Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study

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Summary

Background Nivolumab monotherapy and combination nivolumab plus ipilimumab increase proportions of patients achieving a response and survival versus ipilimumab in patients with metastatic melanoma; however, efficacy in active brain metastases is unknown. We aimed to establish the efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with active melanoma brain metastases.

Methods This multicentre open-label randomised phase 2 trial was done at four sites in Australia, in three cohorts of immunotherapy-naive patients aged 18 years or older with melanoma brain metastases. Patients with asymptomatic brain metastases with no previous local brain therapy were randomly assigned using the biased coin minimisation method, stratified by site, in a 30:24 ratio (after a safety run-in of six patients) to cohort A (nivolumab plus ipilimumab) or cohort B (nivolumab). Patients with brain metastases in whom local therapy had failed, or who had neurological symptoms, or leptomeningeal disease were enrolled in non-randomised cohort C (nivolumab). Patients in cohort A received intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for four doses, then nivolumab 3 mg/kg every 2 weeks; patients in cohort B or cohort C received intravenous nivolumab 3 mg/kg every 2 weeks. The primary endpoint was intracranial response from week 12. Primary and safety analyses were done on an intention-to-treat basis in all patients who received at least one dose of the study drug. This trial is registered with ClinicalTrials.gov, number NCT02374242, and is ongoing for the final survival analysis.

Findings Between Nov 4, 2014, and April 21, 2017, 79 patients were enrolled; 36 in cohort A, 27 in cohort B, and 16 in cohort C. One patient in cohort A and two in cohort B were found to be ineligible and excluded from the study before receiving the study drug. At the data cutoff (Aug 28, 2017), with a median follow up of 17 months (IQR 8–25), intracranial responses were achieved by 16 (46%; 95% CI 29–63) of 35 patients in cohort A, five (20%; 7–41) of 25 in cohort B, and one (6%; 0–30) of 16 in cohort C. Intracranial complete responses occurred in six (17%) patients in cohort A, three (12%) in cohort B, and none in cohort C. Treatment-related adverse events occurred in 34 (97%) of 35 patients in cohort A, 17 (68%) of 25 in cohort B, and eight (50%) of 16 in cohort C. Grade 3 or 4 treatment-related adverse events occurred in 19 (54%) patients in cohort A, four (16%) in cohort B, and two (13%) in cohort C. No treatment-related deaths occurred.

Interpretation Nivolumab combined with ipilimumab and nivolumab monotherapy are active in melanoma brain metastases. A high proportion of patients achieved an intracranial response with the combination. Thus, nivolumab combined with ipilimumab should be considered as a first-line therapy for patients with asymptomatic untreated brain metastases.

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Introduction

Brain metastasis affects 25% of patients at diagnosis of advanced melanoma and has a poor prognosis, with a median survival time of about 4 months.[1,2] Immunotherapy with PD-1 or anti-CTLA4 checkpoint inhibitors, or both, and BRAF-directed targeted therapy have significantly improved the overall survival of patients with advanced melanoma compared with standard therapy.[3–7] However, patients with active brain metastases are largely excluded from clinical trials of these drug therapies because of their poor prognosis, and the activity of immunotherapy in this population is unknown.

Large phase 2 clinical trials of BRAF-directed targeted therapies have shown significant activity in untreated (no previous local brain therapy or drug therapy) melanoma brain metastases with 39% of patients achieving a response with BRAF inhibitors alone and 58% with combined BRAF and MEK inhibitors; however, the responses are short lived.[8–10] A small study of 18 patients with active brain metastases treated with pembrolizumab showed a response in 22% of patients.[11] Stereotactic

Research in context

Evidence before this study

We searched PubMed up to Dec 8, 2017, for clinical trials using the search terms "brain metastases" and "melanoma" and "drug therapy", and excluding "radiotherapy" and "radiation", and identified 103 published articles. Only six were reports of phase 1 or 2 clinical trials of drug therapies (excluding chemotherapies) in patients with active brain metastases, and no phase 3 trials in this population were identified. Four trials tested BRAF inhibitor-based therapies in patients with active brain metastases, and the highest proportion of patients achieving a response and longest progression-free survival was observed for the combination of dabrafenib and trametinib, with 58% of patients achieving an intracranial response and 6-month landmark progression-free survival of 44% in asymptomatic, previously untreated (no local brain-directed therapy) patients with $BRAF^{V600E}$ (ie, Val600Glu) mutation-positive melanoma. Two studies tested ipilimumab or pembrolizumab monotherapy in patients with active brain metastases, showing an intracranial response in eight (16%) of 51 and four (22%) of 18 people, respectively. A single-arm trial of ipilimumab combined with nivolumab in patients with active melanoma brain metastases has been reported at the 2017 American Society for Clinical Oncology Annual Meeting (Chicago, USA), showing an intracranial response in 55% of patients and 6-month progression-free survival in 67% of patients.

Added value of this study

Our study randomly assigned patients with untreated (no local brain-directed therapy) brain metastases to nivolumab monotherapy or combination nivolumab and ipilimumab, and had the largest single cohort of patients ever treated with anti-PD-1 monotherapy (nivolumab). Furthermore, the study included patients previously treated with BRAF and MEK inhibitors.

Implications of all the available evidence

Our results suggest that patients with asymptomatic, untreated (no local brain-directed therapy) brain metastases have a high chance of long-term durable intracranial response when treated with the combination of ipilimumab and nivolumab upfront—higher than reported with BRAF and MEK inhibitors. Additionally, fewer patients have durable responses when treated with first-line anti-PD-1 monotherapy or when previously treated with combined BRAF and MEK inhibitor therapy. Our results suggest that combination therapy with ipilimumab and nivolumab should be considered as first-line therapy in patients with asymptomatic melanoma brain metastases, and induces durable responses in at least 50% of patients. Patients with brain metastases should be included in ongoing clinical trials of novel drug therapies.

radiosurgery and surgery are highly effective for treated metastases, but have no proven effect on the risk of developing further melanoma brain metastases, and thus have little effect on survival, except in patients with isolated monometastatic or oligometastatic brain disease.

We sought to establish the antitumour activity and safety of nivolumab monotherapy and nivolumab combined with ipilimumab in patients with active melanoma brain metastases. We did a phase 2 randomised trial, which included two randomised cohorts of asymptomatic untreated (no previous local brain-directed therapy) patients, as well as a single non-randomised cohort of patients with poor prognostic features, including leptomeningeal disease, neurological symptoms, or disease progression after local brain-directed therapy.

Methods

Study design and participants

This multicentre open-label randomised phase 2 study was done at four cancer centres in Australia (appendix p 14) in three cohorts of patients with histologically confirmed American Joint Committee on Cancer stage IV melanoma (excluding ocular melanoma). The study was administered and monitored by Melanoma Institute Australia and the Australian and New Zealand Melanoma Trials Group. Patients were aged at least 18 years, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, had at least one target intracranial lesion of 5–40 mm on Gadolinium-enhanced MRI, and had no history of severe autoimmune disease; previous BRAF inhibitor therapy with or without MEK inhibitor therapy was allowed if intracranial RECIST 1·1 progression occurred (complete inclusion and exclusion criteria are listed in the appendix p 1). Cohort A and B consisted of patients with asymptomatic melanoma brain metastases who had no previous local brain therapy (surgery, stereotactic radiosurgery, or whole-brain radiotherapy). Cohort C consisted of patients with melanoma brain metastases, who either failed local therapy (ie, had developed new brain metastases or had Response Evaluation Criteria in Solid Tumours [RECIST] 1.1[12] progression in treated brain metastases with new lesions or a ≥20% increase in sum of diameters of previously treated lesions and an absolute increase of ≥5 mm for existing lesions), had symptoms related to brain metastases, or had leptomeningeal disease, or any combination of these. The study protocol was approved by the human research ethics committee at each participating institution. The study was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice. All participants provided written informed consent.

See Online for appendix

Randomisation and masking

Participants were enrolled by study investigators at the individual sites (GVL, VA, SS, ADG, MPB, AMM, and

GAM). Patients were assigned to cohort A (combined nivolumab and ipilimumab), cohort B (nivolumab), or cohort C (nivolumab). The first six patients with asymptomatic, untreated (ie, having received no local brain-directed therapy) brain metastases were assigned to cohort B and were treated for at least 6 weeks. Adverse events were reviewed and the study was confirmed safe to continue by the data and safety monitoring board. Thereafter, all asymptomatic, untreated patients were randomly assigned in a 30:24 ratio to cohort A:B, using the biased coin minimisation method, and stratified by site. Randomisation was centralised, web based, and managed by an independent randomisation team. Treatment allocation was concealed from study staff, investigators, and patients before randomisation, after which, open-label treatment was given. Patients were made aware of their treatment assignment before the start of study therapy. No randomisation was done for cohort C. Patients for cohort C were selected for recruitment at the study sites if they fit the eligibility criteria.

Procedures

Patients in cohort A received intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for four doses, then nivolumab 3 mg/kg every 2 weeks; patients in cohort B or cohort C received intravenous nivolumab 3 mg/kg every 2 weeks. Nivolumab and ipilimumab were manufactured by Bristol-Myers Squibb (Manati, Puerto Rico). Treatment was continued until disease progression, death, unacceptable toxicity, withdrawal of consent, or if recommended by the treating clinician. Patients were allowed to be treated beyond progression with approval from the lead study investigator if clinically beneficial and if the patients had a stable ECOG performance status, according to the investigator. Dose reductions were not permitted; however, dose delays were allowed in response to specified adverse events (appendix p 2). Study treatment was permanently discontinued in patients who had non-skin grade 3 toxicities lasting at least 7 days, grade 4 toxicities, or grade 2 uveitis, eye pain, or blurred vision; specific exceptions are listed in the appendix (p 3). If a toxicity requiring permanent discontinuation occurred during induction with combination ipilimumab and nivolumab, patients were permitted to have ongoing nivolumab after approval by the lead investigator (GVL) if the toxicity was attributed to ipilimumab. Disease progression and response assessments for intracranial and extracranial melanoma

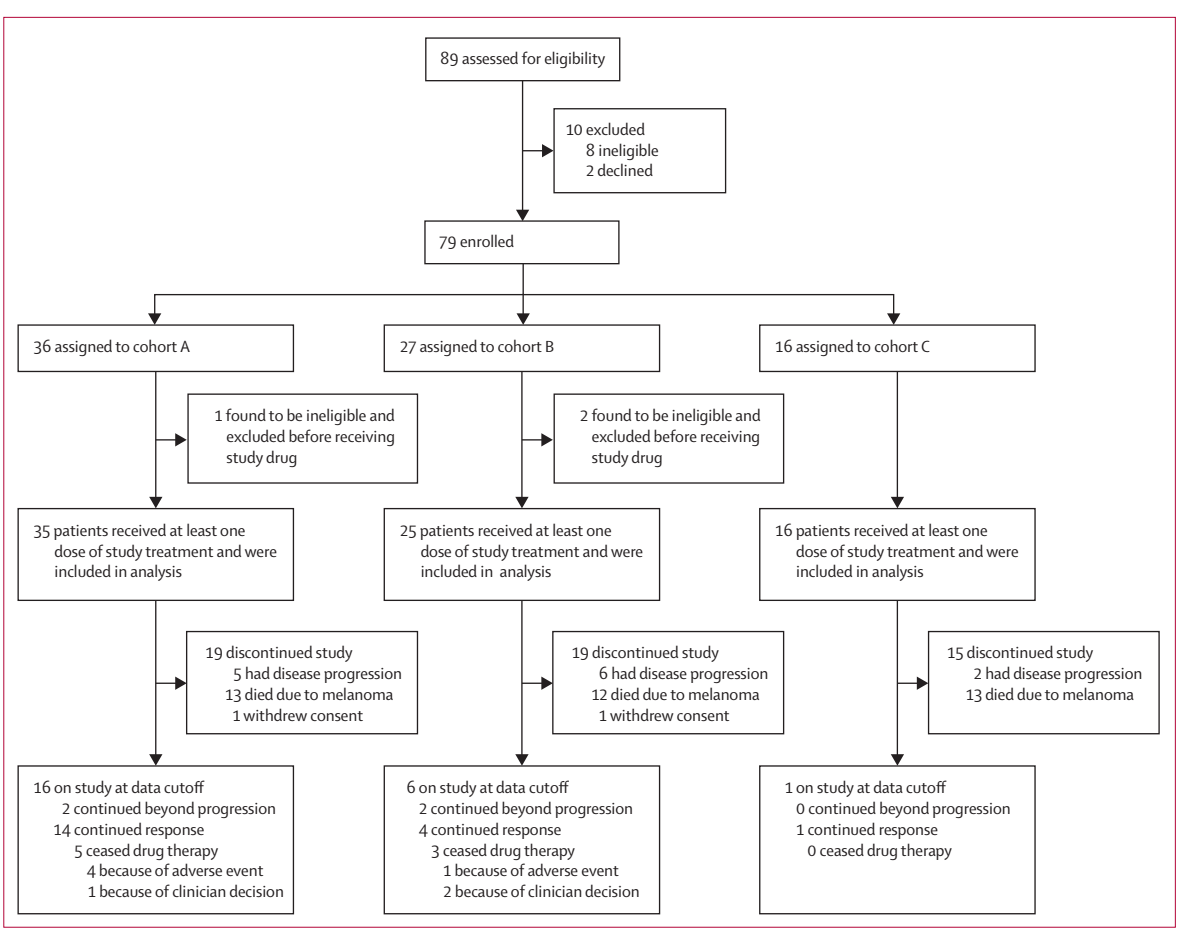

Figure 1: **Trial profile**

metastases were assessed by the investigator using a modified RECIST 1.1,[9] without central review. Intracranial disease (up to five target brain lesions of 5–40 mm in diameter) was assessed by a radiologist up to 14 days before the first study dose, at week 6 (for safety only), week 12, and every 12 weeks thereafter, using gadolinium contrast-enhanced MRI with slices of 1 mm. Extracranial disease was assessed at the same timepoints using contrast-enhanced CT or MRI. Responses were confirmed no less than 4 weeks after first recorded response. Adverse events were graded by the investigator throughout the study using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), from the first study dose until 100 days after discontinuation of study treatment. Laboratory assessments measuring chemistry and haematology parameters were done at screening, start of study drug, and every 3 weeks (cohort A) or 2 weeks (cohorts B and C) for the first 12 weeks, then every 4 weeks thereafter. PD-L1, CD8, Ki67, and SOX10 expression were assessed in baseline tissue, and visualised using Vectra Imaging[13] (appendix p 4), and correlated with the primary and secondary endpoints of the study. Given the need to enrol patients with brain metastases in minimal time, central pathology review of the submitted melanoma tissue was not a requirement for enrolment.

Outcomes

The primary endpoint was best intracranial response at or after week 12 for all cohorts, defined as the percentage of patients with a confirmed intracranial complete or partial response. Secondary endpoints were best extracranial response, defined as the percentage of patients with a confirmed extracranial complete or partial response; best overall response defined as the percentage of patients with a confirmed complete or partial response (combined intracranial and extracranial target lesions); intracranial progression-free survival; extracranial progression-free survival; overall progression-free survival; overall survival; and safety. Responses were assessed by the investigator using modified RECIST version 1.1 criteria. Intracranial and extracranial progression-free survival were calculated separately from the first dose of study treatment until earliest intracranial and extracranial progression or death. Overall survival was calculated from the first dose of study treatment until death. Patients who neither progressed nor died by the data cutoff date were censored at their last tumour assessment. Post-hoc survival analyses were done for BRAF and MEK inhibitor treatment-naive patients.

Statistical analysis

The primary and secondary response endpoints were summarised using frequency and proportion by cohort along with the two-sided 95% Clopper–Pearson exact CIs. No statistical inference was computed because the study was not designed for a formal comparison between cohorts. All analyses were done on an intention-to treat basis in all patients who received at least one dose of study drug. Patients were not evaluable for response if they had not been radiologically assessed for response from week 12, regardless of whether they had survived or not. Survival outcome curves for each cohort were estimated using the Kaplan-Meier product limit method. Median and corresponding two-sided 95% CIs were also computed. Survival rates at 6 months with 95% CIs were estimated using the Kaplan–Meier method. Safety data were summarised by the number and proportions of patients affected in each cohort. Statistical analyses were done using SAS (version 9.3) and R (version 3.4.1). This trial is registered with ClinicalTrials.gov, number NCT02374242.

	Cohort A (n=35)	Cohort B (n=25)	Cohort C (n=16)
Sex			
Men	29 (83%)	19 (76%)	11 (69%)
Women	6 (17%)	6 (24%)	5 (31%)
Age at randomisation, years	59 (53–68)	63 (52–74)	51 (48–56)
ECOG performance status			
0–1	34 (97%)	25 (100%)	15 (94%)
2	1 (3%)	0	1 (6%)
Increased serum lactate dehydrogenase	18 (51%)	14 (56%)	3 (19%)
Number of intracranial metastases (target and non-target)			
1	11 (31%)	6 (24%)	1 (6%)
2–4	10 (29%)	14 (56%)	7 (44%)
>4	14 (40%)	5 (20%)	8 (50%)
Target intracranial RECIST sum of diameters, mm	19 (13–37)	17 (12–29)	34 (21–53)
Presence of extracranial metastases	30 (86%)	21 (84%)	12 (75%)
Target extracranial RECIST sum of diameters, mm	90 (47–120)	46 (28–89)	37 (22–82)
No previous combined BRAF and MEK inhibitor therapy received	27 (77%)	19 (76%)	4 (25%)
Previous combined BRAF and MEK inhibitor therapy received	8 (23%)	6 (24%)	12 (75%)
$BRAF^{V600}$ mutation			
$BRAF^{V600E}$	14 (40%)	11 (44%)	11 (69%)
$BRAF^{V600K}$	4 (11%)	2 (8%)	1 (6%)
$BRAF^{V600R}$	1 (3%)	1 (4%)	1 (6%)
Previous local brain therapy			
Any surgery	0	0	9 (56%)
Any stereotactic radiosurgery	0	0	8 (50%)
Any whole brain radiotherapy	0	0	7 (44%)
Leptomeningeal melanoma	0	0	4 (25%)
Neurological symptoms	0	0	10 (63%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. RECIST=Response Evaluation Criteria in Solid Tumours.

Table 1: **Baseline patient characteristics**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the

	Cohort A		Cohort B		Cohort C (n=16)
	Drug* naive (n=27)	Overall (n=35)	Drug* naive (n=19)	Overall (n=25)	
Intracranial response					
Overall (%; 95% CI)	15 (56%; 35–75)	16 (46%; 29–63)	4 (21%; 6–46)	5 (20%; 7–41)	1 (6%; 0–30)
Complete response	5 (19%)	6 (17%)	2 (11%)	3 (12%)	0
Partial response	10 (37%)	10 (29%)	2 (11%)	2 (8%)	1 (6%)
Stable disease	3 (11%)	4 (11%)	0	0	2 (13%)
Progressive disease	8 (30%)	14 (40%)	14 (74%)	19 (76%)	13 (81%)
Non-evaluable	1 (4%)	1 (3%)	1 (5%)	1 (4%)	0
Extracranial response†					
Overall (%; 95% CI)	15 (63%; 41–81)	17 (57%; 37–75)	5 (29%; 10–56)	6 (29%; 11–52)	3 (25%)
Complete response	0	1 (3%)	1 (6%)	2 (10%)	1 (8%)
Partial response	15 (63%)	16 (53%)	4 (24%)	4 (19%)	2 (17%)
Stable disease	3 (13%)	4 (13%)	2 (12%)	2 (10%)	1 (8%)
Progressive disease	5 (21%)	8 (27%)	9 (53%)	11 (52%)	7 (58%)
Non-evaluable	1 (4%)	1 (3%)	1 (6%)	2 (10%)	1 (8%)
Intracranial progression-free survival					
Number of patients with disease progression	10 (37%)	16 (46%)	15 (79%)	20 (80%)	15 (94%)
Median duration, months (95% CI)	NR (4·7–NR)	NR (2·9–NR)	2·6 (1·8–NR)	2·5 (1·7–2·8)	2·3 (1·4–4·3)
At 6 months (95% CI)‡	60% (44–83)	53% (38–73)	21% (9–50)	20% (9–44)	13% (3–46)
Extracranial progression-free survival†					
Number of patients with disease progression	11 (46%)	15 (50%)	14 (82%)	16 (76%)	9 (75%)
Median duration, months (95% CI)	13·8 (5·3–NR)	13·8 (4·9–NR)	2·5 (1·8–NR)	2·6 (1·8–13·8)	2·6 (2·1–13·6)
At 6 months (95% CI)‡	56% (38–83)	51% (35–76)	35% (19–67)	35% (19–64)	19% (5–65)
Overall survival					
Number of patients with disease progression	8 (30%)	13 (37%)	8 (42%)	12 (48%)	13 (81%)
Median duration, months (95% CI)	NR (11·9–NR)	NR (8·5–NR)	NR (6·9–NR)	18·5 (6·9–NR)	5·1 (1·8–NR)
At 6 months (95% CI)‡	80% (65–98)	78% (65–94)	73% (56–96)	68% (52–89)	44% (25–76)

Data are n (%) unless otherwise stated. NR=not reached. *Drug naive refers to combined MEK and BRAF inhibitor therapy-naive patients. †Denominators for percentages are total patients with extracranial metastases, in cohort A drug-naive patients (24) and total cohort (30), cohort B drug-naive patients (17) and total cohort (21), and cohort C (12). ‡Rate estimated from Kaplan-Meier analysis.

Table 2: **Patient outcomes at data cutoff**

study and had final responsibility for the decision to submit for publication.

Results

Between Nov 4, 2014, and April 21, 2017, 79 patients were enrolled; 36 in cohort A (nivolumab and ipilimumab), 27 in cohort B (nivolumab), and 16 in cohort C (nivolumab; figure 1). One patient in cohort A and two in cohort B were found to be ineligible and removed from the study before receiving the study drug. In December, 2016, nivolumab combined with ipilimumab became widely available in Australia (at which point, 51 patients had been assigned to cohorts A and B), triggering an interim analysis. The data and safety monitoring committee reviewed the interim analysis, which included preplanned decision rules based on the conditional power approach, on Dec 6, 2016, and recommended continuing the trial as planned. Given the availability of the drug combination off study, after approval from the research ethics committee, cohort B was closed and all nine remaining patients were allocated to cohort A.

Baseline characteristics were similar between cohort A and B, including numbers of patients with an increased serum lactate dehydrogenase concentration, with BRAF mutation-positive melanomas, with previous combined BRAF and MEK inhibitor therapy, and with extracranial metastases (table 1). A higher proportion of patients in cohort A than in cohort B had more than four brain metastases (14 [40%] *vs* five [20%]). Fewer patients in cohort C had an increased concentration of lactate dehydrogenase than in cohorts A and B. Of the 60 patients in cohorts A and B combined, 45 (75%) were randomly assigned to the groups (26 to cohort A and 19 to cohort B). Baseline characteristics were similar in the non-randomised and randomised patients, except that the proportion of patients with $BRAF^{V600}$ mutations ($BRAF^{V600E}$ [ie, Val600Glu], $BRAF^{V600K}$ [ie, Val600Lys], and $BRAF^{V600R}$

[ie, Val600Arg]) and the proportion who had previously received BRAF and MEK inhibitor therapy was higher in the non-randomised patients (appendix p 4).

At data analysis cutoff (Aug 28, 2017), the median follow-up was 17 months (IQR 8–25) for all patients; 14 months (8–22) for cohort A, 17 months (13–22) for cohort B, and 31 months (25–35) for cohort C. 16 (46%) patients in cohort A, six (24%) in cohort B, and one (6%) in cohort C remained on study at data cutoff (figure 1).

At data cutoff, 16 (46%; 95% CI 29–63) of 35 patients in cohort A (nivolumab combined with ipilimumab) and five (20%; 7–41) of 25 patients in cohort B (nivolumab alone) had achieved an investigator-assessed intracranial response, with complete responses in six (17%) patients in cohort A and three (12%) in cohort B (table 2, figure 2A, B). Intracranial progression as best response occurred in 14 (40%) patients in cohort A and 19 (76%) in cohort B (table 2). 15 (94%) of 16 responding patients in cohort A, and all five (100%) in cohort B, remained in response at data cutoff (appendix p 15). In the combined BRAF and MEK inhibitor treatment-naive patients, 15 (56%; 95% CI 35–75) of 27 patients in cohort A and four (21%; 6–46) of 19 in cohort B had an investigator-assessed intracranial response, with complete responses in five (19%) patients in cohort A and two (11%) in cohort B (table 2, figure 2C, D). Intracranial tumour reduction correlated with extracranial tumour reduction (appendix pp 5, 10), except in five patients who had discordant responses—ie, a RECIST response in one region (intracranial or extracranial) with RECIST progression in the other (appendix p 5). None had extracranial progression with an intracranial response, and four of the five patients continued the study; three had local brain therapy, and one was rechallenged with nivolumab and responded after a break from treatment because of toxicity (appendix p 5). In contrast to cohort A and B, only one (6%; 95% CI 0–30) of 16 patients in cohort C had an investigator-assessed intracranial response that was ongoing at data cutoff at 22 months (this patient had BRAF wildtype melanoma, no leptomeningeal melanoma, and neurological symptoms only); no patients had complete responses, and 13 (81%) patients had progressive disease as their best response (table 2).

At data cutoff, 16 (46%) of 35 patients in cohort A, and 20 (80%) of 25 patients in cohort B had an intracranial progression event, with a median intracranial progression-free survival that was not reached in cohort A (95% CI 2·9–not reached), and 2·5 months (1·7–2·8) in cohort B (table 2, figure 3A, B). 13 (37%) of 35 patients had died in cohort A, 12 (48%) of 25 had died in cohort B, and 13 (81%) of 16 had died in cohort C (table 2; figure 3 C, D).

A lower baseline intracranial disease burden (sum of diameters ≤19 mm), was associated with a longer progression-free survival in cohort A than high baseline disease burden (>19 mm; appendix p 10). Median intracranial progression-free survival increased from 2·1 months (95% CI 1·3–2·9) in patients with progressive disease to not reached for those with a stable, partial, or complete responses in cohort A (appendix p 11).

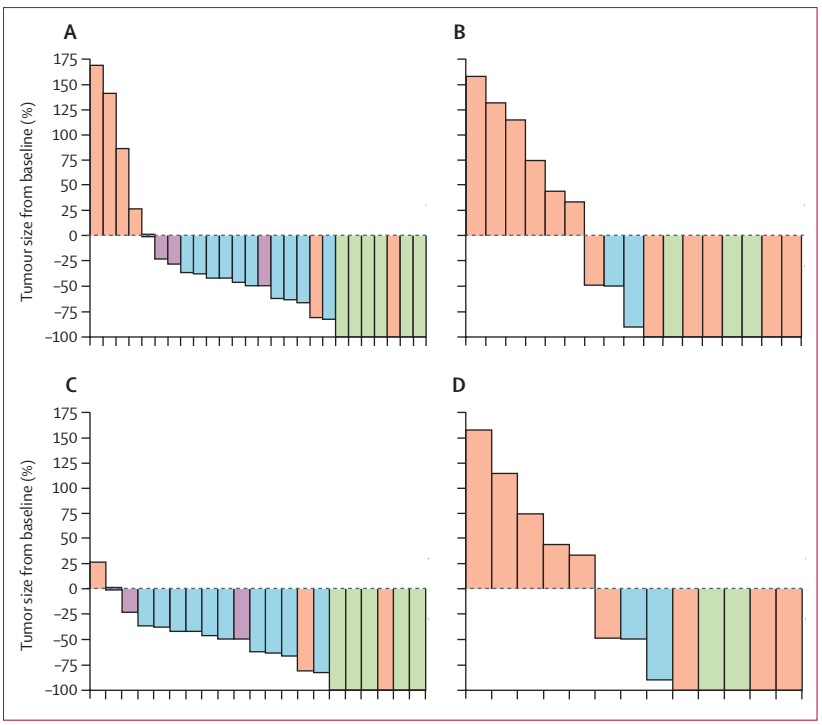

Figure 2: **Best percent reduction in intracranial target lesion sum of diameters**
(A) Cohort A. Nine patients are not included in this figure: eight died before week 12 assessment and one was not evaluable. (B) Cohort B. Eight patients are not included in in this figure: six died before week 12 assessment, one was not evaluable, and one switched drug therapy before week 12 assessment. (C) BRAF and MEK inhibitor treatment-naive patients in cohort A. Six patients are not included in in this figure: five died before week 12 assessment and one was not evaluable. (D) BRAF and MEK inhibitor treatment-naive patients in cohort B. Six patients are not included in in this figure: four died before week 12 assessment, one was not evaluable, and one switched drug therapy before week 12 assessment. Each bar shows one evaluable patient. Orange bars show progressive disease, purple bars indicate stable disease, blue bars show partial response, and green bars show complete response.

The overall pattern of progression did not differ in cohorts A and B; the majority of patients progressed in intracranial and extracranial sites concurrently, and four patients in each cohort (21% of the 19 patients in cohort A and 20% of the 20 in cohort B) progressed in intracranial sites only (appendix p 5). By contrast, six (40%) of 15 patients progressed in intracranial sites only in cohort C. Notably, all progressing patients in cohort B and C (nivolumab only) had intracranial progression, whether alone or concurrently with extracranial progression. The most common pattern of intracranial progression for all cohorts was concurrent growth in existing intracranial metastases and the development of new intracranial metastases; few patients developed new intracranial metastases alone (appendix p 6). Of the patients with intracranial progression, one (6%) of 16 in cohort A, three (15%) of 20 in cohort B, and two (13%) of 13 in cohort C had local therapy (surgery or radiotherapy) to the brain only, and nine (56%), 12 (60%), and

six (40%) commenced a new drug therapy, with or without local therapy (appendix p 6).

Of the 34 patients with intracranial progression at week 6 across cohort A, B, and C (assessed by exploratory brain MRI), 21 remained on study and had a scan at week 12; 17 (81%) of 21 had intracranial progression with further follow-up, and four (19%) of 21 patients subsequently responded or had stable disease at week 12 or later (appendix pp 10–11). Similarly, two (6%) patients in cohort A and one (4%) in cohort B who had intracranial progression as best response at or after week 12 were alive with no new intervening drug therapy 6 months after progression (appendix p 11), although local intracranial radiotherapy or surgery was administered to one patient in cohort A and one in cohort B.

In a subset of 33 (55%) patients from cohort A (n=17) and cohort B (n=16) whose tissue passed quality control, baseline PD-L1, CD8, and proliferating CD8 (Ki67$^+$ CD8$^+$) cell counts did not correlate with response, although analyses were limited by small numbers of samples (appendix p 12). As expected, patients from cohort A and B with baseline PD-L1 expression at least 1% had a numerically higher extracranial and overall progression-free survival than patients with PD-L1 expression less than 1%, but not intracranial progression-free survival (appendix p 13). Notably, for patients with melanoma PD-L1 expression of at least 1%, the extracranial and overall progression-free survival were similar in cohort A and B, but the intracranial progression-free survival was longer in cohort A than B (appendix p 14). By contrast, for PD-L1 expression less than 1%, the extracranial, intracranial, and overall progression-free survival, were longer in cohort A than cohort B (appendix p 14).

Adverse events related to study treatment occurred in 34 (97%) of 35 patients in cohort A, 17 (68%) of 25 in cohort B, and eight (50%) of 16 in cohort C (table 3;

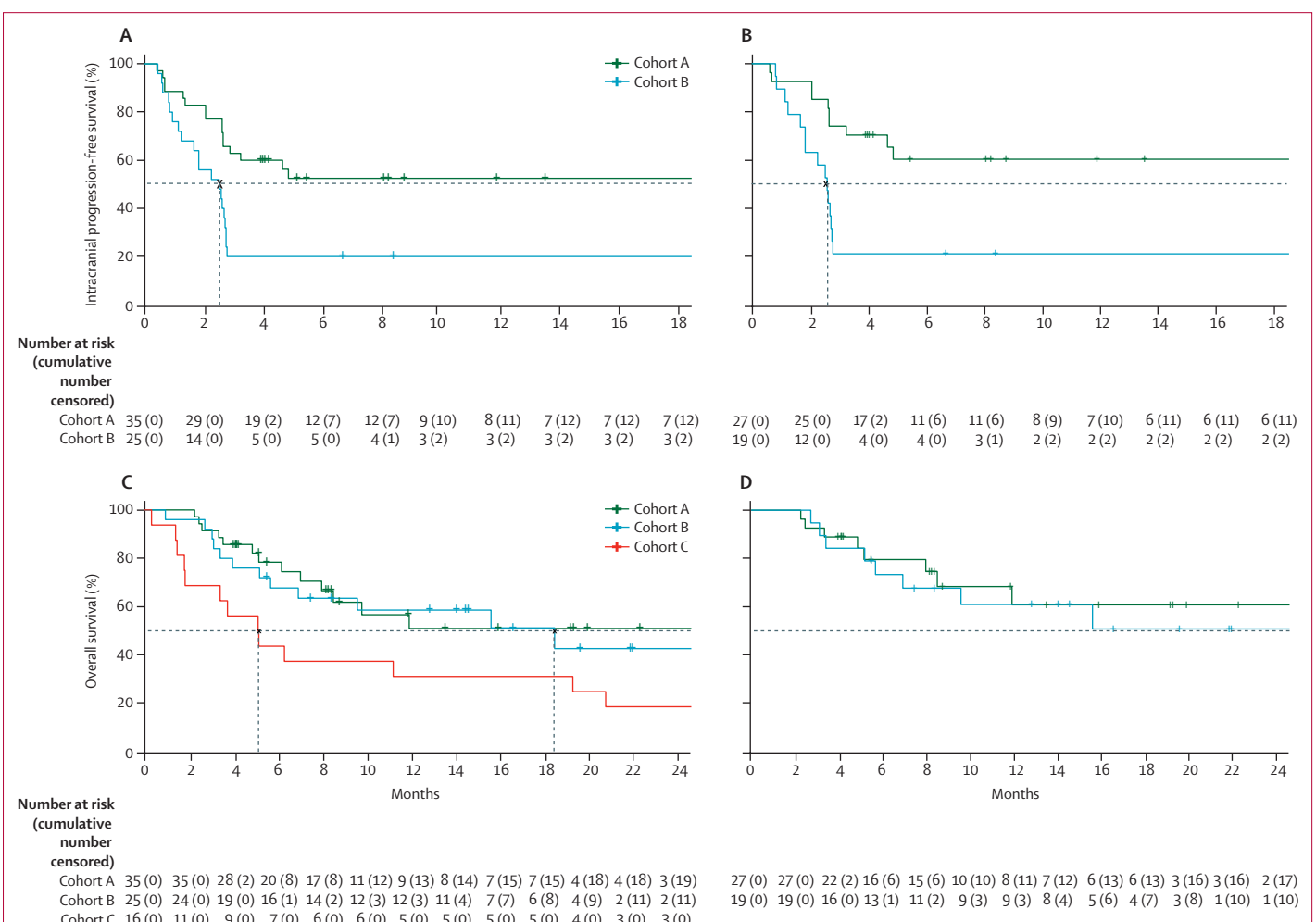

Figure 3: **Progression-free and overall survival**
Intracranial progression-free survival in cohorts A and B: (A) all patients and (B) BRAF and MEK inhibitor treatment-naive patients. Overall survival: (C) all patients in cohorts A, B, and C and (D) BRAF and MEK inhibitor treatment-naive patients in cohorts A and B. Analyses of drug treatment-naive patients in figures B and D are post-hoc.

	Cohort A (n=35)			Cohort B (n=25)		Cohort C (n=16)	
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3
Total number of patients with at least one adverse event	32 (91%)	19 (54%)	3 (9%)†	16 (64%)	4 (16%)	7 (44%)	2 (13%)
Skin	25 (71%)	4 (11%)	0	6 (24%)	0	2 (13%)	0
Rash	20 (57%)	4 (11%)	0	5 (20%)	0	1 (6%)	0
Pruritus	13 (37%)	0	0	2 (8%)	0	2 (13%)	0
Vitiligo	4 (11%)	0	0	2 (8%)	0	1 (6%)	0
Gastrointestinal	24 (69%)	14 (40%)	1 (3%)	11 (44%)	4 (16%)	1 (6%)	0
Diarrhoea or colitis	15 (43%)	7 (20%)	0	5 (20%)	0	1 (6%)	0
Nausea or vomiting	12 (34%)	1 (3%)	0	5 (20%)	0	1 (6%)	0
Hepatitis	10 (29%)	6 (17%)	1 (3%)	4 (16%)	2 (8%)	0	0
Xerostomia	6 (17%)	0	0	1 (4%)	0	0	0
Increased alanine aminotransferase or aspartate aminotransferase	4 (11%)	2 (6%)	0	1 (4%)	0	0	0
Increased amylase	4 (11%)	1 (3%)	0	1 (4%)	0	0	0
Increased lipase	3 (9%)	2 (6%)	0	0	1 (4%)	0	0
Increased alkaline phosphatase or γ-glutamyl transferase	1 (3%)	1 (3%)	0	1 (4%)	1 (4%)	0	0
Fatigue	20 (57%)	1 (3%)	0	9 (36%)	0	1 (6%)	0
Endocrine	11 (31%)	1 (3%)	1 (3%)	1 (4%)	0	1 (6%)	0
Hypophysitis or hypopituitarism	7 (20%)	1 (3%)	1 (3%)	0	0	0	0
Hyperthyroid or thyroiditis	6 (17%)	0	0	1 (4%)	0	1 (6%)	0
Musculoskeletal	12 (34%)	0	0	4 (16%)	0	4 (25%)	0
Arthralgia	7 (20%)	0	0	4 (16%)	0	4 (25%)	0
Myalgia or muscle weakness	6 (17%)	0	0	0	0	0	0
Nervous system	7 (20%)	2 (6%)	0	5 (20%)	0	1 (6%)	2 (13%)
Headache	4 (11%)	0	0	5 (20%)	0	0	1 (6%)
Peripheral neuropathy	3 (9%)	0	0	0	0	1 (6%)	0
Diaphragmatic weakness	0	1 (3%)	0	0	0	0	0
Seizure	0	1 (3%)	0	0	0	0	0
Radionecrosis	0	0	0	0	0	0	1 (6%)
Respiratory	6 (17%)	1 (3%)	1 (3%)	1 (4%)	0	1 (6%)	0
Pneumonitis	4 (11%)	1 (3%)	0	1 (4%)	0	1 (6%)	0
Cough	2 (6%)	0	0	0	0	0	0
Pulmonary oedema	0	0	1 (3%)	0	0	0	0
Other							
Nephritis	2 (6%)	1 (3%)	0	0	0	0	0
Increased creatine phosphokinase	1 (3%)	1 (3%)	0	1 (4%)	0	0	0
Decreased neutrophil	1 (3%)	1 (3%)	0	0	0	0	0

No grade 4 events were reported in cohort B or C and no treatment-related adverse event deaths were reported in any patients. *Some patients had more than one event. †The three patients with grade 4 events also had separate grade 3 events.

Table 3: **Treatment-related adverse events in at least 10% of patients and all grade 3 or 4 events***

appendix p 7). Grade 3 treatment-related adverse events occurred in 19 (54%) patients in cohort A, four (16%) in cohort B, and two (13%) in cohort C, the most common of which were diarrhoea or colitis (seven [20%] in cohort A) and hepatitis (six [17%] in cohort A and two [8%] in cohort B). Three (9%) treatment-related grade 4 events were reported in cohort A (hepatitis, pulmonary oedema, and hypopituitary), and none were reported in cohorts B and C.

Treatment-related serious adverse events occurred in 16 (46%) patients in cohort A, one (4%) in cohort B, and two (13%) in cohort C, of which the most common was colitis in cohort A (eight [23%]), and headache due to cerebral oedema in cohort B (one [4%]) and C (one [6%]; appendix p 9). No deaths occurred because of study treatment, and all deaths were due to progression of melanoma except one patient who died from dementia (appendix p 9). Nine (26%) patients in cohort A, one (4%) in cohort B, and one (6%) in cohort C discontinued study treatment because of adverse events; five due to colitis in cohort A, and one each due to pneumonitis in cohorts B and C.

Discussion

This three-cohort randomised phase 2 trial showed activity of anti-PD-1-based drug therapy in patients with untreated active brain metastases, with an intracranial response achieved by 16 (46%) of 35 patients treated with combined nivolumab and ipilimumab (cohort A) and five (20%) of 25 patients treated with nivolumab monotherapy (cohort B). To our knowledge, our study is the first to investigate anti-PD-1 monotherapy (nivolumab) in patients with brain metastases with the worst prognoses, including those in cohort C with neurological symptoms, progression after previous local brain treatment, or leptomeningeal melanoma; these factors were associated with an intracranial response in one (6%) of 16 patients. Despite the imbalance in baseline characteristics in the randomised cohorts A and B, with nearly double the proportion of patients with four or more brain metastases in cohort A than B, patients in cohort A had durable intracranial responses as shown by the long progression-free survival.

Notably, we showed that the intracranial response, progression-free survival, and overall survival were low after progression on combined BRAF and MEK inhibitors, in keeping with translational evidence that an immune-resistance phenotype develops on progression after BRAF inhibitor-based therapy.[14,15] When patients with asymptomatic untreated brain metastases received combined ipilimumab and nivolumab as their first drug therapy, 15 (56%) of 27 patients achieved an intracranial response, of which five (19%) achieved a complete response. This enhanced intracranial response in the first-line setting was not as apparent with nivolumab monotherapy in cohort B. Given the short duration of response (median 6·5 months) and progression-free survival (median 5·6 months; 44% of patients were progression-free at 6 months) recently reported in a study of first-line dabrafenib combined with trametinib in patients with $BRAF^{V600E}$ asymptomatic untreated brain metastases,[8] our data suggests that first-line treatment for patients with asymptomatic brain metastases should be combination ipilimumab and nivolumab rather than combined BRAF and MEK inhibition.

The phase 3 CheckMate 067 trial of nivolumab with or without ipilimumab versus ipilimumab monotherapy in patients with only active extracranial melanoma showed that the combination was associated with higher proportions of responses, landmark progression-free survival, and overall survival than nivolumab, although the study was not powered to establish statistical significance.[3] Given the toxicity of the combination, and the insufficient power to show significant differences between the nivolumab groups, a post-hoc analysis of the progression-free and overall survival by subgroups suggested that patients with high baseline lactate dehydrogenase, low baseline tumour PD-L1 expression, or a BRAF mutation might benefit from the combination over monotherapy.[3] Our data suggests that the presence of active brain metastases might also be an additional baseline factor in considering combination versus nivolumab monotherapy. Notably, when we examined baseline tumour PD-L1 expression in our study, the combination was associated with a longer intracranial progression-free survival than monotherapy, even for patients with high baseline PD-L1 tumour expression (≥1%). This finding is in contrast to the extracranial and overall progression-free survival, which were only longer with combination therapy than monotherapy in patients with PD-L1-negative tumours, consistent with the CheckMate 067 study.[3]

Analysis of patterns of response in our cohort showed that for most patients, the extracranial and intracranial responses were concordant, suggesting that the role of local therapy might need to be redefined—ie, the brain is not a sanctuary site that is managed separately from other sites of metastases, and that radiotherapy (and the possible increased risk of radionecrosis[16]) perhaps could be avoided in some patients. Additionally, patterns of progression did not differ between the patients who were randomly assigned to cohorts A and B, including type of intracranial progression (existing *vs* new sites *vs* both); however, fewer patients progressed on the combination, and all patients on nivolumab monotherapy had intracranial progression whether alone or concurrently with extracranial progression. However, not all patients who had disease progression in the combination treatment group had intracranial progression (some had extracranial progression only), suggesting that not only is the combination more active than nivolumab alone, but intracranial progression is not inevitable. This fact was reflected in the choice of therapy after intracranial progression—only four (25%) of 16 patients required local brain therapy in the combination group, but 12 (60%) of 20 in the nivolumab group. A clinical trial of upfront combination ipilimumab and nivolumab with salvage radiotherapy in non-responders at 6 weeks is planned (NCT03340129), to examine toxicity and efficacy of this approach. A further point of interest was that early assessment of intracranial progression (brain MRI at week 6), showed that most patients with progression at week 6 still had progression at week 12 (17 [81%] of 21 with available data), whereas four (19%) of the 21 patients had intracranial stable disease or a partial response by week 12. This result suggests that clinicians need to cautiously interpret early scans, although early intervention with local therapy (surgery or radiotherapy, or both) would be the safest clinical course in the setting of progressing brain metastases at week 6.

Notably, no new or unexpected toxicities were associated with drug therapy in this study, specifically no new or unexpected treatment-related neurological adverse events. In terms of efficacy, the study was limited to reporting proportions of responses and survivals within each cohort, and was not powered to compare the

randomised cohorts, although the activity was consistently numerically higher for the combination for all endpoints. Furthermore, the high proportions of responses and long duration of responses, particularly observed in cohort A (combination therapy), might not be generalisable to patients with symptoms due to brain metastases or those requiring corticosteroids to control neurological symptoms. Despite this limitation, the results are consistent with the intracranial response previously reported with pembrolizumab anti-PD-1 monotherapy[11] and the proportion of responses reported in a larger phase 2 study of the combination of ipilimumab and nivolumab,[17] although previous local brain therapy was allowed in each of these studies.

Our study showed that combination nivolumab and ipilimumab and nivolumab monotherapy are active in melanoma brain metastases, with durable responses in most patients who received combination therapy upfront. Given the increasing evidence of efficacy of immunotherapy across many solid tumours, these results might have marked implications for the management of active brain metastases in other solid tumours. Patients with asymptomatic untreated melanoma brain metastases should be considered for combination nivolumab and ipilimumab in the first-line setting.

Contributors

GVL, AMM, and GAM contributed to the study design. GVL, VA, SS, ADG, MPB, MG, AMM, and GAM recruited patients and collected data. SL did the statistical analyses. JSW, JE, and RAS collected and analysed melanoma tissue data. GVL wrote the manuscript. All authors interpreted the data, reviewed the manuscript, and approved the final version.

Declaration of interests

No author has received support for the work in this manuscript. GVL received personal fees as consultant adviser to Bristol-Myers Squibb (BMS), Merck (Merck Sharpe & Dohme [MSD]), Novartis, Roche, Amgen, Pierre-Fabre, and Array. VA received personal fees as a consultant adviser to BMS, Merck (MSD), Merck (Serono), Novartis, and Roche, speaker fees from BMS, Merck (MSD), Novartis, and Roche, and travel support from BMS and Merck (MSD). SS received personal fees as consultant adviser to BMS, Merck (MSD), Novartis, Roche, and Amgen, and research support from Amgen, Pfizer, and Tolmar. ADG received travel support and personal fees as a consultant adviser to BMS. MPB received personal fees as a consultant adviser to BMS, Merck (MSD), Novartis, and Roche. AMM received personal fees as a consultant adviser to BMS, Merck (MSD), Novartis, and Pierre-Fabre, and honoraria from Roche. GAM received research support from Celgene and Pfizer. SL, JSW, JE, MG, and RAS declare no competing interests.

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