AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 62, Issue 02, February, 2022

PROCESSING LOCALIZATION and QUESTIONNARE EORTC QLQ-C30 RESULTS in PATIENTS with BREAST CANCER and METASTASIS

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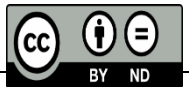
Keywords:
Utility; mapping; non-small cell lung cancer; HRQoL; EQ-5D; QLQ-C30

ABSTRACT

Health utilities summarize a patient's overall health status. This study estimated utilities based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30), a widely used measure of health-related quality-of-life (HRQoL) in oncology, using published mapping algorithms. Data were from the Anaplastic Lymphoma Kinase (ALK) in Lung Cancer Trial of brigatinib (ALTA; NCT02094573), an open-label, international, phase 2 study. ALTA evaluated the efficacy and safety of two randomized dosing regimens of brigatinib in patients with locally advanced or metastatic ALKþ non-small cell lung cancer (NSCLC) that had progressed on prior therapy with crizotinib. QLQ-C30 scores were mapped to European Quality-of-Life-5 Dimensions (EQ-5D) utility scores using two published algorithms (Khan et al. for EQ-5D-5L; Longworth et al. for EQ-5D-3L). The impact of brigatinib treatment on health utilities over time was assessed. The analysis included 208 subjects. Mean baseline utility scores for both algorithms ranged between 0.60 0.71 and increased to 0.78 by cycle 5. Utility improvements were sustained during most of the treatment, before disease progression. Minor variations were observed between utility scores; Khan et al. estimates were approximately 0.01 or 0.02 points lower than Longworth et al. estimates. Algorithms considered were limited to those available in the published literature at the time of the study. This utility analysis was exploratory, and the ALTA trial did not include an internal control group (i.e. standard of care) and was not powered to detect differences in QoL/utility outcomes between treatment arms. Converting QLQ-C30 scores into utilities in trials using established mapping algorithms can improve evaluation of medicines from the patient perspective. Both algorithms suggested that brigatinib improved health utility in crizotinib-refractory ALK þ NSCLC patients, and improvements were maintained during most of the treatment.



1. Introduction

Activating gene rearrangements in anaplastic lymphoma kinase (ALK) have been identified as driver mutations in 3–5% of patients with non-small cell lung cancer (NSCLC) [1], [2]. Tyrosine kinases are key to the regulation of cell differentiation and growth [3]. Crizotinib is an oral ALK inhibitor approved in several countries that is more effective than chemotherapy in patients with metastatic ALK-positive (ALKþ) NSCLC. However, most crizotinib-treated patients will eventually experience disease progression, often within the first year of treatment, leading to tumor relapse that commonly manifests as brain metastases [4]. Next-generation ALK inhibitors such as ceritinib, alectinib, and brigatinib, and sequential therapy with ALK inhibitors or combination therapies targeting ALK plus an alternative signaling pathway, such as epidermal growth factor receptor (EGFR) or heat shock protein 90 (HSP90), have been investigated to treat crizotinib-relapsed patients [5]. Brigatinib is a novel, synthetic, orally active tyrosine kinase inhibitor (TKI) targeting ALK that was approved by the US Food and Drug Administration (FDA) in 2017 and by the European Medicines Agency (EMA) in 2018. Brigatinib has exhibited substantial anti-cancer activity in patients with crizotinib-resistant ALK þ NSCLC. The ALTA study (NCT02094573), an open-label, phase 2, multicenter, international clinical trial, studied the efficacy and safety of two randomized dosing regimens of brigatinib (Arm A: 90 mg once daily [QD] and Arm B: 180 mg QD with a 7-day lead-in of 90-mg QD) in patients with locally advanced or metastatic ALK þ NSCLC that has progressed on therapy with crizotinib [6]. Initial reports from the ALTA study showed that patients in Arm B had a higher investigator-assessed confirmed objective response rate (ORR) than Arm A (54% vs 45%) and Arm A had a longer median duration of response than Arm B (13.8 months vs 11.1 months) with manageable toxicity [6]. This study supported the 180 mg regimen (with lead-in at 90 mg) to be the recommended dose for approval. After this initial reporting, the study remained open to collect longer-term follow-up. With longer follow-up, investigator-assessed confirmed ORR was 46% (97.5% confidence interval [CI] ¼ 35–57%), with a median (range) follow-up time of 19.6 months (0.1–35.2) in Arm A, and 56% (45–67%), with a median follow-up time of 24.3 months (0.1–39.2) in Arm B [7]. The median independent review committee (IRC)-assessed progression-free survival (PFS) was 9.2 months (95% CI ¼ 7.4–12.8) and 16.7 months (11.6–21.4) in Arms A and B, respectively [7].

2. Methods

2.1 Study design

The ALK in Lung Cancer Trial of brigatinib (ALTA trial; NCT02094573) was an open-label, phase 2, multicenter, international study. The trial evaluated the efficacy and safety of two randomized dosing regimens of brigatinib (Arm A: 90 mg QD and Arm B: 180 mg QD with a 7-day lead-in at 90 mg QD) in patients with locally advanced or metastatic ALK þ NSCLC whose disease had progressed on prior therapy with crizotinib. Patients in the ALTA trial were enrolled from 71 sites, including 15 in the US, one in Canada, 38 in Europe, six in Australia, and 11 in Asia. Eligible patients (18 years of age) had locally advanced or metastatic ALK þ NSCLC, investigator-determined disease progression on crizotinib, 1 measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)29, adequate organ and hematologic function, and Eastern Cooperative Oncology Group (ECOG) performance status 230. The detailed exclusion criteria have been published previously [6]. The protocol lists complete inclusion/exclusion criteria and was approved by the local institutional review board (IRB) or ethics committee at each site. This study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonization guidelines for good clinical practice. All patients provided written

ISSN: 0005-2523
Volume 62, Issue 02, February, 2022

informed consent. The primary endpoint was confirmed ORR, as assessed by the investigator per RECIST v1.1.

3. Results

From June 4, 2014 to September 21, 2015, 222 patients were enrolled and randomly assigned to brigatinib in treatment Arm A (*n* ¼ 112) or Arm B (*n* ¼ 110) of the ALTA trial (NCT02094573). The analytical sample in the ITT-PRO population with baseline PRO data and at least one follow-up visit with PRO data included 208 subjects across arm A (n ¼ 105) and Arm B (n ¼ 103). Patient demographic and baseline clinical characteristics of the ITT-PRO sample are shown in Table 2. With the exception of age (Arm A was statistically significantly younger than Arm B), baseline demographic characteristics were balanced between the two dosing arms. It should be noted that the ALK þ NSCLC clinical trial sample tended to be younger and was comprised of more women and more non-smokers relative to the characteristics in the general population of NSCLC patients.

4. Discussion

The ALTA trial has previously demonstrated the treatment Table 3. benefits of brigatinib for patients with crizotinib-refractory ALK þ NSCLC on traditional cancer outcomes, including ORR and median survival [7]. The clinical data from this more recent data extraction (September 29, 2017) confirmed the durable benefit of brigatinib, in particular the increased benefit of Arm B over Arm A compared with an earlier data cut [6]. Findings based on the EORTC QLQ-C30 functional domains46 found that mean GHS/QoL scale scores were statistically significantly improved over time for patients in both treatment arms. In addition, few patients experienced a meaningful worsening of their GHS/QoL scores. In the context of a severe disease such as NSCLC, the fact that treatment did not result in significant reduction of HRQoL is important, given the potential impact of treatment-related toxicities46. These results are consistent with EORTC QLQ-C30 results based on an earlier data cut from the ALTA study that found HRQoL remained at or above baseline levels and did not differ between arms [6]. The current analysis generated utility scores from the EORTC QLQ-C30 using available algorithms to enable evaluation of patients' health utility. This is important because there is literature suggesting that the generic EQ-5D can have variable levels of sensitivity to detecting change in some health conditions47, and it would be practical to have a suitable algorithm identified to use based on a condition specific scale such as the EORTC QLQ-C30. The current study used two published algorithms (Khan et al. 45 and Longworth et al. 43) in this analysis. The key findings from this exploratory analysis of openlabel phase 2 study data were two-fold. First, the availability of appropriate utility mapping algorithms provided an opportunity to estimate utilities in a study where no health utility measure was administered. The EORTC QLQ-C30 is very widely used in oncology and is a condition-specific PRO that is known to be responsive to detecting changes due to treatment48,49, and may be more sensitive to the cancer patient's experience than a generic preference measure. Because of its widespread use, it could be very useful to have reliable methods for generating utilities from the EORTC QLQ-C30. Application of these mapping methods made it possible to evaluate generated utilities based on two separate algorithms. Consistent results were obtained for utilities derived in this study using the Khan et al. 45 algorithm using the expanded EQ-5D-5L system and Longworth et al. 43 based on the standard EQ-5D-3L measure. Very small numeric differences were observed between the estimates, with Khan et al. 45 algorithm-based estimates approximately 0.01 or 0.02 points lower than those generated based on the Longworth et al. 43 method. This minor variation may potentially be related to differences in the utility measure, patient sample, and/or modeling methods used. The Khan et al. 45 estimates were based on the EQ-5D-5L version, with expanded response levels, that has been noted to have less tendency toward over-prediction of utilities, used only NSCLC population of patients rather than a combination of cancer types, and a BB regression approach to develop the model that may provide better estimation over traditional OLS

methods. More accurate prediction for the EQ-5D-5L using the BB model is also corroborated by a recent multi-country survey study comparing alternative statistical approaches to estimating utilities in a sample of 772 patients diagnosed with cancer.

5. Conclusions

Brigatinib at 90 mg to 180 mg standard dose demonstrated sustained clinical benefit after long-term follow-up. The overall pattern of post-baseline increases in utility scores in the ALTA study were found to be similar and consistent using both the Khan et al. 45 and Longworth et al. 43 algorithms to derive utility scores based on the EORTC QLQ-C30. These utilities reflected that mean utility scores in both treatment arms improved over time, and these findings were consistent with analyses conducted using the EORTC QLQ-C3046, and other clinical endpoints such as ORR and PFS that were used to support safety and efficacy for approval of brigatinib [6]. Converting QLQ-C30 scores into utilities in trials using established algorithms can improve the evaluation of medicines by incorporating information from the patient perspective. Both algorithms suggested that brigatinib improved health utility in crizotinib-refractory ALK þ NSCLC patients, and that these improvements were maintained during most of the treatment. Future research may benefit from examination of utilities relative to standard of care for other investigational agents for NSCLC and algorithms for utility derivation that were not available at the time of this analysis.

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ISSN: 0005-2523
Volume 62, Issue 02, February, 2022

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