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Preferences of Canadian patients and physicians for adjuvant treatments for melanoma

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ABSTRACT

Background Past research suggests that patients with early- and late-stage melanoma will endure adverse events and inconvenient treatment regimens for improved survival. Evidence about the preferences of Canadian patients and physicians for novel adjuvant treatments for melanoma is unavailable.

Methods Patient and physician preferences for adjuvant treatments for melanoma were assessed in an online discrete choice experiment (DCE). Treatment alternatives were characterized by 8 attributes with respect to dosing regimen, efficacy, and toxicities, with levels corresponding to those for dabrafenib–trametinib, nivolumab, pembrolizumab, and interferon. For patients, the effects of melanoma on quality of life and ability to work and perform activities of daily living were also assessed. Patients were recruited by Canadian melanoma patient advocacy groups through e-mail and social media. Physicians were recruited by e-mail.

Results Of 94 patients who started the survey, 51 completed 1 or more DCE questions. Of 166 physicians sent the e-mail invitation, 18 completed 1 or more DCE questions. For patients, an increased probability of remaining cancer-free over 21 months was the most important attribute. For physicians, an increased chance of the patient's remaining alive over 36 months was the most important attribute. Patients and physicians chose active treatment over no treatment 85% and 86% of the time respectively and a treatment with attributes consistent with dabrafenib–trametinib 71% and 67% of the time respectively. A substantial proportion of patients reported worrying about future diagnostic tests and their cancer coming back.

Conclusions Canadian patients and physicians are generally concordant in their preferences for adjuvant melanoma treatments, preferring active treatment to no treatment and dabrafenib–trametinib to other options.

Key Words Melanoma, preferences

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INTRODUCTION

Between 1992 and 2013, the melanoma incidence rate in Canada increased approximately 2% annually[1]. In 2017, an estimated 7200 new diagnoses of melanoma and 1250 deaths from the disease occurred in Canada[1].

Surgical resection is recommended for patients with stages IB–III melanoma[2]. Until recently, interferon alfa-2b ("interferon") has been the only therapy approved in Canada for use as adjuvant treatment in patients having a successful resection. However, use of interferon is limited because of relatively modest improvements in the rates of disease recurrence and survival and because of severe toxicities that lead to treatment discontinuation and impaired quality of life.

In recent years, the treatment of metastatic melanoma has been transformed by the introduction of novel therapies targeting the MAPK pathway—in particular, combinations of BRAF and MEK inhibitors (dabrafenib–trametinib, vemurafenib–cobimetinib, and encorafenib–binimetinib)

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and immune checkpoint inhibitors (the anti–CTLA-4 monoclonal antibody ipilimumab, and the PD-1 monoclonal antibodies nivolumab and pembrolizumab). The efficacy and safety of those novel therapies as adjuvant treatment in patients with stage III melanoma is being examined in several ongoing randomized controlled trials, which have reported positive initial findings. The efficacy and safety of dabrafenib–trametinib in patients with resected *BRAF* mutation–positive stage III melanoma is being examined in the COMBI-AD trial (mutations in *BRAF* are detected in 40%–50% of melanoma cases)[3–6]. At the initial data cut-off, with a median follow-up of 34 months, the estimated 3-year relapse-free survival (RFS) was 58% in patients randomized to dabrafenib–trametinib and 39% in those randomized to placebo [hazard ratio (HR): 0.47; 95% confidence interval (CI): 0.39 to 0.58; $p < 0.001$][6]. Based on an updated analysis with median follow-ups of 44 months (dabrafenib–trametinib) and 42 months (placebo), the 3- and 4-year RFS rates were, respectively, 59% and 54% in the dabrafenib–trametinib arm and 40% and 38% in the placebo arm (HR: 0.49; 95% CI: 0.40 to 0.59)[7]. Overall survival (OS) at 3 years was 86% compared with 77% respectively (HR: 0.57; 95% CI: 0.42 to 0.79; $p = 0.000019$, which was above the pre-specified interim analysis boundary)[6]. The risk of pyrexia was increased in patients receiving dabrafenib–trametinib relative to those receiving placebo[6].

In KEYNOTE-054, a randomized, double-blind, placebo-controlled phase III trial of pembrolizumab compared with placebo in adult patients with resected stage III melanoma, the 12-month RFS rate was reported to be 75% for patients receiving pembrolizumab and 61% for those receiving placebo (HR: 0.57; 98.4% CI: 0.43 to 0.74; $p < 0.001$)[8]. In the CheckMate 238 trial, a randomized, double-blind, phase III trial in patients 15 years of age or older with stage IIIB, IIIC, or IV melanoma who had undergone complete resection, the 24-month RFS was 63% for nivolumab and 50% for ipilimumab (HR: 0.66; 95% CI: 0.54 to 0.81; $p < 0.0001$)[9,10]. Although the efficacy of pembrolizumab and nivolumab in improving RFS in the adjuvant setting is promising, data about OS from KEYNOTE-054 and CheckMate 238 are currently not available, and treatments could be associated with potentially severe immune-related adverse events (involving mainly the gut, skin, endocrine glands, liver, and lung) that might persist after discontinuation of treatment[11]. Also, those drugs require intravenous (IV) administration, whereas dabrafenib and trametinib are administered orally.

In light of the differences in efficacy, toxicity, and frequency and mode of administration between existing and novel treatments, patients and physicians have to consider the trade-offs of benefits and risks when choosing treatment options. Past research suggests that patients with early- or late-stage melanoma are willing to endure adverse events and inconvenient treatment regimens for improved survival[12–15]. However, evidence is limited concerning which of the existing and novel treatments might be preferred by Canadian patients with melanoma and by their physicians. The objective of the present study was to estimate patient and physician preferences for attributes of currently available and novel adjuvant treatments for melanoma in Canada.

METHODS

Overview

This descriptive cross-sectional online survey recruited Canadian patients with nonmetastatic (that is, non–stage IV) melanoma and Canadian physicians who treat melanoma patients. The survey was conducted from July 2018 to August 2018. Patient participants were recruited in collaboration with patient advocacy groups—the Save Your Skin Foundation and the Melanoma Network of Canada—through e-mail lists, postings to the Web sites of patient advocacy groups, and postings to social media. Physicians were recruited through e-mail lists provided by the study sponsor. Eligibility of all participants was assessed with a self-completed online screener.

Patient and physician preferences and the relative importance of attributes of adjuvant treatments for melanoma were assessed in a discrete choice experiment (DCE)[16]. In a DCE, individuals are provided with a series of choice-tasks wherein they must choose between hypothetical treatment alternatives that vary in terms of levels of the attributes of interest, with the levels of the attributes being systematically varied for the respondents. Responses to the survey are then used to estimate the degree to which each attribute influences preferences, and to derive utility weights for each attribute level. The attributes and their levels were selected to reflect differences in key characteristics of potential adjuvant treatments for melanoma, including interferon, dabrafenib–trametinib, nivolumab, and pembrolizumab.

The DCE used in this study used a choice-based conjoint approach with identical discrete choice tasks for the patient and physician surveys. For each choice-task, participants were presented with a series of choices between two hypothetical treatments (for example, dabrafenib–trametinib or nivolumab) and the option for no treatment. The patient survey also included a number of questions about the patient's demographic and clinical characteristics, melanoma treatment history, work productivity, and psychological well-being. The DCE was developed in a manner consistent with the recommendations from the Conjoint Analysis Task Force of the International Society for Pharmacoeconomics and Outcomes Research[16–18]. The survey was self-completed and administered and analyzed using Lighthouse Studio, an online survey software and conjoint analysis tool (Lighthouse Studio, version 9.6: Sawtooth Software, Provo, UT, U.S.A.; https://www.sawtoothsoftware.com/products/conjoint-choice-analysis). The study was approved by Quorum Review IRB (Seattle, WA, U.S.A.).

Survey Participants

Patient eligibility criteria included residence in Canada, age 18 years or older, and a current diagnosis of stage I, II, or III melanoma based on self-reporting. Those criteria were selected to match the population of patients who would at that time or at some future point (for example, after progression from stage II to stage III disease) be eligible for adjuvant treatment with interferon, dabrafenib–trametinib, nivolumab, or pembrolizumab. Patients were allowed to have received prior adjuvant treatment for melanoma. To be eligible, physicians had to be 18 years of age or older, to

hold a license to practice medicine in Canada, to specialize in medical oncology, and to have reported seeing at least 1 melanoma patient in the preceding year.

Survey Questionnaire

Attributes and levels in the DCE were determined based on consultation with clinical experts and representatives of patient groups and were designed to capture key differences between the adjuvant treatments of interest, which included interferon, dabrafenib–trametinib, nivolumab, and pembrolizumab. The 8 attributes evaluated included the dosing regimen and estimated improvements in RFS, distant metastases-free survival (DMFS), and OS for treatment compared with no treatment. Each of the foregoing attributes had 4 levels, with 1 level corresponding to each of the 4 treatments of interest. The 4 additional attributes related to the estimated increased risk of experiencing adverse events for treatment compared with no treatment. Each of the latter attributes had 3 levels because the toxicity profiles for nivolumab and pembrolizumab were assumed to be equivalent. Table I shows the attributes and levels included in the survey; Table II presents the attribute profiles corresponding to adjuvant treatments for melanoma.

Levels related to improvements in RFS, DMFS, and OS compared with no treatment were based on reported outcomes from key clinical trials of the treatments of interest[6,8,10,19–22]. At the time that the study was conducted, OS data from trials of nivolumab and pembrolizumab were unavailable. The OS attribute was therefore characterized by levels representing a range of potential improvements including "no proven benefit," "less than 5% improvement," "5%–10% improvement," and "10%–15% improvement." Descriptions of attributes for adverse events were based on the *Common Terminology Criteria for Adverse Events,* version 5.0[23], for grade 2 adverse events. The levels for the increased risks for adverse events were based on the overall incidence of those events (regardless of grade) in the key clinical trials of the treatments of interest[6,8,10,19–22].

The experimental design of the DCE was generated to conform to the principles of minimal overlap (levels that appear multiple times in the same task), level balance (each level appears at approximately the same frequency), and orthogonality (the weight of each attribute level can be measured independently of all other attribute levels). The survey consisted of 14 tasks based on the experimental design and 2 fixed head-to-head tasks: one based on the profiles for dabrafenib–trametinib compared with nivolumab, and one based on the profiles for dabrafenib–trametinib compared with pembrolizumab (both plus the option to receive no treatment). No fixed task had a profile based on interferon because that agent is less efficacious and more toxic than the other adjuvant treatments of interest. For the 14 tasks based on the experimental design, the attribute levels were systematically varied such that each respondent answered a different set of tasks. Treatment labels were omitted from all tasks so that respondents would not be able to discern whether a given concept within a task corresponded to a real or hypothetical treatment.

In addition to the DCE, the patient and physician surveys both included questions about demographics. The patient survey also included questions about clinical characteristics and secondary questions related to personal anxiety and depression[24,25], perceived cancer control[26], and fear of cancer progression[27]. Supplemental Appendix A contains a copy of the survey instrument.

Survey Pretest

A pretest of the survey was conducted to ascertain whether patient and physician participants found the instructions for completing the survey and the descriptions of the characteristics of the treatments easy to understand, and also how much time was required to complete the survey. Most of the 8 patients and 3 physicians who completed the pretest indicated that they completed the survey in 30 minutes or less. Based on responses to the pretest, minor changes were made to the study questions. Because no material changes were made to the survey based on the pretest, the responses from the pretest phase were included in the analysis together with the responses to the final survey instrument.

Analyses

Descriptive statistics were generated to summarize the characteristics of study participants and the relative preferences of the participants for key treatment attributes and for treatment options with profiles corresponding to dabrafenib–trametinib, nivolumab, pembrolizumab, interferon, and no treatment. For patients, descriptive statistics also were generated to summarize the psychological experiences associated with melanoma and melanoma-related impairment of work productivity and activities of daily living. Estimates of relative preferences for attribute levels were estimated separately for patients and physicians using a hierarchical Bayes approach and assuming that preferences were normally distributed across respondents and effects-coded variables[18]. The estimated preference weights (that is, utilities) from the hierarchical Bayes analysis were used to calculate the conditional relative importance of each attribute, which indicates the weight respondents place on that attribute when deciding between treatments.

RESULTS

Study Participants

Of 94 patients who started the survey (including 15 who started the pretest), 68 qualified for the survey, 55 consented to the survey, 51 completed at least 1 DCE question, and 39 completed all survey questions. Of 166 physicians who were sent the e-mail invitation to participate in the survey, 21 started the survey, 19 qualified for the survey, 19 consented to the survey, and 18 completed at least 1 DCE question. All the physicians who completed the 1st DCE task completed all the DCE tasks. Figure 1 summarizes the patient and physician attrition for the survey.

Participant Characteristics

Table III reports patient and physician characteristics. Mean age was 53 years for patients and 50 years for physicians. Of the patients and physicians, 72% and 89% respectively were women. For patients, the mean time since melanoma diagnosis was 4.74 years, and the mean time since the most recent surgery to remove melanoma was

3.26 years. On average, physicians had been in practice 16.6 years and had treated or managed 143 patients in the preceding year. Most patients were from Ontario; of the physicians, 50% were from Quebec, and 22% were from Ontario. Of the physicians, 94% served primarily an urban or suburban population.

DCE Findings

Table IV reports estimated preference weights for each attribute level. It should be noted that the estimated preference weights can be interpreted only in relation to the estimates for the other levels within a given attribute. Within each attribute, the level with the highest preference weight is most preferred, and the level with the lowest preference weight is least preferred. The size of the difference in the preference weights for the most preferred and least preferred levels within an attribute, relative to the size of the differences for other attributes, reflects the importance of that attribute. For example, the effect on patients of a 10%–15% increased chance of remaining

TABLE I Attributes and levels included in the discrete choice experiment[a]

Attribute	Level	Description
Dosing regimen	1	3 Pills in the morning and 1 pill in the evening every day for 1 year
	2	30-Minute intravenous infusion at clinic once every 2 weeks or every 4 weeks for 1 year
	3	30-Minute intravenous infusion at clinic once every 3 weeks for 1 year
	4	60-Minute intravenous infusion at clinic 5 days per week for 1 month and then self-injected under the skin 3 days per week for 1 year
Increased chance of ...		
Remaining cancer-free for 21 months	1	9%
	2	20%
	3	21%
	4	25%
Remaining free of distant metastases for 21 months	1	Not proven to show benefit
	2	14%
	3	16%
	4	18%
Remaining alive for 36 months	1	Not proven to show benefit
	2	<5%
	3	5%–10%
	4	10%–15%
Fever greater than 39.0°C, potentially requiring treatment with steroid medications	1	<10%
	2	52%
	3	81%
Muscle aches, fever, sweating, and malaise causing difficulties with work and daily activities	1	<10%
	2	7%
	3	75%
Diarrhea (4–6 episodes daily), potentially requiring treatment with steroid medications	1	2%
	2	18%
	3	35%
Thyroid problems, with symptoms including sensitivity to heat, cold, or both; weight gain or weight loss; sweating, fatigue, irritability, and insomnia requiring medications and potentially persisting after treatment discontinuation	1	0%
	2	3%
	3	20%

[a] Included regardless of treatment profile.

alive (os rate) for 36 months compared with no treatment is 139.9 [75.1 – (–64.8) = 139.9], which represents twice the utility of an 18% increase in the chance of remaining alive with DMFS status for 21 months compared with no treatment [25.5 – (–45.8) = 71.3]. For physicians, the effect of a 10%–15% increased chance of os for 36 months compared with no treatment is 209.2 [103.8 – (–105.4) = 209.2] or 4.3 times the utility of a 14% increase in the chance of remaining in DMFS status for 21 months compared with no treatment [19.8 – (–28.5) = 48.3].

TABLE II Attribute profiles for adjuvant treatments of melanoma[6,8,10,19–22]

Attribute	Drug	Description
Dosing regimen	Dabrafenib–trametinib	3 Pills in the morning and 1 pill in the evening every day for 1 year
	Nivolumab	30-Minute intravenous infusion at clinic once every 2 weeks or every 4 weeks for 1 year
	Pembrolizumab	30-Minute intravenous infusion at clinic once every 3 weeks for 1 year
	High-dose interferon	60-Minute intravenous infusion at clinic 5 days per week for 1 month and then self-injected under the skin 3 days per week for 1 year
Increased chance of ...		
Remaining cancer-free for 21 months	Dabrafenib–trametinib	25%
	Nivolumab	21%
	Pembrolizumab	20%
	High-dose interferon	9%
Remaining free of distant metastases for 21 months	Dabrafenib–trametinib	18%
	Nivolumab	14%
	Pembrolizumab	16%
	High-dose interferon	Not proven to show benefit
Remaining alive for 36 months	Dabrafenib–trametinib	5%–10%
	Nivolumab	Not proven to show benefit
	Pembrolizumab	Not proven to show benefit
	High-dose interferon	5%–10%
Fever greater than 39.0°C, potentially requiring treatment with steroid medications	Dabrafenib–trametinib	52%
	Nivolumab	<10%
	Pembrolizumab	<10%
	High-dose interferon	81%
Muscle aches, fever, sweating, and malaise causing difficulties with work and daily activities	Dabrafenib–trametinib	7%
	Nivolumab	<10%
	Pembrolizumab	<10%
	High-dose interferon	75%
Diarrhea (4–6 episodes daily), potentially requiring treatment with steroid medications	Dabrafenib–trametinib	18%
	Nivolumab	2%
	Pembrolizumab	2%
	High-dose interferon	35%
Thyroid problems, with symptoms including sensitivity to heat, cold, or both; weight gain or weight loss; sweating, fatigue, irritability, and insomnia requiring medications and potentially persisting after treatment discontinuation	Dabrafenib–trametinib	0%
	Nivolumab	20%
	Pembrolizumab	20%
	High-dose interferon	3%

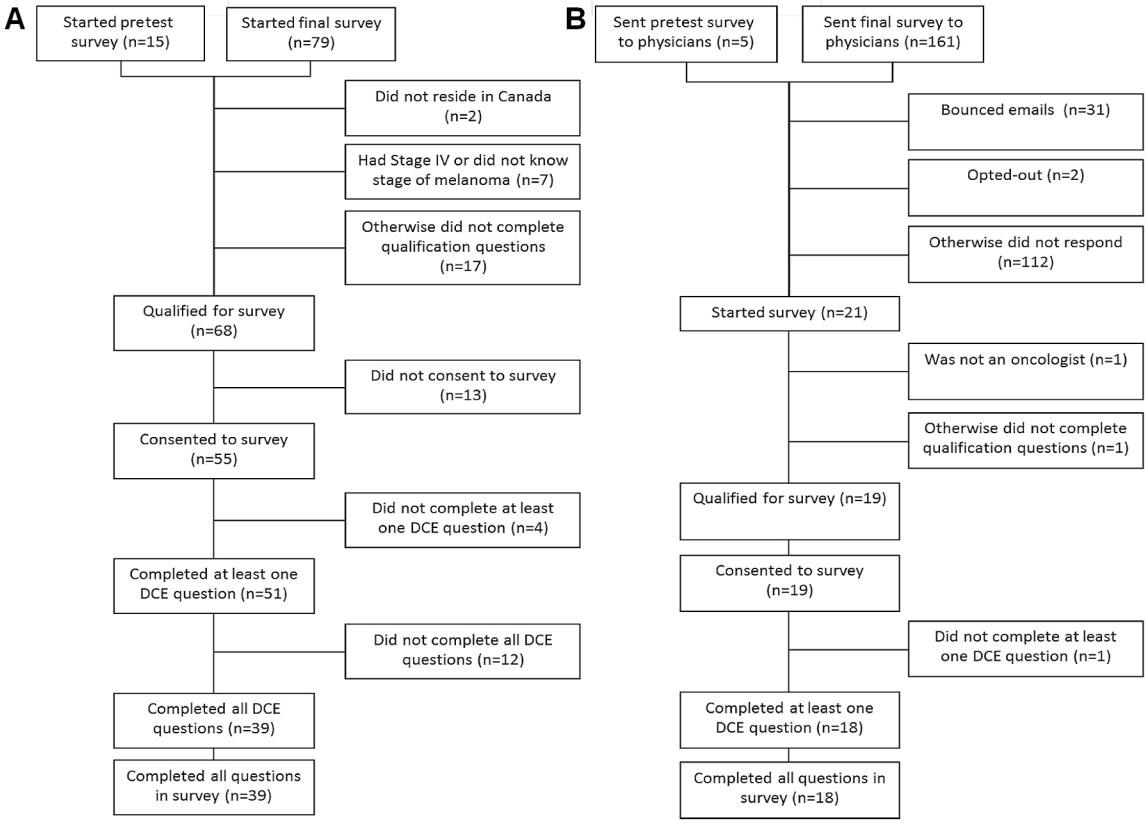

FIGURE 1 (A) Patient and (B) physician attrition. DCE = discrete choice experiment.

Figure 2 shows the mean relative importance of attributes for patients and physicians. Patients valued the increased probability of remaining cancer-free for 21 months highest, followed by the increased probability of remaining alive for 36 months, followed by the dosing regimen. Physicians valued the increased probability of a patient's remaining alive for 36 months highest, followed by the dosing regimen, followed by an increased probability of remaining cancer-free for 21 months.

With respect to preference weights for the various levels of the dosing regimen, physicians assigned the highest preference weights to treatments administered as 3 pills in the morning and 1 pill in the evening every day for 1 year ("orally administered treatment"), corresponding to the dosing regimen for dabrafenib–trametinib. Patients assigned similar preference weights to orally administered treatments and treatments administered by 30-minute IV infusion at the clinic once every 3 weeks for 1 year (mean preference weights of 20.6 and 21.0 respectively), the latter dosing regimen corresponding to pembrolizumab. Patients and physicians both assigned the lowest preference weight to the dosing regimen corresponding to interferon—that is, a 1-hour IV infusion at the clinic 5 days per week for 1 month and then self-injected under the skin 3 days per week for 1 year (–58.1 and –71.1 respectively).

The estimated patient preference weights for the levels of other attributes were generally consistent with expectations, with greater improvements in efficacy and lower risks of adverse events being associated with higher utility values. For physicians, more instances of results being inconsistent with expectations were observed. For example, on average, physicians assigned a lower utility to a 25% improvement than to a 20% improvement in a patient's remaining cancer-free for 21 months. Similarly, on average, physicians assigned lower utilities to 16% and 18% improvements than to a 14% improvement in a patient's remaining in DMFS status for 21 months. The anomalous findings are likely attributable to the small physician sample size.

When asked to choose between two treatment options and the option to receive no treatment, patients and physicians chose one of the active treatments 85% and 86% of the time respectively. Figure 3 reports results of the head-to-head comparisons of treatment alternatives. The treatment alternative whose attributes are consistent with dabrafenib–trametinib was the alternative most frequently selected by patients and physicians alike.

Impact of Melanoma on Quality of Life and Work and Daily Activities

Supplemental Appendix A includes tables summarizing the responses to the questions about the impact of melanoma on quality of life and work and daily activities. Of the patients, 54% reported feeling nervous, anxious, or "on edge" at least some of the time during the preceding 2 weeks, and 49% reported not being able to stop or control worrying at some point during the preceding 2 weeks. Feeling down, depressed, or hopeless during the preceding 2 weeks was reported by 38% of patients, with 21% reporting little interest

TABLE III Demographic characteristics: patients and physicians

Characteristic	Patients	Physicians
Participants *(n)*	39	18
Mean age (years)[a]	53±14	50±8
Female sex [*n* (%)]	28 (71.8)	16 (88.9)
Province of residence [*n* (%)]		
Alberta	6 (15.4)	0
British Columbia	3 (7.7)	3 (16.7)
Ontario	25 (64.1)	4 (22.2)
Quebec	1 (2.6)	9 (50.0)
Other	4 (10.3)	2 (11.2)
Highest education level attained [*n* (%)]		
High school	5 (12.8)	—
Associate's degree	9 (23.1)	—
Bachelor's degree	16 (41.0)	—
Postgraduate degree	9 (23.1)	—
Employment (work for pay) [*n* (%)]		
Full time	17 (43.6)	—
Part time	7 (17.9)	—
Unemployed	15 (38.5)	—
Current stage of melanoma		
I or II	15 (38.5)	—
III	23 (59.0)	—
Free of disease	1 (2.6)	—
Stage of melanoma at diagnosis		
I or II	19 (48.7)	—
III	18 (46.2)	—
IV	2 (5.1)	—
Taking medication for melanoma [*n* (%)]		
Currently	5 (12.8)	—
Not currently, but previously	15 (38.5)	—
Never	19 (48.7)	—
Current or previous medications [*n* (%)]		
Interferon	11 (36.7)	—
Ipilimumab	2 (6.7)	—
Nivolumab	3 (10.0)	—
Pembrolizumab	6 (20.0)	—
Dabrafenib	1 (3.3)	—
Trametinib	1 (3.3)	—
Unknown (clinical trial)	1 (3.3)	—
Chemotherapy	2 (6.7)	—
Other	3 (10.0)	—
Time since most recent physician visit for management of melanoma [*n* (%)]		
<1 Month	11 (28.2)	—
1–3 Months	16 (41.0)	—
3–6 Months	8 (20.5)	—
6–12 Months	4 (10.3)	—
Specialty of physician seen most regularly for management of melanoma [*n* (%)]		
Medical oncologist	24 (61.5)	—
Dermatologist	10 (25.6)	—
Other	5 (12.8)	—
Work setting		
Community-based health centre	—	4 (22.2)
Academic health centre	—	14 (77.8)

[a] Calculated based on mid-points within age categories.

or pleasure in doing things. Some impact of melanoma on the ability to work over the preceding 7 days was indicated by 57%, and 59% indicated some impact on the ability to perform daily activities during that period. Worrying "very much" about their cancer coming back was reported by 56% of patients, with 31% and 15% of patients worrying "very much" about future diagnostic tests and another type of cancer respectively. The extent to which patients worried about future diagnostic tests, other types of cancer, and their cancer coming back declined with time since the diagnosis of melanoma. For example, 48% of patients diagnosed less than 4 years before taking the survey (the median duration since the melanoma diagnosis) reported that they worried "very much" about future diagnostic tests, but only 6% of those diagnosed more than 4 years before taking the survey did so. Of patients who had been diagnosed less than 4 years earlier, 22% reported worrying "very much" about another type of cancer, but only 6% of those diagnosed more than 4 years earlier did so.

Moderate-to-high impact of melanoma on work activities during the preceding 7 days was reported by 24% of patients, and 21% reported that melanoma had a moderate-to-high impact on their activities of daily living. Of the patient respondents, 17% reported missing 1 or more hours from work in the week before taking the survey because of problems associated with their melanoma.

DISCUSSION

Summary

In the present study, we assessed the preferences of Canadian patients and physicians for characteristics of adjuvant treatments for melanoma based on responses to an online survey using a DCE. For patients, the most important attribute of treatment compared with no treatment was the increased probability of remaining cancer-free for 21

TABLE IV Attribute-level preference weights[a]

Attribute	Level	Patients (*n*=39)[b]	Physicians (*n*=18)[b]
Dosing regimen			
	3 Pills in the morning and 1 pill in the evening every day for 1 year	20.6±22	44.1±44
	30-Minute intravenous infusion at clinic once every 3 weeks for 1 year	21.0±33	21.6±47
	30-Minute intravenous infusion at clinic once every 2 weeks or every 4 weeks for 1 year	16.5±21	5.4±38
	60-Minute intravenous infusion at clinic 5 days per week for 1 month and then self-injected under the skin 3 days per week for 1 year	–58.1±37	–71.1±59
Increased chance of ...			
	Remaining cancer–free for 21 months		
	9%	–99.9±64	–52.0±38
	20%	29.0±14	34.2±24
	21%	17.0±13	–3.7±27
	25%	53.9±46	21.4±31
	Remaining free of distant metastases for 21 months		
	Not proven to show benefit	–45.8±23	–28.5±20
	14%	3.1±18	19.8±15
	16%	17.2±34	3.4±31
	18%	25.5±38	5.3±24
	Remaining alive for 36 months		
	Not proven to show benefit	–64.8±25	–49.2±38
	<5%	–41.6±31	–105.4±38
	5%–10%	31.3±30	50.9±34
	10%–15%	75.1±38	103.8±51
	Fever		
	<10%	17.1±27	21.0±27
	52%	0.1±17	–18.8±19
	81%	–17.2±17	–2.2±26
	Flu-like symptoms		
	<10%	17.7±17	–11.9±17
	7%	34.9±19	13.4±20
	75%	–52.6±20	–1.5±30
	Diarrhea		
	2%	20.2±20	–18.4±26
	18%	6.9±26	36.4±24
	35%	–27.1±21	–18.0±20
	Thyroid problems		
	0%	16.1±12	29.5±20
	3%	16.3±20	–21.0±21
	20%	–32.5±18	–8.5±30

[a] Mean with standard deviation.
[b] Not all respondents completed every choice-task.

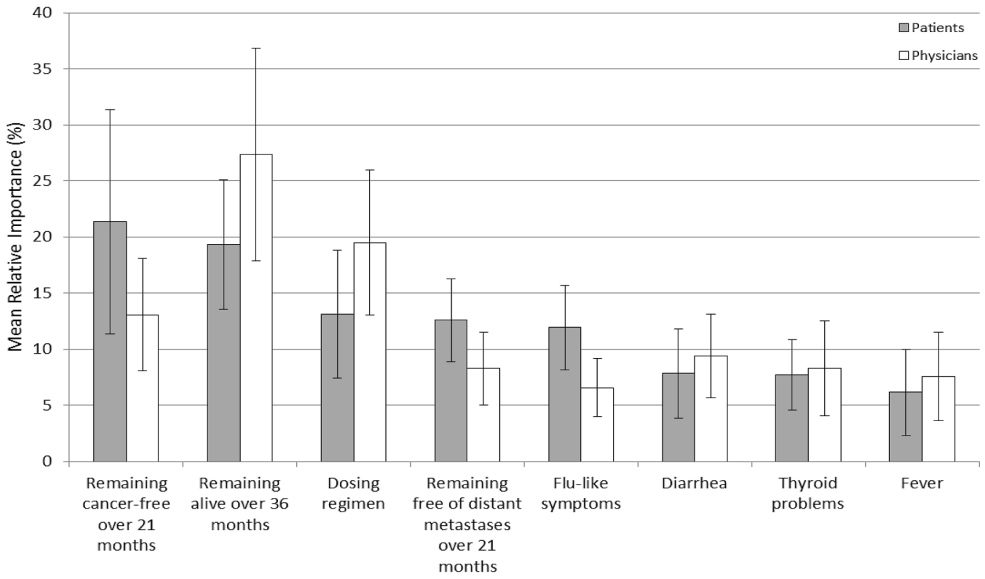

FIGURE 2 Mean (with standard deviation) relative importance of attribute: patients and physicians.

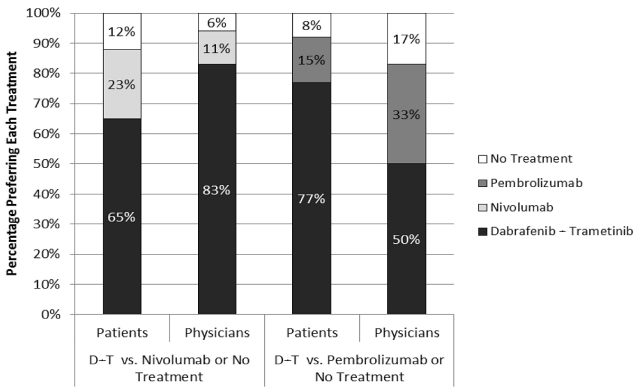

FIGURE 3 Choice of most preferred treatment in head-to-head comparison tasks of dabrafenib–trametinib (D–T) versus nivolumab or pembrolizumab and no treatment.

months. For physicians, the most important attribute of treatment compared with no treatment was an increased chance of remaining alive for 36 months. Whereas physicians assigned the highest preference weights to orally administered treatments (corresponding to the dosing regimen for dabrafenib–trametinib), patients assigned similar preference weights to orally administered treatments and to treatments administered by 30-minute IV infusion at the clinic once every 3 weeks (corresponding to the dosing regimen for pembrolizumab). Patients and physicians were similarly likely to choose an active treatment over no treatment, and patients and physicians alike most frequently chose a treatment alternative that had attributes consistent with dabrafenib–trametinib. Many patients reported that they were bothered by feelings of anxiety, worry, or depression, and that melanoma had some impact on their ability to work or perform daily activities. Importantly, a substantial proportion of patients reported worrying about future diagnostic tests and their cancer coming back. Those feelings of worry were greater for patients who had been diagnosed more recently. Also, 17% of patients reported missing 1 or more hours of work in the week before taking the survey because of problems associated with their melanoma.

Comparison with Prior Studies

Past research has indicated that patients with early- or late-stage melanoma are willing to endure adverse events and inconvenient treatment regimens for an improvement in survival[12–15]. Most recently, Beusterien and colleagues[12] conducted a survey of melanoma patients and physicians in the United States to assess patient preferences with respect to alternative adjuvant therapies for melanoma, including high-dose interferon, pegylated interferon, ipilimumab, and no treatment. As in the study reported here, Beusterien and colleagues found that active treatment is preferred to no treatment and that patients and physicians both prefer ipilimumab to high-dose interferon. However, whereas Beusterien and colleagues reported that improvement in OS is the most important attribute for patients and physicians alike, we found in the present study that improvement in RFS is the most important attribute for patients and that improvement in OS is the most important attribute for physicians. Those observations might be attributable to the fact that our study included a level for OS of "not proven to show benefit." Also, our study found that physicians rated the dosing regimen as relatively important, whereas that attribute was relatively less important in the study by Beusterien and colleagues. The latter observation might reflect the fact that our study included treatments that could be administered orally, whereas Beusterien considered only treatments administered by IV infusion. However, the results for physicians in the present study should be interpreted cautiously because of the relatively small number of physicians who completed the survey.

Limitations

The main limitation of our study is the relatively small sample size, especially for the physician group. Also, many patients failed to complete all the choice-tasks, possibly because of difficulties in understanding the questions or because of the length of the survey. Based on the pretest ($n = 8$), 75% of patients found the instructions for completing the survey and the descriptions of the characteristics of the treatments easy to understand, and most completed the survey in less than 30 minutes. However, 38% reported difficulty in understanding the choice-tasks. In particular, some patients indicated in their comments that it was difficult to choose between hypothetical treatments with very similar characteristics.

Patients were recruited by e-mail and from social media sites owned by two Canadian patient advocacy groups. Patients enrolled through such channels might not be representative of all patients in Canada with early-stage melanoma. Similarly, physicians were recruited based on prior engagement with Novartis and might not be representative of all physicians in Canada treating patients with melanoma. Of the 166 physicians who were recruited for the survey, only 18 (11%) completed at least 1 DCE question. Notably, 72% of patients and 89% of physicians were women, which is not representative of patients with melanoma overall or of Canadian physicians.

The BRAF and MEK inhibitors dabrafenib–trametinib are indicated only for patients with *BRAF* mutation–positive melanoma. However, at the time the study was conducted, testing for a *BRAF* mutation was not universally performed in patients with stage III melanoma. Patient participants were therefore included regardless of *BRAF* mutation status.

CONCLUSIONS

The present study provides important information about patient and physician preferences for novel adjuvant treatments in melanoma, suggesting that patients and physicians might prefer active treatment to observation, and treatments having attributes consistent with those of dabrafenib–trametinib to treatments having attributes consistent with nivolumab or pembrolizumab. That information could be useful for policymakers deliberating reimbursement and access to novel adjuvant treatments for melanoma.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: TED is a partner of Policy Analysis Inc. (PAI) and DS and CE are employees of PAI, which has received research funding from Bristol–Myers Squibb, Novartis, Pfizer, and Merck. MT is an employee of Novartis Pharmaceuticals Corp. and owns stock in Novartis.

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