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Comparison of Chemotherapeutic Regimens Frequently Used in Metastatic Non-squamous NSCLC Treatment

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Abstract. *Background/Aim: Platinum-based chemotherapy with pemetrexed or paclitaxel/bevacizumab are regimens used in combination with checkpoint inhibitors in non-squamous non-small cell lung cancer (NSCLC) treatment. We conducted a real-world study to compare the outcomes of these chemotherapeutic regimens. Patients and Methods: We investigated 1,534 patients with advanced non-squamous NSCLC treated with platin/pemetrexed (n=1212) or platin/paclitaxel/bevacizumab (n=322) in 9 cancer centres in the Czech Republic. Results: The regimen containing platin/paclitaxel/bevacizumab showed significantly better overall response rate (ORR) compared to the platin/pemetrexed [40.8% vs. 32.7% (p=0.008)] in the overall population and [55.0% vs. 38.8% (p=0.002)] in the Eastern Cooperative Oncology Group performance status 0 group. There was no significant improvement in progression-free survival (PFS) and overall survival (OS) in either of these two groups of patients. Conclusion: In our real-world data analysis, patients treated with platin/paclitaxel/bevacizumab had better overall response rate (ORR), but not PFS or OS. Thus, both treatment regimens are similarly effective. Their selection should therefore be based on the potential side effects.*

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Lung cancer is the leading cause of cancer death, with an estimated 1.8 million deaths (18%) and the second most common cancer diagnosis (2.2 million) globally in 2020 (1). Non-small cell lung cancer (NSCLC) represents about 80-85% of cases (2). However, promising achievements have been reached in the lung cancer treatment lately. According to European and American guidelines, immuno-chemotherapy is

the standard of care in metastatic non-squamous NSCLC patients with no proven *EGFR* or *ALK* driver mutations (3). In the absence of direct comparisons between the novel regimens platin plus pemetrexed (PP) and pembrolizumab or platin plus paclitaxel, bevacizumab (PPB) and atezolizumab we decided to compare available real world data of Czech non-squamous NSCLC patients treated with one of the two principal therapeutic chemotherapeutic regimens (PP and PPB), which are nowadays used in combination with check-point inhibitors, such as pembrolizumab and atezolizumab (4-6).

Patients and Methods

Study design and treatment. In this multicenter study conducted in the Czech Republic between 2010 and 2019, we retrospectively analyzed clinical data of patients with cytologically or histologically confirmed advanced non-squamous NSCLC treated with platinum-based therapy. Two intravenous regimens in the approved dosage were administered every 3 weeks – cisplatin (80 mg/m^2) or carboplatin (5 AUC) plus pemetrexed (500 mg/m^2) with possible maintenance of pemetrexed after the 4th cycle or carboplatin (6 AUC) plus paclitaxel (200 mg/m^2) and bevacizumab (7.5 mg/m^2 iv.) with possible maintenance of bevacizumab after the 4th/6th cycle of chemotherapy (depending on the local standards of each center). Therapeutic dose adjustments in case of manageable toxicity were allowed. The treatment was continued until progression defined by RECIST 1.1 (7) or unacceptable toxicity. Clinical follow-up including physical examination, chest X-ray and routine laboratory tests were performed at least every 3 weeks. Computed tomography (CT) or positron-emission tomography (PET)/CT were performed at regular intervals according to the local standards or when progression was suspected based on clinical or chest X-ray examination. The national register TULUNG, a non-interventional post-registration database of epidemiological and clinical data of patients with advanced-stage NSCLC treated with targeted or biological therapies in the Czech Republic, served as the data source. The patients gave their informed consent for use of their data for scientific purposes.

Statistical methods. Patients' demographic and disease characteristics are summarized. Continuous parameters are described using the mean with 95% confidence interval (CI) and the median with minimum and maximum, together with the total number of non-missing observations. Categorical parameters are summarized using absolute and relative frequencies. Overall response rate (ORR, *i.e.* complete response + partial response) was evaluated only for patients with discontinued treatment and tested by Pearson's chi-square test. Overall survival (OS) was defined as the time from treatment initiation to the date of death due to any cause. Progression-free survival (PFS) was defined as the time from treatment initiation to the date of the first documented progression or death due to any cause. OS and PFS were estimated using the Kaplan–Meier method, including 95% confidence intervals (95%CI). Differences between OS and PFS were analysed by log-rank test. Statistical analyses were performed using IBM SPSS, Statistics (version 25.0) and R software (version 3.5.1). Statistical significance was set at α=0.05.

Ethics. The study was approved by the Institutional Ethics Committees of all participating centres of the TULUNG registry [University Hospital Brno, University Hospital Pilsen, University Hospital Olomouc, University Hospital Hradec Kralove, University Hospital Motol (Prague), University Hospital Prague-Bulovka, Thomayer Hospital (Prague), and VFN (Prague)]. This study was approved by the Ethics Committee of University Hospital Hradec Kralove on May 11, 2018, reference number: 201805 I134R.

Results

Patient characteristics. In total, 1,534 patients were stratified according to the PS Eastern Cooperative Oncology Group (ECOG) and the given chemotherapy regimen. A total of 334 patients were PS 0 and 1,168 were PS 1. In addition, 1,212 patients received PP and 322 PPB. In the overall population, significant differences were only seen in the median age and clinical stage proportion. Baseline patient characteristics are summarized in Table I. Of the patients treated with PP, 280 (23.1%) continued maintenance therapy with pemetrexed, and 43 (13.4%) patients continued maintenance therapy in the PPB arm. According to the nature of the TULUNG registry we had data regarding the second line treatment only for a small number of patients. Pemetrexed was used as second line treatment in 160 (49.7%) patients in the PPB arm. Immunotherapy was used in 48 (4.2%) in the PP arm and in 9 (2.8%) patients in the PPB arm. Erlotinib was used as second line treatment in 338 (27.9%) patients in the PP arm and in 13 (4.0%) patients in the PPB arm. Another TKI was used in 32 (2.7%) patients in the PP and in 8 (2.5%) in the PPB arm. The second line treatment used in the rest of the patients is unknown.

ORR, PFS and OS in the overall population. There was a significantly better ORR in the PPB *versus* PP arm (40.8% *vs*. 32.7%; p=0.008). No significant difference was observed in PFS between PPB (median PFS=6.3 months, 95%CI=5.8-7.1) and PP (median PFS=5.2 months, 95%CI=4.9-5.6), p=0.917. A non-significant difference was found in OS in favor of PPB (median OS=16.3 month; 95%CI=14.5-18.4) *vs*. PP (median OS=13.0 month; 95%CI=11.4-14.1), p=0.126. Kaplan–Meier curves for OS and PFS are shown in Figure 1.

ORR, PFS and OS in PS 0 (ECOG) patients. A significantly better ORR was observed with PPB *versus* PP (55.0% *vs*. 38.8%; p=0.012). We did not find a significant difference in PFS between PPB (median PFS=7.6 months, 95%CI=6.6-8.8) and PP (median PFS=7.7 months, 95%CI=6.9-8.9), p=0.199. There was no significant difference in OS between PPB (median OS=20.9 months; 95%CI=17.5-25.5) and PP (median OS=20.6 months; 95%CI=16.9-26.6), p=0.461. Kaplan–Meier curves for OS and PFS are shown in Figure 2.

ORR, PFS and OS in PS 1 (ECOG) patients. There was no significant difference in ORR between PPB and PP (35.9% *vs*. 31.4%; p=0.203). No significant improvement in PFS was found in favor of PPB (median PFS=6.1 months,

Table I. *Baseline patient characteristics (overall population).*

	Pemetrexed + platin* (N=1212)	Bevacizumab + carboplatin + paklitaxel (N=322)	*p*-Value***
Gender			
Male (N; %)	706 (58.3 %)	184 (57.1 %)	0.751
Female (N; %)	506 (41.7 %)	138 (42.9 %)	
Age (therapy start)			
Mean (95%CI)	63.6 (63.1; 64.2)	60.8 (59.7; 61.9)	<0.001
Median (Min–Max)	65.1 (23.7-83.3)	62.2 (23.4-80.9)	
Smoking			
Smoker (N; %)	542 (44.7 %)	145 (45.0 %)	0.983
Former smoker** (N; %)	415 (34.2 %)	111 (34.5 %)	
Never smoker (N; %)	255 (21.0 %)	66 (20.5 %)	
Histology			
Adenocarcinoma (N; %)	1148 (94.7 %)	301 (93.5 %)	0.411
Other histological type (N; %)	64 (5.3 %)	21 (6.5 %)	
ECOG PS (therapy start)			
0 (N; %)	249 (20.5 %)	85 (26.4 %)	0.072
1 (N; %)	940 (77.6 %)	228 (70.8 %)	
2 (N; %)	23 (1.9 %)	9 (2.8 %)	
Clinical stage (therapy start)****			
IIIA (N; %)	25 (2.1 %)	4 (1.2 %)	<0.001
IIIB (N; %)	137 (11.3 %)	14 (4.3 %)	
IIIC (N; %)	3 (0.2 %)	0 (0.0 %)	
IV (without specification) (N; %)	989 (81.6 %)	295 (91.6 %)	
IVA (N; %)	22 (1.8 %)	6 (1.9 %)	
IVB (N; %)	36 (3.0 %)	3 (0.9 %)	

*Platin: Cisplatin or Carboplatin. **Patient stopped smoking at least a year prior to diagnosis. ***Fisher's exact test or Mann-Whitney's test. ****Patients diagnosed until 2018 were staged accorging TNM7 classification, and later patients were diagnosed according to TNM8 classification.

95%CI=5.4-6.7) *versus* PP (median PFS=4.8 months, 95%CI=4.4-5.2), p=0.773. There was no significant difference in OS between PPB (median OS=13.7 months; 95%CI=11.8-17.5) and PP (median OS=11.1 months; 95%CI=10.2-12.4), p=0.124. Kaplan–Meier curves for OS and PFS are shown in Figure 3.

Discussion

Based on retrospective real-live data of 1,534 non-squamous NSCLC patients from several lung cancer centers in Czech Republic, we compared the outcomes of two principal chemotherapy regimens, which are nowadays most frequently used in the first line treatment in combination with checkpoint inhibitors. The analyzed data showed significantly better ORR in the overall population and in the subgroup of PS 0 (ECOG) patients in favor of PPB. There was no significant difference in PFS or OS.

Comparing results of the Czech patients treated with PPB with the data from the registration trial E4599 we reached comparable median PFS and better ORR and median OS in the overall population (6.3 months *vs*. 6.2 months; 40.8% *vs*. 35%; 16.3 months *vs*. 12.3 months) (8). Also, the PP regimen median OS was comparable with the median OS data from the registration trials JMDB and PARAMOUNT, 13.0 months *vs*. 12.6 months and 13.9 months, respectively (9, 10). Highly centralized and controlled care for lung cancer patients in the Czech Republic may be a reason for these achievements.

To the best of our knowledge, there are no other studies directly comparing ORR, PFS or OS between PP and PPB or regimens in combination with pembrolizumab or atezolizumab. However, there are possible indirect comparisons found in several studies (11, 12). There are studies comparing the maintenance part of these regimens, and also some studies evaluating similar regimens (11, 13, 14).

COMPASS and AVAPREL clinical phase III trials showed a possible benefit of the addition of bevacizumab to pemetrexed in the maintenance treatment in terms of PFS (14, 15). This suggests a different mechanism of action and thus possible different efficacies of bevacizumab and pemetrexed. This was also indicated by the phase III PointBreak trial (11), which compared carboplatin, bevacizumab plus paclitaxel or pemetrexed with maintenance of bevacizumab *vs*. pemetrexed plus bevacizumab, respectively. After the addition of bevacizumab to the pemetrexed regimen a significant PFS

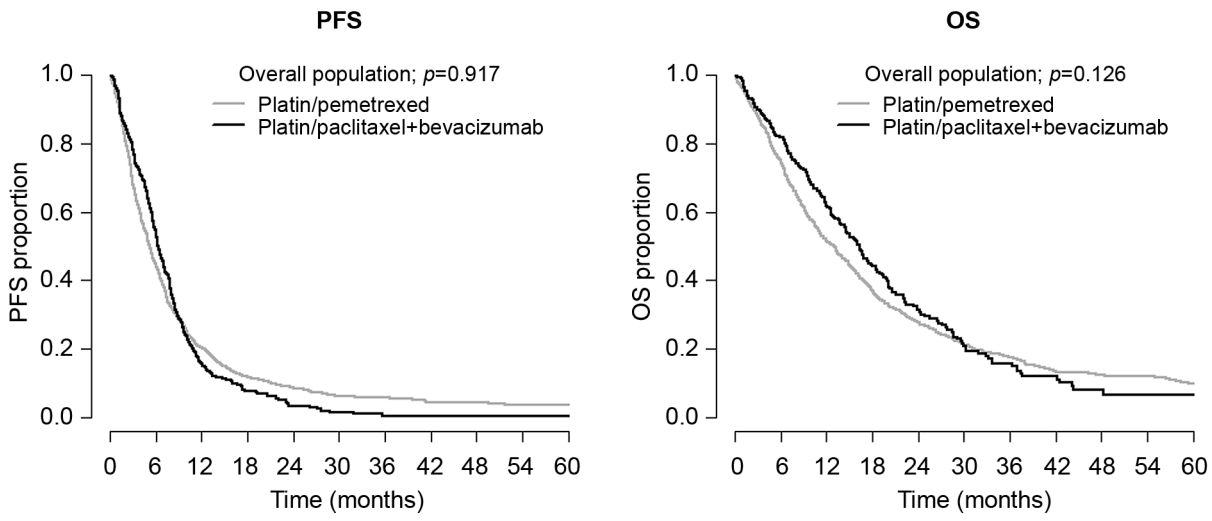

Figure 1. *Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in the overall population.*

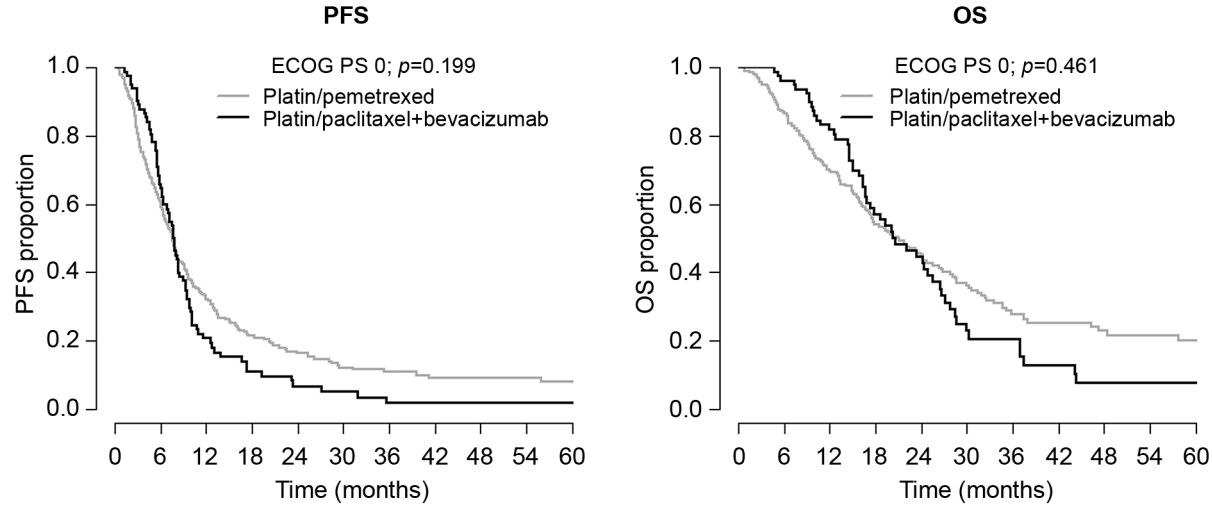

Figure 2. *Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in patients with ECOG PS 0.*

benefit was achieved. However, neither of these three trials showed improvement in OS (11, 13, 14). Moreover, these treatment regimens differed from the basic combinations that commonly used PP or PPB.

Efficacy comparison of cisplatin, gemcitabine plus bevacizumab *vs*. cisplatin and pemetrexed also revealed the bevacizumab combination as more effective, with a 17% progression and death risk reduction (12). Also, the Asian SAil trial suggested a non-significant trend towards the bevacizumab in a platinum-based setting *vs*. cisplatin plus pemetrexed alone in a non-squamous NSCLC East-Asian population (16). However, these studies were performed in the Asian population, which may have different characteristics from Caucasian patients. On the other hand, the PRONOUNCE trial (with a dominant representation of Caucasian patients) primarily did not show a grade 4 toxicity-free PFS (G4PFS) benefit of carboplatin plus pemetrexed *vs*. carboplatin plus paclitaxel and bevacizumab; secondary objectives such as PFS, OS and ORR were also non-significantly different (17). It seems that there is no PFS or OS benefit difference from the use of pemetrexed plus carboplatin neither plus cisplatin, which was used in our trial. Since the cisplatin regimens may be more

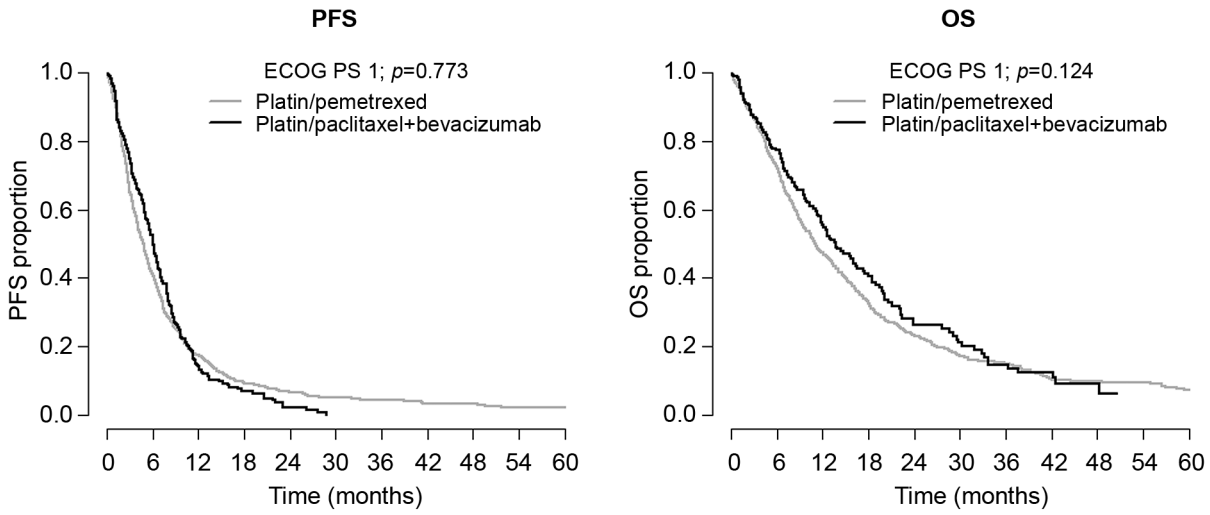

Figure 3. *Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in patients with ECOG PS 1.*

effective than the carboplatin regimens (18), our data provide valuable new information, and suggest the same efficacy of the PP and PPB regimens in terms of PFS and OS.

There were several limitations to our study. First, as it was a retrospective study, the subjective wishes of the clinicians might have affected the therapy choice, which may have impacted the results. Second, the patients treated with platin plus pemetrexed were significantly older than those treated with PPB. However, in a meta-analysis of data from 2,671 non-squamous NSCLC patients (PS 0/1 ECOG) who participated in four pemetrexed phase III clinical trials, showed no impact of age on OS (19). Furthermore, according to the review conducted on bevacizumab use in advanced NSCLC, age or performance status has no impact on the patient's eligibility for bevacizumab (20). Interestingly, the significantly higher number of patients with advanced, stage IV NSCLC in the group treated with PP did not seem to have an effect on the better PPB outcomes in our study. Lastly, we do not know the type of second line treatment in the whole cohort. On the other hand, immunotherapy and targeted therapy (we did not include erlotinib, as it is usually used as a "nontargeted" therapy in the second or third line in the Czech Republic) were used in similar numbers in both treatment arms.

Furthermore, some side effects may play a role in the choice of these treatment regimens (21, 22). Bevacizumab is particularly associated with poor wound healing, the risk of arterial hypertension, proteinuria, hemoptysis, and thromboembolic events. Specific problems with paclitaxel include: neurotoxicity, myalgia/arthralgia, and a higher number of allergic reactions. Pemetrexed with cisplatin may be associated with an increased risk of gastrointestinal toxicity, renal impairment, and myelosuppression. Therefore, the individual profile of each patient should be taken into account when choosing a treatment.

In conclusion, our real-world study demonstrated that PPB for non-squamous NSCLC patients tends to have a higher ORR compared to PP. Overall, however, with insignificant differences in PFS and OS, these treatment regimens appear to be similarly effective. Their selection should therefore be based on the possible side effects.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

DK and MS conceived the presented idea. DK, MS, JK, PO, MZ, PZ, JK, VK, JS, MČ, VK, MH, RV, HČ, LK, DD, LS, MŠ and MP conceived and planned the experiments, and collected the data. KH and MB analyzed the data. DK wrote the article with support from MS. MS helped supervise the project.

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