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COMMENTARY

From ASCEND-5 to ALUR to ALTA-3, an Anti-Climactic End to the Era of Randomized Phase 3 Trials of Next-Generation ALK TKIs in the Crizotinib-Refractory Setting

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Abstract: The competing roles of various next-generation ALK TKIs in the first and second line treatment setting of advanced *ALK*+ NSCLC were based on many phase 3 clinical trials in both the first-line and crizotinib-refractory settings. The approval of all next-generation ALK TKIs was first in the crizotinib-refractory setting, based on a large-scale Phase 2 trial, and was then followed by at least one global randomized phase 3 trial comparing to platinum-based chemotherapy (ASCEND-4) or to crizotinib (ALEX, ALTA-1L, eXalt3, CROWN). In addition, three randomized phase 3 trials in the crizotinib-refractory setting were also conducted by next-generation ALK TKIs that were developed earlier before the superiority of next-generation ALK TKIs was demonstrated in order to secure the approval of these ALK TKIs in the crizotinib-refractory setting. These three crizotinib-refractory randomized trials were: ASCEND-5 (ceritinib), ALUR (alectinib), and ALTA-3 (brigatinib). The outcome of the ATLA-3 trial was recently presented closing out the chapter where next-generation ALK TKIs were investigated in the crizotinib-refractory setting as they have replaced crizotinib as the standard of care first-line treatment of advanced *ALK*+ NSCLC. This editorial summarizes the results of next-generation ALK TKIs in randomized crizotinib-refractory trials and provides a perspective on how natural history of *ALK*+ NSCLC may potentially be altered with sequential treatment. ALTA-3 compared brigatinib to alectinib, showing that both achieved near identical blinded independent review committee (BIRC)-assessed progression-free survival (PFS) (19.2–19.3 months). Importantly, 4.8% of brigatinib-treated patients developed interstitial lung disease (ILD) while no alectinib-treated patients developed ILD. Dose reduction and discontinuation due to treatment-related adverse events were 21% and 5%, respectively, for brigatinib-treated patients compared to 11% and 2%, respectively, for alectinib-treated patients. Upon analysis of these findings, we speculate that brigatinib may have a diminishing role in the treatment of advanced *ALK*+ NSCLC.

Keywords: ALTA-3, ALUR, ASCEND-5, brigatinib, alectinib, ceritinib, crizotinib, advanced *ALK*+ NSCLC

Introduction

When crizotinib received full FDA approval based on the results of the PROFILE 1007 trial, in which crizotinib demonstrated statistically significant improvement in progression-free survival over single-agent chemotherapy (pemetrexed or docetaxel) in the second-line chemotherapy-refractory setting,[1,2] the US FDA approval was not contingent on any particular line of therapy setting.[2] Notably, the initially accelerated US FDA approval of crizotinib on August 26, 2011, was described broadly as "treatment of advanced anaplastic lymphoma kinase fusion positive (*ALK*+) non-small cell lung cancer (NSCLC).[3] Nevertheless, crizotinib quickly demonstrated statistically significant improvement in progression-free survival over platinum-based chemotherapy and established itself as the standard of care (SOC) treatment of advanced *ALK*+ NSCLC in 2014.[4]

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As data of multiple on-target resistance mutations and lack of substantial central nervous system efficacy emerged from the use of crizotinib, more potent next-generation ALK tyrosine kinase inhibitors (TKIs) based on lower concentration to inhibit 50% of the ALK kinase activity (IC_{50}) were developed to overcome resistance to crizotinib.[5] The clinical development of these next-generation ALK TKIs followed the now very standard drug development paradigm, with, first, a phase 2, usually single arm study, demonstrating an impressive overall response rate (ORR) and secondarily long duration of response (DOR) in a molecularly defined cohort of crizotinib-refractory patients. Importantly, all US FDA accelerated approvals require at least one randomized phase 3 trial demonstrating clinical benefit. Given that crizotinib had, by this point, established statistically significant improvement in PFS in the first-line setting (PROFILE1014),[4] in addition to the chemotherapy-refractory setting (PROFILE1007),[1] randomized phase 3 trials involving next generation ALK TKIs had to be designed with a specific line of therapy in mind. While the pharmaceutical sponsor of ALK TKIs aimed to replace crizotinib as the new first-line SOC treatment of advanced *ALK*+ NSCLC, given that the initial approval status of next-generation ALK TKIs were in the crizotinib-refractory setting and the still nascent knowledge base of advanced *ALK*+ NSCLC, three randomized phase 3 trials in the crizotinib-refractory were launched and subsequently completed (ASCEND-5,[6] ALUR,[7,8] and ALTA-3).[9,10] The most recent trial, ALTA-3, reported its results at the ESMO Asia 2022 meeting.

Randomized Second-Line Trials of Next-Generation ALK TKI in Crizotinib-Refractory Settings

ASCEND-5 (NCT01828112)

ASCEND-5 is an open-label randomized trial comparing ceritinib to either single-agent pemetrexed or docetaxel chemotherapy in the post-platinum-based chemotherapy AND post-crizotinib progression settings. The conduct and results of this trial are listed in Table 1. The median PFS achieved by ceritinib was 5.4 months (95% CI: 4.1–6.9), which was significantly better than single-agent chemotherapy, with a median PFS of 1.6 months (1.4–2.8). The hazard ratio of these results was 0.49 (95% CI: 0.36–0.67); $p<0.0001$.[6] The ASCEND-5 results confirmed the accelerated approval of ceritinib for crizotinib-refractory ALK TKI.[11]

ALUR (NCT02604342)

ALUR is a randomized phase 3 trial designed similarly to ASCEND-5 and compared alectinib to single agent docetaxel or pemetrexed chemotherapy.[7] The primary data from ALUR are listed in Table 1. Blinded independent review committee (BIRC)-assessed PFS was significantly longer with alectinib, with a HR of 0.32 (95% CI: 0.17–0.59). Median PFS was 7.1 months (95% CI: 6.3–10.8) with alectinib and 1.6 months (95% CI: 1.3–4.1) with chemotherapy. The final update of ALUR indicated further prolongation of the investigator-assessed PFS of alectinib from 9.6 months[7] to 10.9 months[8] with no change in the BIRC-assessed PFS for alectinib (Table 1).

ALTA-3 (NCT03596866)

Given that ALTA-3 was launched later than ASCEND-5 and ALUR, the use of ceritinib, alectinib, and brigatinib was approved in the crizotinib-refractory setting. Also, the stated purpose of ALTA-3 from the sponsor and clinical investigators was as follows: "if positive, the results of ALTA-3 will build on the ALTA trial data and reaffirm the optimal approach with brigatinib over alectinib in crizotinib-resistant patients".[9] Hence in ALTA-3, *ALK*+ NSCLC patients were randomized 1:1 to either alectinib or brigatinib. ALTA-3 employed two stratification factors, the presence/absence of brain metastases and the best response to crizotinib (CR/PR versus SD/PD/other). While prior chemotherapy was allowed in ALTA-3, prior use of chemotherapy was not a stratification factor. Additionally, ALTA-3 was a globally conducted trial, but race (Asian vs non-Asian) was not a stratification factor. The sample size was calculated to be 246 total patients (164 events) to detect improvement in median PFS from 9 to 15 months (HR=0.60). Interim analysis for efficacy and futility was to be conducted at approximately 70% of target PFS events (~115 of 164 expected events).[9,10]

ALTA-3 was a well-conducted trial, although with a list of patient characteristics that could affect the trial outcome, but were not stratification factors, including sex, race, smoking history, performance status, prior systemic chemotherapy (31% for brigatinib and 35% for alectinib), and distribution of tumor metastasis (Table 1). Furthermore, median time from initial

Table 1 Comparison of Characteristics of ASCEND-5, ALUR, and ALTA-3

	ASCEND-5 (NCT01828112)		ALUR (NCT02604342)		ALTA-3 (NCT03596866)	
Trial Design						
	Ceritinib	**Docetaxel/ pemetrexed**	**Alectinib**	**Docetaxel/ Pemetrexed**	**Brigatinib**	**Alectinib**
N (# patients)	115	116	72	35	125	123
Date of enrollment	June 28, 2013 (started) November 2, 2015 (ended)		September 28, 2018 (ended)			
Stratification factors	WHO PS (0 vs 1–2) and presence of brain metastases at screening (yes vs no).		ECOG PS (0/1 vs 2); baseline CNS metastases (yes vs no); and, for patients with baseline CNS metastases, brain radiotherapy history (yes vs no)		Brain metastases at baseline (yes vs no) and best response to prior crizotinib (CR/PR vs SD/PD/other)	
Randomization ratio	1:1		2:1		1:1	
Primary endpoint	IRC-assessed PFS		Investigator-assessed PFS		BIRC-assessed PFS	
Cross-over	Allowed		Allowed		Not allowed	
	Trial conduct					
Number of lines of chemotherapy	1 line (88%) 2 lines (11%)	1 line (88%) 2 lines (12%)	1 line (100%)	1 line (100%)	1 line (31%)	1 line (35%)
% CNS metastasis	57%	59%	65.3%	74.3%	64%	61%
Never-smoker	62%	53%	48.6%	45.7%	66%	69%
	Trial outcome					
BIRC-ORR (95% CI)	39·1% (30.2–48.7)	6·9% (3.0–13.1)			52 (43–61)	61 (52–70)
BIRC-PFS (95% CI)	5.4 (4.1–6.9)	1.6 (1.4–2.8)	7.1 (6.3–10.8)	1.6 (13–4.1)	19.3 (15.7–NR)	19.2 (12.9–NR)
BIRC-PFS HR (95% CI)	0.49 (0.36–0.67); $p<0.0001$		0.32 (0.17–0.59)		0.97 (0.66–1.42); $p=0.8672$	
Investigator-assessed PFS	6.9 (4.4–7.9)	1.6 (1.4–2.6)	10.9 (8.1–15.5)	1.4 (1.2–1.6)	16.8m (10.9–19.4)	16.6 (13.6–27.6)
Investigator-assessed PFS HR (95% CI)	0.40 (0.29–0.54)		0.2 (10.2–0.33); $p<0.0001$		1.23 (95% CI: 0.86–1.76)	
OS (95% CI)	18.1m (13.4–23.9)	20.1m (11.9–25.1)	12.6m (95% CI=9.7–NR)	NR (95% CI=NR–NR)	1-year survival probability: brigatinib, 89% (95% CI=81–93)	1-year survival probability: alectinib, 96% (95% CI=90–98)
OS HR	0.50		0.89 (95% CI: 0.35–2.24)		NA	

Abbreviations: BIRC, blinded independent review committee; CI, confidence interval; IRC, independent review committee; M, month; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival; PS, performance status.

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diagnosis of *ALK*+ NSCLC and time on treatment with crizotinib, though longer, were similar. Plasma genotyping was successful in 94.4% (118/125) of brigatinib-treated patients and 92.7% (114/123) of alectinib-treated patients.

The primary endpoint of the trial BIRC-assessed median PFS was identical, with 19.2 months in the alectinib-treated patients (95% CI: 12.9–not reached) and 19.3 months in the brigatinib-treated patients (95% CI: 15.7–not reached). The HR achieved by brigatinib-treated patients was 0.97 (95% CI: 0.66–1.42); p=0.8672)[10] (Table 1). Other important endpoints of ALTA-3 are listed in Table 1. Both next-generation ALK TKIs achieved median PFS beyond the expectation of clinicians.

In terms of safety, there was no treatment-related death in both treatment arms. Six out of 125 (4.8%) brigatinib-treated patients developed interstitial lung disease (ILD) (either grade 1 or 2) while no alectinib-treated patients developed ILD. Dose reduction and discontinuation due to treatment-related adverse events were 21% and 5%, respectively, for brigatinib-treated patients compared to 11% and 2%, respectively, for alectinib-treated patients. Quality-of-life improved in the brigatinib and alectinib arms beginning at cycle 2 and was not significantly different between arms. However, the majority of the time alectinib scored numerically above brigatinib. Time to worsening in the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-LC13 Composite Score was similar between arms, with a HR of 0.87 (95% CI: 0.65–1.18). In summary, overall response rate, safety as measured by dose reduction and discontinuation, and quality-of-life numerically favor alectinib over brigatinib, although these results were not statistically significant. Near-identical median PFS was achieved by both alectinib and brigatinib.

Why ALTA-3 Did Not Show Any PFS Improvement of Brigatinib Over Alectinib

The obvious question we are faced with is the reason behind alectinib's and brigatinib's essentially identical performance, given that pre-clinically brigatinib was more potent than alectinib, as demonstrated by longer median PFS in phase 2 trials.[12–14] The only imbalance between the two arms is the proportion of *EML4-ALK* variant 1. There were nine (7.2%; 9/125) *EML4-ALK* variant 1s in the brigatinib-treated arm compared to 17 (13.8%; 17/123) *EML4-ALK* variant 1s in the alectinib-treated arm. There were similar proportions of *EML4-ALK* variant 3 in the brigatinib-treated arm (N = 16; 8.0%; 16/125) compared to the alectinib-treated arm (N = 15; 8.1%; 15/123). It is well-known that *EML4-ALK* variant 3 is more resistant to all ALK TKIs,[15] but the similar and low incidence among the ALTA-3 populations is unlikely to favor one treatment arm over the other. Further analysis of the ORR and PFS by alectinib and brigatinib according to *EML4-ALK* variant will be required to assess how this imbalance may have contributed to the eventual outcome of ALTA-3. Future randomization should take *EML4-ALK* variant (v1 versus v3 versus other) as a stratification factor.

The detection rate of *ALK* fusion from plasma genotyping was lower than has been reported (usually >50%).[16] Hence, while most of the *EML4-ALK* variants were unknown, it is unlikely that the eight known confirmed extra *EML4-ALK* variant 1s that could have conferred a difference in PFS explain the PFS seen in alectinib compared to brigatinib.

One of the more likely reasons that there was no difference between brigatinib and alectinib was that the *ALK*+ NSCLC patients enrolled into ALTA-3 possessed a better prognosis based on three characteristics. First, the median time from diagnosis of *ALK*+ NSCLC to enrollment was relatively long, with a median time in the alectinib group of 21.3 months (range: 2.37–266.2) and 22.2 months (range: 2.3–161.8) in the brigatinib group.[10] We assumed that most patients were stage IV and that the time of second-line treatment from diagnosis was relatively long, at 22 months for advanced *ALK*+ NSCLC. Second and in support of our first observation, the duration of crizotinib treatment was 16.8 (range: 1.0–83.8) months for patients randomized to alectinib and 16.0 (range: 1.3–85.9) months for patients randomized to brigatinib.[10] The median PFS of first-line crizotinib in PROFILE1014, ALEX, J-ALEX, ALESIA, ALTA-1L, and CROWN was between 9 and 11 months.[4,16–20] It is likely that the duration of crizotinib treatment included continuation of crizotinib-beyond progressive disease (CBPD), especially among CNS-only patients, who represent a subgroup of patients with better prognosis. However, a median duration of 16 months in the crizotinib group is still a relatively long time, even taking into consideration CBPD.[21] Third, the detection of *ALK* fusions in the plasma was low, at 27% for brigatinib and 40% for alectinib. The ability to detect *ALK* fusion by plasma genotyping generally represents a higher tumor burden and the positive rate of *ALK* fusions is usually >50%.[15] Indeed, the median PFS between patients with detectable ALK fusion in plasma was only 11.1 months (95% CI: 8.0–19.3) compared to 22.5 months (95% CI: 19.2–NE) for non-detectable *ALK* fusions.

The Dwindling Role of Brigatinib in the Treatment of Advanced *ALK*+ NSCLC from the ALTA Program (ALTA, ALTA-1L, J-ALTA, ALTA-2, ALTA-3)

The first-line approval of alectinib based on ALEX was on December 11, 2017, while the first-line brigatinib approval based on ALTA-1L was on May 27, 2020, almost 30 months later. Prior to that, the approval of alectinib in crizotinib-refractory patients was on November 26, 2015, compared to the approval of brigatinib in crizotinib-refractory patients on April 28, 2017. This was, again, almost 18 months behind alectinib.[15] Thus, the adaptation of brigatinib had always followed that of alectinib, and its uniquely unpredictable rapid-onset pulmonary toxicity within the first week of treatment could have further deterred many oncologists from its use.[22] Thus, despite the much longer median PFS demonstrated by brigatinib in ALTA compared to the alectinib in phase 2 trials, oncologists have eagerly-awaited the ALTA-1L data.

Cross-trial comparisons are admittedly discouraged, but commonly used amongst oncologists to make certain clinical judgments. Thus, it can be said that brigatinib in ALTA-1L has failed to demonstrate a numerical advantage in median PFS (24.0 months)[23] over the median PFS of alectinib in ALEX (25.7 months).[17] Given that the standard of care for advanced *ALK*+ NSCLC has advanced quickly to next-generation ALK TKIs, alectinib has become the primary first-line treatment of advanced *ALK*+ NSCLC. Furthermore, the number of patients treated initially with crizotinib as their first ALK TKI has been dwindling rapidly. Thus, the ALTA-3 data further destabilizes the market share of brigatinib in the ever-disappearing post-crizotinib setting.

Lorlatinib, another potent next-generation ALK TKI, is generally used as ALK TKI post-alectinib and is the only ALK TKI that has this FDA indication based on a phase 2 trial demonstrating a median PFS of 5.5 months post-alectinib.[24] Most recently, ALTA-2, a single arm study of brigatinib in the post-alectinib (and post-ceritinib) setting reported an ORR of 26.2%. However, the lower limit of the 95% CI (18%) dropped below the 20% ORR null hypothesis.[25] Thus, ALTA-2 did not reach its primary endpoint. Furthermore, the median PFS achieved by brigatinib in the post-alectinib setting was 3.8 months (95% CI=1.9–5.4), which is numerically shorter than the median PFS achieved by lorlatinib in a similar setting.[24,25] Hence, we project that the role of brigatinib in the treatment of advanced *ALK*+ NSCLC will continue to shrink, like ceritinib, which has been associated with significant toxicities and which possesses an even shorter median PFS of 16.8 months in the frontline setting based on ASCEND-4.[26]

Our Final Perspectives on ALTA-3

ALTA-3 was designed at a time when crizotinib had begun to cede its role as the standard of care front-line treatment for advanced *ALK*+ NSCLC in the face of next-generation ALK TKIs (alectinib, brigatinib, lorlatinib). As stated in the rationale and perspective of the ALTA-3 trial, "if positive, the results of ALTA-3 will build on the ALTA trial data and reaffirm the optimal approach with brigatinib over alectinib in crizotinib-resistant patients". If true, brigatinib would have at least retained, but not built on, a small role in the treatment of advanced *ALK*+ NSCLC in the ever-dwindling subset of patients who were treated with crizotinib as first-line or first ALK TKI treatment. With the near identical median PFS achieved by both alectinib and brigatinib in ALTA-3, and the disappointing results of ALTA-1L[23] and ALTA-2,[25] unfortunately we venture to speculate that brigatinib, despite being a highly potent ALK TKI, will fall victim to the breakneck pace of oncology and become a footnote in the treatment parlance of *ALK*+ NSCLC.

Disclosure

Professor Sai-Hong Ignatius Ou reports personal fees from Pfizer, AnHeart Therapeutics, JNJ/Janssen, DAVA Oncology LLP; stock ownership from Elevation Oncology and Turning Point Therapeutics, outside the submitted work. The authors report no other conflicts of interest in this work.

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