Research Article

The Clinical Lung Cancer

Erlotinib plus bevacizumab vs erlotinib monotherapy as first-line treatment for advanced EGFR mutation-positive non-squamous non-small-cell lung cancer: Survival follow-up results of the randomized JO25567 study.

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ABSTRACT

Goals: In Japanese patients with chemotherapy-naïve epidermal growth factor receptor mutation-positive (EGFR+) non-small-cell lung cancer (NSCLC), the JO25567 randomized Phase II trial showed a statistically significant benefit in progression-free survival (PFS) with erlotinib plus bevacizumab compared with erlotinib monotherapy. This After a median follow-up of 34.7 months, we offer revised PFS and final overall survival (OS) statistics. Supplies and techniques: Patients with stage IIIB/IV or postoperative recurrent non-small cell lung cancer (NSCLC) were randomized to receive either oral erlotinib 150 mg once daily (n = 77) or erlotinib plus intravenous bevacizumab 15 mg/kg every 21 days (n = 75) until unacceptable toxicity or disease progression. A Cox proportional hazards model that was not stratified was used to assess OS. Results: Bevacizumab with erlotinib was linked to a significant improvement in PFS (hazard ratio [HR] 0.52; 95% confidence interval [CI]: 0.35–0.76; log-rank twosided P = 0.0005; median 16.4 months vs. 9.8 months, respectively), which is in line with the primary study. On the other hand, there was no discernible improvement in OS (HR 0.81; 95% CI, 0.53–1.23; P = 0.3267; median 47.0 months vs. 47.4 months, each). Treatment arms' post-study therapies were comparable, and OS results were unaffected by the kind of EGFR mutation. When erlotinib with bevacizumab was used instead of erlotinib monotherapy, the 5-year OS rate was significantly higher (41% vs. 35%). New safety problems were not found in the previously published tolerable tolerability profile, according to updated safety assessments.In conclusion, Japanese patients with stage IIIB/IV or postoperative recurrent EGFR+ NSCLC did not significantly improve in OS when bevacizumab was added to first-line erlotinib. Regardless of the unique characteristics of each patient, the median OS benefit (up to 4 years) was similar for both treatment arms. We eagerly await the findings of ongoing investigations assessing the synergy of EGFR and VEGF signaling inhibitors. Trial enrollment numbers are JapicCTI-142669 and JapicCTI-111390.

Keywords : Bevacizumab ,EGFR ,Erlotinib ,NSCLC

INTRODUCTION

Activating mutations in the epidermal growth factor receptor (EGFR) gene are present in a significant number of patients with non-small-cell lung cancer (NSCLC), with exons 19 and 21 accounting for the majority of these alterations [1]. Patients with EGFR mutation-positive (EGFR+) non-small cell lung cancer (NSCLC) have shown increased progression-free survival (PFS) when using erlotinib, an EGFR tyrosine kinase inhibitor (TKI), in phase III trials compared to normal chemotherapy dosages [2]. But for patients with EGFR+ NSCLC, resistance and relapse continue to be significant issues; after receiving EGFR TKI treatment, a specific proportion of individuals will develop resistance mutations [3]. One of the main objectives of oncology research is the development of logical synergistic therapeutic combinations to prevent treatment resistance.

In Japanese patients with stage IIIB/IV or recurrent EGFR+ NSCLC, the combination of erlotinib and bevacizumab was studied as first-line therapy in the Phase II JO25567 study (JapicCTI-111390) [4]. With median PFS durations of 16.0 months and 9.7 months, respectively, (hazard ratio [HR] 0.54; 95% confidence interval [CI]: 0.36–0.79; P = 0.0015), the primary analysis of JO25567 showed a statistically significant PFS benefit with erlotinib plus bevacizumab vs erlotinib monotherapy [4]. After a median follow-up period of 20.4 months (13 and 18 events, respectively), the median overall survival (OS) had not yet been reached at the time of the

primary analysis. Following a long-term follow-up period (median duration of 34.7 months), we are reporting revised PFS and final OS results here. We also evaluate the effect of treating with both bevacizumab and erlotinib. The study's design in its entirety has already been published [4].

JO25567 was a multicenter (n = 30), open-label, randomized Phase II trial that looked at bevacizumab in addition to erlotinib as a first-line treatment.

MATERIALS AND METHODS

treatment in Japanese NSCLC patients who have EGFR+. The patients had satisfactory organ function, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and stage IIIB/IV or postoperative recurrent non-squamous EGFR+ disease (either exon 19 deletion or exon 21 L858R mutation) that was validated histopathologically and/or cytologically.

The course of treatment involved either oral erlotinib (150 mg once daily) or intravenous bevacizumab (15 mg/kg) administered once every 21 days.Patients received treatment until either unacceptable toxicity or progressive disease (PD) occurred.Good Clinical Practice principles and the Helsinki Declaration of Helsinki were followed in the conduct of the study. The institutional review boards at the institutions examined and approved the study protocol. institutions that take part. For every patient, written informed permission was acquired. Again, signed informed consent was obtained for the OS follow-up. Using data gathered before the study's conclusion, patients who were unable to give written informed consent for the OS follow-up (because they had passed away or were lost to follow-up) were included in the final analysis. The Japan Pharmaceutical Information Center has JO25567 and the OS follow-up registered under the numbers JapicCTI-111390 and JapicCTI-142669.

RESULTS

In all, 154 patients underwent randomization in the main analysis. Two patients withdrew from the erlotinib monotherapy trial, but all randomized patients (n = 77) received treatment and were eligible for analysis.

prior to starting treatment, there were 75 patients in the erlotinib plus bevacizumab group (Supplementary Fig. S1). In the erlotinib plus bevacizumab arm, three patients were lost to follow-up, compared to zero in the erlotinib arm, according to the revised PFS analysis. The final OS study revealed that the primary explanation for the corresponding numbers of 13 and 12 patients, respectively, was a change in hospital.

Baseline patient characteristics and post-study therapy were generally balanced between the treatment groups (Supplementary Table S1) and S2. Roughly 85% of patients obtained 52% received fourth- and later-line therapy, 68% received third-line therapy, and 28% received second-line therapy. 34.7 months was the median follow-up period. Fig. 1A shows the investigator-assessed PFS against erlotinib alone (HR 0.52; 95% CI: 0.35–0.76; log-rank two-sided P = 0.0005). The median duration was 16.4 months as opposed to 9.8 months. The final median OS, however, was comparable. between the therapy groups (median 47.0 months vs. 47.4 months, respectively; Fig. 1B); HR 0.81; 95% CI: 0.53–1.23; P = 0.3267). Compared to erlotinib monotherapy, the 5-year OS rate with erlotinib + bevacizumab was quantitatively higher (41% [95% CI: 0.29–0.53] vs. 35% [95% CI: 0.24–0.47]).

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Safety

The JO25567 trial's latest safety analysis (data cut-off: March 31, 2014) was previously published [5]. Adverse occurrences (AEs) were constant and generally comparable across the treatment arms. use the principal analysis [4]. With erlotinib plus bevacizumab, the most frequent any-grade adverse events (AEs) were rash (99 %), diarrhea (81 %), hypertension (79 %), and paronychia (79 %). These events also frequently occurred with erlotinib monotherapy, with the highest frequency of rash (99 %), diarrhea (79 %), hypertension (14 %), and paronychia (65 %) occurring. When erlotinib + bevacizumab was used instead of erlotinib alone, the rate of grade ≥3 hypertension was significantly greater (6% vs. 12%, respectively) [5].

When treating EGFR+ NSCLC, erlotinib plus bevacizumab is preferred than erlotinib monotherapy. Combination therapy showed a significant PFS benefit, however this did not transfer into a statistically meaningful OS benefit (47.0). P = 0.3267; HR 0.81; months vs 47.4 months erlotinib alone). This outcome could be explained by a multitude of causes. Most patients were treated with many lines of post-discontinuation medication. The excellent OS statistics in both arms and the lengthy post-progression survival (PPS) seen may have been influenced by the fact that more than 80% of patients in both arms received second-line, two-thirds received third-line, and

half received fourth- or later-line treatment.

DISCUSSION

first-line combo regimen that would free up resources for later lines of treatment for additional medications. Results from the AvaALL trial suggest that bevacizumab treatment may have some advantages for a number of lines. Thus, a plan of erlotinib with bevacizumab as first-line therapy, followed by bevacizumab-containing treatments following Parkinson's disease (PD), may more clearly show the benefit to OS than the study JO25567's final OS analysis. Additional assessment across many therapy axes to maximize the overall treatment plan is necessary.

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