

Oncologist and Patient Preferences for Attributes of CDK4/6 Inhibitor Regimens for the Treatment of Advanced/Metastatic HR Positive/HER2 Negative Breast Cancer: Discrete Choice Experiment and Best–Worst Scaling

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Purpose: To understand and compare preferences for dosing- and toxicity-related attributes associated with selective cyclin-dependent 4/6 kinase inhibitors regimens among US oncologists and patients.

Materials and Methods: Oncologists and patients with mBC participated in an internet-based survey that included a discrete choice experiment (DCE) and a best–worst scaling (BWS) exercise. For the DCE, participants chose between two hypothetical treatment profiles, each with seven attributes: risk of dose reduction due to adverse events (AEs), risk of diarrhea, risk of abdominal pain, need for electrocardiogram (ECG) monitoring to assess heart function, risk of Grade 3/4 neutropenia, dosing regimen, and dosing schedule. The BWS exercise assessed the relative prioritization of a larger set of 16 attributes. Hierarchical Bayesian models were used to estimate preference weights for each attribute level.

Results: Oncologists (N=209) and patients (N=304) rated risks of diarrhea (25% each) and Grade 3/4 neutropenia (20% and 24%, respectively) as the most important attributes for treatment choice. The risks of diarrhea and Grade 3/4 neutropenia were 1.8 to 2.3 times (oncologists: 25% and 20%, respectively vs 11%) and 2.4 to 2.5 times (patients: 25% and 24%, respectively vs 10%) higher in relative importance than the risk of dose reduction due to AEs. Oncologists placed greater importance on the risk of dose reduction due to AEs and the need for ECG monitoring, whereas patients placed greater importance on the risk of Grade 3/4 neutropenia (all, $p < 0.05$). The BWS exercise results were largely consistent with those from the DCE.

Conclusion: The risks of diarrhea and Grade 3/4 neutropenia were key drivers of both oncologist and patient preferences. Overall, the palbociclib + aromatase inhibitor (AI) profile was most preferred, due to its association with a lower risk of diarrhea and no ECG monitoring, compared with abemaciclib + AI and ribociclib + AI profiles, respectively.

Keywords: adverse events, metastatic HR positive/HER2 negative breast cancer, selective cyclin-dependent 4/6 kinase inhibitors, stakeholder preferences, treatment administration, treatment choice

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Introduction

Women in the United States (US) have a 12.4% lifetime risk of breast cancer (BC).¹ BC risk has increased across the past four decades, which may be attributable to longer life expectancy, reproductive pattern changes, hormone use, higher obesity

rates, and contributions from increased screening and detection.¹ Up to 10% of initial BC diagnoses are metastatic at presentation, and roughly 30% of patients treated with endocrine therapy (ET) in the adjuvant setting eventually progress to metastatic disease.³ Overall five-year relative survival is 27% for those diagnosed with advanced or metastatic BC (mBC) in the US.² Treatment for mBC continues as long as a patient is alive or elects only supportive care. For hormone receptor positive, HER2 negative (HR+/HER2-) mBC, ETs, namely selective estrogen receptor modulators (including tamoxifen), aromatase inhibitors (AIs), and selective estrogen receptor down regulators (including fulvestrant) are used for disease control, to delay the need for chemotherapy, and maintain quality of life (QoL).⁴

There has been considerable progress in treatment options for patients with HR+/HER2- mBC with the advent of a new class of drugs with selective inhibition of the cyclin-dependent 4/6 kinases (CDK4/6i; including palbociclib, ribociclib, and abemaciclib) now available to treat these patients.⁴ CDK4/6i regimens have been shown to improve overall survival, progression-free survival, and overall response rate in women with HR+/HER2- mBC, compared with ET alone.^{5–8} While all CDK4/6i have demonstrated efficacy in randomized controlled trials (RCTs), corresponding toxicities, dosing schedules, and label-required monitoring differ among the class.^{4,9–14} All CDK4/6i regimens have the dose-limiting toxicity of neutropenia and require regular complete blood counts. However, for abemaciclib, the risk of diarrhea determined the recommended dose in dose-finding studies. In RCTs, abemaciclib was associated with higher risk of thromboembolic disease, compared with the unexposed control arms.^{4,8} Ribociclib and abemaciclib also require regular monitoring of liver functions; ribociclib requires the monitoring of electrolytes and electrocardiograms (ECGs) to assess for prolongation of the QT interval, both prior to and during treatment, and is contraindicated for use with tamoxifen.

For the practicing oncologist, determining the optimal CDK4/6i regimen may be challenging. Often, comorbidities, physician familiarity, and physician preferences can determine which CDK4/6i regimen is selected.⁴ However, it is vital to consider patient values and preferences in treatment decisions.

Patients and physicians do not always share the same treatment values or preferences,¹⁵ and discrepancies in patient/physician views may predict lower treatment adherence.¹⁶ In turn, treatment nonadherence is associated

with disease progression and mortality among patients with BC.^{17,18} Patient involvement in decision-making has been linked to better health outcomes and lower costs, as patients who were involved in the decision-making process, chose their treatment, or received their preferred treatment reported higher treatment satisfaction, higher rates of treatment completion, and better clinical outcomes across health conditions.¹⁹ Furthermore, greater healthcare engagement among patients is associated with lower medical costs over time via fewer emergency room visits and hospitalizations.²⁰ Determining the extent to which patients and physicians are aligned in their preferences is warranted, particularly in an oncology setting, where available treatment options may be more limited, and it becomes increasingly important to understand what patients value and are willing to endure regarding toxicity risk and inconvenience.¹⁶

Prior research in the US and other countries has examined patient preferences regarding the characteristics of cancer treatments, including those with mBC or other advanced cancers.^{15,21–25} No studies to date have examined or compared the preferences of oncologists and patients regarding the clinical and non-clinical attributes of CDK4/6i regimens. A better understanding of oncologist and patient preferences may help to facilitate both clinical and payer decision-making regarding the selection of CDK4/6i regimens for HR+/HER2- mBC.

To potentially improve communication among oncologists and patients and to inform payer decisions regarding treatment for mBC, this study examined the treatment preferences of oncologists and patients with HR+/HER2- mBC, based on attributes associated with available CDK4/6i regimens. Specifically, this study sought to assess the trade-offs in benefits and risks that oncologists and patients are willing to accept, heterogeneity in preferences among oncologists and patients, and rank order of preferences for treatment attributes.

Materials and Methods

Data Source

The study was conducted in two phases and included four separate, but complementary, studies with oncologists and postmenopausal patients with HR+/HER2- mBC. Study data were collected in two phases: oncologist and patient responses in pilot interviews to test and refine the study instruments (phase 1), and oncologist and patient preferences reported in an online survey (Phase 2).

To be eligible, all participants were required to be able to read and understand English, able to operate a computer

to access the online survey, located in the US, aged ≥ 18 years, and able and willing to provide informed consent. All eligible participants were contacted through e-mail. The study was conducted in accordance with the recommendations of the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Conjoint Analysis Task Force.²⁶ The study protocol was granted an exemption from full or expedited review by Pearl Institutional Review Board (Indianapolis, Indiana) prior to starting data collection based on FDA 21 CFR 56.104 and 45 CFR 46.104(b)(2). Participants provided their informed consent electronically.

Study Samples

The target sample sizes for patients and oncologists were first established by using the formula provided by Orme.²⁷ Target sample sizes were further verified through a simulation study. Specifically, we simulated random choice for samples of the same size and fit a logit regression to the simulated data. This process confirmed that the errors for the preference levels were less than 0.05, which indicated that preference weights would be estimated with adequate precision.

Patients

Patients were recruited using convenience sampling from the Endeavour database, which accrues participants via referrals from physician sites and relationships with patient advocacy groups. Patient recruitment was concurrent with oncologist recruitment. Patient recruitment was also stratified with a mix of 109 patients on first line therapy (de novo Stage IIIB, IIIC, IV; previously-treated, recurrent Stage IIIB, IIIC, IV) and 195 patients on second or later line therapy. To be eligible to participate, patients were required to be female, diagnosed with HR+/HER2- mBC (stage IIIB, IIIC, IV), and postmenopausal. Patients who did not meet all inclusion criteria were considered ineligible.

Oncologists

Oncologists were recruited from Lightspeed Research's All Global physician panel. All Global proprietary panel members are telephone-recruited to become members using hospital books and directories, medical directories, and yellow pages as original sample sources; panel demographics are generally representative of American Medical Association membership. Members undergo a double opt-in process, including a registration process followed by

activation through email. To be eligible for the current study, oncologists were required to be board certified or board eligible, have been in practice between 2 and 35 years, spend at least 75% of time in direct patient care, have been providing services for ≥ 5 patients with mBC with systemic treatments at time of study participation, and have experience using CDK4/6i regimens. Oncologists who were unwilling or unable to comply with study procedures were excluded.

Measures

Variables included sociodemographic, disease, and treatment characteristics for patients, practice characteristics for oncologists, and treatment profile choices, as measured via discrete choice experiment (DCE) and best-worst scaling (BWS) exercise.

Study Design

Two preference elicitation methods using hypothetical scenarios that mimic real-world decision-making were employed (DCE and BWS). The use of two elicitation methods allowed insight into whether preference data would converge.

Discrete Choice Experiment

A DCE was used to assess patient and oncologist preferences regarding CDK4/6i + AI regimen attributes and levels. The DCE modeling approach is designed to assess respondents' willingness to accept trade-offs among hypothetical treatment profiles providing information on key factors (eg, toxicities, efficacy, etc.) that drive treatment choice. DCE has a strong foundation in psychology and economics.²⁸ This approach is based on the principle that treatment options can be decomposed into attributes of interest. The attractiveness of a treatment to individuals will depend on their relative preferences for these attributes, as expressed by the frequency with which they choose profiles with the preferred features; these values are then used to estimate the predictive probabilities that determine whether respondents will be more likely to choose one hypothetical treatment over another. Although there are alternatives for eliciting preferences (eg, revealed preferences, direct ratings/rankings, etc.), DCE is one of the most common approaches for assessing preferences in a healthcare context, and it has become of increasing interest to health authorities and clinicians to facilitate shared decision-making.²⁹

In the DCE, participants considered two hypothetical CDK4/6i + AI regimen profiles, shown side-by-side, and were then asked to choose the one that they preferred. There was no “none” option, so the respondent was forced to make a choice. Each hypothetical treatment profile consisted of combinations of characteristics (“attributes”) and “levels” reflecting the attributes for each hypothetical treatment profile. Respondents’ selections allowed for an assessment of the trade-offs they were willing to make between positive and negative aspects of the treatment profiles. Respondents made several hypothetical treatment decisions over a series of scenarios involving two alternatives, which varied in the levels of each attribute. For example, one medication may have conferred a 33% risk of dose reduction due to AEs, while the other may have conferred a 45% risk. In total, each respondent saw 12 choice tasks. We used a balanced, overlap design to select what combination of levels were shown to a respondent. We generated more choice sets than respondents per survey, so that no respondent saw the same set of choice tasks.

The DCE method is superior to other approaches because it mimics a real-world situation where a medication’s attributes do not occur in isolation. For example, one must weigh both efficacy and toxicities simultaneously among available therapies when selecting treatment. In this study, the seven attributes and their corresponding levels for CDK4/6i + AI regimens (see [Table 1](#)) were carefully chosen based on clinical trial data, literature review, and qualitative interviews. No actual medication names were shown in the DCE. A sample DCE item is shown in [Appendix 1](#). To help familiarize respondents with the DCE attributes and levels prior to completing the choice tasks, they were asked to rate the levels for each attribute on a scale from 1=very bad to 5=very good.

Best–Worst Scaling

Participants completed a separate BWS exercise, which enabled the ranking of a larger set of attributes in order of importance and included attributes associated with CDK4/6i + AI and CDK4/6i + fulvestrant regimens. There was some overlap between items in the DCE and BWS exercise, which provided the opportunity to examine multiple attributes and compare those that were in both exercises. In the BWS exercise, a list of 16 attributes was presented to oncologists and patients, four at a time. To avoid any bias due to ordering effects, randomization was used to select the four attributes in each set presented to respondents in the BWS exercise. The participants selected the most important and least important attribute from among the four presented.

Procedure

Phase 1, Survey Development

Survey content was pilot tested among oncologists and patients in a qualitative study via hour-long telephone interviews and a desktop sharing platform. Eight oncologists and eight patients completed the qualitative study. Interviews assessed comprehension of the DCE/BWS items and appropriate screening thresholds. Pre-testing of the online survey was also conducted to ensure that the language was appropriate for, and could be easily understood by, respondents. Based on qualitative interview results, the survey content was further refined.

Issues were identified among two patients in the comprehension of the instructions for the first task; specifically, they were unsure what we meant by “very bad/very good”. The final survey instructions were revised to clarify that “very good” means “very appealing”. As some respondents mistakenly thought they were supposed to rank the attributes in order of importance, even though they were instructed to rank the most and least important, we programmed the final survey to force respondents to select one attribute per column. After the pilot testing, we also added further details to describe the percentage risk of developing a serious infection after developing a low white blood cell count, as we believed that preferences would be more accurate if this risk was explicitly noted in the attribute definition.

Phase 2, Final Survey Administration

Potential participants were pre-screened for eligibility before being invited to participate in the study. In total, 488 oncologists and 400 patients were eligible to participate. Overall, 209 oncologists and 304 patients with mBC completed the final survey.

Statistical Analysis

Descriptive analyses were used to characterize the oncologist and patient samples. Descriptive statistics (means, standard deviations (SDs), medians, and interquartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables) were calculated for all study measures on the total samples of oncologists and patients. This analysis of the distributions was a part of testing of model assumptions and helped inform the appropriate modeling techniques.

For the DCE, to estimate preference weights for each attribute level, a hierarchical Bayesian (HB) model was fitted to the choice data. The fit for the HB model was done with a Markov Chain Monte Carlo. The underlying

Table I Attributes and Levels Included in the DCE

Attribute	Definition	Levels
Safety-Related Attributes		
Risk of dose reduction due to AEs	[INSERT LEVEL] risk of lowering treatment dose due to side effects	1. 36% 2. 43% 3. 45%
Risk of diarrhea	[INSERT LEVEL] risk of diarrhea with a [INSERT LEVEL] chance of severe diarrhea (increase of seven or more loose or watery stools per day which requires hospitalization)	1. 81%, 9% 2. 35%, 1% 3. 26%, 1%
Risk of abdominal (belly) pain	[INSERT LEVEL] risk of abdominal (belly) pain, with [INSERT LEVEL] chance of severe abdominal pain	1. 29%, 1% 2. 17%, 1% 3. 11%, 1%
Need for ECG monitoring to assess heart function	Requires ECG testing to assess heart function 3 times within the first 3 months of treatment to monitor the 6% risk of arrhythmia Do not require ECG testing to assess heart function	1. yes 2. no
Risk of Grade 3/4 neutropenia	[INSERT LEVEL] chance you will develop low white blood cell counts during treatment that may not cause symptoms, but may result in a [INSERT LEVEL] risk of a serious infection	1. 22%, 4% 2. 60%, 1% 3. 66%, 5%
Non-Clinical Attributes		
Regimen	[INSERT LEVEL]	1. 2 pills per day taken with food 2. 3 pills per day taken with or without food 3. 4 pills per day taken with or without food
Dosing schedule	[INSERT LEVEL]	1. Pills taken everyday 2. Stop taking 1 pill for 7 days per month 3. Stop taking 3 pills for 7 days per month

Abbreviations: AE, adverse event; ECG, electrocardiogram.

HB choice-probability model was conditional logit, using effects coding for the attribute levels. The results were then used to construct the joint posterior distribution of preference weights over the entire sample, including the mean and SD for each level. Independent-samples t-tests were used to evaluate whether the importance estimates differed across stakeholder groups. The BWS data were analyzed as frequencies.³⁰ Specifically, two rates were calculated: the rate that the attribute was selected as the most important for considering a treatment and the rate that an attribute was selected as least important. The difference between these rates was used to rank order the attributes and to estimate the magnitude of attribute preference for oncologists and patients.

HB modeling was performed using Sawtooth's Choice-Based Conjoint HB Lighthouse Studio software, 2018. Descriptive and bivariate analyses were performed using SPSS v23.0.

Relative Preference Weights for Each Attribute Level

Point estimates of HB model coefficients, representing mean utility weights at the aggregate level, SDs, and 95% confidence intervals, were calculated. The HB model produced utility estimates for each respondent. The 95% confidence interval was estimated from the individual utilities with a t-distribution. These utility weights measure relative preference; thus, only changes between attribute-level estimates and the relative size of those changes across attributes have meaningful interpretations. The magnitude of the trade-offs that stakeholders are willing to make among the attribute levels were assessed via these weights.

Relative Importance of Each Attribute

Relative importance estimates demonstrate the unique contribution of each attribute to the total utility of a treatment profile. These were calculated at the respondent level by dividing the range of each attribute (utility of the most favorable level minus utility of the least favorable level) by the sum of the ranges of all attributes and multiplying by 100 to convert to a percentage. The resulting estimates reflect the importance of each attribute, relative to the others. Importance estimates are ratio-scaled; an attribute with an importance of 20% is twice as important as an attribute with an importance of 10%.

Profile Comparisons

Participants evaluated three CDK4/6i + AI regimen profiles corresponding to the specific attributes and levels within the DCE. The utilities for each respondent were derived from their DCE data and then summed to compute a total mean utility for each profile. This enabled head-to-head comparisons of patient preferences among palbociclib + AI, abemaciclib + AI, and ribociclib + AI profiles.

Results

Oncologist Characteristics

Oncologist characteristics (N=209) are presented in Table 2. Most specialized in medical oncology (82.3%) and had been practicing for a median of 15.0 (IQR: 10.0–20.0)

years. The largest proportion practiced in community-based private groups (42.5%) or academically-based practices (38.7%). Oncologists reported spending most of their time in direct patient care (93.3%), and they saw a median of 75.0 (IQR: 50.0–99.0) patients with BC during the past three months, including a median of 40.0 (IQR: 24.0–60.0) patients with mBC.

Patient Characteristics

Patient characteristics (N=304) are shown in Table 2. The median age was 47.0 (IQR: 40.0–55.0) years old. Most were married/in a committed relationship (62.5%), White (63.2%), had completed at least some college (81.9%), were unemployed or retired (51.0%), and had a household income of \geq \$50,000 (52.7%). Most (62.7%) had initially been diagnosed with BC between one to

Table 2 Sample Characteristics

Oncologist Variables		N	%
Practice Location	Major metropolitan/urban area	132	63.2
	Suburb/small city	70	33.5
	Rural/small town	7	3.3
Primary Specialty	Medical oncology	172	82.3
	Hematology oncology	37	17.7
		Mean	SD
Years in Practice		15.75	6.67
Median (IQR)		15.0	10.0, 20.0
Percent of Time Spent in Direct Patient Care		93.33	6.78
Median (IQR)		95.0	90.0, 100.0
Percent of Time in Practice Setting	Community-based solo or group practice	44.95	44.73
	Median (IQR)	40.0	0.0, 100.0
	Out-patient oncology center or clinic	22.39	36.81
	Median (IQR)	0.0	0.0, 30.0
	Academically-based practice	23.06	38.69
	Median (IQR)	0.0	0.0, 25.0
	NCCN designated cancer center	9.17	27.08
	Median (IQR)	0.0	0.0, 0.0
Other setting		0.43	2.78
	Median (IQR)	0.0	0.0, 0.0
Number of Patients with mBC Seen/Treated in Past 3 Months		71.24	24.83
Median (IQR)		75.0	50.0, 99.0
Percent of Time Treating Patients with mBC		57.76	28.60
Median (IQR)		60.0	30.0, 80.0
Number of Patients with HR+/HER2- mBC		41.64	21.79
Median (IQR)		40.0	24.0, 60.0
Number of Patients with HR+/HER2- mBC on Systemic Treatment		36.53	19.83
Median (IQR)		34.0	20.0, 50.0

(Continued)

Table 2 (Continued).

Patient Variables		N	%
Education	Some high school/high school graduate	55	18.1
	Some college or higher	249	81.9
Marital Status	Single/separated/divorced/widowed	114	37.5
	Married/committed relationship	190	62.5
Employment Status	Unemployed/retired	155	51.0
	Employed	130	42.8
	Other	19	6.3
Household Income	<\$50,000	144	47.4
	≥\$50,000	149	49.0
	Prefer not to answer	11	3.6
Race/Ethnicity	African-American/Black	64	21.1
	Asian	22	7.2
	American Indian	39	12.8
	Hispanic	70	23.0
	White	192	63.2
First Diagnosed with Breast Cancer	In the last year/past 12 months	25	8.3
	1 to 2 years ago	71	23.4
	>2 years, but <5 years ago	119	39.3
	≥5 years ago	88	29.0
		Mean	SD
Age		47.35	9.96
Median (IQR)		47.0	40.0, 55.0
Number of months from initial diagnosis when breast cancer reached advanced/metastatic stage		21.34	21.80
Median (IQR)		15.0	8.0, 26.5

Notes: For patient race/ethnicity, the total sums to >100% because multiple options could be selected.

Abbreviations: HR+/HER2-, hormone receptor positive/HER2 negative; IQR, interquartile range; mBC, metastatic breast cancer; NCCN, National Comprehensive Cancer Network; SD, standard deviation.

five years prior to study participation, and the cancer had become metastatic a median of 15.0 (IQR: 8.0–26.5) months from initial diagnosis.

Oncologist and Patient Preferences

Attribute level preference weights by stakeholder group are shown in [Figure 1](#). Among oncologists, the difference between level estimates allowed for the evaluation of the effect of a change within an attribute. For example, lowering the risk of diarrhea/severe diarrhea from 81%/9% to 35%/1% (0.35–[–1.39]=1.74) outweighed lowering the risk of abdominal (belly) pain/severe abdominal pain from 29%/1% to 11%/1% (0.25–[–0.41]=0.66) in importance. Lowering the risk of Grade 3/4 neutropenia/serious infection from 60%/1% to 22%/4% was 6.8 times more important to treatment choice than lowering the risk of dose reduction due to AEs from 43% to 36% (0.88 vs

0.13). Lowering the risk of diarrhea/severe diarrhea from 81%/9% to 35%/1% was 2.1 times more influential to treatment choice than lowering the risk of Grade 3/4 neutropenia/severe infection from 66%/5% to 60%/1% (1.74 vs 0.82).

A similar pattern of results was observed among patients. Specifically, lowering the risk of diarrhea/severe diarrhea from 81%/9% to 35%/1% was 2.2 times more important to treatment choice than lowering the risk of Grade 3/4 neutropenia/serious infection from 66%/5% to 60%/1% (1.58 vs 0.71) and 5.9 times more important than lowering the risk of dose reduction due to AEs from 43% to 36% (1.58 vs 0.27). Lowering the risk of Grade 3/4 neutropenia/serious infection from 60%/1% to 22%/4% was 4.2 times more important to treatment choice than lowering the risk of dose reduction due to AEs from 43% to 36% (1.13 vs 0.27). [Appendix 2](#) shows estimates

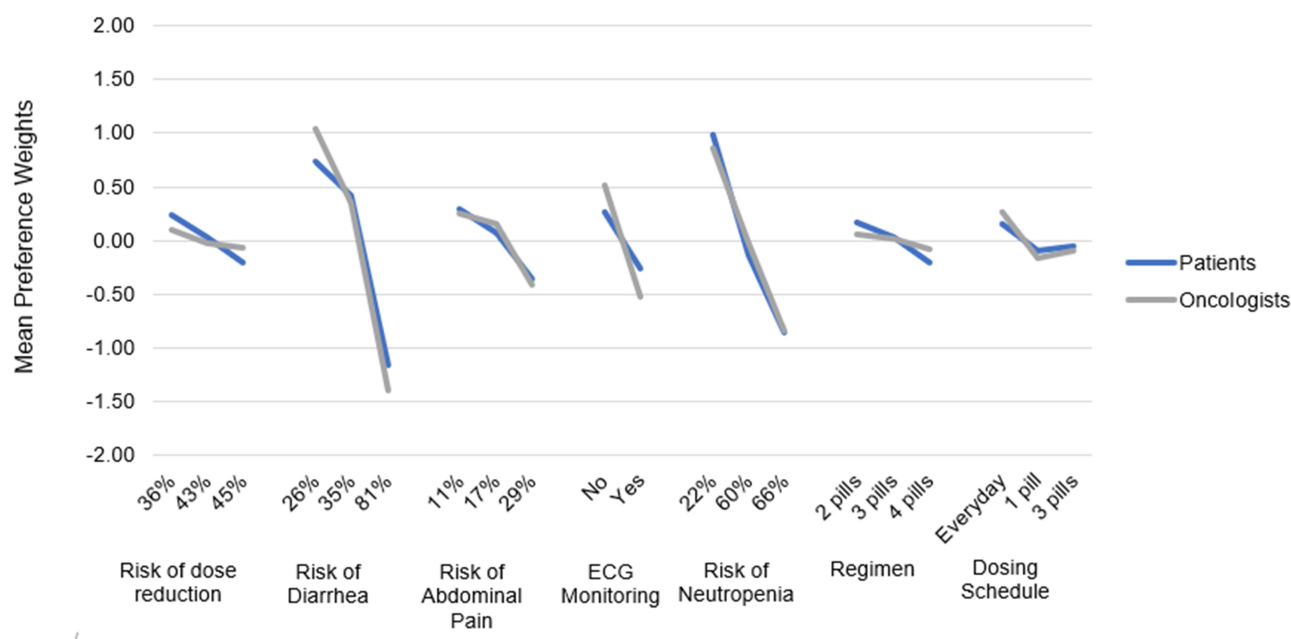


Figure 1 Attribute-level preference weights for oncologists and patients.

Abbreviations: AE, adverse event; ECG, electrocardiogram.

of the relative importance for each attribute by stakeholder group.

Overall, the risks of diarrhea/severe diarrhea and Grade 3/4 neutropenia/serious infection were rated as the most important attributes by both oncologists and patients, and these two attributes were each approximately twice as important as the other attributes included in the DCE. Compared with patients, oncologists rated dose reduction due to AEs (10% vs 11%), need for ECG monitoring to assess heart function (9% vs 11%), and regimen (9% vs 11%) as significantly more important (all, $p < 0.05$). However, patients rated risk of Grade 3/4 neutropenia/serious infection as significantly more important than oncologists did (24% vs 20%, $p < 0.001$). There were no significant differences by stakeholder group on the relative importance of risks of diarrhea/severe diarrhea or abdominal (belly) pain/severe abdominal pain.

Treatment Profile Comparisons

The treatment profiles for the three CDK4/6i + AI regimens are shown in Table 3. Abemaciclib + AI was associated with a lower preference weight than the other CDK4/6i + AI profiles on the risk of diarrhea/severe diarrhea, and palbociclib + AI and ribociclib + AI were associated with lower preference weights than the abemaciclib + AI profile on the risk of Grade 3/4 neutropenia/serious infection. Based on the total utility weights for

each treatment profile, oncologists and patients preferred the overall combination of safety and non-clinical attributes associated with palbociclib + AI. However, the palbociclib + AI (0.97 vs 0.75) and ribociclib + AI (0.50 vs 0.17) profiles were more preferred by oncologists than patients (both, $p < 0.05$).

Best–Worst Scaling

Figure 2 illustrates the BWS exercise results for patients and oncologists, which included attributes of CDK4/6i + AI and CDK4/6i + fulvestrant regimens. While lower risks of moderate diarrhea and Grade 3/4 neutropenia, which may lead to serious infection, were still near the top in importance for patients, three attributes that were not in the DCE were also rated as very high in importance: lower risk of heart dysfunction, which involves having a sudden irregular heartbeat, real-world effectiveness data are available, and patient-reported benefits have been published. For oncologists, the most important attributes were consistent with the results from the DCE. Specifically, lower risks of Grade 3/4 neutropenia, which may lead to serious infection, moderate diarrhea, and heart dysfunction, which involves having a sudden irregular heartbeat, were the top three most important attributes. Monitoring of liver function is required (16% vs 25%) and lower risks of moderate diarrhea (40% vs 32%) and heart dysfunction, which involves having a sudden irregular heartbeat (49% vs

Table 3 Preferences Among Oncologists and Patients for Selected CDK4/6i Treatment Profiles

Attribute	Levels	Palbociclib + AI	Abemaciclib+ AI	Ribociclib+ AI
Oncologist Preferences				
Risk of dose reduction due to AEs	36% 43% 45%	0.10	-0.03	-0.07
Risk of diarrhea	26% (1% severe diarrhea) 35% (1% severe diarrhea) 81% (9% severe diarrhea)	1.04	-1.39	1.04
Risk of abdominal (belly) pain	11% (1% severe diarrhea) 17% (1% severe diarrhea) 29% (1% severe diarrhea)	0.25	-0.41	0.25
Need for ECG monitoring to assess heart function	No Yes	0.52	0.52	-0.52
Risk of Grade 3/4 neutropenia	22% (4% serious infection) 60% (1% serious infection) 66% (5% serious)	-0.84	0.86	-0.02
Regimen	2 pills per day taken with food 3 pills per day taken with or without food 4 pills per day taken with or without food	0.06	0.02	-0.08
Dosing schedule	Pills taken everyday Stop taking 1 pill for 7 days per month Stop taking 3 pills for 7 days per month	-0.16	0.26	-0.10
Total profile utility		0.97	-0.17	0.50
Patient Preferences				
Risk of dose reduction due to AEs	36% 43% 45%	0.24	-0.03	-0.21
Risk of diarrhea	26% (1% severe diarrhea) 35% (1% severe diarrhea) 81% (9% severe diarrhea)	0.74	-1.16	0.74
Risk of abdominal (belly) pain	11% (1% severe abdominal pain) 17% (1% severe abdominal pain) 29% (1% severe abdominal pain)	0.29	-0.36	0.29
Need for ECG monitoring to assess heart function	No Yes	0.26	0.26	-0.26
Risk of Grade 3/4 neutropenia	22% (4% serious infection) 60% (1% serious infection) 66% (5% serious infection)	-0.85	0.99	-0.14
Regimen	2 pills per day taken with food 3 pills per day taken with or without food 4 pills per day taken with or without food	0.17	0.03	-0.20

(Continued)

Table 3 (Continued).

Attribute	Levels	Palbociclib + AI	Abemaciclib+ AI	Ribociclib+ AI
Dosing schedule	Pills taken everyday Stop taking 1 pill for 7 days per month Stop taking 3 pills for 7 days per month	-0.10	0.15	-0.05
Total profile utility		0.75	-0.12	0.17

Abbreviations: AE, adverse event; AI, aromatase inhibitor; ECG, electrocardiogram.

42%), had the largest absolute differences in importance when comparing the ratings of oncologists and patients, respectively. However, these differences did not reach statistical significance.

Discussion

For both oncologists and patients, the most important attributes for selecting from among currently available CDK4/6i + AI regimens were the risks of diarrhea and Grade 3/4 neutropenia, with diarrhea being the most important. Patients placed greater importance than oncologists on the risk of Grade 3/4 neutropenia, whereas oncologists placed greater importance than patients on the risk of dose reduction due to AEs and the need for ECG monitoring. Overall, the palbociclib + AI profile was most preferred, due to its association with a lower risk of diarrhea and no ECG monitoring, compared with abemaciclib + AI and ribociclib + AI profiles, respectively.

Among the attributes explored with the BWS exercise, the risks of Grade 3/4 neutropenia and diarrhea were perceived as near the top in importance by both stakeholder groups. However, oncologists also highly valued a lower risk of heart dysfunction, and patients also placed importance on the treatment having real-world effectiveness data and published patient-reported benefits. Findings regarding both preference “agreements” (risks of diarrhea and Grade 3/4 neutropenia being considered most important by both stakeholder groups) and “disagreements” (level of importance regarding: Grade 3/4 neutropenia, risk of dose reduction due to AEs, need for ECG monitoring, having real-world effectiveness data, and published patient-reported benefits) may potentially help facilitate fruitful conversations between oncologists and patients when selecting a CDK4/6i + AI regimen to treat mBC.

To our knowledge, this is the first study to assess treatment preferences of oncologists and patients with mBC across currently available CDK4/6i regimens.

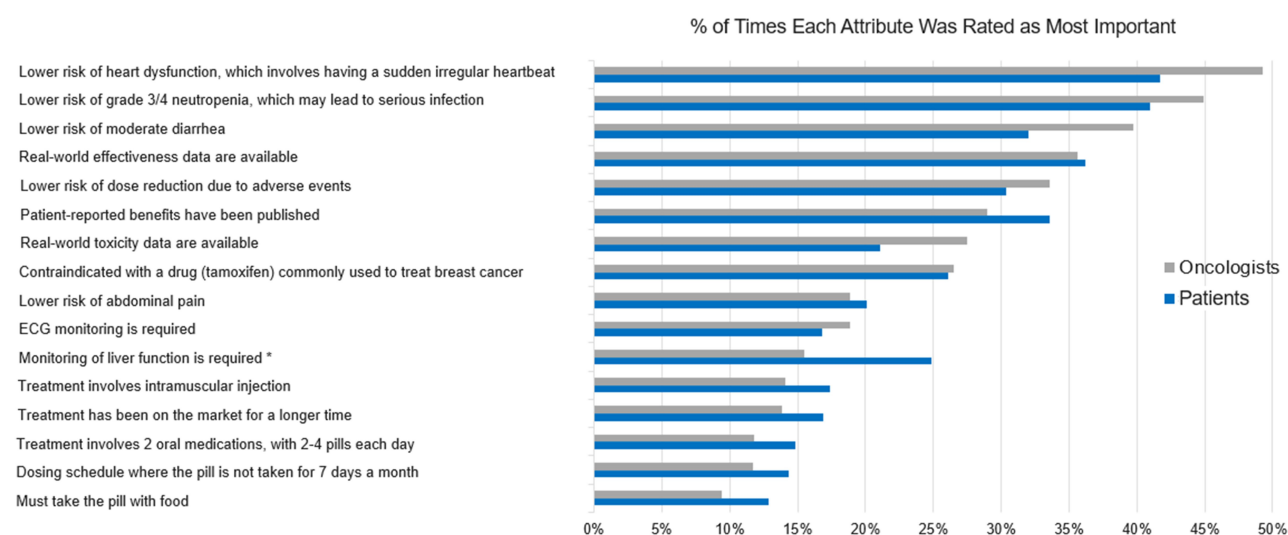


Figure 2 BWS exercise ratings for oncologists and patients.

Note: An asterisk *Indicates that groups significantly differ at $p < 0.05$.

Abbreviation: ECG, electrocardiogram.

Oncologists' preference for less risk of toxicities is not an unexpected finding and has been well documented in the literature.^{15,21,23,24,31} Little data are available regarding patient treatment preferences in the mBC setting. This examination of the decision-influencing attributes of CDK4/6i regimens supports the existing body of literature that describes oncologist and patient preferences for other treatments across cancer sites.

Results of the current study showed diarrhea to be one of the most important drivers of preferences for both stakeholder groups. Although infrequently life-threatening, treatment-induced diarrhea nevertheless has important implications, as it can frequently necessitate supportive therapy, dose reductions, treatment delays, switches, and discontinuations.³² Moreover, among patients using systemic cancer therapy, experiencing moderate to severe diarrhea (vs no diarrhea) was associated with significantly worse QoL.²¹ Dosing frequency was not a key factor in patient and oncologist preferences, which further supports the finding that toxicity-related attributes primarily underlie stakeholder preferences among available CDK4/6i regimens.

When treatment decisions are aligned with patient preferences, patients report higher treatment satisfaction and adherence and have better clinical outcomes.¹⁹ Prior longitudinal research has found that oncologists, relative to their patients with advanced cancer, place stronger emphasis on survival (vs QoL) as the treatment goal that would be best for patients.³³ A systematic literature review of prior DCE studies across 26 disease conditions (including eight types of cancer) reported that mortality was more important to healthcare providers, while medication safety, delivery and timing of treatment, and treatment accessibility were more important to patients.³⁴ Thus, prior research suggests that patients prioritize treatment aspects that can impact their QoL, whereas physicians may prioritize prolonging a patient's life;^{19,33,34} this discordance has implications in the metastatic setting, as patients may potentially be less willing to endure inconvenient treatment regimens with high toxicity risks that could negatively impact the quality of their remaining time. Although there was largely agreement in stakeholder preferences in this study, oncologists should consider those treatment aspects that are most important to patients when making treatment recommendations. Moreover, patients who are more engaged in decisions about their healthcare have fewer emergency room visits and hospitalizations over time.²⁰ This suggests that including the patient perspective

in treatment decision-making may also help to reduce healthcare expenditures, especially those incurred from high-cost medical events.

Limitations

Younger patients and those interested in research may have been more likely to participate in the study. The average age of participants in this study is significantly younger than the average age of a patient with mBC in the US, limiting the generalizability of the results. Therefore, results may not generalize to the entire population of patients with mBC and/or to the population of oncologists who treat these patients. The DCE also may not reflect the same clinical, financial, or emotional consequences of actual decisions, although the DCE was carefully designed to include the feedback of the stakeholder groups of interest, to mimic realistic treatment choices, and to closely align with clinical evidence. BWS is also purported to be an "easier" task comparatively, although this issue was addressed by including two preference elicitation methods to determine the convergence of results. Discrepancies between DCE and BWS results may also reflect that the former only included CDK4/6i + AI regimen attributes, whereas the latter additionally included attributes of CDK4/6i + fulvestrant regimens.

Stated preferences may differ from actual treatment decisions. Moreover, all study variables were reported directly from participants without independent verification; it is possible that patients may have an incomplete understanding of the attributes presented. Self-reported data may potentially be subject to response bias, which can increase measurement error. Because the rate of any grade diarrhea is much higher than that of Grade 3/4, this may have resulted in the overestimation of the importance of the risk of diarrhea, relative to the risk of Grade 3/4 neutropenia, particularly among patients. Oncologists' relative ranking of these two attributes may reflect that Grade 3/4 neutropenia is typically asymptomatic, while patients may not be aware of whether or not symptoms are associated with this AE.

Cost data were not included in the DCE or BWS. Cost can be a predominant factor in treatment choice, thereby greatly overshadowing the effects of other attributes in the model, resulting in biased estimates. Efficacy data were likewise not included in the DCE or BWS, as CDK4/6i + AI regimens were assumed to have similar efficacy, based on clinical data available when the study was conducted. However, we cannot exclude the possibility that incorporating both efficacy and toxicity-related attributes would

have a more meaningful impact on stakeholder preferences. Additionally, it is possible that estimated preferences for the CDK4/6i regimens of interest could differ from those observed had we included an alternative to opt-out of treatment in the choice tasks. Future research should ascertain whether those individuals who would choose to opt-out of mBC treatment systematically differ in demographics, clinical status, attitudes, and other characteristics from those would not opt-out of treatment.

Conclusions

For patients and physicians, the risks of diarrhea and Grade 3/4 neutropenia were the most important attributes driving treatment preferences. The results of the DCE and BWS exercise largely converged regarding the attributes most valued by oncologists and patients. When considering all attributes collectively, the palbociclib + AI profile was most preferred, overall, due to its association with a lower risk of diarrhea and no ECG monitoring, compared with abemaciclib + AI and ribociclib + AI profiles, respectively. Patients and oncologists were willing to make similar trade-offs in potential risks and benefits associated with different treatment profiles, although results revealed subtle differences in attribute importance. This study's findings highlight the importance of understanding oncologist and patient preferences when making mBC treatment decisions in clinical practice.

Abbreviations

AE, adverse event; AI, aromatase inhibitor; BC, breast cancer; BWS, best-worst scaling; CDK4/6i, selective cyclin-dependent 4/6 kinase inhibitor; DCE, discrete choice experiment; ECG, electrocardiogram; ET, endocrine therapy; HB, hierarchical Bayesian; HR+, hormone receptor positive; IQR, interquartile range; mBC, metastatic breast cancer; NCCN, National Comprehensive Cancer Network; QoL, quality of life; RCT, randomized clinical trial; SD, standard deviation; US, United States.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will

also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

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