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Research Article

Pembrolizumab with or without Chemotherapy for First-Line Palliative Treatment for PD-L1 High-Positive Advanced Non-Small Cell Lung Cancer: A Monocentric Analysis

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Abstract

Background: Pembrolizumab alone and pembrolizumab plus chemotherapy are an effective standard of care in first-line palliative therapy for patients with PD-L1 high positive non-small cell lung cancer. There are only two comparisons from clinical practice. However, there is little evidence which patients may benefit more from a combination strategy and for whom a monotherapy is adequate. **Patients and methods:** We conducted a retrospective study of all consecutive patients from a certified lung cancer center in Berlin, who received pembrolizumab alone as first-line palliative therapy for non-small cell lung cancer between 01 January 2017 and 31 December 2020 or a combination of pembrolizumab plus chemotherapy after approval. Overall survival and progression-free survival were compared between the two groups using Kaplan-Meier methodology. **Results:** 102 patients were included during the observation period. Patients in the pembrolizumab monotherapy group (n=71) were slightly older than patients treated with Pembrolizumab in combination with chemotherapy (n=31). Both groups had a slight predominance of male patients and showed mainly former or active smokers. With a median follow-up of 22,1 months for Pembrolizumab alone versus 18,5 months for Pembrolizumab plus chemotherapy, median OS did not differ between the two groups (35,2 months (+/- 7,4 months) vs. 28,3 months (+/- 0 months)), and not between median PFS for patient treated with pembrolizumab and chemotherapy (14,4 months +/- 3,6 vs 20,4 months +/- 0). This analysis suggests worse OS for patients with brain metastases or multiple metastases in both groups. Patients with PD-L1 status >75% tend to have a better OS, as do patients with MET high/int. Overall, it appears that men have a better prognosis, but without statistical significance. There is no statistically significant difference in overall survival for either patient group. **Conclusion:** Both therapies are highly effective and significantly prolong overall survival compared to chemotherapy alone. The decision of which therapy should be preferred for which patient, pembrolizumab alone or in combination with chemotherapy, is influenced by many factors and requires further investigation to better stratify risk.

Keywords: Pembrolizumab; Pembrolizumab Chemotherapy; PD-L1; Lung cancer; Real world data

Introduction

Immunotherapy represents a paradigm shift in the treatment of non-small cell lung cancer. Using the blockade of PD-1 / PD-L1, the treatment has revolutionized a variety of carcinomas and resulted in durable therapeutic responses not usually seen with conventional cytostatic therapy, as is the case with non-small cell lung cancer [7, 13,16].

However, immunotherapy is ineffective in a significant proportion of patients and some, who initially responded, eventually develop resistance to the therapies with resulting tumor progression. To date, PD-L1 expression is the only approved biomarker for the therapy with immune checkpoint inhibitors. Understanding and evaluating possible causes for the development of resistance to PD-1 / PD-L1 blockade may lead to new strategies to prevent or reverse resistance to therapy, which results in improved patient outcomes. Immunotherapy regimes have been available to patients in Germany with PD-L1 expression above 50% as a palliative treatment - since 2017, as a mono therapy with pembrolizumab and since 2019 as a combination of chemotherapy plus pembrolizumab.

An analysis for predictive factors for the course of therapy is useful. To what extent can the combination with chemotherapy influence the course of the disease in patients with PD-L1 expression ≥ 50%? What could be possible clinical factors for the decision to use pembrolizumab alone or the combination with chemotherapy? For which patients does initiating pembrolizumab alone seem more appropriate than administering combination therapy with 4 cycles of platinum-based doublet and pembrolizumab when PD-L1 expression is ≥ 50%? Are there predictive factors for the decision on the respective therapy?

Patients, Methods and Statistical Analysis

Patients and methods

For this analysis, all patients who had relapsed or metastatic non-small cell lung cancer along with PD-L1 expression of ≥ 50% in squamous or non-squamous histology and without a treatable driver mutation (translocation of ALK or ROS1 or BRAF or EGFR mutations) and who started palliative first-line therapy with pembrolizumab between 01 January 2017 and 31 December 2020 or after approval of a combination with platinum-based standard chemotherapy and pembrolizumab at the Lung Cancer Centre (German Cancer Society) of the Evangelische Lungenklinik in Berlin Buch were included.

Patients were identified using the hospital's clinical cancer registry and database. Data on baseline patient demographics (age, sex, ECOG status, smoking history, prior therapies), diagnosis date, histology, PD-L1 expression and molecular profile, initial tumor stage (TMN), treatments and clinical outcome (therapeutic response according to RECIST 1.1., progression date, follow-up date or death date) were collected. The decision on the respective therapy regimen was made by the treating physician on basis of study data, age, ECOG and metastases.

In addition, brain metastases, immune-mediated side effects and, if applicable, a discontinuation of treatment due to these were recorded as possible additional influencing factors. At the time of diagnosis, the assignment to the exact histology, the determination of PD-L1 expression and the molecular pathological examinations were carried out. PD-L1 expression was determined as a percentage of membrane-stained positive tumor cells using 22 C3 (Cell Signaling Technology, Cambridge, UK). Assessment was performed by experienced thoracic pathologists by counting > 100 tumor cells.

The molecular pathological examinations were carried out by means of next generation sequencing (lung panel) in cooperation with the Institute of Pathology -Molecular Diagnostics- of the Charité, Berlin and the Network for Genomic Medicine of the University Hospital Cologne. Inclusion criteria for this analysis were existing molecular pathology tests and that patients received at least 1 cycle of pembrolizumab alone or triple therapy. Patients who had already received one cycle of palliative chemotherapy before a switch to pembrolizumab alone after receiving PD-L1 status results, were included into the pembrolizumab alone Cohort. Patients who received less than the 4 cycles of combination therapy in the triple therapy group were also included.

Evaluated endpoints

Primary endpoint of this retrospective cohort analysis was overall survival (OS) and the secondary endpoint progression-free (PFS). OS was defined as the time (in months) from the start date of pembrolizumab to death from any cause and PFS as the time from the start of pembrolizumab to the first radiologically and/or histologically confirmed disease progression or death from any cause.

Statistical analysis and evaluation

Demographic and disease data were described and compared using the Pearson-Chi2 test. The Kaplan-Meier method was used to estimate median progression-free survival (PFS) and overall survival (OS). P-values comparing survival curves were calculated using log-rank tests. All analyses were performed using IBM SPSS Statistics version 21(IBM, Armonk, NY, USA). A p-value <0.05 (two-sided) was defined as statistically significant.

Results

Baseline characteristics

150 patients were screened for this purpose. 102 patients were identified for the analysis. 71 Patients were treated with

pembrolizumab alone (69,6%) and 31 patients were treated with pembrolizumab plus chemotherapy (30,4%).

In the pembrolizumab mono therapy group there was a slight predominance of male patients (n=39, 54.9%). Mainly former or active smokers (n=67, 94.4%) were represented. The median age was 68 (range 39-83). Non-squamous carcinoma was the most represented histology (n=51, 71.8%). Median PD-L1 expression was 70% (95% CI, 64.5-74.3).

In the group with the combination of chemotherapy and pembrolizumab (triple therapy group), there was also a small predominance of male patients (n=19, 56.9%) and mainly former or active smokers (n=25, 80.6%). The median age was 63 (range 48-76). Non-squamous carcinoma was again the most represented histology (n=22, 70.9) and median PD-L1 expression was 60% (95% CI, 49.2-80.8). Most patients in the combination therapy group received carboplatin plus pemetrexed. The others received carboplatin and paclitaxel. One patient (1.4%) from the pembrolizumab monotherapy group and one patient (3.2%) from the triple therapy group had stage III unresectable tumor and could not receive chemoradiotherapy with curative intent. Thus, 70 patients (98.6%) from the pembrolizumab monotherapy group and 30 patients (96.8%) from the triple therapy group were in a metastatic stage at the onset of the treatment.

Performance status was defined according to Eastern Co-operative Oncology Group (ECOG) performance status. Patients from the pembrolizumab monotherapy group were predominantly (n=58, 81.7%) in good ECOG (0-1) and 13 patients were in reduced general status (ECOG 2, 18.3%). 25 patients (80.6%) from the triple therapy group were in ECOG 0-1 and 6 patients (18.6%) had an ECOG of 2. Compared with the triple-therapy group, the pembrolizumab monotherapy group contained more older patients overall (68 vs. 63 years median; p = 0.018) and had a slightly higher proportion of squamous cell carcinoma (7.0 vs. 3.2%). However, both groups showed a similar proportion of poorly differentiated carcinomas (21.1 vs. 25.8%).

The proportion of patients with PD-L1 expression ≥ 75% was slightly higher in the pembrolizumab monotherapy group (45.1 vs. 35.5%). The number of metastatic sites before the start of therapy was similarly distributed in both groups. 66.2% of patients (n=47) from the pembrolizumab monotherapy group had 0-2 metastatic sites, while 24 of patients (33.8%) had three or more metastatic sites. In the triple therapy group, 61.3% of patients (n=19) showed 0-2 metastatic sites and 38.7% of patients (n=12) showed three or more metastatic sites. The triple therapy group showed a significantly higher proportion of patients with brain metastases (38.7 vs. 19.7).

Details are presented in Table 1.

Patient characteristics	Pearson chisquare P	Pembrolizumab monotherapy n=71		Pembrolizumab Triple therapy n=31	
		No.	%	No.	%
Sex					
Men	0,551	39	54,9	19	56,9
Women		32	45,1	12	43,1
ECOG					
0		9	12,7	2	10,8
1	0,647	49	69,0	23	70,6
2		13	18,3	6	18,6
Age at first diagnosis					
<60	0,018	13	18,3	12	38,7
60 - <75		39	54,9	17	54,8
≥ 75		19	26,8	2	6,5
Histological subtypes					
Non squamous carcinoma		51	71,8	22	71,0
Squamous cell carcinoma	0,006	5	7,0	8	25,8
NOS		15	21,1	1	3,2
PD-L1					
≥ 50 - 75%	0,367	39	54,9	20	64,5
≥ 75 - 100%		32	45,1	11	35,5

Molecular pathology					
BRAF	0,872	4	5,6	2	6,5
EGFR, uncommon mutation	0,384	2	2,8	2	6,5
KRAS, all	0,902	33	46,5	14	45,2
KRAS G12C	0,282	21	29,6	6	19,4
TP53	0,543	39	54,9	15	48,4
MET	<0,0001	17	23,9	21	67,7
Others	0,610	17	23,9	6	19,4
MET					
MET int		2	2,8	8	25,8
MET high		4	5,6	0	0,0
Smoking status					
Non-smoker	0,155	4	5,6	6	19,3
Ex-smoker		48	71,6	14	45,2
Smoker		19	28,4	11	35,5
Pack years					
<30 py	0,777	29	43,3	10	40,0
≥ 30 py		38	56,7	15	60,0
Immune-related events					
Yes	0,500	19	26,8	4	12,9
Discontinuation	0,404	14	19,7	2	6,5
Previous therapies					
Yes (total)	0,006	26	36,6	3	9,7
Surgery	0,008	0	0,0	3	9,7
Radiochemotherapy	0,028	10	14,1	0	0,0
palliative chemotherapy	0,004	16	29,6	0	0,0
T-classification before starting therapy					
0-1	0,728	8	11,3	3	9,7
2		18	25,4	5	16,1
3		15	21,1	7	22,6
4		30	42,3	16	51,6
Metastases before starting therapy					
0	0,209	2	2,8	1	3,2
1a		17	23,9	6	19,4
1b		21	29,6	4	12,9
1c		31	43,7	20	64,5
M1c					
Metastases 1c	0,056	31	43,7	20	51,6
Metastases number					
0-2	0,633	47	66,2	19	61,3
3-8		24	33,8	12	38,7
Brain Metastases					
Brain Metastases	0,043	14	19,7	12	38,7
Response under Therapy					
PD	0,034	28	39,4	10	32,3
SD		12	16,9	6	19,4
PR		19	26,8	15	48,4
CR		12	16,9	0	0,0

Overall Survival alive dead	0,769	39 32	54,9 45,1	18 13	58,1 41,9
Median number of cycles Pembrolizumab	0,451	14		11	
Median observation time OS	0,445	22,1 months		18,5 months	
OS (2 y.) +/- SD [%]	0,280	64,9 +/- 6,0		57,7 +/- 9,7	
Median OS	0,280	35,16 +/- 7,44 months		28,32 +/- 0 months	
PFS (2 y.) +/- SD [%]	0,560	38,0 +/- 5,9		46,0 +/- 9,5	
Median PFS	0,560	14,4 +/- 3,6 months		20,4 +/- 0 months	

Table 1: Patient characteristics: Pembrolizumab alone and pembrolizumab in combination with chemotherapy.

Survival analysis

Progression-free survival (PFS) after two years of observation was 38,0 % (+/- 5,9) in the pembrolizumab monotherapy group and 46,0% (+/- 9.5) in the triple therapy group. After one year, disease progression was evident in 64.8% (+/- 6.1) of the pembrolizumab monotherapy group and in 63.5% (+/- 9.5) of the triple therapy group. The median time to progression was 14,4 months (+/- 3,6) in the pembrolizumab monotherapy group and 20,4 months (+/- 0) in the triple therapy group.

The 2-year survival rate (OS 2y) was 64,9% (+/- 6.0) in the pembrolizumab monotherapy group and 57,7% (+/- 9,7) in the triple therapy group. Median overall survival was 35,2 months (+/- 7,4) in the pembrolizumab monotherapy group and 28,3 months (+/- 0) in the triple therapy group. Comparison between the triple therapy group and the monotherapy group shows no difference in OS (Figure 1).

All patients >70 years of age tended to show improved overall survival in all groups, but without statistical relevance. Once again, there was a predominance of male patients. A positive trend for an improved overall survival in all groups was seen for the men, but without statistical relevance. Overall, there were more smokers in both groups. However, no statistical differences are shown between smokers and nonsmokers, even in the subgroups. Neither does a tendency show up in the subgroups according to packyears.

Prolonged overall survival was seen for patients with triple therapy with a PD-L1 status ≥ 75%. Overall, patients with PD-L1 expression >75% showed improved overall survival compared to patients with PD-L1 expression <75%, but without statistical relevance. This was only evident for patients with a PD-L1 status >85% in all groups regardless of therapy regimen (Figure 2.).

There seems to be an advantage in overall survival for patients with high (METhigh) and intermediate (METint) MET amplification status in the overall group, but this remains without statistical relevance (n=14). Because of the small number of cases, a subgroup analysis was not useful here (n=6 vs. n=8).

There was improved overall survival for patients in all groups for patients with few (0-2) metastatic sites Figure 3) regardless of the regimen of therapy. Patients without brain metastases showed a better overall survival in all groups (Figure 4).

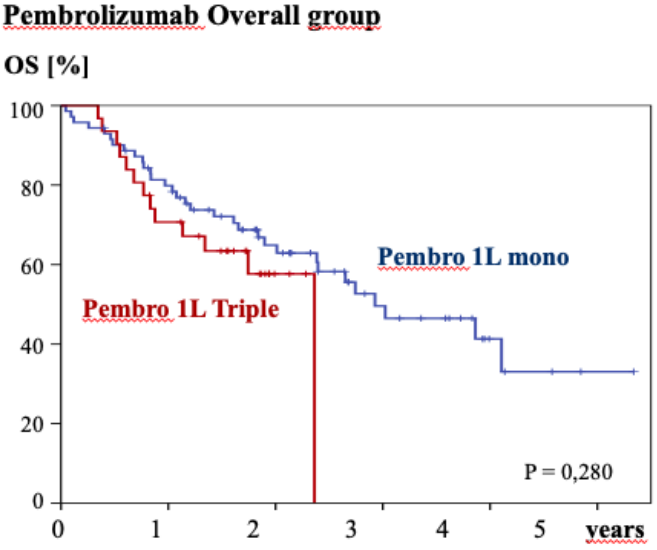
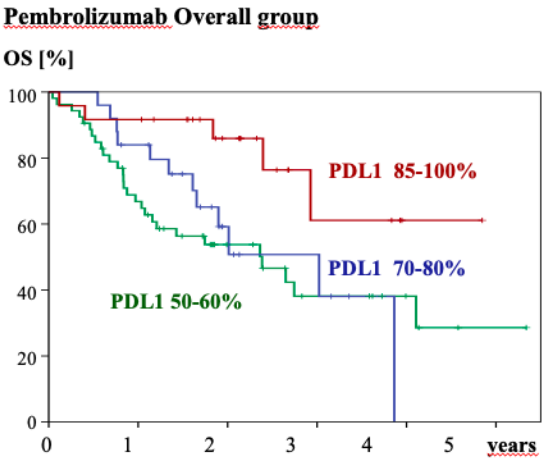
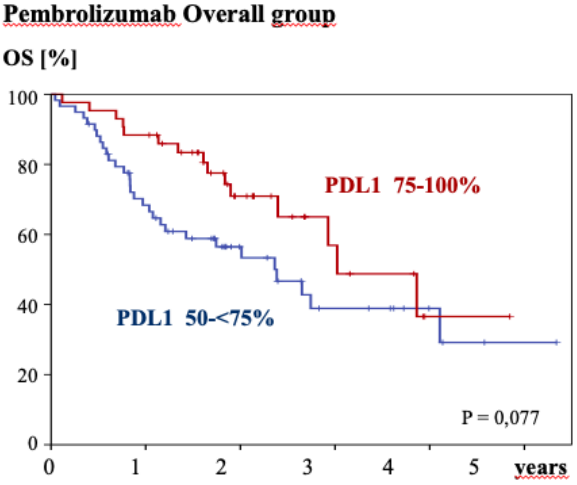


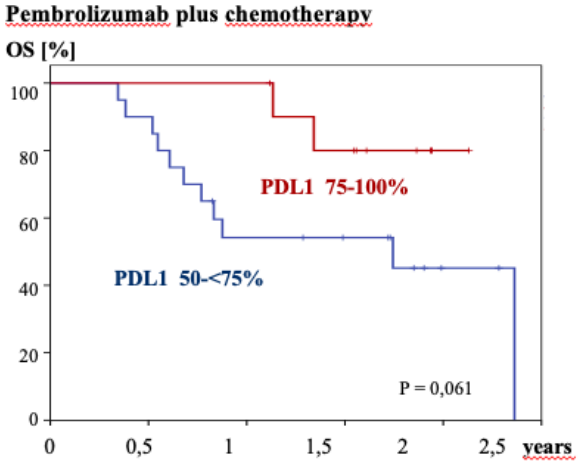
Figure 1: Overall survival pembrolizumab alone vs. triple therapy.



PDL1 85-100% vs PDL1 70-80%: P = 0,032

PDL1 85-100% vs PDL1 50-60%: P = 0,012





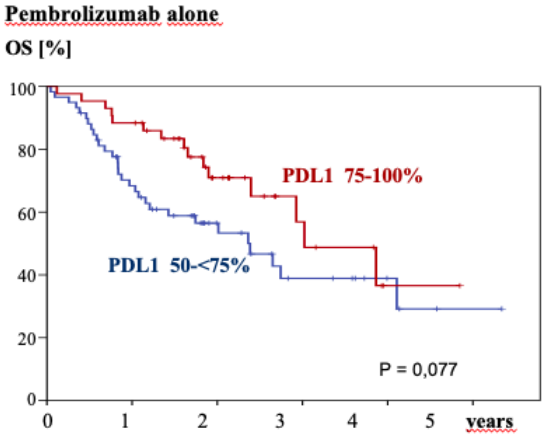
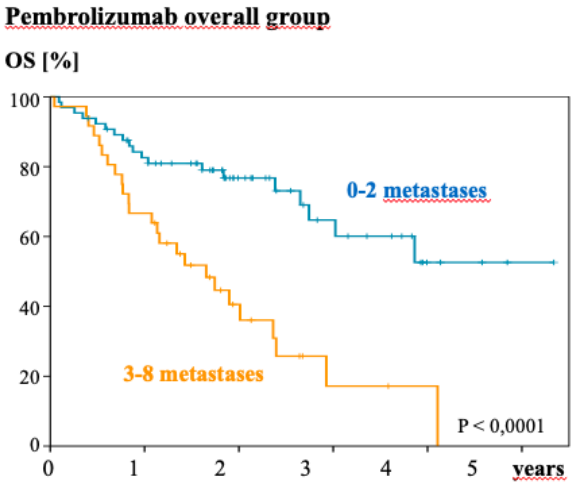
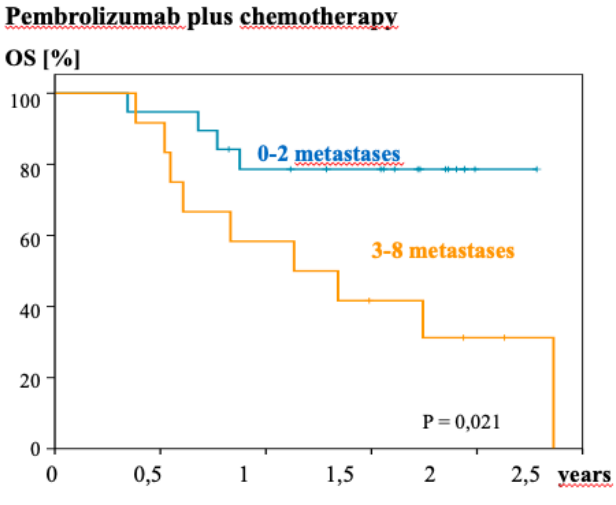
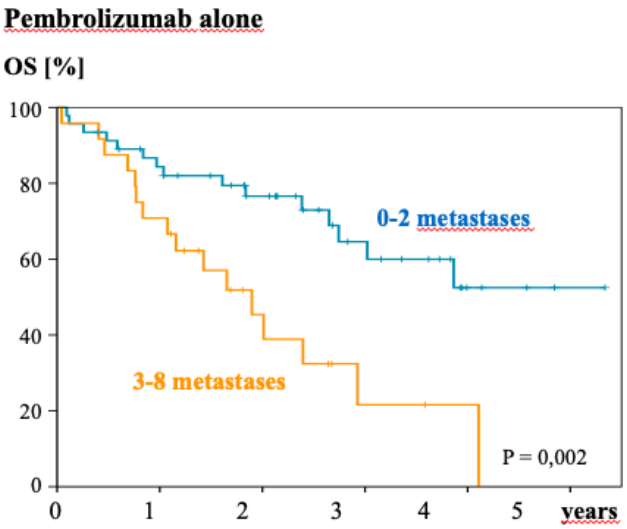


Figure 2: Overall survival in relation to PD-L1 status pembrolizumab alone vs. triple therapy and in the overall group.







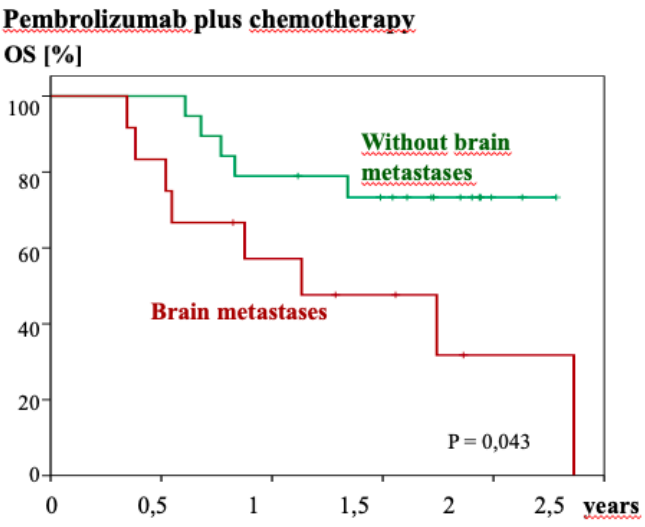
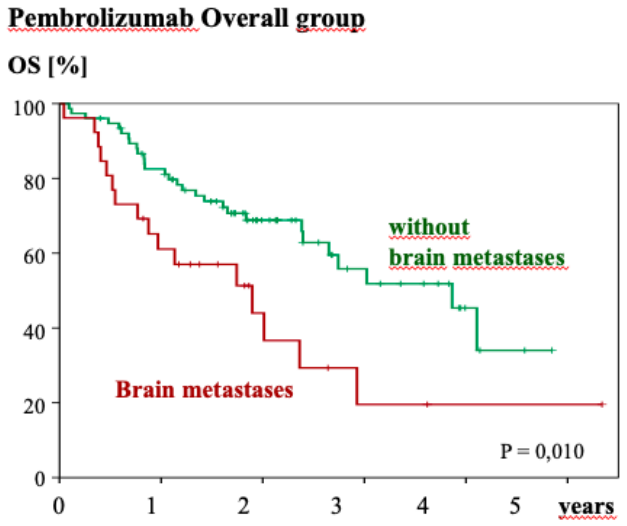


Figure 3: Overall survival as a function of number of metastatic sites pembrolizumab alone vs. triple therapy and the overall group.



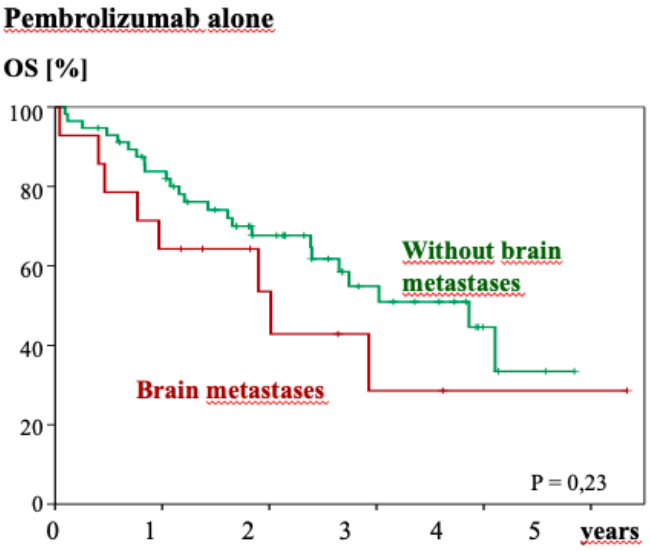


Figure 4: Overall survival depending on brain metastases Pembrolizumab mono vs. triple therapy and overall group.

In the pembrolizumab monotherapy group, there were 23 patients (32,3%) who received more than 20 cycles with a good response and were long-term responders. In the triple therapy group, there were only 7 patients (22%) with more than 15 cycles due to the later approval of the combined therapy regimen and thus the shorter observation period.

Molecular pathology analysis of long-term responders showed 11 patients (55%) in the pembrolizumab monotherapy group with a KRAS G12C mutation, 11 patients (55%) with a TP53 mutation, and 3 (15%) with a KRAS G12C mutation and a TP53 co-mutation. A total of 8 patients (40%) had MET amplification, including 4 (20%) with METhigh and 4 (20%) with METlow amplification status. Among the histologies, adenocarcinomas were predominant (p=51). Three patients (15%) had brain metastases.

In the triple therapy group, long-term responders showed a heterogeneous field with a small number of cases. Two patients (28.6%) showed KRAS G12C mutation, one patient (14.3%) showed KRAS Q61H mutation, and one patient (14.3%) showed KRAS G12A mutation. Five patients (71.4%) had a TP53 mutation, five patients (71.4%) had a METlow amplification status, and three (42.9%) had a METint amplification status. Two patients (28.6%) had brain metastases.

Patients who showed no response (<4 cycles): 7 patients (9.8%) in the pembrolizumab monotherapy group and 3 patients (9.6%) in the triple therapy group.

In the pembrolizumab monotherapy group, molecular pathology analysis showed a TP53 mutation among 4 patients (57.1%). One patient (14.3%) showed a KRAS G12V mutation. One showed a KRAS G12D mutation and one showed a METint amplification. Three patients (42.9%) also had brain metastases.

Molecular pathology results showed a higher proportion of MET-positive patients in the triple therapy group (67.7 vs. 23.9%). In the triple therapy group, 2 patients (66.6%) showed a METlow amplification, one a TP53 mutation (33.3%), and one (33.3%) of the patients had a KRAS G12C mutation with TP53 co-mutation. Two (66.6%) of the "non-responders" also had brain metastases.

The median observation time of patients was 22,1 months in the pembrolizumab monotherapy group and 18,5 months in the triple therapy group.

Discussion

This analysis provides data from a smaller patient cohort on the real-world use of pembrolizumab mono and in combination with platinum-based chemotherapy (triple therapy) as first-line palliative therapy in patients with non-small cell lung cancer and PD-L1 expression of ≥ 50%. The importance of this analysis is underscored by the fact that there are no randomized controlled clinical trials addressing this question.

In KEYNOTE-024, -407 and -189, the efficacy of immunotherapy alone or in combination with chemotherapy versus chemotherapy alone was demonstrated in improvement of overall survival and progression-free survival [7,13,16]. We observed no statistically significant difference in overall survival between pembrolizumab alone and pembrolizumab in combination with platinum-based chemotherapy, but with a trend for a better progression free survival in the group treated with pembrolizumab in combination with chemotherapy. This has been observed in another retrospective analysis [1,2,4,14]. There were more patients with brain metastases in the triple therapy group (38.7 vs. 19.7%). Although survival of patients with non-small cell lung cancer and brain metastases has improved significantly in recent years [18], it remains a poor prognostic factor. Brain metastases have been and continue to be described as limiting prognostic factors in patients with non-small cell lung cancer [8].

Our analysis showed an improved overall survival in the absence of brain metastases in all groups. However, a phase 2 study demonstrated efficacy and activity of pembrolizumab in patients with untreated brain metastases at therapy initiation with PD-L1 expression ≥ 1% [9]. In pooled analyses from KEYNOTE -001, -010, -024, and -042, similar results were seen in patients with and without brain metastases receiving pembrolizumab monotherapy. Objective response rates were similar with pembrolizumab alone compared with chemotherapy, but duration of response was longer with pembrolizumab [11]. Similarly, for the triple therapy group, a clinical benefit was demonstrated for patients with non-small cell lung cancer compared with the chemotherapy group in a subgroup analysis from KEYNOTE-021, -189, and -407, regardless of the presence or absence of stable brain metastases [15]. However, in a real-world use cohort of pembrolizumab alone for frail patients with an ECOG ≥ 2, symptomatic brain metastases, and/or steroids as medication, a disadvantage was shown [5]. In contrast to a larger patient analysis by Dudnik, et al. our patient cohort showed no difference in treatment reg-imen for men and women. In contrast to our analysis, Dudnik et al showed an improvement in overall survival for women on combination therapy. However, this may be due to the larger cohort [4].

In our analysis, there was no statistical difference between smokers and nonsmokers, nor between heavy and light smokers. In a real-world data collection in Europe with PD-L1 highly positive patients, an advantage in favor of the combination had been found in nonsmokers [14]. In our cohort never smokers were under-represented.

The triple therapy group, in contrast to the pembrolizumab monotherapy group, had younger patients overall. The median age in the triple therapy group was 63 years (range 48-76) and 68 years (range 39-83) in the pembrolizumab monotherapy group at therapy initiation. However, younger age may have also caused the

decision to start triple therapy. A higher pressure to treat younger patients with a more complex regimen may need to be discussed here. In our analysis, age appears not to play a role in overall survival.

It is also possible, as already addressed, that prior therapy has an influence on outcome. Two patients in the pembrolizumab monotherapy group had completed radiochemotherapy a few weeks prior to initiation of first-line palliative therapy of pembrolizumab. These showed good long-term outcome and may have positively influenced the better outcome in overall survival for the pembrolizumab monotherapy group. Other factors to be investigated in the analysis were the influences of molecular pathology results. As already shown in the study by Frost, et al. a KRAS G12C mutation is a positive prognostic factor for therapy with pembrolizumab alone [6]. There were 11 patients (55%) with KRAS G12C mutation among the patients with long response (n=20, < 20 cycles of therapy) and three (15%) also had a TP53 co-mutation.

There was a slightly higher proportion of MET-positive patients in the triple therapy group (67.7 vs. 23.9%, p=0.0001). However, this group of patients was also very small (n=8 vs. n=6). There seems to be an advantage in overall survival for patients with high (METhigh) and intermediate (METint) MET amplification status in the overall group, but remains without statistical relevance with overall numbers being too small. An impact on favorable outcome under immunotherapy, independent of smoking history, PD-L1 expression, or KRAS mutation, could already be described with high MET expression [17]. Similarly, Kron et al showed that patients with MET amplification benefit from immunotherapy [10].

The level of PD-L1 expression is known to be one of the predictive factors for immunotherapy response [3]. Moreover, in a multicenter retrospective analysis, patients with non-small cell lung cancer and PD-L1 expression of ≥ 50% who were treated with first-line pembrolizumab showed significantly improved clinical outcomes when PD-L1 expression was ≥ 90% as compared to patients with lower PD-L1 expression [1]. In our patient cohort, overall survival is shown to be prolonged for patients on triple therapy with a PD-L1 status ≥ 75%. Furthermore, the overall group shows a significant prolongation of overall survival with a PD-L1 expression ≥ 85% compared to patients with a PD-L1 expression between 50-60%.

Overall, comparing the pembrolizumab monotherapy group with the triple therapy group and deciding which treatment modality is more appropriate for which patient is difficult based on this analysis.

First, the patient cohort is limited (n=102).

Second, the two subgroups also have very different case sizes (n=71 vs. n=31), so it is possible that the consideration of the overall cohort for individual factors was influenced by the pembrolizumab monotherapy group due to the higher case number and higher statistical security. The difference in case size may certainly be attributable to the later approval of triple therapy.

Furthermore, a pre-selection of patients for the respective therapy group was already made in advance by the physicians of the Evangelische Lungenklinik Berlin Buch. This also influences the further course of the individual groups and leads to a distortion. The decision to administer triple therapy on younger patients with multiple metastases and metastatic sites, a good ECOG, a PD-L1 expression of ≥ 75% and existing brain metastases is understandable. However, these factors, among others, may have favored a worse outcome. Established molecular pathological markers for therapy failure could not be determined, certainly due to the small number of cases. In our comparison, pre-selection for the respective group (pembrolizumab alone vs. triple therapy) was already done initially. Nevertheless, these two groups, even with poorer conditions than in the study cohorts, continued to demonstrate longer overall survival overall than with chemotherapy alone.

Summary

In summary, the therapy with pembrolizumab or the combination of pembrolizumab with standard chemotherapy in patients with PD-L1 expression ≥ 50% leads to significantly longer overall and progression-free survival, a higher response rate and a longer duration of response than with chemotherapy alone. Immunotherapy thus represents a paradigm shift in the tumor therapy of non-small cell lung cancer. There is a lack of identifiable bio-markers to assign patients to either mono or triple therapy.

Overall, our analysis did not detect statistical differences in long-term outcome between pembrolizumab monotherapy and combination therapy. Regardless of the treatment regimen, overall survival was improved, especially for patients with few metastases, few brain metastases and a PD-L1 status > 85%. Deciding which therapy, pembrolizumab alone or in combination with chemotherapy, for which patient would be better, is influenced by many factors and needs further investigation. Furthermore, in order to perform a better risk stratification, a larger patient cohort is needed.

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