ASCO ANNUAL MEETING
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2016
THE FUTURE OF PATIENT-CENTERED CARE AND RESEARCH

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McCormick Place | Chicago, Illinois
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ASCO

ALK y otros biomarcadores

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HGU Elche / H Vega Baja Orihuela
21 de Junio de 2016

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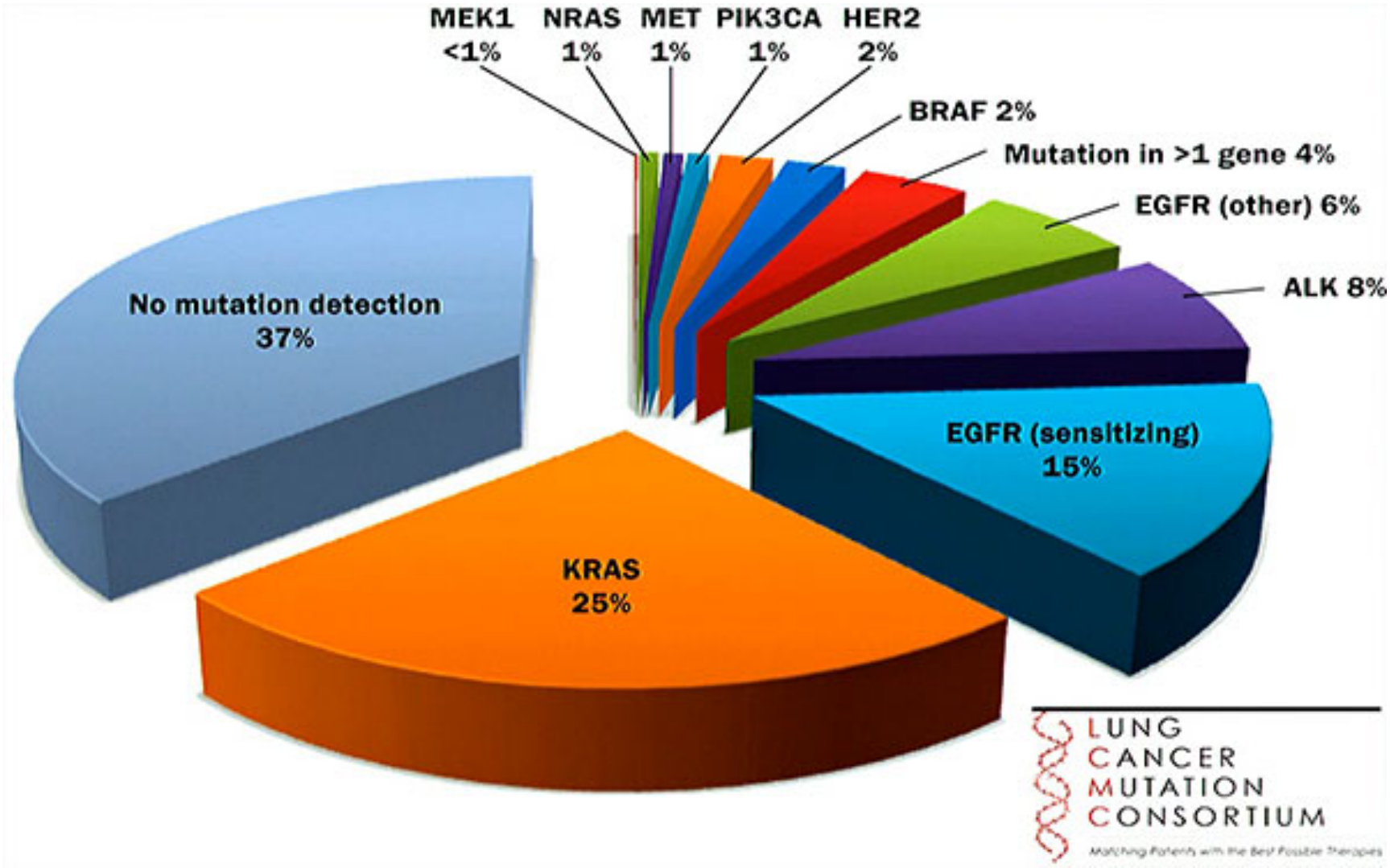
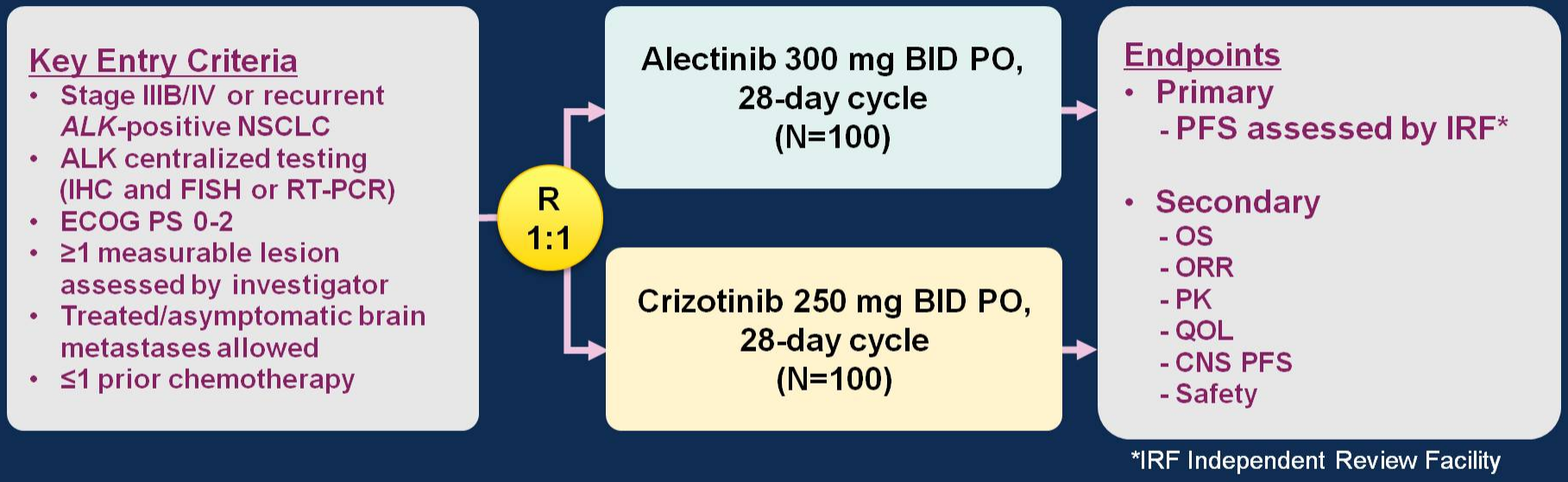

MEK1 <1%
NRAS 1%
MET 1%
PIK3CA 1%
HER2 2%
BRAF 2%
Mutation in >1 gene 4%
EGFR (other) 6%
ALK 8%
EGFR (sensitizing) 15%
KRAS 25%
No mutation detection 37%
LUNG CANCER MUTATION CONSORTIUM
Matching Patients with the Best Possible Therapies


MET
ROS1
BRAF
RET
EGFR
EML4-ALK

Alectinib versus Crizotinib in ALK Inhibitor Naïve *ALK*-Positive Non-Small Cell Lung Cancer: Primary Results from the J-ALEX Study

J-ALEX Phase III Study Design



*IRF Independent Review Facility

Stratification factors: Clinical stage (IIIB/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)

JapicCTI-132316

Oral Abstract Session
Lung Cancer – Non-Small Cell Metastasic

Presented By Hiroshi Nokihara at 2016 ASCO Annual Meeting

Statistical Considerations

- **Events calculation by superiority hypothesis**
  - Targeted HR for PFS = 0.643
    - Assumed median PFS of alectinib: 14 months vs. crizotinib: 9 months
  - Two sided significance level: 0.05, Power: 80%
  - 164 events needed
- **Sample size and interim analysis**
  - Required sample size: 200 patients for 164 events
  - Three interim analyses for efficacy: 33%, 50%, and 75% of final events

Study Overview

- **Accrual period : 20.5 months (Nov 18th, 2013 - Aug 4th, 2015)**
- **Primary analysis was performed in accordance with the results at 2nd interim analysis on the recommendation of the IDMC***
  - Data cut off date: Dec 3rd, 2015
  - Actual PFS events by IRF: 83 (50.6% of required PFS events)
  - Two sided significance level: 0.003174
  - Duration of follow-up, median (range)
    - Alectinib: 12.0 months (1.2 - 23.0)
    - Crizotinib: 12.2 months (0.0 - 20.3)

Baseline Characteristics

		Alectinib (N=103)	Crizotinib (N=104)
Sex	Male / Female	41 (39.8%) / 62 (60.2%)	41 (39.4%) / 63 (60.6%)
Median age (range)		61.0 (27-85)	59.5 (25-84)
ECOG PS*	0	54 (52.4%)	48 (46.2%)
	1	47 (45.6%)	54 (51.9%)
	2	2 (1.9%)	2 (1.9%)
Prior chemotherapy*	0	66 (64.1%)	67 (64.4%)
	1	37 (35.9%)	37 (35.6%)
Clinical stage*	Stage IIIB	3 (2.9%)	3 (2.9%)
	Stage IV	76 (73.8%)	75 (72.1%)
	Postoperative recurrence	24 (23.3%)	26 (25.0%)
Histology	Squamous cell carcinoma	2 (1.9%)	0
	Adenocarcinoma	100 (97.1%)	103 (99.0%)
	Other	1 (1.0%)	1 (1.0%)
Brain metastases by IRF	Yes / No	14 (13.6%) / 89 (86.4%)	29 (27.9%) / 75 (72.1%)
Smoking status	Never smoker	56 (54.4%)	61 (58.7%)
	Past or Current smoker	47 (45.6%)	43 (41.3%)
ALK test method	IHC and FISH	96 (93.2%)	94 (90.4%)
	RT-PCR	7 (6.8%)	10 (9.6%)

*Stratification factors

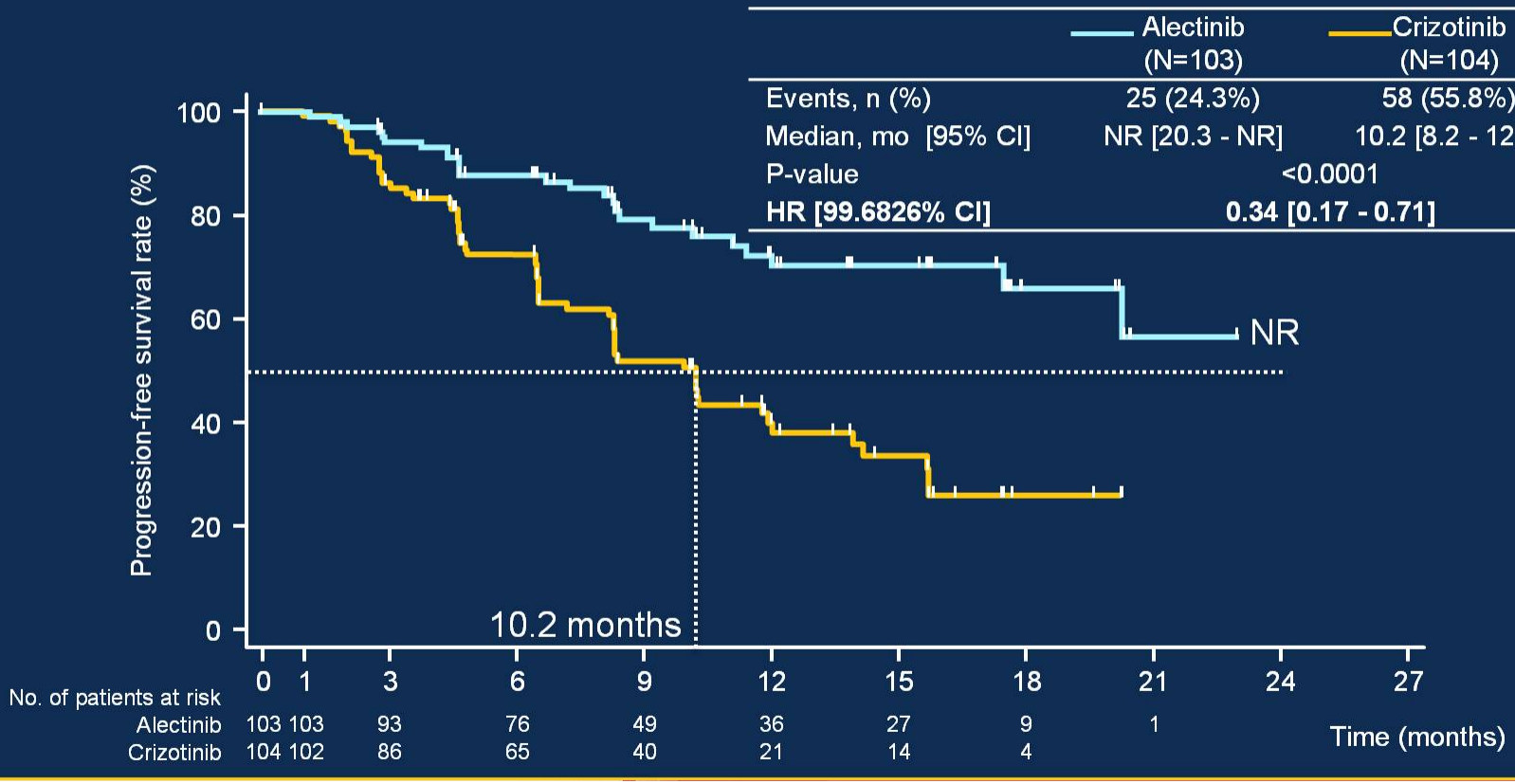
Common AEs, ≥20% of Patients in Either Arm

	All Grade		Grade 3/4	
	Alectinib (N=103)	Crizotinib (N=104)	Alectinib (N=103)	Crizotinib (N=104)
Constipation	36 (35.0%)	46 (44.2%)	1 (1.0%)	1 (1.0%)
Nausea	11 (10.7%)	77 (74.0%)	0	2 (1.9%)
Diarrhea	9 (8.7%)	76 (73.1%)	0	2 (1.9%)
Vomiting	6 (5.8%)	60 (57.7%)	0	2 (1.9%)
Aspartate aminotransferase increased	11 (10.7%)	32 (30.8%)	1 (1.0%)	5 (4.8%)
Alanine aminotransferase increased	9 (8.7%)	33 (31.7%)	1 (1.0%)	13 (12.5%)
Visual disturbance	1 (1.0%)	57 (54.8%)	0	0
Nasopharyngitis	21 (20.4%)	24 (23.1%)	0	0
Dysgeusia	19 (18.4%)	54 (51.9%)	0	0
Pyrexia	10 (9.7%)	21 (20.2%)	1 (1.0%)	0
Decreased appetite	1 (1.0%)	21 (20.2%)	1 (1.0%)	1 (1.0%)

Detail of AEs Leading to Discontinuation of Study Drug

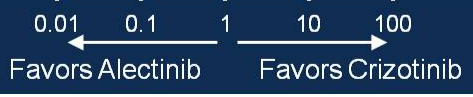
	Alectinib	Crizotinib
Total number of events	**9**	**23**
Interstitial lung disease	8	8
Enterocolitis	1	0
Hepatic function abnormal	0	5
Alanine aminotransferase increased	0	4
Aspartate aminotransferase increased	0	1
Blood bilirubin increased	0	1
Electrocardiogram QT prolonged	0	1
Bradycardia	0	1
Acute myeloid leukemia	0	1
Rash maculo-papular	0	1

Primary Endpoint: PFS by IRF (ITT Population)



Subgroup Analysis of PFS by IRF

Subgroup		Alectinib (N=103) n	Alectinib (N=103) Events	Crizotinib (N=104) n	Crizotinib (N=104) Events	HR [95% CI]
Overall		103	25	104	58	0.34 [0.21 - 0.54]
ECOG performance status	0/1	101	24	102	57	0.33 [0.20 - 0.53]
	2	2	1	2	1	1.41 [0.08 - 23.57]
Prior chemotherapy	0	66	15	67	35	0.30 [0.17 - 0.56]
	1	37	10	37	23	0.39 [0.18 - 0.83]
Clinical stage	Postoperative recurrence	24	6	26	13	0.49 [0.18 - 1.30]
	Stage IIIB/IV	79	19	78	45	0.31 [0.18 - 0.52]
Age group	≥75	12	3	10	5	0.28 [0.06 - 1.19]
	<75	91	22	94	53	0.34 [0.21 - 0.56]
Smoking status	Never smoker	56	18	61	33	0.50 [0.28 - 0.89]
	Past or Current smoker	47	7	43	25	0.18 [0.08 - 0.42]
Brain metastases at baseline	Yes	14	1	29	16	0.08 [0.01 - 0.61]
	No	89	24	75	42	0.39 [0.23 - 0.64]
ALK testing method	IHC and FISH	96	21	94	52	0.30 [0.18 - 0.50]
	RT-PCR	7	4	10	6	0.80 [0.22 - 2.90]
Sex	Female	62	16	63	37	0.31 [0.17 - 0.57]
	Male	41	9	41	21	0.35 [0.16 - 0.77]



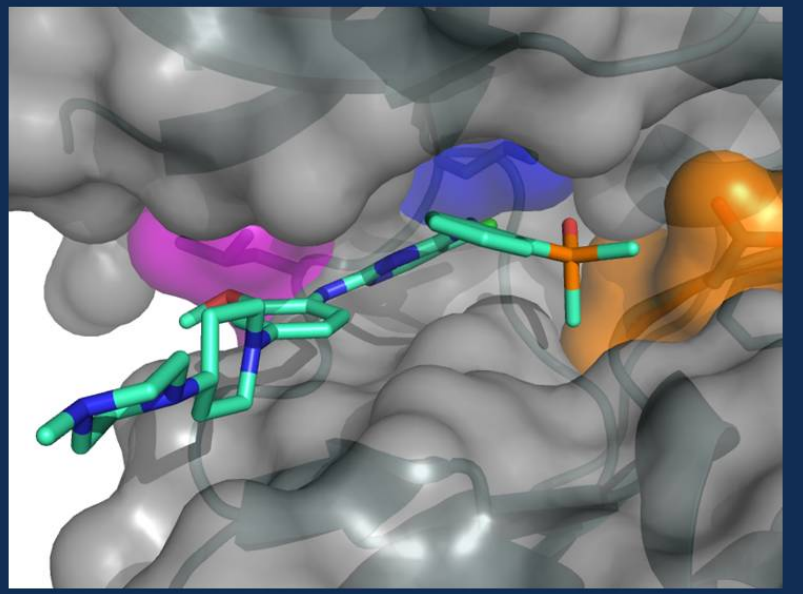
Multiple stratified Cox regression using prognostic factors including brain metastases showed consistent treatment effect (HR = 0.34)

Conclusion

- At a pre-planned interim analysis, J-ALEX met the primary endpoint, demonstrating superiority of alectinib compared with crizotinib in ALK inhibitor naïve patients
  - PFS HR of alectinib vs. crizotinib: 0.34
  - Median PFS in alectinib arm was not reached [95% CI:20.3 - NR]
  - Crizotinib behaved as expected, both PFS and ORR
- Alectinib was well-tolerated with a favorable AE profile
  - Less discontinuation or interruption due to AEs than crizotinib
  - No treatment-related deaths in either arm
- Alectinib has the potential to be a new standard first-line therapy for *ALK*-positive NSCLC

Brigatinib in Patients With Crizotinib-Refractory ALK+ Non–Small Cell Lung Cancer: First Report of Efficacy and Safety From a Pivotal Randomized Phase 2 Trial (ALTA)

- Brigatinib overcomes mechanisms of resistance to first- and second-generation ALK inhibitors in preclinical models[1]
  - Potently inhibited all ALK resistance mutations tested, including G1202R, at clinically achievable levels
  - Significantly prolonged survival and reduced tumor burden in an ALK-dependent orthotopic brain tumor model in mice
- Brigatinib yielded promising clinical activity in crizotinib-treated ALK+ NSCLC patients in a phase 1/2 study[2]



Brigatinib binding ALK kinase domain[6]

(1) Zhang, et al. *Cancer Res*. 2015;75(15 suppl):abstract 781.
(2) Camidge, et al. *J Clin Oncol*. 2015;33(suppl):abstract 8062.
(3) Katayama, et al. *Clin Cancer Res*. 2015;21:2227-35.
(4) Friboulet, et al. *Cancer Discov*. 2014;4:662-73.

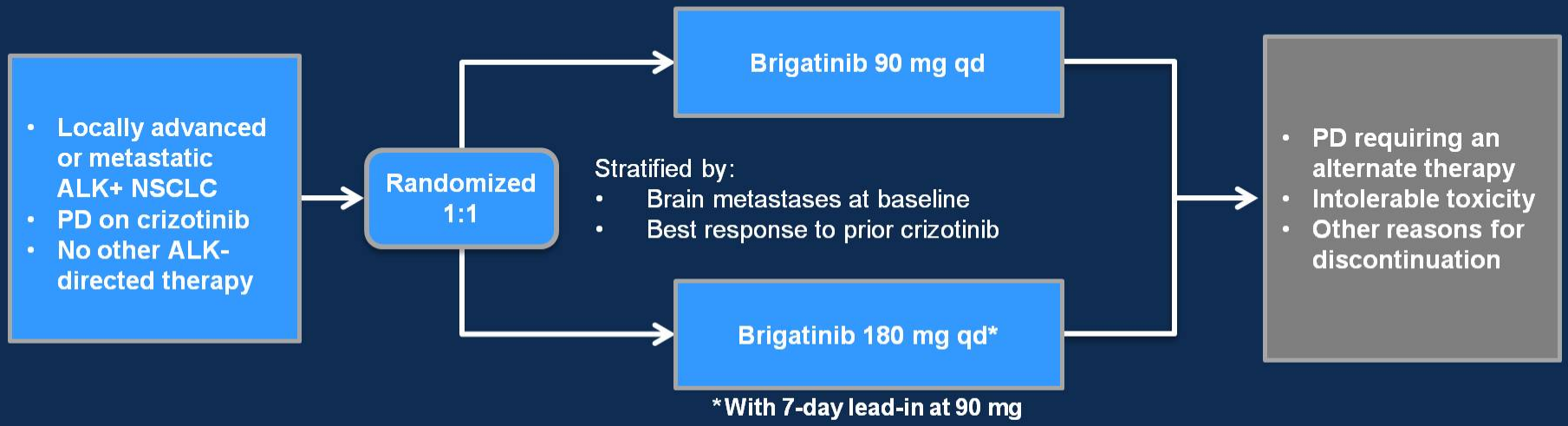
Adapted from Zhang, et al

Presented By Dong-Wan Kim at 2016 ASCO Annual Meeting

Oral Abstract Session
Lung Cancer – Non-Small Cell Metastasic

ALTA: Randomized Dose Evaluation of Brigatinib

A phase 2, open-label, multicenter, international study (NCT02094573)



Primary Endpoint: Confirmed ORR per RECIST v1.1 (assessed by investigator)

Key Secondary Endpoints: Confirmed ORR (assessed by an IRC), CNS response (IRC-assessed intracranial ORR and PFS in patients with active brain metastases†), duration of response, PFS, OS, safety, and tolerability

Randomized phase 2 design not intended for statistical comparisons between arms; however, post hoc comparisons were performed on PFS and OS to support dose selection

- Data as of February 29, 2016

	90 mg qd	180 mg qd*
Randomized, n	112	110
Treated, n (%)	109 (97)	110 (100)
Remain on study, n (%)	64 (57)	76 (69)
Median follow-up, months (range)	7.8 (0.1–16.7)	8.3 (0.1–20.2)

* 180 mg qd with 7-day lead-in at 90 mg

Demographics and Baseline Characteristics

		90 mg qd n=112	180 mg qd* n=110	Total N=222
Median age, y (range)		50.5 (18–82)	56.5 (20–81)	54 (18–82)
Gender, n (%)	Female	62 (55)	64 (58)	126 (57)
Race, n (%)	White	72 (64)	76 (69)	148 (67)
	Asian	39 (35)	30 (27)	69 (31)
	Other	1 (1)	4 (4)	5 (2)
ECOG, n (%)	0/1	105 (94)	101 (92)	206 (93)
	2	7 (6)	9 (8)	16 (7)
Smoking history, n (%)	No	71 (63)	63 (57)	134 (60)
	Yes	40 (36)	47 (43)	87 (39)
	Unknown	1 (1)	0	1 (<1)
Histology, n (%)	Adenocarcinoma	107 (96)	108 (98)	215 (97)
	Other	5 (4)	2 (2)	7 (3)
Prior chemotherapy, n (%)	Yes	83 (74)	81 (74)	164 (74)
Brain metastases at baseline,† n (%)	Present	80 (71)	74 (67)	154 (69)
Best response to prior crizotinib, n (%)	CR or PR	71 (63)	73 (66)	144 (65)
	Other response or unknown	41 (37)	37 (34)	78 (35)

CR = complete response, PR = partial response. * 180 mg qd with 7-day lead-in at 90 mg; † Presence of brain metastases as assessed by the investigator

- Arms balanced for important prognostic factors including gender, ECOG PS (0/1 vs. 2), brain metastases, prior chemotherapy, and prior response to crizotinib

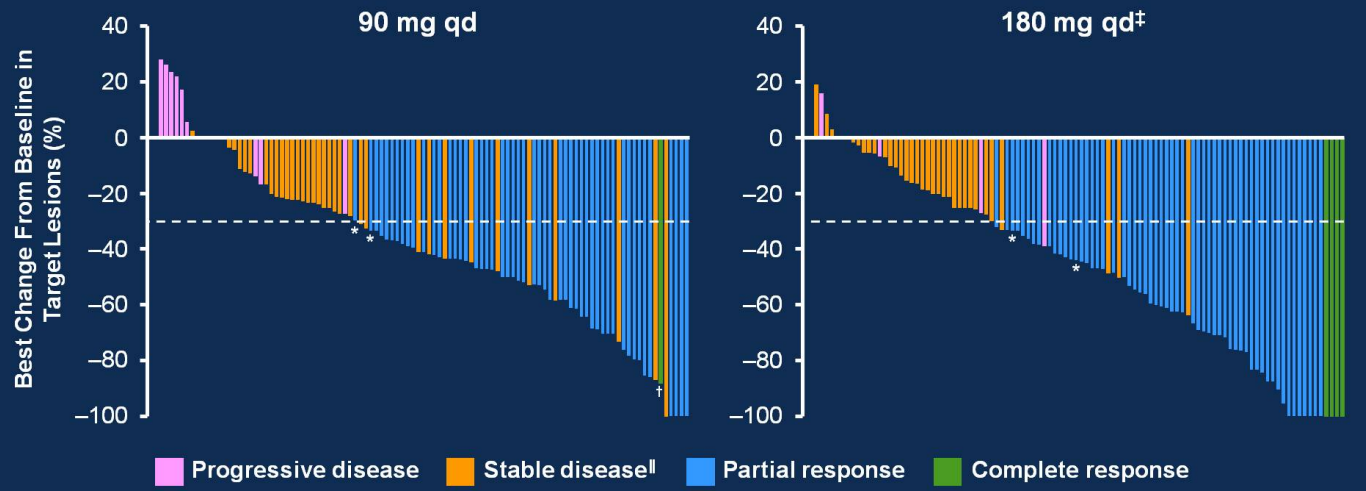
Data as of February 29, 2016

Objective Response Rates in Crizotinib-Resistant Patients by Arm

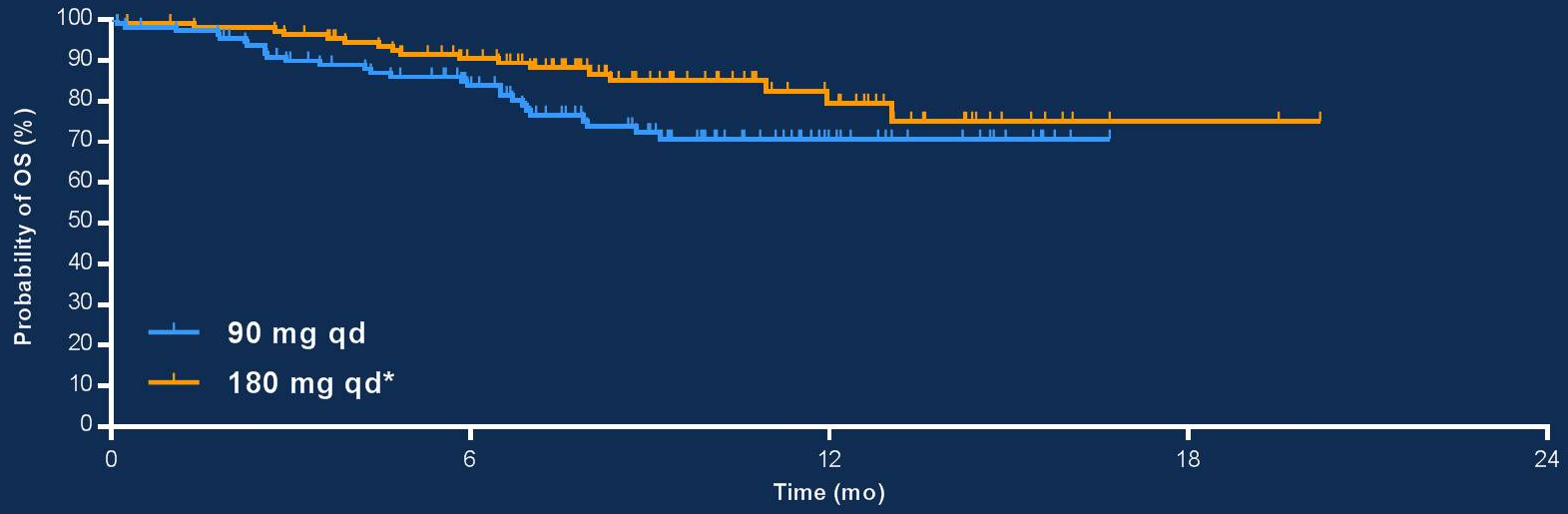
Investigator-Assessed Efficacy Parameter	90 mg qd n=112	180 mg qd* n=110
Confirmed ORR, n (%) [97.5% CI]†	50 (45) [34–56]	59 (54) [43–65]
Confirmed CR, n (%)	1 (1)	4 (4)
Confirmed PR, n (%)	49 (44)	55 (50)
PR awaiting confirmation, n (%)	2 (2)	2 (2)
Disease control rate, n (%) [95% CI]	92 (82) [74–89]	95 (86) [79–92]
Confirmed ORR by history of prior chemotherapy, n/N (%)		
Yes	35/83 (42)	44/81 (54)
No	15/29 (52)	15/29 (52)

CR = complete response, PR = partial response
* 180 mg qd with 7-day lead-in at 90 mg; † Primary endpoint tested at 0.025 level for each dose

Brigatinib Antitumor Activity by Arm



Survival by Arm



	Events / Total (%)	1-Year OS Probability, % (95% CI)	Median OS	Hazard Ratio (95% CI)†
90 mg qd	27/112 (24)	71 (60–79)	Not reached	0.57 (0.31–1.05)
180 mg qd*	17/110 (15)	80 (67–88)	Not reached	

*180 mg qd with 7-day lead-in at 90 mg

†Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Data as of February 29, 2016

IRC-Assessed Intracranial Response Rates

IRC-Assessed Efficacy Parameter	Patients With Measurable (≥10 mm) Brain Metastases		Patients With Only Nonmeasurable Brain Metastases	
	90 mg qd n=25	180 mg qd* n=18	90 mg qd n=54	180 mg qd* n=54
Confirmed intracranial ORR, n (%) [95% CI]	9 (36) [18–58]	12 (67) [41–87]	3 (6) [1–15]	10 (19) [9–31]
Best overall response, n (%)				
Confirmed intracranial CR	2 (8)	0	3 (6)	10 (19)
Confirmed intracranial PR	7 (28)	12 (67)	NA	NA
Intracranial CR awaiting confirmation	0	0	0	1 (2)
Intracranial PR awaiting confirmation	3 (12)	0	NA	NA
Intracranial disease control rate, n (%) [95% CI]	22 (88) [69–98]	15 (83) [59–96]	39 (72) [58–84]	47 (87) [75–95]

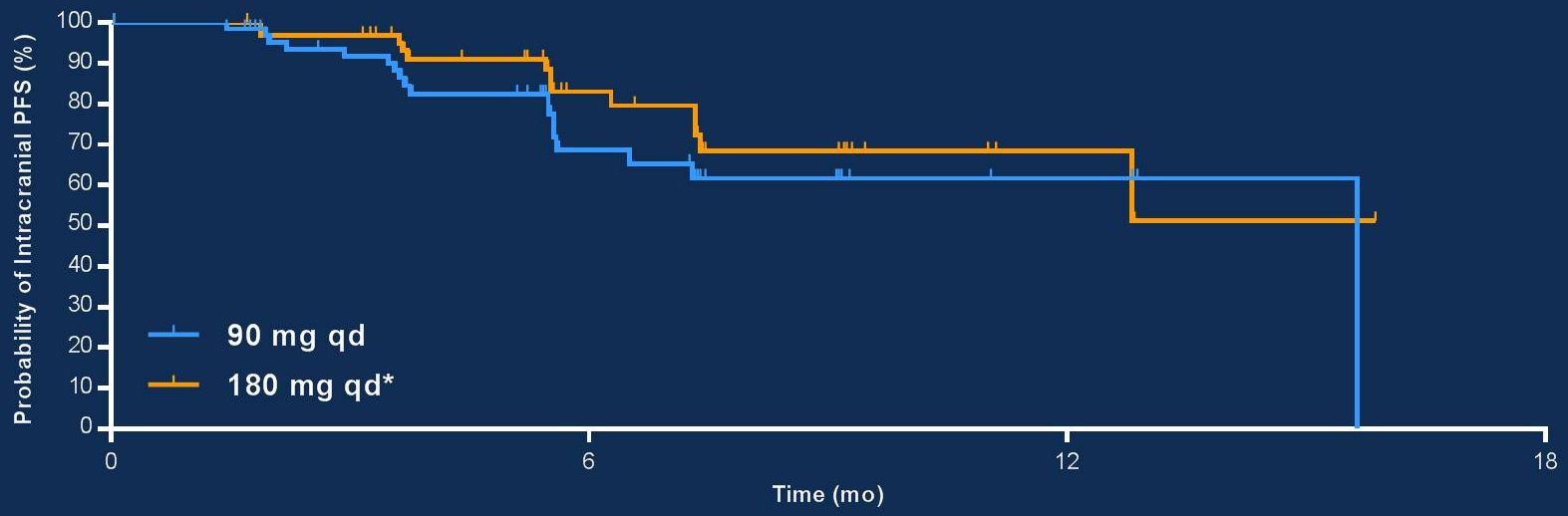
Of 222 randomized patients, 215 had a baseline brain MRI evaluated by the IRC, with 151 identified as having brain metastases at baseline
Intracranial response defined as a ≥30% decrease in measurable lesions or complete disappearance of lesions in patients with only nonmeasurable lesions
NA = not applicable

- Among patients with measurable, active† brain metastases at baseline, IRC-assessed intracranial ORR:
  - 37% (7/19) at 90 mg
  - 73% (11/15) at 180 mg

*180 mg qd with 7-day lead-in at 90 mg
†Active brain metastases were defined as lesions with no prior radiotherapy or those with investigator-assessed progression after prior radiotherapy

Last scan date: February 17, 2016

Intracranial PFS by Arm



	Events / Total (%)	Median Intracranial PFS (95% CI)	Hazard Ratio (95% CI)†
90 mg qd	18/79 (23%)	15.6 months (6.5–15.6)	0.66 (0.32–1.35)
180 mg qd*	13/72 (18%)	Not reached (7.4–not reached)	

*180 mg qd with 7-day lead-in at 90 mg

†Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Last scan date: February 17, 2016

Conclusions

- Brigatinib demonstrated substantial efficacy and an acceptable safety profile in both arms
- At 180 mg (with 7-day lead-in at 90 mg):
  - 54% ORR
  - 67% intracranial ORR (for patients with measurable brain metastases)
  - Median PFS >1 year (12.9 months); 80% 1-year OS
- Observed clinical activity at 180 mg with 7-day lead-in at 90 mg was not associated with an increased risk of additional early pulmonary AEs
- A consideration of efficacy outcomes and AEs supports choice of 180 mg regimen
- Brigatinib has the potential to be a promising new treatment option for patients with crizotinib-resistant ALK+ NSCLC
- A randomized, phase 3 study of brigatinib with 180 mg regimen vs crizotinib in ALK inhibitor–naive patients has been initiated (ALTA-1L, NCT02737501)

Abstract No. 9009

Safety and Efficacy of Lorlatinib (PF-06463922) From the Dose Escalation Component of a Study in Patients With Advanced ALK+ or ROS1+ Non-Small-Cell Lung Cancer

B. Solomon[1], T.M. Bauer[2], E. Felip[3], B. Besse[4], L.P. James[5], J.S. Clancy[6], K. Klamerus[7], J.-F. Martini[7], A. Abbattista[8], A. Shaw[9]

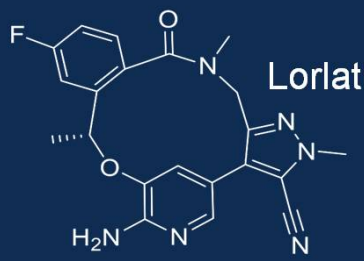
ALK/ROS1+ NSCLC:
Treatment-naïve in advanced setting
or PD after at least 1 prior ALK/ROS1 TKI;
any prior chemotherapy
N=54

→

Lorlatinib
QD or BID*
(Dose Escalation)

- Histologically or cytologically confirmed metastatic NSCLC and either:
  - ALK rearrangement, by FDA-approved FISH assay or by IHC (Ventana Inc.)
  - ROS1 rearrangement, by FISH, RT-PCR, or NGS via a local diagnostic test
- ≥1 measurable extracranial target lesion per RECIST v1.1
  - Patients with asymptomatic CNS metastases (treated or untreated) were eligible

*Treatment until PD or unacceptable toxicity; treatment beyond PD allowed if deriving benefit



Objectives

- Primary objective:
  - Assess safety and tolerability of single-agent lorlatinib at increasing dose levels in patients with advanced ALK+ or ROS1+ NSCLC in order to establish the RP2D

- Additional objectives:
  - Antitumor activity (including intracranial activity)
  - Pharmacokinetics
  - PROs
  - Correlative studies

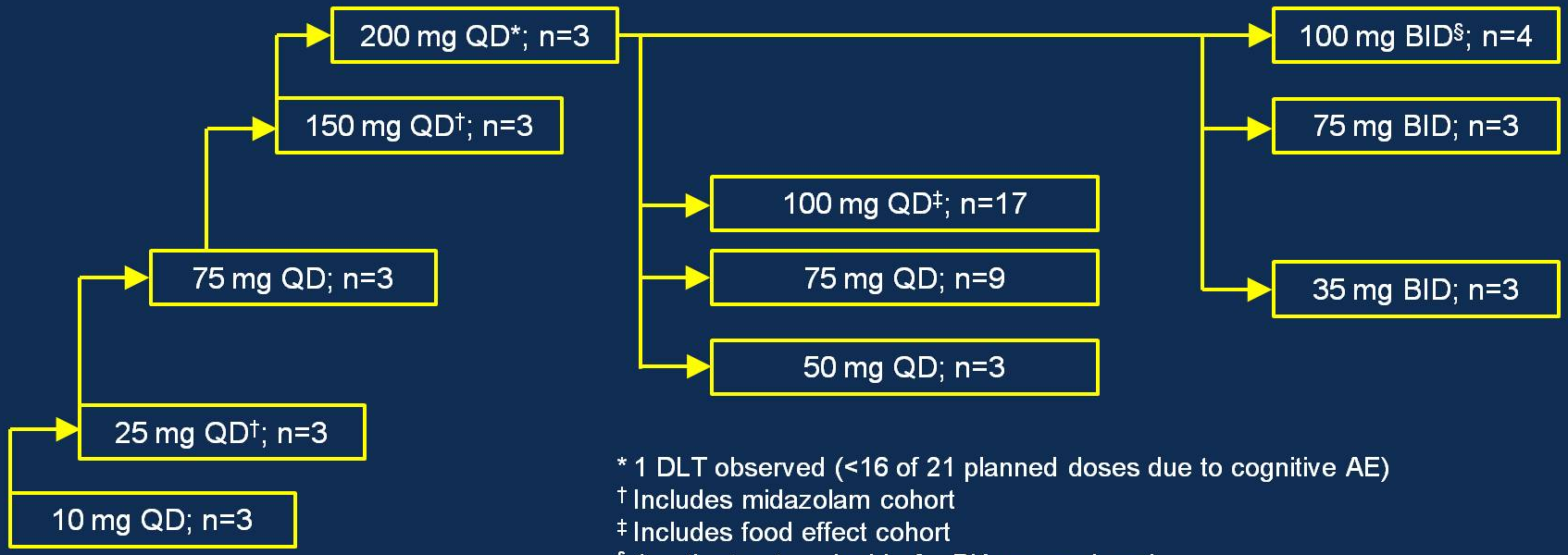
Baseline Patient Characteristics

Characteristic		Lorlatinib (N=54)
Age, years	Mean (±SD)	51.9 (±12.8)
Sex, n (%)	Male	22 (41)
	Female	32 (59)
Race, n (%)	White	42 (78)
	Black	4 (7)
	Asian	7 (13)
	Other	1 (2)
Brain metastases, n (%)	Present	39 (72)
ALK/ROS1 status, n (%)	ALK+	41 (76)
	ROS1+	12 (22)
	Mutation status not confirmed	1 (2)
Prior ALK/ROS1 TKI*, n (%)	0	7 (13)
	1	20 (37)
	≥2	27 (50)

*Number of prior TKIs counted by line; patients may have received the same drug more than once, either sequentially or separated by another therapy

Patient Allocation to Dose Levels in Phase I Portion

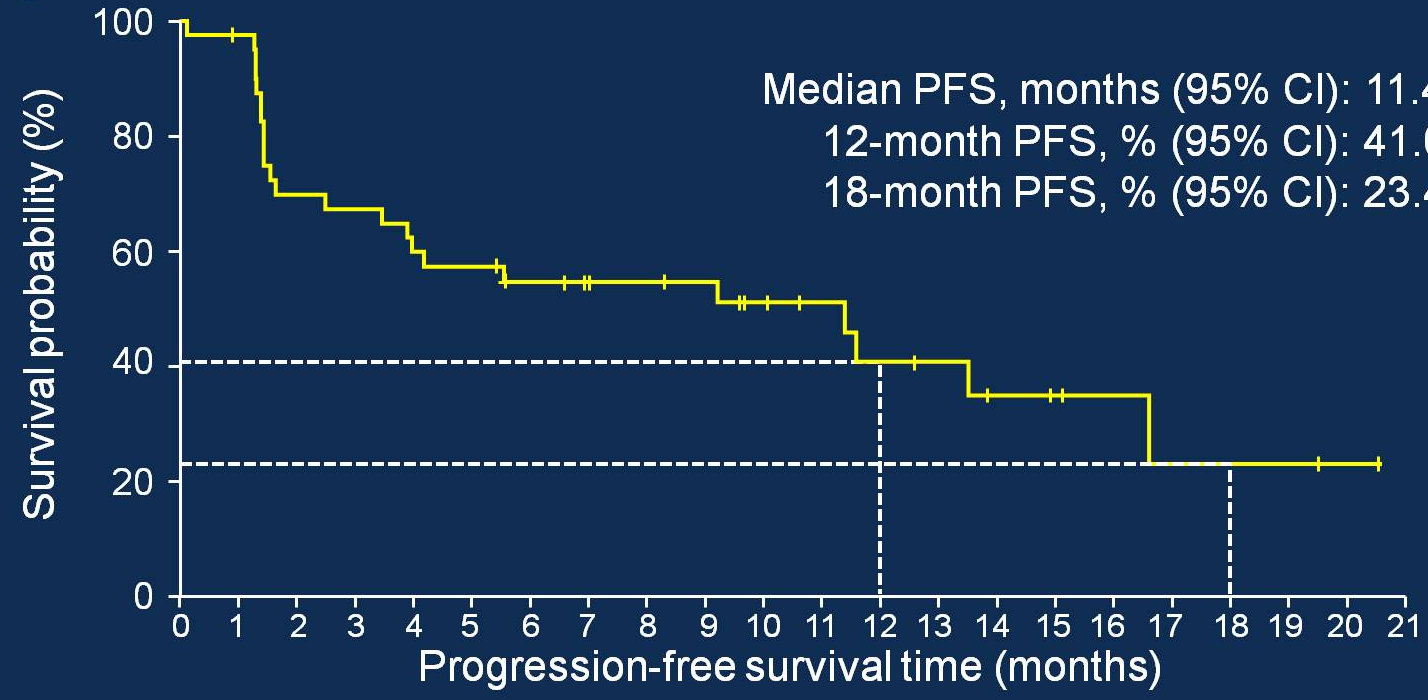
Lorlatinib given day –7; then continuously in 21-day cycles, either QD or BID



* 1 DLT observed (<16 of 21 planned doses due to cognitive AE)
† Includes midazolam cohort
‡ Includes food effect cohort
§ 1 patient not evaluable for PK was replaced

AE, adverse event; BID, twice daily; DLT, dose-limiting toxicity; PK, pharmacokinetics; QD, once daily

Clinical Activity: Progression-Free Survival in ALK+ Patients



Conclusions

- Lorlatinib was well tolerated at the RP2D (100 mg QD) with the most frequent treatment related toxicity of hypercholesterolemia.
- Lorlatinib demonstrated robust clinical activity in both ALK+ and ROS1+ patients with NSCLC, most of whom had brain metastases and had received ≥1 prior ALK TKI
- Significant intracranial responses were observed, showing that lorlatinib can cross the blood–brain barrier to achieve clinically meaningful CNS activity
- The phase II portion of the study is ongoing at 57 centres worldwide
- Novel, broad spectrum, potent ALK and ROS1 inhibitor, active against multiple mutations conferring resistance to other ALK and ROS1 TKIs, including crizotinib, ceritinib, alectinib.

Antitumor Activity and Safety of Crizotinib in Patients with Advanced *MET* Exon 14-Altered Non-Small Cell Lung Cancer

- Incidence
  - 3-4% of nonsquamous NSCLCs
  - 20-30% of sarcomatoid lung carcinomas
- Clinicopathologic Features
  - older patients
  - ↓ proportion of never smokers
  - patients should be screened regardless of these clinical features
  - 15-20% with concurrent *MET* amplification

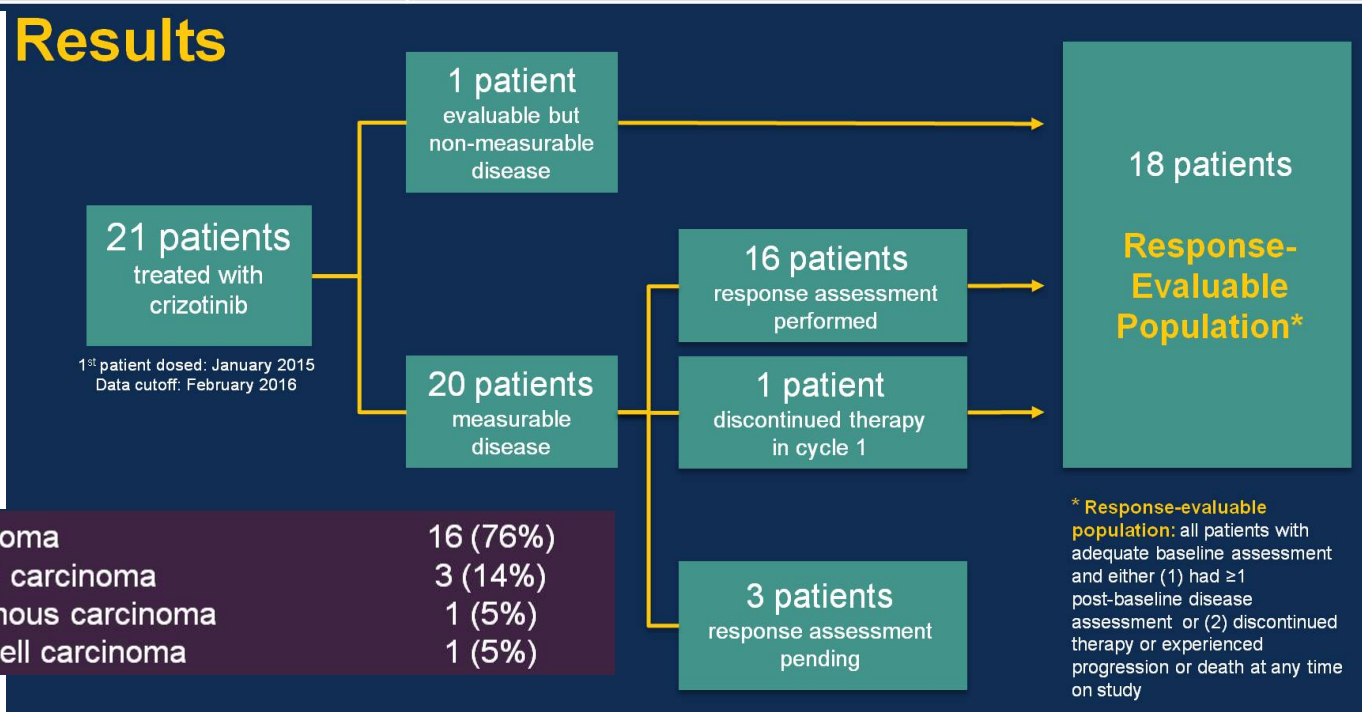
Crizotinib

- potent MET inhibitor
  - ATP-competitive tyrosine kinase inhibitor, IC50 11 nM for MET
  - approved for the treatment of *ALK*- and *ROS1*-rearranged lung cancers
- active in tumors harboring *MET* exon 14 alterations
  - ↓ cell proliferation and downstream signaling *in vitro*
  - case reports of patient responses

PROFILE 1001 Study - Presented By Alexander Drilon at 2016 ASCO Annual Meeting

PROFILE 1001 Study (NCT00585195)	
Eligibility	Advanced non-small cell lung cancer MET exon 14 alteration No prior MET-directed targeted therapy Treated brain metastases allowed
Diagnosis of MET exon 14 alteration	Local molecular profiling Central confirmation - performed if with sufficient tissue but not required - ThermoFisher Oncomine Focus Assay, Ion Torrent (Cancer Genetics Inc., CA)
Treatment	Crizotinib at 250 mg twice daily
Response Assessment	Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 Imaging at baseline and every 8 weeks
Adverse Events	Common Terminology Criteria for Adverse Events (CTCAE) v3.0

Results



Adenocarcinoma	16 (76%)
Sarcomatoid carcinoma	3 (14%)
Adenosquamous carcinoma	1 (5%)
Squamous cell carcinoma	1 (5%)

Patients

Patients with *MET* exon 14-altered lung cancers (n=21)

Age, years	Median (range)	68 (53–87)
Sex, n (%)	Female	15 (71%)
	Male	6 (29%)
Race, n (%)	White	14 (67%)
	Asian	4 (19%)
	Black	1 (5%)
	Other	2 (10%)
Smoking history, n (%)	Former smoker	13 (62%)
	Never smoker	8 (38%)
Tumor histology, n (%)	Adenocarcinoma	16 (76%)
	Sarcomatoid carcinoma	3 (14%)
	Adenosquamous carcinoma	1 (5%)
	Squamous cell carcinoma	1 (5%)
Prior treatments for advanced disease, n (%)	0	3 (14%)
	1	12 (57%)
	2	3 (14%)
	≥3	3 (14%)

Safety

Crizotinib-Related Adverse Events Occurring in ≥10% of Patients

Patients, n (%)	n=21 Patients Evaluable for Safety		
Adverse events†	All Grades	Grade 3	Grade 4
Any adverse event‡	19 (90%)	4 (19%)	0
Edema	9 (43%)	1 (5%)	0
Diarrhea	7 (33%)	0	0
Nausea	7 (33%)	0	0
Vision disorder	7 (33%)	0	0
Vomiting	6 (29%)	0	0
Bradycardia	5 (24%)	1 (5%)	0
Constipation	3 (14%)	0	0
Fatigue	3 (14%)	0	0

†There were no treatment-related grade 5 adverse events.
‡Refers to reports of any frequency of AE and is not limited to AE's that were reported in ≥10% of patients.
One permanent treatment discontinuation was due to an unrelated grade 3 hypoxia.

Summary and Conclusions

- *MET* exon 14 alterations are actionable lung cancer drivers that can be

Response-Evaluable Population (n=18)		
Best overall response n (%)	Complete response (CR)	0
	Partial response (PR)	8 (44%)
	Stable disease (SD)	9 (50%)
	Unconfirmed CR/PR †	5 (28%)
	Progression of Disease (PD)	0
	Indeterminate ‡	1 (6%)
Overall response rate (ORR)		44% (95% CI: 22–69), n=8/18

– accrual goal of up to 50 patients with *MET* exon 14-altered lung cancers

- Screening should be considered for patients with NSCLC.

Targeting RET in patients with RET-rearranged lung cancers: results from a global registry

Gautschi O, Wolf J, Milia J, Filleron T, Carbone D, Camidge R, Shih J, Awad M, Cabillic F, Peled N, Van Den Heuvel M, Owen D, Kris M, Janne P, Besse B, Cho B, Karp D, Rosell R, Mazieres J, Drilon A, on behalf of the GLORY investigators. Coordinating centers: University Hospital Toulouse, France; Cantonal Hospital Lucerne, Switzerland; MSKCC New York, USA.

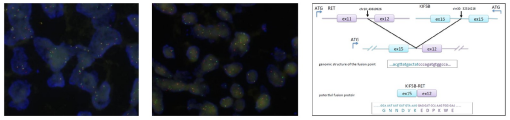
GLORY global RET-NSCLC registry

ABSTRACT

Background: Alongside prospective clinical trials for patients (pts) with non-small cell lung cancers (NSCLC) driven by rare genomic alterations, registries can provide complementary information on response to targeted therapies. We present the results of a global registry of RET-rearranged NSCLC, providing the largest data set on outcomes with RET-directed therapy so far. **Methods**: Pts were identified by a global, multicenter network of thoracic oncologists. IRB approval was obtained according to local requirements. Eligibility included a diagnosis of NSCLC harboring a RET fusion by FISH, RT-PCR or NGS. Anonymized data (age, gender, smoking, histology, stage, systemic therapy, survival) were collected centrally and evaluated by an independent statistician. In an analysis of pts treated off-protocol with multikinase inhibitors known to target RET, the primary endpoint was best objective response (RECIST). **Results**: 132 pts with RET-rearranged NSCLC from the USA, Asia, and Europe were registered. Median age at diagnosis was 61 years (range: 28-89), 52% were female, 62% were never-smokers, 97% had adenocarcinoma, and 91% had stage III/IV disease. 41 pts (31%) received RET inhibitor therapy off-protocol: cabozantinib (14), vandetanib (11), sunitinib (10), sorafenib (2), alectinib (1), lenvatinib (1), nintedanib (1), and ponatinib (1). Most pts received a RET inhibitor in the third-line setting (range: 1st-8th line). Median PFS was 2.9 months (95%CI: 1.3-5.6), OS 6.8 months (95%CI: 3.9-14.3), median duration of therapy 2.2 months (range: 0.5-12.2). 8 pts remain on treatment. In 35 pts with serial imaging evaluated by RECIST, ORR was 23% (1 CR, 7 PR, 12 SD, 14 PD, 1 not measurable) and DCR 57%. Individual ORR (DCR) for cabozantinib and vandetanib was 31% (62%) and 18% (46%), respectively. No unexpected adverse effects were reported. **Conclusions**: RET inhibitors are active in a proportion of pts with RET-rearranged NSCLC. Consistent with results from an ongoing phase II trial of cabozantinib (Drilon, ASCO 2015), this proportion is lower than that observed with targeted therapy for EGFR-mutant and ALK-rearranged NSCLC. New therapeutic approaches and an improved understanding of tumor biology and response are needed.

AIMS & METHODS

This registry was opened to collect information about individual patients with RET-rearranged NSCLC of all stages. Investigators have to obtain consent and can use FISH, RT-PCR or NGS. Data are anonymized, collected in a central database, and evaluated by an independent statistician. Patients treated with tyrosine kinase inhibitors (TKI) known to target RET are eligible only if treated outside of a clinical protocol. Response to TKI was assessed locally by RECIST1.1.



Panel 1: Lung adenocarcinoma with rearrangement of KIF5B and RET by FISH (left and middle). Matched NGS result of the same tumor, confirming the KIF5B-RET fusion (right).

Images: J. Diebold (Lucerne) and F. Leenders (Cologne)

RESULTS

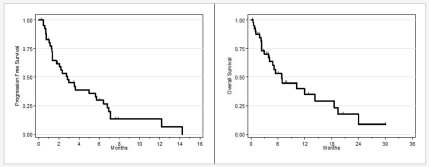
Characteristics	All	With RET inhibitor	P-value*
Eligible Patients	132 (100%)	41 (31%)	
Age [years] median (range) below 70 70 and older	 61 (28 – 89) 102 (77%) 30 (23%)	 58 (29 – 83) 34 (83%) 7 (17%)	 NS
Gender female male	 69 (52%) 63 (48%)	 23 (56%) 18 (44%)	 NS
Smoking status (n=131) never former current	 81 (62%) 37 (28%) 13 (10%)	 26 (65%) 8 (20%) 6 (15%)	 NS
Histology Adenocarcinoma NSCLC NOS Squamous	 128 (97%) 3 (2%) 1 (1%)	 40 (98%) 1 (2%) 0	 NS
UICC stage (n=129) I-II III IV	 12 (9%) 23 (18%) 94 (73%)	 0 6 (15%) 33 (85%)	 0.027
Concomitant driver EGFR mutation KRAS mutation MET amplification	 3 (2%) 2 (2%) 1 (1%)	 0 1 (2%) 1 (2%)	 NS

Panel 2: Patients included in the registry at the first data cutoff in December 2015. NS = not significant by chi2 or Fishers exact test for subgroup "with RET inhibitor" versus "others"

RET inhibitor	Patients	IC50 for RET	Further targets
Cabozantinib	14 (34%)	4 nM	VEGFR2, MET, KIT, AXL
Vandetanib	11 (27%)	130 nM	VEGFR2
Sunitinib	10 (24%)	224 nM	VEGFR2, PDGFRβ, KIT
Sorafenib	2 (5%)	50 nM	RAF1, BRAF, VEGFR2, PDGFR
Alectinib	1 (2%)	5 nM	ALK
Lenvatinib	1 (2%)	35 nM	VEGFR1-3
Nintedanib	1 (2%)	35 nM	VEGFR1-3, PDGFR1-3, FGFR1-3
Ponatinib	1 (2%)	25 nM	ABL, PDGFRα, VEGFR2, FGFR1

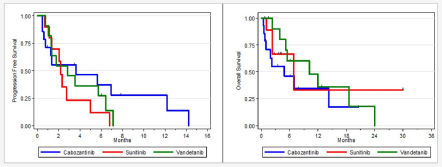
Inhibitor	CR	PR	SD	PD	NE	Missing	Total
Cabozantinib	1	3	4	5	0	1	14
Vandetanib	0	2	3	6	0	0	11
Sunitinib	0	2	3	3	1	1	10
Sorafenib	0	0	2	0	0	0	2
Alectinib	0	0	0	0	0	1	1
Lenvatinib	0	0	0	0	0	1	1
Nintedanib	0	0	0	0	0	1	1
Ponatinib	0	0	0	0	0	1	1

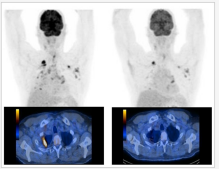
Panel 3: Inhibitors with known target effect for RET kinase used in the registry (top). Best response for individual RET inhibitors in patients with evaluable disease according to RECIST (bottom). NE = not evaluable.



Best RECIST response (N=35)	Progression free survival (N=41)	Overall survival (n=41)
CR = 1 (3%) PR = 7 (20%) SD = 12 (34%) PD = 14 (40%) NE = 1 (3%) ORR = 23% DCR = 57%	 Median 2.9 months [95%CI=1.3;5.6] 33 events (81%)	 Median 6.8 months [95%CI=3.9;14.3] 24 events (59%)

Panel 4 : Kaplan Meier survival curves for all 41 patients with RET inhibitor therapy (top). RECIST response, PFS and OS from the start of first RET inhibitor (bottom). NE = not evaluable.





Panel 5: Survival curves for the 35 patients treated with cabozantinib, vandetanib or sunitinib (top). PET/CT of a patient at baseline (bottom left) and after 2 weeks of vandetanib (bottom right). Images: K. Strobel (Lucerne).

SUMMARY

1. This is the largest database of patients with RET-rearranged NSCLC.
2. Consistent with previous reports, tumor remissions were observed with cabozantinib, vandetanib and sunitinib.
3. The registry remains open for follow up, and inclusion of further patients with RET-targeted therapy.

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Drilon, Ann Oncol. 2016 Apr 7 [Epub ahead of print]

ASCO 2016 abstract 9014
Presenting author: oliver.gautschi@luks.ch

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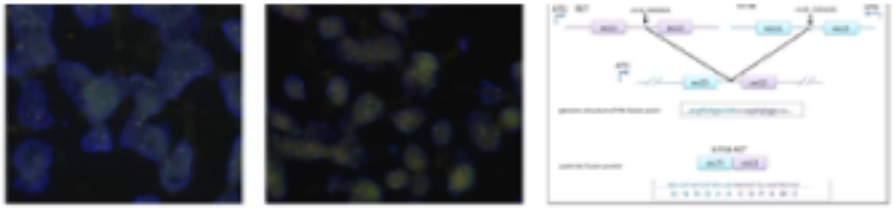
Poster Discussion Session

Lung Cancer – Non-Small Cell Metastasic



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RESULTS

Characteristics	All	With RET inhibitor	P-value*
Eligible Patients	132 (100%)	41 (31%)	
Age [years]			
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below 70	102 (77%)	34 (83%)	NS
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former	37 (28%)	8 (20%)	
current	13 (10%)	6 (15%)	
Histology			
Adenocarcinoma	128 (97%)	40 (98%)	NS
NSCLC NOS	3 (2%)	1 (2%)	
Squamous	1 (1%)	0	
UICC stage (n=129)			
I-II	12 (9%)	0	0.027
III	23 (18%)	6 (15%)	
IV	94 (73%)	33 (85%)	
Concomitant driver			
EGFR mutation	3 (2%)	0	NS
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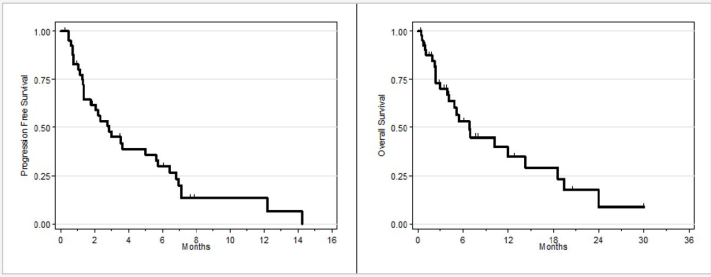

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A Phase II Open-label Single-arm Study of Vandetanib in Patients with Advanced RET-rearranged Non-Small Cell Lung Cancer (NSCLC): LURET study

Abstract ID:9012

Takashi Seto[1], Kiyotaka Yoh[2], Miyako Satouchi[3], Makoto Nishio[4], Noboru Yamamoto[5], Haruyasu Murakami[6], Naoyuki Nogami[7], Kaname Nosaki[1], Yoshiko Urata[3], Seiji Niho[2], Atsushi Horiike[4], Takashi Kohno[8], Shingo Matsumoto[2], Shogo Nomura[9], Sakiko Kuroda[9], Akihiro Sato[9], Yuichiro Ohe[5], Takeharu Yamanaka[10], Atsushi Ohtsu[2], Koichi Goto[2]

1 National Kyushu Cancer Center, 2 National Cancer Center Hospital East; 3 Hyogo Cancer Center; 4 The Cancer Institute Hospital of Japanese Foundation for Cancer Research; 5 National Cancer Center Hospital; 6 Shizuoka Cancer Center; 7 National Hospital Organization Shikoku Cancer Center; 8 National Cancer Center Research Institute; 9 National Cancer Center; 10 Yokohama City University, Japan

BACKGROUND

- RET rearrangements were identified as a new rare oncogenic alteration in 2012 and observed in 1-2% of all NSCLC.[1-4]
- Vandetanib is an oral receptor tyrosine kinase inhibitor that potently inhibits RET, EGFR, and VEGFR tyrosine kinase activity.
- Some case reports have described tumor shrinkage after vandetanib in patients with RET-rearranged NSCLC.[5-6]

METHODS

- This was a multicenter, single-arm phase II study to evaluate the efficacy and safety of vandetanib in patients with advanced RET-rearranged NSCLC who failed at least one prior chemotherapy.

Figure 1. Study design

- Non-squamous NSCLC
- RET fusion-positive
- Advanced disease
- Age ≥20
- ECOG PS 0–2
- At least one prior chemotherapy
- Measurable disease by RECIST

→ Vandetanib 300 mg orally, once daily until PD or unacceptable toxicity

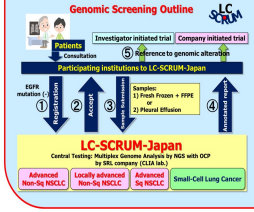
- Clinical trial information: UMIN000010095

Study objectives

- Primary endpoint: Objective response rate (ORR) by independent radiology review committee
- Secondary endpoints: Progression-free survival (PFS), Disease control rate (DCR, CR+PR+SD), Duration of response (DOR), Overall survival (OS), Safety, Response of prior anticancer therapy
- This study required 17 patients, with ORR of 30% considered non-promising and 60% promising (one-sided alpha = 0.05; beta = 0.2).

Genomic Screening by LC-SCRUM-Japan

We initiated a nationwide genomic screening project called LC-SCRUM-Japan in conjunction with this phase 2 study.

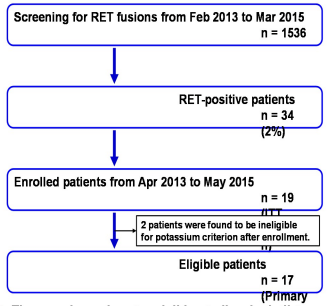


The RET rearrangements were identified using multiplex RT-PCR and a break-apart FISH assay.[7]

The LC-SCRUM-Japan has the participation of over 200 institutions and the collaboration of 14 drug company on May 2016.

RESULTS

Figure 2. Study profile



- The pre-planned protocol did not allow including ineligible patients in the primary efficacy analysis, and for that reason 2 ineligible patients were excluded from the primary analysis .
- Statistical analysis except the primary analysis included all 19 patients in ITT population.
- The data-cutoff date was August 31, 2015.

Table 1. Patient characteristics (n = 19)

Characteristic	n	(%)
Age: Median (range)	59 (41–80)	
Sex: Male/Female	5/14	(26/74)
Smoking status: Never/Former	13/6	(68/32)
Adenocarcinoma histology	19	(100)
Stage: IIIB/IV	1/18	(5/95)
ECOG PS: 0/1/2	9/8/2	(47/42/11)
Previous chemotherapy regimens 1/2/≥3	7/4/8	(37/21/42)
RET fusion partners KIF5B/CCDC6/Unknown	10/6/3	(53/31/16)

Response to prior systemic anticancer therapy

- The response rates of the previous anticancer therapy were as follows:
  - First-line therapy (n=19): 26% (95% CI, 9 to 51)
  - Second-line therapy (n=12): 25% (95% CI, 5 to 57)
  - Third-line therapy (n=8): 0%

Primary analysis in 17 eligible patients

- The ORR was 53% (90% CI, 31 to 74) of which 9 partial responses met the primary endpoint.

Figure 3. Response to vandetanib in RET-rearranged NSCLC (n = 19: ITT population)

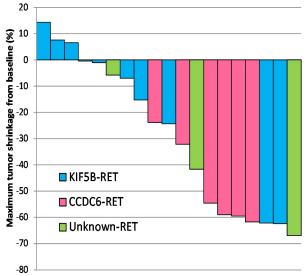
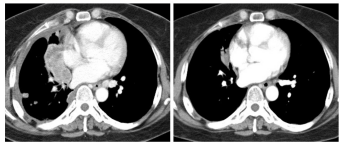


Table 2. Efficacy according to the type of RET fusion

Outcome	All (n = 19)	KIF5B-RET (n = 10)	CCDC6-RET (n = 6)	Unknown (n = 3)
ORR, % (95% CI)	47 (24, 71)	20 (3, 56)	83 (36, 99.6)	67 (9, 99)
DCR, % (95% CI)	90 (67, 99)	90 (56, 99.7)	100 (54, 100)	67 (9, 99)
Median PFS, mo (95% CI)	4.7 (2.8, 8.5)	2.9 (1.1, 15.7)	8.3 (4.7, 8.5)	4.7 (1.0, 10.9)
1-yr OS, % (95% CI)	47 (21, 69)	42 (11, 71)	67 (5, 95)	33 (1, 77)

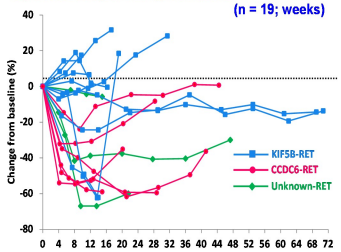
Figure 4. Effect of vandetanib treatment



Baseline After 20 Weeks

- This patient with CCDC6-RET NSCLC had a partial response with a 62% reduction in tumor burden.

Figure 5. Changes of target tumor burden over time (n = 19; weeks)



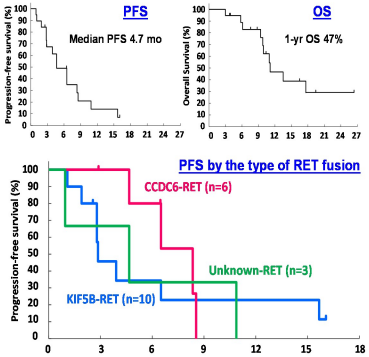
- The median DOR was 5.6 months (range, 1.5 to 9.1).
- On May 2016, 2 responders are ongoing over 1 years.

Table 3. Treatment-related adverse events

NCI-CTCAE Adverse event	Any grade n (%)	Grade 3 ≤ n (%)
Hypertension	16 (84)	11 (58)
Diarrhea	15 (79)	2 (11)
Rash acneiform	12 (63)	3 (16)
Dry skin	8 (42)	1 (5)
QTc prolongation	8 (42)	2 (11)
Anorexia	6 (32)	1 (5)
Creatinine increased	6 (32)	0
Vomiting	5 (26)	0
Paronychia	5 (26)	0
Proteinuria	5 (26)	1 (5)
Mucositis	4 (21)	0
Nausea	4 (21)	1 (5)
Liver dysfunction	4 (21)	0
Hypoalbuminemia	4 (21)	0
Photosensitivity	4 (21)	1 (5)

- Adverse events listed here occurred in at least 20% of patients. Any event of grade 3 or higher was observed in 84% of the patients. Only 1 patient had grade 4 adverse event as QTc prolongation and there was no grade 5 event.
- 4 patients (21%) had an adverse event leading to discontinuation of the study drug; 2 for rash and one each for pneumonitis and corneal opacity.
- 16 patients (84%) had a dose interruption for adverse event and dose reduction was observed in 10 patients (53%); the most common were acneiform rash and hypertension.

Figure 6. Kaplan-Meier plots (n = 19; months)



CONCLUSIONS

- Vandetanib showed marked antitumor activity in patients with advanced RET-rearranged NSCLC.
- In particular, it was indicated that CCDC6-RET showed much higher sensitivity to vandetanib than KIF5B-RET.
- The safety profile of vandetanib was similar to that reported previously.
- A nationwide screening such as LC-SCRUM-Japan is needed to make a successful of targeted therapy trials for NSCLC patients with rare driver mutations.

Acknowledgement

- This research is supported by the Practical Research for Innovation Cancer Control from Japan Agency for Medical Research and Development, AMED and by AstraZeneca.
- In 2015, Sanofi and its subsidiary Genzyme acquired the rights to Caprelsa® (Vandetanib) from AstraZeneca.
- We thank the participating patients and their families, all the site investigator and operations staff, and all hospital in LC-SCRUM-Japan.

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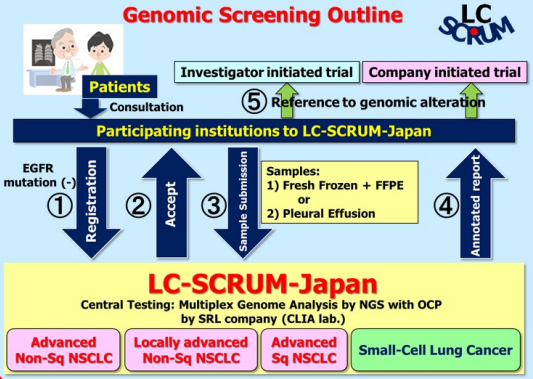

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Study objectives

- **Primary endpoint: Objective response rate (ORR) by independent radiology review committee**
- **Secondary endpoints: Progression-free survival (PFS), Disease control rate (DCR, CR+PR+SD), Duration of response (DOR), Overall survival (OS), Safety, Response of prior anticancer therapy**
- **This study required 17 patients, with ORR of 30% considered non-promising and 60% promising (one-sided alpha = 0.05; beta = 0.2).**

Table 1. Patient characteristics (n = 19)

Characteristic	n	(%)
Age: Median (range)	59 (41–80)	
Sex: Male/Female	5/14	(26/74)
Smoking status: Never/Former	13/6	(68/32)
Adenocarcinoma histology	19	(100)
Stage: IIIB/IV	1/18	(5/95)
ECOG PS: 0/1/2	9/8/2	(47/42/11)
Previous chemotherapy regimens 1/2/≥3	7/4/8	(37/21/42)
RET fusion partners KIF5B/CCDC6/Unknown	10/6/3	(53/31/16)

Primary analysis in 17 eligible patients

- The ORR was 53% (90% CI, 31 to 74) of which 9 partial responses met the primary endpoint.

Figure 3. Response to vandetanib in RET-rearranged NSCLC (n = 19: ITT population)

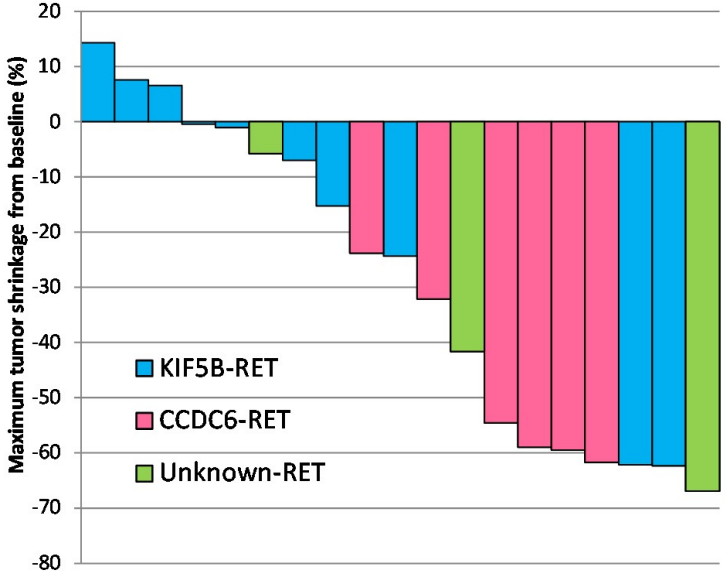
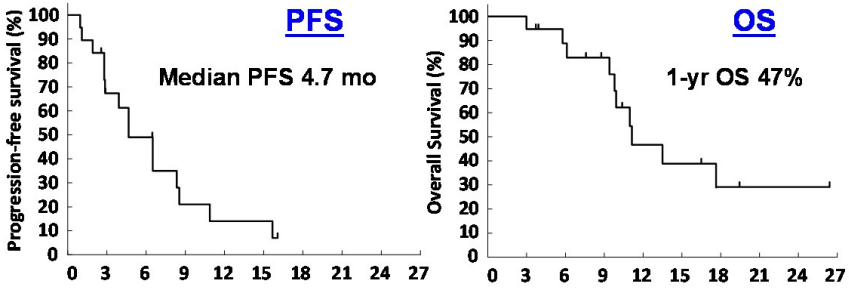


Figure 6. Kaplan-Meier plots (n = 19; months)



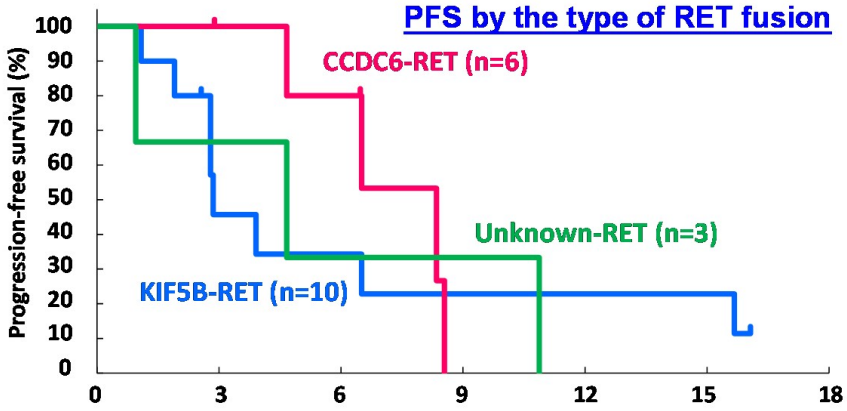


Table 2. Efficacy according to the type of RET fusion

Outcome	All (n = 19)	KIF5B-RET (n = 10)	CCDC6-RET (n = 6)	Unknown (n = 3)
ORR, % (95% CI)	47 (24, 71)	20 (3, 56)	83 (36, 99.6)	67 (9, 99)
DCR, % (95% CI)	90 (67, 99)	90 (56, 99.7)	100 (54, 100)	67 (9, 99)
Median PFS, mo (95% CI)	4.7 (2.8, 8.5)	2.9 (1.1, 15.7)	8.3 (4.7, 8.5)	4.7 (1.0, 10.9)
1-yr OS, % (95% CI)	47 (21, 69)	42 (11, 71)	67 (5, 95)	33 (1, 77)

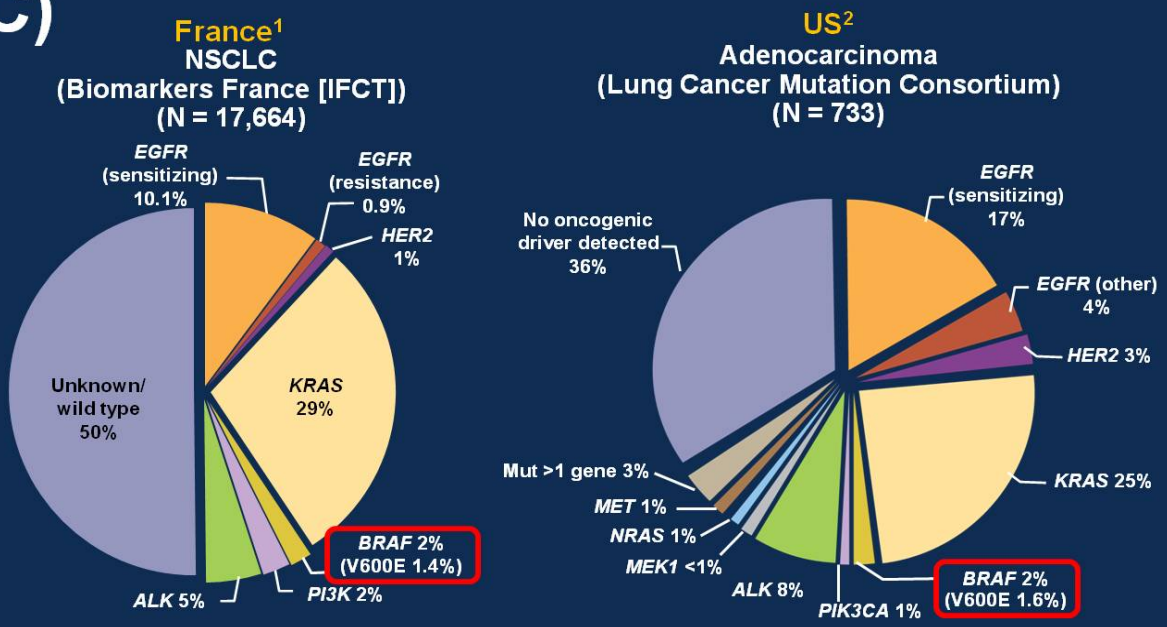
CONCLUSIONS

- Vandetanib showed marked antitumor activity in patients with advanced RET-rearranged NSCLC.
- In particular, it was indicated that CCDC6-RET showed much higher sensitivity to vandetanib than KIF5B-RET.
- The safety profile of vandetanib was similar to that reported previously.
- A nationwide screening such as LC-SCRUM-Japan is needed to make a successful of targeted therapy trials for NSCLC patients with rare driver mutations.

An Open-Label Phase 2 Trial of Dabrafenib in Combination With Trametinib in Patients With Previously Treated *BRAF* V600E–Mutant Advanced Non-Small Cell Lung Cancer (BRF113928)

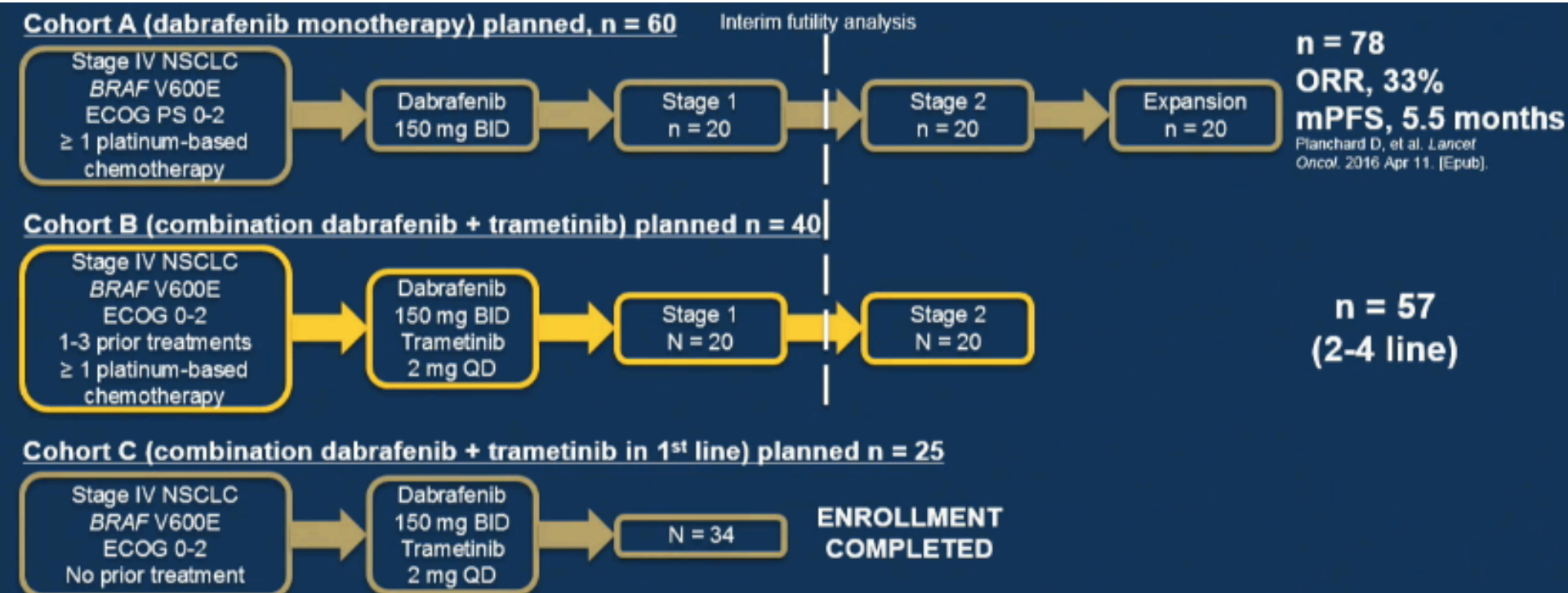
David Planchard,[1] Benjamin Besse,[1] Harry Groen,[2] Pierre-Jean Souquet,[3] Elisabeth Quoix,[4] Christina Baik,[5] Fabrice Barlesi,[6] Tae Min Kim,[7] Julien Mazieres,[8] Silvia Novello,[9] James Rigas,[10] Allison Upalawanna,[11] Anthony M. D'Amelio Jr,[12] Pingkuan Zhang,[12] Bijoyesh Mookerjee,[12] Bruce E. Johnson[13]

BRAF Mutations in Non-Small Cell Lung Cancer (NSCLC)



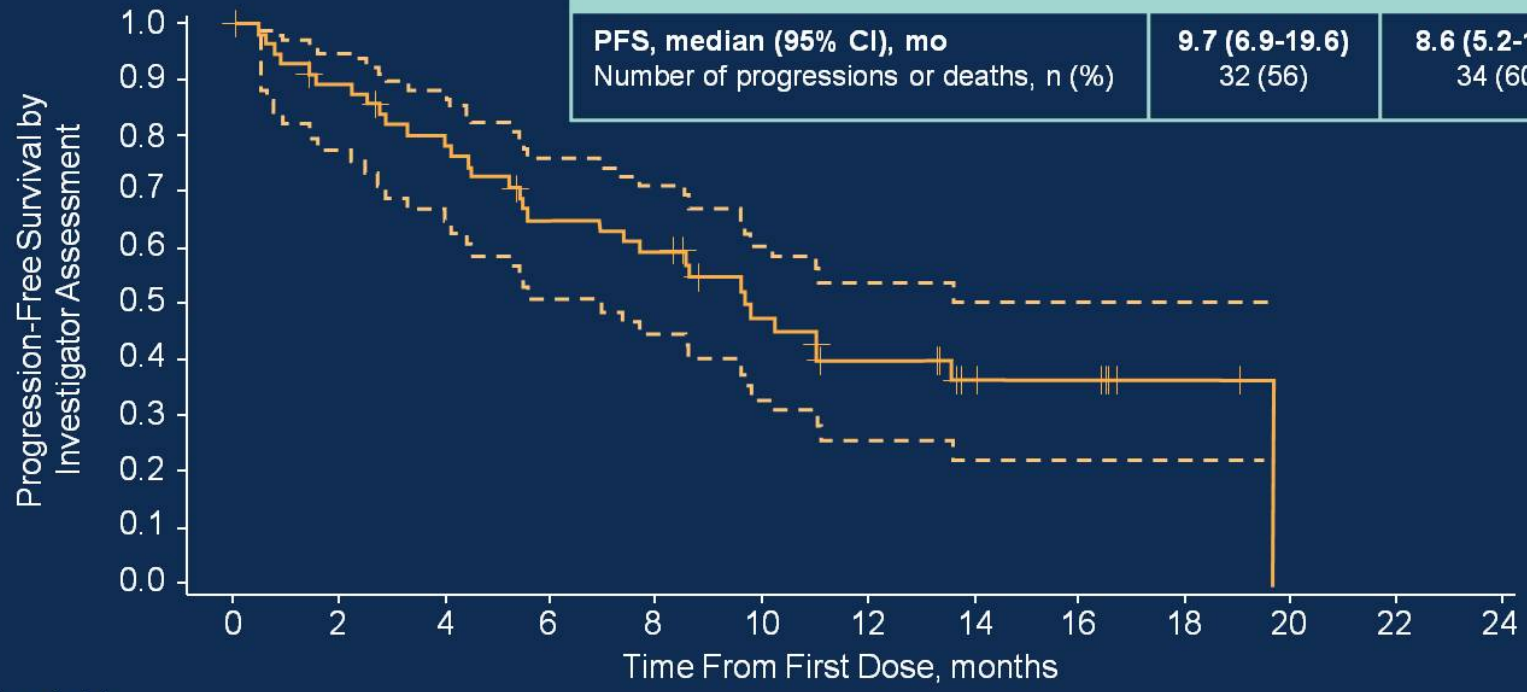
- NSCLC with *BRAF* V600E mutations has histological features suggestive of an aggressive tumor[3]
- Patients with *BRAF* V600E–mutant NSCLC demonstrated less-favorable outcomes with platinum-based chemotherapy[3,4]

- Primary objective: investigator-assessed overall response rate (ORR)
  - All responses had to be confirmed based on RECIST
  - Null hypothesis, ORR ≤ 30%; alternative hypothesis, ORR ≥ 55%
  - Independent review committee was also used
- Secondary objectives
  - Progression-free survival (PFS)
  - Duration of response (DOR)
  - Overall survival (OS)
  - Safety
  - Population pharmacokinetics



Summary

	Investigator	Independent
PFS, median (95% CI), mo	**9.7 (6.9-19.6)**	**8.6 (5.2-19.1)**
Number of progressions or deaths, n (%)	32 (56)	34 (60)



No. at risk													
	57	49	43	34	31	20	13	7	6	2	0	0	0
No. censored													
	0	2	3	4	4	10	14	19	20	24	25	25	25

Dashed lines represent 95% CIs.
Median follow-up of 11.6 months.

1. PI

Conclusiones

- Alectinib tiene el potencial para convertirse en la primera línea de tratamiento de ALK+ (resultados globales de NCT02075840).
- Brigatinib y Lorlatinib necesitan completar sus ensayos Fases III para demostrar su potencial real y encontrar el nicho de pacientes ALK+ más adecuado.
- MET es una diana prometedora en CPNM con diferentes moléculas en desarrollo (mono/politerapia).
- La vía de RET debe explorarse en más ensayos específicos pues existen fármacos con gran actividad (vandetanib).
- Los conocimientos en melanoma y otras neoplasias con biomarcadores establecidos deben servirnos para adaptar en CPNM terapias dirigidas ya conocidas.

Gracias