SUPPLEMENTARY MATERIALS

Supplementary Table 1. Summary of ALK status by central and local laboratory testing (as-treated population; N=1066)

	Central laboratory test results									
	ALK-positive		ALK-negative		ALK uninformative		Not done		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Local laboratory test results										
Positive	163	(15)	52	(5)	36	(3)	70	(7)	321	(30)
Negative	3	(0.3)	0	(0)	0	(0)	0	(0)	3	(0.3)
Uninformative	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
No local test performed	742	(70)	0	(0)	0	(0)	0	(0)	742	(70)
Total	908	(85)	52	(5)	36	(3)	70	(7)	1066	(100)

Supplementary Table 2. Patient disposition at time of data cut-off (as-treated population, N=1066)

Disposition	n (%)
Treatment ongoing	122 (11)
Discontinued treatment	944 (89)
Adverse event	76 (7)
Deterioration of health status	286 (27)
Lost to follow-up	3 (<1)
Objective progression or relapse (progressive disease)	329 (31)
Patient died	134 (13)
Patient refused to continue treatment for reason other than adverse event	64 (6)
Other*	52 (5)

*****Other reasons included: continuing crizotinib off study (38 patients), disease progression / no longer continued benefit (10 patients), pregnancy (1 patient), refused further follow-up (2 patients), and to be enrolled in another study (1 patient).

Supplementary Table 3: Progression-free survival and overall survival by number of prior therapies (as-treated population)

	Central ALK-testing subgroup		Local ALK-testing subgroup		Central ALK-testing subgroup		Local ALK-testing subgroup	
Number of prior therapies	*n/N**	Median PFS** (95% CI)†	*n/N**	Median PFS** (95% CI)†	*n/N**	Median OS** (95% CI)†	*n/N**	Median OS** (95% CI)†
1	170/231	9.7 (8.2, 11.1)	49/67	7.0 (5.5, 9.5)	134/231	26.4 (22.6, 33.0)	50/67	16.0 (12.0, 24.2)
2	273/335	6.9 (5.7, 7.0)	37/49	10.9 (5.0, 15.2)	231/335	17.6 (14.9, 20.6)	34/49	23.0 (13.4, 29.8)
≥3	258/340	10.9 (8.7, 12.4)	33/42	5.5 (2.8, 6.9)	228/340	23.2 (19.2, 27.0)	31/42	13.9 (10.4, 20.2)

ALK=anaplastic lymphoma kinase, CI=confidence interval, OS=overall survival, PFS=progression free survival.

*Number with event/total number of patients.

**Months.

†Based on Brookmeyer and Crowley method.

Supplementary Table 4. Summary of shifts from CTCAE grade ≤2 at baseline to CTCAE grade 3 or 4 postbaseline for clinical laboratory abnormalities (as-treated population, N=1066).

	N	Patients with shift from CTCAE grade ≤2 to grade 3 or 4 n (%)
Hematology		
Lymphopenia	1035	210 (20.3)
Neutrophils (absolute)	1035	152 (14.7)
Anemia	1036	43 (4.2)
White blood cells	1036	42 (4.1)
Platelets	1035	20 (1.9)
Clinical chemistry		
Hypophosphatemia	1032	126 (12.2)
Alanine aminotransferase	1034	101 (9.8)
Aspartate aminotransferase	1035	46 (4.4)
Alkaline phosphatase	1032	29 (2.8)
Creatinine	1038	13 (1.3)
Total bilirubin	1034	9 (0.9)

CTCAE=Common Terminology Criteria for Adverse Events

Supplementary Table 5. Treatment-related adverse events associated with permanent treatment discontinuation (as-treated population; N=1066). All events are shown.

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any	10	(0.9)	3	(0.3)	23	(2)	11	(1)	13	(1)	60	(6)
Interstitial lung disease[a]*	3	(0.3)	2	(0.2)	2	(0.2)	3	(0.3)	3	(0.3)	13	(1)
Elevated transaminases[a]	1	(0.1)	1	(0.1)	7	(0.7)	0	(0)	0	(0)	9	(0.8)
Hepatotoxicity[a]	0	(0)	0	(0)	1	(0.1)	5	(0.5)	1	(0.1)	7	(0.7)
Pneumonia	0	(0)	0	(0)	1	(0.1)	0	(0)	3	(0.3)	4	(0.4)
Dyspnea	0	(0)	0	(0)	2	(0.2)	0	(0)	1	(0.1)	3	(0.3)
Death	0	(0)	0	(0)	0	(0)	0	(0)	3	(0.3)	3	(0.3)
Edema	0	(0)	0	(0)	2	(0.2)	0	(0)	0	(0)	2	(0.2)
Lung infection	0	(0)	0	(0)	1	(0.1)	0	(0)	1	(0.1)	2	(0.2)
Renal cyst[a]	1	(0.1)	0	(0)	1	(0.1)	0	(0)	0	(0)	2	(0.2)
Acute kidney injury	0	(0)	0	(0)	1	(0.1)	0	(0)	0	(0)	1	(0.1)
Atrial fibrillation	0	(0)	0	(0)	1	(0.1)	0	(0)	0	(0)	1	(0.1)
Blood creatinine	0	(0)	0	(0)	1	(0.1)	0	(0)	0	(0)	1	(0.1)
Bradycardia[a]	1	(0.1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.1)
Cellulitis	0	(0)	0	(0)	1	(0.1)	0	(0)	0	(0)	1	(0.1)
Chest wall mass	1	(0.1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.1)
Colitis	0	(0)	0	(0)	1	(0.1)	0	(0)	0	(0)	1	(0.1)
Decreased appetite	0	(0)	0	(0)	1	(0.1)	0	(0)	0	(0)	1	(0.1)
Dysgeusia	1	(0.1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.1)
Fatigue	0	(0)	0	(0)	1	(0.1)	0	(0)	0	(0)	1	(0.1)
Hypokalemia	0	(0)	0	(0)	0	(0)	1	(0.1)	0	(0)	1	(0.1)
Mass	0	(0)	0	(0)	1	(0.1)	0	(0)	0	(0)	1	(0.1)
Neuropathy[a]	1	(0.1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.1)
Neutropenia[a]	0	(0)	0	(0)	0	(0)	1	(0.1)	0	(0)	1	(0.1)
Pulmonary embolism	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.1)	1	(0.1)
Visual loss	0	(0)	0	(0)	0	(0)	1	(0.1)	0	(0)	1	(0.1)
Vomiting	1	(0.1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.1)

[a]Certain preferred terms were analyzed in aggregate using clustered terms, because the frequency of certain medical concepts or conditions may have been underestimated by reliance on single Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. MedDRA Preferred Terms within each clustered term that were actually reported are marked with an asterisk: Bradycardia (Bradyarrhythmia or Bradycardia* or Heart rate decreased* or Sinus arrest or Sinus bradycardia*); Elevated transaminases (Alanine aminotransferase or Alanine aminotransferase abnormal* or Alanine aminotransferase increased* or Aspartate aminotransferase or Aspartate aminotransferase abnormal* or Aspartate aminotransferase increased* or Gamma-glutamyltransferase abnormal or Gamma-glutamyltransferase increased* or Hepatic enzyme abnormal or Hepatic enzyme increased* or Hepatic function abnormal* or Hypertransaminasemia or Liver function test abnormal or Transaminases or Transaminases abnormal or Transaminases increased*); Hepatotoxicity (Acute hepatic failure or Cholestatic liver injury or Coma hepatic or Drug-induced liver injury* or Hepatic encephalopathy or Hepatic failure* or Hepatic necrosis or Hepatic steatosis* or Hepatitis fulminant or Hepatocellular injury* or Hepatorenal failure or Hepatorenal syndrome or Hepatotoxicity* or Liver disorder* or Liver injury* or Mixed liver injury or Subacute hepatic failure); Interstitial lung disease (Acute interstitial pneumonitis or Acute lung injury or Acute respiratory distress syndrome* or Alveolitis* or Alveolitis allergic or Alveolitis necrotising or Diffuse alveolar damage or Eosinophilic pneumonia or Eosinophilic pneumonia acute or Idiopathic pulmonary fibrosis or Interstitial lung disease* or Pneumonitis* or Pulmonary toxicity); Neuropathy (Acute polyneuropathy or Amyotrophy or Areflexia or Autoimmune neuropathy or Autonomic failure syndrome or Autonomic neuropathy or Axonal neuropathy or Biopsy peripheral nerve abnormal or Burning feet syndrome or Burning sensation* or Decreased vibratory sense or Demyelinating polyneuropathy or Dysaesthesia* or Electromyogram abnormal or Formication* or Gait disturbance* or Genital hypoaesthesia or Guillain-Barre syndrome or Hyperaesthesia* or Hypoaesthesia* or Hyporeflexia or Hypotonia* or Ischaemic neuropathy or Loss of proprioception or Miller Fisher syndrome or Mononeuritis or Mononeuropathy or Mononeuropathy multiplex or Motor dysfunction* or Multifocal motor neuropathy or Muscle atrophy* or Muscular weakness* or Myelopathy or Nerve conduction studies abnormal or Nerve degeneration or Neuralgia* or Neuritis* or Neuromuscular toxicity or Neuromyopathy or Neuropathy peripheral* or Neuropathy vitamin B6 deficiency or Neurotoxicity* or Paraesthesia* or Peripheral motor neuropathy* or Peripheral nerve lesion or Peripheral nerve palsy or Peripheral nervous system function test abnormal or Peripheral sensorimotor neuropathy* or Peripheral sensory neuropathy* or Peroneal muscular atrophy or Peroneal nerve palsy* or Phrenic nerve paralysis or Polyneuropathy* or Polyneuropathy chronic or Polyneuropathy idiopathic progressive or Radiation neuropathy or Sensorimotor disorder or Sensory disturbance* or Sensory loss or Skin burning sensation* or Temperature perception test decreased or Tinel's sign or Toxic neuropathy* or Ulnar neuritis); Neutropenia (Febrile neutropenia* or Neutropenia* or Neutrophil count decreased*); Renal cyst (Renal abscess* or Renal cyst* or Renal cyst excision or Renal cyst hemorrhage* or Renal cyst infection* or Renal cyst ruptured).

Supplementary Table 6. Treatment-related serious adverse events (as-treated population; N=1066). Data are shown for SAEs that occurred in ≥0.2% of patients.

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any	9	(0.8)	24	(2)	58	(5)	13	(1)	15	(1)	119	(11)
Renal cyst[a]	5	(0.5)	2	(0.2)	9	(0.8)	0	(0)	0	(0)	16	(2)
Interstitial lung disease[a]	2	(0.2)	3	(0.3)	4	(0.4)	2	(0.2)	4	(0.4)	15	(1)
Hepatotoxicity[a]*	0	(0)	0	(0)	2	(0.2)	4	(0.4)	2	(0.2)	8	(0.8)
Edema	0	(0)	4	(0.4)	3	(0.3)	0	(0)	0	(0)	7	(0.7)
Dyspnea	0	(0)	3	(0.3)	2	(0.2)	0	(0)	1	(0.1)	6	(0.6)
Pneumonia	0	(0)	0	(0)	3	(0.3)	0	(0)	3	(0.3)	6	(0.6)
Elevated transaminases[a]	0	(0)	0	(0)	4	(0.4)	1	(0.1)	0	(0)	5	(0.5)
Deep vein thrombosis	0	(0)	2	(0.2)	1	(0.1)	1	(0.1)	0	(0)	4	(0.4)
Neutropenia[a]	0	(0)	0	(0)	2	(0.2)	2	(0.2)	0	(0)	4	(0.4)
Nausea	0	(0)	1	(0.1)	3	(0.3)	0	(0)	0	(0)	4	(0.4)
Pulmonary embolism	0	(0)	0	(0)	3	(0.3)	0	(0)	1	(0.1)	4	(0.4)
Acute kidney injury	0	(0)	2	(0.2)	1	(0.1)	0	(0)	0	(0)	3	(0.3)
Death	0	(0)	0	(0)	0	(0)	0	(0)	3	(0.3)	3	(0.3)
Cellulitis	0	(0)	0	(0)	2	(0.2)	0	(0)	0	(0)	2	(0.2)
Dehydration	0	(0)	1	(0.1)	1	(0.1)	0	(0)	0	(0)	2	(0.2)
Diarrhoea	0	(0)	1	(0.1)	1	(0.1)	0	(0)	0	(0)	2	(0.2)
Gastrointestinal hemorrhage	0	(0)	1	(0.1)	1	(0.1)	0	(0)	0	(0)	2	(0.2)
Hyponatremia	0	(0)	0	(0)	1	(0.1)	1	(0.1)	0	(0)	2	(0.2)
Lung infection	0	(0)	0	(0)	1	(0.1)	0	(0)	1	(0.1)	2	(0.2)

Event	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Squamous cell carcinoma of the skin	0	(0)	2	(0.2)	0	(0)	0	(0)	0	(0)	2	(0.2)

[a]Certain preferred terms were analyzed in aggregate using clustered terms, because the frequency of certain medical concepts or conditions may have been underestimated by reliance on single Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. MedDRA Preferred Terms within each clustered term that were actually reported are marked with an asterisk:*: Elevated transaminases (Alanine aminotransferase or Alanine aminotransferase abnormal* or Alanine aminotransferase increased* or Aspartate aminotransferase or Aspartate aminotransferase abnormal* or Aspartate aminotransferase increased* or Gamma-glutamyltransferase abnormal or Gamma-glutamyltransferase increased* or Hepatic enzyme abnormal or Hepatic enzyme increased* or Hepatic function abnormal* or Hypertransaminasemia or Liver function test abnormal or Transaminases or Transaminases abnormal or Transaminases increased*); Hepatotoxicity (Acute hepatic failure or Cholestatic liver injury or Coma hepatic or Drug-induced liver injury* or Hepatic encephalopathy or Hepatic failure* or Hepatic necrosis or Hepatic steatosis* or Hepatitis fulminant or Hepatocellular injury* or Hepatorenal failure or Hepatorenal syndrome or Hepatotoxicity* or Liver disorder* or Liver injury* or Mixed liver injury or Subacute hepatic failure); Interstitial lung disease (Acute interstitial pneumonitis or Acute lung injury or Acute respiratory distress syndrome* or Alveolitis* or Alveolitis allergic or Alveolitis necrotising or Diffuse alveolar damage or Eosinophilic pneumonia or Eosinophilic pneumonia acute or Idiopathic pulmonary fibrosis or Interstitial lung disease* or Pneumonitis* or Pulmonary toxicity); Neutropenia (Febrile neutropenia* or Neutropenia* or Neutrophil count decreased*); RENAL CYST (Renal abscess* or Renal cyst* or Renal cyst excision or Renal cyst hemorrhage* or Renal cyst infection* or Renal cyst ruptured).

Supplementary Table 7. Grade 5 treatment-related adverse events (as-treated population; N=1066)

Event	N (%)
Any AE	15 (1.4)
Interstitial lung disease	4 (0.4)
Pneumonia	3 (0.3)
Death 3	(0.3)
Hepatotoxicity	2 (0.2)
Dyspnea	1 (0.1)
Pulmonary embolism	1 (0.1)
Lung infection	1 (0.1)

Supplementary Table 8. Change in EORTC (QLQ-C30 and QLQ-LC13) scales relative to baseline (PRO-evaluable population; N=976)

Scale	Domain	Improved*		Stable**		Worsening***	
		n	(%)	n	(%)	n	(%)
EORTC	Global QOL	415	(43)	376	(39)	179	(18)
QLQ-C30							
Functional	Physical functioning	333	(34)	506	(52)	136	(14)
scales	Role functioning	342	(35)	415	(43)	217	(22)
QLQ-C30	Emotional functioning	338	(35)	509	(52)	122	(13)
	Cognitive functioning	234	(24)	525	(54)	212	(22)
	Social functioning	403	(41)	375	(38)	191	(20)
Symptom	Fatigue	451	(46)	364	(37)	160	(16)
scales/items	Nausea and vomiting	213	(22)	507	(52)	255	(26)
QLQ-C30	Pain	470	(48)	392	(40)	113	(12)
	Dyspnea	411	(42)	408	(42)	154	(16)
	Insomnia	420	(43)	396	(41)	159	(16)
	Appetite loss	355	(36)	420	(43)	200	(21)
	Constipation	185	(19)	356	(37)	428	(44)
	Diarrhea	104	(11)	438	(45)	427	(44)
	Financial difficulties	249	(26)	553	(57)	167	(17)
Symptoms	Dyspnea	403	(41)	430	(44)	139	(14)
scales/items	Coughing	498	(51)	343	(35)	132	(14)
QLQ-LC13	Hemoptysis	89	(9)	863	(88)	21	(2)
	Sore mouth	119	(12)	744	(76)	111	(11)
	Dysphagia	149	(15)	701	(72)	123	(13)
	Peripheral neuropathy	216	(22)	518	(53)	238	(24)
	Alopecia	274	(28)	565	(58)	132	(14)
	Pain in chest	359	(37)	524	(54)	90	(9)
	Pain in arm or shoulder	352	(36)	498	(51)	120	(12)
	Pain in other parts	398	(41)	396	(41)	159	(16)

EORTC=European Organisation for the Research and Treatment of Cancer; PRO=patient-reported outcome; QOL=quality of life. *≥10-point improvement in the average of mean changes. **Neither improved nor worsened. **≥10-point deterioration in the average of mean changes.