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The efficacy and safety of bevacizumab in addition to platinum-based chemotherapy for the first-line treatment of patients with advanced nonsquamous non-small-cell lung cancer: Final results of AVALANCHE, an observational cohort study

EDINA TOLNAY[1*], ÁRON KRISTÓF GHIMESSY[2*], ERZSÉBET JUHÁSZ[3], ZSUZSANNA SZTANCSIK[4], GYÖRGY LOSONCZY[5], PÉTER DOMBI[6], ZSUZSANNA VENNES[7], LÁSZLÓ HELF[8], EDIT CSADA[9] and VERONIKA SÁROSI[10]

[1]2nd Department of Pulmonology, Pest County Institute of Pulmonology, Törökbálint 2045; [2]Department of Thoracic Surgery, National Institute of Oncology, Budapest 1122; [3]14th Department of Pulmonology and Internal Medicine, National Korányi Institute of Pulmonology, Budapest 1121; [4]1st Department, Békés County Pulmonology Hospital, Gyula 5701; [5]Department of Pulmonology, Semmelweis University, Budapest 1125; [6]Department of Oncology, Szent Borbála County Hospital, Tatabánya 2800; [7]2nd Department of Internal Medicine, Uzsoki Hospital, Budapest 1145; [8]Department of Pulmonology, Bonyhád Hospital, Bonyhád 7150; [9]Department of Pulmonology; Faculty of Medicine, University of Szeged, Deszk 6772; [10]Department of Pulmonology, University of Pécs, Pécs 7623, Hungary

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Abstract. The previous results of former clinical studies confirmed that first-line bevacizumab (BEV) in combination with chemotherapy improves clinical outcomes in patients with advanced non-squamous non-small cell lung cancer. The AVALANCHE study (ClinicalTrials.gov Identifier NCT03170284) was undertaken to assess the clinical outcomes of first-line BEV combined with standard platinum-based regimens in the Hungarian clinical practice. This observational study was conducted in 28 Hungarian sites, with patients enrolled between July 2008 and April 2011. Patients with untreated locally advanced, metastatic or recurrent lung adenocarcinoma received BEV (7.5 mg/kg, q3w) with any platinum-doublet for up to 6 cycles, and then non-progressors proceeded to receive BEV until disease progression or unacceptable toxicity. The primary endpoint was time-to-progression, and secondary endpoints included overall survival (OS), tumour control rate and safety. Patients were also analysed as two cohorts (non-progressors vs. progressors) based on whether or not they received BEV maintenance therapy following completion of first-line chemotherapy plus BEV. The study enrolled 283 patients (median age: 58.2 (18-78) years; males: 50.5%; stage: III/B: 18.4%, IV: 79.9%; adenocarcinoma/other: 95.8/4.2%; ECOG PS 0/1/2/≥3: 30.8/59.7/2.6/1.4%). Centrally located tumours were reported in 21.6%. Cisplatin/carboplatin-based regimens: 53.8/46.2%. A total of 43% of patients received BEV maintenance therapy. The median number of BEV cycles was 6. Median progression-free survival (PFS) was 7.2 months and OS was 15.2 months for the entire cohort. Longer PFS and OS were observed in patients who received BEV maintenance therapy [median OS, 26.2 vs. 10.2 months (P<0.001); median PFS, 9.2 vs. 5.8 months (P<0.001)]. Contrary to the results of previous OCS no significant difference was recorded in the different age groups or gender. Best tumour response: Complete remission/partial remission/stable disease/progressive disease/not reported were: 1.5/29.9/26.9/9.1/32.6% of all patients. In conclusion, clinical outcomes obtained in this real-life population were consistent with pivotal studies. BEV maintenance treatment was associated with a significantly longer PFS and OS.

Correspondence to: Dr Áron Kristóf Ghimessy, Department of Thoracic Surgery, National Institute of Oncology, H-1013 Attila út 61, Budapest 1122, Hungary
E-mail: aronghimessy@gmail.com

*Contributed equally

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BEV, bevacizumab; CI, confidence interval; CR, complete response; CRF, case report form; ECOG, Eastern Cooperative Oncology group; EGFR, epidermal growth factor receptor; EMA, European medicines agency; NA, not applicable; NSCLC, non-small cell lung cancer; nsNSCLC, non-squamous non-small cell lung cancer; OCS, observational cohort study; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RCT, randomized clinical trial; SAE, serious adverse event; SD, stable disease; SD, standard deviation; TNM, Internationally accepted classification of malignant tumours; TTP, time-to-progression; VEGF, vascular endothelial growth factor; WHO, World Health Organization

Key words: bevacizumab, non-small cell lung cancer, first-line, observational study

Introduction

Lung cancer is the second most common malignant tumour. However it causes more deaths than breast, prostate and colon cancer combined (1). Hungary has the highest mortality rates of lung cancer in the world regarding both men and women. Hungary, unlike other developed countries, records a growing number of new cases. While the incidence hasn't increased over the last few years in men, it continuously does in women (2).

Survival rates remain poor in non-small cell lung cancer (NSCLC) with 49% 5-year survival rate with early (stage IA) NSCLC and 1% 5-year survival rate in stage IV. One reason for such poor survival is that more than 50% of patients are diagnosed with advanced disease (3).

Although many advances have been made in the treatment of unresectable (stage IIIB), metastatic (stage IV) or recurrent NSCLC, such as the introduction of targeted therapy for specific oncogenic drivers (EGFR, ALK mutations etc.), platinum-based chemotherapy (with or without radiotherapy) still remains the first choice in most cases.

Targeted therapies showed superior survival data, demonstrated improved response rates and are associated with less toxicity. Druggable mutations for EGFR and ALK mutation, however, only occur in 25 and 5%, respectively (4,5). Vascular endothelial growth factor (VEGF) is a key factor to endothelial cell growth and one of the most important regulators of angiogenesis. Increased expression of VEGF can be demonstrated in most solid tumours including NSCLC (6). In many cases, VEGF overexpression is associated with an increased risk of relapse and metastasis (7-10). According to preclinical studies, anti-VEGF monoclonal antibodies are capable of inhibiting the growth of human tumour xenografts both in monotherapy and in combination with chemotherapy (11-14). Bevacizumab (BEV) (Avastin®; Genentech/Roche, San Francisco, CA, USA) is a humanized monoclonal antibody that acts by binding and neutralizing the VEGF-A isoform, thus preventing VEGF ligand-receptor binding. It has demonstrated its efficacy in colorectal (15,16), ovarian (17), breast (18,19) and renal cancer (20,21). This was the first antivascular drug to be licensed for the treatment of NSCLC.

According to a phase II study (22), BEV treatment in combination with chemotherapy in NSCLC was more effective than chemotherapy alone. The combination was also well tolerated, however, the incidence of lung haemorrhage increased. In a post hoc multivariate analysis, squamous cell histology was identified as an independent risk factor for bleeding (23). Consequently, patients with squamous cell histology were excluded from most of the clinical trials of BEV in NCSLC.

Subsequent to the above Phase II study, the Eastern Cooperative Oncology Group (ECOG) E4599 trial was initiated (24). This study, which was the first published Phase III randomized trial of an antiangiogenesis agent in combination with chemotherapy in patients with advanced NSCLC, randomized chemotherapy-naive patients with predominantly non-squamous cell histology were included. In the BEV treatment arm, following completion of chemotherapy, single-agent BEV was continued until disease progression. Results showed that the addition of BEV was associated with a significant improvement in the median overall survival (OS) compared with chemotherapy alone. Progression-free survival (PFS) was also significantly improved.

A second Phase III trial (Avastin® in Lung; AVAiL), evaluating BEV in combination with cisplatin and gemcitabine (25) (another commonly used and efficacious regimen in NSCLC) was originally initiated with a primary end point of OS. However, after the positive OS results of E4599, the study design was amended so as to change the primary end point from OS to PFS. Patients were randomly assigned to receive cisplatin 80 mg/m^2 and gemcitabine 1250 mg/m^2 for up to six cycles plus low-dose BEV (7.5 mg/kg), high-dose BEV (15 mg/kg) or placebo every 3 weeks until disease progression. PFS was significantly prolonged with BEV. Interestingly, according to the final efficacy analysis, OS was >13 months in all treatment groups, which was the longest OS reported for advanced non-squamous NSCLC in a clinical trial setting, although it did not yield a statistically significant prolongation with either BEV dose (26).

As a result of the above trials, BEV in combination with platinum-based chemotherapy was approved for the first-line treatment of patients with advanced NSCLC by the European Medicines Agency (EMA) in August 2007.

Although BEV was approved with platinum-based chemotherapy in NSCLC in 2007, so far no Hungarian data have been available. The AVALANCHE study (ClinicalTrials.gov, identifier: NCT03170284) was undertaken to assess the clinical outcomes of first-line BEV combined with standard platinum-based regimens in Hungarian clinical practice.

Patients and methods

Study design. AVALANCHE (ClinicalTrials.gov, identifier: NCT03170284) was a multi-centre single-arm observational study designed to assess the efficacy and safety of BEV therapy in patients with advanced, unresectable, metastatic or recurrent nsNSCLC (other than predominantly squamous cell histology) in the routine oncology practice in Hungary. Further objective of the study was to assess and identify possible treatment-related prognostic factors.

Patients. This study was originally projected to enrol 150 patients from 40 Hungarian study centres. Fortunately, however, due to the high number of patients recruited by some centres, nearly 300 patients were enrolled.

Patients with histology or cytology proven unresectable advanced, metastatic or recurrent (stage IIIB/IV) NSCLC other than predominantly squamous cell histology were included in the present study. There were 143 male (50.5%) and 135 female (47.7%) patients and no data on gender was available in 5 patients (1.8%) (Table I).

The exclusion criteria were the following: i) hypersensitivity to the active substance or to any of the excipients of Avastin®; ii) hypersensitivity to products derived from Chinese hamster ovary (CHO) cells or to other recombinant human or humanized antibodies; iii) pregnancy and iv) presence of untreated central nervous system metastases. The present study was done in accordance with the Declaration of Helsinki, Good Clinical Practice International Conference on Harmonisation Tripartite Guidelines, laws and regulations of the participating institutes' country. The present study was approved by the Hungarian Ethics Committee and Health Authority. All patients provided written informed consent.

Table I. Patient demographics and treatment.

Characteristics	No. of patients, n (%)
Evaluable patient population	283 (99.6)
Patient population evaluable in terms of PFS	252 (88.7)
Patient population evaluable in terms of OS	250 (88)
Age (years)	
Mean	58.16±9.032
Men	58.30±8.986
Women	58.02±9.113
Gender	
Male	143 (50.5)
Female	135 (47.7)
No data	5 (1.8)
Histologic type	
Adenocarcinoma	271 (95.8)
Bronchoalveolar carcinoma	11 (3.9)
Squamous cell carcinoma	1 (0.4)
Stage	
III B	52 (18.4)
IV	226 (79.9)
No data	5 (1.8)
Previous treatment	
Previous surgery	64 (22.6)
Adjuvant/neoadjuvant chemotherapy	18 (6.4)
Radiotherapy	18 (6.4)
Chemotherapeutic agent during study	
Paclitaxel	132 (46.6)
Gemcitabine	111 (39.2)
Docetaxel	18 (6.4)
Vinorelbine	2 (0.7)
Other	7 (2.5)
No data	13 (4.6)
Reported reasons for ending the study	
Progression of primary disease	172 (60.8)
Deterioration of symptoms	4 (1.4)
Loss of contact with the patient	7 (2.5)
Adverse event associated with BEV treatment	13 (4.6)
Patient's decision	17 (6.0)
Mortality	16 (5.7)
Other	45 (15.9)
No data	9 (3.2)

PFS, progression-free survival; OS, overall survival; BEV, bevacizumab.

Treatment. Eligible patients received first-line BEV with cisplatin or carboplatin in accordance to the approved and reimbursed BEV indication in Hungary (BEV 7.5 mg/kg, every 3 weeks with any platinum-doublet for up to 6 cycles) then non-progressors proceeded to receive BEV until disease progression or unacceptable toxicity. The maintenance therapy regimen was 7,5 mg/kg every 3 weeks until PD or intolerable toxicity. The third component of the combination chemotherapy was one of the following: paclitaxel, gemcitabine, docetaxel or vinorelbine. Based on the therapeutic protocol, patients were followed up until the first progression of their primary disease, or death, or withdrawal of consent, or loss of contact with the patient, or closure of the study, whichever occurred first.

Progression-free and OS. Investigators seemed to be frequently using PFS and time-to-progression (TTP) interchangeably in clinical trials in the early 2000s (27). The protocol of our study defined TTP as the time elapsed from the date of enrolment until the first documented progression or the death of the patient from any cause which is in accordance with the current definition of PFS. To avoid confusion, PFS will be used hereinafter for the denomination of the primary endpoint of the study. Progression was determined by the investigator at the routine clinical practice follow-up examinations. PFS was calculated from the start of BEV treatment.

Secondary endpoints included best tumour response (complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD)), OS (based on retrospective analysis) and indicators of safety (serious and non-serious adverse events). Objective response rate (ORR) was calculated from patients experiencing complete or partial remission.

Basic demographic data, basic vital parameters, primary disease-related historical data, ECOG performance status, data related to BEV treatment, results of the staging assessments as well as the patient's comorbidities and concomitant treatments were recorded in an electronic case-report form.

Following the closure of the study, data for the assessment of the PFS were available for 252 patients. As per the amended protocol, the secondary endpoint (OS) was retrospectively analysed based on data from 250 patients.

During the treatment period regular monitoring visits were conducted to ensure high-quality data collection. Data related to BEV treatment, blood pressure, body weight, concomitant treatments and adverse events were registered.

The following data were recorded at the end-of-treatment visit: End date of BEV treatment, reason for ending treatment, ECOG status, best tumour response observed during treatment, concomitant treatments administered during BEV treatment and adverse events observed during BEV treatment.

Statistical analysis. Continuous variables were compared with Student's t-tests if the sample distribution was normal or with Mann-Whitney U test if the sample distribution was asymmetric. Categorical data were compared using Fisher's exact probability and χ^2 tests. PFS (primary study endpoint) and OS in the total population were analysed using Kaplan-Meier curves. Both PFS and OS were assessed separately in subgroups according to gender, age, ECOG status, the platinum derivate used, the use of maintenance therapy and weather prior surgical intervention was done. Log-rank test was used for comparison between the above mentioned groups.

PFS was defined as the time elapsed from the start of BEV treatment until the first documented progression or the death

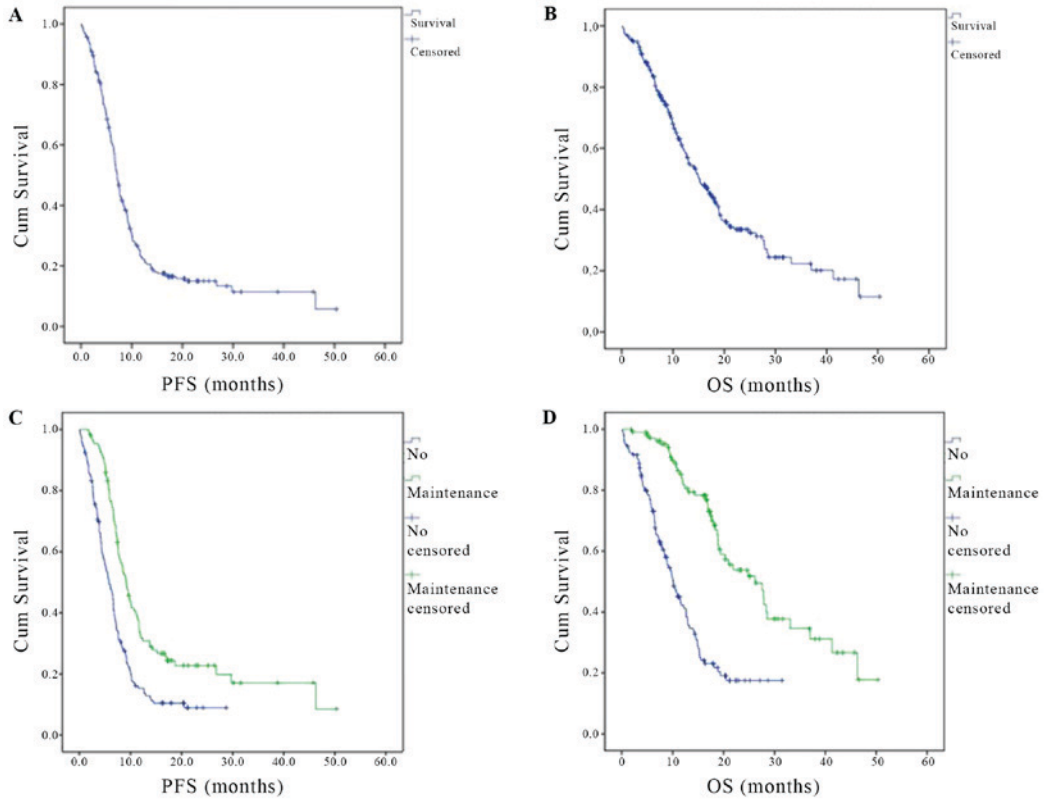

Figure 1. Kaplan-Meier plots of (A) PFS in the total population. (B) OS in enrolled and evaluated patients. (C) Analysis of PFS by Bevacizumab maintenance therapy. (D) Analysis of OS by Bevacizumab maintenance therapy. OS, overall survival; PFS, progression-free survival.

of the patient from any cause. For study subjects who had not shown progression and had not died by the closure of the study, the data were censored at the date of the last contact.

OS was defined as the time elapsed from the date of enrolment until the death of the patient from any cause. Regarding subjects who had not died by the closure of the study, the OS data were analysed retrospectively after the end of the study in the knowledge of their dates of death. Otherwise, data were censored at the date of the last contact.

P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were conducted using Statistica 8.0 (StatSoft, Inc., Tulsa, OK, USA) software program.

Results

Baseline characteristics of the patients. A total of 284 patients with corresponding diagnosis were identified at the Hungarian study sites, and were subsequently enrolled into the study between 17th June 2008 and 3rd May 2011, out of which data of 283 patients were evaluable. From among the 41 study centres originally involved, no patients were enrolled at 16 sites, thus in fact 25 centres participated actively. The highest number of patients enrolled at one centre was 36, whereas the smallest was 1. One patient did not comply with all the inclusion and exclusion criteria: The patient's histological diagnosis was squamous cell carcinoma; therefore evaluable patient population was 283. Central localization of the primary tumour was reported in 61 patients (21.6%) and cavitated tumour in 4 patients (1.4%) in the total patient population.

The study population had to be reduced to 252 in case of PFS and 250 regarding OS. In case of PFS 31 patients and in case of OS 33 patients had to be excluded from the data assessment due to missing or incomplete information. These information could not be recovered retrospectively.

The demographic characteristics of the enrolled and evaluable patients are summarized in Table I.

Treatment. Prior to enrolment, 64 patients (22.6%) had undergone surgical intervention, 18 patients (6.4%) had received adjuvant/neoadjuvant chemotherapy, and 18 patients (6.4%) had received radiotherapy (Table I).

Patients received cisplatin (N=148, 52.3%) or carboplatin (N=124, 43.8%) treatment in accordance with the protocol in approximately half-and-half proportion during the study. No data are available for 11 patients (3.9%). The other components of the combination chemotherapy are shown in Table I.

The vast majority of patients (N=262, 92.6%) received BEV in 3-weekly cycles. A treatment of different cycle frequency was applied in two patients (0.7%), and no data were available for 19 patients (6.7%). The median number of BEV treatment cycles in the retrospectively evaluated patient population was 6.

The most common reason for ending the study was documented as progression of the primary disease in more than half of the study subjects (60.8%). Patient's decision, patient's death, adverse event related to BEV therapy, loss to follow-up, and symptom deterioration accounted for ending the study in 6.0, 5.7, 4.6, 2,5 and 1.4% of the cases, respectively. Other reasons behind ending the study occurred in 15.9%; no data were available in 3.2% of cases.

Table II. Best tumor response reached during the first-line treatment.

Response	N	Patient population with evaluable data (n=133), (%)	Total patient population (n=216), (%)
Complete remission	3	2.3	1.5
Partial remission	59	44.4	29.9
Stable disease	53	39.8	26.9
Progressive disease	18	13.5	9.1
Not assessable	83	-	32.6

Efficacy analysis

PFS. The PFS in the total study patient population was 7.162±0.282 ($CI_{95\%}$: 6.609-7.715) months (Fig. 1A). The subgroup-analysis of PFS by gender showed that the survival time with BEV treatment was longer in women (median: 7.589±0.647, $CI_{95\%}$: 6.321-8.858 months) than in men (median: 6.669±0.375, $CI_{95\%}$: 5.934-7.405 months). This difference, however, was not significant (P=0.542).

The median PFS was higher in patients with an ECOG status of 0 at enrolment (median: 7.326±0.535, $CI_{95\%}$: 6.278±8.375 months) than in patients with a baseline ECOG status of 1 (median: 6.702±0.597 months, $CI_{95\%}$: 5.531-7.873 months). However, the difference between the two groups was not remarkable (P=0.123).

Similarly, PFS was not significantly influenced by the localization of the tumour (central vs. non-central, P=0.813).

Interestingly, the median PFS in patients who had undergone surgical intervention prior to enrolment (median: 8.411±0.947, $CI_{95\%}$: 6.554-10.267 months) was notably higher (P=0.017) compared with patients with no such prior intervention (median: 6.834±0.265, $CI_{95\%}$: 6.314-7.353 months). In contrast, neither adjuvant/neoadjuvant chemotherapy (P=0.165) nor radiotherapy (P=0.165) applied prior to enrolment had a significant impact on median PFS.

The platinum derivative used had no significant influence on median PFS, either (P=0.199).

Nearly 10% of the patient population with evaluable data were over 70 years of age at the time of enrolment. The median PFS was not significantly different between patients under or above 70 years of age (P=0.541).

Of note, median PFS was significantly higher (P<0.001) in patients receiving BEV maintenance therapy (median: 9.166±0.601, $CI_{95\%}$: 7.988-10.345 months) compared with those who received no maintenance therapy (median: 5.815±0.574, $CI_{95\%}$: 4.690-6.940 months) (Fig. 1C).

Secondary endpoints

Tumour response. Disease control was achieved in a remarkable 86.5% with CR in 2.3%, and PR in 44.4% of the cases with evaluable data. PD was recorded in 13.5% of evaluable cases and sufficient data was not available in 32.6% (Table II).

OS. The median OS in the total study population was 15.179±1.377 months ($CI_{95\%}$: 12.480-17.877) (Fig. 1).

As with PFS, we performed subgroup-analysis of OS by gender, ECOG status, prior surgical procedure and chemotherapy. Results can be seen on Table III.

The localization of the tumour had no impact on OS (P=0.992) in the patient population studied.

Surprisingly, we found a tendency towards a higher median OS for patients over 70 years of age (18.398±3.869 months, $CI_{95\%}$: 10.815-25.982 months) compared with patients younger than 70 years (15.014±1.329 months, $CI_{95\%}$: 12.410-17.619 months), although this difference remained not significant (P=0.638).

A remarkably longer (P<0.001) OS was observed in patients receiving BEV maintenance therapy (median: 26.218±3.946 months, $CI_{95\%}$: 18.484-33.952 months) than in those without maintenance BEV therapy (median: 10.152±0.975 months, $CI_{95\%}$: 8.240-12.064 months) (Fig. 1D).

Safety and adverse events. As per the protocol, possible adverse events (AE) encountered during the study were recorded in the Case Report Form. Data on AE were recorded from the start of treatment until the end of treatment.

During the study, a total of 157 AEs were reported for 59 patients, 14 of which were serious (sAE) (Table IV).

Of all the adverse events, 63 (40.1%) events resolved without sequelae, the investigators reported improvement for 61 cases (38.9%) and the event resolved with remaining symptoms in 7 cases (4.5%). 2 AEs (1.3%) had not resolved, 14 AEs (8.9%) persisted unchanged from observation until the last follow-up of the patient, 5 AEs (3.2%) led to the death of the patient, and the outcome was unknown for 4 AEs (2.5%).

Of the above-mentioned AEs, 14 were categorized as sAE, which were the following: Anaemia (3 cases), pulmonary embolism (3 cases), haemoptysis (2 cases), deep vein thrombosis (2 cases), hypertension (1 case), neutropenia (1 case), thrombocytopenia (1 case), uraemia (1 case). 5 of these (two cases of pulmonary embolism, haemoptysis, hypertension and uraemia) led to the death of the patient.

During the study period, 16 (5.6%) of the 283 enrolled and evaluable patients died. The investigators reported the cause of death as disease progression in 11 cases (3.8%), while a serious adverse event was behind the death of the patient in 5 cases (1.7%).

In summary, the participating investigators did not encounter and report on any new information on the safety profile of BEV. Indeed, the rate of reported adverse events falls behind the rate expected based on literature data.

Discussion

Various randomised trials showed superior survival data and acceptable safety results with the use of BEV in

Table III. Subgroup analysis of OS.

Variable	Gender		ECOG status		Prior surgery		Prior chemo-/radiotherapy		Platinum derivative used	
	Male	Female	ECOG 0	ECOG 1	Yes	No	Chemotherapy	Radiotherapy	Cisplatin	Carboplatin
Median OS	12.583	17.511	18.891	13.306	26.218	13.306	Not significant P=0.237	Not significant P=0.237	16.953	12.977
CI 95%	9.544-15.622	14.320-20.703	14.869-22.914	10.385-16.227	18.721-33.714	11.373-15.239			13.475-20.431	9.661-16.294
P-value	0.071		0.004		0.001				0.006	

OS, overall survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

NSCLC (24,25,28,29). Most of these trials, however, were not concluded in an unselected, real-world environment. Of note, there are still several questions yet to be answered regarding the drug's safety, efficacy and optimal treatment protocol. The AVALANCHE observational cohort study (OCS) provided an opportunity to examine the safety and efficacy of BEV in combination with chemotherapy in a real-life setting in Hungarian everyday practice.

Generally the results of observational studies cannot be directly compared with those of a randomized study. However, the indicators of effectiveness in the AVALANCHE study (which included a higher variety of patients) are consistent with those of several randomized trials shown in Table V.

The median PFS and OS in our study were longer than in the AVAiL (25,26), the E4599 (24) or the ARIES (28) studies. These OS outcomes are also comparable with the results of the phase IV SAiL trial conducted between 2006 and 2008 in Europe. SAiL reported 14.6 months (95% CI, 13.8-15.3) OS, that was shorter than the reported OS in AVALANCHE. The PFS in AVALANCHE was 7.162±0.282 months ($CI_{95\%}$: 6.609-7.715). SAiL trial reported TTP of 7,8 months (95% CI, 7.5-8.1) but not PFS. The SAiL study let the choice of platinum doublet chemotherapy regimen to the investigator's decision similarly to our study. However, non-platinum doublets and single-agent chemotherapy regimens were also allowed in SAiL study unlike in AVALANCHE. Other differences included that SAiL enrolled a selected patient population that was generally healthier and younger (29).

ORR outcomes in AVALANCHE were also comparable with the ORR results of the above-mentioned studies. The 46.7% ORR was higher than the 34.6%, 37.8% and the 34.9% of the AVAiL 7.5 mg/kg, AVAiL 15 mg/kg and the E4599 trials, respectively. The SAiL and ARIES trials showed higher ORR. SAiL reported 3% CR and 48% PR (29) which is also comparable to the 2.3% CR and 44.4% PR rate of AVALANCHE.

Sandler *et al* (24) reported that women had significantly lower OS in the E4599 trial. They, however, also stated that this difference could be the result of imbalances of treatment regiments or baseline prognostic factors between the two groups (24). The AVAiL studies (26) and our AVALANCHE trial, on the other hand, found comparable results between women and men. Women had longer PFS and OS than men in the AVALANCHE, however, only OS was on the boundary of significance (P=0.071). Although, OS was reported higher in both AVAiL studies and the AVALANCHE trial, this survival advantage of women can also be accounted for by the generally longer survival of women with lung cancer that has been previously reported in statistical reports (1,30).

As for the patients' age, nearly 10% of the patient population with evaluable data were over 70 years of age and no significant difference was found between the two groups regarding PFS. Surprisingly, however, OS was reported to be longer in patients over 70 years of age, although this difference was not significant. Contrary to our findings, the E4599 study found that patients older than 65 years of age had a significantly higher HR for death and suggested that these patients might not benefit from BEV treatment (24). The AVAiL studies reported similar HRs for OS in both groups. One concern in previous studies was that the risk of bleeding could be higher in older patients, however neither

Table IV. Summary of the adverse events reported in the present study.

Adverse event	n (%)
Anemia	23 (14.7)
Thrombocytopenia	14 (9)
Neutropenia	12 (7.7)
Hypertension	7 (4.5)
Nausea	7 (4.5)
Epistaxis	6 (3.9)
Chest pain	5 (3.2)
Acute bronchitis	4 (2.6)
Weight loss	4 (2.6)
Bone pain	3 (2)
Diarrhea	3 (2)
Pulmonary embolism	3 (2)
Hemoptysis	3 (2)
Hyponatremia	3 (2)
Deep vein thrombosis	3 (2)
Hoarseness	3 (2)
Cough	2 (1.3)
Fever	2 (1.3)
Respiratory infection	2 (1.3)
Obstipation	2 (1.3)
Pneumonia	2 (1.3)
Pyuria	2 (1.3)
Tachycardia	2 (1.3)
Throat pain	2 (1.3)
Lung abscess	1 (0.7)
Agranulocytosis	1 (0.7)
Acute osteomyelitis (jaw)	1 (0.7)
Allergic dermatitis	1 (0.7)
Allergic reaction	1 (0.7))
Hip pain (right-sided)	1 (0.7)
Decubitus	1 (0.7)
Dermatitis (forehead, back)	1 (0.7)
Dermatitis (generalized)	1 (0.7)
Cholesterol increased	1 (0.7)
Exsiccosis	1 (0.7)
Ulcer (in the mouth, tongue)	1 (0.7)
Gastroesophageal reflux disease	1 (0.7)
Weakness	1 (0.7)
Vomiting	1 (0.7)
Abdominal pain	1 (0.7)
Ileus	1 (0.7)
Ischemic cerebral vascular lesions	1 (0.7)
Arthralgia	1 (0.7)
Swelling of arm	1 (0.7)
Hand swelling	1 (0.7)
Leg swelling	1 (0.7)
Laryngotracheitis	1 (0.7)
Febrile neutropenia	1 (0.7)
Prostration	1 (0.7)
Leukopenia	1 (0.7)
Breast swelling	1 (0.7)
Esophageal ulcer	1 (0.7)
Duodenal ulcer	1 (0.7)
Suffusion without trauma	1 (0.7)
Dizziness	1 (0.7)
Thrombosis (left femoral vein)	1 (0.7)
Uremia	1 (0.7)
Urticaria	1 (0.7)
Iron deficiency	1 (0.7)
Bleeding following superficial injury	1 (0.7)
Clear-cell renal carcinoma	1 (0.7)
Numbness (of the soles)	1 (0.7)

the E4599, nor the AVAiL studies nor the SAiL study back up this hypothesis (31).

We observed higher PFS and OS in patients with an ECOG status of 0 at enrolment, although only OS showed a significant difference. This result is not surprising in light of the fact that ECOG performance status is an important prognostic factor in lung cancer (32-35). Of note, the E4599 and the AVAiL studies did not find a significant difference in the HR for OS between the ECOG 0 and the ECOG 1 group (24,26).

Johnson *et al* (22) assumed that central tumour location might cause pulmonary haemorrhage more often thus decreasing the OS. However, this was not supported by subsequent data. Neither SAiL, nor ARIES showed significantly more pulmonary bleeding with centrally located tumours (36,37). Based on a retrospective analysis of the E4599 study data, Sandler *et al* (38) suggested that pulmonary haemorrhage was connected to cavitation of NSCLC instead of central location. Further studies did not support this assumption. Our data do not reinforce any of these suggestions. Neither the PFS, nor the OS was significantly longer with central tumours, and cavitated tumours were not assessed separately.

Although previous chemo- or radiotherapy did not influence PFS or OS, we found significantly longer PFS and OS in the patient group that underwent surgery before enrolment in this study. There is no available data to back up this finding. The most probable reason behind it is that the number of cancer sites is lower in these patients. Further assessment would be needed to draw further conclusions.

Platinum based chemotherapy has been shown in multiple studies to result in a small but significant survival benefit when compared to supportive care (39,40). The most commonly used platinum derivatives are cisplatin and carboplatin. Neither of the above mentioned two drugs were associated with higher PFS, OS or lower toxicity when compared to each other (41-46). Interestingly, patients treated with cisplatin were found to have a longer OS (16.953±1.775 months) than those receiving carboplatin (OS: 12.977±1.692 months). The statistical difference was on the boundary of significance (P=0.06). Santana-Davila *et al* (42) showed that oncologists more often administered cisplatin to relatively younger patients with less comorbidities. This could be a reason for the longer OS. However, it has also been

Table V. Baseline patient characteristics and effectiveness of Bevacizumab with First-Line Chemotherapy for nsNSCLC in the AVALANCHE OCS, ARIES OCS, the Phase IV SAiL Study, and the Phase III Clinical Trials E4599 and AVAiL.

	Baseline patient characteristics									Results				
		Gender (%)		ECOG status (%)			Stage (%)							
Trial	Age (years)	Female	Male	0	1	2	IIIB	IV	Recurrent	Chemotherapy regimen used	Median follow-up (months)	Median PFS (months)	Median OS (months)	ORR[c] (%)
AVAiL 7.5 mg/kg (n=345 ITT) (n=307 PP)	<65: 70.95% >65: 29.05%	35.55	64.45	39.73	60.27	0	14.88	77.02	8.1	Gemcitabine + Cisplatin	≥7 for PFS, ≥12.5 for OS	6.5	13.4 (11.1-15.1)	34.6
AVAiL 15 mg/kg (n=351 ITT) (n=285 PP)	<65: 69.92% >65: 30.08%	36.67	63.33	40.1	59.9	0	15.9	76.64	7.3	Gemcitabine + Cisplatin	≥7 for PFS, ≥12.5 for OS	6.7	13.6 (11.8-15.8)	37.8
E4599 (n=434)	<70: 76%; >70: 24%	48	52	47	53	0	14	86	0	Paclitaxel + carboplatin	19	6.2	12.3 (11.3-13.7)	34.9
SAIL (n=2,212)	58.8 (24-86)[a]	40	60	37	57	6	20	80	0	Investigator's choice	12.5 (SD: 7.1-12.5)	7.8 (7.5-8.1)	14.6 (13.8-15.3)	51.5
ARIES (n=1,967)	>65: 51.5%; >75: 18.8%	46.7	53.3	36	48.7	9.3	Locally advanced =16.6[b]		Metastatic =83.4[b]	Investigator's choice	12.5 (SD: 0.2-65.5)	6.6 (6.3-6.9)	13 (12.2-13.8)	49
AVALANCHE (n=283)	58.16±9.032[b]	49.5	50.5	33	67	0	19.2	80.8	0	Investigator's choice	n.a.	7.162±0.282 (6.609-7.715)	15.179 (12.480-17.877)	46.7

[a]Age was reported as the average in the SAIL and AVALANCHE studies. [b]Stage was reported as such in the ARIES study. ORR, objective response rate [c](patients who experienced a complete or partial response); AVAiL, Avastin in lung; E4599, eastern cooperative oncology group (ECOG) 4599; SAIL, safety of avastin in lung [The SAiL study reported time to progression outcomes instead of PFS]; ARIES, avastin regimens: investigation of effectiveness and safety; PFS, progression-free survival; OS, overall survival; n.a., not available; ITT, intention-to-treat; PP, per protocol; SD, standard deviation.

shown that morbidity is higher in patients receiving cisplatin and they experience a higher need for health care (42).

Our patients receiving BEV maintenance therapy showed significantly higher PFS and OS, which correlates with previous results published by Reck *et al* (25). In addition, Dranitsaris *et al* (47) found that BEV maintenance therapy contributed to a significant OS benefit. In the Phase IIIB AvaALL study, BEV was administered even after disease progression. A significantly higher PFS of 10.1 months was achieved in this experimental arm compared to the control arm where only supportive care was used after disease progression (48). There are several trials debating whether BEV or BEV with pemetrexed is more effective for maintenance therapy. AVAPERL and POINTBREAK, two phase III trials designed to evaluate BEV maintenance therapy with or without pemetrexed, showed significantly longer PFS, however the difference regarding OS was not significant in either of them (49,50).

Our rate of reported adverse events falls behind that of expected based on previous trials. Lynch *et al* (28) reported that in the ARIES trial 19.7% of patients experienced one or more protocol-specified adverse event, which is somewhat lower than the 20.8% of patients reported in AVALANCHE. However, when looking at the serious adverse events, the 10.9% reported in ARIES is appreciably higher than the 0.5% reported in AVALANCHE. Notably, the study protocols can vary in the qualification of serious adverse events. Crinò *et al* (29) reported a rate of 38% for serious adverse events, although only 13% was deemed related to BEV by the investigators. There is a special interest in similar studies regarding pulmonary bleeding, one of the most common serious adverse event following BEV therapy. AVAiL 7.5 mg/kg, AVAiL 15 mg/kg, E4599, ARIES and SAiL reported 4, 5, 4.7, 4.1 and 9.5% for the prevalence of any grade pulmonary haemorrhage, respectively. In contrary to this, pulmonary haemorrhage only occurred in 2 patients (0.7%) in AVALANCHE.

In summary, patients in Hungary commonly receive BEV for advanced NSCLC in combination with a range of chemotherapeutics. Despite the less strictly selected patient population and treatment regimens survival outcomes and treatment response rates are comparable with those of the previous large RCT (randomised clinical trials). In our study, both PFS and OS were significantly longer and ORR significantly higher in patients who received BEV maintenance therapy. The adjuvant/neoadjuvant chemotherapy or radiotherapy received prior to enrolment, the localization of the primary tumour, the presence of metastases or the age of the patient had no influence on the efficacy of BEV treatment. On the other hand, previous surgery and cisplatin chemotherapy were associated with better outcomes. We also found low rates of adverse events and acceptable safety profile.

The study design did not allow the comparison of PFS and OS assessed in the study, with placebo or any active comparator, and the comparative assessment of the significance of the prognostic factors studied, either. Due to the high censoring rate, the median OS could not be determined after the closure of the study; therefore, a retrospective data collection was required.

The Avalanche study, like most OCSs had limitations such as reporting errors, missing data, potential biases regarding data entry and confoundment. In this study, reporting centres were asked to enrol all eligible patients to reduce selection bias, however, unintended selection bias cannot be excluded. All known strong confounders were collected and analysed to reduce confounding bias. Clinical reporting errors were reduced by systematic data reviews occurring every 3 months.

A further limitation of the current study was that in 12/40 planned sites, due to their lower patient turnover, we did not identify eligible patients within the recruiting period. Thus, representing the real life setting, not all centres enrolled patients and there were also smaller centres where fewer patients were recruited.

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Availability of data and materials

The datasets generated and analysed during the present study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request and with permission of F Hoffmann-La Roche AG.

Authors' contributions

ET analysed and interpreted the data and contributed to the study design. ÁKG analysed and interpreted the collected data and wrote the manuscript. EJ, ZS, GL, PD, ZV, LH and EC enrolled the patients to the present study and collected the data. VS enrolled the patients and designed the study.

Ethics approval and consent to participate

The present study was approved by the Hungarian Ethics Committee and Health Authority. All patients provided written informed consent.

Patient consent for publication

All patients provided written informed consent for the publication of any associated data.

Competing interests

The BEV used in the present study was obtained from Genentech/Roche (South San Francisco, CA, USA). The present study was also sponsored by F Hoffmann-La Roche. The funding body contributed to data collection and analysis; however, the sponsor did not influence the content of the report and did not contribute to the writing of this manuscript. The authors declare that they have no competing interests.

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