Abstract 8031

First-in-Human Dose-Finding Study of the ALK/EGFR Inhibitor AP26113 in Patients with Advanced Malignancies: Updated Results

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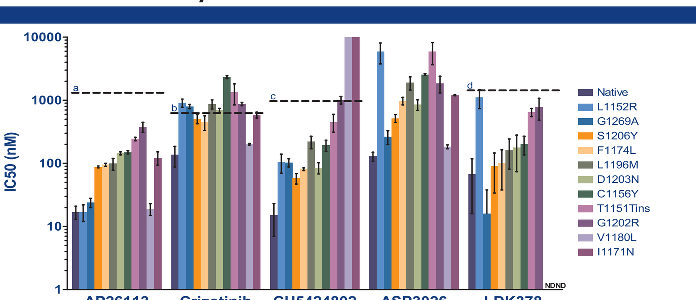
INTRODUCTION

- Anaplastic lymphoma kinase (ALK) and ROS1 translocations and epidermal growth factor receptor (EGFR) activating mutations are oncogenic drivers in subsets of non-small cell lung cancer (NSCLC).[1] ALK and ROS1 rearrangements have also been identified as potential driver abnormalities in subsets of several other solid tumors and lymphomas
- First generation tyrosine kinase inhibitors (TKIs) such as crizotinib (ALK and ROS1) and erlotinib (EGFR) exhibit robust clinical activity in ALK/ROS1+, and EGFR mutant NCSLC, respectively, but acquired resistance develops over time[2]
- In clinical trials, median overall survival in patients following failure of 1 prior EGFR TKI is approximately 9 to 11 months[3,4]; survival data in patients following failure of 1 prior ALK TKI are not yet available
- AP26113 is an ALK, ROS1, and EGFR inhibitor that inhibits native and crizotinib-resistant mutants of ALK (Table 1). AP26113 exhibits pan-ALK inhibitory activity against all 9 clinically-identified crizotinib-resistant mutants, with IC_{50}s from 17 nM (L1152R) to 379 nM (G1202R) (Figure 1). AP26113 selectively inhibits mutant EGFR (EGFRm), including the T790M resistance mutation, without affecting the native receptor, with IC_{50}s from 112 nM (exon 19 deletion) to 694 nM (L858R +T790M)[5,6,7]
- AP26113 also inhibits the insulin-like growth factor 1 receptor (IGF-1R), with an IC_{50} of 148 nM, without affecting the insulin receptor[7]

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



IC_{50}s determined in Ba/F3 cell lines; ND=not determined
The approximate steady-state trough concentrations at the recommended phase 2 dose are indicated by the dashed line, according to the following published data:
[a]AP26113: ~1300 nM at 180 mg QD (see below); [b]Crizotinib: ~620 nM at 250 mg BID (Bang et al, ASCO 2010, Abstract 3); [c]CH5424802: ~960 nM at 300 mg BID (Seto et al, Lancet Oncology, 2013); [d]LDK378: ~1400 nM at 750 mg QD (Shaw et al, ESMO 2012, Abstract 440O)
The recommended phase 2 dose for ASP3026 has not been reported

- Steady-state trough concentrations in patients treated with AP26113 (see below) or other ALK inhibitors at the recommended phase 2 dose are compared to IC_{50} values against defined ALK resistance mutations (Figure 1)
- For AP26113, clinical concentrations substantially exceed IC_{50}s for all 11 EML4-ALK mutants tested

Table 1. AP26113 Activity in Cellular Models

	IC_{50} (nM)
Ba/F3 cell line	
ALK[5]	
EML4-ALK	17
L1152R	17
G1269A	24
S1206Y	88
F1174L	95
L1196M	99
D1203N	144
C1156Y	150
T1151T insertion	244
G1202R	379
V1180L[b]	19
I1171N[b]	123
ROS1[5]	
CD74-ROS1	18
EGFR[6,7]	
DEL[a]	112
DEL[a] +T790M	282
L858R	456
L858R +T790M	694
Native EGFR	>3000
Parental Ba/F3 cell line	>3000

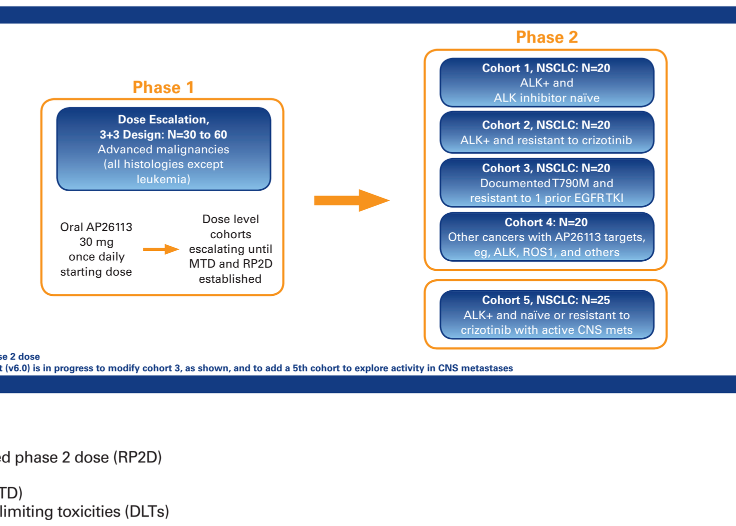
[a]Exon 19 deletion; [b]CH5424802-resistant mutants identified in an in vitro mutagenesis screen[5]

OBJECTIVE

- Assess the safety, tolerability, pharmacokinetics (PK), and preliminary anti-tumor activity of AP26113 in an open label, multi-center phase 1/2 clinical trial in patients with advanced malignancies (except leukemia) refractory to available therapies or for whom no standard treatment exists (ClinicalTrials.gov NCT10449461)

METHODS

Figure 2. Study Design



MTD: maximum tolerated dose; RP2D: recommended phase 2 dose
Enrollment began September 2011; A protocol amendment (v6.0) is in progress to modify cohort 3, as shown, and to add a 5th cohort to explore activity in CNS metastases

Study Endpoints

- Phase 1
  - Primary endpoint: recommended phase 2 dose (RP2D)
  - Secondary endpoints:
    - Maximum tolerated dose (MTD)
    - Safety, tolerability, and dose-limiting toxicities (DLTs)
    - Plasma PK parameters
- Phase 2
  - Primary endpoint: objective response rate (RECIST v1.1)[8]
  - Secondary endpoints:
    - Safety and tolerability
    - Plasma PK parameters
    - Efficacy parameters including: best target lesion response, progression-free survival, time to progression, overall survival, brain response in cohort 5

METHODS

Key Inclusion Criteria

- Histologically confirmed advanced malignancies, all histologies except leukemia (phase 1 only)
- Disease refractory to available therapies or for which no standard or available curative treatment exists (phase 1 only)
- Measurable disease by RECIST v1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (status = 2 excluded in protocol v5.0)
- Adequate renal, hepatic, and bone marrow function
- Tumor tissue available for analysis (could be archival in phase 1)
- No investigational agents or systemic anticancer or radiation therapy within 14 days prior to receiving AP26113 (except for FDA-approved ALK- or EGFR-targeted TKIs, minimum washout 72 hours)
- No symptomatic central nervous system (CNS) metastases (in phase 1)
- No history or presence of pulmonary interstitial disease (effective with protocol v5.0)

Assessments

- Study-related assessments occurred at screening, on days 1, 2, 8, 15, and 22 of Cycle 1 (1 cycle=28 days), days 29, 30, and 31 (days 1, 2, and 3 of Cycle 2), and every 4 weeks thereafter
- Safety assessments included physical and laboratory examinations, vital signs, and ECGs. Adverse events (AEs) are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0)
- Plasma PK assessments were performed on blood samples collected at specified time points pre-dosing (t0hr) and post-dosing (t0.5, 1, 2, 4, 6, 8, 24, and 48hr). Steady-state PK assessments occurred on day 29. For twice daily (BID) dosing, only the first dose on day 29 was administered
- Disease assessment was performed at screening and at 8-week intervals thereafter. RECIST-defined responses were to be confirmed with an imaging assessment at a 4-week interval. Imaging assessment was also to be performed at the end of treatment

Statistical Methods

- Data as of 17 April 2013 are presented
- Analysis populations:
  - Patients were evaluable for safety analyses if they received at least one dose of study drug
  - Patients were evaluable for response if they received at least one dose of study drug and had a post-baseline scan or discontinued from the study
  - Patients were subgrouped according to mutation history (local testing)
    - History of ALK gene rearrangement (ALK+)
    - History of EGFR mutation (EGFRm)
- Definitions:
  - DLT: a drug-related toxicity (possibly, probably, or definitely related) occurring within the first 28 days of treatment, as defined by:
    - Any grade ≥3 non-hematologic toxicity (except for self-limiting or medically controllable toxicities lasting <3 days and excluding alopecia)
    - Hematologic toxicities including febrile neutropenia not related to underlying disease, grade 4 neutropenia >7 days, neutropenic infection, thrombocytopenia grade ≥3 with bleeding or grade 4 ≥7 days
    - Missed ≥25% of planned doses over the first 28 days due to treatment-related AE(s)
  - MTD: highest dose at which ≤1 of 6 evaluable patients experience a DLT within the first 28 days of treatment. MTD evaluable patients completed at least 75% of their planned doses during the first 28 days, unless missed doses were due to related AEs

RESULTS

Table 2. Demographics and Baseline Characteristics

	All Patients N=55	History of ALK+ N=28	History of EGFRm N=20
Median age, yrs (range)	58 (32-83)	54 (32-73)	58 (39-83)
Sex, female, n (%)	34 (62)	17 (61)	13 (65)
Race, n (%)			
White	40 (73)	21 (75)	13 (65)
Asian	9 (16)	5 (18)	3 (15)
Other	6 (11)	2 (7)	4 (20)
Diagnosis, n (%)			
Non-small cell lung cancer (NSCLC)	47 (85)	24 (86)	19 (95)
Adenocarcinoma	45 (82)	23 (82)	18 (90)
Other	8 (15)	4 (14)[a]	1 (5)[b]
ECOG, n (%)			
0	13 (24)	6 (21)	4 (20)
1	38 (69)	20 (71)	14 (70)
2	3 (5)	1 (4)	2 (10)
Prior targeted therapy, n (%)			
Crizotinib	27 (49)	24 (86)[c]	1 (5)
EGFR-targeted TKI	27 (49)	6 (21)	18 (90)
Neither ALK nor EGFR-targeted TKI	7 (13)	4 (14)	1 (5)
Prior systemic therapy, n (%)			
1-2 regimens	16 (29)	9 (32)	6 (30)
≥3 regimens	37 (67)	17 (61)	14 (70)

[a]Inflammatory myofibroblastic tumor (2), neuroendocrine carcinoma (1), adenocarcinoma of unknown primary origin (ACUP; 1)
[b]Small cell lung cancer
[c]3 ALK+ NSCLC patients previously received LDK378 in addition to crizotinib

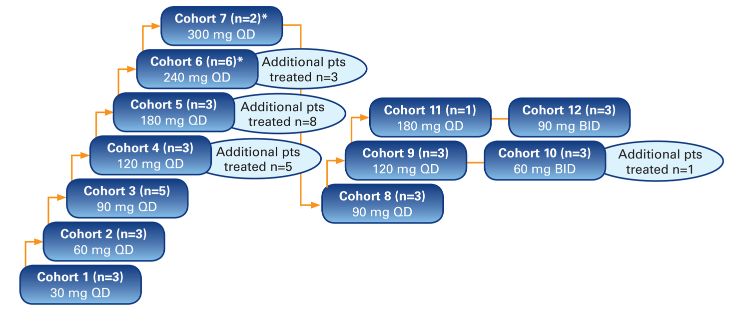
Table 3. Patient Disposition

	All Patients N=55 n (%)	History of ALK+ N=28 n (%)	History of EGFRm N=20 n (%)
Remain on study	22 (40)	18 (64)	4 (20)
Discontinued treatment	33 (60)	10 (36)	16 (80)
Documented progressive disease	16 (29)	4 (14)	6 (30)
Adverse event	6 (11)	2 (7)	4 (20)
Clinical progressive disease	6 (11)	1 (4)	4 (20)
Death[a]	4 (7)	2 (7)	2 (10)
Withdrawal by subject	1 (2)	1 (4)	0

[a]2 deaths were considered possibly related by the investigtor: 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)

RESULTS

Figure 3. Dose Escalation



*1 DLT was observed

Table 4. Dosing Summary

Dose (mg/day)[a]	DLT Evaluable N	DLTs Observed N	Additional Patients Treated N	Total Treated N	Evaluable for Response N
30	3	0	-	3	3
60	3	0	-	3	3
90	5	0	3	8	8
120	3	0	12 (4 BID)	15	13
180	3	0	12 (3 BID)	15	11
240	6	1	3	9	9
300	2	1	-	2	2

[a]Assigned dose

- Doses were escalated using a 3+3 design, with additional patients enrolled for further evaluation of PK and activity
- 2 DLTs have occurred to date:
  - A DLT of grade 3 increased alanine aminotransferase (ALT) was reported in 1 patient at 240 mg; this DLT resolved within 8 days following drug interruption. The patient resumed therapy at 180 mg and ALT remains in the normal range
  - DLTs of grade 4 dyspnea and grade 3 hypoxia were reported concurrently in 1 patient at 300 mg; the events recurred at 180 mg, and the patient discontinued from the study as a result of these events
- In addition, isolated events of dyspnea and hypoxia were observed during expansion at lower doses (120 mg, 180 mg). In 1 case at 180 mg, the event occurred after 1 dose of AP26113 in a patient whose cause of death was adenocarcinoma of the lung, extremely widely metastatic to both lungs; the investigator thought AP26113 may have been a contributory factor. As a result, cohorts from 90 mg to 180 mg, including BID dosing, were expanded using eligibility criteria that were narrowed to exclude patients with history or presence of pulmonary interstitial disease and patients with ECOG performance status ≥2. No further events of this nature have been observed in newly enrolled patients
- The MTD has not been defined according to protocol criteria. However, based on safety, efficacy, and pharmacokinetics (see below), the recommended phase 2 dose is 180 mg QD

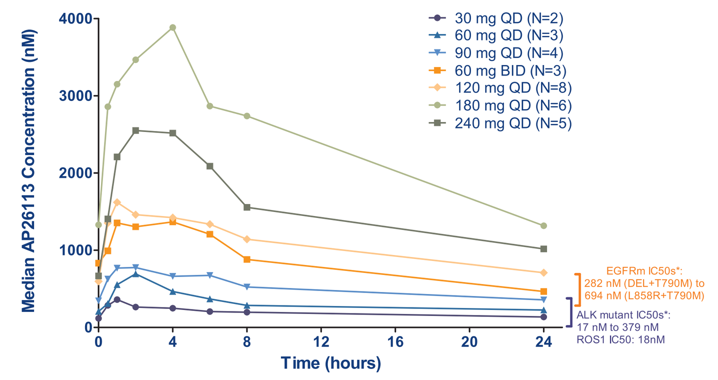
Table 5. Adverse Events, All Causality

Preferred terms (≥10% incidence all grades, ≥3% incidence grade 3/4)	All Grades N=55 n (%)	Grades 3/4 N=55 n (%)
Fatigue	22 (40)	3 (5)
Nausea	20 (36)	0
Diarrhea	18 (33)	2 (4)
Headache	10 (18)	1 (2)
Cough	9 (16)	0
Decreased appetite	8 (15)	0
Muscle spasms	8 (15)	0
Pain in extremity	7 (13)	1 (2)
Peripheral edema	6 (11)	0
Vomiting	6 (11)	0
Pneumonia	5 (9)	3 (5)
Hypoxia	3 (5)	2 (4)

Adverse events are presented regardless of treatment relationship

- AEs considered at least possibly related to treatment occurring in ≥10% of patients were nausea (33%), fatigue (22%), and diarrhea (20%)
- Serious AEs (all causality) occurring in 2 or more patients were pneumonia (7%), cough (4%), dyspnea (4%), hypoxia (4%), and pleural effusion (4%)
- No rash typical of EGFR TKIs was observed
- Increases from baseline in non-fasting glucose and insulin laboratory values were observed in 24/38 and 25/41 patients, respectively; no AEs of increased glucose or insulin were reported

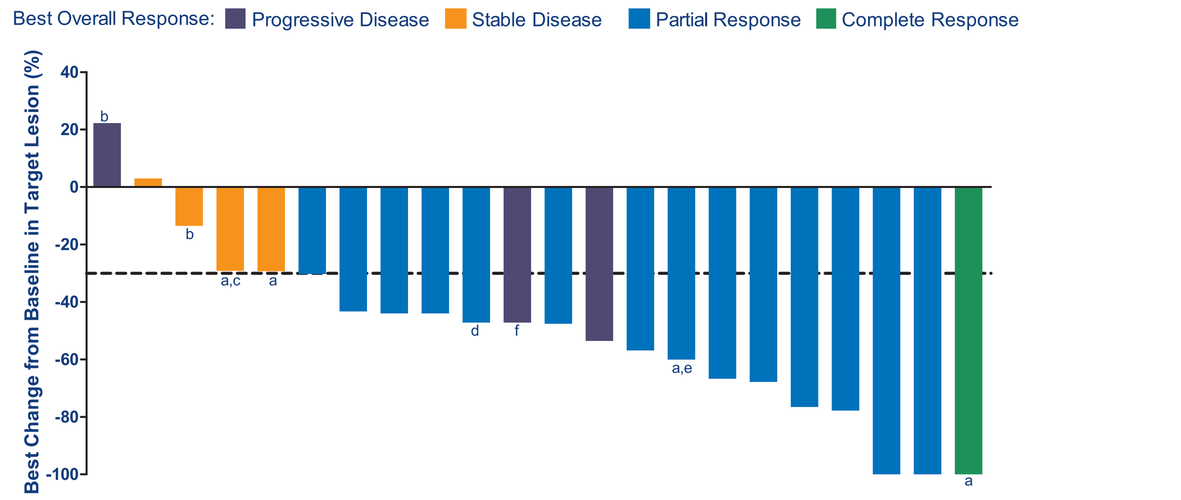
Figure 4. AP26113 Preliminary Pharmacokinetics at Steady State (Day 29)



Median AP26113 Steady State Trough Concentrations (nM)						
30 mg QD	60 mg QD	90 mg QD	60 mg BID	120 mg QD	180 mg QD	240 mg QD
135	226	357	632	706	1317	1017

- Median plasma levels of AP26113 have surpassed preclinically identified IC_{50} values for ALK, ROS1, and mutant EGFR
- Steady state median plasma levels of AP26113 were higher in the 180 mg cohort than in the 240 mg cohort; however, patient numbers are small and there is inter-patient variability. Data from additional patients will be collected

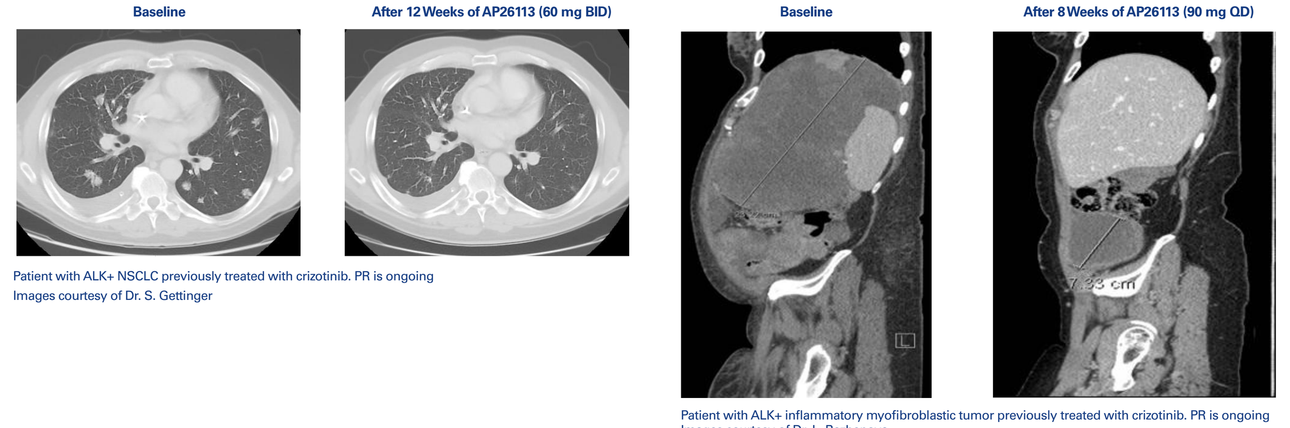
Figure 5. AP26113 Preliminary Anti-Tumor Activity in ALK+ Patients



Patients with follow-up scans are shown (n=22); 24 ALK+ patients were evaluable for response
All patients received prior crizotinib unless otherwise indicated
[a]ALK TKI naive; [b]Received prior crizotinib and prior LDK378; [c,d,e]Non-NSCLC diagnoses: [c]neuroendocrine carcinoma, [d]inflammatory myelofibroblastic tumor, [e]ACUP; [f]Patient was PD by RECIST 1.1 due to 2nd primary tumor of melanoma

- Among ALK+ pts with ≤1 prior ALK TKI, responses were observed in:
  - 2/4 (50%) TKI-naïve patients (1 partial response [PR], 1 complete response [CR], 2 stable disease [SD])
  - 13/17 (76%) patients with prior crizotinib therapy but no other ALK inhibitor exposure (13 PR, 1 SD, 2 progressive disease [PD], 1 no scan)
- Among ALK+ NSCLC pts with prior crizotinib but no other ALK inhibitor exposure, 12/16 (75%) responded
- Three patients received prior crizotinib and LDK378. One remains on study with SD, one discontinued due to PD, and one discontinued prior to a follow-up scan
- Among the 15 patients (all histologies) with PR or CR observed on at least one occasion (5 PR confirmed, 1 CR confirmed, 4 PR unconfirmed, 5 PR awaiting confirmation), at all dose levels from 60 mg to 240 mg daily
  - Response durations ranged from 15+ to 40+ weeks in patients with confirmed responses
  - 10/15 patients remained in response at the time of analysis

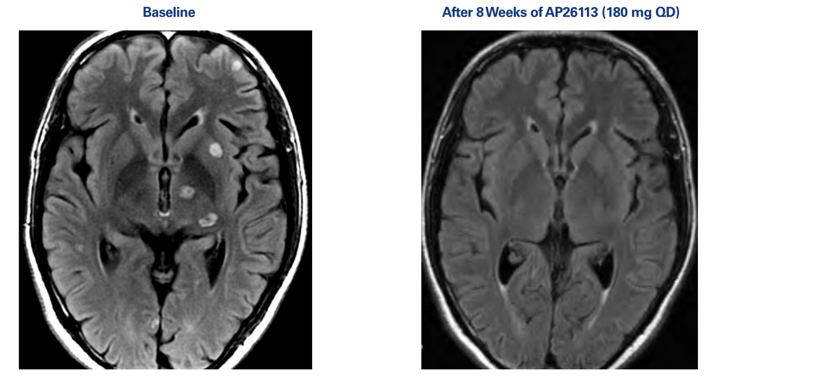
Figure 6. AP26113 Activity in ALK+ Patients



Patient with ALK+ NSCLC previously treated with crizotinib. PR is ongoing. Images courtesy of Dr. S. Gettinger

Patient with ALK+ inflammatory myofibroblastic tumor previously treated with crizotinib. PR is ongoing. Images courtesy of Dr. L. Bazhenova

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



Patient with ALK+ NSCLC previously treated with crizotinib. PR is ongoing. Images courtesy of Dr. D.R. Camidge

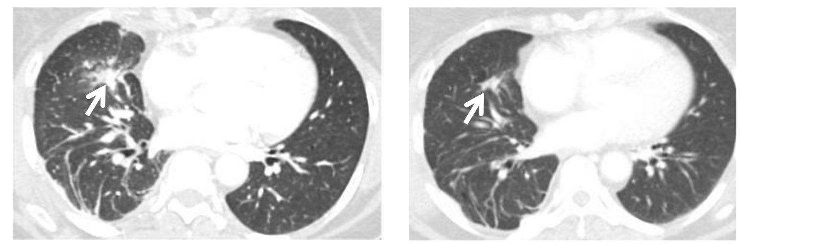
- 4 of 5 ALK+ patients (AP26113 180 mg QD, n=2; 240 mg QD, n=2) with untreated or progressing CNS lesions at baseline and with follow-up scans had evidence of radiographic improvement in CNS, including 1 pt resistant to crizotinib and LDK378 (overall response = stable disease)
- CNS lesion improvements in all 4 patients are ongoing, with durations ranging from 15 to 28 weeks

Table 6. Prior EGFR TKI Therapy and AP26113 Pharmacokinetics and Activity in Evaluable Patients with History of EGFR T790M Mutation

Patient No.	AP26113 Assigned Dose (mg/day)	Mutation History	Prior EGFR TKI Regimen(s)	Treatment Duration of Prior EGFR TKI Regimen(s)	Reported Best Response to Prior EGFR TKI Regimen(s)	EGFR TKI as Last Therapy Prior to AP26113	T790M+ Status Determined During or After Most Recent EGFR TKI	AP26113 Steady State C_{trough}/C_{max} (nM)	Response to AP26113
1	60	DEL +T790M	erlo	1 yr	PR	Yes	Yes[a]	336 / 1277	SD (duration 8 wks)
2	120	DEL +T790M	afa/erlo/afa	1.8 yrs/1.1 yrs/ 1 mos	NK/NK/NK	Yes	No	760 / 1654	PD
3	120	DEL +T790M	erlo/afa	5 yrs/2 mos	PR/SD	Yes	No	656 / 1469	SD (duration 9 mos)
4	120	DEL +T790M	dac/erlo	1.7 yrs/3 mos	PR/PD	Yes	No	1253 / 2911	PD
5	180	DEL +T790M	erlo/erlo	1 yr/1.8 yrs	PR/NK	Yes	Yes	1351 / 3373	SD (duration 7 wks)
6	180	DEL +T790M	erlo	1.6 yrs	NK	Yes	Yes	NA	NS
7	180	L858R +T790M	erlo/erlo	1.3 yrs/4 mos	NK/NK	No	Yes[b]	NA	NS
8	240	DEL +T790M	erlo/erlo	3.3 yrs/2.3 yrs	PR/SD	Yes	No	1013 / 4503	PD
9	240	T790M	erlo	6.4 yrs	PR	Yes	No	NA	SD (duration 16 wks, ongoing)
10	300	T790M	erlo	3 mos	NK	No	Yes[c]	NA	NS

DEL=Exon 19 deletion; erlo=erlotinib; afa=afatinib; dac=dacomitinib; NK=not known; NS=no follow-up scan; NA=not available
[a]Detected 3 months after discontinuation of erlotinib for resistance and 2 months prior to starting AP26113
[b]Detected 2 days after starting 2nd regimen of erlotinib (1 year after end of 1st erlotinib regimen) and 2 years prior to starting AP26113
[c]Detected 1 month after discontinuation of erlotinib for resistance and 1 year prior to starting AP26113

Figure 8. AP26113 Activity in NSCLC Patient with History of EGFR Exon 19 Deletion



Patient with NSCLC previously treated with erlotinib, history of EGFR exon 19 deletion, T790M status unknown. Right middle lobe scan. PR is ongoing (26+ weeks). Images courtesy of Dr. L. Bazhenova

- Among patients with a history of EGFRm that were evaluable for response, 1/18 patients experienced PR and 7/18 experienced SD
  - A PR (ongoing with duration of 26+ weeks) was observed at 120 mg QD in 1 patient with a history of exon 19 DEL (T790M status unknown) and prior erlotinib therapy (best response of PR on erlotinib, discontinued due to resistance)
  - SD was observed in 7 patients (60 mg QD to 300 mg QD), including 4 with T790M by history; SD is ongoing in 1 patient with a history of T790M (240 mg QD, duration 16 weeks), and 1 patient with a history of exon 19 DEL +T790M (120 mg QD) had SD for 7 months prior to discontinuing due to an AE (pneumonitis) and disease remained stable 2 months later
- 3 evaluable patients were treated (Patients 1, 5, and 6 in Table 6) who had an EGFR TKI as their last therapy prior to AP26113 and had T790M detected during/after treatment with that therapy; all 3 started AP26113 more than 1 month after stopping the prior EGFR TKI
  - Patient 1: This patient started AP26113 (60 mg QD) approximately 5 months after stopping erlotinib. The steady-state AP26113 C_{trough} in this patient was 336 nM, which exceeded the preclinically determined exon 19 DEL +T790M IC_{50} of 282 nM. This patient's response to AP26113 was SD (duration 8 weeks). The patient discontinued due to clinical progressive disease
  - Patient 5: This patient started AP26113 (180 mg QD) approximately 7 months after stopping erlotinib. The steady-state AP26113 C_{trough} in this patient was 1351 nM, and the response to AP26113 was SD (duration 7 weeks). The patient discontinued due to clinical progressive disease
  - Patient 6: This patient started AP26113 (180 mg QD) approximately 2 months after stopping erlotinib, received AP26113 for 4 days, experienced an AE of ARDS following lung infection and died 13 days after the last dose of AP26113

SUMMARY

- Based on the observed DLTs at 240 mg and 300 mg, isolated events of hypoxia and dyspnea at 120 mg and 180 mg, and PK observations, cohorts from 90 mg to 180 mg were expanded and included evaluation of BID dosing; entry criteria relating to pulmonary interstitial disease were tightened and no further DLTs or events of hypoxia or dyspnea have been observed
- The MTD has not been defined; however, based on safety, efficacy, and pharmacokinetics, the recommended phase 2 dose is 180 mg
- Most common AEs were fatigue, nausea, and diarrhea, which were generally grade 1 or 2 in severity; the most common serious AE was pneumonia; no rash typical of other EGFR TKIs has been observed
- Median plasma levels of AP26113 have surpassed preclinically identified IC_{50} values for ALK, ROS1, and mutant EGFR
- AP26113 has promising anti-tumor activity in patients with ALK+ NSCLC and other ALK+ tumors, including brain metastases in ALK+ patients
- Activity was not seen in 3 patients with prior LDK378 therapy, but a CNS response was noted in this setting
- Initial evidence of activity (PR) was observed in a patient with a history of exon 19 deletion and unknown T790M status. Cohort 3 in the phase 2 portion of the study will provide an opportunity to test AP26113 activity in a rigorously defined patient population with T790M-mediated resistance to 1 prior EGFR TKI (documented EGFR T790M following disease progression on the most recent EGFR TKI therapy [stopped within 30 days of initiating AP26113], without intervening therapy prior to starting AP26113)
- The phase 2 cohorts are now open for enrollment at the RP2D (180 mg QD)
- Further phase 1 testing at 240 mg will occur in patients with documented EGFR T790M (same enrollment criteria as phase 2 cohort 3)
- A separate, pivotal phase 2 trial in patients with ALK+ NSCLC resistant to crizotinib will begin shortly

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DISCLOSURES

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