Phase 1/2 Study of Brigatinib (AP26113) in Patients With Advanced Malignancies, Including ALK+ NSCLC: Analysis of Safety and Efficacy at Selected Phase 2 Doses

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Abstract 99O

Brigatinib Phase 1/2 Trial: Phase 2 Doses Disclosures

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- Dorer and Kerstein (employment: ARIAD)
- Camidge (honoraria: ARIAD; research funding: ARIAD)

Brigatinib Phase 1/2 Trial: Phase 2 Doses Introduction

- Anaplastic lymphoma kinase (ALK) gene rearrangements are driver mutations in NSCLC and other cancers
- Crizotinib is active in ALK-rearranged (ALK+) NSCLC, but most patients eventually develop disease progression
- Brigatinib (AP26113) is an investigational oral tyrosine kinase inhibitor with preclinical activity against rearranged ALK and clinically identified crizotinib-resistant mutants

Brigatinib Phase 1/2 Trial: Phase 2 Doses Objectives of This Subanalysis

- Report safety and efficacy data for patients treated with selected phase 2 doses evaluated during the phase 1/2 trial:
  - 90 mg qd
  - 90 mg qd for 7 days followed by 180 mg qd (90→180 mg qd)
  - 180 mg/d[a]

[a] Includes 44 patients at 180 mg qd and 4 patients at 90 mg bid

Brigatinib Phase 1/2 Trial: Phase 2 Doses Methods

Overall Trial

- Phase 1/2 single-arm, multicenter study in patients with advanced malignancies (N=137; NCT01449461)
- Brigatinib total daily doses: 30–300 mg
- Phase 2 primary endpoint: ORR by RECIST v1.1
- Secondary endpoints: safety, tolerability, best target lesion response, PFS, time to progression

Specific Methods for This Analysis

- Patients receiving doses of 90 mg qd, 90→180 mg qd, and 180 mg/d were evaluated for efficacy (ALK+ NSCLC) and safety (all patients)
- Data as of 19 Jan 2015

Brigatinib Phase 1/2 Trial: Phase 2 Doses Baseline Characteristics (All Doses)

Characteristic		ALK+ NSCLC n=79	All Patients n=137
Median age, y (range)		54 (29–83)	57 (29–83)
Sex, n (%)	Female	39 (49)	79 (58)
Race, n (%)	White	65 (82)	110 (80)
	Asian	10 (13)	17 (12)
	Other	4 (5)	10 (7)
ECOG, n (%)[a]	0	30 (38)	42 (31)
	1	48 (61)	92 (67)
	2	1 (1)	3 (2)
Prior crizotinib, n (%)		71 (90)	79 (58)
Number of prior chemotherapy regimens, n (%)	1	20 (25)	35 (26)
	2	23 (29)	36 (26)
	≥3	14 (18)	30 (22)

[a] Protocol amendment as of 30 November 2012 restricted enrollment to ECOG 0 or 1

Brigatinib Phase 1/2 Trial: Phase 2 Doses Patient Disposition by Cohort of Interest

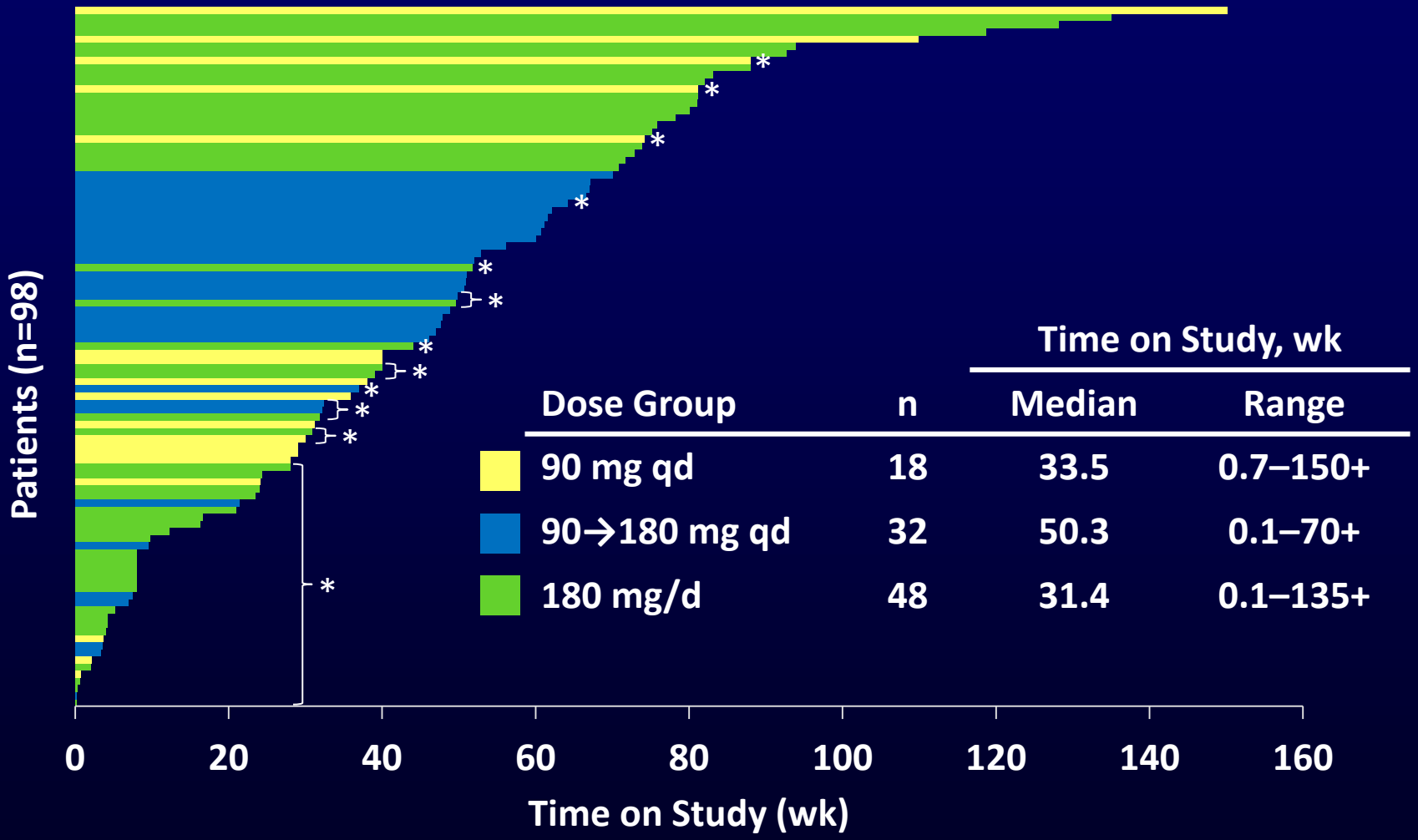
Characteristic	90 mg qd n=18	90→180 mg qd n=32	180 mg/d[a] n=48
Remain on study, n (%)	10 (56)	20 (63)	18 (38)
Discontinued treatment, n (%)	8 (44)	12 (38)	30 (63)
Documented progressive disease	4 (22)	5 (16)	19 (40)
AE	2 (11)	3 (9)	3 (6)
Death[b]	1 (6)	0	4 (8)
Clinical progressive disease	0	0	3 (6)
Physician decision	0	2 (6)	1 (2)
Withdrawal by subject	1 (6)	1 (3)	0
Protocol violation	0	1 (3)	0

[a] Includes 44 patients at 180 mg qd and 4 patients at 90 mg bid

[b] 3 deaths were considered possibly related by the investigator: sudden death (180 mg), hypoxia (180 mg), and unknown cause (90 mg); 2 deaths were considered not related: acute respiratory distress syndrome (180 mg) and progression of neoplasm (90 mg)

Median follow-up = 40 (0.14–150) weeks

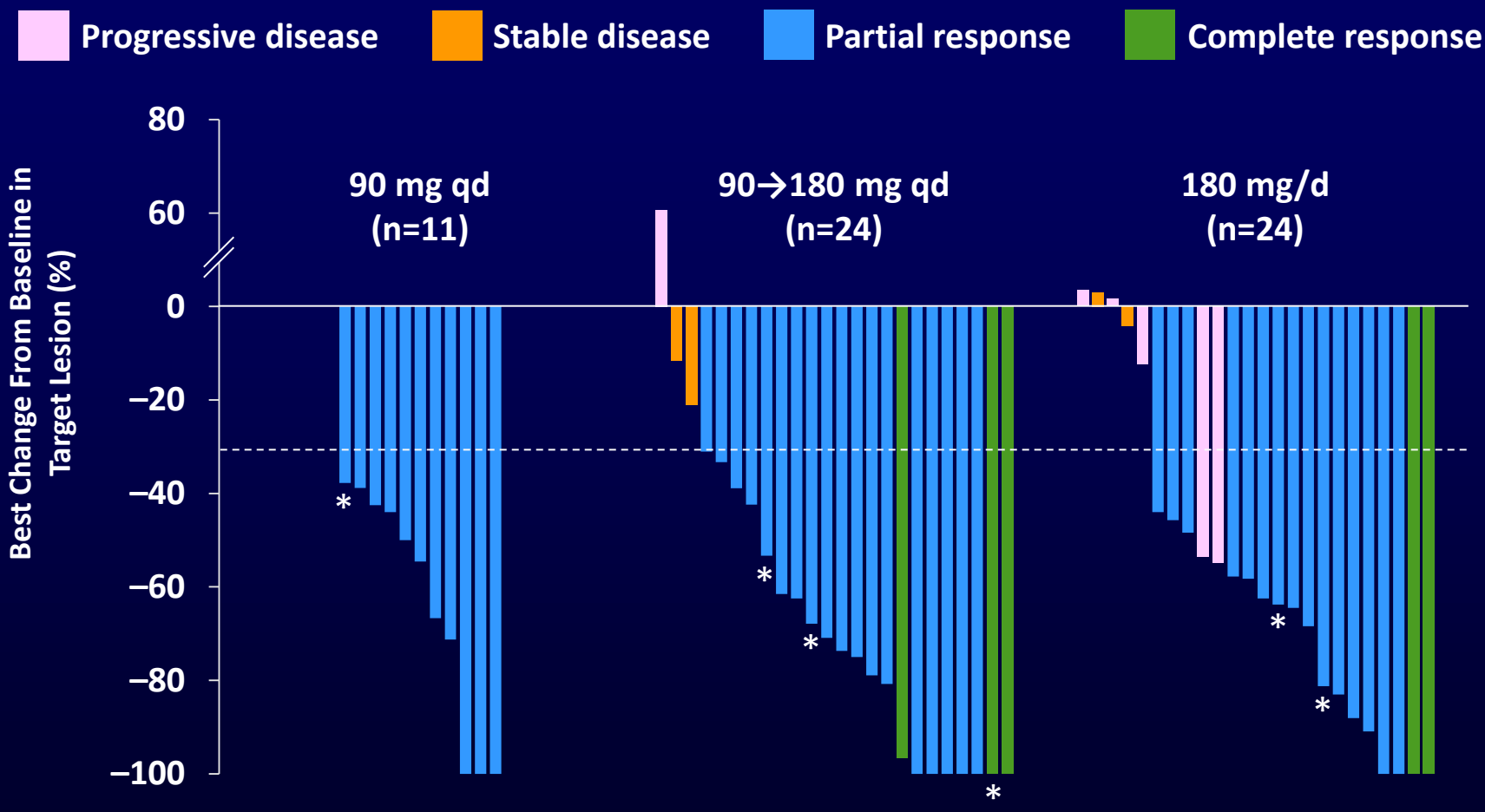
Brigatinib Phase 1/2 Trial: Phase 2 Doses
Time on Study



Dose Group	n	Time on Study, wk	
		Median	Range
90 mg qd	18	33.5	0.7–150+
90→180 mg qd	32	50.3	0.1–70+
180 mg/d	48	31.4	0.1–135+

* Discontinued

Brigatinib Phase 1/2 Trial: Phase 2 Doses Antitumor Activity in ALK+ NSCLC



* Crizotinib-naive patients (n=6)

Brigatinib Phase 1/2 Trial: Phase 2 Doses Responses in ALK+ NSCLC

Endpoint	90 mg qd n=14	90→180 mg qd n=26	180 mg/d[a] n=25
ORR (CR + PR), n (%) [95% CI]	11[b] (79) [49–95]	21[c] (81) [61–93]	17[d] (68) [47–85]
CR, n (%)	0	3 (12)	2 (8)
PR, n (%)	11 (79)	18 (69)	15 (60)
Stable disease, n (%)	3 (21)[e]	2 (8)	3 (12)
Progressive disease, n (%)	0	1 (4)	5 (20)
Discontinued prior to scan, n (%)	0	2 (8)	0

CR = complete response, PR = partial response

[a] Includes 23 patients at 180 mg qd and 2 patients at 90 mg bid

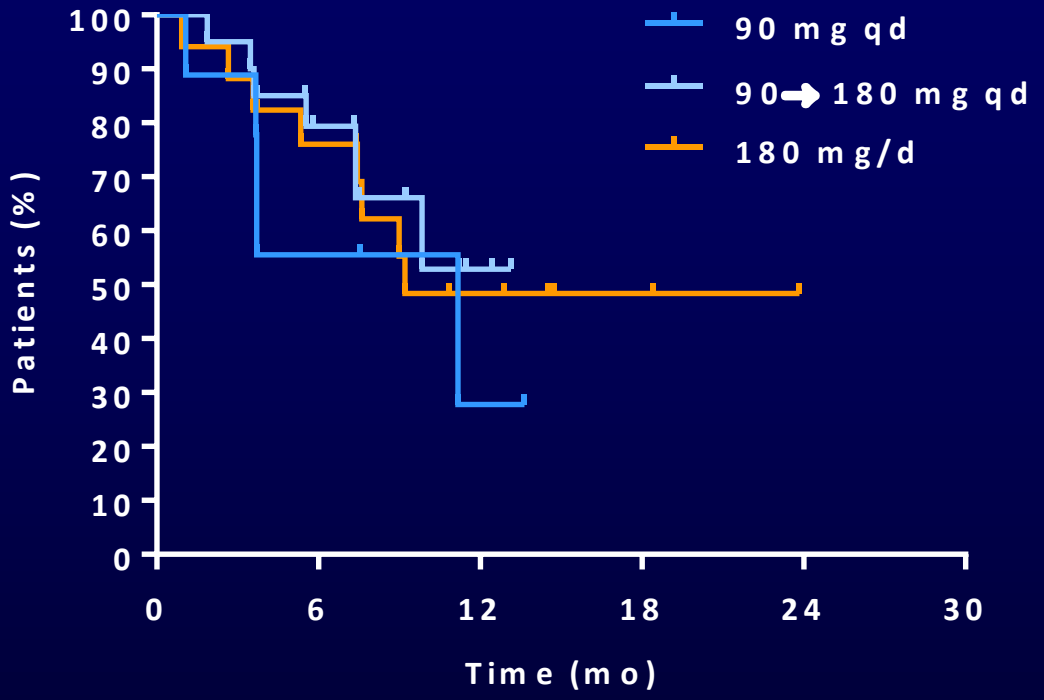
[b] 7 confirmed

[c] 19 confirmed

[d] 16 confirmed

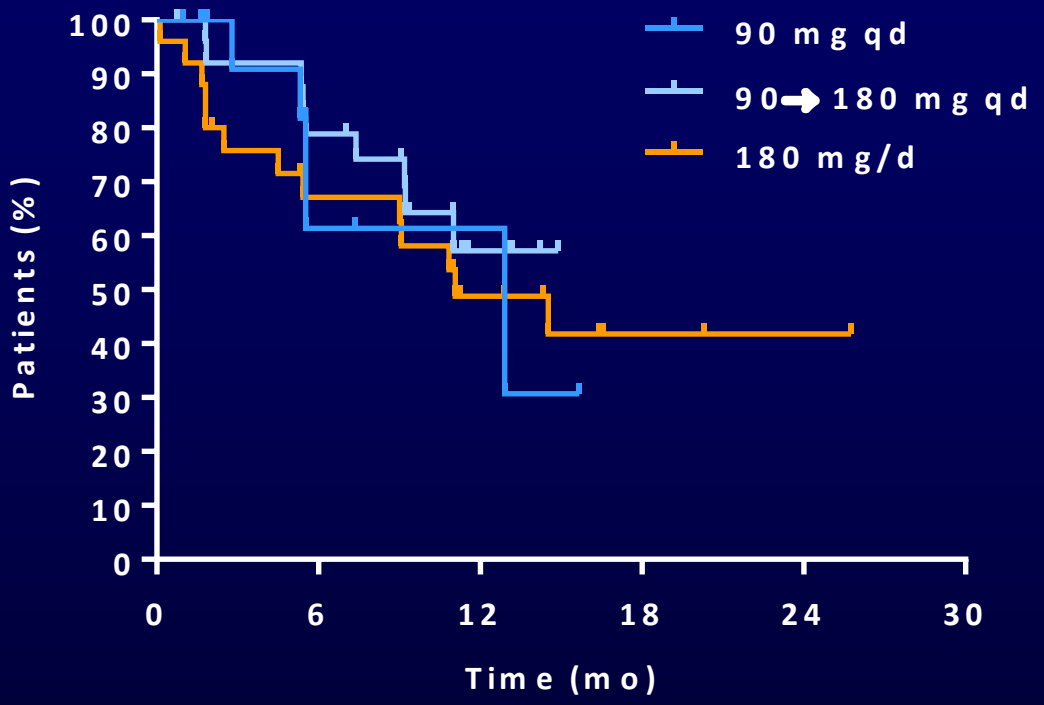
[e] 2 non-CR/non–progressive disease

Brigatinib Phase 1/2 Trial: Phase 2 Doses Duration of Response by Dose in ALK+ NSCLC



Dose Group	n	Median Duration, mo
90 mg qd	9	11.2
90→180 mg qd	20	Not reached
180 mg/d	17	9.2

Brigatinib Phase 1/2 Trial: Phase 2 Doses
PFS by Dose in ALK+ NSCLC



Dose Group	n	Median PFS, mo
90 mg qd	14	12.9
90→180 mg qd	26	Not reached
180 mg/d	25	11.1

Brigatinib Phase 1/2 Trial: Phase 2 Doses Treatment-Emergent AEs, ≥15%[a]

	90 mg qd n=18		90→180 mg qd n=32		180 mg/d[b] n=48	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Nausea	44	0	41	0	63	4
Diarrhea	39	0	44	0	38	0
Fatigue	39	0	38	3	31	2
Headache	44	0	28	0	31	0
Cough	39	0	28	0	25	2
Increased amylase	33	11	28	6	15	2
Arthralgia	17	0	28	0	13	2
Dyspnea	28	6	16	6	17	4
Increased lipase	28	11	25	9	10	8
Vomiting	6	0	9	0	27	0
Increased AST	17	0	19	0	15	2
Back pain	6	0	22	0	17	4
Constipation	22	0	19	0	13	0
Decreased appetite	17	0	13	0	19	2

[a] Among all patients in the dose cohorts of interest combined

[b] Includes 44 patients at 180 mg qd and 4 patients at 90 mg bid

Brigatinib Phase 1/2 Trial: Phase 2 Doses Serious Treatment-Emergent AEs, ≥4%[a]

	90 mg qd n=18 n (%)	90→180 mg qd n=32 n (%)	180 mg/d[b] n=48 n (%)
Dyspnea	1 (6)	2 (6)	2 (4)
Hypoxia	2 (11)	1 (3)	2 (4)
Pneumonia	2 (11)	1 (3)	2 (4)

[a] Among all patients in the dose cohorts of interest combined; neoplasm progression listed as SAE in 1 (6%), 1 (3%), and 4 (8%), respectively

[b] Includes 44 patients at 180 mg qd and 4 patients at 90 mg bid

Brigatinib Phase 1/2 Trial: Phase 2 Doses Early-Onset Pulmonary Events

- Events included dyspnea, hypoxia, and new pulmonary opacities suggestive of pneumonia or pneumonitis
  - Occurred within 7 days of starting brigatinib (usually within 24–48 hours)
  - Required medical intervention
  - Occurred at lower rates with lower doses
- In addition to 180 mg qd, 90 mg qd and 90→180 mg qd were explored in phase 2 expansion
  - 90→180 mg qd regimen was evaluated as events were observed to typically occur within 24–48 hours but did not generally recur with continued exposure to brigatinib, despite drug accumulation

Brigatinib Phase 1/2 Trial: Phase 2 Doses Early-Onset Pulmonary Events (cont'd)

- Early-onset pulmonary events were observed in 13/137 (9%) patients at the following starting doses:
  - 0/6 (0%) at 30 mg or 60 mg qd
  - 2/50 (4%) at 90 mg qd
    - 2/18 at 90 mg qd
    - 0/32 at 90→180 mg qd
  - 1/11 (9%) at 120 mg qd; 0/7 (0%) at 60 mg bid
  - 6/44 (14%) at 180 mg qd; 0/4 (0%) at 90 mg bid
  - 2/10 (20%) at 240 mg qd; 0/3 (0%) at 120 mg bid
  - 2/2 (100%) at 300 mg qd
- **None of the 32 patients in the 90→180 mg qd group had early-onset pulmonary events**

Brigatinib Phase 1/2 Trial: Phase 2 Doses Early-Onset Pulmonary Events (cont'd)

- Early-onset pulmonary events were observed in 13/137 (9%) patients at the following starting doses:
  - 0/6 (0%) at 30 mg or 60 mg qd
  - 2/50 (4%) at 90 mg qd
    - 2/18 at 90 mg qd
    - 0/32 at 90→180 mg qd
  - 1/11 (9%) at 120 mg qd; 0/7 (0%) at 60 mg bid
  - 6/44 (14%) at 180 mg qd; 0/4 (0%) at 90 mg bid
  - 2/10 (20%) at 240 mg qd; 0/3 (0%) at 120 mg bid
  - 2/2 (100%) at 300 mg qd
- **None of the 32 patients in the 90→180 mg qd group had early-onset pulmonary events**

Brigatinib Phase 1/2 Trial: Phase 2 Doses Summary

Response Summary

- In this study, brigatinib was active at daily doses of 90 mg (ORR=79%), 90→180 mg (ORR=81%), and 180 mg (ORR=68%) in ALK+ NSCLC patients
  - Median duration of response: 11.2 months, not reached, and 9.2 months, respectively
  - Median PFS: 12.9 months, not reached, and 11.1 months, respectively

Safety Summary

- Most common AEs included nausea, diarrhea, and fatigue and were similar in incidence across all dose cohorts
  - Early-onset pulmonary events were less frequent at the starting daily dose of 90 mg (4%) vs 180 mg (14%)
  - No early-onset pulmonary events were observed in the 32 patients started at 90 mg and escalated to 180 mg after 7 days

- The results of this brigatinib phase 1/2 trial have guided the dose selection of 90 mg qd and 90→180 mg qd for evaluation in the ongoing pivotal phase 2 study in ALK+ NSCLC (ALTA: ALK in Lung Cancer Trial of AP26113)

Brigatinib Phase 1/2 Trial: Phase 2 Doses Acknowledgments

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