

**ANTIANGIOGENIC THERAPY IN ADVANCED LUNG
ADENOCARCINOMA: EFFICACY AND KRAS MUTATION
AS A PROGNOSTIC BIOMARKER**

PhD Thesis – short version

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1. Introduction

Lung cancer became the second most common malignant tumor in the last century. Recent statistics show that it causes more deaths than breast, prostate and colon cancer combined. It is estimated that the total number of deaths caused by lung cancer was 1.589 million worldwide, which accounts for 17% of all cancer related deaths.

Hungary has one of the highest mortality rates of lung cancer in the world both in 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. In 2014, the registered number of new cases of lung cancer in Hungary was 5189 (60% male, 40% female).

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 tumors including NSCLC. In many cases, VEGF overexpression is associated with an increased risk of relapse and metastasis.

Bevacizumab (BEV; Avastin®; Genentech/Roche, South 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, ovarian, breast and renal cancer. This has also been the first and only anti-vascular drug to be licensed for the treatment of NSCLC so far.

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

Subsequent to the above Phase II study, several randomized phase III studies, including the Eastern Cooperative Oncology Group (ECOG) E4599 trial was initiated. Results showed that the addition of bevacizumab was associated with a significant improvement in the median overall survival (OS) compared with chemotherapy alone. Progression-free survival (PFS) was also significantly improved.

As a result of the above trials, bevacizumab 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 bevacizumab was approved with platinum-based chemotherapy in NSCLC in 2007, so far no Hungarian data have been available. The AVALANCHE (ML21783) study was undertaken to assess the clinical outcomes of first-line bevacizumab combined with standard platinum-based regimens in Hungarian clinical practice.

KRAS protein, encoded by the KRAS proto-oncogene, is a small GTPase which plays a key role in regulating various cell functions. KRAS is frequently mutated in lung adenocarcinoma (LADC). With an incidence of up to 30%. The most prevalent G12C and G12V

KRAS mutation subtypes are associated with smoking-, while the G12D subtype has been observed in never-smokers.

The prognostic and predictive power of KRAS mutation in non-small cell lung cancer (NSCLC) patients remains controversial. Although two different meta-analyses concluded that KRAS mutation is a negative prognosticator in LADC, the most comprehensive study of more than 1500 NSCLC patients (including 300 KRAS mutant cases) from four trials of adjuvant chemotherapy (CHT) reported that KRAS mutation had no clear prognostic or predictive relevance with regards to response to CHT.

Previously, our group performed a mutation subtype-specific analysis of 505 stage III–IV LADC patients treated with platinum-based CHT and found that there were no significant differences in progression-free survival (PFS) and overall survival (OS) among patients with wild type (WT), codon 12 and codon 13 KRAS mutations. Importantly, however, G12V KRAS mutant patients tended to have a higher response rate and a modestly longer median PFS.

Increased expression and the negative prognostic role of vascular endothelial growth factor (VEGF, the key angiogenic cytokine) have been reported in most solid tumors including NSCLC. Although the RAS/RAF/MEK/ERK signaling pathway has been implicated in the regulation of VEGF expression and angiogenesis, only very few studies investigated the effect of KRAS mutation on the efficacy of BEV therapy. Two different groups, demonstrated that G12V, G12A and G12D KRAS mutations are associated with poor outcome in metastatic CRC patients receiving BEV. As for nonsquamous NSCLC, no pathological response was seen to neoadjuvant BEV/CHT in a small study, while in another small study of stage IV NSCLC,

BEV therapy was associated with improved OS and PFS in KRAS WT (n=26) but not in KRAS-mutant (n=16) patients. No study was done on a large cohort of patients to examine the amino acid substitution-specific KRAS mutational status of BEV/CHT-treated stage III-IV Caucasian patients.

2. Objectives

Bevacizumab is a relatively new treatment option in advanced LADC. The addition of BEV to standard platinum based chemotherapy was validated in several international randomized trials, however no Hungarian data was available.

Despite the research effort no validated predictive or prognostic biomarker is known regarding antivasular treatment in NSCLC.

2.1. The safety and efficacy of bevacizumab in addition to platinum based chemotherapy in patients with advanced NSCLC

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. To achieve results that represent the Hungarian practice, a multi-institutional, single-arm observational study was conducted.

The primary endpoint of the study was PFS, the time from first administration of BEV to disease progression. Secondary endpoints included tumor response, OS and safety.

2.2. KRAS mutation as a biomarker for anti-VEGF therapy in NSCLC

Based on international literature and previous findings from a sub-cohort of the AVALANCHE study, anti-VEGF therapy is not effective in all patients. The exact mechanisms of therapy resistance and furthermore, a predictive and prognostic biomarker for antivasular therapy is not yet known.

The molecular connection between the KRAS signaling cascade and the VEGF signaling pathway has been established, however its clinical relevance is not yet studied. The aim of this study was to analyze whether KRAS mutation could be used as a biomarker for anti-VEGF therapy in NSCLC. We examined the amino acid substitution-specific KRAS mutational status in a large cohort of BEV/CHT-treated stage III-IV Caucasian patients and its effect on PFS and OS. Our aim was to show the clinical relevance of subtype specific KRAS mutational status in anti-VEGF therapy and furthermore to establish a predictive biomarker that can help identify therapy resistant patients and thus to give individualized therapy.

3. Methods

3.1. The safety and efficacy of bevacizumab in addition to platinum based chemotherapy in patients with advanced NSCLC

AVALANCHE (ClinicalTrial.gov Identifier NCT03170284) was a multi-center single-arm observational study designed to assess the efficacy and safety of bevacizumab therapy in patients with advanced nsNSCLC (non-squamous NSCLC) in the routine oncology practice in Hungary.

Eligible patients received first-line bevacizumab with cisplatin or carboplatin then non-progressors proceeded to receive bevacizumab until disease progression or unacceptable toxicity. The third component of the combination chemotherapy was one of the following: paclitaxel, gemcitabine, docetaxel or vinorelbine. 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.

The primary endpoint of the study was PFS. PFS was calculated from the start of bevacizumab treatment.

Secondary endpoints included best tumor 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). ORR (Objective Response Rate) was calculated from patients experiencing complete or partial remission.

3.2. KRAS mutation as a biomarker for anti-VEGF therapy in NSCLC

In this single-center, retrospective study, 501 consecutive patients with advanced lung adenocarcinoma (LADC) were included who underwent first-line platinum-based (cisplatin or carboplatin) doublet chemotherapy (CHT) with or without BEV at the National Korányi Institute of Pulmonology, Budapest between 2007 and 2016. According to our inclusion criteria, cytologically or histologically verified unresectable stage IIIB or IV LADC patients were included. Smoking status, TNM stage and molecular tumor characteristics (EGFR and KRAS mutational status) were defined at the time of diagnosis. For the calculation of PFS and OS, date of the first CHT was used. Patients with known EGFR mutations were excluded. Clinical follow-up was closed on the 1st of August, 2017. Median follow up was 21 months in the BEV/CHT group, while 10 months in the CHT group.

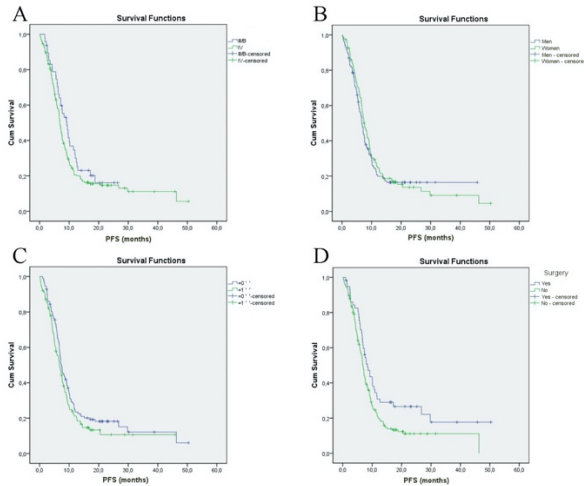
4. Results

4.1. The safety and efficacy of bevacizumab in addition to platinum based chemotherapy in patients with advanced NSCLC

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.

The PFS in the total study patient population was 7.162 ± 0.282 (CI95%: 6.609-7.715) months. There was no significant difference in

PFS regarding gender (median of 7.589 ± 0.647 vs. 6.669 ± 0.375 months, $p=0.542$), ECOG (median of 7.326 ± 0.535 vs. 6.702 ± 0.597 months $p=0.123$), localization of tumor (central vs. non-central, $p=0.813$), the platinum derivative used (cisplatin vs. carboplatin, $p=0.199$), adjuvant/neoadjuvant chemotherapy ($p=0.165$) or radiotherapy ($p=0.165$).



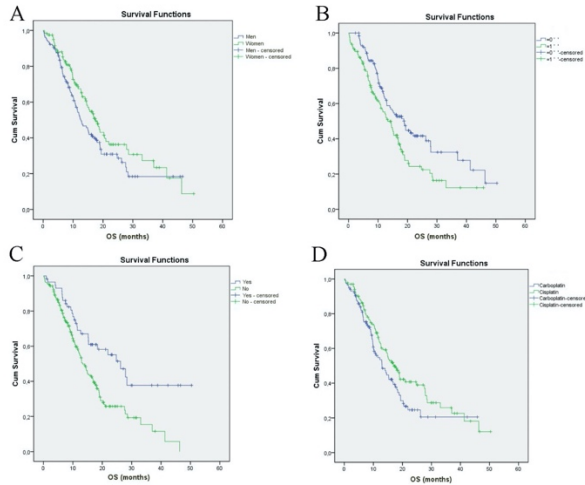
1. Figure - Analysis of progression-free survival. A: in different tumor stages; B: According to gender; C: by ECOG PS and D: by history of surgery (Kaplan-Meier). Avalanche study.

Of note, median PFS was significantly higher ($p<0.001$) in patients receiving bevacizumab maintenance therapy (median: 9.166 ± 0.601 , CI95%: 7.988-10.345 months) compared with those who received no maintenance therapy (median: 5.815 ± 0.574 , CI95%: 4.690-6.940 months).

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%.

The median OS in the total study population was 15.179 ± 1.377 months (CI95%: 12.480-17.877) (Figure 27).



2. Figure - Analysis of overall survival. A: According to gender; B: by ECOG PS; C: by history of surgery and D: according to the platina derivate used (Kaplan-Meier). Avalanche study.

A remarkably longer ($p < 0.001$) OS was observed in patients receiving bevacizumab maintenance therapy (median: 26.218 ± 3.946 months, CI95%: 18.484-33.952 months) than in those without maintenance bevacizumab therapy (median: 10.152 ± 0.975 months, CI95%: 8.240-12.064 months).

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

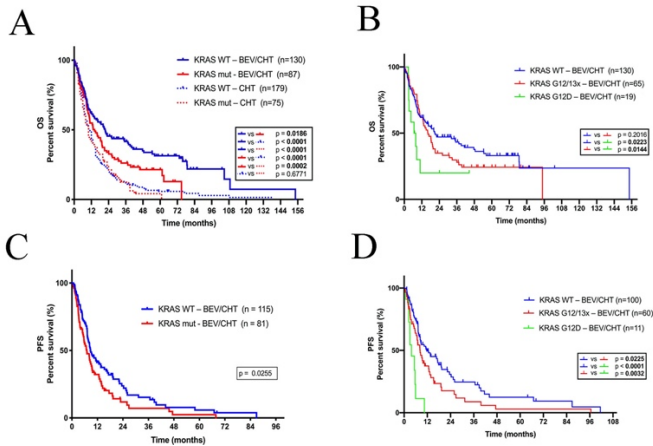
4.2. KRAS mutation as a biomarker for anti-VEGF therapy in NSCLC

All patients had advanced LADC and Caucasian background. Patients with tumors harboring an EGFR mutation were excluded. One hundred and seventy patients of the full cohort of 501 cases were identified as KRAS-mutant (33.9%) and 331 (66.1%) as KRAS WT. 38.5% (n=95) of the patients treated in the BEV/CHT group were KRAS-mutant, whereas in the CHT group (Table 8) this ratio was 29.5% (n=75) (P=0.012). There were no significant differences between the BEV/CHT and CHT groups with respect to age (P=0.193), smoking status (p=0.072), gender (p=0.506) or tumor stage (P=0.610). The only difference was seen in performance status, where there were more ECOG 0 (vs. EVOG 1) patients in the BEV/CHT group than in the CHT alone group (P=0.031; data not shown), which might be due to the BEV selection criteria. In the BEV/CHT sub-cohort, 35 (36.8%), 19 (20%) and 20 (21%) cases were classified as G12C, G12D and G12V mutants, respectively. Other rare (i.e. n<3) KRAS exon 2 mutation subtypes (G12A, G12R, G12S, G13C, G13D) were also found in the BEV group. Subtype specific mutations were technically not assessable in 21 cases.

In order to study the clinical relevance of KRAS mutations, we performed comparative statistical analyses of KRAS status and

clinicopathological variables in both the BEV/CHT and the CHT sub-cohorts. As for the BEV/CHT group, ever-smoking and KRAS mutational statuses showed a significant positive association ($P=0.008$). KRAS mutation was also significantly more common in female BEV/CHT patients (vs. males; $P=0.002$, Table 8). ECOG status and clinical stage did not differ between KRAS-mutant and KRAS WT patients in the BEV/CHT group significantly ($P=0.056$ and $P=0.16$, respectively). The presence of KRAS mutation did not associate with age in the BEV/CHT group ($P=0.09$). Of note, we did not detect significant associations of KRAS mutational status with age, smoking status, gender, ECOG status, stage or OS in the CHT group (Table 8). While reasons for the differences in the associations between KRAS mutational status and clinicopathological variables in the BEV/CHT vs. the CHT sub-cohorts are not entirely clear, a possible explanation is that they are due to the selection criteria for BEV therapy.

As expected, patients in the BEV/CHT group had significantly longer median OS than those receiving CHT only ($P<0.0001$, log-rank test). This difference was even more remarkable when only KRAS WT patients were compared ($P<0.0001$, log-rank test, Figure 3A). Notably, the addition of BEV to CHT was also associated with significant benefit in OS if KRAS-mutant patients were compared with those in the CHT alone sub-cohort ($P=0.0002$, log-rank test, Figure 3A).



3. Figure - Kaplan-Meier plots for the OS (A-B) and PFS (C-D) in LADC patients according to KRAS mutation status.

We next investigated if KRAS mutational status influences the efficacy of CHT with or without BEV in advanced LADC. There was no difference in OS between patients with KRAS-mutant versus KRAS WT tumors in the CHT alone group ($P=0.6771$, log-rank test, Figure 3A). Importantly, however, in the BEV/CHT group we found that KRAS-mutant LADC patients had significantly shorter median PFS and OS than did KRAS WT patients ($P=0.0255$ and $P=0.0186$, respectively, log-rank test; Figures 3C and 3A). In support of this, multivariate Cox regression analyses revealed that KRAS status (mutant vs. WT) at diagnosis influenced OS (HR 0.645, 95% CI 0.458-0.908, $P=0.012$) and PFS (HR 0.597, 95% CI 0.402-0.887, $P=0.011$) independently from age (continuous; P values were 0.081 and 0.628, respectively), gender (female vs. male; P values were 0.005 and 0.001, respectively), smoking status (never- vs. ever-smoker; P values were 0.907 and 0.835, respectively), ECOG PS (0 vs. 1; P

values were 0.193 and 0.177, respectively) and tumor stage (III. vs. IV; P values were 0.048 and 0.617, respectively). These analyses also identified more advanced tumor stage as a significant independent negative prognostic factor for OS but not for PFS (P values were 0.048 and 0.617, respectively). Gender proved to be an independent prognosticator for both OS and PFS in a multivariate Cox regression model as well (P values were 0.005 and 0.001, respectively).

Next, we looked at the clinicopathological characteristics of KRAS codon 12-mutant LADC patients receiving BEV/CHT and performed a statistical analysis on their associations with amino acid-specific mutational status. We identified 35 (36.8%) G12C, 19 G12D (20%), 20 G12V (21%), 3 G12A (3.2%), 1 G12S (1%), 1 G12R (1%), 3 G13D (3.1%), and 1 G13C (1%) cases. Significant associations of subtype-specific KRAS mutational status with age, smoking status, gender, ECOG PS or tumor stage were not detected. Importantly, patients with KRAS G12D mutant tumors had significantly shorter OS than those presenting with KRAS WT or with other KRAS codon 12 or 13 mutant (G12/13x) tumors (P=0.0223 and P=0.0144, respectively; log-rank test, Figure 3C). In line with the OS data, KRAS G12D mutation conferred a significant disadvantage for PFS when compared with KRAS WT (P<0.0001; log-rank test, Figure 3D) or all the other codon 12 or 13 KRAS (G12/13x) mutations (P=0.0032; log-rank test, Figure 3D). Of note, the OS of G12D KRAS mutant patients in the BEV/CHT group was comparable to that of patients in the CHT alone sub-cohort.

5. Conclusion

5.1. The safety and efficacy of bevacizumab in addition to platinum based chemotherapy in patients with advanced NSCLC

To conclude the results of the AVALANCHE study, it can be stated that comparable results were seen in the Hungarian clinical practice as in former international studies. Marked improvement was seen in PFS and OS of patients with locally advanced, metastatic, or recurrent non-small cell lung cancer other than predominantly squamous cell histology when BEV was added to standard platinum based CHT. In the meantime, combination therapy with BEV proved to be safe, with acceptable amount of adverse events and low percentage of treatment discontinuation. BEV is a valid option in the treatment of stage IIIB and IV nsNSCLC in the Hungarian clinical setting.

5.2. KRAS mutation as a biomarker for anti-VEGF therapy in NSCLC

In conclusion, when combined with standard first-line chemotherapy, BEV has led to increased OS and thus has been approved in patients with advanced or recurrent nsNSCLC without targetable molecular abnormalities. However, although serious efforts have been made to identify patients responsive to BEV, there is as yet no validated predictive biomarker in this field.

Here, we present novel evidence for use of BEV in stage III-IV LADC patients with *KRAS*-mutant tumors -and especially with *KRAS* G12D-mutant tumors -, demonstrating inferior activity of this drug compared to that in LADC patients with non-*KRAS*-mutant tumors. Our data may not only help to improve the efficacy of BEV, but through better patient selection, could also help to decrease the unnecessary use of this expensive agent in subgroups of *KRAS*-mutant human LADC patients. Unnecessary and ineffective use of BEV can potentially even harm patients through adverse events while achieving no PFS, OS or quality of life benefit and also putting a financial strain on health care.

Subtype specific *KRAS* mutational status can be an easily accessible marker, since its already part of the routine molecular testing in NSCLC. Using subtype specific *KRAS* mutation status as a biomarker could help clinicians to administer individualized therapy. To validate this potential biomarker prospective studies are needed.

6. Applicants publications related to the thesis

6.1. Publications related to the thesis

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