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Brigatinib vs Crizotinib in ALK TKI–Naive ALK+ NSCLC: Final Results From ALTA-1L

Sanjay Popat,[1] Hye Ryun Kim,[2] Myung-Ju Ahn,[3] James CH Yang,[4] Ji-Youn Han,[5] Maximilian J Hochmair,[6] Ki Hyeong Lee,[7] Angelo Delmonte,[8] Maria Rosario Garcia Campelo,[9] Dong-Wan Kim,[10] Frank Griesinger,[11] Enriqueta Felip,[12] Raffaele Califano,[13] Alexander Spira,[14] Scott N Gettinger,[15] Marcello Tiseo,[16] Huamao M Lin,[17] Yuyin Liu,[17] Florin Vranceanu,[17] D Ross Camidge[18]

[1]Royal Marsden Hospital, London, England, United Kingdom; [2]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [3]Samsung Medical Center, Seoul, South Korea; [4]National Taiwan University Cancer Center, Taipei, Taiwan; [5]National Cancer Center, Goyang, South Korea; [6]Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Department of Respiratory and Critical Care Medicine, Klinik Floridsdorf, Vienna, Austria; [7]Chungbuk National University Hospital, Cheongju, South Korea; [8]Scientific Institute of Romagna for the Study and Treatment of Cancer, Meldola, Italy; [9]University Hospital A Coruña, CHUAC, A Coruña, Spain; [10]Seoul National University Hospital, Seoul, South Korea; [11]Pius-Hospital Oldenburg, University of Oldenburg, Oldenburg, Germany; [12]Vall d'Hebron University Hospital, Barcelona, Spain; [13]The Christie NHS Foundation Trust, Manchester, England, United Kingdom; [14]Virginia Cancer Specialists and US Oncology Research, The Woodlands, TX, USA; [15]Yale Cancer Center, New Haven, CT, USA; [16]University Hospital of Parma, Parma, Italy; [17]Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA; [18]University of Colorado Cancer Center, Aurora, CO, USA

Introduction

- The first-generation anaplastic lymphoma kinase (ALK) inhibitor crizotinib has shown superiority to chemotherapy in patients with treatment-naive advanced ALK-positive (ALK+) non–small cell lung cancer (NSCLC)[1]
  - However, most patients develop progressive disease within 1 year due to acquired ALK resistance mutations and/or poor crizotinib central nervous system (CNS) penetration[2,3]
  - The CNS is the most common site for progression in patients with ALK+ NSCLC treated with crizotinib[4]
- Brigatinib, a single-tablet, once-daily ALK inhibitor with broad preclinical activity against ALK resistance mutations, was evaluated in patients with ALK treatment-naive ALK+ NSCLC in ALK in Lung Cancer Trial of brigAtinib in 1st Line (ALTA-1L)[3,5]
  - The study met statistical significance at the first preplanned interim analysis (50% of expected events)[5]
  - At the second interim analysis (75% of expected events), brigatinib maintained durable BIRC-assessed PFS superiority vs crizotinib (HR: 0.49; *P*<0.0001)[6]
    - Among patients with brain metastases at baseline, the HR for BIRC-assessed PFS was 0.25 (95% CI, 0.14–0.46; *P*<0.0001), favoring brigatinib
    - Overall survival was still maturing at this analysis (HR: 0.92; 95% CI, 0.57–1.47; brigatinib, 24% of events; crizotinib, 27% of events)
- We report the final efficacy and safety data from long-term follow-up of patients in ALTA-1L

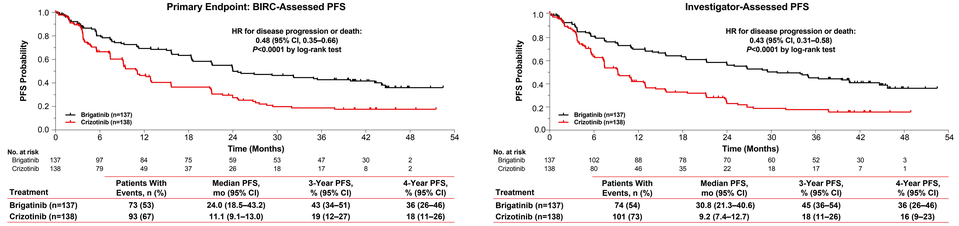
Methods

- Complete methods for ALTA-1L (NCT02737501) have been previously published[5,6]
- ALTA-1L enrolled patients aged ≥18 years with stage IIIB/IV ALK+ NSCLC who had not received prior ALK inhibitor therapy and had received ≤1 prior systemic treatment for locally advanced/metastatic NSCLC[5,6]
  - Patients with asymptomatic, untreated CNS metastases were not excluded
- Patients were randomized 1:1 to receive brigatinib 180 mg qd (with 7-day lead-in at 90 mg qd) or crizotinib 250 mg BID[5,6]
  - Stratification factors: Baseline brain metastases (y/n) and prior chemotherapy for locally advanced/metastatic disease (y/n)
- Disease assessment, including brain MRI for all patients, occurred every 8 weeks through cycle 14, then every 12 weeks[5,6]
- Crossover from crizotinib to brigatinib was permitted at BIRC-assessed disease progression[5,6]
- The primary endpoint was BIRC-assessed PFS per RECIST v1.1; secondary endpoints included confirmed ORR, confirmed intracranial ORR, intracranial PFS, OS, safety, and tolerability[5,6]
- A marginal structural model (MSM) was constructed on OS to adjust for the potential time-dependent confounding effects of treatment crossover after patients discontinued crizotinib
  - The MSM censors switchers at the time of treatment switch and then re-weights the data using information on baseline and time-dependent covariates[7,8]
    - Baseline covariates included in the final model: age, initial diagnosis stage, baseline ECOG score, histopathological class at study entry, measurable intracranial CNS disease (yes/no), race group (Asian vs non-Asian), sex, smoking history, and strata at randomization
    - Time-dependent covariates: intracranial disease progression, target lesion size, and ECOG score

Results

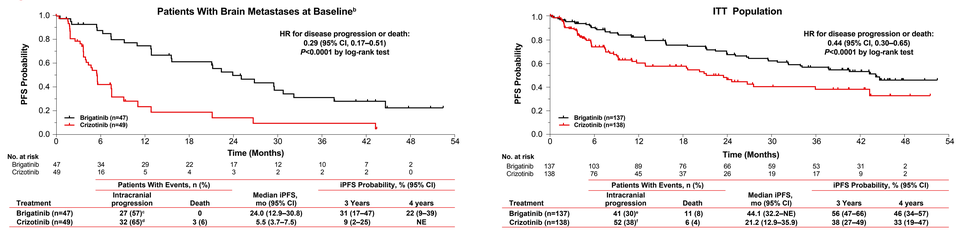
- Last patient last contact was January 2021, approximately 3.5 years after the last patient enrolled
- Median (range) follow-up: brigatinib 40.4 (0–52.4) months; crizotinib 15.2 (0.1–5.7) months
- 58 patients (42%) in the brigatinib arm and 16 patients (12%) in the crizotinib arm were still on study drug before end of study
- 65 patients (47%) from the crizotinib arm crossed over to brigatinib after disease progression on crizotinib
  - Median (range) duration of brigatinib treatment in these 65 patients was 17.3 (0.1–37.5) months
  - Crossover occurred in 46% (19/41) of patients who had brain metastases at baseline per investigators
  - 23/65 patients (35%) remained on brigatinib up to study end

Figure 1. Final Systemic PFS



Treatment	Patients With Events, n (%)	Median PFS, mo (95% CI)	3-Year PFS, % (95% CI)	4-Year PFS, % (95% CI)
Brigatinib (n=137)	73 (53)	24.0 (18.5–43.2)	43 (34–51)	36 (26–46)
Crizotinib (n=138)	93 (67)	11.1 (9.1–13.0)	19 (12–27)	18 (11–26)
Brigatinib (n=137)	74 (54)	30.8 (21.3–40.6)	45 (36–54)	36 (26–46)
Crizotinib (n=138)	101 (73)	9.2 (7.4–12.7)	18 (11–26)	16 (9–23)

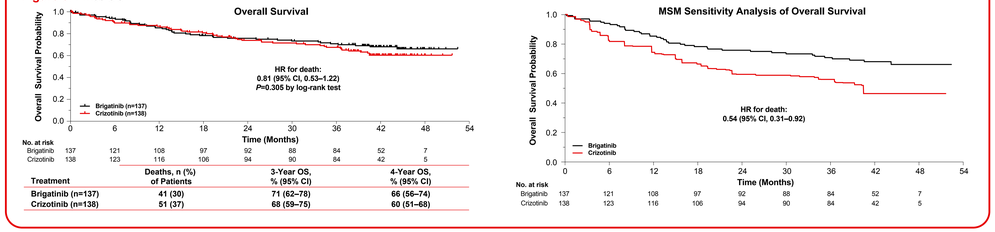
Figure 2. Final BIRC[a]-Assessed Intracranial PFS



Treatment	Patients With Events, n (%)		Median iPFS, mo (95% CI)	iPFS Probability, % (95% CI)	
	Intracranial progression	Death		3 Years	4 years
Brigatinib (n=47)	27 (57)[c]	0	24.0 (12.9–30.8)	31 (17–47)	22 (9–39)
Crizotinib (n=49)	32 (65)[e]	3 (6)	5.5 (3.7–7.5)	9 (2–25)	NE
Brigatinib (n=137)	41 (30)[d]	11 (8)	44.1 (32.2–NE)	56 (47–65)	46 (34–57)
Crizotinib (n=138)	52 (38)[f]	6 (4)	21.2 (12.9–35.9)	38 (27–49)	33 (19–47)

[a] Intracranial reviewers were independent from systemic reviewers. Only brain lesions were reviewed. Patients were counted as having an event if there was radiological progression, radiotherapy to the brain, or death. [b] Per BIRC assessment. [c] Includes 1 patient with radiotherapy to the brain. [d] Includes 3 patients with radiotherapy to the brain. [e] Includes 1 patient with radiotherapy to the brain. [f] Includes 6 patients with radiotherapy to the brain

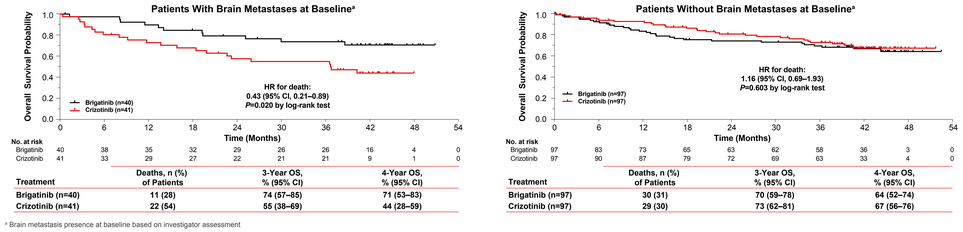
Figure 3. Final OS



Treatment	Deaths, n (%) of Patients	3-Year OS, % (95% CI)	4-Year OS, % (95% CI)
Brigatinib (n=137)	41 (30)	71 (62–78)	66 (56–74)
Crizotinib (n=138)	51 (37)	68 (59–75)	60 (51–68)

- In sensitivity analyses adjusting for treatment crossover in the crizotinib arm, the OS HR was 0.54 (95% CI, 0.31–0.92; *P*=0.023) by the MSM approach

Figure 4. Final OS in Patients With and Without Brain Metastases at Baseline



Treatment	Deaths, n (%) of Patients	3-Year OS, % (95% CI)	4-Year OS, % (95% CI)
Brigatinib (n=40)	11 (28)	74 (57–85)	71 (53–83)
Crizotinib (n=41)	22 (54)	55 (38–69)	44 (28–59)
Brigatinib (n=97)	30 (31)	70 (59–78)	64 (52–74)
Crizotinib (n=97)	29 (30)	73 (62–81)	67 (56–76)

[a] Brain metastasis presence at baseline based on investigator assessment

Table 1. Subsequent Anticancer Therapies

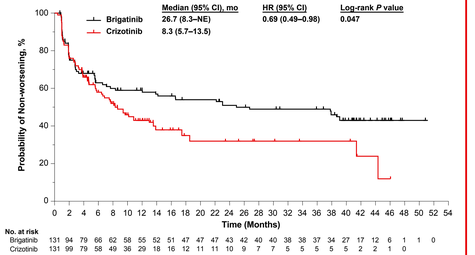
	Brigatinib			Crizotinib		
	Brain Metastases at Baseline[a]			Brain Metastases at Baseline[a]		
	Yes (n=40)	No (n=96)	Total (n=136)	Yes (n=41)	No (n=96)	Total (n=137)
Patients who discontinued study treatment[b], n	27	51	78	39	82	121
No. of subsequent systemic anticancer regimens, n (%[c])						
1	13 (48)	13 (25)	26 (33)	18 (46)	42 (51)	60 (50)
2	2 (7)	2 (4)	4 (5)	7 (18)	13 (16)	20 (17)
3+	4 (15)	12 (24)	16 (21)	7 (18)	16 (20)	23 (19)
Subsequent anticancer treatment, n (%[c])						
Systemic therapy	19 (70)	27 (53)	46 (59)	32 (82)	71 (87)	103 (85)
ALK TKI	19 (70)	23 (45)	42 (54)	31 (79)	68 (83)	99 (82)
Brigatinib[d]	1 (4)	1 (2)	2 (3)	24 (62)	56 (68)	80 (66)
Alectinib	10 (37)	6 (12)	16 (21)	9 (23)	19 (23)	28 (23)
Lorlatinib	10 (37)	12 (24)	22 (28)	9 (23)	12 (15)	21 (17)
Crizotinib	3 (11)	8 (16)	11 (14)	2 (5)	4 (5)	6 (5)
Ceritinib	0	4 (8)	4 (5)	2 (5)	3 (4)	5 (4)
Chemotherapy/other targeted therapy	3 (11)	13 (25)	16 (21)	5 (13)	15 (18)	20 (17)
Carboplatin	1 (4)	8 (16)	9 (12)	3 (8)	8 (10)	11 (9)
Cisplatin	1 (4)	5 (10)	6 (8)	1 (3)	5 (6)	6 (5)
Gemcitabine	0	3 (6)	3 (4)	1 (3)	3 (4)	4 (3)
Paclitaxel	0	2 (4)	2 (3)	1 (3)	1 (1)	2 (2)
Docetaxel	1 (4)	2 (4)	3 (4)	0	0	0
Etoposide	0	2 (4)	2 (3)	0	0	0
Erlotinib	0	1 (2)	1 (1)	0	0	0
Ifosfamide	0	1 (2)	1 (1)	0	0	0
Immunotherapy	0	4 (8)	4 (5)	2 (5)	3 (4)	5 (4)
Atezolizumab	0	2 (4)	2 (3)	1 (3)	1 (1)	2 (2)
Nivolumab	0	1 (2)	1 (1)	1 (3)	0	1 (1)
Pembrolizumab	0	1 (2)	1 (1)	0	2 (2)	2 (2)
VEGF-R inhibitor	2 (7)	2 (4)	4 (5)	2 (5)	3 (4)	5 (4)
Other	0	2 (4)	2 (3)	1 (3)	0	1 (1)
Radiotherapy	0	2 (4)	2 (3)	5 (13)	9 (11)	14 (12)
Surgery	0	0	0	2 (5)	0	2 (2)

[a] Brain metastases at baseline as assessed by the investigator; [b] Patients who discontinued treatment before end of study; [c] Denominator is number of patients who discontinued study treatment; [d] Including crossover brigatinib in patients randomized to first-line crizotinib at enrollment, and any brigatinib use in regular medical practice

Table 2. Safety Overview

Patients with ≥1 event, n (%)	Brigatinib (n=136)	Crizotinib (n=137)
Any grade adverse event	136 (100)	137 (100)
Grade 3–4 adverse event	95 (70)	77 (56)
Adverse event leading to death (grade 5)	11 (8)	11 (8)
Treatment-related	0	0
Adverse event leading to treatment discontinuation	18 (13)	12 (9)
Adverse event leading to dose reduction	60 (44)	34 (25)
Adverse event leading to dose interruption	98 (72)	65 (47)

Figure 5. Time to Worsening of EORTC QLQ-C30 Global Health Status



	Median (95% CI), mo	HR (95% CI)	Log-rank *P* value
Brigatinib	26.7 (8.3–NE)	0.69 (0.49–0.98)	0.047
Crizotinib	8.3 (5.7–13.5)		

Summary

- Final results of ALTA-1L showed efficacy and safety consistent with the 2 interim analyses, with longer duration of therapy (median follow-up 40.4 months in the brigatinib arm)
- Brigatinib continued to show superior BIRC-assessed PFS compared with crizotinib, with a 52% reduction in the risk of progression or death
- Brigatinib continued to demonstrate high intracranial efficacy, with risk of intracranial progression reduced by 56% in all patients and by 71% in patients with any baseline brain metastases compared with crizotinib
- OS was still maturing at the final analysis (30% event rate) and indicated similar OS across both arms (HR: 0.81; 95% CI, 0.53–1.22)
  - An MSM OS sensitivity analysis that adjusted for possible confounding from crossover suggested that brigatinib treatment would have been associated with improved OS if treatment crossover from crizotinib to brigatinib had not been permitted
  - OS HR with brigatinib vs crizotinib in patients with baseline brain metastases was 0.43 despite the high rate of crossover from crizotinib, suggesting a survival benefit in patients with brain metastases who received brigatinib as the first ALK inhibitor
- Greater proportions of patients treated with crizotinib received subsequent anticancer therapy after discontinuation of study drug
- Brigatinib demonstrated health-related quality of life benefits versus crizotinib
- Final ALTA-1L results confirm the significant improvement in PFS with brigatinib compared with crizotinib in ALK-positive NSCLC with no new safety signals
- These results support brigatinib as a standard treatment option for treatment-naive ALK+ NSCLC

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Abbreviations

ALK, anaplastic lymphoma kinase; ALK+, anaplastic lymphoma kinase gene–rearranged; ALTA-1L, ALK in Lung Cancer Trial of brigAtinib in 1st Line; BID, twice daily; BIRC, blinded independent review committee; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HR, hazard ratio; iPFS, intracranial PFS; MRI, magnetic resonance imaging; MSM, marginal structural model; NE, not estimable; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; qd, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; VEGF-R, vascular endothelial growth factor-receptor.

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Disclosures

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Email address for questions or comments: sanjay.popat@rmh.nhs.uk

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