The Option Value of Innovative Treatments for Non–Small Cell Lung Cancer and Renal Cell Carcinoma

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ABSTRACT

OBJECTIVES: To develop a model of the option value a therapy provides by enabling patients to live to see subsequent innovations and to apply the model to the case of nivolumab in renal cell carcinoma (RCC) and non–small cell lung cancer (NSCLC).

STUDY DESIGN: A model of the option value of nivolumab in RCC and NSCLC was developed and estimated.

METHODS: Data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry and published clinical trial results were used to estimate survival curves for metastatic cancer patients with RCC, squamous NSCLC, or nonsquamous NSCLC. To estimate the conventional value of nivolumab, survival with the pre-nivolumab standard of care was compared with survival with nivolumab assuming no future innovation. To estimate the option value of nivolumab, long-term survival trends in RCC and squamous and nonsquamous NSCLC were measured in SEER to forecast mortality improvements that nivolumab patients may live to see.

RESULTS: Compared with the previous standard of care, nivolumab extended life expectancy by 6.3 months in RCC, 7.5 months in squamous NSCLC, and 4.5 months in nonsquamous NSCLC, according to conventional methods. Accounting for expected future mortality trends, nivolumab patients are likely to gain an additional 1.2 months in RCC, 0.4 months in squamous NSCLC, and 0.5 months in nonsquamous NSCLC. These option values correspond to 18%, 5%, and 10% of the conventional value of nivolumab, respectively.

CONCLUSIONS: Option value is important when valuing therapies like nivolumab that extend life in a rapidly evolving area of care.

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Cancer is a leading cause of death in the United States,[1] with rising prevalence. In 1995, there were 7.1 million individuals in the US who had ever been diagnosed with cancer (2.7% of the population)[2]; by 2012, there were 13.4 million such individuals (4.3%).[3] Although cancer mortality rates are declining,[4] prevalence is expected to increase because of population aging,[5,6] advances in cardiovascular care, earlier cancer detection, and life-extending treatment.[7,8]

Increasing cancer prevalence translates to greater demand for oncology care, with implications for payers. Given growing pressures on payers' budgets and debate over the cost of cancer treatment,[9,10] value is an increasingly important consideration in coverage and access decisions. Moreover, the pressures on payers will increase as cancer prevalence rises, further reinforcing the importance of value.[5]

As value has grown in importance in assessing cancer care, organizations have offered recommendations on measuring value. For example, the National Comprehensive Cancer Network and the American Society of Clinical Oncology recently published frameworks for considering a therapy's efficacy and cost to determine its value.[11,12] The Institute of Clinical and Economic Review, an independent health technology assessment (HTA) organization, uses cost-effectiveness analysis (CEA) and budget impact analysis to measure therapies' value,[13] an approach common in Europe.[14,15]

Traditional methods of CEA measure the value of an innovation by comparing benefits such as survival gains and improved quality of life with costs, assuming no other health technology improvements besides the one in question.[16] However, such methods ignore aspects of therapies that matter to patients, like the value of hope, insurance value to healthy individuals, and the increased value people place on life near its end.[17-20]

Such components of value can be difficult to quantify in HTA because they are subjective valuations based on unobserved patient preferences. However, 1 relevant component of value is rooted in real-world survival data, the "option value" of therapy. Option value is the benefit a therapy provides patients by enabling

them to survive to the next innovation. For example, in cancer care, any survival gains today hold additional value because they increase the likelihood that a patient may live to access even more effective treatment in the future. This concept is particularly important in disease areas with traditionally poor outcomes and rapid innovation.

TAKEAWAY POINTS

- Therapies that enable patients to live to see further innovations in care have option value.
- Option value raises the conventionally estimated value of nivolumab to patients with metastatic cancer by 18% in renal cell carcinoma, 5% in squamous non–small cell lung cancer (NSCLC), and 10% in nonsquamous NSCLC.
- Option value is particularly important in disease areas where there is rapid innovation. In such areas, payers and providers should consider option value when gauging the value of new therapies.

Although metastatic non–small cell lung cancer (NSCLC) and metastatic renal cell carcinoma (RCC) have had low survival rates,[21,22] innovation to treat both cancers is currently rapid. A number of breakthrough targeted therapies and immuno-oncology (IO) therapies, which harness the immune system to fight cancer, are available, such as nivolumab, pembrolizumab, osimertinib, and ceritinib for NSCLC and nivolumab and lenvatinib for RCC.[23,24] These therapies are improving 1 or more clinical endpoints, such as survival rates for cancers with traditionally poor survival odds.[23,24] Furthermore, the pipelines for both tumors are active.[25,26]

Given the proliferation of treatment options and the prospect of future innovation, payers, policymakers, clinicians, and patients require multiple criteria to make care-related decisions.[27] A therapy's option value accounts for the future benefits of a life-extending therapy in addition to its immediate survival effects. With that in mind, we looked at the option value of nivolumab, the first IO therapy given breakthrough status and approved by the FDA for NSCLC and RCC.[23,24] NSCLC is histologically divided into squamous and nonsquamous (adenocarcinoma, large cell) tumor types,[21] and individuals face different prognosis and treatment options depending on the histology. Squamous NSCLC (about 25%-30% of all lung cancers) is typically smoking-related, whereas nonsquamous NSCLC is the most common type of lung cancer in nonsmokers (although smokers are still at greater risk than nonsmokers).[28] We examined squamous and nonsquamous NSCLC separately.

METHODS

Study Design

We adapted a framework for estimating a therapy's option value[19,20,29,30] to the contexts of metastatic NSCLC and metastatic RCC. In particular, we examined the option value of nivolumab, the first programmed cell death protein-1 (PD-1) inhibitor in both disease states. In order to estimate nivolumab's option value, a survival curve for patients taking the pre-nivolumab standard of care was needed first. The pre-nivolumab survival curves were modified using mortality hazard ratios (HRs) from clinical trial publications to obtain a nivolumab survival curve in each setting. Forecasting methods were used to project likely future survival improvements patients with either NSCLC or RCC may live to see. The conventional survival gain from nivolumab was obtained by comparing life expectancy with nivolumab, assuming no future innovation, against life expectancy with the pre-nivolumab standard of care. The option value of nivolumab was obtained by comparing life expectancy with nivolumab under 2 scenarios: allowing for likely future survival gains versus assuming no future innovation. Finally, the option value estimates were converted to economic terms. Additional methodological detail is available in the **eAppendix** (eAppendices available at **ajmc.com**).

Data

Survival trends in metastatic NSCLC and metastatic RCC were estimated using the Surveillance, Epidemiology and End Results (SEER) cancer registry.[31] SEER, which tracks cancer incidence and mortality using data reported by registries across the United States, currently covers about 30% of the US population.[32]

Long-term all-cause mortality rates were taken from the Human Mortality Database (HMD).[33] The HMD contains detailed population and mortality data for 37 countries, and currently provides US life tables for 1933 through 2013.

Survival curves from SEER were modified to reflect nivolumab patients' survival using mortality HRs from clinical trial publications.[34-36] Specifically, in both squamous and nonsquamous NSCLC, nivolumab was compared with docetaxel, and in RCC, nivolumab was compared with everolimus. These comparisons reflect those in the trials noted on the nivolumab FDA label.[37] The comparator drugs were assumed to represent the pre-nivolumab standard of care.

Population

We identified 3 study populations: metastatic squamous NSCLC, metastatic nonsquamous NSCLC, and metastatic RCC. First, we identified patients with NSCLC in SEER by requiring a primary cancer site of "lung or bronchus" or "trachea." We distinguished squamous from nonsquamous histology types using *International Classification of Diseases for Oncology, Third Edition* (*ICD-O-3*) histology codes. For both histology types, we defined metastatic NSCLC as American Joint Committee on Cancer (AJCC) stage IV, IIIb, or III with no surgery. The latter category addressed the fact that not all patients have a substage listed (eg, IIIa vs IIIb), and a lack of surgery suggested the case was inoperable.

To identify the RCC population, we required a primary site of "kidney," "renal pelvis," or "ureter," and identified the RCC histology using *ICD-O-3* histology codes. To limit to patients with RCC with metastatic disease, we selected the "distant" stage using "SEER historic stage A." Although AJCC staging is commonly used in clinical practice for treatment decisions and in clinical trials for eligibility,[38] it was not well documented for RCC in SEER before 2004. Because metastatic RCC is a smaller sample than NSCLC, preserving sample size was important. Moreover, in order to track longer-term trends, it was necessary to be able to identify patients before 2004. In general, SEER distant stage approximates AJCC stage IV. Therefore, we identified metastatic RCC using the SEER distant stage.

Statistical Analyses

We estimated the option value of nivolumab in the 3 populations by taking these 5 steps.

Step 1: estimate pre-nivolumab survival curves. To establish a pre-nivolumab baseline, we estimated survival curves using the SEER data. We identified metastatic squamous and nonsquamous NSCLC and metastatic RCC patients diagnosed between 2001 and 2010. Survival curves for each population were estimated parametrically using a log-normal distribution. Covariates included age at diagnosis, age squared, gender, race, ethnicity, marital status, tumor grade, and a quadratic time trend.

Our survival estimation was limited by the patients' duration of follow-up in SEER. Although we preferred using patients with a more recent diagnosis due to the pace of innovation in cancer care, this limited the number of years of follow-up available. Rather than project survival for many years beyond the duration of follow-up in the SEER data, we assumed that the minority of patients surviving more than 20 years past diagnosis had the same mortality rates as the general population, using US life tables from the HMD.

Specifically, we calculated mortality rates in the first 20 years after diagnosis using the estimated survival curves from SEER and then appended the HMD mortality rates. This lifetime mortality table was used as an input in the Lee-Carter model described in Step 2.

Step 2: forecast survival improvements. The SEER survival curves estimated in Step 1 showed a clear trend of improving survival over time in all 3 populations. Based on these trends, we used the Lee-Carter method[39,40] to forecast survival improvements for each population. The Lee-Carter method involves modeling age-specific mortality rates as a function of a long-term trend in overall mortality improvements and an age-specific response to the overall trend. This method is widely used as a benchmark for long-term mortality forecasts, including by the US Census Bureau and the Social Security Administration.[40]

Step 3: estimate survival with nivolumab. To obtain survival curves for patients taking nivolumab in each population, we began with the pre-nivolumab survival curves estimated in Step 1. Based on the FDA label, which calls for second- or later-line use in both the NSCLC and RCC indications,[37] we assumed that nivolumab would be given as a second-line therapy starting 1 year after diagnosis. Following the clinical trial evidence,[34-36] we assumed that nivolumab patients would experience diminished mortality risk compared with patients on the prior standard of care. Specifically, we applied the mortality HRs from nivolumab trial publications to the pre-nivolumab survival curves estimated in Step 1. We conservatively assumed that any mortality benefits of nivolumab would disappear 4 years after beginning nivolumab therapy.

Step 4: calculate option value in terms of life expectancy gains. Using the survival curves from Steps 1 and 3 and the survival forecasts from Step 2, we calculated the undiscounted life expectancies of patients in each population for several scenarios. First, we calculated life expectancy under the pre-nivolumab standard of care, assuming no future innovation; call this $LE_{pre\text{-}nivo}$. Second, we calculated life expectancy with nivolumab, assuming no future innovation; call this LE_{nivo}. Finally, we calculated life expectancy with nivolumab allowing for future innovation based on the forecasts from Step 2; call this EL_{nivo}.

We calculated the conventional survival gain with nivolumab by comparing life expectancy with nivolumab to that with the pre-nivolumab standard of care. Specifically:

$$\text{Conventional survival gain with nivolumab} = LE_{nivo} - LE_{pre\text{-}nivo}$$

To calculate the option value of nivolumab, we compared life expectancy with nivolumab assuming no further innovation to expected lifetime with nivolumab allowing for future innovation. Specifically:

$$\text{Option value of nivolumab} = EL_{nivo} - LE_{nivo}$$

Step 5: calculate option value in economic terms. Finally, we expressed the conventional and option values in economic terms by applying an economic value of a life year to the additional life years gained. We selected a mid-range value from the literature of $150,000 per life year[41,42] and applied a discount rate of 3% to obtain present discounted values. The per-patient option value was multiplied by the estimated size of each patient population to obtain the total economic values in each population. Population sizes were estimated using several sources.[28,43-47]

Sensitivity Analysis

To test the robustness of the study results to the underlying assumptions, several sensitivity analyses were performed. First, we estimated an alternative parametric survival model (log logistic). This tested the sensitivity of the results to our choice of parametric model. Second, we estimated survival exclusively using the parametric model rather than taking HMD mortality rates after 20 years. This tested the effect of our use of the HMD data. Third, we assumed nivolumab would be taken in the first year after diagnosis, rather than the second. This reflected the fact that metastatic cancer

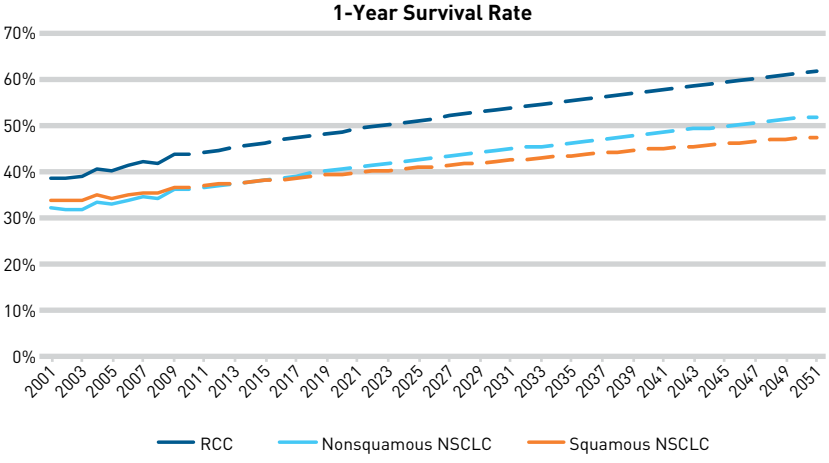
can progress rapidly and, therefore, some patients could potentially reach second-line therapy in the first rather than second year from diagnosis. Fourth, we varied the duration post diagnosis that nivolumab would be effective, from 2 to 10 years. This addressed the limited duration of clinical trial data and the accompanying uncertainty about the duration of nivolumab's effects. Fifth, we estimated nivolumab's mortality benefits using the confidence intervals of the published mortality HRs in order to address uncertainty about the exact magnitude of nivolumab's effects of survival. Sixth, we varied the discount rate from 0% to 6%. Seventh, we varied the value of a life year from $50,000 to $250,000.[26,27] Last, we varied the stage definition used for the selection of the SEER RCC data, using AJCC stage IV instead of the historic "distant" stage. (We used the historic stage definition in our base case analysis because it was better populated and we wanted to test the sensitivity of our results to this choice.)

TABLE. SEER Descriptive Statistics[a]

Diagnosed 2001-2010	Metastatic RCC	Metastatic Squamous NSCLC	Metastatic Nonsquamous NSCLC
Age at diagnosis (years)	64.5 (12.7)	69.0 (10.5)	68.0 (11.4)
Female	33.1%	34.7%	43.6%
Married at diagnosis	59.5%	52.2%	53.3%
Hispanic	12.2%	4.8%	5.3%
White	83.6%	81.3%	80.8%
Black	10.2%	13.8%	12.6%
Asian/Pacific Islander	5.9%	4.8%	6.5%
Median survival (months)	8	7	7
Observations	12,868	49,194	210,419

NSCLC indicates non–small cell lung cancer; RCC, renal cell carcinoma; SEER, Surveillance, Epidemiology, and End Results cancer registry.
[a]Except where otherwise noted, means and standard deviations are given for continuous variables and percentages are given for binary variables.

FIGURE 1. Survival Improvements in SEER[a]



NSCLC indicates non–small cell lung cancer; RCC, renal cell carcinoma; SEER, Surveillance, Epidemiology, and End Results cancer registry.
[a]A parametric survival model was used to estimate historical real-world survival trends from 2001 to 2010, while the Lee-Carter method was employed to forecast survival based on all-cause mortality in the SEER cancer registry.

RESULTS

Study Populations

The **Table** presents descriptive statistics on the 3 study populations in SEER. The nonsquamous NSCLC population was the largest, at 210,419 individuals, followed by squamous NSCLC (49,194) and RCC (12,868). The RCC population was younger than the squamous and nonsquamous NSCLC populations, with average ages of 64.5, 69.0, and 68.0 years, respectively. A higher share of patients with nonsquamous NSCLC (44%) was female compared with squamous NSCLC (35%) and RCC (33%). Patients with RCC were more likely to be married (60%) compared with patients with squamous (52%) or nonsquamous (53%) NSCLC. Racial composition was similar, with whites composing over 80% of all 3 groups. Median survival was 8 months in RCC and 7 months in both squamous and nonsquamous NSCLC.

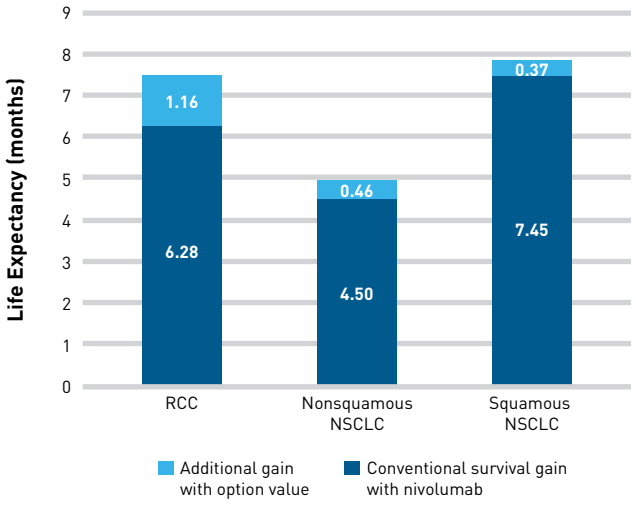
Survival Trends

All 3 populations showed an increasing 1-year survival rate in the 2001 to 2010 SEER data (**Figure 1**). Projected survival in 2011 to 2060 according to the Lee-Carter method is shown via the dashed lines. Survival improved the most quickly in RCC (0.44% per year), followed by nonsquamous NSCLC (0.39%) and squamous NSCLC (0.27%).

Life Expectancy Estimates and Option Value

Life expectancy for patients taking the pre-nivolumab standard of care was estimated to be 18.2 months in RCC, 11.7 months in nonsquamous NSCLC, and 11.6 months in squamous NSCLC. Ignoring future innovations, patients taking nivolumab were expected to survive 24.5 months with RCC, 16.2 months with nonsquamous NSCLC, and 19.1 months with squamous NSCLC, implying gains of 6.3 months, 4.5 months, and 7.5 months, respectively. These

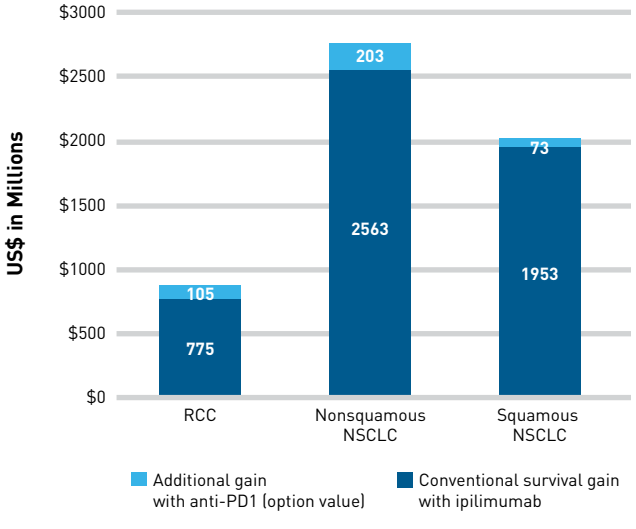
FIGURE 2. Option Value of Nivolumab: Life Expectancy[a]



NSCLC indicates non–small cell lung cancer; RCC, renal cell carcinoma.

[a]Life expectancy estimates are undiscounted. The conventional survival gain with nivolumab represents the additional months the patient could expect to live relative to the previous standard of care, assuming no future improvements in care beyond nivolumab. The additional gain with option value updates the nivolumab life expectancy estimates to take into account forecasted improvements in care.

FIGURE 3. Option Value of Nivolumab: Economic Value[a]



NSCLC indicates non–small cell lung cancer; PD-1, programmed cell death protein-1; RCC, renal cell carcinoma.

[a]Each life year was valued at $150,000. A 3% discount rate was applied to obtain the present value of life expectancy. Population-level numbers were estimated based on age-adjusted incidence data (43.62 per 100,000 population for NSCLC and 14.92 per 100,000 for RCC)[45] reported by the National Cancer Institute for 2010. The incidence estimates were further stratified into the nonsquamous and squamous populations for NSCLC based on American Cancer Society estimates that 61% to 76% of NSCLC is nonsquamous and 24% to 39% of NSCLC is squamous.[27] Metastatic NSCLC is calculated based on the estimate that 60% of all NSCLC diagnosed is advanced-stage.[43] Metastatic RCC is calculated based on the estimates that 90% of all kidney cancers and above 30% of all RCC is advanced-stage.[44,46]

gains are shown in blue in **Figure 2** and represent the conventional survival gains from nivolumab.

However, during the time that nivolumab patients' survival was extended, we allowed for additional innovations to come to market. Incorporating expected innovation, nivolumab extends survival by an additional 1.2 months in RCC, 0.5 months in nonsquamous NSCLC, and 0.4 months in squamous NSCLC. These additional gains due to option value represent 18% of nivolumab's conventionally estimated survival gain in RCC, 10% in nonsquamous NSCLC, and 5% in squamous NSCLC.

Valuing the per-patient survival gains over the full incident metastatic population with each tumor, we found a conventional economic value from nivolumab of $775 million in RCC and an option value of $105 million (**Figure 3**). Due to its higher incidence, economic values were larger in NSCLC. The conventional value of nivolumab was $2.6 billion in nonsquamous NSCLC and $2.0 billion in squamous NSCLC, while the option values were $203 million and $73 million, respectively. Although these valuations are based on a mid-range value of a quality-adjusted life year, it should be noted that debate exists about the best way to provide economic valuations of incremental changes in survival, such as those in this study.[41,42,48]

Sensitivity Analysis

The study results were robust to a variety of specifications. Across the 3 populations, the value of a life year was particularly influential on option value in economic terms. Varying the value from $50,000 to $250,000 changed the option value from $35 to $174 million in RCC, $68 to $339 million in nonsquamous NSCLC, and $24 to $122 million in squamous NSCLC. Varying the discount rate was also influential, with a 0% discount rate leading to the largest option values ($180 million in RCC, $316 million in nonsquamous NSCLC, $118 million in squamous NSCLC) and 6% to the lowest ($67 million in RCC, $141 million in nonsquamous NSCLC, $49 million in squamous NSCLC). The nivolumab mortality HR was particularly influential on option value in life expectancy terms, with values at the lower (higher) end of the confidence intervals producing the highest (lowest) option value (1.42 vs 0.88 months in RCC, 0.56 vs 0.35 in nonsquamous NSCLC, 0.46 vs 0.27 in squamous NSCLC). Assuming a longer duration of benefit from nivolumab and allowing nivolumab therapy to start in the first, rather than second, year after diagnosis also led to greater option value. Results were qualitatively similar regardless of the parametric model used, whether HMD was used, and the stage definition. (Additional detail is available in the eAppendix.)

DISCUSSION

The study results show that incorporating option value can substantially increase the conventionally calculated value of a therapy.

The option value of nivolumab accounts for an additional gain of 1.2 months (18% of conventional survival gain) in metastatic RCC, 0.5 months (10%) in nonsquamous NSCLC, and 0.4 months (5%) in squamous NSCLC. Over the full US incident population, this amounted to an option value of $105 million in metastatic RCC. Given the high incidence of lung cancer, the option value was greater in nonsquamous NSCLC ($203 million) and squamous NSCLC ($73 million). These results show that option value is quantitatively meaningful.

This concept of option value has been introduced in other diseases, such as HIV/AIDS, breast cancer, and chronic myeloid leukemia,[20,29,30] where innovation alters survival and therefore the value of life near its end.[19] This study adds to the existent literature, showing that option value can be important in various healthcare contexts with rapid innovation, as seen in metastatic RCC and NSCLC.

Although our analysis focused on metastatic RCC and NSCLC, the methodology can be applied in other therapeutic areas. The study results demonstrate the need for payers and providers to be aware of attributes of therapies that patients value that are not reflected in traditional value metrics, like the value of hope, the value of life near its end, and the insurance value of therapy.[17-19] Option value is closely related to these concepts, since the option of surviving to see new therapies may give patients hope. Such considerations may be particularly important for patients near the end of life, for example, with a terminal cancer diagnosis. Moreover, option value is especially relevant to patients with metastatic cancer because of rapid innovation in this area.

This study's results suggest promising directions for future research of relevance to payers, providers, and patients. Option value studies can better inform payers and providers of expected survival gains in areas of rapid innovation, as well as their economic value. Further research is needed to understand the patient perspective on innovative therapies and their value. For example, patients could be surveyed on their perceptions and valuations of option value in different disease states. Such research could help to improve the care of patients being treated for serious illnesses, such as cancer.

Limitations

This study has limitations. First, SEER is an incidence sample; therefore, we assumed second-line therapy started 1 year after diagnosis. Second, the SEER population could not be made perfectly comparable with the trial population, thereby affecting life expectancy estimates. In particular, because SEER is an incidence sample and does not report therapies used over time, it was not possible to select only those patients who took the second-line therapies with which nivolumab was compared in the trials (docetaxel in NSCLC and everolimus in RCC). Instead, we obtained the nivolumab survival curves by applying the mortality HRs from the trials to the pre-nivolumab survival curves from SEER. Therefore, both the pre-nivolumab and nivolumab survival estimates in our model are based on the SEER population and should be similarly affected by this assumption. As a result, the effect on our option value estimates should be minimal.

Third, the option value calculations are based on forecasted mortality improvements, which are inherently less accurate than historical data. However, this approach allows us to calculate option value for current treatments rather than focusing on purely historical examples. To do so, we used the Lee-Carter method, which is widely used to forecast improvements in mortality, including by the US Census Bureau and Social Security Administration.[40]

In addition, sensitivity analyses showed that option value was quantitatively important across a range of modeling assumptions. In particular, the results were robust to alternative specifications of the survival model, assumptions on the use of nivolumab and its effects, and alternative stage definitions. ■

CONCLUSIONS

Recent innovations in oncology have allowed patients to live long enough to gain access to more effective future treatments; this is their option value. This study quantifies the option value of nivolumab for metastatic RCC and metastatic NSCLC and shows that it is substantial. Option value is therefore important to patients, payers, providers, and society as a whole.

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eAppendix

Additional Detail on Methods

Identification of study populations in SEER

	Non-squamous NSCLC	Squamous NSCLC	RCC
Primary site	• "lung or bronchus" or "trachea" • ICD-O-3 codes: C339, C340, C341, C342, C343, C348, C349	• "lung or bronchus" or "trachea" • ICD-O-3 codes: C339, C340, C341, C342, C343, C348, and C349	• "kidney," "renal pelvis," or "ureter" • ICD-O-3 codes C649, C659, C669, C680, C681, C688, C689
Histology	• non-squamous • ICD-O-3 histology codes: 8010, 8012, 8013, 8020, 8046, 8050-8052, 8070–8078, 8140, 8141, 8143, 8147, 8250–8255, 8260, 8310, 8430, 8480, 8481, 8490, 8560, 8570–8575	• squamous • ICD-O-3 histology codes: 8051, 8052, 8070-8078, 8560, 8570	• renal cell carcinoma • ICD-O-3 histology codes 8260, 8310, 8316, 8317, 8318, 8319, 8320, 8510, 8959, 8312
Stage	• AJCC stage IV • AJCC stage IIIB • AJCC stage III with no surgery	• AJCC stage IV • AJCC stage IIIB • AJCC stage III with no surgery	• "Distant" stage according to "SEER historic stage A"

Notes: The "SEER historic stage A" variable was used to select metastatic RCC cases in SEER rather than the AJCC variable because it was better populated over the study time period.

AJCC indicates American Joint Committee on Cancer; *ICD-O-3*, *International Classification of Diseases for Oncology, Third Edition*; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.

Implementation of the Lee-Carter method

The Lee-Carter method assumes that the age-specific death rate $m_{x,t}$ pertaining to age x at time t can be modeled as

$$ln\, m_{x,t} = a_x + b_x k_t + \varepsilon_{x,t},$$

where a_x describes the time-invariant shape of the age-specific death rates, k_t describes the improvement in all-cause mortality over time, b_x describes the tendency of mortality at age x to respond to overall improvements in mortality at time t, and $\varepsilon_{x,t}$ is an error term.

The goal is to estimate the coefficients a_x, b_x, and k_t to fit the historical data on the age-specific death rates. Lee-Carter method reduces the time dimension of mortality to a single index, which can be modeled and forecasted using time series methods. In Lee-Carter's application to US mortality, they discovered that, an autoregressive integrated moving average, specifically ARIMA(0,1,0), is the most appropriate model for k_t. We followed the same approach to model a simple random walk with drift, where

$$k_t = k_{t-1} + c + e_t.$$

Here c is the drift and e_t is the error. Empirically, the time trend k_t has been highly linear in time.

We followed this approach to forecast the mortality trends for squamous NSCLC, non-squamous NSCLC, and RCC patients.

Estimation of the size of the incident patient populations in the US

In order to convert our per-patient option value estimates to national estimates, we needed to estimate the size of the incident population with each tumor type in the US.
To do so, first we estimated the size of the incident NSCLC and kidney cancer populations. (Incidence rates were not available specifically for RCC.) Estimates of incident NSCLC and kidney cancer cases in 2010 were obtained based on age-adjusted incidence data (43.62 per 100,000 population ages 19 and over for NSCLC and 14.92 per 100,000 for kidney cancer)[45] reported by the National Cancer Institute and the overall US population ages 19 and over from the Census (308,745,538).[47]

Metastatic NSCLC was calculated based on the estimate that 60% of all diagnosed NSCLC is advanced stage.[43] This produced an estimated population with incident metastatic NSCLC of 80,805.

The NSCLC incidence estimates were further stratified into the non-squamous and squamous populations based on American Cancer Society estimates. Specifically, the American Cancer Society estimates that 85% to 90% of lung cancers are NSCLC, and 25% to 30% of lung cancers are squamous NSCLC.[27] This implies that 28-35% of NSCLC is squamous, while 65-72% is non-squamous. We took the midpoint and assumed 31.5% of NSCLC is squamous, while 69.5% is non-squamous. This produced estimated incident metastatic populations of 25,454 for squamous and 55,351 for non-squamous.

Incident metastatic RCC cases were calculated based on the estimates that 90% of all kidney cancers are RCC and at least 30% of all RCC is advanced stage.[44,46] This produced an estimated population with incident metastatic RCC of 12,438.

Results of the Sensitivity Analysis

eAppendix Table 1. Sensitivity Analysis Results for RCC Population

Alternative specification	**Conventional gains (months)**	**Option value (months)**	**Option value (% of conventional gains)**	**Conventional gains (US$ millions)**	**Option value (US$ millions)**
Base case	6.28	1.16	18.46%	$775	$105
Alternative parametric model (log logistic)	7.46	0.98	13.09%	$886	$77
Using parametric survival model exclusively rather than HMD after 20 years	6.45	1.21	18.77%	$779	$110
Alternative nivolumab mortality hazard ratio					
HR=0.57	10.94	1.42	12.99%	$1,345	$125
HR=0.93	1.45	0.88	60.69%	$180	$82
Discount rate varied from 0-6%					
0%	6.28	1.16	18.46%	$977	$180
6%	6.28	1.16	18.46%	$635	$67
2nd line assumed to start in first year from diagnosis	14.77	1.56	10.58%	$1,895	$141
Duration of nivolumab effect post-diagnosis					
2 years	2.58	0.93	35.89%	$332	$86
10 years	8.68	1.39	15.99%	$1,026	$121
Value of a life year					
$50,000	6.28	1.16	18.46%	$258	$35
$250,000	6.28	1.16	18.46%	$1,291	$174
Stage: AJCC IV	6.56	0.86	13.16%	$806	$73

eAppendix Table 2. Sensitivity Analysis Results for Non-Squamous NSCLC Population

Alternative specification	**Conventional gains (months)**	**Option value (months)**	**Option value (% of conventional gains)**	**Conventional gains (US$ millions)**	**Option value (US$ millions)**
Base case	4.50	0.46	10.14%	$2,563	$203
Alternative parametric model (log logistic)	5.57	0.36	6.55%	$3,026	$133
Using parametric survival model exclusively rather than HMD after 20 years	4.53	0.54	12.00%	$2,549	$243
Alternative nivolumab mortality hazard ratio					
HR=0.57	7.51	0.56	7.48%	$4,256	$244
HR=0.93	1.65	0.35	21.52%	$943	$162
Discount rate varied from 0-6%					
0%	4.50	0.46	10.14%	$3,116	$316
6%	4.50	0.46	10.14%	$2,159	$141
2nd line assumed to start in first year from diagnosis	12.25	0.67	5.51%	$7,267	$300
Duration of nivolumab effect post-diagnosis					
2 years	1.95	0.35	18.04%	$1,157	$162
10 years	5.95	0.56	9.36%	$3,263	$240
Value of a life year					
$50,000	4.50	0.46	10.14%	$854	$68
$250,000	4.50	0.46	10.14%	$4,272	$339

eAppendix Table 3. Sensitivity Analysis Results for Squamous NSCLC Population

Alternative specification	**Conventional gains (months)**	**Option value (months)**	**Option value (% of conventional gains)**	**Conventional Gains (US$ Millions)**	**Option value (US$ millions)**
Base case	7.45	0.37	4.96%	$1,953	$73
Alternative parametric model (log logistic)	9.21	0.36	3.89%	$2,304	$58
Using parametric survival model exclusively rather than HMD after 20 years	7.47	0.45	6.05%	$1,934	$92
Alternative nivolumab mortality hazard ratio					
HR=0.57	11.26	0.46	4.07%	$2,938	$89
HR=0.93	3.34	0.27	8.12%	$879	$56
Discount rate varied from 0-6%					
0%	7.45	0.37	4.96%	$2,372	$118
6%	7.45	0.37	4.96%	$1,645	$49
2nd line assumed to start in first year from diagnosis	20.98	0.63	3.01%	$5,703	$126
Duration of nivolumab effect post-diagnosis					
2 years	2.95	0.25	8.36%	$808	$52
10 years	10.53	0.51	4.89%	$2,638	$97
Value of a life year					
$50,000	7.45	0.37	4.96%	$651	$24
$250,000	7.45	0.37	4.96%	$3,255	$122