REAL-WORLD DATA FROM THE GERMAN PROSPECTIVE CRISP REGISTRY (PROSPECTIVE GERMAN REGISTRY CRISP, AIO-TRK-0315)

EFFECTIVENESS OF MAINTENANCE THERAPY WITH PEMBROLIZUMAB VS. PEMETREXED AND PEMBROLIZUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER

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BACKGROUND

The 5-year update of the phase III KEYNOTE-189 trial reinforce the established standard of care with immunotherapy (IO) plus pemetrexed (PEM) and a platinum-based chemotherapy in metastatic non-squamous Non-small Cell Lung Cancer (NSCLC) without sensitizing EGFR or ALK alterations[1]. Prior to the approval of IO, the PARAMOUNT trial in 2013 demonstrated a significant overall survival benefit by maintenance therapy with pemetrexed in non-squamous mNSCLC[2]. However, the combination of IO and PEM frequently requires dose modifications or treatment discontinuation due to immune-related or chemotherapy-associated toxicities. As the efficacy of the combination vs. immune single-agent maintenance has not been evaluated prospectively, this study aims to assess survival benefits in a real-world data set.

METHODS

CRISP is a prospective, non-interventional, multi-center registry in Germany. In this analysis, patients with histologically confirmed non-squamous NSCLC stage IV (IVA and IVB, UICC 7th) without sensitizing EGFR, ALK, ROS1 or BRAF alterations qualifying for first-line targeted treatment were eligible. Patients starting first line treatment from October 1, 2018 to September 30, 2022 were included, data base cut was September 30, 2023. No progress up to four weeks after end of platinum and at least one dose pembrolizumab (PBZ) with or without PEM as maintenance therapy was required. Inverse probability of treatment weighting was used to adjust the treatment groups for differences in prognostic variables and confounders.

RESULTS

Patients and tumor characteristics

A total of 444 patients were included, of which 286 (64.4 %) received PBZ maintenance with PEM and 158 (35.6 %) without, respectively. Median age at inclusion was 63.5 years, most of the patients were male (57.0 %) and had an ECOG performance status of 0 and 1 (82.2 %).

With respect to the mutational profile, in the PBZ mono group, TP53 alteration was found in 15.2 % and in the PBZ+PEM group 26.6 %; KRAS alteration was documented in 36.1 % (9.5 % KRAS G12C) and 31.1 % (10.8 % KRAS G12C). Regarding the PD-L1 tumor proportion score (TPS), 18.4 % in PBZ mono and 8.4 % in PBZ+PEM had a TPS ≥ 50 % and 36.1 % and 40.2 % a TPS ≥ 1 % and < 50 %; TPS < 1% was documented for 6.3 % and 14.7 % (PBZ mono, PBZ+PEM, **Table 1**).

Primary outcomes

Weighted median OS (mOS) was 22.1 months (95 % CI, 17.4 to 25.4) in the PBZ+PEM and 19.8 months (95 % CI, 15.8 to 26.7) in the PBZ mono group, respectively, with a hazard ratio (HR; PBZ+PEM vs. PBZ mono) for death of 0.89 (95 % CI, 0.69 to 1.15). After 48 months, 29.0 % (95 % CI, 21.9 to 36.4) and 15.0 % (95 % CI, 5.8 to 28.2) of patients were still alive, respectively **(Figure 1)**.

With 335 events of progression or death, weighted median progression-free survival was 10.2 months (95 % CI, 9.0 to 11.8) in the PBZ+PEM group and 9.5 months (95 % CI, 8.1 to 11.0) in the PBZ mono group, respectively. HR (PBZ+PEM vs. PBZ mono) for disease progression or death was 0.81 (95 % CI, 0.65 to 1.01, **Figure 2**).

Secondary outcomes, treatment characteristics

Cox proportional hazards models were used for subgroup analyses. For OS, no significant difference in both treatment groups regarding smoking status (smokers vs. non-smokers: HR 0.66, (95 % CI, 0.40 – 1.07) for PBZ mono and HR 0.81 (95 % CI, 0.51 – 1.29) for PBZ+PEM) could be revealed. In both maintenance groups, the comparison of PD-L1 TPS <1 % to ≥ 50 % revealed a significant benefit in OS in PD-L1 TPS ≥ 50 % (HR 3.57; 95 % CI, 1.70 – 7.49 for PBZ mono and HR 2.80; 95 % CI, 1.08 – 7.24 for PBZ+PEM). **(Figure 3+4)**.

Median treatment duration was 8.0 months in PBZ mono and 8.3 months in PBZ+PEM group. 57.8 % and 51.5 % respectively, ended the treatment due to progressive disease whereas 7.5 % and 10.6 % stopped treatment according to guidelines. Interestingly, toxicity as reason for end of treatment was similar in both groups, 7.5 % in pembrolizumab maintenance and 7.3 % in pemetrexed plus pembrolizumab maintenance.

QUALITY OF LIFE

Quality of life (QoL) was assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire and the Lung Cancer Subscale (LCS). A total of 78.8 % of patients (350 out of 444) completed and returned the questionnaires at initiation. At baseline, FACT-G score in both groups reported the same median of 74.3 points. The highest decrease of median FACT-G score in both groups was documented at four months, 4.2 points (range: -14.0 – 8.5) in PBZ mono and 1.7 points (range: -11.5 – 7.0) in PBZ+PEM. Recovery started earlier at six months in PBZ mono compared to eight months in PBZ+PEM with a greater and continuous improvement in PBZ mono **(Figure 5)**.

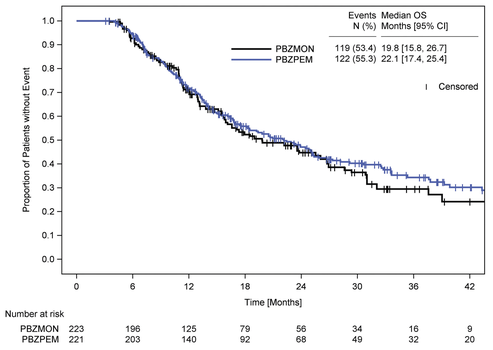
CONCLUSION

Standard of care with immune maintenance therapy in advanced NSCLC has become routine clinical practice, which has raised new questions in the application and optimization of treatment regimen. This analysis addressed the efficacy of pembrolizumab maintenance regimen with or without combination of pemetrexed in non-squamous NSCLC. Our prospective real-world data analysis from the German CRISP Registry suggests no significant or clinically relevant benefit in the overall survival and progression-free survival by the addition of pemetrexed to pembrolizumab maintenance therapy. However, by the combination, toxicity did not appear as a more frequent reason for the end of treatment, although patient's-reported outcomes during maintenance suggest a numerically improvement of quality of life under PBZ monotherapy. The results on 444 patients recruited by the CRISP registry are of clinical relevance since it promotes the practice of immune monotherapy maintenance. Yet, limitations of the non-interventional trial need to be regarded and at the end, the choice of treatment regimen remains a patient's individualized decision.

Table 1: Patient and tumor characteristics

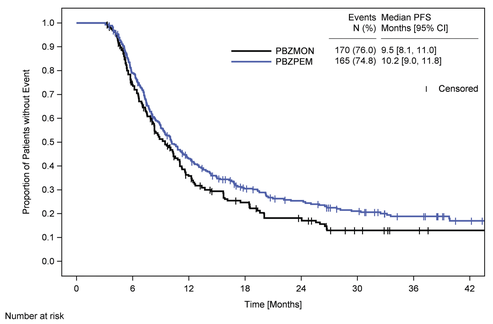
	PBZ Mono	PBZ+PEM	Total
Characteristics at Start of Treatment	**n=158**	**n=286**	**n=444**
Age in years, median (25 % – 75 % quantile)	62.8 (57.7 – 69.0)	64.3 (58.6 – 70.2)	63.5 (58.3 – 69.5)
Age < 70 years n (%)	124 (78.5)	212 (74.1)	336 (75.7)
Age ≥ 70 years n (%)	34 (21.5)	74 (25.9)	108 (24.3)
Sex			
Female n (%)	64 (40.5)	127 (44.4)	191 (43.0)
Male n (%)	94 (59.5)	159 (55.6)	253 (57.0)
BMI (kg/qm), mean (± StD)	**25.4 (5.24)**	**25.6 (5.71)**	**25.5 (5.54)**
Patients with any comorbidity n (%)	**124 (78.5)**	**244 (85.3)**	**368 (82.9)**
Comorbidites according to CCI			
CCI = 0 n (%)	93 (58.9)	166 (58.0)	259 (58.3)
CCI = 1-2 n (%)	57 (36.1)	106 (37.1)	163 (36.7)
CCI = 3-4 n (%)	7 (4.4)	9 (3.1)	16 (3.6)
CCI ≥ 5 n (%)	1 (0.6)	5 (1.7)	6 (1.4)
Performance Status			
ECOG 0 (%)	55 (34.8)	119 (41.6)	174 (39.2)
ECOG 1 (%)	75 (47.5)	116 (40.6)	191 (43.0)
ECOG ≥ 2 (%)	11 (7.0)	19 (6.6)	30 (6.8)
Unknown (%)	16 (10.1)	32 (11.2)	48 (10.8)
Missing (%)	1 (0.6)	0	1 (0.2)
Smoking Status			
Current Smoker (%)	54 (34.2)	88 (30.8)	142 (32.0)
Ex-Smoker (heavy) (%)	57 (36.1)	103 (36.0)	160 (36.0)
Ex-Smoker (intensity unknown) (%)	14 (8.9)	27 (9.4)	41 (9.2)
Ex-Smoker (light) (%)	9 (5.7)	26 (9.1)	35 (7.9)
Never Smoker (%)	14 (8.9)	27 (9.4)	41 (9.2)
Unknown to site (%)	10 (6.3)	15 (5.2)	25 (5.6)
Tumor proportion score (TPS)			
TPS ≥ 50% (or CS 5) (%)	29 (18.4)	24 (8.4)	53 (11.9)
TPS ≥ 5% and < 50% (or CS 2-4) (%)	42 (26.6)	71 (24.8)	113 (25.5)
TPS ≥ 1% and < 5% (or CS 1) (%)	15 (9.5)	44 (15.4)	59 (13.3)
TPS < 1% (or CS 0) (%)	10 (6.3)	42 (14.7)	52 (11.7)
TPS/CS unknown but documented as positive (%)	5 (3.2)	12 (4.2)	17 (3.8)
TPS/CS unknown but documented as negative (%)	24 (15.2)	40 (14.0)	64 (14.4)
Test result documented as unknown (%)	1 (0.6)	1 (0.3)	2 (0.5)
No, unknown or missing test (%)	32 (20.3)	52 (18.2)	84 (18.9)
KRAS test results			
Alteration (%)	57 (36.1)	89 (31.1)	146 (32.9)
Wildtype (%)	49 (31.0)	111 (38.8)	160 (36.0)
No, unknown or missing test (%)	52 (32.9)	86 (30.1)	138 (31.1)
TP53 test results			
Alteration (%)	24 (15.2)	76 (26.6)	100 (22.5)
Wildtype (%)	29 (18.4)	70 (24.5)	99 (22.3)
No, unknown or missing test (%)	105 (66.5)	140 (49.0)	245 (55.2)

Figure 1: Kaplan-Meier survival analysis for overall survival.



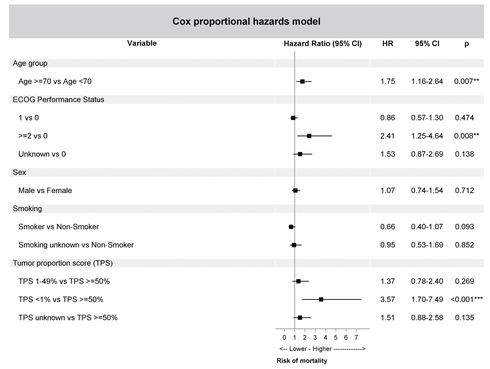
Kaplan-Meier analyses are performed adjusted by IPTW weights.
Therefore, N respective Number at risk denote the sum of IPTW weights and not patient numbers per se.
CI: confidence interval | OS: overall survival | PBZMON: pembrolizumab monotherapy maintenance | PBZPEM: pembrolizumab plus pemetrexed maintenance

Figure 2: Kaplan-Meier survival analysis of progression-free survival.



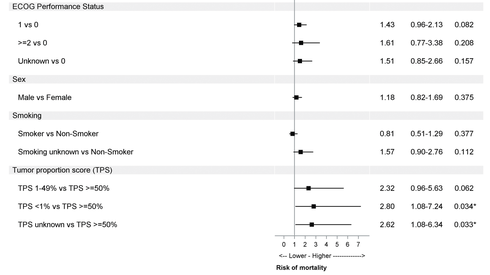
Kaplan-Meier analyses are performed adjusted by IPTW weights.
Therefore, N respective Number at risk denote the sum of IPTW weights and not patient numbers per se.
CI: confidence interval | PBZMON: pembrolizumab monotherapy maintenance | PBZPEM: pembrolizumab plus pemetrexed maintenance | PFS: progression-free survival

Figure 3: Forest Plot for overall survival: PBZ Mono group.



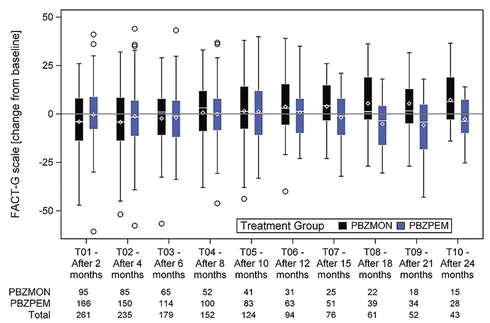
Cox proportional hazards model for overall survival for pembrolizumab monotherapy maintenance.
CI: confidence interval | ECOG: Eastern Cooperative Oncology Group | HR: hazard ratio | TPS: Tumor proportion score

Figure 4: Forest Plot for overall survival: PBZ+PEM group.



Cox proportional hazards model for overall survival for pembrolizumab plus pemetrexed maintenance.
CI: confidence interval | ECOG: Eastern Cooperative Oncology Group | HR: hazard ratio | TPS: Tumor proportion score

Figure 5: Box plot for patient- reported outcome scores by using FACT-G scale (change from baseline) over time.



Legend: the filled box denotes range Q1 to Q3, horizontal dash denotes median,diamond denotes mean, whiskers denote extremes but cannot be longer than 1.5 times the length of the box, open circles denote outliers. N denotes the number at risk.

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1. Speranza G, Felip E, Esteban E, Dómine M, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol. 2023;JCO2201989.
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