Primary Analysis and 4-Year Follow-Up of the Phase III NIBIT-M2 Trial in Melanoma Patients With Brain Metastases

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ABSTRACT

Purpose: Phase II trials have shown encouraging activity with ipilimumab plus fotemustine and ipilimumab plus nivolumab in melanoma brain metastases. We report the primary analysis and 4-year follow-up of the NIBIT-M2 study, the first phase III trial comparing these regimens with fotemustine in patients with melanoma with brain metastases.

Patients and Methods: This phase III study recruited patients 18 years of age and older with *BRAF* wild-type or mutant melanoma, and active, untreated, asymptomatic brain metastases from nine centers, randomized (1:1:1) to fotemustine, ipilimumab plus fotemustine, or ipilimumab plus nivolumab. The primary endpoint was overall survival (OS).

Results: From January, 2013 to September, 2018, 27, 26, and 27 patients received fotemustine, ipilimumab plus fotemustine, and ipilimumab plus nivolumab. Median OS was 8.5 months [95% confidence interval (CI), 4.8–12.2] in the fotemustine arm, 8.2 months (95% CI, 2.2–14.3) in the ipilimumab plus fotemustine arm (HR vs. fotemustine, 1.09; 95% CI, 0.59–1.99; $P = 0.78$), and 29.2 months (95% CI, 0–65.1) in the ipilimumab plus nivolumab arm (HR vs. fotemustine, 0.44; 95% CI, 0.22–0.87; $P = 0.017$). Four-year survival rate was significantly higher for ipilimumab plus nivolumab than fotemustine [(41.0%; 95% CI, 20.6–61.4) vs. 10.9% (95% CI, 0–24.4; $P = 0.015$)], and was 10.3% (95% CI, 0–22.6) for ipilimumab plus fotemustine. In the fotemustine, ipilimumab plus fotemustine, and ipilimumab plus nivolumab arms, respectively, 11 (48%), 18 (69%), and eight (30%) patients had treatment-related grade 3 or 4 adverse events, without treatment-related deaths.

Conclusions: Compared with fotemustine, ipilimumab plus nivolumab significantly improved overall and long-term survival of patients with melanoma with asymptomatic brain metastases.

Introduction

Brain metastases in solid tumors are of increasing clinical concern (1). Metastatic spread to the central nervous system (CNS) occurs in up to 50% of patients with cancer (2–6), with the highest incidence among patients presenting with metastatic disease reported in melanoma (28.2%) and lung adenocarcinoma (26.8%; ref. 5). The survival of patients with brain metastases is scanty, with overall 5-year survival rates across different tumor types of 2.4%; disease spreading to the CNS is the cause of death in more than half of these cases (6). Furthermore, the management of melanoma brain metastases remains clinically challenging because of the limited effectiveness of conventional therapeutic options (1, 4). Because of their poorer prognosis, patients with brain metastases have invariably been excluded from past clinical trials with chemotherapeutic agents and, more recently, with immune checkpoint inhibitors (7). Recent insights into the immune landscape of the CNS, as well as of the brain tumor microenvironment, have increased our understanding of the immune-biology of brain metastases (7). This knowledge, along with the recent availability of effective immunomodulatory mAbs, including anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and anti-programmed death-1 (PD-1)/-ligand (PD-L1) mAbs, has supported the use of these mAbs in patients with brain metastases as well as in primary CNS tumors, challenging the dogma that immunotherapy has limited efficacy in this clinical setting (7, 8). Along this line, we showed in the NIBIT-M1 phase II study that ipilimumab, combined with the standard schedule of fotemustine approved as single agent for patients with melanoma without or with brain metastases (9), appears to be an active therapeutic strategy in patients with melanoma with asymptomatic brain disease, meriting further investigation (10, 11). More recent results from phase II studies in patients with melanoma with asymptomatic brain metastases reported that cotargeting of CTLA-4 and PD-1 induced objective intracranial tumor responses in approximately 50% of patients (12–15), providing initial support for the efficacy of ipilimumab plus nivolumab in this hard-to-treat patient population.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

To the best of our knowledge, the NIBIT-M2 study is the first phase III trial demonstrating that ipilimumab plus nivolumab, unlike ipilimumab plus fotemustine, significantly improves the survival of patients with *BRAF* wild-type or mutant melanoma and untreated, asymptomatic brain metastases, compared with chemotherapy with fotemustine, and with a better safety profile. These findings, along with the substantial proportion of patients treated with ipilimumab plus nivolumab having long-term survival, strongly support the role of this therapeutic combination as a first-line treatment in melanoma with asymptomatic brain metastases, regardless of the tumor BRAF status. Furthermore, the induction of durable, complete, clinical responses suggests that treatment with ipilimumab plus nivolumab should be carefully evaluated and weighed against surgery or radiotherapy for patients with melanoma with asymptomatic brain metastases. Finally, our findings may pave the way to explore treatment with ipilimumab plus nivolumab in other tumor types in which the combination has already shown activity in extracranial disease.

In this article, we report the primary analysis and the long-term follow-up of the NIBIT-M2 study, the first randomized phase III trial designed to investigate the efficacy of the combination of ipilimumab plus nivolumab or ipilimumab plus fotemustine compared with fotemustine alone on the overall and long-term survival of patients with metastatic melanoma and active, asymptomatic, and untreated melanoma brain metastases.

Patients and Methods

Patients

Adult patients (ages ≥18 years) with stage IV, *BRAF* wild-type or mutant melanoma with active, untreated and asymptomatic brain metastases (diameter, 5–20 mm), a life expectancy of ≥12 weeks, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, were eligible for inclusion. No prior therapy for stage IV melanoma is allowed. Symptomatic brain metastases requiring immediate local intervention [radiotherapy (RT) and/or surgery], leptomeningeal disease, ocular melanoma, and autoimmune diseases are exclusion criteria.

Study design and treatment

The Italian Network for Tumor Biotherapy (NIBIT) Foundation conceived and sponsored the NIBIT-M2 trial, a randomized, open-label, phase III trial, comparing the efficacy of ipilimumab plus fotemustine to fotemustine alone. Patients were enrolled at nine centers in Italy. Because of the preliminary results of ipilimumab plus nivolumab in patients with metastatic melanoma (16), enrollment in the NIBIT-M2 trial was halted in November 2013, when six patients had been enrolled in the ipilimumab plus fotemustine arm and four in the fotemustine arm, and the protocol was amended to include an ipilimumab plus nivolumab arm. Study enrollment resumed in November 2014. Eligible patients were randomly assigned in a 1:1:1 ratio to fotemustine, ipilimumab plus fotemustine, or ipilimumab plus nivolumab. All study drugs were administered intravenously. Both as monotherapy and in combination with ipilimumab, the fotemustine dosing regimen was as used by Avril and colleagues (9) in a phase III trial comparing fotemustine with dacarbazine. Fotemustine was administered at a dose of 100 mg/m^2 over 60 minutes, once every week for three doses (weeks 1, 2 and 3; induction phase), and once every 3 weeks from week 9 for six doses (maintenance phase). When given in combination with fotemustine, the ipilimumab dosing schedule was the same as that previously reported for the NIBIT-M1 trial (10, 11), and comprised ipilimumab 10 mg/kg over 90 minutes given as induction every 3 weeks for four doses (weeks 1, 4, 7, and 10), and then as maintenance every 12 weeks from week 24. In the ipilimumab plus nivolumab arm, patients received ipilimumab 3 mg/kg over 90 minutes together with nivolumab 1 mg/kg over 60 minutes every 3 weeks for four doses (weeks 1, 4, 7, and 10; induction phase), and from week 12 received maintenance treatment with nivolumab 3 mg/kg over 60 minutes every 2 weeks (Supplementary Fig. S1). Investigational drugs, ipilimumab and nivolumab, were provided by Bristol Myers Squibb; fotemustine was purchased as standard of care for patients with melanoma with brain metastases through the Italian National Health System.

Dose reduction was allowed only for fotemustine; dose delays were allowed for toxicity management. Treatment was continued until confirmed progressive disease, unacceptable toxicity, or patient refusal. Study treatment was permanently discontinued in patients who reported grade 4 toxicities, any grade 3 nonskin, drug-related adverse event (AE) lasting more than 7 days, or grade 2 drug-related uveitis, eye pain, or blurred vision.

Tumor response, as categorized by the World Health Organization (WHO; for the fotemustine arm) and immune-related response criteria (for the immunotherapy arms; ref. 17), was assessed by investigators based on brain MRI and CT scans with contrast of neck, chest, abdomen, and pelvis, as well as photographic documentation of skin lesions for all patients at the following timepoints: screening, weeks 12, 20, 28, and 36, and then every 12 weeks until disease progression or treatment was discontinued. Responses were confirmed at least 4 weeks later.

The study was done in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. The protocol was approved by appropriate independent ethics committees of participating Institutions. All participants or their legal representatives provided written informed consent before enrollment.

Endpoints and analysis

The primary endpoint was overall survival (OS), calculated from the date of randomization until the date of death. Secondary endpoints were objective response rate (ORR) and disease control rate in and outside the brain; time to response and duration of response; intracranial and global progression-free survival (PFS); intracranial and extracranial PFS; quality of life and multiple translational studies.

Safety was continuously assessed for all patients who received at least one dose of the study treatment, from the date of the first dose until 70 days (five half-lives) after the last dose is received. Clinical assessment of vital signs, physical examination, and clinical laboratory tests was also performed at screening, during treatment and the end of treatment visit. AEs were graded according to the National Cancer Institute Common Terminology Criteria (CTCAE), version 4.0.

Statistical analysis

The primary analysis compared OS in the experimental ipilimumab plus fotemustine arm with the control fotemustine arm, and OS in the experimental ipilimumab plus nivolumab arm with fotemustine only. Each comparison was set to a significance level of 0.025 to verify, with a power of 80%, an increase in median OS from 5 months in the control

arm to 11 months in both experimental arms. We planned to randomize 153 patients 1:1:1 to obtain the required total of 90 events. The design included a planned interim analysis for efficacy after 60 events; according to the O'Brian-Fleming alpha spending function, the *P* value to refuse the null hypothesis was set to 0.0015. The interim analysis was performed after 58 events, because only three events were recorded in the 24 months preceding data cutoff. Ahead of the interim analysis, enrollment in the study was suspended as endorsed by the independent ethics committees of participating institutions. All data reported here are based on this interim analysis. A regular review of the safety data was performed by an independent Data Safety Monitoring Board, including a pre-planned review after the first 15 patients enrolled in each treatment arm; no stopping rules were included in the protocol.

Analyses of efficacy endpoints were to be based on all randomized subjects. However, patients who withdrew informed consent after randomization but before starting treatment were excluded from the study; the remaining patients were included in all analyses of efficacy and safety.

OS was analyzed using an unstratified log-rank test (two-sided), with hazard ratios (HRs) for the combination arms relative to the fotemustine arm and the associated 95% confidence interval (CI) computed using a Cox proportional hazard model. OS was estimated using the Kaplan–Meier Product Limit method and a two-sided 95% CI for median OS was computed using the Brookmeyer and Crowley method. Other time-to-event analyses for secondary endpoints, including PFS (both global and intracranial) and duration of objective immune-related response, and intracranial, were analyzed similarly. The OS rate, defined as the probability that a patient was alive at 12, 24, 36, 48, and 60 months following the date of randomization, was estimated via the Kaplan–Meier method with a corresponding two-sided 95% CI. Secondary efficacy endpoints were evaluated with exploratory intent and no formal hypothesis testing was planned. For the proportion endpoints ORR and disease control rate, exact two-sided 95% CI were calculated using the binomial method. Immune-related duration of response and time to response were estimated only for patients with a confirmed best overall response of immune-related complete or partial response. Median follow-up was estimated with the reverse Kaplan–Meier method. Time to response was summarized using descriptive statistics. All statistical analyses used IBM-SPSS statistical software, version 21.0. This trial is registered with European Union Drug Regulating Authorities Clinical Trials, number 2012–004301–27 and with ClinicalTrials.gov. Number NCT02460068.

Results

From January 24, 2013 to September 4, 2018, 96 patients with metastatic melanoma and active, asymptomatic brain metastases were assessed for eligibility, and 80 patients were enrolled and randomized (27 to fotemustine, 26 to ipilimumab plus fotemustine, and 27 to ipilimumab plus nivolumab). Four patients randomized to fotemustine withdrew their consent before receiving any treatment and were excluded from the study; the remaining 76 patients were treated and

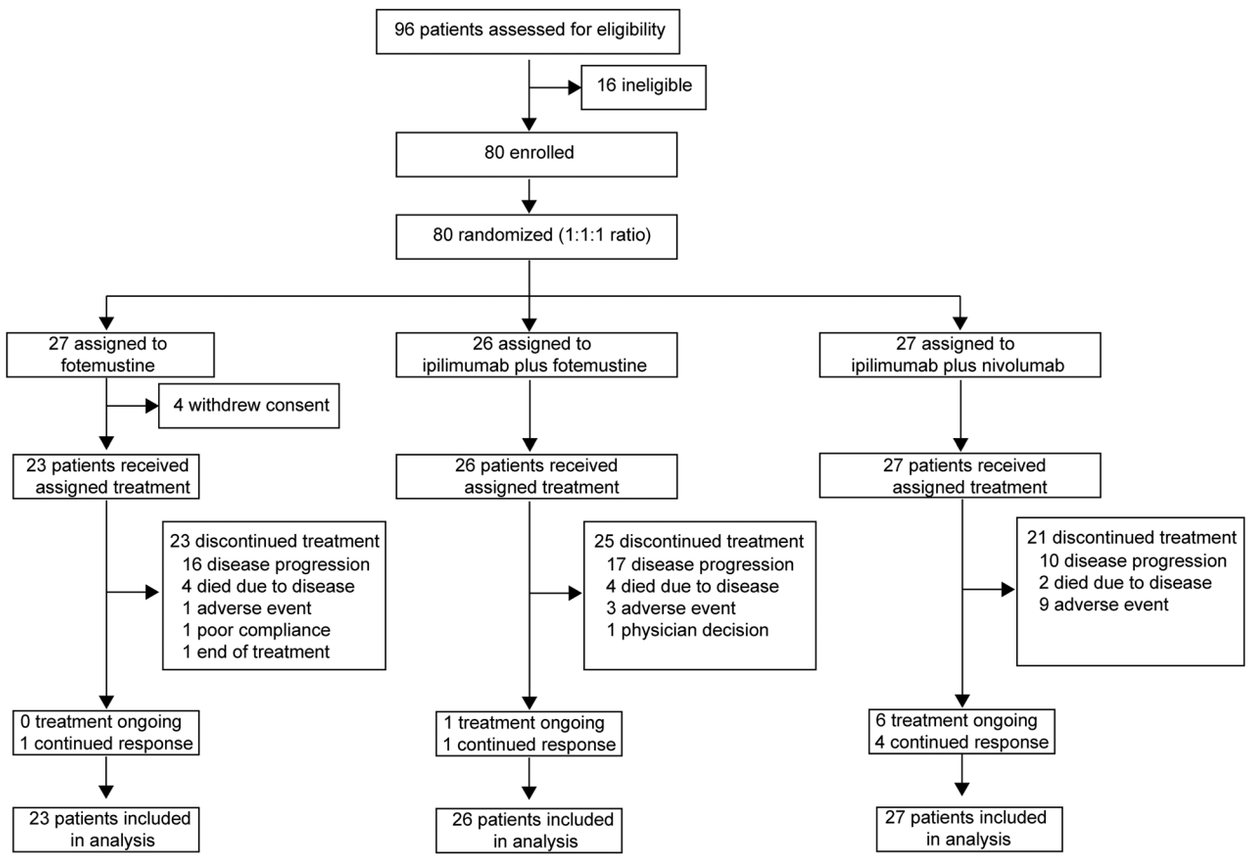

Figure 1.
Trial profile.

Table 1. Baseline characteristics.

	Fotemustine ($n = 23$)[a]	Ipilimumab plus fotemustine ($n = 26$)	Ipilimumab plus nivolumab ($n = 27$)
Sex			
Male	15 (65%)[b]	16 (62%)	17 (63%)
Female	8 (35%)	10 (38%)	10 (37%)
Age, y	57 (20–80)[c]	60 (31–74)	56 (25–79)
ECOG performance status			
0	21 (91%)	18 (69%)	22 (81%)
1	2 (9%)	8 (31%)	5 (19%)
Number of brain lesions			
1	5 (22%)	12 (46%)	7 (26%)
2	3 (13%)	8 (31%)	8 (30%)
3	5 (22%)	1 (4%)	3 (11%)
>3	10 (43%)	5 (19%)	9 (33%)
Target brain lesion diameters (mm)			
5×5	6 (26%)	4 (15%)	5 (19%)
5–20	17 (74%)	22 (85%)	22 (81%)
Previous local treatments for brain metastases			
Surgery	4 (17%)	5 (19%)	7 (26%)
Stereotactic radiosurgery	2 (9%)	0	0
Whole brain radiotherapy	1 (4%)	0	0
BRAF status			
Mutated (*BRAF*–V600)	8 (35%)	11 (42%)	11 (41%)
Wild-type	13 (57%)	15 (58%)	15 (56%)
Unknown	2 (9%)	0	1 (4%)
Serum lactate dehydrogenase			
Elevated	3 (13%)	13 (50%)	7 (26%)
Normal	20 (87%)	13 (50%)	20 (74%)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Number of treated patients per arm.
[b]*n* (%).
[c]Median (range).

included in all analyses (**Fig. 1**). Baseline characteristics are reported in **Table 1** and were similar in the three study arms, apart from a higher proportion of patients with elevated serum lactate dehydrogenase levels and an ECOG performance status of 1 in the ipilimumab plus fotemustine arm.

Efficacy

At data cutoff for the primary analysis (September 1, 2020), with a median follow-up of 52 months (IQR, 38–62), no patients in the fotemustine arm, one (4%) patient in the ipilimumab plus fotemustine arm, and six (22%) patients in the ipilimumab plus nivolumab arm were still on treatment. Twenty-one (91%) of 23 patients in the fotemustine-alone arm (median number of cycles 3; IQR, 3–3) competed induction treatment. In the ipilimumab plus fotemustine arm, 22/26 (85%) patients completed fotemustine induction treatment (median number of cycles 3; IQR, 2–3) and 13/26 (50%) patients completed induction treatment with ipilimumab (median number of cycles 4; IQR, 3–4). Finally, in the ipilimumab plus nivolumab arm, 15/27 (56%) patients completed induction treatment both with ipilimumab and with nivolumab (median number of cycles for each treatment 4; IQR, 3–4). In the maintenance phase, 12 (52%) and 16 (70%) patients received at least one dose of fotemustine in the fotemustine-only and ipilimumab plus fotemustine arms, respectively; seven (27%) and 14 (52%) patients received at least one dose of ipilimumab or nivolumab in the ipilimumab plus fotemustine and ipilimumab plus nivolumab arms, respectively (Supplementary Table S1).

At data cutoff, 69 (91%) patients had discontinued treatment, most frequently because of disease progression (43 patients; 62%) or drug-related AEs (11 patients; 16%; **Fig. 1**). Subsequent therapy was received by 13/23 (57%), 10/26 (38%), and 9/27 (33%) patients in the fotemustine, ipilimumab plus fotemustine, and ipilimumab plus nivolumab arms, respectively (Supplementary Fig. S2). Of note, none of the patients enrolled in the three arms of this study received ipilimumab plus nivolumab as subsequent treatment at disease progression. Furthermore, among 12 patients still alive in the ipilimumab plus nivolumab arm, six remained on study treatment, four had permanently discontinued therapy due to drug-related AEs, and only two had received subsequent treatment (Supplementary Fig. S2).

As of September 1, 2020, with a median follow-up of 52 months, median OS was 8.5 months (95% CI, 4.8–12.2) for the fotemustine-only arm, 8.2 months (95% CI, 2.2–14.3) for the ipilimumab plus fotemustine arm, and 29.2 months (95% CI, 0–65.1) for the ipilimumab plus nivolumab arm (**Fig. 2A**). The 4-year OS rate was 11% (95% CI, 0–24.4) in the fotemustine arm, 10% (95% CI, 0–22.6) in the ipilimumab plus fotemustine arm, and 41% (95% CI, 20.6–61.4) in the ipilimumab plus nivolumab arm (**Table 2**); OS at 4 years was significantly higher with ipilimumab plus nivolumab than with fotemustine ($P = 0.015$). Although the risk of death did not differ for ipilimumab plus fotemustine versus fotemustine only (HR, 1.09; 95% CI, 0.59–1.99; $P = 0.78$), the combination of ipilimumab plus nivolumab resulted in a 56% reduction in risk of death when compared with fotemustine only (HR, 0.44; 95% CI, 0.22–0.87; $P = 0.017$), although it did not reach the per-protocol planned level of significance ($P < 0.0015$).

The intracranial ORR was 0% (0/23; 95% CI, NE), 19% (5/26; 95% CI, 4.1–34.4), and 44% (12/27; 95% CI, 25.7–63.2) in the fotemustine-only, ipilimumab plus fotemustine, and ipilimumab plus nivolumab arms, respectively, and the global ORR was 0% (0/23; 95% CI, NE), 23% (6/23; 95% CI, 6.9–39.3), and 44% (12/27; 95% CI, 25.7–63.2), respectively (**Table 2**). The median intracranial PFS was 3.0 months (95% CI, 2.3–3.6), 3.3 months (95% CI, 1.2–5.4), and 8.7 months (95% CI, 0–19.9) in the fotemustine-only, ipilimumab plus fotemustine, and ipilimumab plus nivolumab arms, respectively (**Fig. 2B** and **Table 2**), and was identical to the median global PFS within each of the three study arms (**Fig. 2C** and **Table 2**). Disease progressed both at intracranial and extracranial sites in all patients with progression, apart from in one patient from the ipilimumab plus fotemustine arm who had progression at extracranial sites only. Among the 73 patients in whom *BRAF* gene mutation status was investigated, 30 (41%) carried a *BRAF*-V600 mutation: eight (35%) in the fotemustine arm, 11 (42%) in the ipilimumab plus fotemustine arm, and 11 (41%) in the ipilimumab plus nivolumab arm (**Table 1**). A *post hoc* analysis of this patient population showed a median OS for *BRAF* mutant melanoma of 19.6 (95% CI, 3.7–35.6), 11.6 (95% CI, 4.9–18.4), and 45.0 (95% CI, 0–100.3) months in the fotemustine, ipilimumab plus fotemustine, and ipilimumab plus nivolumab arms, respectively, and for *BRAF* wild-type patients of 5.3 (95% CI, 1.2–9.4), 4.3 (95% CI, 0.3–8.3), and 19.9 (95% CI, 0–42.4) months, respectively (Supplementary Table S2). The median PFS for *BRAF* mutant and *BRAF* wild-type patients with melanoma is reported in Supplementary Table S2.

Safety

In the fotemustine-only, ipilimumab plus fotemustine, and ipilimumab plus nivolumab arms, respectively, 19 (83%), 21 (81%), and 21 (78%) patients had any grade treatment-related AEs and 11

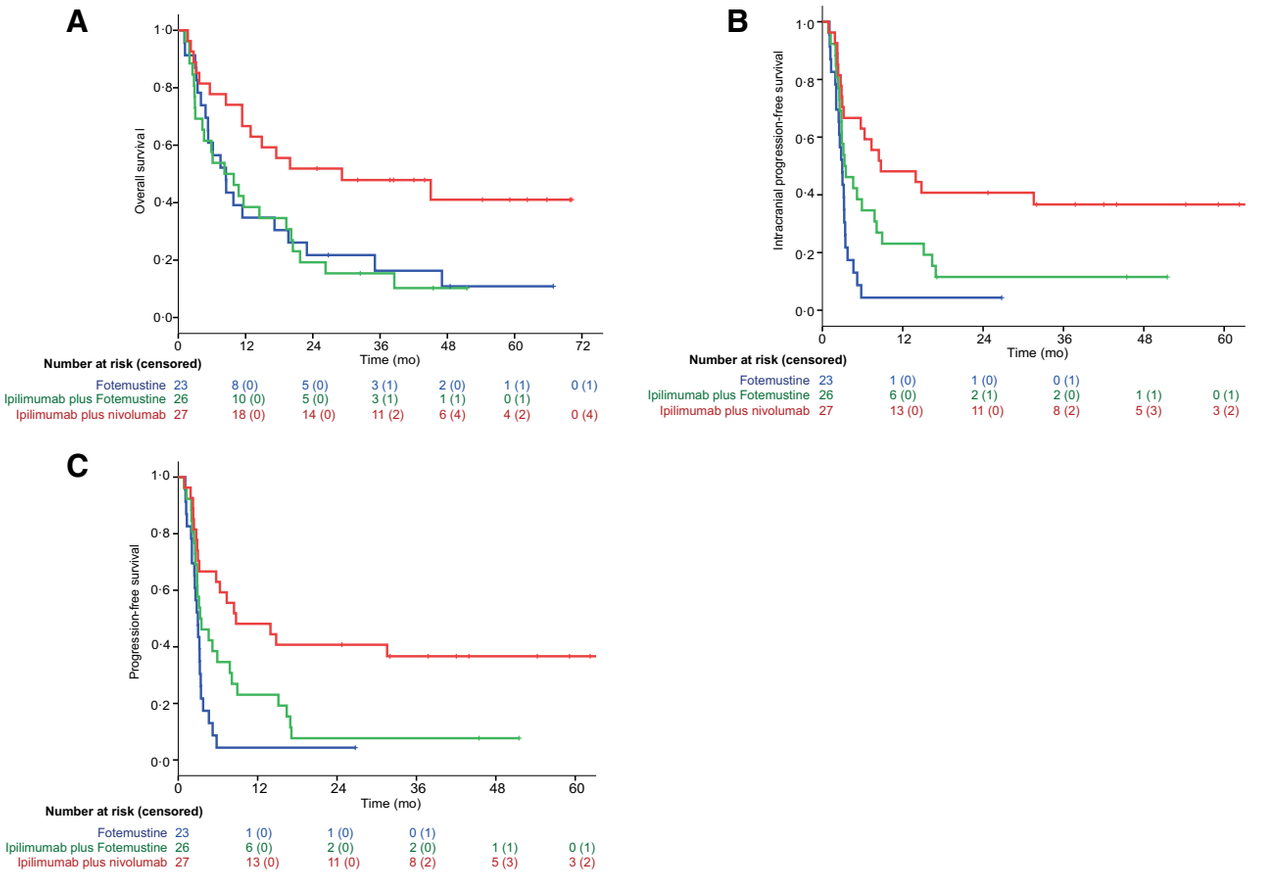

Figure 2.

Kaplan–Meier plots of (**A**) overall survival, (**B**) intracranial progression-free survival (PFS), and (**C**) global PFS of all treated patients. Vertical lines indicate censoring. CI, confidence interval; HR, hazard ratio.

(48%), 18 (69%), and eight (30%) patients had grade 3 or 4 treatment-related AEs across both induction and maintenance (**Table 3**). No treatment-related deaths or unexpected toxicities were observed. The most common AEs were myelotoxicity in the fotemustine-only and ipilimumab plus fotemustine arms, and immune-related AEs in the ipilimumab and fotemustine and the ipilimumab plus nivolumab arms; among the latter, the most common were skin- and liver-related events (**Table 3**). Any grade and grade 3 to 4 immune-related AEs were 58% and 38% for ipilimumab combined with fotemustine, and were 70% and 30% for ipilimumab combined with nivolumab, respectively. Treatment-related nausea and vomiting were also recorded (**Table 3**). During maintenance treatment, the most frequent treatment-related AEs were myelotoxicity in the fotemustine arm (5/12 patients; 42%), diarrhea in the ipilimumab plus fotemustine arm (1/7 patients; 14%), and liver toxicity in the ipilimumab plus nivolumab arm (6/14 patients; 43%). Among these 33 patients, grade 3 to 4 AEs were reported in five (15%) patients, and comprised diarrhea ($n = 2$; 6%), liver toxicity ($n = 2$; 6%), and myelotoxicity ($n = 1$; 3%). In the fotemustine-only, ipilimumab plus fotemustine, and ipilimumab plus nivolumab arms, two (9%), one (4%), and one (4%) patients, respectively, reported CNS events (hemorrhage, headache, and seizure) that were all attributed to disease progression.

Treatment-related AEs and immune-related adverse reactions were generally manageable and reversible as per-protocol guidance. Of the 18 (40%) patients with grade 3 or 4 immune-related adverse reactions, 16 (89%) were treated with steroids, including one patient with liver toxicity who also received mycophenolate mofetil. Median time to resolution of grade 3 to 4 immune-related AEs was 7 days (IQR, 4–25).

Discussion

To our knowledge, NIBIT-M2 is the first randomized phase III study to show that first-line treatment with ipilimumab plus nivolumab significantly ($P = 0.017$) improves OS of patients with metastatic melanoma and active, untreated, asymptomatic brain metastases when compared with fotemustine. Most importantly, the 4-year OS rate was significantly higher in patients receiving ipilimumab plus nivolumab as compared with fotemustine (41% vs. 11%). Furthermore, the incidence of high-grade treatment-related AEs was markedly lower (30%) in patients treated with ipilimumab plus nivolumab than in patients in both fotemustine-containing arms (48% and 69%, respectively).

In the present randomized study, the addition of ipilimumab to fotemustine induced intracranial disease control in 35% of treated patients, although it failed to confer a survival benefit when compared with fotemustine alone. This latter finding is at variance with the long-term survival we observed in a subset of patients with asymptomatic brain metastases treated with ipilimumab combined with fotemustine

Table 2. Summary of survival and tumor response.

	Fotemustine ($n = 23$[a])	Ipilimumab plus fotemustine ($n = 26$)	Ipilimumab plus nivolumab ($n = 27$)
Overall survival			
Deaths	20 (87.0%)[b]	23 (88.5%)	15 (55.6%)
Median OS, mo (95% CI)[c]	8.5 (4.8–12.2)	8.2 (2.2–14.3)	29.2 (0–65.1)
1-y OS rate[d]	34.8% (15.4–54.2)	38.5% (19.9–57.1)	66.7% (48.9–84.5)
2-y OS rate	21.7% (4.9–38.5)	19.2% (4.1–34.3)	51.9% (33.1–70.7)
3-y OS rate	16.3% (0.6–32.0)	15.4% (1.5–29.3)	47.9% (28.9–66.9)
4-y OS rate	10.9% (0–24.4)	10.3% (0–22.6)	41.0% (20.6–61.4)
5-y OS rate[e]	10.9% (0–24.4)	NE	41.0% (20.6–61.4)
Intracranial response[f]			
Overall (95% CI)	0	5 (19.2%; 4.1–34.4)	12 (44.4%; 25.7–63.2)
Complete response	0	2 (7.7%)	10 (37.0%)
Partial response	0	3 (11.5%)	2 (7.4%)
Stable disease	5 (21.7%)	4 (15.4%)	3 (11.1%)
Progressive disease	18 (78.3%)	17 (65.4%)	12 (44.4%)
Global response[f]			
Overall (95% CI)	0	6 (23.1%; 6.9–39.3)	12 (44.4%; 25.7–63.2)
Complete response	0	1 (3.9%)	6 (22.2%)
Partial response	0	5 (19.2%)	6 (22.2%)
Stable disease	4 (17.4%)	2 (7.7%)	3 (11.1%)
Progressive disease	19 (82.6%)	18 (69.2%)	12 (44.4%)
Median time to global response, months (IQR)	NA	3.4 (2.9–4.7)	3.0 (2.7–4.8)
Median duration of global response, months (95% CI)	NA	13.8 (10.5–17.2)	18.2 (NE)
Intracranial PFS			
Patients with disease progression	22 (95.7%)	23 (88.5%)	17 (63.0%)
Median PFS, mo (95% CI)	3.0 (2.3–3.6)	3.3 (1.2–5.4)	8.7 (0.0–19.9)
6-mo PFS rate[d]	4.3% (0–12.7)	34.6% (16.4–52.8)	63.0% (44.8–81.2)
1-y PFS rate	4.3% (0–12.7)	23.1% (6.8–39.4)	48.1% (29.3–66.9)
2-y PFS rate	4.3% (0–12.7)	11.5% (0–23.8)	40.7% (22.1–59.3)
3-y PFS rate	NE	11.5% (0–23.8)	36.7% (18.5–54.9)
4-y PFS rate	NE	11.5% (0–23.8)	36.7% (18.5–54.9)
Global PFS			
Patients with disease progression	22 (95.7%)	24 (92.3%)	17 (63.0%)
Median PFS, mo (95% CI)	3.0 (2.3–3.6)	3.3 (1.2–5.4)	8.7 (0.0–19.9)
6-mo PFS rate[d]	4.3% (0–12.7)	34.6% (16.4–52.8)	63.0% (44.8–81.2)
1-y PFS rate	4.3% (0–12.7)	23.1% (6.8–39.4)	48.1% (29.3–66.9)
2-y PFS rate	4.3% (0–12.7)	7.7% (0–17.8)	40.7% (22.1–59.3)
3-y PFS rate	NE	7.7% (0–17.8)	36.7% (18.5–54.9)
4-y PFS rate	NE	7.7% (0–17.8)	36.7% (18.5–54.9)

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable; NE, not evaluable; OS, overall survival; PFS, progression-free survival.
[a]Number of treated patients per arm.
[b]*n* (%).
[c]% (95% CI).
[d]Rate estimated from Kaplan–Meier analysis.
[e]Projected value.
[f]Objective response by investigator review per WHO criteria (fotemustine arm) or immune-related response criteria (ipilimumab plus fotemustine and ipilimumab plus nivolumab arms; ref. 17).

in the single-arm phase II NIBIT-M1 study in treatment-naïve or pretreated patients with metastatic melanoma (11). The lack of survival benefit we observed in the NIBIT-M2 study for patients treated with ipilimumab combined with fotemustine may possibly be explained, at least in part, by the worse ECOG performance status and higher lactate dehydrogenase levels of patients treated with ipilimumab combined with fotemustine in the NIBIT-M2 study. Nevertheless, the comprehensive efficacy observed with ipilimumab plus nivolumab in the NIBIT-M2 study strongly suggest that chemotherapy with fotemustine, either alone or combined with ipilimumab, is not a strategy to be further pursued in patients with melanoma with brain metastases. This opinion is supported by the higher toxicity rates we observed in both fotemustine-containing arms, compared with the ipilimumab plus nivolumab arm.

The results of this primary analysis of the NIBIT-M2 study at a median follow-up of 52 months, demonstrating a median OS of 29.2 months, a 41% 4-year survival rate, and a projected 41% 5-year survival rate (**Table 2**) for patients treated with ipilimumab plus nivolumab, are obviously clinically meaningful for patients with melanoma with a very dismal prognosis due to brain metastases, although not reaching the per-protocol planned statistical significance versus fotemustine. The long-term efficacy of first-line ipilimumab plus nivolumab in metastatic melanoma patient without brain metastases was first demonstrated by the phase III Checkmate 067 study, in

Table 3. Summary of AEs occurring in the study population.

	Fotemustine ($n = 23$)[a]		Ipilimumab plus fotemustine ($n = 26$)		Ipilimumab plus nivolumab ($n = 27$)	
	Any grade	G3–G4	Any grade	G3–G4	Any grade	G3–G4
Any adverse event[b]	**23 (100%)[c]**	**16 (70%)**	**23 (88%)**	**22 (85%)**	**23(85%)**	**14 (52%)**
Treatment-related adverse events	**19 (83%)**	**11 (48%)**	**21 (81%)**	**18 (69%)**	**21 (78%)**	**8 (30%)**
Nausea	3 (13%)	0	3 (12%)	0	3 (11%)	0
Vomiting	0	0	1 (4%)	0	1 (4%)	0
Myelotoxicity						
Anemia	5 (22%)	0	3 (12%)	1 (4%)	0	0
Thrombocytopenia	11 (48%)	4 (17%)	14 (54%)	10 (38%)	0	0
Neutropenia	10 (43%)	7 (30%)	10 (38%)	6 (23%)	0	0
Leukopenia	10 (43%)	3 (13%)	2 (8%)	2 (8%)	0	0
Other (fever, fatigue, liver)	10 (43%)	3 (13%)	8 (31%)	1 (4%)	12(44%)	0
Any immune-related adverse events	**0**	**0**	**15 (58%)**	**10 (38%)**	**19 (70%)**	**8 (30%)**
Skin						
Rash	0	0	9 (35%)	3 (11.5%)	10 (37%)	1 (4%)
Pruritus	0	0	5 (19%)	0	6 (22%)	0
TEN	0	0	0	0	1 (4%)	1 (4%)
Hepatic						
ALT increase	0	0	8 (31%)	7 (27%)	10 (37%)	5 (19%)
AST increase	0	0	9 (35%)	3 (12%)	8 (30%)	3 (11%)
Bilirubin increase	0	0	2 (8%)	0	0	0
Hepatic failure			1 (4%)	1 (4%)	1 (4%)	1 (4%)
Gastrointestinal (diarrhea or colitis)	0	0	5 (19%)	2 (8%)	7 (26%)	2 (7%)
Endocrine						
Hyperthyroidism	0	0	3 (12%)	2 (8%)	3 (11%)	0
Hypothyroidism	0	0	3 (12%)	0	4 (15%)	0
Hypophysitis	0	0	0	0	1 (4%)	0
Other (amylase or lipase increase)	0	0	0	0	3 (11%)	0

Note: All reported treatment-related and immune-related AEs are shown.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade; TEN, toxic epidermal necrolysis.
[a]Number of treated patients per cohort.
[b]AEs were graded using the NCI Common Terminology Criteria for AEs (version 4.0).
[c] *n* (%).

which 52% of patients were alive at 5 years (18). Consistent with these results is the long-term efficacy of ipilimumab plus nivolumab in the NIBIT-M2 study in melanoma patients with brain metastases, who bear a markedly worse prognosis. This convincing long-term efficacy of ipilimumab combined with nivolumab in patients with melanoma is further supported by the finding that at the time of data cutoff only a minority (17%) of patients alive at 4 years in the ipilimumab plus nivolumab arm of the NIBIT-M2 study had received subsequent therapy. Similarly, only 18% of patients alive at 5 years in the ipilimumab plus nivolumab arm of the CheckMate 067 study had received subsequent treatment (18).

Two recent phase II studies, ABC and CheckMate 204, were designed to investigate the intracranial efficacy of ipilimumab plus nivolumab on brain metastases of patients with melanoma (12, 13). No long-term follow-up is available for the CheckMate 204 study. Of note, however, the 3-year follow-up from the ABC trial has been recently presented (15). Although interstudy comparison needs to be placed in context, the 3-year survival rate was similar for patients enrolled in the NIBIT-M2 and ABC trials (48% and 49%) although, to the best of our knowledge, the impact of potential subsequent treatment(s) in the ABC trial was not reported (15). Additional long-term analyses of both the ABC and CheckMate 204 studies are eagerly awaited to further confirm the long-term efficacy of ipilimumab plus nivolumab in patients with melanoma with brain metastases.

In the NIBIT-M2 study, the intracranial ORR with ipilimumab plus nivolumab was 44% [10 complete responses (CRs) and two partial responses (PRs)], whereas the intracranial ORRs were 46% (six CRs and 10 PRs) and 55% (24 CRs and 28 PRs) in the ABC and CheckMate 204 study, respectively (12, 13). These findings comprehensively demonstrate a relevant clinical efficacy of ipilimumab plus nivolumab in the control of melanoma brain metastases. Of note, and consistent with the concordant intra- and extracranial activity of ipilimumab plus nivolumab in the ABC and CheckMate 204 studies (12, 13), the NIBIT-M2 study intracranial and global ORRs were identical (44%).

Available data on the impact of the *BRAF* gene status on the efficacy of immunotherapy for melanoma brain metastases remain controversial (13, 19, 20); the *post hoc* analysis we performed in the NIBIT-M2 study suggested better efficacy with ipilimumab plus nivolumab in *BRAF* mutant versus *BRAF* wild-type patients with melanoma. These findings, although with intrinsic limitations of a *post hoc* analysis, seem to suggest that prospective studies should be designed to specifically assess the role of *BRAF* status in determining the outcome of therapy with ipilimumab plus nivolumab on melanoma brain metastases.

The safety profiles of treatment in each arm of our study were consistent with those in previous studies in patients with brain metastases (9, 10, 12, 13), and were related to the therapeutic

agents administered, without overlapping toxicities. Importantly, no treatment-related deaths, unexpected or uncommon treatment-related AEs were observed in any cohort of this study; of particular note, there were no unexpected neurological toxicities. All treatment-related adverse were manageable per-protocol guidelines. Our experience thus suggests that first-line treatment with ipilimumab plus nivolumab is a feasible and manageable strategy even in this challenging population of patients with melanoma metastatic to the brain.

The overall and long-term survival results of our phase III NIBIT-M2 study in patients with melanoma with asymptomatic brain metastases strongly contribute breaking the dogma that immunotherapy has limited efficacy in brain metastases. Recognition of the value of immunotherapy in treating asymptomatic melanoma brain metastases suggests that in first-line patients, the role of surgery and RT might be reappraised for this subgroup of patients, and paves the way to broadening investigation of immunotherapy in tumors of different histology when metastatic to the brain.

Authors' Disclosures

A.M. Di Giacomo reports personal fees from BMS and MSD and nonfinancial support from Pierre-Fabre during the conduct of the study as well as personal fees from Incyte, Sanofi, and GSK outside the submitted work. V. Chiarion-Sileni reports other support from BMS during the conduct of the study and other support from MSD (occasional consultant role), Pierre-Fabre (occasional consultant role, invited speaker, accommodations, and travel expenses for medical meeting), Merck-Serono and Novartis (occasional consultant role). M.D. Vecchio reports personal fees from BMS, MSD, Novartis, Pierre-Fabre, and Sanofi outside the submitted work. P.F. Ferrucci reports grants and personal fees from BMS, Novartis, MSD, Pierre-Fabre, and Roche outside the submitted work. M. Guida reports membership on the advisory board for Bristol Meyers Squibb, Novartis, and Merck Sharp & Dohme. P. Quaglino reports personal fees and nonfinancial support from BMS and Novartis, as well as personal fees from MSD and Pierre-Fabre during the conduct of the study. P. Marchetti reports other support from BMS during the conduct of the study as well as other support from Roche, MSD, Novartis, AstraZeneca, and Pfizer outside the submitted work and reports funding from Bristol Myers Squibb, Novartis, Pfizer, Merck Sharp & Dohme, AstraZeneca, Boehringer, Celgene, and Roche. A. Covre reports other support from Epigen Therapeutics S.r.l. outside the submitted work. R. Camerini reports grants from Bristol Myers Squibb during the conduct of the study as well as other support from ReiThera Srl, Alfasigma S.p.A., Cosmo Nbv, and Epigen Therapeutics outside the submitted work. L. Calabrò reports other support from BMS during the conduct of the study as well as other support from AstraZeneca, MSD, Sanofi, and Roche outside the submitted work. M. Maio reports other support from BMS and Astex during the conduct of the study as well as personal fees from BMS, Roche, Incyte, AstraZeneca, Amgen, Pierre-Fabre, Eli Lilly, GSK, Sciclone, Sanofi, Alfasigma, and Merck Serono, other support from Epigen Therapeutics, and other support from Theravance outside the submitted work as well as reports a patent for WO 2014/128245 pending. No disclosures were reported by the other authors.

Authors' Contributions

A.M. Di Giacomo: Conceptualization, data curation, supervision, validation, writing-original draft, writing–review and editing. **V. Chiarion-Sileni:** Data curation, writing–review and editing. **M.D. Vecchio:** data curation, writing–review and editing. **P.F. Ferrucci:** Data curation, writing–review and editing. **M. Guida:** Data curation, writing–review and editing. **P. Quaglino:** Data curation, writing–review and editing. **M. Guidoboni:** Data curation, writing–review and editing. **P. Marchetti:** Data curation, writing–review and editing. **O. Cutaia:** Data curation, writing–review and editing. **G. Amato:** Data curation, writing–review and editing. **A. Covre:** Data curation, writing–review and editing. **R. Camerini:** Data curation, methodology, writing–review and editing. **L. Calabrò:** Data curation, writing–review and editing. **M. Valente:** Data curation, writing–review and editing. **D. Giannarelli:** Data curation, formal analysis, validation, methodology, writing–review and editing. **M. Mandalà:** Data curation, writing–review and editing. **M. Maio:** Conceptualization, data curation, supervision, validation, writing–original draft, writing–review and editing.

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