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Pembrolizumab plus Pemetrexed and Platinum in Metastatic Non-Squamous Non-Small Cell Lung Cancer: A Real-Life Study at a Portuguese Centre

Pembrolizumab com Pemetrexedo e Platina no Cancro do Pulmão Não Pequenas Células Metastático: Um Estudo de Vida Real num Centro Português

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ABSTRACT

First-line therapy for metastatic non-small-cell lung cancer without targetable mutations is platinum-based chemotherapy plus pembrolizumab if programmed death ligand 1 is < 50%. The aim of this real-life retrospective study is to assess the efficacy and safety of this therapy. This retrospective observational study was conducted at the Pulmonary Oncology Department in Unidade Local de Saúde Santa Maria, in Lisbon, Portugal. We included patients with stage IV non-squamous non-small-cell lung cancer with programmed death ligand 1 < 50% that started pembrolizumab plus platinum and pemetrexed between July 2020 and December 2022. Follow-up was carried out until September 2023. Progression-free survival, overall survival, response rate and safety were evaluated. Sixty-six patients were included. Median age 67 years, 72.7% male, 92.4% performance status 0 - 1, 90.9% current/former smokers. Programmed death ligand 1 < 1% in 63.6%. Median overall and progression-free survival were 12.2 months and 6.7 months, respectively. At the time of the cut-off, 21.2% of patients were alive and progression-free. The objective response rate was 42.4% (partial response). The disease control rate was 69.7%. Adverse events occurred in 92.4%, 43.9% had grade 3 - 4 adverse effects. The most common were anemia (50.0%), neutropenia (40.9%), and asthenia (36.4%). Treatment was discontinued in three patients due to adverse effects. There were no treatment-related deaths reported. With median progression-free survival and overall survival of 6.7 and 12.2 months, respectively, and no new safety signals, these results complement data from clinical trials, providing information from a real-world setting.
Keywords: Antibodies, Monoclonal, Humanized; Antineoplastic Combined Chemotherapy Protocols; Carcinoma, Non-Small-Cell Lung/drug therapy; Pembrolizumab; Pemetrexed; Platinum

RESUMO

A terapêutica de primeira linha para cancro do pulmão não pequenas células metastático sem mutações-alvo é quimioterapia à base de platina associada a pembrolizumab se o ligando 1 de morte celular programada (*programmed cell death ligand 1*) < 50%. Este estudo retrospetivo de vida real tem como objetivo avaliar eficácia e segurança desta terapêutica. Este estudo observacional retrospetivo foi realizado no Serviço de Pneumologia Oncológica da Unidade Local de Saúde Santa Maria, em Lisboa, Portugal. Foram incluídos doentes com cancro do pulmão não pequenas células não escamoso estádio IV com ligando 1 de morte celular programada < 50% que iniciaram pembrolizumab com platina/pemetrexedo entre julho 2020 e dezembro 2022. O *follow-up* foi realizado até setembro 2023. Foram analisados: sobrevida livre de progressão, sobrevida global, taxa de resposta e segurança. Foram incluídos 66 doentes. A mediana de idade foi 67 anos, 72,7% sexo masculino, 92,4% *performance status* 0 - 1, 90,9% dos doentes eram fumadores/ex-fumadores. Ligando 1 de morte celular programada < 1% em 63,6%. A mediana de sobrevida global e de sobrevida livre de progressão foi de 12,2 meses e 6,7 meses, respetivamente. À data do *cut-off*, 21,2% dos doentes estavam vivos e sem progressão. A taxa de resposta foi 42,4% (resposta parcial). A taxa de controlo da doença foi 69,7%. Ocorreram efeitos adversos em 92,4% dos doentes, dos quais 43,9% foram de grau 3 - 4. Os mais comuns foram anemia (50,0%), neutropenia (40,9%) e astenia (36,4%). O tratamento foi interrompido em três doentes devido a efeitos adversos. Não se registaram mortes relacionadas com o tratamento. Com mediana de sobrevida livre de progressão e sobrevida global de 6,7 e 12,2 meses, respetivamente, e sem novos sinais de segurança, estes resultados complementam os dados de ensaios clínicos, fornecendo informação sobre um contexto de vida real.
Palavras-chave: Anticorpos Monoclonais Humanizados; Carcinoma Pulmonar de Células não Pequenas/tratamento farmacológico; Pembrolizumab; Pemetrexedo; Platina; Protocolos de Quimioterapia Combinada Antineoplásica

INTRODUCTION

Current treatment for metastatic lung adenocarcinoma is determined according to the presence or absence of oncogenic drivers such as Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK). In their absence, adequate treatment is dependent of programmed death-ligand 1 (PD-L1). Programmed death-ligand 1 inhibitors such as pembrolizumab have proven to be effective in combination with chemotherapy (ChT). In the KEYNOTE-189 trial, pembrolizumab-ChT (versus placebo-ChT) improved overall survival (OS) at 12 months (69.2% *vs* 49.4%) and median progression-free survival (PFS) (8.8 months *vs* 4.9 months).[1] Current guidelines recommend platinum-based ChT plus PD-L1 blockade for stage IV NSCLC with PD-L1 < 50%.[2]

METHODS

Study design

This retrospective observational study was conducted at the Pulmonary Oncology Department in Unidade Local de Saúde Santa Maria, in Lisbon, Portugal. The included patients had stage IV non-squamous NSCLC with PD-L1 < 50% that started pembrolizumab, platinum, and pemetrexed between July 2020 and December 2022. Follow-up was carried out until September 2023. The patients were

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identified through our department databases and data was obtained from medical record files. Since this was a retrospective study with no new intervention research, ethics approval was not necessary.

Treatment

Patients received four cycles of carboplatin or cisplatin, pemetrexed, and pembrolizumab every three weeks, followed by pemetrexed and pembrolizumab every three weeks. At least one dose had to be administered. The treatment was discontinued in case of radiologic progression, unacceptable toxicity or death.

Assessment

Radiological assessment was performed every three to four cycles. Tumour response, including overall response rate, was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1.[3] Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[4]

Statistical analysis

This study evaluated OS (time from the start of treatment until death), PFS (time from treatment start until disease progression or death, whichever occurred first), response rate (percentage of patients with partial/complete response), disease control rate (percentage of patients with complete/partial response or stable disease), duration of response (time from first radiological evaluation with response until progression or death) and safety. The Kaplan–Meier method was used to estimate OS and PFS. Patients who were alive or lost to follow-up were censored for OS at the time they were last known to be alive. Patients who were alive and did not have disease progression or who were lost to follow-up were censored for PFS at the time of the last imaging assessment before the cut-off. Confidence intervals were calculated using the Greenwood formula.

RESULTS

A total of 66 patients met the eligibility criteria, with the following characteristics:

- median age: 67 years, with 12.1% patients being ≥ 75 years old;
- 72.7% patients were male;
- performance status (according to Eastern Cooperative Oncology Group - ECOG) of 0 - 1 in 92.4%;
- 90.9% patients were current/former smokers;
- PD-L1 < 1% in 63.6%;
- 3 patients with EGFR mutation*;
- 1 with ALK translocation*.

The patients highlighted with * were included because the mutational study was only available after therapy was initiated. At the time of this study, first-line targeted therapy was only approved for EGFR and ALK at our center.

Further demographic and disease characteristics are described in Table 1.

At the time of cut-off, 41 patients (62.1%) had died. The median follow-up was 10.9 months. Median OS was 12.2 months (95% CI: 7.1 - 19.8) (Fig. 1A); 11.1 months (95% CI: 6.3 - 27.8) in the PD-L1 < 1% group, 12.2 months (95% CI: 6.5 - NR) in the PD-L1 1% - 49% group (Fig. 1B). Patients who progressed or interrupted therapy before starting maintenance ChT-immunotherapy (≤ 4 cycles) had a median OS of 4.7 months (95% CI: 2.8 - 5.9).

There were 52 events of progression or death; 21.2% of patients were alive and progression-free at cutoff. Median PFS was 6.7 months (95% CI: 4.6 - 10.4) (Fig. 1C); 6.4 months (95% CI: 3.7 - 10.4) in the PD-L1 < 1% group, 8.4 months (95% CI: 5.0 - 13.7) in the PD-L1 1% - 49% group (Fig. 1D).

From the total, 71.2% of patients completed at least four cycles. The median treatment time was 6.5 months (95% CI: 4.7 - 12.5). The objective response rate (ORR) was 42.4%, all with partial response. The disease control rate (DCR) was 69.7%. Tumor response was not assessed in nine patients (Table 2). The median duration of response was 12.0 months (95% CI: 6.0 - 17.7). At the time of cut-off, 15 patients were still receiving stipulated therapy. After disease progression, 28 patients (42.4%) received subsequent treatment.

Adverse events (AE) occurred in 92.4% of patients. The most common were anemia (50.0%), neutropenia (40.9%) and asthenia (36.4%). Thyroidism (four patients with hypothyroidism and three with thyroiditis, representing 10.6%:) and adrenal insufficiency (7.6%) were the most common immune AE. Grade 3 - 4 AE occurred in 43.9%, with 46 events reported, four of which were assumed immune-mediated AE (liver toxicity and colitis). Treatment was discontinued in three patients: immune-mediated colitis, immune-mediated pneumonitis and adrenal insufficiency (G2 AE but treatment was discontinued because the two events were present) and non-immune liver toxicity. There were no treatment-related deaths.

DISCUSSION

To the best of our knowledge, this study is the first real-life study in Portugal to provide data on the efficacy and safety of ChT-pembrolizumab for metastatic NSCLC. The baseline characteristics of patients were similar to patients in the KEYNOTE-189 trial, with a higher prevalence of male patients and similar median age (67 *vs* 65 years).

Median PFS and OS were 6.7 and 12.2 months respectively, lower estimates than those from KEYNOTE-189, but still with a higher PFS than their placebo-ChT group (4.9

Table 1 – Demographic characteristics of patients and disease characteristics at baseline

Demographic characteristic	Value, n = 66
Age (years)	
Median (range)	67 (41 - 79)
≥ 75 years, n (%)	8 (12.1)
Male, n (%)	48 (72.7)
Performance status, n (%)	
0	19 (28.8)
1	42 (63.6)
2	5 (7.6)
Smoking status, n (%)	
Current smoker	34 (51.5)
Former smoker	26 (39.4)
Never smoker	6 (9.0)
Previous cancer, n (%)	13 (19.7)
Arterial hypertension, n (%)	36 (54.5)
Dyslipidemia, n (%)	26 (39.4)
Chronic obstructive pulmonary disease, n (%)	15 (22.7)
Disease characteristics	
Histology, n (%)	
Adenocarcinoma	64 (97.0)
Adenosquamous carcinoma	1 (1.5)
Combined large cell neuroendocrine carcinoma with adenocarcinoma	1 (1.5)
Location, n (%)	
Upper right lobe	20 (30.3)
Medium lobe	4 (6.1)
Lower right lobe	12 (18.2)
Upper left lobe	24 (36.4)
Lower left lobe	6 (9.1)
Stage IV, n (%)	
IV-A, M1a	16 (24.2)
IV-A, M1b	10 (15.2)
IV-B	40 (60.6)
Metastatic sites, n (%)	
Brain	14 (21.2)
Liver	10 (15.2)
Bone	25 (37.9)
Adrenal gland	21 (31.8)
PD-L1 rate, n (%)	
< 1%	42 (63.6)
1% - 49%	24 (36.4)
Mutations, n (%)	
None	22 (33.3)
KRAS	26 (39.4)
EGFR	3 (4.5)
BRAF	3 (4.5)
MET	3 (4.5)
RET	3 (4.5)
ALK	1 (1.5)
Others (SMO, PI3KCA, HER2, TP53, MAP2K1)	6 (9.1)
NA	3 (4.5)

NA: not assessed

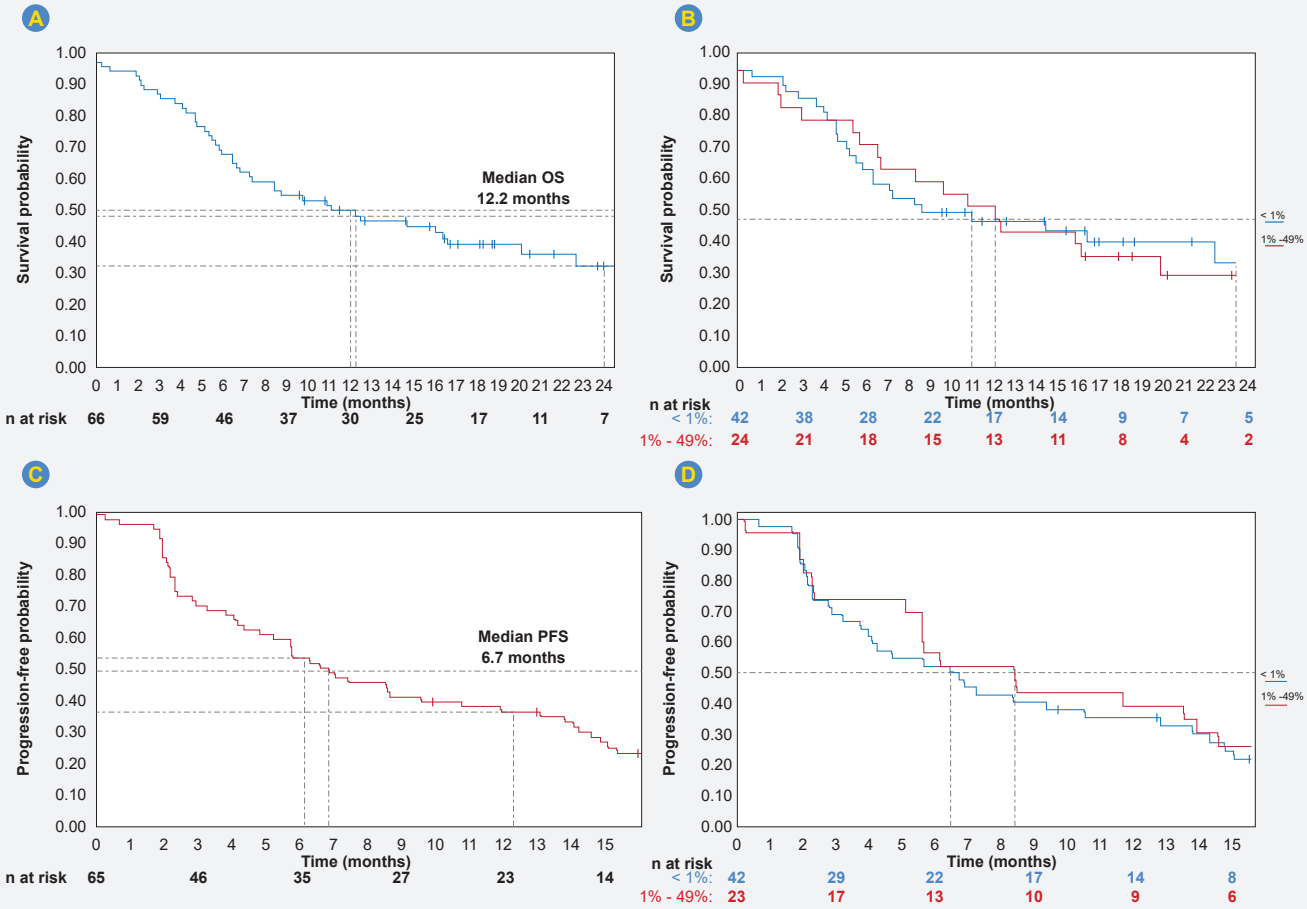

Figure 1 – Overall survival (A), overall survival according to the value of PD-L1 (B), progression-free survival (C), and progression-free survival according to the value of PD-L1 (D) of patients with metastatic non-squamous NSCLC treated with ChT-pembrolizumab

months). Our study did not include PD-L1 ≥ 50%, unlike the KEYNOTE-189 trial, and included an older sample (63.6% patients with ≥ 65 years old *vs* 52.0%), higher prevalence of ECOG 1 and included ECOG 2. Also, real-life studies are limited by hospital resources, which influenced treatment and imaging assessment timings. The OS is consistent with a real-world study by Waterhouse *et al*[5] and the PFS is also similar to Velcheti *et al*.[6] Subanalysis with PD-L1 levels did not reveal a major difference in OS but there was still a two-month difference in PFS favoring the 1% - 49% group. The ORR was 42.4%, similar to the KEYNOTE-189 trial (47.6%), and DCR was 69.7% (*vs* 84.6%). The median duration of response was slightly higher (12.0 *vs* 11.2 months). The AE rates were similar to the KEYNOTE-189 trial but grade ≥ 3 events were lower (43.9% *vs* 67.2%). In light of these results, ChT-pembrolizumab is still the first-line therapy for patients at our center, with benefits in OS and PFS, and an adequate safety profile.

Our study has multiple limitations. It is a retrospective study with a small sample; it did not include a control group; AE, especially grade 1 - 2, may be underreported, as this information is taken from clinical records, and sometimes less serious AE are not registered.

CONCLUSION

With a median PFS and OS of 6.7 and 12.2 months, respectively, and no new safety signals, these results complement data from clinical trials providing information from a real-world setting.

Table 2 – Tumor response

Variable	Value, n = 66
Best response, n (%)	
Complete response	0 (0)
Partial response	28 (42.4)
Stable disease	18 (27.3)
Progressive disease	11 (16.7)
Non-evaluable	9 (13.6)

AUTHOR CONTRIBUTIONS

MJS: Data collection and analysis, writing of the manuscript.

FF: Study design, critical review of the manuscript.

ALM, ASV, DH, PA: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

FF received payment or honoraria from MSD for lectures, presentations, speakers' bureaus, manuscript writing or educational events; received support from Takeda for attending meetings and/or travel.

ALM received payment or honoraria from Takeda, Bristol Myers Squibb, Pfizer and AstraZeneca for lectures, presentations, speakers' bureaus, manuscript writing or educational events; received support from Roche, Daichi Sankyo, Takeda and AstraZeneca for attending meetings and/or travel.

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