Erlotinib and bevacizumab *versus* cisplatin, gemcitabine and bevacizumab in unselected nonsquamous nonsmall cell lung cancer

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ABSTRACT Erlotinib with bevacizumab showed promising activity in recurrent nonsquamous (NS) nonsmall cell lung cancer (NSCLC). The INNOVATIONS study was designed to assess in first-line treatment of unselected cisplatin-eligible patients this combination compared to cisplatin, gemcitabine and bevacizumab.

Stage IIIB/IV patients with NS-NSCLC were randomised on erlotinib (150 mg daily) and bevacizumab (15 mg·kg^{-1} on day 1, every 3 weeks) (EB) until progression, or cisplatin (80 mg·m^{-2} on day 1, every 3 weeks) and gemcitabine (1250 mg·m^{-2} on days 1 and 8, every 3 weeks) up to six cycles and bevacizumab (15 mg·kg^{-1} on day 1, every 3 weeks) (PGB) until progression.

224 patients were randomised (EB n=111, PGB n=113). The response rate (12% *versus* 36%; p<0.0001), progression-free survival (median 3.5 *versus* 6.9 months; hazard ratio (HR) 1.85, 95% CI 1.39–2.45; p<0.0001) and overall survival (median 12.6 *versus* 17.8 months; HR 1.41, 95% CI 1.01–1.97; p=0.04) clearly favoured PGB. In patients with epidermal growth factor receptor mutations (n=32), response rate, progression-free survival and overall survival were not superior with EB.

Platinum-based combination chemotherapy remains the standard of care in first-line treatment of unselected NS-NSCLC. Molecular targeted approaches strongly mandate appropriate testing and patient selection.

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Introduction

The standard of care for unselected patients with advanced nonsmall cell lung cancer (NSCLC) is platinum-based combination chemotherapy [1]. Achievements with chemotherapy are modest and have reached an efficacy plateau envisaging a range of median survival of 8–11 months [2, 3]. In nonsquamous NSCLC (NS-NSCLC) further improvements were reported with the addition of bevacizumab to chemotherapy and continuation until disease progression [4, 5]. Preclinical data showed that this anti-vascular endothelial growth factor (anti-VEGF) strategy might be enhanced in terms of additive anti-tumour effects with an anti-epidermal growth factor receptor (EGFR) therapy [6, 7]. Based on these observations, a phase I/II trial with erlotinib and bevacizumab in advanced NS-NSCLC after failure of at least one platinum-based treatment regimen showed promising results in unselected patients with adenocarcinoma: a 20% response rate, a median progression-free survival (PFS) of 6.2 months and a median overall survival of 12.6 months [8]. The current trial assessed the impact of this regimen in first-line treatment, in a randomised phase II setting. To facilitate a descriptive comparison to an at best first-line approach, we chose cisplatin, gemcitabine and bevacizumab as the comparator for the following reasons. 1) As reflected by the CISCA (Cisplatin *versus* Carboplatin) meta-analysis, a cisplatinum-based regimen is considered the choice of priority in first-line treatment, in patients who are amenable [9]. 2) At the time when the trial was designed, one of the best survival times from a phase III trial was derived from the Eastern Cooperative Oncology Group (ECOG) 4599 study (median 12.3 months) with carboplatin, paclitaxel and bevacizumab in NS-NSCLC [4]. Thus, bevacizumab was integrated in the comparator arm. 3) To resemble the treatment backbone of the AVAiL (Avastin in Lung) trial, gemcitabine was selected as a combination partner to cisplatin [10].

Methods

INNOVATIONS (Inoperable NS-NSCLC (stage IIIB/IV): a randomised phase II study with bevacizumab plus erlotinib or gemcitabine/cisplatin plus bevacizumab) was a multicentre open-label randomised phase II trial conducted in Germany. Eligibility criteria included: histologically proven predominately NS-NSCLC; stage IIIB with pleural or cardiac effusion and no need for intervention or stage IV (6th Union for International Cancer Control staging classification); measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1; age 18–75 years; ECOG performance status 0–2; adequate bone marrow, hepatic and renal function, defined as haemoglobin $\geqslant$10.0 g·dL^{-1}, white blood cell count $\geqslant 3.0\times10^{9}$ cells·L^{-1}, neutrophils $\geqslant 1.5\times10^{9}$ cells·L^{-1}, platelets $\geqslant 100\times10^{9}$ cells·L^{-1}, serum creatinine $\leqslant$1.5 mg·dL^{-1}, estimated creatinine clearance $\geqslant$60 mL·min^{-1}, serum bilirubin $\leqslant$2.0 mg·dL^{-1}, aspartate aminotransferase and alkaline phosphatases $\leqslant$5× upper limit of normal (ULN) with liver metastases and $\leqslant$2.5× ULN without liver metastases; life expectancy of $\geqslant$3 months; written informed consent provided. Patients were excluded if contraindications existed for the use of bevacizumab, erlotinib, cisplatin or gemcitabine according to the official label. The study was approved by the ethics committee of each participating institution and the German regulatory institute Paul Ehrlich. An independent data safety monitoring board (DSMB), reviewing all serious adverse events, was nominated by the steering committee. The DSMB reviewed the study performance at regular intervals. When unfavourable results emerged in the TASK trial (a study of tarceva (erlotinib) in combination with avastin (bevacizumab) in patients with advanced NSCLC) [11], which used similar comparators, the DSMB reviewed current, interim efficacy data from the INNOVATIONS trial and indicated no reason to stop the trial. The study was conducted in accordance with the Declaration of Helsinki (version 1996) and the applicable ICH-GCP (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice) guidelines. It was registered on ClinicalTrials.gov as NCT00536640 (EUDRA-CT 2006-004865-32).

Random assignment

Patients were centrally randomly assigned to one of the two treatment arms *via* fax registration by the Coordinating Center for Clinical Trials at the University of Marburg (Marburg, Germany). Stratification parameters were ECOG performance status (0–1 *versus* 2), sex, smoking status (smoker *versus* nonsmoker) and institution.

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Treatments

Patients randomly assigned to the experimental arm received erlotinib 150 mg daily and bevacizumab 15 mg·kg^{-1} body weight on day 1, every 3 weeks until disease progression (EB treatment arm). After progression a switch to a combination chemotherapy of cisplatin 80 mg·m^{-2} on day 1 and gemcitabine 1250 mg·m^{-2} on days 1 and 8, every 3 weeks for a maximum of six cycles was recommended. Patients randomly assigned to the standard treatment arm received cisplatin, gemcitabine and bevacizumab as outlined, for a maximum of six cycles (PGB treatment arm). Patients with complete response, partial response or no change subsequently received bevacizumab maintenance therapy until disease progression. Patients with progressive disease were recommended to switch to erlotinib 150 mg daily.

In cases with grade 3 or 4 toxicities (CTCAE (Common Terminology Criteria for Adverse Events) version 3.0), erlotinib could be reduced, stepping down in two dose levels (100 mg followed by 50 mg) with the possibility of interrupting treatment for a maximum of 2 weeks. Bevacizumab could be interrupted in cases of uncontrolled hypertension or substantial proteinuria (>2000 mg·day^{-1}) for a maximum of 6 weeks. Reinstitution was allowed after recovery from these symptoms. Bevacizumab was terminated in cases of thromboembolic or bleeding events, haemoptysis or any other grade 3 or 4 toxicity (CTCAE version 3.0). If chemotherapy resulted in a grade IV leuko- or thrombocytopenia (CTCAE), gemcitabine was reduced to 1000 mg·m^{-2}. Nephrotoxicity with a dropping creatinine clearance in the range of 40–60 mL·min^{-1} demanded reduction of cisplatin down to 50% of the recommended dose; when dropping below 40 mL·min^{-1}, systemic treatment was stopped. Impairment of hearing resulted in a switch of cisplatin to carboplatin (carboplatin dosage based on area under the curve 5 mg·mL^{-1}·min).

Assessment procedures

Patients were evaluated at baseline with a complete history and physical examination, routine haematology and biochemistry, chest radiography, computed tomography (CT) scans of the chest and the abdomen, CT scan or magnetic resonance imaging of the brain, and a bone scan. Blood cell examination was performed weekly during the treatment. Complete haematology and biochemistry controls were performed every 3 weeks. Examination of tumour response was performed every 6 weeks by CT scans of the chest and abdomen. Other metastatic sites were assessed as appropriate. The 6-week intervals of control investigations were maintained until disease progression. Objective response was determined using RECIST. Toxicity was graded according to CTCAE version 3.0 and coded according to the Medical Dictionary for Regulatory Activities. Serious adverse events had to be reported immediately.

EGFR *mutation analysis*

For mutational analysis of *EGFR* (exons 19 and 21), serial sections from paraffin blocks of each case were cut. The first section was stained with haematoxylin and eosin for the evaluation of the tumour region and tumour cell content by an experienced pathologist [12]. From the corresponding unstained serial sections, the marked tumour areas were manually microdissected and further processed to fully automated DNA extraction from the proteinase K digested tissues using a QIASymphony SP (Qiagen, Hilden, Germany). Sanger sequencing-based mutation analysis was essentially performed as previously described [13]. In brief, for PCR amplification of *EGFR*, the following primers were used: 5′-gctggtaacatccacccaga-3′ (exon 19 forward), 5′-gagaaaaggtgggcctgag-3′ (exon 19 reverse), 5′-cctcacagcagggtcttctc-3′ (exon 21 forward) and 5′-cctggtgtcaggaaaatgct-3′ (exon 21 reverse). Exons 2 and 3 of *KRAS* were amplified with the following primers: 5′-gtgtgacatgttctaatatagtca-3′ (exon 2 forward), 5′-gaatggtcctgcaccagtaa-3′ (exon 2 reverse), 5′-ccagactgtgtttctcccttc-3′ (exon 3 forward) and 5′ aacccacctataatggtg aatatct-3′ (exon 3 reverse). Direct sequencing of the PCR amplicons was carried out for both strands on an 3500 Genetic Analyzer (Applied Biosystems by Life Technologies Corporation) using the BigDye® Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems by Life Technologies Corporation).

Statistical methods

The sample size calculation was based on median PFS of 6.4 months, as reported in ECOG 4599 [4]. Following the method of Brookmeyer and Crowley [14], 110 patients per therapy arm were necessary to obtain a lower 95% confidence limit of about 5 months for the median PFS in each arm. Time-to-event data were analysed using the Kaplan–Meier method, and the log-rank test was used to compare the distributions between groups. In addition, hazard ratios (HR) with 95% confidence intervals (CI) were estimated using the Cox proportional hazards model [15]. Secondary end-points were analysed using adequate methods. All p-values were two-sided. Efficacy analyses were performed on all randomised patients (intention-to-treat (ITT) basis). Patients receiving at least one treatment cycle were qualified for safety analysis. All statistical analyses were done with SAS (version 9.2; SAS Institute, Cary, NC, USA).

Results

From November 2007 to August 2009 a total of 224 patients were randomised from 37 sites across Germany (113 to PGB and 111 to EB). The demographic and baseline characteristics were balanced between study arms (table 1). As shown in figure 1, a total of 108 patients in the EB arm and 111 in the PGB arm received at least one cycle of the respective regimen. The median number of cycles was five in the EB and five in the PGB arm. The proportions of patients receiving at least six cycles were similar in each treatment group (EB 44.4%, PGB 46.9%).

Treatment conduct and adverse events

The frequency and severity of toxicity according to treatment arm and the frequency of non-cancer-related mortality are shown in tables 2 and 3, respectively. In the EB arm, erlotinib was temporarily stopped due to severe side-effects in 38% of patients, mandating dose reductions in 24%. In 4.6% of bevacizumab cycles, treatment had been delayed by more than 7 days. In the PGB arm this was documented in 13% of bevacizumab cycles and in 16% of chemotherapy cycles.

Further treatment

Second-line and third-line treatments are summarised in table 4. Of the 108 patients treated with EB, two were still on treatment at the time of the analysis. 106 had stopped treatment; of these, 76 had stopped due to progressive disease (fig. 1). 62 (57%) out of 108 patients had received a systemic second-line treatment, 44 of them a platinum-based chemotherapy. Of the 111 patients in the PGB arm, five were still on treatment at the time of the analysis. 106 had stopped treatment; of these, 50 had stopped due to progressive disease (fig. 1). 70 (63%) out of 111 patients received a systemic second-line treatment, 22 of them an EGFR target therapy and 48 a second-line chemotherapy.

TABLE 1 Baseline patient characteristics

	EB arm	PGB arm
Patients	111	113
Age years	62 (40–85)	60 (36–83)
Sex		
Male	63 (56.8)	63 (55.8)
Female	48 (43.2)	50 (44.3)
ECOG performance status		
0	48 (43.2)	53 (46.9)
1	61 (55.0)	56 (49.6)
2	2 (1.8)	4 (3.6)
Stage		
IIIB	15 (13.5)	21 (18.6)
IV	96 (86.5)	92 (81.4)
Lactate dehydrogenase		
<1.5× ULN	98 (88.3)	93 (82.3)
⩾1.5× ULN	10 (9.0)	13 (11.5)
Missing	3 (2.7)	7 (6.2)
Histology		
Adenocarcinoma	97 (87.4)	105 (92.9)
Large cell	4 (3.6)	3 (2.7)
Not specified	10 (9.0)	5 (4.4)
Smoking status		
Current smoker	32 (28.8)	37 (32.7)
Former smoker	50 (45.0)	44 (38.9)
Former light smoker	5 (4.5)	8 (7.1)
Never-smoker	21 (18.9)	19 (16.8)
Missing	3 (2.7)	5 (4.4)
***EGFR* mutation status**		
Not available	34 (30.6)	31 (27.4)
Mutation	20 (18.0)	12 (10.6)
Wild type	57 (51.4)	70 (61.9)

Data are presented as n, mean (range) or n (%). EB: erlotinib/bevacizumab; PGB: cisplatin/gemcitabine/bevacizumab; ECOG: Eastern Cooperative Oncology Group; ULN: upper limit of normal; *EGFR*: epidermal growth factor receptor.

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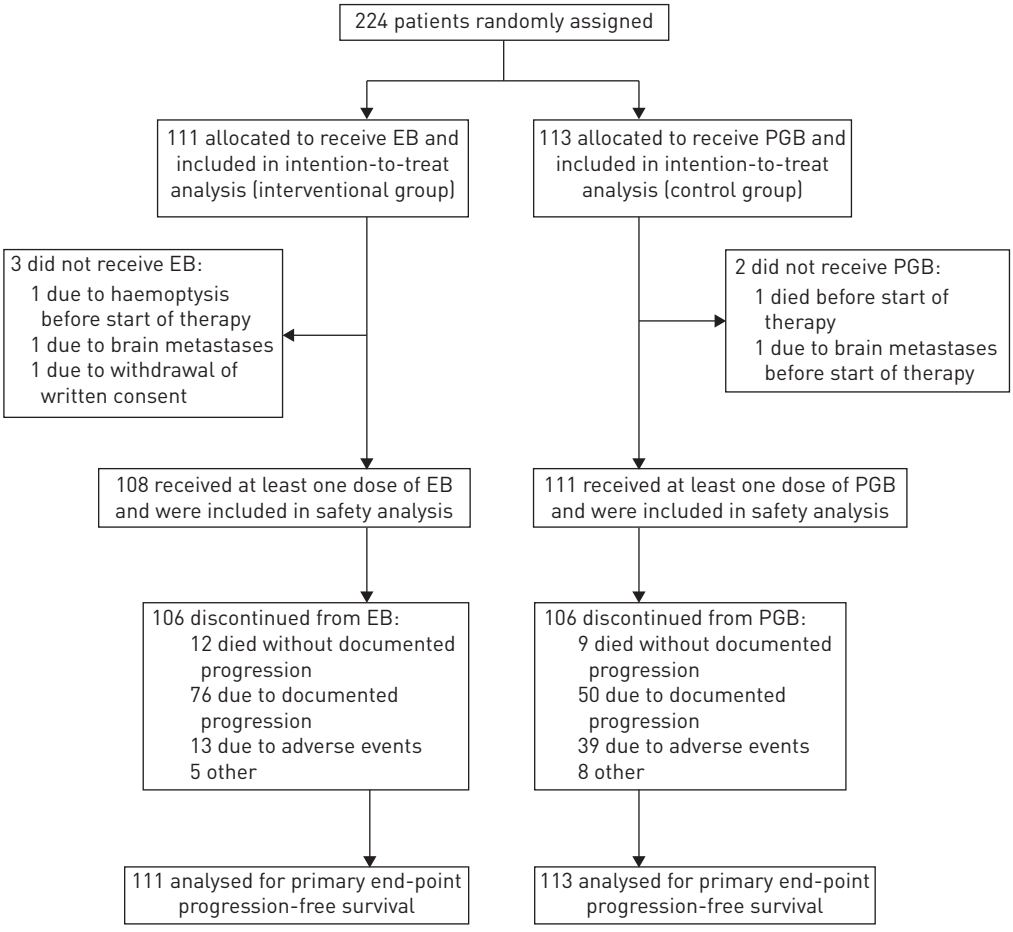

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram. EB: erlotinib/bevacizumab; PGB: cisplatin/gemcitabine/bevacizumab.

TABLE 2 Frequency and severity of toxicity

	EB arm[#] toxicity		PGB arm[¶] toxicity	
	Grade 1+2	Grade 3–5	Grade 1+2	Grade 3–5
Anaemia	0 (0)	0 (0)	18 (16.2)	7 (6.3)
Neutropenia	0 (0)	0 (0)	7 (6.3)	8 (7.2)
Febrile neutropenia[+]	0 (0)	0 (0)	0 (0)	2 (1.8)
Thrombocytopenia	0 (0)	0 (0)	18 (16.2)	16 (14.4)
Nausea/vomiting	19 (17.6)	2 (1.9)	52 (46.8)	11 (9.9)
Hypertension	15 (13.9)	4 (3.6)	12 (10.8)	12 (10.8)
Cardiac disorders	5 (4.6)	4 (3.7)	9 (8.1)	4 (3.6)
Thromboembolism	0 (0)	5 (4.6)	5 (4.5)	16 (14.4)
Rash	61 (56.5)	18 (16.7)	12 (10.8)	1 (0.9)
Diarrhoea	37 (34.3)	3 (2.8)	17 (15.3)	2 (1.8)
Fatigue	18 (16.7)	1 (0.9)	37 (33.3)	5 (4.5)
Dyspnoea	16 (14.8)	5 (4.6)	23 (20.7)	5 (4.5)
Gastrointestinal complaints	9 (8.3)	8 (7.4)	17 (15.3)	1 (0.9)
Infection	24 (22.2)	9 (8.3)	22 (19.8)	9 (8.1)
Bleeding events	13 (12.0)	2 (1.9)	30 (27.0)	1 (0.9)
Epistaxis	11 (10.2)	0 (0)	26 (23.4)	1 (0.9)
Gingival bleeding	3 (2.8)	0 (0)	2 (1.8)	0 (0)
Gastrointestinal haemorrhage	2 (1.9)	1 (0.9)	4 (3.6)	0 (0)
Pulmonary haemorrhage	1 (0.9)	1 (0.9)	0 (0)	0 (0)

Data are presented as n (%). EB: erlotinib/bevacizumab; PGB: cisplatin/gemcitabine/bevacizumab. [#]: n=108; [¶]: n=111; [+]: fever >38.5°C and absolute neutrophil count <1.0×10^9 cells·L^{-1}.

TABLE 3 Frequency of non-cancer-related mortality

	EB arm[#] deaths	PGB arm[¶] deaths
Total non-cancer deaths	6 (5.6)	5 (4.5)
Pulmonary bleeding	1 (0.9)	0 (0)
Gastrointestinal perforation/peritonitis	2 (1.8)	1 (0.9)
Pulmonary embolism	2 (1.8)	0 (0)
Sepsis	0 (0)	2 (1.8)
Sudden cardiac death	1 (0.9)	2 (1.8)

Data are presented as n (%). EB: erlotinib/bevacizumab; PGB: cisplatin/gemcitabine/bevacizumab. [#]: n=108; [¶]: n=111.

Efficacy

The response rate was 12% for EB and 36% for PGB (p=0.0001). The median PFS (ITT population) was 3.5 months in the EB arm and 6.9 months in the PGB arm. This difference was statistically significant (HR 1.85, p<0.0001). The median overall survival (ITT population) was 12.6 months in the EB arm and 17.7 months in the PGB arm, showing a statistically significant difference (HR 1.41, p=0.0409). Kaplan–Meier estimates for PFS and overall survival in the ITT population are shown in figure 2. The minimum follow-up was 2 years for each patient.

EGFR *mutation analysis*

An analysis of *EGFR* mutation status was performed in 159 (71%) patients, 77 (69%) randomised to EB and 82 (73%) to PGB. In 28 (13%) cases, tumour tissue was not available, and in 37 (17%) cases, paraffin blocks were insufficient for analyses. *EGFR* mutations were detected in a total of 32 patients (20% of 159), 20 in the EB group and 12 in the PGB group (fig. 3). The main patient characteristics (age, smoking status, performance status and lactate dehydrogenase distribution) were in balance with the total population.

In the *EGFR*-mutant patient population, the response rate for EB was 25% compared with 17% for PGB. PFS did not differ significantly, with a median of 4.2 months with EB and 4.6 months with PGB. However, overall survival showed a trend for superior survival with EB compared to PGB (median 17.0 *versus* 10.0 months; HR 0.45, 95% CI 0.18–1.16; p=0.092) (fig. 4). All of the 20 patients in the EB group received second-line chemotherapy, whereas only three out of 12 patients in the PGB group received any further treatment. In the *EGFR* wild-type patient population, the response rate was 9% for EB but 39% for PGB, with a PFS of 3.5 months *versus* 7.1 months (HR 2.07, 95% CI 1.42–3.02; p=0.0001) and overall survival of 10.3 months *versus* 18.0 months for PGB (HR 1.76, 95% CI 1.13–2.74; p=0.011) (fig. 4).

TABLE 4 Allocation to and type of second- and third-line treatments

	Second-line		Third-line	
	EB arm	PGB arm	EB arm	PGB arm
Patients	108	111	108	111
Radiation therapy only	4 (4)	3 (3)	3 (3)	3 (3)
Any systemic treatment	62 (57)	70 (63)	40 (37)	34 (31)
EGFR-TKI	3 (3)	22 (20)	3 (3)	11 (10)
Mono chemotherapy	15 (14)	36 (32)	30 (28)	20 (18)
Docetaxel	1 (1)	7 (6)	8 (7)	7 (6)
Pemetrexed	6 (6)	26 (23)	12 (11)	8 (7)
Gemcitabine	4 (4)	0 (0)	2 (2)	0 (0)
Other	4 (4)	3 (3)	8 (7)	5 (5)
Combination chemotherapy	44 (41)	12 (11)	7 (6)	3 (3)
Cisplatinum-based	24 (22)	7 (6)	2 (2)	2 (2)
Carboplatinum-based	20 (19)	5 (5)	3 (3)	1 (1)

Data are presented as n or n (%). EB: erlotinib/bevacizumab; PGB: cisplatin/gemcitabine/bevacizumab; EGFR-TKI: epidermal growth factor receptor tyrosine kinase inhibition.

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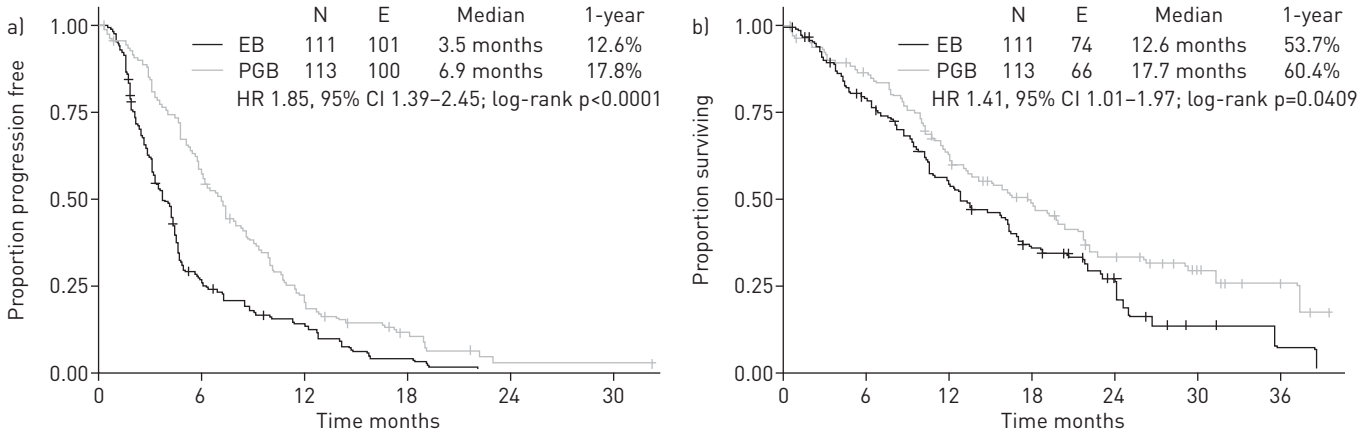

FIGURE 2 a) Progression-free survival and b) overall survival by treatment arm (intention-to-treat population). EB: erlotinib/bevacizumab; PGB: cisplatin/gemcitabine/bevacizumab; N: total patients; E: events; HR: hazard ratio.

Discussion

INNOVATIONS assessed a combination of erlotinib and bevacizumab (EB) compared with cisplatin-based chemotherapy with bevacizumab in first-line treatment of unselected advanced NS-NSCLC patients, amenable to cisplatin. The combination of cisplatin, gemcitabine and bevacizumab (PGB) showed superior overall survival (HR 1.41; p=0.0409), response rate (36% *versus* 12%; p<0.0001) and PFS (HR 1.85; p<0.0001). PFS and overall survival ranged in the most favourable spans reported for combination chemotherapy and bevacizumab in NS-NSCLC [4, 5, 10].

Similar to INNOVATIONS, an HR of 1.24 on overall survival has been derived from the TORCH (Tarceva or Chemotherapy) trial [16], comparing erlotinib (E) with cisplatin and gemcitabine (PG) in first-line treatment of unselected NSCLC patients, amenable to cisplatin. The TORCH trial protocol outlined a strictly linked second-line treatment mandating PG (E arm) and E (PG arm), while in INNOVATIONS this was recommended but not strictly mandated (table 5) [17–19]. Both trials emphasise platin-based combination chemotherapy as the standard of care in first-line treatment of unselected patients with advanced NSCLC. Even with first-line PG, TORCH patients performed similarly to those allocated to EB in INNOVATIONS and worse than those allocated to PGB (table 5). This might be due to the addition of bevacizumab in both arms of INNOVATIONS, providing 1) a treatment effect and 2) a selection effect of patients included. It may be of importance that there was a substantial difference in inclusion patterns in terms of histology, with predominant adenocarcinoma enrolment in INNOVATIONS (89% in INNOVATIONS *versus* 55% in

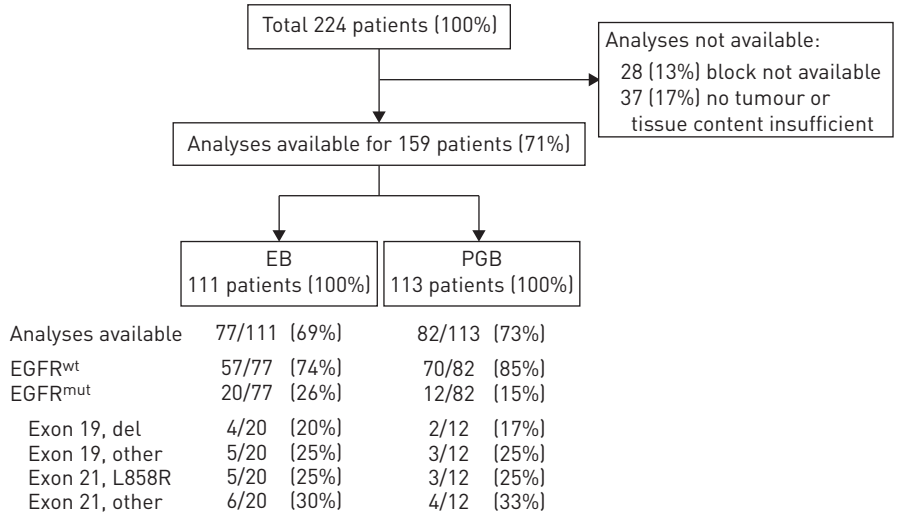

FIGURE 3 Epidermal growth factor receptor (*EGFR*) mutation analysis with Sanger sequencing, by treatment arm. EB: erlotinib/bevacizumab; PGB: cisplatin/gemcitabine/bevacizumab; wt: wild type; mut: mutation. Other mutations were as follows. Exon 19, EB arm: N756H, L747F, L747P, R748K, L730P+A755P; exon 19, PGB arm: D761N, S752F, V742A. Exon 21, EB arm: P848L, D855N, R832C, R831C, T847I, A859S; exon 21, PGB arm: P848L, D855N, L838N, E868G.

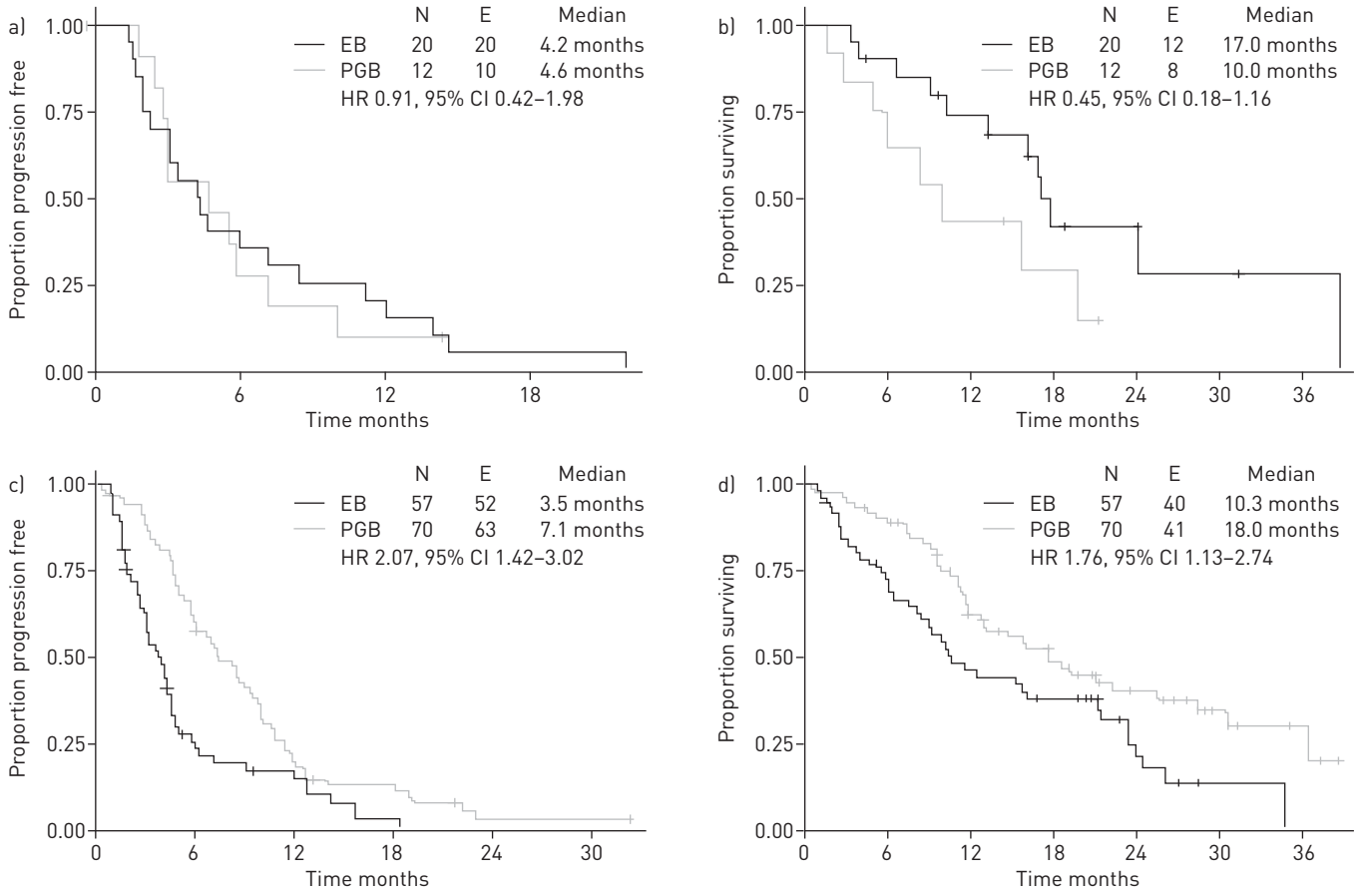

FIGURE 4 a, c) Progression-free survival and b, d) overall survival by treatment arm in patients with a, b) epidermal growth factor receptor (*EGFR*) mutations (n=32) and c, d) *EGFR* wild type (n=127). EB: erlotinib/bevacizumab; PGB: cisplatin/gemcitabine/bevacizumab; N: total patients; E: events; HR: hazard ratio.

TORCH). Even in advanced NSCLC, the prognostic impact of adenocarcinoma is more favourable than other histological subtypes [20]. Moreover, the allocation to and type of further treatment after disease progression might have an impact. In TORCH, proportions of 88% (333 out of 380) in the E arm and 83% (316 out of 380) in the PG arm were documented with progression [16]. However, only 51% (194 out of 380) of E patients and 59% (226 out of 380) of PG patients started with second-line treatment. Similarly, the second-line treatment proportions in INNOVATIONS amounted to 57% (EB) and 63% (PGB), with only 41% of EB patients starting with platinum-based combination chemotherapy after failure of first-line treatment (table 5). Thus, the outcome differences between the trials are not explained by differences of allocation to further treatment. Although in the current trial only 41% of patients in the EB arm received any platinum-based combination chemotherapy, a median survival time of 12.6 months was achieved.

Further trials with first-line EB in NS-NSCLC are summarised in table 5. The TASK trial showed a second-line proportion of 49% after first-line EB [11]. The SAKK (Swiss Group for Clinical Cancer Research) reported on a fixed-sequence protocol with initial EB treatment, showing a higher starting proportion in second-line treatment (62 (61%) out of 101) but a substantial drop down for those receiving four cycles or more (35 (35%) out of 101) [17]. Thus, a start-with-progression treatment strategy, even with a strictly linked treatment sequence, is not effective on all progressors. This is in accordance with the experience derived from maintenance trials after first-line chemotherapy. These revealed in the respective observation arms a second-line treatment proportion ranging between 63% and 72% [21–24]. The deterioration of performance status due to disease progression and the preference of patients were the main reasons for not proceeding to second-line chemotherapy in these trials.

Of tumours successfully analysed for *EGFR* mutations, 20% (32 out of 159) showed molecular alterations of exon 19 or 21, with a high proportion revealing point mutations of uncertain biological significance (18 out of 32) (fig. 3). This substantial proportion might explain the low rates of response and PFS with EB. The trial had finished in 2009 and the *EGFR* mutation analysis has been conducted retrospectively; therefore, it remains unclear whether the low proportion of mutations of biological significance can be delineated from

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TABLE 5 Trials with erlotinib (E) or erlotinib plus bevacizumab (EB) as first-line treatment in unselected patients with advanced nonsmall cell lung cancer (NSCLC)

Trial	Trial type	Histology enrolled	First-line treatment	Second-line treatment	Patients	Proportion with documented progression	Proportion with second-line treatment	Proportion with platinum-based CCT in second line	PFS	Overall survival
TORCH [16]	Phase III	NSCLC	PG	sl E	380	316 (83)	226 (59)	-	5.4 (4.8–6.3)	11.6 (10.2–13.3)
			E	sl PG	380	333 (88)	194 (51)	194 (51)	2.2 (2.1–2.4)	8.7 (7.4–10.5)
INNOVATIONS (current study)	Phase II, randomised	NS-NSCLC	PGB	rec. E	113	100 (88)	70 (63)	12 (11)	6.9 (5.6–8.3)	17.7 (12.1–21.6)
			EB	rec. PG	111	101 (91)	62 (57)	44 (41)	3.5 (2.8–4.1)	12.6 (10.2–16.2)
TASK [11]	Phase II, randomised	NS-NSCLC	CB	Open	63	-	- (66)	-	5.8 (4.8–NR)	NR (-)
			EB	Open	61	-	- (49)	-	4.3 (4.0–5.8)	16.4 (-)
SAKK [17]	Phase II	NS-NSCLC	EB	sl PG	101	-	62 (61)	62 (61)[#]	4.1 (2.9–5.5)	14.1 (10.7–19.0)
Akerley [18]	Phase II	NS-NSCLC	EB	Open	50	45 (90)	28 (56)	26 (52)	3.9 (3.3–4.4)	11.6 (8.1–13.4)
Dingemans [19]	Phase II	NS-NSCLC	EB	Open	47	35 (74)	-	-	3.8 (2.3–5.4)	6.9 (5.5–8.4)

Data are presented as n, n (%) or median (95% CI). CCT: combination chemotherapy after progression; PFS: progression-free survival; TORCH: Tarceva or Chemotherapy; SAKK: Swiss Group for Clinical Cancer Research; PG: cisplatin/gemcitabine; sl: strictly linked; NS: nonsquamous; PGB: cisplatin/gemcitabine/bevacizumab; rec.: recommended; CB: chemotherapy (cisplatin/gemcitabine or carboplatin/paclitaxel)/bevacizumab; -: not reported; NR: not reached. [#]: 35 (35%) patients receiving at least four cycles.

technical difficulties with implementing molecular analyses. Explorative analyses according to treatment arm showed no improvement with EB compared with PGB, in terms of PFS. Nonetheless, stopping EB after disease progression and implementing further treatment resulted in a trend towards superior overall survival (fig. 3). However, salvage treatment was absent in 75% of cases (nine out of 12) in the PGB arm, while all patients in the EB arm received second-line chemotherapy. The low salvage in PGB might be due to quick deterioration but this has to remain open to speculation. The analysis is exploratory and no firm conclusions can be drawn, due to the small patient number and a substantial proportion of mutations with uncertain significance. A subgroup analysis of the BeTa lung trial (assessing the efficacy of bevacizumab plus erlotinib *versus* erlotinib alone in advanced NSCLC after failure of standard first-line chemotherapy) indicated in the second-line setting in 30 *EGFR*-mutated patients (exons 18–21; denaturing high-performance liquid chromatography) an advantageous overall survival with EB compared with E alone [25]. In a further extension, the recently reported JO25567 trial, randomising *EGFR*-mutated patients (del. 19; L858R) in first-line treatment between EB and E, stated a substantial improvement of PFS with EB (median 16.0 *versus* 9.7 months; HR 0.54, p=0.0015) [26]. Thus, in "activating" *EGFR* mutations, the interference with the VEGF pathway, in addition to EGFR tyrosine kinase inhibition (TKI), might have an impact on outcome. The concept of "early interference" has been approached in the FASTACT-2 trial by intercalating chemotherapy with first-line TKI [27]. In the context of this trial, a retrospective analysis on mutation-positive patients revealed a significant survival advantage when intercalating EGFR-TKI upfront with chemotherapy, compared with chemotherapy followed by EGFR-TKI (84% crossover rate to EGFR-TKI after chemotherapy) [27].

Allocating lung cancer patients with tumours harbouring activating *EGFR* mutations or *EML4-ALK* translocations to appropriate TKI treatment is nowadays the standard of care [28, 29]. Molecularly determined treatment options, mandating appropriate assessment and testing, will increasingly move into clinical routine [30]. However, placement of these approaches in the treatment algorithm should be approached thoroughly. Development and overcoming resistance will be an issue [31] and conventional chemotherapy still has potential to show sustained impact. In this regard, randomised trials in selected patients with activating *EGFR* mutations, comparing EGFR-TKI against chemotherapy in first-line treatment, showed no survival advantage between treatment arms, given a crossover to EGFR-TKI after failure of chemotherapy [28]. Nonetheless, recently a combined analysis of two trials comparing chemotherapy with afatinib as upfront TKI (with a 66% crossover rate to EGFR-TKI after failure of chemotherapy) revealed a substantial survival advantage for upfront TKI in cases with del. 19 but not L858R mutations [32].

In conclusion, platinum-based combination chemotherapy remains the standard of care in first-line treatment of unselected NS-NSCLC, showing most favourable survival with the addition of bevacizumab in the current trial. Concise molecular assessment is a prerequisite to implementing molecular targeted approaches in any line of therapy. It clearly has to be emphasised that those approaches strongly mandate appropriate testing and patient selection. Unselected NSCLC patients should not receive TKI as a first-line treatment, as has been shown in further trials (table 5). To derive the most optimal impact on outcome and mitigate resistance, complementing treatments, as well as the sequencing of treatment lines and their effect on overall survival, should be assessed properly.

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