeks of last dose or inability to reduce corticosteroids to ≤10 mg of prednisone or equivalent per day within 12 weeks. Hold treatment until toxicity resolves to Grade ≤1 or baseline, therapy with pembrolizumab may continue while endocrine replacement therapy is instituted. Refer to the ECI Guidance Document for supportive care guidance.
Hyperthyroidism	1/2	Continue crizotinib at the same dose level	Continue pembrolizumab
	3	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.	Hold treatment until toxicity resolves to Grade ≤1 or baseline. Discontinue if toxicity does not resolves within 12 weeks of last dose or inability to reduce corticosteroids to ≤10 mg of prednisone or equivalent per day within 12 weeks. Refer to pembrolizumab ECI Guidance Document for supportive care.
	4	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.	Permanently discontinue pembrolizumab. Refer to pembrolizumab ECI Guidance Document for supportive care.

Toxicity	Severity Grade	Crizotinib Dose Modification	Pembrolizumab Dose Modification[a,]
Renal Failure or Nephritis	1	Continue crizotinib at the same dose level	Continue pembrolizumab. Refer to the ECI Guidance Document for supportive care guidance.
	2	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.	Hold treatment until toxicity resolves to Grade ≤1 or baseline. Discontinue if toxicity does not resolves within 12 weeks of last dose or inability to reduce corticosteroids to ≤10 mg of prednisone or equivalent per day within 12 weeks Refer to pembrolizumab ECI Guidance Document for supportive care.
	3/4	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.	Permanently discontinue Refer to pembrolizumab ECI Guidance Document for supportive care.

a. Intra-patient pembrolizumab dose modifications are not permitted. Permanently discontinue pembrolizumab for any severe or Grade ≥3 drug-related AE that recurs or any life-threatening treatment related adverse event. Re-challenging after delay due to pembrolizumab toxicities may be allowed once for some specific toxicities as in the ECI document but if it recurs, it will require permanent discontinuation. Refer to the ECI Guidance Document for supportive care guidance and Section 5.3.4.2.2.

b. Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue pembrolizumab for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

† Patients who develop Grade 3 or 4 lymphopenia without other dose-limiting events (eg, opportunistic infection) may continue study treatment without interruption.

In case toxicity does not resolve to Grade ≤1 or does not return to baseline within 12 weeks after the last dose of either crizotinib or pembrolizumab, either treatment or both may be discontinued, after consultation with the Sponsor. With investigator and Sponsor agreement, patients with a laboratory adverse event that remains Grade >2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. Patients who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of either crizotinib or pembrolizumab should be discontinued from the study treatment after consultation with the Sponsor.

5.3.4.2.1. Immune-Related Adverse Events

An immune-related adverse event (irAE) may occur after the first dose to several months after starting pembrolizumab treatment. This will need to be monitored by the investigator and Sponsor throughout the time that patients remain on the study. Mild irAEs are treated symptomatically and do not require dosing delays or discontinuation. For irAE management, consult Table 8.

5.3.4.2.2. Supportive Care Guidelines for irAEs Following Pembrolizumab Dosing

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Table 8 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

5.3.4.2.2.1. Pneumonitis

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks.

- For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

5.3.4.2.2.2. Diarrhea/Colitis

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).

- All patients who experience diarrhea/colitis 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. For Grade ≥2 diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.

- For Grade 3 or 4 diarrhea/colitis that persists >1 week, treat with IV steroids followed by high-dose oral steroids.

- When symptoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks.

5.3.4.2.2.3. Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

For T1DM or Grade 3-4 Hyperglycemia

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

5.3.4.2.2.4. Hypophysitis

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.3.4.2.2.5. Hyperthyroidism or Hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Grade 2 hyperthyroidism and Grade 2, 3 and 4 hypothyroidism events:

For hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy.

- For hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

Grade 3-4 hyperthyroidism

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.3.4.2.2.6. Hepatic Events

For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

- Treat with IV or oral corticosteroids.

For Grade 3-4 events,

- Treat with intravenous corticosteroids for 24 to 48 hours.

Monitor liver function tests more frequently until returned to baseline value (consider weekly). When symptoms improve to Grade ≤1, a steroid taper should be started and continued over no less than 4 weeks.

5.3.4.2.2.7. Renal Failure or Nephritis

- For Grade 2 events, treat with corticosteroids.

- For Grade 3-4 events, treat with systemic corticosteroids.

When symptoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks.

5.3.5. Dosing Interruptions

See Table 8 for AEs that require dosing interruptions for crizotinib, respectively.

Appropriate follow-up assessments should be done until adequate recovery as assessed by the investigator.

Doses may be held as needed until toxicity resolution as described in Section 5.3.4.2 (Table 8). Depending on when the AE resolved, an interruption of crizotinib treatment may lead to the patient missing all subsequent planned doses within that same cycle or even to delayed initiation of the subsequent cycle.

If pembrolizumab is to be held according to toxicities described in Section 5.3.4 (Table 8), this will lead to a delay in the initiation of the subsequent cycle or dose modification according to Table 5.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing of crizotinib in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. Dose modification for pembrolizumab will only involve an increase in the time between infusions and will follow the recommendations in Table 8 as the dose pembrolizumab cannot be modified. If the crizotinib dose reduction occurs during the cycle, the patient will need to return to the clinical site to receive a new bottle of crizotinib drug supply.

5.3.6. Pembrolizumab Dosing Delays

Pembrolizumab dosing delays should follow the recommendations in Table 8. If the adverse events are due to crizotinib (per investigator assessment), pembrolizumab may be continued according to the aforementioned tables. If the adverse events are due to pembrolizumab (per investigator assessment), crizotinib may be continued according to the aforementioned tables.

5.3.7. Crizotinib Dosing Reductions

Following dosing interruption or cycle delay due to toxicity, the crizotinib dose may need to be reduced when treatment is resumed. See Table 7 and Table 8 for guidelines.

5.4. 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 email a complete Registration Form to the designated sponsor study team member. The sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other study-related documentation or correspondence referencing that patient and email to the site.

No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- confirmation of the patient's enrollment;
- specification of the dose level for that patient; and
- 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.

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label.

Storage conditions stated in the single reference safety document (SRSD) (eg. IB) will be superseded by the storage conditions stated in the labeling.

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 the study. Even for continuous monitoring systems, a log or site procedure that 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 the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the proper storage requirements for crizotinib.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. Crizotinib must be returned to the investigator by the patient.

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatments

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the investigator.

All concomitant treatments, blood products, as well as non-drug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

Concurrent anticancer therapy with agents other than crizotinib and pembrolizumab is not allowed.

5.7.1. Prohibited Medications When Using Crizotinib

The metabolism of crizotinib is predominantly mediated by the CYP3A isozymes in human liver microsomes and hepatocytes. Coadministration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of crizotinib in humans. The concurrent use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, telithromycin, troleandomycin, saquinavir, voriconazole, and grapefruit or grapefruit juice, are not allowed in the study. The topical use of medications, such as 2% ketoconazole cream, may be allowed when discussed with the Sponsor. The concurrent use of potent CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, are not allowed in the study.

Coadministration of crizotinib with CYP3A4 substrates with narrow therapeutic indices including, but not limited to, dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (* withdrawn from U.S. market) must be avoided from the time of the first dose of crizotinib until treatment discontinuation.

Additionally, the concurrent use of non prescription drugs, complementary medicines (excluding vitamins) or herbal supplements is not recommended.

5.7.2. Prohibited Medications When Using Pembrolizumab

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

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab.
- Radiation therapy (see Section 5.7.3).
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Note: Inhaled steroids are allowed for management of asthma.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.7.3. 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.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study enrollment and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression.

5.7.4. Hematopoietic Growth Factors

Primary use of granulocyte-colony stimulating factors (G-CSF) or erythropoietin/darbopoietin is not permitted during Cycles 1 and 2 of the Dose Finding Phase (the DLT evaluation period). G-CSF may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines. If approved and available for use per country regulations, erythropoietin or darbopoeitin may be used at the investigator's discretion for the supportive treatment of anemia in both the Dose Finding and Dose Expansion Phases.

5.7.5. Anti-Emetic, Anti-Diarrheal Therapy

Supportive care including premedication with anti-emetics to limit treatment-related nausea and vomiting should be considered as consistent with the IBs of crizotinib and pembrolizumab, respectively, and local standards of care. Patients may receive prophylaxis against treatment-induced diarrhea for crizotinib or pembrolizumab.

All patients with diarrhea should be advised to increase oral intake of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. In particular, for pembrolizumab, patients should be carefully monitored for colitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and for bowel perforation (such as peritoneal signs and ileus). Colitis may be related to crizotinib, pembrolizumab or both. The recommended therapy for colitis is described in Table 8.

5.7.6. Other Concomitant Medications

Anti-inflammatory or narcotic analgesics may be offered as needed. Due to the AE of hypothyroidism from pembrolizumab, patients in this study may be supported with appropriate hormone replacement therapy for hypothyroidism and monitored for any changes in thyroid function.

Bisphosphonate therapy for metastatic bone disease is permitted. Bisphosphonate therapy should be given as per local medical practice.

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

The concurrent use of crizotinib with other bradycardic agents, medicinal products that are known to prolong the QT interval, and/or antiarrhythmics should be avoided.

5.7.7. Surgery

5.7.7.1. Crizotinib Guidelines

The effect of crizotinib on wound healing is not known and has not been investigated; therefore, caution is advised on theoretical grounds (potential antiangiogenic effect). In the event elective surgery is necessary during study participation, crizotinib dosing should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery.

5.7.7.2. Pembrolizumab Guidelines

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy such as elective surgery, unrelated medical events, patient vacation and holidays. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for the interruption should be documented..

5.7.8. Pembrolizumab Infusion Reaction

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion Table 9 below shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.

Table 9. Pembrolizumab Infusion Reaction Treatment Guidelines

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 patients 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 hour (±30 minutes) prior to infusion of pembrolizumab 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		

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see Schedule of Activities and ASSESSMENTS section (Table 1 and Table 3 and Section 7).

6.1.1. Mandatory Tumor Biospecimen

Provision of an archival tumor tissue biospecimen is mandatory for all patients, including patients in either the Dose Finding or the Dose Expansion Phases. The archived tumor tissue specimen may be from either a primary or a metastatic lesion, and may represent tissue obtained at the time of, or subsequent to, the initial diagnosis. The most recently obtained archival tissue is preferred.

Archived tumor tissue should be provided as a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block containing sufficient tumor tissue to allow if possible for fifteen (15) slides each containing a 5-micron tissue section. If a tissue block cannot be provided, sites should try to obtain 15 unstained slides each containing a 5-micron tissue section cut serially from the same block. If archived FFPE tissue is not available, every effort should be made to collect a *de novo* (ie, fresh) tumor sample in accordance with local institutional practice for tumor biopsies. Archived or *de novo* tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted (see Section 7.3.1). Additional information on tumor tissue specimen collection procedures is included in the study laboratory manual. Acquisition of the mandatory tumor tissue can be completed outside the 28-day screening window.

6.2. Study Period

For treatment period procedures, see Schedule of Activities and ASSESSMENTS section (Table 1**,** Table 3**,** Table 2 **and** Table 4).

6.3. End of Treatment/Withdrawal and Follow-up Visit

For follow-up procedures see Schedule of Activities and ASSESSMENTS section (Table 1 and Table 3 and Section 7).

At least 28 days but no more than 35 days after the last dose of study treatment, patients will return to undergo review of concomitant medications, vital signs, body weight, and assessment of resolution of any treatment-related toxicity. Any toxicity that continues should be followed at least every 4 weeks until resolution or or new anticancer therapy is started. Any irAEs should be reported to the Sponsor up to 12 months after the last dose of pembrolizumab, or until a new immunologic therapy is started.

Hematology, Blood Chemistry, and Urinalysis: Required tests are listed in Appendix 1 of protocol.

Where possible, laboratory tests should be performed preferably at the clinical site's local laboratory, and, when not possible, patients will provide the laboratory test results copy (from the non-clinical site laboratory) by telephone and bring a copy of the laboratory test results at the next cycle visit; process depends on local medical practice. The copy of the laboratory test results must be retained in the patient's file at the clinical site for documentation purposes.

If ALT or AST becomes Grade ≥3 or ALT or AST Grade ≥2 and total bilirubin Grade ≥2, then liver function tests need to be repeated every 48-72 hours until ALT/AST and total bilirubin recover to Grade <2.

Patients will be followed for post-study survival every 2 months until death or until 18 months after enrollment of the last patient, whichever occurs first. Collection of information on subsequent anti-cancer therapy and the patient's disposition by telephone is acceptable.

Once the primary endpoint for the study has been summarized and reported, ongoing patients on single-agent crizotinib will only need to visit the clinic every other cycle for study assessments instead of every cycle. Hematology and blood chemistry tests are still required in the non-visit cycle ie, approximately 3 weeks after previous laboratory testing. Enough study medication until the next clinic visit will be dispensed at each clinic visit. During the non-visit cycle, patients must telephone the clinical site to provide an update of AEs and concomitant medications, and to provide results of the laboratory tests.

6.4. Patient Withdrawal

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

Reasons for withdrawal of study treatment may include:

- Objective disease progression; unless the patient is considered to be deriving clinical benefit by the investigator;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Refusal of 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;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Telephone contact is acceptable. 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 that the patient return all unused crizotinib capsules, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

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

7.1. Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examinations, ECGs, laboratory assessments, including pregnancy tests and verification of concomitant treatments. For details, refer to the SOA –Table 1, Table 3**,** Table 2 **and** Table 4.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment; once at the start of screening and once at the

baseline visit, immediately before investigational product administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a further negative pregnancy test 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 treatment cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnacy test, the patient will be withdrawn from administration of investigational product and will be withdrawn from the study.

Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

7.1.2. Adverse Events

Assessment of adverse events 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.

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

7.1.2.1. Events of Clinical Interest (ECI): Pembrolizumab

Events of clinical interest (ECI) are non-serious and serious adverse events that may or may not be irAEs. Information on how to identify and report ECIs can be found in the Study Reference Manual.

Events of clinical interest for this trial include:

1. An overdose of Sponsor's product, as defined in Section 5.3, Administration, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT values that is ≥3X the upper limit of normal and an elevated total bilirubin value that is ≥2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is <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 Study Reference Manual (or equivalent).

A separate guidance document has been provided entitled “MK-3475 Events of Clinical Interest and Immune-Related Adverse Event Guidance Document”. This guidance document can be found in the Study Reference Manual 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.

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 indicated a possible immune-related ECI then additional testing should be performed to rule out other etiologic causes. If no other cause was 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 pembrolizumab 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 of the investigator awareness of the event see Section 8.14. Reporting Requirements. Sponsor Contact information can be found in the Study Reference Manual.

7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the SOA (Table 1 and Table 3) and analyzed at local laboratories.

Hematology	**Chemistry**	**Coagulation**	**Urinalysis**	**Pregnancy Test**
Hemoglobin	ALT	PT or INR	Urine dipstick including urine protein or urine blood at screening only. If positivie collect a microscopic (Reflex testing)	For female patients of childbearing potential, serum or urine (to be specified in the protocol)
Platelets	AST	PTT		
WBC	Alk Phos			
Absolute Neutrophils	Sodium			
Absolute Lymphocytes	Potassium			
Absolute Monocytes	Magnesium			
Absolute Eosinophils	Chloride			
Absolute Basophils	Total Calcium			
	Total Bilirubin***			
	BUN or Urea			
	Creatinine			
	Uric Acid			
	Glucose (fasted or non-fasted)			
	Albumin			
	Phosphorous or Phosphate			
	Thyroid Function Tests: TSH, T3, and Free T4			

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

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examinations to include body weight, vital signs, ECG assessments, and height; height will be measured at baseline only.

7.1.5. ECOG Performance Status

ECOG performance status will be performed at baseline and on Day 1 of each study cycle.

7.1.6. (12-Lead) Electrocardiogram

All patients require a single ECG measurement at screening. Triplicate ECGs measurements (approximately 2 minutes apart) will be measured at all other time points with all 3 measurements obtained within a 10 minute time window for each timepoint. ECGs should be performed immediately before PK blood draws at respective time points. See Schedule of Activities Table 1 and Table 3 for more details. Additional ECGs will be performed as clinically indicated

7.2. Pharmacokinetics Assessments

Plasma/serum samples will be obtained from patients for PK analysis of crizotinib, the crizotinib metabolite PF-06260182, pembrolizumab and anti-pembrolizumab-antibodies depending on the treatment cohort that they belong to. Serum samples for pembrolizumab PK[CCI] will be collected from all patients in the study. Plasma samples for crizotinib PK will be collected from all patients in the Dose Finding Phase and at least 8 patients in the Dose Expansion Phase. The PK sampling schedule may be modified based on emerging PK data.

7.2.1. Blood Sample Collection for Pharmacokinetic[CCI] Analysis

Where noted in the Schedule of Activities (SOA – Table 1 and Table 3), blood samples will be collected at approximately the same time as other assessments wherever possible.

Blood samples for crizotinib and PF-06260182 PK, pembrolizumab PK,[CCI] will be collected as outlined in Table 2 and Table 4.

Table 2 indicates PK blood sampling time points for crizotinib given in combination with pembrolizumab at DL0, DL-2, and DL-3. For DL-1 Table 4 indicates PK blood sampling time points for when crizotinib is administered alone and in combination with pembrolizumab. On the days of crizotinib PK sample collection, patients should be instructed to hold morning crizotinib dosing until the pre-dose sample has been drawn. For all collections, the actual time of crizotinib and pembrolizumab dosing, as well as actual times of PK collections will be recorded in the source documents and CRF.

In addition to samples collected at the scheduled times, additional blood samples for crizotinib concentrations and pembrolizumab concentrations[CCI] should be collected from patients experiencing unexpected and/or SAEs. The date and time of sample collection and of last dosing prior to PK collection should be documented in the CRF. 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 complaint, 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 collection may be rescheduled with agreement of the clinical investigator, patient, and Sponsor.

PK samples will be assayed for crizotinib, PF-06260182, pembrolizumab [redacted] using validated analytical method in compliance with Pfizer standard operating procedures. Additional details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual. As part of the understanding of the pharmacokinetics of the study drug, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for crizotinib, pembrolizumab, [redacted]

7.2.2. Collection of Crizotinib PK Samples

At each crizotinib time point, a 3 mL whole blood sample will be collected into an appropriately labeled K_2EDTA tube to provide a minimum of 1 mL plasma for pharmacokinetic analysis.

7.2.2.1. Processing, Storage and Shipment of Crizotinib PK Samples

Special precaution should be taken to minimize crizotinib samples from exposure to visible light, which will cause rapid degradation of crizotinib. The blood collection tube should be covered completely immediately after sample collection. Gently invert the covered tube 8-10 times to mix the blood with the anticoagulant. Place the tube in an ice bath (2°C to 8°C) until sample can be centrifuged. Centrifuge for 10 to 15 minutes at 1700 x g at 4°C or lower to separate the plasma. Plasma should be transferred rapidly to an amber cryovial, with the collection tube covered during the plasma transfer. Place plasma aliquot in an ice bath (2°C to 8°C) until frozen storage. Harvested plasma should be frozen within 1 hour of collection at -20°C or lower in an opaque box to protect from light exposure. If a sample is inadvertently exposed to light (for at least 5 minutes), the sponsor should be notified so that the sample can be flagged for possible spurious results. Once frozen, samples should not be allowed to thaw until assayed.

7.2.3. Collection of Pembrolizumab Pharmacokinetic Samples

At each pembrolizumab timepoint, a 3 mL whole blood sample will be collected into an appropriately labeled Serum Separator Tube (SST) tube to provide a minimum of 1 mL serum for PK analysis.

7.2.3.1. Processing, Storage and Shipment of Pembrolizumab PK Samples

PK sample collection must be from the opposite arm to that used for pembrolizumab infusion. If pembrolizumab was administered via a central venous catheter, the sample collection should be from a different site. Collect 3 mL of blood into a 3.5 mL SST at the designated collection timepoints. The tube should be inverted 5-6 times without shaking. Leave the tube upright at room temperature for 30 minutes but less than 60 minutes to allow coagulation. Centrifuge for 10 to 15 minutes at 1100 to 1300 x g at room temperature until clot and serum are separated. Serum should be aliquoted equally into 2 polypropylene cryovials (at least 0.5 mL per aliquot). Place serum aliquot in an ice bath (2°C to 8°C) until frozen storage. Serum samples should be frozen within 30 minutes of centrifugation at –70°C or colder (alternatively –20°C is acceptable for up to 1 month) and maintained in the frozen state until assayed.

CCI

7.3. Pharmacodynamic Assessments

CCI

7.3.1. Archival Tumor Tissue and Optional *De Novo* End of Treatment Tumor Biopsies

CCI [redacted]

Specifically, tumor expression of PD-L1 will be measured by anti-PD-L1 IHC. CCI [redacted]

The optional end-of-treatment tumor biopsy will also be used to investigate the biomarkers described above with the objective being to determine change from pre-treatment baseline to begin to define potential mechanisms of resistance to treatment with the combination of crizotinib and pembrolizumab.

CCI [redacted]

[redacted]

7.4. Tumor Response Assessments

Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline, then at Week 9 , and every 6 weeks, thereafter, using RECIST v 1.1 (See SOA – Table 1 and Table 3). In addition, radiological tumor assessments will also be conducted to confirm a best response of CR or PR at ≥4 weeks after initial assessment of response, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not performed in the previous 6 weeks). In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions and new lesions according to RECIST v 1.1 (see Appendix 6). The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

If radiologic imaging shows PD and the patient is perceived to be experiencing clinical benefit, repeat tumor assessment is to be performed ≥4 weeks later in order to confirm tumor status; study treatment may be continued at the investigator's discretion.

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

CCI

[redacted]

[redacted]

[redacted]

7.6. Patient-Reported Outcomes

Patient-reported lung cancer specific disease/treatment-related symptoms, functioning and global quality of life will be assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30),[69, 70] and its corresponding module for lung cancer (QLQ-LC13).[71] The visual disturbances experienced by the patient will be characterized using the visual symptom assessment questionnaire (VSAQ-ALK).

Patients will complete the EORTC QLQ-C30, the QLQ-LC13 and VSAQ-ALK on Cycle 1 Day 1 (baseline) and Day 1 of each subsequent cycle until End of Treatment/Withdrawal

The EORTC QLQ-C30, QLQ-LC13 and VSAQ-ALK should be completed by patients prior to any testing, treatment, or discussion with the physician or clinic personnel.

7.6.1. EORTC QLQ-C30 and QLQ-LC13

The EORTC QLQ-C30 (Version 3.0) and the QLQ-LC13 module (Appendix 3 and Appendix 4, respectively) are validated and reliable self-report measures.[69, 70, 71] The EORTC QLQ-C30 consists of 30 questions which assess 5 functional domains (physical, role, cognitive, emotional, and social domains); global quality of life and disease/treatment-related symptoms (fatigue, pain, nausea and vomiting, dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea).[69, 70, 71]

The QLQ-LC13 consists of 1 multi-item scale and 9 single items that assess the specific symptoms (dyspnea, cough, hemoptysis, and site specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of lung cancer patients receiving chemotherapy.[71] The EORTC QLQ-C30 and the QLQ-LC13 module require about 15 minutes to complete and are available in many languages.

7.6.2. VSAQ-ALK

The VSAQ-ALK is a self-report measure that was developed to assess and better understand the visual symptoms that some patients reported experiencing upon starting treatment in a crizotinib monotherapy trial (Appendix 5). These visual symptoms may include the appearance of overlapping shadows and after images; shimmering, flashing or trailing lights; strings, streamers, or floaters; as well as hazy or blurry vision. The VSAQ-ALK consists of 7 items which assess the frequency, duration, bother, and impact of visual disturbances on

activities of daily living. Translation of the VSAQ-ALK into different languages is available. However, if the VSAQ-ALK is not available in the patient's preferred language, the patient does not need to complete this assessment. The VSAQ-ALK should take less than 5 minutes to complete.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious 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 28 calendar days after the administration of crizotinib or 90 calendar days after the last administration of pembrolizumab, whichever is later, and before initiation of a new anti-cancer treatment. The prolonged follow-up is due to the pharmacokinetic properties of pembrolizumab. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

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

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

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 product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

- Medication errors involving patient exposure to the investigational product(s);
- 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 is captured on the medication error version of the AE page and, if applicable, any associated adverse event(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

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

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

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

8.6. Serious Adverse Events

A Serious Adverse Event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see Section 8.8 Severity Assessment).

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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 the Section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

Concurrent with:

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

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see Section 8.14 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 both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

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

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

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

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on anSAE 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 baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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

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

Additional information regarding the EDP 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 AE.

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

8.12. Withdrawal Due to Adverse Events (See also the Section on Patient Withdrawal (Section 6.4))

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

When a patient withdraws because of 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 or legally acceptable representative. In addition, each study patient or legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

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

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

8.14.3. Sponsor's 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 study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis sets

The following patient populations will be assessed:

- Safety analysis population: includes all enrolled patients who receive at least 1 dose of crizotinib or pembrolizumab. This will also be the primary population for the efficacy endpoints of PFS and OS.

- DLT-evaluable population: includes all patients enrolled in the Dose Finding Phase who are in the safety analysis population, and either experience DLT during the first 2 cycles, or complete the observation period for the first 2 cycles of treatment. Patients who do not receive at least 80% of the planned first 2 cycles of crizotinib dosing or both infusions of pembrolizumab within the DLT observation period due to reasons other than treatment-related AEs will not be evaluable for DLT.

- Response-evaluable population: includes all patients in the safety analysis population who have an adequate baseline tumor assessment. This will be the primary population for the efficacy endpoints of ORR, DR and TTR.

- PK analysis population: includes all patients in the safety analysis population who have sufficient concentration data to estimate at least 1 of the PK parameters of interest.

- PRO-evaluable population: includes all patients in the safety analysis population who have completed the patient reported questionnaires both at baseline and at least 1 on-treatment assessment.

- CCI [redacted]

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose De-escalation/Re-Escalation: mTPI

Many alternative designs have been proposed to the standard 3+3 design for Phase 1 dose escalation studies that improve its accuracy, efficiency and statistical validity.

The mTPI design[72] uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target probability (p_T) rate ($p_T = 0.30$). If the toxicity rate of the currently used dose level is far smaller than p_T, the mTPI will recommend escalating the dose level; if it is close to p_T, the mTPI will recommend continuing at the current dose; if it is far greater than p_T, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model.

Being a model-based design, mTPI automatically and appropriately tailors dose re-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose re-escalation/de-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a 2-way table (see Table 6). Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement. Recently, a phase 1 study based on the mTPI design has been published.[73]

Decision rules are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as $(0; p_T\text{-}e_1)$, the over-dosing interval (p_T+e_2), and the proper-dosing interval $(p_T- e_1, p_T+ e_2)$, where e_1 and e_2 are small fractions. Based on the safety profile of crizotinib and pembrolizumab, e_1 is selected as 0.05, and e_2 is selected as 0.03. Therefore, the target interval for the DLT rate is (0.25, 0.33).

The 3 dosing intervals are associated with 3 different dose-escalation decisions. The under-dosing interval corresponds to a dose re-escalation (RE), over-dosing corresponds to a dose de-escalation (D), and proper-dosing corresponds to staying at the current dose (S). Given a dosing interval and a probability distribution, the UPM of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the 1 with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the under-dosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Ji et al.[72] have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

The Dose Finding Phase of the trial is completed when 10 DLT-evaluable patients have been treated at the highest dose associated with a DLT rate <0.33. For this reason, a modification has been applied to the original mTPI decision algorythm so that if 4 DLTs are observed at any dose level, that dose level is considered unacceptable and never used again in the remainder of the study since 4/10 patients with DLTs would be a ≥33% rate. In addition, a further modification will allow re-escalatation and exposure of up to 10 patients at the higher dose in case of ≤3 out of 10 patients experience DLTs.

In case a de-escalation is required from the initial starting DL0, it is estimated that approximately up to 30 DLT-evaluable patients will need to be enrolled to estimate MTD.

9.2.2. Statistical Method for Estimating the MTD

As previously described in Section 9.2.1, the estimated MTD is the highest tested dose level with DLT rate <0.33 in 10 DLT-evaluable patients. It is unknown whether higher doses of either crizotinib or pembrolizumab result in higher toxicity rates. But, due to the relatively low number of patients that may be potentially allocated to any dose combination, this assumption may be violated.

For example, at the end of the study, the dose combination (crizotinib 200 mg BID, pembrolizumab 200 mg Q3weeks) may have a higher proportion of DLTs than, say, (crizotinib 250 mg BID, pembrolizumab 200 mg Q3weeks), and this variability may be simply related to small cohort size alone. To overcome this potential problem, a bivariate isotonic regression is used to smooth the resulting toxicity surface to a monotonically increasing one. The determination of the MTD contour is accomplished using the Dykstra-Roberston algorithm.[73] Once a monotonically increasing toxicity surface is obtained (either observed or smoothed according to the bivariate isotonic regression algorithm), the MTD combinations closest to the targeted DLT rate of 0.30 but still <0.33 are calculated. Clinical judgment will be exercised in taking forward combinations to the Dose Expansion Phase, in case no clear choice exists between more than 1 competing MTD combination. While the limited sample size may result in up to 2 dose combinations of equal potential anti-tumor activity, under the circumstances of this study, likely only 1 will be chosen for the Dose Expansion Phase. This decision will be based upon the combination of data related to safety, available antitumor activity, and clinical judgment of the investigators and the Sponsor

9.3. Sample Size Determination

The sample sizes planned for the study arise from logistic feasibility and past experience with Phase 1b studies in Oncology and are not entirely driven by statistical considerations. It is expected that approximately 70 patients will be required to achieve all study objectives.

As far as the Dose Finding Phase of this study is concerned, due to the dynamic nature of the Bayesian allocation procedure, the sample size of the “Up-and-Down” matrix design using the mTPI approach cannot be determined in advance. It is estimated that 30 DLT evaluable patients will be enrolled in the dose escalation stage in order to have a reliable and accurate estimate of the MTD and determine the RP2D.

Subsequent patients will then enter the Dose Expansion Phase aimed at evaluating safety, antitumor activity and PK at the MTD.

The planned sample size for the Dose Expansion Phase is 50 patients (including 10 patients from the Dose Finding Phase of the study treated at the MTD). Fifty patients will allow to test the hypothesis that the true 18-month PFS probability is ≥50% vs. 32% for historical control (data from the crizotinib arm of Study 1014[8]) with 85% power, an alpha = 0.05 (1-sided), and based on normal approximation.

9.4. Efficacy Analysis

Efficacy analyses will be presented in the form of statistical summaries and data listings for the Dose Expansion Phase (including the 10 patients from the Dose Finding Phase of the study treated at the MTD). For the Dose Finding Phase only data listings will be presented. PFS and OS will be analyzed in the safety analysis population, whereas ORR will be determined in the response-evaluable population, and DR and TTR will be assessed in the subgroup of responding patients.

PFS is defined as the time from the date of the first dose of crizotinib or pembrolizumab to first documentation of objective disease progression or to death due to any cause, whichever occurs first. Six, 12, and 18-month PFS probabilities are defined as the probabilities of being alive and progression free at 6, 12 and 18 months, respectively, after the first dose of the combination treatment based on the Kaplan-Meier estimate.

OS is defined as the time from the date of first dose of crizotinib or pembrolizumab to the date of death due to any cause. Twelve and 18-month survival probabilities are defined as the probabilities of survival at 12-months and 18-months, respectively, after the first dose of the combination treatment based on the Kaplan-Meier estimate.

ORR is defined as the percent of patients with confirmed CR or PR according to RECIST v1.1 relative to the response-evaluable population. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation of response.

DR is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of objective disease progression or to death due to any cause, whichever occurs first.

TTR is defined as the time from the date of first dose of crizotinib or pembrolizumab to first documentation of objective tumor response (CR or PR) that is subsequently confirmed

PFS, OS, and DR will be analyzed by the Kaplan-Meier method while TTR will be summarized with descriptive statistics. Best overall response (BOR) will be summarized and ORR will be calculated along with the corresponding exact 2-sided 95% confidence intervals using the exact method based on the F-distribution.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Pharmacokinetic Analysis of Crizotinib and Pembrolizumab

Standard plasma PK parameters for crizotinib will be estimated using non-compartmental analysis. For crizotinib, standard PK parameters will include; C_{max}, T_{max}, C_{trough}, AUC_{0-8}, AUC_{tau} , and oral plasma clearance (CL/F). For PF-06260182 PK parameters will include; C_{max}, T_{max}, C_{trough}, AUC_{0-8}, AUC_{tau}, $MRAUC_{tau}$, and MRC_{max}. Descriptive statistics for the PK parameters for crizotinib and PF-06260182 will be provided by dose level, cycle and day of assessment in tabular form.

All plasma/serum concentrations will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by dose level, cycle, day and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose level, cycle and day using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

Trough concentrations for pembrolizumab will be plotted for each dose using a box-whisker plot by cycle and day in order to assess the attainment of steady-state.

In addition, Non-linear Mixed Effects Modeling (NONMEM) approaches will be explored to further describe the PK profile of pembrolizumab in combination with criztoinib(See also Section 9.5.1.4).

9.5.1.2. Effect of Pembrolizumab on Crizotinib Pharmacokinetics

For DL-1, the effect of pembrolizumab on crizotinib PK will be evaluated using steady-state crizotinib AUC_{tau} and C_{max} after crizotinib is administered as a single agent (Cycle -1 Day 15, Reference) and in combination with pembrolizumab (Cycle 6 Day 1, Test), respectively, as the primary pharmacokinetic parameters. The AUC_{tau} and C_{max} will be log transformed and analyzed using a mixed effect model with treatment as the fixed effect and patient as the random effect. Ninety percent confidence interval for the ratio of geometric means of AUC_{tau} and C_{max} (crizotinib + pembrolizumab/ crizotinib alone) will be computed to assess the effect magnitude.For the other dose levels that do not incorporate a crizotinib lead-in period, the effect of repeated pembrolizumab doses on crizotinib PK will be evaluated by comparing the steady-state crizotinib and PF-06260182 PK to that observed in prior single-agent crizotinib studies.

CCI [redacted]

CCI [redacted]

[redacted]

9.5.2. Analysis of Patient-Reported Outcomes

The PRO-evaluable population will be the primary population for the analysis of PROs. Change from baseline scores over treatment will be evaluated in the PRO evaluable population.

At each time point, the number and percentage of patients who completed the QLQ-C30, QLQ-LC13 and VSAQ-ALK will be summarized. A questionnaire is considered complete if at least 1 item was answered by the patient. Scoring and handling of missing data for the EORTC QLQ-C30 and QLQ-LC-13 was implemented in line with the scoring manual.[72] Summary statistics (mean, standard deviation, median, range, and 95% CI) of actual scores and change from baseline at each time point will calculated for all scales of the EORTC QLQ-C30 and QLQ-LC13 scores. The number and proportion of patients who improved, worsened, or remained stable as compared to baseline will also be summarized for all of the symptom and functional domains, global QOL, and single items of the EORTC QLQ-C30 and QLQ-LC-13. If less than half of the constituent items on the QLQ-C30 and QLQ-LC13 have been answered for a multi-item subscale, that subscale will be considered missing. Single-item subscales will be considered missing if the constituent item is incomplete. For the VSAQ-ALK questions not answered will be considered missing items and will not be utilized.

Frequency analyses will be performed and reported for each item of the VSAQ.

CCI [redacted]

9.6. Safety Analysis

Summaries and analyses of the primary safety endpoint will be based on the DLT-evaluable analysis population. All other summaries and analyses of safety parameters will be based on the safety analysis population. Safety data will be summarized by dose level using appropriate tabulations and descriptive statistics (pooling together patients treated at the

MTD from both phases of the study). If applicable, safety data collected during the crizotinib lead-in period for patients who are treated at DL-1 will be reported separately.

9.6.1. Primary Endpoint Analysis

The occurrence of DLTs observed in the Dose Finding Phase will be used to estimate the MTD as described in (Section 3.3 and Section 9.2.1). Adverse events meeting the DLT definition in Section 3.2 will be listed per dose level. The RP2D will be based upon a DLT rate <33% as well as the tolerance of the dose in the Dose Expansion Phase.

9.6.2. Secondary Safety Endpoint Analysis

9.6.2.1. Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the NCI CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on treatment-emergent AEs, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any treatment-emergent AE, treatment-emergent SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1, Cycle 2, and Cycles ≥2). In DL-1, the summaries will present AEs during the lead-in period, overall, and by cycle (Cycle 1, Cycle 2, and Cycles ≥2).

9.6.2.2. Laboratory Tests Abnormalities

The number and percentage of patients who experience laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests during the lead-in period (only applicable to DL-1), overall, and by cycle (Cycle 1, Cycle 2, and Cycles ≥ 2). Shift tables will be provided to examine the distribution of laboratory abnormalities.

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

9.6.3. Electrocardiograms

The analysis of ECG results will be based on data collected during the first 3 cycles in all patients except in DL-1 where ECG collection will be performed during the crizotinib lead-in period.

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

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's [QTcF; default correction], or Bazett's [QTcB]). Data will be summarized and listed for HR, RR interval, PR interval, QRS complex, QTcF and QTcB, and by dose level. Categorical analysis of the ECG parameters will be performed as follows:

- The number and percentage of patients with maximum increase from baseline in QTcF/QTcB (<30, 30- 60, and ≥60 ms).
- The number of and percentage patients with maximum post-dose QTcF/QTcB (<450, 450-<480, 480- <500, and ≥500 ms).
- PR changes from baseline ≥50% if absolute baseline value was <200 ms, and ≥25% if absolute baseline value was ≥200 ms.
- QRS changes from baseline ≥50% if absolute baseline value was <100 ms, and ≥25% if absolute baseline value was ≥100 ms.

Shift tables will be provided for baseline vs. worst on treatment for QTcF and QTcB using maximum CTCAE Grade.

9.6.4. Vital signs

Vital signs will be categorized according to the maximum/minimum change from baseline and/or according to the maximum/minimum values on treatment.

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 with medical and statistical capabilities 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 and laboratory test alterations, vital signs, and ECGs abnormalities observed at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and benefit/risk ratio to decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

During study conduct and/or after study completion, 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.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board /Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

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

12.3. Patient Information and Consent

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

When study data are 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 each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

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

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC 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, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, 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 or 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 patient or the patient's legally acceptable representative, before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

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

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

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 trial application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as the last patient last visit in the Dose Expansion Phase of the study.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of combination crizotinib and pembrolizumab 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 7 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), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product.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 of the results of the study (collectively, “Publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication 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 before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. 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.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

16. REFERENCES

1. Siegel R, Ma J, Zou Z, *et al*. Cancer statistics, 2014. *CA Cancer J Clin*. 2014; 64: 9-29.

2. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer. World Health Organization. http://globocan.iarc.fr.

3. Mallath MK, Taylor DG, Badwe RA, *et al*. The growing burden of cancer in India: epidemiology and social context. *Lancet Oncol*. 2014; 15: e205-12.

4. Yang G, Wang Y, Zeng Y, *et al*. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013; 381: 1987-2015.

5. Ou S-H I, Bartlett CH, Mino-Kenudson M, *et al*. Crizotinib for the treatment of *ALK*-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecularly targeted therapy in oncology. *The Oncologis*t. 2012; 17: 1351-75.

6. Shaw AT, Kim DW, Nagawa K, *et al*. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013; 368: 2385-94.

7. Crizotinib (PF-02341066) Investigator's Brochure. Current effective version.

8. Mok T, Kim D-W, Wu Y-L, *et al*. First-line crizotinib versus pemetrexed-cisplatin or pemetrexed-carboplatin in patients (pts) with advanced *ALK*-positive non-squamous non-small cell lung cancer (PROFILE 1014). *J Clin Oncol*. 2014 ; 32 : 5s (suppl ; abstr. 8002).

9. Galluzzi L, Senovilla L, Zitvogel L, *et al*. The secret ally: immunostimulation by anticancer drugs. *Nat Rev Drug Discovery*. 2012; 11: 215-33.

10. Talmadge JE, Donkor M and Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. *Cancer Metastasis Rev*. 2007; 26: 373-400.

11. Usubütün A, Ayhan A, Uygar MC, *et al*. Prognostic factors in renal cell carcinoma. *J Exp Clin Cancer Res*. 1998; 17: 77-81.

12. Garon EB, Balmanoukian A, Hamid O, *et al*. Preliminary clinical safety and activity of MK-3475 monotherapy for the treatment of previously treated patients with non-small cell lung cancer (NSCLC). Abstr. 2416. International Association for the Study of Lung Cancer. 15th World Conference on Lung Cancer. 27-30 October 2013.

13. Ji Y, Liu P, Li Y, and Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clinical Trials. 2010;7:653-63.

14. Raaschou-Nielsen O, Andersen ZJ, Beelen R, *et al*. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol*. 2013; 14: 813-22

15. Fukuoka M, Wu Y-L, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer is Asia (IPASS). J Clin Oncol. 2011; 29: 2866-74.

16. Rosell R, Bivona TG and Karachaliou N. Genetics and biomarkers in personalisation of lung cancer treatment. Lancet. 2013; 382: 720-31.

17. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicenter, open-label, randomised phase 3 trial. Lancet Oncol. 2012; 13: 239-46.

18. Sequist LV, Yang J C-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013; 31: 3327-34.

19. Wu Y-L, Zhou C, Hu C-P, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014; 15: 213-22.

20. Pan H, Liu R, Li S, et al. Effects of icotinib on advanced non-small cell lung cancer with different EGFR phenotypes. Cell Biochem Biophys. 2014; doi 10.1007/s12013-014-9955-y.

21. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007; 448: 561-6.

22. Inamura K, Takeuchi K, Togashi Y, et al. EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. Mod Pathol. 2009; 22: 508-15.

23. Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res. 2008; 14: 4275-83.

24. Shinmura K, Kageyama S, Tao H, et al. EML4-ALK fusion transcripts, but no NPM-, TPM3-, CLTC-, ATIC-, or TFG-ALK fusion transcripts, in non-small cell lung carcinomas. Lung Cancer. 2008; 61: 163-9.

25. Choi YL, Takeuchi K, Soda M, *et al*. Identification of novel isoforms of the EML4-ALK transforming gene in non-small cell lung cancer. *Cancer Res*. 2008; 68: 4971-6.

26. Takeuchi K, Choi YL, Soda M, *et al*. Multiplex reverse transcription-PCR screening for EML4-ALK fusion transcripts. *Clin Cancer Res*. 2008; 14: 6618-24.

27. Soda M, Takada S, Takeuchi K, *et al*. A mouse model for EML4-ALK-positive lung cancer. *Proc Natl Acad Sci USA*. 2008; 105: 19893-7.

28. Rikova K, Guo A, Zeng Q, *et al*. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell*. 2007; 131: 1190-1203.

29. Takeuchi K, Choi YL, Togashi Y, *et al*. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive cancer. *Clin Cancer Res*. 2009; 15: 3143-9.

30. Sundar R, Soong R, Cho B-C, *et al*. Immunotherapy in the treatment of non-small cell lung cancer. *Lung Cancer*. 2014; 85: 101-9.

31. Lynch TJ, Bondarenko I, Luft A, *et al*. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol*. 2012; 30: 2046-54.

32. Disis ML. Immune regulation in cancer. *J Clin Oncol*. 2010; 28: 4531-8.

33. Dong H, Strome SE, Salomao DR, *et al*. Tumor-associated B7-H1promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med*. 2002; 8: 793-800.

34. Sharpe AH and Freeman GJ. The B7-CD28 superfamily. *Nat Rev Immunol*. 2002; 2: 116-26.

35. Brown JA, Dorfman DM, Ma F-R, *et al*. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. *J Immunol*. 2003; 170: 1257-66.

36. Francisco LM, Sage PT and Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev*. 2010; 236: 219-42.

37. Thompson RH, Dong H, Lohse CM, *et al*. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clin Cancer Res*. 2007; 13: 1757-61.

38. Al-Shibli KI, Donnem T, Al-Saad S, *et al*. Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. *Clin Cancer Res*. 2008; 14: 5220-7.

39. Deschoolmeester V, Baay M, Van Marck E, *et al*. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. *BMC Immunol*. 2010; 11: 19.doi:10.1186/1471-2172-11-19.

40. Diez M, Pollán M, Enriquez JM, *et al*. Histopathologic prognostic score in colorectal adenocarcinomas. *Anticancer Res*. 1998; 18: 689-94.

41. Galon J, Costes A, Sanchez-Cabo F, *et al*. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science*. 2006; 313: 1960-4.

42. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. *Int J Clin Oncol*. 2010; 15: 544-51.

43. Nobili C, Degrate L, Caprotti R, *et al*. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. *Tumori*. 2008; 94: 426-30.

44. Hodi FS and Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. *J Cutan Pathol*. 2010; 37 (Suppl 1): 48-53.

45. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. *Lancet Oncol*. 2009; 10: 840-1.

46. Hillen F, Baeten CI, van de Winkel A, *et al*. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. *Cancer Immunol Immunother*. 2008; 57: 97-106.

47. Lee HE, Chae SW, Lee YJ, *et al*. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. *Br J Cancer*. 2008; 99: 1704-11.

48. Leffers N, Gooden MJ, de Jong RA, *et al*. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. *Cancer Immunol Immunother*. 2009; 58: 449-59.

49. Nishimura H, Honjo T and Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. *J Exp Med*. 2000; 191: 891-8.

50. Liotta F, Gacci M, Frosali F, *et al*. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. *BJU Int*. 2011; 107: 1500-6.

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

52. Rizvi NA, Garon EB, Patnaik A, et al. Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2014; 32: 5s (suppl; abstr. 8007)

53. Brahmer JR, Tykodi SS, Chow LQM, et at. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *New Engl J Med*. 2012; 366: 2455-65

54. Rizvi NA, Chow LQM, Borghaei H, et al. Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC. *J Clin Oncol*. 2014; 32: 5s(suppl; abstr. 8022)

55. Ou S-H I, Bang Y-J, Camidge DR, et al. Efficacy and safety of crizotinib in patients with advanced ROS1-rearranged non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2013; 31: suppl; abstr. 8032).

56. Camidge DR, Ou S-H I, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-Met-amplified non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2014; 32: 5s (suppl; abstr. 8001).

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

58. Gandhi L, Balmanoukian A, Hui R, *et al*. MK-3475 (anti-PD-1 antibody) for non-small cell lung cancer: antitumor activity and association with tumor PD-L1 expression. 2014 AACR presentation.

59. Pembrolizumab IB; Current effective version.

60. Pulford K, Falini B, Banham AH, *et al*. Immune response to the ALK oncogenic tyrosine kinase in patients with anaplastic large-cell lymphoma. *Blood*. 2000; 96: 1605-7.

61. Mussolin L, Damm-Welk C, Pillon M, *et al*. Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis. *Leukemia*. 2013; 27: 416-22.

62. Passoni L, Scardino A, Bartozzoli C, *et al*. ALK as a novel lymphoma-associated tumor antigen: identification of 2 HLA-A2.1 restricted CD8+ T-cell epitopes. *Blood*. 2002; 99: 2100-6.

63. Passoni L, Gallo B, Biganzoli E, *et al*. In vivo T-cell immune response against anaplastic lymphoma kinase in patients with anaplastic large cell lymphomas. *Haematologica*. 2006; 91: 48-55.

64. Ait-Tahar K, Barnardo MC and Pulford K. CD4 T-helper responses to the anaplastic lymphoma kinase (ALK) protein in patients with ALK+ ALCL. *Cancer Res*. 2007; 67: 1898-1901.

65. Ait-Tahar K, Damm-Welk C, Burkhardt B, *et al*. Correlation of the autoantibody response to the ALK oncoantigen in pediatric anaplastic lymphoma kinase-positive anaplastic large cell lymphoma with tumor dissemination and relapse risk. *Blood*. 2012; 115: 3314-9.

66. Chiarle R, Martinengo C, Mastini C, *et al*. The anaplastic lymphoma kinase is an effective oncoantigen for lymphoma vaccination. *Nat Med*. 2008; 14: 676-80.

67. Chiarle R. October 16, 2013, webcast. http://labroots.com/user/webinars/details/id/102.

68. Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European Organization for Research and Treatment QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993; 85: 365-76.

69. Aaronson NK, Cull AM, Kaasa S, *et al*. The European Organisation for Research and Treatment of Cancer (EORTC) modular approach to quality of life assessment in oncology: an update. *Quality of Life and Pharmacoeconomics in Clinical Trials*. 2nd Edition. Bert Spilker, Ed. Raven Press. New York. 1996. pp. 179-89.

70. Bergman B, Aaronson NK, Ahmedzai S, *et al*. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. *Eur J Cancer*. 1994; 30: 635-42.

71. Fayers P, Aaronson NK, Bjordal K, *et al*. *The EORTC QLQ-C30 Staging Manual*. 3rd Edition. European Organisation for Research and Treatment of Cancer. Brussels. 2001.

72. Fanale M, Fayad L, Pro B, *et a*l. Phase I study of bortezomib plus ICE (BICE) for the treatment of relapsed/refractory Hodgkin lymphoma. *British Journal of Haematol*. 2011; 154:284-6.

73. Dykstra R, Robertson T. An algorithm for isotonic regression for two or more independent variables. *Ann Stat.* 1982;10:708-716.

74. Poole, R.M., Pembrolizumab: First Global Approval. Drugs, 2014.

17. APPENDICES

Appendix 1. Required Laboratory Tests

	Conventional Units	Conversion Factor	SI Units
Hematology			
Hemoglobin (Hgb)	g/dL	x 10	g/L
Platelet count (Plt)	$10^3/mm^3$	x 10^9	10^{12}/L
White blood count (WBC)	$10^3/mm^3$	x 10^6	10^9/L
White blood cell differential	%	x 0.01	fraction
Chemistry			
Total bilirubin	mg/dL	x 17.1	µmol/L
Alanine aminotransferase (ALT)	U/L	N/A	U/L
Aspartate aminotransferase (AST)	U/L	N/A	U/L
Alkaline phosphatase	U/L	N/A	U/L
Total protein	g/dL	x 10	g/L
Albumin	g/dL	x 10	g/L
Sodium	MEq/L	x 1.0	mmol/L
Potassium	MEq/L	x 1.0	mmol/L
Chloride	MEq/L	x 1.0	mmol/L
Calcium	mg/dL	x 0.25	mmol/L
Phosphorus	mg/dL	x 0.323	mmol/L
Blood urea nitrogen (BUN)*	mg/dL	x 0.357	mmol/L
Urea*	Na	Na	mmol/L
Creatinine	mg/dL	x 88.4	µmol/L
Uric acid	mg/dL	x 0.059	mmol/L
Magnesium	mg/dL	x 0.41	mmol/L
Glucose	mg/dL	x 0.055	mmol/L
LDH	U/L	N/A	U/L
Urinalysis			
Microscopy and Dipstick for Protein/ Blood	(unitless)	N/A	(unitless)
For France only: FibroTest*	(unitless)	N/A	(unitless)
Coagulation			
Protime INR	(unitless)	N/A	(unitless)
* either/or			
In cases of suspected Drug-Induced Liver Injury (DILI) - values eventually to be reported on SAE form and eCRF AE page if appropriate			
Creatine kinase (aka CPK)	U/L	N/A	U/L
Indirect bilirubin	mg/dL	x 17.1	µmol/L
Direct bilirubin	mg/dL	x 17.1	µmol/L
Gamma-glutamyl transferase (GGT)	U/L	N/A	U/L
Acetaminophen level	µg/mL	6.62	µmol/L
Thyroid Functions			
TSH	µU/mL		
T3	Pg/dL		
Free T4	ng/dL		

* For France only, FibroTest: the FibroTest score is calculated from the results of the following blood tests: Alpha-2 macroglobulin, Haptoglobulin, Apolipoprotein A1, Gamma-glutamyl transpeptidase (GGT), Total bilirubin, and ALT.

Appendix 2. ECOG Performance Status

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

Appendix 3. EORTC QLQ-C30 Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4. EORTC QLQ-LC13 Questionnaire

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 5. Visual Symptom Assessment Questionnaire (VSAQ-ALK)

We would like to ask some questions about problems you may be experiencing with your eyesight. These problems are called visual disturbances and may include but are not limited to the appearance of the following: overlapping shadows or after images; shimmering, flashing or trailing lights; streamers, strings, or floaters in your peripheral vision; as well as hazy or blurry vision.

Please select the response that best applies to your experience of visual disturbances in the <u>past three weeks</u>.

1) In the past three weeks, have you experienced any visual disturbances?

☐ Yes If ***yes*** go to Question 2.

☐ No If ***no***, thank you and please return the questionnaire.

2) In the past three weeks, how often did you experience a visual disturbance?

☐ One day a week or less often.

☐ Two or three days a week.

☐ Four to six days a week.

☐ Seven days a week.

3) In the past three weeks, when did **you experience a visual disturbance? (Check <u>all</u> that apply)**

☐ Morning.

☐ Afternoon (from 12 PM -4 PM).

☐ Evening.

4) In the past three weeks, how long did each visual disturbance last on average? (Check only <u>one</u>)

☐ 30 seconds or less.

☐ More than 30 seconds but not longer than one minute.

☐ More than one minute but not longer than five minutes.

☐ More than five minutes but not longer than ten minutes.

☐ More than ten minutes.

☐ Don't remember.

5) In the past three weeks, how often did you experience a visual disturbance when adjusting to changes in lighting (eg, coming indoors on a bright sunny day)?

☐ Never.

☐ Rarely.

☐ Sometimes.

☐ Often.

☐ Always.

6) In the past three weeks, how much have you been bothered by. . . (Check <u>one</u> box on each line below):

		Did not experience	Not at all	A little	Moderately	Quite a bit	Extremely
a.	Visual disturbances?	☐	☐	☐	☐	☐	☐
b.	Appearance of overlapping shadows or after images?	☐	☐	☐	☐	☐	☐
c.	Appearance of shimmering, flashing, or trailing lights?	☐	☐	☐	☐	☐	☐
d.	Appearance of streamers, strings, or floaters?	☐	☐	☐	☐	☐	☐
e.	Difficulty seeing at night?	☐	☐	☐	☐	☐	☐
f.	Hazy or blurry vision?	☐	☐	☐	☐	☐	☐
g.	Difficulty adapting to bright lights (e.g., going out on a bright day)?	☐	☐	☐	☐	☐	☐
h.	Difficulty adapting to dim light (eg, entering a darkened room)?	☐	☐	☐	☐	☐	☐

7) During the past three weeks, how much did visual disturbances affect your ability to do your regular daily activities?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If visual disturbances affected your activities only a little, choose a low number. Choose a high number if visual disturbances affected your activities a great deal.

Consider only how much visual disturbances affected your ability to do your regular daily activities

Visual disturbances had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Visual disturbances completely prevented me from doing my daily activities

CIRCLE A NUMBER

Appendix 6. RECIST version 1.1 Tumor Assessment Criteria

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below (see Table 11):

Measurable Lesions

Lesions that can be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-Measurable Lesions

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥10 but <15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Special Considerations Regarding Specific Lesions

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

- If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as target lesions and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- **Complete Response (CR):** disappearance of all target lesions.
- **Partial Response (PR): at** least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered a sign of progression.
- **Stable Disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG-PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up.

- No FDG-PET at baseline and a positive FDG-PET at follow-up: if the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Confirmation of Tumor Response

Confirmation of response is required for non-randomized trials with primary endpoint of response, but is not required in randomized studies since the control arm serves as appropriate means of interpretation of data.

Determination of Overall Response by RECIST v1.1

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 11.

Table 11. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease,			
PD = progressive disease, and NE = inevaluable.			

Best overall response

The best overall response is determined once all the data for the patient is known. Best response in trials in which confirmation of complete or partial response is not required (ie, randomized trails) is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

When confirmation of CR and PR is required (ie, non-randomized trials with primary endpoint of response), the best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.