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Osimertinib compared docetaxel-bevacizumab as third-line treatment in EGFR T790M mutated non-small-cell lung cancer

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ABSTRACT

Objective: To compare the efficacy and toxicity of osimertinib versus docetaxel-bevacizumab as third-line treatment in EGFR T790M mutated NSCLC.

Methods: In this phase 3, open-label, three-center study, we randomly assigned (1:1) previously treated with TKI-chemotherapy or chemotherapy-TKI recurrent or metastatic advanced non-squamous lung cancer patients into two groups. These patients had acquired EGFR T790M resistance mutation confirmed by tumor tissues or serum. One group received oral osimertinib (80 mg/day) and the other group received intravenous infusion docetaxel (75 mg/m^2) and bevacizumab (7.5 mg/kg) every 21 days until disease progression, unacceptable toxic effects or patient death. The primary endpoint of this study was progression-free survival (PFS) and the secondary endpoints were response rates, toxicities and overall survival (OS). This trial was registered with ClinicalTrials.gov, number NCT02959749.

Results: A total of 147 patients were treated. Among them, 74 were enrolled in the osimertinib group and 73 were in the docetaxel-bevacizumab group. The median progression-free survival was 10.20 months in the osimertinib group versus 2.95 months in the docetaxel-bevacizumab group (hazard ratio 0.23; 95% confidence interval [CI], 0.12–0.38; P < 0.001). The overall response rate in the osimertinib group was significantly better than in the docetaxel-bevacizumab group (61.6%; 95% CI, 55.5–67.7 versus 8.3%; 95% CI, 1.3–15.3; p < 0.001). Because all the progressed patients in the docetaxel-bevacizumab group crossed over to the osimertinib group, there was no significant difference in the median OS between two groups at the time of last follow-up (hazard ratio 0.79; 95% CI, 0.38–1.61; P = .551). The main grade 3 or 4 toxic effects were diarrhea (2.7%) and interstitial lung disease (1.4%) in the osimertinib group and alopecia (15.3%), anorexia (12.5%), neutropenia (9.7%) and nausea (8.3%) in the docetaxel-bevacizumab group.

Conclusions: Osimertinib had higher response rate, longer PFS and milder side effects than docetaxel-bevacizumab in third-line therapy in patients with EGFR T790 M positive advanced NSCLC.

1. Introduction

Acquired epidermal growth factor receptor (EGFR) T790M mutation is the most common genetic change after resistant to first-generation EGFR tyrosine kinase inhibitor (EGFR-TKI) in non-small-cell lung cancer. After 10–14 months with the treatment of first-generation EGFR-TKI, half of the patients will get disease progression [1,2]. The substitution of threonine with methionine at amino acid position 790 (T790M), as the second mutation in EGFR, is the most common resistance mechanism and is detected in tumor cells from more than 50–60% of patients after disease progression. This mutation enhances ATP affinity, reduces the ability of ATP-competitive reversible EGFR-TKI binding to EGFR tyrosine kinase domain, resulting in cancer cells resistant to gefitinib and erlotinib [3].

Osimertinib (Tagrisso, AZD9291, AstraZeneca) is an oral, potent, irreversible EGFR-TKI, which inhibits kinase activity of EGFR sensitive mutation and T790M resistance mutation [4,5]. *In vitro* and *in vivo* study, osimertinib showed strong inhibition of both the EGFR sensitive mutation and EGFR T790M resistance mutation. However, it showed less activity on wild type EGFR compared to first-generation EGFR-TKI (*e.g.*, gefitinib or erlotinib) [6]. It had a high response rate in NSCLC patients who had harbored EGFR T790M mutation [7], and was

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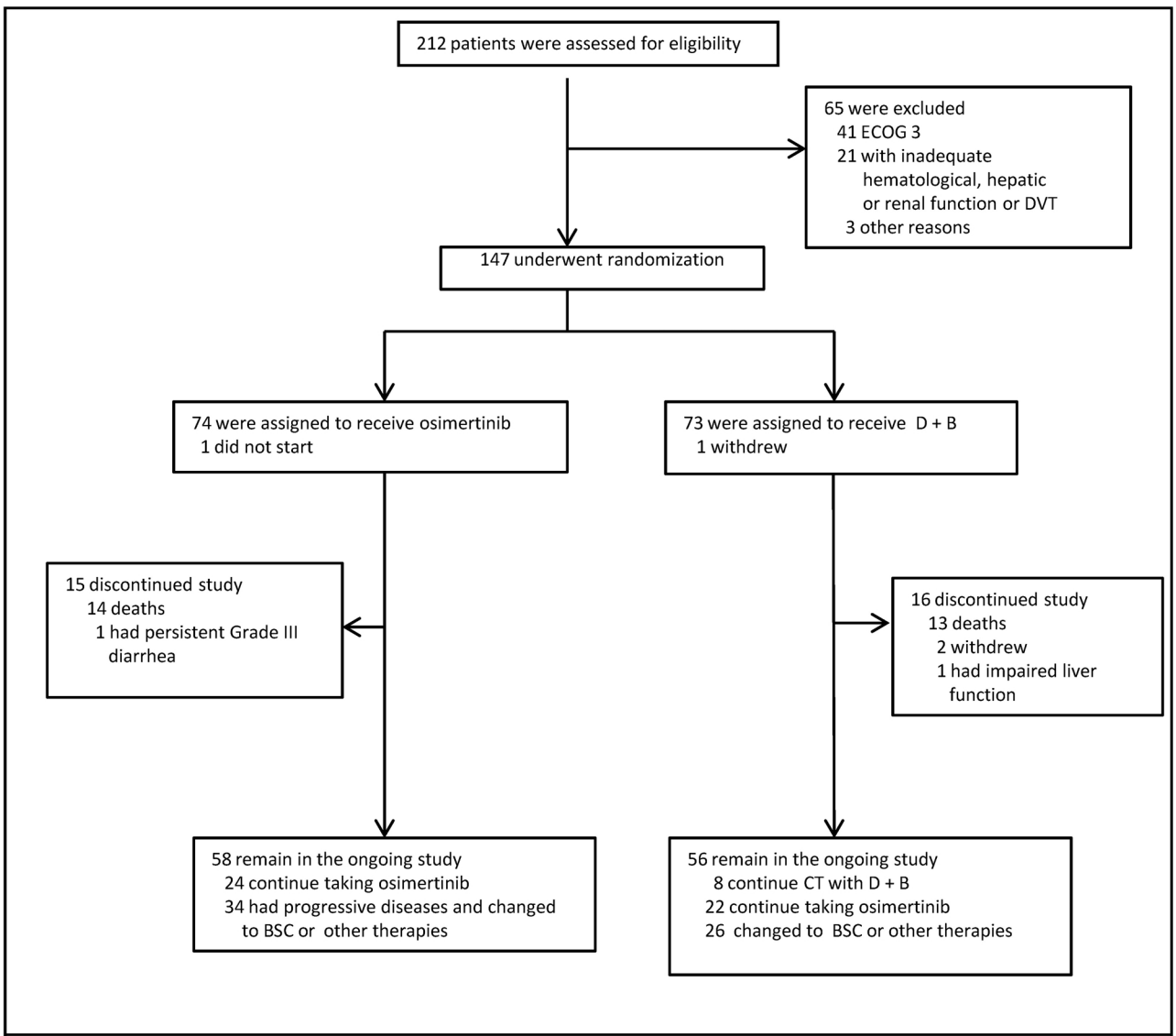

Figure 1. Screening, Group Assignment and Outcomes.
ECOG denotes Eastern Cooperative Oncology Group performance status; DVT denotes Deep Vein Thrombosis; D denotes Docetaxel; B denotes Bevacizumab; PD denotes Progression disease; CT denotes Chemotherapy; BSC denotes of Best Supportive Care.

Fig. 1. Trial profile. Data cutoff date was May 30, 2016. Overall survival data was obtained in Feb. 15, 2017.

approved for clinical use by FDA in November 2015.

For non-squamous NSCLC patients with disease progression after platinum-doublet chemotherapy, docetaxel with or without bevacizumab are suggested agents for the third-line therapy if they are not exposed before [8–10]. Docetaxel combined with bevacizumab had higher response rate than docetaxel alone and the toxicities were tolerable [11,12]. Bevacizumab (Avastin, Roche) is a vascular endothelial growth factor A (VEGFA) monoclonal antibody, inhibits tumor angiogenesis, and is widely used in colorectal cancer and lung adenocarcinoma. Bevacizumab combined with VEGFA, attenuates VEGFA dependent tumor blood vessels formation, normalizes tumor blood vessels, prompts tumor cell apoptosis and finally shrinks tumor [13,14]. Combined with platinum-doublet chemotherapy, bevacizumab could increase ORR, prolong PFS and OS in Caucasian and Asian patients with advanced stage non-squamous NSCLC [8,15,16].

For patients with disease progression after treated with first line EGFR-TKI and second-line platinum-doublet chemotherapy, or chemotherapy and then EGFR-TKI, the optimal third-line therapy is critically important for continuing patients' survival. This study compared the efficacy and toxicity of osimertinib and docetaxel-bevacizumab as the third-line therapy in patients with local advanced or metastatic non-squamous NSCLC.

2. Methods

2.1. Study design and patient selection

This was a three-center open-label randomized study. Study patients were pathologically, or, cytologically confirmed as having local advanced, or metastatic non-squamous NSCLC with acquired EGFR T790M mutation. EGFR T790M mutation was diagnosed at progression of 2nd line therapy, *e.g.*, after chemotherapy in TKI-chemotherapy