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Research Article

Comparison of Single Agent Check-Point Inhibitors as First-Line Treatment in NSCLC Patients with High PD-L1-Expression

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Abstract

Background: Three antibodies directed against programmed cell death receptor 1 (PD-1) or its ligand 1 (PD-L1) are approved for the first-line therapy of metastatic non-small cell lung cancer (NSCLC), but no direct comparison has been performed. **Methods:** The clinicopathological features of 161 locally advanced NSCLC patients with unresectable tumor disease and being unfit to undergo definitive chemo-/radiotherapy or metastatic NSCLC patients, who received atezolizumab, cemiplimab or pembrolizumab as single-agent, first-line, palliative checkpoint-inhibitor (CPI) therapy in a certified German lung cancer center, were analyzed. **Results:** High PD-L1-positive immune cells scores (= 10%) were found in 33 patients (23.8%) with available values. Partial response occurred in 54.4%, stable disease in 21.6% and progressive disease in 24.0% of the assessable 127 patients with significant differences between the treatment groups in the univariate analysis. Median progression-free survival (PFS) and overall survival (OS) of the entire cohort were 10.5 and 15.0 months. There was no difference between the treatment groups. Patients receiving pembrolizumab instead of atezolizumab tended to have a longer PFS (13.0 vs. 9.1 months, p=0.063). In patients with stage IV at initial diagnosis, median PFS and OS were 10.5 and 12.0 months, resp., with a similar trend of a prolonged PFS and OS for treatment with pembrolizumab (PFS: 11.0 vs. 9.1 months, p=0.058; OS: 14.2 vs. 8.7 months, p=0.065). But the differences were not statistically significant. **Conclusion:** Different PD-1/PD-L1 inhibitors as first-line palliative treatment for locally advanced or metastatic NSCLC show a similar effectiveness.

Keywords: Non-Small Cell Lung Cancer; Immune Checkpoint-Inhibitor; First-Line Therapy; Tumor Proportion Score; Immune Cell Score; (Modified) Lung Immune Prognostic Index.

Introduction

Lung cancer is the second most frequent cancer and the cancer with the highest mortality worldwide [1]. Based on morphological features, lung cancer has been historically classified as small cell lung cancer (SCLC: 15%) and non-small cell lung cancer (NSCLC: 75%) [2]. NSCLC patients have often an advanced, unresectable disease stage not amenable to curative treatment or a metastatic disease stage at their initial diagnosis [3]. Historically, chemotherapy has long been the standard of care for the treatment of advanced and metastatic lung cancer. Compared with patients who receive best supportive care only, patients undergoing platinum-based combination chemotherapy have an improved 1-year survival rate from 20 to 29% (hazard ratio [HR]: 0.77, 95% CI: 0.71–0.83) [4].

Until the advent of immune checkpoint inhibitors (CPIs) in the recent treatment of the aforementioned group of NSCLC patients without oncogenic driver mutations systemic therapy was limited to chemotherapy associated with poor survival times and an unfavorable toxicity profile [5]. The availability of CPIs, which are monoclonal antibodies targeting immune systems T cells or ligands on the tumor cells [6], caused a paradigm shift in the treatment landscape of NSCLC opening new perspectives for a relevant number of patients, particularly of those with comorbidities and a reduced performance status [7].

Results from the pivotal clinical studies CheckMate-017, CheckMate-057, KEYNOTE-010 and OAK revealed marked improvements in survival with monoclonal antibodies targeting programmed cell death receptor 1 (PD-1) or programmed cell death receptor-ligand 1 (PD-L1) as compared with standard chemotherapies and led to the approval of nivolumab, pembrolizumab and atezolizumab after platinum-based chemotherapy for the treatment of metastatic NSCLC [8].

Due to the success of the CPIs in previously treated NSCLC patients, their effectiveness unter real life condition of a lung cancer as single agent therapy in the frontline setting was evaluated. Currently, efficacious first-line treatment options with ICI monotherapy can be offered to patients with an expression of PD-L1 on ≥ 50% of the tumor cells or on ≥ 10% of the immune cells according to phase 3 clinical trials with pembrolizumab [9-11], atezolizumab [12, 13], and cemiplimab [14, 15].

Regarding the approval status, there are some differences between atezolizumab, cemiplimab, and pembrolizumab. Pembrolizumab (a PD-1- antibody) was approved on October 24, 2016 by the U.S. Food and Drug Administration (FDA) and on January 31, 2017 by the European Medicines Agency (EMA) as first-line therapy for metastatic NSCLC patients with a PD-L1-Tumor Proportion Score (TPS) of ≥ 50%, after the amazing results of the KEYNOTE-024 trial were presented [9]. In contrast to the EMA, the FDA extended approval of pembrolizumab for every therapy-naïve, metastatic NSCLC patient with any PD-L1 expression in the tumor cells after the KEYNOTE-042 trial met its primary endpoints [16, 17].

The positive results of the IMpower-110 trial led to approval of atezolizumab (a PD-L1 antibody) as first-therapy in metastatic NSCLC patients with a Tumor Cell Score (TCS) of ≥ 50% or an Immune Cell Score (ICS) of ≥10% on May 18, 2020 by the FDA and on May 5, 2021 by the EMA [12, 13].

Only cemiplimab got approval on February 22, 2021 by the FDA and on June 21, 2021 by the EMA for locally advanced stage IIIB/IIIC NSCLC patients with a TPS ≥ 50% and with unresectable tumor disease and who are unfit undergoing definitive chemo-/radiotherapy or for metastatic patients according to the results of the EMPOWER-Lung1 trial [11].

However, from 2016/2017 until 2020/2021 pembrolizumab was the one and only first-line therapy option for metastatic NSCLC patients with a TPS = 50%. After the approval of atezolizumab in a rather similar setting, some treating physicians changed to the administration of atezolizumab or even cemiplimab due to a slightly broader approval status. Furthermore, the lower incidence of pneumonitis in NSCLC patients treated with PD-L1 inhibitors [18] versus those receiving PD-1 inhibitors might have prompted oncologists to prefer atezolizumab. But data about the comparison of these antibodies are very limited. Therefore, we aimed to compare mainly atezolizumab with pembrolizumab as single-agent first-line therapy for patients with metastatic NSCLC and a high PD-L1 expression not only on the tumor cells, but also on the immune cells. Particularly, data about the efficacy of pembrolizumab in NSCLC patients with a high CPS or ICS and in patients with a poor performance status (Eastern Cooperative Oncology Group (ECOG): 2) caused by the underlying malignant disease or serious comorbidities (e.g., chronic obstructive pulmonary disease (COPD), cardiac or renal failure or polyneuropathy) are lacking. The last group of patients tend to be treated with CPIs more often, even if they are more suffering from tumor related symptoms, usually requiring combined chemo-/immunotherapy.

Materials and Methods

Study Design and Patients

Data of a total of 161 locally advanced stage IIIB/IIIC NSCLC patients with unresectable tumor disease who were unfit to undergo definitive chemo-/radiotherapy or metastatic patients, who started their first systemic palliative therapy from January 31, 2017 until April 30, 2024 at the Lung Cancer Center Essen-

Mitte, which is certified by the German Cancer Society (Deutsche Krebsgesellschaft: DKG), were retrospectively analyzed. The clinical data collected for this analysis were age, gender, Eastern Cooperative Oncology Group performance status (ECOG-PS), the pretreatment absolute counts of leukocytes, neutrophil granulocytes and lymphocytes, as well as the serum level of lactate dehydrogenase (LDH), the smoking status and TNM or IASLC/ Union for International Cancer Control (UICC) stages. Some of the values were used to calculate either the Lung Immune Prognostic Index LIPI or the modified LIPI (mLIPI).

As previously defined the LIPI score was calculated [19], using LDH > upper limit of normal and derived neutrophil-to-lymphocyte ratio (dNLR) > 3 as cutoff-points. dNLR is calculated as follows: absolute neutrophil count/(total leukocyte count-absolute neutrophil count). Therefore patients could be assigned a score of 0, 1 or 2 based on their LDH and dNLR values, corresponding to good, intermediate and poor LIPI, respectively. Furthermore, patients were additionally scored on the basis of the mLIPI [20], specifically, NLR =3, LDH >1.5× the upper limit of the normal value, and ECOG-PS =2 were assigned 1 point each. According to the total score, the patients were divided into good (0 points), intermediate (1 point), and poor/very poor (=2 points) groups.

Regarding the retrospective analysis of adverse events (AE), only serious AEs leading to treatment interruption or discontinuation with CPIs were extracted from the patients` records.

All tumor sample evaluations were conducted by board-certified pathologists. All tissues were stained with hematoxylin and eosin (H&E), rabbit monoclonal immunoglobulin as a negative reagent control, and with the VENTANA PD-L1 (SP263) Assay, which is one of the recommended assays for PD-L1 diagnostics [21]. The H&E staining was performed to determine the adequacy of tumor. A tissue sample was adequate for the assay interpretation if it contained at least 100 viable tumor cells. Tumor-associated stroma was not required for tumor cell scoring, but was essential for scoring of immune cells [22]. For each staining run, prequalified human benign tonsil tissue was used as positive and negative tissue control. Tonsil tissue stained with PD-L1 was assessed for staining in lymphocytes and macrophages in germinal centers, and scattered PD-L1 staining cells among PD-L1-negative cells in paracortical regions. Tonsil tissue was also assessed for the presence of diffuse staining observed in the reticulated crypt epithelial cells with the absence of staining of superficial squamous epithelial cells. Patient-matched tissue stained for negative reagent control was evaluated for the presence and acceptability of nonspecific background staining. Once the H&E and the control slides were deemed acceptable, the PD-L1 stained slide was assessed.

In case of the suspicion of lung cancer as the underlying malignant disease leading to probe sampling reflex testing for PD-L1 usually occurs, if specimens contain a sufficient number of vital tumor cells. The PD-L1 Tumor Proportion Score (TPS) was calculated as the percentage of at least 100 viable tumor cells with complete or partial membrane staining and was separated into the following three groups: <1% (no expression: category 0), 1%–49% (low expression: category 1) and =50% (high expression: category 2).

The expression on immune cells was assessed as the proportion of tumor area occupied by PD-L1-positive immune cells of any intensity. Only immune cell staining in the tumor microenvironment was evaluated, including different patterns of staining (aggregates and single cells dispersed among tumor cells) and staining in different immune cell types (lymphocytes, macrophages, dendritic cells, and granulocytes). The coverage of the tumor area by PD-L1 expressing tumor infiltrating immune cells was graded into the following four groups: <1% (ICS 0), 1%–4% (ICS 1), 5%–9% (ICS 2) and =10% (ICS 3) [12, 13, 22].

Initially, the mononuclear immune cell density score (MIDS), defined as the ratio of the number of PD-L1-expressing immune cells to that of all tumor cells, was used in an attempt to capture immune cell expression. However, MIDS demonstrated poor reproducibility in preliminary studies. Given that the TPS is the ratio of the number of PD-L1-expressing tumor cells to that of all tumor cells, it is mathematically feasible to combine it with the MIDS (both are fractions with a common denominator). The result of this combination is the ratio of the number of all PD-L1–expressing cells (tumor cells, lymphocytes, macrophages) to the number of all tumor cells, which is termed the Combined Proportion Score (CPS). As the name implies, CPS considers PD-L1 expression on tumor cells and immune cells combined [23].

From January 31, 2017 (date of first approval of pembrolizumab as first-line therapy for metastatic NSCLC by the EMA) until May, 5 of 2021 (date of first approval of atezolizumab as first-line therapy for metastatic NSCLC by the EMA) only TPS was assessed by the pathologists. Therefore, CPS and ICS had to be retrospectively analyzed for patients who started CPS first-line treatment during this time period.

Immuncyto- and -histochemistry were performed at the Practice for Pathology Essen-Mitte (Zentrum fuer Pathologie Essen-Mitte), Essen, Germany, which is accredited by the German Accreditation Body (Deutsche Akkreditierungsstelle: DAkkS). Furthermore, PD-L1-testing is certified by the Initiative for Quality Assurance in Pathology (Qualitätssicherungsinitiative in der Pathologie: QuIP) of the German Society of Pathology (Deutsche Gesellschaft für Pathologie: DGP).

Next Generation Sequencing (NGS) for DNA and RNA alterations was performed at GENOPATH GbR, Bonn, Germany using the ARCHER panel, if molecular diagnostics were requested by the treating physician. In general, DNA mutations of the BRAF, cMET

(exon 14 skipping mutation), EGFR, Her2 and KRAS gene as well as RNA fusions of the ALK, NTRK, RET, and ROS1 genes were investigated.

Treatment and Assessment

Atezolizumab (1.200 mg, d1, q3w), Cemiplimab (350 mg, d1, q3w) or Pembrolizumab (200 mg, d1, q3w) were intravenously administered according to local standard. Radiological evaluation of response to treatment was carried out using RECIST 1.1 [24]. For progression-free survival (PFS) and overall survival (OS) analysis, patients were followed up until April, the 30th of 2024.

Statistical Analysis

The retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of the DKG-certified Lung Cancer Center (approval on March 11, 2024: ITT-EP-03-2024). Individual consent for this retrospective analysis was waived.

The statistical tests were performed using IBM SPSS Statistics (version 29), the associated figures were created using GraphPad PRISM (version 7). The Chi-square test was used to compare categorical variables (when necessary, Fisher's exact test). Students t-test was used for age, Mann Whitney U test for „pack years" and PD-L1 expression (%). Multivariate logistic regression was used to estimate associations (wald test). Models were adjusted for all variables. Kaplan-Meier methodology was used for estimation of medians, survival curves and their comparisons. Cox proportional hazard model was performed to identify prognostic factors in both the univariate analysis and the multivariate analysis (wald test).

Results

Clinicopathological Features

Detailed clinicopathological information is shown in table 1. A total of 161 patients with locally advanced NSCLC with unresectable tumor disease being unfit to undergo definitive chemo-/radiotherapy or metastatic NSCLC were identified. All patients received atezolizumab, cemiplimab or pembrolizumab as single-agent first-line palliative therapy. The majority of the patients (70.2%) had metastatic disease at the initial diagnosis (table 2). LIPI and mLIPI was calculated in 150 patients (93.2%).

Variable	Atezolizumab	Cemiplimab	Pembrolizumab	total	p-value
Numbers	65 (40.4%)	9 (5.6%)	87 (54.0%)	161 (100%)	
Age in years					**0.019**
Median (range)	74 (52-87)	79 (72-83)	70 (44-89)	72 (44-89)	
<72	28 (43.1%)	0	48 (55.2%)	76 (47.2%)	**0.005**
≥72	37 (56.9%)	9 (100%)	39 (44.8%)	85 (52.8%)	
Gender					0.645
Female	34 (52.3%)	4 (44.4%)	39 (44.8%)	77 (47.8%)	
Male	31 (47.7%)	5 (55.6%)	48 (55.2%)	84 (52.2%)	
ECOG-PS					0.184
Known	63 (96.9%)	0	86 (98.9%)	158 (98.1%)	
Unknown	2 (3.1%)	0	1 (1.1%)	3 (1.9%)	
0	13 (20.0%)	0	27 (31.0%)	40 (24.8%)	
1	42 (64.6%)	9 (100%)	49 (56.3%)	100 (62.1%)	
2	8 (12.3%)	0	10 (11.5%)	18 (11.2%)	
Smoking status					
Known	52 (80%)	9 (100%)	64 (73.6%)	125 (77.6%)	0.138
Unknown	13 (20.0%)	0	23 (26.4%)	36 (22.4%)	
Smoker	50 (96.2%)	9 (100%)	60 (93.8%)	119 (95.2%)	
Non-smoker	2 (3.8%)	0	4 (6.2%)	6 (4.8%)	
Pack years Mean (standard deviation)	46 (7-175)	50 (15-80)	40 (1-120)	45 (1-175)	0.608
1-45	23 (46.0%)	3 (33.3%)	59 (49.6%)	59 (49.6%)	0.384

>45	27 (54.0%)	6 (66.7%)	60 (50.4%)	60 (50.4%)	
TNM stages					
T					0.486
1	11 (16.9%)	1 (11.1%)	17 (19.5%)	29 (18.0%)	
2	17 (26.2%)	1 (11.1%)	17 (19.5%)	35 (21.7%)	
3	15 (23.1%)	2 (22.2%)	12 (13.8%)	29 (18.0%)	
4	22 (33.8%)	5 (55.6%)	41 (47.1%)	68 (42.2%)	
N					0.228
0	21 (32.3%)	2 (22.2%)	16 (18.4%)	39 (24.0%)	
1	6 (9.2%)	3 (33.3%)	11 (12.6%)	20 (12.4%)	
2	15 (23.1%)	1 (11.1%)	24 (27.6%)	40 (24.8%)	
3	23 (35.4%)	3 (33.3%)	36 (41.4%)	62 (38.5%)	
M					**<0.001**
0	13 (20.0%)	8 (88.9%)	26 (29.9%)	47 (29.2%)	
1	52 (80.0%)	1 (11.1%)	61 (70.1%)	114 (70.8%)	
Initial IASLC/ UICC stages					**<0.001**
I	4 (6.2%)	0	5 (5.7%)	9 (5.6%)	
II	3 (4.6%)	2 (22.2%)	4 (4.6%)	9 (5.6%)	
III	6 (9.2%)	6 (66.7%)	17 (19.5%)	29 (18.0%)	
IV	52 (80.0%)	1 (11.1%)	61 (70.1%)	114 (70.8%)	
Histology					0.131
ADC	44 (67.7%)	3 (33.3%)	56 (64.4%)	103 (64.0%)	
Non-ADC	21 (32.3%)	6 (66.7%)	31 (35.6%)	58 (36.0%)	
SCC	17 (26.2%)	4 (44.4%)	27 (31.0%)	48 (29.8%)	
LCNEC	1 (1.5%)	0	0	1 (0.6%)	
NOS	1 (1.5%)	1 (11.1%)	3 (3.4%)	5 (3.1%)	
Other	2 (3.1%)	1 (11.1%)	1 (1.1%)	4 (2.5%)	
PD-L1 TPS					**<0.001**
Median (range)	70 (0-100)	90 (55-100)	80 (55-100)	80 (0-100)	
<50%	12 (18.5%)	0	0	12 (7.5%)	
≥50%	53 (81.5%)	9 (100%)	87 (100%)	149 (92.5%)	
PD-L1 CPS					
Unknown	2 (3.1%)	0	66 (75.9%)	23 (14.3%)	
Known	63 (45.7%)	9 (6.5%)	66 (47.8%)	138 (85.7)	**<0.001**
Median (range)	85 (0-120)	95 (70-110)	90 (57-140)	90(0-140)	
PD-L1 ICS					
Unknown	2 (3.1%)	0	20 (23.0%)	22 (13.7%)	
Known	63 (96.9%)	9 (100%)	67 (77.0%)	139 (86.3%)	
Median (range)	4 (0-100)	4(0-25)	3 (0-60)	3 (0-100)	**0.002**

<10%	43 (66.2%)	6 (66.7%)	62 (71.3%)	111 (86.9%)	**<0.001**
≥10%	20 (30.8%)	3 (33.3%)	10 (14.9%)	33 (23.8%)	
PD-L1					**<0.001**
TPS ≥50% + ICS <10%	43 (66.2%)	6 (66.7%)	57 (65.5%)	106 (65.8%)	
TPS <50% + ICS ≥10%	12 (18.5%)	0	0	12 (7.5%)	
TPS ≥50% + ICS ≥10%	8 (12.3%)	3 (33.3%)	10 (11.5%)	21 (13.0%)	
TPS ≥50% + unknown ICS	2 (3.1%)	0	20 (23.0%)	22 (13.7%)	
Gene mutations					
Unknown	7 (10.8%)	0	35 (40.2%)	42 (26.1%)	
Known	58 (89.2%)	9 (100%)	52 (59.8%)	119 (73.9%)	**<0.001**
Wild type	6 (10.3%)	2 (22.2%)	26 (50.0%)	34 (28.6%)	
Any mutation	52 (89.7%)	7 (77.8%)	26 (50.0%)	85 (71.4%)	
No. of mutations					**0.034**
1	20 (38.5%)	1 (14.3%)	9 (34.6%)	30 (35.3%)	
2	21 (40.4%)	1 (14.3%)	13 (50.0%)	35 (41.2%)	
≥3	11 (21.2%)	5 (71.4%)	4 (15.4%)	20 (23.5%)	
KRAS gene mutation	58 (100%)	9 (100%)	52 (100%)	119 (100%)	0.706
Wild type	38 (65.5%)	7 (77.8%)	33 (63.5%)	78 (65.5%)	
Mutation	20 (34.5%)	2 (22.2%)	19 (36.5%)	41 (34.5%)	
G12C mutation	12 (60.0%)	2 (100%)	11 (57.9%)	25 (61.0%)	0.506
Non-G12C mutation	8 (40.0%)	0	8 (42.1%)	16 (39.0%)	
KEAP1 gene mutation	58 (100%)	9 (100%)	52 (100%)	119 (100%)	0.131
Wild type	55 (94.8%)	8 (88.9%)	52 (100%)	115 (96.6%)	
Mutation	3 (5.2%)	1 (11.1%)	0	4 (3.4%)	
LKB1/STK11 gene mutation	58 (100%)	9 (100%)	52 (100%)	119 (100%)	0.28
Wild type	52 (89.7%)	9 (100%)	50 (96.2%)	111 (93.3%)	
Mutation	6 (10.3%)	0	2 (3.8%)	8 (6.7%)	
TP53 gene mutation	58 (100%)	9 (100%)	52 (100%)	119 (100%)	**<0.001**
Wild type	21 (36.2%)	3 (33.3%)	39 (75.0%)	63 (52.9%)	
Mutation	37 (63.8%)	6 (66.7%)	13 (25.0%)	56 (47.1%)	
LIPI					
Unknown	2 (3.1%)	0	9 (10.3%)	11 (6.8%)	
Known	63 (96.9%)	9 (100%)	78 (89.7%)	150 (93.2%)	0.768
0 factors (good)	13 (20.6)	3 (33.3)	14 (17.9)	30 (20.0)	
1 factors (intermediate)	34 (54.0)	5 (55.6)	46 (59.0)	85 (56.7)	
2 factors (poor)	16 (25.4)	1 (11.1)	18 (23.1)	35 (23.3)	
mLIPI					
Unknown	2 (3.1%)	0	9 (10.3%)	11 (6.8%)	
Known	63 (96.9%)	9 (100%)	78 (89.7%)	150 (93.2%)	0.356

0	13 (20.6%)	3 (33.3%)	10 (12.8%)	26 (17.3%)	
1	28 (44.4%)	5 (55.6%)	48 (61.5%)	81 (54.0%)	
2	21 (33.3%)	1 (11.1%)	19 (24.4%)	41(27.3%)	
3	1 (1.6%)	0	1 (1.3%)	2 (1.3%)	
Treatment cycles					0.092
Median (range)	4 (1-47)	5 (1-21)	8 (1-88)	6 (1-88)	
Response					
Unknown	16 (24.6 %)	2 (22.2%)	18 (20.6%)	36 (22.3%)	
Known	49 (75.4%)	7 (87.8%)	10 (79.6%)	125 (77.7%)	**0.034**
CR	0	0	0	0	
PR	20 (40.8%)	5 (71.4%)	43 (62.3%)	68 (54.4%)	
SD	10 (20.4%)	1 (14.3%)	16 (23.2%)	27 (21.6%)	
PD	19 (38.8%)	1 (14.3%)	10 (14.5%)	30 (24.0%)	

ADC: adenocarcinoma, CPS: Combined Proportion Score, CR: Complete Response, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, IASLC: International Association for the Study of Lung Cancer, ICS: Immune Cell Score, KEAP1: Kelch-like ECH-associated protein 1, KRAS: Kirsten Rat Sarcoma viral oncogene homolog, LCNEC: Large Cell Neuroendocrine carcinoma, LIPI: Lung Immune Prognostic Index, LKB1: Liver Kinase B1, mLIPI: modified Lung Immune Prognostic Index, NSCLC: Non-Small Cell Lung Cancer, NOS: Not Otherwise Specified carcinoma, OTH: Others, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SCC: Squamous Cell Carcinoma, SD: Stable Disease, STK11: Serine/Threonine Kinase 11, TP53: Tumor Protein 53 and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Table 1: Comparison of clinicopathological factors between locally advanced NSCLC patients with unresectable tumor disease being unfit to undergo definitive chemo-/radiotherapy and metastatic NSCLC patients, who received atezolizumab, cemiplimab or pembrolizumab as single-agent first-line therapy for palliative treatment.

PD-L1 TPS was assessed in each patient (table 1). Median PD-L1 TPS was 80%. PD-L1 CPS was analyzed in 138 patients (85.7%) with a median of 90. PD-L1 ICS was determined in 139 patients (86.3%), with a median of 3 %. A high ICS (=10%) was noted in 33 patients (23.8%). Only 21 patients (13.0 %) patients had a high TPS and ICS, 106 patients (65.8%) had a high TPS, but low ICS and only 12 patients (7.5%) had a low TPS, but high ICS.

In the univariate analysis of the clinicopathological features (table 1), significant differences between patients receiving atezolizumab, cemiplimab or pembrolizumab regarding age, synchronous development of metastases, PD-L1 expression (TPS, CPS or ICS) or pathogenic gene mutations (e.g., KEAP1 or TP53) were noted. In contrast, LIPI and mLIPI factor distribution were quite similar. In the subgroup of patients with metastatic disease at primary diagnosis, significant differences between atezolizumab and cemiplimab regarding PD-L1 expression or pathogenic mutations were found (table 2).

Variable	**Atezolizumab**	**Pembrolizumab**	**total**	**p-value**
Numbers	52 (46.0%)	61 (%)	113 (54.0%)	
Age in years				0.557
Median (range)	73 (52-87)	70 (51-89)	72 (51-89)	
<72	24 (46.2%)	32 (52.5%)	56 (49.6%)	0.504
≥72	28 (53.8%)	29 (47.5%)	57 (50.4%)	
Gender				0.621
Female	28 (53.8%)	30 (49.2%)	58 (51.3%)	
Male	24 (46.2%)	31 (50.8%)	55 (48.7%)	

ECOG-PS				0.184
Unknown	1 (1.9%)	1 (1.6%)	2 (1.8%)	
Known	51 (98.1%)	60 (98.4%)	112 (98.2%)	
0	10 (19.2%)	17 (27.9%)	27 (23.9%)	
1	34 (65.4%)	36 (59.0%)	70 (61.9%)	
2	7 (13.5%)	7 (11.5%)	14 (12.4)	
Smoking status				
Unknown	10 (19.2%)	17 (27.9%)	27 (23.9%)	
Known	41 (97.8%)	44 (72.1%)	86 (76.1%)	1
Smoker	50 (76.9%)	42 (95.5%)	83 (96.5%)	
Non-smoker	1 (2.4%)	2 (4.5%)	3 (3.5%)	
Pack years	46 (7-175)	40 (1-120)	45 (1-175)	0.608
Mean (standard deviation)				
1-45	23 (46.0%)	59 (49.6%)	59 (49.6%)	0.384
> 45	27 (54.0%)	60 (50.4%)	60 (50.4%)	
TNM stages				
T				0.306
1	6 (11.5%)	9 (14.8%)	15 (13.3%)	
2	14 (26.9%)	12 (19.7%)	26 (23.0%)	
3	11 (21.2%)	7 (11.5%)	18 (15.9%)	
4	21 (40.4%)	33 (54.1%)	54 (47.8%)	
N				0.425
0	14 (26.9%)	9 (14.8%)	23 (20.4%)	
1	4 (7.7%)	7 (11.5%)	11 (9.7%)	
2	12 (23.1%)	17 (27.9%)	29 (25.7%)	
3	22 (42.3%)	28 (45.9%)	50 (44.2%)	
Histology				0.79
ADC	47 (71.2%)	42 (68.9%)	79 (69.9%)	
Non-ADC	21 (32.3%)	31 (35.6%)	34 (30.1%)	
SCC	12 (23.1%)	16 (26.2%)	28 (24.8%)	
NOS	1 (1.9%)	3 (4.9%)	4 (3.5%)	
Other	2 (3.8%)	0	2 (1.8%)	
PD-L1 TPS				**<0.001**
Median (range)	80 (0-100)	90 (50-100)	80 (0-100)	
<50%	7 (13.5%)	0	17 (6.2%)	**0.003**
≥50%	45 (86.8%)	61 (100%)	106 (93.8%)	
PD-L1 CPS				**<0.001**
Unknown	2 (3.8%)	15 (24.6%)	17 (15.0%)	
Known	50 (96.2%)	46 (75.4%)	96 (85.0%)	

Median (range)	85 (0-120)	95 (57-140)	90 (0-140)	**0.008**
PD-L1 ICS				
Unknown	2 (3.8%)	15 (24.6%)	17(15.0%)	
Known	50 (96.2%)	46 (75.4%)	96 (85.0%)	
Median (range)	4 (0-100)	2.5 (0-65)	3(0-100)	**0.012**
<10%	38 (76.0%)	41 (89.1%)	79 (82.3%)	**<0.001**
≥10%	12 (24.0%)	5 (10.9%)	17 (17.7%)	
PD-L1				**<0.001**
TPS ≥50% + ICS <10%	38 (73.1%)	41 (67.2%)	79 (69.9%)	
TPS <50% + ICS ≥10%	7 (13.5%)	0	7 (6.2%)	
TPS ≥50% + ICS ≥10%	5 (9.6%)	5 (8.2%)	10 (8.8%)	
TPS ≥50% + unknown ICS	2 (3.8%)	15 (24.6%)	17 (15.0%)	
Gene mutations				
Unknown	6 (11.5%)	24 (39.3%)	30 (26.5%)	
Known	46 (88.5%)	37 (70.7%)	83 (73.5%)	
Any mutation	42 (91.3%)	16 (43.2%)	58 (69.9%)	**<0.001**
Wild type	4 (8.7%)	21 (56.8%)	25 (30.1%)	
No. of mutations				0.334
1	16 (38.1%)	6 (37.5%)	22 (37.9%)	
2	17 (40.5%)	9 (56.3%)	26 (44.8%)	
≥3	9 (21.4%)	1 (6.3%)	10 (17.2%)	
KRAS gene mutation				0.708
Wild type	28 (60.9%)	24 (64.9%)	52 (62.7%)	
Mutation	18 (39.1%)	13 (35.1%)	31 (37.3%)	
G12C mutation	11 (61.1%)	8 (61.5%)	19 (61.3%)	0.981
Non-G12C mutation	7 (38.9%)	5 (38.5%)	12 (38.7%)	
KEAP1 gene mutation				0.5
Wild type	44 (95.7%)	37 (100%)	81 (97.6%)	
Mutation	2 (4.3%)	0	2 (2.4%)	
LKB1/STK11 gene mutation				0.125
Wild type	42 (91.3%)	37 (100%)	79 (95.2%)	
Mutation	4 (8.7%)	0	4 (4.8%)	
TP53 gene mutation				**<0.001**
Wild type	14 (30.4%)	28 (75.7%)	42 (50.6%)	
Mutation	32 (69.6%)	9 (24.3%)	41 (49.4%)	
LIPI				
Unknown	2 (3.8%)	8 (13.1%)	10 (8.8%)	
Known	50 (96.2%)	53 (86.9%)	103 (91.2%)	0.963
0 factors (good)	10 (20.0%)	10 (18.9%)	20 (19.4%)	

1 factors (intermediate)	26 (52.0%)	29 (54.7%)	55 (53.4%)	
2 factors (poor)	14 (28.0%)	14 (26.4%)	28 (27.2%)	
mLIPI				
Unknown	2 (3.8%)	8 (13.1%)	10 (8.8%)	
Known	50 (96.2%)	53 (86.9%)	103 (91.2%)	0.527
0	10 (20.0%)	8 (15.1%)	18 (17.5%)	
1	21 (42.0%)	30 (56.6%)	51 (49.5%)	
2	18 (36.0%)	14 (26.4%)	32 (31.1%)	
3	1 (2.0%)	1 (1.9%)	2 (1.9%)	
Treatment cycles				0.11
Median (range)	4 (1-47)	7 (1-88)	4 (1-88)	
Response				
Unknown	16 (30.8%)	16 (26.2%)	32 (28.3%)	
Known	36 (69.2%)	45 (73.8)	81 (71.7%)	
CR	0	0	0	0.133
PR	17 (47.2%)	30 (66.7%)	47 (58.8%)	
SD	7 (19.4%)	8 (17.8%)	15 (18.5%)	
PD	12 (33.3%)	7 (15.6%)	19 (23.5%)	

ADC: adenocarcinoma, CPS: Combined Proportion Score, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, IASLC: International Association for the Study of Lung Cancer, ICS: Immune Cell Score, KEAP1: Kelch-like ECH-associated protein 1, KRAS: Kirsten Rat Sarcoma viral oncogene homolog, LCNEC: Large Cell Neuroendocrine Carcinoma, LIPI: Lung Immune Prognostic Index, LKB1: Liver Kinase B1, mLIPI: modified lung immune prognostic index, NSCLC: non-small cell lung cancer, NOS: not otherwise specified carcinoma, OTH: others, PD-L1: Programmed Death receptor Ligand 1, SCC: Squamous Cell Carcinoma, SD: Stable Disease, STK11: Serine/Threonine Kinase 11, TP53: Tumor Protein 53 and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Table 2: Comparison of clinicopathological factors between metastatic NSCLC patients, who received atezolizumab or pembrolizumab as single-agent first-line therapy for palliative treatment.

Gene Mutations

In 119 patients of the entire cohort (74.5 %), DNA & RNA mutational diagnostics were performed. The majority of these patients suffered from an adenocarcinoma of the lung (90 resp. 75%) or had metastatic disease at the initial diagnosis (84 resp. 70%). Any type of an activating or a pathogenic mutation was observed in 85 patients (70.8%). Of these, activating KRAS gene mutations were

found in 42 patients (49.4%), pathogenic TP53 gene mutations in 56 patients (65.9%) or CDKN2A gene mutations in 12 patients (14.1%). All other gene mutations had a frequency lower than 10% (Suppl. table 1).

Mutation	N (%)
total	85 (100)
TP53	56 (65.9)
KRAS	42 (49.4%)
G12C	25
G12D	5
G12V	4
G12A	1
G12F	2
G12H	1
G12P	1
G13C	1
G61H	1
CDKN2A	12 (14.1%)
STK11	8 (9.4%)
EGFR (non-activating)	7 (8.2%)
PIK3CA	7 (8.2%)
RB1	5 (5.9%)
MET	3 (3.6%)
KEAP1	4 (4.8%)
NFE2L2	4 (4.8%)
PTEN	2 (2.4%)
APC	1 (1.2%)
ATR	1 (1.2%)
BRAC2	1 (1.2%)
BRAF V600E	1 (1.2%)
BRAF non-V600	2 (2.4%)
CDK4	1 (1.2%)
FBXW7	1 (1.2%)
Her2neu	1 (1.2%)
IDH1	1 (1.2%)
IDH2	1 (1.2%)
NRAS	1 (1.2%)

Suppl. Table 1: Genetic mutations (activating or pathogenic mutations) found in patients with DNA- and RNA mutational diagnostics. Of note, in 35 patients only wild type genes were detected. No gene transfusions or translocations were observed. In some patients, several mutations were found (comutations).

Treatment Effectiveness

ORR was assessable in 127 patients (78.9%), but 15 patients (23.1%), 2 patients (22.2%), and 17 patients (19.5%) discontinued therapy with atezolizumab, cemiplimab, or pembrolizumab before radiographic assessment of response, mainly due to clinical deterioration. Partial response (PR) occurred in 54.4%, stable disease (SD) in 21.6% and progressive disease (PD) in 24.0% of the assessable patients (table 1). There were significant differences between the treatment groups (p=0.034, table 1). In the subgroup of stage IV patients ORRs between atezolizumab and pembrolizumab did not differ significantly (table 2).

Median PFS of the entire cohort was 10.5 months and median OS was 15.0 months (figure 1A/B). There were no significant differences between the treatment groups. However, patients receiving pembrolizumab compared to atezolizumab tended to receive longer treatment without progression (13.0 vs. 9.1 months, p=0.063) in the univariate analysis.

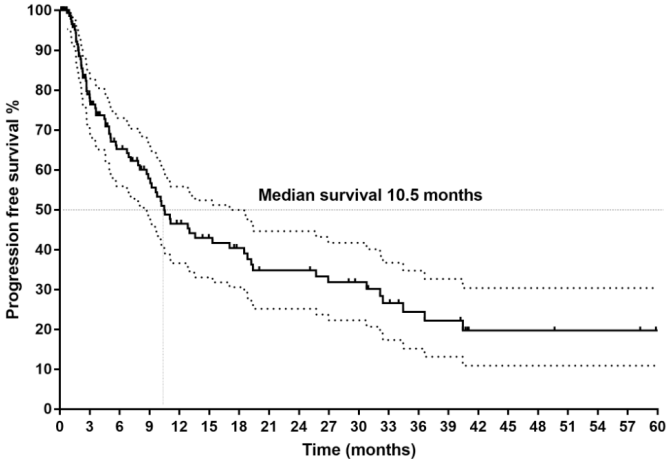

Figure 1A: Progression-free survival (PFS) of locally advanced NSCLC patients with unresectable tumor disease being unfit to undergo definitive chemo-/radiotherapy or metastatic NSCLC patients, who received atezolizumab, cemiplimab or pembrolizumab as single-agent first-line therapy for palliative treatment.

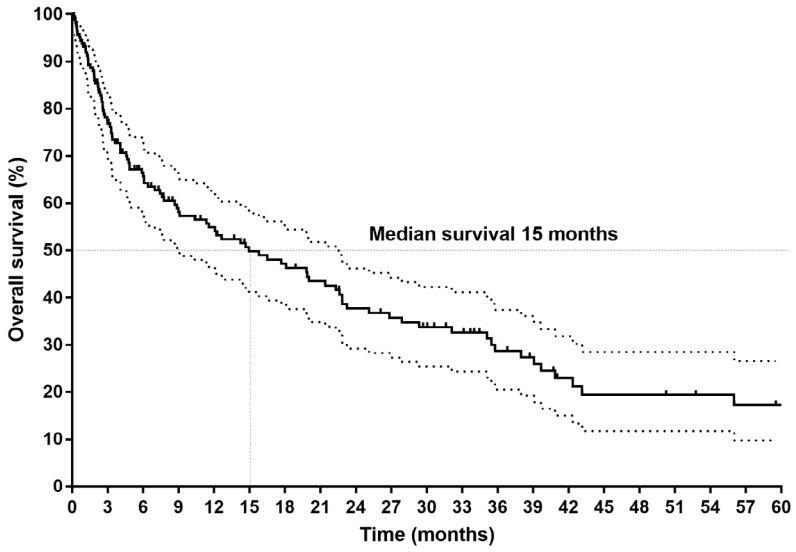

Figure 1B: Overall survival (OS) of locally advanced NSCLC patients with unresectable tumor disease being unfit to undergo definitive chemo-/radiotherapy or metastatic NSCLC patients, who received atezolizumab, cemiplimab or pembrolizumab as single-agent first-line therapy for palliative treatment.

Non-smoking status (p=0.026), a high ICS and low TPS (p=0.002), a lower number of treatment cycles (p<0.001) or progressive disease (p<0.001) as response to therapy resulted in a worse PFS (table 3) in the multivariate analysis. An ECOG PS of 2, detection of at least three genetic mutations (compared to wild type of all genes tested), stage IV at initial diagnosis, 2 factors in the LIPI, 2 or 3 factors in mLIPI, a lower number of treatment cycles or PD as response to CPIs were associated with a poorer OS (table 4) in the multivariate analysis. In contrast, the kind of the used CPI had no influence on OS (p=0.509 for atezolizumab vs. cemiplimab or p=0.0326 for pembrolizumab vs. atezolizumab).

Variable	Median PFS in months	Hazard Ratio (CI 95%)	p-value
total	10.5		
Age in years			
<72	9.2	1 (ref.)	
≥72	13	0.84 (0.54-1.31)	0.441
Gender			
Female	9.6	1 (ref.)	
Male	11	0.87 (0.56-1.37)	0.56
ECOG-PS			
Unknown	2.7	-	-
Known	10.5		
0	8	1 (ref.)	
1	10.5	0.71 (0.43-1.15)	0.166
2	19.4	0.47 (0.16-1.36)	0.165
Smoking status			
Unknown	8		

Known	11		
Smoker	11	1 (ref.)	
Non-smoker	1.8	2.88 (1.13-7.34)	**0.026**
Pack years			
1-45	10	1 (ref.)	
>45	19	0.52 (0.35-0.97)	0.737
TNM stages			
T			
1	7	1 (ref.)	
2	10.5	0.77 (0.40-1.51)	0.452
3	18.8	0.64 (0.31-1.30)	0.217
4	9.2	1.02 (0.57-1.85)	0.934
N			
0	12.8	1 (ref.)	
1	9.1	1.55 (0.73-3.28)	0.251
2	18.5	0.97 (0.49-1.94)	0.94
3	10.2	1.41 (0.80-2.50)	0.231
M			
0	15.3	1 (ref.)	
1	10.5	1.31 (0.80-2.14)	0.283
Initial IASLC/UICC stages			
I-II	9	1 (ref.)	
III	19.4	0.77 (0.34-1.76)	0.538
IV	10.5	1.12 (0.57-2.21)	0.739
Histology			
ADC	10.5	1 (ref.)	
Non-ADC	10.5	0.92 (0.57-1.47)	0.719
PD-L1			
TPS ≥50% + ICS <10%	10.5	1 (ref.)	
TPS <50% + ICS ≥10%	2.7	3.28 (1.52-7.09)	0.002
TPS ≥50% + ICS ≥10%	n.e.	0.44 (0.18-1.11)	0.083
TPS ≥50% + unknown ICS	26.9	0.86 (0.45-1.66)	0.66
Gene mutations			
Unknown	8.7	1 (ref.)	
Known	11	0.84 (0.51-1.37)	0.483
Wild type	10.5	1 (ref.)	
Any mutation	13	0.92 (0.52-1.63)	0.768
No. of mutations			
1	13	1.00 (0.49-2.02)	0.993

2	7	1.17 (0.60-2.28)	0.639
≥3	30.8	0.46 (0.17-1.24)	0.126
KRAS gene mutation			
Wild type	11	1 (ref.)	
Mutation	13	0.73 (0.40-1.31)	0.289
TP53 gene mutation			
Wild type	11	1 (ref.)	
Mutation	11	0.95 (0.56-1.63)	0.854
LIPI			
Known	10	1 (ref.)	
Unknown	10	1.19 (0.43-3.28)	0.733
0 factors (good)	18.5	1 (ref.)	
1 factors (intermediate)	10.5	1.36 (0.76-2.43)	0.306
2 factors (poor)	9.1	1.07 (0.50-2.28)	0.87
mLIPI			
Known	10	1 (ref.)	
Unknown	10	1.19 (0.43-3.28)	0.733
0	18.5	1 (ref.)	
1	10.5	1.34 (0.72-2.48)	0.35
2-3	9.8	0.97 (0.45-2.11)	0.949
Treatment cycles			
Pro+ 1 Cycle		0.95 (0.93-0.97)	**<0.001**
<6	2.7	1(ref.)	
≥6	19	0.09 (0.05-0.16)	**<0.001**
Checkpoint Inhibitor			
Atezolizumab	9.1	1 (ref.)	
Cemiplimab	n.e.	0.20 (0.03-1.45)	0.111
Pembrolizumab	11	0.65 (0.40-1.04)	0.071
Response			
Unknown	10	1 (ref.)	
Known	10	0.74 (0.23-2.40)	0.618
PR	26	1 (ref.)	
SD	9	1.67 (0.85-3.26)	0.134
PD	2.1	31.2 (14.5-66.9)	**<0.001**

ADC: adenocarcinoma, CPS: Combined Proportion Score, CR: Complete Response, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, IASLC: International Association for the Study of Lung Cancer, ICS: Immune Cell Score, KRAS: Kirsten Rat Sarcoma viral oncogene homolog, LIPI: Lung Immune Prognostic Index, LKB1: liver kinase B1, mLIPI: modified Lung Immune Prognostic Index, NSCLC: Non-Small Cell Lung Cancer, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SCC: Squamous Cell Carcinoma, SD: Stable Disease, TP53: Tumor Protein 53 and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Table 3: Multivariate logistic regression analysis by choosing PFS as the terminal point variable.

Variable	Median OS in months	Hazard Ratio (CI 95%)	p-value
total	15		
Age in years			
<72	21	1 (ref.)	
≥72	12	1.27 (0.86-1.88)	0.23
Gender			
Female	13	1 (ref.)	
Male	16	0.99 (0.67-1.47)	0.964
ECOG-PS			
Unknown	4.9		
Known	15.8		
0	15	1 (ref.)	
1	20	1.02 (0.64-1.61)	0.942
2	3	1.96 (1.01-3.82)	0.048
Smoking status			
Unknown	14.6		
Known	15.8		
Smoker	15.8	1 (ref.)	
Non-smoker	63.8	0.64 (0.23-1.79)	0.391
Pack years			
1-45	16	1 (ref.)	
>45	14	0.92 (0.58-1.48)	0.737
TNM stages			
T			
1	20	1 (ref.)	
2	9	1.23 (0.66-2.28)	0.515
3	32	0.84 (0.42-1.70)	0.638
4	11	1.57 (0.91-2.71)	0.104
N			
0	28	1 (ref.)	
1	15	1.15 (0.54-2.46)	0.708
2	9	1.72 (0.98-3.04)	0.058
3	15	1.48 (0.88-2.51)	0.142
M			
0	23	1 (ref.)	
1	12	1.51 (0.96-2.38)	0.072
Initial IASLC/UICC stages			
I-II	77	1 (ref.)	
III	20	2.50 (0.95-6.05)	0.062

IV	12	2.73 (1.18-6.28)	0.018
Histology			
ADC	18	1 (ref.)	
Non-ADC	12	1.15 (0.77-1.74)	0.488
PD-L1			
TPS ≥50% + ICS <10%	16	1 (ref.)	
TPS <50% + ICS ≥10%	9	1.30 (0.52-3.28)	0.574
TPS ≥50% + ICS ≥10%	32	0.74 (0.39-1.41)	0.36
TPS ≥50% + unknown ICS	9	1.07 (0.62-1.83)	0.816
Gene mutations			
Unknown	9.1	1 (ref.)	
Known	18	0.68 (0.45-1.03)	0.066
Wild type	18	1 (ref.)	
Any mutation	22	0.74 (0.45-1.23)	0.247
No. of mutations			
1	16	0.89 (0.47-1.68)	0.724
2	7.4	0.86 (0.48-1.56)	0.623
≥3	40	0.31 (0.11-0.89)	**0.03**
KRAS gene mutation			
Wild type	18	1 (ref.)	
Mutation	28	0.74 (0.43-1.27)	0.276
TP53 gene mutation			
Wild type	18	1 (ref.)	
Mutation	29	0.88 (0.54-1.45)	0.618
LIPI			
Known	15	1 (ref.)	
Unknown	25	1.36 (0.63-2.95)	0.43
0 factors (good)	23	1 (ref.)	
1 factors (intermediate)	18	1.57 (0.89-2.75)	0.116
2 factors (poor)	5	2.44 (1.29-4.58)	**0.006**
mLIPI			
Known	15	1 (ref.)	
Unknown	25	1.36 (0.63-2.95)	0.43
0	38	1 (ref.)	
1	20	1.61 (0.87-2.96)	0.128
2-3	4.1	2.78 (1.44-5.36)	**0.002**
Treatment cycles			
Pro+ 1 Cycle		0.95 (0.93-0.97)	**<0.001**
<6	3.3	1 (ref.)	

≥6	35	0.18 (0.12-0.28)	**<0.001**
Checkpoint Inhibitor			
Atezolizumab	9	1 (ref.)	
Cemiplimab	29	0.67 (0.21-2.19)	0.509
Pembrolizumab	16	0.80 (0.52-1.24)	0.326
Response			
Unknown	2	1 (ref.)	
Known	22	0.10 (0.06-0.16)	**<0.001**
PR	28	1 (ref.)	
SD	23	1.54 (0.85-2.79)	0.152
PD	7.4	3.06 (1.76-5.34)	**<0.001**

ADC: adenocarcinoma, CPS: Combined Proportion Score, CR: Complete Response, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, IASLC: International Association for the Study of Lung Cancer, ICS: Immune Cell Score, KRAS: Kirsten Rat Sarcoma viral oncogene homolog, LIPI: Lung Immune Prognostic Index, LKB1: liver kinase B1, mLIPI: modified Lung Immune Prognostic Index, NSCLC: Non-Small Cell Lung Cancer, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SCC: Squamous Cell Carcinoma, SD: Stable Disease, TP53: Tumor Protein 53 and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Table 4: Multivariate logistic regression analysis by choosing OS as the terminal point variable.

In the subgroup of patients with stage IV at initial diagnosis, median PFS was 10.5 months and median OS was 12.0 months (figure 2A/B). Patients receiving pembrolizumab compared to atezolizumab tended to be longer without progression (11.0 vs. 9.1 months, p=0.058) and to survive longer, although there was no significant difference in OS between pembrolizumab or atezolizumab treatment (14.2 vs. 8.7 months, p=0.065).

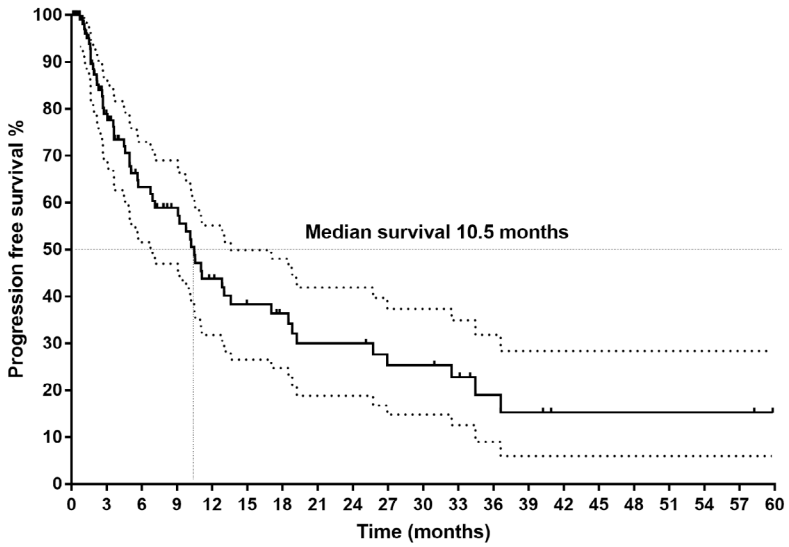

Figure 2A: Progression-free survival (PFS) of metastatic NSCLC patients, who received atezolizumab or pembrolizumab as single-agent first-line therapy for palliative treatment.

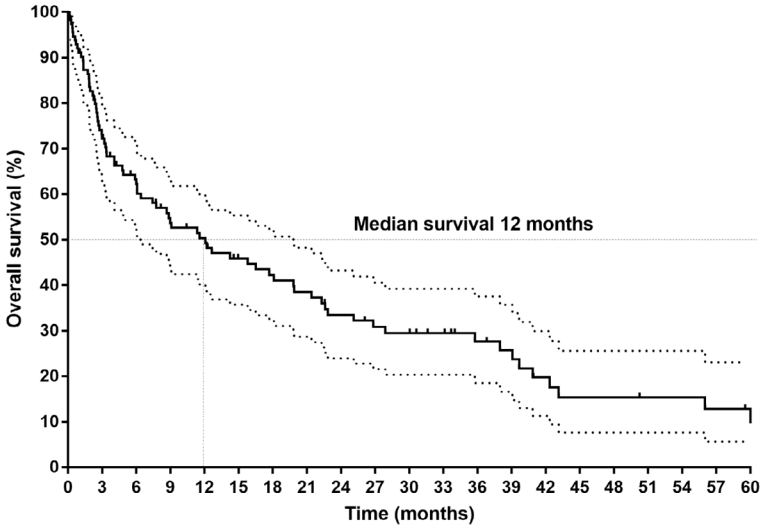

Figure 2B: Overall survival (OS) of metastatic NSCLC patients, who received atezolizumab or pembrolizumab as single-agent first-line therapy for palliative treatment.

Adverse events leading to treatment interruption or permanent discontinuation

In 20 patients (12.4%) treatment was either temporarily or permanently discontinued due to the advent of serious adverse events (Suppl. table 2). The main causes were colitis (6 patients), dermatitis, hepatitis or pneumonitis (each 3 patients). In patients treated with cemiplimab, no serious adverse were noted. Of note, one case of hyperprogression during atezolizumab therapy (proven by CT, the course of serum levels of LDH and tumor markers) was observed.

Serious adverse event	no. of patients	checkpoint inhibitors used
Colitis	6	atezolizumab (2 patients), pembrolizumab (4 patients)
Dermatitis	3	pembrolizumab (3 patients)
Hepatitis	3	atezolizumab (2 patients), pembrolizumab (1 patient)
Pneumonitis	3	atezolizumab (1 patient), pembrolizumab (2 patients)
Coeliac disease	1	pembrolizumab (1 patient)
Mucositis/Stomatitis	1	pembrolizumab (1 patient)
Myocarditis	1	atezolizumab (1 patient)
Polymyalgia rheumatica	1	atezolizumab (1 patient)
Pruritus	1	pembrolizumab (1 patient)
Xerostomia	1	pembrolizumab (1 patient)

Suppl. Table 2: Adverse events leading to temporary or permanent treatment interruption.

Discussion

To the best of our knowledge, this retrospective study is the first comparison of different immune CPIs acting in the PD-1-/PD-L1 pathway as first-line palliative treatment of locally advanced or metastatic NSCLC patients. There were no significant differences in PFS or OS, although ORRs differed significantly between treatment groups. Patients receiving pembrolizumab tended to survive longer without progression in the whole cohort.

Compared to the pivotal trials leading to approval of atezolizumab, cemiplimab and pembrolizumab in this setting [9-15] we observed a higher percentage of responding patients (54.4%). However, similar results were recently published in a retrospective real-world study of non-squamous, metastatic NSCLC patients with pembrolizumab as palliative first line therapy (CR: 3.1%, PR: 49.6%) [25]. In another retrospective trial investigating CPIs as first-line therapy in metastatic (non-squamous and squamous) NSCLC CR was 2.7%, PR was 25%, SD was 22.8% and PD was 19.7%, while evaluation has not been performed in 29.9% of the patients [26].

Our results in terms of PR, SD and PD might be biased by the relatively high number of patients discontinuing treatment during the first three months without any further radiographic assessment.

Some reasons for the early treatment discontinuation beside progression of the underlying malignant disease might be the percentage of patients with an ECOG-PS of 2 (11.2%) and the rather high aged population (median age was 72 years). In the above mentioned study from the German National Network Genomic Medicine Lung Cancer 11% of the patients died within the first three months of treatment without any evaluation, which is similar to our results [25]. Furthermore, patients with advanced or metastatic NSCLC and a poor performance status were consistently found to have clearly worse outcomes in several previously published retrospective studies evaluating pembrolizumab monotherapy, including a meta-analysis of real-world data [27-32].

The majority of patients in our study who received pembrolizumab were treated from 2017 to 2021 and patients receiving atezolizumab or cemiplimab got their treatment in the recent years starting in 2021 after the approval of atezolizumab for this specific setting. Response assessments considered in this monocentric study were performed by the same radiologists since the first approval of pembrolizumab for palliative first-line therapy of metastatic NSCLC patients in 2017. Therefore, we do not expect any influence on the determination of progressive disease in relation to the administered CPI.

Immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) [33] is not standard-of-care. Therefore, we could not compare iRECIST evaluation between the different treatment groups.

Almost no data about associations between CPS or ICS and the efficacy of pembrolizumab in metastatic NSCLC are published. We present some CPS und ICS data of these group of patients. In the multivariate analysis patients with a low TPS and a high ICS had a worse PFS, if they received atezolizumab compared to pembrolizumab. Furthermore, we have proven that patients in the poor prognosis group determined by the LIPI or the mLIPI indead survive significantly shorter – irrespective of the used CPI.

One important weakness is the rather low number of patients with available results of DNA- and RNA sequencing. It is worth mentioning that until 2021 these diagnostics were recommended only in patients with non-sqamous NSCLC. In 41 of 119 patients with DNA- and RNA sequencing data an activating KRAS gene mutation was found (34.5%), which is far higher than the frequency of reported activating KRAS gene mutation in the western population (25.78%) [34]. In a cohort from a German prospective, observational, nation-wide registry trial 160 (15.4 %) patients had KRAS G12C gene mutations and 251 patients (24.2 %) had non-G12C gene mutations. High PD-L1 expression (TPS > 50 %) was documented for 28.0 % and 43.5 % of these patients, respectively, revealing an association between KRAS gene mutations and PD-L1 expression [35] in accordance with our results. The above cited study from the German National Network Genomic Medicine Lung Cancer analyzed the influence of an activating KRAS gene mutation on the presence of comutations in a cohort of non-squamous, metastatic NSCLC patients with pembrolizumab as palliative fist-line therapy. 53% of 696 patients had KRAS gene mutations (KRAS G12C gene mutation in 173 patients and KRAS nonG12C gene mutation in 195 patients, respectively) [25]. Preclinical data showed an upregulation of PD-L1 in lung adenocarcinoma with KRAS gene mutations through p-ERK signaling, thereby providing a rationale for the higher frequency of KRAS gene mutations in our cohort of patients [36]. Superior outcome with CPIs in NSCLC harboring activating KRAS gene mutations has been reported in retrospective cohorts and post hoc analyses of the phase 3 KEYNOTE-42 trial [37, 38].

Another weakness of our study may be the underreporting of adverse events. We extracted only serious adverse events leading to temporary treatment interruption or permanent discontinuation. However, some difference in the frequency of serious adverse events between different CPIs were noted.

To summarize, different PD-1/PD-L1 inhibitors show similar effectiveness and toxicity in first-line palliative treatment of locally advanced or metastatic NSCLC.

Statement of Ethics

This retrospective study protocol was reviewed and approved by the institutional review board of the DKG-certified Lung Cancer Center on March 11, 2024 with the approval number ITT-EP-03-2024. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the World Medical Association Declaration of Helsinki (as revised in 2013). The need for informed consent of the patients was waived by the above mentioned board.

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Author Contributions

FMK and DCC contributed to conception and design of the study.

FMK, LG, GN, IS, JV, IS, AK, FG, KMS and DCC contributed to the acquisition of the data.

FMK, AT and DCC contributed to the analysis and interpretation of data.

FMK, AT and DCC wrote first draft of the manuscript.

FMK, LG, GN, IS, JV, IS, AK, FG, KMS and DCC contributed to the revision of the manuscript.

All the authors made substantial contributions to this work and approved it for publication.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest Statement

Daniel C. Christoph reports consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, and payment for expert testimony from, and participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Ipsen, Janssen, Merck Sharpe & Dohme, Novartis, Novocure, Pfizer, Roche, Sanofi, and Takeda; and support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Ipsen, Janssen, Chugai, Merck Sharpe & Dohme, Novartis, Pfizer, Roche, Sanofi, and Takeda.

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