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ADIS DRUG EVALUATION

Brigatinib: A Review in ALK-Inhibitor Naïve Advanced *ALK*-Positive NSCLC

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Abstract

Brigatinib (Alunbrig®) is an oral, potent and selective anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) tyrosine kinase inhibitor approved for treating adults with advanced *ALK*-positive non-small-cell lung cancer (NSCLC) not previously treated with an ALK inhibitor. In a multinational, phase III study (ALTA-1L) in this patient population, brigatinib significantly improved median blinded independent review committee-assessed progression-free survival (PFS), the confirmed objective response (OR) rate and the confirmed intracranial OR rate compared with crizotinib. Its tolerability profile in this study was manageable and no new safety concerns were identified. Although final analysis data are awaited with interest, brigatinib therapy extends the first-line treatment options available for standard of care in this patient population, including patients with CNS metastases.

Brigatinib: clinical considerations in ALK-inhibitor naïve advanced *ALK*-positive NSCLC

Selective ALK and ROS1 tyrosine kinase inhibitor
Prolongs PFS and improves the intracranial OR rate compared with crizotinib
Generally manageable tolerability profile; may be associated with pulmonary adverse events

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1 Introduction

The anaplastic lymphoma kinase (*ALK*) gene encodes a tyrosine kinase receptor that is primarily involved in neurological developmental processes; in adults, ALK is expressed at low levels [1]. While the oncogenic activation of ALK can result from point mutations in the *ALK* kinase domain, gene fusions (i.e. the exchange of *ALK* chromosomal segments with other genes [2]) are required by most *ALK*-positive malignancies, including *ALK*-positive non-small-cell lung cancer (NSCLC), to induce de novo ALK expression and activation [1]. *ALK* has multiple fusion partners across various *ALK*-positive malignancies; in *ALK*-positive NSCLC, the dominant fusion partner is echinoderm microtubule-associated protein-like 4 (*EML4*) [1, 2].

Rearrangements of *ALK* occur in ≈ 5% of patients with NSCLC [3], and are more frequently seen among younger patients, those with adenocarcinoma histology, and light or non-smokers [1, 2, 4]. Tumours with such rearrangements require continued ALK signalling for growth and survival [4], making ALK a compelling therapeutic target [2]. The first ALK inhibitor to be approved for use in patients with *ALK*-positive NSCLC was crizotinib [5]. However, almost all patients with *ALK*-positive NSCLC treated with crizotinib eventually develop resistance [1, 2], leading to disease progression, including the development of CNS metastases [6]. The latter probably reflects the poor penetration

of crizotinib into the CNS (a dominant site of disease progression in *ALK*-positive NSCLC) [6]. Thus, the potential of newer (next generation) ALK inhibitors resides in their activity in patients with CNS and/or crizotinib-resistant disease [1]. One such next-generation ALK inhibitor is brigatinib (Alunbrig®).

This article discusses pharmacological, therapeutic efficacy and tolerability data relevant to the use of oral brigatinib in adults with advanced *ALK*-positive NSCLC not previously treated with an ALK inhibitor. The use of brigatinib in adults with advanced *ALK*-positive NSCLC previously treated with crizotinib has been summarized previously [7] and is beyond the scope of this review.

2 Pharmacodynamic Properties of Brigatinib

Brigatinib is a potent and selective ALK and c-ros oncogene 1 (ROS1) tyrosine kinase inhibitor (TKI) [8]. In vitro, it inhibited the kinase activity of native ALK [half maximal inhibitory concentration (IC_{50}) 0.6 nmol/L], native ROS1 (IC_{50} 1.9 nmol/L) and native FLT3 (IC_{50} 2.1 nmol/L), as well as mutant variants of ALK and FLT3 ($IC_{50} \leq$ 6.6 nmol/L) and the L858R mutant variant of epidermal growth factor receptor (EGFR) [IC_{50} 1.5 nmol/L]. Brigatinib displayed more modest activity against native EGFR, EGFR with a T790M resistance mutation (L858R/T790M), native insulin-like growth factor-1 receptor (IGF-1R) and native INSR [IC_{50} 29–160 nmol/L], and did not inhibit native MET ($IC_{50} >$ 1000 nmol/L). In cellular assays, brigatinib inhibited native ALK and native ROS1 to a similar degree (IC_{50} 14 and 18 nmol/L); however, its potency against native FLT3 and native IGF-1R was ≈ 11-fold lower (IC_{50} 158 and 148 nmol/L) and that against mutant variants of FLT3 and EGFR was 15- to 35-fold lower (IC_{50} 211–489 nmol/L). Cellular activity against native EGFR and native INSR was lacking ($IC_{50} >$ 3000 nmol/L) [8].

In anaplastic large-cell lymphoma (ALCL) and NSCLC cell lines expressing *EML4–ALK* and nucleophosmin (*NPM*)–*ALK* gene fusions, brigatinib concentrations of 4–31 nmol/L and 1.5–12 nmol/L inhibited growth and ALK phosphorylation, respectively, by 50% (vs crizotinib concentrations of 62–309 nmol/L and 23–55 nmol/L, respectively) [8]. Downstream signalling inhibition by brigatinib was also seen in these cell lines [8]. Both the autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signalling proteins STAT3, AKT, ERK1/2 and S6 have been shown to be inhibited by brigatinib [9].

Brigatinib dose-dependently inhibited tumour growth in xenograft mouse models of *ALK*-positive ALCL and NSCLC [8]. In an orthotopic mouse brain tumour model of *ALK*-positive NSCLC, once-daily oral brigatinib 25 mg/kg and 50 mg/kg significantly ($p < 0.05$ and $p \leq 0.0002$) prolonged median survival compared with vehicle and once-daily oral crizotinib 100 mg/kg (potentially reflecting the enhanced CNS penetration of brigatinib over crizotinib). Therapy with once-daily brigatinib 50 mg/kg also significantly ($p = 0.005$) reduced the tumour burden in the brain compared with crizotinib 100 mg/kg [8].

A multinational, phase I/II study demonstrated the potential of brigatinib in adults with advanced malignancies, including *ALK*-positive NSCLC [10]. In the dose-escalation (phase I) part of the study, brigatinib 180 mg once daily was initially chosen as the recommended phase 2 dosage. However, subsequent to the development of early-onset [i.e. within 7 days of treatment (re-) initiation] pulmonary events (EOPEs; including cough, dyspnea, hypoxia, pneumonia and pneumonitis) during the phase I and initial expansion (phase II) parts of the study, with an increased incidence of EOPEs seen with higher starting dosages (e.g. 180 mg once daily), two additional regimens (90 mg once daily, and 180 mg once daily with a 7-day lead-in at 90 mg once daily) were explored and then recommended for the reminder of the phase II part of the study. Brigatinib demonstrated promising antitumour activity in the cohort of patients with crizotinib-treated or -naïve *ALK*-positive NSCLC participating in this part of the study, with 62% and 100% of 71 and 8 patients achieving a confirmed objective response (OR). None of the 32 patients receiving brigatinib 180 mg once daily (with lead-in) experienced an EOPE following escalation to this dosage [10]. The 90 mg once daily and 180 mg once daily (with lead-in) dosages of brigatinib were further assessed in a multinational, phase II study (ALTA) in crizotinib-treated adults with advanced *ALK*-positive NSCLC, with the 180 mg once daily (with lead-in) dosage not associated with an increased risk of additional EOPEs versus the 90 mg once daily dosage [11]. In a pooled analysis of data [12] from the phase I/II study [10], ALTA [11] and a multinational, phase III study in ALK inhibitor-naïve adults with locally advanced or metastatic *ALK*-positive NSCLC (ALTA-1L; see Sect. 4) [13, 14], 4.5% of 440 patients [treated with a starting dosage of 90 mg once daily (alone or as part of the step-up regimen to 180 mg once daily)] experienced at least a possible EOPE; grade ≥ 3 EOPEs were reported in 3% of patients. The EU SPC [15] states that increased age is independently associated with an increased rate of EOPEs.

Brigatinib was not associated with clinically relevant prolongations in the QT interval when used at sub-therapeutic (30 mg once daily) to supratherapeutic (240 mg once daily) dosages [9].

3 Pharmacokinetic Properties of Brigatinib

Food has no clinically meaningful effect on the pharmacokinetics of brigatinib [16] (see Sect. 6). Brigatinib concentrations peak a median of 1–4 h after single oral doses of 30–240 mg [9,

15]. Systemic exposure to the drug (following a single dose and at steady state) was dose proportional over a 60 mg to 240 mg dose range [15], and the mean accumulation ratio of brigatinib after multiple once-daily dosing was 1.9–2.4 [9]. Brigatinib is 91% bound to human plasma proteins, with binding independent of the concentration [9, 15]. In patients receiving brigatinib 180 mg once daily, the drug was moderately distributed to the tissues (geometric mean apparent volume of distribution at steady state of 307 L). The mean plasma elimination half-life of brigatinib is ≈ 24–25 h [9, 15].

Brigatinib is predominately metabolized by cytochrome P450 (CYP)2C8 and CYP3A4 in vitro, with *N*-demethylation and cysteine conjugation the two major metabolic pathways in healthy volunteers [9, 15]. Unchanged brigatinib accounted for the majority (92%) of circulating radioactivity, with the primary metabolite (AP26123) accounting for only 3.5%, following the administration of a single 180 mg dose of oral radiolabelled brigatinib to healthy volunteers. The major route of elimination is via the faeces, with 65% (41% as unchanged) and 25% (86% as unchanged) of a single oral 180 mg dose of radiolabelled brigatinib excreted in the faeces and urine [9, 15].

There are no clinically relevant effects on the pharmacokinetics of brigatinib based on age, race, sex, bodyweight, mild to moderate renal impairment [creatinine clearance (CL_{CR}) ≥ 30 mL/min)] or mild to moderate hepatic impairment (Child-Pugh Class A or B) [9, 15, 17]. However, systemic exposure [as assessed by the area under the concentration–time curve from 0 to infinity (AUC_{∞})] to brigatinib was 94% higher in patients with severe renal impairment (CL_{CR} < 30 mL/min) and 37% higher in patients with severe hepatic impairment (Child-Pugh Class C) compared with healthy volunteers with normal renal and hepatic function [9, 15]. Thus, dose adjustments of brigatinib are recommended in patients with severe renal impairment and those with severe hepatic impairment [9, 15].

Coadministration of brigatinib and moderate [USA] or strong [EU and USA] CYP3A inhibitors (resulting in elevated brigatinib maximum concentration and AUC_{∞} values) should be avoided; if such concomitant use is unavoidable, the brigatinib dose should be reduced [9, 15]. Patients receiving brigatinib and moderate CYP3A inhibitors in the EU should be monitored [15]. Coadministration of brigatinib with moderate or strong CYP3A inducers should also be avoided [9, 15]. Local prescribing information should be consulted for detailed information regarding these and other potential drug interactions.

4 Therapeutic Efficacy of Brigatinib

A randomized, open-label, multinational, phase III study (ALTA-1L) (Fig. 1) evaluated the first-line efficacy of oral brigatinib compared with oral crizotinib in adults with locally advanced or metastatic *ALK*-positive NSCLC not previously treated with an ALK inhibitor [13, 14]. Patients with asymptomatic, untreated CNS metastases were eligible for this study [13]. Those who had previously received > 1 systemic anticancer therapy regimen for advanced disease, or chemotherapy or radiation therapy (other than stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days prior to the first dose of the study medication [13], or who had a history of interstitial lung disease (ILD), drug-related pneumonitis or radiation pneumonitis [9, 15] were among those excluded.

Randomization to treatment arms [brigatinib (180 mg once daily after a 7-day lead-in period of 90 mg once daily) or crizotinib (250 mg twice daily)] was stratified by brain metastases (present or absent) and the completion of ≥ 1 cycle of previous chemotherapy for locally advanced or metastatic disease (yes or no) [13, 14]. Treatment continued until blinded independent review committee (BIRC)-assessed disease progression, or unacceptable toxicity. Therapy could be extended in the brigatinib group (at the investigator's discretion) following disease progression, with patients in the crizotinib group permitted to crossover to brigatinib [13, 14]. At baseline, patient demographics and clinical characteristics were well balanced between the treatment groups [13, 14]; 90 of 275 patients had brain metastases and 39 had measurable (≥ 10 mm in diameter) brain metastases (as assessed by the BIRC) [13].

The primary efficacy endpoint was BIRC-assessed progression-free survival (PFS) [13, 14]. An initial prespecified interim analysis was conducted after 99 PFS events (36 of 137 brigatinib recipients and 63 of 138 crizotinib recipients) [corresponding to 50% of the prespecified total of 198 events] had occurred (data cut-off date of 19 February 2018; median follow-up duration of 11.0 and 9.3 months) [13]. At this timepoint, 69% of brigatinib recipients and 43% of crizotinib recipients continued to receive the study medication (median treatment duration of 9.2 and 7.4 months), with 35 patients who had discontinued crizotinib treatment because of disease progression crossing over to brigatinib therapy [13]. A second prespecified interim analysis was conducted after 150 PFS events (63 and 87 in the brigatinib and crizotinib groups) [corresponding to 76% of the prespecified total] had occurred (data cut-off date of 28 June 2019; median follow-up duration of 24.9 and 15.2 months) [14]. At this timepoint, 55% and 17% of brigatinib and crizotinib recipients continued to receive the study medication (median treatment duration of 24.3 and 8.4 months) [14]. Analyses were conducted in the intent-to-treat population [13, 14].

4.1 Progression-Free Survival

Brigatinib significantly prolonged median BIRC-assessed PFS, corresponding to a 51% reduction in the risk of disease progression or death relative to crizotinib, at the time

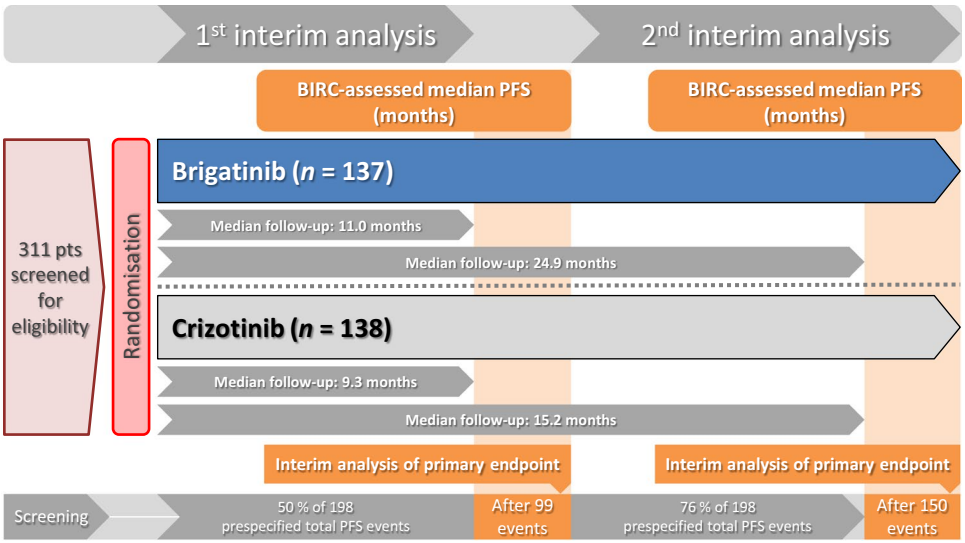

Fig. 1 Design of the ALTA-1L study in adults with locally advanced or metastatic *ALK*-positive NSCLC not previously treated with an ALK inhibitor [13, 14]. Primary endpoint results are reported in the animated figure (available online). Patients received brigatinib (180 mg once daily following a 7-day lead-in period of 90 mg once daily) or crizotinib (250 mg twice daily). *ALK* anaplastic lymphoma kinase, *BIRC* blinded independent review committee, *NR* not reached, *PFS* progression-free survival, *pts* patients

of both the first and second prespecified interim analyses (Table 1). Investigator assessments of PFS corroborated these findings, with significant 55% and 57% reductions in the risk of disease progression or death in the brigatinib group relative to the crizotinib group at the time of the first [HR 0.45 (95% CI 0.30–0.68)] [13] and second [HR 0.43 (95% CI 0.31–0.61)] [14] interim analyses. Estimated BIRC-assessed PFS rates in brigatinib versus crizotinib recipients were 67% versus 43% at 12 months and 48% versus 26% at 24 months, with similar rates seen following investigator assessment (69% vs 40% and 56% vs 24%) [13, 14]. HRs for PFS favoured brigatinib over crizotinib in all prespecified subgroups (based on stratification factors and other baseline characteristics), including the presence or absence of brain metastases at baseline, at the time of the first [13] and second [14] interim analyses. Preliminary data suggest that the improvement in PFS seen with brigatinib versus crizotinib at the time of the first [18] and second [19] interim analyses is similar in Asian and non-Asian patients with ALK inhibitor-naïve, *ALK*-positive NSCLC. Among the currently identified *EML4–AKL* gene fusion variants, variant 3, along with the *TP53* mutation, is considered a poor prognostic biomarker in *ALK*-positive NSCLC [20]. In an exploratory analysis, brigatinib demonstrated a PFS benefit over crizotinib regardless of the *EML4-ALK* fusion variant and *TP53* mutation status. In patients with detectable *EML4-ALK* fusion variant 3, median PFS was 16 months in brigatinib recipients ($n = 25$) and 7 months in crizotinib recipients ($n = 21$) [HR 0.273 (95% CI 0.125–0.597)] [20]. In a Cox regression analysis, brigatinib exposure is not a predictor of BIRC-assessed PFS [14] (Sect. 7).

Brigatinib significantly prolonged median BIRC-assessed intracranial PFS relative to crizotinib in patients with baseline brain metastases [24.0 vs 5.6 months; HR 0.31 (95% CI 0.17–0.56); $p < 0.0001$] ($n = 47$ and 49), but not in those without baseline brain metastases (32.3 months vs not reached) [$n = 90$ and 89] at the time of the second interim analysis [14]. Estimated BIRC-assessed intracranial PFS rates at 24 months were 48% and 15% in brigatinib versus crizotinib recipients with baseline brain metastases and 74% and 67% in those without baseline brain metastases [14].

Among the 61 crizotinib recipients who crossed over to brigatinib (65% of whom did so following BIRC-assessed disease progression), median BIRC-assessed PFS was 15.6 months at the time of the second interim analysis (median follow-up duration of 14.4 months) [14].

4.2 Other Endpoints

The odds of achieving a BIRC-assessed confirmed (i.e. the response was confirmed ≥ 4 weeks after the initial response) OR was only significantly higher with brigatinib versus crizotinib at the time of the second interim analysis (Table 1). BIRC-assessed confirmed complete and partial responses were achieved by 4% and 67% of brigatinib recipients (vs 5% and 55% of crizotinib recipients) at the time of the first interim analysis [13] and by 15% and 59% (vs 9% and 53%) of patients at the time of the second interim analysis [14]. In patients with a BIRC-assessed confirmed OR, the median duration of response had not yet been reached at either timepoint with brigatinib, and was 11.1 and 13.8 months at the respective timepoints with crizotinib [13, 14]. Estimated BIRC-assessed confirmed OR rates in brigatinib versus crizotinib recipients were 75% versus 41% at 12 months [13] and 51% versus 30% at 24 months [14]. At the time of the second interim analysis (median follow-up duration of 14.4 months), the BIRC-assessed confirmed OR rate was

Table 1 First-line efficacy of brigatinib in adults with *ALK*-positive NSCLC not previously treated with an ALK inhibitor

BIRC-assessed endpoint	Brigatinib	Crizotinib	Odds ratio (95% CI)
Median PFS[a] (months)	($n = 137$)	($n = 138$)	
First interim analysis	NR	9.8	Hazard ratio 0.49 (0.33–0.74)***
Second interim analysis	24.0	11.0	Hazard ratio 0.49 (0.35–0.68)***
Confirmed[b] objective response rate (% of pts)	($n = 137$)	($n = 138$)	
First interim analysis	71	60	1.59 (0.96–2.62)
Second interim analysis	74	62	1.73 (1.04–2.88)*
Confirmed[b] intracranial objective response rate (% of pts)	($n = 18/18$[c])	($n = 21/23$[c])	
First interim analysis	78	29	10.42 (1.90–57.05)**
Second interim analysis	78	26	11.67 (2.15 to 63.27) **

Results of the first [13] and second [14] prespecified interim analyses from a multinational, phase III study (ALTA-1L). Median follow-up duration in the brigatinib and crizotinib groups, respectively, of 11.0 and 9.3 months (first interim analysis) and 24.9 and 15.2 months (second interim analysis). Additional information has been obtained from the EMA assessment report [21]

ALK anaplastic lymphoma kinase, *BIRC* blinded independent review committee, *NSCLC* non-small-cell lung cancer, *NR* not reached, *PFS* progression-free survival

*$p < 0.05$, **$p < 0.005$, ***$p < 0.001$ vs crizotinib

[a]Primary endpoint

[b]Responses were confirmed ≥ 4 weeks after the initial response

[c]Patients with measurable brain metastases at baseline, as assessed by BIRC; in the first and second interim analyses, respectively, $n = 18$ and 18 in the brigatinib group and 21 and 23 in the crizotinib group

54% among the 61 crizotinib recipients who had crossed over to brigatinib [14].

In patients with measurable baseline brain metastases, the odds of achieving a BIRC-assessed confirmed intracranial OR were at least 10-fold higher with brigatinib than crizotinib at the time of both the first and second interim analyses (Table 1). BIRC-assessed confirmed intracranial complete and partial responses were achieved by 11% and 67% of brigatinib recipients (vs 0% and 29% of crizotinib recipients) at the time of the first interim analysis [13] and by 28% and 50% (vs 0% and 26%) of patients at the time of the second interim analysis [14]. At the time of the second interim analysis, the median duration of confirmed intracranial OR had not yet been reached with brigatinib and was 9.2 months with crizotinib; the probability of maintaining the BIRC-assessed confirmed intracranial OR rate at 24 months was 64% and undeterminable (owing to an insufficient number of patients) [14]. Preliminary data from an exploratory analysis showed a benefit with brigatinib over crizotinib in terms of OR regardless of the *EML4-ALK* fusion variant and *TP53* mutation status [20].

In patients with any baseline brain metastases, the odds of achieving a BIRC-assessed confirmed intracranial OR were over 11-fold higher with brigatinib than crizotinib at the time of both the first [67% vs 17%; odds ratio (OR) 13.00 (95% CI 4.38–38.61); $p < 0.0001$] ($n = 43$ and 47) [13, 21] and second [66% vs 16%; OR 11.75 (95% CI 4.19–32.91); $p < 0.0001$] ($n = 47$ and 49) [14] interim analyses. At the time of the second interim analysis, the median duration of confirmed intracranial OR was 24.0 months with brigatinib and 9.2 months with crizotinib; the probability of maintaining the BIRC-assessed confirmed intracranial OR rate at 24 months was 55% and undeterminable (owing to an insufficient number of patients) [14].

Median overall survival (OS) had not yet been reached in either treatment group at the time of the first [HR 0.98 (95% CI 0.50–1.93)] or second [HR 0.92 [95% CI 0.57–1.47)] interim analysis [13–15]. Estimated OS rates in brigatinib versus crizotinib recipients were 85% and 86% at 12 months and 76% and 74% at 24 months [13–15]. At the time of the second interim analysis, a sensitivity analysis determined that the HR for OS for brigatinib versus crizotinib was 0.70 (95% CI 0.39–1.26), suggesting that the ability to detect an improvement in OS was affected by the crossover [14].

Brigatinib improved health-related quality of life (HR-QOL) [14, 22]. At the time of the first interim analysis, brigatinib was associated with a significant ($p < 0.05$) estimated mean difference (of 4.1) in the change from baseline in the global health status (GHS)/QOL score [as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire–C30 (version 3.0)] versus crizotinib ($n = 131$ in each treatment group) [22]. Improvements were seen as early as the second cycle, with clinically meaningful improvements (i.e. a ≥ 10-point increase) seen in cycles 5−8, 10−13, 17 and 19 with brigatinib and in cycle 6 with crizotinib. The duration of improvement in the GHS/

QOL score was also significantly ($p < 0.001$) prolonged with brigatinib versus crizotinib at this timepoint [22]. At the time of the second interim analysis, brigatinib had delayed the median time to worsening in the GHS/QOL score [26.7 vs 8.3 months; HR 0.70 (95% CI 0.49–1.00); $p = 0.049$] and, in patients with an improved GHS/QOL score, significantly prolonged the median duration of improvement in GHS/QOL [not reached vs 12.0 months; HR 0.27 (95% CI 0.14–0.49); $p < 0.0001$] compared with crizotinib [14].

5 Tolerability of Brigatinib

Oral brigatinib had a manageable tolerability profile, with no new safety concerns identified, in adults with locally advanced or metastatic *ALK*-positive NSCLC not previously treated with an ALK inhibitor participating in ALTA-1L [13, 14]. Its adverse event profile appears to be consistent between Asian and non-Asian patients [18, 19].

In the brigatinib ($n = 136$) and crizotinib ($n = 137$) groups, 99% and 100% of patients experienced treatment-emergent adverse events (TEAEs) [median duration of treatment of 24.3 and 8.4 months; data cut-off date of 28 June 2019] [14]. Grade ≥ 3 TEAEs occurred in 73% of brigatinib recipients and 61% of crizotinib recipients, with the most common (occurring in > 5% of patients in either treatment group and with a numerically higher incidence in the brigatinib group than the crizotinib group) being increased blood creatine phosphokinase (CPK) levels (24% vs 1%), increased lipase levels (14% vs 7%), hypertension (12% vs 3%) and increased amylase levels (6% vs 1%). Symptoms (e.g. musculoskeletal pain, myalgia) possibly related to the increase in blood CPK levels did not appear to be related to the TEAE grade assigned to these increases. No grade ≥ 3 myalgia or musculoskeletal pain, and no clinical cases of pancreatitis or rhabdomyolysis were reported in either treatment group. Grade 1 or 2 myalgia was reported in 10% and 7% of patients receiving brigatinib or crizotinib, and grade 1 or 2 musculoskeletal pain in 10% and 8% of patients [14].

Severe, life-threatening and fatal pulmonary TEAEs, including those with features consistent with ILD/pneumonitis, have been reported with brigatinib therapy [9, 15]. At the data cut-off date of 28 June 2019 in ALTA-1L, ILD/pneumonitis (all grades) occurred in 5% of brigatinib recipients and 2% of crizotinib recipients; early onset (days 3 to 8 of treatment initiation) ILD/pneumonitis occurred in 3% of patients receiving brigatinib, 2% of 61 patients who had crossed over from crizotinib to brigatinib therapy, and 0% of patients receiving crizotinib [14]. Grade 3 or 4 ILD/pneumonitis was reported in 3% and 1% of patients in the brigatinib and crizotinib groups [14]. Of note, patients with a history of ILD, drug-related pneumonitis or radiation pneumonitis were among those excluded from ALTA-1L [9, 15].

The protocol-specified (see Sect. 4) dose escalation of brigatinib (from 90 to 180 mg) occurred in 94% of patients, although 40% of these subsequently had their dose reduced because of TEAEs [14]. Overall, TEAEs resulting in dose reductions occurred in 38% of brigatinib recipients (vs 25% of crizotinib recipients), most commonly because of changes in laboratory values. In the brigatinib group, the most frequently reported TEAEs resulting in dose reduction were increased blood CPK levels (15% of patients), increased lipase levels (7%), increased amylase levels (4%), hypertension (2%) and increased aspartate aminotransferase levels (2%) [14]. The incidence of dose reductions at this timepoint was numerically higher than that seen after a median treatment duration of 9.2 months (brigatinib) and 7.4 months (crizotinib) [at which timepoint 29% and 21% of patients had experienced TEAEs requiring dose reductions [13]], which for some TEAEs is reflective of the increased treatment duration [14].

At the data cut-off date of 28 June 2019, serious TEAEs occurred in 33% of brigatinib recipients (data from the crizotinib group not reported), with pneumonia (4.4% of patients) and ILD/pneumonitis (3.7%) being the most common serious TEAEs in this patient group [9]. Treatment discontinuations because of TEAEs (all grades) occurred in 13% of patients in the brigatinib group (vs 9% of those in the crizotinib group) [14], with ILD/pneumonitis (3.7%) and pneumonia (2.2%) being the most common TEAEs leading to the discontinuation of brigatinib [9]. TEAEs resulting in death within 30 days of the last dose of study medication occurred in 7% and 8% of patients in the brigatinib and crizotinib groups; none of these TEAEs were considered to be related to the study medication [14].

6 Dosage and Administration of Brigatinib

In the EU [15], oral brigatinib is approved as monotherapy in adults with advanced *ALK*-positive NSCLC not previously treated with an ALK inhibitor, as well as monotherapy in adults with advanced *ALK*-positive NSCLC previously treated with crizotinib. In the USA [9], it is approved for the treatment of adults with metastatic *ALK*-positive NSCLC, as detected by a US FDA-approved test.

The recommended dosage of brigatinib for first-line therapy is 90 mg once daily for the first 7 days, then 180 mg once daily until disease progression or unacceptable toxicity [9, 15]. The tablets should be swallowed whole and may be administered with or without food, although grapefruit or grapefruit juice should be avoided [9, 15]. Local prescribing information should be consulted for detailed information regarding contraindications, missed doses, events for which dosage modifications and/or interruptions are recommended, warnings and precautions, potential drug interactions, and use in special patient populations.

7 Place of Brigatinib in the Management of ALK-Inhibitor Naïve Advanced *ALK*-Positive NSCLC

In patients with NSCLC, the presence of an *ALK* gene fusion is predictive of a therapeutic benefit from ALK inhibitor therapy [3]. Subsequent to the approval of the first-in-class ALK inhibitor crizotinib [5], next-generation ALK inhibitors were developed to address the challenge of resistance to, and CNS progression with, crizotinib therapy [1]. Brigatinib is the latest ALK inhibitor to be approved for the first-line therapy of advanced *ALK*-positive NSCLC (Sect. 6). Current European Society of Medical Oncology [23] and National Comprehensive Cancer Network (NCCN) [3] guidelines recommend [as grade A (alectinib and brigatinib) or B (ceritinib and crizotinib) [23]; as category 1 [3]] the use of alectinib, brigatinib, ceritinib and crizotinib as first-line therapy for patients with advanced *ALK*-positive NSCLC. Alectinib is recommended by both guidelines as the preferred first-line therapy option [3, 23]; brigatinib and ceritinib are considered 'other recommended' options and crizotinib 'useful in certain circumstances' by the NCCN [3]. Most recently, the UK National Institute for Health and Care Excellence recommended brigatinib as an option for treating adults with advanced ALK-positive NSCLC not previously treated with an ALK inhibitor [24].

In vitro, brigatinib exhibited potent and selective inhibitory activity against the tyrosine kinase receptors ALK and ROS1, with its activity against native ALK in *ALK*-positive cell lines ≈ 12-fold greater than that of crizotinib (Sect. 2). In vivo it has demonstrated inhibitory effects in several xenograft models, including an orthotopic mouse brain tumour model of *ALK*-positive NSCLC in which it significantly prolonged medial survival and reduced the tumour burden in the brain compared with crizotinib (Sect. 2).

In the multinational, phase III ALTA-1L study, brigatinib significantly prolonged median BIRC-assessed PFS at the time of the first and second interim analyses (Sect. 4.1) and significantly improved the BIRC-assessed confirmed OR rate at the time of the second interim analysis (Sect. 4.2) relative to crizotinib. Of note, no statistically significant relationship between brigatinib exposure and the risk of disease progression or death has been identified (Sect. 3), suggesting that the efficacy benefit of brigatinib is consistent across the range of systemic exposures achieved with the brigatinib regimen [14]. The beneficial effects of brigatinib over crizotinib treatment were also seen in various CNS-related subgroups (Sects. 4.1 and 4.2), including in patients with any or measurable baseline brain metastases (Sect. 4.2). At both timepoints, median OS had not yet been reached in either treatment group (Sect. 4.2). While mature OS data are awaited with interest, ascertaining the effect of brigatinib on OS was potentially confounded by crizotinib recipients crossing over to brigatinib and by the subsequent use of other TKI therapy following study discontinuation [13]. Brigatinib was associated with significant improvements in HR-QOL compared with crizotinib (Sect. 4.2), which may reflect differences in the efficacy of these drugs on disease-related symptoms and/or differences in treatment-related adverse events [14].

In ALTA-1L, the tolerability profile of brigatinib was manageable and no new safety concerns were identified (Sect. 5). The most common grade ≥ 3 TEAEs reported with brigatinib were increased blood CPK levels, increased lipase levels, hypertension and increased amylase levels; no grade ≥ 3 myalgia or musculoskeletal pain and no clinical cases of pancreatitis or rhabdomyolysis were seen in either treatment group (Sect. 5). Severe, life-threatening and fatal pulmonary TEAEs, including those with features consistent with ILD/pneumonitis, have been reported with brigatinib therapy [9, 15], with grade ≥ 3 ILD/pneumonitis reported in 3% of brigatinib recipients (vs 1% of crizotinib recipients) (Sect. 5). As patients with a history of ILD, drug-related pneumonitis or radiation pneumonitis were among those excluded from ALTA-1L [9, 15], real-world data on the incidence of EOPEs would be of interest, including in populations (e.g. patients with poor pulmonary function or those with organ dysfunction) not well represented in clinical studies [12].

ALTA-1L (for which final analysis data are anticipated) is the only head-to-head comparison between brigatinib and another ALK inhibitor. Like brigatinib, the next-generation ALK inhibitor alectinib [an ALK and RET (Rearranged during Transfection) TKI] has demonstrated efficacy versus crizotinib in patients with metastatic *ALK*-positive NSCLC not previously treated with an ALK inhibitor, including those with CNS metastases [25, 26]. The ALK TKI ceritinib was compared with chemotherapy in this patient population, showing overall and CNS efficacy [27, 28]. The three agents differ in terms of their administration schedule, with brigatinib and ceritinib both administered once daily, although brigatinib requires a 7-day lead-in period (see Sect. 6), and alectinib twice daily [9, 15, 25–28]. Brigatinib may be taken with or without food (see Sect. 6). The tolerability profiles of these agents all appear manageable. As with other TKIs (including brigatinib; see Sect. 5), alectinib and ceritinib are associated with ILD/pneumonitis. Bradycardia is also listed as a warning and precaution for all three agents, with elevated CPK and pancreatic enzyme levels seen with brigatinib, severe myalgia and elevated CPK levels with alectinib, and pancreatitis with ceritinib. Among other warnings and precautions, hepatotoxicity is listed for alectinib and ceritinib, but not brigatinib (USA only [9]), gastrointestinal adverse events and QT interval prolongation for ceritinib, but not brigatinib or alectinib, and hypertension for

brigatinib, but not alectinib or ceritinib. In terms of drug interactions, changes in the plasma concentrations of both brigatinib and ceritinib, but not alectinib, are seen with the coadministration of moderate and/or strong CYP3A inducers and inhibitors [9, 15, 25–28]. Studies comparing brigatinib with next-generation agents (particularly alectinib) would be of interest, especially with regard to comparing the safety profiles of these agents.

In conclusion, in the pivotal phase III study, brigatinib was effective and associated with a manageable tolerability profile in adults with locally advanced or metastatic *ALK*-positive NSCLC. It significantly prolonged PFS and improved confirmed OR rates, including the intracranial OR rate, and HR-QOL relative to crizotinib. Although final analysis data are awaited with interest, brigatinib therapy extends the first-line treatment options available for standard of care in this patient population, including patients with CNS metastases.

Data Selection Brigatinib: 208 records identified	
Duplicates removed	43
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	132
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	6
Cited efficacy/tolerability articles	5
Cited articles not efficacy/tolerability	22
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were brigatinib, ALUNBRIG, ALK-rearranged NSCLC. Records were limited to those in English language. Searches last updated 16 November 2020	

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