First-Line, Fixed-Duration Nivolumab Plus Ipilimumab Followed by Nivolumab in Clinically Diverse Patient Populations With Unresectable Stage III or IV Melanoma: CheckMate 401

Reinhard Dummer, MD[1]; Pippa Corrie, PhD, FRCP[2]; Ralf Gutzmer, MD[3,4]; Tarek M. Meniawy, MD, PhD[5]; Michele Del Vecchio, MD[6]; Céleste Lebbé, MD, PhD[7]; Michele Guida, MD[8]; Caroline Dutriaux, MD[9]; Brigitte Dreno, MD, PhD[10]; Nicolas Meyer, MD, PhD[11]; Pier Francesco Ferrucci, MD[12]; Stéphane Dalle, MD, PhD[13]; Muhammad Adnan Khattak, MD[14,15]; Jean-Jacques Grob, MD, PhD[16]; Karen Briscoe, MD[17]; James Larkin, MD, PhD[18]; Sandrine Mansard, MD[19]; Thierry Lesimple, MD, MSc[20]; Massimo Guidoboni, MD[21]; Silvia Sabatini, MD[22]; Erika Richtig, MD[23]; Rudolf Herbst, MD[24]; Maurice Lobo, PharmD[25]; Margarita Askelson, MSc[25]; Paolo A. Ascierto, MD[26]; and Michele Maio, MD[27]

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ABSTRACT

PURPOSE To address the paucity of data in patients with historically poor outcomes, we conducted the single-arm phase IIIb CheckMate 401 study to evaluate the safety and efficacy of nivolumab plus ipilimumab followed by nivolumab monotherapy in clinically diverse patient populations with advanced melanoma.

METHODS Treatment-naive patients with unresectable stage III-IV melanoma received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks (four doses) followed by nivolumab 3 mg/kg (240 mg following a protocol amendment) once every 2 weeks for ≤24 months. The primary end point was the incidence of grade 3-5 select treatment-related adverse events (TRAEs). Overall survival (OS) was a secondary end point. Outcomes were evaluated in subgroups defined by Eastern Cooperative Oncology Group performance status (ECOG PS), brain metastasis status, and melanoma subtype.

RESULTS In total, 533 patients received at least one dose of study drug. Grade 3-5 select TRAEs affecting the GI (16%), hepatic (15%), endocrine (11%), skin (7%), renal (2%), and pulmonary (1%) systems occurred in the all-treated population; similar incidence rates were observed across all subgroups. At 21.6 months' median follow-up, 24-month OS rates were 63% in the all-treated population, 44% in the ECOG PS 2 subgroup (including patients with cutaneous melanoma only), 71% in the brain metastasis subgroup, 36% in the ocular/uveal melanoma subgroup, and 38% in the mucosal melanoma subgroup.

CONCLUSION Nivolumab plus ipilimumab followed by nivolumab monotherapy was tolerable in patients with advanced melanoma and poor prognostic characteristics. Efficacy was similar between the all-treated population and patients with brain metastases. Reduced efficacy was observed in patients with ECOG PS 2, ocular/uveal melanoma, and/or mucosal melanoma, highlighting the continued need for novel treatment options for these difficult-to-treat patients.

ACCOMPANYING CONTENT

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INTRODUCTION

Advances in immunotherapy have revolutionized clinical outcomes in patients with advanced melanoma.[1] Nivolumab plus ipilimumab followed by nivolumab monotherapy was shown to prolong overall survival (OS) and progression-free survival (PFS) versus ipilimumab monotherapy in treatment-naive patients with advanced melanoma in the phase III CheckMate 067 trial.[2,3] Clinical benefit was sustained as of the 7.5-year trial update (7.5-year OS rate, 48%; 7.5-year PFS rate, 33%).[4] However, combination treatment was associated with increased toxicity; grade 3-4 treatment-related adverse events (TRAEs) were reported in 59% of patients treated with the combination, 24% of those receiving nivolumab, and 28% of those receiving ipilimumab.[5]

Although clinical trials have demonstrated clinical benefit with immunotherapy in patients with advanced melanoma,

CONTEXT

Key Objective

Although previous studies demonstrated clinical benefit with immunotherapy in patients with advanced melanoma, there is a paucity of data in patients with poor prognoses who are typically excluded from clinical trials. CheckMate 401, a single-arm phase IIIb trial, evaluated the safety and efficacy of first-line nivolumab plus ipilimumab followed by nivolumab in clinically diverse patient populations with unresectable stage III-IV melanoma representative of real-life practice.

Knowledge Generated

Nivolumab plus ipilimumab followed by nivolumab administered for ≤24 months was tolerable, regardless of Eastern Cooperative Oncology Group performance status (ECOG PS), brain metastasis status, and melanoma subtype; reduced efficacy was observed in patients with ECOG PS 2, ocular/uveal melanoma, and/or mucosal melanoma.

Relevance *(G.K. Schwartz)*

Despite advances in the treatment of cutaneous melanoma, new treatment approaches are desperately needed to treat patients with rare forms of this disease such as acral/mucosal and uveal melanoma and those patients with poor performance status.*

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

these trials generally excluded patients with poor prognoses, such as those with ocular/uveal melanoma, brain metastases, or Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2.[6] The exclusion of such patients from melanoma clinical trials has resulted in a paucity of data regarding outcomes with immunotherapy in those who typically have poorer prognoses. The phase IIIb CheckMate 401 study (ClinicalTrials.gov identifier: NCT02599402) aimed to address this gap by characterizing the safety and efficacy of first-line nivolumab plus ipilimumab followed by nivolumab monotherapy in clinically diverse patient populations with unresectable stage III-IV melanoma. Here, we report final safety and efficacy results, including key patient subgroup analyses.

METHODS

Trial Design

CheckMate 401 was a multinational, single-arm, phase IIIb trial (Data Supplement [Fig A1], online only) performed in accordance with the Declaration of Helsinki and Good Clinical Practice as defined by the International Council for Harmonisation. The trial Protocol (online only) and amendments were approved by the institutional review board at each site. Patients provided written informed consent before initiating trial procedures.

Patients

Treatment-naive adult patients with measurable, histologically confirmed, unresectable stage III-IV melanoma (per American Joint Committee on Cancer seventh edition [AJCC-7]) and an ECOG PS ≤2 were eligible for enrollment, including patients with cutaneous, ocular/uveal, mucosal, or acral melanoma and/or those with asymptomatic brain metastases, regardless of *BRAF* mutation status. Additional eligibility criteria are provided in the Data Supplement (Supplemental Methods).

Treatments and Assessments

Initially, patients received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks for four doses (induction phase), followed by nivolumab 3 mg/kg once every 2 weeks for ≤24 months (or ≤50 cycles if treatment was temporarily discontinued) from the first combination dose or until disease progression or development of unacceptable toxicity (maintenance phase). After a protocol amendment, the maintenance phase dosing regimen was changed to nivolumab 240 mg once every 2 weeks because simulated population pharmacokinetic and exposure-response analyses predicted similar activity between nivolumab 240 mg and 3 mg/kg.[7,8]

The primary end point was the incidence of grade 3-5 (per Common Terminology Criteria for Adverse Events v4.0) select TRAEs (adverse events [AEs] of potentially immune-mediated etiology in the following categories: pulmonary, GI, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity). Secondary end points included time to select AE onset/resolution, OS, investigator-assessed objective response rate (ORR) and PFS, and safety and tolerability. Although the initial tumor assessment was performed using RECIST v1.1, subsequent assessments were performed per local standard of care or investigator discretion, limiting ORR and PFS evaluations. Given that the inconsistent timing of tumor assessments limited the reliability of time-to-event analyses, PFS will not be reported. After the collection of sufficient safety data, a protocol amendment shortened follow-up duration from 5 years to 2 years after treatment initiation.

Statistical Analysis

All end points were evaluated in the primary analysis (all-treated) population and predefined patient subgroups on the basis of ECOG PS, brain metastasis status, and melanoma subtype; efficacy analyses in the ECOG PS 2 subgroup were restricted to patients with cutaneous melanoma. Post hoc safety analyses were performed according to baseline age and lactate dehydrogenase (LDH). Post hoc efficacy analyses were performed according to baseline age, LDH (in the all-treated and *BRAF*-mutant melanoma populations), *BRAF* mutation status, and treatment-completion status. Two-sided 95% CIs for median OS were calculated using the Brookmeyer and Crowley method. The Clopper-Pearson method was used to calculate binomial ORRs and corresponding two-sided 95% CIs. Sample size calculations and methods for determining exposure-adjusted TRAEs are provided in the Data Supplement (Supplemental Methods). Analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients

Of 637 patients enrolled between December 2015 and August 2017, 533 received at least one dose of study drug (all-treated population; Data Supplement [Fig A2]). Among patients in the all-treated population, 10% had ECOG PS 2; 20% had ocular/uveal, mucosal, or acral melanoma; 12% had *other melanoma*; 44% had LDH >upper limit of normal (ULN); and 8% had brain metastases (5% previously treated; 3% untreated) at baseline (Table 1). Baseline characteristics by age, LDH, and treatment-completion status, and information on hepatic/extrahepatic involvement in patients with ocular/uveal melanoma are provided in the Data Supplement (Tables A1-A3).

As of the October 1, 2020, data cutoff, minimum study follow-up (from the first dose date of the last treated patient) was 27.3 months, and median OS follow-up (median time between the first dose and date of death/last known alive for all patients) was 21.6 months. During the induction phase, the median number of nivolumab plus ipilimumab doses received was four (range, 1-4), with 53% of the all-treated population receiving all four doses. In total, 45% of the all-treated population transitioned to the maintenance phase, including 12% who received one to three doses of combination therapy. Median duration of nivolumab plus ipilimumab treatment in the all-treated population was 2.4 months (95% CI, 2.1 to 2.8). All patients had discontinued treatment by the data cutoff date, with 84 patients completing 24 months of treatment (Data Supplement [Table A4]). The most common reasons for treatment discontinuation within the first 12 months of treatment were study drug toxicity (33%), disease progression (25%), and death (5%; Data Supplement [Table A5]). Overall, 193 patients (36%) received subsequent systemic therapy, including 106 (20%) who received immunotherapy and 57 (11%) who received combination BRAF/MEK inhibitors (Data Supplement [Table A6]). Most subsequent immunotherapy regimens (101/106; 95%) were anti–PD-1–based.

Safety

All patients experienced at least one all-cause AE, with the most common being diarrhea (43%), fatigue (34%), and nausea (29%; Data Supplement [Table A7]). Any-grade and grade 3-4 TRAEs were reported in 91% and 60%, respectively, of the all-treated population; similar frequencies were observed across predefined patient subgroups (Table 2). The most common any-grade TRAEs were diarrhea (35%), pruritus (25%), and fatigue (25%), while the most frequent grade 3-4 TRAEs were elevated lipase (8%), diarrhea (7%), and colitis (6%). In patients age younger than 75 years and patients age 75 years and older, grade 3-4 AE rates were 73% and 79%, any-grade TRAE rates were 91% and 92%, and grade 3-4 TRAE rates were 59% and 62%, respectively (Data Supplement [Tables A8 and A9]). Similar trends were observed in subgroups on the basis of LDH (≤ULN and >ULN). Exposure-adjusted TRAE incidence rates decreased from month 2 (approximately 2,250/100 patient-years) to month 4 (approximately 600/100 patient-years) and to month 28 (approximately 50/100 patient-years; Data Supplement [Fig A3]). AEs of special interest (eg, myocarditis, Guillain-Barré syndrome) occurred infrequently in the all-treated population, with the most common being uveitis (2%; Data Supplement [Table A10]). The most common immune-mediated endocrine AEs in the all-treated population were hypothyroidism (24%), hyperthyroidism (20%), and hypophysitis (11%), and the most common immune-mediated nonendocrine AEs were rash (25%), diarrhea/colitis (25%), and hepatitis (21%; Data Supplement [Table A11]).

Select TRAEs are reported in Table 3. Patients in the all-treated population reported any-grade select TRAEs affecting the skin (56%), endocrine (43%), GI (40%), hepatic (29%), renal (5%), and pulmonary (4%) systems. Grade 3-5 select TRAEs (the primary end point) affecting the GI (16%), hepatic (15%), endocrine (11%), skin (7%), renal (2%), and pulmonary (1%) systems were also reported in this population. The incidences of any-grade and grade 3-5 select TRAEs in the predefined subgroups are reported in Figure 1. Grade 5 select TRAEs occurred in one patient with cutaneous melanoma (acute kidney injury) and one patient with mucosal melanoma (colitis).

Median time to onset of any-grade and grade 3-5 select TRAEs ranged from 14 (skin) to 128 days (pulmonary) and from 31 (skin) to 76 days (endocrine), respectively (Fig 2). Median time to resolution of any-grade and grade 3-5 select TRAEs ranged from 20 days (GI) to not reached (NR; endocrine) and from 23 days (GI; renal) to NR (endocrine), respectively.

Altogether, 86% of the all-treated population required immunomodulating agents to manage AEs, with corticosteroids

TABLE 1. Baseline Characteristics in the All-Treated Population and Predefined Patient Subgroups

Characteristic	All Patients (N = 533)	Melanoma Subtype[a]				ECOG PS 2 (n = 55)	BM (n = 42)
		Cutaneous (n = 365)	Ocular/Uveal[b] (n = 64)	Mucosal (n = 32)	Acral (n = 10)		
Age, years, median (range)	59.0 (20-84)	58.0 (20-84)	63.0 (27-84)	64.0 (34-80)	67.5 (44-82)	55.0 (25-84)	54.5 (23-84)
Male, No. (%)	316 (59)	231 (63)	35 (55)	11 (34)	5 (50)	20 (36)	31 (74)
Region, No. (%)							
Europe	459 (86)	305 (84)	61 (95)	28 (88)	9 (90)	54 (98)	37 (88)
Australia	74 (14)	60 (16)	3 (5)	4 (12)	1 (10)	1 (2)	5 (12)
ECOG PS, No. (%)							
0	370 (69)	258 (71)	53 (83)	14 (44)	5 (50)	0	28 (67)
1	107 (20)	70 (19)	8 (12)	12 (38)	5 (50)	0	7 (17)
2	55 (10)	37 (10)	2 (3)	6 (19)	0	55 (100)	7 (17)
Not reported	1 (<1)	0	1 (2)	0	0	0	0
AJCC-7 M stage,[c] No. (%)							
M0, M1a, or M1b	143 (27)	140 (38)	—	—	3 (30)	8 (15)	0
M1c (with BM)	33 (6)	33 (9)	—	—	0	5 (9)	33 (79)
M1c (without BM)	196 (37)	189 (52)	—	—	7 (70)	24 (44)	0
Unknown/not reported	3 (1)	3 (1)	—	—	0	0	0
Treated BM, No. (%)	27 (5)	20 (5)	0	1 (3)	0	3 (5)	27 (64)
LDH level, No. (%)							
≤ULN	280 (53)	204 (56)	25 (39)	14 (44)	3 (30)	20 (36)	24 (57)
>ULN	237 (44)	150 (41)	35 (55)	18 (56)	6 (60)	34 (62)	18 (43)
Unknown/not reported	16 (3)	11 (3)	4 (6)	0	1 (10)	1 (2)	0
>2× ULN	78 (15)	48 (13)	13 (20)	6 (19)	2 (20)	19 (35)	8 (19)
BRAF status, No. (%)							
Mutant	175 (33)	155 (42)	1 (2)	4 (12)	2 (20)	15 (27)	18 (43)
Wild-type	291 (55)	188 (52)	26 (41)	26 (81)	7 (70)	33 (60)	22 (52)
Not reported	67 (13)	22 (6)	37 (58)	2 (6)	1 (10)	7 (13)	2 (5)
cKIT status, No. (%)							
Mutant	9 (2)	4 (1)	0	4 (12)	1 (10)	0	1 (2)
Wild-type	138 (26)	81 (22)	13 (20)	15 (47)	3 (30)	16 (29)	14 (33)
Not reported	386 (72)	280 (77)	51 (80)	13 (41)	6 (60)	39 (71)	27 (64)
Prior systemic treatment setting, No. (%)							
Adjuvant	50 (9)	38 (10)	3 (5)	1 (3)	0	0	5 (12)
Metastatic	2 (<1)	2 (1)	0	0	0	0	0
Patients with quantifiable PD-L1 at baseline,[d] No.	170	111	15	11	4	27	16
PD-L1 expression, No. (%)							
≥1%	67 (39)	43 (39)	6 (40)	3 (27)	0	7 (26)	10 (62)
<1%	103 (61)	68 (61)	9 (60)	8 (73)	4 (100)	20 (74)	6 (38)

NOTE. Percentages may not total 100 because of rounding.

Abbreviations: AJCC-7, American Joint Committee on Cancer seventh edition; BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PD-L1, programmed death ligand-1; ULN, upper limit of normal.

[a]Sixty-two patients (12%) were classified by investigators as having a melanoma subtype of *other melanoma*. Examples of *other melanoma* were melanoma of an unknown primary site, amelanotic melanoma, lentigo melanoma, meningeal melanoma, nodular melanoma, spitzoid melanoma, subcutaneous melanoma, superficial spreading melanoma, and vulvar melanoma.

[b]Case report forms did not capture conjunctival melanoma as a distinct melanoma subtype. Instead, patients with conjunctival melanoma were classified as having ocular/uveal melanoma.

[c]AJCC-7 M stage information specific to ocular/uveal and mucosal melanoma was not available. On the basis of reported baseline tumor lesion data, all patients had unresectable or metastatic disease, including 64/64 patients (100%) with ocular/uveal melanoma and 28/32 patients (88%) with mucosal melanoma who had metastatic (stage IV) disease; 4/32 patients (12%) with mucosal melanoma had locally advanced unresectable disease.

[d]Denominator for PD-L1 subgroups below.

(systemic or topical) being the most commonly used (80% and 30%, respectively; Data Supplement [Table A12]). GI and hepatic events were the most common causes of treatment discontinuation due to select TRAEs in the all-treated population (14% and 9%, respectively) and all predefined subgroups except for the acral melanoma subgroup in which only one patient (10%) discontinued treatment due to a select TRAE (Stevens-Johnson syndrome; Data Supplement [Table A13]).

Overall, 199 patients (37%) in the all-treated population died (Data Supplement [Table A14]). Most deaths (179/199; 90%) were attributed to melanoma, while five (3%) were due to study drug toxicity and/or grade 5 TRAEs (two due to myocarditis and one each due to aplastic anemia, acute kidney injury, and colitis).

Efficacy

At data cutoff, median OS was NR in the all-treated population (95% CI, 33.9 to NR; Fig 3); censoring within the first 12 months of treatment is provided in the Data Supplement (Table A15). The 24-month OS rate was 63% (95% CI, 59 to 68; Fig 3), and the ORR was 44% (95% CI, 40 to 49), with 11% of patients experiencing complete response (CR; Data Supplement [Table A16]). Among 237 responders in the all-treated population, median duration of response was NR.

Median OS was 11.0, NR, 15.3, 12.6, and 20.8 months in the ECOG PS 2 with cutaneous melanoma (n = 37), brain metastasis, ocular/uveal melanoma, mucosal melanoma, and acral melanoma subgroups, respectively (Fig 3). OS rates varied between these subgroups; 24-month OS rates were 44%, 71%, 36%, 38%, and 47%, respectively. Similarly, ORRs and CR rates varied between these subgroups, with ORRs being 30%, 52%, 9%, 44%, and 30%, and CR rates being 3%, 17%, 2%, 9%, and 0%, respectively (Data Supplement [Table A16]). Median duration of response was NR among responders in most subgroups, except for patients with ocular/uveal (11.5 months) or acral melanoma (5.6 months).

Post hoc analyses found that 24-month OS rates were 65% and 53% in patients age younger than 75 years and patients age 75 years and older, respectively; 74% and 49% in patients in the all-treated population with LDH ≤ULN and >ULN, respectively; 68% and 65% in patients with *BRAF*-mutant and wild-type disease, respectively; and 77% and 55% in patients who had *BRAF*-mutant melanoma with LDH ≤ULN and >ULN, respectively (Data Supplement [Table A17]). All patients who completed the 24-month treatment regimen were still alive at data cutoff (Data Supplement [Fig A4]).

DISCUSSION

To our knowledge, CheckMate 401 was the first phase III trial to assess the safety and efficacy of nivolumab plus ipilimumab followed by nivolumab monotherapy in clinically diverse patient populations with advanced melanoma that included patients with poor prognostic characteristics. No substantive differences in grade 3-5 select TRAEs were observed between the all-treated population and the patient subgroups, suggesting that patients with relatively poor prognoses were not at a greater risk of nivolumab/ipilimumab toxicity. Select TRAEs typically occurred within 3 months of treatment initiation, with the exception of pulmonary AEs, and were manageable with immunomodulating agents (most often corticosteroids). Efficacy data demonstrated clinical benefit with nivolumab plus ipilimumab followed by nivolumab monotherapy in the all-treated population. Although efficacy was comparatively poor in patients with ECOG PS 2, ocular/uveal melanoma, and/or mucosal melanoma (ie, patients with typically poor prognoses),[6,9] outcomes in patients with brain metastases were similar to those in the all-treated population.

CheckMate 401 differed in key ways from similar studies, such as CheckMate 067[4] and CheckMate 069 (a phase II study that assessed the safety and efficacy of nivolumab plus ipilimumab versus ipilimumab in treatment-naive patients with advanced melanoma).[10] To our knowledge, CheckMate 401 was the first study to evaluate nivolumab plus ipilimumab followed by nivolumab monotherapy for a fixed maximum duration of 24 months, whereas treatment duration was unrestricted in previous trials evaluating this regimen.[4,10] Furthermore, there were greater proportions of patients with ECOG PS 2 (10%), asymptomatic brain metastases (5% previously treated; 3% untreated), or ocular/uveal melanoma (12%) in CheckMate 401 than in either of the earlier studies,[2,10] suggesting that the present findings may have broader relevance in clinical practice.

Despite the differences in patient characteristics and treatment duration noted previously, the overall safety of nivolumab plus ipilimumab in CheckMate 401 was consistent with previous reports.[5,10] The relatively high incidence of select hepatic TRAEs in patients with ocular/uveal melanoma was expected because these patients often present with hepatic metastases.[11] With the exception of select endocrine TRAEs, time to select TRAE onset in CheckMate 401 was generally similar to that reported in pooled[12-14] and real-world analyses.[15,16] By contrast, select endocrine TRAEs in CheckMate 401 occurred sooner than those reported previously.[12-14,16] Further evaluation of nivolumab plus ipilimumab safety may be warranted because endocrinopathies are typically irreversible, thereby necessitating long-term hormone replacement therapy.[17,18]

OS in the CheckMate 401 all-treated population was consistent with that in CheckMate 067 and CheckMate 069.[3,10] When examined by patient subgroup, notable trends emerged in OS, especially when compared with findings of other studies, noting that between-study differences in trial design and patient characteristics limit substantial conclusions from being drawn. For example, median OS in the

TABLE 2. Treatment-Related Adverse Events in the All-Treated Population and Predefined Patient Subgroups

			Melanoma Subtype											
	All Patients (N = 533)		Cutaneous (n = 365)		Ocular/Uveal (n = 64)		Mucosal (n = 32)		Acral (n = 10)		ECOG PS 2 (n = 55)		BM (n = 42)	
Event	Any Grade,[a] No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)
Any	484 (91)	318 (60)	332 (91)	222 (61)	61 (95)	41 (64)	26 (81)	16 (50)	8 (80)	4 (40)	40 (73)	19 (35)	33 (79)	23 (55)
Diarrhea	186 (35)	38 (7)	127 (35)	27 (7)	26 (41)	4 (6)	8 (25)	3 (9)	3 (30)	0	14 (25)	3 (5)	10 (24)	4 (10)
Pruritus	134 (25)	2 (<1)	95 (26)	1 (<1)	12 (19)	0	10 (31)	0	3 (30)	0	11 (20)	1 (2)	10 (24)	0
Fatigue	133 (25)	3 (1)	96 (26)	1 (<1)	13 (20)	0	6 (19)	0	1 (10)	0	2 (4)	0	7 (17)	0
Nausea	104 (20)	3 (1)	70 (19)	2 (1)	17 (27)	1 (2)	5 (16)	0	1 (10)	0	5 (9)	0	4 (10)	0
Hypothyroidism	102 (19)	2 (<1)	67 (18)	1 (<1)	8 (12)	0	9 (28)	0	2 (20)	0	6 (11)	0	7 (17)	0
Hyperthyroidism	97 (18)	8 (2)	71 (19)	6 (2)	13 (20)	1 (2)	7 (22)	0	0	0	2 (4)	0	6 (14)	0
Increased ALT	85 (16)	29 (5)	60 (16)	18 (5)	15 (23)	6 (9)	3 (9)	2 (6)	1 (10)	0	8 (15)	5 (9)	6 (14)	2 (5)
Rash	80 (15)	7 (1)	56 (15)	3 (1)	8 (12)	2 (3)	3 (9)	0	3 (30)	0	6 (11)	0	5 (12)	0
Pyrexia	72 (14)	4 (1)	51 (14)	3 (1)	7 (11)	1 (2)	4 (12)	0	1 (10)	0	9 (16)	0	3 (7)	1 (2)
Increased lipase	69 (13)	42 (8)	54 (15)	33 (9)	6 (9)	4 (6)	2 (6)	1 (3)	0	0	5 (9)	3 (5)	8 (19)	5 (12)
Increased AST	69 (13)	16 (3)	50 (14)	11 (3)	11 (17)	2 (3)	3 (9)	1 (3)	1 (10)	0	7 (13)	3 (5)	5 (12)	1 (2)
Asthenia	67 (13)	4 (1)	45 (12)	3 (1)	8 (12)	0	3 (9)	0	1 (10)	0	7 (13)	0	5 (12)	1 (2)
Decreased appetite	67 (13)	1 (<1)	49 (13)	0	7 (11)	0	3 (9)	0	0	0	1 (2)	0	5 (12)	0
Vitiligo	65 (12)	2 (<1)	53 (15)	1 (<1)	1 (2)	0	2 (6)	0	1 (10)	0	9 (16)	0	7 (17)	0
Maculopapular rash	60 (11)	11 (2)	45 (12)	8 (2)	5 (8)	1 (2)	4 (12)	1 (3)	1 (10)	0	6 (11)	1 (2)	5 (12)	1 (2)
Headache	58 (11)	7 (1)	41 (11)	5 (1)	6 (9)	1 (2)	3 (9)	0	1 (10)	0	3 (5)	0	4 (10)	2 (5)
Colitis	55 (10)	34 (6)	39 (11)	25 (7)	4 (6)	3 (5)	3 (9)	2 (6)	0	0	3 (5)	2 (4)	2 (5)	1 (2)
Arthralgia	48 (9)	3 (1)	36 (10)	2 (1)	6 (9)	0	1 (3)	0	1 (10)	0	1 (2)	0	2 (5)	0
Vomiting	47 (9)	1 (<1)	33 (9)	1 (<1)	5 (8)	0	4 (12)	0	0	0	2 (4)	0	7 (17)	1 (2)

NOTE. Treatment-related adverse events occurring in ≥10% of patients (and ≥2 patients) in any subgroup between the first dose and 30 days after the last dose of therapy are shown.
Abbreviations: BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]The following grade 5 events were reported: aplastic anemia (n = 1; cutaneous), acute kidney injury (n = 1; cutaneous), and colitis (n = 1; mucosal).

TABLE 3. Select Treatment-Related Adverse Events in the All-Treated Population and Predefined Patient Subgroups

Event	All Patients (N = 533)		Melanoma Subtype								ECOG PS 2 (n = 55)		BM (n = 42)	
			Cutaneous (n = 365)		Ocular/Uveal (n = 64)		Mucosal (n = 32)		Acral (n = 10)					
	Any Grade,[a] No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)
Skin	296 (56)	35 (7)	212 (58)	20 (5)	30 (47)	7 (11)	16 (50)	3 (9)	7 (70)	1 (10)	23 (42)	4 (7)	21 (50)	1 (2)
Pruritus	134 (25)	2 (<1)	95 (26)	1 (<1)	12 (19)	0	10 (31)	0	3 (30)	0	11 (20)	1 (2)	10 (24)	0
Rash	80 (15)	7 (1)	56 (15)	3 (1)	8 (12)	2 (3)	3 (9)	0	3 (30)	0	6 (11)	0	5 (12)	0
Vitiligo	65 (12)	2 (<1)	53 (15)	1 (<1)	1 (2)	0	2 (6)	0	1 (10)	0	9 (16)	0	7 (17)	0
Maculopapular rash	60 (11)	11 (2)	45 (12)	8 (2)	5 (8)	1 (2)	4 (12)	1 (3)	1 (10)	0	6 (11)	1 (2)	5 (12)	1 (2)
Pruritic rash	30 (6)	4 (1)	27 (7)	3 (1)	0	0	3 (9)	1 (3)	0	0	2 (4)	1 (2)	0	0
Macular rash	29 (5)	3 (1)	20 (5)	3 (1)	2 (3)	0	3 (9)	0	1 (10)	0	2 (4)	1 (2)	2 (5)	0
Erythema	15 (3)	1 (<1)	11 (3)	1 (<1)	1 (2)	0	0	0	0	0	0	0	4 (10)	0
Eczema	13 (2)	0	11 (3)	0	0	0	1 (3)	0	0	0	0	0	4 (10)	0
Erythematous rash	10 (2)	0	8 (2)	0	0	0	0	0	0	0	0	0	0	0
Pustular rash	4 (1)	2 (<1)	1 (<1)	0	2 (3)	2 (3)	0	0	0	0	0	0	0	0
Endocrine	227 (43)	58 (11)	157 (43)	43 (12)	26 (41)	6 (9)	15 (47)	2 (6)	4 (40)	1 (10)	11 (20)	0	18 (43)	5 (12)
Hypothyroidism	102 (19)	2 (<1)	67 (18)	1 (<1)	8 (12)	0	9 (28)	0	2 (20)	0	6 (11)	0	7 (17)	0
Hyperthyroidism	97 (18)	8 (2)	71 (19)	6 (2)	13 (20)	1 (2)	7 (22)	0	0	0	2 (4)	0	6 (14)	0
Hypophysitis	42 (8)	22 (4)	30 (8)	14 (4)	5 (8)	5 (8)	2 (6)	1 (3)	0	0	3 (5)	0	3 (7)	1 (2)
Adrenal insufficiency	25 (5)	6 (1)	19 (5)	4 (1)	1 (2)	0	2 (6)	0	1 (10)	1 (10)	2 (4)	0	1 (2)	0
Thyroiditis	15 (3)	2 (<1)	13 (4)	1 (<1)	0	0	1 (3)	0	0	0	1 (2)	0	0	0
Hypopituitarism	10 (2)	4 (1)	8 (2)	4 (1)	1 (2)	0	1 (3)	0	0	0	0	0	1 (2)	0
Decreased blood TSH	9 (2)	0	5 (1)	0	2 (3)	0	0	0	1 (10)	0	1 (2)	0	1 (2)	0
Increased blood TSH	9 (2)	0	6 (2)	0	1 (2)	0	0	0	0	0	1 (2)	0	3 (7)	0
Autoimmune thyroiditis	7 (1)	0	3 (1)	0	2 (3)	0	1 (3)	0	0	0	0	0	1 (2)	0
Lymphocytic hypophysitis	7 (1)	6 (1)	7 (2)	6 (2)	0	0	0	0	0	0	0	0	2 (5)	1 (2)
Type 1 diabetes mellitus	3 (1)	2 (<1)	2 (1)	1 (<1)	0	0	0	0	0	0	0	0	2 (5)	2 (5)
GI	214 (40)	83 (16)	148 (41)	57 (16)	29 (45)	9 (14)	9 (28)	5 (16)	4 (40)	1 (10)	14 (25)	4 (7)	11 (26)	5 (12)
Diarrhea	186 (35)	38 (7)	127 (35)	27 (7)	26 (41)	4 (6)	8 (25)	3 (9)	3 (30)	0	14 (25)	3 (5)	10 (24)	4 (10)
Colitis	55 (10)	34 (6)	39 (11)	25 (7)	4 (6)	3 (5)	3 (9)	2 (6)	0	0	3 (5)	2 (4)	2 (5)	1 (2)
Autoimmune colitis	14 (3)	9 (2)	6 (2)	3 (1)	3 (5)	2 (3)	1 (3)	1 (3)	1 (10)	0	1 (2)	1 (2)	1 (2)	0
Immune-mediated enterocolitis	9 (2)	6 (1)	8 (2)	5 (1)	0	0	0	0	0	0	0	0	0	0
Hepatic	155 (29)	82 (15)	110 (30)	56 (15)	27 (42)	17 (27)	5 (16)	2 (6)	1 (10)	1 (10)	10 (18)	7 (13)	12 (29)	6 (14)
Increased ALT	85 (16)	29 (5)	60 (16)	18 (5)	15 (23)	6 (9)	3 (9)	2 (6)	1 (10)	0	8 (15)	5 (9)	6 (14)	2 (5)
Increased AST	69 (13)	16 (3)	50 (14)	11 (3)	11 (17)	2 (3)	3 (9)	1 (3)	1 (10)	0	7 (13)	3 (5)	5 (12)	1 (2)

(continued on following page)

TABLE 3. Select Treatment-Related Adverse Events in the All-Treated Population and Predefined Patient Subgroups (continued)

	All Patients (N = 533)		Melanoma Subtype											
			Cutaneous (n = 365)		Ocular/Uveal (n = 64)		Mucosal (n = 32)		Acral (n = 10)		ECOG PS 2 (n = 55)		BM (n = 42)	
Event	Any Grade,[a] No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)	Any Grade, No. (%)	Grade 3 or 4, No. (%)
Autoimmune hepatitis	23 (4)	18 (3)	18 (5)	14 (4)	3 (5)	2 (3)	0	0	0	0	1 (2)	1 (2)	3 (7)	2 (5)
Immune-mediated hepatitis	20 (4)	15 (3)	13 (4)	9 (2)	3 (5)	3 (5)	0	0	0	0	0	0	2 (5)	2 (5)
Increased blood alkaline phosphatase	19 (4)	1 (<1)	14 (4)	1 (<1)	2 (3)	0	2 (6)	0	0	0	1 (2)	1 (2)	1 (2)	0
Increased blood bilirubin	17 (3)	2 (<1)	14 (4)	1 (<1)	3 (5)	1 (2)	0	0	0	0	3 (5)	1 (2)	0	0
Increased GGT	17 (3)	5 (1)	16 (4)	5 (1)	0	0	0	0	1 (10)	0	1 (2)	1 (2)	2 (5)	0
Hepatitis	14 (3)	5 (1)	12 (3)	4 (1)	1 (2)	1 (2)	1 (3)	0	0	0	0	0	0	0
Increased transaminases	14 (3)	7 (1)	7 (2)	4 (1)	5 (8)	2 (3)	0	0	0	0	0	0	0	0
Hepatotoxicity	4 (1)	4 (1)	2 (1)	2 (1)	2 (3)	2 (3)	0	0	0	0	0	0	0	0
Renal	28 (5)	10 (2)	24 (7)	8 (2)	1 (2)	1 (2)	0	0	0	0	1 (2)	1 (2)	2 (5)	1 (2)
Increased blood creatinine	10 (2)	1 (<1)	8 (2)	1 (<1)	1 (2)	0	0	0	0	0	0	0	0	0
Pulmonary	23 (4)	7 (1)	16 (4)	6 (2)	3 (5)	1 (2)	2 (6)	0	0	0	1 (2)	0	2 (5)	0
Pneumonitis	19 (4)	7 (1)	15 (4)	6 (2)	2 (3)	1 (2)	1 (3)	0	0	0	1 (2)	0	1 (2)	0

NOTE. Treatment-related adverse events of potential immune-mediated etiology occurring in ≥2% of patients (and ≥2 patients) in any subgroup between the first dose and 30 days after the last dose of therapy are shown.

Abbreviations: BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; GGT, gamma-glutamyl transferase; TSH, thyroid-stimulating hormone.

[a]The following grade 5 events were reported: acute kidney injury (n = 1; cutaneous) and colitis (n = 1; mucosal).

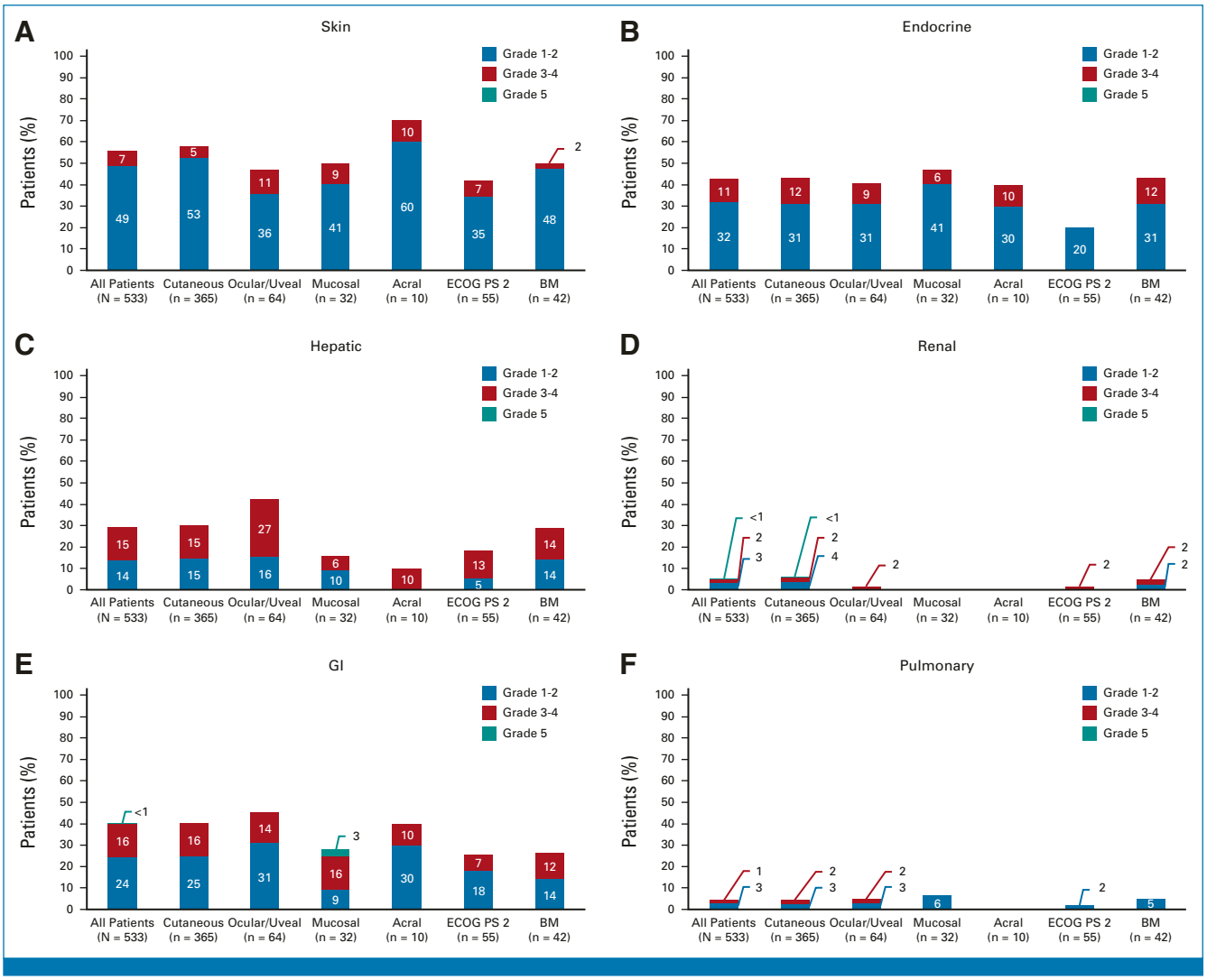

FIG 1. Frequencies of select TRAE categories in the all-treated population and predefined patient subgroups: (A) skin, (B) endocrine, (C) hepatic, (D) renal, (E) GI, and (F) pulmonary. Select AEs are AEs of potential immune-mediated etiology. AE, adverse event; BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; TRAE, treatment-related adverse event.

CheckMate 401 ECOG PS 2 subgroup (11.0 months) compared favorably against similar patients in a real-world study evaluating nivolumab plus ipilimumab (2.1 months).[15] Median OS in patients with asymptomatic brain metastases in CheckMate 401 (NR) aligned with findings from phase II and III studies evaluating nivolumab plus ipilimumab in patients with advanced melanoma and active brain metastases (29.2, 45.8 months, and NR),[19-21] further supporting clinical benefit with nivolumab plus ipilimumab in patients with intracranial disease.[22] Although median OS in patients with ocular/uveal melanoma in CheckMate 401 (15.3 months) was comparatively poor relative to the all-treated population (NR) and patients with cutaneous melanoma (NR), similar findings were observed in phase II (12.7 and 19.1 months)[23,24] and real-world studies (15 months)[25] investigating this patient subgroup. In patients with mucosal melanoma, median OS in CheckMate 401 (12.6 months) was lower than that in the nivolumab plus ipilimumab arm of CheckMate 067 (22.7 months).[26] This may have been due to a greater proportion of patients with mucosal melanoma in CheckMate 401 having an ECOG PS ≥1 (CheckMate 401, 56%; CheckMate 067, 36%) and/or small sample sizes in both studies (CheckMate 401, n = 32; CheckMate 067, n = 28) amplifying minor variations,[26] but further analyses are needed to test these hypotheses.

Consistent with previous studies,[27,28] OS in patients age 75 years and older and/or with baseline LDH >ULN was poorer than in patients age younger than 75 years and/or with LDH ≤ULN, respectively, in CheckMate 401. In particular, 24-month OS rates in CheckMate 401 and CheckMate 067 were similar between patients who received nivolumab plus ipilimumab and had LDH ≤ULN (74% and 74%, respectively) or >ULN (49% and 46%, respectively).[3] As baseline characteristics were generally similar between these patient subgroups within CheckMate 401, the present findings further support that increased age and LDH are associated with poorer outcomes.

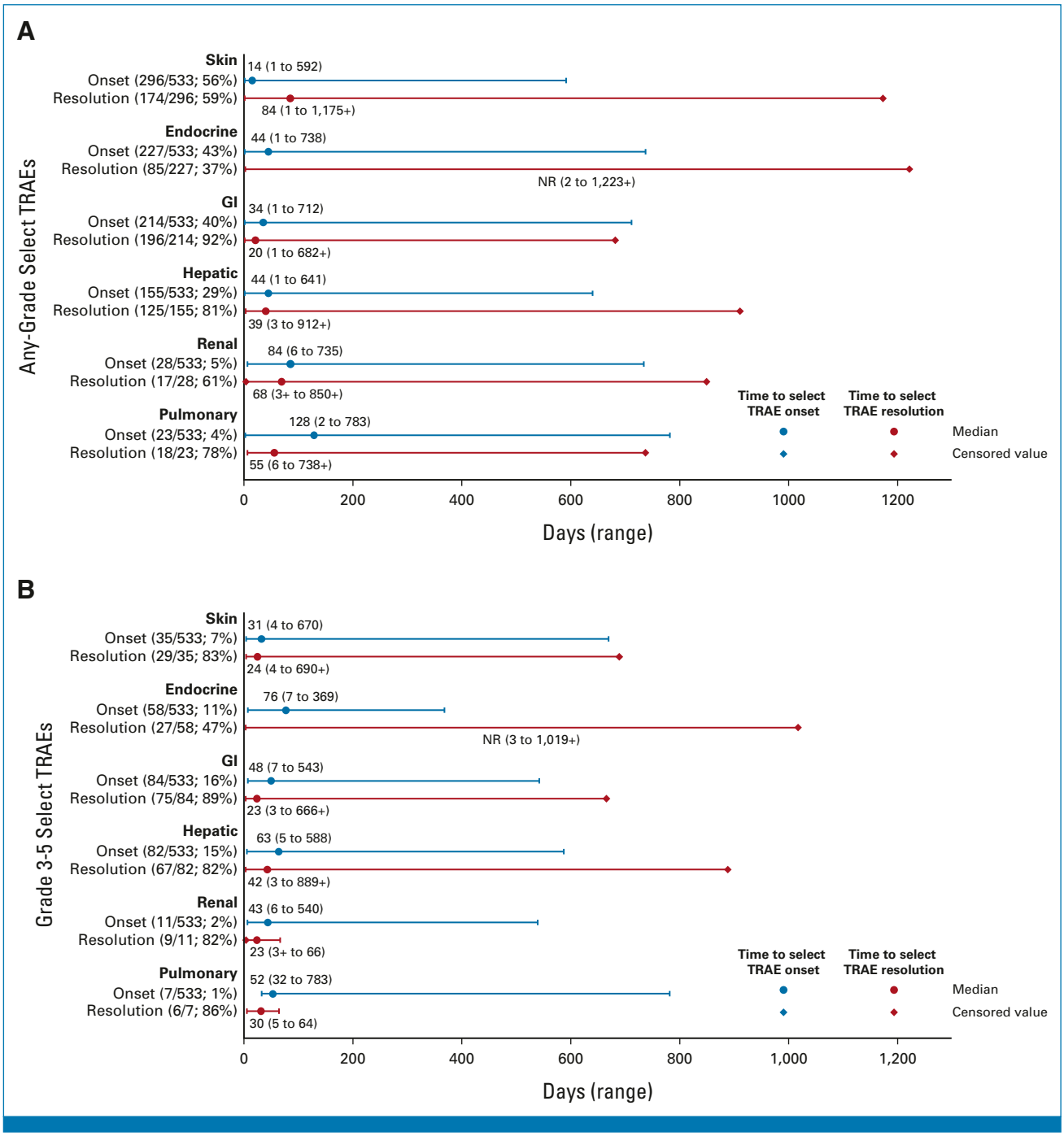

FIG 2. Time to onset and time to resolution of (A) any-grade and (B) grade 3-5 select TRAEs in the all-treated population. Select AEs are AEs of potential immune-mediated etiology. Circles represent medians, and bars indicate ranges (values shown above bars). Percentages of select AEs that resolved were calculated using the numbers of patients who experienced a select AE in the same category as the denominator; + in ranges and ♦ on bars indicate censored values. AE, adverse event; NR, not reached; TRAE, treatment-related adverse event.

The 24-month OS rates in patients with *BRAF*-mutant or wild-type melanoma in CheckMate 401 (68% and 65%, respectively) were similar to those observed in patients treated with nivolumab plus ipilimumab in CheckMate 067 (71% and 61%, respectively),[3] further demonstrating clinical benefit with this treatment regimen in patients with advanced melanoma, regardless of *BRAF* mutation status. Nevertheless, additional studies are needed to evaluate the long-term efficacy of fixed-duration treatment in these patient subgroups.

None of the patients who completed the 24-month treatment regimen died during CheckMate 401, and baseline characteristics were broadly similar between those who

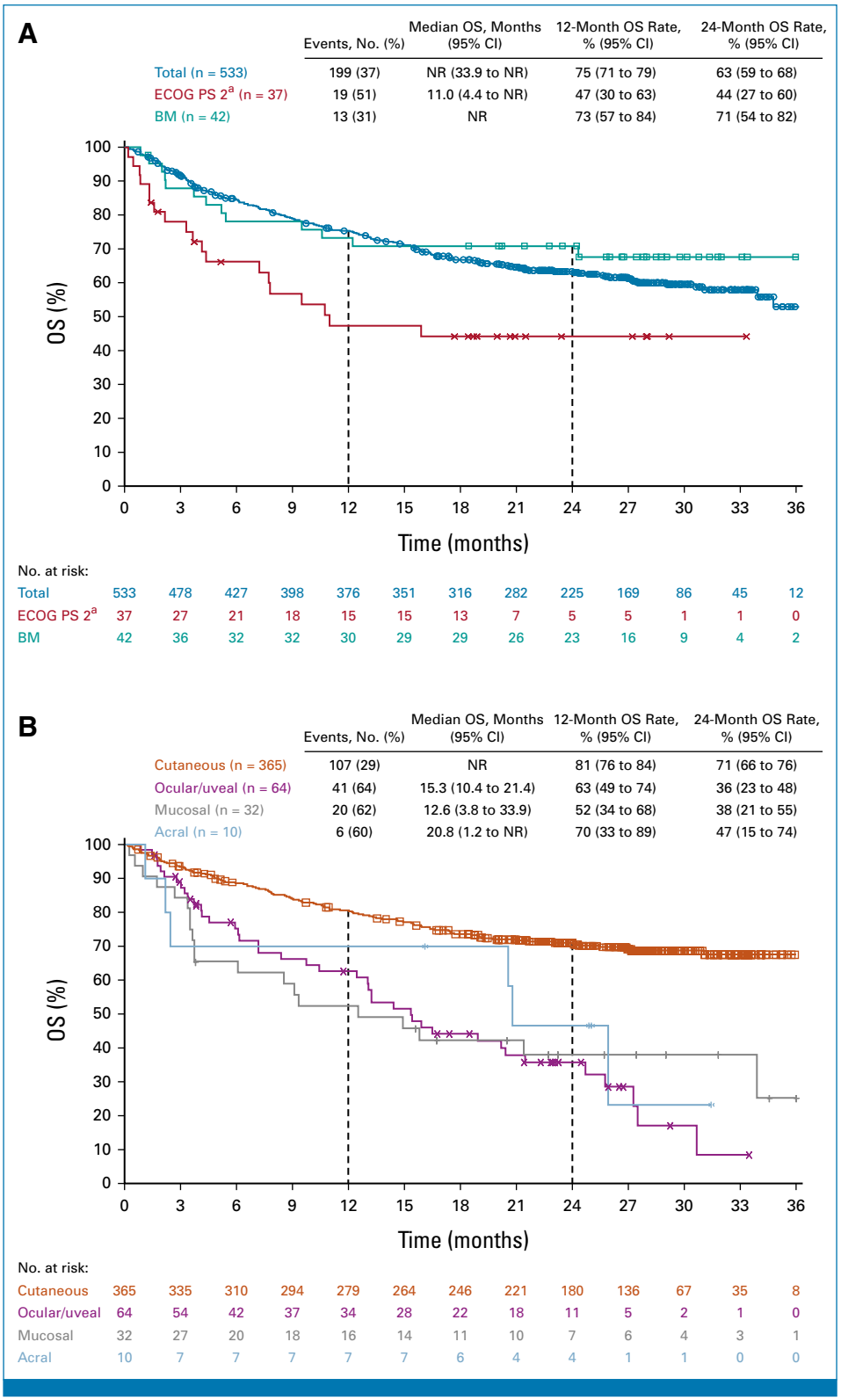

FIG 3. OS in the all-treated population and predefined patient subgroups: (A) ECOG PS 2[a] and BM; (B) mucosal, ocular/uveal, cutaneous, and acral melanoma. [a]Including patients with cutaneous melanoma only. BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reached; OS, overall survival.

completed treatment and those who did not. Although these results address some questions about optimal immunotherapy duration in patients with advanced melanoma,[29,30] limited time between treatment completion and censoring prevents firm conclusions. Additional analyses, such as those being conducted in the phase III DANTE study,[31] are needed to determine if clinical benefit with fixed-duration treatment persists over longer periods of time.

Various limitations should be considered when interpreting results from CheckMate 401. The distribution of disease characteristics in the all-treated population may not have been representative of real-world populations with advanced melanoma (eg, 8% of patients in CheckMate 401 had brain metastases, while approximately 28% of patients with metastatic melanoma in real-world populations have brain metastases at diagnosis),[32] thereby limiting generalizability. Similarly, the limited number of patients within each subgroup prevented us from making definitive conclusions regarding particular melanoma subpopulations. However, the proportions of patients with ECOG PS 2, brain metastases, or ocular/uveal melanoma in this trial were comparable with those in real-world analyses evaluating immunotherapy.[15,33] Protocol amendments that shortened follow-up duration also limited the collection of long-term data. Furthermore, ORRs in CheckMate 401 may not be directly comparable with those of similar trials because tumor assessments (excluding the baseline assessment) were performed per local standard of care or investigator discretion rather than a standardized protocol; however, investigator-assessed ORR may be more indicative of real-world outcomes. Although all patients in CheckMate 401 had unresectable or metastatic disease, AJCC-7 M stage information specific to ocular/uveal and mucosal melanoma was not available. Per protocol, ocular melanoma and uveal melanoma were also classified as a single melanoma subtype.

In conclusion, CheckMate 401 demonstrated the utility of nivolumab plus ipilimumab followed by nivolumab monotherapy in clinically diverse patient populations more representative of real-life practice than previous melanoma clinical trials. Patients with relatively poor prognoses appeared to be at no greater risk of developing select TRAEs than the all-treated population. Although efficacy in the all-treated population and patients with brain metastases was similar, reduced efficacy was observed in patients with ECOG PS 2 and/or certain melanoma subtypes, such as ocular/uveal and mucosal melanoma, highlighting the continued need for novel treatment options for these patients. Further investigation is warranted to evaluate the clinical activity of this treatment regimen administered over a fixed duration >24 months.

AFFILIATIONS

[1]University Hospital Zurich, Zurich, Switzerland
[2]Addenbrooke's Hospital, Cambridge, United Kingdom
[3]Medizinische Hochschule Hannover, Hannover, Germany
[4]Johannes-Wesling Medical Center, Ruhr University Bochum Campus, Minden, Germany
[5]Sir Charles Gairdner Hospital and the University of Western Australia, Nedlands, Western Australia, Australia
[6]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[7]Université Paris Cité and AP-HP, Department of Dermato-oncology, INSERM U976, Hôpital Saint Louis, Paris, France
[8]IRCCS Giovanni Paolo II, Bari, Italy
[9]Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France
[10]Nantes University Hospital, Nantes, France
[11]Institut Universitaire and CHU de Toulouse, Toulouse, France
[12]European Institute of Oncology, IRCCS, Milan, Italy
[13]Hospices Civils de Lyon, Lyon, France
[14]Fiona Stanley Hospital, Murdoch, Australia
[15]Edith Cowan University, Perth, Western Australia, Australia
[16]Aix-Marseille University and Hospital de la Timone AP-HM, Marseille, France
[17]North Coast Cancer Institute, Coffs Harbour, New South Wales, Australia
[18]The Royal Marsden NHS Foundation Trust, London, United Kingdom
[19]CHU Clermont-Ferrand, Clermont-Ferrand, France
[20]Eugène Marquis Centre, Rennes, France
[21]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRCCS, Meldola, Italy
[22]Azienda Ospedaliera Santa Maria di Terni, Terni, Italy
[23]Medical University of Graz, Graz, Austria
[24]Helios Hauttumorzentrum Erfurt, Erfurt, Germany
[25]Bristol Myers Squibb, Princeton, NJ
[26]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy
[27]University of Siena and Center for Immuno-Oncology, Department of Oncology, University Hospital, Siena, Italy

CORRESPONDING AUTHOR

Reinhard Dummer, MD, University Hospital Zurich Gloriastrasse 31, Zurich 8091, Switzerland; e-mail: reinhard.dummer@usz.ch.

EQUAL CONTRIBUTION

P.A.A. and M.M. contributed equally to this work.

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DATA SHARING STATEMENT

Bristol Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

AUTHOR CONTRIBUTIONS

Conception and design: Reinhard Dummer, Pippa Corrie, Michele Guida, Maurice Lobo, Michele Maio
Provision of study materials or patients: Ralf Gutzmer, Tarek M. Meniawy, Céleste Lebbé, Caroline Dutriaux, Nicolas Meyer, Brigitte Dreno, Pier Francesco Ferrucci, Muhammad Adnan Khattak, Thierry Lesimple, Massimo Guidoboni, Silvia Sabatini, Erika Richtig, Rudolf Herbst, Michele Maio
Collection and assembly of data: Reinhard Dummer, Pippa Corrie, Ralf Gutzmer, Tarek M. Meniawy, Michele Del Vecchio, Céleste Lebbé, Michele Guida, Caroline Dutriaux, Brigitte Dreno, Pier Francesco Ferrucci, Stéphane Dalle, Muhammad Adnan Khattak, Jean-Jacques Grob, Karen Briscoe, Sandrine Mansard, Thierry Lesimple, Massimo Guidoboni, Silvia Sabatini, Erika Richtig, Maurice Lobo, Paolo A. Ascierto, Michele Maio
Data analysis and interpretation: Reinhard Dummer, Pippa Corrie, Tarek M. Meniawy, Michele Del Vecchio, Céleste Lebbé, Nicolas Meyer, Brigitte Dreno, Pier Francesco Ferrucci, Muhammad Adnan Khattak, Jean-Jacques Grob, James Larkin, Rudolf Herbst, Maurice Lobo, Margarita Askelson, Paolo A. Ascierto, Michele Maio
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

First-Line, Fixed-Duration Nivolumab Plus Ipilimumab Followed by Nivolumab in Clinically Diverse Patient Populations With Unresectable Stage III or IV Melanoma: CheckMate 401

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Reinhard Dummer
Honoraria: Roche, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, Alligator Bioscience, MaxiVax, touchIME, T3 Pharmaceuticals, Pfizer
Consulting or Advisory Role: Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Alligator Bioscience, touchIME, MaxiVax, Regeneron, Pfizer, T3 Pharmaceuticals
Research Funding: Roche (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Merck Sharp & Dohme (Inst), Amgen (Inst)

Pippa Corrie
Honoraria: Novartis, Merck Sharp & Dohme, Pierre Fabre, Bristol Myers Squibb
Consulting or Advisory Role: Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Microbiotica
Speakers' Bureau: Merck Sharp & Dohme, Pierre Fabre
Research Funding: Merck Sharp & Dohme (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Iovance Biotherapeutics (Inst), Pfizer (Inst), AstraZeneca (Inst)

Ralf Gutzmer
Honoraria: Bristol Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, Novartis, Merck Serono, Almirall Hermal GmbH, Amgen, Sun Pharma, Pierre Fabre, Sanofi/Regeneron, Immunocore
Consulting or Advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, Novartis, Almirall Hermal GmbH, 4SC, Amgen, Pierre Fabre, Merck Serono, Sun Pharma, Sanofi, Immunocore
Research Funding: Novartis (Inst), Amgen (Inst), Merck Serono (Inst), Sun Pharma (Inst), Sanofi (Inst), Kyowa Kirin (Inst), Almirall Hermal GmbH (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Pierre Fabre, Sun Pharma, Boehringer Ingelheim

Tarek M. Meniawy
Consulting or Advisory Role: Novartis, GlaxoSmithKline, Bristol Myers Squibb, Eisai, Regeneron, Sanofi, Merck Sharp & Dohme
Research Funding: Bristol Myers Squibb (Inst), Incyte (Inst), BeiGene (Inst), AstraZeneca/MedImmune (Inst), Regeneron (Inst), Bayer (Inst), Merck Serono (Inst), Roche/Genentech (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb

Michele Del Vecchio
Consulting or Advisory Role: Novartis, Bristol Myers Squibb, Merck, Pierre Fabre, Immunocore

Céleste Lebbé
Honoraria: Roche, Bristol Myers Squibb, Novartis, Amgen, Merck Sharp & Dohme, Pierre Fabre, Pfizer, Incyte
Consulting or Advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Amgen, Roche, Merck Serono, Sanofi, Pierre Fabre
Speakers' Bureau: Roche, Bristol Myers Squibb, Novartis, Amgen, Merck Sharp & Dohme
Research Funding: Roche (Inst), Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Sanofi, Pierre Fabre
Other Relationship: Avantis Medical Systems, InflaRx, Sanofi, Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Novartis, Jazz Pharmaceuticals

Michele Guida
Consulting or Advisory Role: Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, Pierre Fabre

Caroline Dutriaux
Honoraria: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre
Consulting or Advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre
Travel, Accommodations, Expenses: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre

Brigitte Dreno
Consulting or Advisory Role: Bristol Myers Squibb, Roche/Genentech, Pierre Fabre, Almirall, Sun Pharma
Research Funding: Roche (Inst), Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Roche/Genentech

Nicolas Meyer
Consulting or Advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme Oncology, Novartis, Pierre Fabre, Sun Pharma, Merckle GmbH
Research Funding: Bristol Myers Squibb (Inst), Merck Sharp & Dohme Oncology (Inst)

Pier Francesco Ferrucci
Expert Testimony: Delcath Systems

Stéphane Dalle
Employment: Sanofi Pasteur
Stock and Other Ownership Interests: Sanofi
Consulting or Advisory Role: Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst)
Speakers' Bureau: Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst)
Research Funding: Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst), Roche (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb

Muhammad Adnan Khattak
Travel, Accommodations, Expenses: Pierre Fabre

Jean-Jacques Grob
Consulting or Advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme Oncology, Roche/Genentech, Novartis, Amgen, Pierre Fabre, Sun Pharma, Merck KGaA, Sanofi, Roche, Philogen, Ultimovacs
Speakers' Bureau: Novartis, Pierre Fabre
Travel, Accommodations, Expenses: Bristol Myers Squibb, Merck Sharp & Dohme Oncology, Novartis, Pierre Fabre

Karen Briscoe
Speakers' Bureau: Pierre Fabre

James Larkin
Honoraria: Bristol Myers Squibb, Pfizer, Novartis, Incyte, Merck Serono, Eisai, touchIME, touchEXPERTS, Royal College of Physicians, Cambridge Healthcare research, RCGP, VJOncology, Agence Unik
Consulting or Advisory Role: Bristol Myers Squibb, Incyte, iOnctura, Apple Tree Partners, Merck Serono, Eisai, Debiopharm Group, Pierre Fabre, Ipsen, Roche, EUSA Pharma, Novartis, Aptitude Health, AstraZeneca, GlaxoSmithKline, Calithera Biosciences, Ultimovacs, eCancer, Insel Gruppe, Pfizer, Goldman Sachs, Merck Sharp & Dohme Oncology, Agence Unik
Research Funding: Pfizer (Inst), Novartis (Inst), Merck Sharp & Dohme (Inst), Bristol Myers Squibb (Inst), Achilles Therapeutics (Inst), Roche (Inst), Nektar (Inst), Covance (Inst), Immunocore (Inst), AVEO (Inst), Pharmacyclics (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, GlaxoSmithKline, Pierre Fabre, immatics, ESMO

Sandrine Mansard
Consulting or Advisory Role: Sanofi, Novartis
Travel, Accommodations, Expenses: Bristol Myers Squibb, Pierre Fabre, Novartis

Thierry Lesimple
Consulting or Advisory Role: Novartis, Bristol Myers Squibb
Speakers' Bureau: Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, Pierre Fabre

Massimo Guidoboni
Consulting or Advisory Role: Bristol Myers Squibb, Novartis, Pierre Fabre
Speakers' Bureau: Bristol Myers Squibb, Novartis, Pierre Fabre
Research Funding: Merck Sharp & Dohme

Erika Richtig
Stock and Other Ownership Interests: Roche Pharma AG
Honoraria: Amgen, Bayer, Bristol Myers Squibb, Merck Sharp & Dohme, Merck, Novartis, Pierre Fabre, Roche, Sanofi
Consulting or Advisory Role: Amgen, Bayer, Bristol Myers Squibb, Merck Sharp & Dohme, Merck, Novartis, Pierre Fabre
Speakers' Bureau: Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Merck, Novartis, Pierre Fabre, Sanofi
Research Funding: Amgen (Inst), Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst), Novartis (Inst), Pierre Fabre (Inst), Roche (Inst), CureVac (Inst), Incyte (Inst), Regeneron (Inst), Delcath Systems (Inst)
Travel, Accommodations, Expenses: Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Merck, Novartis, Pierre Fabre, Roche, Sanofi

Rudolf Herbst
Employment: Helios Kliniken

Maurice Lobo
Employment: Bristol Myers Squibb/Celgene
Stock and Other Ownership Interests: Bristol Myers Squibb/Celgene

Margarita Askelson
Employment: Bristol Myers Squibb/Celgene
Stock and Other Ownership Interests: Bristol Myers Squibb/Celgene

Paolo A. Ascierto
Consulting or Advisory Role: Bristol Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre Fabre, AstraZeneca, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Italfarmaco, Nektar, Boehringer Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, OncoSec, Nouscom, Lunaphore Technologies, Seagen, ITeos Therapeutics, Medicenna, Bio-AI Health, ValoTx, Replimune, Bayer
Research Funding: Bristol Myers Squibb (Inst), Roche/Genentech (Inst), Sanofi (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Pfizer, Bio-AI Health, Replimune

Michele Maio
Stock and Other Ownership Interests: Theravance, Epigen Therapeutics
Honoraria: Bristol Myers Squibb, AstraZeneca, Roche, Merck Sharp & Dohme, Merck, Amgen, Pierre Fabre, Alfasigma, Sanofi, Lilly
Consulting or Advisory Role: Bristol Myers Squibb, Roche, AstraZeneca, Merck Sharp & Dohme, Merck, Pierre Fabre, Alfasigma
Patents, Royalties, Other Intellectual Property: DNA Hypomethylating agents for cancer therapy
Travel, Accommodations, Expenses: Bristol Myers Squibb, AstraZeneca, Roche, Merck Sharp & Dohme, Merck, Amgen, Pierre Fabre, Alfasigma

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