Case Report

Brief Report: First-line Pembrolizumab in Metastatic Non-Small Cell Lung Cancer Habouring *MET* Exon 14 Skipping Mutation and PD-L1 ≥50% (GFPC 01-20 Study)

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Clinical PracticePoints

- Pembrolizumab is a valid option for first-line treatment of stage IV NSCLC with PD-L1≥ 50% and *MET* exon 14 skipping mutation.
- Best outcomes were seen in adenocarcinomas (vs. squamous cell carcinoma or sarcomatoïd carcinoma)

Clinical Lung Cancer, Vol. 000, No.xxx, 1–5 © 2022 The Author(s). Published by Elsevier Inc.

Keywords: Immunotherapy, MET exon 14 skipping mutation, non-small cell lung cancer, oncogenic addiction, biomarker

Introduction

Genomic studies of large cohorts have unraveled a complex molecular landscape of lung tumors. Targeted therapies for several oncogenic alterations have been developed and improve patients' outcomes. In stage IV non-squamous non-small cell lung cancer (NSCLC) patients, *MET* exon 14 skipping mutations (METΔ14) were described in 2003 and is found in 1% to 4% NSCLC. The resulting protein escapes ubiquitination and degradation and confers cell survival, proliferative and invasive properties to the cell.[1] Several MET inhibitors have been evaluated for the treatment of METΔ14 NSCLC.[2-4]

Since 2015, anti-Programmed Death 1 (PD1) and anti-Programmed Death Ligand 1 (PD-L1) immunotherapy has emerged as a gold-standard treatment for second-line treatment and more recently for first- line treatment for of stage IV NSCLC, either in monotherapy or in combination with chemotherapy. In these studies, no information was reported regarding the METΔ14 NSCLC subgroup. Efficacy of anti-PD1/PD-L1 in these patients is largely unknown. Pathophysiologically, *MET* alterations may induce PD-L1 expression,[2] hence METΔ14 may affect response to anti-PD1/PD-L1 immunotherapy. In 147 METΔ14 NSCLC patients, Sabari et al. found a higher PDL1 expression than expected, with 22%, and 41% having PD-L1 expression of 1% to 49%, and ≥ 50%, respectively.[5] Nevertheless, median TMB of METΔ14 NSCLC was lower than that of unselected NSCLCs. Similar results were recently reported in 2 series of 14 and 20 METΔ14 NSCLC.[6,7]

Several observational studies reported the results of anti-PD1/PD-L1 immunotherapy in molecularly defined subgroups including METΔ14 NSCLC, mainly in second and more lines, with mixed results. In the above-mentioned study by Sabari et al. 24 patients (11 as first-line treatment) were treated with anti-PD1/PD-L1 immunotherapy. Among 22 patients evaluable for response, objective response rate (ORR) was 17% and median progression free survival (PFS) and overall survival (OS) were 1.9 months and 18.2 months (95% CI 12.9-NR), respectively.[5] The Immunotarget study reported results from 36 patients treated with anti-PD1/PD-L1 in second line and more: ORR was 16%, PFS 3.4 months.[7] In a similar study, we reported 30 more patients treated in first line (n = 4), second line (n = 15) or more (n = 11), with ORR 36% and PFS 4.9 months.[8] Recently, a series of 6 METΔ14 NSCLC

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Submitted: Jun 25, 2022; Revised: Sep 4, 2022; Accepted: Sep 5, 2022; Epub: xxx

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https://doi.org/10.1016/j.cllc.2022.09.002

Please cite this article as: Florian Guisier et al, Brief Report: First-line Pembrolizumab in Metastatic Non-Small Cell Lung Cancer Habouring MET Exon 14 Skipping Mutation and PD-L1 ≥50% (GFPC 01-20 Study), Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2022.09.002

patients with long-term benefit of anti-PD1 therapy in ≥ 2nd line was also reported.[9]

To further evaluate the efficacy of anti-PD1 immunotherapy in METΔ14 NSCLC in the first-line setting, we gathered data from 3 academic cohorts conducted by the French lung cancer group (GFPC) that included a subgroup of patients who received pembrolizumab as first-line treatment for metastatic METΔ14 NSCLC with PDL1≥ 50%.

Materials and Methods

Study Design

We collected data from 3 independent retrospective, multicenter cohorts conducted: IMAD2 (GFPC 01-2018),[8] AFONMET (GFPC 03-2018)[10] and ESCKEYP (GFPC 05-2018).[11]

From these 3 cohorts, patients who met the following criteria were included in the present study: age > 18 years, metastatic NSCLC with *MET*Δ14 mutation, PDL1≥ 50%, first-line treatment with pembrolizumab. Patients included in a clinical immunotherapy trial were excluded.

Data Collection

Patients' demographic and clinical characteristics at NSCLC diagnosis were obtained from patient files and included: age; sex; smoking status; cancer stage; number and sites of metastases; presence of *MET*Δ14 mutation; the Eastern Cooperative Oncology Group performance status (ECOG PS) at immunotherapy onset; clinical response to pembrolizumab; adverse event (AE) type and grade on pembrolizumab; and post-immunotherapy treatment.

Statistical Analyses

PFS was defined as the time from pembrolizumab initiation to first subsequent tumor progression. Progression was defined as Response Evaluation Criteria In Solid Tumors version 1.1 criteria (RECIST 1.1) radiological or clinical progression (deteriorated clinical status preventing systemic treatment) or death. Assessments were done in each participating center without centralized imaging review. OS was calculated from pembrolizumab introduction to death. ORR to pembrolizumab was defined as the best response according to RECIST1.1 (radiological assessment was done every 6 weeks). AEs were reported according to Common Terminology Criteria for Adverse Events (CTCAEs) version 4.

The Kaplan–Meier method was used to estimate PFS and OS.

All statistical analyses were computed with the RStudio statistical software (Version 1.1.383).

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Participating centers were responsible for obtaining patient consent and institutional approval. All contributors were trained in good clinical practices. The study was purely an academic collaboration and was not funded by industry.

Results

Patients Characteristics

Twenty-four advanced *MET*Δ14 NSCLC patients were included in the study.

Table 1 Patients Characteristics

	Patients (n = 24)
Age (median, range, yr)	73.0 (53-89)
Male	13 (56%)
Smoking status	
Never smoker	8 (33%)
Former smoker	11 (46%)
Active smoker	5 (21%)
Performance status	
0-1	21 88%)
> 1	3 (12%)
Histology	
Adenocarcinoma	17 (71%)
Squamous cell carcinoma	3 (13%)
Sarcomatoïd carcinoma	2 (8%)
Others	2 (8%)
Metastatic sites	
Number (median, range)	3 (1-5)
Lymph nodes	11 (46%)
Bone	9 (38%)
Lung	9 (38%)
Pleura	7 (29%)
Adrenal glands	5 (21%)
Brain	4 (17%)
Liver	3 (13%)

Patients characteristics are summarized in Table 1. Median age was 73, 54% were male, 33% were never-smoker, 71% had adenocarcinoma. Median number of metastatic sites was 3 (range: 1-5). Four (17%) patients had brain metastasis, of whom 2 received SBRT before immunotherapy onset. Co-mutations in *BRAF, KRAS* and *P53* were identified in 1 patient each.

ICI Therapy and Clinical Outcomes

Median follow up was 12.0 months (IC96 [10.5-NR]). Median duration of first line Pembrolizumab therapy was 3.4 months (IC96 [1.9-8.9]) (Figure 1).

Among 21 of 24 (87.5%) evaluable patients, ORR was 43% (complete response: 14%, partial response: 29%) and disease control rate was 57%. Nine patients (43%) had progressive disease at first tumor assessment. All tumor responses were seen in adenocarcinomas. Median DoR was 13.9 months (95%CI = [8.3-NR]).

Treatment was stopped in 21 of 24 (87.5%) patients: 13 (54%) for tumor progression, 5 (21%) for toxicity and 2 (8%) for having reach 2 years of treatment. Three patients were still on treatment at data cut-off. Nine (38%) patients received a MET inhibitor as subsequent therapy.

Median PFS and OS in the overall cohort were 3.5 months (95%CI = [2.0 – NR]) and 12.1 months (95%CI = [9.1-NR]), respectively (Figure 2); in the adenocarcinoma subgroup PFS and OS were 5.3 months (95%CI = [2.1-NR]) and 17.9 months (95%CI = [10.5-NR]), respectively. One-year PFS and OS were 35.8% (95%CI = [20.3-63.1]) and 55.0%

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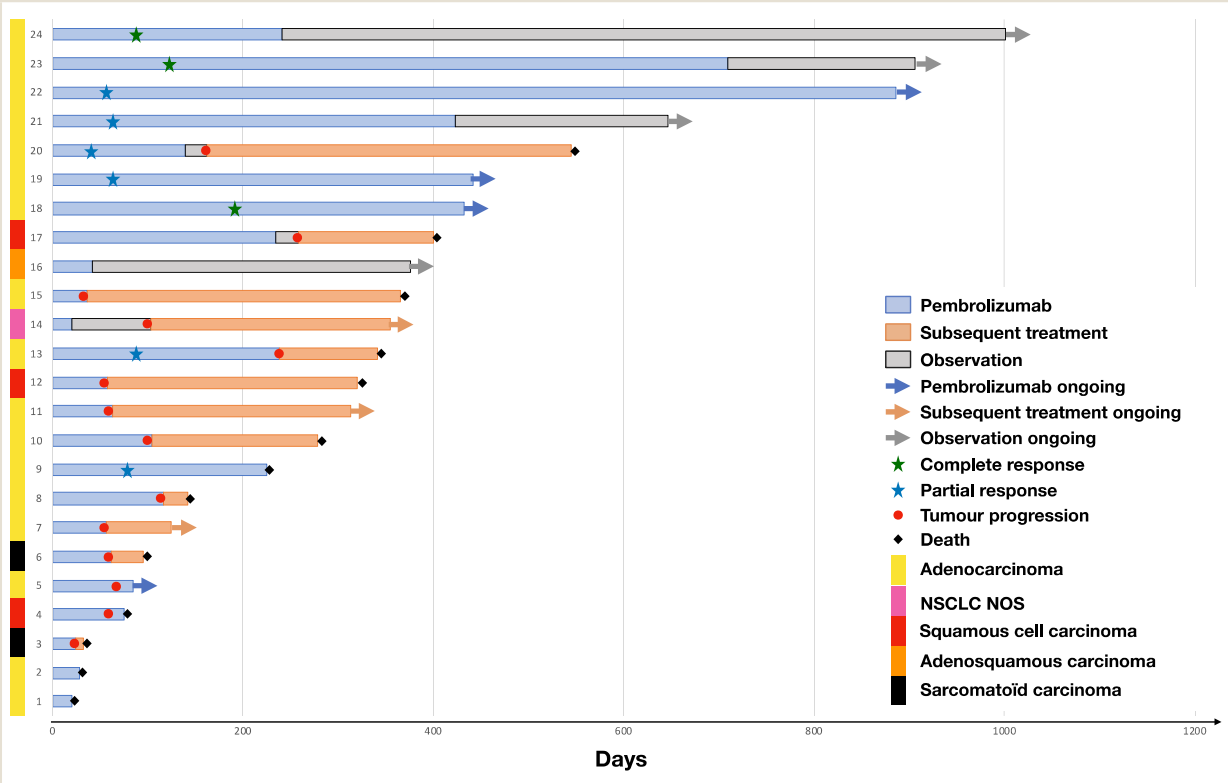
Figure 1 Swim-lane plot showing patients treatments and outcomes.



(95%CI = [37.6-80.5]), respectively, in the overall population and 46.7%(95%CI = [27.2-80.2]) and 63.8%(95%CI = [42.8-95.2]), respectively, in the adenocarcinoma subgroup. Two-year OS was 30.8% (95%CI = [15.2-62.6]) in the overall population and 44.7% (95%CI = [23.3-85.5]) in the adenocarcinoma subgroup.

Safety

Grade 2 toxicity was reported in 2 (8%) patients (cutaneous and pneumonitis, 1 each), and 3 (12%) patients developed a grade 3 toxicity (cutaneous, renal insufficiency and pneumonitis, 1 each). No grade 4 or 5 toxicity was observed.

Discussion

In this real-world series of 24 stage IV *MET*Δ14 NSCLC patients with PLD1 > 50%, first-line treatment with pembrolizumab resulted in a median OS of 12.1 months in the entire cohort and 17.9 months in the subgroup of 17 patients with adenocarcinoma. PFS were 3.5 (95%CI = [2.0-NR]) and 5.3 months (95%CI = [2.1-NR]), respectively. These results are worse than those reported from the KEYNOTE 024 and 042 studies, where median OS in patients with PDL1 TPS ≥ 50% receiving first-line Pembrolizumab were 30.0 (C95, [18.3-NR]) and 20.0 months (95%CI = [15.4-24.9]), respectively.[12,13] Nevertheless, real-world studies reporting the efficacy of first-line Pembrolizumab in stage IV NSCLC showed contrasted results. In a French retrospective multicenter longitudinal study of 108 consecutive NSCLC patients with PD-L1 TPS ≥ 50% and without EGFR/ALK alterations treated with first-line pembrolizumab, median PFS was 10.1 months (95% CI, 8.8-11.4), ORR was 57.3% and 6-months OS was 86.2%.[14] In a US medico-administrative study of 423 NSCLC patients with PDL1 TPS ≥ 50% who received first-line pembrolizumab, median PFS and OS were respectively 6.8 months (95%CI = [5.3-8.1]) and 18.9 months (95%CI = [14.9-25.5]) and ORR was 48%.[15] These results are in line with ours, especially for adenocarcinomas.

The efficacy of anti-PD1/PD-L1 treatment in *MET*Δ14 NSCLC patients has also to be discussed in the context of emerging targeted therapies. First generation anti-MET inhibitors were not specifically designed for this purpose but rather targeted ALK, RET or ROS-1. Their clinical activity in *MET* exon 14 skipping mutated NSCLC was usually weak.[2] Nevertheless, an updated analysis of the PROFILE-1001 study, in which 69 *MET*Δ14 NSCLC patients were treated with crizotinib, showed 3 complete responses and 18 partial responses (ORR, 32% [95%CI = [21-45]) with median PFS of 7.3 months (95%CI = [5.4-9.1]).

Results of Capmatinib, a new-generation MET inhibitor, were reported in 28 *MET*Δ14 NSCLC patients treated in the first-line setting (median age 71 years, 55% females, PS 0 23%, adenocarcinoma 77%, never smoker 89%, brain metastasis 11%). ORR was 68% (95% CI, 48-84) in 20 evaluable patients, PFS was 12.6 months (95%CI=[5.6-NR]) and median DoR was 12.4 months (95%CI = [8.2-NR]).[4] In a phase II trial evaluating Tepotinib, another new-generation MET inhibitor, 43 *MET*Δ14 NSCLC

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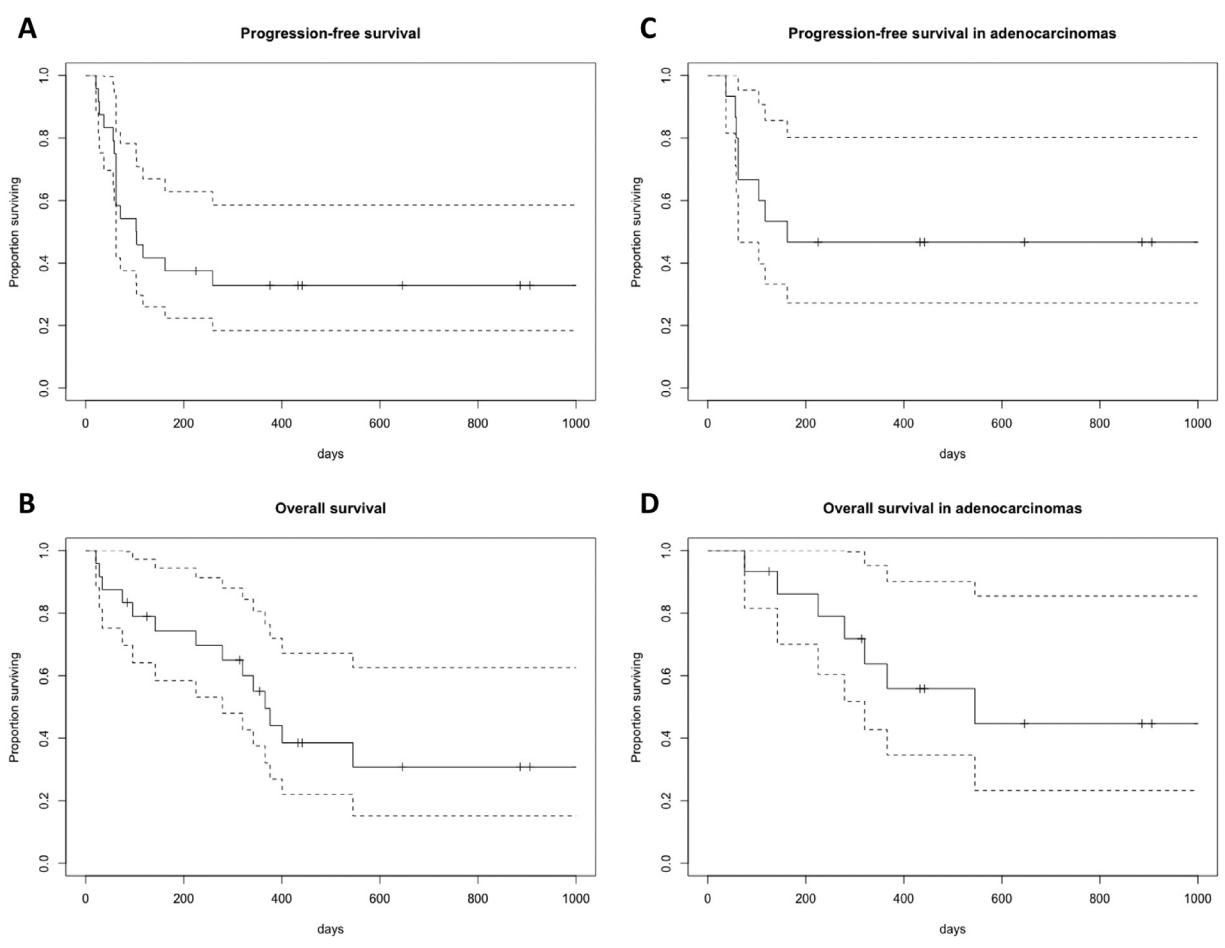
Figure 2 Kaplan-Meier estimates for progression-free (A, C) and overall survival (B, D) in the overall population (A, B) and among adenocarcinoma patients (C, D).



patients were treated in the first-line setting. Efficacy results were reported for the overall 152 NSCLC patients included in the trial[3]; showing an ORR of 46% (95%CI = [36%-57%]) and a median DoR of 11.1 months (95%CI = [7.2 -NR]).[3] The phase 1 CHRYSALIS study also included a cohort of patients with *MET*Δ14 NSCLC, that were treated with Amivantamab, a bispecific MET and EGFR antibody. Patients received 2 (range, 0-10) prior lines of therapy in median. In 36 evaluable patients, overall response rate was 33% (50% [3/6] in treatment-naïve patients, 46% [5/11] in patients with no prior MET inhibitor, and 21% [4/19] in patients with prior MET inhibitor therapy).[16] Nevertheless PD-L1 status was not reported in these 3 studies, as well as ICI treatment.

Our study has limitations, notably its retrospective nature and the absence of independent review committee. ORR might be overestimated by investigators, whereas AEs might be under-estimated because of the retrospective nature of the study. The size of the cohort is also limited but *MET*Δ14 NSCLC is a rare subtype and we included only patients with PDL1 TPS≥ 50%.

In conclusion, first-line treatment with Pembrolizumab in PDL1≥50% NSCLC with *MET* exon 14 skipping mutation may represent a treatment option, especially in adenocarcinoma. This treatment regimen should be assessed prospectively together with chemo-immunotherapy and targeted therapies.

Disclosure

The study was purely an academic collaboration and was not funded by industry.

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