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Intracerebral efficacy and tolerance of nivolumab in non–small-cell lung cancer patients with brain metastases

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ABSTRACT

Objectives: Although nivolumab has shown efficacy against non–small-cell lung cancers (NSCLCs), patients with active brain metastases (BMs) were excluded from pivotal clinical trials. Hence, data regarding nivolumab intracerebral activity and safety in NSCLC patients with BMs are scarce.

Materials and methods: We conducted a retrospective multicenter study on NSCLC patients with BMs treated with nivolumab. The primary endpoint was intracerebral objective response rate (IORR), according to RECIST criteria. Secondary endpoints included intracerebral control rate, intracerebral and general progression-free survival (PFS), overall survival (OS) and tolerance.

Results and conclusion: Forty-three patients were included. BMs were locally pretreated in 34 (79%) patients and active in 16 (37%) patients. Median follow-up was 5.7 (95% CI: 2.7–8.4) months. IORR and extracerebral response rate were, respectively, 9% (95% CI: 3–23%) and 11% (95% CI: 4–26%). Intracerebral control rate was 51% (95% CI: 37–66%). Median intracerebral and general PFS lasted 3.9 (95% CI: 2.8–11.1) and 2.8 (95% CI: 1.8–4.6) months, respectively. Median OS was 7.5 (95% CI: 5.6–not reached) months. Five neurological adverse events occurred, including 1 grade-4 transient ischemic attack of uncertain imputability and 1 grade-3 neurological deficit; neither required nivolumab discontinuation. Nivolumab intracerebral activity was similar to its reported extracerebral efficacy, with an acceptable safety profile. Prospective and controlled data are needed to determine nivolumab's place in treatment of NSCLC patients with BMs.

1. Introduction

Immunotherapy, especially checkpoint inhibitors, like anti-programmed death-1 (anti-PD1), constitutes a major strategy for management of non–small-cell lung cancers (NSCLCs) [1–4]. In pivotal phase III studies on second-line therapies, the anti-PD1 antibody nivolumab prolonged progression-free survival (PFS) and overall survival (OS) of patients with metastatic squamous cell NSCLCs [5]. Compared to docetaxel for non-squamous–cell NSCLCs, nivolumab significantly prolonged OS but not PFS [6]. Furthermore, again as second-line therapy versus chemotherapy, pembrolizumab was beneficial for PDL1-positive patients, as was atezolizumab for unselected, pretreated NSCLC patients [7], Therefore, the most recent European Society of Medical Oncology guidelines included anti-PD1 antibodies as a part of a systemic strategy for pretreated locally advanced or metastatic NSCLCs [1]. However, whether those results can be extrapolated to real-life patients remains challenging, because all trials evaluating anti-PD1 excluded patients with active or non-pretreated brain metastases (BMs) [5–9]. More precisely, nivolumab efficacy in patients with brain metastases remains unknown.

BMs are common in NSCLC patients, being found in up to 40% of patients in some studies [10]. Moreover, BMs have been associated with poor prognosis [11]. BM treatment has long been considered to rely wholly on local strategies, such as whole brain radiation therapy,

Abbreviations: BM, brain metastasis; AE, adverse event; CI, confidence interval; CTLA4, cytotoxic T-lymphocyte antigen-4; CT, computed-tomography; GPA, Graded Prognostic Assessment score; IORR, intracerebral objective response rate; IQR, interquartile range; NSCLC, non–small-cell lung cancer; OS, overall survival; PD1, programmed death–1; PDL1, programmed death-ligand–1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

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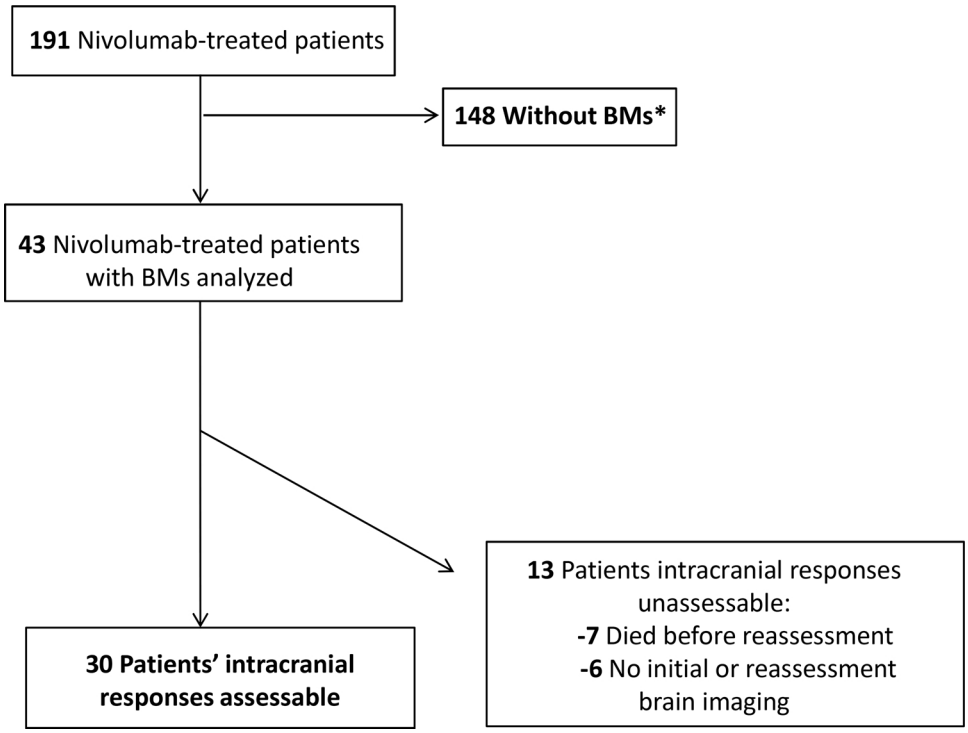

Fig. 1. Flow chart of NSCLC patients. BM, brain metastasis.

surgery or stereotaxic radiosurgery [12] but intracerebral responses were also observed in patients treated exclusively with chemotherapy [13] or epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors [14,15] in several trials. Indeed, the intracerebral objective response rate (IORR) was similar with or without whole brain radiation therapy for patients who had received first-line cisplatin and vinorelbine in a trial evaluating whether radiation should be delivered before or after chemotherapy [16]. Notably, doubts regarding the ability of newly developed drugs to flow across the blood–brain barrier often leads to the non-inclusion in trials of patients with BMs, especially when the latter are active or not pretreated [17]. This situation also applied to nivolumab, whose safety and intracerebral activity in NSCLC patients with BMs is unknown.

Therefore, the goal of this study was to assess nivolumab intracerebral efficacy and tolerance in NSCLC patients with BMs in a real-life setting.

2. Methods

We conducted a retrospective, observational study in 2 tertiary thoracic oncology centers in France. All patients with advanced NSCLCs and BMs who started nivolumab between May 2015 and August 2016 were included. BMs had to be present either on brain magnetic resonance imaging or brain computed-tomography (CT) scans obtained before the first nivolumab dose. BMs could be treated or not and active (defined as growing or newly appeared) or not.

The nivolumab dose was 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The tumor response was assessed every 2 months (4 nivolumab injections) by brain imaging similar to that performed at baseline, a chest CT scan and other investigations depending on the localization of tumor metastases. Intracerebral and extracerebral tumor responses were evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST). The following information was collected: patient demographics, tumor characteristics including number of metastatic sites, PDL1 expression when available, treatments received before nivolumab, Graded Prognostic Assessment (GPA) score, numbers of BMs and their previous treatment, presence of edema and BM activity.

The primary objective was to provide an estimation of intracerebral objective response rate (IORR), as assessed by RECIST criteria after 4 nivolumab infusions in this population. IORR was then compared to the global disease objective response rate (ORR). If patients could not be assessed for brain response (i.e., brain imaging not performed at re-evaluation or death occurring before first follow-up visit), they were still included in the study population and considered to have presented intracerebral progression so as not to overestimate the IORR or intracerebral control rate.

Secondary outcomes included the intracerebral control rate (i.e., response and stable disease), intracerebral PFS, general PFS and OS. Adverse events (AEs) were recorded, including immune-related AEs and signs suggestive of poor brain tolerance (e.g., epilepsy, neurological deficit, worsening edema or intracerebral hemorrhage). All symptoms were graded according to the Common Terminology Criteria for Adverse Events.

Qualitative variables are expressed as numbers (%) and corresponding 95% confidence interval (95%CI) were calculated using the Pearson's chi-squared test. IORR and extra-cerebral ORR were compared with a McNemar test for matched data. $P < 0.05$ defined significance. Quantitative data are described by their means ± standard deviation when a normal distribution could be assumed and by their medians (interquartile range [IQR]) otherwise.

3. Results

Between May 2015 and August 2016, 191 patients with advanced NSCLCs started nivolumab treatment in the 2 centers. Among them, 43 had BMs and were enrolled in this study, including 30 who were assessable for brain responses. Exact size and number of BMS at nivolumab onset were not evaluable in 3 and 2 patients, respectively, and one patient lacked follow-up imaging, and brain response was therefore not assessable in these patients. Furthermore, seven patients died before the first follow-up visit (Fig. 1). All non assessable patients were considered as cerebral progressors (worst case scenario). Baseline characteristics of the patients are given in Table 1. Median age was 59.5 ± 8.4 years; most patients were males (76%) and had adenocarcinoma (82%), and 26% of the NSCLCs harbored a V-Ki-ras2 Kirsten