The Value of Novel Immuno-Oncology Treatments

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ABSTRACT

OBJECTIVES: To assess the value to society of improved survival from novel immuno-oncology (I-O) treatments.

STUDY DESIGN: Case studies of ipilimumab for the treatment of advanced unresectable melanoma and nivolumab for advanced previously treated squamous non–small cell lung cancer (NSCLC).

METHODS: Published data and survival analysis were used to estimate survival gains. We valued the gains using an economic model developed for application to discrete changes in life expectancy. We estimated aggregate utilization and value to society using cancer registry data and literature. We assessed the share of social value that flowed to the pharmaceutical manufacturer as sales revenue based on publicly available prices.

RESULTS: For advanced melanoma, our analysis estimated an average real-world life expectancy (discounted at a 3% rate) of 32.4 months with ipilimumab versus 14.2 months with an existing standard of care. Treatment of advanced NSCLC with nivolumab generated a life expectancy of 28.1 months versus 14.3 months with an existing standard of care. Depending on model assumptions, the value of these survival gains ranged from $232,000 to $697,000 for a patient with melanoma and from $180,000 to $586,000 for one with NSCLC. Using a midpoint value to aggregate across treated patients over a 5-year window, the total value to society was estimated at $1.9 billion for ipilimumab in advanced melanoma and $1.7 billion for nivolumab in NSCLC. Less than 30% of the total value flowed to the pharmaceutical manufacturer in the form of profit.

CONCLUSIONS: The novel I-O treatments studied here generate substantial survival gains and, thus, social value. Less than half of this value accrued to the pharmaceutical manufacturer as sales revenue.

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For more than 150 years, it has been hypothesized that the human immune system plays an important role in oncogenesis.[1,2] As long ago as the 19th century, it was hoped that the immune system could be made to combat the disease, and in this century, the hope of immuno-oncology (I-O) therapy has finally begun to be borne out. The FDA approved ipilimumab in 2011 for the treatment of unresectable or metastatic melanoma.[3] This monoclonal antibody inhibits a protein receptor that acts as a brake on immune response and thus promotes the availability of lymphocytes that target and kill cancer cells.[4] Since the launch of ipilimumab, several other I-O treatments have been introduced. For example, nivolumab, another monoclonal antibody, came to market in 2014 for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600–mutation positive, a BRAF inhibitor.[5] In 2015, nivolumab was approved in the United States for treating metastatic squamous non–small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.[6]

In the past, the prognosis for these specific cancers has been quite poor. The advent of I-O treatment offers the prospect of substantial improvements in efficacy and tolerability in cancer care, with early evidence pointing to sizable gains in life expectancy. For example, a recent pooled analysis of long-term survival with ipilimumab for advanced melanoma indicates that roughly 1 of 6 patients can expect to live as long as 10 years, which is a degree of durable survival that borders on a cure for this subgroup of patients.[7] Furthermore, I-O treatments may prove efficacious in treating a range of cancers. Nivolumab has been approved in the United States for the treatment of advanced renal cell carcinoma and other cancers,[8,9] and as of November 2018, ClinicalTrials.gov reported 654 open studies involving nivolumab.[10]

Although the clinical promise of I-O treatment is well appreciated, its economic value remains controversial. In the United States, there are acute and growing concerns about the rising costs of both branded and generic drugs and the rising share of national health spending that drugs comprise.[11] Costs represent one side of the equation. The economic approach compares costs with

benefits in order to ascertain value. In some instances, the high cost of a new therapy may be dwarfed by the substantial benefits that the therapy provides to society in terms of improved outcomes. As an example, first-line treatment of chronic myeloid leukemia with tyrosine kinase inhibitors has been shown to produce survival gains worth $2.6 billion to a cohort of incident patients compared with a treatment cost of just $0.7 billion.[12] In another context, the use of statins in cardiovascular care has been found to generate quite substantial value for society.[13] At this time, however, evidence on the economic value of I-O treatments is lacking.

TAKEAWAY POINTS

Immuno-oncology is a new paradigm in cancer treatment whose value to society is not well understood.

- Case studies of ipilimumab for melanoma and nivolumab for squamous non–small cell lung cancer point to substantial improvements in life expectancy compared with existing standards of care.
- The value of these survival gains is substantial.
- Revenues from sales of these drugs represent only a fraction of their value to society.

The present study investigates the potential of this new treatment paradigm for cancer care to provide value to society, in the sense that the willingness of individuals to pay for the survival gains that come from I-O treatments exceeds their cost. Specifically, this study evaluates 2 case studies, with corresponding analyses, of ipilimumab for the treatment of advanced unresectable melanoma and nivolumab for advanced previously treated squamous NSCLC. To do so, we use the best available evidence to quantify survival gains over an existing standard of care and value the gains based on an economic model developed for application to discrete changes in longevity. We then compare the value of the survival gains to society with the profits received by the pharmaceutical manufacturer.

METHODS

Assessing the value of I-O treatment to society is challenging because this paradigm of cancer treatment is novel and rapidly evolving.[1] To develop meaningful insights, this study undertook 2 case studies corresponding to their approved indications: (1) ipilimumab for unresectable or metastatic melanoma and (2) nivolumab for advanced previously treated squamous NSCLC. For simplicity, we will frequently refer to these I-O treatments as ipilimumab for melanoma and nivolumab for NSCLC. These case studies represented relatively old versus new I-O treatments, with more versus less extensive evidence on survival and utilization. It should be noted that for melanoma, combination I-O therapy (nivolumab + ipilimumab) has been approved, but data on survival are relatively limited.[14]

Each case study involved several analytic steps. First, we characterized the real-world gain in life expectancy that a patient experiences from the I-O treatment. Second, we quantified the value of the survival gain to each patient and the aggregate value of the gains to the patient cohort and society. Finally, we determined the share of social value that flows to pharmaceutical manufacturers in the form of sales revenue. Following is a description of our methods for each step.

Survival Gains From I-O Treatment

For each case study, we compared expected survival with the select I-O treatment with survival with an existing standard of care (glycoprotein 100 [gp100] for advanced unresectable melanoma and docetaxel for advanced previously treated squamous NSCLC) using published studies with the longest available follow-up of these patients.[7,15-17] Survival curves from these studies were extracted using graph-reading software.

It is also relevant to incorporate survival beyond the end of follow-up. For melanoma, follow-up with ipilimumab is approximately 10 years (with somewhat less than 20% of patients still alive); with gp100, follow-up is approximately 4 years (with approximately 5% of patients still alive). With ipilimumab, the **eAppendix** (available at **ajmc.com**) shows that mortality becomes rare among patients who survive 36 months. We estimated the survival gain from ipilimumab by assuming that any patient alive at the end of follow-up was cured of cancer. This approach understates the survival gains from ipilimumab insofar as gp100 is less curative than ipilimumab, as noted above. To provide some perspective, we quantified survival gains through 44 months, when follow-up for gp100 ended.[15]

Under our approach, a cured patient survives according to rates of all-cause mortality from recent US life tables.[18] These mortality rates are age specific, so we assumed that patients were diagnosed at the mean/median age for each cancer in the key studies.[16,17] In sensitivity analysis, we used the average age at diagnosis reported in the Surveillance, Epidemiology, and End Results (SEER) registry from 2008 to 2012.[19] (Details on cohort identification are provided in the eAppendix.) In addition, we addressed heterogeneity in age at diagnosis by calculating average survival gains among those diagnosed younger than average and those diagnosed older than average in the SEER data.

For advanced previously treated squamous NSCLC, follow-up of nivolumab in current literature extends to 66 months.[15] As with ipilimumab for melanoma, mortality becomes rare among patients who survive 36 months. We therefore assumed that patients with NSCLC using nivolumab who are still alive at the end of follow-up are cured. For docetaxel, follow-up is just 24 months.[16] We addressed this issue in 3 main ways. First, we estimated survival gains from docetaxel through 24 months. Next, we estimated alternative survival functions using available data with the longest follow-up and projected long-term survival (details are presented in the eAppendix). We also considered a scenario in which some patients did not respond differently to nivolumab. Third, we considered a scenario in which some patients experienced durable survival. In

this durable survival scenario, we started with the head-to-head survival data.[16,17] Beginning at 24 months for both treatments, we applied mortality hazard rates from the survival analyses. Then, at 36 months, we assumed that all patients alive were cured and survived according to all-cause mortality rates. We also considered a scenario in which half of the patients were cured and the other half survived according to the estimated hazard rates.

Each year of survival was discounted at a rate of 3%, consistent with the recommendation of the US Public Health Service's Panel on Cost-Effectiveness in Health and Medicine.[20] Finally, life expectancies in trials were translated into real-world survival using a recent comparison of mean survival in trials and observational studies (specifically, mean survival in the real world was found to be 95% of the survival seen in trials).[21]

Value of Survival Gains

To determine the value of improved survival to a patient, we applied an economic model developed for application to discrete changes in life expectancy, which has been previously applied in the health context to antiretroviral therapy for HIV/AIDS and tamoxifen for breast cancer.[22-24] This model is calibrated to standard parameters, such as risk aversion and willingness to substitute consumption across time periods (details are provided in the eAppendix).

A key input into the model is "full income" as a measure of economic resources, as it is distinct from actual income. Full income represents the full range of economic possibilities and exceeds actual income, which ignores the value of household production, nontraded goods, and leisure. Notably, leisure is "purchased" by working fewer hours and receiving a lower actual income.[25] Allowing for 8 hours of sleep per night, total hours exceed full-time work by a factor of 2.8, and average actual family income annually among patients with cancer exceeded $70,000 in the Medical Expenditure Panel Survey during the 2010 to 2013 period.[26] In our survival valuation model, we focused on a full income of $200,000, but we also considered the sensitivity of the value estimates to full incomes of $100,000 and $300,000. A prominent analysis of the US context estimated full income within this range for individuals of the average ages at melanoma and NSCLC diagnosis in key studies.[16,17]

To determine the value of improved survival to society, we aggregated the estimated value to a patient across the number of patients treated in each cohort. We considered value over a window of 5 years of incident cases, because the I-O paradigm is evolving rapidly and may render the treatments considered in our case studies less relevant in the near future. We started by determining the number of patients diagnosed based on primary site, histology, American Joint Committee on Cancer staging, and surgical treatment in the most recent SEER data (2008-2012),[19] and we used the SEER coverage rate (28% of the US population in 2010) to produce a national estimate of the size of each cohort of patients diagnosed at an advanced stage. Where relevant data were missing, we conservatively excluded potential cases (detailed in the eAppendix).

In the past, patients with advanced NSCLC have frequently foregone treatment, and so we applied the historical rate of second-line treatment among patients with advanced squamous NSCLC from the literature (16%).[27] However, the availability of more efficacious and/or better-tolerated treatment could encourage higher utilization, so a sensitivity analysis considered a scenario in which the treatment rate increased by one-fourth. For advanced melanoma, nontreatment is minimal. However, in sensitivity analyses (detailed in the eAppendix), we addressed the approval of BRAF inhibitors in 2013 for first-line use in specific populations and also the potential use of ipilimumab by patients with early-stage disease that progresses to advanced disease.

Share of Social Value Flowing to the Manufacturer

We focused on revenues minus production costs—that is, profits. To calculate revenues for the manufacturer, we first determined the typical dose of an infusion treatment from our reference studies[17,28]; this dose accounts for the average weight of US adults of the same age, adjusted for gender composition in the studies.[29] We then multiplied dose per infusion by number of infusions from the 2 published studies. Ipilimumab was administered over 4 infusions; for nivolumab, the median number of infusions was 8. Finally, total dosage was multiplied by the Average Sales Price used to determine payments under Medicare Part B and decreased by 10% to reflect the typical manufacturer rebate for oncology drugs.[30,31] Industry reporting points to a cost of $100 per gram for a well-established production line.[32] Estimated profits per patient were then aggregated across the patient cohorts and divided by social value from the preceding analytic step to quantify the share of value flowing to the pharmaceutical manufacturer.

RESULTS

Based on the literature and our analytic approach, we estimate that an individual with advanced unresectable or metastatic melanoma could expect real-world survival of 65.6 months with ipilimumab treatment compared with 23.1 months with an existing standard of care (gp100). Within 45 months of treatment, when gp100 follow-up ended, average survival was 17.4 months with ipilimumab versus 11.2 months with gp100. Overall, discounting future years at a 3% rate, life expectancies were 32.4 months and 14.2 months, respectively, as **Figure 1** shows. Based on average age at diagnosis from SEER (as described previously), the life expectancy estimates are 31.7 and 13.9 months; further allowing for variability in age at diagnosis, the estimates are 30.7 and 13.5 months.

For advanced previously treated squamous NSCLC, average survival through 24 months is estimated to be 7.9 months on a discounted real-world basis for an existing standard of care (docetaxel). Based on our preferred survival functions, life expectancy is projected to be 11.4 months for the existing standard of care and 27.7 months with nivolumab, for a survival gain of 16.3 months. If patients who are alive at 36 months are cured of cancer, survival is

estimated to increase to 14.3 months with docetaxel compared with 28.1 months with nivolumab, as shown in Figure 1. This survival gain (13.9 months) is smaller because the survival analysis of patients receiving docetaxel points to continued cancer mortality beyond 36 months. If just half of patients are cured, the survival gain with nivolumab would grow to 15.6 months. In the remainder of our analysis, we use the estimated gain of 13.9 months from the durable survival scenario.

As **Figure 2** shows, based on the economic model for valuing discrete changes in longevity, the total (present discounted) value of the expected survival gain from treating a patient with melanoma with ipilimumab, as in the reference studies, is estimated to be $465,000, assuming a full income level (described previously) of $200,000. If full income were $100,000, the value of the survival gain would be $232,000, and the value would be $697,000 if full income were $300,000. Similarly, the value of the survival gain from treating a patient with NSCLC with nivolumab is estimated to range from $180,000 to $586,000, according to the magnitude of full income.

Aggregating across patients over a 5-year window, the total value to society of the survival gains from treating patients with melanoma with ipilimumab is estimated to be $1.9 billion, based on a full income of $200,000, as shown in **Figure 3**. In sensitivity analysis, we estimated that aggregate utilization would decrease 36% if all patients with melanoma who had the BRAF V600 mutation were first treated with BRAF inhibitors. On the other hand, we estimated that the potential treatment of patients with early-stage melanoma who survive but progress to advanced disease could increase the size of the treated cohort by 70%, generating a social value of $3.2 billion under our survival projections. Turning to nivolumab treatment of NSCLC, the total social value of survival gains is $1.7 billion. If the rate of second-line NSCLC treatment increased 25% in response to the availability of a more effective therapy, this figure would be $2.2 billion.

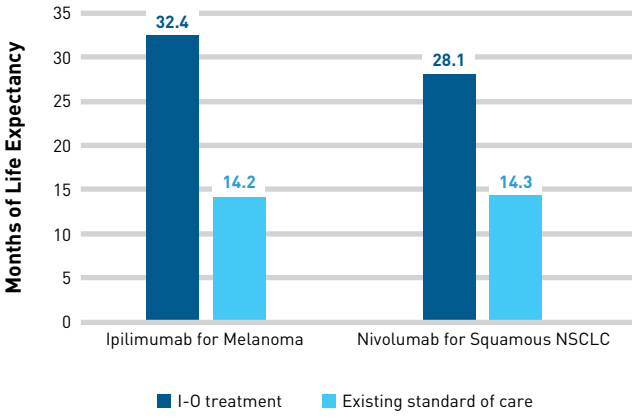
Finally, we estimate that the pharmaceutical manufacturer receives $132,000 in profits from each patient with melanoma treated with ipilimumab and $45,000 from each patient with NSCLC treated with nivolumab. Thus, as **Figure 4** shows, less than 30% (28.4%) of the value of treating melanoma patients with ipilimumab flows to the manufacturer as profits. For nivolumab treatment of NSCLC, the manufacturer's profits are a notably smaller share (11.8%) of the value of the survival gains experienced by patients.

DISCUSSION

This study investigated the social value of the survival gains from novel I-O treatments, specifically, ipilimumab for advanced unresectable melanoma and nivolumab for advanced previously treated squamous NSCLC.

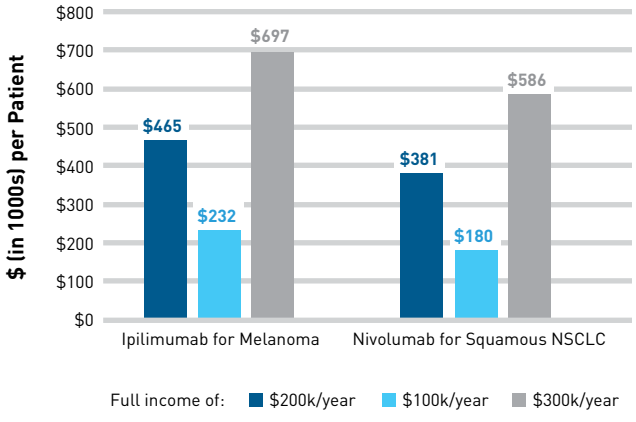
We estimate that ipilimumab substantially improves real-world discounted life expectancy over an existing standard of care, and nivolumab for NSCLC would also generate substantial gains if durable survival comparable with ipilimumab for melanoma resulted.

FIGURE 1. Life Expectancy With Novel I-O Treatment Versus Comparative Standard of Care[a]



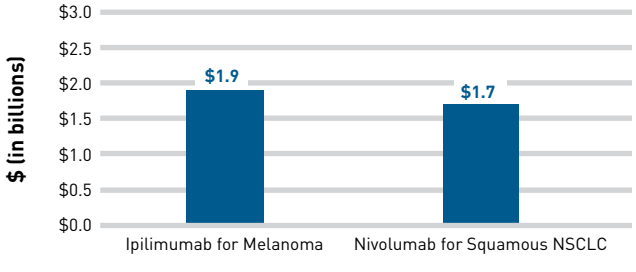
I-O indicates immuno-oncology; NSCLC, non–small cell lung cancer.
[a]Estimates are for discounted real-world life expectancy.

FIGURE 2. Patient Value of Survival Gains From Novel I-O Treatments, Under Alternative Assumptions About Full Income



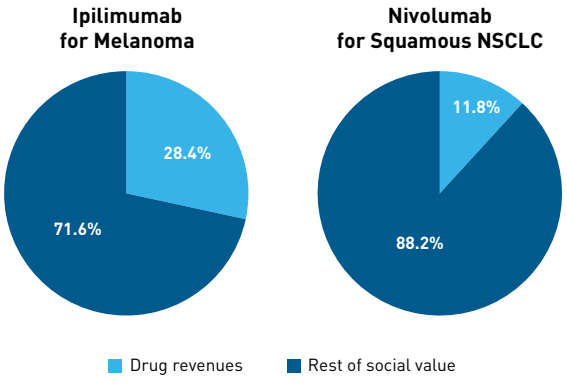
I-O indicates immuno-oncology; NSCLC, non–small cell lung cancer.

FIGURE 3. Aggregate Value of Survival Gains to Society Over 5-Year Window[a]



NSCLC indicates non–small cell lung cancer.
[a]Results are based on midpoint value for full income ($200k/year).

FIGURE 4. Drug Revenues as Share of Social Value[a]



NSCLC indicates non–small cell lung cancer.

[a]Results are based on midpoint value for full income ($200k/year).

An economic model for valuing discrete changes in longevity indicates that the improvement in life expectancy is worth $465,000 to a patient with melanoma and $381,000 to a patient with NSCLC, based on an intermediate value for a key model input (income).

These findings are consistent with a value of a statistical life-year of approximately $230,000. Reviews of the literature on the value of occupational and nonoccupational safety point to a value of a statistical life-year of anywhere from $150,000 to $360,000, and out-of-pocket health spending by patients with cancer reveals a willingness to pay for survival of a comparable magnitude.[33-35]

Aggregating value per case across the patients treated over a 5-year window, we estimate that ipilimumab treatment of melanoma generates $1.9 billion in value for society, whereas nivolumab treatment of NSCLC would generate $1.7 billion in value for patients with durable survival. We estimate that profits to the pharmaceutical manufacturer represent 28% of the total social value of ipilimumab treatment in melanoma and 12% of the value from nivolumab in NSCLC.

Limitations

Our analysis has a number of limitations. Our approach to estimating long-term survival likely understated survival gains from I-O treatment because it assumed that patients were cured at the end of follow-up under an existing standard of care, as well as I-O treatment. In addition, recent evidence on 5-year survival with nivolumab for NSCLC is more favorable than our own estimates applying findings from an earlier analysis of pooled studies.[15,36] These studies were based on dosing according to weight. The most recent label specifies flat dosing, at a level below what would be typical under the original label[9]; on the other hand, our estimate of the cost of nivolumab treatment used the median number of infusions from the pooled studies, which understates the actual average with durable survival and maintenance therapy per the current label. Due to uncertainty about real-world utilization of these treatments, as well as ongoing developments in cancer treatment, we considered a relatively short time horizon (5 years of new cases) and explored the sensitivity of our results to alternative scenarios for utilization. Another limitation is that this study has not addressed quality of life. Existing evidence is limited but nevertheless suggests that I-O treatment can maintain baseline quality of life and thus contribute to value.[37]

CONCLUSIONS

Despite these limitations, this study has important implications for patients, payers, and policy makers. The National Academy of Medicine and numerous stakeholders have emphasized the need for better value in healthcare.[38,39] Certainly, I-O treatment is not low-cost; we estimated that ipilimumab treatment of a typical case of advanced unresectable melanoma cost nearly $147,000 for drug acquisition. However, the question of value is always: Where do the benefits stand in relation to the costs?[40] In healthcare, the benefits are the health outcomes achieved for patients—in our case, substantial survival gains. As has been found in the context of traditional chemotherapy, as well as chronic medication, spending on the I-O treatments studied here represents a modest fraction of the economic value of the survival gains produced by the treatments.[12,13] Our findings suggest that novel I-O treatments have strong potential to yield not only favorable prognoses but also good value. ■

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Identifying patient cohorts

To identify patients in SEER over 2008-2012, the following inclusion criteria are used:

- Advanced squamous NSCLC
    - Primary site "lung or bronchus" or "trachea," as identified through International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes: C339, C340, C341, C342, C343, C348, C349
    - Histology: squamous non-small cell lung cancer, as identified through ICD-O-3 codes 8070–8078.
- Advanced unresectable melanoma
    - Primary site "melanoma" as identified through ICD-O-3 codes: C440, C441, C442, C443, C444, C445, C446, C447, C448, C449, C510, C511, C512, C518, C519, C600, C601, C602, C608, C609, C632
    - Histology: melanomas, as identified through ICD-O-3 codes 8720-8790

Patients first diagnosed in advanced stage are identified based on American Joint Committee on Cancer staging, 6th edition (specifically, IIIB or higher). Cases with unknown stage at diagnosis are excluded (5 and 6 percent of melanoma and squamous NSCLC cases, respectively). For melanoma, stage IIIB/C cases that were initially treated by resection are excluded.

Survival curves

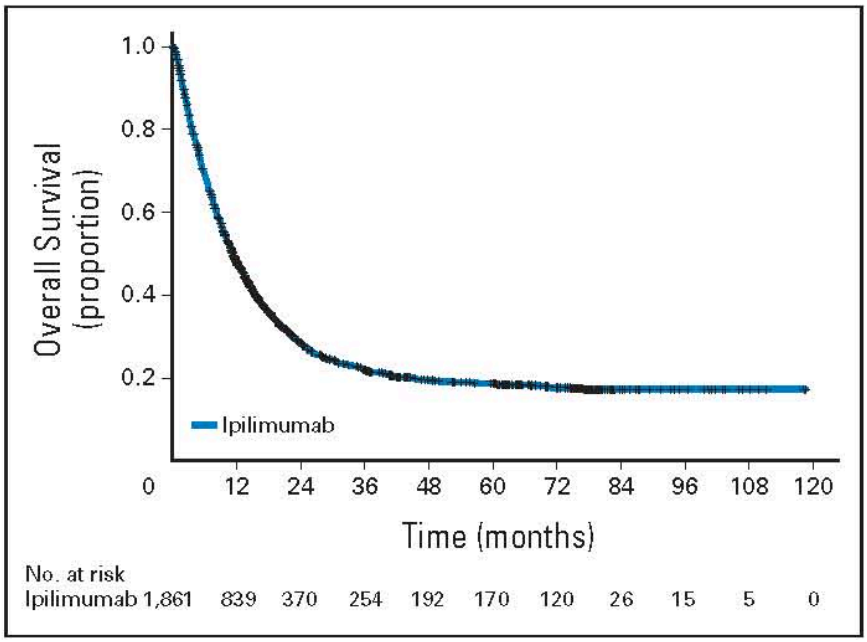
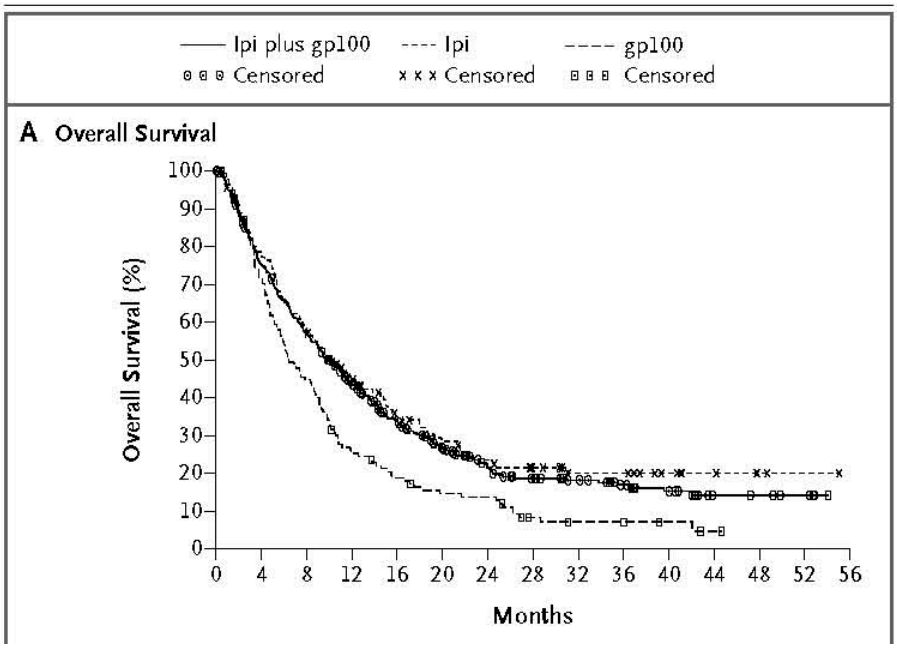


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

Schadendorf et al. (2015)



Hodi et al. (2010)

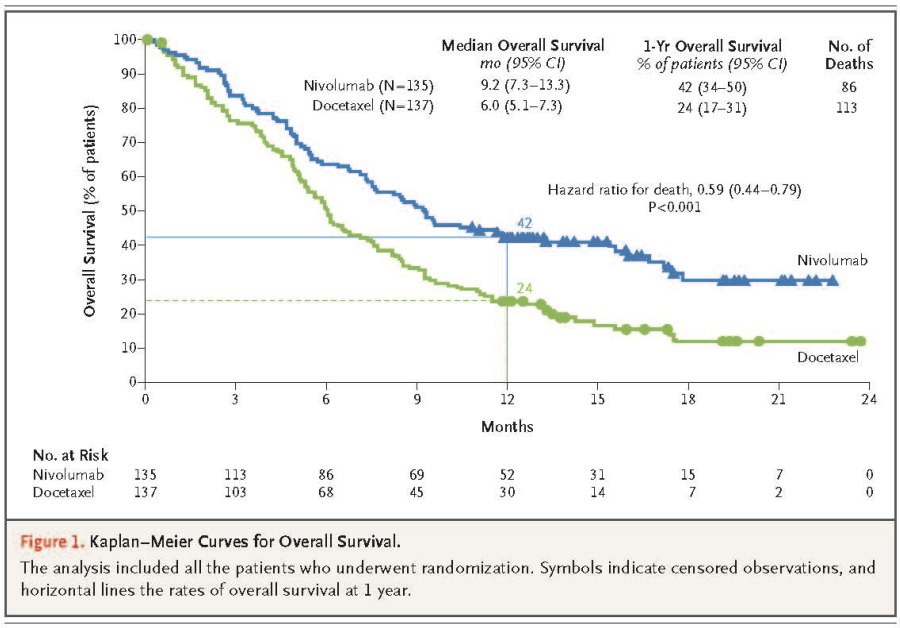
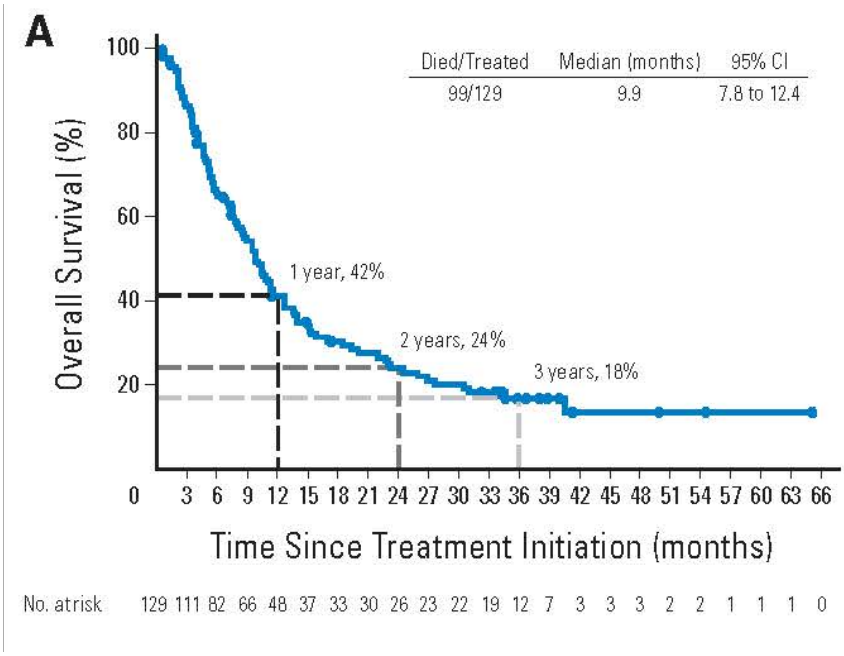


Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Brahmer et al. (2015)



Gettinger et al. (2015)

Projecting long-term survival

For both treatments, we consider five parametric survival functions in Stata for which mean life expectancy can be calculated. Two of these (exponential and Weibull) can be viewed as either proportional hazard or accelerated failure time (AFT) models, while the other three (lognormal, loglogistic and gamma) are AFT-only models. The table below reports the loglikelihood, Akaike Information Criterion (AIC) and discounted real-world life expectancy for each specification. For both treatments, the loglogistic specification had the lowest AIC, and was therefore used. The difference in discounted real-world life expectancy was estimated to be 16.3 months.

Model	Loglikelihood	AIC	LE	Converged?
Docetaxel				
Exponential	-1.47E+09	2.94E+09	9.0	Yes
Weibull	-1.46E+09	2.93E+09	8.8	Yes
Loglogistic	-1.41E+09	2.82E+09	11.4	Yes
Lognormal	-1.41E+09	2.83E+09	10.0	Yes
Gamma	-1.42E+09	2.83E+09	N/a	No
Nivolumab				
Exponential	-1.68E+09	3.36E+09	18.7	Yes
Weibull	-1.67E+09	3.33E+09	19.3	Yes
Loglogistic	-1.57E+09	3.13E+09	27.7	Yes
Lognormal	-1.57E+09	3.14E+09	21.9	Yes
Gamma	-1.59E+09	3.18E+09	N/a	Yes

Notes: "LE" is discounted real world life expectancy estimate in months. "N/a" means not available, because LE could not be calculated at final parameter values.

In a supplemental analysis, we estimate a model in which the overall survival curve for nivolumab reflects a mixture of two types of patients, those who benefit from nivolumab instead of docetaxel and others who respond according to the survival function for docetaxel. The patient shares are parameterized using a logistic function, ensuring that the shares lie strictly between zero and one. Our starting values for this estimation are derived from the parameters of the independently estimated survival curves and a conjectured 50:50 mix of patient types. After 25 iterations, this analysis produced an estimated share of nivolumab responders that is essentially equal to one. The loglikelihood of this model with heterogeneous response was indistinguishable from the sum of the loglikelihoods of the independently estimated survival models.

Valuing life expectancy gains

Following Philipson et al.,[1] let an individual's lifetime indirect utility function *V(S,y)* depend on annual full income of *y* and survival profile *S*. Suppose that an I-O treatment improves survival from *S* to *S´*. Define the individual's willingness to pay (WTP) *w* as the monetary value that satisfies *V(S,y) = V(S´,y-w)*.

We assume that the individual's utility function in a given time period takes the form

$$u(c) = \frac{c^{1-\frac{1}{\gamma}}}{1-\frac{1}{\gamma}} + \alpha,$$

where *c* is consumption in the period, α is a parameter that normalizes the consumption value of death to zero, and γ is the inter-temporal elasticity of substitution (equivalently, the degree of risk aversion in this constant relative risk aversion utility function.) Given these assumptions, we can the compute the annual WTP for the survival gain with constant consumption equal to full income *y* as:

$$w = y - \left[\left(\frac{1}{1-\gamma}\right)\left(\frac{A(S)}{A(S')}u(y) - \alpha\right)\right]^{\frac{\gamma}{\gamma-1}},$$

where *A(S)* is the value of an annuity that pays one dollar in perpetuity under survival curve *S*. The lifetime willingness to pay is the present value of the annual willingness to pay over the lifetime: *A(S)w*. Following the calibration of the model in the literature, we assume that $\gamma = 1.25$ and $\frac{u'(y)y}{u(y)} = 0.346$, and consider alternative values of *y* as explained in the body of the study.

Sensitivity analysis

For melanoma, we assess the potential impact of the approval of BRAF inhibitors in 2013 on utilization of ipilimumab. To do so, we suppose that all patients whose tumor is positive for the BRAF V600 mutation use a BRAF inhibitor first line; the prevalence of this mutation has been estimated at 43 percent in the literature.[2] We multiplied this prevalence by the proportion of patients in a key trial of BRAF inhibitors who did not use ipilimumab after first-line treatment (83 percent).[3]

We also explore the impact of potential utilization of ipilimumab among early-stage patients who survive but progress to advanced disease on the size of the cohort and thus

aggregate value to society. To do so, we determine the number of individuals diagnosed at stage 0 in the SEER registry over 2008-2012, and apply a rate of survival with distant recurrence from the literature.[4]

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