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ORIGINAL ARTICLE

Sequencing of Checkpoint or BRAF/MEK Inhibitors on Brain Metastases in Melanoma

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Abstract

BACKGROUND The impact of the order of treatment with checkpoint inhibitors or BRAF/MEK inhibitors on the development of brain metastases in patients with metastatic unresectable *BRAF* V600-mutant melanoma is unknown. The SECOMBIT trial examined the impact of the order of receipt of these treatments in such patients.

METHODS In this three-arm trial, we reviewed patients without brain metastases who received the BRAF/MEK inhibitors encorafenib and binimetinib until they had progressive disease followed by the immune checkpoint inhibitors ipilimumab and nivolumab (arm A); or treatment with ipilimumab and nivolumab until they had progressive disease followed by encorafenib and binimetinib (arm B); or treatment with encorafenib and binimetinib for 8 weeks followed by ipilimumab and nivolumab until they had progressive disease followed by retreatment with encorafenib arm binimetinib (arm C).

RESULTS Brain metastases were discovered during the trial in 23/69 patients in arm A, 11/69 in arm B, and 9/68 in arm C. At a median follow-up of 56 months, the 60-month brain metastases–free survival rates were 56% for arm A, 80% for arm B (hazard ratio [HR] vs. A: 0.40, 95% confidence interval [CI] 0.23 to 0.58), and 85% for arm C (HR vs. A: 0.35, 95% CI 0.16 to 0.76).

CONCLUSIONS In patients with unresectable metastatic melanoma, the treatment sequence of immune checkpoint inhibition followed by BRAF/MEK inhibitors was associated with longer periods of new brain metastases–free survival than the reverse sequence. A regimen in which immune checkpoint inhibition was sandwiched between BRAF/MEK inhibition also appeared to be protective against brain metastases. (ClinicalTrials.gov number NCT02631447.)

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Introduction

Based on historical data, brain metastases are detected in 40% to 50% of patients with cutaneous melanoma; it is the third most common site of metastasis in such patients.[1,2] The prognosis of these patients is poor; before the introduction of checkpoint inhibitors and targeted therapies median overall survival (OS) as low as 4 months after discovery of brain metastases was not uncommon.[3,4]

Among patients with melanoma and brain metastases, especially those whose tumors harbor *BRAF* mutation, the choice of treatment is challenging. Combination blockade of programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte antigen-4[5,6] and dual BRAF/MEK inhibition[7,8] are all approved by the U.S. Food and Drug Administration and the European Medicines Agency as the first-line treatment options for *BRAF* V600-mutant melanoma, but the role of the sequence of these treatments to prevent and treat brain metastases is still debated.

A registry-based prospective trial and a retrospective trial on patients with metastatic *BRAF* V600-mutated melanoma found brain metastases–free survival (BMFS) and OS were longer after initial treatment with immunotherapy than with targeted therapy.[9,10] In addition, the incidence of brain metastases at 24 months was higher when first-line therapy was BRAF/MEK inhibition compared with checkpoint inhibition.[9]

Herein, we report the 5-year BMFS and OS from the SECOMBIT trial, which compared anti-cytotoxic T-lymphocyte antigen-4 and anti-PD-1 treatments administered until patients had progressive disease and then followed by treatment with BRAF/MEK inhibitors, with the same drugs given in the reverse order. A third "sandwich" arm in which BRAF/MEK inhibitors were given first, followed by checkpoint inhibitors, followed by repeat treatment with BRAF/MEK inhibitors was also examined. Data from an ancillary exploratory analysis of potential biomarkers and clinical prognostic factors are also reported.

Methods

TRIAL DESIGN

The design of the phase II, open-label randomized SECOMBIT trial has been previously published.[11,12] Figure 1 shows the trial design. Patients were randomized 1:1:1 across treatment arms. Arm A received encorafenib plus binimetinib until they had progressive disease, followed by ipilimumab plus nivolumab until second progressive disease. Arm B received ipilimumab plus nivolumab until they had progressive disease followed by encorafenib plus binimetinib until second progressive disease. Arm C ("sandwich" or "induction/maintenance") received encorafenib plus binimetinib for 8 weeks followed by ipilimumab plus nivolumab until they had progressive disease followed by encorafenib plus binimetinib until second progressive disease. The protocol had no formal comparative test and a single-stage design for each arm. Patients were enrolled at 37 academic medical centers in 9 countries. The trial protocol was approved by the appropriate ethics body at each participating institution and is available in the Supplemental Appendix, with the statistical analysis plan available at evidence.nejm.org. Patients gave informed consent to participate and to the publication of anonymous data.

An independent data monitoring committee oversaw the trial. Quality measures included centralized remote monitoring and contact with sites on a regular basis and remote data checking and management. SECOMBIT is registered at ClinicalTrials.gov (NCT02631447).[13]

Tumor assessments include measurable and nonmeasurable lesions — computed tomography (CT) or magnetic resonance imaging (MRI) of the brain at all baselines, CT/MRI of the chest, abdomen, and pelvis; CT/MRI of the chest, abdomen, and pelvis was performed at baseline and at each assessment. All measurable and nonmeasurable lesions were documented at screening (within 28 days prior to randomization) and reassessed at each subsequent tumor evaluation (every 8 weeks (±1 week) for the first year, every 12 weeks (±1 week) while the patient was on the trial). Tumor assessments with CT or MRI scans of the brain, chest, abdomen, and pelvis were performed until disease progression after the second combined treatment per RECIST v1.1. Imaging of the neck was included if clinically indicated. In the event that a positron emission tomography (PET)-CT scan was used for tumor assessments, the CT portion of the PET-CT must meet the criteria for diagnostic quality for that image to be included in the trial outcomes. All scans were collected for possible independent review.

BMFS was defined as the time between treatment start date and the date of diagnosis of brain metastases, censored at the last follow-up or death. Survival after brain metastases was defined as the time from the diagnosis of brain metastasis to death or the last follow-up. All analyses were performed according to an intention to treat design as prespecified in the protocol.

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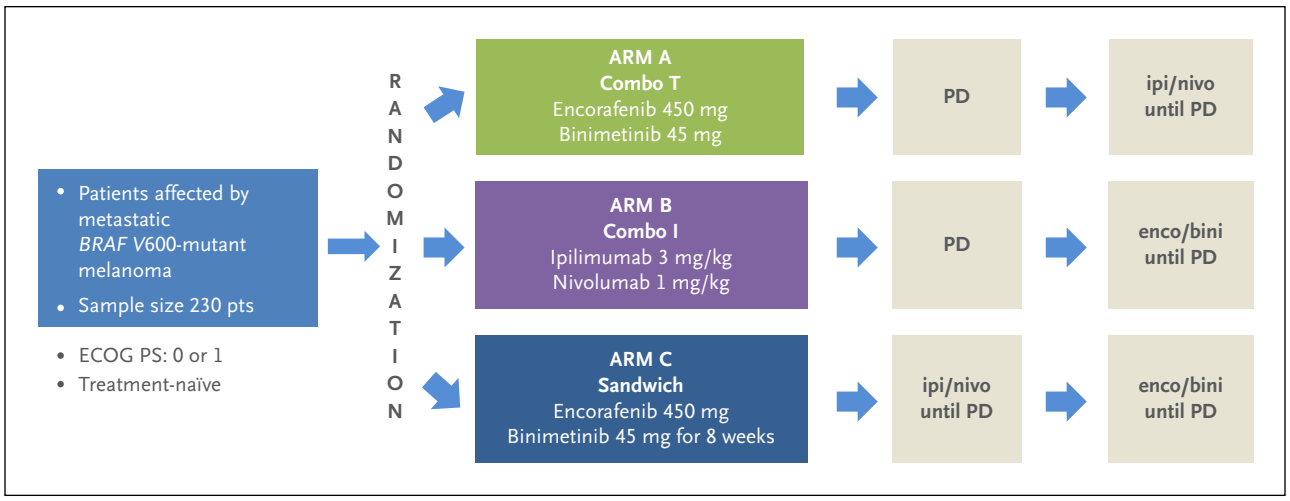

Figure 1. Trial Design.

ECOG PS denotes the Eastern Cooperative Oncology Group Performance Scale; bini, binimetinib; enco, encorafenib; ipi, ipilimumab; nivo, nivolumab; and PD, progressive disease.

An ancillary trial of potential biomarkers and clinical prognostic factors was performed to help identify subgroups of patients who may have benefited from each of the treatment approaches studied in the trial.

Methods for patient selection, randomization, procedures, statistical analysis, formalin-fixed paraffin-embedded (FFPE) DNA extraction and next-generation sequencing, and cytokine analysis can be found in the Supplemental Appendix (2.1, 2.2, 2.3, 2.4, 2.5, 2.6 to 2.8, 2.9, respectively).

Information on author contributions can be found in Section 1 of the Supplemental Appendix. Confidentiality agreements are in place between the sponsor funding the trial and the authors as well as the institutions named in the credit lines.

Results

PATIENTS AND TREATMENT

The disposition of patients in the trial has been published previously; it can be viewed in the CONSORT diagram in the Supplemental Appendix.[11,14] Briefly, between November 2016 and May 2019, 251 patients with untreated, metastatic *BRAF* V600-mutant melanoma were screened, and 209 patients were enrolled and randomized (by June 2019) across the three treatment arms: 69 in arm A (encorafenib plus binimetinib until progressive disease followed by ipilimumab plus nivolumab), 71 in arm B (ipilimumab plus nivolumab until progressive disease followed by encorafenib plus binimetinib), and 69 in arm C ("sandwich," encorafenib plus binimetinib for 8 weeks followed by ipilimumab plus nivolumab until progressive disease followed by encorafenib plus binimetinib). Overall, 206 patients received at least one dose of the trial sequence (n=69, n=69, and n=68 in arms A, B, and C, respectively).

The median age of patients in arms A, B, and C was 55.0 (range 19 to 77), 55.0 (range 18 to 81), and 51.0 years (range 28 to 80), with 60.9%, 47.9%, and 60.9% of male patients in the arms, respectively (Table 1). Patients were representative of the population affected with the disease in Italy (Table S1). No patient had active brain metastases, that is, metastases that were enlarging on CT/MRI scans compared with the previous assessment at baseline; one patient in arm B and one in arm C had had brain metastases that had previously resolved, and these patients were excluded from the analysis of BMFS.

At database lock, by May 31, 2023, the median follow-up was 56 months (interquartile range [IQR] 48 to 63 months). Among the 206 patients who received at least one dose of the trial sequence, 61 remained on treatment (n=16, n=22, and n=23 in arms A, B, and C, respectively). The numbers of patients who completed the entire sequence (i.e., who reached progressive disease on treatment 1 and treatment 2) were 20, 11, and 20 in arms A, B, and C, respectively. During treatment across the arms, there were 12 deaths in arm A (7 during encorafenib plus binimetinib treatment and 5 during ipilimumab plus nivolumab treatment), 11 deaths in arm B (3 during the ipilimumab plus nivolumab

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Table 1. Baseline Characteristics of the Intention-to-Treat Population*

Characteristics	Arm A (n=69)	Arm B (n=71)	Arm C (n=69)
Age (years), median (range)	55.0 (19–77)	55.0 (18–81)	51.0 (28–80)
Sex — male, n (%)	42 (60.9)	34 (47.9)	42 (60.9)
ECOG PS 0, n (%)	57 (82.6)	62 (87.3)	62 (89.9)
CNS metastases at baseline, n (%)	0 (0)	1 (1)	1 (1)
LDH levels, n (%)			
≤1×ULN	41 (59.4)	37 (52.1)	44 (63.8)
>1×ULN	28 (40.6)	34 (47.9)	25 (36.2)
>2×ULN	7 (10.1)	9 (12.7)	7 (10.1)
Stage, n (%)			
M0–M1a–M1b	29 (42)	28 (39.4)	29 (42)
M1c	40 (58.0)	42 (59.1)	39 (56.5)
Not reported	0	1 (1.5)	1 (1.5)
Metastatic sites, n (%)			
<3	43 (62.3)	41 (57.7)	43 (62.3)
≥3	25 (36.2)	29 (40.8)	25 (36.2)
Not evaluated	1 (1.5)	1 (1.4)	1 (1.5)

*The stage is reported as described in the American Joint Commission on Cancer Staging Manual, Version 7. CNS denotes central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Scale; LDH, lactate dehydrogenase; and ULN, upper limit of normal.

treatment and 8 during encorafenib plus binimetinib treatment), and 4 deaths in arm C (2 during the ipilimumab plus nivolumab treatment and 2 during second treatment of encorafenib plus binimetinib). Adverse events led to treatment discontinuation in 12 patients in arm A, 10 patients in arm B, and 11 patients in arm C.

BRAIN METASTASES PROGRESSION-FREE SURVIVAL AND SURVIVAL AFTER BRAIN METASTASES

Two patients were excluded from these analyses, as they had brain metastases at baseline. Overall, brain metastases were discovered during the trial in 23 (33.3%) patients in arm A, 11 (15.5%) in arm B, and 9 (13.0%) in arm C (Table S2). The median time to detection of brain metastases was 14 months. This analysis showed that brain metastases were detected at first progression in 17 patients in arm A, 6 in arm B, and 8 in arm C, and at second progression in 6 patients in arm A, 5 in arm B, and 1 in arm C. Five patients in arm A, one in arm B, and one in arm C had leptomeningeal disease; symptomatic brain metastases were noted in 13, 5, and 4 patients of arms A, B, and C, respectively; whole brain radiotherapy was administered to 5, 0, and 1 patient(s), and dexamethasone at over 2 mg/day was administered to 13, 4, and 1 patient(s), respectively (Table S1). The numbers of patients who had brain metastases as the only site of new metastasis were 16/20, 6/11, and 7/9 in arms A, B, and C, respectively.

At first progressive disease, patients in arm A received BRAF/MEK inhibitors, and in arms B and C checkpoint inhibitors were given. At the second progressive disease, patients in arm A received checkpoint inhibitors while patients in arms B and C received BRAF/MEK inhibitors.

The new data in this report show that the 60-month BMFS rates were 56% for arm A, 80% for arm B (hazard ratio [HR] vs. A: 0.40, 95% CI 0.23 to 1.00), and 85% for arm C (HR vs. A: 0.36, 95% CI, 0.17 to 0.77) (Fig. 2A).

The 2-year survival rates after brain metastasis detection (the time from the first discovery of brain metastases to death or the last follow-up) were 9% in arm A, 27% in arm B (HR vs. arm A: 0.52, 95% CI 0.23 to 1.19), and 33% in arm C (HR vs. arm A: 0.53, 95% CI 0.22 to 1.28) (Fig. 2B).

5-YEAR SURVIVAL OUTCOMES

As previously published, at a median follow-up of 32.2 months (range 27.9 to 41.6), more than 30 patients were alive in all arms. The 2-year and 3-year OS rates were 65% (95% CI 54 to 76) and 54% (95% CI 41 to 67) in arm A, 73% (95% CI 62 to 84) and 62% (95% CI 48 to 76) in arm B, and 69% (95% CI 59 to 80) and 60% (95% CI 58 to 72) in arm C.[11]

This new analysis of data showed that at a median follow-up of 56 months, the total 60-month progression-free survival (TPFS; the time from randomization to the second progression or death) rate was 27% for arm A, 50% for arm B (HR vs. arm A: 0.61, 95% CI 0.39 to 0.95), and 50% for arm C (HR vs. arm A: 0.58, 95% CI 0.37 to 0.90) (Fig. 3A).

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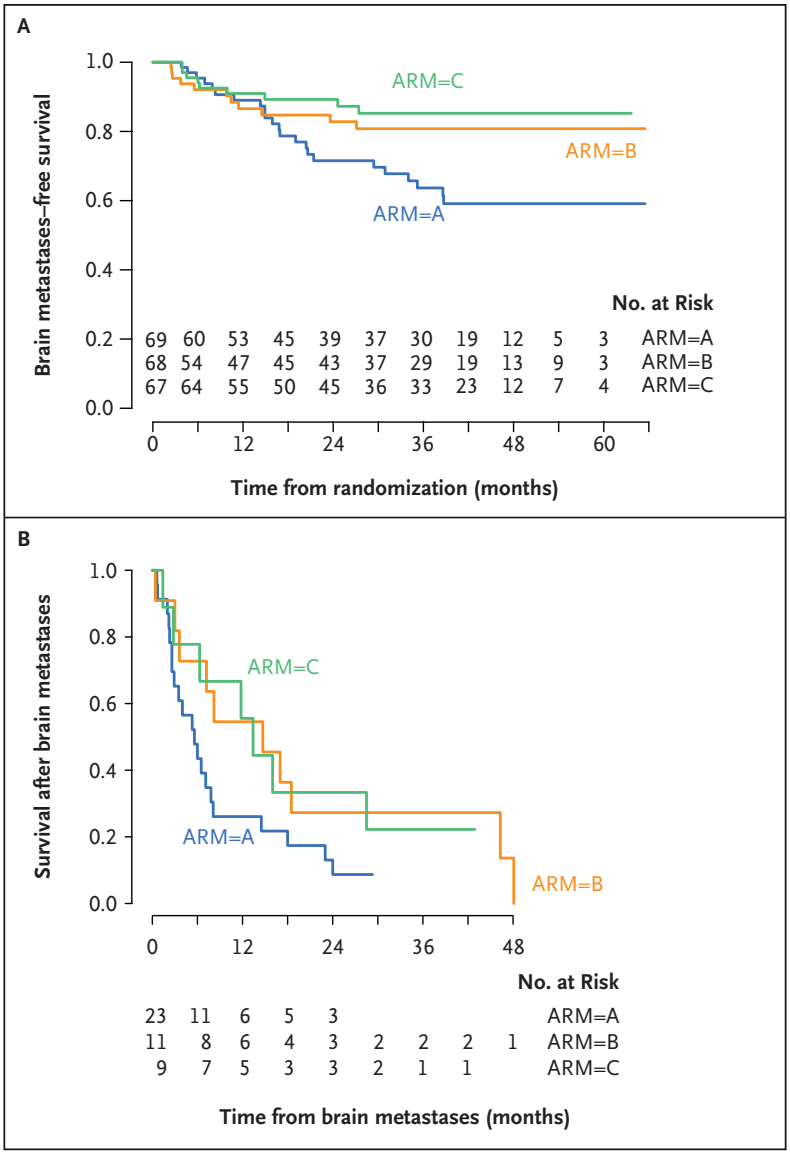

Figure 2. Kaplan–Meier Curves for 5-Year Brain Metastases–Free Survival (Panel A) and Survival After Brain Metastases (Panel B) by Treatment Arm.

The total 60-month OS rate was 45% for arm A, 52% for arm B (HR vs arm A: 0.75, 95% CI 0.46 to 1.22), and 57% for arm C (HR vs. arm A: 0.71, 95% CI 0.43 to 1.16) (Fig. 3B).

BIOMARKER ANALYSIS

Targeted next-generation sequencing was performed on tumor tissue obtained at baseline from 84 patients, of whom 29 from arm A (28 were analyzed for Janus kinases [JAK] and tumor mutational burden [TMB] and only 1 for JAK alone), 25 from arm B, and 30 from arm C were included in the analysis for TMB and deleterious *JAK* mutations.

Patients from arms A and B who had high TMB (≥10 mut/Mb, limits according to Mo et al.)[15] had a 5-year BMFS of 100%, while those with low TMB (<10 mut/Mb) had a 5-year BMFS of 46% and 66%, respectively, while patients from arm C had similar BMFS independent of TMB level (Fig. S1).

In addition, patients from arms A and B who harbored *JAK* mutation had a 5-year BMFS of 100% while patients with wild-type *JAK* in the tumors had a 5-year BMFS of 56% and 67%, respectively; patients from arm C had comparable BMFS with mutated and wild-type *JAK* (Fig. S2).

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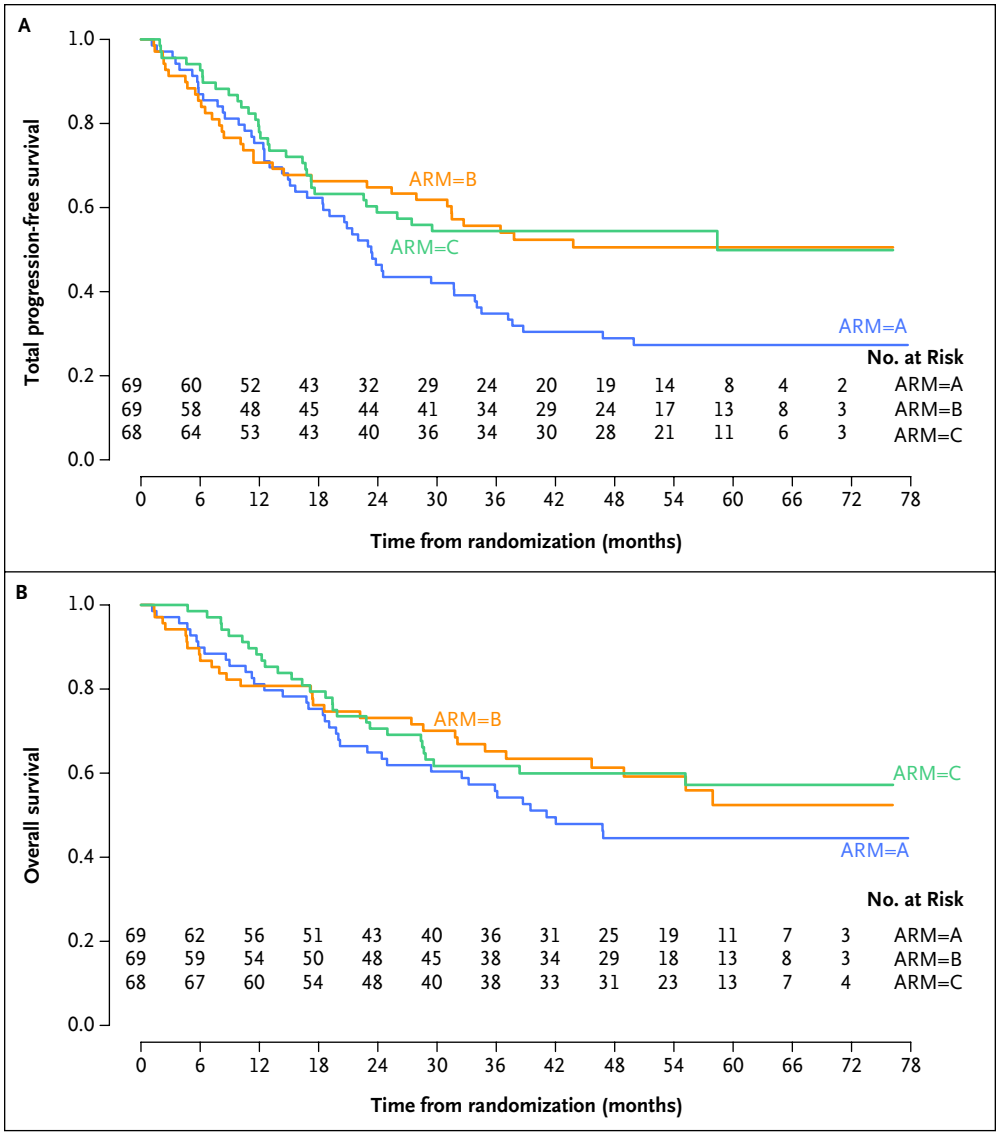

Figure 3. Kaplan–Meier Curves for 5-Year Total Progression-Free Survival (Panel A) and Overall Survival (Panel B) by Treatment Arm.

The 5-year BMFS rate was 66% in patients with low (<10) TMB and 92% in those with high (≥10) TMB (HR: 0.23, 95% CI 0.05 to 1.00) in the overall population (Fig. S3). In addition, the 5-year BMFS rate was 67% in patients with wild-type *JAK* and 92% in those with a deleterious *JAK* mutation (HR: 0.24, 95% CI 0.06 to 1.04) (Fig. S4).

Five-year TPFS and OS were analyzed in each treatment arm according to lactate dehydrogenase (LDH) level at baseline; patients in arm C who had elevated levels of LDH had TPFS and OS rates of 60% and 65%, respectively, and those with normal LDH levels had TPFS and OS rates of 43% and 52%, respectively. In contrast, the TPFS rate of patients in arm A was 15% with elevated LDH and 36% with normal LDH, and in arm B it was 46% versus 51%. In addition, the OS rate of patients in arm A was 40% with elevated LDH and 50% with normal LDH, and in arm B it was 44% versus 57%. A trend was observed for better TPFS and survival in arm C than in arm A when the LDH baseline level was high, while no difference between arms was evident when the LDH level was normal (Fig. S5).

Among patients with metastases at three or more sites, median TPFS was 19%, 48%, and 46% in arms A, B, and C, respectively. Among patients with metastases at fewer than three sites, median TPFS was 32%, 52%, and 53% in

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arms A, B, and C respectively. The OS was similar across the arms, in patients with metastases both in three or more sites and in fewer than three sites (Fig. S6).

Discussion

This analysis of the results of the SECOMBIT trial at 60 months extends our prior reports on the impact of the order of treatment with checkpoint or BRAF/MEK inhibitors in the appearance of brain metastases. Our data suggest that patients receiving checkpoint inhibitors first had fewer brain metastases and longer survival after brain metastases diagnosis than those receiving the reverse sequence of treatment. Brain metastases developed by patients receiving targeted therapy first seemed not only to be more frequent but also to have poorer characteristics (more leptomeningeal disease, more symptomatic lesions, more often leading to whole brain radiotherapy and dexamethasone treatment at a dose of over 2 mg/day). In the IMspire150 trial, the addition of the immune checkpoint inhibitor atezolizumab to the BRAF/MEK inhibitors vemurafenib and cobimetinib was associated with a lower rate of development of brain metastases in patients with *BRAF* 600-mutated advanced melanoma without brain involvement at baseline.[16] The results reported here are in agreement with those findings and add information on the role of treatment timing.

The SECOMBIT trial investigated a third arm of treatment with a BRAF/MEK inhibitor course preceding checkpoint inhibitor treatment up until the onset of progressive disease (sandwich sequence). An exploratory analysis also suggested that the treatment strategy of this last arm might further increase the benefit of preventing new brain metastases associated with administering checkpoint inhibitor treatment in the first line, followed by BRAF/MEK inhibitors in the second line.

The phase 2 ImmunoCobiVem trial showed that, in patients with *BRAF* V600-mutated advanced melanoma, a planned switch to the anti-PD-L1 agent after achieving tumor control with targeted therapy was associated with an increased PFS but with a lower 2-year survival.[17] In contrast, we observed that a short course of targeted therapy before checkpoint inhibition was associated with a high 5-year survival, comparable to the survival of the group receiving immunotherapy in the first line; we speculate that the sandwich schedule could have even better results than first-line immunotherapy in some subgroups, such as those with high LDH or brain metastases.

This trial has some limitations. The SECOMBIT trial has a phase II design, and a small sample size. Here we present results obtained from a subgroup analysis, allowing us to generate a hypothesis. The biomarkers analysis is exploratory only due to the small number of patients included and the lack of high-resolution information on cellular populations and cytokine levels within the tumor metastatic environment. All samples available for the biomarker analysis were used, without exclusion, and, although the samples were equally distributed in the treatment arms, no comparisons may be significant.

The original analysis of data from SECOMBIT showed that TPFS and OS outcomes were superior in patients receiving combination checkpoint inhibitor treatment with ipilimumab/nivolumab as a first-line treatment and combination BRAF/MEK therapy with encorafenib/binimetinib after the first disease progression, compared with the reverse sequence, in agreement with results from the DREAMseq trial.[11,18] This article reports an analysis of data from SECOMBIT with a median follow-up of 56 months (IQR 48 to 63). Data confirmed that outcomes continued to show this difference in treatment arms B and C (first-line checkpoint inhibitor therapy without or with a planned period of BRAF/MEK therapy before switching to ipilimumab/nivolumab) than in arm A (targeted therapy as a first-line treatment followed by checkpoint inhibition after progression). Indeed, the long-term results of SECOMBIT are still in agreement with those of the DREAMseq trial.[18]

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

This trial was supported by unconditional grants from Bristol-Myers Squibb (Princeton, NJ) and Array Biopharma/Pfizer (Boulder, CO).

Data Sharing Statement

All data generated in this trial have been deposited in Zenodo (https://doi.org/10.5281/zenodo.10623983); the variant allele–frequency data have been deposited in the European Variation Archive at EMBL-EBI under the accession number PRJEB70957. The accession associated with the submission is project PRJEB70957. Accession is public in both databases. Anonymous characteristics of patients at baseline are shared. Clinical values and biomarkers reported in the manuscript are shared.

The trial protocol is available in the Trial Protocol file. The informed consent form is available in the Informed Consent Form file. The remaining data are available within the Article and Supplemental files.

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