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Immunotargeted therapy in melanoma: patient, provider preferences, and willingness to pay at an academic cancer center

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New melanoma therapies have shifted the expectations of patients and providers. Evaluating the impact of treatment characteristics may enhance shared decision making. A survey, including a discrete choice experiment, was utilized to evaluate perceived trade-offs of different melanoma treatments and to estimate out-of-pocket (OOP) willingness-to-pay (WTP) thresholds (January 2016 to March 2016). Participants included patients with melanoma at Huntsman Cancer Institute and their cancer care providers. Stakeholder focus groups were conducted to identify treatment attributes. Descriptive and comparative statistics and multinomial logit model were used to evaluate responses. Response rates were 41.9% (*N*=220) for patients and 37.7% (*N*=20) for providers. Immunotherapy and targeted therapy attributes considered important by participants were overall survival, immunotherapy-related side effects, and skin toxicities. Patients and providers had significantly different views of quality-of-life expectations, anxiety toward melanoma, trust to make treatment decisions, sharing concerns about treatment, time to discuss treatment, understanding OOP costs, and willingness to undergo/recommend treatment (half of the patients would undergo treatment if it was effective for >24 months). Among patients, the average monthly OOP WTP for combination immunotherapy with nivolumab+ipilimumab was $2357 and for BRAF/MEK inhibitor was $1648. Among providers, these estimates were $2484 and $1350, respectively. Discordance existed between patients' and providers' perceptions about quality of life expectations, degree of anxiety, sharing of opinions, and progression-free survival. Our study suggests that patients and providers exhibit a higher OOP WTP for combination immunotherapy treatment compared with BRAF/MEK inhibitors, influenced predominately by overall survival expectations. *Melanoma Res* 29:626–634 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

In the USA, skin cancer is a major public health problem with increasing incidence and annual treatment costs estimated at $8.1 billion [1]. Melanoma, the most serious type of skin cancer, is listed as the fifth most common cancer in the USA. Once it metastasizes, it has historically been considered a treatment-resistant malignancy.

The armamentarium of melanoma treatments, previously limited to traditional surgery, radiation therapy, and chemotherapy, has now expanded to include immunotherapy and targeted therapy. Until 2011, dacarbazine and high-dose interleukin 2 were the only agents for metastatic melanoma approved by the US Food and Drug Administration. Presently, there are four approved immunotherapy agents (ipilimumab, pembrolizumab, nivolumab, and interleukin 2) and four approved targeted therapy agents (vemurafenib, dabrafenib, trametinib, cobimetinib) approved by the Food and Drug Administration [2–7]. A recent publication reported a 3-year overall survival (OS) rate of 58% for combination nivolumab and ipilimumab in patients with advanced melanoma [2]. New agents afford patients with advanced melanoma more treatment choices.

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Corollary to this expansion is an increase in the complexity of healthcare decision-making. The Institute of Medicine defines high-quality healthcare as good communication, shared decision-making, and respect for patients' values and preferences [8]. Although value assessment of therapy has traditionally focused on survival advantage and economic gain, the real-world definition of value may differ by what is important to a particular audience (patient, provider, payer, policy maker, etc.) [9]. For example, among patients with solid tumors, 77% indicate a preference for 'hopeful gambles' in treatment selection, where a low percentage of patients derive long-term survival, compared with 'safe bet' treatments conferring a higher percentage of patients with an average survival benefit but no chance at a large gain [9].

As the molecular underpinnings of melanoma continue to be explored, new therapies will become available. Thus, it is important to understand how patients value therapy and to elucidate what facets of treatment are important to them. A personalized treatment strategy that incorporates patients' perceptions about melanoma, prognosis, treatment characteristics, expected clinical outcomes, and overall desired quality-of-life may contribute to treatment acceptance, utilization, and adherence. To address these gaps in patient and provider preferences surrounding melanoma treatment, we performed a prospective survey study using a discrete choice experiment (DCE) design that was administered to both patients with melanoma and their corresponding providers. In addition to characterizing patient and provider preferences, we calculated the respective willingness-to-pay (WTP) for immunotherapy and targeted therapy for melanoma treatment.

Patients and methods

A three-part tailored survey was built separately for patients and providers (see 'Patient and Provider Surveys' section, Supplemental digital content 1, *http://links.lww.com/MR/A106*). The first part of the survey assessed patient and provider demographics, disease and treatment characteristics (patients only), and perceptions and concerns toward melanoma care, treatment, and costs. The second part of the survey assessed the willingness of patients and providers to receive and/or recommend different systemic melanoma treatments, respectively, based on differing effectiveness and safety parameters. The last portion of the survey was the DCE. The questionnaire was developed at a fifth grade literacy level, and the contents were validated by provider focus groups and patient interviews. In addition, patient-friendly graphics were included to help illustrate/visualize the patient's experience.

Discrete choice experiment

DCE is a rigorous method for examining preference and WTP in healthcare [10]. It includes various choice sets, with each one consisting of different hypothetical treatment alternatives. These alternatives differ by treatment attributes, such as efficacy, side effects, cost, and levels of attributes. For each choice set, alternatives are compared and one alternative is selected. Based on random utility theory, a multinomial logit model was developed to determine the influences of attributes on patient preference and WTP for each level of change across all attributes.

Attribution and level identification

A literature review of studies reporting efficacy and safety of immunotherapy and targeted therapy in metastatic melanoma was conducted to determine treatment attributes. The initial list of attributes included: 5-year OS, 3-year OS, median OS, median progression-free survival, time to response, duration of response, immunotherapy-related side effects, skin toxicity, and gastrointestinal (GI) side effects. This list of attributes was discussed with providers and patients (details below). Eventually, six attributes including median OS, immunotherapy-related side effects, skin toxicity, GI toxicity, route of administration, and monthly out-of-pocket cost (OOP) were selected for the study (Table 1). For each attribute included in the DCE, the minimum and maximum values were obtained by literature review (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/MR/A106*). Each attribute had three levels, except the route of administration and cost attributes, which had two and six levels, respectively. The

Table 1 Attributes and levels of melanoma treatments and example discrete choice experiment choice set

Attributes	Levels		
Overall survival (years)	1, 2, 3		
Immunotherapy-related side effect (%)	0, 10, 20		
Skin toxicity (%)	0, 10, 20		
Gastrointestinal toxicity (%)	0, 5, 10		
Route of administration	Oral, intravenous		
Monthly out-of-pocket cost ($)	0, 500, 1000, 1500, 2000, 2500		
Treatment characteristics	**Treatment A**	**Treatment B**	**Neither**
Example discrete choice experiment choice set			
Average time you would live	3 years	2 years	Neither treatment A nor treatment B
Immune system side effects	10%	0%	
			
Skin side effects	10%	10%	
			
Gastrointestinal side effects	0%	0%	
			
How treatment is given	Through the vein	Oral	
Monthly out-of-pocket cost	$500	$0	
Which treatment would you choose?			
Treatment A			
Treatment B			
Neither treatment A nor treatment B			

route of administration included oral and intravenous dosage forms given the type of treatment availability for melanoma. The ranges for each treatment attribute were divided equally per level. The cost attribute was defined as the patient's monthly OOP cost derived from an estimated annual systemic treatment cost of $150 000 with an 80% insurance coverage rate. OOP costs were defined to patients and providers as the monthly amount for medications they would be responsible for paying OOP above and beyond their medical or prescription drug insurance benefits. It has been reported that 15 and 19% of cancer patients indicate spending from $2500 to less than $5000 to treat their cancer, including medications, in the past 12 months and since initial diagnosis, respectively [11].

As it was not feasible to present all possible combinations of selected attributes and levels (3×3×3×3×2×6) to each individual patient or provider, Ngene software (version 1.1.1, Choice-Metrics, Sydney, Australia) was used to draw a subset of all combinations using an orthogonal and level balance design. Two different 36-choice sets were generated and divided into six and two blocks for patients and providers, respectively. Therefore, there were six and two different versions of the questionnaires for patients and providers, respectively. Each patient questionnaire contained six different choice sets, and each provider questionnaire contained 18 different choice sets. Each choice set consisted of two hypothetical melanoma treatments and an opt-out alternative to allow patients and providers to choose neither treatment. Pictograms were added to help patients understand the attributes, particularly the adverse events associated with the treatments. Table 1 shows an example of the choice sets. Each questionnaire also contained an additional choice that served as a validity check. This choice set contained a dominant alternative (highest OS, lowest immunotherapy-related side effect, skin toxicity, GI toxicity, oral formulation, and lowest OOP cost) that patients or providers who understood the DCE questions must choose.

Focus groups, patient interviews, and pilot study

Two focus groups were conducted with melanoma specialists and three interviews with patients with melanoma. In total, two medical oncologists and two surgical oncologists provided important aspects of melanoma care from the provider perspective. Three individual patients were interviewed, who were receiving care from the specialists and who collectively represented the spectrum of melanoma disease and treatment exposure. During the focus groups and interviews, providers and patients were asked to review the initial list of attributes of melanoma treatments. They were also asked to rank the importance of the efficacy and safety attributes of melanoma treatment to gain consensus in determining the most important attributes to include in the survey. After the survey was developed, it was fielded in a pilot phase. A convenient sample of 10 patients from the eligible cohort, not including the three patients previously interviewed, evaluated the survey's layout, comprehensibility, graphics, content relevance, and questions.

Study cohort

The cohort of eligible study participants with melanoma was created using the University of Utah Health Sciences Enterprise Data Warehouse and the Huntsman Cancer Institute Tumor registry (HCI-TR). Inclusion criteria included the following: patients at least 18 years at the time of diagnosis; at least 2 ICD-9 codes for melanoma; inclusion in the HCI-TR with International Classification of Diseases for Oncology, 3rd ed., site and histology codes indicative of melanoma with stage I–IV disease between 2013 and 2014; and at least two encounters in the Enterprise Data Warehouse, with one encounter at least 30 days from the index date; a valid e-mail address on record; and patients were required to be alive to actively participate in the survey. Eligible providers included physicians, pharmacists, and nurses at HCI involved in providing direct care to patients with melanoma or whose clinical activities involved immunotherapy or targeted therapy. Institutional Review Board approval was granted from the University of Utah.

Survey dissemination

The final self-administered questionnaire was built using Qualtrics software (Provo, Utah, USA). Survey dissemination spanned January 2016 to March 2016. Institutional Review Board approved recruitment and survey materials were initially distributed by e-mail to eligible patients and providers. The introductory e-mail included a survey link and a study telephone number, which was followed up with a reminder phone call or e-mail ~2 weeks later. Phone calls were placed to patients to ensure receipt of the e-mail invitation and to answer any questions. Patients who remained interested in the study could complete the survey electronically or were offered a duplicate paper version of the survey mailed with a prestamped return envelope. Instead of follow-up phone calls to providers, reminder e-mails were sent and paper versions of the survey were delivered to their offices. All study participants were offered a nominal monetary incentive or a donation to a cancer organization on their behalf as a token of appreciation. Participants were given 3 months to complete the survey. Surveys completed through the e-mail link were automatically captured. Responses provided on the paper version were manually entered into Qualtrics.

Statistical analysis

Survey responses for the demographics and general survey sections were descriptively analyzed using χ^2-test or Fisher's exact test as appropriate. Demographics were compared between patient responders and nonresponders using data contained in the Enterprise Data Warehouse to determine underlying differences.

According to good DCE research practice, the aim was for 150 complete and valid responses from at least 150 patient participants to ensure study precision [12]. For the DCE section, a multinomial logit model based on random utility theory was developed to estimate the following utility model: U_{ij}, that either a patient or a provider i assigned to an alternative I, from patients' and providers' responses for choice sets using NLOGIT version 4.

$$U_{ij} = \beta_0 + \beta_1 OS_j + \beta_2 IM_j + \beta_3 SK_j + \beta_4 GI_j + \beta_5 AD_j + \beta_6 Cost_j + \varepsilon_{ij},$$

where β_0 is the constant reflecting patients' or providers' preference for selecting melanoma treatment relative to no treatment, and β_1, β_2, β_3, β_4, β_5, and β_6 are the coefficients or the mean attribute weights of OS, immunotherapy-related side effect (IM), skin toxicity (SK), GI, route of administration (AD), and monthly OOP cost (cost), respectively, and ε_{ij} is error term. The magnitude of each coefficient indicated the relative importance of each attribute, whereas the sign of the coefficient reflected whether the attribute had a positive or a negative effect on utility or preference, as compared with the base level. The level of statistical significance was set at 0.05.

For each attribute, the marginal WTP, which indicates how much a patient or a provider is willing to pay for a one-unit change in the attribute, was calculated by taking the ratio of the mean attribute coefficient to the mean coefficient of cost attribute. The Krinsky and Robb [13] method was used to estimate the 95% confidence interval of the WTP for each attribute. Finally, the WTP for each existing melanoma treatment was calculated by multiplying the marginal WTP for all attributes and their level changes, which were obtained from literature (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/MR/A106*). Simple one-way sensitivity analysis was performed, varying attribute levels from the lowest to highest point estimates.

Table 2 Patient respondent demographics and disease characteristics

Patient characteristics	Patients (N=233)
Current age [median (IQR)] (years)	64 (50–74.5)
Male [*n* (%)]	145 (62)
Highest level of education [*n* (%)]	
College/university	98 (42)
Graduate school	58 (25)
High school	66 (28)
Other	11 (5)
Marital status [*n* (%)]	
Married	180 (77)
Not married	34 (15)
Widowed	18 (8)
Not reported	1 (<1)
Report having children [*n* (%)]	206 (88)
Currently employed [*n* (%)]	103 (44)
Current health insurance [*n* (%)][a]	
Government plan	108 (46)
Supplemental	56 (24)
Private	133 (57)
None	2 (<1)
Insurance covers melanoma treatment (yes) [*n* (%)]	218 (94)
Annual household income [*n* (%)]	
<$49 999	83 (36)
$50 000–$99 999	79 (34)
>$100 000	58 (25)
Not reported	13 (6)
Annual healthcare insurance out-of-pocket cost [median (IQR)]	$2500 ($355–$5000)
Patient reported stage at diagnosis [*n* (%)]	
I–II	174 (75)
III–IV	46 (19)
Missing/unknown	13 (5)
Year of diagnosis [*n* (%)]	
2013	129 (55)
2014	104 (45)
Current melanoma treatment status [*n* (%)][a]	
Receiving treatment	21 (9)
Not receiving treatment	199 (85)
In remission	182 (78)
Cancer still present	5 (2)
Prior treatment [*n* (%)][a]	
Surgery	215 (92)
Systemic treatment	27 (12)
Radiation	16 (7)
Immunotherapy	18 (8)
Chemotherapy	12 (5)
BRAF/MEK inhibitor	4 (2)

IQR, interquartile range.
[a]Categories not exclusive.

Results

Patient and provider characteristics and their perceptions of melanoma treatments

An eligible cohort of 557 patients was initially identified for the study from 2013 to 2014. A total of 233 patients completed the survey (electronic version, n=91; paper version, n=142) reflecting a 42% response rate. Fifty-three providers were invited to participate in the study, with 20 providers completing the survey (electronic version, n=15; paper version, n=5) for a 38% response rate.

Table 2 presents the demographics and disease characteristics of the patient respondents, demonstrating no difference compared to nonrespondents (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/MR/A106*). The median age was 64 years and 62% were male. The majority of respondents were well-educated (42% college education), had insurance to cover their melanoma treatment (94%), and their annual median OOP cost for medical treatment was $2500 (mean $4621). A majority of respondents were diagnosed with early-stage melanoma, stage I or II (75%), and most were not currently receiving active treatment for their disease (85%). Prior treatments for melanoma were reported as surgery (92%), systemic treatment (12%), and radiation (7%). Immunotherapy was administered to 18 (8%) patients, 12 (5%) patients had received chemotherapy, and BRAF/MEK inhibitors were administered to four (2%) patients.

Table 3 presents the provider respondents' characteristics. The median age of providers was 38.5 years and 40% were male. Seven oncologists, nine oncology pharmacists, and four nurses responded to the survey. The average number of patients treated per year was 390 patients and

Table 3 Provider respondent characteristics

Provider characteristics	Providers (*N*=20)
Current age (median) (years)	38.5
Male [*n* (%)]	8 (40)
Provider type [*n* (%)]	
Oncologist	7 (35)
Oncology pharmacist	9 (45)
Nurse	4 (20)
Average number of patient treated per year (range)	390 (5–1000)
Average number of years treating cancer patients (range)	7.3 (1–26)

the average number of years treating cancer patients was 7.3 years.

Figure 1 presents patient and provider quality-of-life expectations, relations, and perceptions toward melanoma and its treatment. More providers than patients selected 'feeling less pain' as a quality-of-life indicator (65.0 vs. 28.6%; $P<0.001$; Fig. 1a). Most providers perceived patients were 'very anxious' about their melanoma, whereas most patients reported feeling 'not anxious' ($P<0.0001$; Fig. 1b). Almost half of patients responded that they 'always' have enough time to discuss their melanoma treatment with their provider, while only one provider felt similarly ($P<0.001$; Fig. 1c). Approximately 70% of patients indicated 'always' trusting their providers to make the best treatment decision compared with 15% of providers that felt they 'always' trusted themselves ($P<0.0001$; Fig. 1d). Additionally, most patients (74%) reported 'always' feeling that their providers share their opinions about melanoma, compared with most providers (39%) selecting 'rarely' ($P<0.0001$; Fig. 1e). Conversely, patients reported 'always' or 'most of the time' sharing their concerns, whereas most providers felt this was 'sometimes' true ($P<0.0001$; Fig. 1f). Patients most frequently responded that providers 'sometimes' understand the impact of their OOP costs for melanoma treatment, whereas providers most frequently responded 'most of the time' ($P=0.002$; Fig. 1g). Sixty percent of providers would recommend melanoma treatment that would be effective for 6–11 months. Approximately 50% of patients would only elect to undergo treatment if it was effective long-term, specifically for more than 24 months ($P=0.007$; Fig. 1h).

Patients' and providers' preferences and their willingness to pay

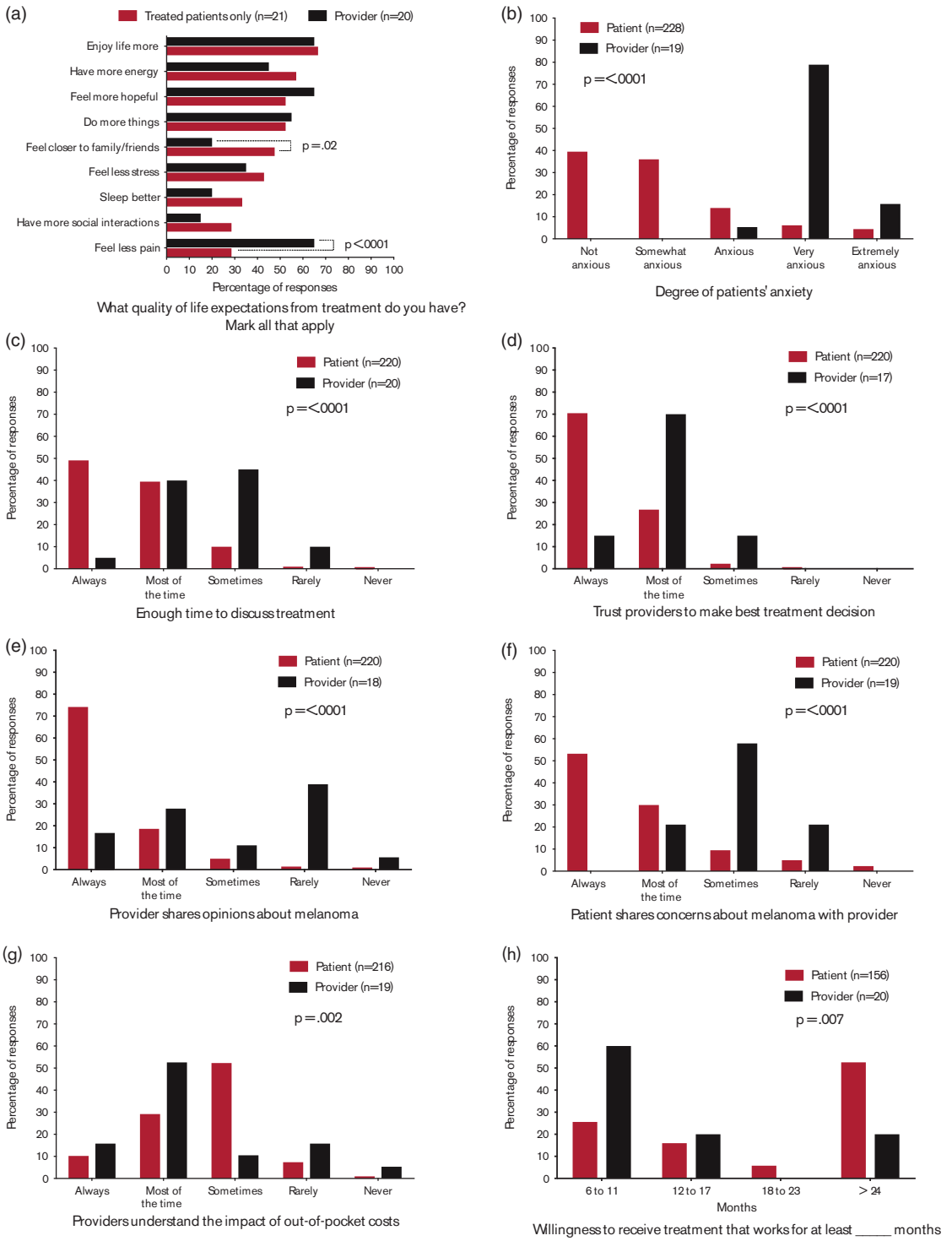
Table 4 shows the estimated parameters from the multinomial logit models. No bad observations (failing validity check) were included in the DCE analyses for both patient and provider groups. Approximately 29% of patients and 8% of providers chose the no treatment alternative, respectively, meaning they would not choose either treatment. For each group, the remainder of the selected treatment alternatives were distributed similarly between the two treatment alternatives. Among the six tested attributes, only OS, immunotherapy-related side effect, skin toxicity, and monthly OOP cost were statistically significant and had expected signs in both models. The positive sign of the estimated coefficients for OS reflects that both patients and providers preferred melanoma treatments that extended survival. Conversely, the negative signs of the estimated coefficients for immunotherapy-related side effects, skin toxicity, and monthly OOP cost indicated respondents prefer less frequent side effects and toxicity, and lower monthly OOP cost. Among all four significant attributes, only the coefficient magnitudes of the immunotherapy-related side effect and skin toxicity can be compared directly because their levels had the same unit (frequency of side effect). The patients weighted the immunotherapy-related side effect almost three times the weight of skin toxicity (0.033 vs. 0.013), whereas the provider evenly weighted these attributes (0.075 vs. 0.070).

Table 5 shows the patients' and providers' marginal WTP per month per unit change in the attribute's level. The patients and providers were willing to pay \$932 and \$1008 per month, respectively, for every 1-year increase in OS. The patients and providers were willing to pay \$50 and \$55 per month, respectively, to reduce the occurrence of immunotherapy-related side effects by 1%. The providers were willing to pay \$31 more per month than patients to reduce the occurrence of skin toxicities by 1% (\$51 vs. \$20). Finally, the attribute levels of combination immunotherapy (nivolumab + ipilimumab) and BRAF/MEK inhibitors extracted from the literature (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/MR/A106*) were used to calculate the WTP for these treatments. Patients and providers were willing to pay \$2357 and \$2484 per month OOP, respectively, for combination immunotherapy. For BRAF/MEK inhibitors, patients and providers were willing to pay \$1648 and \$1350 per month OOP, respectively. Based on the 95% confidence intervals for survival estimates for immunotherapy and BRAF/MEK inhibitors, one-way sensitivity analysis determined patient's WTP for immunotherapy ranged from \$1700 to \$3020 for an OS distribution of 2.0–3.7 years. For BRAF/MEK inhibitors it ranged from \$1072 to \$2547 for an OS distribution of 1.5–3.0 years. The sensitivity analysis for the adverse event attributes are presented in the Supplementary Fig. (Supplemental digital content 1, *http://links.lww.com/MR/A106*).

Discussion

Shared decision-making between patient and provider is integral to providing optimal cancer care. Previous findings demonstrate a discord between perceived and actual patient requests. Physicians often feel 'patients who demand interventions or treatments' promote utilization of costly treatments, despite evidence to the contrary [14]. Other studies have demonstrated that patients prefer treatment that affords a 'hopeful gamble' for a small chance to obtain large gains in health outcomes.

Fig. 1



Patient and provider relations and perceptions regarding melanoma treatment decisions including: quality of life expectations from treatment (a); degree of patients' anxiety (b); having enough time to discuss treatment goals (c); trust in providers to make best treatment decision (d); provider shares opinions about melanoma or melanoma treatment (e); patient shares concerns about melanoma or melanoma treatment with provider (f); providers understand the impact of out-of-pocket costs (f); and willingness to receive treatment that works for at least _____ months (h).

Table 4 Discrete choice experiment parameter estimates from multinomial logit model

	Patients[a]		Providers[b]	
Attributes	Estimate	Standard error	Estimate	Standard error
Constant	0.43	0.24	2.50[c]	0.59
Overall survival	0.62[c]	0.062	1.37[c]	0.16
Immunotherapy-related side effect	−0.033[c]	0.006	−0.075[c]	0.014
Skin toxicity	−0.013[c]	0.006	−0.070[c]	0.014
Gastrointestinal toxicity	−0.0036	0.012	−0.014	0.026
Route of administration	−0.13	0.099	0.086	0.23
Out-of-pocket cost	−0.00067[c]	0.00006	−0.0014[c]	0.00015

[a]Number of observations=1050, log-likelihood=−1010.81, akaike information criterion=1.94, pseudo-R^2=0.12.
[b]Number of observation=339, log-likelihood=−185.78, akaike information criterion=1.83, pseudo-R^2=0.40.
[c]$P<0.05$.

Table 5 Patients' and providers' willingness-to-pay per month for one level change of each attribute

	WTP per month average $US (95% confidence interval)	
Attributes	Patient	Provider
Overall survival (per 1-year increase)	$932 (721–1175)	$1008 (781–1273)
Immunotherapy-related side effects (per 1% increase in frequency of occurrence)	$–50 (–69 to –31)	$–55 (–77 to –36)
Skin toxicities (per 1% increase in frequency of occurrence)	$–20 (–38 to –2)	$–51 (–74 to –31)

WTP per month by treatment			
Immunotherapy average $US (minimum–maximum)		BRAF/MEK inhibitor average $US (minimum–maximum)	
Patient WTP	Provider WTP	Patient WTP	Provider WTP
$2357 (1462–3352)	$2484 (1498–3552)	$1648 (943–2419)	$1350 (539–2196)

WTP, willingness-to-pay.

This contrasts with providers who tend to prefer 'safer bets' for small, incremental benefits in health outcomes with relatively high chance of occurrence [9,15]. In our study, exploration of these patient and provider relationships showed a similar discordance, where ~70% of patients 'always' trust their providers to make the best treatment decision for them compared with 15% of providers responses who feel that they actually do. This discordance in perception between patients and providers may likely contribute to differing beliefs toward therapeutic decision-making. Contributing factors to these differences, which were demonstrated in our study, include perceptions of patient anxiety toward melanoma treatment, conflicting perspectives on adequate time to discuss melanoma treatment options, and ultimately, optimism for outcomes of various treatment options.

Among the observed attributes in the DCE, OS, immunotherapy-related side effects, skin toxicity, and monthly OOP cost were statistically significant. As expected, our study demonstrated both patient and provider preference for survival benefit in the DCE, which is commonly reported in DCEs in oncology [16–18]. OS was included as an attribute in the DCE due to the profound change in long-term survival with the introduction of these novel treatment options. In clinical trial setting, patients with advanced melanoma have demonstrated a 3-year OS rate of 58% for combination nivolumab and ipilimumab [19], 44% for combined BRAF/MEK inhibitors [20], and 21% with ipilimumab + dacarbazine, or 12% with dacarbazine alone [19]. Patients preferred to avoid immunotherapy-related side effects almost three times more than skin toxicity (0.033 vs. 0.013), whereas providers evenly weighted these treatment attributes (0.075 vs. 0.070). Route of administration and mild side effects did not carry as much weight in both patients' and providers' decision-making.

WTP was predominantly driven by gains in survival. These data are again similar to prior reports demonstrating the value patients place on survival time [9,15,21]. However, our study was able to explore the subtleties around survival beyond the DCE. Sixty percent of providers would recommend melanoma treatment that would be effective for 6–11 months compared with ~50% of patients who would only elect to undergo treatment if it was effective for more than 24 months. This finding highlights the need for thoughtful discussions with patients about treatment preferences when recommending therapy. Despite the differences in survival expectations for treatment, patients and providers had similar OOP WTP thresholds for OS of ~$900–$1000 per month per 1-year increase in survival. Patients and providers had similar WTP for immunotherapy ($2357 and $2484, respectively). In contrast, patients and providers were willing to pay $1648 and $1350, respectively for BRAF/MEK inhibitors, stemming from the difference in perceived OS benefit between these treatment modalities. Interestingly, providers' WTP for BRAF/MEK inhibitors was nearly half that of immunotherapy, which may be explained by

providers' knowledge of high resistance rates with BRAF/MEK inhibitors compared with the durable responses that have been observed with immunotherapy [2,22,23]. Overall these OOP WTP costs represent significant portions of the patients' reported monthly income considering 36% of respondents reported an annual household income of less than $49 999. In addition, both patients and providers were willing to pay, or have their patient's pay, approximately the same amount to avoid immunotherapy-related side effects suggesting that they viewed immunotherapy-related side effects similarly. Regarding skin toxicities, the providers' WTP was more than that of the patients. Providers value avoiding skin toxicities more than patients, a preference likely rooted in their experience with managing skin toxicities resulting from melanoma treatments, especially BRAF/MEK inhibitors.

Our study was unique in demonstrating a more granular understanding of the important attributes of treatment options for melanoma compared with other DCEs [16,17]. Unlike previous studies, our study also incorporated a spectrum of oncology-specialized clinicians, including oncology-trained pharmacists and nurse practitioners in addition to the more commonly investigated physicians. This diversification adds greater context to the findings given that pharmacists have intimate knowledge of therapies and nurse practitioners have vast patient interactions in clinical applications. Investigating this wider spectrum of oncology clinicians brings greater context to decision-making in regards to adverse events, common trends in patient preference, and procurement of therapies. However, including a broad spectrum on oncology practitioners may contribute to greater heterogeneity in the expectations of patient outcomes influencing the outcomes of the study.

Three limitations of the study warrant mention. First, our study was performed at an academic cancer center in the Intermountain West staffed by melanoma physicians who are specialists in surgery and oncology. Therefore, the results may not be generalizable to community cancer centers or regions with differing ethnicities. Homogeny in a sample population is often preferable for comparing results in a variety of study types [18]. Our study population included primarily European American, well-educated, insurance-carrying patients with early-stage melanoma. Patients' overall lack of exposure to systemic treatment would likely minimize bias from previous treatment; however, patients were required to weigh attributes of treatment reserved for advanced melanoma with which they may have little or no actual experience. For example, patients' WTP to avoid skin toxicities was less compared with providers' WTP and may reflect lack of personal familiarity with this particular adverse effect. In addition, our study did not control for differences in the cultural background of patients and clinicians or annual incomes levels which could have influenced outcomes and WTP [13]. More heterogeneity in the sample population would have also increased generalizability to a broader population. Second, our one-time survey dissemination represented a snapshot in time of the patient experience with immunotherapy and targeted therapy. The comparative unfamiliarity with systemic treatments and their associated toxicity profile among patients with early-stage melanoma may be addressed in the future with a larger study of patients with advanced disease and treatment experience. Given the more durable response of systemic therapies now reported in recent publications, it is possible to have a larger study comparing the preferences and WTP of patients with early-stage disease with those with advanced disease. Last, a limitation to all DCEs is not being able to investigate all attributes related to a treatment decision. Other attributes such as additional side effects, progression-free survival, and lower-grade adverse events were not assessed in our study, as these were eliminated by the patient or clinician focus groups. In addition, an emerging attribute of combination immunotherapy, treatment-free survival (i.e. being able to maintain durable benefit after stopping treatment), was not assessed and would warrant future study on the value patients and providers place on it.

Conclusion

There was discordance between the patient-provider relationship and perceptions around melanoma treatment. Patients understandably want treatment with longer survival advantage and remain more optimistic, whereas providers tend to make decisions based on reported survival benefit and personal experience using these therapies. Long-term durable benefit is very important to patients, with 50% indicating that they would only elect to undergo treatment if it was effective for more than 24 months. Patient-provider preferences may enrich shared decision-making, especially as more efficacious treatments become available and there is a need to balance survival benefits with side effects and costs. As expected, patients and providers were willing to accept all risk levels from adverse effects of immunotherapy and BRAF/MEK inhibitors for improved survival. Patients and providers exhibited a greater WTP for combination immunotherapy as compared to BRAF/MEK inhibitor therapy, indicating a greater perceived survival benefit with combination immunotherapy.

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Conflicts of interest

David D. Stenehjem reports relevant research funding from Bristol-Myers Squibb during the course of the study; personal consulting fees from Bristol-Myers Squibb, Salarius Pharmaceuticals, and Iterion Therapeutics outside the submitted work. Dr Diana I. Brixner reports a relevant research grant from BMS, during the conduct of the study; personal fees from AbbVie, Becton Dickinson, Abbott, and Millcreek Outcomes Group, outside the submitted work. Joshua Schwartz, Constance M. Pfeiffer, and Beata Korytowsky are employees and shareholders of Bristol-Myers Squibb, Inc. For the remaining authors there are no conflicts of interest.

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