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

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Abstract 439O

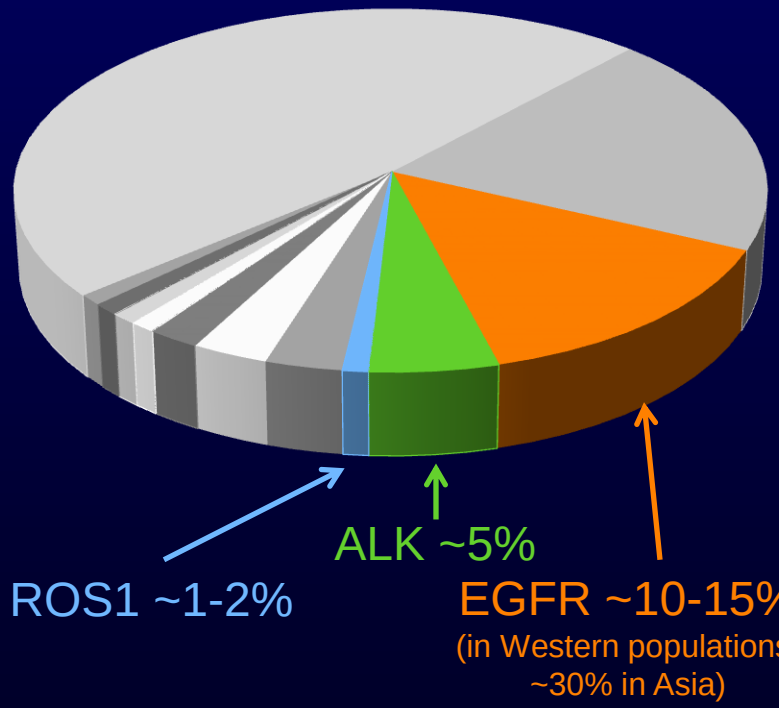
Disclosures

- Dr. Gettinger has no conflict of interest to disclose.

ALK, ROS1, and EGFR: Validated Targets in Non-Small Cell Lung Cancer

- ALK and ROS1 translocations and EGFR activating mutations are oncogenic drivers in subsets of NSCLC patients
- 1st generation inhibitors such as crizotinib (ALK/ROS1) and erlotinib (EGFR) exhibit robust clinical activity
- Mutation-based resistance develops over time

Potential Oncogenic Targets in NSCLC

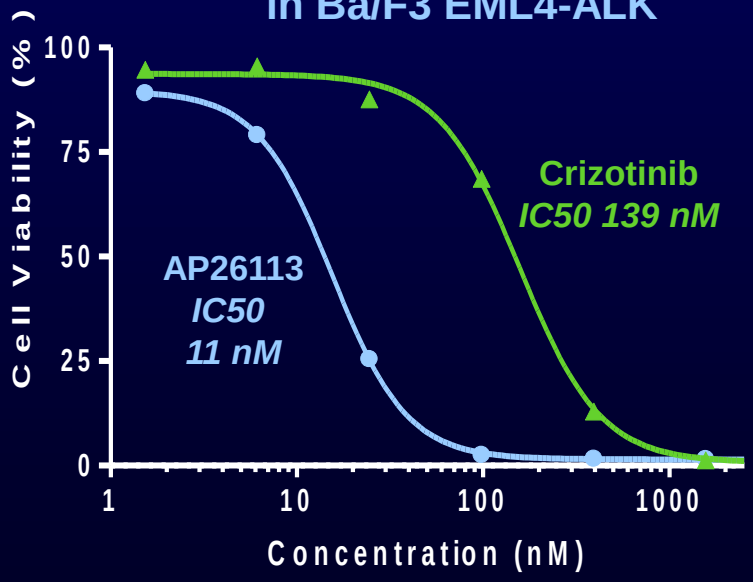


Pao and Hutchinson, *Nature Med,* 2012;3:349-351; Custodio et al, *Cancer Treat Rev*, 2011;38:36-53.

AP26113 is a Potent ALK and ROS1 Inhibitor

- Ten-fold more potent inhibitor of ALK fusions than crizotinib
- Inhibits crizotinib-resistant mutants, including the L1196M gatekeeper
- Also potently inhibits ROS1 fusions at concentrations similar to ALK

Potency of AP26113 vs. Crizotinib in Ba/F3 EML4-ALK



AP26113 Activity in Cellular Models

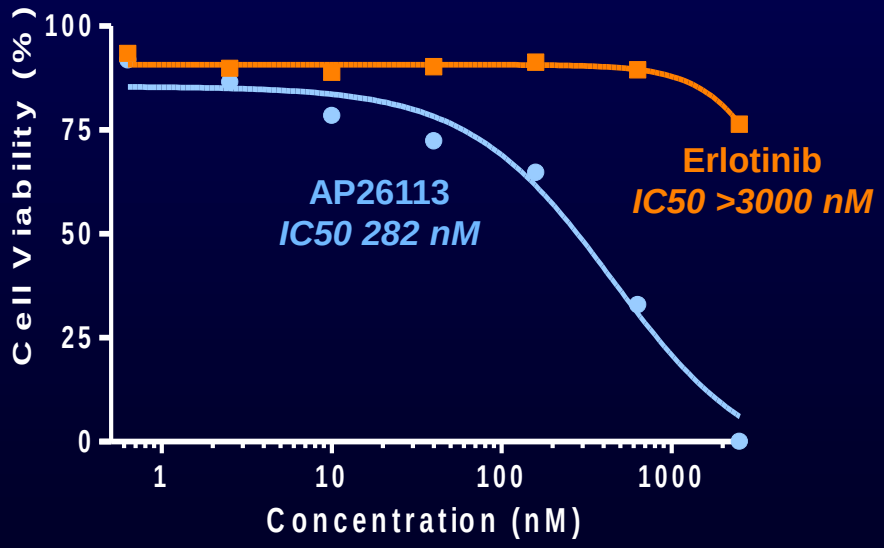
Ba/F3 Cell Line	IC50 (nM)
EML4-ALK	11
EML4-ALK L1196M	40
CD74-ROS1	18

Zhang et al, presented at AACR 2010, Abstract LB-298; Data on file, ARIAD Pharmaceuticals, Inc.

AP26113 Inhibits Activated and Gatekeeper Mutant EGFR

- Potently inhibits most common activated EGFR variants
  - Exon 19 deletion (DEL) and L858R exon 21 mutation
- Also inhibits activated variants with T790M gatekeeper mutations
- Does not inhibit native EGFR

Potency of AP26113 vs. Erlotinib in Ba/F3 EGFR-DEL+T790M



AP26113 Activity in Cellular Models

EGFR Ba/F3 Cell Line	IC50 (nM)
DEL	112
DEL + T790M	282
L858R	456
L858R + T790M	694
Native EGFR	>3000
(Parental Ba/F3)	>3000

Rivera et al, presented at AACR 2012, Abstract 1794; Data on file, ARIAD Pharmaceuticals, Inc.

AP26113 Phase 1/2 Study
Study Objectives

- To determine the safety profile, including identification of the maximum tolerated dose and dose-limiting toxicities
- To determine the recommended phase 2 dose
- To examine the pharmacokinetic profile
- To describe preliminary anti-tumor activity in NSCLC with ALK gene rearrangement (ALK+) or mutant EGFR (EGFRm)
- To perform exploratory analyses including molecular assessments

AP26113 Phase 1/2 Study
Study Design

Phase 1

Dose Escalation,
3+3 Design: N=30 to 50
Advanced malignancies
(all histologies except leukemia)

Oral AP26113 30 mg once daily starting dose → Dose level cohorts escalating until recommended phase 2 dose is established

Phase 2

Cohort 1, NSCLC: N=20
ALK+ and
ALK inhibitor naïve

Cohort 2, NSCLC: N=20
ALK+ and resistant to ≥1 prior ALK inhibitor

Cohort 3, NSCLC: N=20
EGFRm and
resistant to ≥1 prior EGFR inhibitor

Cohort 4: N=20
Other cancers with AP26113 targets
eg, ALK, ROS1, and others

AP26113 Phase 1/2 Study
Key Inclusion Criteria

- Histologically confirmed advanced malignancies, all histologies except leukemia (phase 1 only)
- Disease that is refractory to available therapies or for which no standard or available curative treatment exists (phase 1 only)
- Measurable disease by RECIST 1.1
- ECOG score ≤2
- Minimum life expectancy ≥3 months
- No active brain metastases
- Adequate renal, hepatic, and bone marrow function
- Normal QT interval
- Tumor tissue available for analysis

AP26113 Phase 1/2 Study Patient Characteristics

	All Patients N=34	History of ALK+ N=15	History of EGFRm N=12
Median age, yrs (range)	60 (32-77)	54 (32-73)	58 (39-77)
Sex, male, n (%)	14 (41)	5 (33)	6 (50)
Race, n (%)			
White	26 (76)	12 (92)	8 (67)
Asian	5 (15)	2 (13)	2 (17)
Other	3 (9)	1 (7)	2 (17)
Diagnosis, n (%)			
NSCLC[a]	29 (85)	14 (93)	11 (92)
Other	5 (15)	1 (7)[b]	1 (8)[c]
Prior targeted therapy, n (%)			
Crizotinib	16 (47)	13 (87)	1 (8)
EGFR-targeted TKI	17 (50)	4 (27)	10 (83)
Neither crizotinib nor EGFR-targeted TKI	5 (15)	2 (13)	1 (8)
Prior systemic therapy, n (%)			
1-2 regimens	8 (24)	4 (27)	3 (25)
≥3 regimens	26 (76)	11 (73)	9 (75)

[a] 28 adenocarcinoma and 1 squamous cell carcinoma
[b] Adenocarcinoma of unknown primary origin (ACUP)
[c] Small cell lung cancer

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study Cohort Summary

Dose (mg/d)[a]	DLT Evaluable N	DLTs Observed N	Additional Patients Treated N	Total Treated N	Evaluable for Response[b] N
30	3	0		3	3
60	3	0		3	3
90	5	0		5	5
120	3	0	5	8	6
180	3	0	6	9	7
240	3+3[c]	1[d]		6	3

[a] Assigned dose; Four patients escalated to the next dose level
[b] Patients were evaluable for response if they had a post-baseline tumor assessment or discontinued from the study
[C] 3 patients in the 240 mg cohort are under evaluation for development of DLTs in cycle 1
[d] A DLT of grade 3 increased ALT was reported in 1 patient at 240 mg; this DLT resolved within 8 days following drug interruption, and the patient resumed therapy at 180 mg and achieved PR

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study
Patient Disposition

	All Patients N=34	History of ALK+ N=15	History of EGFRm N=12
Ongoing, n (%)	19 (56)	12 (80)	4 (33)
Discontinued, n (%)	15 (44)	3 (20)	8 (67)
Documented progressive disease, n (%)	10 (29)	1 (7)	5 (42)
Clinical progressive disease, n (%)	1 (3)	0 (0)	1 (8)
Adverse events, n (%)	3 (10)	2 (15)	1 (8)
Death, n (%)	1 (3)[a]	0 (0)	1 (8)

[a] 1 patient (EGFRm, 180 mg) experienced sudden death (possibly related)

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study
Adverse Events (Treatment Emergent)

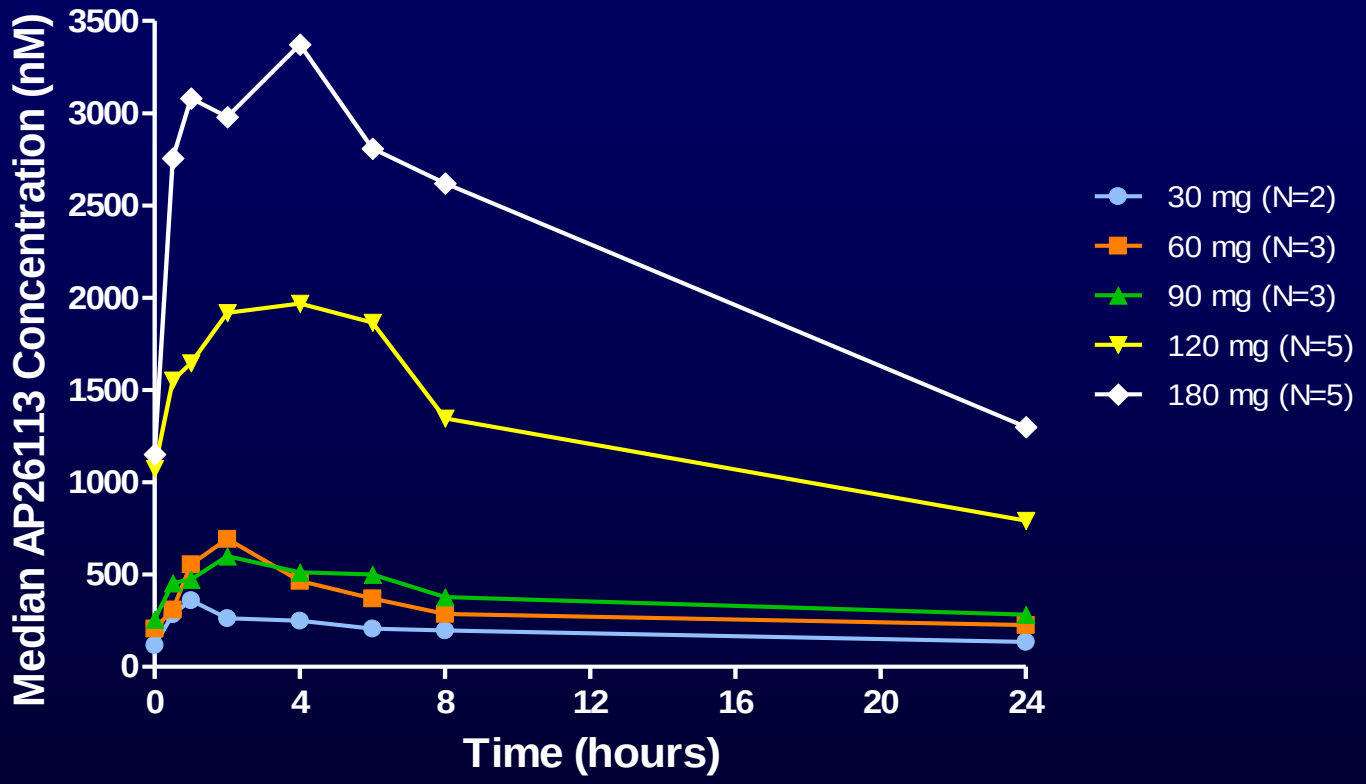
Preferred term (AEs with ≥10% incidence)	All Grades N=34 n (%)	Grades ≥3 N=34 n (%)
Nausea	11 (32)	0 (0)
Fatigue	9 (26)	1 (3)
Diarrhea	6 (18)	1 (3)
Pain in extremity	6 (18)	1 (3)
Vomiting	5 (15)	0 (0)
Abdominal pain	4 (12)	1 (3)
Constipation	4 (12)	0 (0)
Decreased appetite	4 (12)	0 (0)
Muscle spasms	4 (12)	0 (0)
Peripheral edema	4 (12)	0 (0)
Pneumonia	4 (12)	4 (12)

- The only treatment-related AEs occurring in ≥10% of patients were nausea (26%), diarrhea (18%), decreased appetite (12%), and vomiting (12%)
- No rash typical of EGFR TKIs observed, no visual disturbances typical of crizotinib observed

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study Pharmacokinetics

Median Plasma Concentrations (Day 29)



- At 180 mg:
  - Median C_{max} 3373 nM
  - Median C_{trough} 1243 nM
  - Median T_{half} 21 hours

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study
Preliminary Anti-Tumor Activity

Mutation Status History	Patients Evaluable for Response[a] N	Partial Response N
ALK+ (translocation)	11[b] (60, 90, 90, 90, 120, 180, 180, 180, 180, 240, 240 mg)	8 (60, 90, 90, 90, 180, 180, 240, 240 mg)
Crizotinib-resistant	9	6
Crizotinib-naive	2	2
EGFRm (7 T790M by history)	11[c] (60, 60, 90, 120, 120, 120, 120, 180, 180, 180, 240 mg)	1 (120 mg)
EGFR TKI-resistant	9[d]	1
EGFR TKI-naive	2	0
Neither ALK nor EGFRm	5 (30, 30, 30, 90, 120 mg)	0

[a] Patients were evaluable for response if they had a post-baseline tumor assessment or discontinued from the study
[b] 9 patients were assessed, 1 responded but was PD by RECIST 1.1 due to melanoma; 2 discontinued due to AE and did not reach the first scheduled Cycle 3 Day 1 assessment,
[c] 9 patients were assessed; 2 discontinued due to AE or death and did not reach the first scheduled Cycle 3 Day 1 assessment
[d] 3 patients received prior erlotinib + [afatinib or dacomitinib]

Data as of 25 Sept 2012

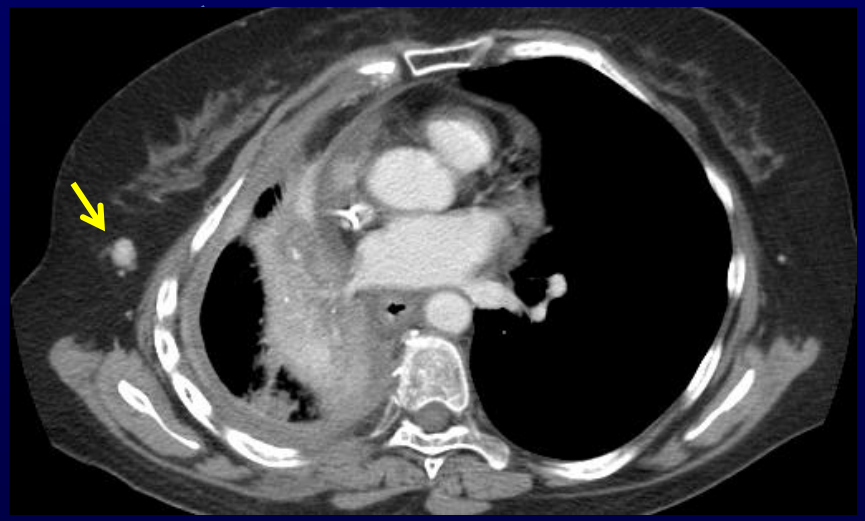
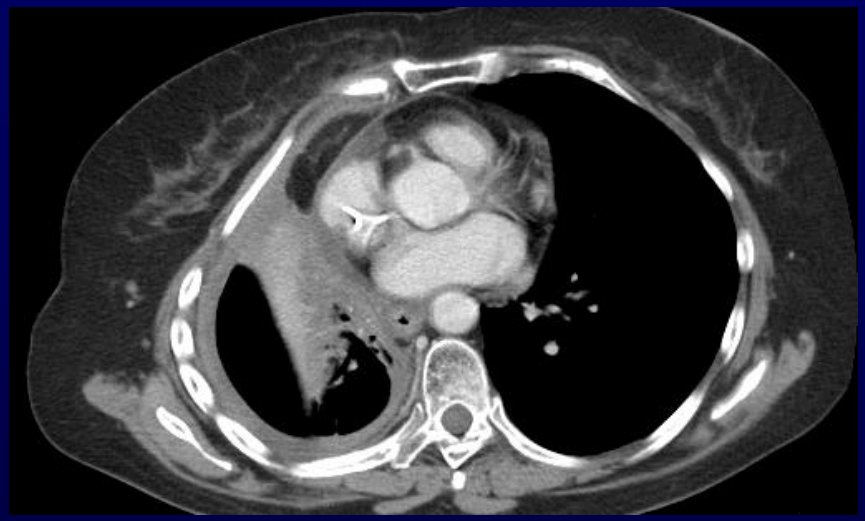
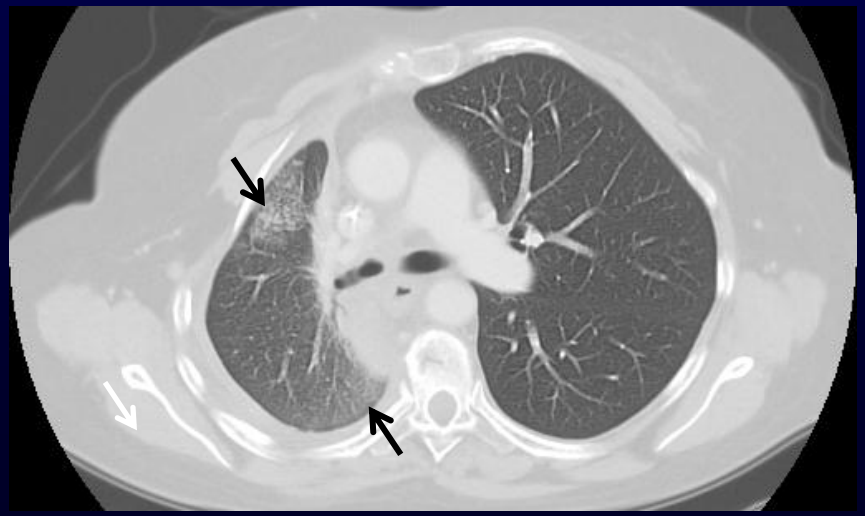
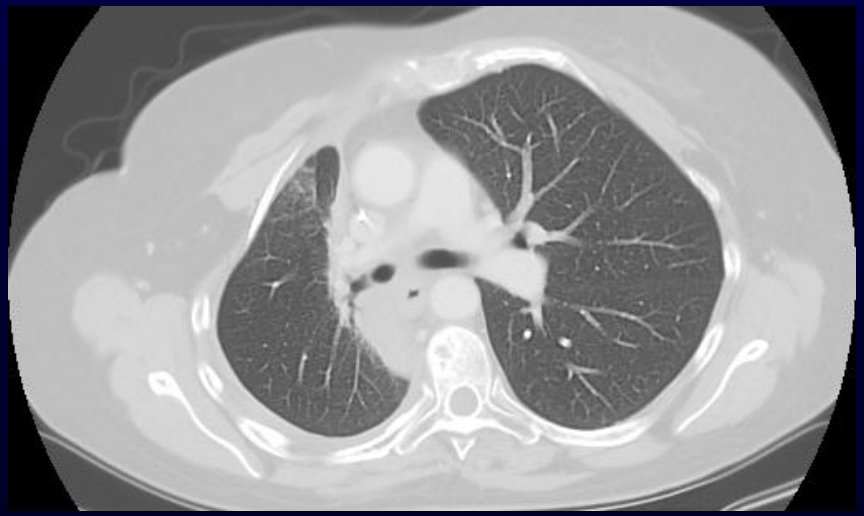
AP26113 Phase 1/2 Study Response Overview

- **ALK** patient responses observed at 60 mg and above
  - Responses observed in patients naïve to and resistant to crizotinib
  - Responses observed in all patients who have been assessed
  - Longest PR durations are 9 months (crizotinib-naïve patient) and 6 months (crizotinib-resistant patient); both responses are ongoing
- **EGFR** patient response observed at 120 mg
  - EGFR patients heterogeneous with regard to timing of prior therapy at study entry, and potentially to EGFR dependence
  - Six patients have received 120 mg or higher doses and have been assessed; all had failed erlotinib, bevacizumab, and ≥1 round of chemotherapy
  - Of these 6, 1 patient has ongoing PR (2 month duration; exon 19 deletion by history), 2 patients have stable disease (2 and 4 months duration) and remain on study, 3 patients had disease progression

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study
PR at 90 mg in Crizotinib-resistant ALK+ NSCLC

Baseline | **After 7 Weeks of AP26113**

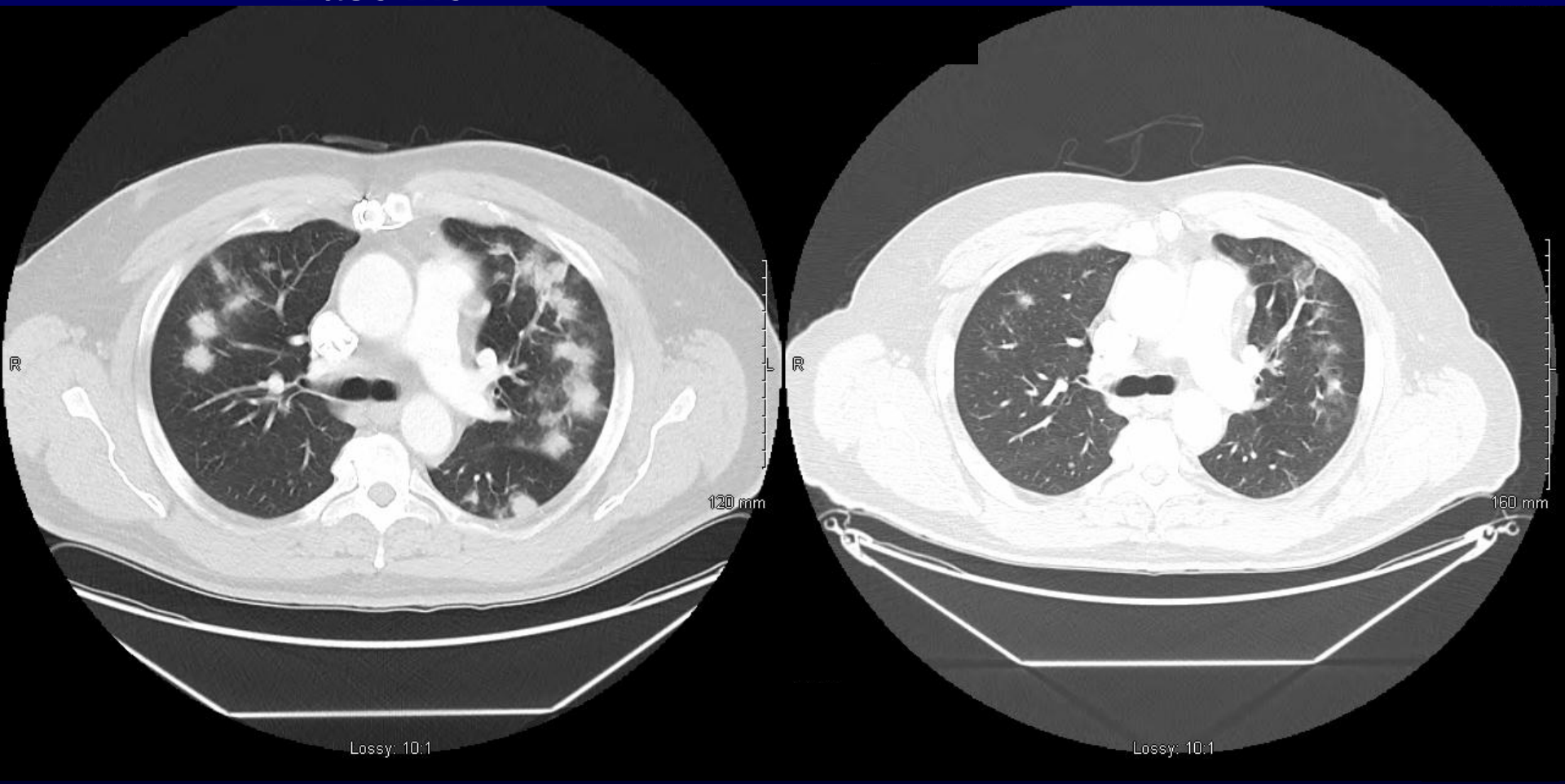





PR=partial response, RECIST 1.1; Images courtesy of Dr. S. Gettinger

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study
Response at 180 mg in
Crizotinib-resistant ALK+ NSCLC

Baseline **After 4 Weeks of AP26113**

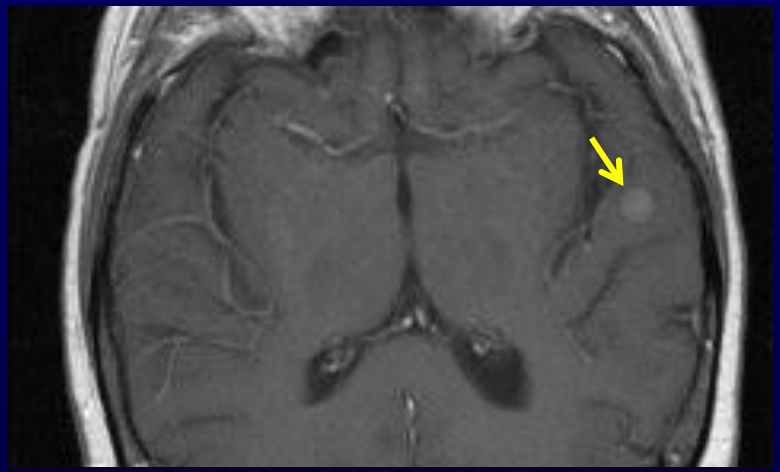


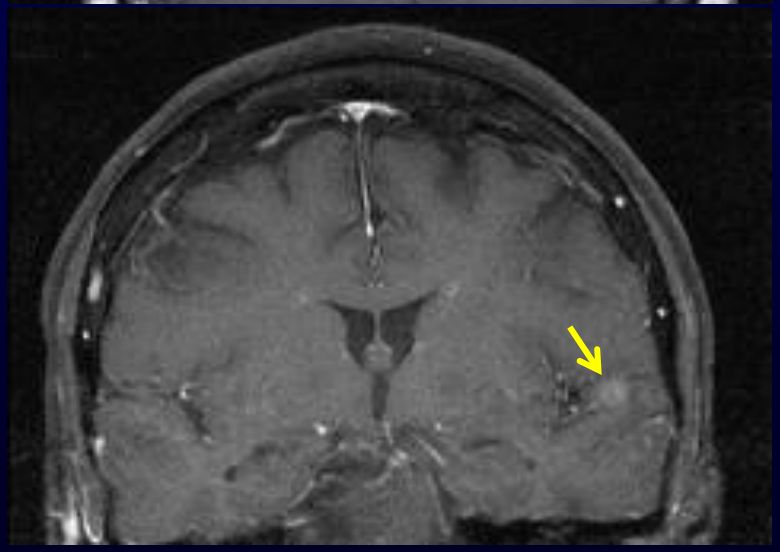
Response assessment PD per RECIST 1.1 due to CNS progression from second primary (melanoma – confirmed at resection); images courtesy of Dr. D. R. Camidge

Data as of 25 Sept 2012

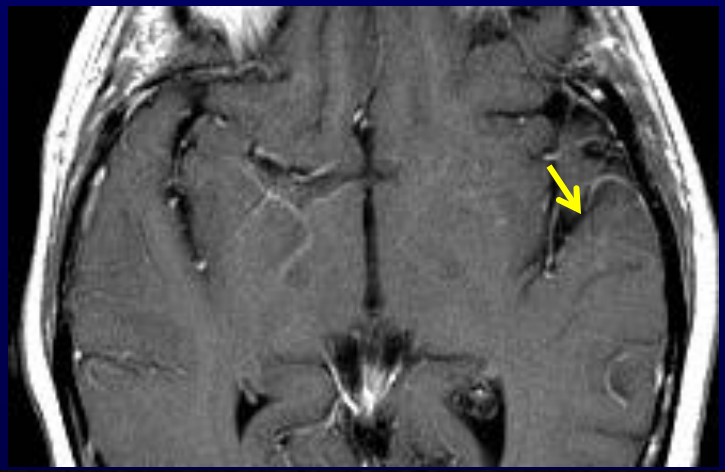
AP26113 Phase 1/2 Study
Response at 180 mg in Crizotinib-resistant ALK+ NSCLC Brain Metastasis

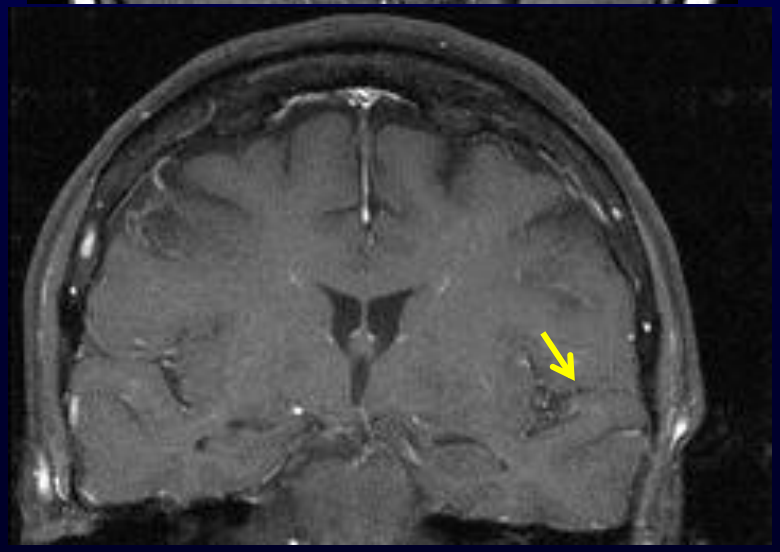
Baseline





After 8 Weeks of AP26113





Patient enrolled under protocol waiver; Images courtesy of Dr. L. Bazhenova

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study Summary

- The most common AEs were nausea and fatigue, which were generally grade 1 or 2 in severity; no rash typical of other EGFR TKIs has been observed
- One DLT identified at 240 mg (increased ALT); this cohort has been expanded, further dose escalation may occur pending ongoing evaluation of the 240 mg cohort
- The MTD has not yet been identified
- The blood levels of AP26113 have reached preclinically identified IC50 values for ALK, ROS1, and mutant EGFR
- AP26113 exhibited preliminary anti-tumor activity in patients with ALK+ and EGFRm NSCLC during dose escalation phase of study
- AP26113 is active in ALK+ brain metastases

Data as of 25 Sept 2012

AP26113 Phase 1/2 Study Acknowledgements

We thank the following for their contributions to this trial:

- Patients, along with their families and caregivers, for participation in the trial
- Clinical sites, including study investigators and their team members
- AP26113 Study Team (ARIAD Pharmaceuticals, Inc.)