Patient Preference and Adherence

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ORIGINAL RESEARCH

The Value of Hope: Patients' and Physicians' Preferences for Survival in Advanced Non-Small Cell Lung Cancer

This article was published in the following Dove Press journal:
Patient Preference and Adherence

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Purpose: Immuno-oncology treatments offer patients with advanced non-small cell lung cancer (NSCLC) treatment options with greater probability of durable survival and a different toxicity profile compared with traditional chemotherapy. The objective of this study was to explore the importance of increases in the probability of long-term survival versus changes in expected (median) survival and treatment toxicities among patients with advanced NSCLC and physicians.

Patients and Methods: In a discrete-choice experiment, oncologists and patients diagnosed with NSCLC chose between profiles of treatments for advanced NSCLC offering different combinations of benefits (expected, best-case, and worst-case survival) and risks. We analyzed preference data from each sample using a random-parameters logit model that controls for preference heterogeneity and the panel nature of the data.

Results: Both patients and physicians expressed a strong preference for improving the probability of best-case survival; however, patients viewed increases in the probability of long-term survival as more important than increases in expected survival, while the opposite was true for physicians. Both patients and physicians weighted survival to be more important than toxicities.

Conclusion: This study identified a potentially important divergence between physician and patient perspectives on survival statistics. Physicians placed more importance on increases in expected survival than did patients with NSCLC. The importance patients placed on long-term survival reinforce previous research identifying the primacy of hope as a value among seriously ill patients. The findings underscore the importance of considering patients' priorities and in shared decision-making when choosing treatment.

Keywords: non-small cell lung cancer, patient preferences, physician preferences, immunotherapy, survival, discrete-choice experiment

Introduction

Lung cancer, the leading cause of cancer death among both men and women globally,[1] also results in a high symptom burden and greatly reduced quality of life during and after treatment.[2] The most recent data available indicate that the 5-year survival rate of patients with advanced or metastatic forms of non-small cell lung cancer (NSCLC), which accounts for the majority of patients diagnosed, was 4.7% in the United States from 2008 to 2014.[3]

Immuno-oncology has now begun to move that bar for patients diagnosed with lung cancer. Several treatment options enlisting the immune system to combat

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http://doi.org/10.2147/PPA.S248295

tumor growth are now widely available. Specifically, the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors (eg, nivolumab and pembrolizumab) harness the body's immune system to fight tumor growth, leading to increases in durable treatment response and longer survival for a subset of patients diagnosed with NSCLC.[4–6] For example, data from an early, Phase 1, dose-escalation study of nivolumab revealed a 5-year survival rate of 16%,[7] a tripling of the historic rate for such patients.[8] In addition, a pooled analysis of two Phase 3 trials comparing treatment with nivolumab and treatment with docetaxel showed that the 3-year survival rate with nivolumab was roughly twice that with docetaxel (17% vs 8%).[9] Similarly, the 2-year survival rate for patients with PD-L1 tumor proportion score ≥ 50% was greater with pembrolizumab (51.5%) than with chemotherapy (34.5%).[10]

Research in the social sciences suggests that when people are faced with a potentially fatal disease, their tolerance for risk increases, and they may be more willing to gamble on the possibility of a large gain in life expectancy than persons in relatively good health.[11] A patient-preference study in the advanced melanoma and advanced breast cancer context showed that most (but not all) patients preferred a treatment with the potential for longer survival compared with a treatment with the same average benefit but without the possibility of long-term survival.[12] This phenomenon has been termed the value of hope.[12] Several studies have explored the value that patients, providers, or both place on aspects of benefits and burdens of treatment, including progression-free survival (PFS), landmark overall survival (OS), or toxicities in lung cancer,[13–22] melanoma,[12,20,23,24] and renal cell carcinoma.[25–28] However, no study to date has been designed to elicit how patients and their physicians value a set of attributes with the unique profile of immuno-oncologic treatments, including how patients and physicians trade off increases in mean or median survival versus an increased chance of remission or durable survival or avoiding toxicities associated with cytotoxic chemotherapy.

To further explore these earlier findings, we developed a study to quantify the extent to which both patients and physicians weigh the distribution of survival outcomes offered by an NSCLC treatment against treatment-related risks of adverse events. We conducted a discrete-choice experiment (DCE) in which patients diagnosed with NSCLC and oncologists were asked to choose between hypothetical treatment profiles offering tradeoffs between expected (median) survival, the probability of durable survival, worst-case survival, and treatment toxicities. By characterizing preferences for the distribution of potential survival rather than simply expected OS, this study was designed to extend previous work quantifying the value of hope to patients and to provide greater insight into what matters to patients with NSCLC and the physicians who treat these patients.

Methods

Study Population

Eligible patient respondents included individuals ≥ 18 years of age who had a self-reported physician diagnosis of NSCLC. Eligible physician respondents included board-certified oncologists who currently treat patients with NSCLC. Both patients and physicians were required to be residents of the United States and to read and understand English. There were no specific exclusion criteria.

Eligible patient respondents were invited by Survey Sampling International (Shelton, Connecticut) through its online panel. Physicians were invited by All Global (New York, New York), which maintains a health-care panel, through e-mails and follow-up phone calls to be screened and to confirm eligibility.

All respondents provided electronic informed consent and received payment for time spent participating. The study was approved by the RTI International institutional review board (IRB ID Number 13746, dated 16 December 2016 [physicians] and 22 June 2017 [patients]) and complied with the Declaration of Helsinki.

Survey Instrument

We developed and administered a DCE survey instrument following guidelines for good research practices.[29] The experiment was designed to elicit tradeoffs respondents are willing to make among treatment attributes by observing choice patterns. Treatments were defined by attributes, which were assigned varying levels (Table 1). In consultation with clinical experts, we selected attributes and attribute levels that reflected evidence gathered in two published studies comparing an immunotherapy treatment to standard-of-care chemotherapy.[9,30] Side-effect attributes were chosen to be relatively common side effects that differ between immunotherapy and platinum-based chemotherapies.

We identified three efficacy endpoints that, when taken together, describe the distribution of potential survival outcomes: worst-case survival, defined as life expectancy at the 15th percentile; expected survival, defined as life

Table 1 Attributes and Levels for the Treatment Profiles

Attribute	Levels	Variable Name	Description in Patient Survey	Description in Physician Survey
Expected survival	6 months 9 months 12 months	EXP	No one can say for certain how long a person receiving treatment for advanced lung cancer can expect to live. However, doctors have information from clinical trials that can help them understand how cancer medicines may help patients live longer. Clinical trials are studies designed by doctors to learn how patients respond to specific medicines. In this survey, we would like you to consider how well lung cancer medicines work based on the following: • How long your doctor expects that patients live after taking a cancer medicine • How much longer patients can live if a lung cancer medicine works better than expected • How much less time patients might live if the medicine work worse than expected	We will ask you to think about the expected survival for a patient who undergoes a specific NSCLC treatment. For the purposes of this survey, assume that this expected survival is based on information from phase 3 clinical trials.
Best-case survival	14 months 24 months 48 months	BEST	Worse or better than expected responses to medicine: Doctors also consider other information from clinical trials to understand how well a cancer medicine works. From these trials, your doctor can tell you how long patients with lung cancer taking a specific medicine might live if the medicine works better or worse than expected. For the purpose of this survey, we would like you to consider the following: • Patients who live the longest time in a clinical trial represent how long patients live if the medicine works better than expected (better than expected response) • Patients who live the shortest time in a clinical trial represent how long patients live if the medicine works worse than expected (worse than expected response)	We want you to consider (1) the top 15% of patients in terms of survival after starting the treatment (patients at or above the 85th percentile) and (2) the bottom 15% of patients in terms of survival after starting the treatment (patients at or below the 15th percentile). Specifically, we will ask you to consider the levels of survival that define these percentiles. These levels will be presented for different hypothetical NSCLC treatments, and we will ask you to assume that the information is obtained from head-to-head phase 3 trials.
Worst-case survival	1 month 2 months 5 months	WORST		
Fatigue	None Mild to moderate (grades 1 and 2)[a] Severe (grade 3)[a]	TIRED1 TIRED2 TIRED3[b]	Patients with cancer may experience some tiredness (they have less energy or strength) that does not go away and cannot be relieved by sleeping. Some cancer medicines make patients feel even more tired. No tiredness: A person with no tiredness is not more tired than usual and is able to do all usual physical activities, work, or social activities. Mild to moderate tiredness: A person with mild to moderate tiredness: Has difficulty with strenuous physical activities such as exercising, climbing several flights of stairs, or running; May have difficulty with moderate physical activities such as walking, housework, and shopping; May not be able to perform normal work activities; Can participate in normal social activities. Severe tiredness: A person with severe tiredness: Has difficulty with moderate physical activates like walking, housework, and shopping; Is not able to perform normal work activities; Cannot participate in normal social activities.	Fatigue associated with treatments for advanced NSCLC will be consistent throughout treatment and will be described as none, mild to moderate (grades 1–2), or severe (grade 3). No fatigue: This patient has no fatigue. Mild to moderate fatigue (grades 1–2): A patient with mild to moderate (grades 1–2) fatigue: Has difficulty with strenuous physical activities, such as exercising, climbing several flights of stairs, or running; May have difficulty with moderate physical activities, such as walking, housework, and shopping; May not be able to perform normal work activities; Can participate in normal social activities. Severe fatigue (grade 3): A patient with severe (grade 3) fatigue: Has difficulty with strenuous physical activities, such as exercising, climbing several flights of stairs, or running; Has difficulty with moderate physical activities, such as walking, housework, and shopping; Is not able to perform normal work activities; Cannot participate in normal social activities.

(*Continued*)

Table 1 (Continued).

Attribute	Levels	Variable Name	Description in Patient Survey	Description in Physician Survey
Nausea	None Mild to moderate (grades 1 and 2)[a] Severe (grade 3)[a]	NAUS1 NAUS2 NAUS3[b]	Some medicines to treat advanced lung cancer can cause nausea. Nausea is the sensation of uneasiness in the stomach that can make you feel like you have to vomit. No nausea: This person experiences no nausea. Mild to moderate nausea: With this level of nausea, the uneasiness in the stomach affects how much you eat, but the nausea does not cause significant weight loss or dehydration. Severe nausea: With this level of nausea, the uneasiness in the stomach affects how much you eat, causing significant weight loss and dehydration. If this level of nausea persists for more than 24 hours, IV fluids or tube feedings may be indicated.	Nausea associated with NSCLC treatments will be consistent throughout treatment and described as none, mild to moderate (grades 1–2), or severe (grade 3). No nausea: This person experiences no nausea. Mild to moderate nausea (grade 1–2): A patient with mild to moderate (grades 1–2) nausea may have decreased oral intake without significant weight loss, dehydration, or malnutrition. Severe nausea (grade 3): A patient with severe (grade 3) nausea may have inadequate oral caloric or fluid intake; IV fluids, tube feedings, or total parenteral nutrition are indicated.
Risk of febrile neutropenia (fever)	No risk 10% risk (2 of 20) 40% risk (8 of 20)	FEVER0 FEVER10 FEVER 40[b]	Some medicines used to treat advanced lung cancer can also affect your body's ability to make white blood cells that protect you from infections. With a low count of white blood cells, you may develop a severe fever that can peak at 104°F with severe chills, which may make you dehydrated. Although this severe fever may be associated with infections, often doctors cannot determine what causes it. The severe fever can be treated with over-the-counter medicines. However, your doctor may require that you are hospitalized for up to 7 days to bring the fever down, and/or prescribe antibiotics to help with any potential infection causing the fever.	We will ask you to think about the probability that a patient may develop febrile neutropenia.

Notes: [a]Based on the Common Terminology Criteria for Adverse Events, version 3. [b]This level was omitted for model identification during estimation and recovered after estimation (as the negative sum of the included-category parameters).
Abbreviation: NSCLC, non-small cell lung cancer.

expectancy at the 50th percentile; and best-case, or durable survival, defined as life expectancy at the 85th percentile. In addition, we included three common toxicities of treatments for NSCLC—fatigue, nausea, and febrile neutropenia—based on clinical input from medical reviewers and prescribing information.

Treatment profiles were then created as combinations of attribute levels, and profiles were paired following an experimental design developed following good research practices[31] using Sawtooth Software (Orem, Utah). The experimental design contained four blocks of 12 choice questions. Both patient and physician respondents saw the same design and were randomly assigned to one of the four blocks.

We pretested patient and physician survey instruments using in-person qualitative pretest interviews with five patients with NSCLC and five oncologists who treat NSCLC. On the basis of feedback from these interviews, we made minor survey revisions to improve comprehension and readability and increased the highest level of the risk of febrile neutropenia from 15% to 40% to ensure that the highest level of this risk was sufficient that this risk would be considered when patients and physicians were evaluating the treatment alternatives in the survey.

Patient Survey

For each treatment pair, patient respondents were asked to select the treatment they would choose for themselves if they were a patient with advanced NSCLC who had experienced at least one treatment failure. Because not all patient respondents would currently be considering second-line treatment for advanced NSCLC, each patient respondent was asked to assume that "you are a patient with advanced lung cancer, your first treatment for advanced lung cancer is not working

anymore, and you have to start a new medicine" when answering survey questions. In addition to the choice questions, patient respondents were asked to report disease and treatment experience and demographic characteristics.

Physician Survey

In each choice question, physician respondents were asked to indicate which treatment option they would recommend for a prototypical patient defined with input from clinical experts and additional input from the five pretest interviews conducted with oncologists. That individual was described as a 65-year-old male with well-controlled hypertension and a pulmonary disorder (mild chronic obstructive pulmonary disease). This individual was described as having quit smoking 3 years ago. The patient's clinical profile included stage IV NSCLC at diagnosis 2 years ago that had progressed following a platinum-based treatment with metastases in regional lymph node(s), liver, and lungs; an Eastern Cooperative Oncology Group (ECOG) score of 1; and no brain metastasis confirmed by a recent magnetic resonance imaging scan. Figure 1 presents an example choice question from the physician survey.

Statistical Analyses

We analyzed preference data from each sample following good research practices using a random-parameters logit model that controls for preference heterogeneity and the panel nature of the data.[32] We used a main-effects model with the following model specification: best-case survival, expected survival, and worst-case survival were modeled as continuous linear variables after specification tests confirmed that the marginal effects of these attributes could be assumed to be constant over the range of levels shown to respondents. In other words, relative preferences for a 1-month increase in survival were constant across the range of levels for each of the survival attributes included in the study. Fatigue, nausea, and risk of febrile neutropenia were modeled as effects-coded, categorical variables. Effects coding produces a preference-parameter estimate for each level of an attribute in which the estimate of the preference parameter on the omitted level is

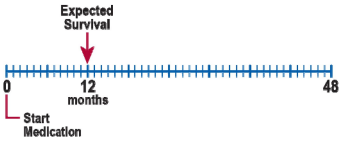
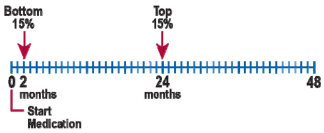
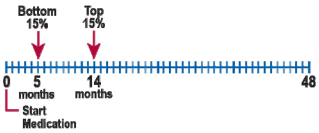
Treatment Feature	Treatment A	Treatment B
Expected survival with treatment		
Survival for bottom 15% of patients Survival for top 15% of patients		
Fatigue	No fatigue	Mild to moderate fatigue (Grades 1 and 2)
Nausea	Mild to moderate nausea (Grades 1 and 2)	No nausea
Risk of febrile neutropenia	 10% (2 out of 20)	 40% (8 out of 20)
Which would you choose	☐	☐

Figure 1 Example choice question (physician version).

the negative sum of the parameters on the other levels of the attribute.

For all analyses, a main-effects specification of the utility function as described in Equation 1 was used in estimations, and parameters estimated for each attribute level were assumed to be normally distributed across respondents to capture heterogeneity:

$$V = \beta_{EXP} \times EXP + \beta_{BEST} \times BEST + \beta_{WORST} \times WORST + \beta_{TIRED1} \times TIRED1 + \beta_{TIRED2} \times TIRED2 + \beta_{NAUS1} \times NAUS1 + \beta_{NAUS2} \times NAUS2 + \beta_{FEV0} \times FEV2 + \beta_{FEV10} \times FEV10 \quad (1)$$

where V is the value function for a particular treatment profile (specified as a function of the attributes as in Eq. 1), and β is a parameter estimate (ie, preference weight) for each attribute level.

We tested for systematic differences in preferences between subgroups of patient respondents based on gender, age, tumor spread (metastatic disease vs nonmetastatic disease), and time since diagnosis. To test for differences in preferences between each subgroup pair, we created a dummy-coded variable that was equal to 1 if the respondent belonged to one of the two groups and interacted with the dummy variable with each explanatory variable. To determine whether preferences were systematically statistically different between the subgroups in each pair, we used a joint test of significance of all interaction terms. Specifically, we applied a Wald test with a chi-squared distribution.

Results from the DCE provided preference weight estimates used to calculate the importance of each attribute in the survey relative to the other attributes conditional on the ranges of the attribute levels presented in the study. To compare the conditional relative importance between the physician and patient samples, we set the conditional relative importance of the best-case survival attribute to 10 for both samples.

Results

Study Populations

Survey Sampling International invited 8900 individuals via e-mail to be screened for eligibility to participate in the patient study between July and August 2017. Of the 462 individuals who responded to the invitation, 248 (53.7%) were eligible and consented to participate. Once the target of 200 completed surveys was met, the survey link was deactivated, and no more surveys were accepted. All Global invited 1110 physicians through e-mails and follow-up phone calls to be screened for study eligibility between December 2016 and January 2017. Of the 112 individuals who responded to the invitation, 105 (93.8%) were eligible and consented to participate. The final sample size was 102 physicians. Three individuals did not complete the survey.

Table 2 presents patient and physician characteristics. Patients had a mean age of 47.2 years (standard deviation [SD], 16.7), and 48.5% were female; 47.5% of patients had metastatic NSCLC (with regional or distant tumor spread), and 64.0% had NSCLC that was diagnosed at least 1 year before the survey. Physicians had a mean age of 47.7 years (SD, 10.9), and 29.7% were female.

Preference Weights

Figure 2 presents the mean estimated preference weights for physicians and patients. In general, the preference weights

Table 2 Patient and Physician Respondent Characteristics

Patient Characteristics	**Respondents (N = 200)**
Age, years	
Mean (SD)	47.2 (16.7)
Median (range)	44.0 (19–83)
Female, n (%)	97 (48.5)
Time since diagnosis, n (%)	
< 6 months	26 (13.0)
≥ 6 months to < 1 year	46 (23.0)
≥ 1 year to < 2 years	68 (34.0)
≥ 2 years to < 5 years	38 (19.0)
≥ 5 years to < 10 years	16 (8.0)
≥ 10 years	6 (3.0)
Unknown/not sure	0
Disease progression, n (%)	
Tumor has not spread from lungs	103 (51.5)
Tumor has spread to tissue around lungs (eg, lymph nodes)	66 (33.0)
Tumor has spread to other parts of the body (eg, liver, kidneys, or brain)	29 (14.5)
Unknown	2 (1.0)
Physician Characteristics[a]	**Respondents (N = 102)**
Age, years	
Mean (SD)	47.7 (10.9)
Median (range)	45 (29–72)
Female, n (%)	30 (29.7)
Less than 10 years in practice, n (%)	34 (33.3)

Note: [a]One respondent is missing from the age- and gender-characteristic categories.
Abbreviation: SD, standard deviation.

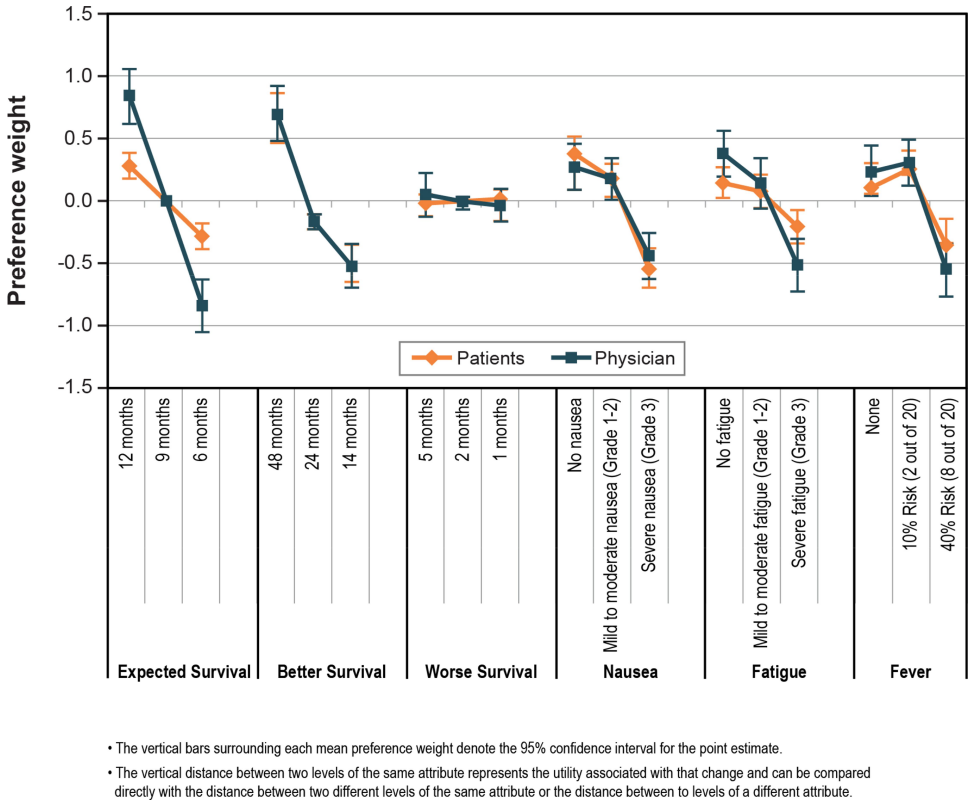


Figure 2 Preferences of patients with non-small cell lung cancer and treating physicians.
Notes: This graph compares the relative weight placed on the attribute levels represented on the x-axis. Vertical distance between levels of the same attribute represents the weight placed on a relative change in that attribute. Calculated mean preference estimates for each value can be compared within each attribute and across different attributes. The vertical bars surrounding each mean preference weight denote the 95% CI about the point estimate.
Abbreviation: CI, confidence interval.

reflected the natural order of the outcomes; that is, better clinical outcomes were preferred to worse clinical outcomes. Both patients and physicians expressed a strong preference for improving the probability of best-case survival and conversely placed little value on worst-case survival. The only area of discordance between physicians and patients occurred in expected survival. Physicians preferred improving expected survival to improving best-case survival, while patients perceived improvements in best-case survival to be preferable to improvements in expected survival.

As expected, both patients and physicians wanted to avoid the worst levels of potential toxicities. For both patients and physicians, preferences for reducing the risk of febrile neutropenia were not ordered as expected. Specifically, the mean preference weight for a 10% treatment-related risk of febrile neutropenia was slightly higher than the mean preference weight for no risk in each sample. However, the difference between these preference weights was not statistically significant in either sample. Physicians expressed a slightly higher preference for avoiding increases in the severity of fatigue than did patients, but the difference was not statistically significant.

Conditional Relative Importance

The difference between the preference weight of the most-preferred and the preference weight of the least-preferred levels of each attribute represents its conditional relative importance. When we compared the estimates of conditional relative attribute importance between physicians and patients, we found that physician respondents placed more weight on longer expected survival than did patients (Figure 3). Patient respondents, in contrast, placed relatively greater weight on best-case survival. Specifically, among physicians, increasing expected survival by 6 months (from 6 months to 12 months) was viewed as approximately 38.5% more important than increasing best-case survival by 34 months (from 14 months to 48 months). Among patients, a 6-month increase in expected survival was less than half as important as a 34-month increase in best-case survival. In addition, patient respondents placed more value on avoiding nausea and reducing the risk of febrile neutropenia than they did on avoiding

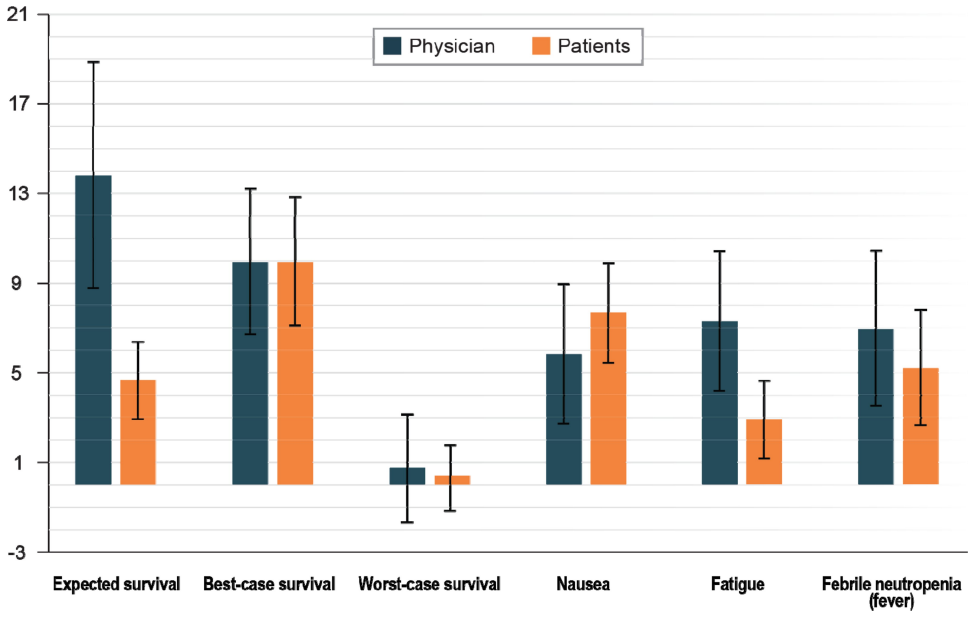


Figure 3 Conditional relative importance for patients and physicians.
Notes: This graph plots the conditional relative importance of each attribute, calculated as the difference between the most- and least-preferred levels of each attribute. The vertical bars surrounding each mean preference weight denote the 95% CI about the point estimate.
Abbreviation: CI, confidence interval.

fatigue. In contrast, physicians saw changes all toxicities to be approximately equally important.

Subgroup Analysis

When we compared the results for subgroups of patients by gender, age, tumor spread (metastatic vs nonmetastatic disease), and time since diagnosis. The only statistically significant difference we found between any subgroup pair was that patients above the median age of 44 years in our sample placed a relatively greater emphasis on achieving best-case survival and avoiding the worst toxicities than did patients below the median age (Table 3).

Discussion

In this study, we compared how physician and patient preferences vary when faced with cancer treatment decisions in which the treatments offer different distributions of survival. Our aim was to assess the relative value placed by physicians and patients on increasing the probability of durable survival, a treatment benefit offered by immuno-oncology treatments now available to patients with NSCLC. These treatments work through a substantially different mechanism than that of chemotherapy agents. Results of clinical trials have shown that for a subset of patients, immuno-oncology treatments produce a durable response that can extend life expectancy significantly for those patients.[4–6] As such, changes in oncologic practice patterns offer a different set of variables for patients and physicians to consider when initiating treatment.

Use of a DCE to elicit preferences allowed us to vary multiple parameters of the distribution of survival simultaneously and weigh these against one another and against common toxicities. Our results revealed that patients and clinicians had similar preferences for durable survival, but

Table 3 Descriptions of Patient Subgroups Analyzed (N = 200)

Subgroup	Description (Dummy Variable = 1)	Respondents, n (%)	Statistically Significant Systematic Difference in Preferences
Gender	Female	97 (48.5)	No
Age	Older than median age of 44 years	98 (49)	Yes
Tumor spread[a]	Tumor has not spread	103 (51.5)	No
Time since diagnosis	Patients diagnosed less than 1 year ago	72 (36)	No

Notes: [a]Tumor spread had two missing respondents and was excluded from the subgroup analysis. All other response categories were complete.

patients valued expected survival less than clinicians. This result indicates that when trading off between expected survival and durable survival, patients are more willing than physicians to forgo expected survival for gains in durable survival. Previous patient-preference research has documented that patients and physicians preferred to gamble on a long shot that offered a small chance of living well beyond the median survival rather than take a sure bet, even if the two options provided the same median survival benefit.[23,24] Simply reframing survival in terms of improvements in landmark survival rather than median survival increased patients' perceptions of the value of a hypothetical treatment.[33] The results of this study add to this body of work, providing further evidence of the value of hope to both patients and physicians.

Patients in our sample above the median age of 44 years placed greater emphasis than patients below the median age on best-case survival, avoiding nausea, and reducing the risk of febrile neutropenia. This finding could reflect that patients above the median age of the sample are still relatively younger than those in the overall NSCLC population. As such, they are in their prime working years and possibly in their "prime of life" years and view durable survival as key to achieve the life goals and family-oriented milestones they have begun to pursue. Additional examination of the effect of age on patients' NSCLC treatment preferences may be warranted.

For both patients and physicians, the preference weights on the lower two levels of the risk of febrile neutropenia were disordered but not statistically significantly different. This result indicates that both patients and physicians may not be concerned about what are perceived to be relatively low risks of febrile neutropenia (<10%) and are only concerned about this adverse event when the risk of occurrence is higher. This result is consistent with the observation that respondents did not appear to trade off increases in the risk of febrile neutropenia for improvements in the levels of other attributes when the risk of febrile neutropenia was less than 15%.

This study identified a potentially important divergence between physician and patient perspectives on survival statistics. While both groups valued a best-case outcome, physicians placed more importance on expected survival than did patients. Physicians preferred increases in expected survival to increases in best-case survival. The opposite was true for patients. This finding may reflect physician familiarity with assessing survival based on mean or median PFS or OS typically measured in clinical trials. It may also reflect the desire of patients in the metastatic setting to reach for a best-case outcome if one is possible. An additional difference in ordering of priorities occurred in assessing toxicities. Physicians placed relatively equal weight on all toxicities presented, whereas patients placed greater relative importance on avoiding nausea and reducing the risk of febrile neutropenia than on avoiding fatigue. The conditional relative importance that patients and physicians placed on nausea and febrile neutropenia was similar between samples and across these two toxicities. The reason that patients placed lower conditional relative importance on fatigue is not entirely clear. One potential explanation is that a minority (44.5%) of patients in the sample had experienced fatigue of any kind since being diagnosed with NSCLC and many patients may not have experienced significant fatigue at any time in their lives. If this is the reason for the lower weight placed on avoiding fatigue, then it may suggest that patients who have not experienced fatigue may not perceive it to be as bad as those patients who have experienced it.

Previous studies exploring patient and provider priorities in the treatment of advanced cancer also have found that these groups value treatment attributes differently. A DCE study exploring the relative importance of seven attributes—treatment mode, dosing schedule, duration of therapy, objective response rate, PFS, OS, and grade 3 or 4 (undefined) adverse events—among patients with advanced lung cancer and oncology nurses found that both groups considered OS the most important treatment attribute, followed by adverse events, objective response rate, and PFS.[23] In contrast, a companion study comparing oncologists' perspectives on these attributes with the same patients' perspectives found adverse events to be the most important attribute to physicians, followed by OS, objective response rate, and PFS.[24] Further, a survey study comparing survival preferences among patients with advanced lung cancer or melanoma and among oncologists found that a treatment with variable survival—or a 50% chance of survival for less than 1 year, a 30% chance of survival for 4 to 7 years, and a 20% chance of durable survival for more than 7 years—was preferable for most patients (63.0% of those with melanoma and 65.5% of those with lung cancer) over a treatment with a fixed survival gain of 4 years. A minority of oncologists, on the other hand, would select the therapy with a chance of durable survival for patients with melanoma (29.7%) or

lung cancer (40.8%).[20] Although the hypothetical treatment profiles evaluated in these studies and in our study differed, the results reveal consistently divergent priorities between patients and physicians.

Our findings underscore the importance of considering the attributes patients value in treatment. The patient voice should be included in the process of weighing a course of treatment, particularly when several options are available, each offering a different profile of risks and benefits. Given the time pressures associated with clinical encounters, and the inherent stress to the patient in such encounters, patient-oriented decision aids have been developed to assist in presenting treatment options.[34] Such an approach acknowledges the need to reconcile just such a physician-patient mismatch in value prioritization as we found in this study.

These novel findings have policy implications as health-care systems and/or reimbursement policies shift to value-based frameworks for determining treatment coverage. In the United States, the Patient-Focused Drug Development (Section 3002) of the twenty-first Century Cures Act incorporates the integration of patient experience.[35] In the realm of oncology, the emergence of treatments enlisting the immune system to fight tumor growth presents a new kind of challenge to physicians, policymakers, and patients alike. Uncertainty remains over which patients' tumors are most likely to respond to treatment, which treatment combinations are most likely to be effective, and how to ensure treatment-related toxicities are properly managed.[5,36]

The American Society of Clinical Oncology value framework includes a scaled approach that includes the patient's perspective on the most valuable therapeutic option.[37] Incorporating the patient perspective in coverage decision-making is currently evolving.[38] The results of this study suggest that traditional cost-effectiveness analysis, which typically uses mean or median overall survival as the basis for determining quality-adjusted life years may be insufficient to capture the full value of immuno-oncologic agents. Specifically, to the extent that cost-effectiveness analyses neglect the value of increases in the probability of longer-term survival, however small, such analyses may understate the impact of these novel agents on patients. All of these factors should be properly communicated to patients weighing their treatment options.

A 2016 Proceedings of a National Academy of Sciences' National Cancer Policy Forum on immunotherapy summarized the challenges facing physicians, patients, policymakers, and payers.[39] The report points to the need for more communication between providers and patients, as well as shared decision-making, given the differing trajectories of treatment response that patients sometimes experience with immuno-oncology treatments. A survey of cancer patients within the Cancer Support Community Cancer Experience Registry, presented during the Forum, highlighted the need for quality communication by revealing that many cancer patients have knowledge gaps and misinformation about immunotherapy treatment. In the same survey, patients stated that they highly valued communication with their health-care team. Participants recommended both prioritizing the patient perspective and improving physician-patient communication. Given these challenges and changing treatment landscape, longer-term study of patient preferences for immuno-oncology treatments is warranted.

Limitations

When interpreting the results of a DCE, it is important to consider the method's limitations. While its use in health services research is now well established,[40–42] DCE patient respondents were asked to choose among hypothetical treatments, and their choices do not carry the same weight as actual treatment choices. Patient respondents were asked to consider a second-line treatment for advanced NSCLC even if they did not have advanced NSCLC. Patients facing a non-hypothetical second-line treatment for advanced NSCLC might value treatment options differently. In addition, actual patient choices may reveal different implicit preference weights than those observed here because the choice of an actual treatment includes contextual factors beyond the scope of this study.

Similarly, in this experiment physician respondents were asked to evaluate a single patient profile. Physicians' treatment preferences could change if a patient presented with different history and clinical characteristics.

Patient respondents were self-selected, and their diagnosis was self-reported. We did not seek physician or medical records confirmation. Therefore, we cannot determine how representative our patient population is compared to a broader sample of NSCLC patients. An important limitation is that the average age of patient respondents (47 years) in our sample was younger than the average age of patients (70 years) diagnosed with lung

cancer in the United States, which limits the generalizability of these data.

Conclusions

This study identified a potentially important divergence between physician and patient perspectives on survival statistics. Physicians placed more importance on increases in expected survival than did patients with NSCLC. The importance patients placed on long-term survival reinforces previous research identifying the primacy of hope as a value among seriously ill patients. The findings underscore the importance of considering patients' priorities and in shared decision-making when choosing treatment.

Acknowledgments

Kimberly Moon of RTI Health Solutions proved overall project management for this study. Kate Lothman of RTI Health Solutions provided medical writing services, which were funded by Bristol Myers Squibb.

Disclosure

The research reported in this paper was funded by a research contract between Bristol Myers Squibb and RTI Health Solutions. Financial support for this study was provided entirely by Bristol Myers Squibb. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The following authors are employed by the sponsor: John Penrod and Lina Musallam. Bristol Myers Squibb participated in study design, research, data collection, analysis and interpretation of data, writing, reviewing, and approving the publication. Brett Hauber is an employee of RTI Health Solutions, and David Gebben was an employee of RTI Health Solutions at the time of the study.

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