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A phase II study of erlotinib in combination with bevacizumab versus chemotherapy plus bevacizumab in the first-line treatment of advanced non-squamous non-small cell lung cancer☆,☆☆

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ABSTRACT

Background: Molecularly targeted agents for non-small cell lung cancer (NSCLC) can provide similar efficacy to chemotherapy without chemotherapy-associated toxicities. Combining two agents with different modes of action could further increase the efficacy of these therapies. The TASK study evaluated the efficacy and safety of the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in combination with the anti-angiogenic agent bevacizumab as first-line therapy in unselected, advanced non-squamous NSCLC patients.

Methods: Patients were recruited from December 2007 to September 2008. Planned sample size was 200 patients, a total of 124 patients were randomized. Patients were randomized using a minimization algorithm 1:1 to receive bevacizumab (iv 15 mg/kg day 1 of each 21-day cycle) plus chemotherapy (gemcitabine/cisplatin or carboplatin/paclitaxel standard doses, 4–6 cycles) (BC arm) or bevacizumab plus erlotinib (p.o. 150 mg/day; BE arm) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). If the hazard ratio (HR) of PFS for BE relative to BC was above 1.25 at the pre-planned interim analysis in favor of BC, the study would be re-evaluated. Secondary endpoints included overall survival, response rate and safety.

Results: All randomized patients ($n = 63$ BE; $n = 61$ BC) were evaluated for the efficacy analyses. At the updated interim analysis, median PFS was 18.4 weeks (95% confidence interval [CI] 17.0–25.1) versus 25.0 weeks (95% CI 20.6–[not reached]) for BE versus BC, respectively (HR for death or disease progression, BE relative to BC, 2.05, $p = 0.0183$). The incidence of death was 19% for BE treatment compared with 11.5% for BC treatment. The HR for PFS at the updated interim analysis was above 1.25, therefore patients on the BE arm were permitted to change arms or switch to another drug and the study was terminated. Adverse events reported were as expected.

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Conclusions: The TASK study did not show a benefit in terms of PFS for the combination of erlotinib with bevacizumab in unselected first-line advanced non-squamous NSCLC compared with chemotherapy plus bevacizumab.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1], with recent statistics projecting 226,160 new cases in the US alone in 2012 [2]. Current therapeutic options for first-line non-small cell lung cancer (NSCLC) treatment are based on platinum doublet chemotherapy, which provide overall survival (OS) of ~8 months [3]. Advances in treatments include personalized NSCLC therapies that focus on molecular targets to improve outcomes and reduce cumulative toxicities seen with chemotherapies. For patients with epidermal growth factor (*EGFR*) mutations, EGFR tyrosine-kinase inhibitors (TKIs) are recommended as first-line therapy, for those with non-squamous disease without these driver mutations, agents such as pemetrexed and bevacizumab are available [4].

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF). VEGF is a key signaling molecule in developmental angiogenesis, promoting survival of endothelial cells and new vessel growth [5]. Tumor dependency on VEGF makes VEGF an attractive target for anticancer treatments. The addition of bevacizumab to chemotherapy, improved OS with first-line paclitaxel and carboplatin (12.3 months for bevacizumab plus chemotherapy, hazard ratio [HR] 0.79, 95% confidence interval [CI]: 0.67–0.92; $p = 0.003$) [6]. The first-line AVAiL study showed increased progression-free survival (PFS) with the addition of bevacizumab to cisplatin–gemcitabine (HR 0.75, 95% CI: 0.64–0.87; $p = 0.0003$) [7]. In a phase IV trial bevacizumab-based therapy resulted in median OS of 14.6 months (95% CI 13.8–15.3) [8].

Erlotinib is an EGFR TKI. EGFR is critical in pathways used in cell proliferation and survival and increased expression is often seen in tumor cells [9]. Erlotinib demonstrated a significant OS benefit versus placebo (HR 0.70, 95% CI: 0.58–0.85; $p < 0.001$) in patients with advanced NSCLC who had failed prior chemotherapy in a randomized, double-blind trial (BR.21) [10,11]. This led to approval of erlotinib for NSCLC patients who have failed at least one prior chemotherapy regimen. Erlotinib was also shown to be effective in the post-marketing single-arm phase IV TRUST study [12]. Additionally, data for erlotinib [13,14] have resulted in its approval as first-line therapy for *EGFR* mutation-positive NSCLC, and as maintenance treatment in unselected NSCLC patients after first-line platinum-based chemotherapy [15]. Similar benefits have not been observed with first-line treatment of NSCLC with TKIs in populations not selected by *EGFR* mutation. In a study comparing first-line erlotinib with chemotherapy in patients with advanced NSCLC not selected for *EGFR* mutations, median OS was 6.5 months for erlotinib and 9.7 months for chemotherapy (HR 1.73, 95% CI: 1.09–2.73, $p = 0.018$) [16]. The TORCH study showed median OS of 8.7 months for first-line erlotinib versus 11.6 months for chemotherapy in *EGFR* unselected patients [17]. In the non-inferiority studies iPASS and First-SIGNAL, comparing the TKI gefitinib with chemotherapy, progression-free survival (PFS) and OS in populations not selected by *EGFR* mutation were similar [18,19].

Combining bevacizumab with erlotinib has shown promising activity in second-line treatment [20,21]. Preclinical and clinical trial data suggest the combination of erlotinib and bevacizumab has similar efficacy to standard platinum-based chemotherapy plus bevacizumab (median PFS of 6.2–6.3 months) but with reduced toxicity [22,23]. The SAKK 19/05 study suggested that bevacizumab and erlotinib first-line treatment was feasible with acceptable toxicity and activity (PFS 4.1 months, OS 14.1 months) [24]. However, in another study the first-line combination of bevacizumab and erlotinib resulted in a non-progression rate of 75%, PFS of 3.8 months (95% CI: 2.3–5.4) and OS of 6.9 months (95% CI: 5.5–8.4) [25]. These data warranted further investigation of the optimal setting for a bevacizumab and erlotinib combination regimen.

The BO20571 (TASK) study evaluated the efficacy and safety of bevacizumab in combination with either erlotinib or chemotherapy as first-line therapy in advanced NSCLC (ClinicalTrials.gov identifier: NCT00531960).

2. Methods

2.1. Patients

TASK was a phase II, open-label, multicenter, randomized, two-arm, first-line study in patients with advanced non-squamous NSCLC. The trial was approved by the medical ethics committee of each participating center and was performed in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. All patients provided written informed consent prior to any study-related procedure. The study had a planned sample size of 200 patients.

Patients aged ≥18 years were eligible if they had advanced or recurrent, untreated, stage IIIB/IV NSCLC, with Eastern Co-operative Oncology Group (ECOG) performance status (PS) 0–1. Formalin-fixed paraffin-embedded primary tumor samples were mandatory. Patients were excluded if they had squamous cell histology, central pulmonary lesions, central nervous system metastases, history of grade ≥2 hemoptysis, received prior treatment with an EGFR inhibitor, chemotherapy or anti-angiogenic therapy, received prior radiotherapy or surgery within 4 weeks, significant ophthalmic abnormalities, or had abnormal blood cell count, liver function tests or creatinine clearance. Patients receiving anticoagulants, acetylic salicylic acid, dipyramidole, ticlopidine, clopidogrel or cilostazol at baseline were also excluded.

2.2. Study treatment

Patients were randomized to receive erlotinib (p.o. 150 mg/day) plus bevacizumab (i.v. 15 mg/kg, day 1 of each 21-day cycle) until disease progression or unacceptable toxicity (BE arm) or 4–6 cycles of gemcitabine/cisplatin (gemcitabine 1250 mg/m^2 days 1 and 8 and cisplatin 80 mg/m^2 on day 1 of each 21-day cycle) or carboplatin/paclitaxel (carboplatin AUC 6 on day 1 and paclitaxel 200 mg/m^2 on day 1 of each 21-day cycle), plus bevacizumab (i.v. 15 mg/kg on day 1 of each 21-day cycle; BC arm). Following 4–6 cycles of chemotherapy, single-agent bevacizumab was continued until disease progression or unacceptable toxicity. Patients were centrally randomized and allocated drug packs via an Interactive Voice Response System.

2.3. Efficacy and safety analyses

The primary endpoint was assessment of the HR for PFS with BE relative to BC. Secondary endpoints included OS, objective response rate (ORR) and safety profile. A pre-specified exploratory biomarker