Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients With Advanced *BRAF*-Mutant Melanoma: The DREAMseq Trial—ECOG-ACRIN EA6134

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PURPOSE Combination programmed cell death protein 1/cytotoxic T-cell lymphocyte-4–blockade and dual BRAF/MEK inhibition have each shown significant clinical benefit in patients with *BRAFV600*-mutant metastatic melanoma, leading to broad regulatory approval. Little prospective data exist to guide the choice of either initial therapy or treatment sequence in this population. This study was conducted to determine which initial treatment or treatment sequence produced the best efficacy.

PATIENTS AND METHODS In a phase III trial, patients with treatment-naive *BRAFV600*-mutant metastatic melanoma were randomly assigned to receive either combination nivolumab/ipilimumab (arm A) or dabrafenib/trametinib (arm B) in step 1, and at disease progression were enrolled in step 2 to receive the alternate therapy, dabrafenib/trametinib (arm C) or nivolumab/ipilimumab (arm D). The primary end point was 2-year overall survival (OS). Secondary end points were 3-year OS, objective response rate, response duration, progression-free survival, crossover feasibility, and safety.

RESULTS A total of 265 patients were enrolled, with 73 going onto step 2 (27 in arm C and 46 in arm D). The study was stopped early by the independent Data Safety Monitoring Committee because of a clinically significant end point being achieved. The 2-year OS for those starting on arm A was 71.8% (95% CI, 62.5 to 79.1) and arm B 51.5% (95% CI, 41.7 to 60.4; log-rank $P = .010$). Step 1 progression-free survival favored arm A ($P = .054$). Objective response rates were arm A: 46.0%; arm B: 43.0%; arm C: 47.8%; and arm D: 29.6%. Median duration of response was not reached for arm A and 12.7 months for arm B ($P < .001$). Crossover occurred in 52% of patients with documented disease progression. Grade ≥ 3 toxicities occurred with similar frequency between arms, and regimen toxicity profiles were as anticipated.

CONCLUSION Combination nivolumab/ipilimumab followed by BRAF and MEK inhibitor therapy, if necessary, should be the preferred treatment sequence for a large majority of patients.

INTRODUCTION

BRAFV600 mutations are present in approximately 50% of patients with metastatic melanoma and drive cell proliferation and survival through constitutive activation of the MAP kinase pathway.[1] BRAF/MEK inhibitor combinations (dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib) produce a higher number of objective responses, and demonstrate improved median progression-free survival (PFS) and overall survival (OS) relative to BRAF-inhibitor monotherapy leading to FDA approval.[2-4] Although these regimens have distinct toxicity profiles, the PFS hazard ratios (HRs) for the three combinations versus vemurafenib monotherapy were similar, ranging from 0.54 to 0.58. Although benefits are particularly noted in early end points (objective response rate [ORR] and median PFS), 5-year OS has been noted in 71% of patients with complete response to treatment and in 51% of patients

CONTEXT

Key Objective

This trial sought to determine the optimal treatment sequence between combination nivolumab/ipilimumab checkpoint inhibitor immunotherapy and combination dabrafenib/trametinib molecularly targeted therapy for patients with treatment-naive *BRAFV600*-mutant metastatic melanoma using 2-year overall survival rate as the primary end point.

Knowledge Generated

This study established that the sequence beginning with combination nivolumab/ipilimumab resulted in a 20% absolute improvement in 2-year overall survival (72% *v* 52%) compared with the sequence beginning with dabrafenib/trametinib. A trend toward 2-year overall benefit was seen across all patient subsets, and other efficacy end points (progression-free survival and duration of response) also favored first-line immunotherapy.

Relevance (*G.K. Schwartz*)

The optimal sequence of targeted molecular therapy versus checkpoint inhibitor immunotherapy as first-line treatment for patients with *BRAFV600*-mutant metastatic melanoma has represented a major therapeutic challenge. This study addresses this issue and settles this question by showing that immunotherapy should precede targeted therapy as the first-line treatment for patients with *BRAFV600* metastatic disease.*

*Relevance section written by *JCO* Associate Editor Gary K. Schwartz, MD.

with normal lactate dehydrogenase (LDH) and < three organ sites of metastases at baseline.[5,6]

The combination of nivolumab/ipilimumab was shown to be superior to ipilimumab in terms of ORR, PFS, and OS leading to FDA approval in patients with metastatic melanoma in 2015, regardless of tumor *BRAF* mutation status.[7] Although the CheckMate 067 study was not powered to show differences between combination nivolumab/ipilimumab versus nivolumab monotherapy, 6.5-year follow-up results showed significant benefits in median PFS (16.8 *v* 5.6 months; HR, 0.62 [95% CI, 0.44 to 0.89]) and OS (not reached [NR] *v* 45.5 months; HR, 0.68 [95% CI, 0.46 to 1.0]) together with an absolute 14% difference between both 6.5-year PFS (37% *v* 23%) and OS (57% *v* 43%) rates in favor of the combination in the subset of patients with *BRAF*-mutated tumors.[8]

In general, BRAF/MEK inhibitor therapy tends to produce high tumor shrinkage rates and to prolong median PFS, whereas nivolumab/ipilimumab tends to have its major impact on response durability, 2-year and beyond PFS and OS rates, and treatment-free survival,[9] complicating cross-trial comparisons. Several nonrandomized retrospective comparisons of either matched trial data or real-world data suggested improved clinical outcomes and cost-effectiveness of immunotherapy as initial treatment[10-15]; however, these studies were subject to selection biases that could not be controlled for, as well as inconsistent availability and use of second-line treatments leading the authors, and the field in general, to call for prospective validation. Despite this information, marketing data showed that in 2021, half of all patients in the United States with metastatic *BRAF*-mutant melanoma received BRAF/MEK inhibitors and only one quarter received nivolumab/ipilimumab as initial therapy (data on file [Melanoma Treatment Report, 1L Metastatic Melanoma BRAF MT Patients; data collected from September 2020-September 2021], IQVIA BrandImpact, Durham, NC). Therefore, prospectively randomized data were necessary to determine which treatment approach is preferred. The EA6134 (DREAMseq) trial was launched in 2015 within the NCI-supported US National Clinical Trials Network to address this question.[16]

PATIENTS AND METHODS

DREAMseq (EA6134) is a two-arm, two-step, open-label, randomized phase 3 trial led by the ECOG-ACRIN Cancer Research Group (NCT02224781). The study was conducted in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The Protocol (online only) was approved by the NCI Central IRB. All patients provided written informed consent before study enrollment.

Treatment

The treatment schema is shown in the Data Supplement (online only). Eligible patients were stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 and LDH level normal or elevated and randomly assigned 1:1 to receive step 1 with either nivolumab/ipilimumab (arm A) or dabrafenib/trametinib (arm B) and at disease progression were enrolled in step 2 to receive the alternate therapy, dabrafenib/trametinib (arm C) or nivolumab/ipilimumab (arm D). Patients received nivolumab 1 mg/kg and ipilimumab 3 mg/kg once every 3 weeks for four doses followed by nivolumab 240 mg intravenously once every 2 weeks for up to 72 weeks (arms A and D) or dabrafenib 150 mg twice a day and trametinib 2 mg orally once daily until progressive disease (arms B and C). In 2019, investigators were given the option to use alternate induction doses of nivolumab 3 mg/kg and ipilimumab 1 mg/kg once every 3 weeks for four doses for arms A and D.

Cycles were every 6 weeks to enable visits, blood tests, and correlative studies to match between the arms. Imaging for investigator-assessed tumor measurements was obtained at baseline and every 12 weeks (two cycles) on each arm while patients were on treatment. For patients on any arm who stopped treatment before 2 years in the absence of disease progression, tumor imaging was performed every 12 weeks until 2 years and then every 6 months from years 2 to 5. Patients on arm B or C who stopped treatment for reasons other than disease progression after 2.5 years from study arm entry were followed every 3 months for 1 year, then every 6 months until 5 years.

Patients

Eligible patients had to have histologically confirmed, RECISTv1.1-measurable, unresectable stage III or IV melanoma containing a *BRAFV600E/K* mutation by a Clinical Laboratory Improvement Amendments–approved assay. Patients had to be treatment-naive for metastatic disease, but could have received adjuvant therapy that did not include a programmed cell death protein 1 (PD-1)/programmed death-ligand 1, cytotoxic T-cell lymphocyte-4, BRAF, or MEK inhibitor. Patients were further required to have ECOG PS 0 or 1, age $\geq$ 18 years, and adequate organ and bone marrow function. Pre-existing brain metastases had to have been treated with either surgery or stereotactic radiosurgery (SRS) and patients had to be off steroids for at least 10 days before treatment assignment and have no evidence of disease progression on a repeat brain magnetic resonance imaging (MRI) obtained 4 weeks following radiation or surgery. With Amendment 13 in 2019, potential central nervous system (CNS) metastases that were too small for SRS or surgery were permitted, and repeat brain MRI following SRS or surgery was not required so long as the original MRI was within 4 weeks of study enrollment.

Patients were excluded if they had major surgery or radiation therapy within 14 days (shortened to 7 days for radiation in 2019) of starting study treatment, autoimmune disease that might recur and affect vital organ function or require immunosuppressive treatment, cardiovascular disease, history of retinal vein occlusion, or use of medications that were strong inhibitors or inducers of CYP3A or CYP2C8. Patients were initially excluded if they had an LDH > 10 times the upper limit of normal, but this restriction was subsequently removed.

To enroll onto step 2, patients needed to have RECISTv1.1-documented progressive disease and had to meet the relevant step 1 eligibility criteria. Patients crossing over from arm A to arm C were required to have any immune-related adverse events (irAEs) resolve to grade 1 or less, but were permitted to still be on immunosuppressive therapy. Initially, patients were required to be at least 2 weeks and no more than 12 weeks from documented disease progression; however, this was subsequently amended to a minimum of 1 week and no maximum. Patients not enrolled in

step 2 were followed for toxicity resolution and OS. They could receive any treatment available to their oncology team including the agents being tested in this study.

Toxicity assessment was based on Common Terminology Criteria for Adverse Events v4 throughout the course of the study. Patients experiencing grade 3 toxicity during nivolumab/ipilimumab induction therapy (excluding endocrine toxicity managed with replacement hormones) received no further induction therapy and if this toxicity involved either the heart, lungs, kidney, or neurologic system, or was grade 4, they received no further immunotherapy on protocol. For other irAEs resolving to grade 1 by week 16, patients could receive nivolumab maintenance therapy according to the original schedule. Patients experiencing grade 3 toxicity on dabrafenib/trametinib typically held the presumed causative agent(s) until toxicity resolved to grade $\leq$ 1 and then restarted treatment at a lower dose (dabrafenib 100, 75, or 50 mg twice a day; trametinib 1.5 or 1 mg once daily). Patients experiencing grade 3 toxicity despite three dose reductions of dabrafenib or two dose reductions of trametinib permanently discontinued that treatment. Patients stopping therapy for toxicity in step 1 were considered for crossover to step 2 only if progressive disease was subsequently documented.

Full eligibility and exclusion criteria and toxicity management guidelines are provided in the protocols available in the Data Supplement (Table S1) describing the components of each protocol amendment.

End Points

Because of the anticipated nonproportional hazards of OS, the primary end point was 2-year landmark OS rate among patients followed for at least 2 years. Secondary end points included 3-year OS; ORR by RECISTv1.1, duration of response, PFS and safety for each arm and in first-line versus second-line; and feasibility of crossover from step 1 to step 2.

Statistical Analysis

With 300 patients enrolled (270 evaluable), there would be 90% power to show a difference in 2-year OS rate of 70% with the nivolumab/ipilimumab first sequence versus 50% with the dabrafenib/trametinib first sequence using a chi-square test with a two-sided type 1 error rate of 0.05. The 2-year OS rates were compared using the Mantel-Haenszel chi-square test among the patients with at least 2-year follow-up time per study design, and using the 2-year OS estimates from the Kaplan-Meier plot for all patients at the time of analysis. Hazards for OS were estimated as a function of time by treatment. An intent-to-treat analysis was conducted in all comparisons. Kaplan-Meier curves were also used for calculating PFS and duration of response. Duration of response was estimated for patients with a response from the time of response to progression or last assessed. Binary end points, such as response rate or toxicity rate, were compared using Fisher's exact test. Multiple testing has not been adjusted. Two-sided *P* values

were reported for all analyses. SAS software version 9.4 (SAS Institute, Cary, NC) and R software version 3.5.2 (SAS Institute, Cary, NC) were used.

Interim analyses by an independent Data Safety Monitoring Committee (DSMC) were planned beginning 2 years after enrollment of 100 patients with subsequent efficacy and futility analyses every 6 months. The Lan and DeMets spending function with O'Brien and Fleming boundaries were used. Repeated CIs were constructed for the futility analysis.[17]

RESULTS

The study was activated on July 13, 2015. At the time of the 4th interim DSMC analysis (cutoff date: July 16, 2021), at the median follow-up time of 27.7 months (IQR, 41.9-11.9 = 30 months), 265 patients had enrolled in step 1 (arm A = 133; arm B = 132) and 73 in step 2 (arm C = 27; arm D = 46; Figs 1A and 1B). The two initial arms were

balanced for most characteristics (Table 1). Of note, more patients on arm B had *BRAFV600K*-mutant tumors than those on arm A (25.2% *v* 12.1%). Study accrual was halted on September 30, 2021, on the basis of the DSMC recommendation.

Efficacy

OS curves for the combined sequences showed a biphasic pattern (Fig 2A). HRs over time were similarly biphasic (Data Supplement). One hundred patients had died, of which 62 had dabrafenib/trametinib as initial therapy. The 2-year OS rate was 71.8% (95% CI, 62.5 to 79.1) for patients who started on nivolumab/ipilimumab and 51.5% (95% CI, 41.7 to 60.4) for those who started on dabrafenib/trametinib ($P = .010$, log-rank). At the time of the 4th DSMC interim analysis, 176 patients had 2-year follow-up data (arm A = 87; arm B = 89; 59% information) and there were 74 deaths (arm A/C = 32; arm B/D = 42). The
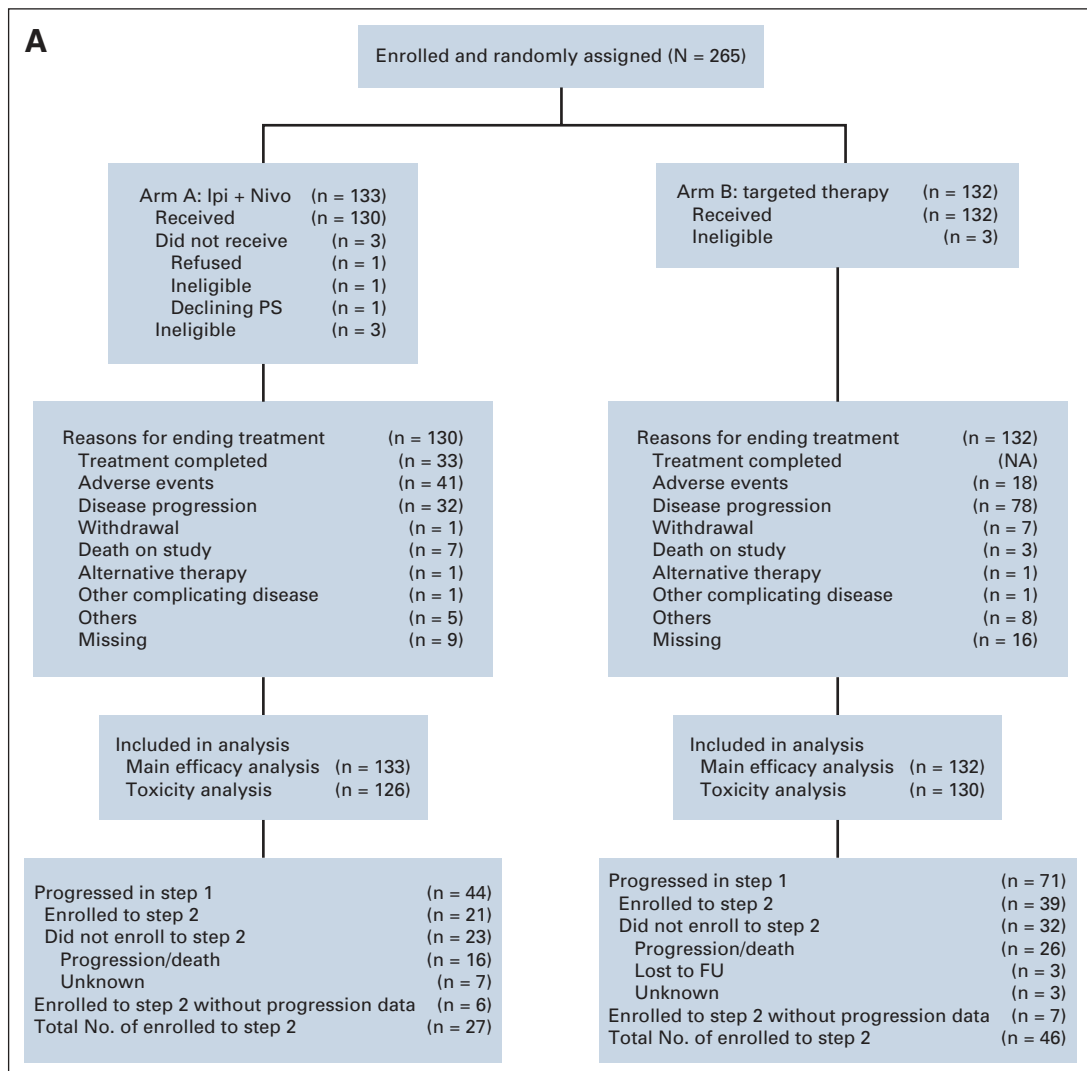

FIG 1. CONSORT diagrams for (A) step 1—initial random assignment and (B) step 2—crossover enrollment. [a]All cases with data included. FU, follow-up; Ipi, ipilimumab; NA, not applicable; nivo, nivolumab; PS, performance status. (continued on following page)
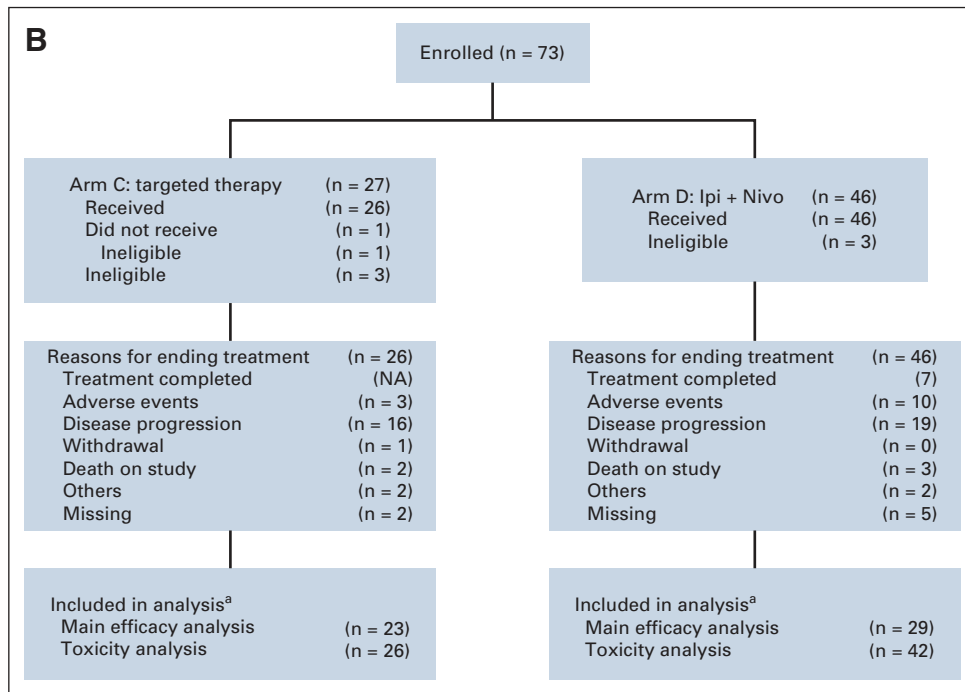
B

Enrolled (n = 73)

Arm C: targeted therapy	(n = 27)
Received	(n = 26)
Did not receive	(n = 1)
Ineligible	(n = 1)
Ineligible	(n = 3)

Arm D: Ipi + Nivo	(n = 46)
Received	(n = 46)
Ineligible	(n = 3)

Reasons for ending treatment	(n = 26)
Treatment completed	(NA)
Adverse events	(n = 3)
Disease progression	(n = 16)
Withdrawal	(n = 1)
Death on study	(n = 2)
Others	(n = 2)
Missing	(n = 2)

Reasons for ending treatment	(n = 46)
Treatment completed	(7)
Adverse events	(n = 10)
Disease progression	(n = 19)
Withdrawal	(n = 0)
Death on study	(n = 3)
Others	(n = 2)
Missing	(n = 5)

Included in analysis[a]	
Main efficacy analysis	(n = 23)
Toxicity analysis	(n = 26)

Included in analysis[a]	
Main efficacy analysis	(n = 29)
Toxicity analysis	(n = 42)

FIG 1. (Continued).

protocol-specified comparison of 2-year OS rates by the Mantel-Haenszel chi-square test did not cross the efficacy boundary ($P = .163$); however, 2-year OS rates from a Kaplan-Meier analysis indicated a significant difference and crossed the O'Brien Fleming boundary at 59% information time. Furthermore, the 95% repeated CI around the 2-year OS difference remained positive (95% CI, 2.6% to 37.9%). Therefore, the DSMC deemed this difference in OS to be clinically meaningful and recommended that the study be closed to accrual and patients currently on arm B be given the option to switch to arm D without the need for disease progression. Three-year OS rates continued to favor those beginning with nivolumab/ipilimumab (Table 2).

Twenty-four patients had earlier death (< 10 months) on arm A relative to arm B (Fig 2A). These individuals tended to have poor prognostic features relative to the general study population, received limited treatment either because of early disease progression or toxicity, and none successfully crossed over to arm C. Similarly, the 25 patients who died within 10 months on arm B tended to have more aggressive disease at baseline and limited (only 20%) crossover to immunotherapy (arm D). However, these patients tended to stop step 1 treatment because of disease progression, particularly in the brain, compared with those on the immunotherapy-first sequence (Data Supplement).

Table 3 presents the 2-year OS rates in relevant patient subsets. Data are presented graphically in the Data Supplement. A forest plot was not felt to be applicable because of nonproportional hazards for OS between the arms. For all subsets, including those with *BRAFV600E* and *K*-mutant tumors, OS was numerically better for the sequence

beginning with nivolumab/ipilimumab. Of note, even in the group resembling those for whom dabrafenib/trametinib is purported to do best (those with performance status 0, normal LDH, and lower stage, perhaps a surrogate for < 3 disease sites), starting with nivolumab/ipilimumab showed a trend for improved OS.

PFS curves for step 1 also exhibited a biphasic pattern with the curves crossing at 6 months and then nivolumab/ipilimumab showing increasing benefit till the 2-year time point (Fig 2B). Median PFS favored nivolumab/ipilimumab (11.8 months [95% CI, 5.9 to 33.5] v 8.5 months [95% CI, 6.5 to 11.3] [$P = .054$, log-rank]). The 2-year PFS rates were 41.9% (95% CI, 31.2 to 52.3) for arm A versus 19.2% (95% CI, 12.1 to 27.5) for arm B (Table 2). Median PFS for step 2 was 9.9 months (95% CI, 8.3 to 20.8) in arm C and 2.9 months (95% CI, 2.6 to 8.9) in arm D.

ORRs were similar between the step 1 regimens and for dabrafenib/trametinib whether used in step 1 or step 2 (Table 2). By contrast, nivolumab/ipilimumab appeared less effective after progression on dabrafenib/trametinib than first-line. Among the patients in step 1 who had a response to therapy, median duration of response was significantly longer for nivolumab/ipilimumab (NR [29.3, NR]) than for dabrafenib/trametinib (12.7 months [8.2, NR] [$P < .001$; Fig 2C). Of note, 37 of 42 nivolumab/ipilimumab responders remain in response, while 19 of 37 dabrafenib/trametinib responders have progressed.

Feasibility of Crossover

Data were submitted on 115 of 145 patients who had experienced disease progression. Of these, 60 (52%) had

TABLE 1. Demographics of Step 1 Population

Characteristic	Arm A (n = 133)	Arm B (n = 132)
Age, years		
Median (range)	61 (25-85)	61 (30-84)
Sex, No. (%)		
Male	81 (60.9)	86 (65.2)
Female	52 (39.1)	46 (34.8)
Race, No. (%)		
White	127 (95.5)	126 (95.5)
Non-White	6 (4.5)	6 (4.5)
Ethnicity, No. (%)		
Hispanic	2 (1.5)	6 (4.5)
Non-Hispanic	127 (95.5)	120 (90.9)
Unknown/missing	4 (3.0)	6 (4.5)
ECOG PS, No. (%)		
0	90 (67.8)	89 (67.4)
1	43 (32.2)	43 (32.6)
Stage, No. (%)[a]	n = 130	n = 130
III unresectable	9 (6.9)	17 (13.1)
M1A	16 (12.3)	14 (10.7)
M1B	24 (18.5)	23 (17.7)
M1C	81 (62.3)	76 (58.5)
LDH, No. (%)		
> ULN	53 (39.9)	53 (40.1)
Normal	80 (60.1)	79 (59.9)
BRAF mutation, No. (%)	n = 132	n = 131
V600E	108 (81.8)	89 (67.9)
V600K	16 (12.1)	33 (25.2)
Other	8 (6.1)	9 (6.9)
Prior treatment (adjuvant),[b] No. (%)	16 (12.0)	21 (15.9)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; M, metastasis.

[a]AJCC v7. Only four subjects had a history of brain metastases (three were on arm B).

[b]Almost all interferon.

registered to step 2: 21 of 44 (48%) from arm A and 39 of 71 (55%) from arm B. The median time from disease progression to crossover was 20 days (range, 5-83 days) for arm A to arm C and 21 days (range, 7-109 days) for arm B to arm D. Reasons for not registering to step 2 by initial treatment arm are provided in the Data Supplement. The majority of patients on each arm who did not register to step 2 died within 6 months of step 1 progression (arm A = 65.2%, arm B = 78.1%), many because of brain metastases.

Safety

The incidence of grade ≥ 3 treatment-related adverse events was 59.5% in arm A, 53.1% in arm B, 53.8% in arm C, and 50.0% in arm D (Table 4). Toxicity profiles were as previously reported for the specific regimens.[1,18] The differences in grade ≥ 3 treatment-related AEs in arm A versus B (step 1) and C versus D (step 2) were not significant, although numerically more grade 4 toxicities were seen in arm A. Treatment-related AEs on arms A and D were primarily immune-related and for arms B and C were primarily fevers, leukopenia, and hyponatremia. There were two treatment-related deaths on arm A (myocarditis and colitis), one on arm B (cerebral vascular event), and one on arm C (thromboembolic event). All grade toxicity is displayed in the Data Supplement.

The summary of treatment is shown in the Data Supplement. Median duration of treatment on arm A was 8.9 weeks (range < 1-86.9 weeks) and arm B was 28.5 weeks (range, 3.7-192.1 weeks). The principal reason for stopping treatment on arms B, C, and D was disease progression, whereas for arm A, treatment was halted in relatively equal parts for toxicity, treatment completion, and disease progression (Data Supplement). Of note, no patient in the current database had received the alternate immunotherapy induction regimen.

DISCUSSION

On the basis of this prospectively randomized phase III trial, the sequence of therapy commencing with nivolumab/ipilimumab followed by dabrafenib/trametinib is associated with greater 2-year OS than the inverse sequence. In all clinical subgroups examined (age, sex, ECOG PS, LDH level, or disease stage), including those purported to have the best outcomes with BRAF-targeted therapy[5,6] or the worst outcomes with immunotherapy,[19] at least a trend toward better 2-year OS for the nivolumab/ipilimumab initial sequence was seen. Thus, these clinical variables do not identify a population that should receive BRAF-targeted therapy as initial treatment.

OS for the nivolumab/ipilimumab first sequence was initially inferior to that for the dabrafenib/trametinib first sequence, with 24 patients (18%) dying within the first 10 months of starting immunotherapy. This population was notable for having relatively more aggressive disease and receiving less therapy (median one cycle) than the study population as a whole. Although this observation might suggest that patients with more aggressive disease should receive BRAF/MEK inhibitor therapy first (even for a brief course as was tested in the SECOMBIT trial[20] or is being further explored in the EBIN EORTC trial NCT03235245), the fact that none of these patients were able to enroll onto step 2 suggests that this rapid demise was as much a result of the relatively strict protocol eligibility criteria for crossover (eg, progressive disease confirmed by RECISTv1.1, minimum 2-week wait following disease progression, resolution of irAEs to grade ≤ 1, and treatment of brain metastases) as of disease biology. Therefore, rather than subjecting all patients with aggressive disease to initial BRAF/MEK-targeted therapy, better therapeutic outcomes might be attained by lowering
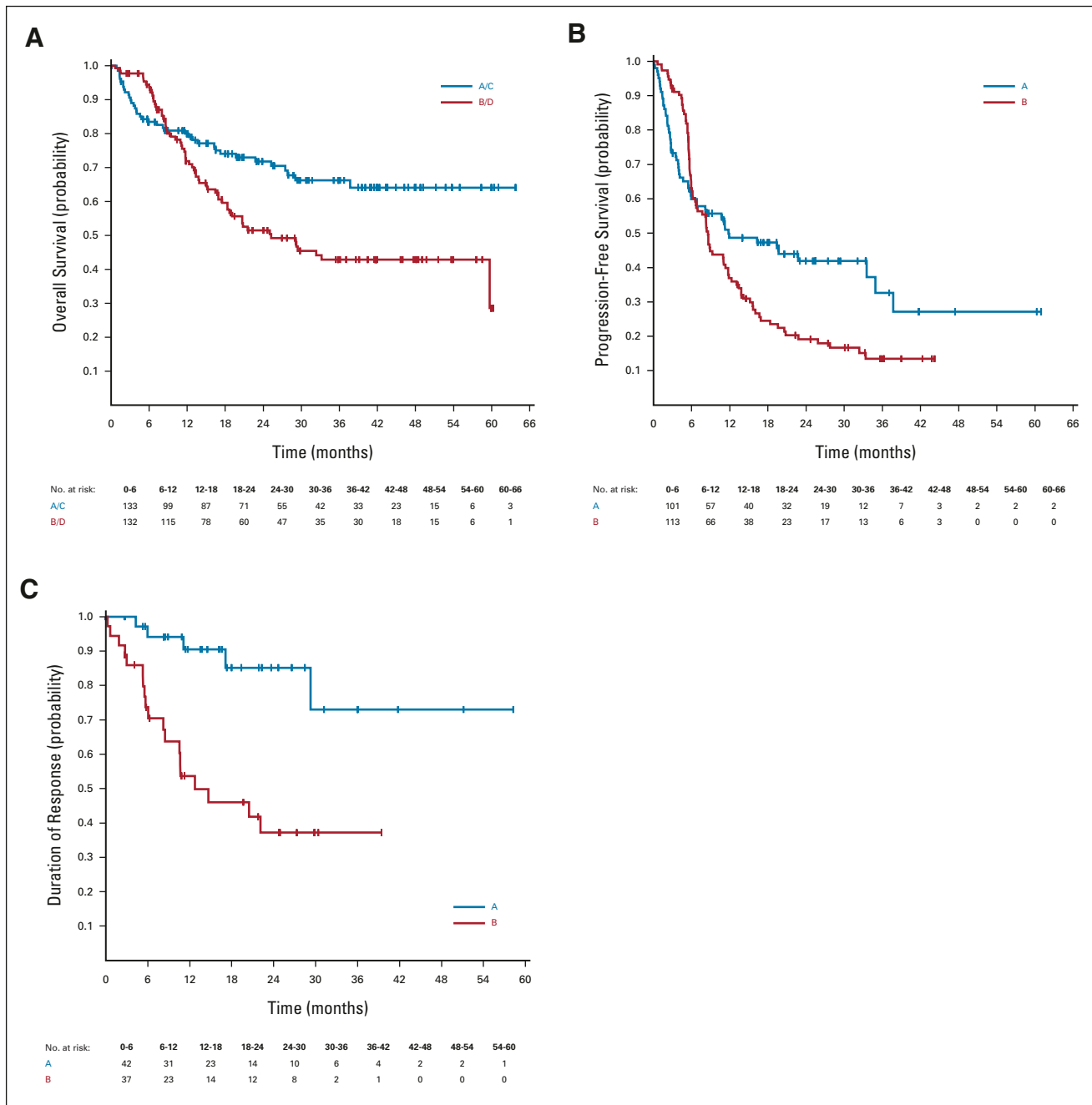
FIG 2. (A) Kaplan-Meier curve of overall survival for the two treatment sequences; (B) Kaplan-Meier curve of progression-free survival for the step 1 regimens; (C) Kaplan-Meier curve of duration of response on the step 1 regimens.

the threshold for switching to second-line therapy in those who appear not to be responding to frontline immunotherapy. Alternatively, correlative studies on baseline tumor tissue or blood analyzed for circulating tumor DNA early in the course of therapy may identify patients for whom earlier application of BRAF-targeted therapy might be beneficial.

Similarly, patients on the dabrafenib/trametinib first sequence who died within 10 months tended to have more aggressive disease at baseline and limited crossover to immunotherapy (arm D), frequently because of disease

progression within the CNS. As combination nivolumab/ipilimumab has shown antitumor activity against asymptomatic brain metastases roughly equivalent to its activity against extracranial disease,[21] prevention of isolated CNS relapse in systemic responders may be an important contributor to the benefit of the immunotherapy first sequence.

Other reasons for the superiority of immunotherapy first sequence were the durability of responses to frontline nivolumab/ipilimumab (88% of the responses ongoing compared with < 50% with dabrafenib/trametinib) and the

TABLE 2. Efficacy End Points

End Point	Treatment	
Primary end point		
2-year overall survival rate (95% CI)	Starting with arm A (n = 133) 71.8% (62.5 to 79.1)	Starting with arm B (n = 132) 51.5% (41.7 to 60.4)
Difference in 2-year overall survival between sequences	20.3% (95% repeated CI [2.6% to 37.9%] at 59% information time, log-rank *P* value = .010)	
Secondary end point		
2-year PFS rate (95% CI)	Step 1—arm A (n = 133) 41.9% (31.2 to 52.3)	Step 1—arm B (n = 132) 19.2% (12.1 to 27.5)
Median PFS, months (95% CI)	Step 1—arm A (n = 133) 11.8 (5.9 to 33.5)	Step 1—arm B (n = 132) 8.5 (6.5 to 11.3)
	Step 1 PFS: Log-rank *P* value = .054	
	Step 2—arm C (n = 27) 9.9 (8.3 to 20.6)	Step 2—arm D (n = 46) 2.9 (2.6 to 8.9)
ORR (95% CI)	Step 1—arm A (n = 113) 46.0% (36.6 to 55.6)	Step 1—arm B (n = 114) 43.0% (33.8 to 52.6)
	Step 1 ORR: Fisher's exact test *P* value = .690	
	Step 2—arm C (n = 23) 47.8% (26.8 to 69.4)	Step 2—arm D (n = 29) 29.6% (12.7 to 47.2)
Median duration of response, months	Step 1—arm A (n = 42) NR (29.3, NR)	Step 1—arm B (n = 37) 12.7 (8.2, NR)
	Step 1 response duration: Log-rank *P* value < .001	
3-year overall survival rate (95% CI)	Starting with arm A (n = 133) 66.2% (56.0 to 74.6)	Starting with arm B (n = 132) 42.8% (32.9 to 52.4)

Abbreviations: NR, not reached; ORR, objective response rate; PFS, progression-free survival.

comparable efficacy of BRAF-targeted therapy (in contrast to immunotherapy) in the second-line setting. This latter finding is supported by the results of the SECOMBIT trial, where the ORR for nivolumab/ipilimumab in the frontline was 45% versus 25% following disease progression on BRAF-targeted therapy[20] as well as some retrospective analyses.[13] In addition, recent tumor biology studies suggest that resistance to BRAF/MEK-inhibitor therapy results in an immunosuppressive tumor microenvironment that lacks functional CD103+ dendritic cells, preventing effective antigen presentation to the immune system[22] and that immunotherapy may actually enhance *BRAF*-mutated melanoma responsiveness to targeted therapy.[23]

Another approach to the treatment of patients with *BRAF*-mutated metastatic melanoma has been to combine BRAF/MEK inhibitors with programmed cell death protein 1 (PD-1)–pathway inhibitors. Studies of triplet regimens have shown either a trend or a statistically significant improvement in median PFS compared with combination BRAF/MEK inhibitors[24-26] and the FDA has approved the combination of vemurafenib, cobimetinib, and atezolizumab. However, the results of the DREAMseq trial suggest that a more appropriate comparison for these regimens would be nivolumab/ipilimumab followed by BRAF/MEK-targeted therapy as well as providing data that

inform the design of such a trial. Furthermore, cross-trial comparisons suggest that these triplet regimens would not exceed the 2-year landmark PFS seen with nivolumab/ipilimumab—and given the lack of an established effective second-line therapy for those with disease progression, would likely have inferior OS at and beyond 2 years.

Nivolumab/ipilimumab was administered safely and effectively in a cooperative group trial setting with toxicity profile similar to what has been previously reported including two deaths from irAEs.[18] Although toxicity profiles differ greatly between the two regimens in the DREAMseq study, the incidence of grade ≥ 3 toxicities were similar between treatment arms, as well as within each treatment approach whether used in the frontline or second-line. Although severe toxicities from immunotherapy frequently required early treatment cessation, they were not associated with more treatment-related mortality and most importantly, did not appear to negatively affect patient OS. In fact, several analyses suggest that irAEs to nivolumab/ipilimumab therapy are associated with better efficacy.[27,28] These findings should encourage physicians and patients to consider nivolumab/ipilimumab as the preferred immunotherapy in patients with *BRAF*-mutant melanoma and be confident that even when treatment needs to be held or stopped because of toxicity, there remains a realistic likelihood of sustained melanoma control.

TABLE 3. Two-Year OS Rate by Subgroup

| Factor | Subgroup | 2-Year OS Rate, % (95% CI) | | P (Log-Rank) |
		Arm A/Arm C	Arm B/Arm D	
Age, years	< 40	(n = 12) 90.9 (50.8 to 98.7)	(n = 17) 36.3 (12.6 to 60.8)	.053
	40-60	(n = 60) 77.8 (64.1 to 86.8)	(n = 46) 56.9 (40.5 to 79.3)	.136
	> 60	(n = 61) 62.5 (47.8 to 74.2)	(n = 69) 51.6 (37.5 to 64.0)	.221
ECOG PS	0	(n = 90) 78.1 (67.4 to 85.6)	(n = 89) 54.9 (43.0 to 65.2)	.011
	1	(n = 43) 57.1 (38.2 72.2)	(n = 43) 44.3 (26.9 to 60.3)	.394
Sex	Male	(n = 81) 70.3 (57.9 79.7)	(n = 86) 49.0 (37.0 to 60.0)	.044
	Female	(n = 52) 74.0 (58.5 to 84.5)	(n = 46) 56.5 (39.3 70.5)	.181
BRAF mutation	*V600E*	(n = 108) 71.4 (60.9 to 79.5)	(n = 89) 43.9 (37.5 to 60.2)	.020
	V600K	(n = 16) 80.3 (50.1 to 93.2)	(n = 33) 53.2 (32.9 to 69.9)	.075
	V600 (not defined)	(n = 8) 60.0 (19.6 to 85.2)	(n = 9) 66.7 (28.2 to 87.3)	.461
LDH	> ULN	(n = 53) 57.3 (41.0 to 70.6)	(n = 53) 32.5 (18.3 to 47.6)	.174
	Normal	(n = 80) 80.5 (69.1 to 88.0)	(n = 79) 61.8 (49.3 72.0)	.035
Stage	< M1c	(n = 49) 81.1 (65.3 to 90.2)	(n = 54) 57.1 (40.5 to 70.6)	.099
	M1c	(n = 81) 66.9 (54.6 to 76.6)	(n = 76) 47.2 (34.8 to 58.6)	.033
Favorable? PS = 0, LDH = WNL, < M1c	Yes	(n = 30) 86.2 (67.3 to 94.6)	(n = 34) 54.1 (35.0 to 69.8)	.059
	No	(N = 100) 67.4 (56.1 to 76.4)	(n = 96) 49.8 (38.1 to 60.4)	.045

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; M, metastasis; OS, overall survival; PS, performance status; ULN, upper limit of normal; WNL, within normal limits.

Study limitations include slow accrual (265 patients over 6 years), which may have skewed the study population toward those with worse prognosis and *V600K*-mutated tumors relative to prior industry-sponsored trials[3] and contributed to the lower-than-anticipated efficacy seen on all arms of the study, especially arm B. However, this concern is mitigated by (1) a median PFS of 8.8 months and a 52% 2-year OS result for patients starting with BRAF-targeted therapy, which closely align with the results of the combined dabrafenib/trametinib arms of the COMBI-D and COMBI-V trials[3] and (2) subset analyses showing that all patient subsets had numerically higher 2-year OS with the immunotherapy first sequence. Given these other efficacy similarities, the most likely reason for the lower-than-anticipated ORR in arm B is the delay in initial response assessment from 8 to 12 weeks to match the typical response assessments used for anti-PD-1–based trials. A second limitation relates to the crossover rate of only 52%. This may be due to the higher-risk patient population and frequent CNS progression mentioned above, but also might reflect issues that distinguish clinical trial design from clinical practice, eg, the need to document progressive disease on step 1 to obtain PFS data and for patients to meet eligibility criteria related to safety before enrolling in step 2. As feasibility of crossover was a secondary end point in this trial, we conclude that crossover to the alternative therapy is frequently not feasible, at least in the context of a clinical trial, further emphasizing the need to choose the best initial therapy. Nonetheless, as the inability to crossover was roughly balanced between the two sequences, and patients who did not crossover within the trial likely received the best off-protocol therapy available to them (which included the treatment approach proposed in the trial), this limitation is unlikely to have affected the primary

TABLE 4. Toxicity by Treatment Arm[a]

| | Treatment Arm | | | | | | | | | | | |
| | A (n = 126) Grade, % | | | B (n = 130) Grade, % | | | C (n = 26) Grade, % | | | D (n = 42) Grade, % | | |
Toxicity Type	3	4	5	3	4	5	3	4	5	3	4	5
Anemia	2	—	—	4	—	—	—	—	—	2	—	—
Disseminated intravascular coagulation	—	1	—	—	—	—	—	—	—	—	—	—
Cardiac disorders—other, specify	—	1	—	1	—	—				—		
Endocrine disorders—other, specify[b]	2	1	—	—	—	—	—	—	—	5	—	—
Colitis[b]	6	—	1	—	—	—	—	—	—	—	—	—
Diarrhea[b]	17	1	—	2	—	—	4	—	—	2	—	—
Enterocolitis[b]	3	—	—	—	—	—	—	—	—	—	—	—
Nausea	6	—	—	—	—	—	4	—	—	—	—	—
Vomiting	3	—	—	2	—	—	4	—	—	—	—	—
Pancreatitis	1	—	—	—	—	—	—	—	—	5	—	—
Fatigue	8	—	—	6	—	—	4	—	—	7	—	—
Fever[c]	1	—	—	7	—	—	8	—	—	2	—	—
Sepsis	—	2	—	—	1	—	—	4	—	—	—	—
Alanine aminotransferase increased[b]	5	2	—	2	—	—	—	—	—	5	—	—
Aspartate aminotransferase increased[b]	6	1	—	2	—	—	—	—	—	5	—	—
Bilirubin increased	1	2	—	—	—	—	—	—	—	—	—	—
CPK increased	—	—	—	—	1	—	—	—	—	—	—	—
Lipase increased	5	8	—	5	2	—	4	—	—	2	5	—
Lymphopenia[c]	1	—	—	2	—	—	8	—	—	5	—	—
Neutropenia[c]	—	—	—	5	1	—	—	—	—	2	—	—
Serum amylase increased	6	1	—	—	1	—	4	—	—	2	—	—
White blood cell decreased	—	—	—	2	1	—	—	—	—	—	—	—
Ejection fraction decreased	—	—	—	4	—	—	4	—	—	—	—	—
Dehydration	3	—	—	2	—	—	4	—	—	2	—	—
Hypernatremia	—	—	—	—	—	—	4	—	—	—	—	—
Hypocalcemia	—	—	—	—	—	—	4	—	—	—	—	—
Hyperglycemia	2	1	—	2	—	—	—	—	—	—	—	—
Hyponatremia[c]	3	—	—	6	1	—	12	—	—	2	—	—
Arthralgia[b]	6	—	—	1	—	—	—	—	—	2	—	—
Generalized muscle weakness	2	—	—	—	—	—	4	—	—	—	—	—
Dyspnea	1	—	—	—	—	—	—	—	—	—	2	—
Syncope	—	—	—	2	—	—	4	—	—	2	—	—
Acute kidney injury	2	—	—	—	—	—	4	—	—	—	—	—
Adult distress syndrome	—	1	—	—	—	—	—	—	—	—	—	—
Rash maculopapular	7	—	—	5	—	—	12	—	—	—	—	—
Hypotension	3	—	—	2	—	—	4	—	—	2	—	—
Thromboembolic event	—	—	—	2	—	—	—	—	4	—	—	—
Myocarditis	—	—	1	—	—	—	—	—	—	—	—	—
Cerebral vascular event	—	—	—	—	—	1	—	—	—	—	—	—
Worst degree	45	13	2	47	5	1	46	4	4	43	7	0

Abbreviation: CPK, creatinine phosphokinase.
[a]Limited to toxicities reported in > 3% of subjects on either arm or with any grade 4 or 5 events.
[b]More for arm A and/or D.
[c]More for arm B and/or C.

trial end point of 2-year OS. Finally, the sequencing conclusions of this trial may not apply to patients treated with other immunotherapy regimens or to patients who have received adjuvant anti–PD-1, anti–cytotoxic T-cell lymphocyte-4, or BRAF/MEK inhibitor therapy.

We conclude that in this population with an oncogene-driven tumor and effective targeted therapy available, combination nivolumab/ipilimumab followed by BRAF/MEK inhibitor therapy, if necessary, should be the preferred treatment sequence for a majority of patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients With Advanced *BRAF*-Mutant Melanoma: The DREAMseq Trial—ECOG-ACRIN EA6134

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Jeffrey A. Sosman
Honoraria: Jazz Pharmaceuticals, Apexian Pharmaceuticals, Iovance Biotherapeutics
Consulting or Advisory Role: Apexigen, Jazz Pharmaceuticals, Iovance Biotherapeutics

Andrew L. Pecora
Employment: Regional Cancer Care Associates, Cota Healthcare, Celularity Inc
Leadership: Regional Cancer Care Associates, Cota Healthcare
Stock and Other Ownership Interests: Regional Cancer Care Associates, Cota Healthcare, Celularity Inc
Honoraria: Bristol Myers Squibb
Consulting or Advisory Role: Bristol Myers Squibb
Speakers' Bureau: Bristol Myers Squibb
Research Funding: Bristol Myers Squibb (Inst)
Patents, Royalties, Other Intellectual Property: Cd34 patents COTA patents
Travel, Accommodations, Expenses: Bristol Myers Squibb

Sunandana Chandra
Honoraria: Bristol Myers Squibb, Array BioPharma, EMD Serono, Novartis, Pfizer, Sanofi/Regeneron, Exicure
Consulting or Advisory Role: Bristol Myers Squibb, EMD Serono, Array BioPharma, Novartis, Pfizer, Sanofi/Regeneron, Exicure
Research Funding: Bristol Myers Squibb Foundation (Inst), Novartis (Inst), Pfizer (Inst), Exicure (Inst), EMD Serono (Inst), Sanofi/Regeneron (Inst)

Jedd D. Wolchok
Stock and Other Ownership Interests: Tizona Therapeutics, Inc, Imvaq Therapeutics, Beigene, Linnaeus Therapeutics, Arsenal IO, Georgiamune, Apricity Therapeutics, Maverick Therapeutics, Trieza Therapeutics, Ascentage Pharma
Consulting or Advisory Role: Bristol Myers Squibb, Sellas Life Sciences, Tizona Therapeutics, Inc, Amgen, Ascentage Pharma, PsiOxus Therapeutics, Surface