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Nivolumab in routine practice for older patients with advanced or metastatic non-small cell lung cancer

Renaud Sabatier [a,b,*], Emanuel Nicolas [a,b], Maria Paciencia [c], Annie-Pierre Jonville-Béra [d], Anne Madroszyk [a], Maud Cecile [a], Cecile Braticevic [a], Ségolène Duran [e], Louis Tassy [a], Franck Rouby [f,g], Joëlle Micallef [f,g], Frédérique Rousseau [a]

[a] Department of Medical Oncology, Institut Paoli-Calmettes, 13009 Marseille, France
[b] Aix-Marseille Univ, CNRS U7258, INSERM U1068, Institut Paoli-Calmettes, CRCM, 13009 Marseille, France
[c] Department of Biopathology, Institut Paoli-Calmettes, 13009 Marseille, France
[d] Department of Clinical Pharmacology, Regional center of Pharmacovigilance, CHRU, Tours, France
[e] Pharmacovigilance unit, Department of Pharmacy, Institut Paoli-Calmettes, 13009 Marseille, France
[f] Department of Clinical Pharmacology, régional center of Pharmacovigilance Marseille - Provence – Corse, Assistance Publique - Hôpitaux de Marseille, Marseille, France
[g] Aix-Marseille Univ, Neurosciences Institute, UMR CNRS 7289, Marseille, France

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ABSTRACT

Background: Nivolumab is approved worldwide as second-line treatment for metastatic non-small cell lung cancer (NSCLC). Despite the fact that most of these cancers are being diagnosed in the older patients, few of the patients were included in pivotal trials. We aimed to describe efficacy and safety in a "real-world" older population.
Patients and Methods: We retrospectively collected data from older patients (≥70 years old) with advanced or metastatic NSCLC treated with Nivolumab in our institution. We analyzed safety (CTCAE v4.0 criteria), efficacy (clinical benefit rate, progression-free survival, and overall survival), and correlated these features to geriatric parameters and PD-L1 expression. Along with this cohort, we assessed safety at a national level by retrieving all cases of Nivolumab (prescribed for NSCLC) induced adverse events analyzed by the French pharmacovigilance network during the inclusion period.
Results: From July 2015 to September 2016, 30 patients were enrolled with a median age of 75.2. Clinical benefit rate was 30.6%. Median progression-free survival and overall survival were 3.3 and 7.1 months, respectively. Fifteen patients (50%) presented an immune-related adverse event (IrAE) of any grade, including four high grade IrAEs. Two hundred and eighty IrAEs had been notified to the French pharmacovigilance network including 91 (35.2%) concerning older patients. Frequency and pattern of IrAEs were similar for older patients and younger subjects.
Conclusions: Even though frequency and patterns of IrAEs are different from pivotal studies, these results don't seem specific to older patients. Further prospective investigations are needed to better characterize and predict the impact of Nivolumab on older patients with NSCLC.

1. Introduction

Recent advances have led to the introduction of immunotherapy as a new standard for non-small cell lung cancers (NSCLC) in second line treatment after platinum failure. Immune checkpoint inhibitors have dramatically improved survival when compared to previous standard-of-care second line chemotherapies [1,2]. PD1 blocker Nivolumab is approved in Europe for advanced melanoma, refractory Hodgkin disease, advanced renal cell cancer, platinum-resistant urothelial cancer, and head and neck cancers. In addition, it is approved for both squamous and non-squamous non-small cell lung carcinoma in the 2nd line setting. Concerning tolerance, in the two pivotal trials of nivolumab, grade 3–5 treatment-related adverse events (AEs) were less common with immunotherapy than with Docetaxel. Treatment related AEs of any grade occurred in up to 69% of patients. Severe AEs of grade 3 or higher (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version4.0) were reported in 7%–13% of patients [1,2].

Abbreviations: NSCLC, non-small cell lung cancer; IrAE, immune-related adverse event; PFS, progression-free survival; OS, overall survival; CMI, Charlson's comorbidity index; ECOG, Eastern Cooperative Oncology Group; ADR, adverse drug reaction; SAE, serious adverse event; FFPE, formalin-fixed paraffin-embedded.

* Corresponding author at: Department of Medical Oncology, Institut Paoli Calmettes, 232 Bd Sainte Marguerite, 13009 Marseille, France.
E-mail address: sabatierr@ipc.unicancer.fr (R. Sabatier).

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More than half of the patients diagnosed with advanced NSCLC are over the age of 65 [3–5]. Until recently, international guidelines recommended using carboplatin-paclitaxel doublet as first line treatment for older patients (over 70 years old) with stage IV NSCLC with good performance status and limited co-morbidities [6]. However, overall survival is 10 months with this regimen [7], and no other chemotherapy has shown to be more beneficial [8,9]. There was moreover no standard second-line treatment for older patients. On the basis of the results of clinical trials, immune checkpoint inhibitors could be considered as an alternative in second line treatment of NSCLC for older patients. However as it has been underlined by registration agencies [10], there is a lack of data concerning efficacy and tolerance in this population due to its underrepresentation in pivotal clinical trials [11–13]. Indeed in the two pivotal studies of Nivolumab, patients between 64 and 75 years old represented 30% of the population and patients over 75 years old represented 8% of the population [1,2]. As a result, the overall survival benefits of Nivolumab in patients over 75 years old remain contradictory in these two pivotal studies.

A recent study focused on older patients included in the prospective CheckMate 153 trial has been recently presented [14]. This study suggests that older patients included in this prospective study had similar safety and efficacy profiles when compared to the younger patients. However there is a need of data obtained from unselected patients. Biological specificities have indeed be described for the older population such as alterations of cellular functions and metabolism [15]. It has also been recently published that there could be a higher incidence of hyper progressive diseases under immune checkpoint inhibitors in older patients that could lead to pulmonary deficiency in patients with NSCLC [16].

Given the probable increase in the use of immune checkpoint inhibitors in the upcoming years, and the lack of specific data concerning the older patient population, we aimed to evaluate safety and efficacy (progression-free survival (PFS) and OS) of Nivolumab for “real-world”, routinely treated, unselected older patients with NSCLC. We present in this article the analyzation of data from a French comprehensive cancer center as well as from the national French pharmacovigilance database.

2. Patients and Methods

2.1. Data Collected from IPC Cohort

We first conducted a monocentric retrospective study among the population of the Institut Paoli Calmettes (IPC, Marseille, France), analyzing the medical files of all the patients diagnosed with stage IIIB or IV non-small cell lung cancer, 70 years and older, who had started on Nivolumab anytime between July 2015 (date of European Medicine Agency approval in Europe) and September 2016. Follow-up data collection was stopped on March 31, 2017. The patients were given Nivolumab at a dose of 3 mg/kg every two weeks until disease progression or unacceptable toxicity.

Because this was a retrospective non-interventional study, formal informed consent was not required. This work was performed after approval of our institutional review board (IPC *Comité d'Orientation Stratégique*). All procedures were done in accordance with the French ethical standards.

Comorbidities were described using the Charlson's comorbidity index (CMI). The CMI includes all comorbidities to predict 10-year mortality [17,18]. Performance status was defined by Eastern Cooperative Oncology Group (ECOG) score. We also described the G8 questionnaire to explore the incidence of patients displaying a G8 score of 14 or lower, *i.e.* requiring a deeper geriatric assessment [19]. CMI was retrospectively defined according to patients' medical files. G8 score was prospectively collected in clinical routine practice and retrieved from medical files for this work.

2.2. End Points and Assessments

The primary aim was to evaluate the safety of immunotherapy. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. We detailed frequency, grade, and characteristics of AEs. We also described corticosteroids use as well as malnutrition rate during Nivolumab treatment. Serum albumin was prospectively evaluated as routine standard of care. Malnutrition was defined as a minimal albumin level lower than 30 g/l or a weight loss of >10% from Nivolumab introduction. We considered fatigue as a symptom of advanced lung cancer, and not as an immune-related AE (IrAE), only after having exclude that fatigue could be related to endocrine toxicities.

Another important objective of this work was to evaluate the õefficacy (PFS and OS) of immunotherapies for older patients. Treatment efficacy was evaluated by conventional Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria [20] every four cycles (usually 8 weeks) or whenever clinically indicated. PFS was defined as the time from the first Nivolumab cycle until objective tumor progression or death from any cause. OS was defined as the time from the first Nivolumab cycle to death from any cause. We also described rates of complete and partial responses, as well as stable disease and progressive disease according to RECIST 1.1 criteria. Clinical benefit rate was defined as the rate of patients with an objective response or with disease stabilization for >6 months.

2.3. PD-L1 Immunohistochemical Analysis

The PD-L1 assessment was retrospectively performed on formalin-fixed paraffin-embedded (FFPE) samples using DAKO 22C3 antibody and reviewed by a trained pathologist (MP). Biopsy samples were retrieved from archives and could have been collected at lung cancer diagnosis or before Nivolumab initiation. We looked at PD-L1 expression (membranous staining) in both tumor cells and tumor-infiltrating immune cells. PD-L1 staining was quantified as the percentage of positive cells.

2.4. Safety Data from the French Pharmacovigilance Database

The French pharmacovigilance network includes 31 Regional Pharmacovigilance Centers that collect and analyze spontaneous reports of adverse drug reactions (ADRs) from health care professionals and patients. All validated cases are stored in a common computerized database using MedDRA (Medical Dictionary for Regulatory Activities) terminology for ADRs coding. This database is called the “French Pharmacovigilance Network Database”. Cases are graded according to seriousness (the factors in the criteria to define serious cases are death, life-threatening, hospitalization (initial or prolonged), disability, and congenital abnormalities). We reviewed all cases of Nivolumab (prescribed for NSCLC)-induced IrAE analyzed by the French pharmacovigilance network from September 1st 2015 (date of first commercialization of Nivolumab in France) to December 31st 2016. We compared patients and IrAEs characteristics (demographics, patterns of IrAEs, seriousness, date of onset, evolution) for two populations split according to age (under 70 *versus* 70 and older).

2.5. Statistical Analyses

Categorical variables were described using counts and frequencies, and quantitative variables were described using medians and ranges. PFS and OS rates were estimated using the Kaplan–Meier method and two-sided 95% confidence intervals (95CI) were presented. Patients without progression or death were censored at date of last news. Correlations between geriatric features and safety data were assessed using the bilateral Fisher's exact test or the Chi-squared test as usually recommended. Correlations between geriatric features and PD-L1 expression

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