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Integrated biomarker analysis of brigatinib efficacy in anaplastic lymphoma kinase-positive non–small cell lung cancer refractory to alectinib

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Introduction

- The anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) alectinib is a standard-of-care option for *ALK* gene-rearranged (*ALK*+) non–small cell lung cancer (NSCLC); however, most patients eventually develop disease progression on alectinib, often through the development of secondary *ALK* resistance mutations such as G1202R[1]
- Emerging evidence suggests echinoderm microtubule-associated protein-like 4-*ALK* (*EML4-ALK*) fusion status and secondary *ALK* mutations may influence the efficacy of ALK inhibitors[2]
- Brigatinib is a next-generation ALK TKI with potent activity against *ALK* fusions and broad coverage of *ALK*-acquired resistance mutations[3,4]

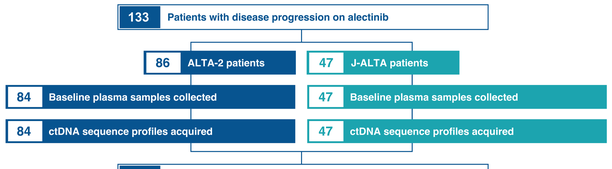
Objective

- To examine the impact of *ALK* fusion variants and secondary *ALK* mutations on clinical efficacy with brigatinib from two phase 2 studies in patients with *ALK*+ NSCLC with disease progression on alectinib
  - ALTA-2 (NCT03535740): Patients with locally advanced or metastatic *ALK*+ NSCLC with disease progression on alectinib or ceritinib[5]
  - J-ALTA (NCT03410108): Japanese patients with locally advanced or metastatic *ALK*+ NSCLC; the main cohort enrolled patients with disease progression on alectinib (± crizotinib)[6]

Methods

- ALTA-2 and J-ALTA enrolled 133 patients (ALTA-2, n=86; J-ALTA, n=47) with advanced *ALK*+ NSCLC that progressed on alectinib; **Figure 1** describes plasma circulating tumor DNA (ctDNA) collected at screening
- ctDNA molecular profiling was determined by next-generation sequencing of actionable genes from the Resolution ctDX Lung™ panel (Agilent, formerly Resolution Biosciences)
- Blinded independent review committee (BIRC)-assessed clinical efficacy (confirmed ORR, DoR, PFS, and OS) was assessed according to molecularly defined populations, including *ALK* fusion and mutation status

Figure 1. Summary of plasma specimens analyzed



Results

- Baseline characteristics for all patients in the integrated population are shown in **Table 1**

Table 1. Baseline patient characteristics

Characteristic, n (%)	Integrated population N=133
Age, median (range), y	54 (22–82)
Female, n (%)	68 (51)
Brain metastases at baseline by BIRC	66 (50)
Stage IV disease at study entry	131 (98)
Prior anticancer therapies	
Alectinib only	77 (58)
Crizotinib and alectinib	56 (42)
Chemotherapy for metastatic disease	41 (31)
2 prior therapies	53 (40)
3 prior therapies	24 (18)
Duration of prior alectinib, median (range), months	15 (1–65)
Best response to prior alectinib as CR/PR	96 (72)

CR, complete response; PR, partial response

ALK fusions

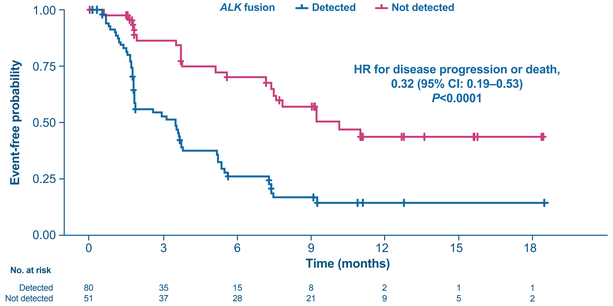
- An *ALK* fusion was detected in 80/131 patients (61%) in plasma ctDNA at screening **(Table 2)**
- *EML4-ALK* fusion represents the majority of detected *ALK* fusions (90%; 72/80), with variant 1 (V1) and variant 3 (V3) comprising 32% (23/72) and 54% (39/72)
- Patients without a detectable *ALK* fusion at screening had better clinical outcomes compared with patients with a detectable *ALK* fusion
  - ORR: 39% vs 25%
  - Median PFS: 10.2 months vs 3.5 months **(Figure 2)**
  - Median OS: Not reached vs 16.2 months

Table 2. *ALK* fusion status at screening and brigatinib clinical efficacy[a]

ALK fusion at screening	Patients, n (%) (n=131)	Confirmed ORR, % (95% CI)	Median PFS, months (95% CI)	Median DoR, months (95% CI)	Median OS, months (95% CI)
Plasma samples without a detectable *ALK* fusion	51 (39)	39 (26–54)	10.2 (7.5–NR)	NR (9.2–NR)	NR (NR–NR)
Plasma samples with a detectable *ALK* fusion	80 (61)	25 (16–36)	3.5 (1.8–5.2)	5.3 (3.7–NR)	16 (11–NR)
EML4-ALK V1	23 (29)[b]	13 (2.8–34)	3.7 (1.9–NR)	7.3 (1.9–NR)	12 (11–NR)
EML4-ALK V2	4 (1)[b]	75 (19–99)	5.4 (0.7–NR)	3.7 (3.7–NR)	NR (NR–NR)
EML4-ALK V3	39 (49)[b]	26 (13–42)	2.6 (1.8–5.2)	5.6 (3.8–NR)	NR (10–NR)
Other *EML4-ALK* variants (eg, V5)	6 (1)[b]	17 (0.42–64)	1.8 (1.1–NR)	3.8 (NR–NR)	6.2 (2.5–NR)

[a] Assessed by BIRC
[b] Denominator is the number of patients with a detectable *ALK* mutation (n=80)
NR, not reached; V, variant

Figure 2. Kaplan-Meier–estimated median PFS by *ALK* fusion detected versus not detected in ctDNA at screening



ALK mutations

- Baseline CNS disease and prior therapy in patients with *ALK* mutations are shown in **Table 3**
- *ALK* mutations were detected in 34/131 patients (26%) in ctDNA at screening **(Table 4)**
- G1202 mutations were the most frequent *ALK* mutation detected (47%; 16/34 patients)
- Patients with or without a detected *ALK* mutation benefited similarly from brigatinib treatment
  - ORR: 32% vs 30%
  - Median PFS: 3.7 months vs 5.6 months **(Figure 3)**
  - Median OS was not reached in either subgroup

Table 3. CNS disease and prior treatment in patients with *ALK* secondary mutations at screening[a]

ALK mutation at screening	Patients, n (%) (n=34)	Patients with multiple *ALK* mutations, n (%) (n=34)	CNS disease,[a] n (%)	Prior chemotherapy, n (%)	Prior crizotinib, n (%)
G1202 mutations	16 (47)	6 (18)	8 (50)	4 (25)	7 (44)
L1196(M/Q) mutations	8 (24)	3 (1)	7 (88)	4 (50)	4 (50)
I1171(N/T/S) mutations	9 (26)	5 (15)	6 (67)	3 (33)	4 (44)

[a] Assessed by BIRC

Table 4. *ALK* secondary mutations at screening and brigatinib clinical efficacy[a]

ALK mutation at screening	Patients, n (%) (n=131)	Confirmed ORR, % (95% CI)	Median PFS, months (95% CI)	Median DoR, months (95% CI)	Median OS, months (95% CI)
Patients without a detectable *ALK* mutation	97 (74)	30 (21–40)	5.6 (3.8–9.2)	NR (5.7–NR)	NR (16–NR)
Patients with a detectable *ALK* mutation	34 (26)	32 (17–51)	3.7 (1.8–7.4)	5.6 (3.5–NR)	NR (10–NR)
G1202 mutations	16 (47)[b]	13 (1.6–38)	1.8 (1.7–5.6)	4.6 (3.5–NR)	NR (7.2–NR)
L1196(M/Q) mutations	8 (24)[b]	25 (3.2–65)	9.2 (1.7–NR)	7.3 (7.3–NR)	NR (2.3–NR)
I1171 mutations	9 (26)[b]	67 (30–93)	5.2 (3.5–NR)	3.5 (3.4–NR)	NR (12–NR)

[a] Assessed by BIRC
[b] Denominator is the number of patients with a detectable *ALK* mutation (n=34)

Figure 3. Kaplan-Meier–estimated median PFS by *ALK* mutation detected versus not detected in ctDNA at screening

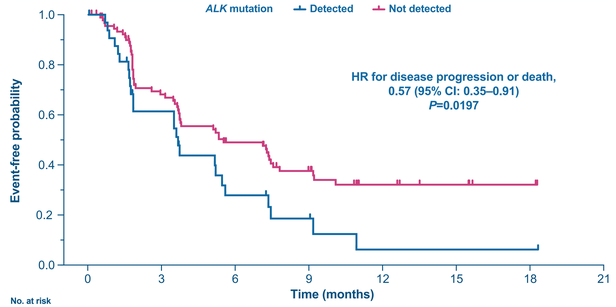
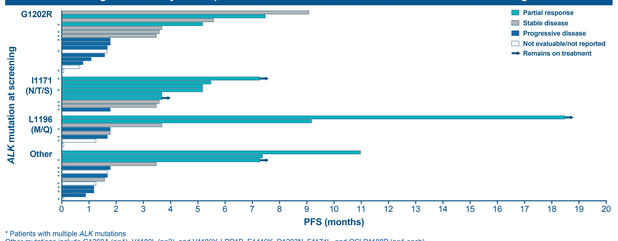
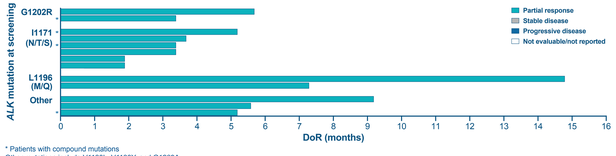


Figure 4. PFS by IRC in patients with detected *ALK* mutations in ctDNA at screening



* Patients with multiple *ALK* mutations
Other mutations include G1269A (n=4), V1180L (n=3), and V1180Y, LRP1B, E1419K, D1203N, F1174L, and QSLP1188P (n=1 each).
IRC, independent review committee

Figure 5. DoR by IRC in patients with detected *ALK* mutations in ctDNA at screening

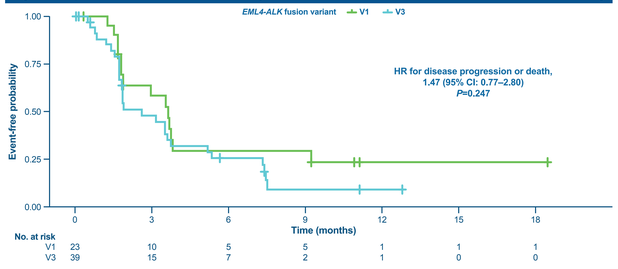


* Patients with compound mutations
Other mutations include V1180L, V1180Y, and G1269A.

EML4-ALK fusion variants

- *EML4-ALK* fusion variant status (V1 vs V3) did not impact PFS in patients treated with brigatinib **(Figure 6)**

Figure 6. Kaplan-Meier–estimated median PFS by *EML4-ALK* fusion variant 1 versus variant 3 in ctDNA at screening



Conclusions

- Brigatinib showed clinical activity in a pooled population of patients with disease progression on alectinib treatment
- The presence of a detectable *ALK* fusion in ctDNA at screening was associated with reduced clinical activity compared with the absence of a detectable *ALK* fusion
- The presence of secondary *ALK* mutations at screening did not impact response
  - Limited clinical activity was observed in patients with G1202R mutations
  - Improved ORR, DoR, PFS, and OS were observed in patients with the alectinib resistance mutation I1171N
  - Clinical activity was similar in patients with the dominant *EML4* variants 1 and 3

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Abbreviations

ALK, anaplastic lymphoma kinase; *ALK*+, anaplastic lymphoma kinase gene–rearranged; BIRC, blinded independent review committee; CI, confidence interval; CNS, central nervous system; CR, complete response; ctDNA, circulating tumor DNA; DoR, duration of response; *EML4-ALK*, echinoderm microtubule-associated protein-like 4-*ALK*; HR, hazard ratio; IRC, independent review committee; NR, not reached; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TKI, tyrosine kinase inhibitor; V, variant

Disclosures

S-HIO: Stock and other ownership interests (Turning Point Therapeutics, Elevation Oncology); honoraria (Pfizer, Roche Pharma AG, Genentech/Roche, ARIAD/Takeda, AstraZeneca, Janssen/JNJ); speakers' bureau (AstraZeneca, Genentech/Roche); research funding (all to institution: Pfizer, Roche Pharma AG, AstraZeneca/MedImmune, ARIAD, Revolution Medicines, Mirati Therapeutics, Janssen/JNJ); **MN:** Grant funding and personal fees (Ono Pharmaceutical, Bristol Myers Squibb, Pfizer, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, MSD, Novartis, Daiichi Sankyo, Takeda Pharmaceutical Company Limited); personal fees (Boehringer-Ingelheim, Merck Biopharma, Teijin Pharma Limited, AbbVie); **TY:** Honoraria (AstraZeneca, MSD Oncology, Ono Pharmaceutical, Chugai/Roche, Lilly Japan, Nippon Boehringer Ingelheim, Bristol Myers Squibb Japan, Novartis, Archer DX, Takeda, Pfizer); consulting or advisory role (Lilly Japan, Chugai/Roche, Novartis, Boehringer Ingelheim, AstraZeneca); research funding (all to institution: Chugai/Roche, AstraZeneca, AbbVie, Amgen, MSD, Bristol Myers Squibb, Ono Pharmaceutical, Takeda, Daiichi Sankyo, Novartis); **M-JA:** Honoraria (AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, MSD, Novartis); consulting or advisory role (AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, MSD, Novartis); **TM:** Consulting or advisory role (AbbVie, ACEA Pharma, Alpha Biopharma, Amgen, Amoy Diagnostics Co., AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Blueprint Medicines, CStone Pharmaceuticals, Daiichi Sankyo, Eisai, Fishawack Facilitate, GeneDecode, Gritstone Oncology Inc., Guardant Health, Hengrui Therapeutics, Ignyta Inc., IQVIA, Incyte, Janssen, Lilly, Loxo Oncology, Lunit USA, Merck Serono, Merck Sharp & Dohme, Mirati Therapeutics, MORE Health, Novartis, OrigiMed, Pfizer, Puma Biotechnology, Roche, Sanofi-Aventis R&D, Takeda, Virtus Medical Group, Yuhan Corp., SFJ Pharmaceuticals, Curio Science, Inivata, Berry Oncology, G1 Therapeutics Inc., Qiming Development (HK) Ltd., Gilead Sciences, Vertex Pharmaceuticals, Covidien LP, Elevation Oncology, C4 Therapeutics); lectures (ACEA Pharma, Alpha Biopharma Co, Amgen, Amoy Diagnostics, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Fishawack Facilitate, GeneDecode, InMed Medical Communication, Janssen, Lilly, Lunit USA, MD Health, Medscape/WebMD, Merck Serono, MSD, Novartis, OrigiMed, PeerVoice, Physicians' Educational Resource, P Permanyer SL, Pfizer, PriME Oncology, Research to Practice, Roche, Sanofi-Aventis R&D, Takeda, Touch Medical Media, Daz Group, Lucence Health, Merck Pharmaceuticals HK Ltd., Shanghai BeBirds Translation & Consulting Co, Lianyihui Network Technology Co., Taiho); board of directors (Lunit USA, AstraZeneca PLC, Hutchison Chi-Med; Act Genomics-Sanomics Group, Aurora); grant funding (Clovis Oncology, Xcovery); **KK:** Employment (Takeda); **TA:** Employment (Takeda); **HY:** Employment (Takeda); **XT:** Employment (Takeda); **SV:** Employment (Takeda); **PZ:** Employment (Takeda); **NY:** Honoraria (AstraZeneca, Ono Pharmaceutical, Chugai Pharma, Pfizer, Boehringer Ingelheim, Lilly Japan, MSD, Novartis, Takeda, Nippon Kayaku, Merck Biopharma, JASMIN, Amgen, GSK, Sanofi, Hisamitsu Pharmaceutical, Bristol Myers Squibb Japan, Janssen, Tsumura & Co., Taiho Pharmaceutical, Kyowa Kirin International); consulting or advisory role (AstraZeneca, Chugai Pharma, Ono Pharmaceutical, MSD, Boehringer Ingelheim, Takeda, Thermo Fisher Scientific, Lilly Japan, Amgen, Novartis); research funding (all to institution: Lilly, AstraZeneca, Chugai Pharma, Toxin Corporation, MSD, Shionogi, Taiho Pharmaceutical, Astellas Pharma, Tsumura & Co., Daiichi Sankyo, Boehringer Ingelheim, Novartis, AbbVie, Amgen, Eisai, Asahi Kasei, Nippon Kayaku, Sanofi, Janssen, Bristol Myers Squibb Japan); **ESK:** Consulting and research (AstraZeneca, Roche/Genentech, Mirati)

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