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## Real-world outcomes in patients with melanoma brain metastasis: a multisite retrospective chart review study of systemic treatments

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# Real-world outcomes in patients with melanoma brain metastasis: a multisite retrospective chart review study of systemic treatments

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**ABSTRACT**

**Objective** This study examined real-world treatment patterns and outcomes in patients with melanoma brain metastasis (MBM) treated with first-line immunotherapy consisting of nivolumab plus ipilimumab or anti-programmed death-1 (PD-1) monotherapy (nivolumab or pembrolizumab) or targeted therapy consisting of BRAF/MEK inhibitors.

**Design** Retrospective chart review study.

**Setting** Academic medical centers, community hospitals, and private practice offices.

**Participants** Included patients diagnosed with melanoma with brain metastasis in the United States.

**Outcome measures** Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method and compared between treatments in a univariate Cox proportional hazards model.

**Results** In total, 472 patients with MBM who received first-line nivolumab plus ipilimumab (n=246), anti-PD-1 monotherapy (n=112), or BRAF/MEK inhibitors (n=114) were identified. Median follow-up times were 15.4 months (range 0.1 to 37.0), 13.3 months (range 0.3 to 36.6), and 13.9 months (range 1.9 to 36.5), respectively. Patients demonstrated trends toward longer OS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.47, 95% CI 0.34 to 0.67) or BRAF/MEK inhibitors (HR 0.72, 95% CI, 0.50 to 1.04), and trends toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.74, 95% CI 0.53 to 1.02) or BRAF/MEK inhibitors (HR 0.82, 95% CI 0.60 to 1.12). With nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, 1-year OS rates were 79%, 60%, and 72%, respectively; 1-year PFS rates were 68%, 58%, and 59%.

**Conclusions** In this real-world study, first-line nivolumab plus ipilimumab appeared to provide benefit vs anti-PD-1 monotherapy and BRAF/MEK inhibitors in patients with MBM, consistent with pivotal trial data.

**Keywords** Immunotherapy; Skin cancer (metastatic melanoma)

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This retrospective chart review study collected real-world data of US patients diagnosed with melanoma brain metastasis (MBM) and treated by medical oncologists with different types of first-line systemic therapy options, including immunotherapy and targeted therapy.
- These results may supplement data from clinical trials and provide valuable insights for clinical decision-making.
- Limitations of this study included heterogeneity in patient characteristics between the treatment groups, inconsistencies in investigator assessments, small sample sizes in the outcome analyses, a retrospective collection of safety data, and a lack in the timeliness of results due to changes in treatment practices since study initiation.

## INTRODUCTION

Metastasis to the brain is a common sequela of metastatic melanoma, with 35% of patients presenting with brain metastasis at diagnosis,<sup>1</sup> more than 40% developing brain metastasis during their disease,<sup>2</sup> and up to 75% having brain metastasis at the time of death.<sup>3</sup> Historically, patients with melanoma brain metastasis (MBM) have demonstrated a poor prognosis, with a median overall survival (OS) of approximately 4 months.<sup>4</sup> *BRAF* mutations are present in the tumors of approximately half of the patients with advanced (unresectable or metastatic) melanoma, and patients with *BRAF* mutations have a higher likelihood of developing brain metastasis and experiencing shorter OS than those without these mutations.<sup>5</sup> Prognosis for

patients with MBM has improved in recent years with therapeutic advances,<sup>6</sup> but outcomes remain poor in a substantial number of patients, suggesting an area of unmet clinical need.

Primary therapeutic approaches for patients with MBM have traditionally consisted of surgery, whole-brain radiotherapy, and stereotactic radiosurgery.<sup>7</sup> Over the last decade, several systemic treatments showing activity in MBM have been introduced, including immunotherapy (immune checkpoint inhibitors) with the combination of nivolumab (an anti-programmed death-1 [PD-1] antibody) plus ipilimumab (an anti-cytotoxic T lymphocyte antigen-4 [CTLA-4] antibody),<sup>8–11</sup> the combination of pembrolizumab (an anti-PD-1 antibody) plus ipilimumab,<sup>12</sup> and nivolumab<sup>9,10</sup> or pembrolizumab<sup>13</sup> monotherapy, as well as targeted therapy with BRAF plus MEK inhibitor combinations (indicated for patients with tumors harboring a *BRAF* mutation) such as dabrafenib plus trametinib<sup>14</sup> and encorafenib plus binimetinib.<sup>15</sup> Patients with MBM enrolled in clinical trials have been broadly separated into those with and without symptoms, with symptomatic patients showing worse outcomes than asymptomatic patients.<sup>8,10,14</sup> Steroids are the mainstay treatment for symptoms of MBM, such as headache, weakness, and focal neurologic deficits, although steroid therapy may abrogate the clinical effects of immunotherapy.<sup>16</sup>

Nivolumab plus ipilimumab has demonstrated intracranial activity in patients with MBM, especially those with asymptomatic disease.<sup>8–11</sup> In the phase 2 CheckMate 204 trial, patients with asymptomatic (n=101) and symptomatic (n=18) MBM treated with nivolumab plus ipilimumab demonstrated 3-year OS rates of 72% and 37%, respectively.<sup>8</sup> In the phase 2 ABC trial, patients with asymptomatic MBM treated with nivolumab plus ipilimumab (n=35) demonstrated a 5-year OS rate of 51%.<sup>9,10</sup> In the phase 3 Italian NIBIT-M2 trial, patients with untreated, asymptomatic MBM receiving nivolumab plus ipilimumab (n=27) showed a 7-year OS rate of 43%.<sup>11</sup> According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), nivolumab plus ipilimumab is the preferred systemic therapy option for patients

with asymptomatic MBM who do not require steroids in comparison with anti-PD-1 monotherapy or dabrafenib plus trametinib, based on superior intracranial activity.<sup>17</sup>

Until recently, comparative data on the use of systemic agents for the treatment of patients with MBM were limited, as this population was often excluded from randomized clinical trials. Furthermore, there are no prospective head-to-head trials comparing nivolumab plus ipilimumab with anti-PD-1 monotherapy or BRAF/MEK inhibitors in patients with MBM. There is interest in examining the effectiveness and use of these first-line systemic treatments among patients with MBM in the real-world setting because these patients may more closely reflect routine clinical practice compared with patients in clinical trials. The objective of this retrospective chart review study is to examine real-world treatment patterns and clinical outcomes in United States (US) patients with MBM treated with different types of systemic therapy options in the first-line setting.

## METHODS

### Study design

This study collected the real-world data of patients diagnosed with melanoma with brain metastasis who were treated by US medical oncologists in academic/cancer centers, community hospital/cancer centers, and private practice offices. Study recruitment employed a two-part design in which a random sample of patients with *BRAF* mutant or wild-type metastatic melanoma with brain metastases (n=250) was identified first, followed by the identification of an augment *BRAF* mutant sample (n=113) and an augment *BRAF* wild-type sample (n=125) (online supplemental figure 1).

Physicians who met the study requirements were contacted by a recruitment group (Global Perspectives), and those who were interested in participating were screened to confirm eligibility. A total of 44 oncologists who were currently treating patients with advanced



melanoma were recruited, 40 of whom identified patients. Participating physicians were responsible for chart data abstraction and resolution of data-related queries.

Patients

To be eligible, patients were required to have been diagnosed with both metastatic/stage IV melanoma and MBM between June 2017 and June 2019; to be 18 years of age or older; and to have a medical history available for medical chart abstraction from initial melanoma diagnosis through the most recent visit, current therapy, or death. Patients were excluded if they had used systemic therapy in the metastatic setting prior to the development of brain metastasis (see criteria for adjuvant therapy below); had received whole brain radiotherapy (other forms of radiotherapy, such as stereotactic radiosurgery, as allowed); had undergone surgical resection for brain metastasis; had a diagnosis of concurrent malignancy (other than nonmelanoma skin cancer or *in situ* cervical carcinoma); or were enrolled in a cancer-related clinical trial since diagnosis of metastatic melanoma. Prior use of adjuvant or neoadjuvant therapy with anti-PD-1 monotherapy, anti-CTLA-4 monotherapy, or BRAF/MEK inhibitors was allowed if 6 or more months had elapsed between the last dose of therapy and diagnosis of brain metastasis, as previously defined.<sup>18</sup> The study was conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices.

Endpoints

Primary endpoints included treatment patterns in the first-line setting. Secondary endpoints included OS and progression-free survival (PFS). OS was defined as the time from index date (start of first-line treatment in the metastatic setting) to date of death from any cause. PFS was defined as the time from index date to date of first disease progression. OS and PFS were described by type of first-line treatment, which were nivolumab plus ipilimumab, anti-PD-1 monotherapy (nivolumab or pembrolizumab), and BRAF/MEK inhibitors (only for patients with

*BRAF* mutant disease). Patients were stratified by *BRAF* wild-type or mutant status and by asymptomatic or symptomatic MBM. Concurrent steroid use was evaluated to identify patients with symptomatic MBM, which was defined as any steroid therapy received within 15 days before the start of first-line treatment. The 15-day window was selected to ensure that steroid administration was not likely because of immune-related adverse events (AEs) associated with immunotherapy. OS and PFS for the three types of systemic treatments were also estimated for patients according to use of radiation, with concurrent radiation defined as radiation therapy that was initiated less than 30 days before or after the start of first-line treatment and sequential radiation defined as radiation that started 30 days or more before/after first-line systemic treatment initiation. Tumor response was not reported because response evaluation was inconsistent among investigators, on-treatment lesion measurements were not collected, response criteria were not defined in the case report form (CRF), and centralized confirmation of radiographic images was not conducted. Information for treatment-related adverse events (TRAEs) and grading based on Common Terminology Criteria for Adverse Events version 3.0 was collected from patient charts for the *BRAF* mutant subgroup, as specified in the study protocol.

### Statistical analysis

The primary objectives of this study were descriptive in nature, and precision estimates were determined using the 95% CI rather than power calculations for each cohort. Median OS and PFS were estimated using the Kaplan–Meier product-limit method. Hazard ratios (HRs) and corresponding CIs were estimated using a univariate Cox proportional hazards model to compare OS and PFS between the three types of systemic treatments. All analyses were performed using SAS Enterprise Version 9.4.

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3 **Patient and public involvement**

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5 Patients or the public were not involved in the design, conduct, reporting, or dissemination plans

6 of this research.

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11 **RESULTS**

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13 **Baseline patient characteristics**

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15 In total, 488 patients were identified for the analysis (online supplemental figure 1). A total of

16 472 patients with a confirmed diagnosis of metastatic/stage IV melanoma with MBM received

17 first-line systemic treatment with nivolumab plus ipilimumab (n=246), anti-PD-1 monotherapy

18 (nivolumab or pembrolizumab; n=112), or BRAF/MEK inhibitors (n=114) (table 1). Among the

19 472 patients, 50% (n=236) had *BRAF* wild-type disease, 45% (n=212) had *BRAF* mutant

20 disease, and 5% (n=24) had missing *BRAF* status. Patients treated with nivolumab plus

21 ipilimumab tended to be younger than those treated with anti-PD-1 monotherapy or BRAF/MEK

22 inhibitors (median age, 61.0 years vs 69.0 years and 62.0 years, respectively). At baseline,

23 patients treated with anti-PD-1 monotherapy or BRAF/MEK inhibitors were more likely to have a

24 greater number of or larger brain metastases, poorer Eastern Cooperative Oncology Group

25 performance status (ECOG PS), greater frequency of increased lactate dehydrogenase (LDH),

26 and worse Charlson Comorbidity Index (CCI) scores than patients treated with nivolumab plus

27 ipilimumab. No patient received prior combination immunotherapy therapy in the adjuvant or

28 neoadjuvant setting per the data collected in charts.

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**Table 1.** Baseline characteristics of patients with MBM by first-line systemic therapy\*†

	Nivolumab plus ipilimumab (n=246)	Anti-PD-1 mono- therapy (n=112)‡	BRAF/MEK inhibitors (n=114)
Median age, years (range)	61.0 (33.0–82.0)	69.0 (29.0–92.0)	62.0 (35.0–84.0)
Sex, n (%)			
Male	147 (60)	57 (51)	59 (52)
Female	99 (40)	55 (49)	55 (48)
Race, n (%)			
White	213 (87)	98 (88)	105 (92)
Black	22 (9)	8 (7)	6 (5)
Asian	11 (4)	4 (4)	3 (3)
Other	0	2 (2)	0
Median (range) number of brain lesions	2.0 (1.0–10.0)	3.0 (1.0–10.0)	3.0 (1.0–10.0)
Mean (SD) size of largest brain metastatic site, mm	8.3 (8.8)	11.9 (10.2)	12.7 (11.7)
ECOG PS, n (%)			
0	66 (27)	9 (8)	22 (19)
1	100 (41)	48 (43)	49 (43)
2	63 (26)	40 (12)	38 (33)
3	15 (6)	14 (3)	5 (4)
4	1 (<1)	0	0
Missing	1 (<1)	1 (1)	0
Serum LDH, n (%)			
Normal	107 (43)	27 (24)	31 (27)
1–2 times ULN	79 (32)	63 (56)	52 (46)
>2 times ULN	60 (24)	22 (20)	31 (27)
BRAF status, n (%)			
Wild-type	159 (65)	77 (69)	0
Mutant	76 (31)	23 (21)	113 (99)
Missing	11 (4)	12 (11)	1 (1)
Mean (SD) CCI scores§	0.47 (0.73)	1.10 (1.33)	0.96 (1.37)
Steroid use, n (%)			
None	198 (80)	86 (77)	85 (75)
Started before index datell	18 (7)	15 (13)	19 (17)
Other	30 (12)	11 (10)	10 (9)
Radiation use, n (%)			
None	192 (78)	80 (71)	75 (66)
Concurrent	43 (17)	24 (21)	34 (30)
Sequential	11 (4)	8 (7)	5 (4)

\*Among 488 patients who were identified, 472 patients received first-line treatment with nivolumab plus ipilimumab, anti-PD-1 monotherapy, or BRAF/MEK inhibitors and were included in the analysis. First-line systemic therapies used in 16 of the 488 patients who were not included in the analysis were dacarbazine (n=3), pegylated interferon alfa-2b (n=3), pembrolizumab plus other systemic therapy (n=3), temozolomide (n=3), paclitaxel (n=2), carboplatin (n=1), cisplatin (n=1), larotrectinib (n=1), and trametinib (n=1). †Percentages may not add up to 100 because of rounding. ‡Nivolumab or pembrolizumab monotherapy.

¶American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander. §Higher scores indicate increased comorbidity burden. ||Start of first-line treatment in the metastatic setting. CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group

performance status; LDH, lactate dehydrogenase; MBM, melanoma brain metastasis; PD-1, programmed death-1; SD, standard deviation; ULN, upper limit of normal.

**Follow-up time**

Median follow-up times from treatment initiation were 15.4 months (range 0.1 to 37.0), 13.3 months (range 0.3 to 36.6), and 14.0 months (range 1.9 to 36.5) with first-line nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, respectively.

**Concurrent steroid use**

Concurrent steroid use was used to identify patients with symptomatic MBM. Among the 472 patients included in the analysis, 369 patients (78%) did not receive steroids (and were considered asymptomatic), 52 patients (11%) received concurrent steroids (and were considered symptomatic), and 51 patients (11%) received steroids outside of the concurrent steroid definition (ie, not within the 15 days before the start of first-line treatment) (table 1).

**Concurrent radiation use**

Among the 472 patients included in the analysis, 347 patients (74%) did not receive concurrent radiation, 101 patients (21%) received concurrent radiation (stereotactic, intensity-modulated, three-dimensional conformal, and gamma knife radiation), and 24 patients (5%) received sequential radiation (defined as radiation that started 30 days or more before/after first-line systemic treatment initiation) (table 1). The median time from first dose of systemic therapy (with nivolumab plus ipilimumab, anti-PD-1 monotherapy, or BRAF/MEK inhibitors) to radiation therapy or vice versa was 12 days (range -671 to 160). Types of first radiation therapy were stereotactic (74%), intensity-modulated (17%), and three-dimensional conformal (9%) radiation (online supplemental table 1).

## OS and PFS in the overall study group

In the overall study group, patients treated with nivolumab plus ipilimumab demonstrated trends toward longer OS vs those treated with anti-PD-1 monotherapy (HR 0.47, 95% CI 0.34 to 0.67) or BRAF/MEK inhibitors (HR 0.72, 95% CI 0.50 to 1.04) (figure 1A). Median OS was 36.0 months (95% CI 32.1 to not reached [NR]) with nivolumab plus ipilimumab, 18.8 months (95% CI 13.0 to 26.0) with anti-PD-1 monotherapy, and NR (95% CI 19.4 to NR) with BRAF/MEK inhibitors. One-year OS rates were 79%, 60%, and 72% with nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, respectively.

Patients treated with nivolumab plus ipilimumab demonstrated trends toward longer PFS vs those treated with anti-PD-1 monotherapy (HR 0.74, 95% CI 0.53 to 1.02) or BRAF/MEK inhibitors (HR 0.82, 95% CI 0.60 to 1.12) (figure 1B). Median PFS was 22.7 months (95% CI 19.3 to 28.3) with nivolumab plus ipilimumab, 16.8 months (95% CI 11.6 to 24.9) with anti-PD-1 monotherapy, and 15.4 months (95% CI 12.7 to NR) with BRAF/MEK inhibitors. One-year PFS rates were 68%, 58%, and 59% with nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, respectively.

## OS in patients with asymptomatic MBM

Patients with *BRAF* wild-type, asymptomatic MBM demonstrated trends toward longer OS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.48, 95% CI 0.30 to 0.78) (figure 2A). Median OS was 32.1 months (95% CI 27.5 to NR) with nivolumab plus ipilimumab and 18.8 months (95% CI 11.8 to NR) with anti-PD-1 monotherapy. One-year OS rates were 80% and 58%, respectively.

Patients with *BRAF* mutant, asymptomatic MBM demonstrated trends toward longer OS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.48, 95% CI 0.16 to 1.41) or BRAF/MEK inhibitors (HR 0.40, 95% CI 0.19 to 0.84) (figure 2B). Median OS was 36.0 months (95% CI 36.0 to NR) with nivolumab plus ipilimumab, 26.0 months (95% CI 16.0 to NR) with



anti-PD-1 monotherapy, and NR (95% CI NR to NR) with BRAF/MEK inhibitors. There were few patients treated with nivolumab plus ipilimumab at 36 months, resulting in a drop in the Kaplan–Meier curve for that group. One-year OS rates were 93%, 86%, and 75%, respectively.

### OS in patients with symptomatic MBM

Patients with *BRAF* wild-type, symptomatic MBM demonstrated trends toward longer OS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.16, 95% CI 0.05 to 0.53), although sample sizes were small (online supplemental figure 2A). Median OS was NR (95% CI 9.2 to NR) with nivolumab plus ipilimumab and 4.7 months (95% CI 2.3 to NR) with anti-PD-1 monotherapy. One-year OS rates were 69% and 18%, respectively.

Patients with *BRAF* mutant, symptomatic MBM demonstrated a trend toward longer OS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.27, 95% CI 0.06 to 1.25) and a trend toward shorter OS with nivolumab plus ipilimumab vs BRAF/MEK inhibitors (HR 1.59, 95% CI 0.42 to 6.04), although sample sizes were small (online supplemental figure 2B). Median OS was 11.1 months (95% CI 7.7 to NR) with nivolumab plus ipilimumab, 4.1 months (95% CI 2.8 to NR) with anti-PD-1 monotherapy, and 23.0 (95% CI 21.4 to NR) with BRAF/MEK inhibitors. One-year OS rates were 40%, 25%, and 68%, respectively.

### PFS in patients with asymptomatic MBM

Patients with *BRAF* wild-type, asymptomatic MBM demonstrated a trend toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.80, 95% CI 0.50 to 1.26) (figure 3A). Median PFS was 24.1 months (95% CI 18.8 to NR) with nivolumab plus ipilimumab and 23.0 months (95% CI 13.6 to NR) with anti-PD-1 monotherapy. One-year PFS rates were 71% and 63%, respectively.

Patients with *BRAF* mutant, asymptomatic MBM demonstrated trends toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.80, 95% CI 0.35 to 1.85)

or BRAF/MEK inhibitors (HR 0.83, 95% CI 0.51 to 1.35) (figure 3B). Median PFS was 21.5 months (95% CI 17.9 to 28.3) with nivolumab plus ipilimumab, 16.3 months (95% CI 16.2 to NR) with anti-PD-1 monotherapy, and 28.9 (95% CI 12.8 to NR) with BRAF/MEK inhibitors. One-year PFS rates were 77%, 79%, and 62%, respectively.

### PFS in patients with symptomatic MBM

Patients with *BRAF* wild-type, symptomatic MBM demonstrated a trend toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.21, 95% CI 0.07 to 0.66), although sample sizes were small (online supplemental figure 3A). Median PFS was NR (95% CI 7.5 to NR) with nivolumab plus ipilimumab and 4.5 months (95% CI 3.1 to NR) with anti-PD-1 monotherapy. One-year PFS rates were 62% and 11%, respectively.

Patients with *BRAF* mutant, symptomatic MBM demonstrated a trend toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.37, 95% CI 0.05 to 2.76) and a trend toward shorter PFS with nivolumab plus ipilimumab vs BRAF/MEK inhibitors (HR 1.29, 95% CI 0.27 to 6.15), although sample sizes were small (online supplemental figure 3B). Median PFS was NR (95% CI 5.4 months to NR) with nivolumab plus ipilimumab, 11.6 months (95% CI 3.5 to NR) with anti-PD-1 monotherapy, and 22.5 months (95% CI 14.0 to NR) with BRAF/MEK inhibitors. One-year PFS rates were 50%, 0%, and 72%, respectively.

### OS and PFS in patients with MBM without or with concurrent radiation

Sample sizes were small in patients with MBM without or with concurrent radiation. Patients without concurrent radiation and *BRAF* wild-type MBM demonstrated a trend toward longer OS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.44, 95% CI 0.28 to 0.72) (online supplemental figure 4A). Patients without concurrent radiation and *BRAF* mutant MBM demonstrated a trend toward longer OS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.48, 95% CI 0.15 to 1.56) or BRAF/MEK inhibitors (HR 0.43, 95% CI 0.20 to



0.90) (online supplemental figure 4B). Patients with concurrent radiation and *BRAF* wild-type MBM demonstrated a trend toward longer OS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.29, 95% CI 0.12 to 0.68) (online supplemental figure 5A). Patients with concurrent radiation and *BRAF* mutant MBM demonstrated a trend toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.85, 95% CI 0.31 to 2.31) and a trend toward shorter PFS with nivolumab plus ipilimumab vs BRAF/MEK inhibitors (HR 1.30, 95% CI 0.60 to 2.81) (online supplemental figure 5B).

Patients without concurrent radiation and *BRAF* wild-type MBM demonstrated a trend toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.76, 95% CI 0.48 to 1.22) (online supplemental figure 6A). Patients without concurrent radiation and *BRAF* mutant MBM demonstrated trends toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.82, 95% CI 0.31 to 2.15) or BRAF/MEK inhibitors (HR 0.72, 95% CI 0.43 to 1.21) (online supplemental figure 6B). Patients with concurrent radiation and *BRAF* wild-type MBM demonstrated a trend toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.32, 95% CI 0.13 to 0.75) (online supplemental figure 7A). Patients with concurrent radiation and *BRAF* mutant MBM demonstrated a trend toward longer PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.96, 95% CI 0.37 to 2.50) and a trend toward shorter PFS with nivolumab plus ipilimumab vs BRAF/MEK inhibitors (HR 1.78, 95% CI 0.88 to 3.61) (online supplemental figure 7B).

**TRAEs in the *BRAF* mutant subgroup**

In the *BRAF* mutant subgroup, any-grade TRAEs were reported in 43% (33/76) of patients receiving nivolumab plus ipilimumab, 30% (7/23) of patients receiving anti-PD-1 monotherapy, and 53% (60/113) of patients receiving BRAF/MEK inhibitors (online supplemental table 2). Grade 3–4 TRAEs were reported in 9% (7/76) of patients receiving nivolumab plus ipilimumab,

none of patients receiving anti-PD-1 monotherapy, and 4% (4/113) of patients receiving BRAF/MEK inhibitors (online supplemental table 2).

## DISCUSSION

This retrospective chart review study collected real-world data of US patients diagnosed with MBM and treated by medical oncologists with different types of systemic therapy options in the first-line setting. Given that there is no prospective head-to-head trial comparing nivolumab plus ipilimumab with anti-PD-1 monotherapy or BRAF/MEK inhibitors in patients with MBM, this study may provide valuable insights for clinical decision-making.

In this study, first-line treatment with nivolumab plus ipilimumab resulted in improved effectiveness compared with first-line treatment with anti-PD-1 monotherapy or BRAF/MEK inhibitors in patients with MBM, of whom 78% had asymptomatic disease (symptomatic disease was based on any steroid therapy received within the 15 days prior to the start of first-line treatment to ensure that steroid administration was not likely due to immune-related AEs; however, steroids may still have been administered during that time period for managing immune-related AEs). Patients demonstrated trends toward longer OS/PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy and BRAF/MEK inhibitors. At 1 year, OS rates were 79%, 60%, and 72% with nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, respectively, and PFS rates were 68%, 58%, and 59%, respectively. Trends toward efficacy in this real-world study were generally consistent with data across clinical trials involving patients with MBM, although cross-trial comparisons are difficult because of differences in study populations and methodologies. For example, among patients with asymptomatic MBM, 1-year OS rates were 63% and approximately 80% with nivolumab plus ipilimumab in the phase 2 ABC trial<sup>10</sup> and CheckMate 204 trial,<sup>8</sup> respectively; 60% with nivolumab in the ABC trial<sup>10</sup> and approximately 60% with pembrolizumab in another phase 2 trial<sup>13</sup>; and 46% with dabrafenib plus trametinib in the phase 2 COMBI-MB trial.<sup>14</sup> Results from the current study were also consistent

with those from the real-world German DeCOG and NICO studies in which 1-year OS rates were 69% and 59%, respectively, in patients with MBM treated with nivolumab plus ipilimumab.<sup>19,20</sup> In addition, these real-world results are in line with findings of two separate meta-analyses using data from clinical trials and real-world studies, respectively, that suggested advantages with nivolumab plus ipilimumab compared with other systemic treatments in patients with MBM.<sup>21,22</sup> Furthermore, OS in patients with MBM treated with nivolumab plus ipilimumab in this real-world study and the ABC and CheckMate 204 trials was similar to that in patients with advanced melanoma not having active brain metastases who were treated with nivolumab plus ipilimumab in the phase 3 CheckMate 067 trial,<sup>23</sup> suggesting that nivolumab plus ipilimumab is effective regardless of the presence of brain metastasis.

Effectiveness was evaluated in this real-world study in subgroups according to asymptomatic or symptomatic MBM and *BRAF* wild-type or mutant status. Patients demonstrated trends toward longer OS and PFS with nivolumab plus ipilimumab vs anti-PD-1 monotherapy, regardless of symptom or *BRAF* status. In addition, patients demonstrated trends toward longer OS and PFS with nivolumab plus ipilimumab vs BRAF/MEK inhibitors with asymptomatic, *BRAF* mutant MBM, but trends toward shorter OS and PFS vs BRAF/MEK inhibitors with symptomatic, *BRAF* mutant MBM. However, sample sizes for patients with symptomatic MBM were small. OS was longer in patients with asymptomatic than symptomatic MBM, consistent with results in clinical studies.<sup>8–10,14</sup> Among patients with *BRAF* wild-type or mutant symptomatic MBM, 1-year OS rates with nivolumab plus ipilimumab were 69% and 40%, respectively, which were consistent with results from the CheckMate 204 trial showing a 1-year OS rate of approximately 40% in patients with symptomatic (*BRAF* wild-type or mutant) MBM treated with nivolumab plus ipilimumab.<sup>8</sup>

OS and PFS were estimated in this real-world study in subgroups without or with concurrent radiation by *BRAF* mutation status, although sample sizes were too small to allow confident interpretation of the results. Patients demonstrated trends toward longer OS and PFS

with nivolumab plus ipilimumab vs anti-PD-1 monotherapy, regardless of use of concurrent radiation or *BRAF* mutation status. In addition, patients demonstrated trends toward longer OS and PFS with nivolumab plus ipilimumab vs BRAF/MEK inhibitors with *BRAF* mutant MBM and no concurrent radiation use, but trends toward shorter OS and PFS with nivolumab plus ipilimumab vs BRAF/MEK inhibitors with *BRAF* mutant MBM and concurrent radiation use.

Safety was evaluated in this real-world study among patients with *BRAF* mutant disease. In this subgroup, any-grade TRAEs were reported less frequently with nivolumab plus ipilimumab (43%) or anti-PD-1 monotherapy (30%) than with BRAF/MEK inhibitors (53%). However, the percentage of patients with grade 3–4 TRAEs was higher with nivolumab plus ipilimumab (9%) than with BRAF/MEK inhibitors (4%). These real-world results are inconsistent with those from clinical trials in which frequencies of any-grade TRAEs were higher.<sup>8–10,14</sup> For instance, in the ABC trial, any-grade TRAEs were reported in 97% and 68% of patients with asymptomatic MBM treated with nivolumab plus ipilimumab and nivolumab monotherapy, respectively.<sup>10</sup> The discrepancy in the frequency of TRAEs between this real-world study and the clinical trials may have been due to the methodology for retrospectively collecting safety information from patient charts in this study.

New therapies have emerged for the treatment of patients with advanced melanoma, and in the phase 2/3 RELATIVITY 047 trial, a novel, dual immune checkpoint inhibitor combination of nivolumab plus relatlimab (a lymphocyte-activation gene 3 inhibitor) appeared to have central nervous system (CNS) activity in patients with advanced melanoma.<sup>24</sup> In that trial, new CNS metastases developed less frequently in patients treated with nivolumab plus relatlimab than with nivolumab alone (5% vs 9%) and time to development of new CNS lesions was longer with the combination than with nivolumab monotherapy (patients with new CNS lesions at 2 years, 6.5% and 10.0%, respectively).<sup>24</sup> However, those results were limited by the low occurrence of new CNS metastases in both treatment groups. The safety and efficacy of

nivolumab plus relatlimab in patients with active MBM is being investigated in a single-arm, open-label, phase 2 BLUEBONNET trial (ClinicalTrials.gov identifier: NCT05704647).<sup>25</sup>

This real-world study had certain limitations. First, the study may have been limited by heterogeneity in baseline patient characteristics between the treatment groups. For example, the nivolumab plus ipilimumab group may have had a survival advantage compared with the anti-PD-1 monotherapy and BRAF/MEK inhibitor groups, given that patients treated with nivolumab plus ipilimumab were younger and had better baseline prognostic factors. At baseline, patients treated with anti-PD-1 monotherapy or BRAF/MEK inhibitors were more likely to have a greater number of or larger brain metastases, poorer ECOG PS, or greater frequency of increased LDH than patients treated with nivolumab plus ipilimumab. In addition, there may have been inconsistencies between the treatment groups in investigator assessments (eg, ECOG PS assessment) and in treatment selection based on clinical trial evidence and therapeutic guidelines. Interpretation of OS and PFS results in certain subgroups was impeded by small sample sizes. Furthermore, tumor response was not reported because of variability in investigator assessments. Although dates of progression were collected in the CRF, progression was based on investigator assessment and not on Response Evaluation Criteria in Solid Tumors, version 1.1. As the CRF did not distinguish between asymptomatic and symptomatic MBM, concurrent steroid use served as a surrogate method for identifying patients with symptomatic MBM. Although concurrent steroid use was defined as any steroid therapy received within the 15 days prior to the start of first-line treatment to ensure that steroid administration was not likely due to immune-related AEs, it was still possible that steroids were administered during that time period for managing immune-related AEs. As mentioned, the safety analysis was limited by the retrospective collection of safety data. Finally, treatment practices for MBM may have changed since patients in this study began treatment (June 2017 through June 2019).

In conclusion, results from this retrospective chart review study, which collected real-world data of US patients diagnosed with MBM and treated by medical oncologists, supplement data from clinical trials evaluating this subset of patients. Patients with MBM in this real-world study demonstrated trends toward longer OS and PFS with first-line nivolumab plus ipilimumab than with first-line anti-PD-1 monotherapy or BRAF/MEK inhibitors. These results are generally consistent with those in clinical trials and real-world studies with these treatments in patients with MBM. Given that there are no prospective head-to-head trials comparing nivolumab plus ipilimumab with anti-PD-1 monotherapy or BRAF/MEK inhibitors in patients with MBM, this real-world study may provide valuable insights for clinical decision-making. Additional studies are required to investigate first-line treatments for patients with MBM.

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**Patient consent for publication** Not applicable.

**Ethics approval** The protocol, amendments, and subject informed consent received appropriate approval by the Institutional Review Board/Independent Ethics Committee or other applicable review board as required by local law prior to initiation of study at the site. Investigators were to ensure that patients, or, in those situations where consent could not be given by patients, their legally acceptable representatives, were clearly informed about the purpose, potential risks, and other critical issues regarding this study. The study was conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices.

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**Data availability statement** The Bristol Myers Squibb policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html>.

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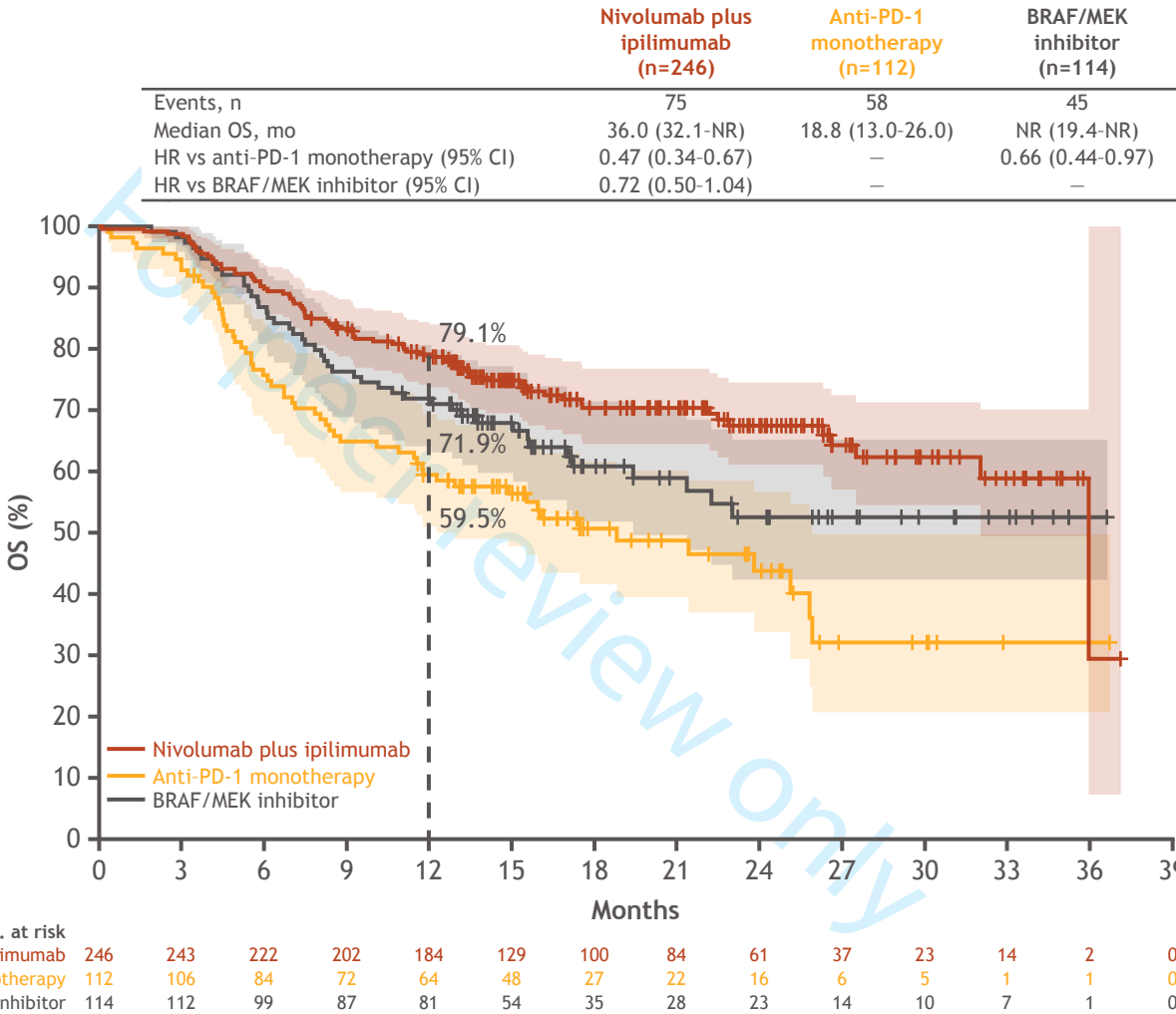
## FIGURE LEGENDS

**Figure 1.** OS and PFS in the overall study group (patients with asymptomatic or symptomatic patients MBM) by first-line treatment. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1; PFS, progression-free survival.

**Figure 2.** OS in patients with asymptomatic MBM by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.

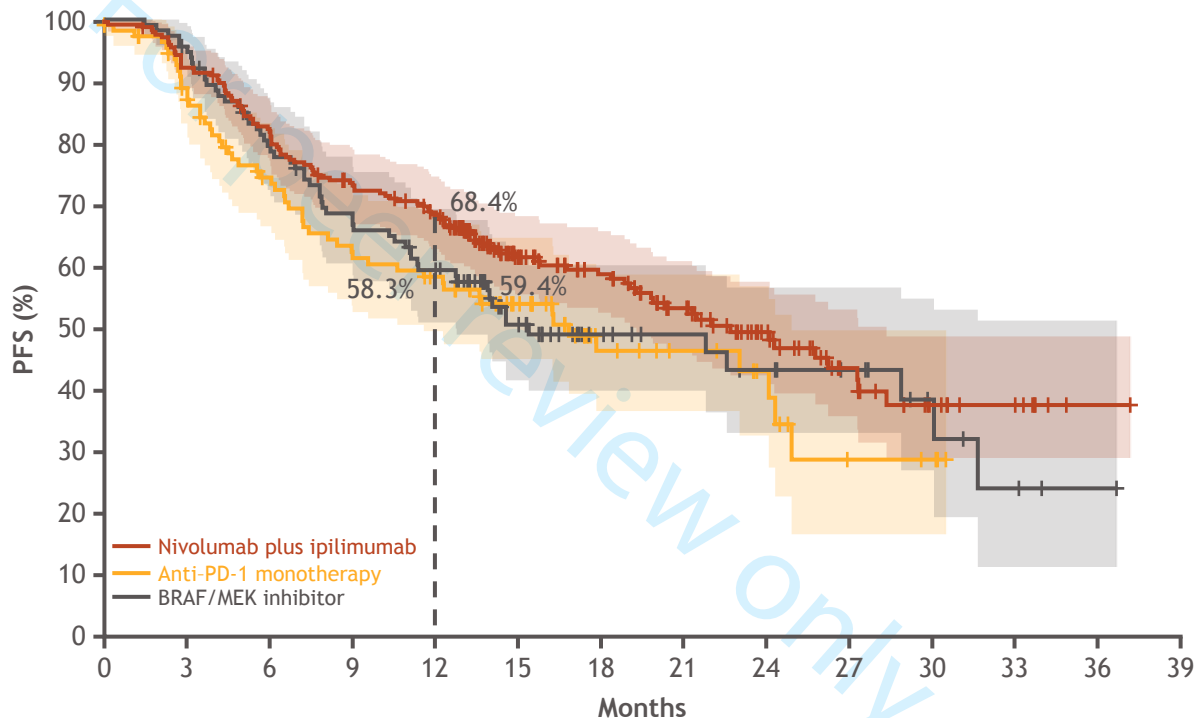
**Figure 3.** PFS in patients with asymptomatic MBM by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; PD-1, programmed death-1; PFS, progression-free survival.

A. OS



## B. PFS

	Nivolumab plus ipilimumab (n=244)	Anti-PD-1 monotherapy (n=111)	BRAF/MEK inhibitor (n=114)
Events, n	112	55	58
Median PFS, mo	22.7 (19.3-28.3)	16.8 (11.6-24.9)	15.4 (12.7-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.74 (0.53-1.02)	—	0.90 (0.62-1.30)
HR vs BRAF/MEK inhibitor (95% CI)	0.82 (0.60-1.12)	—	—

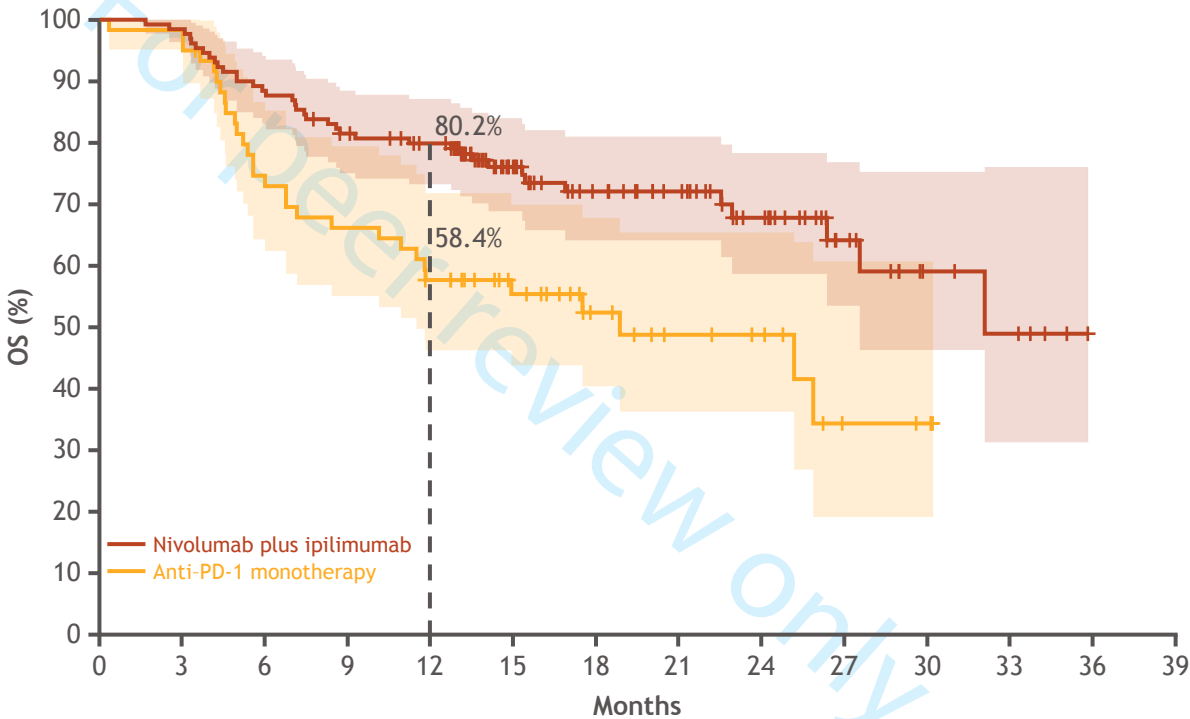


No. at risk

Nivolumab plus ipilimumab	244	224	197	173	158	99	80	60	40	23	12	7	1	0
Anti-PD-1 monotherapy	111	94	74	61	56	39	19	15	10	4	3	0	0	0
BRAF/MEK inhibitor	114	108	88	73	64	35	21	17	14	11	6	3	1	0

A. *BRAF* wild-type disease

	Nivolumab plus ipilimumab (n=132)	Anti-PD-1 monotherapy (n=61)
Events, n	38	30
Median OS, mo	32.1 (27.5-NR)	18.8 (11.8-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.48 (0.30-0.78)	—

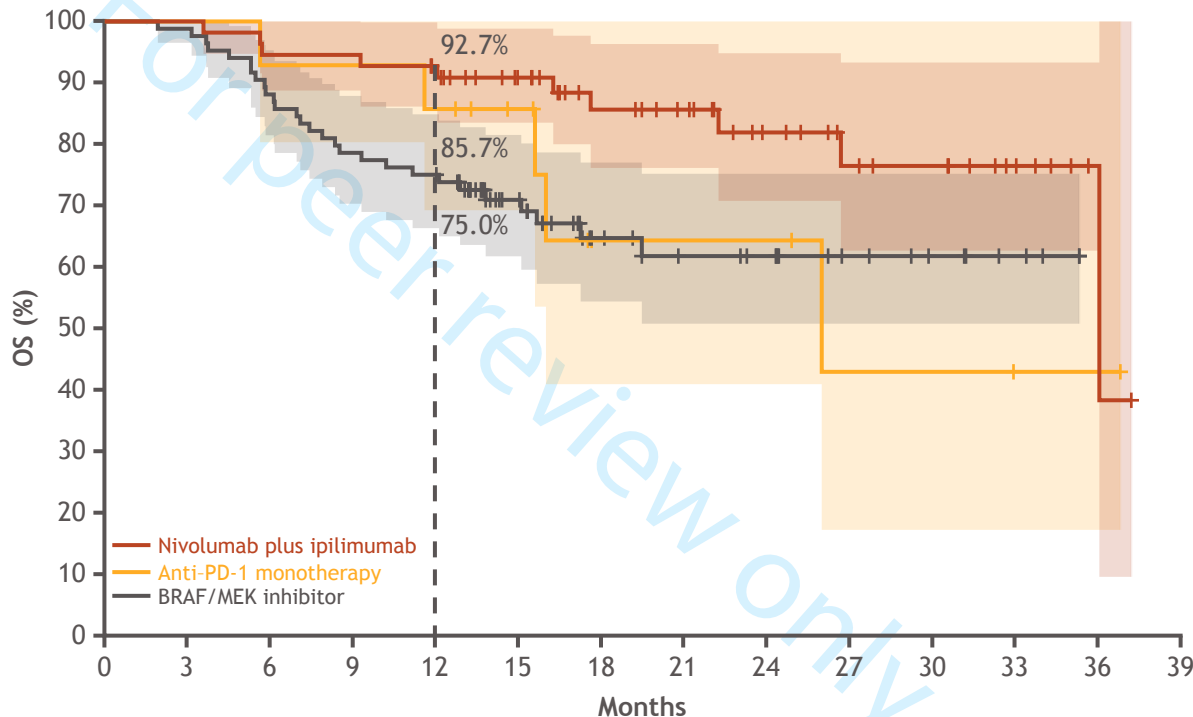


No. at risk

Nivolumab plus ipilimumab	132	130	117	106	99	63	49	41	29	15	7	5	0	0
Anti-PD-1 monotherapy	61	60	44	40	34	25	16	11	9	3	2	0	0	0

B. *BRAF* mutant disease

	Nivolumab plus ipilimumab (n=55)	Anti-PD-1 monotherapy (n=14)	BRAF/MEK inhibitor (n=84)
Events, n	10	5	28
Median OS, mo	36.0 (36.0-NR)	26.0 (16.0-NR)	NR (NR-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.48 (0.16-1.41)	—	1.19 (0.45-3.14)
HR vs BRAF/MEK inhibitor (95% CI)	0.40 (0.19-0.84)	—	—



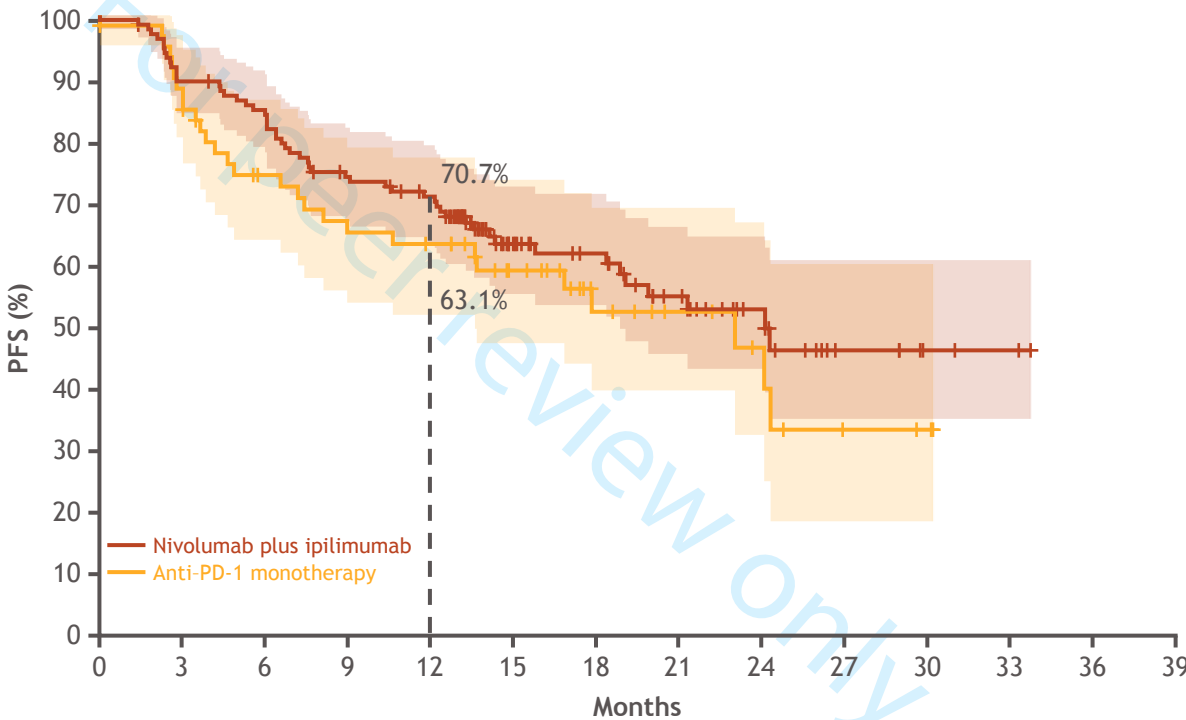
No. at risk

Nivolumab plus ipilimumab	55	55	52	52	49	40	31	27	19	14	12	6	2	0
Anti-PD-1 monotherapy	14	14	13	13	12	9	4	4	4	2	2	1	1	0
BRAF/MEK inhibitor	84	83	74	66	63	39	24	19	17	10	7	4	0	0



A. *BRAF* wild-type disease

	Nivolumab plus ipilimumab (n=132)	Anti-PD-1 monotherapy (n=60)
Events, n	54	28
Median PFS, mo	24.1 (18.8-NR)	23.0 (13.6-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.80 (0.50-1.26)	—

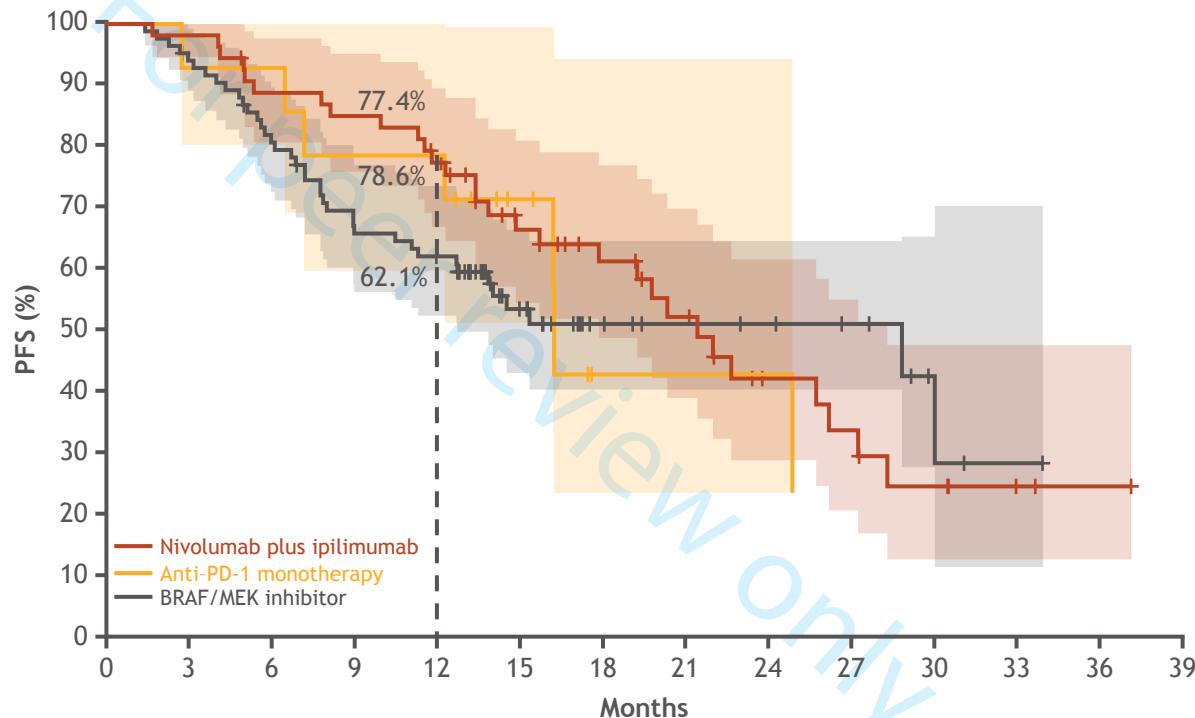


No. at risk

Nivolumab plus ipilimumab	132	117	109	94	87	46	38	27	17	7	3	2	0	0
Anti-PD-1 monotherapy	60	52	40	35	33	24	14	10	7	3	2	0	0	0

B. *BRAF* mutant disease

	Nivolumab plus ipilimumab (n=54)	Anti-PD-1 monotherapy (n=14)	BRAF/MEK inhibitor (n=84)
Events, n	29	7	39
Median PFS, mo	21.5 (17.9-28.3)	16.3 (16.2-NR)	28.9 (12.8-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.80 (0.35-1.85)	—	0.96 (0.43-2.16)
HR vs BRAF/MEK inhibitor (95% CI)	0.83 (0.51-1.35)	—	—



No. at risk

Nivolumab plus ipilimumab	54	53	47	45	40	28	22	17	10	8	5	2	1	0
Anti-PD-1 monotherapy	14	13	13	11	11	6	1	1	1	0	0	0	0	0
BRAF/MEK inhibitor	84	79	67	54	50	25	13	10	9	7	3	1	0	0

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**SUPPLEMENT**

**Real-world outcomes in patients with melanoma brain metastasis:  
a multisite retrospective chart review study of systemic treatments**

Isabella C. Glitza Oliva,<sup>1</sup> Jennell Palaia,<sup>2</sup> Leon A. Sakkal,<sup>2</sup> Divya Patel,<sup>2</sup> Andriy Moshyk,<sup>2</sup>  
Natalia Han,<sup>3</sup> Shardul Odak,<sup>3</sup> Jordana K. Schmier,<sup>4</sup> Ning Ning,<sup>4</sup> Sunandana Chandra<sup>5</sup>

<sup>1</sup>The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>2</sup>Bristol Myers Squibb, Princeton, NJ, USA; <sup>3</sup>RTI Health Solutions, Research Triangle Park, NC, USA; <sup>4</sup>Open Health, Bethesda, MD, USA; <sup>5</sup>Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

**Supplemental table 1.** Types of radiation therapy

	<b>Nivolumab plus ipilimumab (n=246)</b>	<b>Anti-PD-1 monotherapy (n=112)</b>	<b>BRAF/MEK inhibitor (n=114)</b>	<b>Overall (n=472)</b>
Type of first radiation therapy,* n (%)	n=54	n=33	n=40	n=127
Stereotactic	37 (69)	24 (73)	33 (82)	94 (74)
IMRT	13 (24)	6 (18)	3 (8)	22 (17)
3D-CRT	4 (7)	3 (9)	4 (10)	11 (9)
Type of second radiation therapy, n (%)	n=1	n=0	n=4	n=5
Stereotactic	1 (100)	0	4 (100)	5 (100)
IMRT	0	0	0	0
3D-CRT	0	0	0	0

\*Two patients had two types of radiation therapy starting on the same date, and both types were accounted as the first radiation therapy.

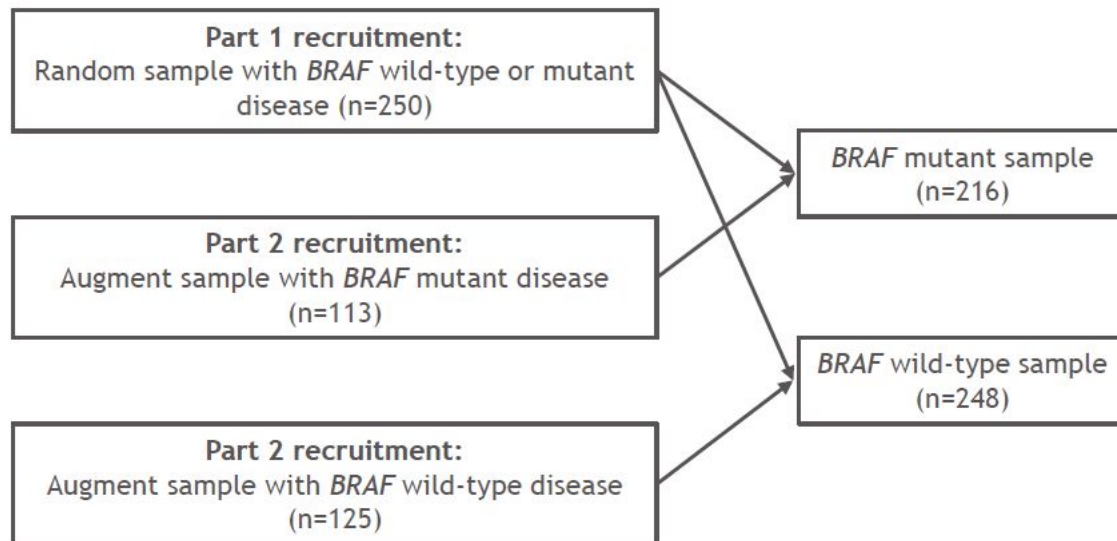
3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PD-1, programmed death-1.

**Supplemental table 2.** TRAEs in the *BRAF* mutant subgroup by type of first-line treatment

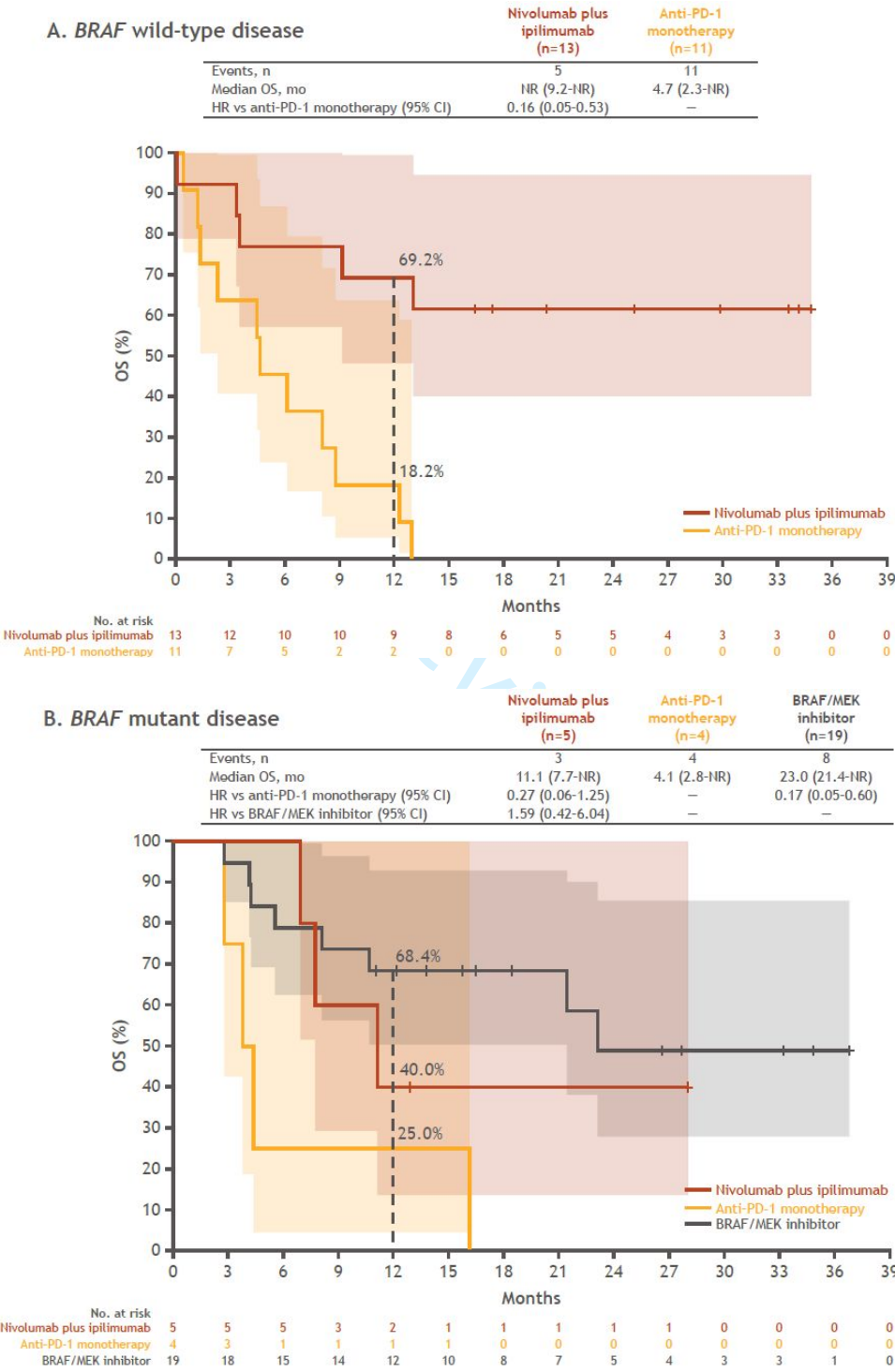
	Nivolumab plus ipilimumab (n=76)	Anti-PD-1 monotherapy (n=23)	BRAF/MEK inhibitors (n=113)
Any-grade TRAE, n (%)	33 (43)	7 (30)	60 (53)
TRAEs by grade, n (%)*			
1	4 (5)	4 (17)	34 (30)
2	22 (29)	3 (13)	21 (19)
3/4	7 (9)	0	4 (4)
Unknown	0	0	1 (1)

\*Grading based on Common Terminology Criteria for Adverse Events version 3.0.  
PD-1, programmed death-1; TRAE, treatment-related adverse event.

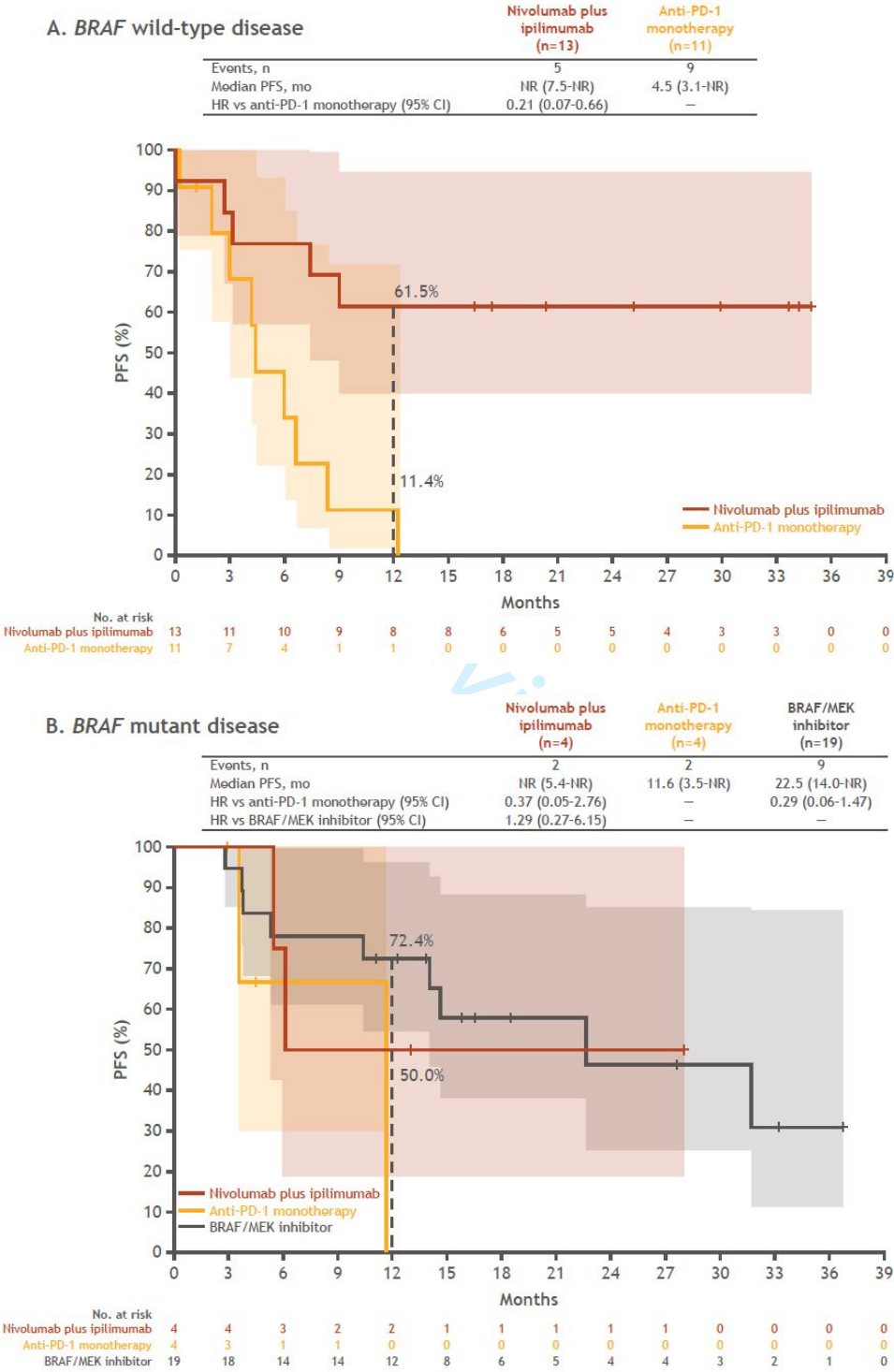
**Supplemental figure 1.** Study design. Study recruitment employed a two-part design in which a random sample of patients with *BRAF* mutant or wild-type metastatic melanoma with brain metastases (n=250) was identified first, followed by the identification of an augment *BRAF* mutant sample (n=113) and an augment *BRAF* wild-type sample (n=125).



**Supplemental figure 2.** OS in patients with symptomatic MBM by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.

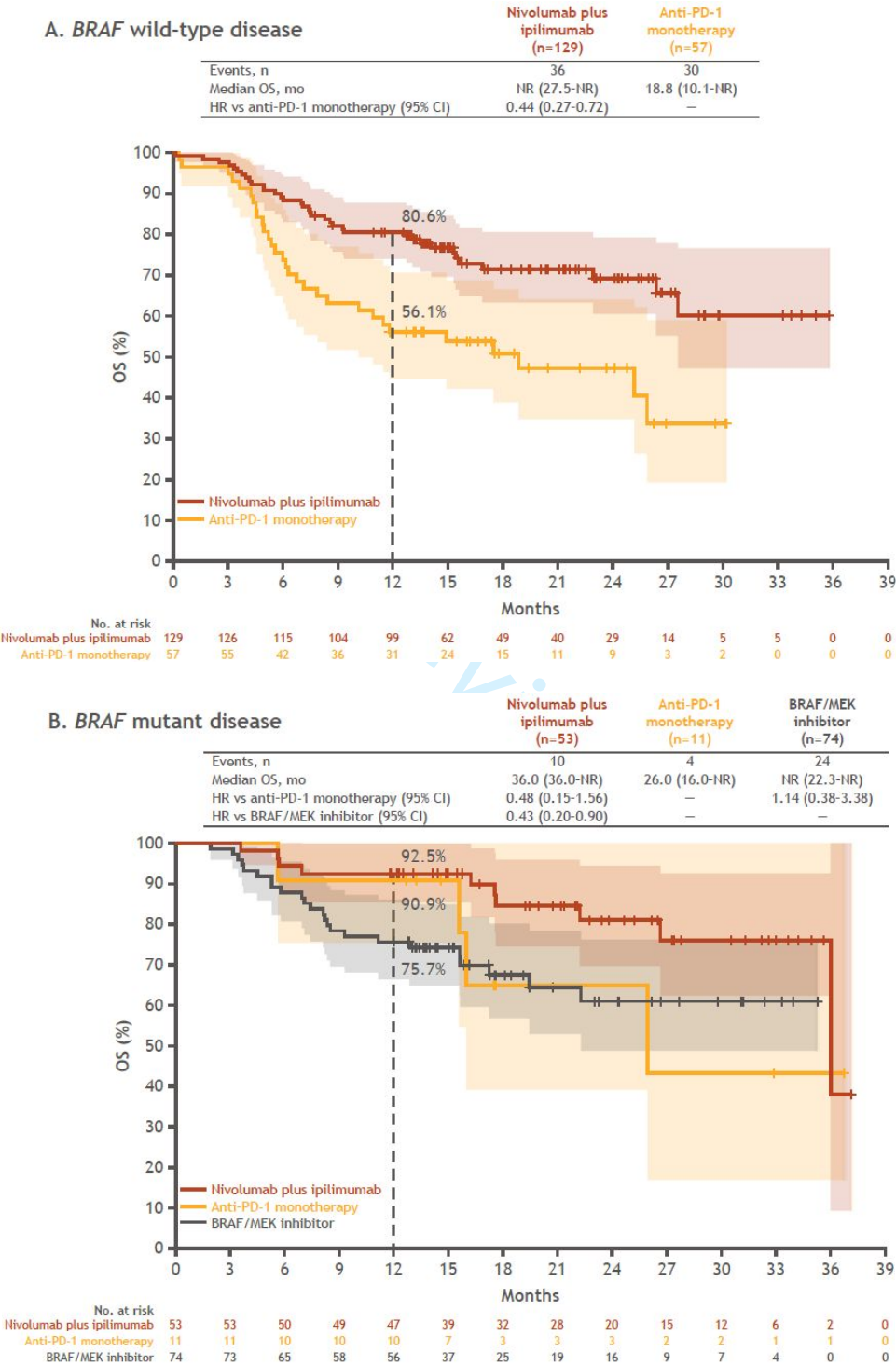


**Supplemental figure 3.** PFS in patients with symptomatic MBM by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; PD-1, programmed death-1; PFS, progression-free survival.

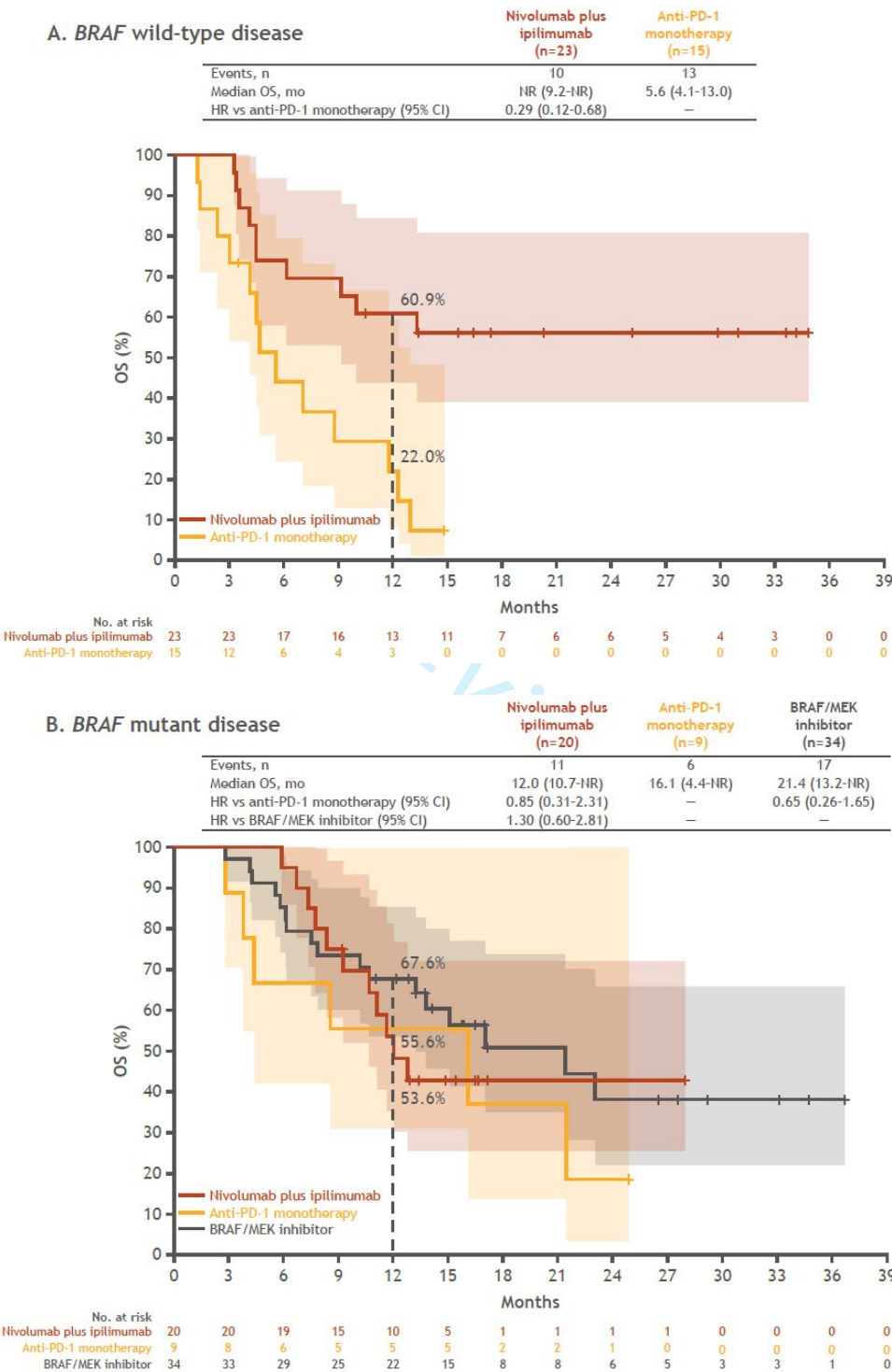




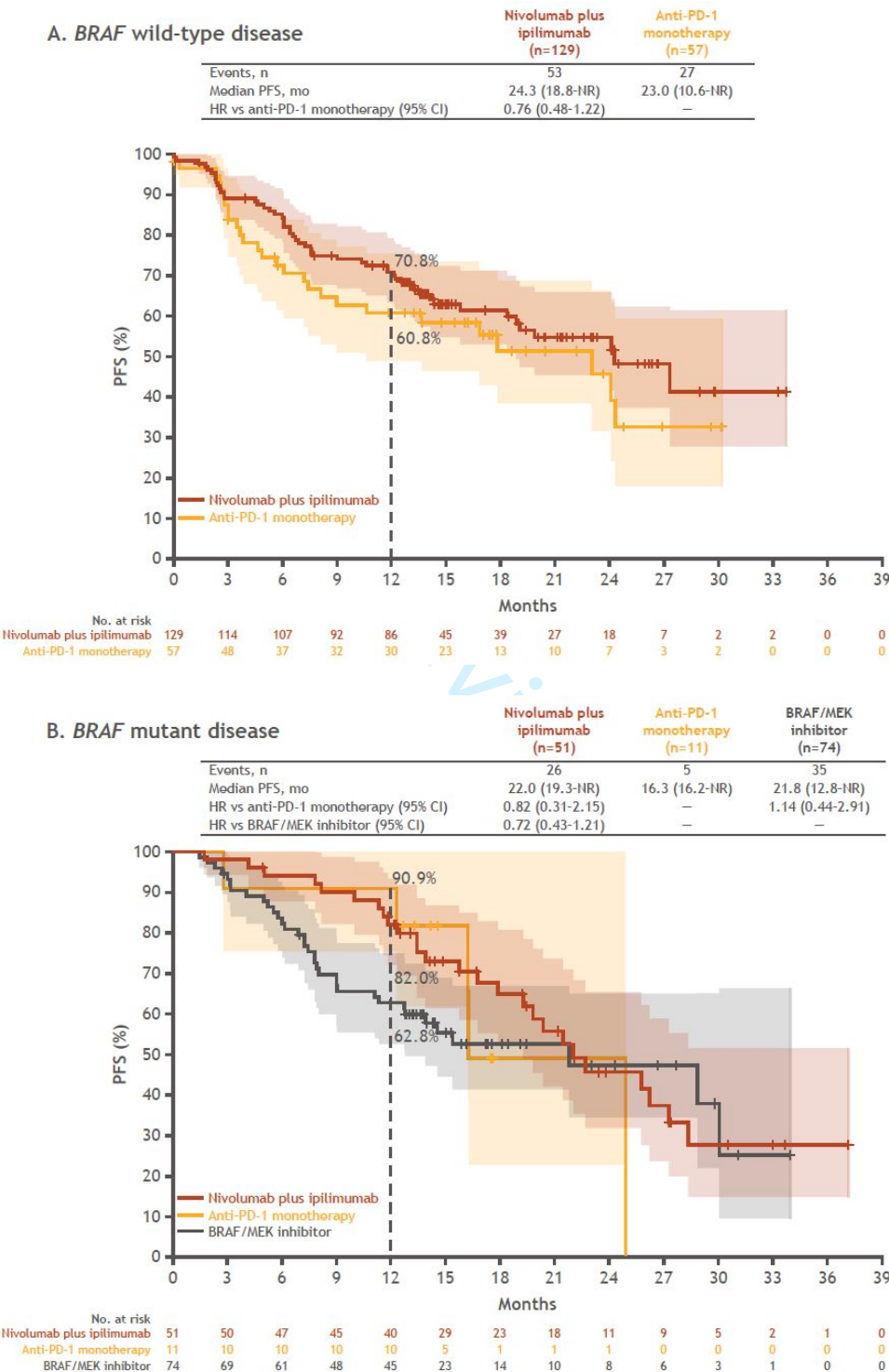
**Supplemental figure 4.** OS in patients with MBM without concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.



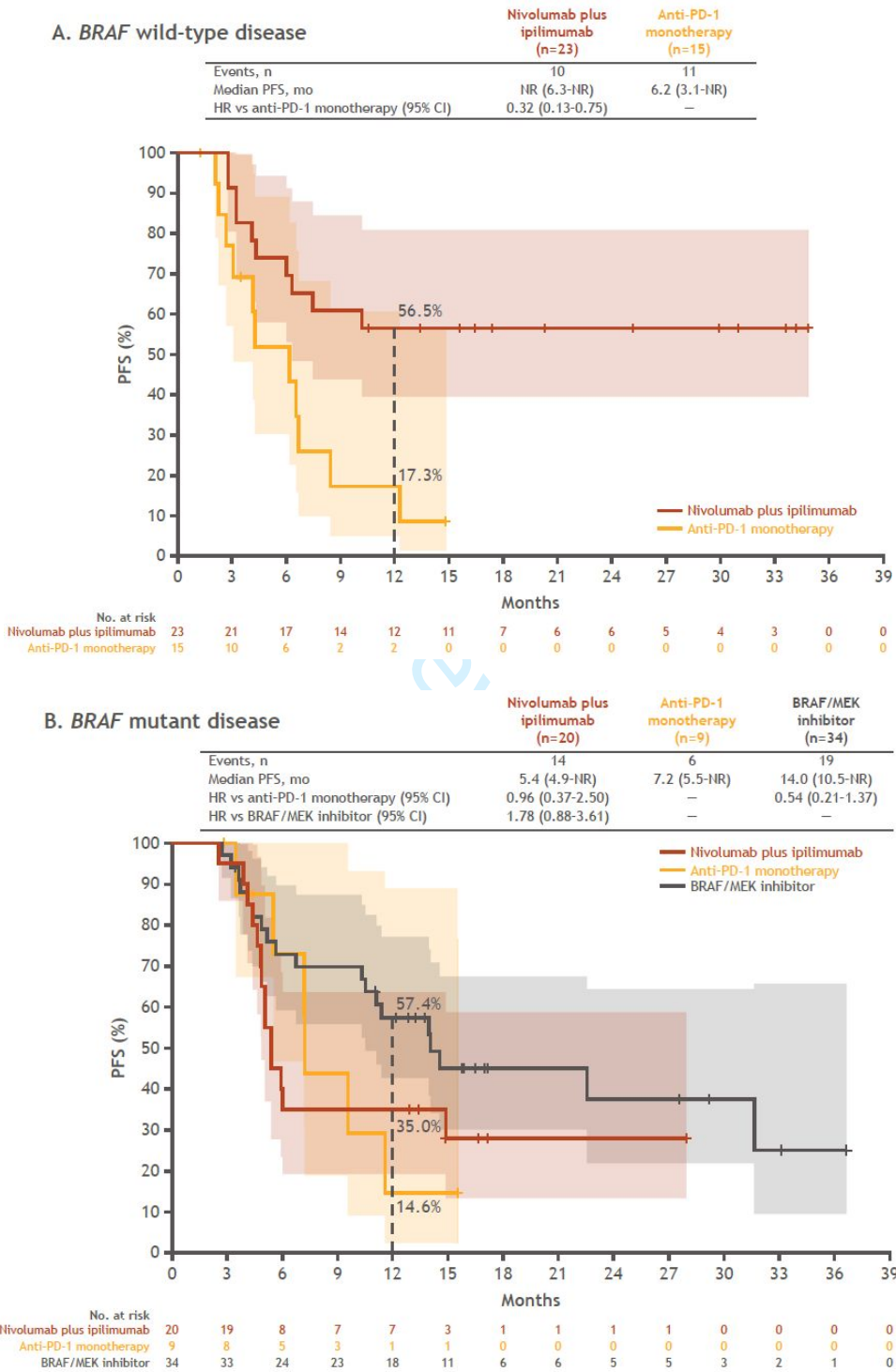
**Supplemental figure 5.** OS in patients with MBM with concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.



**Supplemental figure 6.** PFS in patients with MBM without concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; PD-1, programmed death-1; PFS, progression-free survival.



**Supplemental figure 7.** PFS in patients with concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; mo, month; NR, not reached; PD-1, programmed death-1; PFS, progression-free.



# BMJ Open

## Real-world outcomes in patients with melanoma brain metastasis: a US multisite retrospective chart review study of systemic treatments

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# Real-world outcomes in patients with melanoma brain metastasis: a US multisite retrospective chart review study of systemic treatments

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**ABSTRACT**

**Objective** This study examined real-world treatment patterns and outcomes in patients with melanoma brain metastasis (MBM) treated with first-line immunotherapy consisting of nivolumab plus ipilimumab or anti-programmed death-1 (PD-1) monotherapy (nivolumab or pembrolizumab) or targeted therapy consisting of BRAF/MEK inhibitors.

**Design** Retrospective chart review study.

**Setting** Academic medical centers, community hospitals, and private practice offices.

**Participants** Included patients diagnosed with melanoma with brain metastasis in the United States.

**Outcome measures** The statistical analysis was descriptive in nature. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method and compared between treatments in a univariate Cox proportional hazards model.

**Results** In total, 472 patients with MBM who received first-line nivolumab plus ipilimumab (n=246), anti-PD-1 monotherapy (n=112), or BRAF/MEK inhibitors (n=114) were identified. Patients receiving nivolumab plus ipilimumab, compared with patients receiving anti-PD-1 monotherapy or BRAF/MEK inhibitors, had favorable baseline prognostic factors, such as younger age, fewer or smaller brain metastases, better Eastern Cooperative Oncology Group performance status, and less frequently elevated lactate dehydrogenase. Median follow-up times were 15.4 months (range 0.1 to 37.0), 13.3 months (range 0.3 to 36.6), and 13.9 months (range 1.9 to 36.5), respectively. Numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.47, 95% CI 0.34 to 0.67) or BRAF/MEK inhibitors (HR 0.72, 95% CI 0.50 to 1.04), and numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.74, 95% CI 0.53 to 1.02) or BRAF/MEK inhibitors (HR 0.82, 95% CI 0.60 to 1.12). With nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, 1-year OS rates were 79%, 60%, and 72%, respectively; 1-year PFS rates were 68%, 58%, and 59%.

**Conclusions** In this real-world study, first-line nivolumab plus ipilimumab appeared to provide benefit vs anti-PD-1 monotherapy and BRAF/MEK inhibitors in patients with MBM, consistent with pivotal trial data. However, the observed benefit may have been due to confounding and selection bias, given that patients receiving nivolumab plus ipilimumab had favorable baseline prognostic factors compared with patients receiving anti-PD-1 monotherapy or BRAF/MEK inhibitors.

**Keywords** Immunotherapy; Skin cancer (metastatic melanoma)

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This retrospective chart review study collected real-world data of US patients diagnosed with melanoma brain metastasis (MBM) and treated by medical oncologists with different types of first-line systemic therapy options, including immunotherapy and targeted therapy.
- This real-world study may have been limited by heterogeneity in baseline patient characteristics between the treatment groups.
- There may have been inconsistencies in investigator assessments and treatment selection between the treatment groups.
- Interpretation of these results was impeded by small sample sizes in certain subgroups.
- Treatment practices may have changed since patients began treatment in this study.

## INTRODUCTION

Metastasis to the brain is a common sequela of metastatic melanoma, with 35% of patients presenting with brain metastasis at diagnosis,<sup>1</sup> more than 40% developing brain metastasis during their disease,<sup>2</sup> and up to 75% having brain metastasis at the time of death.<sup>3</sup> Historically, patients with melanoma brain metastasis (MBM) have demonstrated a poor prognosis, with a

median overall survival (OS) of approximately 4 months.<sup>4</sup> *BRAF* mutations are present in the tumors of approximately half of the patients with advanced (unresectable or metastatic) melanoma, and patients with *BRAF* mutations have a higher likelihood of developing brain metastasis and experiencing shorter OS than those without these mutations.<sup>5</sup> Prognosis for patients with MBM has improved in recent years with therapeutic advances,<sup>6</sup> but outcomes remain poor in a substantial number of patients, suggesting an area of unmet clinical need.

Primary therapeutic approaches for patients with MBM have traditionally consisted of surgery, whole-brain radiotherapy, and stereotactic radiosurgery.<sup>7</sup> Over the last decade, several systemic treatments showing activity in MBM have been introduced, including immunotherapy (immune checkpoint inhibitors) with the combination of nivolumab (an anti-programmed death-1 [PD-1] antibody) plus ipilimumab (an anti-cytotoxic T lymphocyte antigen-4 [CTLA-4] antibody),<sup>8–11</sup> the combination of pembrolizumab (an anti-PD-1 antibody) plus ipilimumab,<sup>12</sup> and nivolumab<sup>9,10</sup> or pembrolizumab<sup>13</sup> monotherapy, as well as targeted therapy with BRAF plus MEK inhibitor combinations (indicated for patients with tumors harboring a *BRAF* mutation) such as dabrafenib plus trametinib<sup>14</sup> and encorafenib plus binimetinib.<sup>15</sup> Patients with MBM enrolled in clinical trials have been broadly separated into those with and without symptoms, with symptomatic patients showing worse outcomes than asymptomatic patients.<sup>8,10,14</sup> Steroids are the mainstay treatment for symptoms of MBM, such as headache, weakness, and focal neurologic deficits, although steroid therapy may abrogate the clinical effects of immunotherapy.<sup>16</sup>

Nivolumab plus ipilimumab has demonstrated intracranial activity in patients with MBM, especially those with asymptomatic disease.<sup>8–11</sup> In the phase 2 CheckMate 204 trial, patients with asymptomatic (n=101) and symptomatic (n=18) MBM treated with nivolumab plus ipilimumab demonstrated 3-year OS rates of 72% and 37%, respectively.<sup>8</sup> In the phase 2 ABC trial, patients with asymptomatic MBM treated with nivolumab plus ipilimumab (n=35) demonstrated a 5-year OS rate of 51%.<sup>9,10</sup> In the phase 3 Italian NIBIT-M2 trial, patients with

untreated, asymptomatic MBM receiving nivolumab plus ipilimumab (n=27) showed a 7-year OS rate of 43%.<sup>11</sup> According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), nivolumab plus ipilimumab is the preferred systemic therapy option for patients with asymptomatic MBM who do not require steroids in comparison with anti-PD-1 monotherapy or dabrafenib plus trametinib, based on superior intracranial activity.<sup>17</sup>

Until recently, comparative data on the use of systemic agents for the treatment of patients with MBM were limited, as this population was often excluded from randomized clinical trials. Furthermore, there are no prospective head-to-head trials comparing nivolumab plus ipilimumab with anti-PD-1 monotherapy or BRAF/MEK inhibitors in patients with MBM. There is interest in examining the effectiveness and use of these first-line systemic treatments among patients with MBM in the real-world setting because these patients may more closely reflect routine clinical practice compared with patients in clinical trials. The objective of this retrospective chart review study is to examine real-world treatment patterns and clinical outcomes in United States (US) patients with MBM treated with different types of systemic therapy options in the first-line setting.

## METHODS

### Study design

This study collected the real-world data of patients diagnosed with melanoma with brain metastasis who were treated by US medical oncologists in academic/cancer centers, community hospital/cancer centers, and private practice offices. Study recruitment employed a two-part design in which a random sample of patients with *BRAF* mutant or wild-type metastatic melanoma with brain metastases (n=250) was identified first, followed by the identification of an

augment *BRAF* mutant sample (n=113) and an augment *BRAF* wild-type sample (n=125) (online supplemental figure 1).

Physicians who met the study requirements were contacted by a recruitment group (Global Perspectives), and those who were interested in participating were screened to confirm eligibility. A total of 44 oncologists who were currently treating patients with advanced melanoma were recruited, 40 of whom identified patients. Participating physicians were responsible for chart data abstraction and resolution of data-related queries. Physicians were instructed to identify and enroll patients with advanced melanoma diagnosed with brain metastasis who met the inclusion and exclusion criteria. No additional direction or restrictions were provided to physicians for identifying patients.

## Patients

To be eligible, patients were required to have been diagnosed with both metastatic/stage IV melanoma and MBM between June 2017 and June 2019; to be 18 years of age or older; and to have a medical history available for medical chart abstraction from initial melanoma diagnosis through the most recent visit, current therapy, or death. Patients were excluded if they had used systemic therapy in the metastatic setting prior to the development of brain metastasis (see criteria for adjuvant therapy below); had received whole brain radiotherapy (other forms of radiotherapy, such as stereotactic radiosurgery, as allowed); had undergone surgical resection for brain metastasis; had a diagnosis of concurrent malignancy (other than nonmelanoma skin cancer or *in situ* cervical carcinoma); or were enrolled in a cancer-related clinical trial since diagnosis of metastatic melanoma. Prior use of adjuvant or neoadjuvant therapy with anti-PD-1 monotherapy, anti-CTLA-4 monotherapy, or BRAF/MEK inhibitors was allowed if 6 or more months had elapsed between the last dose of therapy and diagnosis of brain metastasis, as

previously defined.<sup>18</sup> The study was conducted in accordance with International Society for Pharmacoeconomics Guidelines for Good Pharmacoeconomics Practices.

## Endpoints

Primary endpoints included treatment patterns in the first-line setting. Secondary endpoints included OS and progression-free survival (PFS). OS was defined as the time from index date (start of first-line treatment in the metastatic setting) to date of death from any cause. PFS was defined as the time from index date to date of first disease progression. OS and PFS were described by type of first-line treatment, which were nivolumab plus ipilimumab, anti-PD-1 monotherapy (nivolumab or pembrolizumab), and BRAF/MEK inhibitors (only for patients with *BRAF* mutant disease). Patients were stratified by *BRAF* wild-type or mutant status and by asymptomatic or symptomatic MBM. Concurrent steroid use was evaluated to identify patients with symptomatic MBM, which was defined as any steroid therapy received within 15 days before the start of first-line treatment. The 15-day window was selected to ensure that steroid administration was not likely because of immune-related adverse events (AEs) associated with immunotherapy. OS and PFS for the three types of systemic treatments were also estimated for patients according to use of radiation, with concurrent radiation defined as radiation therapy that was initiated less than 30 days before or after the start of first-line treatment and sequential radiation defined as radiation that started 30 days or more before/after first-line systemic treatment initiation. Tumor response was not reported because response evaluation was inconsistent among investigators, on-treatment lesion measurements were not collected, response criteria were not defined in the case report form (CRF), and centralized confirmation of radiographic images was not conducted.



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3 **Statistical analysis**

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5 The statistical analysis was descriptive in nature, and precision estimates were determined

6 using the 95% CI rather than power calculations for each cohort. Median OS and PFS were

7 estimated using the Kaplan–Meier product-limit method. Hazard ratios (HRs) and corresponding

8 CIs were estimated using a univariate Cox proportional hazards model to compare OS and PFS

9 between the three types of systemic treatments. All analyses were performed using SAS

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20 **Patient and public involvement**

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22 Patients or the public were not involved in the design, conduct, reporting, or dissemination plans

23 of this research.

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28 **RESULTS**

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30 **Baseline patient characteristics**

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32 In total, 488 patients were identified for the analysis (online supplemental figure 1). A total of

33 472 patients with a confirmed diagnosis of metastatic/stage IV melanoma with MBM received

34 first-line systemic treatment with nivolumab plus ipilimumab (n=246), anti–PD-1 monotherapy

35 (nivolumab or pembrolizumab; n=112), or BRAF/MEK inhibitors (n=114) (table 1). Among the

36 472 patients, 50% (n=236) had *BRAF* wild-type disease, 45% (n=212) had *BRAF* mutant

37 disease, and 5% (n=24) had missing *BRAF* status. Patients treated with nivolumab plus

38 ipilimumab tended to be younger than those treated with anti–PD-1 monotherapy or BRAF/MEK

39 inhibitors (median age, 61.0 years vs 69.0 years and 62.0 years, respectively). At baseline,

40 patients treated with anti–PD-1 monotherapy or BRAF/MEK inhibitors were more likely to have a

41 greater number of or larger brain metastases, poorer Eastern Cooperative Oncology Group

42 performance status (ECOG PS), greater frequency of increased lactate dehydrogenase (LDH),

43 worse Charlson Comorbidity Index (CCI) scores, and greater frequency of steroid use before

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the index date than patients treated with nivolumab plus ipilimumab. No patient received prior combination immunotherapy therapy in the adjuvant or neoadjuvant setting per the data collected in charts.

**Table 1.** Baseline characteristics of patients with MBM by first-line systemic therapy\*†

	Nivolumab plus ipilimumab (n=246)	Anti-PD-1 monotherapy (n=112)‡	BRAF/MEK inhibitors (n=114)
Median age, years (range)	61.0 (33.0–82.0)	69.0 (29.0–92.0)	62.0 (35.0–84.0)
Sex, n (%)			
Male	147 (60)	57 (51)	59 (52)
Female	99 (40)	55 (49)	55 (48)
Race, n (%)			
White	213 (87)	98 (88)	105 (92)
Black	22 (9)	8 (7)	6 (5)
Asian	11 (4)	4 (4)	3 (3)
Other	0	2 (2)	0
Median (range) number of brain lesions	2.0 (1.0–10.0)	3.0 (1.0–10.0)	3.0 (1.0–10.0)
Mean (SD) size of largest brain metastatic site, mm	8.3 (8.8)	11.9 (10.2)	12.7 (11.7)
ECOG PS, n (%)			
0	66 (27)	9 (8)	22 (19)
1	100 (41)	48 (43)	49 (43)
2	63 (26)	40 (36)	38 (33)
3	15 (6)	14 (12)	5 (4)
4	1 (<1)	0	0
Missing	1 (<1)	1 (1)	0
Serum LDH, n (%)			
Normal	107 (43)	27 (24)	31 (27)
1–2 times ULN	79 (32)	63 (56)	52 (46)
>2 times ULN	60 (24)	22 (20)	31 (27)
BRAF status, n (%)			
Wild-type	159 (65)	77 (69)	0
Mutant	76 (31)	23 (21)	113 (99)
Missing	11 (4)	12 (11)	1 (1)
Mean (SD) CCI scores§	0.47 (0.73)	1.10 (1.33)	0.96 (1.37)
Steroid use, n (%)			
None	198 (80)	86 (77)	85 (75)
Started before index date	18 (7)	15 (13)	19 (17)
Other	30 (12)	11 (10)	10 (9)
Radiation use, n (%)			
None	192 (78)	80 (71)	75 (66)
Concurrent	43 (17)	24 (21)	34 (30)
Sequential	11 (4)	8 (7)	5 (4)

\*Among 488 patients who were identified, 472 patients received first-line treatment with nivolumab plus ipilimumab, anti-PD-1 monotherapy, or BRAF/MEK inhibitors and were included in the analysis. First-line systemic therapies used in 16 of the 488 patients who were not

included in the analysis were dacarbazine (n=3), pegylated interferon alfa-2b (n=3), pembrolizumab plus other systemic therapy (n=3), temozolomide (n=3), paclitaxel (n=2), carboplatin (n=1), cisplatin (n=1), larotrectinib (n=1), and trametinib (n=1). †Percentages may not add up to 100 because of rounding. ‡Nivolumab or pembrolizumab monotherapy. ¶American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander. §Higher scores indicate increased comorbidity burden. ||Start of first-line treatment in the metastatic setting. CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; MBM, melanoma brain metastasis; PD-1, programmed death-1; SD, standard deviation; ULN, upper limit of normal.

**Follow-up time**

Median follow-up times from treatment initiation were 15.4 months (range 0.1 to 37.0), 13.3 months (range 0.3 to 36.6), and 14.0 months (range 1.9 to 36.5) with first-line nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, respectively.

**Concurrent steroid use**

Concurrent steroid use was used to identify patients with symptomatic MBM. Among the 472 patients included in the analysis, 369 patients (78%) did not receive steroids (and were considered asymptomatic), 52 patients (11%) received concurrent steroids (and were considered symptomatic), and 51 patients (11%) received steroids outside of the concurrent steroid definition (ie, not within the 15 days before the start of first-line treatment) (table 1).

**Concurrent radiation use**

Among the 472 patients included in the analysis, 347 patients (74%) did not receive concurrent radiation, 101 patients (21%) received concurrent radiation (stereotactic, intensity-modulated, three-dimensional conformal, and gamma knife radiation), and 24 patients (5%) received sequential radiation (defined as radiation that started 30 days or more before/after first-line systemic treatment initiation) (table 1). The median time from first dose of systemic therapy (with nivolumab plus ipilimumab, anti-PD-1 monotherapy, or BRAF/MEK inhibitors) to radiation therapy or vice versa was 12 days (range -671 to 160). Types of first radiation therapy were

stereotactic (74%), intensity-modulated (17%), and three-dimensional conformal (9%) radiation (online supplemental table 1).

### OS and PFS in the overall study group

In the overall study group, numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.47, 95% CI 0.34 to 0.67) or BRAF/MEK inhibitors (HR 0.72, 95% CI 0.50 to 1.04) (figure 1A). Median OS was 36.0 months (95% CI 32.1 to not reached [NR]) with nivolumab plus ipilimumab, 18.8 months (95% CI 13.0 to 26.0) with anti-PD-1 monotherapy, and NR (95% CI 19.4 to NR) with BRAF/MEK inhibitors. One-year OS rates were 79%, 60%, and 72% with nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, respectively.

Numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.74, 95% CI 0.53 to 1.02) or BRAF/MEK inhibitors (HR 0.82, 95% CI 0.60 to 1.12) (figure 1B). Median PFS was 22.7 months (95% CI 19.3 to 28.3) with nivolumab plus ipilimumab, 16.8 months (95% CI 11.6 to 24.9) with anti-PD-1 monotherapy, and 15.4 months (95% CI 12.7 to NR) with BRAF/MEK inhibitors. One-year PFS rates were 68%, 58%, and 59% with nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, respectively.

### OS in patients with asymptomatic MBM

Among patients with *BRAF* wild-type, asymptomatic MBM, numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.48, 95% CI 0.30 to 0.78) (figure 2A). Median OS was 32.1 months (95% CI 27.5 to NR) with nivolumab plus ipilimumab

and 18.8 months (95% CI 11.8 to NR) with anti-PD-1 monotherapy. One-year OS rates were 80% and 58%, respectively.

Among patients with *BRAF* mutant, asymptomatic MBM, numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.48, 95% CI 0.16 to 1.41) or BRAF/MEK inhibitors (HR 0.40, 95% CI 0.19 to 0.84) (figure 2B). Median OS was 36.0 months (95% CI 36.0 to NR) with nivolumab plus ipilimumab, 26.0 months (95% CI 16.0 to NR) with anti-PD-1 monotherapy, and NR (95% CI NR to NR) with BRAF/MEK inhibitors. There were few patients treated with nivolumab plus ipilimumab at 36 months, resulting in a drop in the Kaplan–Meier curve for that group. One-year OS rates were 93%, 86%, and 75%, respectively.

### OS in patients with symptomatic MBM

Among patients with *BRAF* wild-type, symptomatic MBM, numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.16, 95% CI 0.05 to 0.53), although sample sizes were small (online supplemental figure 2A). Median OS was NR (95% CI 9.2 to NR) with nivolumab plus ipilimumab and 4.7 months (95% CI 2.3 to NR) with anti-PD-1 monotherapy. One-year OS rates were 69% and 18%, respectively.

Among patients with *BRAF* mutant, symptomatic MBM, numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.27, 95% CI 0.06 to 1.25), and numerically shorter OS was observed with nivolumab plus ipilimumab vs BRAF/MEK inhibitors (HR 1.59, 95% CI 0.42 to 6.04), although sample sizes were small (online supplemental figure 2B). Median OS was 11.1 months (95% CI 7.7 to NR) with nivolumab plus ipilimumab, 4.1 months (95% CI 2.8 to NR) with anti-PD-1 monotherapy, and 23.0 (95% CI 21.4 to NR) with BRAF/MEK inhibitors. One-year OS rates were 40%, 25%, and 68%, respectively.

### PFS in patients with asymptomatic MBM

Among patients with *BRAF* wild-type, asymptomatic MBM, numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.80, 95% CI 0.50 to 1.26) (figure 3A). Median PFS was 24.1 months (95% CI 18.8 to NR) with nivolumab plus ipilimumab and 23.0 months (95% CI 13.6 to NR) with anti-PD-1 monotherapy. One-year PFS rates were 71% and 63%, respectively.

Among patients with *BRAF* mutant, asymptomatic MBM, numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.80, 95% CI 0.35 to 1.85) or BRAF/MEK inhibitors (HR 0.83, 95% CI 0.51 to 1.35) (figure 3B). Median PFS was 21.5 months (95% CI 17.9 to 28.3) with nivolumab plus ipilimumab, 16.3 months (95% CI 16.2 to NR) with anti-PD-1 monotherapy, and 28.9 months (95% CI 12.8 to NR) with BRAF/MEK inhibitors. One-year PFS rates were 77%, 79%, and 62%, respectively.

### PFS in patients with symptomatic MBM

Among patients with *BRAF* wild-type, symptomatic MBM, numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.21, 95% CI 0.07 to 0.66), although sample sizes were small (online supplemental figure 3A). Median PFS was NR (95% CI 7.5 to NR) with nivolumab plus ipilimumab and 4.5 months (95% CI 3.1 to NR) with anti-PD-1 monotherapy. One-year PFS rates were 62% and 11%, respectively.

Among patients with *BRAF* mutant, symptomatic MBM, numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.37, 95% CI 0.05 to 2.76), and numerically shorter PFS was observed with nivolumab plus ipilimumab vs BRAF/MEK inhibitors (HR 1.29, 95% CI 0.27 to 6.15), although sample sizes were small (online supplemental figure 3B). Median PFS was NR (95% CI 5.4 months to NR) with nivolumab plus ipilimumab, 11.6 months (95% CI 3.5 to NR) with anti-PD-1 monotherapy, and 22.5 months

(95% CI 14.0 to NR) with BRAF/MEK inhibitors. One-year PFS rates were 50%, 0%, and 72%, respectively.

**OS and PFS in patients with MBM without or with concurrent radiation**

Sample sizes were small in patients with MBM without or with concurrent radiation. Among patients without concurrent radiation and with *BRAF* wild-type MBM, numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.44, 95% CI 0.28 to 0.72) (online supplemental figure 4A). Among patients without concurrent radiation and with *BRAF* mutant MBM, numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.48, 95% CI 0.15 to 1.56) or BRAF/MEK inhibitors (HR 0.43, 95% CI 0.20 to 0.90) (online supplemental figure 4B). Among patients with concurrent radiation and *BRAF* wild-type MBM, numerically longer OS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.29, 95% CI 0.12 to 0.68) (online supplemental figure 5A). Among patients with concurrent radiation and *BRAF* mutant MBM, numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.85, 95% CI 0.31 to 2.31), and numerically shorter PFS was observed with nivolumab plus ipilimumab vs BRAF/MEK inhibitors (HR 1.30, 95% CI 0.60 to 2.81) (online supplemental figure 5B).

Among patients without concurrent radiation and with *BRAF* wild-type MBM, numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.76, 95% CI 0.48 to 1.22) (online supplemental figure 6A). Among patients without concurrent radiation and with *BRAF* mutant MBM, numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.82, 95% CI 0.31 to 2.15) or BRAF/MEK inhibitors (HR 0.72, 95% CI 0.43 to 1.21) (online supplemental figure 6B). Among patients with concurrent radiation and *BRAF* wild-type MBM, numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.32, 95% CI 0.13 to 0.75) (online supplemental figure 7A). Among patients with concurrent radiation and *BRAF* mutant MBM,



numerically longer PFS was observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy (HR 0.96, 95% CI 0.37 to 2.50), and numerically shorter PFS was observed with nivolumab plus ipilimumab vs BRAF/MEK inhibitors (HR 1.78, 95% CI 0.88 to 3.61) (online supplemental figure 7B).

## DISCUSSION

This retrospective chart review study collected real-world data of US patients diagnosed with MBM and treated by medical oncologists with different types of systemic therapy options in the first-line setting. Given that there is no prospective head-to-head trial comparing nivolumab plus ipilimumab with anti-PD-1 monotherapy or BRAF/MEK inhibitors in patients with MBM, this real-world study may provide valuable insights for clinical decision-making.

Certain baseline patient characteristics differed among the three treatment groups in this nonrandomized study. Specifically, patients receiving nivolumab plus ipilimumab, compared with patients receiving anti-PD-1 monotherapy or BRAF/MEK inhibitors, had favorable baseline prognostic factors, such as younger age, fewer or smaller brain metastases, better ECOG PS, less frequently elevated LDH, better CCI scores, and less frequent steroid use before the index date. It is possible that, in some cases, physicians may have reserved therapy with nivolumab plus ipilimumab for patients who had favorable baseline prognostic factors and were therefore considered more likely to tolerate toxicities associated with combination immunotherapy.

In this study, first-line treatment with nivolumab plus ipilimumab appeared to provide benefit compared with first-line treatment with anti-PD-1 monotherapy or BRAF/MEK inhibitors in patients with MBM, of whom 78% had asymptomatic disease (symptomatic disease was based on any steroid therapy received within the 15 days prior to the start of first-line treatment to ensure that steroid administration was not likely due to immune-related AEs; however, steroids may still have been administered during that time period for managing immune-related AEs). Numerically longer OS and PFS were observed with nivolumab plus ipilimumab vs anti-



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PD-1 monotherapy and BRAF/MEK inhibitors. At 1 year, OS rates were 79%, 60%, and 72% with nivolumab plus ipilimumab, anti-PD-1 monotherapy, and BRAF/MEK inhibitors, respectively, and PFS rates were 68%, 58%, and 59%, respectively. However, the observed benefit may have been due to confounding and selection bias, given that patients receiving nivolumab plus ipilimumab had favorable baseline prognostic factors compared with patients receiving anti-PD-1 monotherapy or BRAF/MEK inhibitors.

Effectiveness results in this real-world study were generally consistent with data across clinical trials involving patients with MBM,<sup>8,10,13,14,19–22</sup> although cross-trial comparisons are difficult because of differences in study populations and methodologies. For example, among patients with asymptomatic MBM, 1-year OS rates were 63% and approximately 80% with nivolumab plus ipilimumab in the phase 2 ABC trial<sup>10</sup> and CheckMate 204 trial,<sup>8</sup> respectively; 60% with nivolumab in the ABC trial<sup>10</sup> and approximately 60% with pembrolizumab in another phase 2 trial<sup>13</sup>; and 46% with dabrafenib plus trametinib in the phase 2 COMBI-MB trial.<sup>14</sup> Results from the current study were also consistent with those from the real-world German DeCOG and NICO studies in which 1-year OS rates were 69% and 59%, respectively, in patients with MBM treated with nivolumab plus ipilimumab.<sup>19,20</sup> In addition, these real-world results are in line with findings of two separate meta-analyses using data from clinical trials and real-world studies, respectively, that suggested advantages with nivolumab plus ipilimumab compared with other systemic treatments in patients with MBM.<sup>21,22</sup> Furthermore, 1-year OS rates in patients with MBM treated with nivolumab plus ipilimumab in this real-world study and the ABC trial<sup>10</sup> and the CheckMate 204 trial<sup>8</sup> were similar to that in patients with advanced melanoma not having active brain metastases who were treated with nivolumab plus ipilimumab in the phase 3 CheckMate 067 trial,<sup>23</sup> suggesting that nivolumab plus ipilimumab is effective regardless of the presence of brain metastasis.

Effectiveness was evaluated in this real-world study in subgroups according to asymptomatic or symptomatic MBM and *BRAF* wild-type or mutant status. Numerically longer

OS and PFS were observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy, regardless of symptom or *BRAF* status. In addition, numerically longer OS and PFS were observed with nivolumab plus ipilimumab vs BRAF/MEK inhibitors with asymptomatic, *BRAF* mutant MBM, but numerically shorter OS and PFS were observed with nivolumab plus ipilimumab vs BRAF/MEK inhibitors with symptomatic, *BRAF* mutant MBM. However, sample sizes for patients with symptomatic MBM were small. Numerically longer OS was observed among patients with asymptomatic than symptomatic MBM, consistent with results in clinical studies.<sup>8–10,14</sup> Among patients with *BRAF* wild-type or mutant symptomatic MBM, 1-year OS rates with nivolumab plus ipilimumab were 69% and 40%, respectively, which were consistent with results from the CheckMate 204 trial showing a 1-year OS rate of approximately 40% in patients with symptomatic (*BRAF* wild-type or mutant) MBM treated with nivolumab plus ipilimumab.<sup>8</sup>

OS and PFS were estimated in this real-world study in subgroups without or with concurrent radiation by *BRAF* mutation status, although sample sizes were too small to allow confident interpretation of the results. Numerically longer OS and PFS were observed with nivolumab plus ipilimumab vs anti-PD-1 monotherapy, regardless of use of concurrent radiation or *BRAF* mutation status. In addition, numerically longer OS and PFS were observed with nivolumab plus ipilimumab vs BRAF/MEK inhibitors with *BRAF* mutant MBM and no concurrent radiation use, but numerically shorter OS and PFS were observed with nivolumab plus ipilimumab vs BRAF/MEK inhibitors with *BRAF* mutant MBM and concurrent radiation use.

New therapies have emerged for the treatment of patients with advanced melanoma, and in the phase 2/3 RELATIVITY 047 trial, a novel, dual immune checkpoint inhibitor combination of nivolumab plus relatlimab (a lymphocyte-activation gene 3 inhibitor) appeared to have central nervous system (CNS) activity in patients with advanced melanoma.<sup>24</sup> In that trial, new CNS metastases developed less frequently in patients treated with nivolumab plus relatlimab than with nivolumab alone (5% vs 9%) and time to development of new CNS lesions

was longer with the combination than with nivolumab monotherapy (patients with new CNS lesions at 2 years, 6.5% and 10.0%, respectively).<sup>24</sup> However, those results were limited by the low occurrence of new CNS metastases in both treatment groups. The safety and efficacy of nivolumab plus relatlimab in patients with active MBM is being investigated in a single-arm, open-label, phase 2 BLUEBONNET trial (ClinicalTrials.gov identifier: NCT05704647).<sup>25</sup>

This real-world study had certain limitations. First, because this was a nonrandomized comparison of three treatment regimens, there was likely substantial confounding and selection bias. Thus, the study may have been limited by heterogeneity in baseline patient characteristics between the treatment groups. As previously stated, the observed benefit in patients receiving nivolumab plus ipilimumab may have been due to confounding and selection bias, given that those patients had favorable baseline prognostic factors. At baseline, patients treated with anti-PD-1 monotherapy or BRAF/MEK inhibitors were more likely to have a greater number of or larger brain metastases, poorer ECOG PS, or greater frequency of increased LDH than patients treated with nivolumab plus ipilimumab. In addition, there may have been inconsistencies among the treatment groups in investigator assessments (eg, ECOG PS assessment) and in treatment selection based on clinical trial evidence and therapeutic guidelines. Interpretation of OS and PFS results in certain subgroups was impeded by small sample sizes. Furthermore, tumor response was not reported because of variability in investigator assessments. Although dates of progression were collected in the CRF, progression was based on investigator assessment and not on Response Evaluation Criteria in Solid Tumors, version 1.1. The date of progression was determined by the treating physician based on chart review and not necessarily any radiologic confirmation. As the CRF did not distinguish between asymptomatic and symptomatic MBM, concurrent steroid use served as a surrogate method for identifying patients with symptomatic MBM. Although concurrent steroid use was defined as any steroid therapy received within the 15 days prior to the start of first-line treatment to ensure that steroid administration was not likely due to immune-related AEs, it was still possible that steroids were

administered during that time period for managing immune-related AEs. Additionally, patients selected by the study physicians may not have been representative of the general melanoma population because of selection bias, and physicians who chose to participate in the study may not have accurately represented the broader population of melanoma-treating oncologists. Moreover, despite efforts to minimize missing or inaccurate data, the retrospective nature of this chart review study may still have resulted in some missing or inaccurate data points. Finally, treatment practices for MBM may have changed since patients in this study began treatment (June 2017 through June 2019).

In conclusion, results from this retrospective chart review study, which collected real-world data of US patients diagnosed with MBM and treated by medical oncologists, supplement data from clinical trials evaluating this subset of patients. Among patients with MBM in this real-world study, numerically longer OS and PFS were observed with first-line nivolumab plus ipilimumab vs first-line anti-PD-1 monotherapy or BRAF/MEK inhibitors. These results are generally consistent with those in clinical trials and real-world studies with these treatments in patients with MBM. Given that there are no prospective head-to-head trials comparing nivolumab plus ipilimumab with anti-PD-1 monotherapy or BRAF/MEK inhibitors in patients with MBM, this real-world study may provide valuable insights for clinical decision-making. Additional studies are required to investigate first-line treatments for patients with MBM.

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**Patient consent for publication** Not applicable.

**Ethics approval** The protocol, amendments, and subject informed consent received appropriate approval by the Institutional Review Board/Independent Ethics Committee (WCG Clinical Services, Princeton, NJ, USA) or other applicable review board as required by local law prior to initiation of study at the site. Investigators were to ensure that patients, or, in those situations where consent could not be given by patients, their legally acceptable representatives, were clearly informed about the purpose, potential risks, and other critical issues regarding this study. The study was conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices.

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**Data availability statement** Interested researchers may request access by contacting the corresponding author or Bristol Myers Squibb directly by submitting an inquiry through the following link: <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>. Access will be subject to Bristol Myers Squibb's policies and may require a data use agreement.

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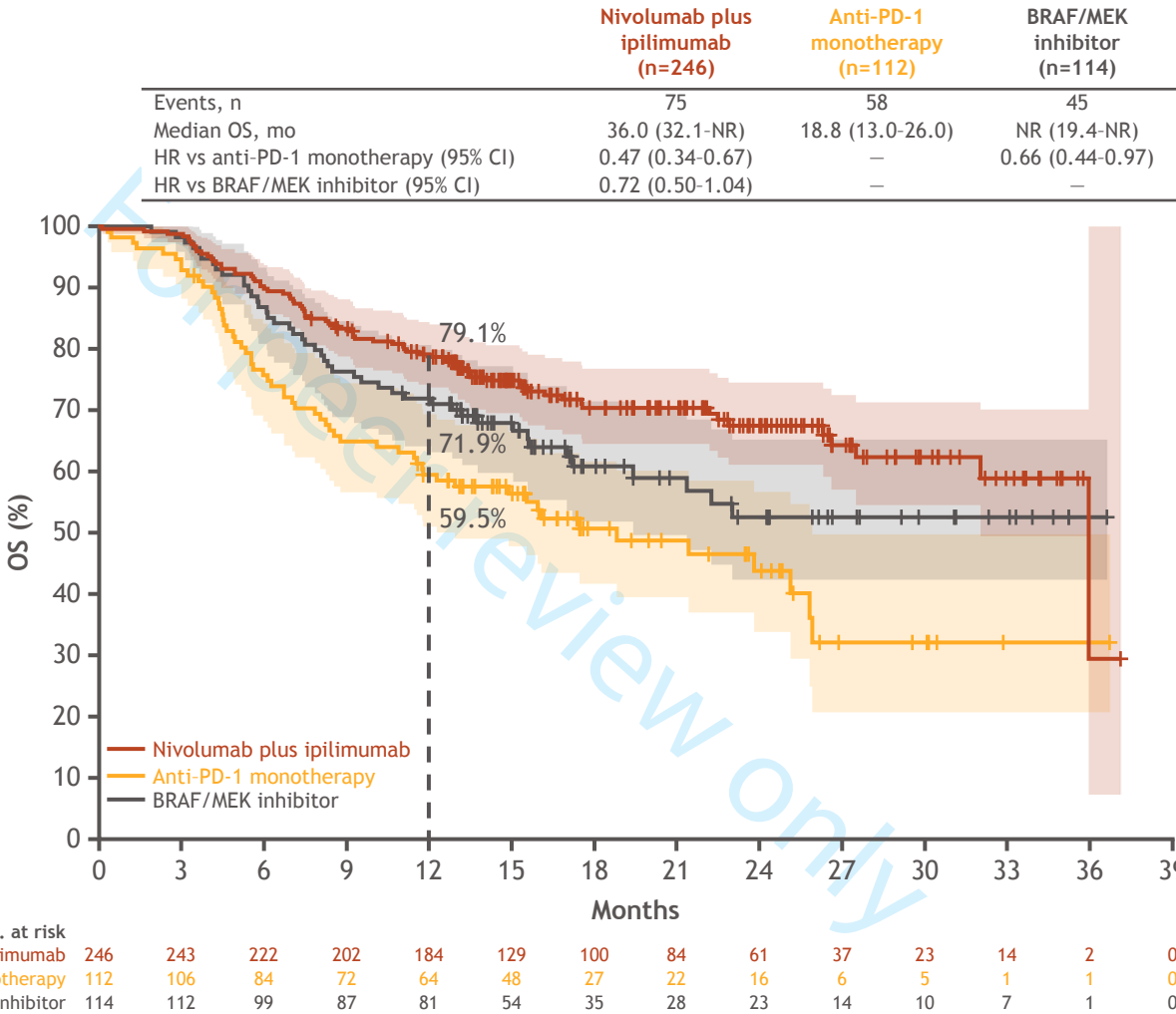
## FIGURE LEGENDS

**Figure 1.** OS and PFS in the overall study group (patients with asymptomatic or symptomatic patients MBM) by first-line treatment. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1; PFS, progression-free survival.

**Figure 2.** OS in patients with asymptomatic MBM by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.

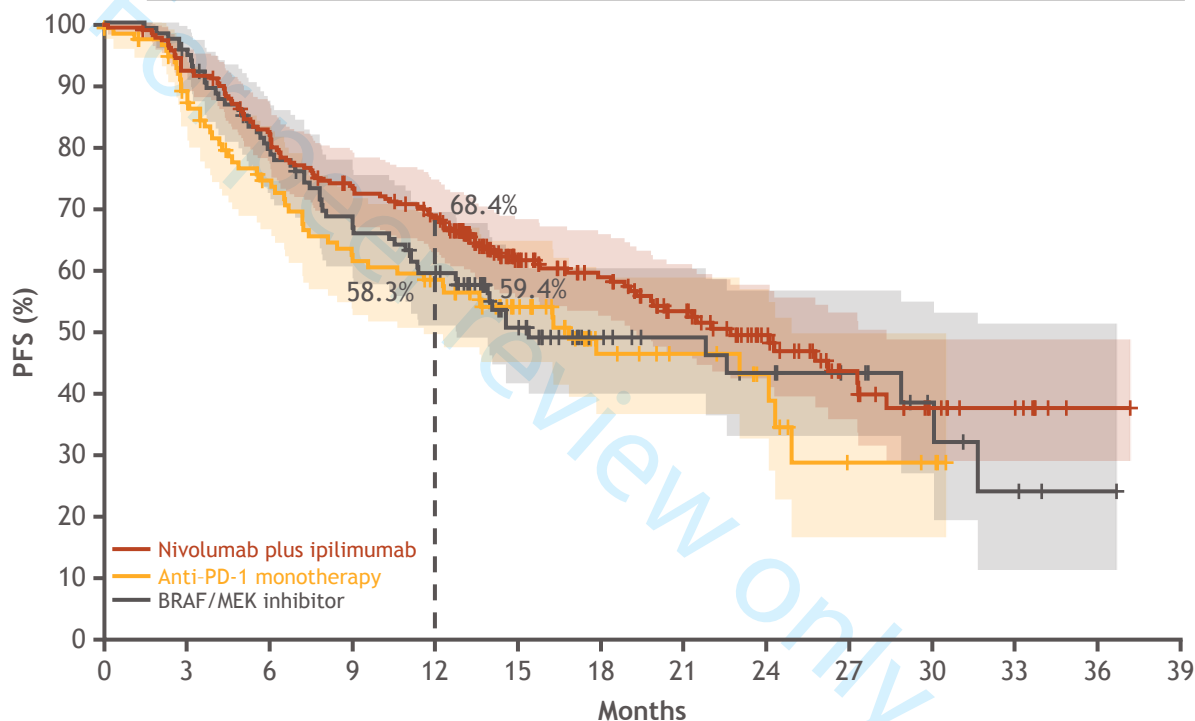
**Figure 3.** PFS in patients with asymptomatic MBM by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; PD-1, programmed death-1; PFS, progression-free survival.

A. OS



## B. PFS

	Nivolumab plus ipilimumab (n=244)	Anti-PD-1 monotherapy (n=111)	BRAF/MEK inhibitor (n=114)
Events, n	112	55	58
Median PFS, mo	22.7 (19.3-28.3)	16.8 (11.6-24.9)	15.4 (12.7-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.74 (0.53-1.02)	—	0.90 (0.62-1.30)
HR vs BRAF/MEK inhibitor (95% CI)	0.82 (0.60-1.12)	—	—

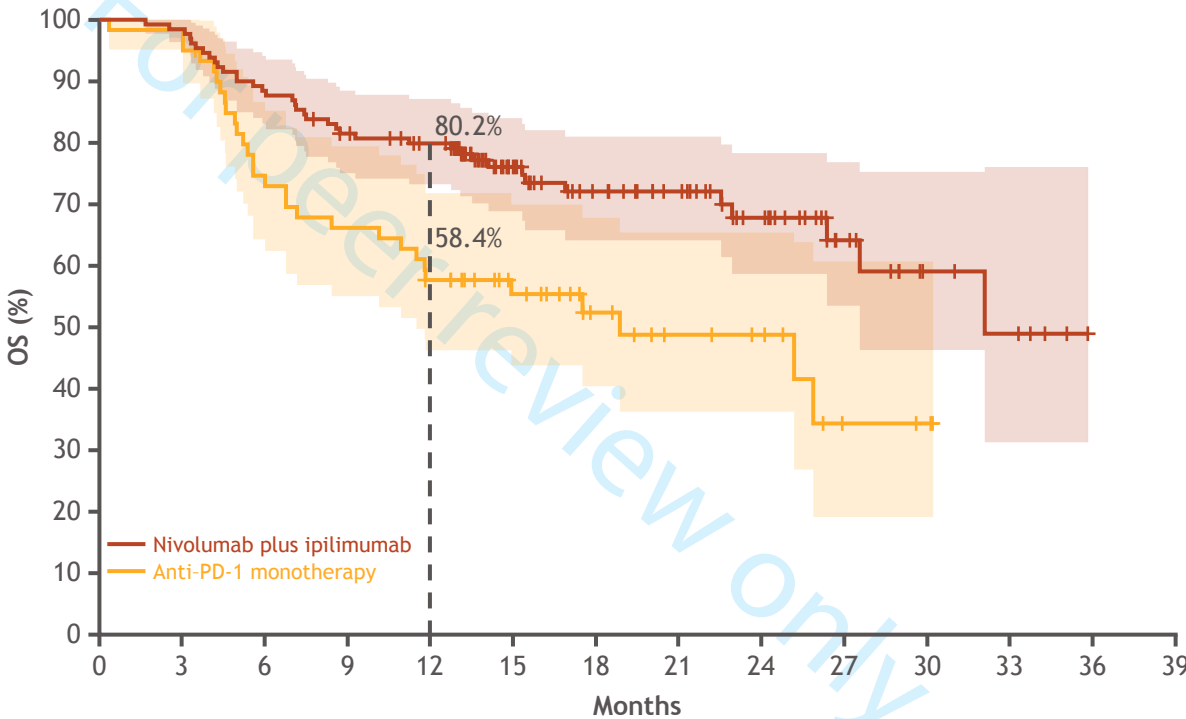


No. at risk

Nivolumab plus ipilimumab	244	224	197	173	158	99	80	60	40	23	12	7	1	0
Anti-PD-1 monotherapy	111	94	74	61	56	39	19	15	10	4	3	0	0	0
BRAF/MEK inhibitor	114	108	88	73	64	35	21	17	14	11	6	3	1	0

A. *BRAF* wild-type disease

	Nivolumab plus ipilimumab (n=132)	Anti-PD-1 monotherapy (n=61)
Events, n	38	30
Median OS, mo	32.1 (27.5-NR)	18.8 (11.8-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.48 (0.30-0.78)	—

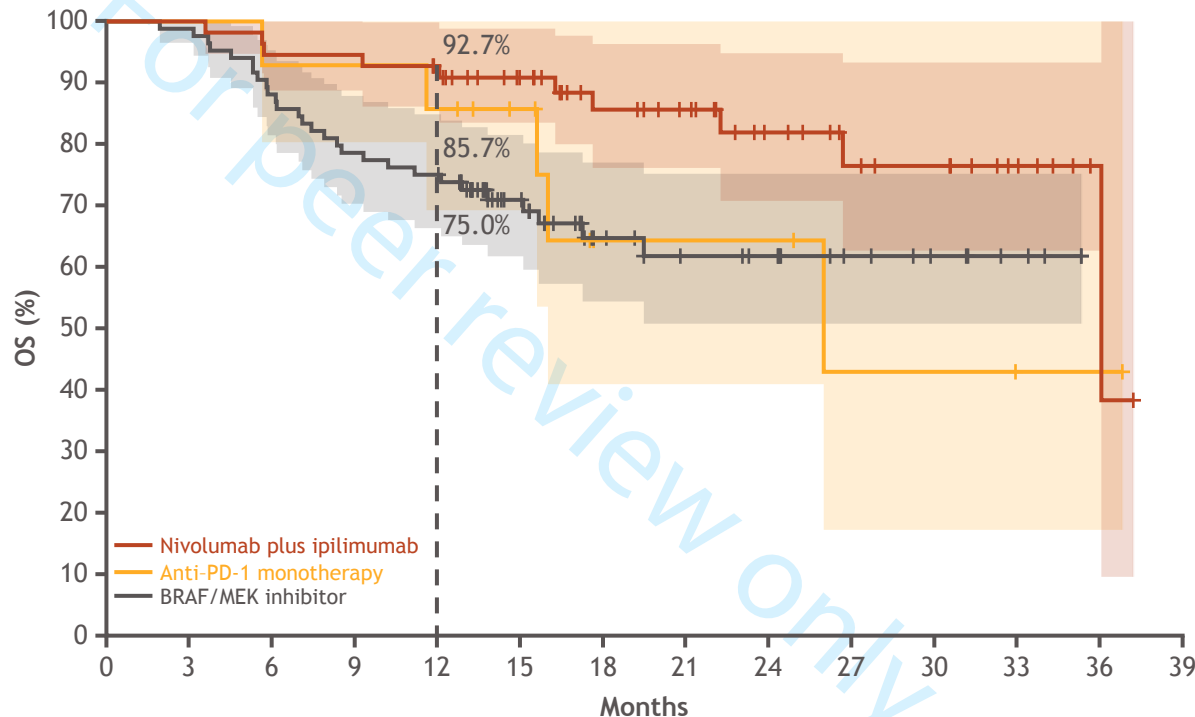


No. at risk

Nivolumab plus ipilimumab	132	130	117	106	99	63	49	41	29	15	7	5	0	0
Anti-PD-1 monotherapy	61	60	44	40	34	25	16	11	9	3	2	0	0	0

B. *BRAF* mutant disease

	Nivolumab plus ipilimumab (n=55)	Anti-PD-1 monotherapy (n=14)	BRAF/MEK inhibitor (n=84)
Events, n	10	5	28
Median OS, mo	36.0 (36.0-NR)	26.0 (16.0-NR)	NR (NR-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.48 (0.16-1.41)	—	1.19 (0.45-3.14)
HR vs BRAF/MEK inhibitor (95% CI)	0.40 (0.19-0.84)	—	—



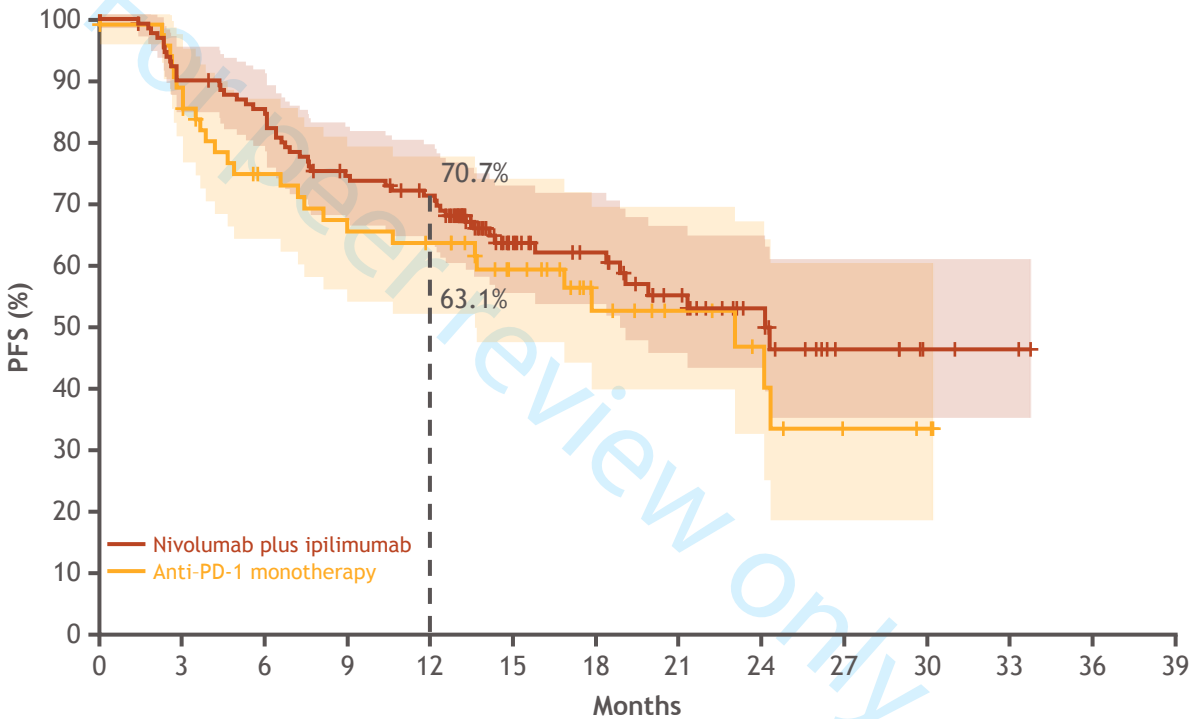
No. at risk

Nivolumab plus ipilimumab	55	55	52	52	49	40	31	27	19	14	12	6	2	0
Anti-PD-1 monotherapy	14	14	13	13	12	9	4	4	4	2	2	1	1	0
BRAF/MEK inhibitor	84	83	74	66	63	39	24	19	17	10	7	4	0	0



A. *BRAF* wild-type disease

	Nivolumab plus ipilimumab (n=132)	Anti-PD-1 monotherapy (n=60)
Events, n	54	28
Median PFS, mo	24.1 (18.8-NR)	23.0 (13.6-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.80 (0.50-1.26)	—

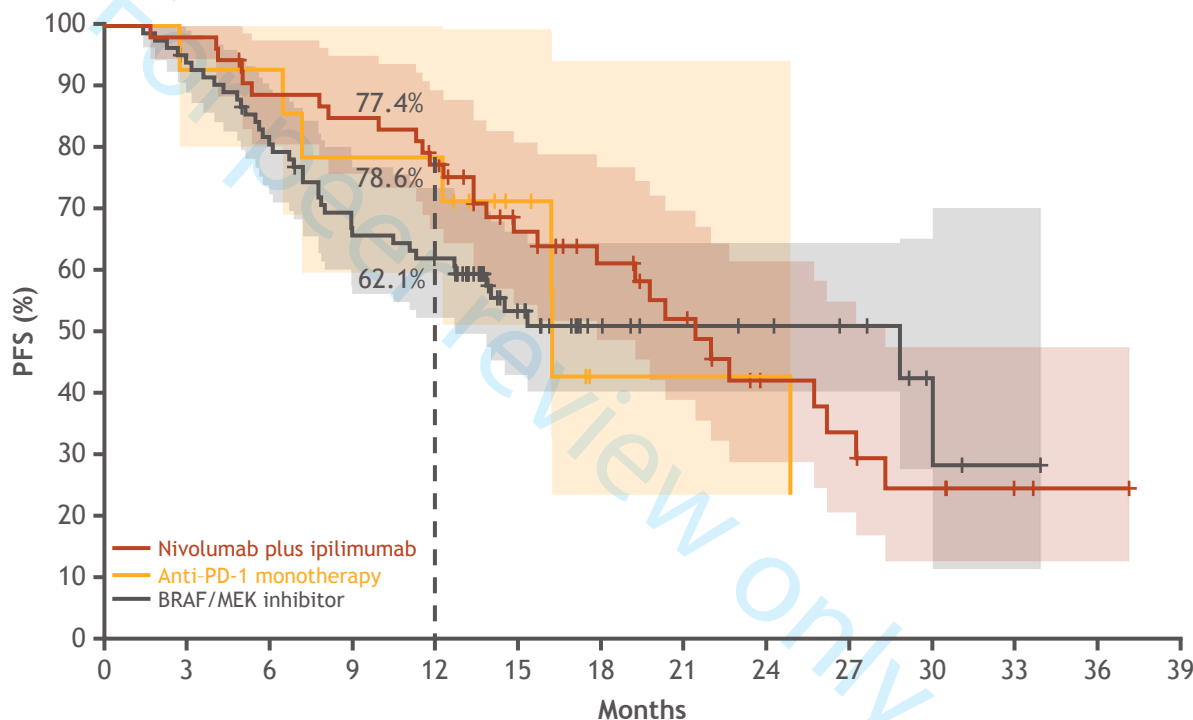


No. at risk

Nivolumab plus ipilimumab	132	117	109	94	87	46	38	27	17	7	3	2	0	0
Anti-PD-1 monotherapy	60	52	40	35	33	24	14	10	7	3	2	0	0	0

B. *BRAF* mutant disease

	Nivolumab plus ipilimumab (n=54)	Anti-PD-1 monotherapy (n=14)	BRAF/MEK inhibitor (n=84)
Events, n	29	7	39
Median PFS, mo	21.5 (17.9-28.3)	16.3 (16.2-NR)	28.9 (12.8-NR)
HR vs anti-PD-1 monotherapy (95% CI)	0.80 (0.35-1.85)	—	0.96 (0.43-2.16)
HR vs BRAF/MEK inhibitor (95% CI)	0.83 (0.51-1.35)	—	—



No. at risk

Nivolumab plus ipilimumab	54	53	47	45	40	28	22	17	10	8	5	2	1	0
Anti-PD-1 monotherapy	14	13	13	11	11	6	1	1	1	0	0	0	0	0
BRAF/MEK inhibitor	84	79	67	54	50	25	13	10	9	7	3	1	0	0

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**SUPPLEMENT**

**Real-world outcomes in patients with melanoma brain metastasis:  
a US multisite retrospective chart review study of systemic treatments**

Isabella C. Glitza Oliva,<sup>1</sup> Jennell Palaia,<sup>2</sup> Leon A. Sakkal,<sup>2</sup> Divya Patel,<sup>2</sup> Andriy Moshyk,<sup>2</sup>  
Natalia Han,<sup>3</sup> Shardul Odak,<sup>3</sup> Jordana K. Schmier,<sup>4</sup> Ning Ning,<sup>4</sup> Sunandana Chandra<sup>5</sup>

<sup>1</sup>The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>2</sup>Bristol Myers Squibb, Princeton, NJ, USA; <sup>3</sup>RTI Health Solutions, Research Triangle Park, NC, USA; <sup>4</sup>Open Health, Bethesda, MD, USA; <sup>5</sup>Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

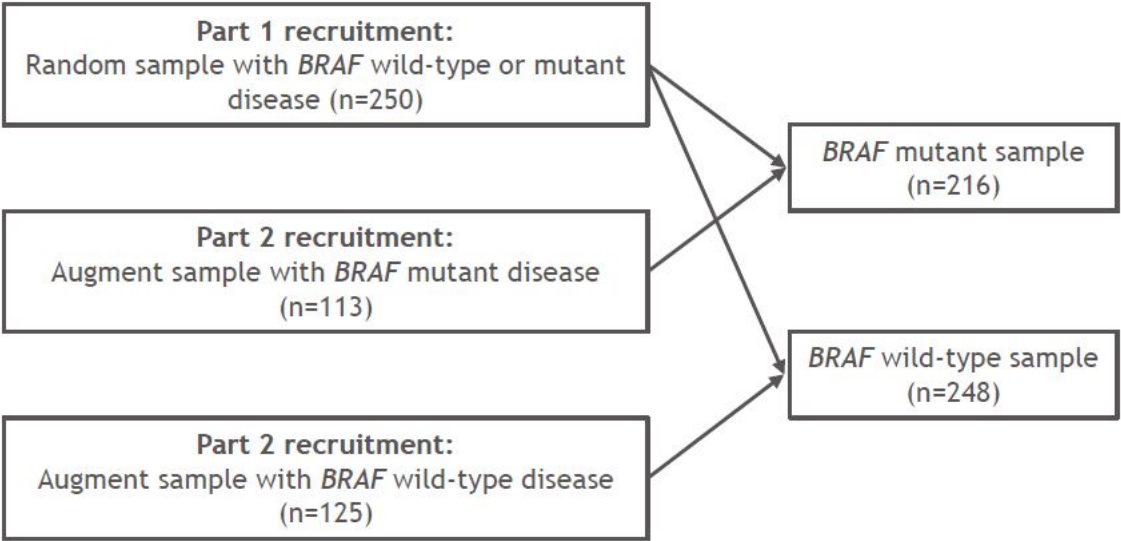
**Supplemental table 1.** Types of radiation therapy

	<b>Nivolumab plus ipilimumab (n=246)</b>	<b>Anti-PD-1 monotherapy (n=112)</b>	<b>BRAF/MEK inhibitor (n=114)</b>	<b>Overall (n=472)</b>
Type of first radiation therapy,* n (%)	n=54	n=33	n=40	n=127
Stereotactic	37 (69)	24 (73)	33 (82)	94 (74)
IMRT	13 (24)	6 (18)	3 (8)	22 (17)
3D-CRT	4 (7)	3 (9)	4 (10)	11 (9)
Type of second radiation therapy, n (%)	n=1	n=0	n=4	n=5
Stereotactic	1 (100)	0	4 (100)	5 (100)
IMRT	0	0	0	0
3D-CRT	0	0	0	0

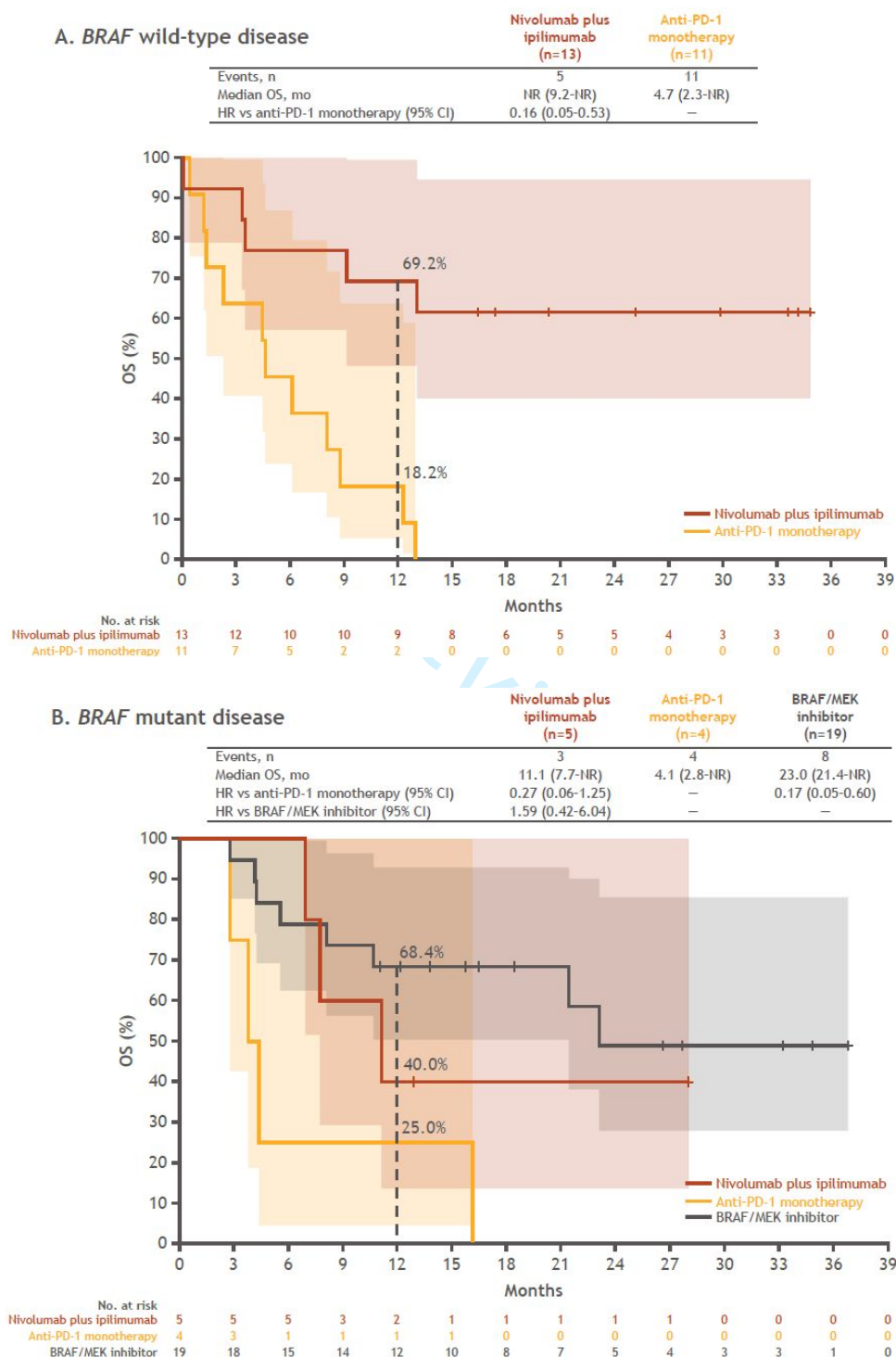
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3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PD-1, programmed death-1.

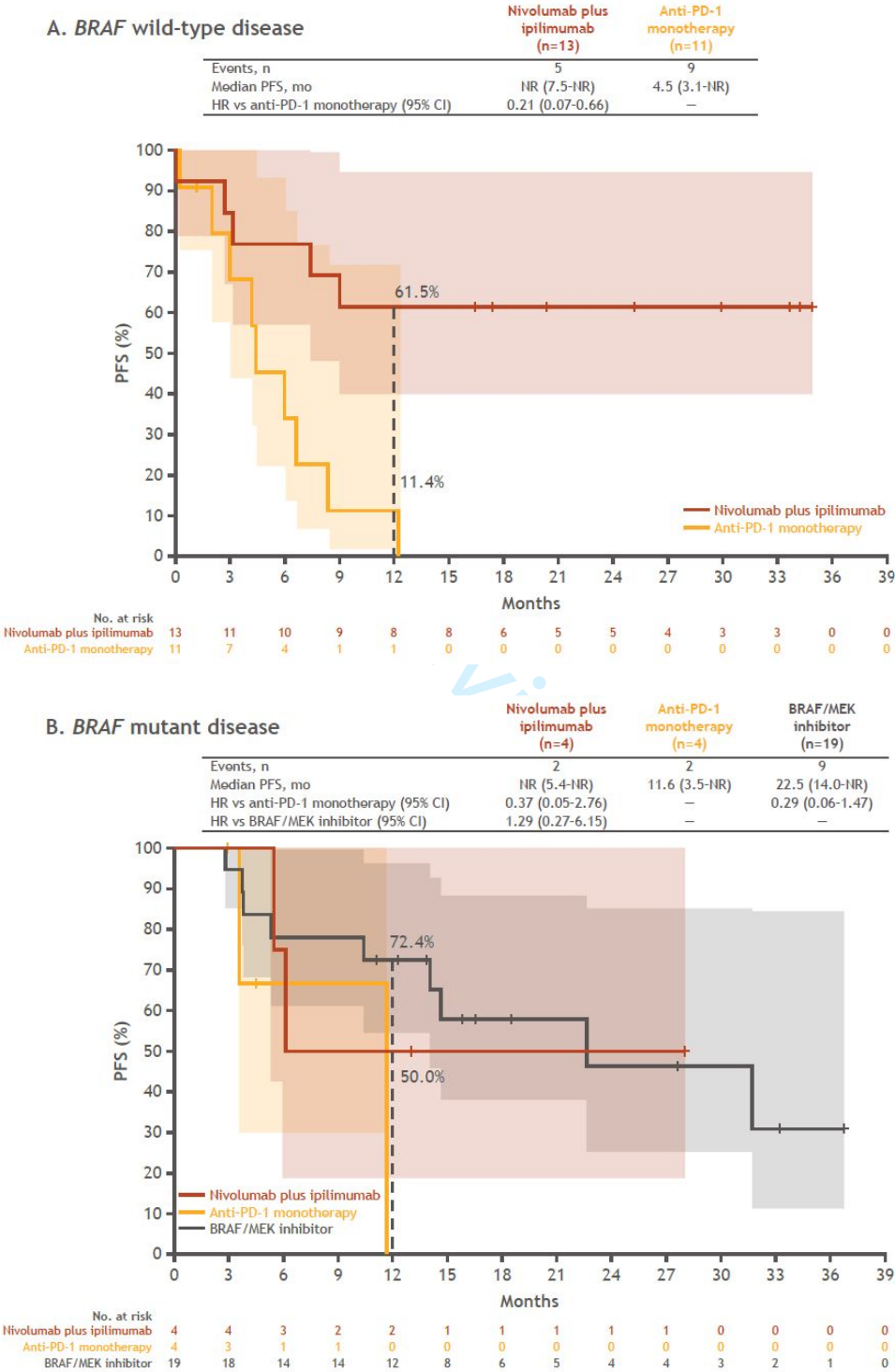
**Supplemental figure 1.** Study design. Study recruitment employed a two-part design in which a random sample of patients with *BRAF* mutant or wild-type metastatic melanoma with brain metastases (n=250) was identified first, followed by the identification of an augment *BRAF* mutant sample (n=113) and an augment *BRAF* wild-type sample (n=125).



**Supplemental figure 2.** OS in patients with symptomatic MBM by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.

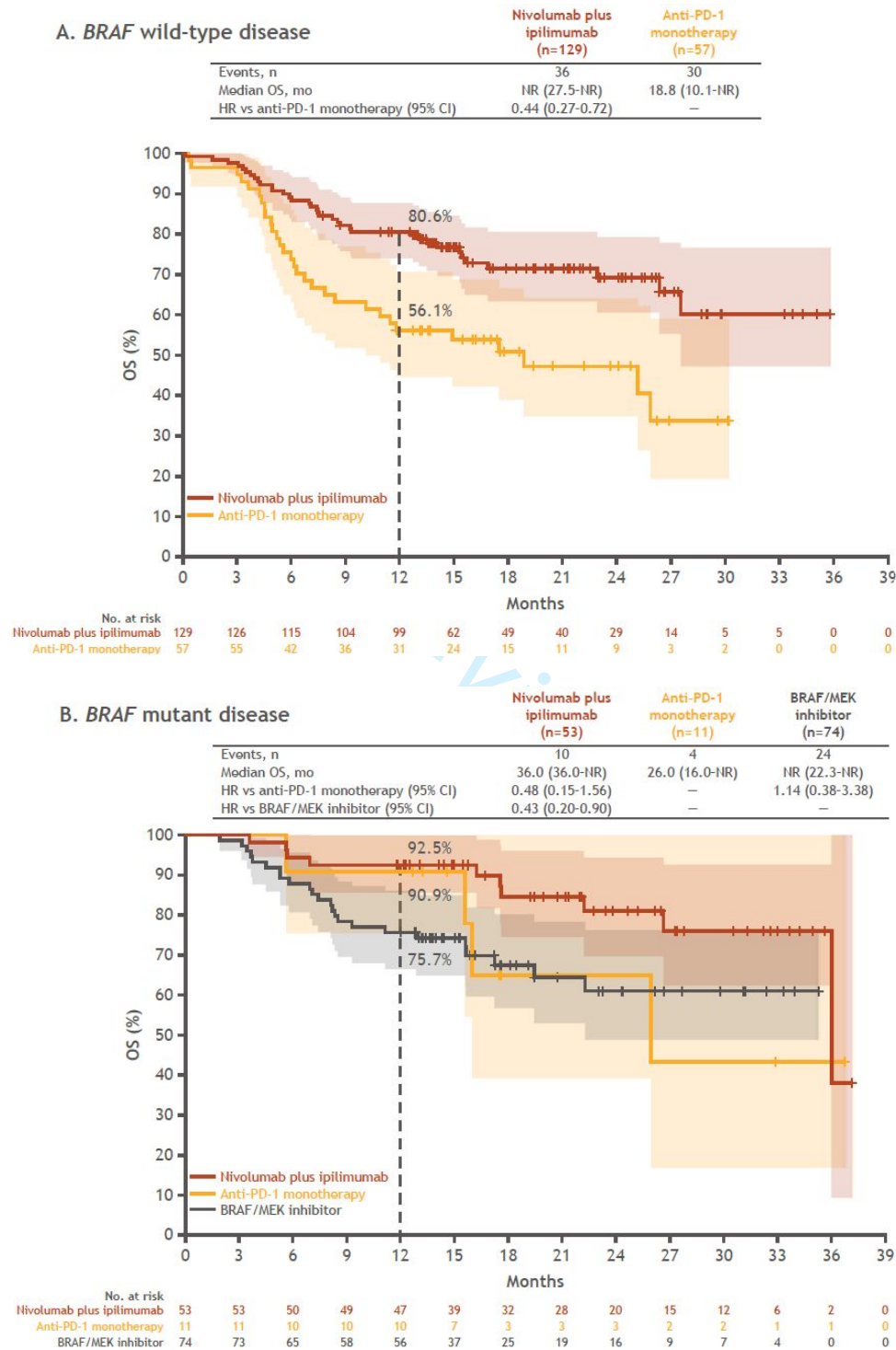


**Supplemental figure 3.** PFS in patients with symptomatic MBM by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; PD-1, programmed death-1; PFS, progression-free survival.

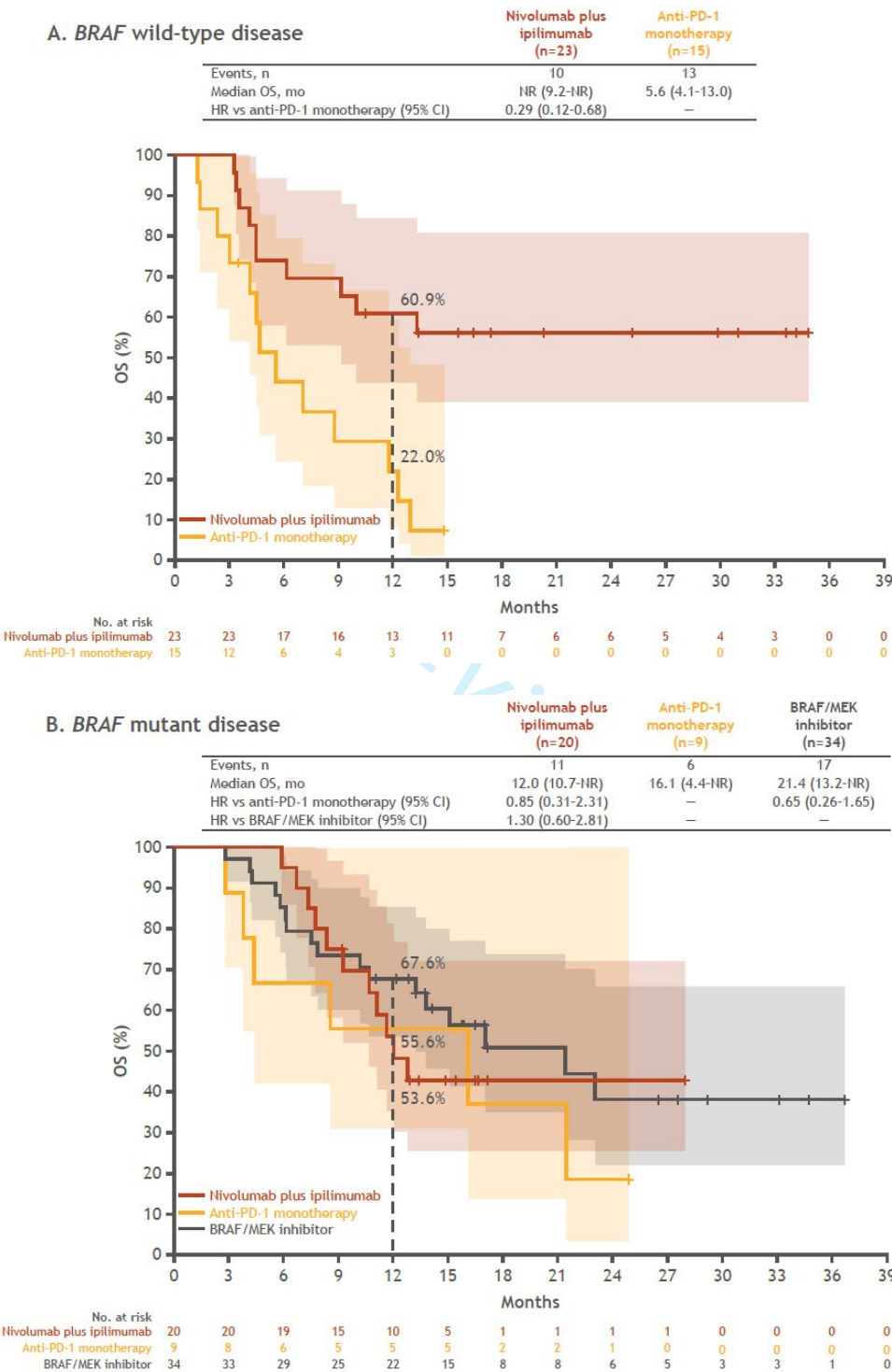




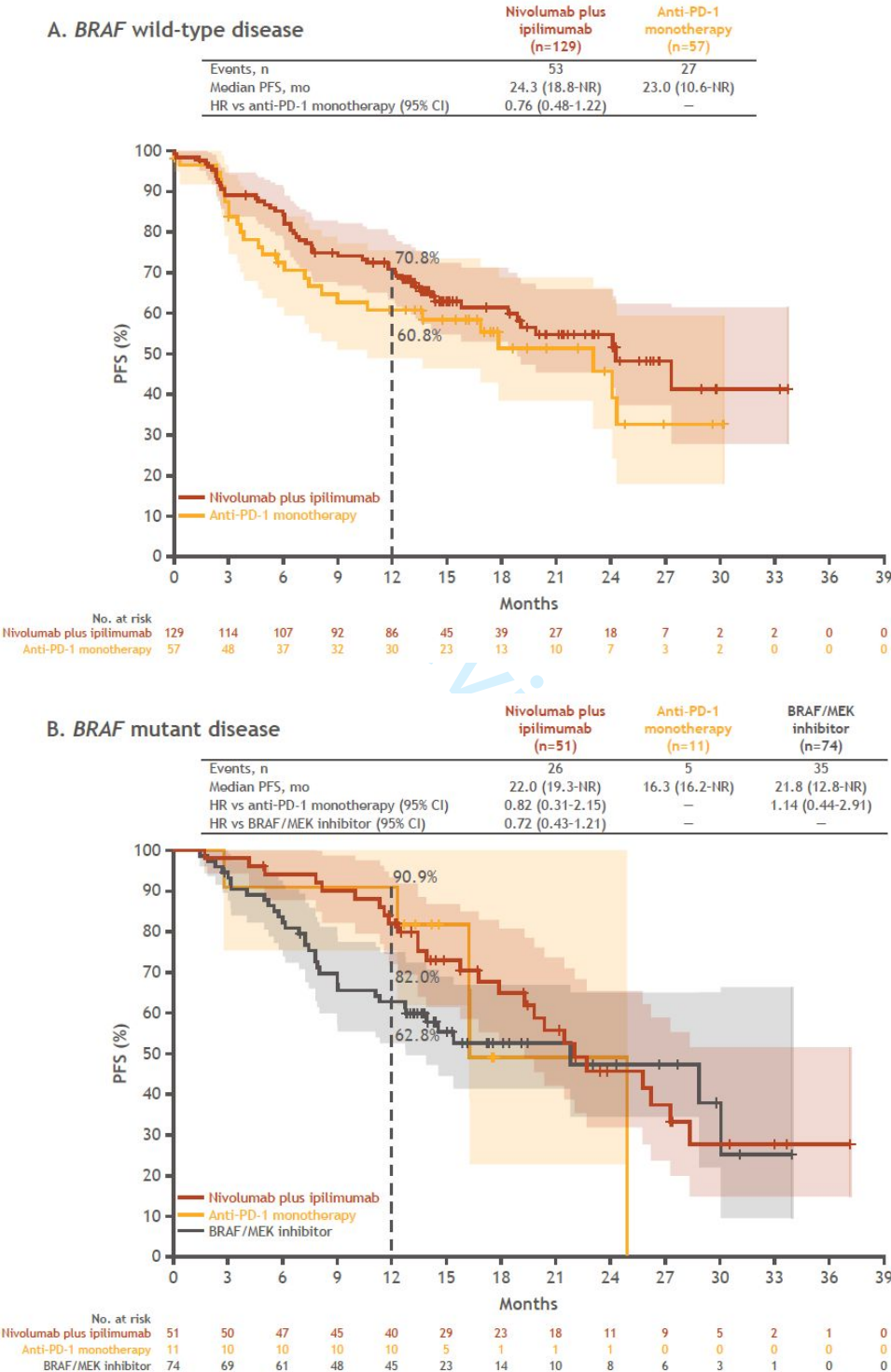
**Supplemental figure 4.** OS in patients with MBM without concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.



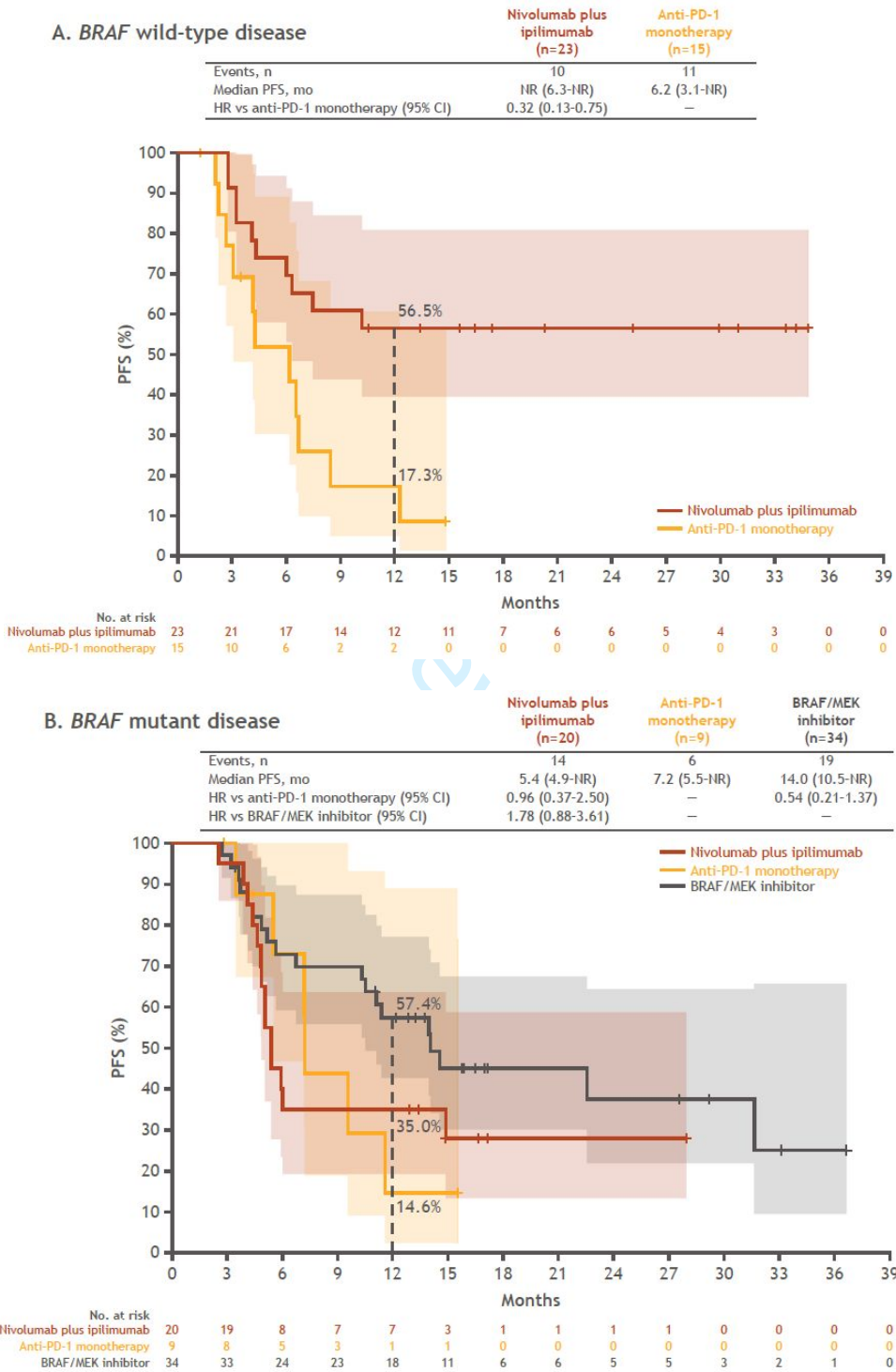
**Supplemental figure 5.** OS in patients with MBM with concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.



**Supplemental figure 6.** PFS in patients with MBM without concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; PD-1, programmed death-1; PFS, progression-free survival.



**Supplemental figure 7.** PFS in patients with concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; mo, month; NR, not reached; PD-1, programmed death-1; PFS, progression-free.



## SUPPLEMENT

### Real-world outcomes in patients with melanoma brain metastasis: a multisite retrospective chart review study of systemic treatments

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\*Two patients had two types of radiation therapy starting on the same date, and both types were accounted as the first radiation therapy.  
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**Supplemental table 2.** TRAEs in the *BRAF* mutant subgroup by type of first-line treatment

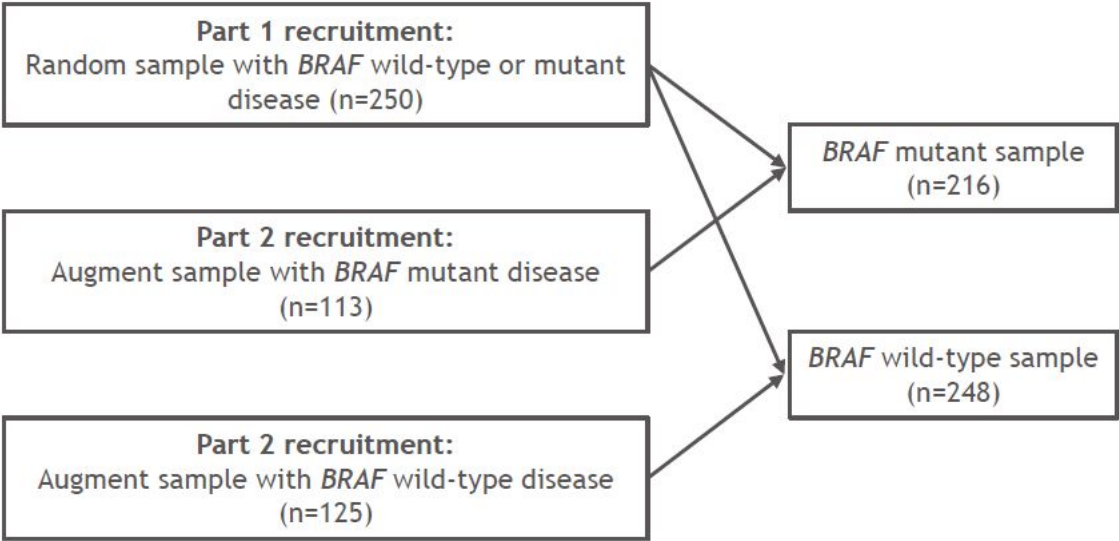
	<b>Nivolumab plus ipilimumab (n=76)</b>	<b>Anti-PD-1 monotherapy (n=23)</b>	<b>BRAF/MEK inhibitors (n=113)</b>
Any-grade TRAE, n (%)	33 (43)	7 (30)	60 (53)
TRAEs by grade, n (%)*			
1	4 (5)	4 (17)	34 (30)
2	22 (29)	3 (13)	21 (19)
3/4	7 (9)	0	4 (4)
Unknown	0	0	1 (1)

\*Grading based on Common Terminology Criteria for Adverse Events version 3.0.

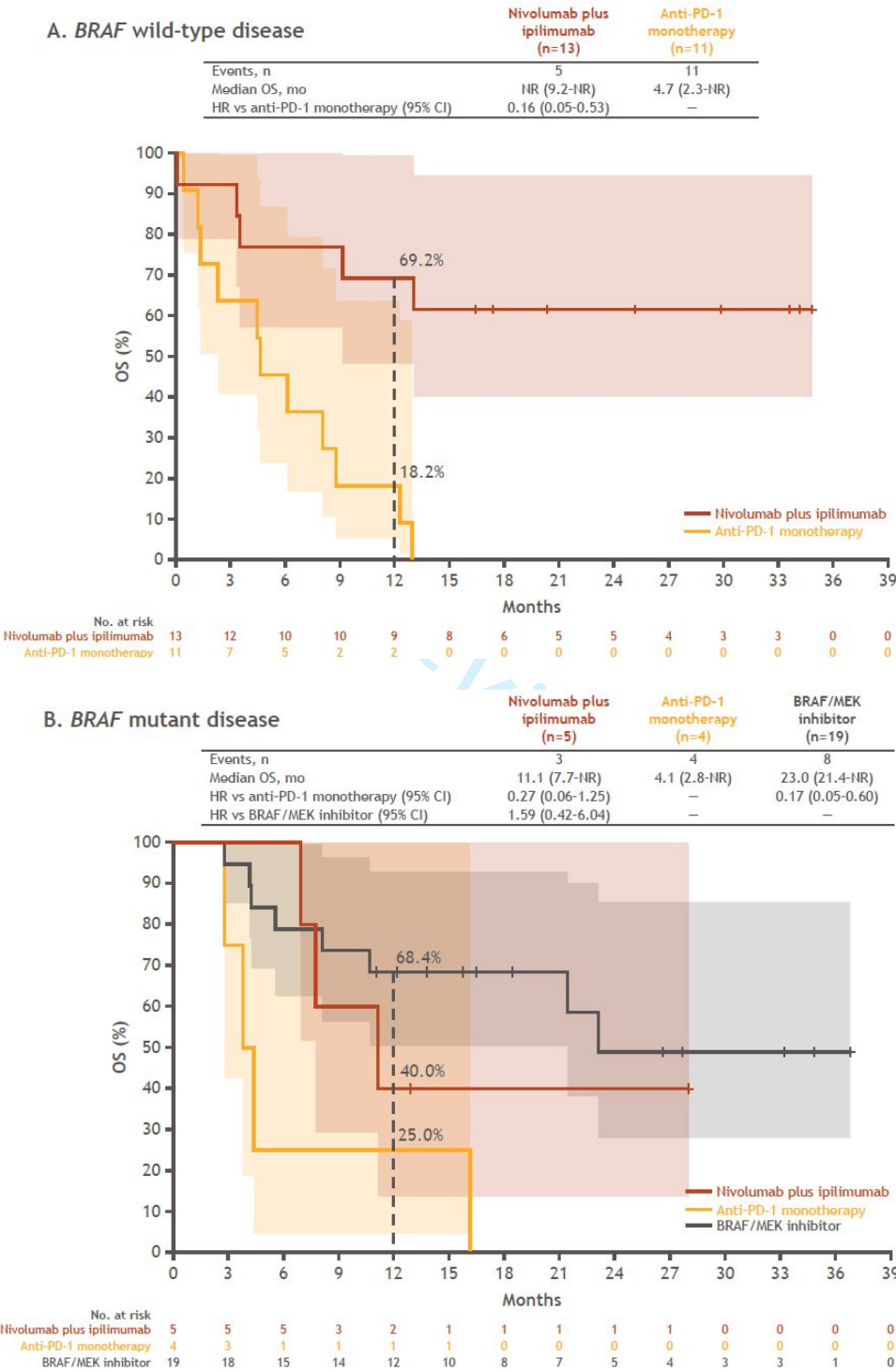
PD-1, programmed death-1; TRAE, treatment-related adverse event.



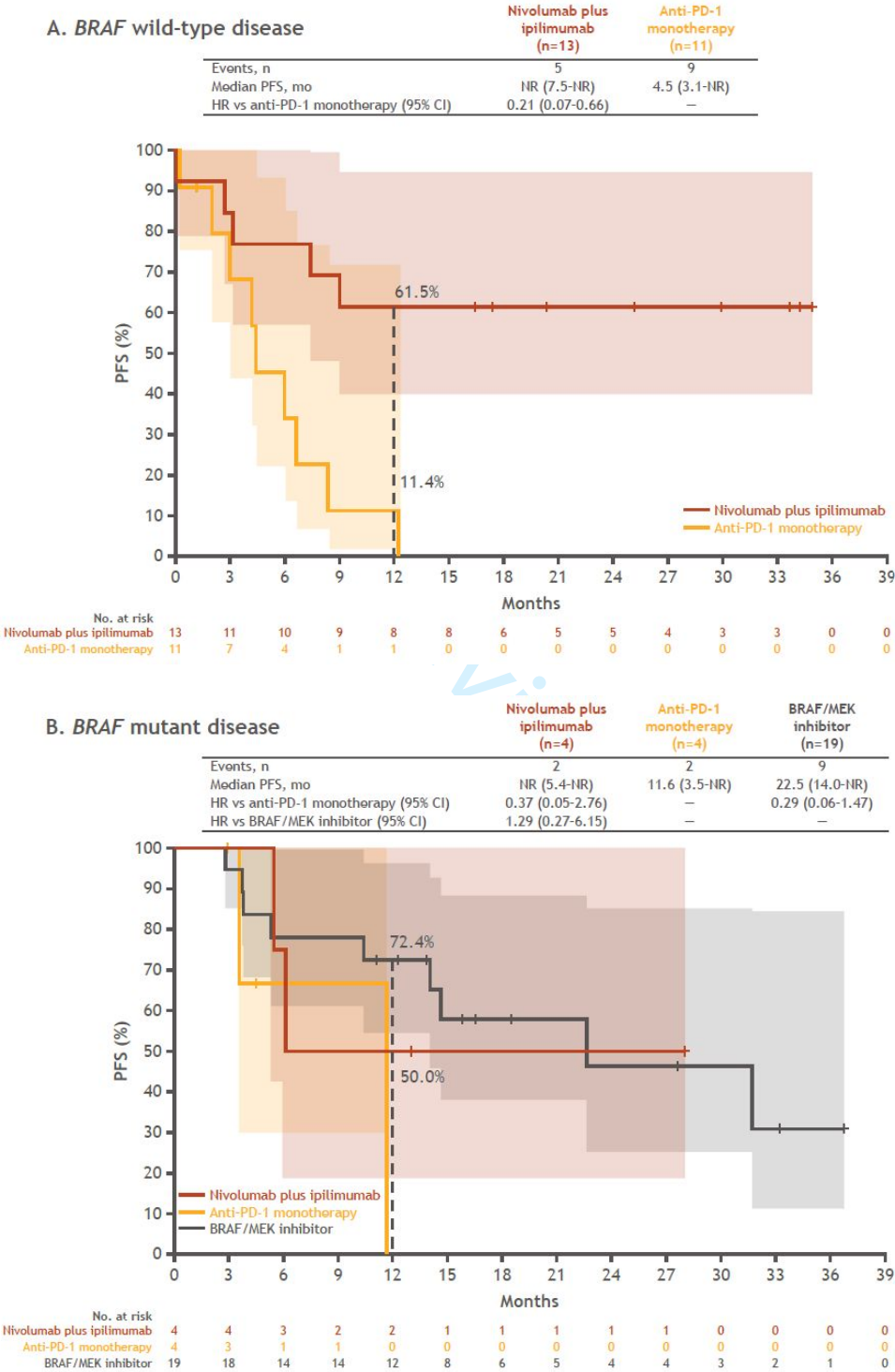
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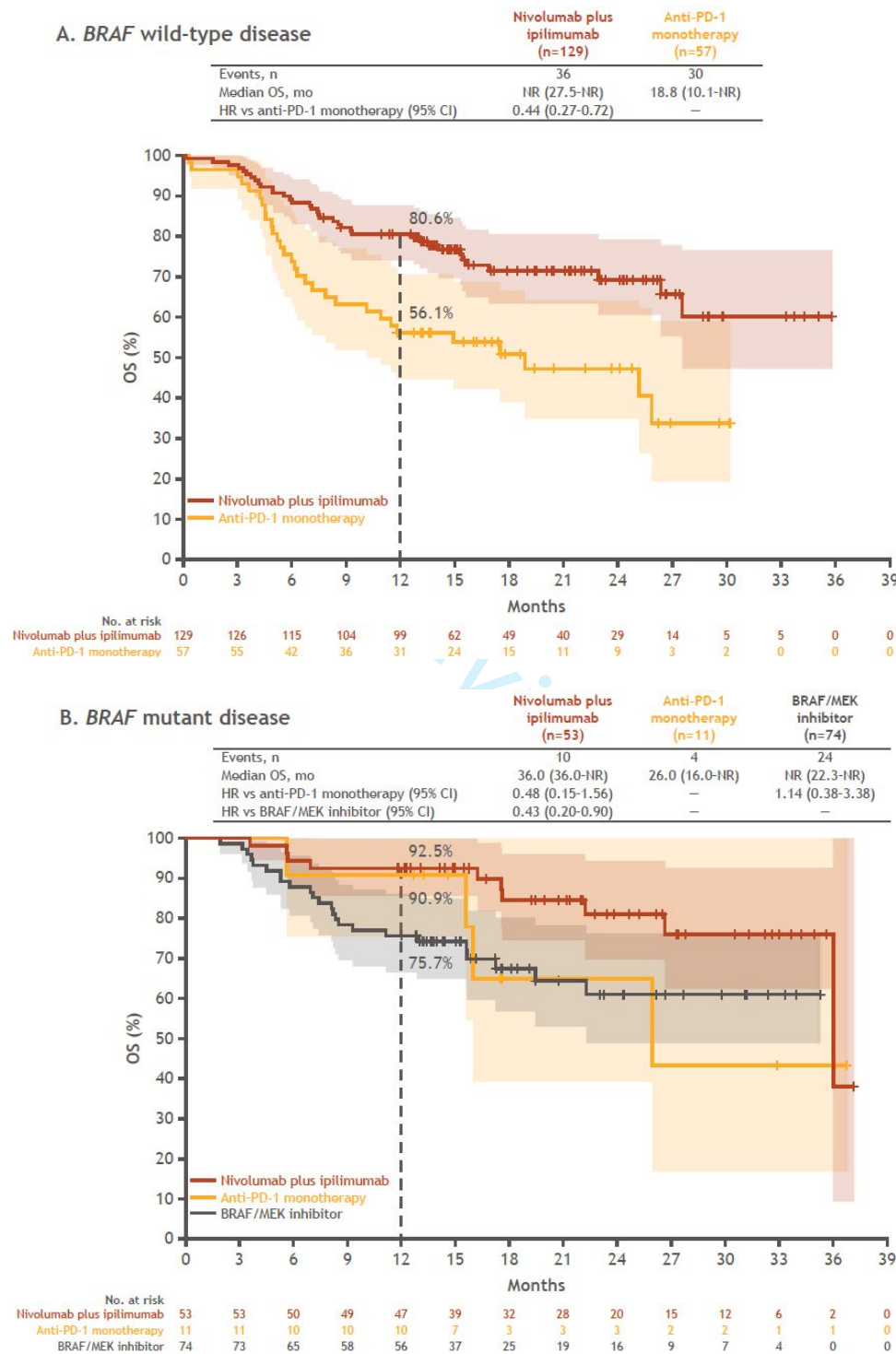
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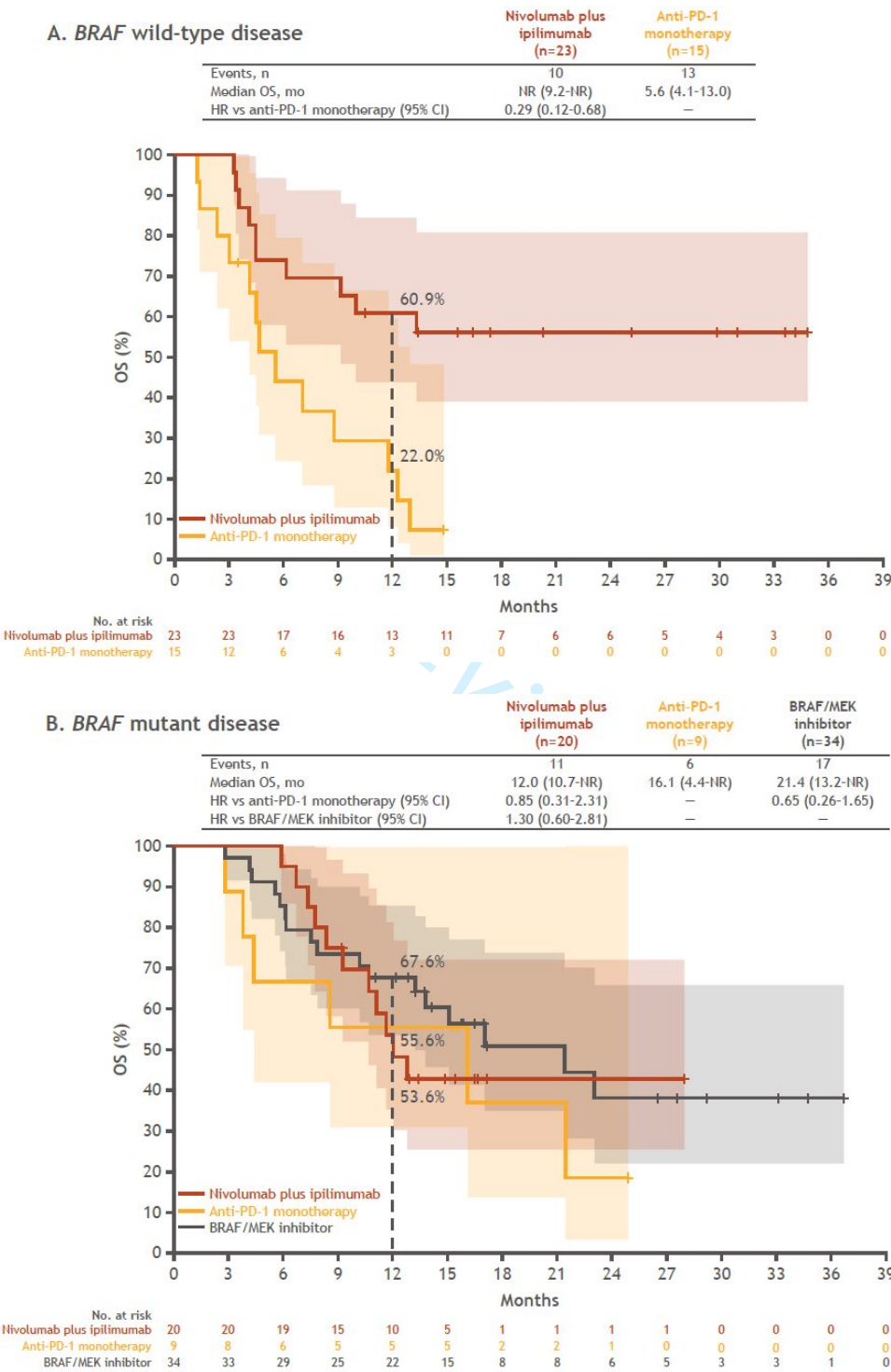
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**Supplemental figure 4.** OS in patients with MBM without concurrent radiation by first-line treatment and *BRAF* status. Shaded areas indicate 95% CIs. CI, confidence interval; HR, hazard ratio; MBM, melanoma brain metastasis; mo, month; NR, not reached; OS, overall survival; PD-1, programmed death-1.

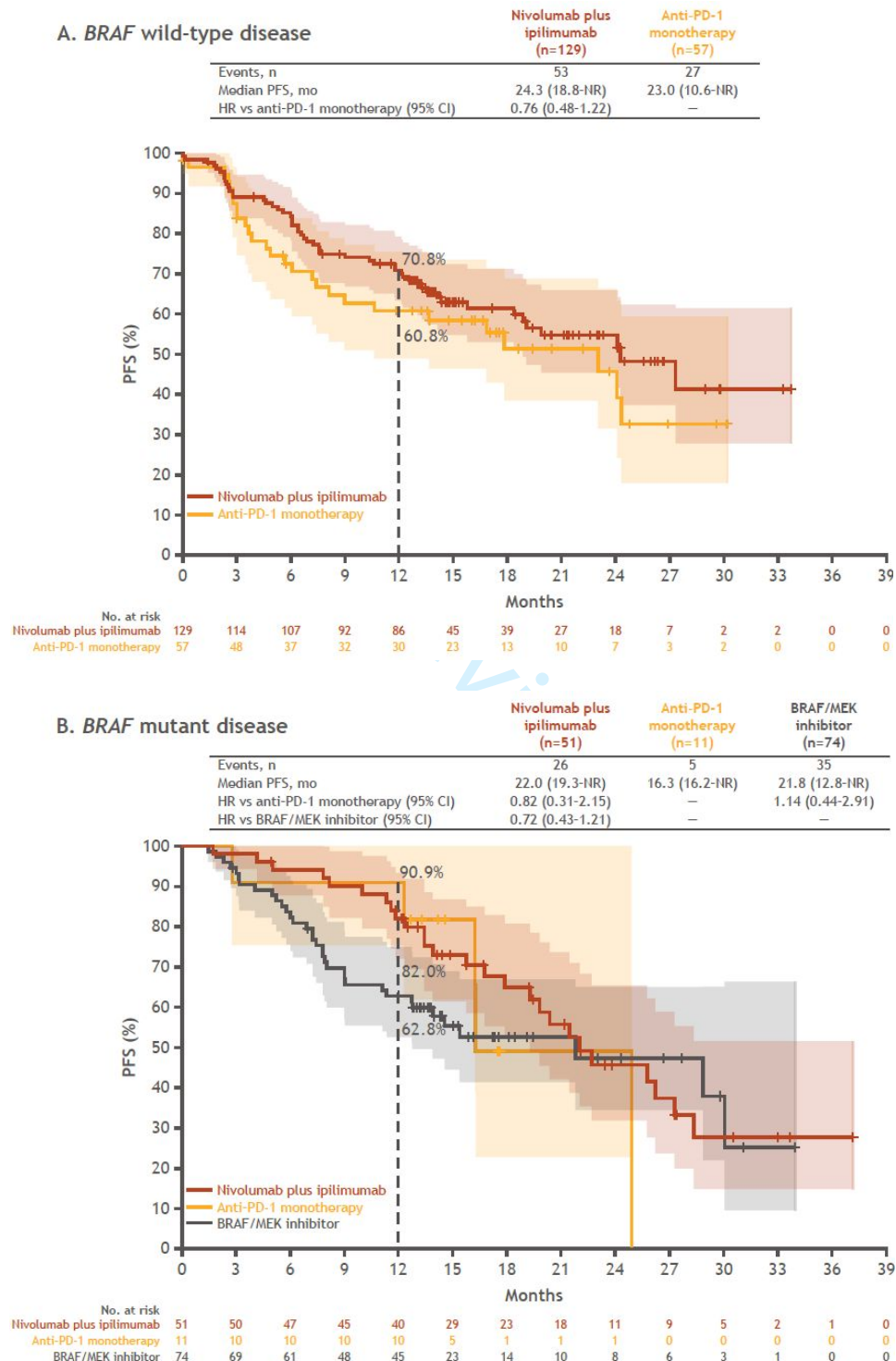


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