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Canadian cohort expanded-access program of nivolumab plus ipilimumab in advanced melanoma

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ABSTRACT

Background The combination of nivolumab and ipilimumab is approved in several jurisdictions (United States, European Union, Canada) for the first-line treatment of patients with advanced melanoma. CheckMate 218 is a North American expanded-access program (EAP) of nivolumab plus ipilimumab in patients with advanced melanoma. Here, we report safety and survival outcomes for the Canadian cohort in the EAP.

Methods Eligible patients were those 18 years of age or older with unresectable stage III or IV melanoma, an Eastern Cooperative Oncology Group performance status of 0 or 1, and no prior anti–PD-1 or anti–CTLA-4 therapy. Patients were treated with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 cycles (induction phase); they then continued with nivolumab 3 mg/kg every 2 weeks (maintenance phase) until progression, unacceptable toxicity, or a maximum of 48 weeks, whichever occurred first. Safety and overall survival (OS) data were collected.

Results Of 194 patients enrolled, 174 were treated, and 51% continued on nivolumab maintenance. Median follow-up was 12.9 months. All-grade and grades 3–4 treatment-related adverse events were reported in 98% and 60% of patients respectively and led to treatment discontinuation in 40% and 28% of patients. Two treatment-related deaths were reported. The 12- and 18-month OS rates were 80% [95% confidence interval (CI): 73% to 86%] and 76% (95% CI: 67% to 82%) respectively.

Conclusions In this Canadian population, nivolumab plus ipilimumab demonstrated a safety profile and survival outcomes consistent with phase II and III clinical trial data.

Key Words Expanded-access programs, immune checkpoint inhibitors, ipilimumab, nivolumab, melanoma

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INTRODUCTION

Immune checkpoint inhibitors such as nivolumab, an anti–PD-1 antibody, and ipilimumab, an anti–CTLA-4 antibody, have changed the treatment paradigm for advanced melanoma. Before the era of immune checkpoint inhibition, median overall survival (OS) for patients with advanced melanoma ranged from 6 months to 12 months[1]; today, it is 4 years or longer[2]. Nivolumab with or without ipilimumab is used for the first-line treatment of patients with advanced melanoma[3,4].

Results from randomized clinical trials (RCTs) indicate that, compared with ipilimumab alone, the combination of nivolumab and ipilimumab is associated with improved OS in patients with treatment-naïve advanced melanoma, but with a higher frequency of treatment-related adverse events (TRAEs) than occur with monotherapy[2,5–7]. In the randomized, phase II CheckMate 069 study, treatment with nivolumab plus ipilimumab was compared with ipilimumab alone and was associated with a significant improvement in the objective response rate and median progression-free survival in patients with treatment-naïve *BRAF* wild-type advanced melanoma[5,6]. In the randomized, phase III CheckMate 067 study, nivolumab plus ipilimumab or nivolumab alone, compared with ipilimumab alone, was associated with a significant improvement in the

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objective response rate, median progression-free survival, and median OS in patients with treatment-naïve advanced melanoma[2,7]. The combination of nivolumab and ipilimumab was approved for advanced melanoma in 2015 in the United States and in 2016 in Canada.

CheckMate 218 (see NCT02186249 at https://ClinicalTrials.gov/) is a North American expanded-access program (EAP) for nivolumab plus ipilimumab in patients with unresectable stage III or IV melanoma, including cutaneous, ocular or uveal, mucosal, and acral melanoma. The EAP provided the combination to patients with treatment-naïve disease or disease that progressed with other therapies, excluding anti–CTLA-4 or anti–PD-1 therapies, until market authorization was granted for the combination. The overall patient population for the EAP included 754 patients: 580 treated in the United States and 174 treated in Canada. We previously reported earlier OS data for the combined U.S. (1-year follow-up) and Canadian (6-month follow-up) cohorts[8]. Here, we report updated safety and OS data for the Canadian cohort, with a median follow-up of 12.9 months. Results from the Canadian cohort support reimbursement decisions in Canada related to this approved treatment. Results from the total North American population (United States and Canada combined) will be published separately.

METHODS

Patients

Eligible patients were 18 years of age or older with unresectable stage III or IV metastatic melanoma per the American Joint Committee on Cancer staging system (7th edition)[9]. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and to be treatment-naïve to anti–CTLA-4 and anti–PD-1 agents. Patients could have received other systemic treatments for localized or metastatic disease, including BRAF or MEK inhibitors. (Initially, patients with *BRAF* mutation–positive tumours who had received prior treatment with targeted therapy were excluded, but the protocol was amended within a few weeks to remove that exclusion.) Patients were excluded if they had active (symptomatic) or untreated brain metastases or leptomeningeal metastases, a life expectancy of less than 6 weeks, autoimmune disease, or conditions requiring systemic corticosteroids or other immunosuppressive medications within 14 days of drug administration. Patients were also excluded if they required other systemic antineoplastic therapy while receiving nivolumab.

EAP Design and Treatment

An EAP protocol was used for administration of sequential doses of nivolumab plus ipilimumab. Investigators had previous experience with the administration of nivolumab and ipilimumab, either as monotherapy or in combination. Patients received nivolumab (intravenously over 60 minutes at 1 mg/kg) and ipilimumab (intravenously over 90 minutes at 3 mg/kg every 3 weeks) for 4 doses during the induction phase. Subsequently, they continued with single-agent nivolumab (intravenously over 60 minutes at 3 mg/kg every 2 weeks) during the maintenance phase, until disease progression or unacceptable toxicity, or until a maximum of 48 weeks from the first nivolumab monotherapy dose, whichever occurred first (supplemental Figure 1).

In Canada, patients who stopped combination therapy because of toxicity were allowed to resume nivolumab monotherapy if toxicities had resolved and upon discussion with the medical monitor. Patients who discontinued treatment were followed for adverse events (AEs). After U.S. approval of the combination treatment, the EAP was closed in the United States because patients were transitioned to the commercial supply of nivolumab, and data collection was continued only for the Canadian cohort. The EAP was subsequently closed in Canada, and some patients experiencing clinical benefit at EAP completion were provided nivolumab through a post-EAP drug access program funded by the Bristol Myers Squibb Company.

EAP Endpoints

Safety parameters—collected according to health authority regulations starting at cycle 1 and recommended for monitoring until 100 days after discontinuation of therapy—were AEs, physical examination, ECOG PS, and laboratory results. Evaluation of AEs commenced with the first dose and ended 30 days after the last dose of therapy. Severity was assessed according to the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events,* version 4.0. Serious AEs were those that resulted in death, that were life-threatening, that resulted in persistent or significant disability or incapacity, or that required intervention or hospitalization.

Overall survival was defined as the time from treatment start to death from any cause. Collection of survival data was recommended for up to 5 years from the first nivolumab monotherapy dose, but the EAP was closed early when a safety analysis determined that patient safety was consistent with observations across the nivolumab program. Response data were not collected.

Statistical Analysis

A descriptive statistical analysis was performed on the collected safety and OS data; no formal hypothesis-testing was conducted. The overall study sample size for the descriptive analysis was based on the projected number of patients meeting the enrolment criteria during a specific period, because one of the objectives was to provide access to therapy. In the overall study population (United States and Canada), it was estimated that, with a screening failure rate of 15%, 1000 patients would have to enrol, provide informed consent, and be screened to allow for 850 patients to be treated for a maximum of 48 weeks in the maintenance phase or until the first of disease progression, loss to follow-up, death, withdrawal of consent, or unacceptable toxicity.

RESULTS

Patients and Treatment

From October 2015 to December 2016, 194 Canadian patients were enrolled at 18 sites throughout Canada, and 174 were treated (Figure 1). Results from a database lock at 24 January 2018 were based on a median follow-up time of

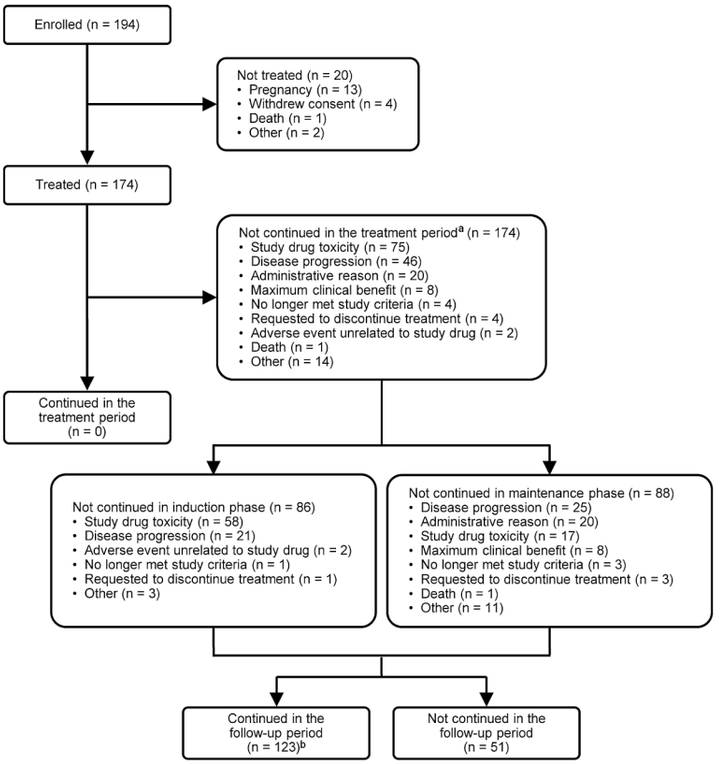

FIGURE 1 Patient disposition. [a]At end of the expanded-access program, 21 of these patients who were experiencing clinical benefit were provided nivolumab through a separate post-study drug access program without drug interruption. [b]After expanded-access program end, still being followed for adverse events.

12.9 months (range: 0.3–21.2 months). All patients discontinued EAP therapy throughout the on-EAP treatment period, with the most common reasons for discontinuation being drug toxicity (n = 75, 43%) and disease progression (n = 46, 26%). Discontinuations during the induction phase totalled 86 [including 21 (24%) because of disease progression and 58 (67%) because of toxicity] and 88 during the maintenance phase [including 25 (28%) because of disease progression and 17 (19%) because of toxicity]. At database lock, 123 patients (71%) continued to be followed for AEs. At the end of the EAP, 21 of the 174 patients who discontinued were experiencing clinical benefit and were provided nivolumab through a separate post-EAP drug access program, without interruption in treatment.

Median age of the 174 treated patients was 56 years (range: 27–81 years; Table I). Most patients (n = 113, 65%) were men; 109 (63%) had a history of cutaneous melanoma; 161 (93%) were diagnosed with stage IV disease; and 119 (68%) were treatment-naïve. Slightly more than half (n = 89, 51%) had *BRAF* mutation–positive tumours. Metastases to the brain were present in 5 patients (2%). Prior therapies, which could have been administered in combination, were received by 29 patients in the adjuvant setting (17%) and by 30 patients in the metastatic setting (17%). Prior therapy received by 55 patients (32%) included targeted therapy, reported as dabrafenib (n = 23), trametinib (n = 17), dabrafenib–trametinib (n = 2), and vemurafenib (n = 2).

Median treatment duration of nivolumab and ipilimumab in the induction phase was 1.7 months (range: 0.03–3.9 months) and 1.6 months (range: 0.03–3.9 months) respectively. The median number of nivolumab and ipilimumab doses received during the induction phase was 3.0 each (range: 1–4), and the median number of nivolumab doses received during the maintenance phase was 1.0 (range: 0–35). From the induction phase, 85 patients (51%) went on to receive maintenance nivolumab monotherapy. Median duration of nivolumab treatment in the maintenance phase was 6.6 months (range: 0.03–16.6 months). In 86 patients (49%), no nivolumab doses were administered during the maintenance phase; 48 patients (28%) received more than 10 doses. In the overall EAP, 57 patients (33%) received more than 10 doses of nivolumab. Overall, a relative dose intensity of 90% or greater with nivolumab and ipilimumab was achieved by 47 patients (27%) and 133 patients (76%) respectively. A dose delay with nivolumab and ipilimumab occurred in 102 patients (59%) and 47 patients (27%) respectively, with the most common reason being occurrence of an AE.

Safety

Any-grade TRAEs were reported in 170 patients (98%), the most common being fatigue in 86 patients (49%), diarrhea in 80 (46%), and nausea in 58 (33%, Table II). Grades 3–4 TRAEs were reported in 104 patients (60%), the most common

TABLE I Demographic and clinical characteristics of 174 patients receiving nivolumab plus ipilimumab through an expanded-access program (EAP)

Variable	Value
Age (years)	
Median	56
Range	27–81
Age group [*n* (%)]	
≥65 Years	35 (20)
≥75 Years	7 (4)
Sex [*n* (%)]	
Men	113 (65)
Women	61 (35)
ECOG PS [*n* (%)]	
0	101 (58)
1	73 (42)
Subtype of melanoma [*n* (%)]	
Cutaneous	109 (63)
Ocular or uveal	15 (9)
Mucosal	10 (6)
Acral	3 (2)
Other	37 (21)
BRAF mutation status [*n* (%)]	
Mutant	89 (51)
Wild type	65 (37)
Not reported	20 (11)
Disease stage at EAP entry [*n* (%)]	
IIIB	13 (7)
IV	161 (93)
M Stage at EAP entry [*n* (%)]	
M0/1a/1b	79 (45)
M1c	94 (54)
Unknown	1 (1)
Brain metastasis [*n* (%)]	
Yes	5 (2)
No	160 (92)
Unknown	9 (5)
Serum LDH at baseline [*n* (%)]	
≤ULN	108 (62)
>ULN	62 (36)
>2×ULN	18 (10)
Not done	3 (2)
Not reported	1 (1)
Number of prior therapies [*n* (%)]	
0	119 (68)
1	29 (17)
2	21 (12)
≥3	5 (3)
Time from prior therapy to first dose [*n* (%)][a]	
<6 Months	37 (21)
≥6 Months	18 (10)
Not reported	119 (68)

[a] Percentages are based on the number of patients who received prior therapies.

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; ULN = upper limit of normal.

TABLE II Adverse event summary for 174 patients receiving nivolumab plus ipilimumab through an expanded-access program (EAP)[a]

Event type	Event grade [*n* (%)]	
	Any	3–4
Any-cause adverse event	174 (100)[b]	128 (74)
Any treatment-related adverse event	170 (98)	104 (60)
Treatment-related adverse events in >5% of patients		
Fatigue	86 (49)	6 (3)
Diarrhea	80 (46)	18 (10)
Nausea	58 (33)	2 (1)
Maculopapular rash	57 (33)	12 (7)
Pruritus	43 (25)	1 (1)
Pyrexia	42 (24)	1 (1)
Increased AST	39 (22)	15 (9)
Decreased appetite	37 (21)	1 (1)
Vomiting	27 (21)	3 (2)
Increased ALT	36 (21)	16 (9)
Pruritus generalized	31 (18)	3 (2)
Hypothyroidism	27 (16)	0
Arthralgia	26 (15)	0
Headache	26 (15)	0
Rash	24 (14)	2 (1)
Increased lipase	23 (13)	16 (9)
Myalgia	21 (12)	2 (1)
Hyperthyroidism	20 (11)	1 (1)
Autoimmune hepatitis	19 (11)	13 (7)
Cough	17 (10)	0
Chills	16 (9)	0
Decreased weight	16 (9)	1 (1)
Hypophysis	16 (9)	2 (1)
Colitis	15 (9)	9 (5)
Abdominal pain	14 (8)	1 (1)
Dyspnea	14 (8)	0
Pneumonitis	14 (8)	3 (2)
Vitiligo	14 (8)	1 (1)
Dry mouth	13 (8)	0
Macular rash	12 (7)	0
Acneiform dermatitis	11 (6)	0
Blurred vision	11 (6)	0
Dehydration	11 (6)	2 (1)
Dysgeusia	9 (5)	0
Increased amylase	9 (5)	5 (3)
Influenza-like illness	9 (5)	0
Hepatitis	9 (5)	4 (2)
Any treatment-related adverse event leading to discontinuation of treatment	70 (40)	48 (28)
Treatment-related adverse events in >5% of patients leading to discontinuation of treatment		
Autoimmune hepatitis	11 (6)	10 (6)
Diarrhea	10 (6)	8 (5)
Increased ALT	8 (5)	7 (4)

[a] Includes adverse events reported between the first dose and 30 days after the last dose of EAP therapy.

[b] Grade 5 adverse events occurred in 2 patients (1%), in both cases because of malignant neoplasm progression.

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

being diarrhea in 18 patients (10%), increased alanine aminotransferase in 16 (9%), increased lipase in 16 (9%), and increased aspartate aminotransferase in 15 (9%). Any-grade and grades 3–4 TRAEs led to treatment discontinuation in 70 patients (40%) and 48 patients (28%) respectively. Serious TRAEs of any grade and grades 3–4 were reported in 58 patients (33%) and 49 patients (28%) respectively. Among patients less than 65 years of age (n = 139) and 65 years of age and older (n = 35), grades 3–4 AEs of any type were reported in 103 (74%) and 25 (71%) patients respectively. The most common grades 3–4 AEs were increased alanine aminotransferase (11%) and diarrhea (10%) in patients less than 65 years of age, and diarrhea (9%) and colitis (7%) in patients 65 years of age and older.

Select TRAEs of any grade (those with a potential immunologic cause) occurred most frequently in skin in 118 patients (68%) and in the gastrointestinal system in 84 patients (48%, Table III). Of the select TRAEs of any grade, the most common were diarrhea in 80 patients (46%), maculopapular rash in 57 (33%), and pruritus in 43 (25%). Of the select TRAEs of grades 3–4, the most common were diarrhea in 18 patients (10%), increased alanine aminotransferase in 16 (9%), and increased aspartate aminotransferase in 15 (9%).

Most patients (n = 154, 89%) required immune-modulating medications for any-grade AEs (supplemental Table I). More than half (n = 95, 55%) required immune-modulating medications for grades 3–4 AEs. Those medications included systemic steroids in 144 patients (83%), infliximab in 15 (9%), and mycophenolic acid in 10 (6%, supplemental Table II).

During the treatment period, 37 patients died (21%). The primary causes of death were disease progression in 31 patients (18%), EAP drug toxicity in 2 (1%), and "other" in 4 (2%). The 2 treatment-related deaths were sepsis from grade 4 colitis (n = 1) and severe skeletal myositis and myocarditis (n = 1).

TABLE III Select treatment-related adverse events (those with a potential immunologic cause) in 5% or more of 174 patients receiving nivolumab plus ipilimumab through an expanded-access program

Event type	Event grade [*n* (%)]	
	Any	3–4
Skin	118 (68)	20 (11)
Maculopapular rash	57 (33)	12 (7)
Pruritus	43 (25)	1 (1)
Generalized pruritus	31 (18)	3 (2)
Rash	24 (14)	2 (1)
Vitiligo	14 (8)	1 (1)
Macular rash	12 (7)	0
Generalized rash	8 (5)	4 (2)
Pruritic rash	8 (5)	0
Gastrointestinal	84 (48)	25 (14)
Diarrhea	80 (46)	18 (10)
Colitis	15 (9)	9 (5)
Hepatic	67 (39)	37 (21)
Increased AST	39 (22)	15 (9)
Increased ALT	36 (21)	16 (9)
Autoimmune hepatitis	19 (11)	13 (8)
Hepatitis	9 (5)	4 (2)
Endocrine	54 (31)	6 (3)
Hypothyroidism	27 (16)	0
Hyperthyroidism	20 (12)	1 (1)
Hypophysis	16 (9)	2 (1)
Pulmonary	14 (8)	3 (2)
Pneumonitis	14 (8)	3 (2)
Hypersensitivity or infusion reaction	9 (5)	0
Infusion-related reaction	8 (5)	0
Renal	7 (4)	1 (1)

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Efficacy

With a median follow-up of 12.9 months, median OS was 20.5 months [95% confidence interval (CI): 20.5 months to not reached], and 12-month and 18-month survival rates were 80% (95% CI: 73% to 86%) and 76% (95% CI: 67% to 82%) respectively (Figure 2). The drop in OS after 18 months is an artefact and reflects the end of follow-up, as patients transitioned to post-EAP drug access.

The OS rates for patients who discontinued treatment during the induction phase (26 of 86 patients) were 71% at 12 months (95% CI: 60% to 80%) and 64% at 18 months (95% CI: 50% to 74%). The OS rates for patients who discontinued during the induction phase because of any TRAEs (15 of 81 patients) were 84% at 12 months (95% CI: 74% to 91%) and 76% at 18 months (95% CI: 62% to 85%). For those who discontinued because of grade 3 or 4 TRAEs (11 of 56 patients), OS rates were 85% at 12 months (95% CI: 72% to 92%) and 73% at 18 months (95% CI: 55% to 85%).

Survival outcomes were numerically different for some subgroups (Figure 3): 12-month OS rates were 87% for male patients (95% CI: 78% to 92%) and 69% for female patients (95% CI: 55% to 79%); they were 86% for the ECOG PS 0 group (95% CI: 76% to 91%) and 73% for the ECOG PS 1 group (95% CI: 61% to 82%); they were 84% for patients with lactate dehydrogenase (LDH) at or below upper limit of normal (95% CI: 75% to 90%), 72% for those with LDH above the upper limit of normal (95% CI: 59% to 82%), and 58% for those with LDH greater than twice the upper limit of normal (95% CI: 31% to 78%); and they were 79% for patients with cutaneous melanoma (95% CI: 70% to 86%), 73% for those

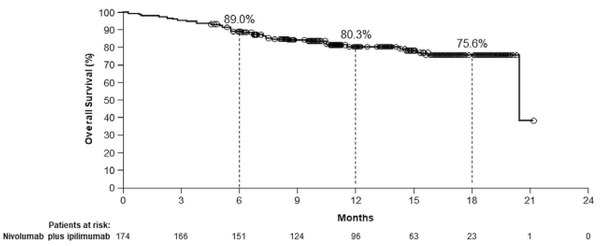

FIGURE 2 Survival in the overall population. The Kaplan–Meier curve reflects the overall population (37 events in 174 patients) with a median overall survival (OS) of 20.5 months (95% confidence interval: 20.5 months to not reached). The drop in OS after 18 months is artefactual, reflecting the end of follow-up, as patients transitioned to a separate post-study drug access program.

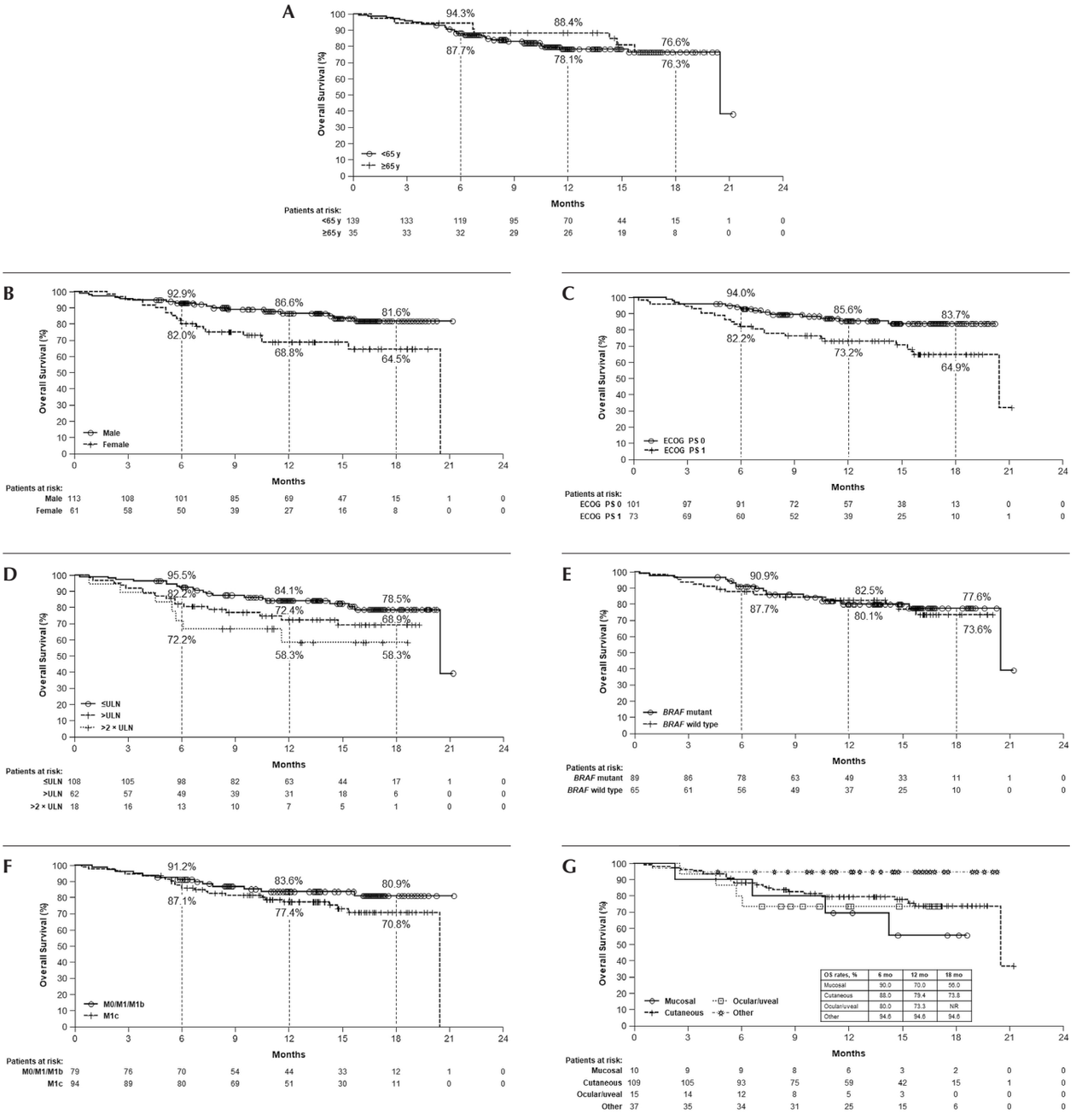

FIGURE 3 Overall survival (OS) outcomes (Kaplan–Meier curves) in key subgroups. (A) Age, with a median OS of 20.5 months [95% confidence interval (CI): 20.5 months to not reached (NR)] for patients less than 65 years of age (30 events, 139 patients) and NR for patients 65 years of age and older (7 events, 35 patients). (B) Sex, with a median OS of NR for male patients (17 events, 113 patients) and 20.5 months (95% CI: 15.3 months to 20.5 months) for female patients (20 events, 61 patients). (C) Eastern Cooperative Oncology Group (ECOG) performance status (PS), with a median OS of NR for patients with PS 0 (14 events, 101 patients) and 20.5 months (95% CI: 20.5 months to NR) for patients with PS 1 (23 events, 73 patients). (D) Serum lactate dehydrogenase, with a median OS of 20.5 months (95% CI: 20.5 months to NR) for the upper limit of normal (ULN) or less (20 events, 108 patients), NR for greater than the ULN (17 events, 62 patients), and NR (95% CI: 5.7 months to NR) for more than 2×ULN (7 events, 18 patients). (E) *BRAF* status, with a median OS of 20.5 months (95% CI: 20.5 months to NR) for mutated status (18 events, 89 patients) and NR for wild-type status (14 events, 65 patients). (F) M Stage, with a median OS of NR for M0/1a/1b disease (13 events, 79 patients) and 20.5 months (95% CI: NR to NR) for M1c disease (24 events, 94 patients). (G) Melanoma subtype, with a median OS of NR (95% CI: 2.3 months to NR) for mucosal melanoma (4 events, 10 patients), 20.5 months (95% CI: 20.5 months to NR) for cutaneous melanoma (25 events, 109 patients), NR (95% CI: 5.8 months to NR) for ocular or uveal melanoma (4 events, 15 patients), and NR for other subtypes (2 events, 37 patients). Of the 37 patients reported to have other forms of melanoma, 13 were reported to have unknown primary melanoma, and 11, nodular melanoma.

with ocular or uveal melanoma (95% CI: 44% to 89%), 70% for those with mucosal melanoma (95% CI: 33% to 89%), and 95% for those with an "other" melanoma subtype (95% CI: 80% to 99%). (Of the 37 patients reported to have an "other" melanoma subtype, 13 had an unknown primary melanoma, and 11 had nodular melanoma.) The 12-month OS rate was numerically lower for patients less than 65 years of age (78%; 95% CI: 70% to 84%) than for those 65 years of age or older (88%; 95% CI: 72% to 95%); rates were similar for patients with *BRAF* mutation–negative tumours (82%; 95% CI: 76% to 86%) and those with *BRAF* mutation–positive tumours (82%; 95% CI: 77% to 85%).

DISCUSSION

This large Canadian EAP allowed patients to access life-prolonging medications while physicians were provided with experience in managing the toxicities associated with the novel agents. Moreover, real-world safety and efficacy data were collected to ensure that the results accorded with those from registrational RCTs[2,5–7].

Compared with patient populations in the CheckMate 069 and CheckMate 067 trials[5,7], the EAP population was younger (median age: 56 years vs. 59–64 years), consisted of proportionally fewer patients with an ECOG PS of 0 (58% vs. 73%–83%), and had a higher incidence of *BRAF* mutation–positive tumours (51% vs. 24%–32%). The relatively high proportion of patients with *BRAF* mutation–positive tumours is likely explained by the inclusion criteria, which allowed enrolment of patients who had progressed on BRAF- or MEK-targeted therapy. However, the incidence of elevated baseline serum LDH was similar in the EAP and RCT populations (36% vs. 25%–36%). In contrast to the CheckMate 069 and CheckMate 067 trials, CheckMate 218 enrolled patients who could previously have received other prior systemic treatment. Overall, the EAP population had some prognostic features that were more negative than those in the RCT populations, but outcomes for the EAP population were comparable.

Despite differences between the EAP and the RCT populations, survival outcomes with nivolumab plus ipilimumab for the patients in the EAP compared favourably. The 12-month OS rate was 80% in the EAP population and 73% for those who received nivolumab plus ipilimumab in the CheckMate 069 and CheckMate 067 trials[6,10]. Further underscoring the survival benefit, the 12-month OS rate was greater than 70% in groups with poor prognostic characteristics (elevated LDH and ocular or uveal melanoma, for instance). Patients with ocular or uveal melanoma were not eligible to enrol in the RCTs, and although such patients constituted a small proportion (9%) of the EAP, survival in that subgroup was better than expected. Ocular or uveal melanoma typically demonstrates an aggressive course[11], with a 5-year relative survival rate of 19% in the metastatic setting[12]. Our observations accord with those in a retrospective study of 8 patients in whom ipilimumab plus nivolumab was active in uveal melanoma[13]. In addition, compared with female patients, male patients experienced increased survival, consistent with a recent systematic review of immune checkpoint inhibitors[14]. Survival rates were higher for patients 65 years of age and older than for patients less than 65 years of age, suggesting that the combination might be of benefit in elderly patients. A similar trend of an increased response to anti–PD-1 therapy in elderly patients has also been observed in another study[15]. Furthermore, survival rates were similar for patients with *BRAF* mutation–negative and *BRAF* mutation–positive tumours, suggesting that *BRAF* mutation status is not predictive of response. However, because of the observational nature of the present EAP and its short follow-up, OS data from this EAP should be interpreted with caution. Notably, the OS differences observed between patients with *BRAF* mutation–negative and *BRAF* mutation–positive tumours in CheckMate 067 were not readily evident at 12 and 18 months, beginning to emerge only at 2 years of follow-up.

Because of the nature of the study design, response data were not collected in the present EAP. The absence of response and progression-free survival data restricts further comparisons with clinical studies and represents a limitation.

Nivolumab plus ipilimumab was well tolerated. Safety results were consistent with those in the RCTs[5,7]. Grades 3–4 TRAEs were reported in 60% of patients and led to treatment discontinuation in 28% of the population. In CheckMate 069 and CheckMate 067[5,7], grades 3–4 TRAEs were reported in 54%–55% of patients and led to treatment discontinuation in 29%–38%. The most common grades 3–4 TRAEs included diarrhea (10%) and increased alanine aminotransferase and aspartate aminotransferase (9% each), which were also among the most common AEs, occurring at similar rates in CheckMate 069 and CheckMate 067[5,7]. Two treatment-related deaths were reported, but no new safety signals were identified.

CONCLUSIONS

CheckMate 218 was an observational EAP evaluating the safety and efficacy of the nivolumab plus ipilimumab combination in real-world patients with advanced melanoma. Its results provide additional insights into the use of the combination in patients with advanced melanoma in the real-world setting, including subpopulations not studied in RCTs. Clinical benefit was noted in patients with various melanoma subtypes and in those who had received prior treatments. The unexpected benefit in uveal melanoma—albeit in a limited number of patients—suggests that the combination should be explored further in that melanoma subtype. The results of the EAP are consistent with RCT data, further supporting the use of the nivolumab plus ipilimumab combination for the treatment of advanced melanoma.

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DATA AVAILABILITY

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

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: DH reports personal fees for advisory board roles from Bristol Myers Squibb, EMD Serono, Merck, Novartis, and Roche, and for a lecture role from Novartis. JGM reports personal fees for advisory board roles from Bristol Myers Squibb, Celgene, EMD Serono, Merck, Novartis, and Roche, and grant funding from Merck. SE reports personal fees for advisory board roles from Bristol Myers Squibb, EMD Serono, Merck, Novartis, and Sanofi. XS reports personal fees for advisory board roles from Bristol Myers Squibb, Merck, and Novartis, and has served as a research investigator for trials sponsored by Bristol Myers Squibb, Merck, Novartis, and Roche. EM reports personal fees for advisory board roles from Bristol Myers Squibb, Merck, Novartis, and Roche. KJS reports personal fees for advisory board roles from AbbVie, AstraZeneca, Bristol Myers Squibb, Merck, and Seattle Genetics; honoraria from AbbVie, AstraZeneca, Bristol Myers Squibb, Merck, Seattle Genetics, and Verastem; a consulting role with Servier; and institutional trial research funding from Bristol Myers Squibb, Merck, and Novartis. MS reports personal fees (honoraria) from Bristol Myers Squibb, EMD Serono, Merck, and Novartis. BS and FR are employees of Bristol Myers Squibb.

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