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Post-progression outcomes of NSCLC patients with PD-L1 expression  $\geq$  50% receiving first-line single-agent pembrolizumab in a large multicentre real-world study

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## Short/brief report

**Running title:** post-progression outcomes after first-line immunotherapy

# Post-progression outcomes of NSCLC patients with a PD-L1 expression $\geq$ 50% receiving first-line single-agent pembrolizumab in a large multicenter real-world study.

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## Abstract

**Background:** Treatment sequencing with first-line immunotherapy, followed by second-line chemotherapy, is a viable option for patients with a PD-L1 expression  $\geq$  50%.

**Methods:** In a large real-world cohort of metastatic NSCLC patients with a PD-L1 expression  $\geq$  50% treated with first-line pembrolizumab monotherapy, we evaluated post-progression treatments and clinical outcomes.

**Results:** In total, 974 patients were included. With a median follow-up of 22.7 months (95%CI: 21.6 – 38.2), the median overall survival (OS) of the entire population was 15.8 months (95%CI: 13.5-17.5; 548 events). Among the 678 patients who experienced disease progression, 379 (55.9%) had not received any further treatment, and 359 patients (52.9%) had died. Patients who did not receive post-progression therapy were older ( $p = 0.0011$ ), had worse ECOG-PS ( $p < 0.0001$ ) and were on corticosteroids prior to pembrolizumab ( $p = 0.0024$ ). The median post-progression OS (ppOS) of patients who received a switched approach was 8.2 months (95%CI: 7.1-9.1; 131 events), while the median ppOS of those who received pembrolizumab beyond progression alone and with the addition of local ablative treatments were 8.0 months (95%CI: 5.4-11.8; 8 events) and 13.9 months (95%CI: 6.1-14.3; 18 events), respectively ( $p = 0.0958$ ). 241 patients (35.5%) received a second-line systemic treatment. As compared to first-line treatment commencement patients features at initiation of second-line showed a significantly higher proportion of patients aged under 70 years ( $p = 0.0244$ ), with a poorer ECOG-PS ( $p < 0.0001$ ), with CNS ( $p = 0.0001$ ), bone ( $p = 0.0266$ ) and liver metastases ( $p = 0.0148$ ).

**Conclusions:** In the real-world scenario NSCLC patients with a PD-L1 expression  $\geq$  50% treated in routine clinical practice with first-line single-agent pembrolizumab, may achieve worse outcomes as compared to the Keynote-024 trial. High attrition post first-line and

second-line treatment options are major determinants of outcomes that should be considered when counselling patients for first-line choices.

**Keywords:** non-small cell lung cancer; immunotherapy; PD-L1; pembrolizumab, Performance Status, post-progression.

## Introduction

The Keynote-024 trial established single-agent pembrolizumab as the standard of care for advanced non-small-cell lung cancer (NSCLC) patients with a programmed cell death-ligand1 (PD-L1) expression  $\geq 50\%$  [1-2]. However, since the Keynote-189 and Keynote-407 trials, this has been challenged by chemo-immunotherapy combinations [3-4], as no head-to-head randomized controlled trial (RCT) has compared the two strategies in the PD-L1 high subgroup.

Even though some meta-analyses suggest there is an incremental benefit of the addition of chemotherapy to first-line immunotherapy, with respect to response rate and progression-free survival (PFS) in patients with high PD-L1 expression [5-7], the absence of OS advantage and the increased toxicity of a triplet regimen compared to a single-agent immune-checkpoint inhibitor (ICI) should be considered.

In this scenario, treatment sequencing with first-line immunotherapy, followed by second-line chemotherapy, might be a viable option for patients with a PD-L1 expression  $\geq 50\%$ . Post-progression analyses of RCTs revealed conflicting results. Among the 154 patients of the experimental arm of the Keynote-024 trial, 51.9% received a further treatment line at the last data-analysis [8], while 38% of the 637 patients of the experimental arm of the Keynote-042 trial received subsequent anticancer therapy [9].

In clinical practice, a non-negligible proportion of NSCLC patients experiences life-threatening progressive disease (PD), without reaching the subsequent treatment line. This is true in all treatment settings, including immunotherapy [10-11]. Recently, we published a large real-world multicentre study of metastatic NSCLC patients with PD-L1 expression  $\geq 50\%$ , receiving first-line single-agent pembrolizumab at 34 European institutions, aimed at investigating the clinicopathologic correlates of efficacy [12-14].

To provide further insights into clinical outcomes of NSCLC patients with high PD-L1 expression after PD, we performed an updated analysis of the aforementioned cohort, with a particular focus on post-progression outcomes.

## Materials and Methods

### Study Design

Following a request for data updating of the cohort of metastatic NSCLC patients with PD-L1 expression  $\geq 50\%$ , treated with first-line pembrolizumab monotherapy, from January 2017 to May 2020, 31 institutions participated (Supplementary file 1).

The aim of this analysis was to evaluate the post-progression clinical outcomes including both treatment beyond PD and further treatment lines. The measured clinical outcomes were post-progression overall survival (ppOS), second-line PFS (II line PFS) and second-line overall survival (II line OS). Methods regarding clinical outcomes estimation have been already detailed [12-14]. In order to be closer to the real-life scenario, both patients who experienced radiological PD and those with clinical progression according to the investigators have been included.

PpOS was defined as the length of time between the first occurrence of PD during pembrolizumab and death (resulting from any cause), or to the last contact; ppOS was evaluated according to the therapeutic strategies chosen by clinicians at the moment of PD, categorized as: patients who received pembrolizumab beyond PD (ByPD), with or without local ablative treatments (LATs) and patients who received other post-progression systemic treatments (switched approach).

Considering the possible positive selection bias associated with oligo-PD [15], investigators were also asked to clarify whether or not patients who received pembrolizumab ByPD had experienced oligo-progression (defined as progression of a single metastasis already present and/or progression that can be safely treated with ablative treatments).

The possible relationship between baseline patients' features and post-progression outcomes (categorized as no post-progression treatments, pembrolizumab ByPD and switched approach) was evaluated. We used the following clinicopathologic characteristics: age ( $<70$  vs  $\geq 70$  years old) [16], gender (male vs female), Eastern Cooperative Oncology Group-PS (ECOG-PS) (0 vs 1 vs  $\geq 2$ ), central nervous system (CNS) metastases (yes vs no), bone metastases (yes vs no), liver metastases (yes vs no), Body Mass Index (BMI) according to the World Health Organization (WHO) categories [16-17], PD-L1 tumour expression ( $< 90\%$  vs  $\geq 90\%$ )[12], smoking status (current vs former vs never smoker) [17], and corticosteroids administration within the 30 days before treatment commencement (dose equivalent or higher to 10 mg prednisone per day) (yes vs no) [12].

Further analyses were performed only among patients who received a second-line systemic treatment (regardless of previous treatment with pembrolizumab beyond PD). II-line PFS was defined as the time from second-line treatment initiation to disease progression/death (whichever occurred first) or to the last contact. II-line OS was defined as the time from second-line treatment initiation to death or to the last contact.

Second-line treatments were categorized as platinum-based doublet chemotherapy, single-agent chemotherapy and other regimens. Those patients' characteristics which could have changed over time, including ECOG-PS, age, CNS metastases, bone metastases and liver metastases, were re-assessed at the second-line treatment commencement. All patients' features were then compared to their baseline distribution. To evaluate whether some of the clinical characteristics affected clinical outcomes, univariate and multivariate analyses of II line PFS and II line OS were performed (using a stepwise selection of covariates, with an entry significance level of 0.05). Having received previous pembrolizumab ByPD (yes vs no) was also considered as a covariate. Patients without events were considered as censored at the time of the last follow-up. The data cut-off period was September 2020.

### **Statistical analysis**

Descriptive statistics were used to report patients' characteristics. Median ppOS, II line PFS and II line OS were evaluated using the Kaplan-Meier method. The median period of follow-up was calculated according to the reverse Kaplan-Meier method.  $\chi^2$  test was used for the correlation analyses. Log-rank test was used to compare median survivals and Cox regression was used to estimate the hazard ratios (HRs) estimation with 95% confidence intervals (CIs) in univariate and multivariate analysis. All statistical analyses were performed using MedCalc Statistical Software version 18.11.3 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2019).

## **Results**

### **Post-progression overall survival analysis**

The entire cohort consisted of 974 metastatic NSCLC patients with a PD-L1 expression  $\geq$  50%. With a median follow-up of 22.7 months (95%CI: 21.6-38.2), median PFS and OS of the entire population were 7.0 months (95%CI: 6.1-8.2; 678 events) and 15.8 months (95%CI: 13.5-17.5; 548 events), respectively.

At the data cut-off, 678 patients (69.6%) experienced disease progression; the post-progression median follow-up was 14.4 months (95%CI: 11.9-33.1). Figure 1 reports the study's flow diagram. Baseline characteristics of patients who experienced disease progression are summarized in table 1.

At the data cut off, 379 (55.9%) had not received any further treatment, and 359 patients (52.9%) had died; 198 patients (29.2%) received a switched approach and 101 (14.9%) received pembrolizumab ByPD either alone (64 [9.4%]) or in combination with LATs (37 [5.5%]). One patient (2.7%) received surgery, 1 (2.7%) radiation therapy (RT) plus surgery and 35 (94.6%) RT; 18 patients (28.1%) among those who received pembrolizumab ByPD alone, and 28 patients (75.7%) among those who received pembrolizumab ByPD in combination with LATs, were marked as oligo-progressive patients ( $p < 0.0001$ ).

Table 1 also reports the correlation analysis between baseline clinicopathologic characteristics and the post-progression outcome. There was a significant association between older age ( $p = 0.0011$ ), higher ECOG-PS ( $p < 0.0001$ ), baseline corticosteroid administration ( $p = 0.0024$ ) and not having received post-progression treatments.

The median ppOS of patients who received a switched approach was 8.2 months (95%CI: 7.1-9.1; 131 events), while the median ppOS of those who received pembrolizumab ByPD alone and with the addition of LATs were 8.0 months (95%CI: 5.4-11.8; events) and 13.9 months (95%CI: 6.1-14.3; 18 events), respectively (log-rank test:  $p = 0.0958$ ) (Figure 2). At the univariate Cox regression, the median ppOS of patients who received pembrolizumab ByPD in combination with LATs resulted to have a significantly lower risk of death as compared to patients who received a switched approach (HR 0.61 [95%CI: 0.37-0.99],  $p = 0.0457$ ) and those who received pembrolizumab ByPD alone (HR = 0.56 [95%CI: 0.32-0.98],  $p = 0.0419$ ).

### **Second-line PFS and OS analysis.**

At the data cut off, 241 (35.5%) among the 678 patients who had experienced PD, received a second-line systemic treatment; 191 patients (79.3%) received platinum-based doublet chemotherapy, 44 (18.3%) single-agent chemotherapy and 6 (2.5%) other regimens. Forty-six patients (19.1%) had previous pembrolizumab ByPD.

Patients' characteristics are summarized in Table 2. As compared to the baseline (at the first-line treatment commencement), at the second-line there was a significantly higher proportion of patients aged under 70 years old ( $p = 0.0244$ ), with CNS ( $p = 0.0001$ ), bone

( $p = 0.0266$ ) and liver metastases ( $p = 0.0148$ ). Noteworthy, they also had a significantly poorer ECOG-PS ( $p < 0.0001$ ).

With a second-line median follow-up of 12.1 months (95%CI: 10.5-32.5), II-line PFS and OS overall were 3.9 months (95%CI: 3.1-4.8; 206 events) and 6.7 months (95%CI: 5.7-7.9; 158 events), respectively.

Patients who received platinum-based doublet chemotherapy had a median II-line PFS of 4.1 months (95%CI: 3.2-5.3; 162 events), while those received single-agent chemotherapy and other regimens had a median II-line PFS of 2.8 months (95%CI: 1.8-4.0; 39 events) and 4.0 months (95%CI: 4.3-5.3; 5 events), respectively (log-rank test:  $p = 0.5628$ ) (Figure 3A). II-line OS was 7.5 months (95%CI: 5.9-8.9; 119 events) for patients treated with platinum-based doublet chemotherapy, 5.3 months (95%CI: 2.7-6.9; 34 events) for those with single-agent chemotherapy and 3.4 months (95%CI: 1.3-7.9; 5 events) for other regimens (log-rank test: 0.0289) (Figure 3B).

Table 3 summarized the univariate and multivariate analyses of II-line PFS and OS. At the multivariate analysis only ECOG-PS  $\geq 2$  was confirmed to be significantly associated with an increased risk of PD as compared to ECOG-PS 0 (HR = 3.09 [95%CI: 1.84-5.19],  $p < 0.001$ ). Patients receiving other regimens had an increased risk of death as compared to platinum-based doublet chemotherapy (HR = 2.53 [95%CI: 1.02-6.27];  $p = 0.0447$ ), as well as patients with an ECOG-PS  $\geq 2$  compared to ECOG-PS 0 (HR = 3.61 [95%CI: 1.90-6.83],  $p = 0.0001$ ).

## Discussion

Clinical decision making in advanced disease has always been a contentious topic in NSCLC, and while the advent of ICIs has been a game-changer, it does not simplify treatment algorithms. Recently, a review of real-world observational studies reported a median OS ranging from 4.6 to 12.8 months in the second-line setting [18]. We report ppOS ranging from 8.0 months to 13.9 months, findings that somehow mirror the incremental benefit already reported in the post-immunotherapy setting [19-22].

Our study conveys a credible portrait of contemporary routine clinical practice in advanced NSCLC. In our study the median OS for the entire population was 15.8 months, a significantly worse estimate compared to the 26.3 months reported in Keynote-024 [8]. These results are not unsurprising, considering the higher proportion of patients with adverse prognostic factors present in our cohort (i.e. those with ECOG-PS  $\geq 2$ , receiving corticosteroids, aged more than 70 year old). Whilst accounting for the OS discrepancy,

data on real world populations are highly important to confirm RCT findings, where participants are highly selected for lower co-morbid burden and features portending to indolent disease. To this respect, it has been already demonstrated that NSCLC patients with PD-L1 expression  $\geq 50\%$  and poor baseline PS, particularly if related to disease burden [23], experience inferior outcomes with first-line single-agent pembrolizumab [24]. Considering that with a shorter follow-up, the OS of our cohort was 17.2 months [12], it can be assumed that post-progression outcomes played their specific detrimental role, reflecting the downside of having included frail patients.

The impressively high proportions of patients who did not receive any further treatment at the data cut off (55.9%), and who died without receiving any subsequent treatments (52.9%), which are worse than reported in clinical trials [8-9], mirror these findings.

Accordingly, the correlation analysis revealed that baseline (at the first-line treatment) characteristics significantly associated with post-progression outcomes and no further treatments, are typical features of patients' frailty including older age ( $p = 0.0011$ ), higher ECOG-PS ( $p = 0.0001$ ) and baseline corticosteroids administration ( $p = 0.0024$ ). These results suggest that NSCLC patients with a PD-L1 expression  $\geq 50\%$  aged  $\geq 70$  year old, with an ECOG-PS  $\geq 2$ , and receiving systemic corticosteroids before starting first-line pembrolizumab, are at higher risk of life-threatening PD, therefore the treatment sequencing approach (first-line immunotherapy followed by second-line chemotherapy) is unlikely to be completely pursued. However, a tailored decision-making process at the first-line treatment commencement, should also take into account that frail/older patients are unlikely to be treated with a first-line chemo-immunotherapy combination without experiencing limiting side effects.

Our results regarding the ppOS are partially aligned with similar studies reported in this setting [25]. Based on the longer ppOS observed with pembrolizumab ByPD in combination with LATs, a combinational approach should be considered at PD when feasible, as confirmed in a recent prospective study [26], particularly in oligo-PD. Indeed, LATs were more likely performed in patients with oligo-PD ( $p < 0.0001$ ), which is known to have a better prognosis [15].

The II-line PFS and II line OS analyses revealed that patients who had reached the second-line setting tended to be younger. Patients receiving second-line treatments had also more frequently CNS, bone and liver metastases, with a significant trend towards a poorer ECOG-PS, as compared to the first-line. This is probably due to the natural history of the disease, which tends to worsen throughout treatment lines. These negative baseline

characteristics could explain the low median II-line PFS and II-line OS in absolute terms and when compared to other studies in the post-immunotherapy setting [21-22, 27]. Nevertheless, we found an incremental benefit for patients who received platinum-based doublet chemotherapy, while ECOG-PS remains the major determinant of II-line survival outcomes.

Several limitations of the present study must be acknowledged. The retrospective design and the lack of centralized imaging review, which exposes to selection biases. Moreover, patients' outcomes assessment performed according to the respective clinical practice of the participating centers, might have affected the analysis, including the definition of oligo-progression.

## **Conclusion**

Our study portrays the significant heterogeneity in the outcome of NSCLC patients with a PD-L1 expression  $\geq 50\%$  treated with first-line single-agent pembrolizumab in routine practice as compared to RCTs. These findings provide an important benchmark that is characteristic of patients of older age, with poorer PS and who were receiving corticosteroids prior to immunotherapy. Attrition between first- and second-line is common and the post-progression outcome is a major determinant of the global outcome. Among patients who are able to receive further treatments, pembrolizumab ByPD +/- LATs represents a viable option. Among patients who reach a second-line treatment, ECOG-PS still remains the major determinant of clinical outcomes.

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### **Ethics approval and consent to participate**

All patients provided written, informed consent to treatment with immunotherapy. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center (Comitato Etico per le province di L'Aquila e Teramo, verbale N.15 del 28 Novembre 2019).

### **Authors' contributions**

All authors contributed to the publication according to the ICMJE guidelines for the authorship (study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision). All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Each author have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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**Availability of data and materials:** the datasets used during the present study are available from the corresponding author upon reasonable request.

### **Consent for publication**

Not applicable.

**Conflicts of Interest:** Dr Alessio Cortellini received speaker fees and grant consultancies by Astrazeneca, MSD, BMS, Roche, Novartis, Istituto Gentili and Astellas. Dr Alessandro Leonetti received speaker fees by Astrazeneca. Dr Raffaele Giusti received speaker fees and grant consultancies by Astrazeneca and Roche. Dr Alex Friedlaender received grant consultancies by Roche, Pfizer, Astellas and BMS. Dr Alfredo Addeo received grant consultancies by Takeda, MSD, BMJ, Astrazeneca, Roche and Pfizer. Dr Rita Chiari received speaker fees by BMS, MSD, Takeda, Pfizer, Roche and Astrazeneca. Dr Carlo Genova received speaker fees/grant consultancies by Astrazeneca, BMS, Boehringer-Ingelheim, Roche and MSD.

### **References.**

1. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* 2016;375(19):1823-1833. doi:10.1056/NEJMoa1606774
2. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell

Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *J Clin Oncol*. 2019;37(7):537-546. doi:10.1200/JCO.18.00149

3. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 May 31;378(22):2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Apr 16.

4. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 Nov 22;379(21):2040-2051. doi: 10.1056/NEJMoa1810865. Epub 2018 Sep 25.

5. Zhou Y, Lin Z, Zhang X, et al. First-line treatment for patients with advanced non-small cell lung carcinoma and high PD-L1 expression: pembrolizumab or pembrolizumab plus chemotherapy. *Journal for immunotherapy of cancer* 2019;7:120.

6. Addeo A, Banna GL, Metro G, et al. Chemotherapy in Combination With Immune Checkpoint Inhibitors for the First-Line Treatment of Patients With Advanced Non-small Cell Lung Cancer: A Systematic Review and Literature-Based Meta-Analysis. *Frontiers in oncology* 2019;9:264.

7. Pathak R, De Lima Lopes G, Yu H, et al. Comparative efficacy of chemoimmunotherapy versus immunotherapy for advanced non-small cell lung cancer: A network meta-analysis of randomized trials. *Cancer*. 2020 Oct 29. doi: 10.1002/cncr.33269.

8. Brahmer JR, Rodríguez-Abreu D, Robinson AG, et al. KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS)  $\geq 50\%$ . *Annals of Oncology* (2020) 31 (suppl\_4): S1142-S1215. 10.1016/annonc/annonc325.

9. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830. doi:10.1016/S0140-6736(18)32409-7

10. Cortellini A, Ficorella C, Crisci R, Divisi D. A reflection on the actual place of osimertinib in the treatment algorithm of EGFR-positive non-small cell lung cancer patients. *Journal Of Thoracic Disease*. 2020. 12(2). doi:10.2103/jtd-20-1733.

11. Freeman AT, Lesperance M, Wai ES, et al. Treatment of non-small-cell lung cancer after progression on nivolumab or pembrolizumab. *Curr Oncol*. 2020;27(2):76-82. doi:10.3747/co.27.5495

12. Cortellini A, Tiseo M, Banna GL, et al. Clinicopathologic correlates of first-line pembrolizumab effectiveness in patients with advanced NSCLC and a PD-L1 expression of  $\geq 50\%$ . *Cancer Immunol Immunother*. 2020 Nov;69(11):2209-2221. doi: 10.1007/s00262-020-02613-9. Epub 2020 May 30.
13. Cortellini A, Friedlaender A, Banna GL, et al. Immune-related Adverse Events of Pembrolizumab in a Large Real-world Cohort of Patients With NSCLC With a PD-L1 Expression  $\geq 50\%$  and Their Relationship With Clinical Outcomes. *Clin Lung Cancer*. 2020 Jun 21:S1525-7304(20)30204-7. doi: 10.1016/j.clcc.2020.06.010. Epub ahead of print.
14. Cortellini A, Ricciuti B, Tiseo M, et al. Baseline BMI and BMI variation during first line pembrolizumab in NSCLC patients with a PD-L1 expression  $\geq 50\%$ : a multicenter study with external validation. *J Immunother Cancer*. 2020 Oct;8(2):e001403. doi: 10.1136/jitc-2020-001403.
15. Kim C, Hoang CD, Kesarwala AH, Schrupp DS, Guha U, Rajan A. Role of Local Ablative Therapy in Patients with Oligometastatic and Oligoprogressive Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2017 Feb;12(2):179-193. doi: 10.1016/j.jtho.2016.10.012. Epub 2016 Oct 22
16. Gridelli C, Balducci L, Ciardiello F, et al. Treatment of Elderly Patients With Non-Small-Cell Lung Cancer: Results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology. *Clin Lung Cancer*. 2015 Sep;16(5):325-33.
17. Cortellini A, De Giglio A, Cannita K, et al. Smoking status during first line immunotherapy and chemotherapy in NSCLC patients: a case-control matched analysis from a large multicenter study. SUBMITTED 2020.
18. Davies J, Patel M, Gridelli C, de Marinis F, Waterkamp D, McCusker ME. Real-world treatment patterns for patients receiving second-line and third-line treatment for advanced non-small cell lung cancer: A systematic review of recently published studies. *PLoS One*. 2017;12(4):e0175679. Published 2017 Apr 14. doi:10.1371/journal.pone.0175679
19. Park SE, Lee SH, Ahn JS, et al. Increased Response Rates to Salvage Chemotherapy Administered after PD-1/PD-L1 Inhibitors in Patients with Non-Small Cell Lung Cancer, *J. Thorac. Oncol*. 13 (2018) 106–111. <https://doi.org/10.1016/j.jtho.2017.10.011>.
20. Schvartsman G, Peng SA, Bis G, et al. Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer, *Lung Cancer*. 112 (2017) 90–95. <https://doi.org/10.1016/j.lungcan.2017.07.034>.

21. Kato R, Hayashi H, Chiba Y, et al. Propensity score-weighted analysis of chemotherapy after PD-1 inhibitors versus chemotherapy alone in patients with non-small cell lung cancer (WJOG10217L). *J Immunother Cancer*. 2020;8(1):e000350. doi:10.1136/jitc-2019-000350
22. Bersanelli M, Buti S, Giannarelli D, et al. Chemotherapy in non-small cell lung cancer patients after prior immunotherapy: The multicenter retrospective CLARITY study. *Lung Cancer*. 2020 Oct 22;150:123-131. doi: 10.1016/j.lungcan.2020.10.008. Epub ahead of print.
23. Facchinetti F, Mazzaschi G, Barbieri F, et al. First-line pembrolizumab in advanced non-small cell lung cancer patients with poor performance status. *Eur J Cancer*. 2020 May;130:155-167. doi: 10.1016/j.ejca.2020.02.023. Epub 2020 Mar 25.
24. Friedlaender A, Metro G, Signorelli D, et al. Impact of performance status on non-small-cell lung cancer patients with a PD-L1 tumour proportion score  $\geq 50\%$  treated with front-line pembrolizumab. *Acta Oncol*. 2020 Sep;59(9):1058-1063. doi: 10.1080/0284186X.2020.1781249. Epub 2020 Jun 17.
25. Metro G, Addeo A, Signorelli D, et al. Outcomes from salvage chemotherapy or pembrolizumab beyond progression with or without local ablative therapies for advanced non-small cell lung cancers with PD-L1  $\geq 50\%$  who progress on first-line immunotherapy: real-world data from a European cohort. *J Thorac Dis*. 2019 Dec;11(12):4972-4981. doi: 10.21037/jtd.2019.12.23.
26. Campbell AM, Cai WL, Burkhardt D, et al. Final Results of a Phase II Prospective Trial Evaluating the Combination of Stereotactic Body Radiotherapy (SBRT) with Concurrent Pembrolizumab in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) *International Journal of Radiation Oncology\*Biography\*Physics*. 2019. Vol: 105, Issue: 1, Page: S36-S37
27. Talbot D, Fish SM, Jin Ong T, et al. 1497P - Second-line (2L) real-world treatment (tx) patterns and outcomes in patients (pts) with advanced/metastatic non-small cell lung cancer (NSCLC) treated with first-line (1L) immuno-oncology (IO) monotherapy (mono tx). *Annals of Oncology* (2019) 30 (suppl\_5): v602-v660. 10.1093/annonc/mdz260.

**Tables/Figures legend:**

**Table 1:** Patients' characteristics. \* available for 488 patients; ¥ available for 617 patients.

**Table 2:** Patients' characteristics at second line treatment commencement. \* available for 488 patients; ¥ available for 154 patients.

**Table 3:** Univariate and multivariate analyses for II line PFS and II line OS. ¥ available for 154 patients. UVA: univariate analysis; MVA: multivariate analysis.

**Supplementary Table 1:** List of the participating centres.

**Figure 1:** Study's flow diagram

**Figure 2:** Kaplan-Meier survival estimate of post-progression overall survival according to the therapeutic strategies chosen by clinicians at the moment of progressive disease (PD): patients who received pembrolizumab beyond PD (ByPD), (with or without local ablative treatments - LATs) and patients who received other post-progression systemic treatments (switched approach).

**Figure 3:** Kaplan-Meier survival estimate of II line progression free survival (PFS) (A) and II line overall survival (OS) (B) according to the received second-line regimen: platinum-based doublet chemotherapy, single-agent chemotherapy and other regimens.