VEGF inhibitors in *EGFR*-mutated lung cancer: a never-ending story?

Mariam Alexander, Balazs Halmos

Department of Oncology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA
Correspondence to: Balazs Halmos, MD. Department of Oncology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA.
Email: bahalmos@montefiore.org.
Comment on: West HL, Moon J, Wozniak AJ, *et al.* Paired Phase II Studies of Erlotinib/Bevacizumab for Advanced Bronchioloalveolar Carcinoma or Never Smokers With Advanced Non-Small-cell Lung Cancer: SWOG S0635 and S0636 Trials. Clin Lung Cancer 2018;19:84-92.

Over the last 15 years, multiple generations of EGFR tyrosine kinase inhibitors (TKIs) have completely transformed the landscape of management of *EGFR*-mutated lung cancers but are rarely used in other settings. In the pre-molecular testing era, the 1st generation reversible EGFR inhibitor, erlotinib, was shown to prolong survival in patients with stage IIIB/IV non-small cell lung cancer (NSCLC) after failure of first- or second-line chemotherapy compared to placebo [overall survival (OS) was 6.7 *vs.* 4.7 months, hazard ratio (HR) 0.70, P<0.001] (1). This led to FDA approval and broad usage as a result, up until withdrawal of this indication (2). Bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF) inhibits angiogenesis and regresses pre-existing tumor blood vessels (3). It also improves drug delivery by decreasing interstitial fluid pressure (4). When administered in combination with platinum-based chemotherapy in patients with advanced NSCLC, a significant survival benefit (OS 12.3 *vs.* 10.3 months in favor of the group receiving bevacizumab, HR 0.79; P=0.003) was noted in the ECOG4599 study leading to FDA approval and common use of this agent (5). As bevacizumab and erlotinib target these key tumor pathways in complementary mechanisms and there is little overlap in their toxicities, it was a reasonable hypothesis that combining the two agents would improve outcomes compared to each agent alone. In 2005, Herbst et al. undertook a phase I/II study to evaluate the efficacy of combining erlotinib and bevacizumab in patients with advanced NSCLC who had progressed on at least one line of chemotherapy (6). The median OS was a promising 12.6 months [1-year survival 54.2% with progression-free survival (PFS) of 6.2 months] with the most common adverse effects being rash, diarrhea and proteinuria. The non-molecularly selected ATLAS trial assessed the efficacy of combining erlotinib and bevacizumab in patients with recurrent or refractory NSCLC after failure of combination chemotherapy (7). Even though there was no improvement in OS (HR 0.92, P=0.5341), the median PFS was significantly, albeit modestly, prolonged to 4.8 months with the combination compared to 3.7 months with bevacizumab alone (HR 0.71, P<0.001). These results were confirmed in the similarly designed phase 3 BeTa trial where there was no improvement in OS (9.3 months in the combined group compared to 9.2 months in control groups) (8). In this study, subgroup analysis of patients with *EGFR*-mutated tumors did not show a statistically significant improvement in overall survival (P=0.1826). The lack of OS benefit might have been partly related to the lack of power in this subset for an OS benefit as well as confounding effect of active subsequent therapies.

Although these results were promising, it was unclear at the time which patients would benefit from an EGFR TKI before molecular testing became widely available providing the backdrop and context to the concurrently conducted SWOG studies focusing on a combination of erlotinib/bevacizumab in two distinct patient subsets (9). The first study, S0635 focused on patients with advanced bronchioloalveolar carcinoma (BAC), recently renamed to adenocarcinoma-in-situ, which is a unique entity where the entire tumor grows along alveolar septae (lepidic growth pattern) and lacks features of invasion (10). On

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radiographic imaging, it can appear as ground glass opacities in a single mass/nodular form versus presenting in a consolidative or multinodular form and these tumors are often fluorodeoxyglucose (FDG) negative on PET/CT. A retrospective analysis showed that BAC was an independent predictor of response to the 1st generation EGFR TKI, gefitinib (P<0.001) (11). Moreover, *EGFR* mutations are frequently present in BACs (12) justifying using this lung cancer subtype as the "enrichment" factor in this trial. The second study enrolled never smokers with advanced lung cancer as these patients, which make up about 10% of the overall advanced NSCLC population were shown to have a longer survival benefit with erlotinib compared to smokers (1) and non-smoking status was similarly found to be an independent predictor of response to 1st generation EGFR TKIs (11). Based on these results and scientific considerations that were relevant at the time, the phase II trials SWOG S0635 and S0636 were designed to investigate if there was a meaningful survival extension of the combination of erlotinib/bevacizumab in advanced lung cancer specifically in patients with BAC or never smokers (9).

These twin trials enrolled patients with BAC/AdenoBAC (S0635) or never smokers (S0636) with stage IIIB/IV lung adenocarcinoma, who had no previous biologic therapy with an EGFR or angiogenesis inhibitor or have received chemotherapy in the 4 weeks before enrollment. The targeted median OS below which the regimen would not be of interest was 12 months, which led to a target population of 80 patients in each trial providing a power of 0.86 to rule out the null hypothesis. The cutoff for which the regimen would warrant testing in the phase III setting was an improved OS >16 months. 84 patients in the S0635 trial and 85 patients in the S0636 trial received erlotinib with bevacizumab until progression or toxicity. The study included patients with brain metastases and progression of disease was measured using CT scans after every 2 cycles and then with increased intervals after 6 months without evidence of progression.

In the S0635 trial, the median cycles delivered was 7, with a median follow up of 37.6 months. Median PFS was 5 months (95% CI: 4–7 months) and median OS was 21 months (95% CI: 14–26 months) with a survival rate of 67% at 1 year. For the S0636 trial with a median of 10.5 cycles delivered, the median follow-up was 41.5 months. Median PFS was 7.4 months (95% CI: 6.1–10.9 months) and median OS was 29.8 months (95% CI: 22.5–37.8 months) with a survival rate of 78% at 1 year. The main grade 3/4 toxicities were rash (13%), diarrhea (10%) and fatigue (9%). Post hoc

analysis showed a correlation of better OS in patients who had developed diarrhea. Unfortunately, in the S0635 trial only 32/85 patients had tissue available for EGFR molecular marker testing and meaningful conclusions could not be drawn as to correlations with biomarkers, such as *EGFR* mutation status. In the S0636 trial, 42 patients had enough tissue for FISH/mutation analysis. There was a significantly higher response rate in *EGFR*-mutant tumors (89% *vs.* 33% in EGFR wild type, P=0.01) but this was not associated with PFS or OS.

All in all, these studies met their primary endpoint demonstrating a promising OS in both studies with the combination. Given the lack of a comparator group and the generally significantly better OS of the two subsets of patients, it is still hard to reach very firm conclusions from either study and from the optic of recognizing the advances made since, the study results lack significant impact. However, these studies represented a tremendous effort on the part of the authors demonstrating the ability to conduct and complete studies on small lung cancer patient subsets and were based on the relevant knowledge during the time of study design. Of course, since the trial was initiated the field has moved to molecular detection of *EGFR* mutations for EGFR TKI therapy selection and the understanding of other key oncogenic alterations enriched in non-smokers, for example ALK/ROS alterations as well as key subsets of BACs, such as K-Ras mutations and NRG1-fusions present in mucinous types with specific targeted treatment considerations.

Since the initial OPTIMAL and EURTAC trials using 1st generation EGFR TKIs erlotinib and gefitinib, the field has rapidly progressed (13-15). The second generation irreversible TKIs, which provide a broader inhibition of the ERBB family, afatinib and dacomitinib have shown unique benefits in tumors with exon 19 deletion and certain uncommon *EGFR* mutations (16) and now also a survival benefit over gefitinib in the case of dacomitinib (17,18). The third generation TKI, osimertinib, which has unique activity in T790M mutated NSCLC showed superiority over chemotherapy in the acquired resistance setting as seen in the AURA3 and over 1st generation EGFR TKIs in the FLAURA study (19,20). However, given the broad range of resistance mechanisms that now are emerging on osimertinib, there is a strong need to re-consider combination strategies using alternative options such as immuno-oncology agents, MET inhibitors, MEK1/2 inhibitors or angiogenesis inhibitors re-igniting the interest in the results of studies such as S0635 and S0636 and it is quite

Table 1 Selected studies combining EGFR and VEGF inhibitors in lung cancer patients

Study/investigator	Phase	Drug combination/ comparison	N	Line of therapy/EGFR mutation-based selection (yes/no)	Primary EP	Clinical outcomes
Herbst et al., 2007 (21)	I/II	B+E vs. B+C vs. C	120	2nd line/no	PFS	PFS: 4.4 m in B+E vs. 4.8 m in B+C vs. 3.0 m for C alone (HR 0.72); OS: 13.7 vs. 12.6 vs. 8.6 m (HR 0.78)
BeTA/Herbst et al., 2011 (8)	III	B+E vs. E	636	2nd line/no	OS	OS: 9.3 m in B+E vs. 9.2 m in E alone (HR 0.97, 95% CI: 0.80–1.18, P=0.7583); PFS: 3.4 m in B+E vs. 1.7 m in E (HR 0.62, 95% CI: 0.52–0.75)
NTR528/Dingemans et al., 2011 (22)	II	B vs. E	47	1st line/no*	NPR	NPR: 75%; mPFS: 3.8 m (95% CI: 2.3–5.4); mOS: 6.9 m (95% CI: 5.5–8.4)
SAKK19/Zappa et al., 2012 (23)	II	B+E → C at progression	103	2nd line/no	DSR	DSR: 54.5%; mTTP: 4.1 m; OS: 14.1 m
TASK/Ciuleanu et al., 2013 (24)	II	B+E vs. B+C	124	1st line/no	PFS	PFS: 18.4 vs. 25.0 w (HR 2.05, P=0.0183)
ATLAS/Johnson et al., 2013 (7)	III	(C+B) ×4 cycles → B vs. B+E	746	2nd line/no	PFS	PFS: 3.7 m in B vs. 4.8 m in B+E (HR 0.71, P<0.001); OS: 13.3 vs. 14.4 m (HR 0.92; P=0.5341)
JO25567/Seto et al., 2014 (25); Yamamoto et al., 2018 (26)	II	B+E vs. E	154	1st line/yes	PFS	PFS: 16.0 m in B+E vs. 9.7 m in E (HR 0.54, P=0.0015); OS: 47.0 vs. 47.4 m (HR 0.81, P=0.3257)
LUN04-77/Riggs et al., 2013 (27)	II	B+E (PS ≥2 or age ≥70)	25	1st line/no	rNPD	rNPD was 28%
INNOVATIONS/ Thomas et al., 2015 (28)	II	B+E/B+C	224	1st line/no	PFS	PFS: 3.5 m in B+E vs. 6.9 m in B+C (HR 1.85, P<0.0001); OS: (12.6 vs. 17.8 m (HR 1.41, P=0.04)
BELIEF/Rossell et al., 2017 (29)	II	B+E (stratified by T790M)	109	2nd line/yes	PFS	PFS: 16.0 m in T790M vs. 10.5 m in T790M-negative
Wang et al., 2017 (30)	III	E+B+P vs. E	297	2nd line/no	PFS	PFS: 4.6 m in E+B+P vs. 1.9 m in E (P=0.003); OS: 10.4 vs. 8.9 m (P=0.031)
ABC/Hata et al., 2018 (31)	II	B+A	32	Any/yes	PFS	PFS: 6.3 m (95% CI: 3.9–9.7); ORR: 18.8% (95% CI: 7.2–36.4%)
JVDL (NCT02789345)/Yu et al., 2017 (32)	Ib	O+R vs. O+N	25	2nd line or after TKI/yes (T790M)	Safety	Ongoing
OLCSG1404/ Harada et al., 2017 (33)	Ib	A+B	6	2nd line/yes	Safety	Ongoing
RELAY/Reck et al., 2018 (34)	Ib	E+R	14	1st line/yes	Safety	PFS: 17.1 m (95% CI: 8.8 m–NR)
BEVERLY/Gridelli et al., 2016 (35)	III	B+E vs. E	200	1st line/yes	PFS	Ongoing

Table 1 (*continued*)

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Study/investigator	Phase	Drug combination/ comparison	N	Line of therapy/EGFR mutation-based selection (yes/no)	Primary EP	Clinical outcomes
NEJ026/Furuya *et al.*, 2018 (36); Maemondo *et al.*, 2016 (37)	III	B+E *vs.* E	Ongoing	1st line/yes	PFS	PFS: 16.9 m in B+E *vs.* 13.3 m in E (HR 0.605, P=0.0157)
NCT02803203/Yu *et al.*, 2017 (38)	I	O+B	15	1st line/yes	PFS	Ongoing

*, EGFR mutation status assessed after treatment. m, months; w, weeks; E, erlotinib; B, bevacizumab; C, chemotherapy; A, afatinib; O, osimertinib; R, ramucirumab; N, necitumumab; P, panitumumab; PFS, median progression-free survival; ORR, objective response rate, OS, overall survival; NPR, non-progression rate at 6 weeks; DSR, disease stabilization rate; rNPD, rate of non-progressive disease at 4 months.

possible that addition of these agents to a front-line TKI could potentially delay resistance mechanisms (*Table 1*) (39).

Indeed, in studies where patients were molecularly selected specifically for *EGFR* mutations, there was a notable improvement in PFS with the combination of EGFR TKI/bevacizumab. For instance, the phase 2 JO25567 study assessed the efficacy of combining erlotinib with bevacizumab as first-line therapy in patients with advanced NSCLC with an activating *EGFR* mutation (25). Promisingly, the median PFS was very significantly prolonged to 16.0 months with the combination compared to 9.7 months with erlotinib alone (HR 0.54, 95% CI: 0.36–0.79, P=0.0015). However, at the ASCO 2018 meeting, after longer follow-up, no notable OS benefit was reported in the combination regimen [OS 47.0 *vs.* 47.4 months (HR 0.81, P=0.3257)] (26). The single arm, phase 2 BELIEF trial corroborated these findings with overall PFS of 13.2 months (95% CI: 10.3–15.5 months) in patients with EGFR activating mutation receiving both erlotinib and bevacizumab (29). Interestingly, there was a further benefit in patients who later were noted to harbor a T790M resistance mutations achieving a PFS of 16.0 months [95% CI: 12.7 months–not reached (NR)]. These data suggest that the combination of erlotinib and bevacizumab is beneficial at least in terms of achieving more durable remissions and delaying resistance in the first-line setting in patients with activating *EGFR* mutations.

Most recently, the phase III NEJ026 trial assigned patients with advanced NSCLC with activating *EGFR* mutations, who were treatment naive to erlotinib/bevacizumab versus erlotinib alone (36). There was again

significant improvement in PFS in the combined group compared to erlotinib alone (16.9 *vs.* 13.3 months, HR 0.61, P=0.016) and OS results will be eagerly awaited. The most common toxicities were hypertension, proteinuria and hemorrhage and as in prior studies, the combination appeared generally well tolerated. Although the above listed trials show an impressive improvement in PFS with the combination of EGFR TKI with VEGF inhibitors, it has not translated into an overall survival benefit as of yet possibly related to extended survival of these patients and effective subsequent therapies confounding the results. However, the standard of care for first-line management of advanced *EGFR*-mutated NSCLC in the US is now the third generation osimertinib, which makes the control arm in these trials also obsolete. A phase 1/2 study combining osimertinib with bevacizumab is ongoing, with preliminary results showing that the combination was tolerable and effective in the first-line setting with potential follow-up studies being planned (38). The combination of osimertinib and the VEGFR2 inhibiting monoclonal antibody, ramucirumab is also being investigated in a phase Ib study, with preliminary results showing median PFS not reached (90% CI: 5.49–NR) and PFS at 6 months of 64% (90% CI: 43.7–78.6%) (40).

There is currently a rapid paradigm shift towards combining immune checkpoint inhibitors with chemotherapy in patients with advanced NSCLC. Based on the positive results of the Keynote-021 and 189 studies, the immune checkpoint inhibitor, pembrolizumab is approved for front line treatment of metastatic non-squamous NSCLC in combination with chemotherapy irrespective

of PD-L1 expression (41,42). Tumor survival requires vascularisation, which is usually abnormal in architecture. VEGF inhibitors can lead to the normalization of this vasculature leading to increased T-cell infiltration, possibly enhancing an immune response against the tumor (43). Therefore, combining immune check point inhibitors with VEGF inhibitors may help enhance immunotherapy efficacy and decrease modes of resistance. While the listed Keynote studies excluded *EGFR*-mutated patients as prior data suggested lack of activity of checkpoint inhibitors in these oncogene-driven, low mutation burden tumors, the phase III, IMpower150 trial combining the PD-L1 inhibitor atezolizumab with bevacizumab and platinum doublet chemotherapy did permit the enrolment of patients with EGFR/ALK positive tumors and demonstrates unique promise for this concept (44). The median PFS for the entire group was improved by 1.5 months with the four-drug regimen compared to the control arm of carboplatin/Taxol/bevacizumab (8.3 *vs.* 6.98 months, P<0.001) with an associated significant improvement in OS (19.2 *vs.* 14.7 months, P=0.0164). The data was furthermore quite striking in the subset of patients with EGFR and ALK mutations (PFS 9.7 months for the 4 drugs *vs.* 6.1 months in those with bevacizumab and chemotherapy alone). Interestingly, the PFS curves separate more over time following completion of the chemotherapy suggesting that there may be an ongoing synergy between bevacizumab and atezolizumab providing now hope for a variety of chemo/immunotherapy/anti-angiogenic combinations as an effective strategy for *EGFR*-mutated tumors. While this study does not allow the separation of benefit driven by bevacizumab but certainly continues to provide fodder for a continued role into studies of VEGF-directed therapy.

All in all, more than 10 years following the publication of the pivotal ECOG4599 study, we continue to see intriguing signals of benefit of VEGF-directed therapy in multiple settings, such as combination with front-line and second-line chemotherapy, in synergy with chemo/immunotherapy as well as EGFR TKI therapy. While studies such as the S0635/0636 studies might not have yielded conclusive answers, they provided further data to support ongoing investigations of this subject as well as demonstration that collaborative efforts can permit completion of important studies on small patient subsets and thereby West et al., should be commended for their significant contributions to the body of literature on the utility of anti-angiogenic therapy in advanced NSCLC and we need to hope that over the next few years we will be able to reach final conclusions

to this never-ending story.

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Footnote

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