Abstract 8047

Updated Efficacy and Safety of the ALK Inhibitor AP26113 in Patients with Advanced Malignancies, Including ALK+ Non-Small Cell Lung Cancer (NSCLC)

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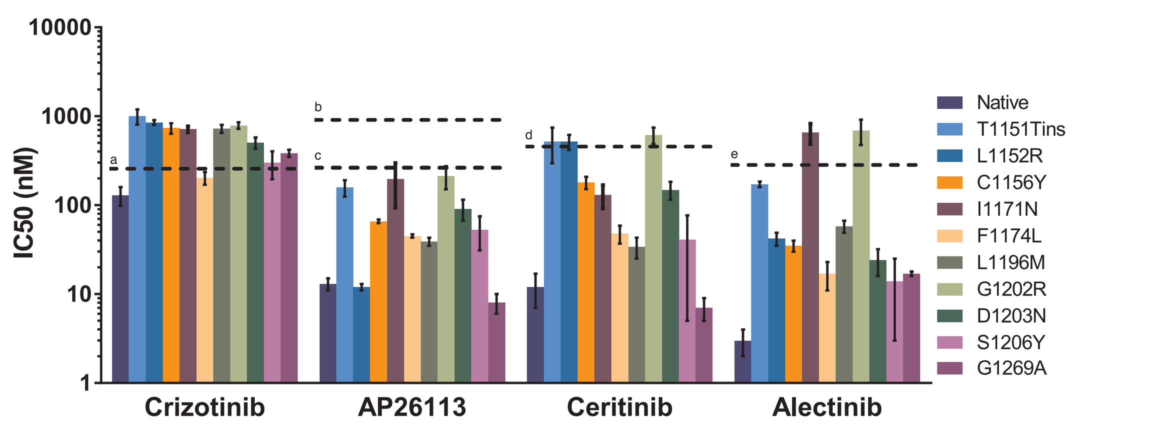
INTRODUCTION

- Anaplastic Lymphoma Kinase (ALK) gene rearrangements have been identified as driver events in non-small cell lung cancer (NSCLC)[1] and other cancers[2]
- Crizotinib is active in patients with ALK rearranged (ALK+) NSCLC[3], but most patients eventually develop disease progression
  - ~46% of patients first progress in brain, suggesting inadequate CNS exposure[4]
  - Systemic progression usually occurs later, through diverse mechanisms, including multiple ALK mutations[4,5,6]
- AP26113 is an investigational orally-active tyrosine kinase inhibitor with potent preclinical activity against native ALK (13 nM) and a broad range of activity against resistant mutants
  - Including all 10 clinically-identified crizotinib-resistant mutants identified to date[7,8]

Figure 1. AP26113 Exhibits a Pan-ALK Inhibitory Profile in Cellular Models



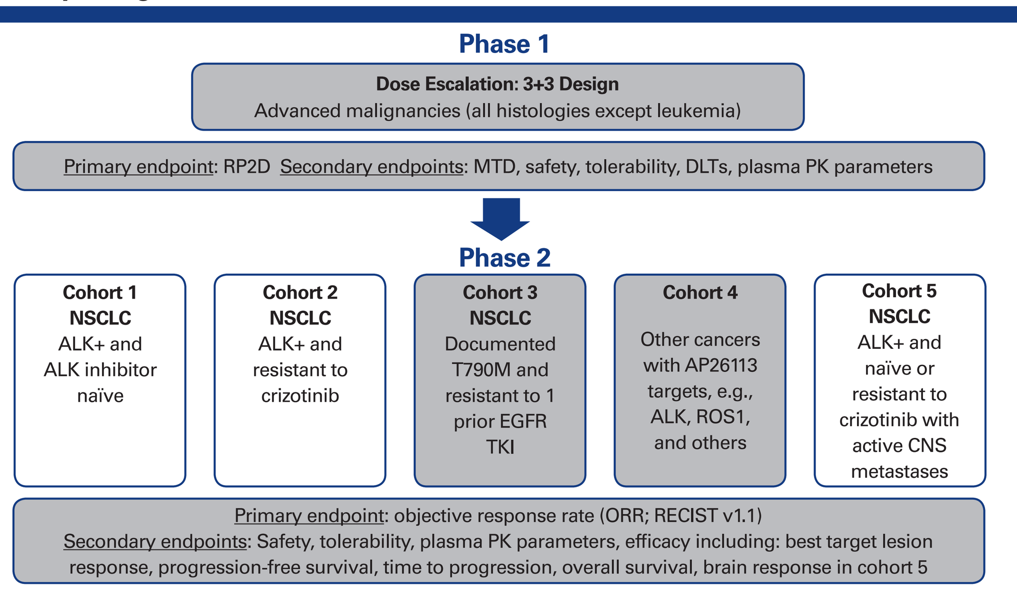
50% maximal inhibitory concentration (IC50) values of Ba/F3 cells dependent on expression of EML4-ALK (native) or kinase domain mutated EML4-ALK variants (n=10). Data for each cell line is derived from at least 4 independent experiments (error bars=standard error). Dashed horizontal lines indicate the mean steady-state exposure concentrations of each drug corrected for the functional effects of protein binding at the recommended phase 2 doses: [a]Crizotinib: 250 mg bid, 259 nM[9]; AP26113: [b]180 mg qd, 899 nM and [c]90 mg qd, 264 nM[10]; [d]Ceritinib: 750 mg qd, 456 nM[11]; [e]Alectinib: 600 mg bid, 277 nM[12]

OBJECTIVE

The Phase 2 portion of a Phase 1/2 single arm, multicenter study in patients with advanced malignancies is underway. We report updated safety for all treated patients and efficacy data for ALK+ NSCLC patients (ClinicalTrials.gov NCT01449461).

METHODS

Figure 2. Study Design



RP2D=recommended phase 2 dose, MTD=maximum tolerated dose, DLT= dose limiting toxicity. White boxes indicate open to enrollment. Safety data reported for all treated patients and efficacy data reported for ALK+ NSCLC patients, with a focus on cohorts 1, 2, and 5.

Key Inclusion Criteria:

- Histologically confirmed advanced malignancies, all histologies except leukemia (phase 1 only)
- Disease refractory to available therapies or for which no standard treatment exists (phase 1 only)
- Tumor tissue available for analysis
- Must have measurable disease by RECIST v1.1[13]
- Must meet all the criteria for the cohort for which entry is proposed (see Figure 2)

Study Dynamics:

- Data as of 17 March 2014 are presented
- Analysis populations:
  - Patients were evaluable for safety analyses if they received at least 1 dose of AP26113
  - Patients were evaluable for response analyses if they received at least 1 dose of AP26113 and had a post-baseline scan or discontinued from the study
- Adverse events (AEs) were graded per NCI CTCAE v4.0
- Plasma PK assessments were performed on blood samples collected at specified time points pre-dosing and post-dosing (0.5, 1, 2, 4, 6, 8, 24, and 48 hr). Steady-state PK assessments occurred on day 29. For twice daily (bid) dosing, only the first dose on day 29 was administered.

RESULTS

Table 1. Demographics and Baseline Characteristics

	All Patients N=125	History of ALK+ N=71
Median age, yrs (range)	57 (29-83)	54 (29-73)
Sex, female, n (%)	72 (58)	37 (52)
Race, n (%)		
White	100 (80)	58 (82)
Asian	15 (12)	9 (13)
Other	10 (8)	4 (6)
Diagnosis, n (%)		
Non-small cell lung cancer (NSCLC)	117 (94)	67 (94)
Adenocarcinoma	108 (86)	62 (87)
Other	8 (6)	4 (6)[b]
ECOG[a], n (%)		
0	38 (30)	25 (35)
1	82 (66)	43 (61)
2	3 (2)	1 (1)
Prior crizotinib, n (%)	69 (55)	63 (89)[c]
Prior chemotherapy, n (%)		
1 regimen	32 (26)	17 (24)
2 regimens	29 (23)	19 (27)
≥3 regimens	27 (22)	12 (17)

[a]Protocol amendment as of 30 November 2012 restricted enrollment to ECOG 0 or 1.
[b]Inflammatory myofibroblastic tumor (2), neuroendocrine carcinoma (1), adenocarcinoma of unknown primary origin (ACUP; 1)
[c]3 ALK+ NSCLC patients previously received ceritinib in addition to crizotinib

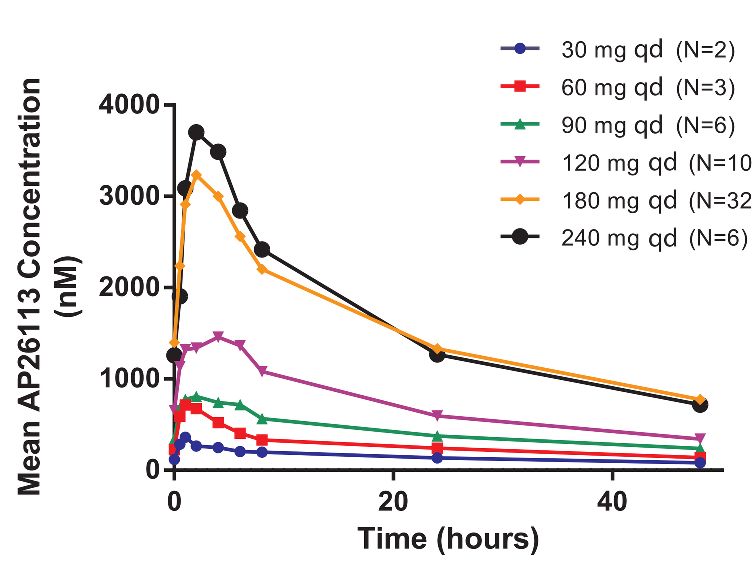
Table 2. Patient Disposition

	All Patients N=125 n (%)	History of ALK+ N=71 n (%)
Remain on study	62 (50)	53 (75)
Discontinued treatment	63 (50)	18 (25)
Documented progressive disease	38 (30)	8 (11)
Adverse event	12 (10)	5 (7)
Clinical progressive disease	6 (5)	2 (3)
Death[a]	4 (3)	2 (3)
Withdrawal by subject	2 (2)	1 (1)
Physician decision	1 (1)	0

[a]2 deaths were considered possibly related by the investigator: sudden death in 1 patient (180 mg) on day 3 (last dose day 2), hypoxia in 1 patient (180 mg) on day 5 (last dose day 1); 2 deaths were considered not related: acute respiratory distress syndrome following lung infection in 1 patient (180 mg) on day 17 (last dose day 4), pneumonia in 1 patient (120 mg) on day 15 (last dose day 1). No deaths reported as a reason for discontinuation since 17 April 2013.

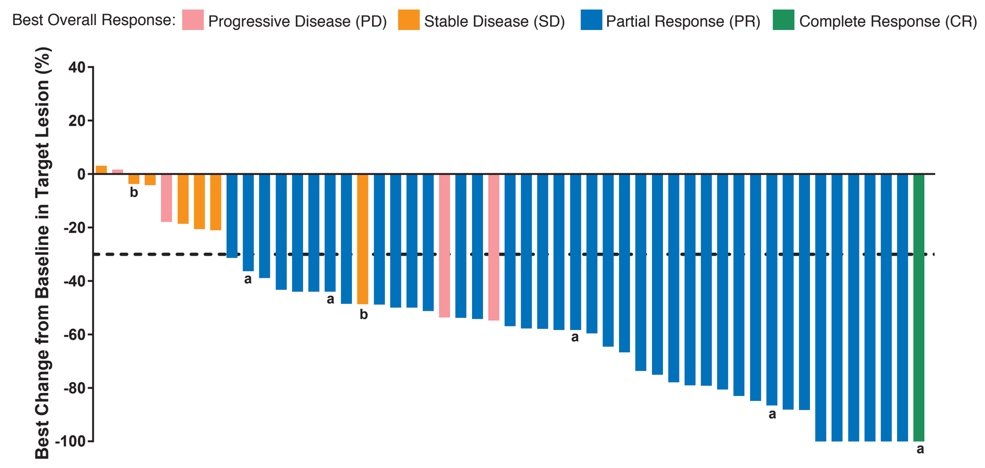
- Median time on treatment for all patients is 3.1 months (max= 24.4 months, ongoing)

Figure 3. AP26113 Pharmacokinetics at Steady State (Day 29)



- At doses of 90 mg and higher, mean plasma steady-state trough drug concentrations exceeded levels predicted preclinically to inhibit crizotinib-resistant ALK mutants.

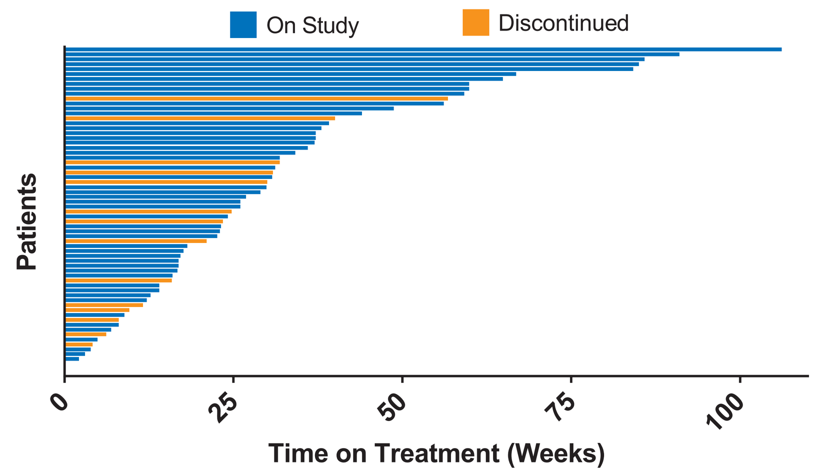
Figure 4. AP26113 Anti-Tumor Activity in ALK+ NSCLC Patients



N=51. All patients received prior crizotinib unless otherwise indicated; Doses ranged from 60-240 mg/d (43 pts 90-180mg/d);
[a]TKI-naïve- 5 of 6 TKI-naïve patients had best target lesion response data entered at time of analysis; [b]Received prior crizotinib and ceritinib

- Among 57 evaluable ALK+ NSCLC patients, 41 (72%) responded (95% CI: 59-83%)
  - Among 51 evaluable ALK+ NSCLC patients with prior crizotinib, 35 (69%) responded (95% CI: 54-81%)
    - 23 patients had confirmed responses; 7 await confirmation
    - 5 patients are not confirmed: 1 had a partial response and then discontinued; 4 had partial responses and then progressive disease
    - Duration of response was 1.6 – 14.7 months (ongoing)
    - 27 (53%) responded by the first 8 week assessment; among patients who responded, the average time to response was 9.3 weeks (+/- 3.72 weeks)
    - Among 49 patients with follow-up scans, median progression-free survival (Kaplan-Meier estimate) is 10.9 months
  - Among 6 evaluable ALK+, crizotinib-naïve NSCLC patients, 6 (100%) responded (including 1 CR)
    - All responses are ongoing. Of the 4 with a confirmed response, the duration of response is 1.9 – 12.9 months
    - 5 (83%) responded by first 8 week assessment and, among patients who responded, the average time to response was 9.2 weeks (+/- 3.22 weeks)

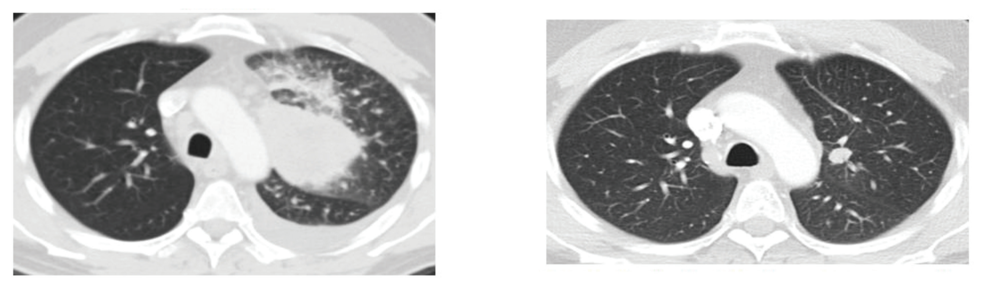
Figure 5. ALK+ NSCLC Time on Treatment



First dose to last dose if discontinued, first dose to date of data cut if on study

- 50/67 (75%) ALK+ NSCLC patients remain on therapy
- 31 ALK+ NSCLC patients have received treatment for at least 6 months; of these, 26 (84%) continue on study

Figure 6. AP26113 Activity in an ALK+ NSCLC Patient



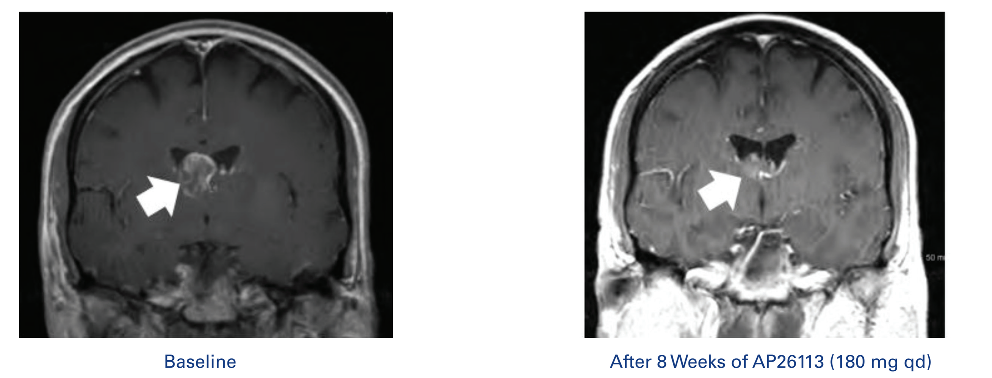
Baseline — After 16 Weeks of AP26113 (180 mg qd)

Patient with ALK+ NSCLC, TKI naïve. PR is ongoing.

Images courtesy of Dr. C. Langer

Figure 7. AP26113 Activity in ALK+ NSCLC Patients with Brain Metastases

A.

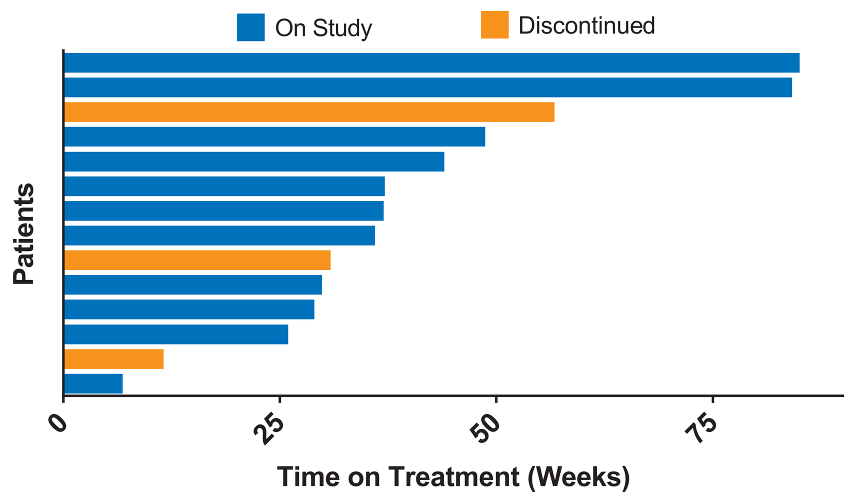


Baseline — After 8 Weeks of AP26113 (180 mg qd)

Patient with ALK+ NSCLC previously treated with crizotinib. PR is ongoing.

Images courtesy of Dr. D.R. Camidge

B. Time on Treatment - ALK+ NSCLC Patients with Brain Metastases



- 14 (13 evaluated; 1 not evaluable) patients were analyzed for regression in the brain:
  - 10 patients enrolled with untreated or progressive brain metastases were included in an independent review of their brain scans
  - 4 patients (3 evaluable) were enrolled in cohort 5
- 9/13 (69%) patients had regression of their brain metastases following treatment with AP26113
  - By independent review
    - 4 patients had CR (undetectable brain metastases following AP26113)
    - 2 patients had PR
    - 4/10 patients included in the independent review did not have regression of their brain metastases following treatment with AP26113
      - 2 patients had SD
      - 2 patients progressed
  - 3 more patients evaluated from cohort 5 had evidence of regression
- The longest time on treatment was 85 weeks
- 11/14 (79%) patients remain on study
- In addition, improvement in a patient with leptomeningeal metastasis (LMD) was observed

Table 3. Treatment-Emergent Adverse Events, All Causality

Preferred terms (≥10% incidence, all grades)	30, 60 mg N= 6 n (%)	90 mg N= 10 n (%)	90 mg → 180 mg N= 28 n (%)	120 mg N= 18 n (%)	180 mg N= 48 n (%)	240, 300 mg N= 15 n (%)	Total N= 125 n (%)
Nausea	3 (50)	3 (30)	5 (18)	7 (39)	25 (52)	7 (47)	50 (40)
Fatigue	2 (33)	3 (30)	7 (25)	6 (33)	13 (27)	12 (80)	43 (34)
Diarrhea	1 (17)	4 (40)	8 (29)	8 (44)	14 (29)	7 (47)	42 (34)
Cough	1 (17)	3 (30)	4 (14)	6 (33)	10 (21)	8 (53)	32 (26)
Headache	0	4 (40)	4 (14)	6 (33)	11 (23)	6 (40)	31 (25)
Vomiting	1 (17)	1 (10)	2 (7)	5 (28)	12 (25)	5 (33)	26 (21)
Dyspnea	0	2 (20)	1 (4)	6 (33)	8 (17)	6 (40)	23 (18)
Amylase increased	0	2 (20)	7 (25)	4 (22)	6 (13)	2 (13)	21 (17)
Decreased appetite	0	3 (30)	1 (4)	1 (6)	10 (21)	5 (33)	20 (16)
Constipation	1 (17)	2 (20)	2 (7)	4 (22)	4 (8)	5 (33)	18 (14)
Muscle spasms	1 (17)	1 (10)	2 (7)	2 (11)	9 (19)	3 (20)	18 (14)
AST increased	0	1 (10)	2 (7)	6 (33)	7 (15)	1 (7)	17 (14)
Peripheral edema	1 (17)	2 (20)	0	3 (17)	5 (10)	5 (33)	16 (13)
Arthralgia	1 (17)	2 (20)	6 (21)	0	5 (10)	0	14 (11)
Back pain	1 (17)	0	3 (11)	3 (17)	5 (10)	1 (7)	13 (11)
Lipase increased	0	1 (10)	4 (14)	3 (17)	3 (6)	2 (13)	13 (11)

- AEs considered at least possibly related to treatment occurring in ≥10% of patients were nausea (34%), diarrhea (26%), fatigue (22%), vomiting (16%), amylase increased (13%), AST increased (13%), dyspnea (12%), cough (10%), and decreased appetite (10%)
  - Treatment-related AEs Grade ≥3 occurring in 3 or more patients were dyspnea (4%), hypoxia (4%), and fatigue (2%)
- Serious AEs (all causality) occurring in 3 or more patients were dyspnea (7%), hypoxia (4%), pneumonia (4%), neoplasm progression (2%), and pulmonary embolism (2%)
- Treatment-emergent AEs of hypertension were reported in 10/125 (8%) patients (1.6% Grade 3 and no reported Grade 4 or 5 hypertension AEs)
  - 13/45 (29%) patients who had low or normal systolic blood pressure (≤120 mmHg) at baseline had a measurement of high systolic blood pressure (≥140 mmHg) on study
  - 17/80 (21%) patients who had low or normal diastolic blood pressure (≤80 mmHg) at baseline had a measurement of high diastolic blood pressure (≥90 mmHg) on study

Clinical Presentation of Early Onset Pulmonary Symptoms

- Early onset pulmonary events included dyspnea, hypoxia, and new pulmonary opacities on chest CT suggestive of pneumonia or pneumonitis
- Symptoms occurred within 7 days following initiation of AP26113, required medical intervention, and occurred at lower rates with lower doses
- Early onset pulmonary symptoms were observed in 12/125 (10%) patients at the following starting doses:
  - 1/38 (3%) at 90 mg qd
    - 1/10 at 90 mg qd
    - 0/28 at 90 mg qd →180 mg qd
  - 1/11 (9%) at 120 mg qd
  - 6/44 (14%) at 180mg qd
  - 2/10 (20%) at 240mg qd
  - 2/2 (100%) at 300mg qd
- Of 28 patients started at 90 mg for 7 days followed by an escalation to 180 mg, none had pulmonary symptoms within the first 7 days at 90 mg or within the first 7 days of escalation to 180 mg
- Patients continue to be enrolled at 90 mg qd

SUMMARY

- 35/51 (69%) crizotinib refractory ALK+ NSCLC patients responded to treatment with AP26113
  - Among 49 patients with follow-up scans, median progression-free survival is 10.9 months
- 9/13 (69%) patients had regression of untreated or progressing brain lesions following AP26113
- Most common AEs were nausea, fatigue and diarrhea, which were generally grade 1 or 2 in severity; the most common serious AE was dyspnea
- Early onset pulmonary symptoms were observed in 3% (1/38) of patients started at 90 mg qd and 14% (6/44) of patients started at 180 mg qd
- No early onset pulmonary symptoms were observed in 28 patients started at 90 mg and escalated to 180 mg after 7 days
- A separate, pivotal randomized phase 2 trial in patients with ALK+ NSCLC resistant to crizotinib (ALTA: **A**LK in **L**ung Cancer **T**rial of **A**P26113) has been initiated. Patients will receive either 90 mg qd continuously, or 90 mg qd for 7 days followed by 180 mg qd continuously

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DISCLOSURES

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