Immune-related Adverse Events of Pembrolizumab in a Large Real-world Cohort of Patients With NSCLC With a PD-L1 Expression ≥ 50%

Journal Pre-proof

Immune-related adverse events of pembrolizumab in a large real-world cohort of NSCLC patients with a PD-L1 expression ≥ 50% and their relationship with clinical outcomes.

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MICROABSTRACT

Immune-related adverse event profile of pembrolizumab in a large real world cohort of NSCLC patients with a PDL1 expression of ≥ 50% and their relationship with clinical outcomes.

The role of immune-related adverse events (irAEs) occurrence, as surrogate predictor of checkpoint inhibitors clinical efficacy has not yet been described in the setting of first line single agent pembrolizumab for metastatic non-small-cell-lung-cancer (NSCLC) patients with a PD-L1 (programmed death-ligand 1) expression of ≥ 50%. 1010 patients were evaluated and after a 6-weeks landmark selection, 877 patients were included We confirmed irAEs profile of first-line single agent pembrolizumab, in a large real-life cohort of NSCLC patients with PD-L1 expression of ≥ 50%. The occurrence of irAEs might be considered a surrogate of clinical activity and improved outcomes also in this setting.

Running title: irAEs during first line pembrolizumab in NSCLC patients.

Immune-related adverse events of pembrolizumab in a large real-world cohort of NSCLC patients with a PD-L1 expression ≥ 50% and their relationship with clinical outcomes.

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Abstract

Background: The role of immune-related adverse events (irAEs), as a surrogate predictor of the efficacy of checkpoint inhibitors has not yet been described in the setting of first line, single agent pembrolizumab for metastatic non-small-cell-lung-cancer (NSCLC) patients with a PD-L1 (programmed death-ligand 1) expression of ≥ 50%.

Methods: We previously conducted a multicenter retrospective analysis in patients with treatment-naïve metastatic NSCLC and a PD-L1 expression of ≥ 50% receiving first line pembrolizumab. Here we report the results of the irAEs analysis and the potential correlation between irAEs and clinical outcomes.

Results: 1010 patients were included in this analysis; after a 6-weeks landmark selection, 877 patients (86.8%) were included in the efficacy analysis. Any grade irAEs ($p < 0.0001$), G3/G4 irAEs ($p = 0.0025$), LTD (leading to discontinuation) irAEs (0.0144), multiple-site and single-site irAEs ($p < 0.0001$), cutaneous irAEs ($p = 0.0001$), endocrine irAEs ($p = 0.0227$), pulmonary irAEs ($p = 0.0479$) and rheumatologic irAEs ($p = 0.0018$), were significantly related to a higher ORR (objective response rate). Any grade irAEs ($p < 0.0001$), single-site irAEs ($p < 0.0001$), multiple-site irAEs ($p = 0.0005$), cutaneous irAEs $p = 0.0042$), endocrine irAEs ($p < 0.0001$), GI irAEs ($p = 0.0391$), rheumatologic irAEs ($p = 0.0086$) were significantly related to PFS (Progression Free Survival). Any grade irAEs ($p < 0.0001$), single-site irAEs ($p < 0.0001$), multiple-site irAEs ($p = 0.0003$), cutaneous irAEs $p = 0.0002$), endocrine irAEs ($p = 0.0001$) and rheumatologic irAEs ($p = 0.0214$) were significantly related to OS (Overall Survival).

Conclusions: This study confirms the feasibility and the safety of first-line, single agent pembrolizumab, in a large real-world cohort of NSCLC patients with PD-L1 expression ≥ 50%. The occurrence of irAEs may be a surrogate of clinical activity and improved outcomes in this setting.

Keywords: PD-L1, pembrolizumab, NSCLC, irAEs, first line.

Introduction

The role of immune-related adverse events (irAEs), as a surrogate predictor of the efficacy of immune-checkpoint inhibitors has previously been described in a variety of malignancies [1, 2]. Studies reported an association between the incidence of irAEs and improved outcomes, including among patients with non-small-cell-lung-cancer (NSCLC) receiving PD-1/PD-L1 (programmed death-1/programmed death-ligand 1) inhibitors in different treatment lines [3-6]. Metastatic NSCLC patients with a PD-L1 expression ≥50%, lacking *EGFR* mutations and *ALK* rearrangements, are a subset of patients for which there are limited data about the association between irAEs and clinical outcomes.

Since the publication of the Keynote-024 trial, single agent pembrolizumab has become the standard of care for patients with PD-L1 ≥ 50% [7-9], while the combination of pembrolizumab with platinum-based doublets is an alternative [10-12].

Recently, we published a large real-world, multicenter study of metastatic NSCLC patients with PD-L1 ≥ 50%, receiving first line, single agent pembrolizumab at 34 European institutions, and aiming to investigate the clinical-pathologic correlates of efficacy [13].

In this report, we present the results of the irAEs analysis, with the assessment of a potential correlation between irAEs and clinical outcomes within the study population.

Materials and Methods

Study design

We evaluated the irAE profile within the study population of a real world multicenter retrospective study evaluating metastatic NSCLC patients with a PD-L1 expression ≥ 50%, consecutively treated with first line pembrolizumab monotherapy, from January 2017 to October 2019, at 34 institutions (Supplementary file 1) [13]. The aim of this analysis was to evaluate the incidence of irAEs in the real-world setting and to assess the correlation between irAEs and clinical outcomes.

Measured clinical outcomes were: objective response rate (ORR), median progression free survival (PFS) and median overall survival (OS). Patients were assessed with radiological imaging according to the local clinical practice; RECIST (v. 1.1) criteria were used [14], but treatment beyond disease progression was allowed when clinically

indicated. ORR was defined as the portion of patients experiencing an objective response (complete or partial response) as best response to immunotherapy. PFS was defined as the time from treatment initiation to disease progression or death, whichever occurred first. OS was defined as the time from treatment initiation to death.

Univariate and multivariate analyses (using a stepwise selection of covariates, with an entry significance level of 0.05) were performed according to the following covariates: sex (male *vs* female), Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0-1 *vs* ≥ 2), age (< 70 *vs* ≥ 70 years old) [15], disease burden (≤ 3 *vs* > 3 systems/organs involved, including the primary tumor) and histology (Squamous *vs* Non-squamous).

A $\chi 2$ test was used to compare ORR and the incidence of irAEs among subgroups and the odds ratios (OR) with 95% confidence intervals (95%CI) were computed. Logistic regression was used for the multivariate analysis of ORR. Median PFS and median OS were evaluated using the Kaplan-Meier method. Median follow-up was calculated according to the reverse Kaplan-Meier method. Cox proportional hazards model was used to evaluate predictor variables in univariate and multivariate analysis for PFS and OS.

As the incidence of irAEs is "time-dependent" [16], we can suppose that patients who progressed or interrupted anti-PD-1 therapy quickly, were exposed to the potential "triggering effect" for a shorter time. Therefore, these patients had a lower risk of experiencing irAEs. In order to overcome the lack of data availability regarding the timing of irAEs, the efficacy analysis was performed after a 6-week landmark selection [4-6], including only patients with a minimum follow-up of PFS of 6 weeks, regardless of disease progression.

The data cut-off period was January 2020. All statistical analyses were performed using MedCalc Statistical Software version 18.6 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

PD-L1 determination

PD-L1 expression evaluation was performed using a variety of immunohistochemical antibodies and platforms according to local institutional clinical practice (including the 22C3, SP263, E1L3N, and 28-8 antibodies) as previously reported [13]. As the tumor

proportion score (TPS) evaluation is validated only with the 22C3 antibody [17], we referred only to "PD-L1 expression" in our study.

Categorization and definition of single/multiple-site irAEs

Immune-related AEs were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE; version 4.0) and cumulatively reported. Subgroup analyses were performed according to any grade irAEs, G3/G4 irAEs and irAEs leading to discontinuation (LTD). LTD irAEs were defined as any irAEs which caused a permanent interruption of the immunotherapy, regardless of the severity. As there have been reports that irAEs with a clinical impact (such as LTD irAEs and pulmonary irAEs) are related to worse clinical outcomes [18-20], we added an ancillary analysis of ORR, PFS and OS according to the G3/G4 irAEs, pulmonary irAEs and LTD irAEs, among patients who experienced at least one irAEs of any grade.

We categorized irAEs on the basis of the organ/system involved as follows: cutaneous irAEs, endocrine irAEs (including thyroid disorders), gastro-intestinal (GI) irAEs, hepatic irAEs, pulmonary irAEs, rheumatologic irAEs, neuro-muscular irAEs and others irAEs, which include fever, anorexia and asthenia [21]. We defined irAEs as “single-site” if the patient experienced just one category of irAEs and “multiple-site” among patients who experienced irAEs belonging to different categories [6]. Patients were monitored clinically at every pre-administration visit (according to the technical files of the drugs) and, subsequently, as clinically indicated by the investigators.

Results

Patient characteristics

One thousand and ten consecutive patients with metastatic NSCLC with a PD-L1 expression ≥ 50% were included in this analysis. After the 6-week landmark selection, 877 patients (86.8%) were included in the efficacy analysis. Patient characteristics of the entire study population and of the landmark-selected cohort are summarized in Table 1.

Immune-related adverse events analysis

In the overall study population, 333 patients (32.9%) experienced any grade irAEs and 101 patients (10.0%) experienced G3/G4 irAEs. 92 patients (9.1%) experienced LTD irAEs. Among the landmark-selected patients, 326 patients (37.2%) experienced any

grade irAEs, 97 patients (11.1%) experienced G3/G4 irAEs and 89 patients (10.1%) experienced LTD irAEs. All irAEs are summarized in Table2.

In Table 3, we detail the incidence of irAEs and patient characteristics. Patient sex ($p = 0.4877$), age ($p = 0.7670$) and histology ($p = 0.4260$) were not significantly related to the incidence of any grade irAEs. On the other hand, ECOG-PS ≥ 2 ($p = 0.0003$) and burden of disease ($p < 0.0001$) were related to a lower incidence of any grade irAEs.

Efficacy analysis

Univariate and multivariate analysis for ORR are detailed in Table 4. Overall, after the 6-week landmark selection, 805 patients were evaluable for disease response and the ORR was 48.9% (95%CI: 44.2-54.0). At the univariate analysis any grade irAEs ($p < 0.0001$), G3/G4 irAEs ($p = 0.0025$), LTD irAEs (0.0144), multiple-site and single-site irAEs ($p < 0.0001$), cutaneous irAEs ($p = 0.0001$), endocrine irAEs ($p = 0.0227$), pulmonary irAEs ($p = 0.0479$) and rheumatologic irAEs ($p = 0.0018$), were associated with a significantly higher ORR. After adjusting for ECOG-PS and burden of disease, all but pulmonary irAEs were confirmed independent predictor of an increased ORR at the multivariate analysis.

The median follow-up was 14.8 months (95%CI: 13.7 – 15.8); median PFS was 12.7 months (95% CI: 10.7 – 14.2; 435 events) and median OS was 27.4 moths (95% CI: 19.9 – 27.4; 575 censored patients).

Median PFS in patients who experienced irAEs of any grade was 19.9 months (95% CI: 16.4 – 26.3), while median PFS in patients who did not was 7.8 months (95% CI: 6.5 – 9.8) (Figure 1A). Median PFS in patients who experienced G3/G4 irAEs was 17.4 months (95% CI: 10.9 – 26.2), while median PFS in patients who did not was 12.2 months (95% CI: 9.8 – 13.9) (Figure 1B). Median PFS in patients who experienced LTD irAEs was 15.2 months (95% CI: 10.7 – 19.9), while median PFS in patients who did not was 12.7 months (95% CI: 9.8 – 14) (Figure 1C). As shown in Table 5, any grade irAEs ($p < 0.0001$), single-site irAEs ($p < 0.0001$), multiple-site irAEs ($p = 0.0005$), cutaneous irAEs p = 0.0042), endocrine irAEs ($p < 0.0001$), GI irAEs ($p = 0.0391$), rheumatologic irAEs ($p = 0.0086$) were significantly related to PFS at the univariate analysis, as well as ECOG-PS ($p < 0.0001$) and disease burden ($p < 0.0001$). Any grade irAEs, single-site and multiple-site irAEs, endocrine irAEs, GI irAEs and rheumatologic irAEs were confirmed independent predictor of prolonged PFS at the multivariate analysis.

Median OS in patients who experienced any grade irAEs was not reached, while median OS in patients who did not was 16.1 months (95%CI: 13.6 – 27.4) (Figure 2A). Median OS in patients who experienced G3/G4 irAEs was not reached, while median OS in patients who did not was 27.4 months (95%CI: 19.1 – 27.5) (Figure 2B). Median OS in patients who experienced LTD irAEs was not reached, while median OS in patients who did not was 27.5 months (95%CI: 19.1 – 27.4) (Figure 2C). As shown in Table 6, any grade irAEs ($p < 0.0001$), single-site irAEs ($p < 0.0001$), multiple-site irAEs ($p = 0.0003$), cutaneous irAEs $p = 0.0002$), endocrine irAEs ($p = 0.0001$) and rheumatologic irAEs ($p = 0.0214$) were significantly related to OS at the univariate analysis, as well as ECOG-PS ($p < 0.0001$) and disease burden ($p < 0.0001$). Any grade irAEs, single-site and multiple-site irAEs, cutaneous irAEs, endocrine irAEs and rheumatologic irAEs were confirmed independent predictor of prolonged OS at the multivariate analysis.

Ancillary analysis of more clinical impacting irAEs

Table 7 summarizes the ancillary analysis performed on the patients who experienced at least one irAE of any grade, according to the occurrence of G3/G4 irAEs, LTD irAEs and pulmonary irAEs. Contrary to what was found in the overall population, neither G3/G4, LTD nor pulmonary irAEs were significantly associated with ORR. There was a statistically significant association between LTD irAEs and shorter PFS in the univariate analysis (HR = 1.55 [95%CI: 1.08-2.22], $p = 0.0169$), but not the multivariate analysis. No other significant findings regarding PFS and OS were reported (Table 7).The HRs for disease progression and death among patients who experienced G3/G4, LTD and pulmonary irAE was worse than in the overall population.

Discussion

Compared to the Keynote-024 trial [7], the incidence of any grade irAEs, G3/G4 irAEs and LTD irAEs in our study population was slightly higher. Moreover, the spectrum of irAEs is in line with what has been described in both clinical trials and real life studies with PD-1/PD-L1 inhibitors across different malignancies [6, 22-24]. Therefore, we confirm the feasibility and safety of first-line, single agent pembrolizumab, in a large real-world cohort of NSCLC patients with PD-L1 expression ≥ 50%, including frail patients with poor performance status, who are usually not enrolled in clinical trials.

As previously described [6, 24], single-site irAEs were more frequent than multiple-site irAEs. IrAEs result from an aberrant immune self-response, and it is reasonable to assume that, as in autoimmune disorders [25], the pathologic mechanisms of irAEs are based on tissue-specific T-cell and B-cell mediated cross-reactions. Berner *et al.* confirmed the association between cutaneous irAEs in NSCLC patients treated with PD-1 inhibitors and the likelihood to respond. They identified highly immunogenic antigens shared both by the skin and lung tumor [26].

As stated, several studies have described a significant association between irAEs and improved clinical outcomes with checkpoint inhibitors, even in NSCLC patients [1-2]. However, to date, only one real world study, with a relatively small sample size, investigated this association in the setting of NSCLC patients with PD-L1 expression ≥ 50% receiving first line pembrolizumab, finding a significant association with improved PFS [18]. Contrary to what was reported in previous studies with PD-1/PD-L1 inhibitors [6, 23, 27-28], sex was not related to the incidence of any grade irAEs, while ECOG-PS and burden of disease were [29]. Nevertheless, we have to take into account that in the study population sex did not affect survival, while the greater incidence of irAEs among female patients in other studies could result from increased drug exposure, since females had a longer PFS.

Thanks to the large sample size, our analysis revealed a concordant correlation between irAEs occurrence and ORR, PFS and OS in the multivariate analyses. In contrast to what we reported in our previous study in NSCLC patients [6], GI irAEs were not associated with an improved ORR and OS. Within the overall population, G3/G4 irAEs and LTD irAEs were significantly associated with a higher ORR, but not with prolonged PFS and OS. Similarly, pulmonary irAEs were predictive of higher ORR, but not a prolonged PFS and OS. We did not detect improved clinical outcomes among patients who experienced G3/G4, LTD and pulmonary irAEs. Moreover, the HRs for disease progression and death in these groups were increased compared to the overall population. From this perspective, it appears as though more clinically impacting irAEs, may lead to more serious sequelae, impairing the clinical benefit, countering the potential benefit of immune activation. On the other hand, data emerging from clinical trials revealed that patients who discontinued immunotherapy due to irAEs achieved similar outcomes to those who continued therapy [30, 31], suggesting that even after discontinuation, many patients may continue to derive clinical benefit.

As a whole, the evidence supporting that irAEs could be considered a surrogate of clinical benefit with immune checkpoint inhibitors, might affect the clinical management of irAEs. If it is true that patients experiencing irAEs achieve better response and survival, clinicians may more readily discontinue immunotherapy in case of adverse events, precisely because they reassured by this evidence. However, we must not reach hasty conclusions, and strict adherence to international guidelines for the management of irAEs is always recommended [32, 33].

Even performing the 6-week landmark analysis, we were not able to completely prevent the immortal time bias, which states that longer exposure time, equates a greater risk of toxicity, namely irAEs [34]. In a recent post-hoc analysis of the Keynote-054 trial, Eggermont *et al.* used a time-dependent Cox model to confirm that the occurrence of irAEs was strongly related to an improved relapse-free survival in melanoma patients who received 12-months of adjuvant pembrolizumab [35]. Although PD-1/PD-L1 checkpoint inhibitors seem to have a dose-independent relationship with regards to the incidence and severity of irAEs [36], without the data about the timing of irAEs in our cohort, we cannot perform a time-adjusted analysis. Therefore, we are unable to draw firm conclusions. Among the limits of our study, we must also recognize the retrospective design which exposes us to the risk of selection bias, as data are lacking regarding pre-existing autoimmune disease [23], the management of the irAEs, and the lack of centralized data review (imaging and toxicity).

Conclusion

This study confirms the feasibility and the safety of first-line, single agent pembrolizumab, in a large real-world cohort of NSCLC patients with PD-L1 expression $\geq$ 50%, including frail patients, who are usually not enrolled in clinical trials. The occurrence of irAEs may be a surrogate of clinical activity and improved outcomes in this setting.

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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, Astellas and Ipsen. Dr. Melissa Bersanelli received research funding by Roche, Pfizer, Seqirus, AstraZeneca, Bristol-Myers Squibb, Novartis and Sanofi; she also received honoraria for advisory role and as speaker at scientific events by Bristol-Myers Squibb, Novartis and Pfizer. Dr. Marco Russano received honoraria for scientific events byRoche, Astrazeneca, Bristol-Myers Squibb, Merck Sharp & Dohme and Boehringer Ingelheim. Dr Emilio Bria received speaker and travel fees from MSD, Astra-Zeneca, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche. Dr Emilio Bria received grant consultancies by Roche and Pfizer. Dr. Alessandro Morabito received speaker fees by

Astra, Roche, BMS, MSD, Boehringer, Pfizer, Takeda. Dr Francesca Mazzoni received grant consultancies by MSD and Takeda. Dr Raffaele Gisti received speaker fees and grant consultancies by Astrazeneca and Roche. Dr Francesco Passiglia received grant consultancies by MSD and Astrazeneca.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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Table and Figure legend

Table 1: Patients' characteristics.

Table 2: Summary of immune-related adverse events.

Table 3: Univariate analyses of incidence of immune related adverse events of any grade.

Table 4: Univariate and multivariate analyses for Overall Response Rate. ¥ Chi-square for trend. * ECOG-PS and burden of disease were used as adjusting factor for the munltivariate analysis of each irAEs category.

Table 5: Cox proportional-hazards regression: univariate and multivariate analyses of Progression Free Survival. * ECOG-PS and burden of disease were used as adjusting factor for the multivariate analysis of each irAEs category.

Table 6: Cox proportional-hazards regression: univariate and multivariate analyses of Overall Survival. * ECOG-PS and burden of disease were used as adjusting factor for the multivariate analysis of each irAEs category.

Table 7: Clinical outcomes analysis according to G3/G4 irAEs, LTD irAEs and pulmonary irAEs among the patients who experience at least one irAEs. UVA:

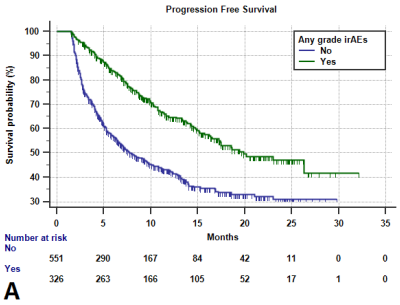
univariate analysis. MVA: multivariate analysis. * ECOG-PS and burden of disease were used as adjusting factor for the multivariate analysis of PFS.

Figure 1: Progression Free Survival Kaplan-Meier survival curves according to any grade irAEs occurrence (A), G3/G4 irAEs occurrence (B), LTD irAEs occurrence (C).

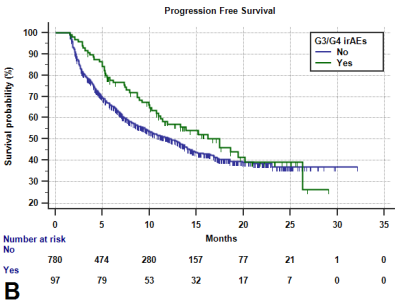
Figure 2: Overall Survival Kaplan-Meier survival curves according to any grade irAEs occurrence (A), G3/G4 irAEs occurrence (B), LTD irAEs occurrence (C).

Supplementary Table 1: list of the participating institutions.

Supplementary Figure 1: Patients flow diagram.



A



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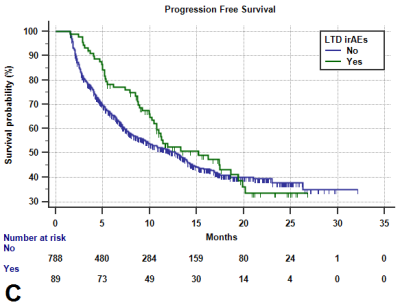

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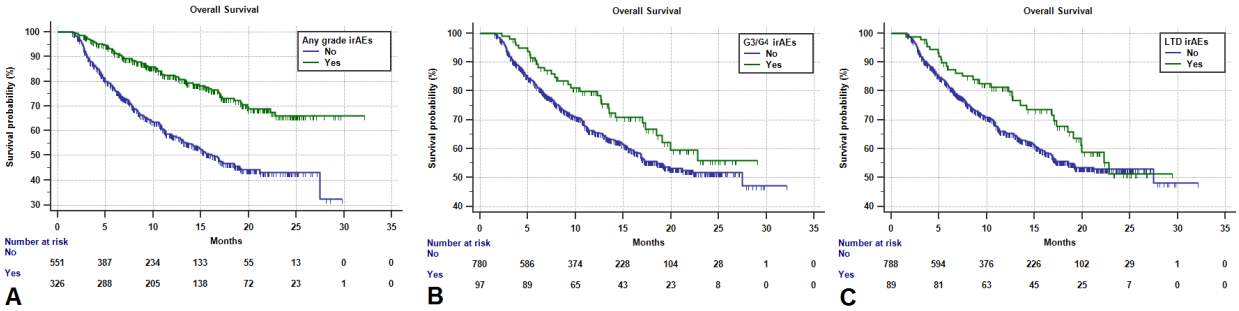
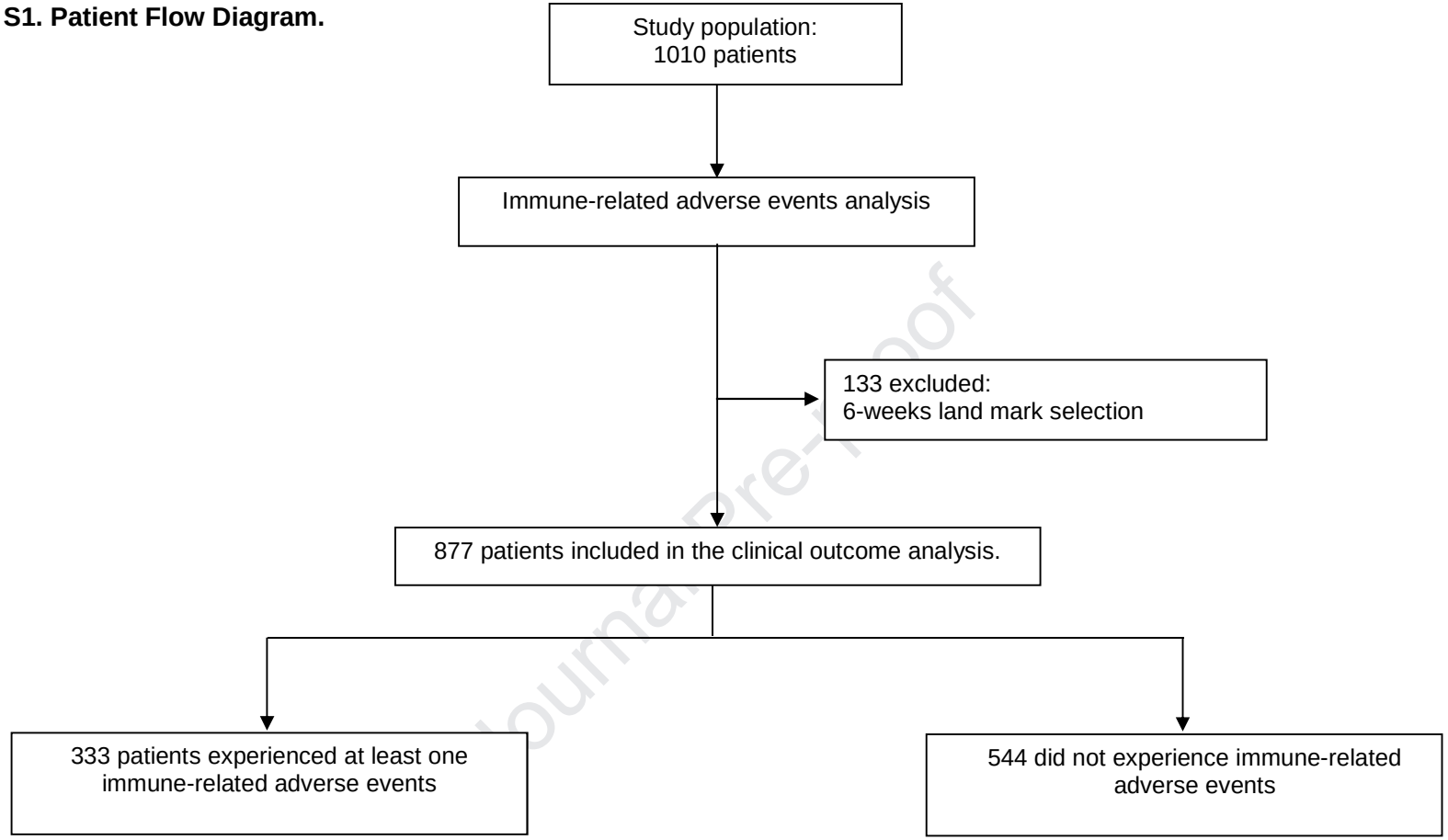


Figure S1. Patient Flow Diagram.



Institution	Department
St. Salvatore Hospital, University of L'Aquila, L'Aquila	Medical Oncology
SS Annunziata Hospital, Chieti	Medical Oncology
University Hospital of Parma, Parma	Medical Oncology
St. Camillo Forlanini Hospital, Rome	Pulmonary Oncology
University Hospital of Modena, Modena	Medical Oncology
S Maria Goretti Hospital, Latina	Medical Oncology
St. Andrea Hospital, Rome	Medical Oncology
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan	Medical Oncology
Campus Bio-Medico University, Rome	Medical Oncology
"Ospedali Riuniti" Hospital, Ancona	Medical Oncology
Policlinico Umberto I, Rome	Medical Oncology
Clinical Cancer Centre "Giovanni Paolo II", Bari	Thoracic Oncology Unit
Hospital of Fabriano, Fabriano	Medical Oncology
"Augusto Murri" Hospital, Fermo	Medical Oncology
St. Gerardo Hospital, Monza	Medical Oncology
IRCCS – Istituto Nazionale Tumori, Fondazione "G. Pascale", Napoli	Medical Oncology
IRCCS Sacro Cuore Don Calabria, Negrar	Medical Oncology
University Hospital of Udine, Udine	Medical Oncology
ASST-Sette Laghi, Varese	Medical Oncology
University Hospital "A.Gemelli", Rome	Comprehensive Cancer Center
"Madre Teresa Di Calcutta" Hospital Padova Sud, Monselice	Medical Oncology
Hospital of Macerata	Medical Oncology
"F. Spaziani" Hospital, Frosinone	Medical Oncology
"Careggi" University Hospital, Florence	Medical Oncology
AUSL Romagna, Ravenna	Department of Oncology and Hematology
"Monaldi" Hospital, Naples	Pneumo-Oncology Unit
Erasmus Medical Center, Rotterdam, the Netherlands	Department of Pulmonary Diseases
"San Luigi-Gonzaga" University Hospital, Orbassano	Department of Oncology
"Fondazione IRCCS Istituto Nazionale dei Tumori", Milan	Department of Medical Oncology
University Hospital of Cagliari, Cagliari	Medical Oncology
University Hospital of Geneva, Geneva	Medical Oncology
United Lincolnshire Hospital Trust, Lincoln	Medical Oncology

CLINICAL PRACTICE POINT

Immune-related adverse event profile of pembrolizumab in a large real world cohort of NSCLC patients with a PDL1 expression of ≥ 50% and their relationship with clinical outcomes.

What is already known about this subject?

Immune-related adverse events (irAEs) occurrence, might be considered a surrogate predictor of checkpoint inhibitors clinical efficacy, even in NSCLC. This association has not yet been described in the setting of first line single agent pembrolizumab for metastatic non-small-cell-lung-cancer (NSCLC) patients with a PD-L1 (programmed death-ligand 1) expression of ≥ 50%.

What are the new findings?

We analyzed 1010 treatment-naïve metastatic NSCLC and a PD-L1 expression of ≥ 50% receiving first line pembrolizumab, and after a 6-weeks landmark selection, 877 patients were included in the efficacy analysis. We confirmed the irAEs profile of first-line single agent pembrolizumab, in a large real-life cohort of NSCLC patients with PD-L1 expression of ≥ 50%. The occurrence of irAEs might be considered a surrogate of clinical activity and improved outcomes also in this setting.

How might it impact on clinical practice in the foreseeable future?

The safety profile of first line pembrolizumab is confirmed in a large real-life cohort, therefore outside the clinical trial framework. Even in this setting, irAEs occurrence might be considered a surrogate predictor of clinical benefit.

	Overall study population	Landmark-selected population
	N° (%) 1010	**N° (%) 877**
AGE, (years)		
Median	70.2	70.3
Range	28 – 92	28 – 92
Elderly (≥ 70)	518 (51.3)	456 (52.0)
Smoking status		
Never smokers	103 (10.2)	90 (10.3)
Former smokers	568 (56.2)	491 (56.0)
Current smokers	339 (33.6)	296 (33.7)
SEX		
Male	664 (65.7)	573 (65.3)
Female	346 (34.3)	304 (34.7)
ECOG PS		
0 - 1	836 (82.8)	760 (86.7)
≥ 2	174 (17.2)	117 (13.3)
Histology		
Squamous	246 (24.4)	211 (24.1)
Non-squamous	764 (75.6)	666 (75.9)
Burden of disease		
> 3 organs involved	515 (51.0)	414 (47.2)
≤ 3 organs involved	495 (49.0)	463 (52.8)

	Overall study population	Landmark-selected patients
	IrAEs of any grade (patients-%)	
All grade irAEs (any)	**333 (32.9)**	**326 (37.2)**
Cutaneous	100 (30.0)	100 (30.7)
Endocrine	89 (26.7)	89 (27.3)
Gastro-intestinal	70 (21.0)	68 (20.9)
Haepatic	28 (8.4)	28 (8.6)
Pulmonary	35 (10.5)	35 (10.7)
Rheumatologic	42 (12.6)	40 (12.3)
Neuro-muscular	14 (4.2)	13 (4.0)
Others	33 (9.9)	30 (9.1)
Single-site irAEs	269 (80.8)	263 (80.7)
Multiple-site irAEs	64 (19.2)	63 (19.3)
	G3/G4 irAEs (patients-%)	
G3/G4 irAEs (any)	**101 (10.0)**	**97 (11.1)**
Cutaneous	14 (13.9)	14 (14.4)
Endocrine	8 (7.9)	8 (8.2)
Gastro-intestinal	24 (23.8)	23 (23.7)
Haepatic	20 (19.8)	20 (19.8)
Pulmonary	23 (22.8)	23 (23.7)
Rheumatologic	1 (1.0)	1 (1.0)
Neuro-muscular	3 (3.0)	3 (3.1)
Others	16 (15.8)	13 (13.8)
Single-site irAEs	94 (93.1)	89 (91.8)
Multiple-site irAEs	7 (6.9)	6 (8.2)

irAEs of any grade (overall stuty population)			
Variable	**Events Ratio**	**Incidence (95% CI)**	***p - value***
Overall	333/1010	32.9 (29.5 – 36.7)	-
Sex			
Female	119/346	34.4 (28.5 – 41.1)	*0.4877*
Male	214/664	32.2 (28.1 – 36.8)	
Age			
Elderly	173/518	33.4 (28.6 – 38.7)	*0.7670*
Non-elderly	160/492	32.5 (27.6 – 37.9)	
ECOG-PS			
0-1	296/836	35.4 (31.5 – 39.7)	*0.0003*
≥ 2	37/174	21.2 (14.9 – 29.3)	
Histology			
Squamous	76/246	30.9 (24.3 – 38.7)	*0.4260*
Non-squamous	257/764	33.6 (29.6 – 38.1)	
Burden of disease			
< 3 organs involved	196/495	39.6 (34.2 – 45.5)	*<0.0001*
≥ 3 organs involved	137/515	26.6 (22.3 – 31.1)	

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
Variable (comparator)	**Response-Ratio**	**ORR (95% CI)**	**OR (95%CI) *p - value***	**Coeff.**	**St. Err.**	***p - value***
Overall	394/805	48.9 (44.2–54.0)	-	-	-	-
irAEs of any grade						
Yes	187/304	61.5 (53.0–70.9)	2.27 (1.69-3.03) *p<0.0001*	-0.7607	0.1522	*< 0.0001*
No	207/501	41.3 (35.8–47.3)				
G3/G4 irAEs						
Yes	57/89	64.0 (48.5–82.9)	2.01 (1.26-3.16) *p=0.0025*	-0.7261	0.2393	*0.0024*
No	337/716	47.1 (42.1–52.3)				
LTD irAEs						
Yes	49/79	62.0 (45.9–82.0)	1.80 (1.12-2.91) *p=0.0144*	-0.6476	0.2501	*0.0096*
No	345/726	47.5 (42.6–52.8)				
Type of irAEs						
No irAEs	207/501	41.2 (35.8-47.3)		-0.6884	0.1628	*<0.0001*
Single site	146/244	59.8 (50.5-70.3)	*p<0.0001*			
Multiple site	41/60	68.3 (49.0-92.7)	*p<0.0001¥*	-1.0672	0.2980	*0.0003*
Cutaneous irAEs						
Yes	65/97	67.0 (51.7–85.4)	2.34(1.49-3.66) *p=0.0001*	-0.7196	0.2332	*0.0020*
No	329/708	46.5 (41.6-51.7)				
Endocrine irAEs						
Yes	51/84	60.3 (42.7–82.8)	1.70 (1.07-2-70) *p=0.0227*	-0.5342	0.2432	*0.0281*
No	343/721	47.5 (42.7-52.8)				
GI irAEs						
Yes	38/63	60.3 (42.7–82.8)	1.64 (0.97-2.78) *p=0.0601*	-	-	-
No	356/742	47.9 (43.1-53.2)				
Hepatic irAEs						
Yes	13/25	52 (27.7–88.9)	1.13 (0.51-2.51) *p=0.7563*	-	-	-
No	381/780	48.8 (44.1-54.0)				
Pulmonary irAEs						
Yes	20/30	66.7 (40.7–102.9)	2.15 (1.01-4.6) *p=0.0479*	-0.6512	0.4041	*0.1071*
No	374/775	48.2 (43.5-53.4)				
Rheumatologic irAEs						
Yes	28/38	73.6 (48.9–106.4)	3.06 (1.46-6.40) *p=0.0018*	-1.0545	0.3822	*0.0058*
No	366/767	47.7 (42.9-52.8)				
Neuro-muscular irAEs						
Yes	5/11	45.4 (14.7–106.1)	0.86 (0.26-2.86) *p=0.8158*	-	-	-
No	389/794	48.9 (44.2-54.1)				
Others irAEs						
Yes	19/30	63.3 (38.1–98.9)	1.84 (0.86-3.93) *p=0.1067*	-	-	-
No	374/774	48.3 (43.5-53.4)				
ECOG-PS						
0-1	361/699	51.6 (46.4–57.2)	2.36 (1.52-3.65) *p=0.0001**	-	-	-
≥ 2	33/106	31.1 (21.4–43.7)				
Burden of disease						
< 3 organs involved	251/438	57.3 (50.4–64.8)	2.10 (1.58-2.79) *p<0.0001**	-	-	-
≥ 3 organs involved	143/367	38.9 (32.8–45.9)				
Sex						
Female	134/275	48.7 (40.8–57.7)	1.01 (0.75-1.35) *p=0.9294*	-	-	-
Male	260/530	49.0 (43.2–55.4)				
Age						
Elderly	206/420	49.1 (42.6–56.2)	1.01 (0.76-1.33) *p=0.9511*	-	-	-
Non-elderly	188/385	48.8 (42.1–56.3)				
Histology						
Squamous	99/197	50.2 (40.8–61.2)	1.07 (0.77–1.47) *p=0.6724*	-	-	-
Non-squamous	295/608	48.5 (43.1–54.4)				

	PROGRESSION FREE SURVIVAL	
	Univariate Analysis	**Multivariate Analysis**
VARIABLE (Comparator)	**HR (95% CI) *p - value***	**HR (95% CI) *p - value***
irAEs of any grade Yes vs No	0.48 (0.39–0.59) *p<0.0001*	0.49 (0.39–0.61) *p<0.0001*
G3/G4 irAEs Yes vs No	0.78 (0.57–1.05) *p=0.1066*	-
LTD irAEs Yes vs No	0.84 (0.62-1.13) *p=0.2687*	-
Type of irAEs (No irAEs) Single site Multiple site	 0.47 (0.38–0.60) *p<0.0001* 0.48 (0.32–0.73) *p=0.0005*	 0.49 (0.39–0.61) *p<0.0001* 0.49 (0.32–0.73) *p=0.0007*
Cutaneous irAEs Yes vs No	0.62 (0.44–0.86) *p=0.0042*	0.72 (0.51–1.01) *p=0.0512*
Endocrine irAEs Yes vs No	0.43 (0.29–0.64) *p<0.0001*	0.40 (0.27–0.59) *p<0.0001*
GI irAEs Yes vs No	0.66 (0.44–0.97) *p=0.0391*	0.58 (0.39–0.86) *p=0.0076*
Hepatic irAEs Yes vs No	1.31 (0.83–2.06) *p=0.2314*	-
Pulmonary irAEs Yes vs No	0.65 (0.39–1.09) *p=0.1092*	-
Rheumatlogic irAEs Yes vs No	0.47 (0.27–0.82) *p=0.0086*	0.50 (0.29–0.87) *p=0.0158*
Neuro-muscular irAEs Yes vs No	0.50 (0.18–1.34) *p=0.1694*	-
Others irAEs Yes vs No	0.73 (0.42–1.28) *p=0.2788*	-
ECOG-PS ≥ 2 vs 0-1	2.08 (1.63–2.66) *p<0.0001**	-
Burden of disease ≥ 3 vs < 3 organs involved	2.07 (1.71–2.50) *p<0.0001**	-
Sex Female vs Male	0.95 (0.78–1.15) *p=0.6234*	-
Age Elderly vs Non-elderly	1.07 (0.89–1.30) *p=0.4391*	-
Histology Squamous vs Non-squamous	1.01 (0.81–1.25) *p=0.9392*	-

	OVERALL SURVIVAL	
	Univariate Analysis	**Multivariate Analysis**
VARIABLE (Comparator)	**HR (95% CI) *p - value***	**HR (95% CI) *p - value***
irAEs of any grade Yes vs No	0.39 (0.30–0.51) *p<0.0001*	0.41 (0.31–0.53) *p<0.0001*
G3/G4 irAEs Yes vs No	0.70 (0.48–1.03) *p=0.0692*	-
LTD irAEs Yes vs No	0.73 (0.50-1.07) *p=0.1099*	-
Type of irAEs (No irAEs) Single site Multiple site	 0.41 (0.30–0.54) *p<0.0001* 0.36 (0.21–0.62) *p=0.0003*	 0.41 (0.31–0.55) *p<0.0001* 0.36 (0.21–0.63) *p=0.0003*
Cutaneous irAEs Yes vs No	0.41 (0.25–0.65) *p=0.0002*	0.48 (0.30–0.78) *p=0.0032*
Endocrine irAEs Yes vs No	0.33 (0.19–0.57) *p=0.0001*	0.30 (0.17–0.52) *p<0.0001*
GI irAEs Yes vs No	0.67 (0.42–1.07) *p=0.0999*	-
Hepatic irAEs Yes vs No	0.82 (0.43–1.54) *p=0.5442*	-
Pulmonary irAEs Yes vs No	0.59 (0.30–1.14) *p=0.1194*	-
Rheumatologic irAEs Yes vs No	0.43 (0.21–0.88) *p=0.0214*	0.47 (0.23–0.96) *p=0.0396*
Neuro-muscular irAEs Yes vs No	0.52 (0.16–1.62) *p=0.2624*	-
Others irAEs Yes vs No	0.57 (0.27–1.22) *p=0.1498*	-
ECOG-PS ≥ 2 vs 0-1	2.43 (1.84–3.19) *p<0.0001**	-
Burden of disease ≥ 3 vs < 3 organs involved	2.11 (1.67–2.65) *p<0.0001**	-
Sex Female vs Male	1.09 (0.86–1.39) *p=0.4521*	-
Age Elderly vs Non-elderly	1.20 (0.95–1.50) *p=0.1141*	-
Histology Squamous vs Non-squamous	1.04 (0.80–1.36) *p=0.7434*	-

	Objective Response Rate			Progression Free Survival			Overall Survival
Variable	**Response-Ratio**	**ORR (95% CI)**	**UVA OR (95% CI) *p - value***		**UVA HR (95% CI) *p - value***	**MVA HR (95% CI) *p - value***	**UVA HR (95% CI) *p - value***
G3/G4 irAEs Yes No	57/89 130/215	64.0 (48.5–82.9) 60.5 (50.5–71.)	1.16 (0.69-1.94) *p=0.5601*	**G3/G4 irAEs** Yes vs. No	1.42 (0.99–2.03) *p=0.0537*	-	1.46 (0.91–2.33) *p=0.1097*
LTD irAEs Yes No	49/79 137/225	62.0 (45.9–82.0) 60.9 (51.1–71.9)	1.05 (0.62-1.78) *p=0.8587*	**LTD irAEs** Yes vs. No	1.55 (1.08–2.22) *p=0.0169*	1.39 (0.97–2.01) p=0.0713*	1.51 (0.94–2.41) *p=0.0844*
Pulmonary irAEs Yes No	20/30 166/274	66.7 (40.7–102.9) 60.6 (51.7-70.5)	1.30 (58.7-2.88) *p=0.5170*	**Pulmonary irAEs** Yes vs. No	1.02 (0.59–1.76) *p=0.9192*	-	1.09 (0.54–2.20) *p=0.7995*