Patient Versus Physician Valuation of Durable Survival Gains: Implications for Value Framework Assessments

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ABSTRACT

Background: Previous research indicates that patients value therapies that provide durable or tail-of-the-curve survival gains, but it is unclear whether physicians share these preferences. Objective: To compare patient and physician preferences for treatments with a positive probability of durable survival gains relative to those with fixed survival gains. Methods: Patients with advanced stage melanoma or lung cancer and the oncologists who treated these patients were surveyed. The primary end point was the share of respondents who selected a therapy with a variable survival profile, with some patients experiencing long-term durable survival and others experiencing much shorter survival, compared to a therapy with a fixed survival duration. Parameter estimation by sequential testing was applied to calculate the length of nonvarying survival that would make respondents indifferent between that survival and therapy with durable survival. Results: The sample comprised 165 patients (lung = 84, melanoma = 81) and 98 physicians. For lung cancer, 65.5% of patients preferred the therapy with a variable survival profile, compared with 40.8% of physicians (Δ = 24.7%; P < 0.001). For melanoma, these figures were 63.0% for patients and 29.7% for physicians (Δ = 33.3%; P < 0.001). Patients’ indifference point implied that therapies with a variable survival profile are preferred unless the treatment with fixed survival had 13.6 months (melanoma) or 11.6 months (lung) longer mean survival; physicians would prescribe treatments with a fixed survival if the treatment had 7.5 months (melanoma) or 1.0 month (lung) shorter survival than the variable survival profile. Conclusions: Patients place a high value on therapies that provide a chance of durable or “tail-of-the-curve” survival, whereas physicians do not. Value frameworks should incorporate measures of tail-of-the-curve survival gains into their methodologies. Keywords: cancer, preferences, survival, value framework.

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Introduction

Prior research indicates that patients place substantial value on a modest chance of a durable survival response, over and above average survival [1]. Almost four-fifths of patients preferred a therapy with a greater chance of durable survival gain, holding constant its effect on average survival. Put differently, patients are willing to risk premature mortality in pursuit of a chance at a durable survival gain.

This research topic is of more than academic interest. Value frameworks for oncology treatments have been developed by a number of organizations, including the American Society of Clinical Oncology, the European Society for Medical Oncology, the Institute for Clinical and Economic Review, the Memorial Sloan Kettering Cancer Center, and the National Comprehensive Cancer Network [2–6]. Most of these frameworks rely on efficacy measures based on improvements in survival for the median patient. A revised version of the American Society of Clinical Oncology framework [7], however, also takes into account improvements in “tail-of-the-curve” survival.

To better understand attitudes toward durable or tail-of-the-curve survival benefits, this study surveyed cancer patients and physicians and extends previous research in three ways. First, we compared patient treatment preferences against physician preferences for treating patients. Second, we examined preferences for patients with non–small cell lung cancer (NSCLC), a tumor site not studied in previous research on patient valuations for durable survival gains. Third, although many studies have compared patient and physician preferences [8–12], this study specifically assessed whether physicians view a chance of durable survival, independent of mean survival, in the same way that patients do. Thus, this study highlights whether there were differences in patient and physician attitudes toward tail-of-the-curve survival (i.e., durable survival) and how such differences could inform current treatment decision making and value framework development.
Methods

This prospective survey of cancer patients and physicians aimed to determine how each group values therapies that offer a positive probability of durable survival gains. The durable survival therapies had variable survival profiles, wherein some patients’ survival after treatment is significantly below mean survival and other patients have durable response to treatment and live much longer than the mean patient.

Durable survival treatments were calibrated based on survival profiles from pivotal trials of nivolumab among patients with advanced NSCLC and ipilimumab among patients with advanced melanoma. Ipilimumab was selected because it had the longest study follow-up time (10 years) of available immuno-oncology therapies [13]. Patient treatment preferences and physician prescribing preferences for therapies with a chance of durable survival were compared with therapies with fixed survival duration. A fixed survival therapy is a hypothetical therapy under which all patients live for a specified period of time and then die immediately afterward.

Survey Design

The analytic approach relied on direct solicitation of respondent preferences across nonvarying survival and varying survival treatments. Economists often call propositions with the chance of both a good and bad outcome “lotteries,” and numerous studies have measured risk aversion using respondent preferences over different lotteries [19]. Respondents chose between a treatment with a varying survival profile and one with a fixed survival outcome. This study set the fixed survival value of the first scenario presented to be equal to the mean survival of the durable survival therapy.

The survey calibrated the variable survival profiles based on two immuno-oncology treatments for advanced melanoma and NSCLC. Immuno-oncology agents offer the prospect of durable survival gains for a subset of patients treated. For patients with lung cancer, the survey calibrated the durable survival therapy for a nivolumab clinical trial of patients with NSCLC that included 66 months of follow-up survival data [20]. This study calibrated the durable survival therapy presented to patients with advanced-stage melanoma to the results of an ipilimumab clinical trial of unresectable or metastatic melanoma that reported 120 months of follow-up survival data [13].

Patients were asked which therapy they preferred for their own treatment (Fig. 1). Initially, the value of the fixed survival therapy (Therapy A) was set to equal the mean survival of the therapy with a variable survival profile (Therapy B)—specifically, 48 months for melanoma and 30 months for lung cancer. This approach replicated an earlier study that measured patient (but not physician) preferences for variable survival compared with fixed survival profiles [1].

Next, parameter estimation by sequential testing (PEST) was used to identify the point at which respondents were indifferent between the therapy with fixed and variable survival (i.e., the indifference point) [21]. PEST is an adaptive elicitation technique that determines the stimulus value for each new question via the participant’s response to the previous question. Under the PEST algorithm, if a survey respondent (patient or physician) preferred the durable survival therapy, the survival of the fixed survival therapy was increased. This process continued until a respondent who initially preferred the variable survival treatment switched to preferring the fixed survival therapy. If the fixed survival therapy was preferred, the value decreased in subsequent questions until an indifference point was reached. Respondents continued to receive questions until an indifference point was reached or until 10 questions were answered.

The patient survey included an eligibility screener to ensure a sample that met the inclusion/exclusion criteria, a burden of cancer module that provided data about the patient’s cancer and treatment, and a demographics and backgrounds module to elicit data for exploratory analysis. The latter two modules were administered after the therapy valuation module.

The physician survey contained three modules. In the treatment preferences (PEST) module, physicians were asked which therapies they would prescribe for their patients. The varying and fixed survival treatments were calibrated identically to those in the patient module, but physicians received both advanced melanoma and lung cancer treatment scenarios. Additional sections included an eligibility screener to ensure a sample that met the inclusion/exclusion criteria and a demographics and backgrounds module to elicit data for exploratory analysis.

Outcomes

There were two primary end points: 1) whether the respondent preferred a durable survival therapy compared with a fixed survival therapy; and 2) the indifference point in terms of certain survival between a durable survival therapy and a fixed survival

Study Population

Survey respondents comprised 1) patients with advanced stage lung cancer; 2) patients with advanced stage melanoma; and 3) oncologists who treated patients with lung cancer or melanoma. Patients had to have a diagnosis of cancer or malignant tumor or advanced stage (i.e., stages III or IV) lung cancer or melanoma, be aged ≥ 18 years, be a resident of the United States, and sign an informed consent form.

The physicians surveyed were practicing medical oncologists who treated ≥ 5 patients with cancer per month, had a medical degree, were board certified in oncology, regularly prescribed chemotherapy and/or targeted cancer treatment to patients with cancer, and signed an informed consent form.

Data Collection Process

Respondents were recruited, and the survey was hosted through a MedPanel patient and physician database. Patients were recruited using HIPAA-compliant methods through their physician network and professional relationships with patient support and advocacy organizations. Researchers have used the MedPanel database to elicit physician opinions across a variety of conditions, including cardiovascular disease [14], hepatitis C [15], chronic pain [16], diabetes [17], and cancer [18].

After the patients were contacted, their current cancer stage was confirmed through screening questions prior to they were sent a unique link to the survey that could not be sent to other individuals. MedPro identification software was used to check physicians’ licenses and verify that inclusion criteria were met. Survey recruitment occurred throughout the United States, covering 42 states. The survey was programmed and hosted using survey building software (Jibinu, Fitchburg, MA).

Before the full data collection began, six patients (three with advanced melanoma and three with lung cancer) and four physicians were selected for pilot study interviews to further hone the survey instrument that collected all data necessary to achieve the research objectives. Patients and physicians who completed the survey and physicians who referred patients received remuneration for their time.

The institutional review board approval process was completed through One Health, LLC.
therapy with no survival variability around the mean. The first end point examined whether the respondent preferred a therapy with a chance of durable survival compared with a fixed survival therapy. The second end point measured the strength of this preference.

**Statistical Analysis**

The two primary analyses measured differences between the patient and physician arms with respect to 1) the share of respondents who preferred a durable survival therapy; and 2) the indifference point (in months of life expectancy) between the therapies with fixed compared to variable survival profiles. For the former, we conducted (by cancer type) an independent sample t test to test whether the percentage of patients who preferred the durable survival therapy was equal to the percentage of physicians who were inclined to prescribe the durable survival treatment.

To describe the indifference point between cancer types and patient and physician samples, sample means for the patients with melanoma and their physicians were calculated and compared using an independent sample t test.

Finally, we calculated patient and physician preferences with respect to uncertainty. We assumed a constant relative risk aversion utility function [22] and based the distribution of risky preferences on the Kaplan-Meier curve from which the survey preferences were drawn; t tests were conducted to compare the indifference point in the survey to the certainty equivalent.

**Sensitivity Analysis**

In the baseline specification, patients and physicians who selected the durable survival or fixed survival therapy in all scenarios, regardless of any difference in survival, were excluded. A sensitivity analysis that did not remove these individuals from the analysis was conducted. In addition, we measured whether the share of patients and physicians who preferred the varying therapy (logistic regression) and mean indifference point (ordinary least squares regression) depended on respondent characteristics.

Patient characteristics included in the regressions were patient demographics, socioeconomic factors, marital status, cancer stage, and share of income spent on health care; for physicians, demographics, practice types (e.g., ownership, single specialty), and beliefs surrounding the importance of efficacy and safety for informing treatment decisions were included in the analysis.

**Results**

Respondents comprised 100 patients with lung cancer, 100 patients with melanoma, and 100 physicians. Respondents were dropped from the analysis if they always selected either the durable survival therapy or the fixed survival therapy because the fixed survival value was varied according to the PEST procedure. The analytical sample comprised 84 patients with lung cancer, 81 patients with melanoma, and 98 physicians. Two physicians were dropped in both the melanoma and lung cancer samples, yielding n = 98. Four physician respondents were dropped from the lung cancer sample (n = 96), and nine melanoma physicians were dropped from the melanoma sample (n = 91) because physicians were dropped from cancer-specific samples if they always selected either the therapy with varying or fixed survival for either scenario (see Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.11.028).

A majority of patient respondents was female and white, with a mean age of approximately 50 years (Table 1). Among physician respondents (Table 2), the majority of respondents was male and treated > 50 patients with advanced-stage cancer per month. About half of physicians had ownership stake in their practice.

Among these respondents, patients had a strong preference for therapies with a durable survival. In the patient sample, 63.0% of patients with melanoma and 65.5% of patients with lung cancer preferred the therapy with a probability of durable survival compared with the therapy with fixed survival (Fig. 2). On the other hand, a minority of physicians reported an inclination to prescribe the therapy with durable survival for both melanoma (29.7%) and lung cancer (40.8%). The percentage of patients who preferred the durable survival therapy was significantly different from the percentage of physicians who preferred the durable survival therapy in both the melanoma (P < 0.001) and lung cancer cases (P < 0.001).

Patients were willing to give up 1 year or more of mean survival in exchange for the therapy with the potential for durable, tail-of-the-curve survival gains. In the case of melanoma, the mean survival for the therapy with durable survival was 48 months, but the patients’ indifference point between the
treatments with variable and fixed survival was 61.6 months. In other words, patients preferred the durable survival therapy unless the fixed survival therapy had 13.6 months longer survival (Fig. 3).

On the other hand, the physicians’ indifference point was 40.5 months. In other words, a physician would prescribe the durable survival therapy to patients only when fixed survival therapy was 7.5 months shorter than the durable survival therapy. The difference between patient and physician indifference points was 21.1 months (P < 0.001).

The patients’ indifference point between lung cancer therapies with durable and fixed survival was 41.6 months, which is 11.6 months greater than the 30-month mean survival for the durable survival therapy. In contrast, the physicians’ indifference point was 29.0 months, equivalent to 1.0 month shorter than the mean survival gains for the variable therapy. The indifference

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GED, general educational development; SD, standard deviation.

difference between patient and physician indifference points...

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HMO, health maintenance organization; PEST, parameter estimation by sequential testing; SD, standard deviation.
utility function was u(x) = x\(^2\) for melanoma; for the lung cancer case, the patient’s implied utility function was u(x) = x\(^{0.39}\) and the physician’s utility function for selecting patient treatments was u(x) = x\(^{0.97}\).

The robustness of the results was assessed by recalculating the results after including respondents who were previously excluded for always selecting either the therapy with durable or fixed survival in all 10 PEST questions. The results were fairly similar after these respondents were included in the sample. Whereas 63.0% of melanoma patients and 65.5% of lung cancer patients preferred the durable survival therapy in the baseline approach, when this broader sample was examined, these figures increased to 65.0% and 68.0%, respectively. For physicians, adding the excluded individuals did not change the results materially.

Our regression analysis by patient and physician characteristics showed that preferences are largely consistent across all characteristics (see Appendix I in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.11.028). The only statistically significant exceptions were that male patients with melanoma had higher indifference points (stronger preference for therapies with more variable outcomes) and physicians who owned a business had lower indifference points when treating patients with lung cancer.

Discussion

A majority of patients with lung cancer or advanced melanoma prefers therapies with a positive probability of a durable or “tail-of-the-curve” survival gain, whereas the majority of physicians prefer prescribing therapies with less variable outcomes. Patients with melanoma prefer therapy with a “tail-of-the-curve” survival option even if the fixed survival offered 13.6 months’ longer survival than the mean value for the durable survival therapy. For patients with lung cancer this figure was 11.6 months.

These large values indicate considerable preference for the chance of “tail-of-the-curve” survival. In other words, patients would be willing to give up 28.3% (melanoma) or 38.7% (lung) of mean survival for a chance of durable survival. This evidence is consistent with a recent study that reported that patients with breast cancer, melanoma, or other solid tumors would be willing to pay a substantial amount of money to receive a treatment that offers a hope of durable survival instead of a treatment with the same mean life expectancy but no chance of prolonged survival or early mortality [1].

In many situations, individuals prefer outcomes that are less variable and more certain. Such risk aversion explains why patients purchase health insurance to protect against the probability of a high-cost illness. Yet in assessing treatments, patients with cancer seem to embrace risk. One explanation for this is the long-standing conjecture that normally risk-averse individuals can become risk loving when they have relatively little to lose [23]. The patient preferences reported in this study are also consistent with prospect theory, which predicts that individuals are risk loving when they start at outcomes below their reference point [24,25]. It is plausible that patients’ reference points were likely their anticipated life expectancy before receiving their cancer diagnoses. Applying a utility function framework produced strong evidence of a preference for treatment outcome risk (P < 0.001 for both types of patients.)

On the other hand, we found that physicians were risk neutral or risk averse. Physicians would prescribe an advanced melanoma therapy with a variable survival profile only if the fixed therapy’s survival was 7.5 months shorter than the mean survival of the variable therapy for melanoma; for the lung cancer case, the corresponding figure was 1.0 month shorter. Physicians may be risk averse due to prior disposition, loss aversion due to malpractice risk, or many other factors.

This contrast between patients’ risk preferences and those of their physicians must be put in the context of a sizable literature that compares patient and physician preferences [8–12]. Numerous studies have found discordance between patient and physician preferences, particularly in the context of acute health conditions. Although there is some evidence that patients value the chance of durable survival [1], the present study adds to the knowledge and the literature by investigating whether physicians assess variability in the survival gains from a therapy in the same way that patients do. In addition, we are able to interpret these incongruent preferences toward treatment within an intuitive framework on attitudes toward risk.

Within the US health care system as a whole, the degree of congruence between patients and physicians has increased as patient centeredness has been recognized as a key element of high-quality health care [26,27]. In the context of cancer...
treatment, this study suggests that physicians are more likely to focus on mean or median survival and fail to fully take into account the value patients place on durable survival gains. Value frameworks typically ignore patient risk-related preferences but rather try to maximize mean or median health benefit—often measured using quality-adjusted life-years—subject to budget constraints. The focus of such value frameworks is an open question for society. For oncologists to provide patient-centered cancer treatment [28], however, physicians should consider treatment gains not only to mean or median survival but also the likelihood of producing durable survival gains. In fact, this study provides evidence that the American Society for Clinical Oncology’s value framework approach of giving “bonus points” for treatments that improve tail-of-the-curve survival is appropriate for capturing the patient perspective.

This study has a number of limitations. First, a majority of the patient sample was female, and a majority of physician respondents was males. Eighty-five percent of physicians in our sample were male compared with 70% of oncologists nationally based on data from the 2015 AMA Physician Masterfile [29]; because male and female physicians had similar preferences in our study, this limitation is unlikely to undermine external validity. On the other hand, 2011 national incidence rates are higher for men compared with women for both NSCLC (49.7 per 100,000 vs. 37.2 per 100,000) and melanoma (28.9 per 100,000 vs. 18.4 per 100,000) [30].

In our study, male patients had a stronger preference for durable survival therapies, which aligns with previous research showing that women are generally more risk averse than men [31–33]. If this study reweighted the analysis so that the composition of males and females was representative of the broader US population across both patients and physicians, an even larger difference between patient and physician preferences would be found as a larger share of the patient sample is female.

Second, these findings may not extend to other treatments of disease beyond advanced melanoma or lung cancer. Third, the survey was conducted online, and a higher proportion of our sample had at least a college degree compared with national data [34,35]. The sensitivity analysis, however, did not find consistent differences in preferences based on income or education levels. Finally, discordant preferences do not necessarily mean that physicians override their patients’ desires. Although patients generally prefer to provide input into the decision-making process, some patients prefer that physicians make treatment decisions for them [36].

On the other hand, extensive evidence that physicians respond to financial incentives indicates that physician decision making is not fully aligned with patients’ interests, at least in some circumstances [37]. In our view, whether, when, and how physicians substitute their perspective for that of patients in real-world decision making about treatments are important issues that need to be fully understood.

Conclusion
Cancer patients place a high value on therapies that provide a chance of “tail-of-the-curve” overall survival. In contrast, physicians report an inclination to prescribe therapies with less variability in survival outcomes. Patient-centered care and value frameworks should evaluate treatments not only based on survival improvement for the mean or median patient, but also based on their ability to produce tail-of-the-curve, durable, long-term survival gains.

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Supplemental Materials
Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2016.11.028 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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