Original Article

Pembrolizumab plus pemetrexed-carboplatin combination in first-line treatment of advanced non-squamous non-small cell lung cancer: a multicenter real-life study (CAP29)

Emmanuelle Renaud[1], Charles Ricordel[2], Romain Corre[3], Guillaume Leveiller[4], Florence Gadby[5], Hélène Babey[6], Josselin Annic[1], François Lucia[7], Vincent Bourbonne[7], Gilles Robinet[1], Renaud Descourt[1], Charles Orione[8], Gilles Quéré[1], Margaux Geier[1]

[1]Department of Medical Oncology, CHRU Morvan, University Hospital of Brest, Brest, France; [2]Department of Pulmonary Diseases, CHU Pontchaillou, University Hospital of Rennes, Rennes, France; [3]Department of Pulmonary Diseases, CH Cornouaille, Quimper, France; [4]Department of Pulmonary Diseases, CH Yves Le Foll, Saint-Brieuc, France; [5]Department of Pulmonary Diseases, Hospital of Morlaix, Morlaix, France; [6]Department of Medical Oncology, Hospital of Landerneau, Landerneau, France; [7]Department of Radiation Oncology, CHRU Morvan, University Hospital of Brest, Brest, France; [8]Department of Pulmonary Diseases, CHRU Cavale Blanche University Hospital of Brest, Brest, France

Contributions: (I) Conception and design: E Renaud, G Quéré, R Descourt, G Robinet, M Geier, C Orione; (II) Administrative support: E Renaud, G Quéré, M Geier; (III) Provision of study materials or patients: E Renaud, G Quéré, C Ricordel, R Corre, H Babey, G Leveiller, F Gadby, F Lucia, V Bourbonne, M Geier, R Descourt, G Robinet; (IV) Collection and assembly of data: E Renaud, G Quéré, M Geier, C Orione; (V) Data analysis and interpretation: E Renaud, G Quéré, M Geier, C Orione; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Margaux Geier, MD. Institut de Cancérologie, Hôpital Morvan, 2, Avenue Foch, 29200 Brest, France.
Email: margaux.geier@chu-brest.fr.

Background: Pembrolizumab combined with chemotherapy is now first-line standard of care in advanced non-small cell lung cancer. This real-life study aimed to assess efficacy and safety of carboplatin-pemetrexed plus pembrolizumab in advanced non-squamous non-small cell lung cancer.

Methods: CAP29 is a retrospective, observational, multicenter real-life study conducted in 6 French centers. We evaluated efficacy of first-line setting chemotherapy plus pembrolizumab (November 2019 to September 2020) in advanced (stage III-IV) non-squamous non-small cell lung cancer patients without targetable alterations. Primary endpoint was progression-free survival. Secondary endpoints were overall survival, objective response rate and safety.

Results: With a median follow-up of 4.5 months (0 to 22 months), a total of 121 patients were included. Baseline characteristics were: median age of 59.8 years with 7.4% ≥75 years, 58.7% of males, 91.8% PS 0-1, 87.6% of stage IV with ≥3 metastatic sites in 62% of cases. Patients had brain and liver metastases in 24% and 15.7% of cases, respectively. PD-L1 was <1% (44.6%), 1–49% (28.1%) and ≥50% (21.5%). Median progression-free survival and overall survival achieved 9 and 20.6 months, respectively. Objective response rate was 63.7% with 7 prolonged complete responses. Survival benefit seemed to be correlated with PD-L1 expression. Brain and liver metastases were not statistically associated with decreased overall survival. Most common adverse events were asthenia (76%), anemia (61.2%), nausea (53.7%), decreased appetite (37.2%) and liver cytolysis (34.7%). Renal and hepatic disorders were the main causes of pemetrexed discontinuation. Grade 3–4 adverse events concerned 17.5% of patients. Two treatment-related deaths were reported.

Conclusions: First-line pembrolizumab plus chemotherapy confirmed real-life efficacy for patients with advanced non-squamous non-small cell lung cancer. With median progression-free survival and overall survival of 9.0 and 20.6 months, respectively and no new safety signal, our real-life data are very close to results provided by clinical trials, confirming the benefit and the manageable toxicity profile of this combination.

Keywords: Non-small cell lung cancer; pembrolizumab; chemo-immunotherapy; first-line treatment; real-life efficacy

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Introduction

Lung cancer is the leading cause of death from cancer worldwide and accounts for 1,796,144 deaths in 2020 (1). The burden of lung cancer mortality remains a major public concern (1). Patients face mostly to advanced non-small cell lung cancer (NSCLC), whose main histological subtype is adenocarcinoma (2,3). A better understanding of tumor immunity pathways has led to the development of immune checkpoint inhibitors (ICI), that enhance the immune system against cancer cells. The advent of ICI has revolutionized strategies for the management of metastatic NSCLC. Three drugs targeting the programmed cell death protein-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) axis (nivolumab, pembrolizumab, and atezolizumab) were initially approved as second-line treatment (4-6). Immunotherapy has then supplanted chemotherapy for upfront treatment and pembrolizumab became first-line standard of care for the specific population of NSCLC with high PD-L1 expression (tumor proportion score ≥50%).

ICI combined with chemotherapy (CT) moved recently into the front line. Indeed, research provided insight into pathophysiological mechanisms that involved a variety of immunogenic pathways via activation of PD(L)-1 axis (e.g., blockade of the STAT pathway, increase of cytotoxic lymphocyte/regulatory T cell ratio) (7). Studies have also reported that pemetrexed might induce acute systemic intratumor immune responses by increasing T-cell activation and sensitizing cancer cells to cytotoxic immune cells (8). The results of the phase 3 KEYNOTE-189 trial led to approval of pembrolizumab plus pemetrexed-platinum in first-line treatment for adult patients [performans status (PS) 0-1] with metastatic non-squamous NSCLC, in the absence of *EGFR* or *ALK* mutation and irrespective of PD-L1 expression (9). The CT-pembrolizumab combination significantly improved overall survival (OS) (HR =0.49; P<0.001) regardless of the level of PD-L1 expression (<1%, ≥1%, 1–49% and ≥50%). The rate of grade 3–4 adverse events (AE) was consistent with the placebo group (67.2% *vs.* 65.8% in the CT-placebo arm). Discontinuation of one of the three drugs due to toxicity occurred in 13.8% of cases in the pembrolizumab arm versus 7.8% in the placebo arm. Gandhi *et al.* warned about the increased risk of acute kidney injury and nephritis (6.2% *vs.* 0.5% in the CT-placebo arm) (9). Three immune-mediated AE led to death in the combination group. Broadly similar results were obtained in the KEYNOTE-407 trial for advanced squamous NSCLC (10). Results of these two pivotal phase 3 trials have altered the therapeutic landscape, highlighting a new upfront for advanced NSCLC patients without targetable alteration (11).

To our knowledge, few studies have assessed the efficacy of first-line pembrolizumab plus pemetrexed-carboplatin regimen in a real-life setting. The aim of our observational multicenter study was to assess efficacy and safety of CT-pembrolizumab combination in a real-life cohort of advanced non-squamous NSCLC patients. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-556/rc).

Highlight box

Key findings

- In a cohort of 121 patients with advanced non-squamous NSCLC, real-life frontline pembrolizumab plus chemotherapy demonstrated median progression-free survival and overall survival of 9 and 20.6 months, respectively. No new safety signal appeared. Renal and hepatic disorders were the main causes of pemetrexed discontinuation during the maintenance phase.

What is known and what is new?

- Pembrolizumab plus chemotherapy is now first-line standard of care for patients with advanced NSCLC. Data are lacking concerning efficacy and safety of this association in real-life.
- Our results confirmed real-life efficacy of this association in advanced non-squamous NSCLC with median PFS and OS of 9 and 20.6 months. No new safety signal was reported. Particular attention was suggested during maintenance phase concerning renal and hepatic disorders with cumulative pemetrexed.

What is the implication, and what should change now?

- These results confirmed the predominant place of this therapeutic strategy as first-line for advanced NSCLC patients.
- Particular caution should be observed during maintenance phase due to risk of cumulative toxicity of pemetrexed.

Methods

Study design and patients

CAP29 is a retrospective observational multicenter study conducted in 6 French centers. Patients were included if they were at least 18 years of age, with confirmed advanced (stage III not eligible to surgery or radiotherapy and stage IV) non-squamous NSCLC and if they did not receive any previous systemic anti-cancer treatment for metastatic disease. Exclusion criteria were: uncontrolled autoimmune disease, active infection (Hepatitis B, C, HIV), organ or bone marrow transplant, contraindication to ICI or to carboplatin/pemetrexed, incapacity to give informed consent or refusal to participate, patients with activating *EGFR* mutation or *ALK* and *ROS* translocations.

Patients were first identified via CHIMIO® software database. Then, they were recruited at time of first visit in Oncology Department. They had to give a non-opposition agreement before enrollment.

Treatment

The maximum number of cycles and dose adjustments were made according to current guidelines (9). All patients received a maximum of 4 cycles of carboplatin AUC 5 plus pemetrexed 500 mg/m^2, both administered intravenously every 3 weeks, followed by pemetrexed maintenance therapy at 500 mg/m^2 every 3 weeks. All patients received premedication with folic acid, vitamin B_{12}, and glucocorticoids administered according to guidelines for pemetrexed use (12). All patients received at least one dose of pembrolizumab at 200 mg administered intravenously every 3 weeks for up to 35 cycles or disease progression or unacceptable toxicity. All patients had to receive at least one dose of chemo-immunotherapy to be included in our study. If toxicity was clearly attributed to one drug, this one could be discontinued.

Centers were asked to include all eligible patients consecutively over the period of inclusion from November, 2019 to September, 2020.

Data collection

Patients' data were obtained from medical files and included baseline demographics and disease characteristics, tumor response to combination therapy, treatments after progression and toxicities. AE were graded according to CTACE version 5.0 (13). Histology, PD-L1 score and driver alterations were evaluated at each institution.

Radiological assessment was performed according to recommendations: every 2 cycles (i.e., every 6 weeks) for the first 4 cycles corresponding to the induction phase; then every 3 cycles during the maintenance phase (i.e., every 9 weeks). Objective response rate (ORR) was assessed by investigators according to RECIST, version 1.1. (14).

Ethical considerations

This non-interventional study was approved by a regional ethics committee and France's national data protection authority (CNIL) (No. B2020CE30) according to French law. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (15). All patients alive provided written informed consent before enrollment. Opposition should be expressed within 15 days in case of refusal.

Outcomes

Primary end point was progression-free survival (PFS), defined as the time duration between the initiation of treatment to disease progression or death. Secondary end points included OS, ORR, duration of response (DOR), disease control rate (DCR), and safety. Exploratory end points included the effect of PD-L1 expression on efficacy.

Statistical analysis

No theoretical calculation of the number of patients was performed in this descriptive study. Efficacy and safety were assessed in all included patients who received at least one infusion of the combination treatment. Continuous variables were described by the number of no missing data, median, minimum and maximum. Categorical variables were described as the total number and percentage per category. PFS and OS curves were calculated with a survival analysis using the Kaplan-Meier method. An evaluation of variables influencing PFS was done using a univariate and then multivariate Cox model. A P value <5% was considered significant, and tests were two-tailed. Hazard ratios and associated 95% confidence intervals (CIs) were calculated with the use of a stratified Cox proportional-hazards model.

Results

Baseline characteristics

A total of 121 patients were included between November 26,

Table 1 Demographic characteristics of patients at baseline

Characteristic	Value, N=121
Age (years)	
Median	59.8
≥75 years, n (%)	9 (7.4)
Female, n (%)	50 (41.3)
Performans Status, n (%)	
0	41 (33.9)
1	70 (57.9)
2	10 (8.2)
Smoking status, n (%)	
Current smoker	73 (60.3)
Former smoker	42 (34.7)
Never smoker	6 (5.0)
Auto-immune disorders, n (%)	7 (5.8)
Baseline corticosteroids, n (%)	15 (12.4)
Antibiotic prior to the start of treatment, n (%)	8 (6.6)
Previously treated cancer, n (%)	8 (6.6)

Table 2 Disease characteristics at baseline

Characteristics	Value, N=121
Stages, n (%)	
Stage IIIB/IIIC	15 (12.4)
Stage IV	106 (87.6)
One site	11 (9.1)
2 sites	20 (16.5)
3 or more sites	75 (62.0)
Metastatic sites, n (%)	
Brain	29 (24)
Meningitis	5 (4.1)
Liver	19 (15.7)
Bone	58 (47.9)
PD-L1 rate, n (%)	
<1%	54 (44.6)
1–49%	34 (28.1)
≥50%	26 (21.5)
NA	7 (5.8)
Mutations, n (%)	
None	70 (57.8)
KRAS	36 (29.7)
BRAF	2 (1.7)
MET	2 (1.7)
EGFR†	4 (3.3)
Co-mutations	1 (0.8)
ROS1	1 (0.8)
Others (*PI3KCA, TP53, HER2*)	3 (2.5)
NA	2 (1.7)
Prior radiotherapy, n (%)	50 (41.3)
Brain	17 (14)
Bone	25 (20.7)
Thoracic	7 (5.8)
Other	1 (0.8)
Prior surgery, n (%)	16 (13.2)
Brain	8 (50.0)
Bone	8 (50.0)

†, rare mutations of *EGFR*. NA, not assessed.

2019 and September 09, 2020. Median age was 59.8 years and 9 (7.4%) patients were ≥75 years; 58.7% of patients were male, 91.8% PS 0-1 and 95% were current or former smokers (*Table 1*). Seven patients had a history of autoimmune disease, 15 patients had received prior corticosteroid therapy and 8 had received antibiotics. Fifteen patients (12.4%) had locally advanced NSCLC (not eligible to surgery or radiotherapy), 75 (62%) had 3 or more metastatic sites (*Table 2*). Twenty-nine patients (24%) had brain metastasis and 19 (15.7%) had liver metastases. Four patients with rare *EGFR* mutation were included because they were not eligible to first-line *EGFR* inhibitor. *KRAS* mutation was the most frequent alteration and found in 29.7% of cases. Patients were classified according to PD-L1 level. PD-L1 was <1% in 44.6% of cases. Seven patients had unknown PD-L1 status.

Survival outcomes

Median PFS and OS achieved 9.0 months (95% CI: 7.6–13.5) (*Figure 1A*) and 20.6 months (17.0–NR), respectively (*Figure 1B*).

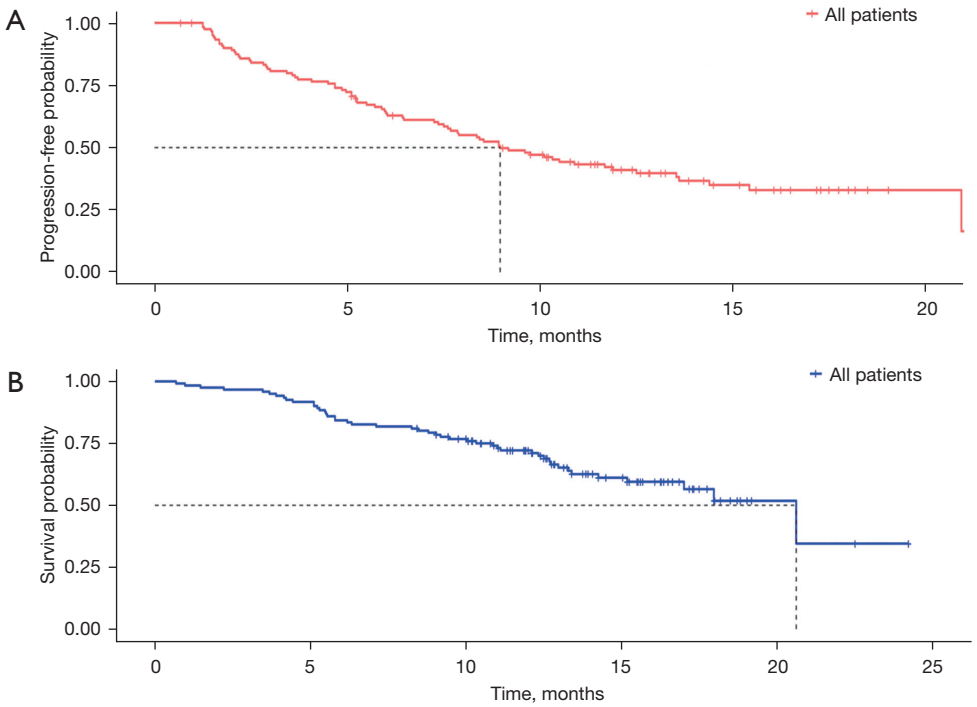

Figure 1 Progression-free survival (A) and overall survival (B) of patients (intention-to-treat population) with advanced non-squamous NSCLC treated with the association of pembrolizumab plus chemotherapy. NSCLC, non-small cell lung cancer.

Median PFS was 6.0 months (95% CI: 5.1–10.1) in PD-L1 <1% group, 8.4 months (95% CI: 7.5–NR) in PD-L1 1–49% group and 20.9 months (95% CI: 9.8–NR) in PD-L1 ≥50% group (*Figure 2A*). Patients with unknown PD-L1 status were censored (n=7).

Median OS was 15.1 months (95% CI: 13.0–NR) in PD-L1 <1% group, 18.0 months (95% CI: 17.0–NR) in PD-L1 1–49% group and not reached in PD-L1 ≥50% group (*Figure 2B*).

Median PFS was 15.4 months (10.9–NR) for patients with locally advanced NSCLC. Median PFS was 8.9 months (3.7–NR) if patients had 1 metastatic site, 9.8 months (4.9–NR) if they had 2 and 7.7 months (5.7–10.5) if they had 3 or more metastatic sites (P=0.032) (Figure S1). Median PFS for patients with and without liver metastases were 7.4 months (5.3–NA) *vs.* 10.3 months (7.9–12.9) respectively (P=0.25). Brain metastases did not appear to be a poor prognostic factor: PFS was 8.4 months (6.5–13.5) in the group without brain metastasis *vs.* 10.9 months (8.5–NA) in the group with brain metastasis or leptomeningeal disease (P=0.24) (Figure S2).

Treatment and tumor response

Median follow-up achieved 4.5 months (0–22 months). Time of treatment (median) was 2.5 months (0–20 months) with 19.4 weeks (6.7 courses) for pemetrexed and 22.0 weeks (10.8 courses) for pembrolizumab (Table S1).

Early discontinuation of carboplatin was either related to AE, mainly hematological, either related to clinical deterioration. The main reason for discontinuation of maintenance pemetrexed was poor clinical and biological tolerance, such as renal and hepatic disorders. For these patients, pembrolizumab was pursued alone until progression. Only 9 patients had received more maintenance courses of pemetrexed than pembrolizumab due to immune-related AE (pneumonitis, hepatic cytolysis or skin toxicities). In these cases, the treatment maintenance was shorter compared to patients who received pembrolizumab alone.

ORR achieved 63.7%: 7 patients with complete response and 70 with partial response (*Table 3*). Median DOR was 2.3 months. Twenty-four (19.8%) patients had stable disease

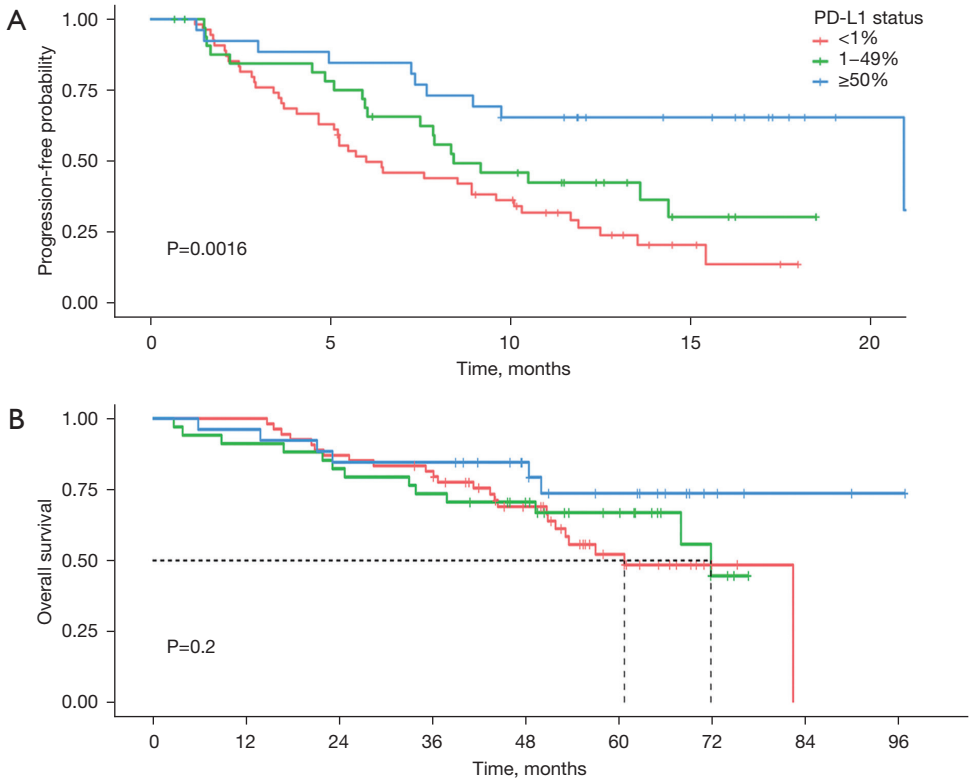

Figure 2 Progression-free survival (A) and overall survival (B) of patients with advanced non-squamous NSCLC treated with the association of pembrolizumab plus chemotherapy, according to the intensity of programmed cell-death-1-ligand-1 expression. NSCLC, non-small cell lung cancer.

Table 3 Tumor response

Variable	Value, N=121
Best response, n (%)	
Complete response	7 (5.8)
Partial response	70 (57.9)
Stable disease	24 (19.8)
Progressive disease	18 (14.9)
Non-evaluable	2 (1.6)
Objective response rate (%)	63.7
Disease control rate (%)	83.5

and 18 (14.9%) patients had disease progression. Seventeen patients continued treatment beyond progression, some of them received concomitant local treatment, mostly radiotherapy. The median duration of treatment after progression was 3 months (0–14 months). At the time of data cut-off, 74 patients (61.2%) had experienced disease progression, 46 patients (38%) died, including 7 (5.8%) during chemo-immunotherapy combination, 2 from AE (pneumonitis and vasculitis) and one patient from a massive pulmonary embolism.

Safety

The most common AE were asthenia (76%), anemia (61.2%), nausea (53.7%), decreased appetite (37.2%) and liver cytolysis (34.7%). Grade 3–4 AE concerned 17.5% of patients (*Table 4*). Two treatment-related deaths (interstitial lung disease and vasculitis) were reported. Sixty-seven events led to permanent discontinuation of one of the treatments (10.5%). Specifically immune-mediated AE included one case of hypereosinophilia, hyperthermia, vasculitis, sarcoidosis-like, encephalitis, adrenal insufficiency and Gougerot-Sjögren syndrome (details are reported in *Table 4*).

Table 4 Non-immune adverse events and immune adverse events in the as-treated population

Event, n (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Lead to discontinuation	Lead to temporary suspension
Non-immune adverse events							
Nausea	65 (53.7)	37 (30.6)	37 (30.6)	37 (30.6)	–	1 (0.8)	1 (0.8)
Vomiting	24 (19.8)	11 (9.1)	11 (9.1)	2 (1.7)	–	1 (0.8)	–
Diarrhea	14 (11.6)	9 (7.4)	3 (2.5)	2 (1.7)	–	–	3 (2.5)
Decreased appetite	45 (37.2)	16 (13.2)	25 (20.7)	4 (3.3)	–	–	1 (0.8)
Constipation	17 (14.0)	12 (9.9)	4 (3.3)	1 (0.8)	–	–	1 (0.8)
Cytolysis	40 (33.0)	21 (17.4)	11 (9.1)	8 (6.6)	–	2 (1.7)	10 (8.3)
Cough	8 (6.6)	8 (6.6)	–	–	–	–	–
Dyspnea	17 (14.0)	2 (1.7)	7 (5.8)	7 (5.8)	1 (0.8)	6 (5.0)	8 (6.6)
Skin reactions	26 (21.5)	13 (10.7)	12 (9.9)	1 (0.8)	–	11 (9.0)	2 (1.7)
Kidney toxicity	22 (18.1)	7 (5.8)	10 (8.3)	5 (4.1)	–	9 (7.4)	6 (5.0)
Asthenia	92 (76.0)	44 (36.4)	39 (32.2)	9 (7.4)	–	6 (5.0)	3 (2.5)
Anemia	74 (61.2)	43 (35.5)	20 (16.5)	10 (8.3)	1 (0.8)	4 (3.3)	3 (2.5)
Thrombocytopenia	19 (15.8)	5 (4.1)	7 (5.8)	3 (2.5)	4 (3.3)	2 (1.7)	6 (5.0)
Neutropenia	41 (33.9)	6 (5.0)	8 (6.6)	10 (8.3)	17 (14.0)	6 (5.0)	10 (8.3)
Neuropathy	11 (9.1)	9 (7.4)	1 (0.8)	1 (0.8)	–	1 (0.8)	1 (0.8)
Stomatitis	14 (11.6)	10 (8.3)	4 (3.3)	–	–	–	–
Lacrimation increased	30 (24.8)	15 (12.4)	15 (12.4)	–	–	–	–
Pneumonitis	7 (5.8)	–	5 (4.1)	2 (1.7)	–	6 (7.4)	1 (0.8)
Arthralgia	6 (5.0)	4 (3.3)	1 (0.8)	1 (0.8)	–	1 (0.8)	–
Peripheral edema	17 (14.0)	12 (9.9)	4 (3.3)	1 (0.8)	–	7 (5.8)	2 (1.7)
Immune adverse events							
Diarrhea	2 (1.7)	–	–	2 (1.7)	–	2 (1.7)	–
Cytolysis	2 (1.7)	–	–	2 (1.7)	–	2 (1.7)	–
Dyspnea	1 (0.8)	–	–	1 (0.8)	–	1 (0.8)	–
Skin reactions	4 (3.3)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.7)	–
Kidney toxicity	1 (0.8)	–	–	1 (0.8)	–	1 (0.8)	–
Thyroidism	24 (19.8)	11 (9.1)	10 (8.3)	3 (2.5)	–	–	1 (0.8)
Pneumonitis	4 (3.3)	–	1 (0.8)	1 (0.8)	2 (1.7)	4 (3.3)	–
Colitis	2 (1.7)	–	–	1 (0.8)	1 (0.8)	–	2 (1.7)
Arthralgia	3 (2.5)	–	2(1.7)	1 (0.8)	–	2 (1.7)	–
Adrenal insufficiency	1 (0.8)	–	–	1 (0.8)	–	1 (0.8)	–
Encephalitis	1 (0.8)	–	1 (0.8)	–	–	–	1 (0.8)

Renal disorders occurred at a median time of 16.6 weeks and were mainly related to pemetrexed. Six patients (5%) experienced grade 3 renal AE but no grade 4 was reported. Discontinuation of treatment occurred in 10 cases. Only one case of immune-mediated nephritis was noted.

Subsequent treatments

When disease progression occurred, 66 patients received subsequent treatment: radiotherapy (n=17), chemotherapy (n=44), targeted therapies (n=3) and rechallenge of immunotherapy (n=2). Most often, subsequent chemotherapies were docetaxel or paclitaxel with or without bevacizumab. The average number of cycles administered was 2.7 cycles.

Discussion

This study, although retrospective, is one of the first real-life studies to provide additional data on the efficacy and safety of first-line pembrolizumab combined with chemotherapy for advanced NSCLC patients. Despite a short follow-up, patients experienced median PSF and OS of 9.0 and 20.6 months, respectively and encouraging ORR of 63.7% with several prolonged complete response. CT-immunotherapy demonstrated a benefit irrespective of PD-L1 expression, although better outcomes were observed for PD-L1 ≥50% patients. No new safety signal was reported.

Although this real-life population was broadly similar to the KEYNOTE-189 in terms of demographics characteristics (5), some notable differences were noticed. Indeed, patients with PS 2 were included and represented 8.3% of the study population. In randomized trials, maximal authorized dose of prednisone was between 7.5 and 10 mg/day because of the supposed risk of decreased efficacy of immunotherapy (16). In CAP29, 12.4% of patients received corticosteroid at the beginning of treatment. In the same way, the use of antibiotics before chemo-immunotherapy initiation should be done with caution; here 6.6% of patients were concerned (17). Finally, it is important to note that a small number of stage III NSCLC patients were included because they were not eligible to surgery or radiotherapy. Despite these differences, PFS was interestingly similar to results provided by Ghandi *et al.* (8.8 months) (9). Nonetheless, OS was slightly lower in real-life (20.6 *vs.* 22 months) (9,11). Although survival outcomes of locally advanced NSCLC patients could have improved our results, because the number of metastatic sites appeared to be directly correlated with survival (18), it was probably counterbalanced by a less selected population and PS 2 patients, compared to clinical trials. Nonetheless, our results confirmed the advances of anti-cancer immunotherapy in a population with historical poor prognosis (16).

In our study, PD-L1 level was a predictive factor of survival with an improvement of PFS and OS, especially in patients with PD-L1 expression over 50%. These data are similar to those observed in patients treated with ICI monotherapy or ICI combined with CT (19-22). Interestingly, the number of patients with a PD-L1 level <1% was higher in CAP29 than in the literature. This might be explained by the frequent use of pembrolizumab as monotherapy in patients with PD-L1 ≥50%, according to guidelines (23). Concerning PD-L1 1–49% population, median PFS and OS achieved here 8.4 (7.5–NR) and 18.0 months (17.0–NR). In an exploratory analysis of KEYNOTE-042 trial, Mok *et al.* evaluated efficacy of single agent pembrolizumab in untreated patients with PD-L1 score 1–49% and reported a nonsignificant OS benefit versus chemotherapy (13.4 *vs.* 12.1 months, respectively) (22,24). Our study suggests the interest of the combination of carboplatin, pemetrexed and pembrolizumab for patients with PD-L1 <50%, for which the benefit of ICI alone has not been significantly demonstrated. Here, patients with PD-L1 ≥50% seemed to derive a greater benefit of CT-immunotherapy with median PFS of 20.9 months (OS not reached), although no strategy has been validated for this specific population. In KEYNOTE-024 study that compared pembrolizumab to platinum doublet in patients with PD-L1 ≥50%, median OS achieved 30 *vs.* 14.2 months, respectively (21). More recently, a retrospective study compared the use of pembrolizumab alone or in combination with CT in patients with PD-L1 ≥50% (25). This study showed no significant difference between the 2 groups. However, the combination of CT-ICI tended to provide a better tumor response. OS was 13.3 months (6.8–20.3) in the pembrolizumab group *vs.* 20.4 months (10.8–NR) in the CT-immunotherapy group (P=0.18). Few data are currently available concerning the benefit of the combination compared to ICI monotherapy. A French prospective multicenter study is currently undergoing to try to answer this question (26).

Liver and brain metastases are known to be poor prognostic factors (19,20,27). Here, the presence of brain or liver metastases did not appear to have a significant impact on survival outcomes. Effective local treatments could have balanced the pejorative nature of brain metastases. Similarly, no conclusion can be formally drawn because of a

small number of patients.

To our knowledge, only three published studies provided real-life data of pembrolizumab combined with platinum-based CT in first-line treatment of advanced NSCLC (20,27,28). Two of them were US real-life retrospective studies. Waterhouse *et al.* published the most consequent study including a total of 4,271 patients treated with pembrolizumab plus CT (20). Median OS of the 3,457 non-squamous NSCLC patients was only 12.0 months, less important than in our study. Velcheti *et al.* reported a median OS of 16.5 months in a cohort of 283 patients (28). These results were lower compared to clinical trials, but also correlated with PD-L1 rate. A Japanese study reported similar survival and tolerance data, with a focus on the elderly population (27).

Finally, no new safety signals emerged in a real-life setting. The rate of grade 3–4 AE was low compared to KEYNOTE-189 (17.5% *vs.* 67.2%), where two toxic deaths were reported (29). Renal toxicity was important (23%) compared to clinical trial and was mainly related to pemetrexed. It led to interruption of treatment for 10 patients only (5%). Our study data confirmed the risk of nephrotoxicity with cumulative pemetrexed dose (30). The mechanisms of toxicity are different between ICI and CT and their effects may be amplified when combined (31). Ghandi *et al.* reported however immuno-induced mechanisms that could minimize renal toxicity (9). Finally, pemetrexed discontinuation rates were higher and occurred earlier than in KEYNOTE-189, although not due to disease progression. This early discontinuation was mostly explained by poor clinical and biological tolerance of this treatment (29). In our real-life study, clinicians tended to stop CT early during maintenance phase in order to limit the risk of pemetrexed-induced toxicity and to continue ICI.

Our study has several limitations. First, it was a retrospective study with a small cohort. In addition, the median follow-up was relatively short. The study design did not allow for a comparative group to assess efficacy of pembrolizumab monotherapy for PD-L1 ≥50% patients. Previous studies have nevertheless suggested similar efficacy of single agent pembrolizumab compared to CT-ICI (25,32). As mentioned above, several patients had stage III NSCLC and received the triplet. Some of them received sequential radiotherapy depending on tumor response. Results observed in this subgroup may have improved survival data. However, this therapeutic choice is part of clinical daily practice. Early discontinuation of pemetrexed to limit toxicity may also have negatively influenced survival (29) but this hypothesis deserves further investigations.

Conclusions

This study is one of the first to provide real-life data on the efficacy and safety of first-line pembrolizumab plus chemotherapy for patients with advanced non-squamous NSCLC. With median PFS and OS of 9.0 and 20.6 months respectively and no new safety signal, our real-life data are very close to results provided by clinical trials, confirming the benefit and the manageable toxicity profile of this combination.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-556/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-556/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-556/coif). RC reports support for attending meetings from Lilly, and participation on a Data Safety Monitoring Board or Advisory Board of MSD. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This non-interventional study was approved by a regional ethics committee and France's national data protection authority (CNIL) (No. B2020CE30) according to French law. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients alive provided written informed consent before enrollment.

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