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Brigatinib in Japanese patients with anaplastic lymphoma kinase–positive non–small cell lung cancer: First results from the J-ALTA tyrosine kinase inhibitor-naive expansion cohort

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Introduction

- Alectinib is the preferred first-line anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) therapy for ALK-positive (ALK+) non–small cell lung cancer (NSCLC) in Japan
- In the phase 3 J-ALEX trial in Japanese patients with ALK TKI-naive ALK+ NSCLC, alectinib demonstrated improved progression-free survival (PFS) vs crizotinib (median 34.1 vs 10.2 months; hazard ratio [HR], 0.37)[1,2]
- Brigatinib is a next-generation ALK TKI that has broad, potent activity against ALK resistance mutations[3,4]
  - Brigatinib has shown robust responses and long median PFS (16.7 months) in the post-crizotinib setting[5-7]
  - In patients with ALK TKI-naive ALK+ NSCLC (ALTA-1L; NCT02737501), brigatinib demonstrated superior PFS vs crizotinib as assessed by a blinded independent review committee (BIRC) (HR, 0.49; 2-year PFS rate: 48% brigatinib; 26% crizotinib)[8,9]

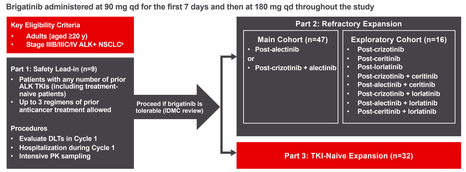
Objective

- This primary analysis from the phase 2 J-ALTA study was conducted to evaluate the efficacy and safety of brigatinib in Japanese patients with advanced ALK+ NSCLC who had not previously been treated with an ALK TKI

Methods

Study Design

Figure 1. J-ALTA: Phase 2, Single-arm, Open-label, Multicenter Study (NCT03410108)



[a] Patients must have had documentation of ALK+ by Vysis ALK Break Apart FISH Probe Kit, Nichirei Histofine ALK iAEP Kit, or Ventana ALK (D5F3) CDx Assay, or have adequate tissue available for confirmation by Vysis ALK Break Apart FISH. Central confirmation of ALK rearrangement was not required before enrollment

Endpoints

- Primary endpoint for TKI-naive expansion cohort: 12-month PFS rate as assessed by IRC per RECIST v1.1[10]
- Key secondary efficacy endpoints in TKI-naive expansion cohort:
  - IRC-assessed confirmed ORR
  - Investigator-assessed confirmed ORR
  - IRC-assessed DoR, PFS, DCR, and time to response
  - OS
  - IRC-assessed intracranial PFS in all patients (regardless of the presence of CNS metastases)
- Demographics, baseline characteristics, and TEAEs for the brigatinib arm from the second interim analysis of the ALTA-1L study are included as a benchmark for the J-ALTA TKI-naive cohort
  - The global phase 3 ALTA-1L study evaluated efficacy and safety with brigatinib vs crizotinib in patients with ALK TKI-naive advanced ALK+ NSCLC

Statistical Considerations

- For the primary endpoint, 12-month PFS rate assessed by an IRC and its 2-sided 90% CI were calculated based on complementary log-log transformation
  - The primary analysis was planned to be performed at approximately 10 months after the enrollment of the last subject in the TKI-naive expansion cohort to provide maturity to report the primary endpoint of 12-month PFS rate
- For all secondary endpoints, variables were summarized descriptively; time-to-event variables were summarized using KM methodology, with KM estimates and 95% CIs calculated for quantiles and some specified time points
- A sample size of 32 patients in the TKI-naive expansion cohort provided approximately 80% power to rule out the threshold PFS rate (42.6%), referred from the crizotinib arm in the ALTA-1L study, when the true 12-month PFS rate was 66.5% or higher, at a 1-sided alpha level of 0.05

Results

Table 1. Demographics and Baseline Characteristics in the J-ALTA TKI-Naive Cohort and the ALTA-1L Study

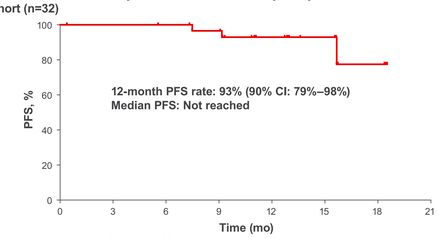
		J-ALTA TKI-Naive Expansion Cohort n=32	ALTA-1L Brigatinib Arm n=137
Median age (range), y		61 (29–85)	58 (27–86)
Sex, %	Female	53	50
ECOG performance status, %	0, 1, 2	50, 47, 3	39, 55, 5
Smoking history, %	Never, Former, Current	63, 38, 0	61, 37, 2
Stage of disease at study entry, %	IIIB, IV	0, 100	6, 94
Histologic type of NSCLC, %	Adenocarcinoma, Adenosquamous carcinoma, Other	94, 3, 3	92, 2, 6
Brain metastases at baseline, %		22	29
Time from initial diagnosis to brigatinib treatment, median (range), mo		1 (0.3–232)	2 (0.1–145)
Prior radiotherapy to the brain, %		9	13
Prior chemotherapy, %[a]		25	26[b]
Detected fusion partner on ALK, %	EML4, Unknown	9, 91	46, 54[c]

Note: Percentages may not sum to 100% due to rounding. [a] Chemotherapy includes immune checkpoint inhibitor monotherapy; [b] Chemotherapy for locally advanced or metastatic disease only; [c] n=124 of 137 patients had samples available for ALK fusion detection

- As of September 29, 2020 (primary analysis), 27 of the 32 patients with TKI-naive ALK+ NSCLC continued to receive brigatinib
- Among all 32 patients in this expansion cohort, median follow-up was 14.2 (range, 3–19) months at primary analysis
- Patients were treated for a median of 15 treatment cycles (range, 1–22), with all but 1 patient (97%) treated for ≥6 cycles (1 cycle=1 month)

Efficacy

Figure 2. IRC-Assessed Systemic PFS in the Primary Analysis of the TKI-Naive Cohort (n=32)



- At primary analysis, 1-year OS probability was 97% (95% CI, 79.8%–99.6%)

Table 2. IRC-Assessed Systemic Objective Response

	TKI-Naive Expansion Cohort n=32
Confirmed ORR, % (95% CI)	97 (84–100)
Confirmed CR, %	6
Confirmed PR, %	91
DCR, % (95% CI)	97 (84–100)
Median time to response in confirmed responders, mo (range)	1.8 (0.95–12.9)

- Median DoR as assessed by IRC was not mature

Figure 3. Overall Response in the Primary Analysis of the TKI-Naive Cohort and Time on Treatment, by Patient

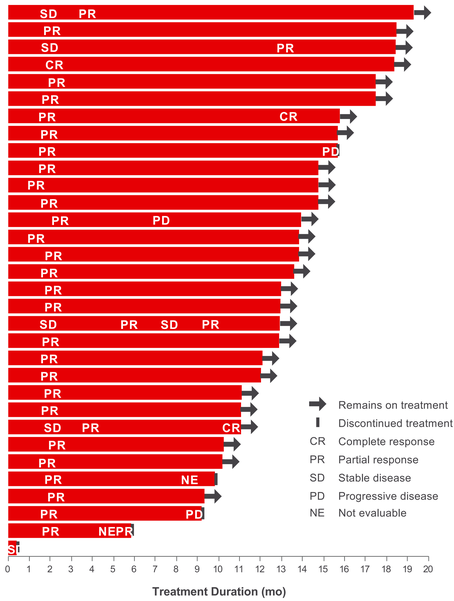
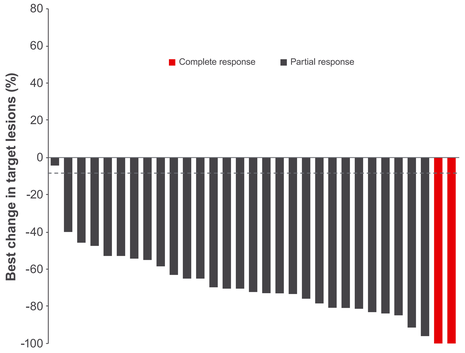


Figure 4. Best Percent Change From Baseline in Sum of Target Lesions in the Primary Analysis of the TKI-Naive Cohort[a]



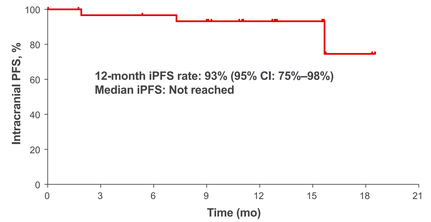
Dotted line at -30% indicates threshold for partial response per RECIST v1.1
[a] 31 of the 32 patients in the TKI-naive cohort had a measurable lesion at baseline and at least 1 post-baseline assessment result

- Median best response in target lesions was −72% as assessed by IRC

Table 3. IRC-Assessed Intracranial Responses in Patients With Measurable CNS Metastases at Baseline: TKI-Naive Expansion Cohort

	TKI-Naive Expansion Cohort n=5
Confirmed intracranial ORR (95% CI), %	40 (5–85)
Confirmed intracranial CR, %	0
Confirmed intracranial PR, %	40
Intracranial SD, %	60

Figure 5. IRC-Assessed Intracranial PFS in the Primary Analysis of the TKI-Naive Expansion Cohort (Regardless of CNS Metastases at Baseline)



Safety

Table 4. Most Common TEAEs at Primary Analysis in the J-ALTA TKI-Naive Cohort and the ALTA-1L Study

TEAEs (Any Grade) in >15% of All Patients or Grade ≥3 Reported in >2 Patients in J-ALTA	J-ALTA TKI-Naive Expansion Cohort (n=32)		ALTA-1L Brigatinib Arm n=136	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Increased blood CPK	81	44	46	24
Hypertension	59	34	32	12
Diarrhea	47	0	52	2
Increased AST	44	6	26	4
Increased lipase[a]	34	19	23	14
Stomatitis	44	0	8	1
Increased amylase[a]	34	9	18	6
Nausea	16	0	30	2
Increased ALT	34	13	21	4
Rash	22	3	15	0
Pyrexia	25	0	15	1
Constipation	25	0	18	0
Headache	9	0	21	2
Vomiting	13	0	21	1
Pneumonia	13	3	7	4
Increased GGT	9	9	2	1
Hypophosphatemia	9	6	5	1
Dyspnea	0	0	21	2

[a] No clinical cases of pancreatitis were reported

- All 32 patients in the TKI-naive expansion cohort experienced ≥1 TEAE; grade ≥3 TEAEs were reported in 91% of patients in this cohort
- As of the primary analysis, no deaths due to TEAEs had been reported in the TKI-naive cohort
- No patients in the TKI-naive cohort discontinued brigatinib due to TEAEs; 94% of patients in this cohort experienced dose interruptions, and 66% had dose reductions due to TEAEs

ILD/Pneumonitis

- Three cases (9.4%) of ILD/pneumonitis were reported in the TKI-naive expansion cohort
  - All cases were grade 1 and occurred after day 15 of brigatinib treatment
  - All patients resumed brigatinib without dose reduction after resolution of pneumonitis/ILD, and all have had no recurrence

Summary

- This study of the expansion cohort of the phase 2 J-ALTA study is the first to evaluate the efficacy of brigatinib in Japanese patients with TKI-naive ALK+ NSCLC
- In this analysis, brigatinib demonstrated substantial efficacy, with IRC-assessed 12-month PFS rate of 93%
  - IRC-assessed confirmed ORR: 97%; 2 complete and 29 partial responses
- The safety profile of brigatinib in this population was consistent with the global ALTA-1L study[8,9] and manageable
  - Treatment duration in the TKI-naive cohort is much longer than in the treatment-refractory cohort[11]
  - There were no treatment discontinuations due to TEAEs in the TKI-naive expansion cohort at this data cut
- These results support the use of brigatinib as a first-line treatment option for Japanese patients with TKI-naive ALK+ NSCLC

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Abbreviations

ALK, anaplastic lymphoma kinase; ALK+, ALK positive; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIRC, blinded independent review committee; CI, confidence interval; CNS, central nervous system; CPK, creatine phosphokinase; CR, complete response; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EML4, echinoderm microtubule-associated protein-like 4; FISH, fluorescence in situ hybridization; GGT, gamma-glutamyltransferase; HR, hazard ratio; IAEP, intercalated antibody-enhanced polymer; IDMC, independent data monitoring committee; ILD, interstitial lung disease; IPFS, intracranial progression-free survival; IRC, independent review committee; KM, Kaplan Meier; mo, month; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor

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