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# Size matters: Early progression of melanoma brain metastases after treatment with immune checkpoint inhibitors

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**Abstract**

**Background**. Immune checkpoint inhibitors (ICIs) are effective treatments for patients with metastatic melanoma, including patients with brain metastasis (BM). However, half of patients with melanoma BM have intracranial progression within 6 months after the start of ICIs. We investigated whether size affects response to ICIs in patients with melanoma BM.

**Methods**. In this single-center cohort study, patients with melanoma BM who were treated with ICIs between 2012 and 2021 were included. Clinical and radiologic features were collected at baseline. Longest axial diameter of all BMs was measured on baseline and follow-up MRI, and segmentation was performed for all BMs on baseline MRI. Lesion-level logistic regression analysis and patient-level survival analysis were performed for early BM progression (ie, within 6 months after start of ICIs) and intracranial progression-free survival (PFS), respectively.

**Results**. A total of 82 patients were included with a total of 464 BMs. At baseline, 37.8% of patients had ≥ 4 BMs and 53.7% of patients had at least one BM with a diameter ≥ 10 mm. In multivariable analysis on the lesion level, baseline BM diameter was associated with early BM progression (odds ratio 1.10, 95%CI 1.05–1.15, $P < .001$). On the patient level, having at least one BM ≥ 10mm was associated with shorter intracranial PFS (hazard ratio 2.08, 95%CI 1.64–5.56, $P < .001$).

**Conclusions**. Large BM diameter was associated with a higher risk of early progression after the start of ICIs. Therefore, local therapy should be considered for patients who are treated with ICIs and who have melanoma BMs ≥ 10 mm.

## Key Points

- Larger size of melanoma brain metastases (BMs) is associated with earlier intracranial progression after the start of immune checkpoint inhibitors (ICIs).
- For patients with melanoma BMs ≥ 10 mm who start with ICIs, additional local treatment should be considered.

Brain metastasis (BM) is commonly diagnosed in patients with metastatic melanoma, with a lifetime prevalence ranging from approximately 40% to 50%.[1–4] This frequency is increasing due to more routine screening of the brain and the improved control of extracranial disease, resulting in a higher risk of developing melanoma BM. The overall survival (OS) of patients with melanoma BM, which was historically 4 to 5 months, mainly relies on response to systemic treatments.[1]

Currently, immune checkpoint inhibitors (ICIs) are the most effective systemic treatments for patients with metastatic

## Importance of the Study

Our study demonstrated that larger baseline brain metastasis (BM) size (≥ 10 mm) was strongly associated with early BM progression, that is, within 6 months after the start of immune checkpoint inhibitors (ICIs). In addition, having at least one BM ≥ 10 mm was independently associated with shorter intracranial progression-free survival and overall survival in patients. This highlights the need to consider local treatment in patients who are treated with ICIs and who have at least one melanoma BM ≥ 10 mm.

melanoma. With ICIs, more than half of patients with metastatic melanoma survive > 5 years.[5,6] Although most pivotal trials with ICIs for metastatic melanoma excluded patients with BM, intracranial benefit was demonstrated. For monotherapy with anti-CTLA4 (ipilimumab) or anti-PD1 (nivolumab or pembrolizumab), intracranial response rates of 20–24% were described for patients with melanoma and asymptomatic BM.[7–9] For combination treatment with nivolumab-ipilimumab, intracranial response was > 50% and the reported intracranial progression-free survival (PFS) rates were 53–64% at 6 months, 54% at 3 years and 43% at 5 years.[7,10–12]

However, these PFS rates demonstrate that approximately half of the patients with melanoma BM have intracranial progressive disease (PD) within the first 6 months after the start of ICIs. Moreover, the number of non-responders is even higher in the real-world setting, since prospective trials usually select patients with a good performance status and stable and asymptomatic BM.[13] In addition, since ICIs are associated with immune related adverse events (irAEs) which can be severe, irreversible or even fatal, a better understanding of characteristics associated with intracranial disease progression is needed.[14]

Currently, it is unknown whether clinical or radiological determinants of melanoma BM are associated with early progression after the start of ICIs. Because large melanoma BMs are associated with neurological symptoms and are more difficult to control with local treatment, we investigated whether BM size at baseline is a determinant of early BM progression after the start of ICIs.[15]

## Methods

### Cohort Selection

This study was conducted at the Erasmus MC Cancer Institute, Rotterdam, the Netherlands, and approved by the local Institutional Review Board (MEC-2020-0681). Two cohorts were defined: a patient cohort and a lesion cohort.

For the patient cohort, all consecutive patients with parenchymal melanoma BM and first-time treatment with ICIs between January 1, 2012 and August 1, 2021, were identified (Flowchart, Supplementary Figure S1). All patients had to discontinue steroids prior to the start of ICIs. Patients of whom no baseline MRI of the brain was available within 2 months of the start of ICIs, who received simultaneous *BRAF*- and *MEK*-inhibitors or who died of extracranial disease prior to the first intracranial response assessment, were excluded. Last follow-up was on August 15, 2023.

For the lesion cohort, all BMs from the patient cohort were selected. Brain metastases with surgical resection or stereotactic radiotherapy (SRT) prior to the start of ICIs were excluded from lesion-level analysis (Figure 1). Brain metastases were also excluded from the lesion cohort in case of non-BM related death or a treatment switch for extracranial PD prior to intracranial response assessment.

### Data Collection

At baseline (ie, start of ICIs), the following clinical patient variables were collected: age, sex, WHO performance status, *BRAF*-mutation status, presence of BM symptoms, presence of MRI-suspected leptomeningeal disease, and status of extracranial metastasis (ECM) as described in radiology reports of computed tomography (CT) and/or positron emission tomography (PET)-CT. In addition, data of the administered ICIs and other anti-cancer treatments prior to and after start of ICIs were collected.

### Image Analysis

Baseline and follow-up MRIs were collected, which required to have at least a post-contrast T1-weighted (T1w) image with ≤ 5 mm slice thickness and 0 mm inter-slice gap. The following imaging variables were assessed for all BMs at baseline MRI: number of BMs, longest axial BM diameter, and BM volume. In addition, the number of BMs and longest axial BM diameter were measured in follow-up MRIs during the study period, including all BMs that were detected since baseline and all newly detected BMs. For volumetric measurement, all BMs on the post-contrast T1w sequence at baseline were manually segmented with Pysnap,[16] by a clinical researcher (S.D.) and a data manager (L.H.), supervised by a senior neuro-radiology resident (S.K.) and an experienced neuro-radiologist (M.S.). Additional MRI features, based on the VASARI criteria, were also collected.[17]

### Endpoints for Lesion-level Analysis

For analysis at the lesion level, the primary endpoint was early BM progression, defined as having PD according to the RANO-BM criteria within 6 months after the start of ICIs.[18] In the absence of available follow-up imaging, but with clear clinical signs of BM progression (ie, neurological focal deficits), PD was defined as BM-related clinical progression even without confirmation by imaging. In case of PD and if available, further MRIs were assessed to confirm PD according to the RANO-BM criteria for the response assessment of immunotherapy.[18]

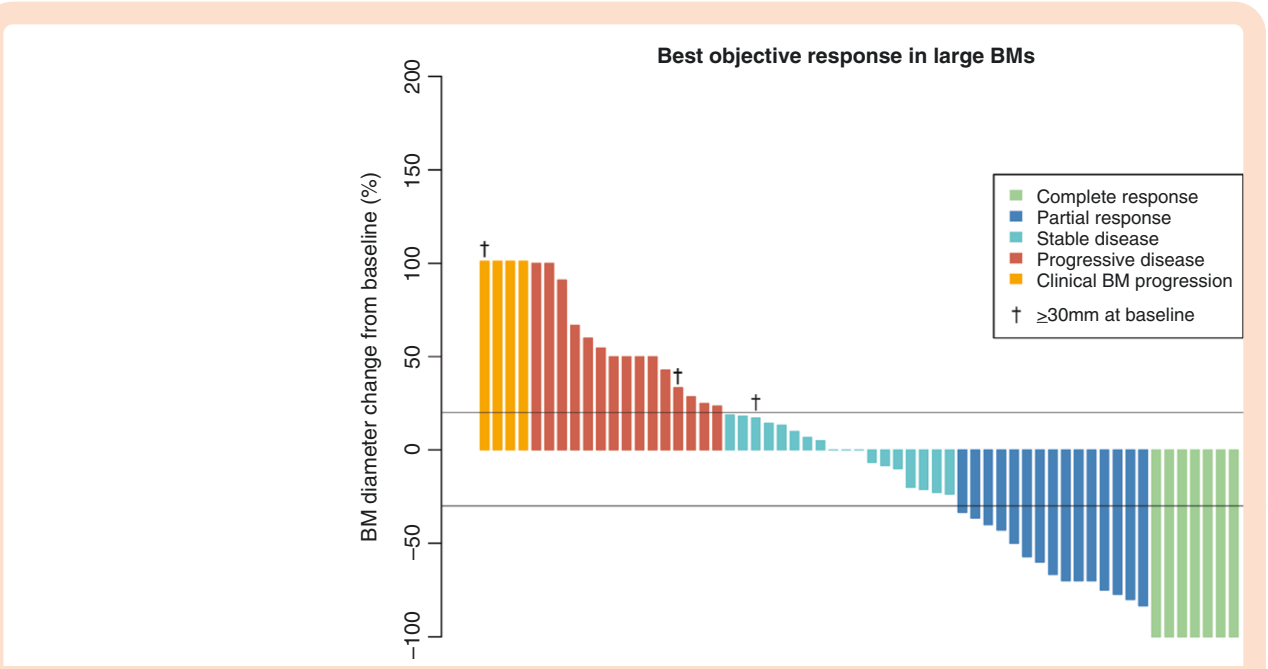


**Figure 1.** Waterfall plot with best objective response rate (bORR) of large BMs (≥ 10 mm, $n = 59$). Horizontal lines: +20% and −30%, representing the RANO-BM cutoff values for response assessment of BMs ≥ 10 mm.

A secondary lesion-level endpoint was the best overall response rate (bORR), defined as the best response per BM according to the RANO-BM since the start of ICIs until data cutoff.[18] On the lesion level, complete response (CR) was defined as 100% disappearance of the BM. For large BMs (≥ 10 mm), partial response (PR) was defined as a decrease in diameter of at least 30%, stable disease (SD) as a change in diameter between −30% and +20%, and PD as an increase of at least 20% in longest axial diameter. For small lesions (< 10 mm), PR was defined as a decrease in diameter > 3 mm, SD as a change between −3 and +3mm, and PD as an increase > 3 mm in longest axial diameter.

### Endpoints for Patient-level Analysis

In patients, the primary endpoint was intracranial PFS, defined as the time since the start of ICIs until intracranial PD according to the RANO-BM criteria or, intracranial PD requiring a treatment switch or, central nervous system (CNS)-related death.[18]

Secondary outcomes in patients were bORR, defined as the best recorded response according to the RANO-BM criteria since the start of ICIs until data cutoff, and OS, defined as the time since start of ICIs until death by any cause.[18]

### Statistical Analysis

For descriptive analyses, medians (interquartile range [IQR] or range) were used for continuous variables and frequencies (percentage) for categorical variables. Normality was tested using the Shapiro–Wilks test. The Mann–Whitney *U* test was used for hypothesis testing in continuous data. The Chi-squared test was used for categorical data, unless groups had < 10 patients, in which case the Fisher-exact test was used.

For lesion-level analysis, univariable and multivariable logistic regression models were used to assess clinical and radiologic variables associated with early BM progression. Spearman's correlation analysis was used to assess the association between longest axial BM diameter and BM volume. In case of a correlation coefficient > 0.7, further analyses would be conducted using longest axial BM diameter, as this is clinically more feasible than volumetric measurement. In addition, cut point analysis was performed to assess the association of longest axial BM diameter at baseline with early BM progression. The Youden index was used for area under the curve (AUC) analysis of the optimal cut point.

For patient-level analysis, median follow-up time was calculated using the Kaplan-Meier statistic. Time-to-event analyses were furthermore performed using univariable and multivariable Cox proportional hazards models with Likelihood ratio testing. Input for the multivariable model was obtained by using backward selection of univariable variables with *P*-values < .2. Results were defined as significant with *P*-values < .05 and highly significant with *P*-values < .001.

## Results

### Baseline Characteristics

We included 82 patients with a total of 464 melanoma BMs at the start of ICIs (Supplementary Figure S1). At data cutoff, the median follow-up was 24.6 (IQR 11.4–44.1) months and 46 (56.1%) of 82 patients were still alive. In these survivors, the median follow-up was 45.6 (IQR 40.6–60.0) months.

**Table 1.** Baseline Characteristics of the Patient Cohort

| Variable | Patients |
|---|---|
| Total (%) | 82 (100) |
| **Clinical variables** | |
| Median age (range) | 61 (29–89) |
| Sex | |
| Female (%) | 42 (51.2) |
| Male (%) | 40 (48.8) |
| WHO performance status | |
| 0–1 (%) | 72 (87.8) |
| ≥ 2 (%) | 10 (12.2) |
| Symptomatic BM (%) | 28 (34.1) |
| *BRAF* mutation status | |
| V600E/K+ (%) | 48 (58.5) |
| Wildtype (%) | 32 (39.0) |
| Other (%) | 4 (4.9) |
| Leptomeningeal disease (%) | 2 (2.4) |
| Status of extracranial metastasis (ECM) | |
| No ECM (%) | 14 (17.1) |
| ECM (%) | 68 (82.9) |
| Newly diagnosed ECM (within 1 month of BM diagnosis; %) | 32 (39.0) |
| Progressive ECM (%) | 19 (23.2) |
| Stable ECM (%) | 17 (20.7) |
| **Imaging variables** | |
| Number of BMs | |
| 1 (%) | 30 (36.6) |
| 2–3 (%) | 21 (25.6) |
| ≥ 4 (%) | 31 (37.8) |
| Median number of BMs (range) | 2 (1–57) |
| At least one BM ≥ 10 mm (%) | 44 (53.7) |
| Median total BM volume of in ml (IQR) | 10.3 (1.82–48.19) |

**Table 2.** Previous Therapies and Type of Immune Checkpoint Inhibitors (ICIs) at Baseline

| Variable | Patients |
|---|---|
| Total (%) | 82 (100) |
| **Previous therapies (prior to ICIs)** | |
| Systemic | |
| BRAF- and MEK-inhibitors (%) | 18 (22.0) |
| Local | |
| WBRT (%) | 8 (9.8) |
| SRT (%) | 19 (23.2) |
| Surgical resection (%) | 13 (15.9) |
| **Type of ICIs at baseline** | |
| Nivolumab-ipilimumab (%) | 40 (48.8) |
| No. of doses (median, range) | *3 (1–4)* |
| Followed by nivolumab maintenance (%) | 17 (42.5[a]) |
| Anti-PD1 monotherapy (%) | 39 (47.6) |
| Nivolumab (%) | 25 (64.1[b]) |
| Pembrolizumab (%) | 14 (35.9[b]) |
| Anti-CTLA4 monotherapy (Ipilimumab; %) | 3 (3.7) |
| Median interval (months) between baseline MRI and start of ICIs (range) | 0.49 (–0.76–1.81) |

[a]percentage of patients with nivolumab-ipilimumab.
[b]percentage of patients with anti-PD1 monotherapy.

Baseline characteristics of the patient cohort are presented in Table 1. The median age was 61 years and 51.2% of patients were female. At baseline, WHO performance status was 0–1 in 87.8% of patients and 34.1% of patients had symptomatic BMs. Extracranial metastasis at baseline was present in 82.9% of patients, which was diagnosed synchronously with BM in 39.0% of patients. Thirty (36.6%) patients had a single BM, 21 (25.6%) patients had 2 or 3 BMs, and 31 (37.8%) patients had at least 4 BMs. The median number of BMs was 2 (range 1–57) and 44 (53.7%) patients had at least one BM with a longest diameter of ≥ 10 mm. Per patient, the median total BM volume (ie, the sum of volumes of all BMs in one patient) was 10.3 mL (IQR 1.82–48.19 mL).

Eighteen (22.0%) patients had received BRAF- and MEK-inhibitors prior to the start of ICIs (Table 2). Nineteen (22.6%) patients had SRT and thirteen (15.9%) patients had surgical resection of BMs prior to the start of ICIs (Table 2, Supplementary Textbox S1). Treatment with ICIs at baseline consisted of combination therapy with anti-PD1 and anti-CTLA4 (48.8%), or monotherapy with anti-PD-1 (47.6%) or anti-CTLA4 (3.7%; Table 2). Baseline BM characteristics were similar between patients with combination therapy and monotherapy (Supplementary Table S1). Monotherapy instead of combination therapy was given because of unapproved combination therapy at that time ($n = 24$), comorbidities ($n = 11$), limited tumor burden ($n = 4$), or patient preference ($n = 3$).

We selected a lesion cohort out of the patient cohort ($n = 82$) with 464 BMs (Supplementary Figure S1). Thirty-five BMs were excluded because of local treatments, including SRT ($n = 21$) and surgical resection ($n = 14$) prior to the start of ICIs (Supplementary Figure S1). Another 73 BMs were excluded from analysis because of non-BM related death ($n = 63$) or systemic disease progression ($n = 10$) prior to intracranial response assessment. As a result, lesion-level analysis was performed with a total of 356 BMs.

Baseline characteristics of the lesion cohort ($n = 356$) are presented in Supplementary Table S2. The median longest axial diameter was 5 mm (range 2–36 mm). Of all 356 BMs, 297 (83.4%) were < 10 mm in longest axial diameter and 59 (16.6%) were ≥ 10 mm. The median BM volume was 0.95 mL (IQR 0.21–3.51 mL). Most BMs were located supratentorially ($n = 316$, 88.8%).

## Lesion-level Analysis

In the lesion cohort with 356 BMs, unidimensional measurements of the longest axial BM diameter correlated well

**Table 3.** Best Objective Response Rates (bORR) of Individual Lesions and Individual Patients

| Response category[a] | Lesion level | | | | Patient level |
|---|---|---|---|---|---|
| | **All** ***n*** **= 356** | BMs < 10 mm ***n*** = 297 | BMs ≥ 10 mm ***n*** = 59 | ***P*-value[b]** | **All** ***n*** **= 82** |
| **Complete response** | 88 (24.7%) | 81 (27.3%) | 7 (11.9%) | **<.001** | 12 (14.6%) |
| **Partial response** | 39 (11.0%) | 24 (8.0%) | 15 (25.4%) | | 27 (32.9%) |
| **Stable disease** | 174 (48.9%) | 156 (52.5%) | 18 (30.5%) | | 9 (11.0%) |
| **Progressive disease** | 55 (15.4%) | 36 (12.1%) | 19 (32.2%) | | 34[c] (41.5%) |

[a]In line with the RANO-BM recommendation.[REF Lin2015]
[b]Chi-square test for comparison of BM response in smaller (< 10mm) versus larger (≥ 10mm) lesions.
[c]For more detail, see Table 5. Significant *P*-values are **bold**.
BMs: brain metastases.

with volumetric measurements (Spearman's rho 0.91, $P < .001$, Supplementary Figure S2). Because unidimensional measurements are more feasible in clinical practice, the longest axial diameter was applied for further lesion-level analyses.

Best overall response consisted of CR in 88 (24.7%), PR in 39 (11.0%), SD in 174 (48.9%), and PD in 55 (15.4%) of all 356 BMs (Table 3). Large BMs (≥ 10 mm, $n = 59$) at baseline had a significantly ($P < .001$) different bORR as compared to small BMs (< 10 mm, $n = 297$): CR in 7 (11.9%) versus 81 (27.3%) BMs, PR in 15 (25.4%) versus 24 (8.0%) BMs, SD in 18 (30.5%) versus 156 (52.5%) BMs, and PD in 19 (32.2%) versus 36 (12.1%) BMs (Table 3).Three of the large BMs had a baseline longest axial diameter of ≥ 30 mm and all 3 BMs had increased in diameter at bORR assessment (Figure 1).

Larger BM diameter (continuous variable; Odds ratio [OR] 1.10 [95% confidence interval, CI, 1.05–1.15], $P < .001$) and previous treatment with BRAF- and MEK-inhibitors (OR 2.28 [95%CI 1.40–3.77], $P = .001$) were independently associated with early BM progression (Table 4, Supplementary Figure S3). Additional MRI features in large BMs, based on the VASARI criteria, were not associated with early BM progression in univariable analyses (Supplementary Table S3).[17]

Cut point analysis showed that baseline BMs with a longest axial diameter of ≥ 6 mm had a higher association with early BM progression (Supplementary Figure S4a,b). However, performance of the model with the cut point at 6 mm was comparable to that of the cut point as recommended by the RANO-BM working group, which is 10 mm for measurable disease (Supplementary Table S4, Supplementary Figure S4b).

### Patient-level Analysis

Best ORR assessment in patients showed that 39 (47.6%) of 82 patients had an intracranial response according to the RANO-BM criteria: 12 (14.6%) patients had CR and 27 (32.9%) patients had PR (Table 3). In addition, 9 (11.0%) patients had SD and 34 (41.5%) patients had PD as bORR. Eight (23.5%) of 34 patients had PD based on clinical deterioration (Table 5). Six (17.6%) of 34 patients with intracranial PD started with dexamethasone after diagnosis of PD (Table 5). Intracranial PD was associated with the development of new BMs in 17 (50%) of 34 patients (Table 5). Five of these 17 patients also had progression of target lesions (ie, BMs at baseline with a longest axial diameter ≥ 10 mm). In total, 1171 new BMs were detected during follow-up of all 82 patients (Supplementary Figure S5). At the time of bORR assessment, 12 (14.6%) of 82 patients were treated with steroids because of irAES.

In intracranial PFS analysis of the total of 82 patients, 57 (70.0%) patients had an event during follow-up and the median intracranial PFS was 7.8 months (interquartile range [IQR] 2.8–NA; Figure 2a). Univariable analysis demonstrated a poorer intracranial PFS for patients with at least one large BM (≥ 10 mm; median intracranial PFS 5.9 months [IQR 3.4–12.3]) compared to patients with only small BMs (< 10 mm; median intracranial PFS 19.0 months [IQR 9.7-NA], hazard ratio [HR] 2.12 [95%CI 1.23–3.65], $P = .0065$; Figure 2b, Supplementary Table S5). Intracranial PFS was not significantly different between patients having combination treatment (nivolumab-ipilimumab; median intracranial PFS 9.2 months [IQR 2.8-NA]) and monotherapy (anti-PD1 or anti-CTLA4; median intracranial PFS 7.3 months [IQR 5.9–19.2], HR 0.99 [95%CI 0.59–1.69], $P = .99$; Supplementary Table S5).

For multivariable analysis of intracranial PFS and OS, we selected baseline variables with *P*-values < .2 from univariate analyses (Supplementary Table S5). Having at least one BM ≥ 10 mm (HR 2.06 [95%CI 1.98–3.55], $P = .009$) and previous treatment with *BRAF*- and *MEK*-inhibitors (HR 2.46 [95%CI 1.37–4.41], $P = .003$) were associated with a shorter intracranial PFS (Table 6). Multivariable analysis of OS showed that older age (HR 1.03 [95%CI 1.01–1.06], $P = .006$), having at least one BM ≥ 10 mm (HR 1.99 [95%CI 1.07–3.70], $P = .029$) and previous *BRAF*- and *MEK*-inhibitors (HR 2.53 [95%CI 1.29–4.95], $P = .007$) were associated with shorter OS, whereas having a single BM (ref. > 1 BM, HR 0.42 [95%CI 0.23–0.76], $P = .004$) was associated with longer OS (Table 6).

## Discussion

In this study, we assessed whether BM size or other clinical determinants at the start of treatment with ICIs were associated with outcome in patients with melanoma BM. The strongest association with intracranial disease progression

**Table 4.** Uni- and Multivariable Logistic Regression for Brain Metastasis (BM) Progression Within 6 Months, at the Lesion Level

| Variables | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95%CI | *P*-value | OR | 95%CI | *P*-value |
| BM diameter (continuous, in mm) | 1.09 | 1.04–1.14 | **<.001** | 1.10 | 1.05–1.15 | **<.001** |
| Infratentorial location (ref. supratentorial) | 0.70 | 0.19–2.04 | .54 | | | |
| Previous *BRAF*- and *MEK*-inhibitors (ref. no) | 1.90 | 1.19–3.05 | **.007** | 2.28 | 1.40–3.77 | **.001** |
| Combination ICIs (ref. monotherapy ICIs) | 0.73 | 0.34–1.58 | .42 | | | |

Significant *P*-values are in **bold**.
ICIs: immune checkpoint inhibitors.

**Table 5.** Specified RANO-BM Criteria and Dexamethasone Use of Patients with Progressive Disease (PD)

| Variables | No. of patients (%) |
|---|---|
| Total of patients with intracranial PD | 34 (100) |
| New intracranial lesions | 17 (50) |
| At least 20% increase of target laesion diameter | 6 (17.6) |
| Unequivocal progression of non-target laesions | 3 (8.8) |
| Clinical deterioration[a] | 8 (23.5) |
| Started dexamethasone treatment for intracranial PD | 6 (17.6) |

[a]Neurological deterioration within days ($n = 6$), neurologic deterioration based on an increase of hemorrhage within a brain metastasis on imaging ($n = 1$), and a diagnosis of leptomeningeal disease ($n = 1$).

was found for longest axial BM diameter. At the lesion level, BMs ≥ 10 mm were significantly associated with early progression of melanoma BMs (ie, within 6 months). At the patient level, patients with at least one melanoma BM ≥ 10 mm had a poorer intracranial PFS after the start of ICIs.

There is an ongoing debate whether volumetric measurements are superior to unidimensional measurements in the response assessment of brain tumors.[19,20] Our results show that the unidimensional longest axial diameter of melanoma BMs correlated strongly with volume. Therefore, unidimensional measurement of BMs, which is more feasible in clinical practice, seems sufficient for response evaluation according to the current RANO-BM criteria.[18]

Complete response was twice more often observed in small BMs (< 10 mm) compared to large BMs (≥ 10 mm), whereas PD was twice more often observed in large BMs compared to small BMs. In 50% of patients with intracranial PD, new BMs were detected. This indicates that, regardless of features of the BMs present at baseline, ICIs were not effective for intracranial disease control in these patients. Because large BMs (≥ 10 mm) at baseline had a higher risk of PD after starting ICIs as compared to small BMs (< 10 mm), local treatments for large BMs including surgical resection and SRT should be considered in addition to ICIs. Moreover, since BM diameter was independently associated with early BM progression, additional local treatment might even be considered in the absence of BM symptoms, which is not often done in clinical practice.

Most patients had a good performance status (88%) and asymptomatic (66%), small (median diameter 5 mm) BMs, which is common even for non-selected real-world populations of patients with melanoma BM at the start of ICIs.[13,21] The improved sensitivity and standardization of modern MRI has increased the detection of small BMs over the past years.[22] It is likely that the increased screening for BMs in patients with metastatic melanoma has further contributed to early detection of BMs and of BMs with a small size. In this cohort, over 80% of BMs were smaller than 10 mm and only 50% of patients had measurable BMs (≥ 10 mm) according to the RANO-BM criteria.[18] These percentages show that formal response evaluation of melanoma BMs is challenging for a substantial number of patients with melanoma BMs, as most patients only have non-measurable BMs.

However, our results show that small BMs (< 10 mm) have a low risk of early BM progression, and patients with only non-measurable BMs have a longer PFS, suggesting that the response assessment of small BMs (< 10 mm) is clinically less relevant. These findings even suggest that a lower scan frequency of the brain during follow-up might be considered for patients with non-measurable intracranial disease. Nevertheless, this hypothesis needs to be confirmed by other studies.

For patients with metastatic melanoma, the diagnosis of BM, even as non-measurable disease, will often lead to a change in treatment plan.[23,24] According to the current guidelines, combination treatment with nivolumab-ipilimumab is recommended over monotherapy in patients with melanoma BM.[23,24] In the present study, a comparable number of patients started with monotherapy with a single-agent anti-PD1 or anti-CTLA4 (51.2%) and combination treatment with nivolumab-ipilimumab (48.8%). These 2 groups had a similar number of BMs and presence of measurable disease (BM diameter ≥ 10 mm) at baseline, allowing a comparison in outcome. Intracranial PFS was comparable between patients with monotherapy and combination treatment. Although this retrospective study could have selection bias and patients with more favorable disease characteristics may have been treated with monotherapy, these results and other studies demonstrate that even in an era where combination therapy is recommended in patients with melanoma BMs, monotherapy can still be effective.[7]

This retrospective study has some limitations. First, ICIs given at baseline consisted of combination treatment with nivolumab-ipilimumab in only half of our cohort, while this combination is now the standard of care for treatment of patients with melanoma BM.[25] Second, a considerable

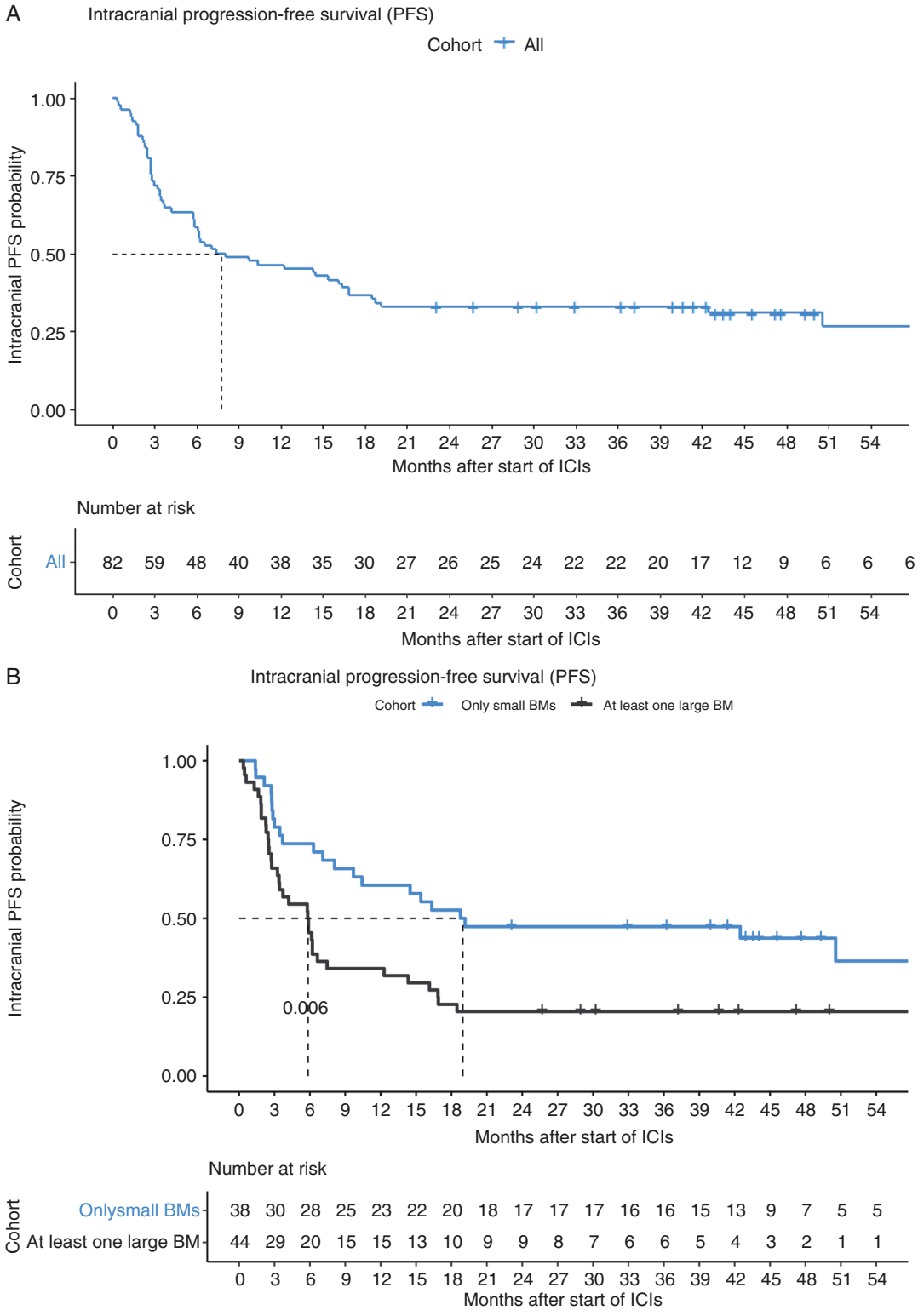


**Figure 2.** Intracranial progression-free survival (PFS) curves for (a) all patients; (b) subgroups of patients with and without at least one large lesion (≥ 10 mm). ICIs: immune checkpoint inhibitors.

number of BMs had to be excluded from lesion-level analysis because of a treatment switch or death that did not enable proper response assessment of these BMs. Third, our results need to be confirmed in an external validation cohort. Nevertheless, both on the lesion and patient level, BM size was an important and independent determinant of early intracranial progression after the start of ICIs, which if confirmed is highly relevant for clinical decision making.

**Table 6.** Multivariable analysis of intracranial progression-free survival (PFS) and overall survival (OS) on the patient level

| | Intracranial PFS | | | OS | | |
|---|---|---|---|---|---|---|
| Variable | Hazard Ratio | 95% CI | *P*-value | Hazard ratio | 95% CI | *P*-value |
| Age (per year, continuous) | | | | 1.03 | 1.01–1.06 | **.006** |
| WHO status ≥ 2 (ref. < 2) | | | | 2.12 | 0.93–4.84 | .075 |
| A single BM (ref. > 1 BM) | | | | 0.42 | 0.23–0.76 | **.004** |
| At least one BM ≥ 10 mm in longest diameter (ref. no) | 2.06 | 1.98–3.55 | **.009** | 1.99 | 1.07–3.70 | **.029** |
| Previous *BRAF*- and *MEK*-inhibitors (ref. no) | 2.46 | 1.37–4.41 | **.003** | 2.53 | 1.29–4.95 | **.007** |

Univariate analyses can be found in the supplements (Table S3). Significant p-values are in **bold**.
BM: brain metastasis.

## Conclusions

Size of melanoma BM at the start of ICIs is an important clinical determinant of early intracranial progression, and BMs ≥ 10 mm are significantly associated with worse outcome. Therefore, local treatments should be considered for patients who are treated with ICIs and have melanoma BMs ≥ 10 mm.

## Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).


## Keywords:

immune checkpoint inhibitors | magnetic resonance imaging | melanoma brain metastasis | response assessment



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## Conflict of interest statement

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## Authorship Statement

**Sophie H.A.E. Derks:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Visualization, Writing. **Li Shen Ho**: Data Curation, Formal analysis. **Stephan R. Koene**: Methodology, Validation, Formal analysis. **Martijn P.A. Starmans**: Methodology. **Esther Oomen-de Hoop**: Formal Analysis, Writing. **Arjen Joosse**: Writing. **Maja J.A. de Jonge**: Writing. **Kishan A.T. Naipal**: Writing. **Joost L.M. Jongen**: Writing. **Martin J. van den Bent**: Conceptualization, Methodology, Writing, Supervision. **Marion Smits**: Conceptualization, Methodology, Writing, Supervision. **Astrid A.M. van der Veldt**: Conceptualization, Methodology, Validation, Investigation, Writing, Supervision, Project administration.

## Data Availability

The data presented in this study will be available upon reasonable request.


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