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

ARTICLE TYPE

Running title: smoking status during immunotherapy.

TITLE

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Abstract

Background:
Methods:
Results:
Conclusions:
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Keywords: non-small cell lung cancer; immunotherapy; smoking; pembrolizumab.

Introduction

The Keynote-024 trial has established single agent pembrolizumab as the standard of care for advanced NSCLC patients with a PD-L1 expression ≥ 50% [1-2]. However, after the Keynote-189 and Keynote-407 trials, this algorithm is currently challenged by the chemo-immunotherapy combination [3-4], since no head-to-head randomized controlled trial (RCT) has compared the two strategies in the PD-L1 high subgroup.

Even though some metanalyses suggested that there is an incremental benefit for the addition of chemotherapy to first-line immunotherapy, with respect of response rate and progression free survival (PFS) [5], and among patient with PD-L1 low expression [6], also the increased toxicity of a triplet regimen, compared to a single-agent checkpoint inhibitor, has to be considered.

Against 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

≥ 50%. From that perspective, post-progression analyses of RCTs revealed conflicting results. Among the 154 patients of the experimental arm of the Keynote-024 trial, 51.9% had received a further treatment line at the last data-analysis [7], while among the 637 patients of the experimental arm of the Keynote-042 trial, 38% had received a subsequent anticancer therapy [8].

Importantly, it is well known that in NSCLC clinical practice, a not negligible portion of patients is used to experiencing life threatening disease progression, without reaching the subsequent treatment line, in all disease settings, including immunotherapy [9-10]. Recently, we published a large real-world multicentre study of metastatic NSCLC patients with PD-L1 expression ≥ 50%, receiving first line single agent pembrolizumab at 34 European institution, aimed at investigating the clinicopathologic correlates of efficacy [11-13].

To provide a further insight about clinical outcomes of NSCLC patients with PD-L1 high expression after disease progression, we performed an update of the abovementioned cohort, with a particular focus on post-progression outcomes.

Materials and Methods

Study Design

We performed a data update of a cohort of metastatic NSCLC patients with PD-L1 expression ≥ 50%, consecutively treated with first line pembrolizumab monotherapy, from January 2017 to May 2020. 31 institutions participated to this analysis (Supplementary file 1).

The aim of this analysis was to evaluate the post-progression clinical outcomes including treatment beyond disease progression 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 [11-13]. In order to be closer to the real-life scenario, both patients who experienced radiological disease progression and those who experienced clinical progression according to the investigators have been included.

PpOS was defined as the length of time between the first occurrence of progressive disease 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 disease progression, categorized as: patients who received pembrolizumab beyond disease

progression (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-progressive disease [14], 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 relationships between baseline patients' features and the post-progression outcome (categorized as no post-progression treatments, pembrolizumab ByPD and switched approach), were evaluated for the following clinicopathologic characteristics: age (<70 vs ≥ 70 years old) [15], gender (male vs female), Eastern Cooperative Oncology Group—PS (ECOG-PS) (0 vs 1 vs ≥2), central nervous system (CNS) metastases (yes vs no), bone metastases (yes vs no), liver metastases (yes vs no), BMI according to the World Health Organization categories [16-17], PD-L1 tumour expression (< 90% vs ≥ 90%)[11], smoking status (current vs former vs never smoker) [18], and corticosteroids administration within the 30 days before treatment commencement (dose equivalent or higher to 10 mg prednisone per day) (yes vs no) [11].

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. Data cut-off period was September 2020.

Statistical analysis

Descriptive statistic was used to report patients' characteristics. Median ppOS, II line PFS and II line OS were evaluated using the Kaplan-Meier method. Median period of follow-up was calculated according to the reverse Kaplan-Meier method. $\chi 2$ test was used for the correlation analyses. Long-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 ≥ 50%. At the median follow-up of 22.7 months (95%CI: 21.6 – 38.2), 678 patients (69.6%) experienced disease progression and the post-progression median follow-up was 14.4 months (95%CI: 11.9 – 33.1). Figure 1 reports the study's flow diagram. All the baseline characteristics of the patients who experienced disease progression are summarized in table 1.

At the data cut of, 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%]). Table 1 also reports the correlation analysis between baseline clinicopathologic characteristics and the post-progression outcome. There was a significant association with older age ($p = 0.0011$), higher ECOG-PS ($p < 0.0001$) and baseline corticosteroids administration ($p = 0.0024$), particularly towards patients who did not received further treatments.

1 patient (2.7%) received surgery, 1 patient (2.7%) received radiation therapy (RT) plus surgery and 35 patients (94.6%) received 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 ($p < 0.0001$).

The median ppOS of the 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 Cox regression, the median ppOS of patients who received pembrolizumab ByPD in combination with LATs resulted to be significantly longer compared to median ppOS of patients 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).

II line PFS and II line OS analysis.

At the data cut off, 241 (35.5%) among the 678 patients who had experienced disease progression, received a second line systemic treatment. 191 patients (79.3%) received a platinum-based doublet chemotherapy, 44 patients (18.3%) a single agent chemotherapy and 6 patients (2.5%), other regimens. 46 patients (19.1%) had received previous pembrolizumab ByPD, while 195 (80.9%) had not.

The updated patients' characteristics are summarized in Table 2. Compared to the baseline (at the first line treatment commencement), at the second line commencement there was a significantly higher portion of patients aged under 70 years old (p = 0.0244), with CNS metastases (p = 0.0001), with bone metastases (p = 0.0266) and with liver metastases (p = 0.0148). Importantly, there was also a significant trend towards a poorer ECOG-PS (p < 0.0001).

The second line median follow-up was 12.1 months (95%CI: 10.5 – 32.5). Patients who received platinum-based doublet chemotherapy had a median II-PFS of 4.1 months (95%CI: 3.2 – 5.3; 162 events), while patients who 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 who received platinum-based doublet chemotherapy, 5.3 months (95%CI: 2.7 – 6.9; 34 events) for patients who received single agent chemotherapy and 3.4 months (95%CI: 1.3 – 7.9; 5 events) for patients who received other regimens (log-rank test: 0.0289) (Figure 3B).

Table 3 summarized the univariate and multivariate analyses of II line PFS and II line OS. At the multivariate analysis only ECOG-PS ≥ 2 was confirmed to be significantly associated to an increased risk of disease progression compared to ECOG-PS 0 (HR = 3.09 [95%CI: 1.84 – 5.19], p < 0.001). On the contrary, patients receiving other regimens were confirmed to have an increased risk of death compared to those receiving platinum-based doublet chemotherapy (HR = 2.53 [95%CI: 1.02 – 6.27]; p = 0.0447), as well as patients

with an ECOG-PS ≥ 2 compared to ECOG-PS 0 (HR = 3.65 [95%CI: 1.93 – 6.92], p = 0.0001).

Discussion

The advanced line setting has been always considered a sticking point, nevertheless the advent of immune checkpoint inhibitors in the treatment algorithm of NSCLC patients has been changing the game. Recently, a review of real-world observational studies reported a median OS ranging from 4.6 to 12.8 months for the second line setting [19], and our ppOS results, ranging from 8.0 months to 13.9 months, are somehow aligned to the incremental benefit already reported in the post-immunotherapy setting [20-23].

However, the findings to consider first are the 55.9% of patients who had not received any further treatment at the data cut off, and the 52.9% who died without receiving subsequent treatments. These results are slightly worse than what reported in clinical trial [7-8], reflecting the real-world scenario. It has been already confirmed that NSCLC patients with a PD-L1 expression ≥ 50% and poor baseline PS, particularly those whose PS is related to the burden of disease [24], are used to experiencing worse outcomes with first line single agent pembrolizumab [25]. Considering that patients with ECOG-PS ≥ 2 are usually not enrolled in RCT, our results can probably be considered the downside of having included patients with poor PS.

Concordantly, the correlation analysis revealed that baseline characteristics which resulted to be significantly associated to the post-progression outcome, particularly to not having received further treatments, are typical features of patients' frailty, including older age (p = 0.0011), ECOG-PS (p 0.0001) and baseline corticosteroids administration (p = 0.0024). These results suggest that older patients, with a poor baseline PS and on systemic corticosteroids, are more likely to experience life-threatening disease progression, with higher chances of not receiving further treatments. Therefore, with respect of treatment sequencing for patients with a PD-L1 expression ≥ 50% (first line immunotherapy, followed by second line chemotherapy), an as much as possible tailored decision making process should be considered at the first line treatment commencement. However, we would do well to consider that unfit 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 to similar studies reported in the setting [26]. Considering that patients who received pembrolizumab ByPD in combination with LATs experienced a significantly longer ppOS, a combinational approach should

always be taken into consideration at disease progression. However, LATs were more likely performed in patients with oligo-progressive disease ($p < 0.0001$), and we must not fail in taking into consideration the prognostic implication of oligoprogression [14].

The II line PFS and II line OS analysis revealed that patients who had reached the second line setting tend to be younger, as older patients are more likely to did not receive further treatments. II line patients were also characterized by a higher proportion of CNS, bone and liver metastases, with a significant trend towards a poorer ECOG-PS, probably due to the natural history of the disease, which tends to get worse across treatment lines.

The negative baseline characteristics might 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 [22-23, 27]. Even though we found an incremental benefit for patients who received platinum-based doublet chemotherapy, ECOG-PS remains the major determinant of II line PFS and II line OS.

Conclusion

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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 provice 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.

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Tables/Figures legend:

Table 1:

Supplementary Table 1:

Supplementary Table 2:

Figure 1:

Figure 2:

Figure 3: