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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ARTICLE INFO

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.

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
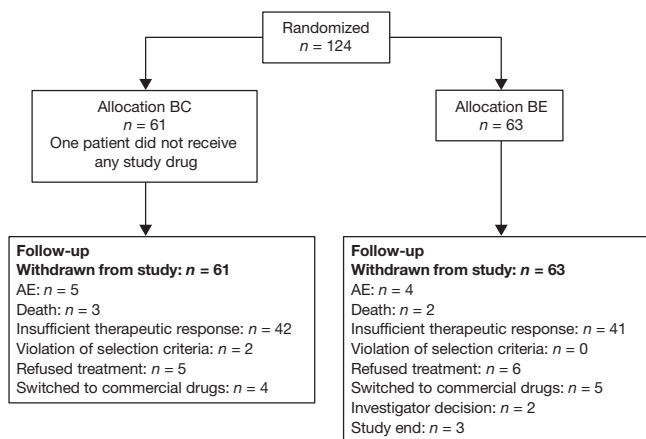
Fig. 1. Summary of patient disposition. AE, adverse event; BC, bevacizumab plus chemotherapy; BE, bevacizumab plus erlotinib

Table 1
Baseline demographics in the overall population.

Characteristic	BC arm ($n = 61$)	BE arm ($n = 63$)
Age, years		
Mean (range)	58 (39–78)	61 (30–77)
Gender, n (%)		
Male	36 (59)	37 (59)
Female	25 (41)	26 (41)
ECOG PS, n (%)		
0	20 (33)	28 (44)
1	41 (67)	35 (56)
Smoking status, n (%)		
Smoker	24 (39)	22 (35)
Non-smoker	23 (38)	21 (33)
Former smoker	14 (23)	20 (32)
Histology, n (%)		
Adenocarcinoma	53 (88)	56 (89)
Other	7 (12)	7 (11)
Disease stage, n (%)		
Unresectable stage IIIB	15 (25)	10 (16)
Stage IV	46 (75)	53 (84)

BC, bevacizumab plus chemotherapy; BE, bevacizumab plus erlotinib; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

analysis was planned for patients with immunohistochemistry EGFR protein expression-positive tumors, patients with high *EGFR* gene copy number measured by fluorescence in situ hybridization, and patients with *EGFR* mutations. Due to early termination of the study only PFS/OS correlation with *EGFR* mutation status was assessed.

Tumor response was assessed at 6 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, then every 6 weeks until week 24, following which tumor response was measured every 12 weeks. A physical examination and vital signs were assessed at baseline and on day 1 of every cycle (cycle 2 until withdrawal). Adverse events (AEs) were assessed at each clinical visit and followed until 6 months after the last drug administration.

2.4. Statistical analyses

Based on the E4599 trial results [6], BC-treated patients were expected to have a median PFS of ~6.4 months. Approximately 200 patients were therefore needed to give an adequate number of patients [26,27]. Assuming a PFS of 6.4 months (27.8 weeks) in each arm, 141 events were estimated for 200 patients, giving a standard error for the log HR of ~0.168. If treatment arms had equivalent efficacy the 95% CI of an HR of 1 would be 0.72–1.39.

The full analysis set included all randomized patients ($n = 63$ BE; $n = 61$ BC), analyzed according to the therapy to which they were randomized. The safety population included all patients who received ≥ 1 dose of study drug and completed ≥ 1 safety follow-up.

PFS was defined as time between randomization and first occurrence of disease progression or death, whichever occurred first. PFS was analyzed according to the investigators' assessments using RECIST plus clinical progression criteria.

A pre-planned interim analysis was undertaken on 17 September 2008. This analysis was to assess whether to stop or evaluate the study if efficacy in the BE arm was worse than the BC arm. If the HR was greater than 1.25, indicating BC treatment was better than BE, the study would be re-evaluated. An updated analysis was performed on 6 January 2009 in order to increase the follow-up period of the randomized patients. The final analysis was on 9 September 2011.

3. Results

3.1. Patient population

From 31 December 2007 to 17 September 2008, 124 patients were randomized (BE, $n = 63$; BC, $n = 61$; Fig. 1); 14 patients were

withdrawn from trial treatment for safety reasons (8 BC and 6 BE). After results of the updated interim analysis were communicated, 10 patients were withdrawn due to administrative reasons in the BE arm (5 patients switched to commercially available erlotinib, 2 patients were withdrawn due to investigator decision and 3 patients were withdrawn due to study end). In the BC arm 4 patients switched to commercially available erlotinib.

At the pre-planned interim analysis (data cut-off 17 September 2008) there were no post-baseline PFS assessments for 20 BE patients and 18 BC patients due to <6 weeks between randomization and data cut-off. A further 12 patients in each arm were censored after randomization but before week 6. The HR for PFS for BE relative to BC treatment was above the predefined threshold of 1.25 (HR 2.17, 95% CI: 0.88–5.34). To account for the patients with no PFS events or insufficient time between randomization and cut-off to be accurately assessed, an updated interim analysis (data cut-off 6 January 2009) was performed. Recruitment was kept on hold but enrolled patients continued treatment. The HR for PFS at the updated interim analysis was above the pre-defined value of 1.25 (HR 2.05, 95% CI: 1.11–3.77; $p = 0.0183$). Therefore recruitment was stopped permanently.

Baseline demographics and patient characteristics for the intent-to-treat population are shown in Table 1. Both arms had a higher proportion of males than females, and more patients with ECOG PS 1 compared with PS 0. Most patients had adenocarcinoma histology and most had stage IV disease.

3.2. Efficacy outcomes

By the final analysis (9 September 2011) all patients had been withdrawn from trial treatment, therefore final analysis data are not available for some endpoints. All presented results are from the updated interim analysis (6 January 2009) unless otherwise stated.

At the updated analysis, the risk of disease progression or death was significantly higher with BE compared with BC (HR 2.05, 95% CI: 1.11–3.77; log rank $p = 0.0183$). A total of 30 events in the BE arm (47.6%) and 16 events in the BC arm (26.2%) were observed. Median PFS was 18.4 weeks (95% CI: 17.0–25.1) with BE and 25.0 weeks (95% CI: 20.6–[not reached]) with BC. The p value of 0.0183 indicated a significant difference in PFS in favor of BC (Fig. 2). No subgroups particularly benefited from the BE combination. In the subgroup analysis by *EGFR* mutation

Table 2
HR and 95% CI for PFS by EGFR subgroups.

Subgroup	BC arm ($n = 61$)			BE arm ($n = 63$)			HR	95% CI
	Patients per group	No. events	Median PFS, weeks	Patients per group	No. events	Median PFS, weeks		
EGFR IHC positive	26	5	NR	29	15	18	3.03	1.10–8.36
EGFR IHC negative	14	5	24.1	11	4	NR	0.96	0.26–3.59
EGFR FISH positive	23	6	NR	28	12	23.4	1.21	0.44–3.33
EGFR FISH negative	13	5	24.1	11	7	12.1	2.62	0.75–9.10
EGFR mutation positive	11	0	NR	13	2	NR	>100	0.00–NA
EGFR wild type	29	11	24.1	30	19	16.0	2.07	0.98–4.40

BC, bevacizumab plus chemotherapy; BE, bevacizumab plus erlotinib; EGFR, epidermal growth factor receptor, IHC, immunohistochemistry; NR, not reached; FISH, fluorescence in situ hybridization; NA, not available.
EGFR mutation status data was not available for all patients.

status ($n = 13$ BE, $n = 11$ BC), there were two PFS events in the BE arm and no PFS events in the BC arm for patients with *EGFR* mutation-positive tumors (Table 2). At the final analysis 9 patients (69.2%) with an *EGFR*-activating mutation had a PFS event in the BE arm and 8 patients (72.7%) had an event in the BC arm.

At the updated interim analysis, the incidence of death (mainly due to disease progression, PD) was higher with BE compared with BC ($n = 12$ [19%; 5 PD, 1 AE, 1 unknown] versus $n = 7$ [11.5%; 10 PD, 2 AE], respectively), although no significant difference was seen (HR 1.63; 95% CI: 0.64–4.15, log rank $p = 0.2994$). Median OS was not reached in either arm (Kaplan–Meier curves did not drop below 50%). At the final analysis, median OS was 16.4 months for BE and not reached for BC (HR 1.24, 95% CI: 0.75–2.05; log rank $p = 0.4063$); the incidence of death was higher with BE compared with BC ($n = 33$ [52.4%] versus $n = 28$ [45.9%], respectively). In the subgroup of patients with *EGFR* mutations, there was one death (due to pneumonia) in the BE group and none in the BC group by the final analysis. Second-line or further therapy was received by 66% of BC patients (most common was TKI, 38%) and 49% of BE patients (most common was antimetabolites, 24%).

The ORR was 23.8% ($n = 15$) with BE (95% CI: 14.0–36.2) compared with 34.4% with BC ($n = 21$) (95% CI: 22.7–47.7; chi-squared $p = 0.19$) at the updated analysis (all partial responses). The estimated odds ratio for response with BE versus BC was 0.60 (95% CI: 0.27–1.30) indicating a higher response with BC. No patient achieved a complete response in either arm. The rate of stable disease was similar in the BE and BC arms (47.6% [$n = 30$] versus 49.2% [$n = 30$], respectively). Patients not achieving a response or stable disease were $n = 13$ for BE and $n = 5$ for BC.
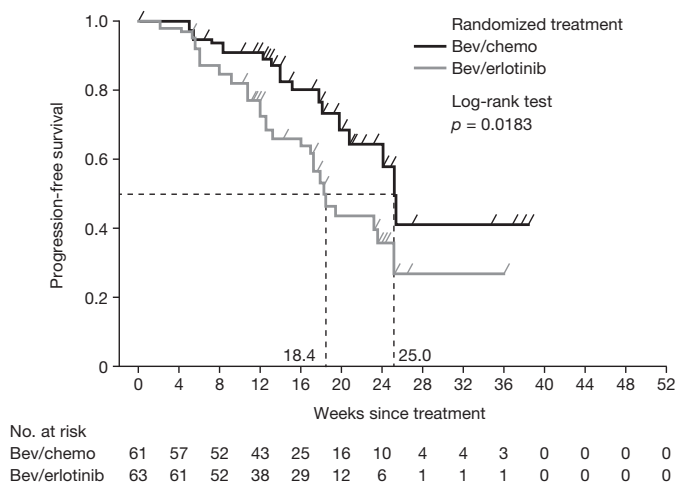
3.3. Safety and tolerability

AEs in the safety population were reported by 84.1% of patients in the BE arm and 82.0% in the BC arm (Table 3), with no unexpected AEs reported. A higher proportion of BE-treated patients experienced events that were considered related to study treatment compared with BC-treated patients (81.0% versus 75.4%, respectively; study treatment includes chemotherapy or bevacizumab or erlotinib). More BC-treated patients experienced a serious AE (29.5% versus 23.8%) or a related serious AE (24.6% versus 11.1%) than BE-treated patients, however, there were more deaths during the treatment period with BE (8 patients, 12.7%) compared with BC (4 patients, 6.6%), mostly due to disease progression. The higher number of serious AEs in the BC arm was due mainly to abnormalities in blood parameters.

The most frequently reported AEs were gastrointestinal events (Table 4); more BC-treated patients reported events in this class (67.2% versus 50.8% in the BE arm). A higher proportion of BE-treated patients reported diarrhea (31.7% versus 19.7% in the BC arm), while a higher proportion of BC-treated patients reported vomiting (29.5% versus 7.9% in the BE arm). A higher incidence of abnormal blood parameters (neutropenia, anemia, thrombocytopenia and leucopoenia) was seen in the BC arm and there were more cases of epistaxis. Consistent with the known safety profile for erlotinib, more events of rash and pruritus were reported in the BE arm. No cases of interstitial lung disease were reported during the study.

At the updated interim analysis, two patients from each treatment arm had withdrawn due to AEs considered related to study treatment. From the BC arm, one patient with reversible posterior leukoencephalopathy syndrome and one patient with thrombosis withdrew. From the BE arm two patients with pulmonary embolisms withdrew; one patient suffering an ischemic stroke also withdrew, however, this was not considered related to study

Fig. 2. Kaplan–Meier curves of PFS (updated interim analysis). Bev, bevacizumab; chemo, chemotherapy. Dashed lines denote median PFS.

Table 3
Summary of AEs in the overall population.

n (%)	BC arm ($n = 61$)	BE arm ($n = 63$)
Patients with at least one AE	50 (82.0)	53 (84.1)
Deaths	4 (6.6)	8 (12.7)
Study withdrawals due to an AE	2 (3.3)	3 (4.8)
Patients with at least one:		
AE leading to death	2 (3.3)	2 (3.2)
Serious AE	18 (29.5)	15 (23.8)
Treatment-related serious AE	15 (24.6)	7 (11.1)
AE leading to withdrawal	4 (6.6)	4 (6.3)
AE leading to dose modification	27 (44.3)	21 (33.3)
Treatment-related AE	46 (75.4)	51 (81.0)
Related AE leading to withdrawal	3 (4.9)	2 (3.2)
Severe AE	28 (45.9)	22 (34.9)

AE, adverse event; BC, bevacizumab plus chemotherapy; BE, bevacizumab plus erlotinib.

Table 4
Summary of AEs with an incidence rate >5% in the overall study population.

Body system/AE, n (%)	BC arm (n = 61)	BE arm (n = 63)
Gastrointestinal disorders		
Nausea	31 (50.8)	10 (15.9)
Diarrhea	12 (19.7)	20 (31.7)
Vomiting	18 (29.5)	5 (7.9)
Constipation	7 (11.5)	4 (6.3)
Stomatitis	4 (6.6)	7 (11.1)
Abdominal pain	3 (4.9)	5 (7.9)
Dyspepsia	3 (4.9)	4 (6.3)
Abdominal pain upper	4 (6.6)	1 (1.6)
Skin and subcutaneous tissue disorders		
Rash	6 (9.8)	31 (49.2)
Alopecia	12 (19.7)	7 (11.1)
Pruritus	1 (1.6)	9 (14.3)
Dry skin	–	4 (6.3)
Respiratory and thoracic disorders		
Cough	4 (6.6)	11 (17.5)
Dyspnea	6 (9.8)	9 (14.3)
Epistaxis	12 (19.7)	1 (1.6)
Hemoptysis	5 (8.2)	4 (6.3)
Dysphonia	2 (3.3)	5 (7.9)
Oropharyngeal pain	1 (1.6)	6 (9.5)
Blood system disorders		
Neutropenia	21 (34.4)	–
Anemia	12 (19.7)	1 (1.6)
Thrombocytopenia	12 (19.7)	1 (1.6)
Leucopenia	11 (18.0)	–
General disorders		
Asthenia	9 (14.8)	5 (7.9)
Fatigue	9 (14.8)	5 (7.9)
Mucosal inflammation	3 (4.9)	5 (7.9)
Vascular disorders		
Hypertension	7 (11.5)	9 (14.3)
Nervous systems disorders		
Headache	3 (4.9)	6 (9.5)
Neuropathy	6 (9.8)	–
Infections		
Paronychia	1 (1.6)	6 (9.5)
Upper respiratory tract infection	1 (1.6)	5 (7.9)
Musculoskeletal disorders		
Myalgia	6 (9.8)	2 (3.2)
Back pain	4 (6.6)	–
Psychiatric disorders		
Insomnia	4 (6.6)	3 (4.8)
Renal disorders		
Proteinuria	2 (3.3)	4 (6.3)

AE, adverse event; BC, bevacizumab plus chemotherapy; BE, bevacizumab plus erlotinib.

treatment. The majority of deaths were due to progression, occurring during safety follow-up.

4. Discussion

This study evaluated efficacy and safety of erlotinib plus bevacizumab compared with bevacizumab plus chemotherapy as first-line treatment in patients unselected for *EGFR* mutation status with advanced non-squamous NSCLC. At the interim analysis, the HR for death or disease progression (2.17) was above the pre-defined threshold of 1.25. An updated analysis was undertaken to allow longer follow-up as some patients could not be evaluated due to insufficient follow-up time from randomization. The updated analysis showed that the BE combination did not produce a PFS benefit compared with BC therapy (HR 2.05); therefore the primary endpoint was not met. Subgroup findings, including patients with *EGFR* mutation-positive disease were consistent with those for the overall randomized population. One reason that no benefit with erlotinib treatment was seen in the *EGFR* mutation-positive group may be due to the low patient numbers in this subgroup. As well as a shorter PFS benefit, a higher incidence of death was reported in

the BE arm than the BC arm (interim analysis HR 1.63; final analysis HR 1.24).

As the results of the updated interim analysis were communicated to investigators with guidance that patients could discontinue BE treatment or switch to an alternative treatment, the final analysis data may be subject to bias, and must be interpreted with caution. The results of the updated interim analysis are considered the most valid assessment of the BE treatment combination in this instance. The Kaplan–Meier curves for PFS are clearly separated at the updated interim analysis.

No new safety findings were identified for either combination in this study. As expected, a higher proportion of patients in the BE arm reported diarrhea than in the BC arm, while a higher incidence of blood disorders were reported in the BC arm.

Other trials have investigated the combination of bevacizumab and erlotinib in different settings for the treatment of advanced NSCLC. Herbst et al. investigated bevacizumab plus erlotinib or chemotherapy versus chemotherapy plus placebo for the treatment of recurrent/refractory NSCLC (n = 120) [21]. Median PFS was 4.4 months (HR 0.72 [95% CI: 0.42–1.23]) for BE versus 4.8 months (HR 0.66 [95% CI: 0.38–1.16]) for BC. These data suggested that the BE combination had similar efficacy to chemotherapy in a second-line setting. The BRAIN study of BE in second-line treatment of NSCLC patients with asymptomatic brain metastases (n = 24) demonstrated a median PFS of 6.3 months (95% CI: 2.5–8.4) and a 6-month PFS rate of 58% [23].

INNOVATIONS investigated first-line BE in NSCLC and also showed no benefit with the BE combination compared with BC regimen. Median PFS was 3.5 months for BE versus 7.7 months for BC. OS was 12.6 months versus 16.3 months for BE versus BC [28]. The first-line SAKK 19/05 study showed a BE combination resulted in PFS of 4.1 months and OS of 14.1 [24].

In previous studies investigating the use of the single-agent TKIs for the treatment of first-line NSCLC, the results in unselected patients were not encouraging [16,18,19,29]. While the combination of bevacizumab and erlotinib showed promise in second-line treatment, the TASK and INNOVATIONS studies suggest that the addition of bevacizumab to first-line erlotinib does not improve outcomes for unselected patients with NSCLC. A recent editorial highlighted that combining more agents is not necessarily better when designing clinical trials and using agents with different modes of action should only be done when preclinical data support the combination in that particular setting [30].

5. Conclusions

This study did not show a PFS benefit for the BE combination in first-line advanced NSCLC compared with BC. Subgroup findings were consistent with the overall population. The premature termination of study treatment in the BE arm does not allow for a reliable assessment of efficacy in the smaller subgroups of patients, including those with *EGFR* mutations. Based on these findings the erlotinib plus bevacizumab combination is not currently recommended for first-line NSCLC.

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