The Value of Progression-Free Survival in Metastatic Breast Cancer: Results From a Survey of Patients and Providers

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Abstract

Background. Value assessments and treatment decision making typically focus on clinical endpoints, especially overall survival (OS). However, OS data are not always available, and surrogate markers may also have some value to patients. This study sought to estimate preferences for progression-free survival (PFS) relative to OS in metastatic breast cancer (mBC) among a diverse set of stakeholders—patients, oncologists, and oncology nurses—and estimate the value patients and providers place on other attributes of treatment. Methods. Utilizing a combined conjoint analysis and discrete choice experiment approach, we conducted an online prospective survey of mBC patients and oncology care providers who treat mBC patients across the United States. Results. A total of 299 mBC patients, 100 oncologists, and 99 oncology nurses completed the survey. Virtually all patients preferred health state sequences with contiguous periods of PFS, compared with approximately 85% and 75% of nurses and oncologists, respectively. On average, longer OS was significantly ($P < 0.01$) preferred by the majority (75%) patients, but only 15% of nurses preferred longer OS, and OS did not significantly affect oncologists’ preferred health state. However, in the context of a treatment decision, whether a treatment offered continuous periods of stable disease holding OS constant significantly affected nurses’ treatment choices. Patients and providers alike valued reductions in adverse event risk and evidence from high-quality randomized controlled clinical trials. Conclusions. The strong preference for observed PFS suggests more research is warranted to better understand the reasons for PFS having positive value to patients. The results also suggest a range of endpoints in clinical trials may have importance to patients.

Keywords

surrogate endpoints, discrete choice experiment, patient preferences, provider preferences

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Overall survival (OS) has long been the gold standard in establishing the efficacy of oncology therapies. Yet, due to improvements in the standard of care, along with constraints on study duration and design, clinical trials often provide incomplete data on the OS benefits of new therapies. To compensate, clinical trials often include one or more “surrogate endpoints” to quantify the potential value offered by new therapies when OS is unlikely to be shown conclusively. Progression-free survival (PFS), defined in clinical trials as the time from randomization until first evidence of tumor progression or death from any cause, is one of the most commonly used surrogate endpoints in oncology clinical trials. The use of PFS in clinical trials has risen rapidly since the mid-1970s, serving as a primary endpoint in 20% of clinical trials in major cancers conducted in the mid to late 2000s.

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Despite the now common use of surrogate endpoints in oncology trial designs, the value of surrogate endpoints has been questioned by some cancer researchers, and often without an evaluation of patient preferences.²,⁴,⁵ Some studies have shown a poor or modest correlation with OS in the majority of surrogate endpoints, but other studies have found that surrogate endpoints can correlate with real-world outcomes.⁹,¹⁰ Furthermore, data on surrogate endpoints can be collected in studies of shorter duration, which shortens access time to new therapies for patients.¹¹,¹² A great deal of controversy remains, however, as to the use of PFS as a surrogate for OS, with the association being weak in some cancers, yet strong in others.¹³

How data from clinical trials, including primary endpoints such as OS, and surrogate endpoints such as PFS, factor into treatment decision-making has also been questioned.¹⁴ Previous research has shown that patients often take into account a wide range of factors when making a choice of therapeutic options, and do not focus solely on OS.¹⁵,¹⁶ For example, patients consider aspects of treatment including mode of administration and dosing schedule, as well as other factors such as the impact of treatment side effects on ability to work, or a spouse or family member’s opinion. Endpoints such as PFS may factor more heavily in a patient’s decision about therapeutic options than OS benefit alone as PFS has implications in terms of quality of life not considered with OS. Physicians, on the other hand, have been shown to place heavy weight on survival when making treatment recommendation, without fully considering how treatment may affect patients’ quality of life.¹⁷,¹⁸ High levels of discordance between patients and providers have been shown to exist across the cancer treatment spectrum and tumor sites, with providers more likely to accept side effects in exchange for increased survival.¹⁹–²² These mismatched priorities may lead to suboptimal decision making when patient and provider understanding of the important attributes of therapy differ widely.

Hence, understanding the priorities patients and providers place on clinical data and treatment attributes in oncology care decision making is critical to improving the patient–provider alliance; which, when the relationship is strong, has been demonstrated to improve outcomes.²³ The collection of relevant data in trials and its use in real-world decisions is of particular importance when patients are faced with potentially life-threatening diseases such as advanced cancer.

With these issues in mind, we conducted a study of metastatic breast cancer (mBC) patients and providers (oncologists and oncology nurses) across the United States to study the role information on PFS (or stable disease) plays in treatment decision making and how patients and providers weigh PFS relative to other treatment attributes. To our knowledge, the value of stable disease to patients and providers, independent from OS, has yet to be measured.

Methods

Study Design and Setting

A study of mBC patients and oncology care providers (nurses and oncologists) was conducted to evaluate the value of OS, PFS, and other treatment attributes in treatment decision making. Three individual, but complementary, surveys were developed, each tailored to the specific respondent populations. All surveys included an eligibility screener, questions about preferences for and perceptions of patient treatment decision making, a module to assess preferences for OS and PFS/stable disease, a module to assess preferences and willingness-to-pay (WTP) for specific treatment attributes, and a set of sociodemographic questions. The Chesapeake Institutional Review Board reviewed study procedures and exempted the study from full review because of low/no risk to the study participants.

A convenience sample of mBC patients, oncology nurses, and oncologists currently treating patients with mBC was invited by email or through social media postings to participate in the study. We arrived at a target sample size of \( n = 300 \) mBC patients, \( n = 100 \) oncology nurses, and \( n = 100 \) oncologists based on methodology outlined by Louviere and colleagues about minimal sample size required to conduct the main and sub-analyses for the study.²⁴

Eligible patients were those who had been told by a doctor that they have mBC, were aged ≥18 years, and were current residents of the United States. Eligible
oncology nurses were registered nurses who treated ≥5 mBC patients per month and held a nursing degree. Eligible oncologists included individuals with a medical degree who were board certified in oncology, treated ≥5 mBC patients per month, and regularly prescribed chemotherapy and/or targeted cancer treatment to cancer patients. Study participants received an email with a link to the online survey website. After providing informed consent, participants were directed to a set of instructions and then asked a series of questions to determine whether they met study inclusion criteria. Those who failed to provide informed consent or who did not meet the eligibility criteria were excluded. All respondents who successfully completed the survey, including pilot test participants, were compensated for their time and effort.

We performed the study in two phases: a pilot phase, conducted from January to February 2017, and a primary data collection phase, conducted from March to June 2017. Eight respondents participated in pilot testing and debriefing interviews to further hone the survey instrument and assess respondent comprehension of the background content and survey questions. This testing included ensuring that patients understood the definitions for PFS and OS, as well as the iconography used to represent PFS and OS in the study design. Results from the pilot testing and consultation with clinical and patient experts informed revisions to the final versions of the three surveys, which were all hosted on a web-based survey platform.

Decision Scenarios

To establish survival preferences, we used a stated preference approach. For establishing preferences for a set of treatment attributes, we used a discrete choice experiment (DCE). Discrete choice experiments are based on economic (random utility) theory about how consumers make choices among goods given a limited budget.25–27 This design allows for the estimation of consumer WTP, or value, for distinct product attributes. These methods are well established in the literature and endorsed by the ISPOR Conjoint Analysis Good Research Practices Task Force for Pharmacoeconomic Research.28 Both the conjoint analysis and DCE were designed using the AlgDesign software package for R based on the D-efficiency criteria.

Survival Preference Scenarios.

To assess patient and provider preferences for PFS versus OS, measured as the timing and duration of stable disease versus progressive disease and death, a set of choice alternatives were presented to survey participants. Nine choice alternatives were presented, each differing in terms of the number of periods of stable disease (PFS), number of periods of progressive disease, and OS (time to death). Choices also varied in terms of the sequencing of periods of stable and progressive disease. The nine choice alternatives presented are depicted in Figure 1. Respondents were asked to select which sequence they preferred for each of the nine combinations.

A pictorial example of choice alternative four is shown in Figure 2. Instructions provided to participants are detailed in the Online Appendix.

Treatment Attribute Preference Scenarios.

To gain additional insights into patient and provider treatment preferences, 12 choice sets comparing two hypothetical treatment plans varying on four key attributes were...
presented to survey participants. The attributes included in the survey were generated from a review of the literature and qualitative data collected through focus groups conducted with mBC patients, oncology nurses, and oncologists. Findings from the focus groups have been reported previously. To arrive at an appropriate and feasible number of attributes, we considered six primary factors: 1) relevance of the attribute to patient’s choice of mBC treatment, 2) relevance of the attribute to physician’s choice of mBC treatment, 3) ease of quantifying the attribute in the survey, 4) overlap or correlation with other attributes, 5) relevance to the objectives of the study, and 6) variation in the attribute across currently available mBC treatments. We aimed to have a parsimonious list of attributes to make the questions as simple as possible for the study population. Most DCE surveys in the health care literature use six or fewer attributes. To arrive at an appropriate and feasible number of attributes, we considered six primary factors: 1) relevance of the attribute to patient’s choice of mBC treatment, 2) relevance of the attribute to physician’s choice of mBC treatment, 3) ease of quantifying the attribute in the survey, 4) overlap or correlation with other attributes, 5) relevance to the objectives of the study, and 6) variation in the attribute across currently available mBC treatments. We aimed to have a parsimonious list of attributes to make the questions as simple as possible for the study population. Most DCE surveys in the health care literature use six or fewer attributes.

The attribute levels were selected based on the characteristics of currently available mBC treatments. Treatments considered in the development of the attribute descriptions were hormone therapy, chemotherapy, and targeted therapies such as mTOR inhibitors, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, and anti-HER2/neu targeted therapies. For each choice set, respondents were asked which of the two unlabeled treatment options they preferred for themselves or for their patients, as depicted in Figure 3.

Using the DCE design, attributes included in the choice sets were the following: 1) risk of moderate to severe side effects, 2) monthly out-of-pocket cost, 3) evidence credibility, and 4) health state sequences reflecting OS, PFS, and, implicitly, health-related quality of life. The health state sequence attribute allowed us to test whether respondents were willing to pay significantly more for contiguous periods of stable disease holding OS constant. The module was not designed, however, to measure marginal willingness to substitute periods of OS for PFS.

**Other Study Measurements**

**Demographics.** For patients, we queried respondents about age, marital status, education, ethnicity, employment status, type of health insurance, and household income. For providers, we queried respondents about age, gender, ethnicity, medical training, and licensure.

**Clinical History.** For patients, we queried respondents about mBC disease diagnosis and duration, past and current therapies, line of treatment, hormone receptor status, presence of comorbid conditions, functional ability, and receipt of palliative or hospice care. These were included to explore whether specific patient characteristics influenced treatment preferences.

**Practice Characteristics.** We queried provider respondents about their practice setting (e.g., academic center, private general hospital, solo office practice) and the average number of breast cancer and mBC patients treated each month.

**Analysis**

Our first objective was to establish a baseline understanding of whether the timing and sequencing of stable disease/PFS intervals was meaningful to respondents, that is, whether patients/providers preferred PFS sooner and/or contiguous periods of PFS. Positive (negative) time preference implies patients prefer their stable disease in earlier (later) periods rather than later (earlier) periods. The health state/survival preference module was designed to meet the first study objective. The second objective was to estimate patient preferences for cancer treatments and WTP for changes in cancer treatment attribute levels, for example, reduced risk of side effects. The DCE module was designed to meet the second objective. All analyses were conducted using statistical software package Version 14.0 (Stata Corporation, College Station, TX).

Responses to the health state/survival preference choice sets were evaluated and patient preferences were estimated using a random utility model. In a random utility model, utility has a deterministic (observable) component separable in price (if applicable) and nonprice attributes, as well as a random (unobservable) component that is distributed as an independent and identically distributed extreme value type I (Gumbel). The health state/survival attributes included in the utility model included the following: 1) an indicator for the health state sequence containing any contiguous periods of PFS, 2) length of OS, 3) cumulative periods of PFS, 4) an indicator for the contiguous periods of PFS occurring at the beginning of the health state sequence, 5) and an indicator for the contiguous periods of PFS occurring at the end of the health state sequence. A random parameters/mixed logistic model was used to estimate utility weights based on responses to the survival preference scenarios.

Responses to the treatment attribute choice scenarios were evaluated and patient preferences and WTP for specific attributes were also estimated using a random utility model. As noted previously, the attributes selected are risk of treatment side effects, evidence credibility, health state sequence over remaining life, and monthly...
out-of-pocket cost. A random parameters/mixed logistic model was used to estimate attribute utility weights and WTP based on responses to the treatment attribute choice scenarios. We explored specifications that were linear and quadratic in the risk of adverse events. Utility was linear in all other treatment attributes. WTP was estimated as the ratio of the nonprice attribute utility weight and the price attribute disutility weight from the random parameter logit model. Goodness of fit was evaluated based on the log-likelihood ratio statistic.
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**Results**

**Participant Characteristics**

Of 519 patient respondents screened, 189 (36.4%) did not meet study eligibility criteria, 330 (63.6%) were enrolled into the study, and 300 (57.8%) completed the survey. Of 515 oncology nurse respondents screened, 244 (47.3%) met study eligibility criteria, and 101 (19.6%) completed the survey. Of 238 oncologist respondents screened, 73 (30.7%) did not meet study eligibility criteria, and 100 (42.0%) completed the survey. We excluded providers who reported not seeing at least five mBC patients per month. Brief email reminders were sent to noncompleters on a weekly basis for up to 4 weeks. We closed each survey as soon as the accrual targets for the sample population were achieved. Ultimately, we excluded from the final data set one nurse because he/she reported not treating mBC patients, and one patient who reported having an earlier stage of breast cancer. Hence, in the completed sample data were analyzed for 299 patients, 100 oncologists, and 99 oncology nurses. We were unable to calculate the overall response rate because we employed a combination of direct invitation, social media advertising, and snowball sampling. Respondent demographic characteristics are presented in Table 1.

**Survival Preferences: Utility parameters**

Table 2 displays the estimated coefficients from the random parameters/mixed logistic regression where all health state attribute coefficients were treated as normally distributed random variables. Figure 4 illustrates the share of respondents with positive utility weights by health state attribute and respondent group. One nurse, two oncologists, and six patients were excluded from the analysis because they chose the same option (A or B) in every choice scenario. All else equal, health states with consecutive periods of PFS were on average preferred across the three respondent groups; however, there was significant variation among nurses and oncologists, as indicated by the significant standard deviations estimated for these respondent groups. Virtually all patients preferred health state sequences with contiguous periods of PFS (i.e., had an estimated coefficient >0), compared with approximately 85% and 75% of nurses and oncologists, respectively (Figure 4). On average, longer OS was significantly preferred by the majority (75%) patients, but only 15% of nurses preferred longer OS, and OS did not significantly affect oncologists’ preferred health state. Relative to health states with no contiguous periods of stable disease/PFS, no respondent group had significant preferences for health states with the contiguous periods of PFS in the first half of the health state sequence; however, all three respondent groups preferred on average not to have the contiguous periods of PFS at the end (Table 2). Last, the cumulative periods of PFS only significantly influenced health state sequence choices among patients, for whom 89% preferred longer cumulative periods of PFS (Figure 4).

**Treatment Attribute Preferences: Utility parameters**

Table 3 displays the estimated coefficients from the random parameters/mixed logistic regression where all treatment attribute coefficients were treated as normally distributed random variables. This model had better goodness of fit than the simple logistic model or the random parameters logit where only the non-cost attributes were included as random parameters based on the log likelihood statistic. The significance of the estimated standard deviations suggests significant preference heterogeneity in the three populations and justifies the use of the random parameter logistic specification (Table 2). In the baseline scenario, two patients and two providers were excluded from the DCE analysis because they chose the same option, A or B, in every DCE choice set.

In the random parameter logit model, we found that the contiguity of periods of PFS only significantly influenced nurses’ treatment preferences. Approximately half (51.2%) of patients were less likely to choose a treatment if the health state sequence had non-contiguous periods of PFS, all else equal.* A similar share of oncologists (52.2%) were less likely to choose a treatment if the health state sequence had non-contiguous periods of PFS; however, only about one third (33.7%) of nurses were less likely to choose a treatment if the health state sequence had non-contiguous periods of PFS. This is consistent with the finding that a majority of nurses preferred health state sequences with contiguous periods of

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*The share of respondents with an estimated coefficient/utility parameter falling below zero was calculated using the estimated mean and standard deviation for the cumulative normal distribution.
### Table 1  Respondent Demographic Characteristics

|                         | Patient ($N = 299$) | Provider ($N = 199$) |
|-------------------------|---------------------|----------------------|
|                         | $n$ | %      | $n$ | %  |
| **Age in years, mean (SD)** | 47.5 (10.1) | 49.7 (10.1) |
| **Race**                |     |        |     |     |
| White/Caucasian         | 250 | 83.6   | 146 | 73.4|
| African American        | 22  | 7.4    | 2   | 1.0 |
| Asian                   | 3   | 1.0    | 35  | 17.6|
| Mixed/Other             | 23  | 7.6    | 8   | 4.0 |
| Missing/refused         | 1   | 0.3    | 8   | 4.0 |
| **Hispanic ethnicity**  |     |        |     |     |
| Hispanic                | 15  | 5.0    | 10  | 5.0 |
| Not Hispanic            | 282 | 94.3   | 175 | 87.9|
| Missing/refused         | 2   | 0.7    | 14  | 7.0 |
| **Marital status**      |     |        |     |     |
| Married or living as married | 207 | 69.2    |     |     |
| Not married (separated, divorced, widowed, single) | 90  | 30.1   |     |     |
| Missing/refused         | 2   | 0.7    |     |     |
| **Education**           |     |        |     |     |
| Some high school        | 2   | 0.7    |     |     |
| High school graduate    | 22  | 7.4    |     |     |
| Some college or associate degree | 106 | 35.5   |     |     |
| College graduate        | 76  | 25.4   |     |     |
| Some graduate           | 21  | 7.0    |     |     |
| Graduate degree         | 71  | 23.7   |     |     |
| Missing/refused         | 1   | 0.3    |     |     |
| **Employment status**   |     |        |     |     |
| Full time               | 81  | 27.1   |     |     |
| Part time               | 19  | 6.4    |     |     |
| Unemployed: medical reasons | 154 | 51.5   |     |     |
| Unemployed: nonmedical reasons | 22  | 7.4    |     |     |
| Retired                 | 22  | 7.4    |     |     |
| Missing/refused         | 1   | 0.3    |     |     |
| **Household income**    |     |        |     |     |
| Less than $25,000       | 67  | 22.5   |     |     |
| $25,000-$49,999         | 50  | 16.7   |     |     |
| $50,000-$99,999         | 87  | 29.0   |     |     |
| $100,000 or more        | 80  | 26.8   |     |     |
| Missing/refused         | 15  | 5.0    |     |     |
| **Insurance**           |     |        |     |     |
| Medicare                | 32  | 10.7   |     |     |
| Medicaid                | 34  | 11.4   |     |     |
| Private plan (employer or self-purchased) | 178 | 59.5   |     |     |
| Multiple (one or more types) | 48  | 16.1   |     |     |
| Other                   | 5   | 1.6    |     |     |
| Missing/refused/none    | 2   | 0.7    |     |     |
| Stages I–III            | 170 | 56.9   |     |     |
| Stage IV (de novo)      | 129 | 43.1   |     |     |
| ER/PR positive          | 220 | 73.6   |     |     |
| HER2/neu positive       | 77  | 25.8   |     |     |
| Triple positive<sup>a</sup> | 33  | 11.0   |     |     |
| Triple negative<sup>b</sup> | 30  | 10.1   |     |     |
| First                   | 95  | 31.8   |     |     |
| Second                  | 46  | 15.4   |     |     |
| Third or more           | 110 | 36.8   |     |     |
| Currently in hospice or palliative care | 47  | 15.7   |     |     |

(continued)
PFS and the contiguity of periods of PFS being a key determinant of nurses’ survival preferences. All respondents were significantly more likely to choose a therapy with efficacy demonstrated in a randomized controlled trial (RCT) versus patient/provider experience. Evidence from RCTs was especially influential for nurses, with nearly 92% of nurses preferring treatments with efficacy demonstrated by RCT evidence, as compared with approximately 77% of both patients and oncologists. A higher risk of adverse events decreased the probability of choosing a treatment, for all respondent groups, as did the patient out-of-pocket cost of treatment. Nearly all (97.6%) nurses preferred lower risk of adverse events, as did the majority of patients (85.9%) and oncologists (88.6%).

**Treatment Attribute Preferences: Willingness-to-Pay**

In the random parameter model, only oncology nurses had a significant (negative) WTP for contiguous periods...
Table 2  Breast Cancer Survival Attribute Mixed Logit Model Coefficients by Respondent Group

| Patients | | Nurses | | Oncologists | |
|----------|----------------|----------------|----------------|----------------|
| Mean     | SD             | Mean           | SD             | Mean           | SD             |
| Contiguous periods of PFS | 0.918** (0.139) | -0.0024 (0.169) | 1.274** (0.336) | 1.196** (0.373) | 0.569* (0.257) | 0.915** (0.340) |
| OS       | 1.003** (0.293) | 1.467** (0.225) | -1.732** (0.415) | 1.699** (0.299) | -0.221 (0.336) | -0.832* (0.403) |
| Consecutive periods of PFS at beginning | 0.0129 (0.115) | -0.676** (0.138) | -0.103 (0.201) | -0.604 (0.319) | 0.332 (0.184) | 0.880** (0.192) |
| Consecutive periods of PFS at the end | -1.154** (0.238) | 2.792** (0.263) | -1.377** (0.342) | 1.775** (0.423) | -1.434** (0.362) | 1.683** (0.450) |
| Cumulative PFS | 2.440** (0.324) | 2.006** (0.220) | 0.141 (0.238) | 0.296 (0.227) | 0.530 (0.338) | 1.108** (0.262) |
| Observations | 5274 | 1764 | 1764 | |
| Log likelihood | -1304 | -395.1 | -467.0 | |

OS, overall survival; PFS, progression-free survival; SD, standard deviation.

*Robust standard errors in parentheses. The sign of the estimated standard deviations is irrelevant. Although in practice the estimates may be negative, interpret them as being positive.

**P < 0.01. *P < 0.05.

Table 3  Breast Cancer Treatment Attribute Mixed Logit Model Coefficients by Respondent Group

| Patients | | Nurses | | Oncologists | |
|----------|----------------|----------------|----------------|----------------|
| Mean     | SD             | Mean           | SD             | Mean           | SD             |
| Non-contiguous PFS health state sequence | -0.0142 (0.0650) | -0.479** (0.101) | 0.237* (0.115) | 0.563** (0.203) | -0.0195 (0.0922) | -0.360* (0.181) |
| RCT evidence | 1.208** (0.108) | -1.636** (0.132) | 1.815** (0.213) | -1.304** (0.198) | 0.867** (0.157) | -1.139** (0.147) |
| Risk of adverse events, % | -0.0395** (0.0029) | 0.0367** (0.0031) | -0.0432** (0.0048) | 0.0218** (0.0049) | -0.0291** (0.0036) | -0.0241** (0.0038) |
| Out-of-pocket cost per month, ($100s) | -0.0626** (4.73e-03) | 0.0610** (5.26e-03) | -0.0598** (7.54e-03) | 0.0629** (0.0119) | -0.0438** (5.12e-03) | 0.0308** (4.46e-03) |
| Observations | 7,128 | 2,376 | 2,376 | |
| Log likelihood | -1533 | -497.9 | -593.8 | |

PFS, progression-free survival; RCT, randomized controlled trial.

*Robust standard errors in parentheses. The sign of the estimated standard deviations is irrelevant. Although in practice the estimates may be negative, interpret them as being positive.

**P < 0.01. *P < 0.05.
of PFS holding OS constant, as depicted in Table 3. All respondents significantly valued efficacy evidence demonstrated in clinical trials over patient/provider experience, and were willing to pay approximately $67 per one-percentage point reduction in the risk of side effects (Table 4). In particular, willingness to pay for reducing the risk of side effects was very similar across the three respondent groups.

**Discussion**

Our study of mBC patients and oncology providers in the United States demonstrates the value information on PFS plays in treatment decision making and how patients and providers weigh PFS in the context of other treatment attributes. Our analysis of survival and treatment preferences demonstrates that there is significant variation in preferences among and across patients and providers. Contiguous periods of stable disease/PFS, the timing of contiguous periods of stable disease/PFS, OS, and cumulative periods of stable disease/PFS were all significant drivers of average patient preferences for survival. Nurses’ preferences were also driven by contiguous periods of stable disease/PFS, the timing of the contiguous PFS, and OS, but not by cumulative periods of PFS. Oncologists’ preferences were driven primarily by contiguous periods of stable disease/PFS and their timing. All respondents were willing to pay significant amounts to reduce the risk of side effects and for efficacy demonstrated in clinical trials rather than provider experience. Willingness to pay for reduced risk of side effects was notably aligned across the three respondent groups. Our analysis of treatment attribute preferences demonstrates that the sequencing of periods of stable disease (PFS) across remaining life (OS) significantly influences the treatment decisions of nurses only when considered jointly with other treatment characteristics. The results also suggest that patients and providers alike value high-quality clinical evidence in their decision making, and prefer treatments with fewer side effects. This study points not only to the challenge of surrogate endpoints in clinical trials, but also to their potential value. Rarely do patients consider their therapy choices as merely a decision between survival and progression.

As demonstrated in previous research, patients value a host of factors when choosing a therapy.\textsuperscript{15,29} It is possible that patients start with a baseline assumption about PFS and OS—assuming any therapy they are offered will at a minimum provide survival benefits. When respondents are asked to choose between survival scenarios alone, it is possible to parse out preferences for PFS versus OS, but in the context of a treatment decision when a variety of treatment characteristics are considered—specifically side effects, strength of evidence, and cost—the PFS/OS benefit may be assumed and other factors take precedence. WTP for a lower risk of side effects is not inconsistent with a preference for PFS. Progression-free survival is in part a question of health-related quality of life, where stable disease allows patients to proceed with their daily lives in a predictable way. Similarly, a

![Figure 4](image.png)

*Figure 4* Proportion of respondents with positive utility weights for timing, sequencing, overall survival, and stable disease. OS, overall survival; PFS, progression-free survival/stable disease.
lower risk of side effects also suggests a more predictable health-related quality of life and ability to carry on with typical life events. Thus, stable disease and fewer side effects may give patients a sense of control over their disease and improve their quality of life. These findings were consistent with our previously published qualitative work in that patients and providers recognized the benefits associated with having fewer side effects—or even having to monitor for side effects, thus allowing patients to live as “normal” a life as possible, and maintain independence and overall functioning.16

In the assessment of disease progression and survival preferences, patients placed more emphasis on the cumulative periods of PFS than OS. This is an important finding as this indicates the continued value of surrogate endpoints in clinical trials and the critical nature of communicating PFS benefits to patients making choices about treatment. Again, this is bolstered by the WTP analysis whereby high-quality clinical trial data are highly valued by patients and providers alike.

However, our finding that the length, timing, and contiguity of PFS, as well as OS, all strongly influence patient survival preferences highlights the importance of patient–provider communication to ensure alignment around treatment. One approach found to be effective in addressing gaps in patient–provider communication is shared decision making, a collaborative process that allows patients and their providers to make health care decisions together, while taking into account the best clinical evidence available and the patient’s individual values and preferences.30–33 Shared decision making has been proven to demonstrate positive outcomes among patients diagnosed with preference sensitive conditions and is increasingly deployed in the oncology setting.17,34,35 The present study highlights the critical need for providers to broaden their lens beyond primary endpoints such as OS, and to elicit patient preferences associated with surrogate endpoints such as PFS.

This study has several limitations and future research would benefit from a deeper exploration of the tradeoffs between PFS and OS, as well as the individual determinants of survival and treatment preferences. Importantly, we did not explicitly ask patients if they would be willing to trade a shorter period of survival for a longer period of stable disease, but instead used a stated preferences approach. While a stated preferences survey design provides insights into what patients value, the level of detail achieved through this approach can leave questions unanswered. For example, beyond pilot testing, we did not evaluate patient understanding of the meaning and interpretation of PFS (stable disease) or progressive

| Table 4 | Willingness-to-Pay for Breast Cancer Treatment Attributes by Respondent Group |
|---------|--------------------------------------------------------------------------------|
| **WTP for** | **Attribute** | **Patients** | **Nurses** | **Oncologists** |
| | Contiguous PFS (v. non-contiguous PFS) | | | |
| | Evidence credibility | $22.7 [±8.1, 1.9] | $938.0 [±775.1, 1.1] | $44.4 [±86.7, 54.7] |
| | One percentage point reduction in risk of side effects | $63.1 [±52.1, 74.0] | $597.3 [±529.9, 71.7] | $66.4 [±47.5, 85.1] |
| | Evidence demonstrated in patient/provider experience | $1930.1 [±1529.2, 31.1] | $72.3 [±52.9, 91.7] | $1977.3 [±2139.6, 61.1] |
| **Evidence credibility** | RCT (v. patient/provider experience) | $1307.2 [±2170.4, 84.0] | $522.0 [±251.2, 231.1] | $1977.3 [±2139.6, 61.1] |
| | One percentage point reduction in risk of side effects | $66.4 [±47.5, 85.1] | $66.4 [±47.5, 85.1] | $66.4 [±47.5, 85.1] |
| **AE/side event risk** | PFS, progression-free survival (v. OS) | | | |
| | Contiguous PFS (v. non-contiguous PFS) | $22.7 [±8.1, 1.9] | $938.0 [±775.1, 1.1] | $44.4 [±86.7, 54.7] |
| | Evidence credibility | $1930.1 [±1529.2, 31.1] | $72.3 [±52.9, 91.7] | $1977.3 [±2139.6, 61.1] |
| | One percentage point reduction in risk of side effects | $63.1 [±52.1, 74.0] | $66.4 [±47.5, 85.1] | $66.4 [±47.5, 85.1] |

AE, adverse event; PFS, progression-free survival; RCT, randomized controlled trial; WTP, willingness to pay.
disease. Some patients may have interpreted stable disease to mean a period of high function and good health, whereas others may have interpreted stable disease to mean a period of continued poor health, but with higher functional ability than periods of progressive disease. Patients may have not made a connection between stable disease and functioning, but instead interpreted stable disease as their condition simply not getting worse. Such interpretation may substantially influence preference choices made by the patient.

Furthermore, the omission of an opt-out choice in the discrete choice experiment may also have an influence on the treatment choices patient respondents made, particularly in the context of treatment for mBC. Prior research shows that approximately 1% to 3.5% of all breast cancer patients opt out of treatment.36–38 Late-stage breast cancer patients have higher treatment refusal rates, with 7% of stage III or IV breast cancer patients opting out of treatment in one study.39 Comparatively, late-stage lung cancer patients opt out of treatment at rates of 19% to 24%.39–41

In reviewing the utilization of an opt-out option in discrete choice experiments, we found that several studies examining treatment preferences in breast cancer patients included an opt-out choice in their surveys. Notably, Ngorsuraches and Thongkeaw found that participants selected the opt-out choice in 42% of all observations.42 The high usage of the opt-out choice is consistent with past research finding that people are more likely to select the opt-out choice when the tradeoff is complex or emotionally difficult.43

Furthermore, Veldwijk et al. found that inclusion of opt-out option in discrete choice experiments may skew results and lead to lower data quality.44 Thus, numerous studies examining treatment preferences in breast cancer patients do not include an opt-out choice.29,45,46 For example, daCosta DiBonaventura et al. found that 35% of their sample of mBC patients either had discontinued or were nonadherent to treatment at the time of their study.29

Similarly, 29% of participants in the study by Lalla et al. were not receiving any treatment for mBC at the time of survey completion.46 Despite these rates, neither study included a hypothetical opportunity to forego treatment options presented in their DCE, thereby forcing participants to select between hypothetical treatment scenarios, as we did in the present study.

Caution should be exercised when extrapolating our results to other patient and provider populations. While our study did not draw from a nationally representative sample of oncology providers, provider respondent characteristics are generally consistent with the oncology workforce.47,48 Race, ethnicity, and gender characteristics of our sample are similar to those of the oncology workforce.48 Furthermore, as our study design was an online convenience sample, our patient population was more highly educated, more likely to be Caucasian, and more likely to be fluent in English than the general mBC patient population. Thus, our results may not be generalizable to the perspectives of mBC patients from other socioeconomic, cultural, or non-English-speaking backgrounds and results may not be generalizable to the larger population of patients and oncology care providers.

Patients face complex decisions and tradeoffs about treatment, and their goals for treatment may not always align with clinicians’ goals for treatment. Previous research has demonstrated that when attitudes are aligned and the patient–physician alliance is strong, patients are more satisfied with their care, adherent to treatment, and optimistic about the usefulness of treatment.23 For breast cancer patients specifically, providers’ ability to effectively communicate information about treatment options has been shown to reduce treatment delays while increasing patients’ knowledge about breast cancer and receipt of breast conserving surgery.49 Despite weak evidence of the correlation between PFS and OS, these data suggest that OS is not the only priority for patients or providers. Clinical trials that focus only on prolonged longevity will likely fail to capture attributes of treatment that are important to these populations.50

Conclusion

Researchers and clinicians often presume that the value of surrogate endpoints like stable disease/PFS only have value if they increase OS. In contrast, our results suggest that mBC patients demonstrated a strong preference for longer periods of stable disease, even when OS was held fixed, highlighting the value of PFS to mBC patients even when it does not contribute to OS. Providers did not share this preference and were not WTP for stable disease. This suggests the critical need for improved patient-provider communication and shared decision-making in the oncology setting.

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