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Nivolumab and brain metastases in patients with advanced non-squamous non-small cell lung cancer

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ABSTRACT

Objectives: Brain metastases are common among patients with non-squamous non-small-cell lung cancer (NSCLC) and result in a poor prognosis. Consequently, such patients are often excluded from clinical trials. In Italy an expanded access program (EAP) was used to evaluate nivolumab efficacy and safety in this subpopulation outside a clinical trial.

Materials and methods: In this EAP, nivolumab was available for patients with non-squamous NSCLC in progression after at least one systemic treatment for stage IIIB/IV disease. Nivolumab 3 mg/kg was administered intravenously every 2 weeks. Patients with brain metastases could be included if they were asymptomatic, neurologically stable and either off corticosteroids or on a stable or decreasing dose of ≤10 mg/day prednisone.

Results: 409 out of 1588 patients included had asymptomatic or controlled brain metastases. A median of 7 doses (range 1–45) were delivered. Median follow-up was 6.1 months (range 0.1–21.9). The disease control rate was 39%: 4 patients had a complete response, 64 a partial response and 96 showed stable disease. At baseline, 118 patients were on corticosteroids and 74 were undergoing concomitant radiotherapy. The median overall survival

Abbreviations: NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed death ligand 1; OS, overall survival; RR, response rate; PFS, progression-free survival; CR, complete response; PR, partial response; SD, stable disease; CNS, central nervous system; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; EAP, expanded access program; ECOG PS, Eastern cooperative oncology group performance status; AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; CTCAEs, common terminology criteria for adverse events; CI, confidence interval

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in this subpopulation was 8.6 months (95% CI: 6.4–10.8). 337 discontinued treatment for various reasons, 23 (7%) of whom due to adverse events, in line with that observed in the overall population and in previous studies. *Conclusions:* Our results confirm that nivolumab is active in non-squamous NSCLC patients with brain metastases, despite their poor prognosis. Its safety profile is also concordant with results in the EAP overall population and in patients with other malignancies.

1. Introduction

The choice of first-line treatment for advanced non-small cell lung cancer (NSCLC) without oncogene addiction (epidermal growth factor receptor [EGFR] wild-type, non-rearranged anaplastic lymphoma kinase [ALK], c-ros proto-oncogene [ROS1]) is currently based on programmed death ligand 1 (PD-L1) expression. If expression levels of this biomarker are ≥50%, the anti-PD-1 immune checkpoint inhibitor pembrolizumab is generally used, whereas platinum-based chemotherapy is the standard treatment when PD-L1 expression is > 50%. First-line chemotherapy for non-squamous NSCLC comprises pemetrexed plus cisplatin or another platinum-based doublet plus bevacizumab [1–3].

Docetaxel had long been regarded as the standard treatment for NSCLC in progression after first-line chemotherapy. Second-line treatment has radically changed over time and now includes pembrolizumab if PD-L1 expression is at least 1% or another anti-PD-1 immune checkpoint inhibitor, nivolumab, regardless of PD-L1 expression, or docetaxel plus nintedanib. The use of second-line nivolumab after first-line chemotherapy was confirmed in 2 phase III clinical trials, CheckMate 017 for squamous histology [4] and CheckMate 057 for non-squamous disease [5]. Docetaxel was the control arm in both studies. CheckMate 017 met both the primary endpoint (overall survival, OS) and the other endpoints (progression-free survival, PFS, and response rate, RR). PD-L1 expression was neither prognostic or predictive. Checkmate 057 met its primary (OS) and secondary endpoints (RR), but not PFS. Interestingly, OS improved in all pre-specified subgroups, with the exception of patients undergoing third-line treatment, those with brain metastases, and those with EGFR mutations.

Around 10% of patients diagnosed with metastatic NSCLC present with brain metastases (half of these with multiple lesions) and around 30% subsequently develop brain metastases [6,7]. Central nervous system (CNS) metastases are associated with poor prognosis and patients with untreated CNS metastases are generally excluded from clinical trials [8]. Although local control of brain metastases has improved thanks to recent advances in local therapies such as stereotactic radiosurgery (SRS) [9], the effects of SRS are still limited and long-term complications may occur. Whole brain radiation therapy (WBRT) is the main alternative to SRS. However, given the limitations of local therapies, systemic therapy can also be used effectively for brain metastases whilst simultaneously treating extracranial disease.

In a pooled analysis of data from the CheckMate 017, CheckMate 057 and CheckMate 063 (phase 2 trial of nivolumab in NSCLC) studies, median OS was longer in the nivolumab group (8.4 months; 95% CI: 5.0, 11.6) than in the docetaxel group (6.2 months; 95% CI: 4.4, 9.2) for patients with pretreated CNS metastases [10].

An expanded access program (EAP) in Italy [11] offered an opportunity to evaluate nivolumab treatment in patients with CNS metastases outside of a controlled clinical trial. We present the results from this EAP for the subgroup of patients with CNS metastases.

2. Materials and methods

2.1. Patients

Inclusion criteria: 1) diagnosis of stage IIIB/IV non-squamous NSCLC confirmed by histology or cytology; 2) age ≥18 years; 3) life expectancy ≥6 weeks; 4) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤2; 5) normal blood, kidney and liver function; 6) progressive disease during or after at least one systemic chemotherapy (platinum-based or alternative cytotoxic regimen if not amenable to platinum) for advanced or metastatic non-squamous NSCLC, also including patients who received definitive chemoradiation therapy for locally advanced disease or platinum-containing neoadjuvant or adjuvant chemotherapy and progressed or relapsed within 6 months of the end of therapy. Any prior anticancer therapy had to be concluded at least 2 weeks before the administration of nivolumab, and all related adverse events (AEs) had to be stabilized or resolved. Patients were eligible if they did not have neurologic symptoms relating to metastatic CNS lesions ≥2 weeks before enrolment. A maximum dose of prednisone 10 mg/day or equivalent was permitted.

Exclusion criteria: 1) symptomatic interstitial lung disease; 2) carcinomatous meningitis; 3) any prior immunotherapy (anti–PD-1, anti–PD-L1, anti-programmed death-ligand 2 (PD-L2), anti-CD137, or anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, any other drugs targeting checkpoint pathways or T-cell co-stimulation); 4) patients eligible for another trial with nivolumab; 5) HIV infection; 6) known autoimmune disease (with the exception of residual hypothyroidism on an autoimmune basis, diabetes mellitus type 1, psoriasis not requiring systemic treatment).

2.2. Study design and treatment

Nivolumab could only be provided upon physician request. All participating centers approved EAP guidelines and all physicians adhered to good clinical practice and the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all patients. Nivolumab 3 mg/kg was administered intravenously every 2 weeks until disease progression, unacceptable toxicity or consent withdrawal, for a maximum of 24 months. In the event of toxicity the administration of nivolumab could be delayed but its dose could not be reduced. If, in the physician's opinion, the patient experienced a clinical benefit, nivolumab could also be continued beyond initial radiological progression, with the exception of patients experiencing rapid disease progression. Concurrent radiotherapy was allowed. Nivolumab had to be suspended for at least 1 week before, during and 1 week after radiotherapy.

2.3. Assessments

Although endpoints were not pre-specified, physicians were required to carefully check for disease progression by assessing RR, disease control rate (DCR; combined rates of complete response [CR], partial response [PR] and stable disease [SD]), PFS and OS. Every 8–12 weeks disease status was assessed using total body CT scan (brain, chest and abdomen) or chest and abdomen CT scan and brain MRI, according to the routine clinical practice of each participating center. The safety profile of treatment was evaluated by physical examination and blood tests including thyroid function, according to standards of care. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAEs) version 4.0. Smoking habits were recorded through behavioral anamnesis: patients who had smoked fewer than 100 cigarettes in their life were defined as never smokers, those who had stopped smoking at least 12 months before the diagnosis of cancer as former smokers, and those who smoked or had stopped smoking < 1 year before diagnosis as current

smokers. EGFR mutations in exons 18–21 were detected using local standard methods (e.g. Sanger Sequencing, pyrosequencing or Next Generation Sequencing), based on the availability of cytological or histological specimens.

2.4. Statistical analysis

The current analysis included patients with at least one CNS metastasis from the Italian EAP cohort who had received at least one dose of nivolumab. The cut-off date was September 2017. PFS and OS were estimated using the Kaplan-Meier method. Median time-to-event values were reported together with 95% confidence intervals (95% CI). PFS was estimated from the start of nivolumab until any evidence of progressive disease, or death, whichever occurred first. OS was calculated from the start of nivolumab until death from any cause or last follow-up. Statistical analyses were performed with IBM SPSS Statistics 21.0 statistical software (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

1588 patients with non-squamous NSCLC from 153 Italian centers participated in the EAP. Patients in the overall cohort received a median of 7 doses (range 1–55) of nivolumab, with a median follow-up of 8.1 months (range 0.1–27.4). The 409 (26%) patients with asymptomatic and controlled CNS metastases received a median of 7 doses (range: 1–54) of nivolumab, with a median follow-up of 6.4 months (range: 0.1–27.2). Baseline characteristics of patients with CNS metastasis and of the overall population are shown in Table 1. 117 (29%) patients were undergoing steroid therapy and 74 (18%) concomitant steroid therapy and radiotherapy. 242 out of 409 patients with brain metastases received brain radiotherapy, mainly before nivolumab (69%).

3.2. Efficacy

ORR and DCR were 17% and 39% in CNS metastasis patients, respectively, with CR in 4 patients, PR in 64 and SD in 96. Results were similar inthe overall population (Table 2) [11]. Median PFS, one-year PFS and median OS for the CNS group

was 3.0 months (95% CI: 2.7–3.3), 20% and 8.6 months (95% CI: 6.4–10.8), respectively, compared to 3.0 months (95% CI: 2.9–3.1), 22% and 11.3 months (95% CI: 10.2, 12.4) for the entire cohort. One-year OS was 43% for CNS patients and 48% for all patients. Kaplan–Meier estimates of OS are shown in Fig. 1. We also report the imaging of a case of response in CNS lesions during treatment with nivolumab without radiotherapy (Fig. 2).

3.3. Safety

Safety outcomes for CNS metastasis patients and the overall population are shown in Table 3. Grade 3–4 treatment-related AEs were reported in 7% of patients with CNS metastasis and in 6% of the overall population. These events were managed using protocol-defined toxicity management algorithms. 344 (84%) patients with CNS metastasis and 1300 (82%) in the overall population discontinued treatment (Table 4). Of these, 11 (3%) in the former and 65 (5%) in the latter stopped treatment because of treatment-related AEs.

4. Discussion

Up to now systemic therapy has played a limited role in targeting brain metastases because of the inability of drugs to reach and target malignant lesions in the CNS, with the exception of some cytotoxic agents such as platinum compounds. As hydrophilic cytotoxic agents only have limited access through the blood brain barrier (BBB), chemotherapy is not usually able to reach primary brain malignancies. However, brain metastases can cause BBB disruption so that chemotherapy may be more effective in secondary brain lesions than in primary brain malignancies [12].

Immune checkpoint inhibitors work by activating the immune system against tumor cells, which may explain the potential effect of immunotherapy on CNS metastases [13]. Moreover, NSCLC-derived brain lesions show a higher expression of PD-L1 than the respective primary tumor [14]. The presence of tumor infiltrating lymphocytes in brain metastases are also an indicator of better prognosis [15].

There is evidence to support the effectiveness of immune checkpoint inhibitors in NSCLC patients with CNS metastases. In their 2016 non-randomized phase 2 trial evaluating pembrolizumab in NSCLC and melanoma patients with untreated brain metastases, Goldberg et al. reported a strong concordance between CNS and systemic response, with 33% of NSCLC patients achieving generally durable response in brain lesions. Neurological AEs in NSCLC patients were grade 1–2 and not related to treatment. However, this study did not provide any information on the effects and safety of pembrolizumab in symptomatic or larger CNS metastases [16]. The authors provided an update of trial results at the 2018 ASCO Annual Meeting, reporting a CNS-related PFS of 10.7 months (95% CI 6.6-not reached) among patients experiencing a brain metastasis response or stable disease. None of the 5 patients with negative PD-L1 had a brain response, but 2 lived for more than 12 months [17]. Dudnik et al. reported that, among 5 of 85 CNS NSCLC patients treated with nivolumab, one experienced a CR, one PR, one SD (leptomeningeal carcinomatosis), and 2 progressed [18]. These authors did not observe any grade ≥3 adverse events, whereas 7% of our EAP experienced grade 3–4 AEs. The 2 responders were a former female smoker with adenocarcinoma (CR) and an elderly male ex-smoker with squamous-cell lung carcinoma (PR). Systemic and intracranial responses were largely concordant [18].

A case report by Pluchart et al. reported on a 64-year-old Caucasian male with pulmonary adenocarcinoma and brain metastases who received 4 courses of nivolumab as 5th-line treatment concomitant with high-dose corticosteroids for the related neurological symptoms.

Table 1
Demographics and baseline patient characteristics.

Characteristic	CNS metastases (n = 409)	All patients (n = 1,588)
Male, n (%)	264 (65)	1029 (65)
Median age, years (range)	63 (29–84)	66 (27–89)
≥75, n (%)	31 (8)	232 (15)
Smoking status, n (%)		
Smoker	98 (27)	360 (23)
Former smoker	193 (47)	765 (48)
Never smoker	72 (18)	305 (19)
Unknown	46 (11)	158 (10)
ECOG PS, n (%)		
0	152 (37)	648 (41)
1	225 (55)	815 (51)
2	30 (7)	108 (7)
Unknown	2 (1)	17 (1)
Metastasis site, n (%)		
CNS	409 (100)	409 (26)
Bone	191 (47)	327 (21)
Liver	115 (28)	626 (39)
No. of prior systemic therapies, n (%)		
1	74 (18)	378 (24)
2	147 (36)	562 (36)
3	99 (24)	332 (21)
≥4	88 (22)	307 (19)
Unknown	1 (1)	9 (1)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; CNS, central nervous system.

Table 2
Response outcomes.

Response, n (%)	CNS metastasis (n = 409)	All patients (n = 1588)
Objective response rate	68 (17)	290 (18)
Disease control rate	164 (40)	704 (44)
Complete response	4 (1)	12 (1)
Partial response	64 (16)	278 (18)
Stable disease	96 (23)	414 (26)
Progressive disease	192 (47)	688 (43)
Death	35 (9)	130 (8)
Not determined	18 (4)	66 (4)

Despite the extent of disease he experienced a PR in the brain lesions and shrinkage of the metastases in other sites [19].

Läubli et al. described a case of cerebral vasculitis with the development of anti-endothelial cell antibodies as a severe complication during nivolumab treatment. The event occurred in a lung adenocarcinoma patient who showed regression in peripheral lesions and an improvement in quality of life after some courses with nivolumab. Subsequent cranial MRI revealed metastatic spread that was initially treated with radiotherapy and then with corticosteroids and surgery. Histopathological analysis revealed necrotizing encephalitis with no evidence of metastatic lung cancer. No antibodies against neuronal antigens were detected, but high titers of antinuclear anti-SSA/Ro and anti-SSB/La antibodies were found. It is interesting to note that high titers against SSA/Ro were already present in serum samples taken before the start of anti-PD1 treatment [20]. Another important report on nivolumab for the treatment of CNS metastases was the Italian EAP for advanced squamous NSCLC [21]. Of 372 patients, 38 with asymptomatic brain metastases received nivolumab. PFS was 5.5 months and OS was 6.5 months (in the Italian EAP for non-squamous NSCLC, PFS was 3 months and OS 8.6 months [11]). There were one CR, 6 PR and 11 SD diseases. Only one patient discontinued treatment because of an adverse event, in contrast to patients with non-squamous histology and CNS lesions where we recorded 4 CR, 64 PR and 96 SD among 409 patients. Although the total number of patients with CNS metastases differs substantially in these 2 EAPs with distinct histological populations, the DCR was similar (47% and 40%, respectively).

The case series in the present report was the largest including non-squamous NSCLC patients with brain metastases treated with immunotherapy. Specifically, the proportion of patients with CNS lesions was one third of the overall population (409/1588), which can be considered as fairly representative of patients seen in daily clinical practice.

However, our study has some limitations. Complete information was not available on the features of brain metastases (e.g. number and site of lesions, brain prognostic scores). Even though inclusion criteria for the EAP were not as strict as those of clinical trials, the patients included with brain metastases were still a selected group given that those with symptomatic brain involvement were excluded because they often require high doses of steroids. Brain MRI was performed in accordance with the standard clinical practice of each center and so this information was not available for all patients. Furthermore, as no distinction was made between intracranial and extracranial response, there were no data on brain response evaluation.

Notwithstanding these limitations, in our opinion these results are sufficiently robust to conclude that patients with asymptomatic brain metastases treated with nivolumab showed outcomes and safety similar to those of the overall population. This has already been seen in other studies on immunotherapy in patients with brain metastases [16,17]. We hypothesize that these findings were the result of the innovative mechanism of action of immune checkpoint inhibitors, perhaps because the BBB is not an obstacle for activated immune cells. However, few papers have compared the immune phenotype of brain metastasis specimens with that of the primary tumor. A higher percentage of "ignorant" immune phenotypes has been observed in brain metastases and this feature could influence the efficacy of immune checkpoint inhibitors rather than PD-L1 expression or tumor mutational burden [13,22]. Although the combination of chemotherapy and immunotherapy is destined to become the standard treatment in NSCLC patients, further studies are warranted to evaluate the efficacy and safety of this new approach in patients with brain metastases.

5. Conclusions

This EAP represents a sizeable real-world experience with nivolumab in previously treated patients with advanced non-squamous NSCLC and CNS metastases. The efficacy of nivolumab in CNS patients was similar to that of the overall cohort of this EAP and of the Checkmate 057 trial population [5]. Safety was comparable between patients with CNS metastasis and the overall EAP population, and is consistent with that previously reported in the CheckMate 057 trial. Despite the limitations of this type of study, our results suggest that patients with CNS metastases could benefit from treatment with nivolumab.

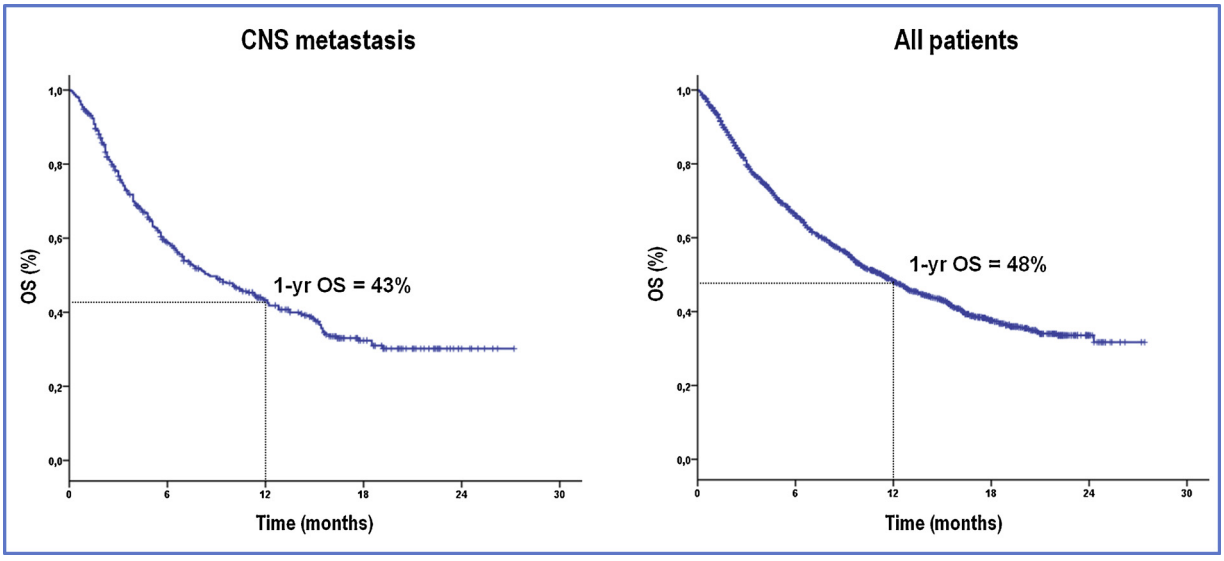

Fig. 1. Kaplan-Meier estimate of overall survival (OS) for patients with central nervous system (CNS) metastases and the overall population.

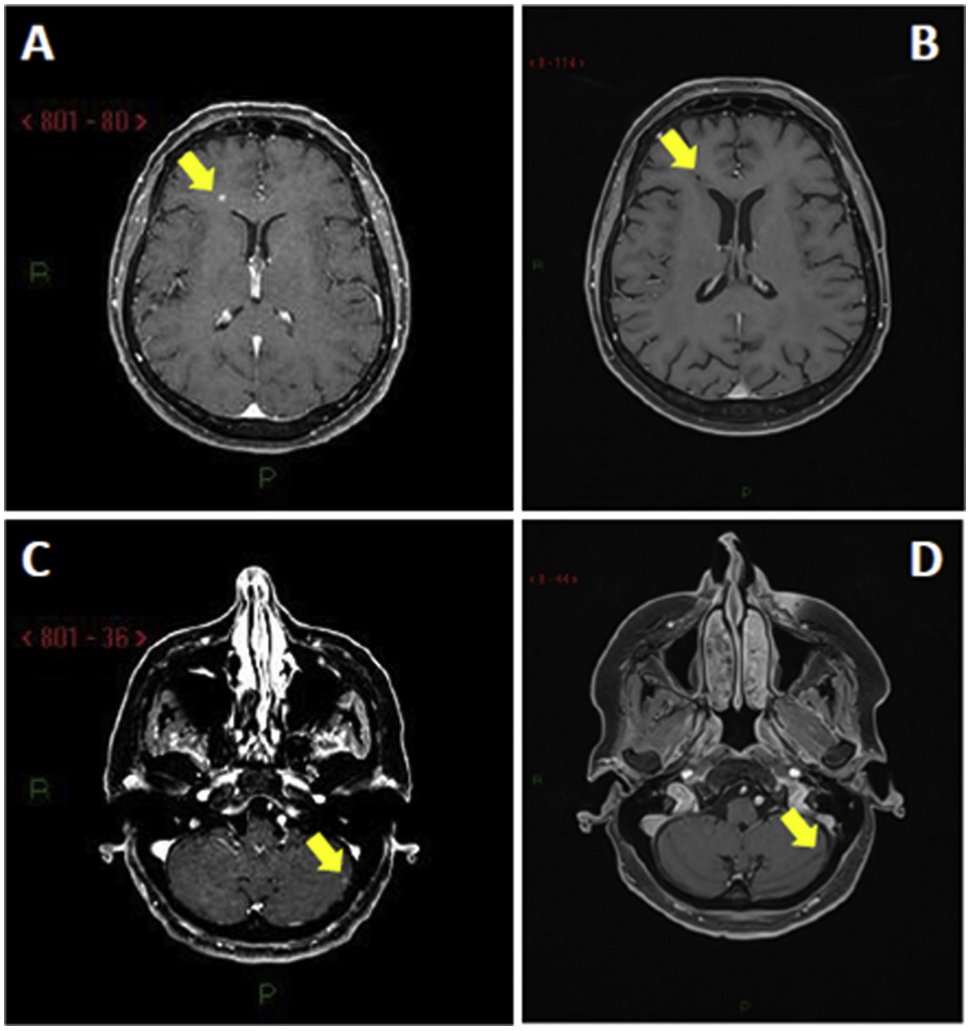

Fig. 2. Magnetic Resonance Imaging of response of CNS lesions in a patient during treatment with nivolumab without radiotherapy. At baseline the patient had a frontal brain metastasis (**A**) and cerebellar metastasis (**C**). After 3 years of treatment with nivolumab without radiotherapy both metastases had disappeared (**B, D**), the frontal lesion substituted by a necrotic area (**B**).

Table 3
Safety results.

Treatment-related AE	CNS metastases (n = 409)		All patients (n = 1588)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Any treatment-related AE	143 (35)	27 (7)	523 (33)	102 (6)
Fatigue/asthenia	47 (11)	6 (1)	175 (11)	26 (2)
Rash	7 (2)	2 (< 1)	52 (3)	6 (< 1)
Diarrhea	20 (5)	1 (< 1)	73 (5)	6 (< 1)
Pyrexia	12 (3)	0	58 (4)	2 (< 1)
Anemia	2 (< 1)	1 (< 1)	22 (1)	6 (< 1)
Nausea/vomiting	25 (6)	1 (< 1)	69 (4)	2 (< 1)
Pain	23 (6)	0	83 (5)	8 (< 1)
Hypothyroidism	7 (2)	1 (< 1)	37 (2)	2 (< 1)
Hyperthyroidism	6 (1)	0	37 (2)	2 (< 1)
Increased transaminase	5 (1)	2 (< 1)	20 (1)	9 (< 1)
Increased lipase/amylase	5 (1)	2 (< 1)	17 (1)	6 (< 1)
Lack of appetite/anorexia	17 (4)	1 (< 1)	57 (4)	2 (< 1)
Dyspnea	21 (5)	5 (1)	79 (5)	19 (1)
Pneumonitis	10 (2)	4 (1)	31 (2)	9 (< 1)

AE, adverse event.

Table 4
Summary of discontinuations.

Discontinuation	CNS metastases (n = 409)	All patients (n = 1,588)
Discontinued treatment, n (%)	344 (84)	1300 (82)
Reason for discontinuation, n (%)		
Progressive disease	246 (72)	954 (73)
Death	43 (12)	130 (10)
AEs or serious AEs	23 (7)	101 (8)
Treatment-related AEs	11 (3)	65 (5)
Other*	32 (9)	115 (9)

AE, adverse event.
* Could include consent withdrawal, lost to follow-up, patient request.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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