



Adherence to Adjuvant Therapy in Patients with Resected Melanoma: An Application of the Theory of Planned Behavior

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ABSTRACT

Introduction: Adherence to adjuvant therapy is crucial for effective disease management in patients with resected melanoma. This study assessed patient-reported adherence to adjuvant therapy and identified behavioral/belief constructs associated with adherence in patients with resected melanoma.

Methods: Patients with resected stage III/IV melanoma were recruited through the Melanoma Research Foundation and a patient panel to complete an online survey. Patient characteristics, medical history, and adherence to therapy were captured. In accordance with the

theory of planned behavior (TPB), the survey measured behavioral, normative, and control beliefs, and intention to adhere to therapy. Structural equation modeling (SEM) examined their relationships with adherence.

Results: Among all patients who received adjuvant therapy and completed the survey ($n = 184$), 69% received intravenous and 31% received oral therapy; the majority (85.3%) were somewhat involved in deciding to start therapy. Mean age was 45 years, 44% of patients were female, and 83% had stage III/IV disease at diagnosis. Patients had a mean disease duration of 1.5 years, a time since complete resection of 10 months, and an adjuvant therapy duration of 8 months. Adherence to adjuvant therapy was high overall and higher with intravenous than with oral therapy (98.4% versus 91.2%, $P = 0.002$). All underlying TPB constructs were significant in the SEM model, which explained 60.3% of the variance in intention to adhere. Control beliefs had the strongest association with intention to adhere (standardized estimate = 0.47, $P < 0.001$) and intravenous therapy was associated with greater adherence than oral therapy (standardized estimate = 0.26, $P < 0.001$).

Conclusions: This study found that patients with resected melanoma are highly engaged in the decision to initiate systemic adjuvant therapy, with an overall high adherence rate to prescribed adjuvant treatment. Enhancing patients' view of their capability to adhere to

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treatments may further improve the adherence rate to melanoma adjuvant therapy.

Keywords: Adherence; Adjuvant therapy; Cancer; Melanoma; Oncology; Theory of planned behavior

Key Summary Points

Why carry out this study?

An increasing number of patients with melanoma are being treated with complete surgical resection followed by adjuvant therapy, and adherence to therapies in the real-world setting may not be adequate.

Understanding the extent of adherence to adjuvant therapy and patients' considerations when receiving adjuvant therapy may improve decision-making to initiate adjuvant treatment and patient outcomes.

What was learned from the study?

Patients with resected melanoma were highly engaged in the decision to initiate systemic adjuvant therapy.

Adherence to prescribed adjuvant treatment was generally high, with a higher proportion in patients treated with intravenous compared with oral therapy (98.4% versus 91.2%).

Enhancing patients' view of their capability to adhere to treatments (control beliefs) may further improve the adherence rate to melanoma adjuvant therapy.

287,700 cases worldwide [1], with 106,110 new cases, excluding in situ carcinomas, in the USA in 2021 [2]. Even with surgical excision as routine care for localized and regionally metastatic melanoma involving lymph nodes, patients remain at a high risk for disease recurrence after complete resection [3].

Systemic adjuvant therapy can lower the risk of recurrence of melanoma and consequently improve survival [4–6]. According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), the recommended adjuvant therapy options for resected stage III or stage IV disease include the programmed death 1 (PD-1) inhibitors nivolumab or pembrolizumab, the BRAF plus MEK inhibitor combination of dabrafenib plus trametinib (for disease having a *BRAF* V600-activating mutation), and observation, among others [7]. Nivolumab and pembrolizumab are administered intravenously every 2 to 6 weeks, whereas dabrafenib and trametinib are taken orally. Two capsules of dabrafenib are taken twice a day and one tablet of trametinib is taken once daily 1 h before or 2 h after a meal. In addition to routine clinical follow-up, adherence to these treatment regimens is crucial for effective disease management. However, patients may not adhere to systemic therapy. Published data on adherence to adjuvant therapies in patients with stage III or stage IV resected melanoma are limited.

A number of factors can affect patient adherence to adjuvant cancer therapy. For example, systematic reviews assessing adherence to adjuvant therapy in breast cancer showed that side effects, forgetfulness, inconvenience, cost, and beliefs about efficacy were associated with low adherence [8], whereas good patient–physician communication and self-efficacy for taking medication were associated with greater adherence [9]. In addition, adjuvant therapies differ in their route of administration, which may also affect patient adherence [10, 11]; however, the literature examining the direct impact of route of administration on adherence is sparse. Given the various factors that affect adherence, a theoretical social-behavioral model framework may offer a comprehensive guide for evaluating the

INTRODUCTION

Melanoma is a severe form of malignant skin cancer, with incidence rates rising in recent years. Estimates suggest an annual incidence of

impact of these factors among patients with resected melanoma.

In this study, we applied the theory of planned behavior (TPB) [12] to explore the factors associated with adherence to adjuvant therapy. The TPB suggests that the intention to engage in a behavior (e.g., medication adherence) results from the following three key underlying constructs: behavioral beliefs, normative beliefs, and perceived control beliefs, which can directly influence the actual behavior. Under this framework, TPB defines behavioral beliefs as a person's positive or negative attitude toward performing the behavior, normative beliefs as the perception of other people (peers) approving or disapproving of the behavior, and perceived control beliefs as a person's view of their capability to perform the behavior. The TPB has been previously used to assess adherence to medications for chronic conditions [13, 14], including cancer; for example, among patients with breast cancer, the TPB explained a substantial proportion of intentions to adhere to adjuvant endocrine therapy [15] and provided a useful framework for understanding adherence [16]. To the best of our knowledge, no previous study has applied the TPB to the adjuvant setting for resected melanoma.

Given the availability of several adjuvant therapies for resected melanoma, we conducted an online survey for patients with resected melanoma to assess patient-reported adherence to adjuvant therapies, as well as describe patients' perceived barriers to adherence and identify constructs associated with adherence.

METHODS

Study Participants

This cross-sectional survey was conducted in patients living in the USA who were members of the Melanoma Research Foundation, a patient advocacy group, or of a patient panel maintained by Dynata, a well-established market research firm that routinely carries out online healthcare surveys. Adult patients diagnosed with self-reported stage III or stage IV melanoma since

January 2018 with no evidence of disease after complete surgical resection and without subsequent recurrence or metastases were included; eligible patients must have received adjuvant therapy for at least 2 months. Patients were further classified by the following routes of administration: intravenous therapy (nivolumab or pembrolizumab) or oral therapy (dabrafenib plus trametinib). Patients who were previously treated with other adjuvant therapies were also eligible. Patients were excluded if they were unable to read English or had participated in a clinical trial for melanoma within the past 2 years. The survey captured patients' socio-demographic and clinical characteristics (including medical and treatment history related to melanoma, comorbidities, overall general well-being, and the extent of engagement when deciding to start adjuvant therapy following complete surgical resection), adherence to adjuvant therapy, and TPB constructs (behavioral, normative, and perceived control beliefs and intentions to adhere). Patients responded to the survey via a secure online portal between November 2019 and January 2020.

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments and was granted an exemption from a full review by the New England Institutional Research Board. All patients consented to participate.

Measures

Adherence

Adherence to adjuvant therapy was self-reported according to the route of administration. Patients treated with oral adjuvant therapy self-reported how often they took their tablets or capsules on time and as instructed by their physician over the past 2 months, using the following categories: always (100%), almost all of the time (80–99%), just over half of the time (51–79%), about half of the time (50%), slightly less than half of the time (25–49%), or rarely (less than 25%). Patients treated with intravenous adjuvant therapy were asked to report the number of infusions missed over the entire duration of the therapy specified. The number

of infusions received was calculated as the difference between the number of prescribed infusions and the number of self-reported missed infusions. Adherence was presented as a percentage, calculated by dividing the number of infusions received by the number of infusions prescribed, according to the dosing schedule. The calculated adherence to intravenous therapy was then characterized using the same categories as oral therapy to allow for comparisons among these measures.

Adherence Barriers

Barriers to adherence were identified through a series of 15 items, which listed reasons for previous and expected future nonadherence, as identified in the literature [17]. These items included the following categories: forgetfulness (forgot the infusion appointment or to take the oral medication), safety and side effect concerns (worried about potential side effects, did not want to become dependent on the medication, on a break from therapy due to side effects), affordability (not covered by insurance or high out-of-pocket costs), avoidance (did not want to be reminded of melanoma, melanoma was out of one's control, melanoma was not bothering respondent, wanted to take a break from treatment), concerns about efficacy, inconvenience, time constraints (childcare or work-related), and other.

Constructs in the TPB

The survey questions were designed on the basis of targeted literature reviews [12–14, 18], patient focus group discussions, and a clinical expert interview. Specifically, to identify the relevant constructs within the melanoma adjuvant therapy setting, the literature review focused on systemic adjuvant therapy options for patients with completely resected melanoma, factors affecting treatment adherence, adherence among patients with cancer treated with adjuvant therapy (with resected melanoma or with other types of advanced cancer), applications of social/behavioral models for adherence in the cancer adjuvant setting, and specific applications of TPB in patients receiving cancer adjuvant therapies. The initial list of constructs

was subsequently developed and facilitated the development of semi-structured interview guides for focus group discussions. The applicability of TPB among this patient population was confirmed in the focus group discussions, and direct inputs/feedback from the patients were used to develop the items for each of the constructs.

The question development for TPB constructs were guided by the TPB framework [12]. Responses to all TPB questions used the 5-point Likert scale (e.g., strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree) on behavioral, normative, and perceived control beliefs related to adjuvant therapy and their intent to adhere. Intent to adhere to adjuvant therapy was assessed using the following two items: "I have every intention to follow the dosing schedule for my adjuvant therapy exactly as prescribed" and "In general, how likely are you to take your medication(s) or receive treatments as prescribed?" The draft survey was pretested among two patients who met the same eligibility criteria as study participants.

Statistical Analysis

All analyses were performed using SAS Enterprise Guide software, Version 7.15 of the SAS system for Unix (Copyright© 2017 SAS Institute Inc., Cary, NC, USA). Categorical and continuous variables were summarized descriptively for all participants and for route of administration (intravenous versus oral). Comparisons between cohorts were made using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

Structural equation modeling (SEM) with maximum likelihood estimation was used to evaluate the TPB for factors associated with adherence and to assess the relationship between route of administration (i.e., intravenous versus oral) and adherence. The following two models were run: a base model that examined core TPB concepts and an expanded model that incorporated the route of administration. First, exploratory factor analysis was used to select items that best described the TPB

latent constructs. Second, confirmatory factor analysis was used to confirm that the selected items represented the intended factors. These models also included age, sex, race, and education as control variables. Fit indices were used to evaluate model validity (i.e., goodness of fit index [GFI], adjusted GFI, chi-square, Bentler comparative fit index [CFI], root mean square error of approximation [RMSEA], and standardized root mean square residual [SRMR]).

RESULTS

Patient Characteristics

A total of 184 patients completed the survey, including 127 (69.0%) recently/currently treated with intravenous adjuvant therapy (86 with nivolumab and 41 with pembrolizumab) and 57 (31.0%) with an oral adjuvant combination therapy (dabrafenib plus trametinib) (Table 1). The mean age was 44.9 years at the time of the survey, 44.0% of patients were female, and 21.7% were non-White, followed by 9.8% black/African American. On average, participating patients had a disease duration from the initial diagnosis of 18 months, time since complete surgical resection of 10.3 months, and adjuvant treatment duration of 8.1 months. Stage III or stage IV disease at first diagnosis was reported by 83% of patients, and stage III disease at the time of complete resection surgery was reported by 65.8% of patients. Sociodemographic and clinical characteristics were mostly similar between the two cohorts of patients who were treated with intravenous compared with oral combination adjuvant therapy, except for education and employment status. Most patients (81.0%) reported that they felt “good,” “very good,” or “excellent” about their overall well-being. The most commonly self-reported comorbidity among patients was anxiety (11.4%), followed by depression (9.8%).

Patients treated with intravenous therapy compared with those treated with oral therapy were more likely to be employed full-time (66.9% versus 47.4%, $P = 0.012$) and to have commercial insurance (75.6% versus 47.4%, $P < 0.001$) (Table 1). A higher proportion of

patients treated with oral therapy compared with those treated with intravenous therapy had a higher educational attainment ($P = 0.030$) and reported involvement in the decision-making process to start adjuvant therapy ($P = 0.005$; 40.4% versus 23.6% reported a great deal of involvement, and 42.1% versus 31.5% reported quite a bit of involvement) (Table 1).

Adherence to Adjuvant Therapy

The majority of patients (90.2%; 166 of 184) were receiving adjuvant therapy (112 were treated with intravenous therapy and 54 were treated with oral therapy). Self-reported adherence to adjuvant therapy was high, with 96.2% of patients following their regimens always or almost all of the time (Table 2). Adherence was higher in patients treated with intravenous therapy than in those treated with oral therapy ($P = 0.002$), with 98.4% and 91.2% of patients, respectively, following their regimens always or almost all of the time. In this analysis, 19% of patients treated with intravenous therapy reported missing an infusion compared with 42% of those treated with oral therapy reporting not always following their regimens as instructed ($P < 0.001$).

Among patients with low adherence (less than 80%), the most common reason for non-adherence was forgetfulness (50.0%) followed by safety and side effect concerns (35.4%; Table 2). Only patients with oral therapy expressed concerns about affordability (45.8% versus 0% in those with intravenous therapy, $P < 0.001$). A substantial proportion of patients (39.8% overall, 36.6% with intravenous therapy, and 46.3% with oral therapy) anticipated not being able to follow their regimens as prescribed in the future. The largest barriers to adherence in the future were expected to be safety and side effects (66.7%) and affordability (59.1%). A higher proportion of patients treated with oral therapy compared with those treated with intravenous therapy had expected that forgetfulness would be a reason for nonadherence (28.0% versus 4.9%, $P = 0.021$).

Table 1 Patient characteristics

	All patients N = 184	Intravenously treated patients n = 127	Orally treated patients n = 57	P value
Age (years), mean (SD)	44.9 (9.3)	45.1 (9.8)	44.4 (8.3)	0.801
Female sex, <i>n</i> (%)	81 (44.0)	61 (48.0)	20 (35.1)	0.102
Geographic region, <i>n</i> (%)				0.050
Northeast	23 (12.5)	10 (7.9)	13 (22.8)	
Midwest	9 (4.9)	7 (5.5)	2 (3.5)	
South	31 (16.8)	22 (17.3)	9 (15.8)	
West	121 (65.8)	88 (69.3)	33 (57.9)	
White or Caucasian race, <i>n</i> (%)	144 (78.3)	97 (76.4)	47 (82.5)	0.355
Education level, <i>n</i> (%)				0.030*
High school graduate or less	4 (2.2)	1 (0.8)	3 (5.3)	
Some college or associate's degree	45 (24.5)	37 (29.1)	8 (14.0)	
College graduate or bachelor's degree	96 (52.2)	61 (48.0)	35 (61.4)	
Advanced degree	39 (21.2)	28 (22.0)	11 (19.3)	
Household income level, <i>n</i> (%)				0.958
Less than \$25,000	4 (2.2)	3 (2.4)	1 (1.8)	
\$25,000 to \$49,999	8 (4.3)	6 (4.7)	2 (3.5)	
\$50,000 to \$74,999	27 (14.7)	17 (13.4)	10 (17.5)	
\$75,000 to \$99,999	37 (20.1)	24 (18.9)	13 (22.8)	
\$100,000 to \$149,999	53 (28.8)	39 (30.7)	14 (24.6)	
\$150,000 and over	28 (15.2)	20 (15.7)	8 (14.0)	
Decline to answer	27 (14.7)	18 (14.2)	9 (15.8)	
Employment status, <i>n</i> (%)				
Paid full-time (40 h/week) employee	112 (60.9)	85 (66.9)	27 (47.4)	0.012*
Paid part-time (temporary or seasonal) employee	18 (9.8)	6 (4.7)	12 (21.1)	< 0.001*
Commercial health insurance, <i>n</i> (%)	123 (66.8)	96 (75.6)	27 (47.4)	< 0.001*
Extent of patient involvement in decision-making process to start or not start adjuvant therapy, <i>n</i> (%)				0.005*
A great deal	53 (28.8)	30 (23.6)	23 (40.4)	
Quite a bit	64 (34.8)	40 (31.5)	24 (42.1)	
Somewhat	41 (22.3)	36 (28.3)	5 (8.8)	
Very little	17 (9.2)	15 (11.8)	2 (3.5)	
Not at all	5 (2.7)	3 (2.4)	2 (3.5)	
Unknown	4 (2.2)	3 (2.4)	1 (1.8)	

Table 1 continued

	All patients <i>N</i> = 184	Intravenously treated patients <i>n</i> = 127	Orally treated patients <i>n</i> = 57	<i>P</i> value
Level of well-being, <i>n</i> (%)				0.436
Poor or very poor	5 (2.7)	3 (2.4)	2 (3.5)	
Fair	30 (16.3)	19 (15.0)	11 (19.3)	
Good	84 (45.7)	55 (43.3)	29 (50.9)	
Very good	48 (26.1)	38 (29.9)	10 (17.5)	
Excellent	17 (9.2)	12 (9.4)	5 (8.8)	
Time since complete resection surgery (months), mean (SD)	10.3 (3.9)	10.4 (4.3)	10.0 (3.0)	0.722
Melanoma stage at time of complete resection surgery, <i>n</i> (%)				0.398
Stage III	121 (65.8)	81 (63.8)	40 (70.2)	
Stage IV	63 (34.2)	46 (36.2)	17 (29.8)	
Comorbidities, ^a <i>n</i> (%)				
Anxiety	21 (11.4)	15 (11.8)	6 (10.5)	0.800
Asthma	12 (6.5)	10 (7.9)	2 (3.5)	0.347
Depression	18 (9.8)	13 (10.2)	5 (8.8)	0.757
Rheumatoid arthritis	11 (6.0)	7 (5.5)	4 (7.0)	0.741

*Indicates statistical significance

^aComorbidities present in more than 5% patients are reported

Constructs in the Theory of Planned Behavior

Overall, on a scale from 1 to 5 (strongly agree), patients indicated strong agreement with respect to the importance of behavioral beliefs, including actively managing their melanoma (mean, 4.5 [standard deviation, 0.6]), receiving adjuvant therapy (4.2 [0.7]), and following instructions exactly as prescribed (4.6 [0.6]; Table 3). Patients also strongly agreed with the value of perceived control beliefs, such as having the capability (4.1 [0.8]), having the necessary resources (4.2 [0.8]), and planning ahead (4.3 [0.8]) to follow instructions for adjuvant therapy. Respondents were less concerned about normative beliefs (views of peers), as

follows: other patients similar to them have had adjuvant therapy (3.7 [0.9]) and follow therapy exactly as prescribed (3.9 [0.9]). Patients generally showed strong intentions to follow instructions (4.3 [0.8]) and take medications or receive treatments as prescribed (4.7 [0.6]). Patients responded similarly to items of the underlying TPB constructs, except that more patients treated with intravenous therapy indicated, “I plan ahead to make it easier to follow instructions for adjuvant therapy,” than those treated with oral therapy (4.4 [0.7] versus 4.1 [1.0], *P* = 0.012).

The base model and the expanded model examining the TBP concepts showed acceptable fit. CFIs were 0.95 and RMSEAs were less than 0.08 (0.0604 and 0.0586, respectively). The

Table 2 Adherence in patients treated with intravenous therapy or oral therapy

	All patients <i>N</i> = 184	Intravenous therapy <i>n</i> = 127	Oral therapy <i>n</i> = 57	<i>P</i> value
Adherence, <i>n</i> (%)				0.002*
Always (100%)	136 (73.9)	103 (81.1)	33 (57.9)	
Almost all of the time (80% to 99%)	41 (22.3)	22 (17.3)	19 (33.3)	
Half to just over half of the time (50% to 79%)	6 (3.3)	2 (1.6)	4 (7.0)	
Just under half of the time (25% to 49%)	1 (0.5)	0	1 (1.8)	
Reasons for non-adherence (< always), <i>n</i> (%)				
Forgetfulness	24 (50.0)	13 (54.2)	11 (45.8)	0.564
Safety and side effect concerns	17 (35.4)	7 (29.2)	10 (41.7)	0.365
Affordability	11 (22.9)	0	11 (45.8)	< 0.001*
Avoidance	7 (14.6)	1 (4.2)	6 (25.0)	0.097
Concerns about efficacy	7 (14.6)	1 (4.2)	6 (25.0)	0.097
Inconvenience	4 (8.3)	0	4 (16.7)	0.109
Time constraints (childcare or work)	1 (2.1)	1 (4.2)	0	1.000
Other	5 (10.4)	4 (16.7)	1 (4.2)	0.348
Currently treated patients who do not expect to be able to follow future adjuvant therapy exactly as instructed, ^a <i>n</i> (%)	66 (39.8)	41 (36.6)	25 (46.3)	0.232
Expected reasons for non-adherence in the future, <i>n</i> (%)				
Safety and side effect concerns	44 (66.7)	28 (68.3)	16 (64.0)	0.720
Affordability	39 (59.1)	25 (61.0)	14 (56.0)	0.690
Avoidance	19 (28.8)	11 (26.8)	8 (32.0)	0.653
Concerns about efficacy	12 (18.2)	5 (12.2)	7 (28.0)	0.186
Forgetfulness	9 (13.6)	2 (4.9)	7 (28.0)	0.021*
Inconvenience	6 (9.1)	5 (12.2)	1 (4.0)	0.396
Time constraints (childcare or work)	2 (3.0)	2 (4.9)	0	0.522
Other	3 (4.5)	3 (7.3)	0	0.283
Mean time on most recent adjuvant therapy, months (SD)	8.1 (3.5)	8.3 (3.7)	7.7 (3.0)	0.509

*Indicates statistical significance

^aA total of 112 patients were treated with intravenous therapy and 54 patients were treated with oral therapy; percentages were calculated among this subsample

Table 3 Item responses to constructs of the theory of planned behavior

	All patients	Intravenously treated patients	Orally treated patients	<i>P</i> value
Behavioral beliefs, mean score (SD)				
It is important to actively manage current stage of melanoma	4.5 (0.6)	4.5 (0.6)	4.4 (0.6)	0.085
Even though most patients with melanoma do not experience symptoms after complete surgical resection, it is important to have adjuvant therapy	4.2 (0.7)	4.3 (0.7)	4.1 (0.8)	0.140
It is important to follow instructions for adjuvant therapy exactly as a doctor prescribed	4.6 (0.6)	4.6 (0.6)	4.5 (0.6)	0.344
Normative beliefs, mean score (SD)				
Most other patients with melanoma like me have had adjuvant therapy	3.7 (0.9)	3.7 (0.9)	3.7 (0.8)	0.904
Most other patients with melanoma like me follow their adjuvant therapy routine exactly as prescribed by their doctors	3.9 (0.9)	3.8 (0.8)	4.0 (1.0)	0.208
Control beliefs, mean score (SD)				
I follow the instructions for adjuvant therapy exactly as prescribed despite whatever barriers are encountered	4.1 (0.8)	4.2 (0.7)	4.1 (0.9)	0.437
I have the resources needed to follow the instructions for adjuvant therapy exactly as prescribed	4.2 (0.8)	4.2 (0.8)	4.2 (0.9)	0.694
I plan ahead to make it easier to follow instructions for adjuvant therapy	4.3 (0.8)	4.4 (0.7)	4.1 (1.0)	0.012*
Behavioral intentions, mean score (SD)				
I have every intention to follow instructions for adjuvant therapy exactly as prescribed	4.3 (0.8)	4.3 (0.6)	4.2 (1.0)	0.552
I am likely to take medications or receive treatments as prescribed	4.7 (0.6)	4.7 (0.6)	4.6 (0.6)	0.445

Items were scored on a 5-point Likert scale: 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree

*Indicates statistical significance

base and expanded models had SRMRs of 0.0491 (Fig. 1a) and 0.0484 (Fig. 1b), respectively. All coefficients were positive and significant in both models. In the base model, behavioral, normative, and perceived control beliefs explained a substantial proportion of the variance in intention to adhere to adjuvant

therapy (60.3%), and all were significantly associated with intention to adhere. Perceived control beliefs were more strongly associated with intention (standardized estimate = 0.47, $P < 0.001$) than behavioral and normative beliefs (standardized estimates = 0.30 and 0.24, respectively, $P < 0.05$ for both). Stronger

intention to adhere was significantly associated with higher adherence (standardized estimate = 0.23, $P < 0.05$). In the expanded model, results between the theoretical constructs were consistent with the base model. Additionally, route of administration had a significant impact on adherence, with intravenous administration being associated with greater adherence than oral administration (standardized estimate = 0.26, $P < 0.001$).

DISCUSSION

This study conducted an in-depth evaluation of the use of adjuvant therapy among real-world patients with resected melanoma. Self-reported adherence to adjuvant therapy was high for patients with resected melanoma. These results differed from those reported in a systematic review of breast cancer survivors, in which adherence to adjuvant endocrine therapy was suboptimal (41–72%) [8]. There are multiple potential reasons for the lower adherence reported among breast cancer survivors, such as the overall drug profile differences between adjuvant therapy for breast cancer versus that for melanoma, the perceived risk–benefit profile, and in particular a much longer recommended adjuvant treatment course for breast cancer (more than 5 years versus up to 1 year for melanoma).

This study also showed that the route of administration was significantly associated with patients' adherence to treatment. Patients treated with intravenous adjuvant therapy reported higher adherence than those treated with oral adjuvant therapy. This finding is similar to results in patients with metastatic colon cancer; for instance, claims data showed that adherence to chemotherapy was significantly higher with treatments administered intravenously than orally [19]. In the current study, this difference in adherence may be attributable to several factors. First, the oral combination adjuvant therapy comprises two capsules of dabrafenib taken twice a day in combination with one tablet of trametinib taken once a day 1 h before or 2 h after a meal. In addition, trametinib must be refrigerated in the original bottle. These

complexities may make it challenging for some patients to adhere to the oral treatment schedule. A review of current literature and clinical experience identified greater regimen complexity as a major barrier to adherence of oral therapies for melanoma, especially in the adjuvant setting, due to the different dosing schedules and storage requirements of dabrafenib and trametinib [10]. These findings appear to align with our results in that only patients treated with oral therapy reported inconvenience as a barrier to adherence, despite the apparent ease of administration. Second, oral medications may require higher co-pays than intravenous therapies, since they are covered under prescription insurance plans instead of major medical plans [10, 20]. This is consistent with our results, which showed that patients treated with oral therapy indicated affordability as a common barrier to adherence, whereas those treated with intravenous therapy did not. Third, patients treated with intravenous therapy may interact with their healthcare providers more frequently as a result of treatment administration, which may enhance feelings of accountability to adhere. In contrast, for patients who are prescribed oral therapy, the responsibility and management of treatment shifts from the clinical team to the patient, which may affect adherence. Although more patients in this study treated with oral therapy anticipated not being able to follow future treatments as instructed, this difference was not statistically significant.

As this study did not evaluate clinical outcomes and their association with adherence rates, it is difficult to speculate whether the difference in adherence rates between intravenous and oral therapy (98.4% versus 91.2%, respectively) would influence clinical outcomes. On the other hand, results from indirect treatment comparisons suggest that intravenous adjuvant therapy with the PD-1 inhibitors nivolumab or pembrolizumab may be more effective than oral adjuvant therapy with the BRAF plus MEK inhibitor combination of dabrafenib plus trametinib, especially over the long term [21, 22]. Therefore, in the real-world setting, the small improvement in adherence with intravenous versus oral therapy may

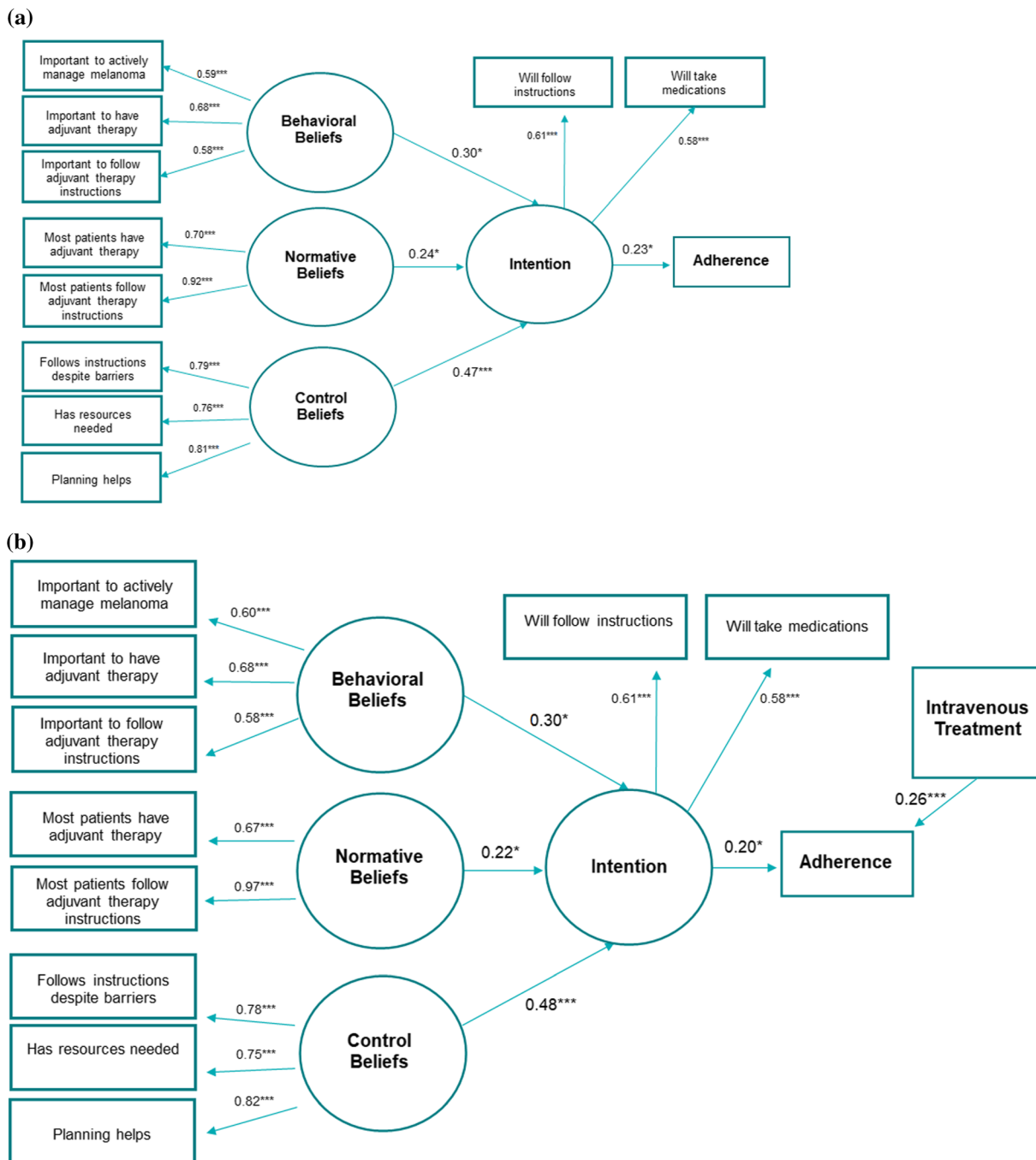


Fig. 1 Base model examining core TPB concepts; R -square = 0.603 for intention and 0.081 for adherence (a) and expanded model that incorporated route of drug administration; R -square = 0.580 for intention and 0.144 for adherence (b). Standardized path estimates shown. Errors were modeled for all observed indicators and the dependent latent variable (i.e., disturbance is modeled for intention). Covariances were also modeled among all

exogenous variables (i.e., variables that only influence another parameter). Errors and covariances not shown. Covariates, including age, sex, white race, education (college graduate versus less than college graduate) were also included but not shown. *TBP* theory of planned behavior. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$

augment the apparent superior treatment effect with PD-1 inhibitors versus the BRAF plus MEK inhibitor.

To the best of our knowledge, this is the first study that utilized a social behavioral model, the TPB, to systematically evaluate underlying factors associated with adherence to adjuvant therapy in patients with resected melanoma. The proposed models had satisfactory fit indices, indicating that the TPB can be useful in understanding medication adherence in patients with resected melanoma. It is a valid theoretical framework for this context, as behavioral, normative, and perceived control beliefs explained a substantial proportion of intention to adhere to adjuvant therapy [15], and intention was significantly associated with actual adherence [16]. These results align with previous findings, which showed that knowledge, attitudes, beliefs, perceptions, and expectations of patients with cancer regarding the course of the disease and their capability to manage their illness and treatment regimen can affect adherence [23, 24].

We found that perceived control beliefs (a patient's perceived capability to perform a behavior) had the strongest association with intention to adhere, followed by behavioral beliefs, and then normative beliefs, similar to previous findings [15, 16, 18]. Other studies have found behavioral beliefs or attitudes to be the strongest predictor of intention [13, 25]. In the adjuvant setting for breast cancer, self-efficacy, attained through more knowledge about taking the medication, has been associated with increased odds of self-reported adherence [9]. It is worth noting that the majority of patients in our study felt their general well-being was good or very good regardless of adjuvant treatment and that they had been involved in the decision-making process about whether or not to start adjuvant therapy. It is possible that the high adherence observed in this study is in part due to patients' high level of involvement in the decisions related to their care and a positive attitude toward their health (feeling good about general well-being). When patients feel empowered in their ability to take control of their care, they have more intention to adhere to treatment, which could lead to a greater

adherence. This may imply that, in clinical practice, communication that increases a patient's sense of control can be an effective channel for improving adherence. Examples of such approaches have been incorporated in patient-tailored counseling at the initiation of adjuvant therapy to help patients overcome perceived barriers and establish treatment routines through goal setting and confidence-building [9].

Despite the strengths of this study, including the collection of patient-reported data to inform adjuvant therapy patterns and beliefs in patients with melanoma, there were several limitations. First, all measures were self-reported and may have been subject to recall biases. As a result of social desirability bias, for instance, adherence may have been overestimated by patients. Second, the adherence measures differed by route of administration: in patients treated with intravenous therapy, missed infusions were considered; whereas, in those treated with oral therapy, adherence was based on estimates of taking medication on time and as instructed. Third, results might not be generalizable to all patients with melanoma treated with adjuvant therapies in the USA. The sample may have been subject to selection bias: patients who were able and willing to participate could have differed from those who were not able to participate because of factors such as patient engagement and internet access. In particular, this group of patients may represent those who are highly engaged in advocacy for their care because of their affiliation with the Melanoma Research Foundation. In addition, this sample includes a limited representation of racial/ethnic minorities and was, on average, younger than other populations of patients with resected melanoma [4, 5, 26]. Assessing adherence in a patient population with a broader range of characteristics would provide greater insights as poorer clinical outcomes with melanoma have been associated with older age, certain racial/ethnic groups (e.g., African Americans), and lower socioeconomic status [27–29]. Finally, we found that while intention to adhere significantly contributed to adherence, this construct explained a limited proportion of the variation observed in adherence.

This suggests that there are factors not currently captured in our study that warrant further research to fully appreciate adherence behavior in these patients.

CONCLUSION

Results from this study indicate that patients with resected melanoma are highly engaged in the decision to initiate systemic adjuvant therapy, with an overall high adherence rate to prescribed adjuvant treatment. Intravenous administration and enhanced patient perception of control are associated with better adherence. Future studies are warranted to fully evaluate factors associated with adherence to adjuvant therapy, as well as the impact that adherence may have on safety and long-term outcomes among patients with completely resected melanoma.

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Data Availability. Bristol Myers Squibb's policy on data sharing is available at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

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