

THE LANCET **Oncology**

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mossé YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol* 2013; published online April 16. [http://dx.doi.org/10.1016/S1470-2045\(13\)70095-0](http://dx.doi.org/10.1016/S1470-2045(13)70095-0).

Supplementary material

Goals and Objectives

Primary Aims

- To estimate the maximum tolerated dose (MTD) and recommend a Phase 2 dose of PF-02341066 administered orally twice daily to children with relapsed/refractory solid tumors and anaplastic large cell lymphoma (ALCL).
- To define and describe the toxicities of PF-02341066 administered on this schedule.
- To characterize the pharmacokinetics of PF-02341066 in children with refractory cancer.

Secondary Aims

- To preliminarily define the anti-tumor activity of PF-02341066 within the confines of a Phase 1 study.
- To obtain initial Phase 2 data on the anti-tumor activity of PF-02341066 in children with relapsed/refractory neuroblastoma and ALCL.
- To preliminarily examine the relationship between ALK status (e.g, the presence of a mutation, duplication, amplification, and/or translocation) in patients with NB or ALCL and response to PF-02341066.
- To preliminarily examine the relationship between MRD status and clinical response to PF-02341066 in patients with ALCL.

Patient eligibility

Age: Patients must be > than 12 months and ≤ 21 years of age at the time of study enrollment.

Diagnosis:

- Part A1: Patients with relapsed or refractory solid tumors or ALCL (excluding patients with primary or metastatic CNS tumors or patients with primary cutaneous ALCL).
- Part A2: Patients with confirmed ALK fusion proteins, ALK mutations, ALK amplification (defined as greater than 4-fold increase in the *ALK* signal number as compared to reference signal number on chromosome 2q arm) or MET mutation or amplification. Testing to confirm the presence of ALK fusion proteins, ALK mutations, ALK amplification or evidence of MET mutation or amplification for eligibility purposes must be performed as a CLIA-certified assay. ALK immunohistochemistry can be used as a surrogate for FISH for patients with IMT or ALCL.
- Part A3: Patients with relapsed or refractory neuroblastoma, with or without bone marrow involvement, who are not eligible for Part A1 or A2 or cannot enroll on Part A1 because of stratum suspension or lack of available spots. These patients were enrolled at one dose level below the dose level at which patients on Part A1 were actively enrolling.

Organ Function Requirements:

Patients must have Adequate Bone Marrow Function Defined as:

Patients on Part A1 of the study:

- a. For patients with solid tumors or ALCL without bone marrow involvement:

- Peripheral absolute neutrophil count (ANC) $\geq 1000/\text{mm}^3$
- Platelet count $\geq 75,000/\text{mm}^3$ (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

b. Patients with known bone marrow metastatic disease:

- Peripheral absolute neutrophil count (ANC) $\geq 750/\text{mm}^3$
- Platelet count $\geq 25,000/\text{mm}^3$ (may receive platelet transfusions)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)
- Not known to be refractory to red cell or platelet transfusions

Transfusions are permitted to meet both the platelet and hemoglobin criteria. Note: Patients with known bone marrow metastatic disease are not evaluable for hematological toxicity for the purposes of dose escalation.

Patients on Part A2 and Part A3 of the study:

- Peripheral absolute neutrophil count (ANC) $\geq 750/\text{mm}^3$
- Platelet count $\geq 25,000/\text{mm}^3$ (may receive platelet transfusions)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)
- Not known to be refractory to red cell or platelet transfusions

Transfusions are permitted to meet both the platelet and hemoglobin criteria.

Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR $\geq 70\text{ml}/\text{min}/1.73\text{ m}^2$ or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR¹⁸ utilizing child length and stature data published by the CDC.

Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x ULN for age
- SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

Adequate Cardiac Function defined as:

- QTc ≤ 480 msec

Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of Part A1 of this study.* Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	Decision
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	Decision
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.

** If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped.

Since this agent is not expected to be associated with dose-limiting myelosuppression, at least 2 of every cohort of 3 or 5 of every cohort of 6 patients must be evaluable for hematologic toxicity. If hematologic dose limiting toxicity is observed, all subsequent patients who are enrolled in Part A1 must be evaluable for hematologic toxicity. Patients in Part A2 or A3 may be enrolled irrespective of whether or not they have bone marrow involvement.

* Rolling six design reference:

Skolnik JM, Barrett JS, Jayaraman B, et al: Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol. 26(2):170-1, 2008

Supplemental Table 1. Maximum grade of Toxicities by Stratum, Irrespective of Attribution, Observed in Patients during First Cycle of Treatment (Total Cycles =65)

Toxicity Type	Dose Level	Maximum grade of patient-toxicity			
		1	2	3	4
Stratum A1		Total Number of Cycles, 31			
Anemia	100 mg/m ²	1			
	165 mg/m ²	2			
	215 mg/m ²	1	2		
	280 mg/m ²		1		
	365 mg/m ²	3	1		
Lymphocyte count decreased	130 mg/m ²	1			
	165 mg/m ²	1	2		
	215 mg/m ²	1	1	1	
	280 mg/m ²	2			
	365 mg/m ²	1			
Neutrophil count decreased	165 mg/m ²	1	2		
	215 mg/m ²		1	2	
	280 mg/m ²			1	
	365 mg/m ²		1	3	1
White blood cell decreased	165 mg/m ²	3			
	215 mg/m ²	1	1		
	280 mg/m ²	1			
	365 mg/m ²	2	1	1	
Abdominal distension	130 mg/m ²	1			
	280 mg/m ²	1			
	365 mg/m ²	1			
Abdominal pain	100 mg/m ²	2			
	130 mg/m ²	1			
	165 mg/m ²	2			
	215 mg/m ²		1		
	280 mg/m ²	2			
	365 mg/m ²	1			
Acidosis	130 mg/m ²	1			
	165 mg/m ²	1			
Activated PTT prolonged	215 mg/m ²			1	
Agitation	280 mg/m ²	1			
Alanine aminotransferase increased	100 mg/m ²	2			
	130 mg/m ²		1		
	165 mg/m ²	5	1		
	215 mg/m ²	3	1		
	280 mg/m ²	4	1		
	365 mg/m ²	4	1		1

Alkaline phosphatase increased	165 mg/m ²		1		
	215 mg/m ²	1			
	365 mg/m ²	1		1	
Allergic rhinitis	100 mg/m ²	1	1		
Alopecia	365 mg/m ²	1			
Anaphylaxis	215 mg/m ²			1	
Anorexia	215 mg/m ²	3			
	280 mg/m ²	1			
	365 mg/m ²	1	2		
Anxiety	165 mg/m ²			1	
Aspartate aminotransferase increased	100 mg/m ²	2			
	130 mg/m ²	1			
	165 mg/m ²	5			
	215 mg/m ²	5	2		
	280 mg/m ²	1	1		
	365 mg/m ²	4			1
Ataxia	165 mg/m ²			1	
Back pain	130 mg/m ²	1			
Bloating	365 mg/m ²	1			
Blood bilirubin increased	100 mg/m ²	1			
Blurred vision	130 mg/m ²		1		
	165 mg/m ²	1			
	215 mg/m ²	2			
	280 mg/m ²	2			
Bronchospasm	100 mg/m ²		1		
Cheilitis	165 mg/m ²	1			
Constipation	215 mg/m ²	3			
	280 mg/m ²	2			
Cough	100 mg/m ²	2			
	165 mg/m ²	1			
	280 mg/m ²	1			
Creatinine increased	100 mg/m ²	1	1		
	165 mg/m ²	1			
	215 mg/m ²	2			
	280 mg/m ²	3			
	365 mg/m ²	2	1		
Cushingoid	165 mg/m ²		1		
Dehydration	100 mg/m ²		1		
	215 mg/m ²	1			
Diarrhea	100 mg/m ²	1			
	130 mg/m ²	1			

	165 mg/m ²	4			
	215 mg/m ²	1	1		
	280 mg/m ²	1		1	
	365 mg/m ²	4	1		
Dizziness	165 mg/m ²	1			
	215 mg/m ²			1	
	280 mg/m ²	1			
	365 mg/m ²	2			
Dry skin	165 mg/m ²	1			
Dysgeusia	100 mg/m ²	1			
	215 mg/m ²	2			
	365 mg/m ²	1			
Dyspepsia	165 mg/m ²		1		
Dysphagia	165 mg/m ²		1		
Dyspnea	165 mg/m ²		1		
Epistaxis	165 mg/m ²	1			
Esophagitis	215 mg/m ²	1			
	365 mg/m ²		1		
Euphoria	165 mg/m ²	1			
Eye disorders - Other, specify (farsighted with astigmatism)	130 mg/m ²		1		
Eye disorders - Other, specify (esotropia)	165 mg/m ²	1			
Eye disorders - Other, specify (palinopsia)	215 mg/m ²		1		
Eye disorders - Other, specify (images dragging across visual field)	215 mg/m ²	1			
Eye disorders - Other, specify (bloodshot eyes)	365 mg/m ²	1			
Eye disorders - Other, specify (seeing stars)	365 mg/m ²	1			
Eye pain	280 mg/m ²	1			
Fatigue	100 mg/m ²	1			
	165 mg/m ²	3			
	215 mg/m ²	7			
	280 mg/m ²	1			
	365 mg/m ²	2	1		
Febrile neutropenia	100 mg/m ²			1	
Fever	215 mg/m ²	1			

Flashing lights	130 mg/m ²	1			
	215 mg/m ²	1			
Flatulence	165 mg/m ²	2			
	215 mg/m ²	1			
Floaters	365 mg/m ²	2			
Flushing	165 mg/m ²		1		
	280 mg/m ²	1			
Gait disturbance	365 mg/m ²	1			
Gastrointestinal disorders - Other, specify (Abdominal Cramping)	215 mg/m ²	1			
GGT increased	100 mg/m ²	1			
	280 mg/m ²	1			
	365 mg/m ²	1			1
Headache	165 mg/m ²	1			
	215 mg/m ²	1	1		
	365 mg/m ²	2			
Hematuria	280 mg/m ²	1			
Hypercalcemia	280 mg/m ²	1			
Hyperglycemia	100 mg/m ²	1			
	165 mg/m ²		1		
	215 mg/m ²	1			
	365 mg/m ²	2			
Hyperkalemia	130 mg/m ²	1			
	165 mg/m ²	1			
Hypermagnesemia	130 mg/m ²	2			
	215 mg/m ²	2			
	365 mg/m ²	2			
Hypernatremia	365 mg/m ²	1			
Hypertension	165 mg/m ²	1			
Hyperuricemia	365 mg/m ²	1			
Hypoalbuminemia	100 mg/m ²	2			
	165 mg/m ²	2			
	215 mg/m ²	1			
	280 mg/m ²	1			
	365 mg/m ²	3			
Hypocalcemia	130 mg/m ²	1			
	165 mg/m ²	2			
	215 mg/m ²		1		
	280 mg/m ²	1			
	365 mg/m ²	2			

Hypoglycemia	100 mg/m ²	1			
	365 mg/m ²	2	1		
Hypokalemia	100 mg/m ²	1			
	130 mg/m ²	1			
Hypomagnesemia	165 mg/m ²	1			
	365 mg/m ²	1			
Hyponatremia	100 mg/m ²	1			
	165 mg/m ²	1			
	280 mg/m ²	1			
Hypophosphatemia	100 mg/m ²	1			
	165 mg/m ²	1			
	215 mg/m ²	4			
	365 mg/m ²	3			
Hypotension	100 mg/m ²	1			
	215 mg/m ²	2			
	280 mg/m ²	1			
Hypoxia	165 mg/m ²		1		
Infections and infestations - Other, specify (Influenza A)	100 mg/m ²		1		
Infections and infestations - Other, specify (Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L): Urinary tract NOS)	280 mg/m ²		1		
Intracranial hemorrhage	215 mg/m ²	1			
Investigations - Other, specify (increased BUN)	130 mg/m ²	1			
Irritability	365 mg/m ²	1			
Lipase increased	215 mg/m ²			1	
Myositis	365 mg/m ²			1	
Nausea	100 mg/m ²	2			
	130 mg/m ²	3			
	165 mg/m ²	4			
	215 mg/m ²	3	1		
	280 mg/m ²	1	1		
	365 mg/m ²	3	2		
Nervous system disorders - Other, specify (Nystagmus)	130 mg/m ²	1			
Nervous system disorders - Other, specify (presyncope)	280 mg/m ²		1		

Non-cardiac chest pain	165 mg/m ²		1		
	365 mg/m ²	1			
Oral pain	365 mg/m ²	1			
Otitis media	365 mg/m ²		1		
Pain	100 mg/m ²	1			
	280 mg/m ²	1			
	365 mg/m ²			1	
Pain in extremity	215 mg/m ²	1			
	280 mg/m ²	1			
	365 mg/m ²	2			
Palpitations	165 mg/m ²		1		
Peripheral motor neuropathy	100 mg/m ²	1			
	165 mg/m ²		1		
Peripheral sensory neuropathy	215 mg/m ²		1		
Pharyngolaryngeal pain	280 mg/m ²	1			
Photophobia	165 mg/m ²	1			
Proteinuria	280 mg/m ²		1		
Pyramidal tract syndrome	165 mg/m ²	1			
Respiratory, thoracic and mediastinal disorders - Other, specify (crackles)	100 mg/m ²	1			
Respiratory, thoracic and mediastinal disorders - Other, specify (Upper Respiratory Infection Symptoms)	130 mg/m ²	1			
Serum amylase increased	215 mg/m ²	1			
Sinus disorder	215 mg/m ²	1			
Sinus tachycardia	100 mg/m ²	1			
	165 mg/m ²	1			
Skin and subcutaneous tissue disorders - Other, specify (hair growth noted on face, fine and dark)	130 mg/m ²	1			
Skin and subcutaneous tissue disorders - Other, specify (Abrasions noted on right forearm and right lower leg)	280 mg/m ²	1			

Skin infection	280 mg/m ²		1		
Sore throat	365 mg/m ²	1			
Stomach pain	365 mg/m ²	2			
Tinnitus	215 mg/m ²		1		
Urinary frequency	165 mg/m ²	1			
Urinary incontinence	165 mg/m ²	1			
Vomiting	100 mg/m ²	1			
	130 mg/m ²	1			
	165 mg/m ²	2	1		
	215 mg/m ²	2		1	
	280 mg/m ²		1		
	365 mg/m ²	5			
Weight gain	165 mg/m ²		1		
Weight loss	100 mg/m ²	1			
	365 mg/m ²	1			
Stratum A2		Total Number of Cycles, 24			
Anemia	100 mg/m ²		1		
	165 mg/m ²	1	1		
	280 mg/m ²	2	1		
Lymphocyte count decreased	100 mg/m ²				1
	165 mg/m ²			1	
Neutrophil count decreased	100 mg/m ²		1		
	165 mg/m ²		2	1	1
	280 mg/m ²	1	1	1	
Platelet count decreased	165 mg/m ²	1			
	280 mg/m ²	1			
White blood cell decreased	100 mg/m ²		1		
	165 mg/m ²	1			
	280 mg/m ²	2			
Abdominal distension	165 mg/m ²			1	
Abdominal pain	165 mg/m ²	3			
	280 mg/m ²	2			
Activated partial thromboplastin time prolonged	165 mg/m ²	1			
Agitation	165 mg/m ²		1		
Alanine aminotransferase increased	100 mg/m ²	1	1		
	165 mg/m ²	2	2		
	280 mg/m ²	4	1		
Allergic reaction	280 mg/m ²	1			
Allergic rhinitis	100 mg/m ²	1			
	280 mg/m ²	1			

Alopecia	100 mg/m ²	1	1		
	165 mg/m ²	1			
Anorexia	165 mg/m ²	1	1		
	280 mg/m ²	3			
Aspartate aminotransferase increased	100 mg/m ²		1		
	165 mg/m ²	4			
	215 mg/m ²	1			
	280 mg/m ²	5	1	1	
Back pain	165 mg/m ²		1		
Blurred vision	165 mg/m ²	2			
	280 mg/m ²	3			
Bone pain	280 mg/m ²	1			
Burn	165 mg/m ²	1			
Chronic kidney disease	165 mg/m ²	1			
Conjunctivitis	165 mg/m ²		1		
Constipation	165 mg/m ²	4			
	280 mg/m ²	1			
Cough	100 mg/m ²	1			
	165 mg/m ²	3			
	280 mg/m ²	5			
CPK increased	165 mg/m ²	1			
Creatinine increased	165 mg/m ²	4		1	
	280 mg/m ²	1			
Dehydration	165 mg/m ²		2		
Depressed level of consciousness	165 mg/m ²		1		
Depression	165 mg/m ²	1	1		
Diarrhea	100 mg/m ²	1			
	165 mg/m ²	4	2		
	280 mg/m ²	2			
Dizziness	165 mg/m ²	1			
	280 mg/m ²	1			
Dry skin	280 mg/m ²	1			
Dyspepsia	165 mg/m ²	2			
Edema face	165 mg/m ²	1			
	280 mg/m ²	1			
Edema limbs	165 mg/m ²	1			
	280 mg/m ²	1			
Edema trunk	165 mg/m ²	1			
Electrocardiogram QT corrected interval prolonged	165 mg/m ²	1			

Epistaxis	280 mg/m ²	1			
Erectile dysfunction	165 mg/m ²		1		
Eye disorders - Other, specify (halos around objects)	165 mg/m ²	1			
Eye disorders - Other, specify (Seeing shadows in eye field)	165 mg/m ²	1			
Eye disorders - Other, specify (Shadows in peripheral vision, particularly upon waking)	280 mg/m ²	1			
Eye pain	280 mg/m ²	1			
Fatigue	165 mg/m ²	1	1		
	215 mg/m ²	1			
	280 mg/m ²	3			
Fever	165 mg/m ²	3	1		
	280 mg/m ²			1	
Fracture	280 mg/m ²		1		
Gastrointestinal disorders - Other, specify (gastroenteritis)	280 mg/m ²	1			
GGT increased	165 mg/m ²	1	1	1	
	280 mg/m ²		1		
Headache	165 mg/m ²	1	1		
	280 mg/m ²	2			
Hemoglobinuria	165 mg/m ²	1			
Hyperglycemia	100 mg/m ²		1		
	165 mg/m ²	4			
	280 mg/m ²	1			
Hypermagnesemia	280 mg/m ²	3			
Hypertension	165 mg/m ²	2			
Hyperuricemia	165 mg/m ²	1			
Hypoalbuminemia	100 mg/m ²	1	1		
	165 mg/m ²	1	2		
	280 mg/m ²	1	1		
Hypocalcemia	165 mg/m ²	2	3		
	280 mg/m ²	1			
Hypoglycemia	280 mg/m ²	1			
Hypokalemia	100 mg/m ²	1			
	165 mg/m ²			2	
	280 mg/m ²	1	1		

Hypomagnesemia	165 mg/m ²	2			
Hyponatremia	100 mg/m ²	1			
	165 mg/m ²	1			
	280 mg/m ²	2			
Hypophosphatemia	165 mg/m ²	2			
	215 mg/m ²	1			
	280 mg/m ²	1			
Hypotension	165 mg/m ²	1	1		
Hypoxia	165 mg/m ²			1	
Infections and infestations - Other, specify (Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L): Catheter-related)	165 mg/m ²			1	
Infections and infestations - Other, specify (Viral gastroenteritis)	280 mg/m ²		1		
Investigations - Other, specify (increased C-reactive protein)	280 mg/m ²	1			
Investigations - Other, specify (increased neutrophil count)	280 mg/m ²	1			
Lip infection	280 mg/m ²	1			
Localized edema	280 mg/m ²	1			
Metabolism and nutrition disorders - Other, specify (decreased AN-GAP)	280 mg/m ²	1			
Metabolism and nutrition disorders - Other, specify (increased chloride)	280 mg/m ²	1			
Metabolism and nutrition disorders - Other, specify (hyperphosphatemia)	280 mg/m ²	1			
Mucositis oral	165 mg/m ²	1			
Muscle weakness lower limb	280 mg/m ²	1			
Nausea	100 mg/m ²	1			
	165 mg/m ²	5	2		
	215 mg/m ²	1			
	280 mg/m ²	7			
Neuralgia	165 mg/m ²			1	

Non-cardiac chest pain	165 mg/m ²	1		1	
	280 mg/m ²	1			
Oral hemorrhage	280 mg/m ²	1			
Oral pain	280 mg/m ²	1			
Pain	165 mg/m ²		1		
	280 mg/m ²	2			
Pain in extremity	165 mg/m ²	1			
	280 mg/m ²	1			
Papilledema	280 mg/m ²	1			
Pelvic pain	165 mg/m ²		1		
Pericardial effusion	165 mg/m ²		1		
Peripheral sensory neuropathy	165 mg/m ²	1			
Pharyngolaryngeal pain	165 mg/m ²	3			
Pleural effusion	165 mg/m ²	1			
Pruritus	280 mg/m ²	1			
Rash acneiform	165 mg/m ²	1			
Rash maculo-papular	165 mg/m ²	3			
	280 mg/m ²	1			
Respiratory, thoracic and mediastinal disorders - Other, specify (tachypnea (breaths fast when she sleeps))	280 mg/m ²	1			
Rhinitis infective	280 mg/m ²	1			
Sinus bradycardia	165 mg/m ²	1			
Skin and subcutaneous tissue disorders - Other, specify	165 mg/m ²	1			
	280 mg/m ²	1			
Skin ulceration	165 mg/m ²		1		
Sneezing	280 mg/m ²	1			
Sore throat	280 mg/m ²	1			
Stomach pain	165 mg/m ²	1			
	280 mg/m ²	1			
Toothache	280 mg/m ²	1			
Tremor	165 mg/m ²	1			
Upper respiratory infection	165 mg/m ²		1		
	280 mg/m ²		1		
Urinary tract pain	280 mg/m ²	1			
Vascular access complication	280 mg/m ²		1		
Vomiting	100 mg/m ²	1			

	165 mg/m ²	7	2	1	
	215 mg/m ²	1			
	280 mg/m ²	6	2		
Weight gain	165 mg/m ²	1			
Weight loss	165 mg/m ²	1			
	280 mg/m ²	1			
Stratum A3		Total Number of Cycles, 10			
Anemia	215 mg/m ²	1			
Neutrophil count decreased	215 mg/m ²		1		
White blood cell decreased	215 mg/m ²	1			
Abdominal distension	280 mg/m ²	1			
Agitation	165 mg/m ²	1			
Alanine aminotransferase increased	165 mg/m ²	1	1		
	215 mg/m ²	3			
	280 mg/m ²	1		1	
Alkaline phosphatase increased	215 mg/m ²	1			
Anorexia	215 mg/m ²	1			
	280 mg/m ²	2			
Aspartate aminotransferase increased	165 mg/m ²		1		
	215 mg/m ²	3			
	280 mg/m ²	1		1	
Back pain	280 mg/m ²	1			
Blurred vision	130 mg/m ²	1			
	165 mg/m ²	1			
	280 mg/m ²	2			
Bone pain	165 mg/m ²			1	
Confusion	165 mg/m ²	1			
	280 mg/m ²	1			
Constipation	280 mg/m ²	1			
Cough	280 mg/m ²	1			
Creatinine increased	165 mg/m ²	2			
	280 mg/m ²	1			
Diarrhea	165 mg/m ²	1			
	215 mg/m ²	2			
	280 mg/m ²	2			
Dry skin	215 mg/m ²	1			
Dysesthesia	280 mg/m ²	1			
Dyspepsia	215 mg/m ²		1		
Edema limbs	280 mg/m ²	1			

Extraocular muscle paresis	215 mg/m ²		1		
Eye disorders - Other, specify (Jumping vision.)	280 mg/m ²	1			
Eye disorders - Other, specify (seeing trails)	280 mg/m ²	1			
Fatigue	280 mg/m ²	3			
Fever	280 mg/m ²	1			
Flashing lights	165 mg/m ²	1			
GGT increased	280 mg/m ²		1		
Hallucinations	280 mg/m ²	1			
Hyperglycemia	165 mg/m ²	1			
	280 mg/m ²	1			
Hyperkalemia	165 mg/m ²		1		
Hypermagnesemia	215 mg/m ²	1			
	280 mg/m ²	1			
Hypoalbuminemia	165 mg/m ²		1		
	215 mg/m ²	1			
	280 mg/m ²		1		
Hypocalcemia	165 mg/m ²	2			
	215 mg/m ²	1			
	280 mg/m ²		1		
Hypoglycemia	280 mg/m ²	1			
Hypokalemia	130 mg/m ²	1			
	165 mg/m ²	1			
	215 mg/m ²	1			
Hyponatremia	165 mg/m ²	1			
	280 mg/m ²	2			
Hypophosphatemia	165 mg/m ²	1			
	280 mg/m ²	1			
Nausea	130 mg/m ²	1			
	165 mg/m ²	1			
	215 mg/m ²	1	1		
	280 mg/m ²	3			
Non-cardiac chest pain	165 mg/m ²	1			
Pain	280 mg/m ²			1	
Pain in extremity	280 mg/m ²		2		
Personality change	215 mg/m ²	1			
Postnasal drip	215 mg/m ²	1			
Renal and urinary disorders - Other, specify (Polyuria)	280 mg/m ²	1			

Respiratory, thoracic and mediastinal disorders - Other, specify (upper respiratory infection)	165 mg/m ²	1			
Respiratory, thoracic and mediastinal disorders - Other, specify (rhinorrhea)	280 mg/m ²	1			
Scalp pain	280 mg/m ²	1			
Sinus tachycardia	165 mg/m ²	1			
Toothache	280 mg/m ²	1			
Tremor	280 mg/m ²	1			
Vomiting	165 mg/m ²	2			
	215 mg/m ²	1	1		
	280 mg/m ²	2			
Watering eyes	165 mg/m ²	1			
Weight loss	165 mg/m ²	1			
	280 mg/m ²	1			

Maximum grade of Toxicities by Stratum, Irrespective of Attribution, Observed in Patients across All Cycles of Treatment (Excluding Follow-up). Total Patient-Cycles=524[MOU1].

Toxicity Type	Dose Level	Maximum grade of patient-toxicity across all cycles				
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Stratum A1		Total Number of Patient-Cycles, 208				
Anemia	100 mg/m ²	1				
	130 mg/m ²	1				
	165 mg/m ²	3	1			
	215 mg/m ²	2	3			
	280 mg/m ²		1			
	365 mg/m ²	3	1			
Lymphocyte count decreased	130 mg/m ²	1	1		1	
	165 mg/m ²	2	2			
	215 mg/m ²	2	1	1		
	280 mg/m ²	2				
	365 mg/m ²	4				
Neutrophil count decreased	130 mg/m ²				1	
	165 mg/m ²	1	1	2		
	215 mg/m ²	1		3		
	280 mg/m ²	1	1	1		
	365 mg/m ²		1	3	2	
Platelet count decreased	100 mg/m ²	1				
	130 mg/m ²	2				

White blood cell decreased	130 mg/m ²			1		
	165 mg/m ²	1	2			
	215 mg/m ²	3	1			
	280 mg/m ²	2	1			
	365 mg/m ²	1	3	1		
Abdominal distension	130 mg/m ²		1			
	165 mg/m ²	1				
	280 mg/m ²	1				
	365 mg/m ²	1				
Abdominal pain	100 mg/m ²	2				
	130 mg/m ²		1			
	165 mg/m ²	3				
	215 mg/m ²		1			
	280 mg/m ²	3				
	365 mg/m ²	1				
Abducens nerve disorder	165 mg/m ²			1		
Acidosis	130 mg/m ²	1				
	165 mg/m ²	1				
Activated partial thromboplastin time prolonged	215 mg/m ²			1		
Agitation	165 mg/m ²	1				
	280 mg/m ²	1				
Alanine aminotransferase increased	100 mg/m ²	3				
	130 mg/m ²		1	1		
	165 mg/m ²	5	1			
	215 mg/m ²	4	1			
	280 mg/m ²	4	1			
	365 mg/m ²	4	1			1
Alkaline phosphatase increased	130 mg/m ²	1				
	165 mg/m ²		1	1		
	215 mg/m ²	3				
	280 mg/m ²	2				
	365 mg/m ²	1			2	
Allergic rhinitis	100 mg/m ²	1	1			
	165 mg/m ²	2				
Alopecia	365 mg/m ²	2				
Amnesia	280 mg/m ²	1				
Anaphylaxis	215 mg/m ²			1		
Anorexia	215 mg/m ²	3				
	280 mg/m ²	1				
	365 mg/m ²	1	2			

Anxiety	165 mg/m ²			1		
	215 mg/m ²	1				
Arthralgia	100 mg/m ²	1				
	165 mg/m ²	1				
	215 mg/m ²		1			
Aspartate aminotransferase increased	100 mg/m ²	3				
	130 mg/m ²	1	1			
	165 mg/m ²	6				
	215 mg/m ²	5	2			
	280 mg/m ²	2	1			
	365 mg/m ²	4			1	
Ataxia	165 mg/m ²			1		
Back pain	130 mg/m ²	1				
	215 mg/m ²	1				
	365 mg/m ²		1			
Bloating	365 mg/m ²	1				
Blood and lymphatic system disorders - Other, specify (cervical lymphadenopathy)	165 mg/m ²	1				
Blood and lymphatic system disorders - Other, specify (Lymphadenopathy)	280 mg/m ²	1				
Blood bilirubin increased	100 mg/m ²	1				
	165 mg/m ²	1				
Blurred vision	130 mg/m ²		1			
	165 mg/m ²	1				
	215 mg/m ²	2				
	280 mg/m ²	2				
Bone pain	215 mg/m ²	1				
Bronchospasm	100 mg/m ²	1	1			
Bruising	100 mg/m ²	1				
	365 mg/m ²	1				
Buttock pain	165 mg/m ²	1				
	215 mg/m ²	1				
Cheilitis	165 mg/m ²	1				
Chills	215 mg/m ²	1				
Chronic kidney disease	215 mg/m ²		1			
Constipation	130 mg/m ²	1				
	165 mg/m ²		1			
	215 mg/m ²	3				
	280 mg/m ²	2				

	365 mg/m ²	1				
Cough	100 mg/m ²	3				
	130 mg/m ²	1				
	165 mg/m ²	4				
	215 mg/m ²		1			
	280 mg/m ²	2				
	365 mg/m ²	1				
Creatinine increased	100 mg/m ²	1	1			
	130 mg/m ²	1				
	165 mg/m ²	1				
	215 mg/m ²	3				
	280 mg/m ²	2	1			
	365 mg/m ²	2	1			
Cushingoid	165 mg/m ²		1			
Dehydration	100 mg/m ²		1			
	130 mg/m ²		1			
	215 mg/m ²	1				
Depressed level of consciousness	130 mg/m ²		1			
Depression	215 mg/m ²	1				
Diarrhea	100 mg/m ²	1				
	130 mg/m ²	1	1			
	165 mg/m ²	3		1		
	215 mg/m ²	1	2			
	280 mg/m ²	2		2		
	365 mg/m ²	5	1			
Dizziness	165 mg/m ²	2				
	215 mg/m ²	1		1		
	280 mg/m ²	1				
	365 mg/m ²	2				
Dry eye	100 mg/m ²		1			
Dry skin	165 mg/m ²	1				
	280 mg/m ²	1				
	365 mg/m ²	1				
Dysgeusia	100 mg/m ²	1				
	215 mg/m ²	2				
	365 mg/m ²	1				
Dyspepsia	100 mg/m ²	1				
	165 mg/m ²		1			
Dysphagia	165 mg/m ²		1			
Dysphasia	165 mg/m ²			1		
Dyspnea	165 mg/m ²	1			1	

	365 mg/m ²			1		
Edema limbs	130 mg/m ²	1				
	165 mg/m ²		1			
	280 mg/m ²	1				
Epistaxis	165 mg/m ²	1				
Esophagitis	215 mg/m ²	1				
	365 mg/m ²		1			
Euphoria	165 mg/m ²	1				
Extraocular muscle paresis	130 mg/m ²		1			
Eye disorders - Other, specify (Difficulty with color perception)	100 mg/m ²	1				
Eye disorders - Other, specify (farsighted with astigmatism)	130 mg/m ²		1			
	165 mg/m ²	1				
	215 mg/m ²	1				
	215 mg/m ²		1			
	365 mg/m ²	1				
	365 mg/m ²	1				
	365 mg/m ²	1				
Eye pain	165 mg/m ²	1				
	280 mg/m ²	1				
Facial nerve disorder	165 mg/m ²			1		
Fatigue	100 mg/m ²	1				
	130 mg/m ²	1				
	165 mg/m ²	3		1		
	215 mg/m ²	7				
	280 mg/m ²	2				
	365 mg/m ²	2	1			
Febrile neutropenia	100 mg/m ²			1		
Fever	130 mg/m ²	1				
	165 mg/m ²	1				
	215 mg/m ²	1				
	280 mg/m ²	1				
	365 mg/m ²		1			
Flashing lights	130 mg/m ²		1			
	215 mg/m ²	1				
Flatulence	165 mg/m ²	2				
	215 mg/m ²	1				

Floaters	365 mg/m ²	2				
Flushing	165 mg/m ²		1			
	280 mg/m ²	1				
Gait disturbance	365 mg/m ²	1				
Gastrointestinal disorders - Other, specify (Abdominal Cramping)	215 mg/m ²	1				
GGT increased	100 mg/m ²	1				
	130 mg/m ²		1			
	280 mg/m ²	1				
	365 mg/m ²	1			1	
Headache	100 mg/m ²	1				
	130 mg/m ²			1		
	165 mg/m ²	3				
	215 mg/m ²	1	2			
	365 mg/m ²	3				
Hematuria	280 mg/m ²	1				
Hemoglobinuria	165 mg/m ²	1				
Hot flashes	130 mg/m ²		1			
Hypercalcemia	280 mg/m ²	1				
	365 mg/m ²	1				
Hyperglycemia	100 mg/m ²	2				
	165 mg/m ²	1	3			
	215 mg/m ²		1			
	365 mg/m ²	3				
Hyperkalemia	130 mg/m ²	1				
	165 mg/m ²	2				
Hypermagnesemia	130 mg/m ²	2				
	165 mg/m ²	1				
	215 mg/m ²	2				
	365 mg/m ²	2				
Hypernatremia	100 mg/m ²	1				
	365 mg/m ²	1				
Hypertension	165 mg/m ²		1			
Hyperuricemia	365 mg/m ²	1				
Hypoalbuminemia	100 mg/m ²	1	1			
	130 mg/m ²	1				
	165 mg/m ²	2				
	215 mg/m ²	3				
	280 mg/m ²	2				
	365 mg/m ²	4				
Hypocalcemia	100 mg/m ²	1				

	130 mg/m ²	2				
	165 mg/m ²	3				
	215 mg/m ²	1	1			
	280 mg/m ²	1				
	365 mg/m ²	2				
Hypoglycemia	100 mg/m ²	1	1			
	215 mg/m ²		1			
	365 mg/m ²	2	1			
Hypokalemia	100 mg/m ²	1				
	130 mg/m ²	2				
	165 mg/m ²	1				
Hypomagnesemia	165 mg/m ²	1				
	365 mg/m ²	1				
Hyponatremia	100 mg/m ²	1				
	130 mg/m ²	1				
	165 mg/m ²	2				
	280 mg/m ²	1				
	365 mg/m ²	1				
Hypophosphatemia	100 mg/m ²	2				
	165 mg/m ²	1				
	215 mg/m ²	4				
	365 mg/m ²	4				
Hypotension	100 mg/m ²	2				
	130 mg/m ²		1			
	215 mg/m ²	2				
	280 mg/m ²	1				
	365 mg/m ²	1				
Hypoxia	165 mg/m ²			1		
Ileus	130 mg/m ²		1			
Infections and infestations - Other, specify (Influenza A)	100 mg/m ²		1			
Infections and infestations - Other, specify (Chest wall bacterial cellulitis)	215 mg/m ²			1		
Infections and infestations - Other, specify (Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L): Urinary tract NOS)	280 mg/m ²		1			
Insomnia	215 mg/m ²	2				
	365 mg/m ²	1				
Intracranial hemorrhage	130 mg/m ²				1	
	215 mg/m ²	1				

Investigations - Other, specify (increased BUN)	130 mg/m ²	1				
Irritability	365 mg/m ²	2				
IVth nerve disorder	165 mg/m ²			1		
Lipase increased	215 mg/m ²			1		
Lower gastrointestinal hemorrhage	130 mg/m ²	1				
Lung infection	130 mg/m ²		1			
Lymph node pain	130 mg/m ²	1				
Memory impairment	130 mg/m ²	1				
Metabolism and nutrition disorders - Other, specify (Hyperbilirubinemia)	165 mg/m ²	1				
Mucositis oral	165 mg/m ²	1				
	215 mg/m ²		1			
Myalgia	100 mg/m ²	1				
Myositis	365 mg/m ²			1		
Nail loss	215 mg/m ²	1				
Nasal congestion	165 mg/m ²	1				
	215 mg/m ²		1			
Nausea	100 mg/m ²	2				
	130 mg/m ²	3				
	165 mg/m ²	5				
	215 mg/m ²	4	1			
	280 mg/m ²	3	1			
	365 mg/m ²	3	2			
Nervous system disorders - Other, specify (Nystagmus)	130 mg/m ²	1				
Nervous system disorders - Other, specify (diminished reflexes)	165 mg/m ²	1				
Nervous system disorders - Other, specify (presyncope)	280 mg/m ²		1			
Non-cardiac chest pain	165 mg/m ²	1	1			
	215 mg/m ²		1			
	365 mg/m ²	1				
Oral pain	365 mg/m ²	1				
Otitis media	365 mg/m ²		1			
Pain	100 mg/m ²	1				
	165 mg/m ²	1	1			
	215 mg/m ²		1			
	280 mg/m ²	1				
	365 mg/m ²				1	

Pain in extremity	100 mg/m ²	1				
	165 mg/m ²	1				
	215 mg/m ²		1			
	280 mg/m ²	3				
	365 mg/m ²	2				
Palpitations	165 mg/m ²		1			
Papulopustular rash	280 mg/m ²	1				
Periorbital edema	165 mg/m ²	1				
Peripheral motor neuropathy	100 mg/m ²	1				
	165 mg/m ²			1		
Peripheral sensory neuropathy	215 mg/m ²		1			
Personality change	365 mg/m ²		1			
Pharyngitis	165 mg/m ²		1			
Pharyngolaryngeal pain	280 mg/m ²	1				
Photophobia	165 mg/m ²	1				
	280 mg/m ²	1				
Pneumonitis	165 mg/m ²	1				
Productive cough	365 mg/m ²	1				
Proteinuria	130 mg/m ²	2				
	165 mg/m ²	1				
	280 mg/m ²		1			
	365 mg/m ²	1				
Pruritus	280 mg/m ²	1				
	365 mg/m ²	1				
Pyramidal tract syndrome	165 mg/m ²	1				
Rash acneiform	215 mg/m ²	1				
Rash maculo-papular	100 mg/m ²	1				
	165 mg/m ²	2				
	280 mg/m ²	1				
	365 mg/m ²	1				
Respiratory, thoracic and mediastinal disorders - Other, specify (crackles)	100 mg/m ²	1				
Respiratory, Other, specify (Upper Respiratory Infection Symptoms)	130 mg/m ²	1				
Serum amylase increased	215 mg/m ²	1				
Sinus bradycardia	165 mg/m ²	1				
	215 mg/m ²	1				
Sinus disorder	215 mg/m ²	2				
Sinus tachycardia	100 mg/m ²	1				
	165 mg/m ²	1				

Skin and subcutaneous tissue disorders - Other, specify (hair growth noted on face, fine and dark)	130 mg/m ²	1				
Skin and subcutaneous tissue disorders - Other, specify (mottled skin)	165 mg/m ²	1				
Skin and subcutaneous tissue disorders - Other, specify (Abrasions noted on right forearm and right lower leg)	280 mg/m ²	1				
Skin infection	215 mg/m ²			1		
	280 mg/m ²		1			
Small intestine infection	130 mg/m ²		1			
Sore throat	165 mg/m ²	1				
	280 mg/m ²	1				
	365 mg/m ²	1				
Stomach pain	100 mg/m ²	1				
	365 mg/m ²	2				
Tinnitus	215 mg/m ²		1			
Toothache	165 mg/m ²	1				
Tumor pain	100 mg/m ²	1				
Upper respiratory infection	100 mg/m ²		1			
	165 mg/m ²		1	1		
	215 mg/m ²		1			
	280 mg/m ²		1			
	365 mg/m ²		1			
Urinary frequency	165 mg/m ²	1				
Urinary incontinence	165 mg/m ²	1				
Urinary retention	165 mg/m ²	1				
Urinary tract infection	130 mg/m ²		1			
Urinary tract pain	165 mg/m ²	1				
Vaginal infection	130 mg/m ²		1			
Vomiting	100 mg/m ²	1				
	130 mg/m ²	1		1		
	165 mg/m ²	3	1			
	215 mg/m ²	3		1		
	280 mg/m ²	1	1			
	365 mg/m ²	5				
Watering eyes	100 mg/m ²	1				
Weight gain	165 mg/m ²		2			
Weight loss	100 mg/m ²	1				
	165 mg/m ²	1				

	215 mg/m ²	2				
	280 mg/m ²	1				
	365 mg/m ²	1				
Anemia	100 mg/m ²		1			
	165 mg/m ²	4	2			
	280 mg/m ²	4	1	1		
Lymphocyte count decreased	100 mg/m ²				1	
	165 mg/m ²	2		1		
	280 mg/m ²	1		2		
Neutrophil count decreased	100 mg/m ²		1			
	165 mg/m ²	1	4	2	2	
	215 mg/m ²			1		
	280 mg/m ²	1	1	3	2	
Platelet count decreased	100 mg/m ²	1				
	165 mg/m ²	2				
	215 mg/m ²	1				
	280 mg/m ²	1			1	
White blood cell decreased	100 mg/m ²		1			
	165 mg/m ²	7	1			
	215 mg/m ²			1		
	280 mg/m ²	2	2	1		
Abdominal distension	165 mg/m ²	1		1		
	280 mg/m ²	1				
Abdominal pain	165 mg/m ²	4	1			
	280 mg/m ²	3				
Acidosis	165 mg/m ²	1				
Activated partial thromboplastin time prolonged	165 mg/m ²	1				
Agitation	165 mg/m ²	1	2			
Alanine aminotransferase increased	100 mg/m ²	1		1		
	165 mg/m ²	6	2			
	215 mg/m ²	1				
	280 mg/m ²	4	2			
Alkaline phosphatase increased	165 mg/m ²	4	1			
	280 mg/m ²	1				
Allergic reaction	280 mg/m ²	1				
Allergic rhinitis	100 mg/m ²	1				
	165 mg/m ²	2				
	280 mg/m ²	3				
Alopecia	100 mg/m ²	1	1			
	165 mg/m ²	1				

Ankle fracture	280 mg/m ²	1				
Anorexia	165 mg/m ²	6	2			
	280 mg/m ²	3				
Anxiety	165 mg/m ²	2				
	280 mg/m ²		1			
Arthralgia	165 mg/m ²	1				
Ascites	100 mg/m ²		1			
Aspartate aminotransferase increased	100 mg/m ²	1		1		
	165 mg/m ²	9				
	215 mg/m ²	1				
	280 mg/m ²	5	1	1		
Ataxia	165 mg/m ²			1		
Atelectasis	280 mg/m ²		1			
Back pain	165 mg/m ²	1	1			
	215 mg/m ²	1				
Blood bilirubin increased	165 mg/m ²	1				
Blurred vision	165 mg/m ²	2				
	280 mg/m ²	3				
Bone pain	280 mg/m ²	1				
Bruising	165 mg/m ²	1				
Burn	165 mg/m ²	1				
Catheter related infection	165 mg/m ²			2		
Chest wall pain	165 mg/m ²		1			
Chills	165 mg/m ²	4				
Cholesterol high	215 mg/m ²	1				
Chronic kidney disease	165 mg/m ²	1				
Conjunctivitis	165 mg/m ²	1	1			
Constipation	165 mg/m ²	5	1	1		
	215 mg/m ²	1				
	280 mg/m ²	1				
Cough	100 mg/m ²	1				
	165 mg/m ²	6	1			
	215 mg/m ²	1				
	280 mg/m ²	7				
CPK increased	165 mg/m ²	2				
Creatinine increased	165 mg/m ²	7	1	1		
	280 mg/m ²	1				
Death NOS	280 mg/m ²					1[M12]
Dehydration	165 mg/m ²		2	1		
Depressed level of consciousness	165 mg/m ²		1			
Depression	165 mg/m ²	1	1			

Diarrhea	100 mg/m ²	1				
	165 mg/m ²	3	5			
	215 mg/m ²	1				
	280 mg/m ²	2	1			
Dizziness	165 mg/m ²	1	2			
	280 mg/m ²	2				
Dry skin	165 mg/m ²	1				
	280 mg/m ²	1				
Dyspepsia	165 mg/m ²	4				
Dysphasia	165 mg/m ²		1			
Dyspnea	165 mg/m ²	4				
Ear pain	165 mg/m ²	1				
	280 mg/m ²	1				
Edema face	165 mg/m ²	1				
	280 mg/m ²	1				
Edema limbs	165 mg/m ²	1				
	280 mg/m ²	1	1			
Edema trunk	165 mg/m ²	1				
Electrocardiogram QT corrected interval prolonged	165 mg/m ²	1				
Enterocolitis infectious	100 mg/m ²		1			
	165 mg/m ²		1			
Epistaxis	280 mg/m ²			1		
Erectile dysfunction	165 mg/m ²		1			
External ear inflammation	165 mg/m ²	1	1			
External ear pain	165 mg/m ²	1	1			
Extrapyramidal disorder	165 mg/m ²	1				
Eye disorders - Other, specify (halos around objects)	165 mg/m ²	1				
Eye disorders - Other, specify (Seeing shadows in eye field)	165 mg/m ²	1				
Eye disorders - Other, specify (erythma of the sclera)	165 mg/m ²	1				
Eye disorders - Other, specify (Conjunctival Irritation)	165 mg/m ²	1				
Eye disorders - Other, specify (Blue discoloration to vision)	165 mg/m ²		1			

Eye disorders - Other, specify (Shadows in peripheral vision, particularly upon waking)	280 mg/m ²	1				
Eye disorders - Other, specify (Double vision)	280 mg/m ²	1				
Eye infection	165 mg/m ²		1			
Eye pain	280 mg/m ²	1				
Fatigue	165 mg/m ²	3	2			
	215 mg/m ²	1				
	280 mg/m ²	3				
Febrile neutropenia	165 mg/m ²			1		
Fever	165 mg/m ²	4	2	1		
	280 mg/m ²	2		1		
Flashing lights	215 mg/m ²	1				
Flatulence	215 mg/m ²		1			
Floaters	165 mg/m ²	1				
Flu like symptoms	165 mg/m ²		1			
Flushing	165 mg/m ²	2				
Fracture	280 mg/m ²		2			
Gait disturbance	100 mg/m ²	1				
	280 mg/m ²	1				
Gastrointestinal disorders - Other, specify (cramping)	215 mg/m ²	1				
Gastrointestinal disorders - Other, specify (gastroenteritis)	280 mg/m ²	1				
General disorders and administration site conditions - Other, specify (Hepatosplenomegaly)	280 mg/m ²	1				
Generalized muscle weakness	165 mg/m ²		2			
GGT increased	165 mg/m ²	1	1	1		
	280 mg/m ²		1			
Glossopharyngeal nerve disorder	165 mg/m ²	1				
Headache	165 mg/m ²	5	2	1		
	280 mg/m ²	2				
Hearing impaired	215 mg/m ²	1				
Hemoglobinuria	165 mg/m ²	1				
Hoarseness	165 mg/m ²	1				
Hot flashes	280 mg/m ²	1				
Hypercalcemia	165 mg/m ²	1				

Hyperglycemia	100 mg/m ²		1			
	165 mg/m ²	4	2			
	280 mg/m ²	3				
Hyperhidrosis	165 mg/m ²	2	1			
Hyperkalemia	165 mg/m ²	2				
	280 mg/m ²	1				
Hypermagnesemia	165 mg/m ²	1				
	215 mg/m ²	1				
	280 mg/m ²	3				
Hypernatremia	280 mg/m ²	2				
Hypertension	165 mg/m ²	3	2			
	280 mg/m ²		1			
Hyperuricemia	165 mg/m ²	2				
Hypoalbuminemia	100 mg/m ²	1	1			
	165 mg/m ²	5	4			
	280 mg/m ²	2	3			
Hypocalcemia	100 mg/m ²	1	1			
	165 mg/m ²	4	6			
	215 mg/m ²		1			
	280 mg/m ²	2	3			
Hypoglycemia	165 mg/m ²	3				
	280 mg/m ²	1				
Hypokalemia	100 mg/m ²	1			1	
	165 mg/m ²	2		2		
	215 mg/m ²	1				
	280 mg/m ²	1	1			
Hypomagnesemia	165 mg/m ²	4				
Hyponatremia	100 mg/m ²	2				
	165 mg/m ²	3				
	280 mg/m ²	4				
Hypophosphatemia	100 mg/m ²	1				
	165 mg/m ²	3				
	215 mg/m ²	1				
	280 mg/m ²	1				
Hypotension	165 mg/m ²	2	2			
Hypoxia	165 mg/m ²			1		
Immune system disorders - Other, specify (Rhinitis)	165 mg/m ²	1				
Immune system disorders - Other, specify (Runny nose)	165 mg/m ²	1				
Infections and infestations - Other, specify (Sinusitis)	165 mg/m ²	1				

Infections and infestations - Other, specify (Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L): Mucosa)	165 mg/m ²		1			
Infections and infestations - Other, specify (ear infection)	165 mg/m ²		1			
Infections and infestations - Other, specify (Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L): Catheter-related)	165 mg/m ²			1		
Infections and infestations - Other, specify (Disseminated Varicella Zoster)	165 mg/m ²			1		
Infections and infestations - Other, specify (Viral gastroenteritis)	280 mg/m ²			1		
Insomnia	280 mg/m ²		1			
Investigations - Other, specify (decreased bilirubin)	280 mg/m ²	1				
Investigations - Other, specify (hyperphosphatemia)	280 mg/m ²	1				
Jejunal ulcer	100 mg/m ²		1			
Laryngeal inflammation	215 mg/m ²	1				
Lip infection	280 mg/m ²	1				
Localized edema	280 mg/m ²	1				
Lung infection	165 mg/m ²		2			
	280 mg/m ²		1			
Malaise	165 mg/m ²	1				
Memory impairment	165 mg/m ²		1			
Metabolism and nutrition disorders - Other, specify (increased chloride)	280 mg/m ²	1				
Metabolism and nutrition disorders - Other, specify (decreased AN-GAP)	280 mg/m ²	1				
Metabolism and nutrition disorders - Other, specify (decreased total protein)	280 mg/m ²	1				
Metabolism and nutrition disorders - Other, specify (hyperphosphatemia)	280 mg/m ²	1				
Mucositis oral	165 mg/m ²	2				
Muscle weakness lower limb	165 mg/m ²	1				
	280 mg/m ²	1				
Musculoskeletal and connective tissue disorder - Other, specify (muscle spasms- chest)	165 mg/m ²		1			

Musculoskeletal and connective tissue disorder - Other, specify (muscle stiffness in back)	215 mg/m ²	1				
Myalgia	165 mg/m ²		1			
	280 mg/m ²	1				
Nasal congestion	165 mg/m ²	3				
	280 mg/m ²	1				
Nausea	100 mg/m ²	1				
	165 mg/m ²	6	3			
	215 mg/m ²		1			
	280 mg/m ²	7				
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify (Ovarian cyst)	280 mg/m ²	1				
Neuralgia	165 mg/m ²			1		
Non-cardiac chest pain	165 mg/m ²	3		1		
	280 mg/m ²	1				
Oral hemorrhage	280 mg/m ²	1				
Oral pain	280 mg/m ²	1				
Pain	165 mg/m ²	2	3			
	215 mg/m ²	1				
	280 mg/m ²	3				
Pain in extremity	100 mg/m ²	1				
	165 mg/m ²	1	1			
	280 mg/m ²	2		1		
Pain of skin	165 mg/m ²	1				
Papilledema	280 mg/m ²	1				
Papulopustular rash	165 mg/m ²	2				
Paresthesia	165 mg/m ²	1				
Pelvic pain	165 mg/m ²		1			
Penile pain	165 mg/m ²	1				
Pericardial effusion	165 mg/m ²		1			
Peripheral motor neuropathy	165 mg/m ²		1			
Peripheral sensory neuropathy	165 mg/m ²		1			
Pharyngitis	165 mg/m ²		1			
Pharyngolaryngeal pain	165 mg/m ²	4	1			
Photophobia	165 mg/m ²	3				
Pleural effusion	165 mg/m ²	2				
Pruritus	165 mg/m ²	3				
	280 mg/m ²	2				

Rash acneiform	165 mg/m ²	1				
Rash maculo-papular	165 mg/m ²	5	1			
	280 mg/m ²	1	1			
Renal and urinary disorders - Other, specify	165 mg/m ²		1			
Respiratory, thoracic and mediastinal disorders - Other, specify (Runny Nose)	165 mg/m ²	1				
Respiratory, thoracic and mediastinal disorders - Other, specify (Upper respiratory infection)	280 mg/m ²	1				
Respiratory, thoracic and mediastinal disorders - Other, specify (tachypnea (breaths fast when she sleeps))	280 mg/m ²	1				
Rhinitis infective	280 mg/m ²	1				
Sinus bradycardia	165 mg/m ²	1				
Sinus tachycardia	165 mg/m ²	4				
Skin and subcutaneous tissue disorders - Other, specify	165 mg/m ²	2				
	280 mg/m ²	1				
Skin induration	165 mg/m ²	1				
Skin infection	165 mg/m ²		1			
Skin ulceration	165 mg/m ²		1			
Sneezing	280 mg/m ²	1				
Sore throat	165 mg/m ²	3				
	280 mg/m ²	1	1			
Stomach pain	165 mg/m ²	2				
	280 mg/m ²	1				
Supraventricular tachycardia	165 mg/m ²	1				
Testicular pain	165 mg/m ²	1				
Toothache	280 mg/m ²	1				
Tremor	165 mg/m ²	1				
Upper respiratory infection	165 mg/m ²		5			
	280 mg/m ²		1			
Urinary tract infection	280 mg/m ²		1			
Urinary tract pain	280 mg/m ²	1				
Urticaria	280 mg/m ²	1				
Vascular access complication	280 mg/m ²		1			
Vomiting	100 mg/m ²	1				
	165 mg/m ²	4	6	1		
	215 mg/m ²	1				

	280 mg/m ²	6	2			
Watering eyes	280 mg/m ²	1				
Weight gain	165 mg/m ²		2	1		
	280 mg/m ²	1	1			
Weight loss	165 mg/m ²	2				
	280 mg/m ²		1			
Wheezing	165 mg/m ²		1			
Stratum A3	Total Number of Patient-Cycles, 52					
Anemia	165 mg/m ²		1	1		
	215 mg/m ²	1				
Lymphocyte count decreased	165 mg/m ²			1		
	215 mg/m ²	1				
Neutrophil count decreased	165 mg/m ²		1			
	215 mg/m ²		1		1	
Platelet count decreased	165 mg/m ²	1	1			
White blood cell decreased	165 mg/m ²	2				
	215 mg/m ²	2				
Abdominal distension	280 mg/m ²	1				
Abdominal pain	280 mg/m ²	1				
Acidosis	165 mg/m ²	1				
Agitation	165 mg/m ²	1				
Alanine aminotransferase increased	165 mg/m ²	2	1			
	215 mg/m ²	3				
	280 mg/m ²	1		1		
Alkaline phosphatase increased	165 mg/m ²	1				
	215 mg/m ²	2				
Allergic reaction	165 mg/m ²		1			
Anorexia	215 mg/m ²	2				
	280 mg/m ²	2				
Arthralgia	165 mg/m ²	1				
Aspartate aminotransferase increased	165 mg/m ²	1	1			
	215 mg/m ²	3				
	280 mg/m ²	1		1		
Back pain	280 mg/m ²	1				
Blurred vision	130 mg/m ²	1				
	165 mg/m ²	1				
	280 mg/m ²	2				
Bone marrow hypocellular	165 mg/m ²	1				
Bone pain	165 mg/m ²			1		
Bruising	215 mg/m ²	1				
Burn	165 mg/m ²	1				

Cardiac troponin I increased	215 mg/m ²	1				
Catheter related infection	165 mg/m ²			1		
Chest pain - cardiac	215 mg/m ²		1			
Confusion	165 mg/m ²	1				
	280 mg/m ²	1				
Constipation	215 mg/m ²	1				
	280 mg/m ²	1				
Cough	165 mg/m ²	1				
	215 mg/m ²	1				
	280 mg/m ²	1				
CPK increased	215 mg/m ²	1				
Creatinine increased	165 mg/m ²	2				
	215 mg/m ²	1				
	280 mg/m ²	1				
Dehydration	165 mg/m ²			1		
Dental caries	165 mg/m ²	1				
Diarrhea	165 mg/m ²	1				
	215 mg/m ²	2				
	280 mg/m ²	2				
Dry skin	215 mg/m ²	1				
Dysesthesia	280 mg/m ²	1				
Dyspepsia	215 mg/m ²		1			
Dysphagia	280 mg/m ²	1				
Ear pain	165 mg/m ²		1			
Edema limbs	280 mg/m ²	1				
Extraocular muscle paresis	215 mg/m ²		1			
Eye disorders - Other, specify (Jumping vision)	280 mg/m ²	1				
Eye disorders - Other, specify (seeing trails)	280 mg/m ²	1				
Fatigue	165 mg/m ²	1				
	280 mg/m ²	3				
Fever	165 mg/m ²			1		
	215 mg/m ²	1	1			
	280 mg/m ²	2				
Flashing lights	165 mg/m ²	1				
GGT increased	280 mg/m ²		1			
Hallucinations	280 mg/m ²	1				
Headache	165 mg/m ²	1				
	215 mg/m ²	1				
Hyperglycemia	165 mg/m ²	2				

	215 mg/m ²	1				
	280 mg/m ²	1				
Hyperkalemia	165 mg/m ²	1	1			
	215 mg/m ²	1	1			
Hypermagnesemia	165 mg/m ²	1				
	215 mg/m ²	1				
	280 mg/m ²	1				
Hypertension	165 mg/m ²	1	1			
Hypoalbuminemia	165 mg/m ²	1	1			
	215 mg/m ²	1	1			
	280 mg/m ²		1			
Hypocalcemia	165 mg/m ²	3				
	215 mg/m ²	2				
	280 mg/m ²		1			
Hypoglycemia	280 mg/m ²	1				
Hypokalemia	130 mg/m ²	1				
	165 mg/m ²	1				
	215 mg/m ²	1				
Hyponatremia	165 mg/m ²	2				
	280 mg/m ²	2				
Hypophosphatemia	165 mg/m ²	1				
	280 mg/m ²	1				
Hypotension	165 mg/m ²		2			
Infections and infestations - Other, specify (ear infection)	165 mg/m ²		1			
Infections and infestations - Other, specify (Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L): Catheter-related)	165 mg/m ²			1		
Nausea	130 mg/m ²	1				
	165 mg/m ²	3				
	215 mg/m ²	2	1			
	280 mg/m ²	3				
Neck pain	280 mg/m ²	1				
Non-cardiac chest pain	165 mg/m ²	2				
Pain	280 mg/m ²			1		
Pain in extremity	165 mg/m ²	1				
	215 mg/m ²	1				
	280 mg/m ²		2			
Penile pain	215 mg/m ²	1				
Personality change	215 mg/m ²	1				
Pharyngolaryngeal pain	165 mg/m ²	1				

Postnasal drip	215 mg/m ²	1				
Pruritus	215 mg/m ²	1				
Renal and urinary disorders - Other, specify	280 mg/m ²	1				
Respiratory, thoracic and mediastinal disorders - Other, specify (upper respiratory infection)	165 mg/m ²	1				
Respiratory, thoracic and mediastinal disorders - Other, specify (rhinorrhea)	280 mg/m ²	1				
Scalp pain	280 mg/m ²	1				
Sinus tachycardia	165 mg/m ²	1				
Skin and subcutaneous tissue disorders - Other, specify (Erythema from hangnails)	165 mg/m ²		1			
Skin ulceration	215 mg/m ²	1				
Sore throat	215 mg/m ²	1				
	280 mg/m ²	1				
Toothache	280 mg/m ²	1				
Tremor	280 mg/m ²	1				
Urinary tract pain	165 mg/m ²	1				
Vomiting	165 mg/m ²	1	1			
	215 mg/m ²	1	1			
	280 mg/m ²	2				
Watering eyes	165 mg/m ²	1				
	215 mg/m ²	1				
Weight gain	280 mg/m ²	1				
Weight loss	165 mg/m ²	1				
	280 mg/m ²	1				

Maximum grade of Toxicities by Stratum, Irrespective of Attribution, Observed in patients in the 30-day period following completion of crizotinib (n=42 total).

Toxicity Type	Dose Level	Maximum grade of patient-toxicity				
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Stratum A1		n=26				
Anemia	100 mg/m ²	1			1	
	130 mg/m ²		1	1		
	165 mg/m ²	1	1			
	215 mg/m ²	1				
	280 mg/m ²	1				
	365 mg/m ²	4	2			

Lymphocyte count decreased	100 mg/m ²			1	1	
	130 mg/m ²		2	2		
	165 mg/m ²		1			
	215 mg/m ²	1		1		
	280 mg/m ²		1			
	365 mg/m ²		1			
Neutrophil count decreased	100 mg/m ²				2	
	130 mg/m ²		1		1	
	165 mg/m ²		1			
	215 mg/m ²			1		
	280 mg/m ²			1		
	365 mg/m ²			1	1	
Platelet count decreased	100 mg/m ²				2	
	130 mg/m ²				1	
	165 mg/m ²	1				
White blood cell decreased	100 mg/m ²				1	
	130 mg/m ²			1	1	
	165 mg/m ²	2				
	280 mg/m ²	2				
	365 mg/m ²	2				
Abdominal pain	165 mg/m ²	1				
Acidosis	215 mg/m ²	1				
Activated partial thromboplastin time prolonged	365 mg/m ²	1				
Agitation	130 mg/m ²		1			
Alanine aminotransferase increased	130 mg/m ²	1				
	165 mg/m ²	1				
	365 mg/m ²		1			
Alkaline phosphatase increased	365 mg/m ²	1				
Alkalosis	215 mg/m ²	1				
Allergic rhinitis	100 mg/m ²	2				
	165 mg/m ²	1				
Alopecia	100 mg/m ²		1			
Amnesia	365 mg/m ²	1				
Anorexia	130 mg/m ²		1	1		
	165 mg/m ²		1			
	215 mg/m ²	1				
	365 mg/m ²	1				
Anxiety	130 mg/m ²		1			
	215 mg/m ²	1				

	365 mg/m ²	2				
Arthralgia	165 mg/m ²	1				
Aspartate aminotransferase increased	100 mg/m ²	1				
	215 mg/m ²		1			
Aspiration	165 mg/m ²				1	
Back pain	100 mg/m ²	1				
	165 mg/m ²	1				
	365 mg/m ²		1			
Bladder spasm	130 mg/m ²		1			
Blurred vision	365 mg/m ²	2				
Bronchopulmonary hemorrhage	130 mg/m ²	1				
Bruising	365 mg/m ²	1				
Cerebrospinal fluid leakage	365 mg/m ²	1				
Cholesterol high	100 mg/m ²	1				
Confusion	130 mg/m ²			1		
Constipation	130 mg/m ²		1			
	165 mg/m ²		1			
	365 mg/m ²	1				
Cough	100 mg/m ²	1				
	130 mg/m ²	1				
	165 mg/m ²	1				
	215 mg/m ²	1				
	365 mg/m ²	1				
Creatinine increased	165 mg/m ²	1				
	215 mg/m ²	1				
	365 mg/m ²	1				
Death NOS	165 mg/m ²					1[MI3]
	215 mg/m ²					1[MI4]
Dehydration	130 mg/m ²		1	1		
	165 mg/m ²	1				
Depressed level of consciousness	130 mg/m ²		1			
Depression	130 mg/m ²	1				
	365 mg/m ²	1				
Diarrhea	130 mg/m ²	1				
Dizziness	165 mg/m ²	1				
	365 mg/m ²	1				
Dysphagia	130 mg/m ²		1			
	165 mg/m ²				1	
Dyspnea	215 mg/m ²	1				
	365 mg/m ²		1			

Edema face	215 mg/m ²	1				
	365 mg/m ²	1				
Epistaxis	100 mg/m ²	1				
	365 mg/m ²	1				
Extraocular muscle paresis	130 mg/m ²		1			
Extrapyramidal disorder	130 mg/m ²	1				
Eye pain	365 mg/m ²	1				
Fatigue	130 mg/m ²			1		
	165 mg/m ²			1		
	365 mg/m ²	2				
Febrile neutropenia	100 mg/m ²			1		
	130 mg/m ²			1		
Fever	130 mg/m ²	1				
	165 mg/m ²	2				
Flashing lights	130 mg/m ²		1			
Gait disturbance	100 mg/m ²		1			
	130 mg/m ²		1			
GGT increased	165 mg/m ²	1				
	365 mg/m ²	1				
Gum infection	130 mg/m ²		1			
Headache	130 mg/m ²			1		
Hyperglycemia	100 mg/m ²	1				
	165 mg/m ²	1	1			
	215 mg/m ²		2			
	280 mg/m ²	1				
	365 mg/m ²	3				
Hyperhidrosis	365 mg/m ²	1				
Hypermagnesemia	165 mg/m ²	1				
Hypernatremia	215 mg/m ²	1				
Hypertriglyceridemia	100 mg/m ²	1				
Hypoalbuminemia	130 mg/m ²	1				
	165 mg/m ²	1				
	365 mg/m ²		1			
Hypocalcemia	130 mg/m ²	1				
	215 mg/m ²	2				
	365 mg/m ²		1			
Hypoglycemia	365 mg/m ²	1				
Hypokalemia	100 mg/m ²	1				
	215 mg/m ²	1				
	365 mg/m ²	3				
Hyponatremia	100 mg/m ²	1				

	165 mg/m ²	1				
Hypophosphatemia	165 mg/m ²	1				
	215 mg/m ²	2				
	280 mg/m ²	1				
	365 mg/m ²	2				
Hypotension	215 mg/m ²	1				
Hypoxia	130 mg/m ²		1			
	365 mg/m ²			1		
Insomnia	130 mg/m ²		1			
Intracranial hemorrhage	215 mg/m ²					1[M15]
Joint range of motion decreased	130 mg/m ²	1				
	280 mg/m ²	1				
Lethargy	365 mg/m ²		1			
Lipase increased	365 mg/m ²		1			
Malaise	365 mg/m ²	1				
Memory impairment	130 mg/m ²	1				
Muscle weakness lower limb	100 mg/m ²			1		
Nausea	100 mg/m ²	1				
	215 mg/m ²	1	1			
	365 mg/m ²	2				
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify (Progressive disease)	365 mg/m ²					1[M16]
Non-cardiac chest pain	130 mg/m ²		1			
	215 mg/m ²	1				
Pain	365 mg/m ²		1			
Pain in extremity	100 mg/m ²			1		
	280 mg/m ²		1			
Palpitations	365 mg/m ²	1				
Paresthesia	280 mg/m ²	1				
Peripheral motor neuropathy	100 mg/m ²	1				
Peripheral sensory neuropathy	365 mg/m ²	1				
Personality change	165 mg/m ²		1			
Respiratory failure	365 mg/m ²				1	
Respiratory, thoracic and mediastinal disorders - Other, specify (URI)	100 mg/m ²	1				

Seizure	130 mg/m ²		2			
Sinus bradycardia	165 mg/m ²		1			
	365 mg/m ²	1				
Sinus tachycardia	365 mg/m ²	1				
Tremor	130 mg/m ²		1			
	365 mg/m ²	1				
Tumor pain	130 mg/m ²			2		
Urinary retention	130 mg/m ²		1			
	365 mg/m ²		1			
Urinary tract pain	165 mg/m ²	1				
Vomiting	215 mg/m ²	1				
	365 mg/m ²	1				
Weight loss	165 mg/m ²	1				
	215 mg/m ²	1				
Stratum A2		n=8				
Anemia	165 mg/m ²	1	1	1		
	280 mg/m ²	1		1		
Lymphocyte count decreased	165 mg/m ²		1	1	2	
	280 mg/m ²		1	1		
Neutrophil count decreased	165 mg/m ²				3	
Platelet count decreased	165 mg/m ²	1			3	
	280 mg/m ²	1				
White blood cell decreased	165 mg/m ²				3	
	280 mg/m ²			1		
Abdominal distension	165 mg/m ²		1			
Abdominal pain	165 mg/m ²	1		1		
Agitation	165 mg/m ²	2		1		
	280 mg/m ²	1				
Alanine aminotransferase increased	165 mg/m ²	2				
	280 mg/m ²	1				
Alkaline phosphatase increased	165 mg/m ²	1				
Alopecia	165 mg/m ²	1				
Anorexia	165 mg/m ²			2		
Anxiety	165 mg/m ²		1			
Arthralgia	165 mg/m ²	1				
Aspartate aminotransferase increased	165 mg/m ²		1			
	280 mg/m ²	1				
Back pain	280 mg/m ²	1				

Blood antidiuretic hormone abnormal	165 mg/m ²	1				
Blood bilirubin increased	165 mg/m ²			1		
Bruising	165 mg/m ²	1				
Chills	165 mg/m ²	1				
Colonic obstruction	165 mg/m ²			1		
Colonic stenosis	165 mg/m ²			1		
Constipation	165 mg/m ²	1				
Cough	280 mg/m ²	1				
Creatinine increased	280 mg/m ²	1				
Cushingoid	165 mg/m ²	1				
Cystitis noninfective	165 mg/m ²	1				
Dehydration	165 mg/m ²			1		
	280 mg/m ²	1				
Diarrhea	165 mg/m ²	1	1			
Dizziness	165 mg/m ²		1			
Dry skin	165 mg/m ²	1				
Dyspnea	165 mg/m ²	1				
Edema limbs	280 mg/m ²			1		
Electrocardiogram QT corrected interval prolonged	165 mg/m ²			1		
Epistaxis	165 mg/m ²	1				
Esophageal pain	165 mg/m ²			1		
Esophagitis	165 mg/m ²			1		
Fall	280 mg/m ²	1				
Fatigue	165 mg/m ²	1				
	280 mg/m ²	1				
Febrile neutropenia	165 mg/m ²			1		
Flatulence	165 mg/m ²	1				
General disorders and administration site conditions - Other, specify (Death NOS)	280 mg/m ²					1[M17]
Headache	165 mg/m ²		1	1		
Hematoma	165 mg/m ²		1			
Hypercalcemia	165 mg/m ²	1				
Hyperglycemia	165 mg/m ²			1		
	280 mg/m ²	2				
Hyperhidrosis	165 mg/m ²	1				
Hypermagnesemia	165 mg/m ²	1				
	280 mg/m ²	2				

Hypertension	165 mg/m ²		1		1	
Hypertriglyceridemia	165 mg/m ²	1				
Hypoalbuminemia	165 mg/m ²	3	1			
	280 mg/m ²		2			
Hypocalcemia	165 mg/m ²	1	1			
	280 mg/m ²	2				
Hypoglycemia	280 mg/m ²	1				
Hypokalemia	165 mg/m ²	1		1		
	280 mg/m ²	1				
Hypomagnesemia	165 mg/m ²	2	1			
Hyponatremia	165 mg/m ²			1		
	280 mg/m ²	1				
Hypophosphatemia	165 mg/m ²	1		1		
	280 mg/m ²	1				
Infections Other, specify (documented clinically or microbiologically with ANC<1.0x10e9/L)	165 mg/m ²			1		
Infections and infestations - Other, specify (Adenovirus in blood)	165 mg/m ²			1		
Infusion related reaction	165 mg/m ²		1			
INR increased	165 mg/m ²		1			
Irritability	165 mg/m ²	1				
Mucositis oral	165 mg/m ²			2		
Nausea	165 mg/m ²		1			
Non-cardiac chest pain	280 mg/m ²		1			
Pain	280 mg/m ²	1				
Pain in extremity	165 mg/m ²	1				
	280 mg/m ²	1				
Pain of skin	165 mg/m ²	1				
Penile pain	165 mg/m ²	1				
Pruritus	165 mg/m ²	1	1			
Rash maculo-papular	165 mg/m ²	2		1		
Seizure	165 mg/m ²			1		
Sinus tachycardia	165 mg/m ²	2				
	280 mg/m ²	1				
Skin infection	165 mg/m ²			1		
Urinary incontinence	165 mg/m ²	1				
Vomiting	165 mg/m ²	2	1	1		

Stratum A3		n=8				
Anemia	165 mg/m ²	1				
	215 mg/m ²	1		1		
Lymphocyte count decreased	165 mg/m ²		1			
	215 mg/m ²		1			
Neutrophil count decreased	165 mg/m ²		1			
Platelet count decreased	215 mg/m ²			1		
White blood cell decreased	165 mg/m ²	1				
	215 mg/m ²			1		
Alanine aminotransferase increased	215 mg/m ²	1				
Anorexia	165 mg/m ²		1			
Anxiety	280 mg/m ²	1				
Ataxia	280 mg/m ²	1				
Back pain	280 mg/m ²			1		
Bone pain	280 mg/m ²			1		
Chest pain - cardiac	280 mg/m ²			1		
Constipation	215 mg/m ²	1				
Cough	280 mg/m ²	1				
Edema limbs	280 mg/m ²	1				
Headache	215 mg/m ²	1				
	280 mg/m ²			1		
Hyperglycemia	165 mg/m ²	1				
	280 mg/m ²		1			
Hypoalbuminemia	280 mg/m ²	1				
Hypocalcemia	215 mg/m ²	1				
Hypoglycemia	280 mg/m ²	1				
Hypokalemia	165 mg/m ²	1				
	215 mg/m ²	1				
Hyponatremia	165 mg/m ²	1				
Hypophosphatemia	215 mg/m ²	1				
Nausea	215 mg/m ²	1				
Rash maculo-papular	165 mg/m ²	1				
Respiratory Other, specify (Sore Throat)	215 mg/m ²	1				
Urinary incontinence	130 mg/m ²	1				
Vomiting	215 mg/m ²	1				
	280 mg/m ²	1				

Supplemental Table 2. Crizotinib dose reductions due to toxicity.

Accession No.	Dose Level mg/m ² /dose BID	Part	Patient diagnosis	Age (years)	Total number of cycles received	Cycle(s) at which dose reduction occurred	Adverse Event(s) leading to dose reduction (Grade)
13	165	A1	Neuroblastoma	8	>39*	2	Diarrhea (G3)
31	215	A1	Hepatocellular carcinoma	17	3	1	Dizziness (G3)
48	280	A1	IMT	1	>19*	8	Diarrhea (G3), Skin infection (G2)
56	365	A1	Neuroblastoma	2	8	7	Neutrophil count decreased (G4)
71	365	A1	Osteosarcoma	11	2	1	Neutrophil count decreased (G4)
30	165	A2	NSCLC [^]	17	5	1	Neutrophil count decreased (G4)
37	165	A2	ALCL [#]	13	>30*	19	Eye disorders, other - Blue discoloration to vision (G2)
73	280	A2	IMT [@]	10	5	2	Neutrophil count decreased (G4)

*Patient still on protocol therapy; [^]NSCLC = non-small cell lung cancer; [#]ALCL = anaplastic large cell lymphoma; [@]IMT= inflammatory myofibroblastic tumor

Supplemental Table 3. AdEERs-reported Adverse Events

Accession No	Part	Dose Level (mg/m ² /dose)	Cycle	Adverse Event	Grade	Attribution	DLT
1	A1	100	1	Febrile neutropenia	3	UNLIKELY	NO
				Neutrophil count decreased	4	UNLIKELY	NO
3	A1	100	Follow-up	Lymphocyte count decreased	3	UNRELATED	NO
				Febrile neutropenia	3	UNRELATED	NO
				Pain in extremity	3	UNLIKELY	NO
				Neutrophil count decreased	4	UNRELATED	NO
				Platelet count decreased	4	UNRELATED	NO
5	A1	130	1	Bronchospasm	3	UNLIKELY	NO
			Follow-up	Tumor pain	3	UNRELATED	NO
6	A1	130	2	Abdominal distension	2	POSSIBLE	NO
				Ileus	2	POSSIBLE	NO
				Abdominal pain	2	POSSIBLE	NO
				Vomiting	3	POSSIBLE	NO
			4	Neutrophil count decreased	4	POSSIBLE	YES
			Follow-up	Gait disturbance	2	UNLIKELY	NO
				Confusion	3	UNRELATED	NO
				Tumor pain	3	UNRELATED	NO
				Anorexia	3	UNLIKELY	NO
				Dehydration	3	UNLIKELY	NO
				Fatigue	3	UNLIKELY	NO
Headache	3	UNLIKELY		NO			
Anemia	3	POSSIBLE	NO				
10	A1	130	2	GGT increased	2	POSSIBLE	NO
				Intracranial hemorrhage	4	UNLIKELY	NO
11	A2	100	1	Hyperglycemia	2	POSSIBLE	NO
			4	Hypokalemia	4	UNRELATED	NO
15	A1	165	2	Hypoxia	3	UNLIKELY	NO
				Peripheral motor neuropathy	3	UNLIKELY	NO
				Dyspnea	4	UNLIKELY	NO
			Folow-up	Fatigue	3	UNRELATED	NO
				Aspiration	4	UNRELATED	NO
				Dysphagia	4	UNRELATED	NO
				Death NOS	5	UNRELATED	NO
16	A1	165	1	Neutrophil count decreased	2	POSSIBLE	NO
				Pain in extremity	3	UNRELATED	NO
18	A1	165	1	Neutrophil count decreased	2	POSSIBLE	NO
			3	White blood cell decreased	2	POSSIBLE	NO

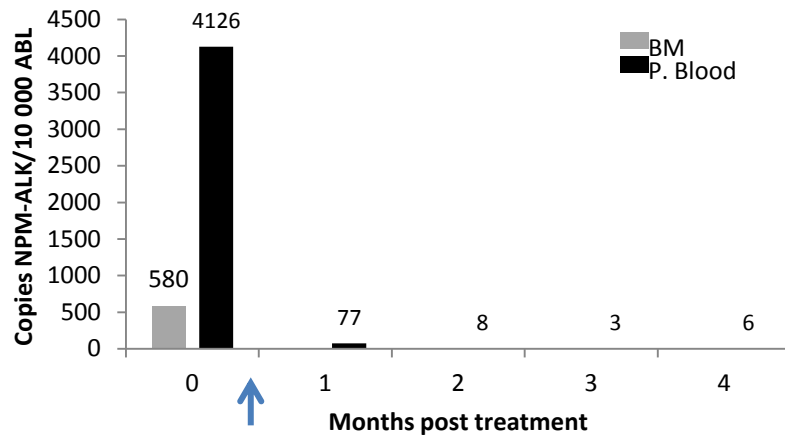
				Neutrophil count decreased	3	POSSIBLE	NO
22	A1	165	3	White blood cell decreased	2	POSSIBLE	NO
				Neutrophil count decreased	3	POSSIBLE	NO
			4	Neutrophil count decreased	2	POSSIBLE	NO
			5	Neutrophil count decreased	2	POSSIBLE	NO
23	A2	165	1	GGT increased	3	UNLIKELY	NO
			3	Constipation	3	UNLIKELY	NO
			Follow-up	Anorexia	3	UNRELATED	NO
				Colonic obstruction	3	UNRELATED	NO
				Colonic stenosis	3	UNRELATED	NO
				Esophageal pain	3	UNRELATED	NO
				Esophagitis	3	UNRELATED	NO
				Febrile neutropenia	3	UNRELATED	NO
				Hyponatremia	3	UNRELATED	NO
				Hypophosphatemia	3	UNRELATED	NO
				Infections and infestations - Other, specify (documented clinically or microbiologically with Grade 3 or 4 neutrophils with ANC<1.0x10e9/L: Blood)	3	UNRELATED	NO
				Blood bilirubin increased	3	UNLIKELY	NO
				Hyperglycemia	3	UNLIKELY	NO
				Hypokalemia	3	UNLIKELY	NO
				Seizure	3	UNLIKELY	NO
Neutrophil count decreased	4	UNRELATED	NO				
Hypertension	4	UNLIKELY	NO				
24	A2	165	1	Abdominal distension	3	UNLIKELY	NO
				Creatinine increased	3	UNLIKELY	NO
				Hypokalemia	3	UNLIKELY	NO
				Hypoxia	3	UNLIKELY	NO
25	A1	215	2	Neutrophil count decreased	3	POSSIBLE	NO
28	A1	215	1	Vomiting	3	UNLIKELY	NO
			Follow-up	Death NOS	5	UNRELATED	NO
30	A2	165	1	Neutrophil count decreased	4	POSSIBLE	YES
			Follow-up	Anorexia	3	UNLIKELY	NO
				Dehydration	3	UNLIKELY	NO
				Headache	3	UNLIKELY	NO
				Vomiting	3	UNLIKELY	NO
31	A1	215	1	Peripheral sensory neuropathy	2	PROBABLE	NO
				Tinnitus	2	PROBABLE	NO
				White blood cell decreased	2	PROBABLE	NO
				Dizziness	3	PROBABLE	YES

				Neutrophil count decreased	3	PROBABLE	NO
32	A3	165	3	Catheter related infection	3	UNLIKELY	NO
33	A1	215	Follow-up	Intracranial hemorrhage	5	POSSIBLE	YES
34	A1	215	2	Neutrophil count decreased	2	POSSIBLE	NO
			3	Nail loss	1	POSSIBLE	NO
				Vomiting	1	POSSIBLE	NO
				Pain	2	POSSIBLE	NO
				Pain	2	POSSIBLE	NO
				Skin infection	3	UNLIKELY	NO
				Neutrophil count decreased	3	POSSIBLE	NO
			4	Headache	2	POSSIBLE	NO
Neutrophil count decreased	3	POSSIBLE		NO			
5	Neutrophil count decreased	2	POSSIBLE	NO			
35	A3	165	1	Hypoalbuminemia	2	POSSIBLE	NO
				Bone pain	3	UNRELATED	NO
			2	Hypotension	2	UNRELATED	NO
				Anemia	3	UNLIKELY	NO
				Fever	3	UNLIKELY	NO
Infections and infestations - Other, specify (with normal ANC: Blood)	3	POSSIBLE	NO				
36	A2	165	Follow-up	Skin infection	3	UNRELATED	NO
37	A2	165	1	Neutrophil count decreased	2	PROBABLE	NO
			4	Neutrophil count decreased	2	PROBABLE	NO
			5	Neutrophil count decreased	2	PROBABLE	NO
			6	Neutrophil count decreased	2	PROBABLE	NO
			7	Neutrophil count decreased	2	PROBABLE	NO
			8	Neutrophil count decreased	2	POSSIBLE	NO
			19	Eye disorders - Other, specify (Blue discoloration to vision)	2	PROBABLE	YES
39	A2	165	3	Neutrophil count decreased	2	PROBABLE	NO
			5	Neutrophil count decreased	3	POSSIBLE	NO
			6	Catheter related infection	3	UNRELATED	NO
				Neutrophil count decreased	3	UNLIKELY	NO
9	Renal and urinary disorders - Other, specify (enlarged kidneys)	2	POSSIBLE	NO			
40	A2	165	1	Infections and infestations - Other, specify (Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L): Catheter-related)	3	UNLIKELY	NO
			3	Fever	3	UNLIKELY	NO
			5	Infections and infestations - Other, specify (Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L): Catheter-related)	3	UNLIKELY	NO
				Neutrophil count decreased	4	UNLIKELY	NO

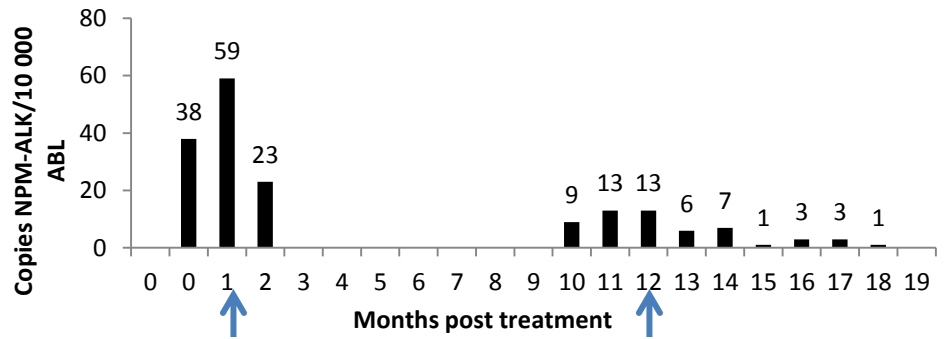
			16	Infections and infestations - Other, specify (Disseminated Varicella Zoster)	3	UNRELATED	NO
				Febrile neutropenia	3	POSSIBLE	NO
42	A2	165	2	Hypoalbuminemia	2	POSSIBLE	NO
44	A1	215	6	Infections and infestations - Other, specify (Chest wall bacterial cellulitis)	3	UNRELATED	NO
			9	Infections and infestations - Other, specify (Chest wall abscess requiring drainage.)	3	UNLIKELY	NO
48	A1	280	8	Skin infection	2	PROBABLE	YES
50	A1	280	1	Nervous system disorders - Other, specify (presyncope)	2	POSSIBLE	NO
51	A2	215	6	Flatulence	2	POSSIBLE	NO
62	A2	280	2	Infections and infestations - Other, specify (Viral gastroenteritis)	3	UNLIKELY	NO
64	A1	365	1	Alanine aminotransferase increased	4	PROBABLE	YES
				Aspartate aminotransferase increased	4	PROBABLE	YES
				GGT increased	4	PROBABLE	YES
67	A1	365	Follow-up	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify (Progressive disease)	5	UNLIKELY	NO
70	A1	365	Follow-up	Respiratory failure	4	UNRELATED	NO
71	A1	365	1	Pain	3	UNRELATED	NO
				Myositis	3	UNLIKELY	NO
72	A1	365	2	Personality change	2	POSSIBLE	NO
76	A2	280	Follow-up	General disorders and administration site conditions - Other, specify (Death NOS)	5	UNRELATED	NO
79	A2	280	2	Anemia	3	UNLIKELY	NO
			2	Epistaxis	3	UNLIKELY	NO
			2	Platelet count decreased	4	UNLIKELY	NO
			3	Death NOS	5	UNRELATED	NO

Figure

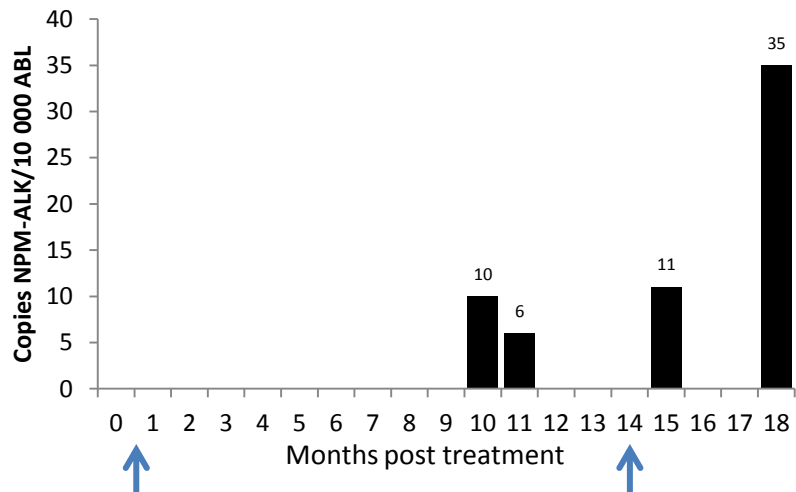
A.



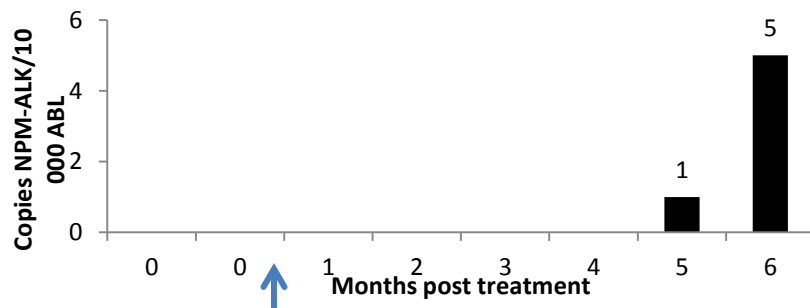
B.



C.



D.



Crizotinib Dose assignment: 280 mg/m²/dose (RP2D)

BSA (m ²)	Crizotinib (mg/day)	Crizotinib (mg PO BID)	
	Total Daily Dose	mg q am	mg q hs
0.30-0.33	180	90	90
0.34-0.37	200	100	100
0.38-0.41	220	110	110
0.42-0.45	240	120	120
0.46-0.48	260	130	130
0.49-0.51	280	140	140
0.52-0.55	300	150	150
0.56-0.58	320	160	160
0.59-0.62	340	170	170
0.63-0.66	360	180	180
0.67-0.69	380	190	190
0.70-0.73	400	200	200
0.74-0.76	420	210	210
0.77-0.80	440	220	220
0.81-0.83	460	230	230
0.84-0.87	480	240	240
0.88-0.91	500	250	250
0.92-0.94	520	260	260
0.95-0.98	540	270	270
0.99-1.03	560	280	280
1.04-1.09	600	300	300
1.10-1.12	620	310	310
1.13-1.16	640	320	320
1.17-1.21	660	330	330
1.22-1.26	700	350	350
1.27-1.30	720	360	360
1.31-1.37	740	370	370
1.38-1.44	800	400	400
1.45-1.48	820	410	410
1.49-1.55	840	420	420
1.56-1.62	900	450	450
1.63-1.71	920	460	460
1.72-1.80	1000	500	500
1.81-1.89	1020	510	510
≥ 1.90	1100	550	550