Brigatinib activity in alectinib-resistant ALK-positive NSCLC according to ALK plasma mutation status from the J-ALTA trial

Toyoaki Hida

Aichi Cancer Center

Japan

1. Toyoaki Hida, Department of Thoracic Oncology, Aichi Cancer Center, Aichi, Japan; **2. Ryohei Katayama**, Division of Experimental Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Tokyo, Japan; **3. Makoto Nishio**, Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; **4. Tatsuya Yoshida**, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; **5. Toru Kumagai**, Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan; **6. Ryo Toyozawa**, Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; **7. Tadasuke Shimokawaji**, Department of Thoracic Oncology, Kanagawa Cancer Center, Kanagawa, Japan; **8. Koichi Goto**, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; **9. Kazuhiko Nakagawa**, Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan; **10. Takashi Seto**, Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; **11. Nobuyuki Yamamoto**, Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan; **12. Takayuki Asato**, Oncology Clinical Research Department, Oncology Therapeutic Area Unit for Japan and Asia, Takeda Pharmaceutical Company Limited, Osaka, Japan; **13. Kei Hiraoka**, Japan Medical Affairs, Japan Oncology Business Unit, Takeda Pharmaceutical Company Limited, Tokyo, Japan; **14. Pingkuan Zhang**, Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; **15. Yuichiro Ohe**, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

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DISCLOSURES

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Objective

- **This analysis was conducted to determine the relationship of *ALK* mutation status with brigatinib treatment outcome in order to guide future treatment strategies for individual patients with different *ALK* mutation profiles**

Introduction

- Brigatinib is a next-generation ALK TKI with broad, potent activity against ALK resistance mutations[1,2]
- Multiple molecular mechanisms cause resistance to ALK TKIs, including acquisition of secondary mutations in *ALK*, amplification of the ALK fusion gene, and upregulation of secondary signaling pathways[3,4]
- This phase 2 trial (J-ALTA) includes Japanese patients with advanced ALK–positive NSCLC refractory to other ALK TKIs[5]
- As an exploratory correlative analysis, we examined the relationship of *ALK* mutation status with brigatinib treatment outcome by next-generation sequencing analysis of cell-free DNA using plasma specimens at baseline (BL) prior to brigatinib treatment in J-ALTA ALK+ NSCLC patients who progressed on alectinib or other ALK TKIs

Methods

Study design and sample collection

- J-ALTA: phase 2, single-arm, open-label, multicenter study (NCT03410108).
- Brigatinib was administered at 90 mg qd for the first 7 days then at 180 mg qd throughout
- Key eligibility criteria: Adults (aged ≥20 y) with stage IIIB/IIIC/IV ALK+ NSCLC
- Collect the plasma samples at BL and EOT for biomarker analysis

Sample analysis

- ctDNA was isolated from patient plasma samples at BL and EOT
- ctDNA was analyzed using the PGDx elioTM plasma resolve (Personal Genome Diagnostics, Baltimore, MD, USA) to determine ALK kinase domain mutations and EML4-ALK fusion status
- Brigatinib activity was defined by the confirmed objective response rate (ORR) (RECIST v1.1). Data are reported as of January 22, 2019 for the J-ALTA trial. Clinical efficacy was reported for the safety evaluation lead-in and refractory expansion groups

ctDNA: circulating tumor DNA; TKI: tyrosine kinase inhibitor; BL: baseline; EOT: end of treatment.

J-ALTA patient flow and sample collection

- Plasma samples were obtained from patients during the J-ALTA study at the points described, for the purpose of determining *ALK* mutation, ALK fusion and *TP53* mutation status.
- Of the 72 ALK+ NSCLC patients enrolled, evaluable plasma samples were obtained from 70 patients at BL

Part 1: Safety Evaluation Lead-in
n=9 DLT evaluable pts
(Any line of prior ALK inhibitor allowed, including treatment naive pts)
3 regimens of anti-cancer treatment allowed
- Evaluate DLT in cycle 1 (28days)
- Hospitalization in cycle 1
- Intensive PK

Proceed to expansion if brigatinib tolerated (IDMC review)

Part 2: Refractory Expansion

Main Cohort n=47
- post alectinib
- post crizotinib and alectinib

Exploratory-Cohort n=16
- post crizotinib
- post ceritinib
- post lorlatinib
- post crizotinib and ceritinib
- post alectinib and ceritinib
- post crizotinib and lorlatinib
- post alectinib and lorlatinib
- post ceritinib and lorlatinib

TKI naïve Expansion Cohort n=32
The first-line study in Japan is a bridging study to ALTA-first-line. The primary endpoint is PFS rate at 12 months.

Collected plasma samples at BL; n=70

Collected plasma samples at EOT; n=49

Prior treatment with alectinib with or without prior crizotinib; n=51

Detected ALK fusion in plasma; n=36

ctDNA: circulating tumor DNA; TKI: tyrosine kinase inhibitor; BL: baseline; EOT: end of treatment.

EML4-ALK fusion status at BL

- BL EML4-ALK fusion was detected in 51.4% (36/70) of the post-ALK TKI patients
- Of these, 25.0% (9/36) had secondary *ALK* mutations

Post-ALK TKI patients with BL EML4-ALK fusion (N=36)	n	%
Variant 1 (E13; A20)	11	30.6
Variant 2 (E20; A20)	1	2.8
Variant 3 (E6a/b; A20)	18	50.0
Variant 5 (E2; A20&ins117A20)	1	2.8
Variant 5’ (E18; A20)	1	2.8
Undetermined	4	11.1

BL: baseline; TKI: tyrosine kinase inhibitor.

Relationship between ALK status at BL and subsequent clinical response to brigatinib treatment

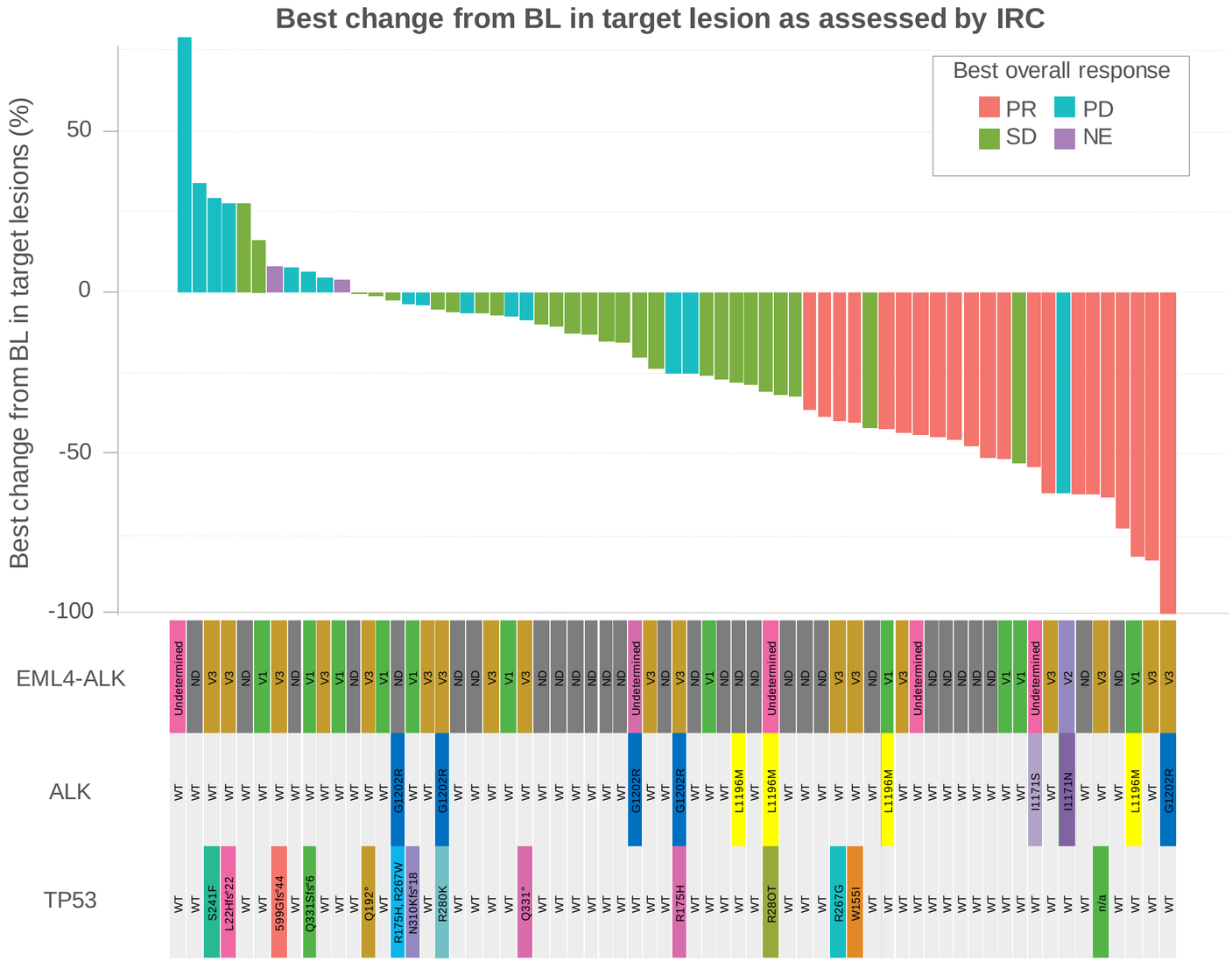
	ORR, % (95% CI)	n/N
All with evaluable BL data	30.0 (19.6–42.1)	21/70
patients treated with prior alectinib	35.3 (22.4–49.9)	18/51
without detectable ALK fusion with detectable ALK fusion	26.5 (12.9–44.4) 33.3 (18.6–51.0)	9/34 12/36
without *ALK* mutation with *ALK* mutation	27.1 (16.4–40.3) 45.5 (16.7–76.6)	16/59 5/11
with ALK fusion and WT ALK with ALK fusion and ALK mutation	25.9 (11.1–46.3) 55.6 (21.2–86.3)	7/27 5/9

- Of the 70 patients evaluated, 30.0% (21) had confirmed response to brigatinib as assessed by IRC

BL: baseline; IRC: independent research committee; ORR: objective response rate.

Best change from BL in target lesion

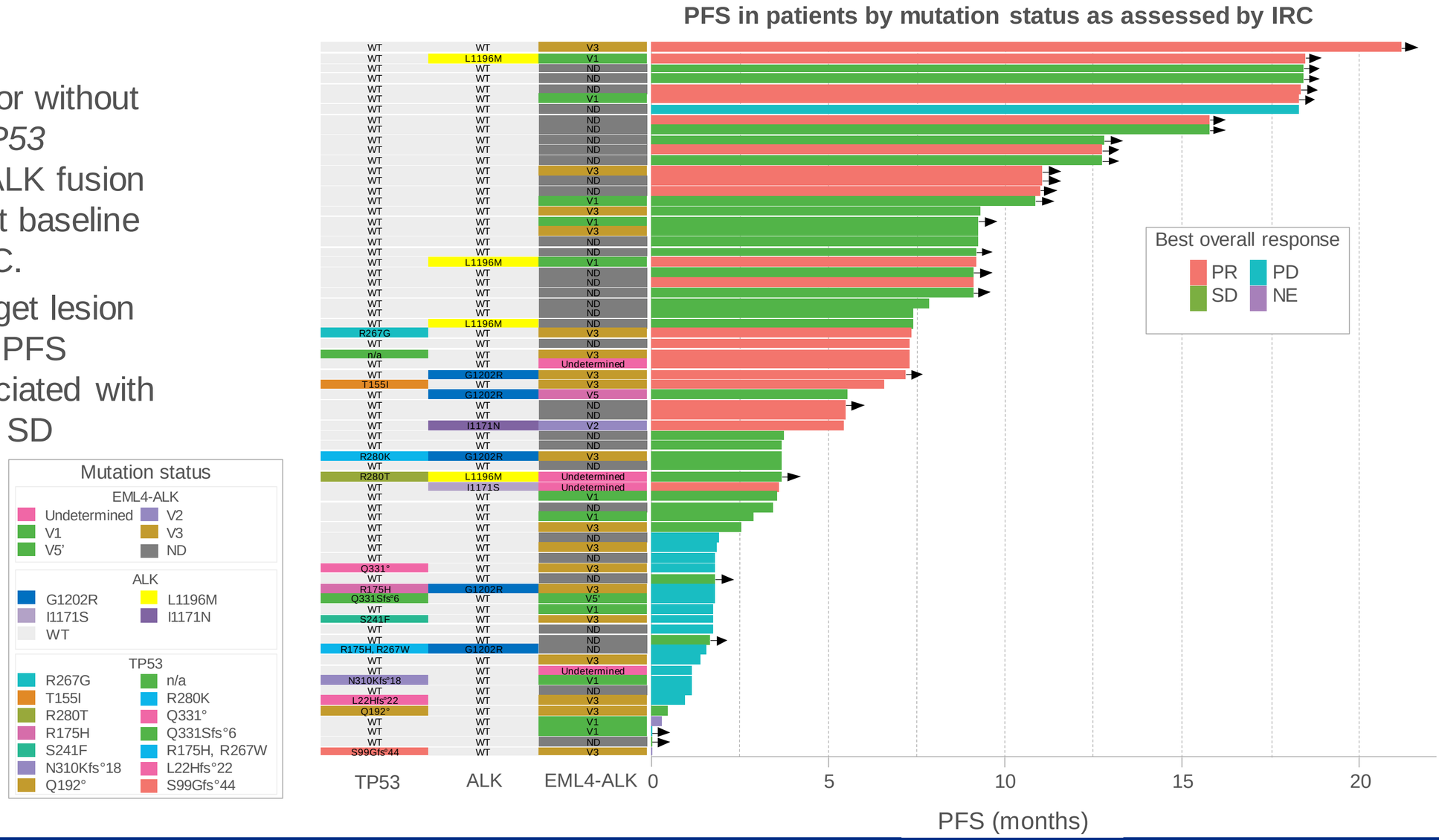
- Best percentage change from BL in target lesion size, compared with best overall response, as determined by IRC per EML4-ALK fusion, ALK mutation and TP53 mutation status
- As expected, greatest percentage reductions in target lesions from BL appeared to be associated with patients with PR and SD



BL: baseline; IRC: independent review committee; ND: not detected V1: EML4-ALK variant 1; V2: EML4-ALK variant 2; V3: EML4-ALK variant 3; WT: wild type.

PFS in patients by mutation status

- PFS in patients with or without secondary *ALK* or *TP53* mutations or EML4-ALK fusion detected in plasma at baseline as determined by IRC.
- As observed with target lesion reduction, increased PFS appeared to be associated with patients with PR and SD

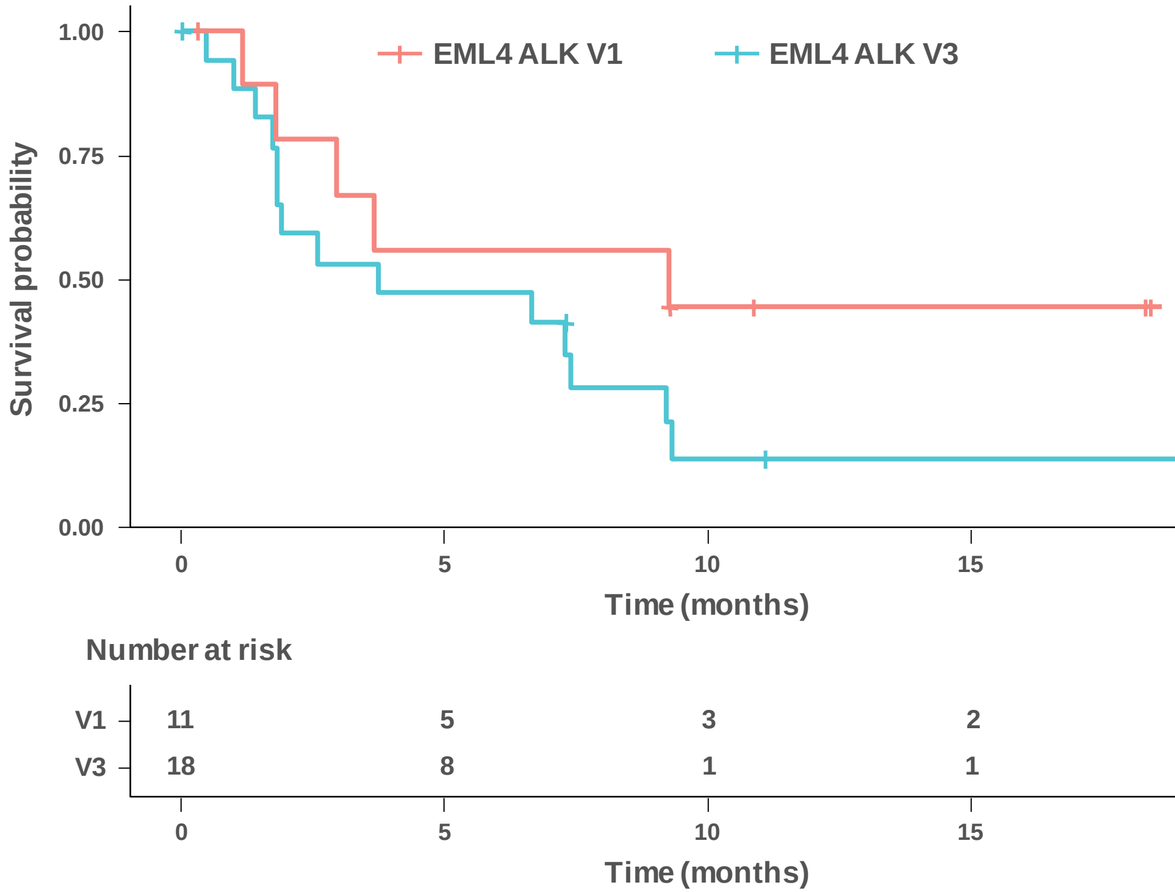


IRC: independent review committee; ND: not detected; PFS: progression-free survival; PR: partial response; SD: stable disease; WT: wild type.

Efficacy of brigatinib by EML4-ALK variant at BL

- Patients with EML4-ALK fusion V1 had longer PFS compared with those carrying EML4-ALK V3

EML4-ALK variant at BL	IRC-assessed efficacy
V1, n=11	
ORR, %	27.3 (6.0–61.0)
mPFS, months	9.2 (1.2–NR)
V3, n=18	
ORR, %	33.3 (13.3–59.0)
mPFS, months	3.7 (1.8–7.4)
Others, n=7	
ORR, %	42.9 (9.9–81.6)
mPFS, months	5.5 (1.2–7.3)

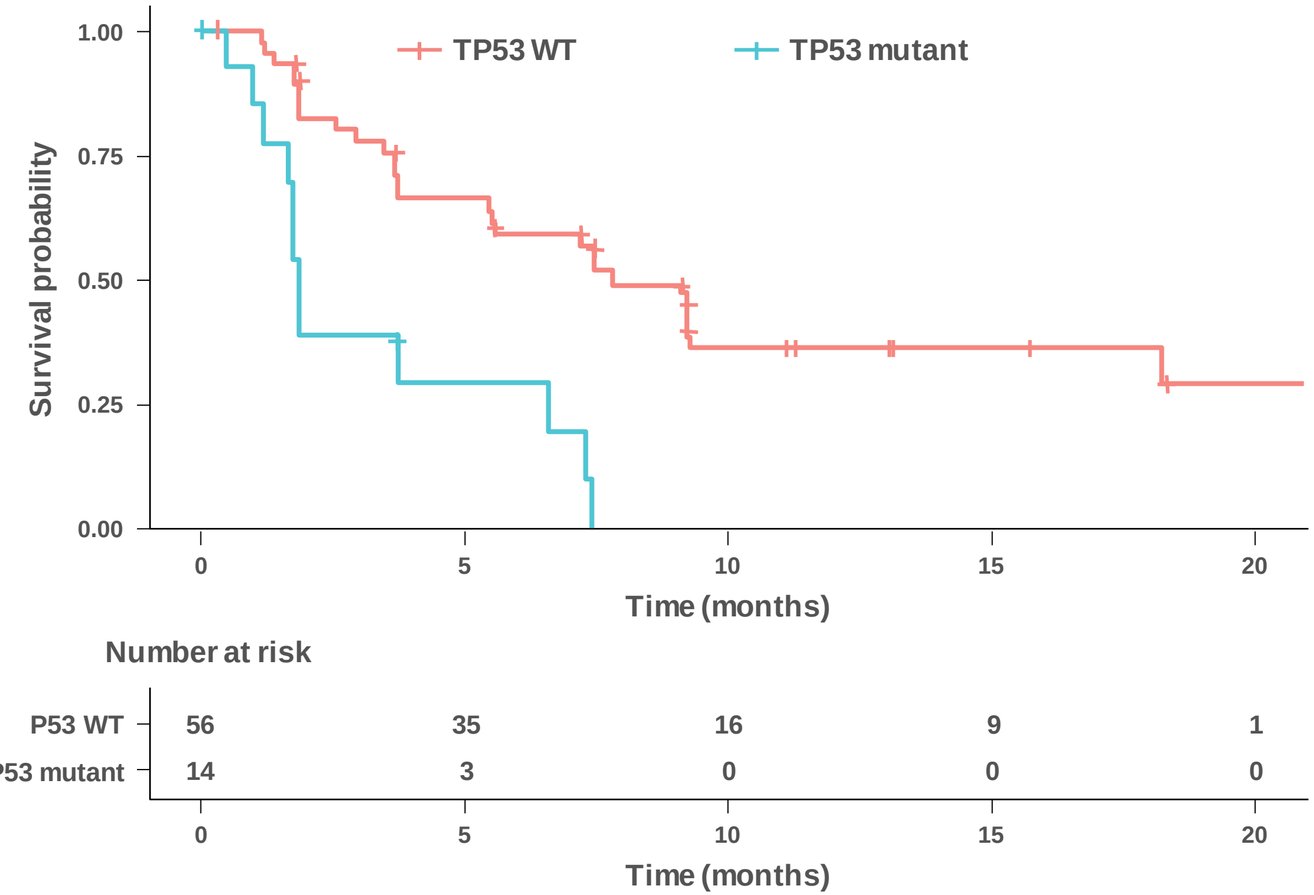


BL: baseline; IRC: independent review committee; mPFS: median progression-free survival; NR: not reached; ORR: objective response rate; V1: EML4-ALK variant 1; V3: EML4-ALK variant 3.

Efficacy by *TP53* mutation status at BL

- PFS was longer in patients with WT *TP53* at baseline compared with patients observed to have mutant *TP53*

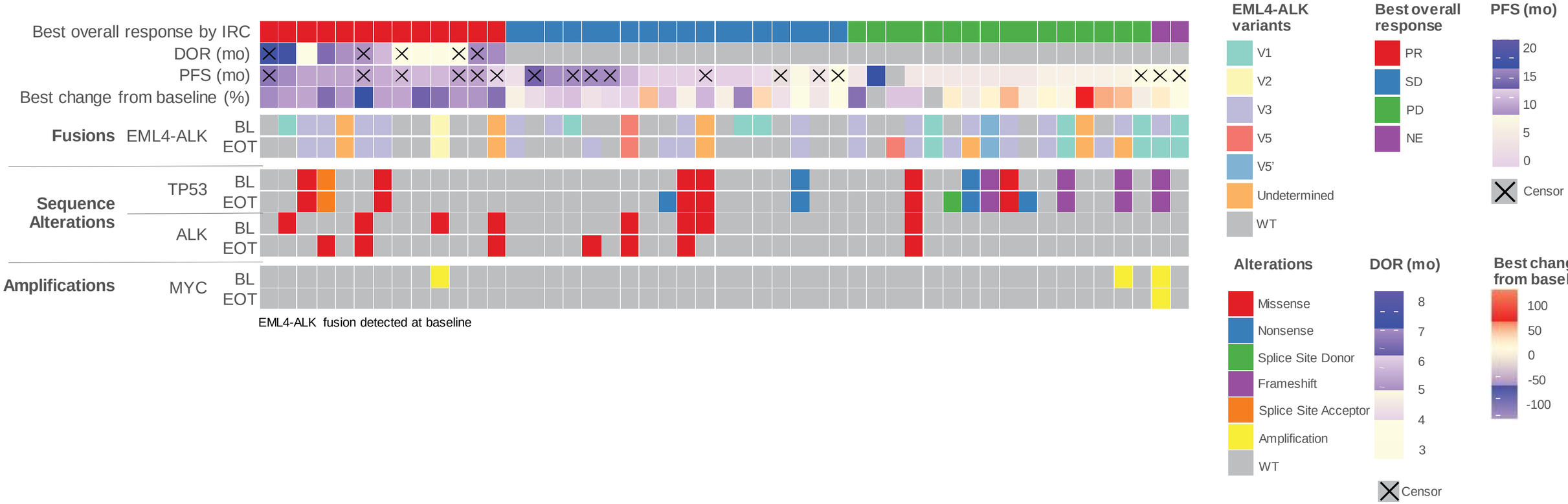
TP53 mutation status at BL	IRC-assessed efficacy
Mutant, N=14	
ORR, %	21.4 (4.7–50.8)
mPFS, months	1.8 (1.2–6.6)
WT, N=56	
ORR, %	32.1 (20.3–46.0)
mPFS, months	9.3 (5.6–NR)



BL: baseline; IRC: independent review committee; mPFS: median progression-free survival; ORR: objective response rate; WT: wild-type.

Oncomap of mutation status and response to treatment

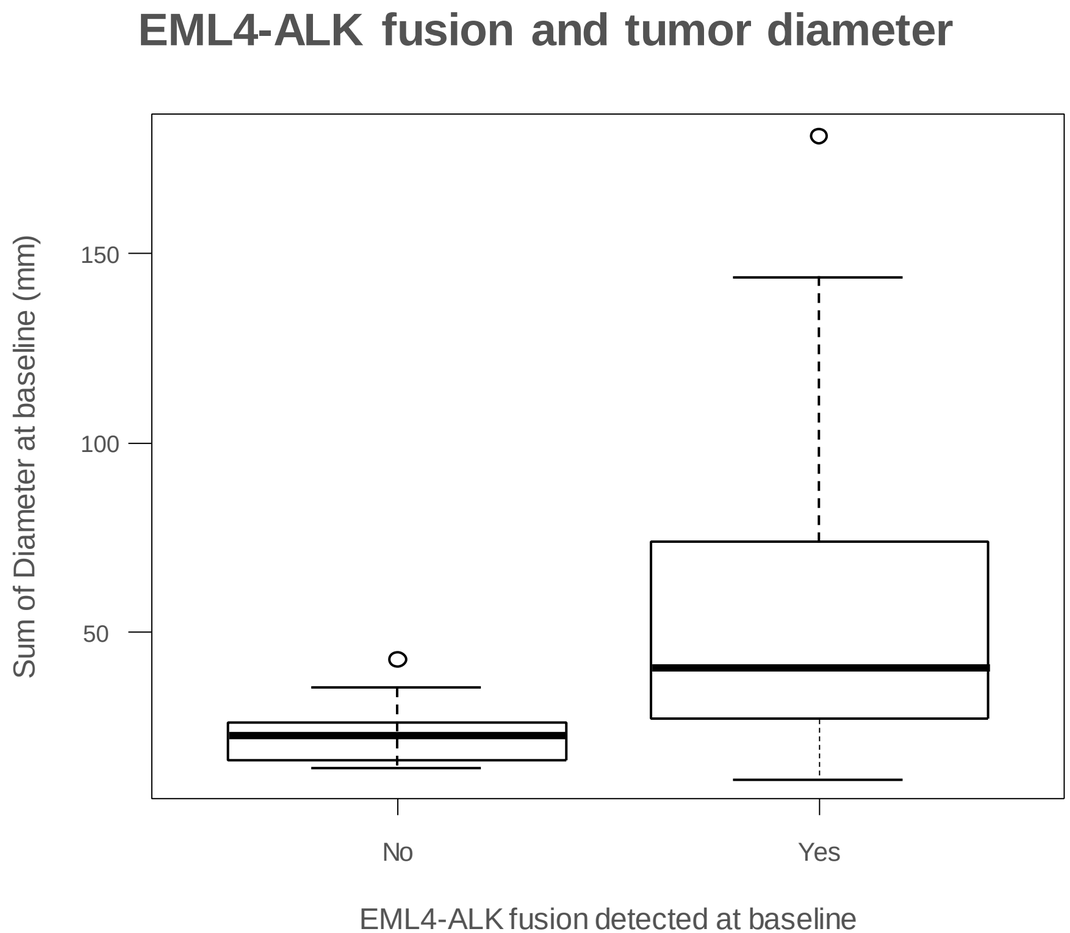
- Stratification of mutation status at BL and EOT by best overall responses to treatment by investigator and IRC, duration of response, PFS and best change from baseline in target lesions



BL: baseline; DOR: duration of response; EOT: end of treatment; IRC: independent review committee; PFS: progression-free survival.

Tumor diameter by EML4-ALK fusion status at BL

- EML4-ALK fusion tended to be detected in the plasma samples of patients with larger sum of target tumor diameters at baseline



BL: baseline.

Summary of ALK mutation status

- Detected ALK mutation patients from plasma samples at BL and/or EOT and response to protocol treatment

No	Pre-treatment regimen	Best Confirmed Response	PFS (mo)	BL			EOT*
				Secondary ALK Mutation	TP53 mutation	ALK fusion variant	Secondary ALK Mutation
1	Alectinib	SD	7.5	L1196M	WT	ND	N/A†
2	Alectinib → Ceritinib	PR	7.2	G1202R	WT	V3	G1202R + S1206F‡
3	Alectinib	PR	18.5	L1196M	WT	V1	N/A†
4	Alectinib	PR	5.5	I1171N	WT	V2	WT
5	Alectinib	PR	3.7	I1171S	WT	Undetermined	E1210K
6	Crizotinib → Alectinib	PR	9.2	L1196M	WT	V1	WT
7	Crizotinib → Ceritinib	SD	9.2	WT	WT	ND	G1202R
8	Alectinib	SD	5.6	G1202R	WT	V5	G1202R
9	Alectinib	PD	1.6	G1202R	R175H,R267W	ND	N/A†
10	Alectinib	PD	1.8	G1202R	R175H	V3	F1174L
11	Crizotinib → Alectinib	SD	3.7	G1202R	R280K	V3	G1202R
12	Alectinib	SD	3.7	L1196M	R280T	Undetermined	WT
13	Alectinib	PR	7.3	WT	TP53_n/a	V3	G1202R

* no patients discontinued due to AE; † Treatment ongoing; ‡ in the cis position.

BL: baseline; EOT: end of treatment; N/A: not applicable; ND: not detected; PD: progressive disease; PR: partial response; SD: stable disease; WT: wild type.

Results summary

Plasma ALK mutation status at BL and after progression on brigatinib therapy

- Secondary *ALK* mutations were detected in 15.7% (11/70) of patients (10 post-alectinib and 1 post-ceritinib) at baseline
  - ORR was higher (45.5% (5/11)) in patients with baseline mutation from plasma samples than those without (27.1%, 16/59) although the sample size is small. Response was observed in patients with G1202R mutation (1PR, 2SD)
  - Gene amplification was detected in only 1 patient (*MYC* gene amplification) at baseline
- The samples were also collected from 49 patients at the end of brigatinib treatment
  - Secondary *ALK* mutations were detected in 7 patients at EOT: 1 with F1174L (also had G1202R at BL); 1 with E1210K (also had I1171S at BL); 5 with G1202R (2 not present at BL; 2 present at BL; 1 present at BL (PR) and compound mutation (G1202R+S1206F) detected in the cis position
  - *MYC* gene amplification was detected in 2 patients at EOT

BL: baseline; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.

Conclusions

- **ALK fusions were detected in the plasma of over 50% of ALK+ NSCLC patients resistant to alectinib and/or other TKIs**
- **Brigatinib demonstrated meaningful activity in ALK TKI-resistant patients regardless of the presence of secondary ALK mutations and EML4-ALK fusion status in plasma**

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Clinical trial registration number NCT03410108

Abbreviations

ALK, Anaplastic lymphoma kinase; ALK+, ALK positive; BL, baseline; ct-DNA, circulating tumor DNA; DLT, dose-limiting toxicity; EOT, end of treatment; FAS, full analysis set; HR, hazard ratio; IDMC, independent data monitoring committee; IRC, independent review committee; mo, months; NE, not evaluated; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PD, progressive disease; PR, partial response; qd, once daily; SD, stable disease; TKI, tyrosine kinase inhibitor; WT, wild type.

Conflicts of interest

Professional medical writing assistance was provided by Ben Searle, PhD, of MIMS MedComms, Hong Kong, the statistics analysis assistance for biomarker analysis of J-ALTA study was provided by Dynacom Co., Ltd, Japan which were funded by Takeda Pharmaceutical Company Limited.

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Corresponding author

Yuichiro Ohe: yohe@ncc.go.jp

Abstract

Background: Brigatinib is a selective and potent ALK tyrosine kinase inhibitor (TKI) with preclinical activity against wild-type *ALK* and a broad spectrum of *ALK* secondary mutants, known to confer clinical resistance to crizotinib, ceritinib, and alectinib. Brigatinib has shown promising efficacy in Japanese patients with ALK+ NSCLC previously treated with alectinib in a phase 2 trial (J-ALTA). As an exploratory correlative analysis, we examined the relationship of *ALK* mutation status with brigatinib treatment outcome by NGS analysis of cell free DNA (cfDNA) using plasma specimens at baseline prior to brigatinib treatment (baseline [BL]) in ALK+ NSCLC patients who progressed on alectinib or other ALK TKIs and enrolled in this study.

Methods: Plasma samples were analyzed using the PGDx elio^{TM} plasma resolve (Personal Genome Diagnostics, Baltimore, MD, USA) to determine *ALK* kinase domain mutations and EML4-ALK fusion status. Brigatinib activity was defined by the confirmed objective response rate (ORR) (RECIST v1.1). Data are reported as of January 22, 2019 for J-ALTA trial.

Results: Of the 72 ALK+ NSCLC patients enrolled, evaluable plasma samples were obtained from 70 patients at BL; alectinib was the most recent ALK TKI (with or without prior crizotinib) in 51 patients. Of these, 30.0% (21/70) of patients had confirmed response to brigatinib, and 35.3% (18/51) of post-alectinib patients responded to brigatinib. Secondary *ALK* mutations were detected in plasma in 15.7% (11/70) of patients (10 post-alectinib and 1 post-ceritinib). ORR was confirmed in 45.5% (5/11) of these patients. Best responses in patients with secondary *ALK* mutations were: 5 confirmed partial responses (PRs); 4 stable disease (SD); 2 progressive disease (PD), including 1 confirmed PR and 2 SD in patients with *ALK* G1202R mutation at BL. No secondary *ALK* mutations were detected in 84.2% (59/70), ORR was confirmed in 27.1% (16/59) of these. Gene amplification was detected in only 1 patient (*MYC* gene amplification).

BL EML4-ALK fusion was detected in 51.4% (36/70) of the post-ALK TKIs patients; 25.0% (9/36) of these had secondary *ALK* mutations. Post-BL samples were also collected from 49 patients at the end of brigatinib treatment. Secondary *ALK* mutations were detected in 7 patients: 1 with F1174L (also had G1202R at BL); 1 with E1210K (also had I1171S at BL); 5 with G1202R (2 not present at BL; 2 present at BL; 1 present at BL and S1206F also detected). *MYC* gene amplification was detected in 2 patients.

Conclusions: ALK fusions were detected in the plasma of over 50% of ALK+ NSCLC patients resistant to alectinib and/or other TKIs. Brigatinib demonstrated meaningful activity in ALK TKI-resistant patients regardless of the presence of secondary *ALK* mutations and EML4-ALK fusion status in plasma. Clinical trial information: NCT03410108.