Original Investigation

Necitumumab in Metastatic Squamous Cell Lung Cancer
Establishing a Value-Based Cost

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IMPORTANCE The SQUIRE trial demonstrated that adding necitumumab to chemotherapy for patients with metastatic squamous cell lung cancer (mSqCLC) increased median overall survival by 1.6 months (hazard ratio, 0.84). However, the costs and value associated with this intervention remains unclear. Value-based pricing links the price of a drug to the benefit that it provides and is a novel method to establish prices for new treatments.

OBJECTIVE To evaluate the range of drug costs for which adding necitumumab to chemotherapy could be considered cost-effective.

DESIGN, SETTING, AND PARTICIPANTS We developed a Markov model using data from multiple sources, including the SQUIRE trial, which compared standard chemotherapy with and without necitumumab as first-line treatment of mSqCLC, to evaluate the costs and patient life expectancies associated with each regimen. In the analysis, patients were modeled to receive gemcitabine and cisplatin for 6 cycles or gemcitabine, cisplatin, and necitumumab for 6 cycles followed by maintenance necitumumab. Our model's clinical inputs were the survival estimates and frequency of adverse events (AEs) described in the SQUIRE trial. Log-logistic models were fitted to the survival distributions in the SQUIRE trial. The cost inputs included drug costs, based on the Medicare average sale prices, and costs for drug administration and management of AEs, based on Medicare reimbursement rates (all in 2014 US dollars).

MAIN OUTCOMES AND MEASURES We evaluated incremental cost-effectiveness ratios (ICERs) for the use of necitumumab across a range of values for its cost. Model robustness was assessed by probabilistic sensitivity analyses, based on 10,000 Monte Carlo simulations, sampling values from the distributions of all model parameters.

RESULTS In the base case analysis, the addition of necitumumab to the treatment regimen produced an incremental survival benefit of 0.15 life-years and 0.11 quality-adjusted life-years (QALYs). The probabilistic sensitivity analyses established that when necitumumab cost less than $563 and less than $1309 per cycle, there was 90% confidence that the ICER for adding necitumumab would be less than $100,000 per QALY and less than $200,000 per QALY, respectively.

CONCLUSIONS AND RELEVANCE These findings provide a value-based range for the cost of necitumumab from $563 to $1309 per cycle. This study provides a framework for establishing value-based pricing for new oncology drugs entering the US marketplace.
In 2015, there will be more than 220,000 new cases of lung cancer in the United States. Approximately 45% of these will be adenocarcinomas; 25% will be the squamous cell subtype; and the remaining 30% will be small cell, large cell and other rare cancers. In recent years, great advances have been made in identifying driver mutations such as the epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) gene rearrangement. The approval of tyrosine kinase inhibitors such as erlotinib and crizotinib has greatly changed the outcomes for patients harboring these mutations. However, these mutations are generally found in patients with histologically confirmed adenocarcinoma.

Patients without driver mutations in advanced disease are treated with conventional chemotherapy consisting of a platinum compound in addition to gemcitabine, vinorelbine, paclitaxel, or docetaxel, all with comparable levels of efficacy. In patients with metastatic squamous cell lung cancer (mSqCLC) treated with cisplatin and gemcitabine, the median overall survival is 11 months. Given the lack of progress in the treatment of squamous cell carcinoma, development of novel anticancer agents is urgently needed.

Necitumumab is a human IgG1 monoclonal antibody directed against the ligand binding site of the anti–epidermal growth factor receptor (EGFR), thereby inhibiting downstream targets of the EGFR pathway that are important for cancer cell proliferation, invasion, and metastasis. The SQUIRE study was a phase 3 multicenter trial that enrolled 1093 previously untreated patients with mSqCLC to evaluate the survival benefit of necitumumab in combination with first-line chemotherapy. Patients were randomized to receive gemcitabine-cisplatin or gemcitabine-cisplatin in addition to necitumumab followed by maintenance necitumumab alone. The study demonstrated an improvement of 1.6 months in median overall survival (hazard ratio [HR], 0.84) when necitumumab was added to chemotherapy, which exceeded the trial’s pre-specified criteria for clinical benefit. Patients receiving necitumumab experienced the following grade 3 or 4 adverse events (AEs) more frequently than controls: hypomagnesemia (9% vs 1%), rash (7% vs 0%), arterial thromboembolic events (4% vs 2%), and venous thromboembolic events (5% vs 3%). Slightly higher rates of thromboembolic events were reported in a similar study evaluating the safety and efficacy of necitumumab in patients with nonsquamous, non–small-cell lung cancer.

The high cost of recently approved anticancer drugs has raised the importance of value as a consideration in treatment decisions in oncology. Cost-effectiveness studies can help to identify opportunities to improve value in clinical decision making. In the United States, the conventional paradigm is to study the cost-effectiveness of a drug after it is approved by the US Food and Drug Administration (FDA) and available in the marketplace. These analyses are rarely used to guide coverage decisions. If necitumumab gains FDA approval, the incremental costs for the drug and management of AEs will be added to the current cost of managing patients with mSqCLC. The objective of the present study was to prospectively identify the range of drug costs from a US perspective within which adding necitumumab to first-line chemotherapy could be considered cost-effective.

Methods

We developed a Markov model to analyze the costs and effectiveness of management of mSqCLC. The model evaluated 2 first-line treatment options: (1) gemcitabine and cisplatin for 6 cycles and (2) gemcitabine, cisplatin, and necitumumab for 6 cycles followed by maintenance necitumumab alone. In both arms of the model, following progression of disease, patients could receive second-line therapy. As observed in the SQUIRE trial, docetaxel, erlotinib, and vinorelbine were the most commonly used second-line therapies. Based on the reported distribution of each treatment, patients were modeled to receive docetaxel (30.6% for necitumumab arm vs 23.2% for control arm), erlotinib (10.5% vs 13.7%), vinorelbine (7.3% vs 6.0%), or no therapy for second-line treatment. Patients could progress to death at any point in the model.

Each model cycle represented 3 weeks. The primary clinical inputs to the model were survival estimates and the frequency of AEs, as described in the SQUIRE trial. The primary cost inputs included drug costs, administration costs, and the costs of AEs. The primary outputs of the model included total costs, life-years, quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratios (ICERs). The Markov models were implemented in C++ language, and statistical analyses were performed in R.

Model Patients and Treatment Regimens

To project the outcomes for a population of patients with mSqCLC, we sampled a patient’s initial age at diagnosis based on the age distribution for metastatic lung cancer from the Surveillance, Epidemiology, and End Results (SEER) data between 2000-2011.

Mortality and Progression Risk Estimates

The overall mortality rate for each arm was derived from the corresponding overall survival curve from the SQUIRE trial. Engauge Digitizer software, version 4.12014, was used to extract the data points from the overall survival plots, and these data points were then used to fit parametric survival models. Log-logistic models provided a good fit for all curves according to the Akaike information criterion and the Schwarz Bayesian criterion (see eFigure 1 and eFigure 2 in the Supplement). We also considered the age-specific background mortalities from other causes, which were estimated from the US life tables.
In the model, the probability of transition from any state to the death state was defined as the maximum value of observed mortality rate and the background mortality during each cycle. We estimated the progression risks for each arm based on the progression-free survival curves in the SQUIRE trial using the same approach. Estimates of mortality and progression risk beyond the follow-up time in the clinical trial were extrapolated based on the fitted survival models and mortality rates from US life tables.

**Utility Estimates**

To compute the total QALYs in the Markov model, survival time was adjusted by utility. Given the lack of direct utility assessment in the SQUIRE trial, we used quality-of-life data from another published study based on a similar patient cohort. We assigned a utility of 0.71 for all patients in first-line therapy and a utility of 0.74 for all patients in second-line therapy. This slightly higher but not clinically relevant increase in the utility during second-line treatment may reflect the relative physical fitness of the patients in the quality-of-life study who move on to a second line of treatment. These estimates provided base case values for our analysis, although they may not exactly match the health outcomes of the study cohort in the SQUIRE trial. The uncertainty in utility estimates was addressed in sensitivity analyses.

We modeled AEs for first-line therapy that had significantly different rates between the arms of the SQUIRE trial. These included arterial and venous thromboembolic events, rash, and hypomagnesemia. The probabilities of AEs occurring for patients during therapy in the model were based on the reported frequency of AEs in the SQUIRE trial. A disutility of 0.116 was assigned to patients experiencing a rash based on a prior study that established corresponding utility values for individual AEs. This was estimated to last for 28 days, and the total disutility over this period was subtracted from the baseline utility. Further information regarding utilities is available in Table 1. We did not include in the model AEs with similar rates in both arms of the SQUIRE trial. Although these AEs might influence the total costs of therapy, they would not influence the incremental cost-effectiveness of necitumumab.

**Cost Estimates**

To estimate drug costs, we used the 2014 average sales price as reported by the Centers for Medicare and Medicaid services (CMS). This surrogate for reimbursement rates provides a useful assessment of medical costs that has been applied commonly in cost-effectiveness analyses. Direct costs included drug costs, administration costs, and AE costs valued in 2014 US dollars. In the first-line setting, the intravenous (IV) drug costs for each 3-week cycle of treatment were based on the following doses: gemcitabine, 1250 mg/m² on day 1 and day 8, and cisplatin, 75 mg/m² on day 1. When necitumumab was given, it was dosed at 800 mg on day 1 and day 8. Whenever cisplatin was administered, IV supportive medicines included palonosetron (0.25 mg), fosaprepitant (150 mg), dexamethasone (12 mg), and normal saline (1 L). Oral medications included dexamethasone, 8 mg twice daily for 4 days following cisplatin, ondansetron, 8 mg as needed, and prochlorperazine, 8 mg as needed. Drug costs are listed in eTable 1 in the Supplement. Administration of gemcitabine-cisplatin on day 1 was assumed to last 5 hours. Administration of gemcitabine on day 8 was assumed to last 1 hour. Whenever necitumumab was added, an additional hour was added to the administration time.

In the second-line treatment, the following dosing strategies were used: IV docetaxel, 75 mg/m² every 3 weeks; oral erlotinib, 150 mg/d; IV vinorelbine, 25 mg/m² weekly. We used a body surface area of 1.86 m² based on mean US values. We did not round drugs up to the full vial size. Administration costs and AE costs were calculated according to the Medicare physician fee schedule for 2014. The fees for outpatient physician visits were based on Current Procedural Terminology codes. The methods used for these cost calculations were previously described by Tumeh et al. The fees for physician visits and chemotherapy administration are listed in eTable 2 in the Supplement. All costs and health outcomes were discounted by 3% annually.

We assumed that skin rash was treated with clobetasol cream, 0.05%, and hypomagnesemia was treated with 2 g of IV magnesium sulfate injection. We assumed that venous thromboembolic events were managed with enoxaparin, 1 mg/kg twice daily for 6 months, and arterial thromboembolic events were managed with aspirin, 81 mg/d (Table 1).

**Model Validation**

We performed internal model validations demonstrating that the overall survival curves generated by the Markov model simulation closely approximated those presented in the SQUIRE trial and the fitted survival models (see eFigure 3 and eFigure 4 in the Supplement).

**Sensitivity Analysis**

We performed probabilistic sensitivity analysis to evaluate the robustness of the model and to address uncertainty in the estimation of variables. Values of all variables were sampled from recommended distributions: gamma distribution for the cost parameters and beta distribution for parameters bounded between 0 and 1. We assumed the mean value of each distribution to be the base case value of the
corresponding variable, and the standard deviation to be half of the 95% confidence intervals for utility and 20% of the mean values for other variables.25,26 The baseline values, ranges, and distributions of model parameters are listed in Table 1. From the probabilistic sensitivity analyses, we developed cost acceptability curves for given “willingness-to-pay” (WTP) values. Each curve represents the probability that the ICER is below the WTP value for different costs of necitumumab (Figure 2).

Variations in the Cost of Necitumumab

We ran the base case model multiple times, each time varying the cost of necitumumab and analyzing the effect on the ICER. We present data for results that produced ICERs below commonly accepted benchmarks for cost-effectiveness: $50 000 per QALY, $100 000 per QALY, $150 000 per QALY, and $200 000 per QALY.24,26

Variations in the Overall Survival Hazard Ratio

To provide data for the design of future clinical trials, we examined the effect on the ICER of the HR for overall survival comparing the intervention and control arms and aimed to establish the HR range where expected costs for novel first-line therapies for mSqCLC are likely to be cost-effective. The reported HR in the SQUIRE study was 0.84.14 We explored a range of HRs between 0.5 and 0.95 and examined the effect on the ICER. We ran the model multiple times under these scenarios, with variation in the cost of necitumumab.

Results

In the base case analysis, the survival benefit with the addition of necitumumab was 0.15 life-years. When adjusted for utility, the survival benefit with the addition of necitu-
mumab was 0.11 QALYs (6 quality-adjusted life-weeks). When necitumumab cost $850 or $1850 per cycle, the ICER approximated $100 000 per QALY or $200 000 per QALY, respectively (Table 2).

In the probabilistic sensitivity analyses, we established the cost ranges such that necitumumab is cost-effective at different costs per QALY threshold. By interpolating values in the cost acceptability curves (Figure 2), we determined that when necitumumab cost less than $563 or $1309 per cycle, there was a 90% likelihood that the ICER for adding necitumumab to gemcitabine and cisplatin would be less than $100 000 per QALY or $200 000 per QALY, respectively. When the cost of necitumumab was greater than $6628 per cycle, there was greater than 99% likelihood that the ICER exceeded $500 000 per QALY.

In analyses without adjustment for quality of life, for WTP values of $100 000 per life-year or $200 000 per life-year, adding necitumumab was cost-effective with a 90% likelihood at a cost of $7030 per cycle, respectively. The ICER was higher than $500 000 per life-year with a 99% likelihood if the cost was at least $7030 per cycle.
Figure 3 illustrates the sensitivity of the relationship between the cost of necitumumab and the ICER to the assumption about the overall survival HRs for necitumumab vs standard therapy. With an HR of 0.5 to 0.8, the ICER remained below $100,000 per QALY at all simulated costs of necitumumab.

Discussion

The current cost for new oncology agents entering the US marketplace usually exceeds $10,000 per month. For example, ceritinib, approved by the FDA in April 2014 for patients with ALK-positive metastatic lung cancer whose disease progressed during treatment with crizotinib, costs approximately $13,000 per month.37 Necitumumab is currently not approved by the FDA. However, given that the recently completed SQUIRE trial14 met the prespecified end points for clinical effectiveness, it may soon gain approval. Data regarding necitumumab have been reviewed by the Oncology Drug Advisory Committee (ODAC) and are now undergoing FDA review. We performed a prospective assessment to establish the cost for necitumumab such that necitumumab, when added to standard chemotherapy, would be considered cost-effective by conventional standards.

The current system of paying for cancer drugs provides little incentive for manufacturers and physicians to consider value when pricing and using drugs. Medicare and other payers have recently outlined payment system reforms designed to shift risk from payers to clinicians.36,39 Several alternative payment systems have been suggested. For example, bundled payments provide a specified amount of money to physicians to care for a patient with a particular disease, encouraging physicians to select less expensive drugs.40 Accountable care organizations have been developed to focus on covering the costs incurred by institutions that care for populations of patients and rewarding these institutions when they adhere to guidelines and demonstrate improved outcomes.40 Value-based insurance design and shared savings have been suggested, rewarding clinicians and patients for using cost-effective therapy.41-43 Another mechanism used in Germany is reference pricing, whereby all treatments are available to patients, but reimbursement to physicians is at the level of the lowest-cost option.44

These strategies all deserve consideration. However, they do not have direct effect on the cost of new cancer drugs entering the marketplace, which is more appropriately addressed by alternative pricing systems. Value-based pricing is a concept dating back to at least 1992,45,46 and with escalating cancer drug prices, it is becoming increasingly relevant today. Currently, elements of value-based pricing described in this study are used in the Netherlands, Norway, The United Kingdom, Sweden, Belgium, France, Denmark, Italy, and Germany.47 It is expected that more European Union countries will soon convert to value-based pricing.48

We also note the common practice of international reference pricing, ie, using the price of a drug in one country to negotiate the price in another country.47 It is therefore crucial that new drugs such as necitumumab entering the US marketplace are appropriately priced because there are implications not only for US payers but also possibly for global payers.

We recognize that the costs in our study were generated for necitumumab only and do not compare this to other commonly used oncology drugs. It is likely that many oncology drugs in clinical practice in the United States would fare poorly in cost-effectiveness analyses. For example, when added to platinum-doublet chemotherapy for patients with...
metastatic lung cancer, bevacizumab has an ICER of $560 000 per QALY.26 We also recognize that many cancer drugs, but not all, are priced above the value-based cut point. A recent study has suggested that many hematologic cancer drugs are cost-effective,49 but these conclusions have recently been challenged.50 A value-based pricing system could establish incentives for pharmaceutical manufacturers that lead to the development of drugs that are expected to provide a more meaningful clinical benefit.

We used reimbursement rates provided by Medicare, the largest public payer in the United States, which are generally lower than reimbursement rates for private insurers.51 Our model was developed using data from a clinical trial, and may not fully reflect the real-world experience of a population of patients. However, the ranges used in our sensitivity analyses will likely account for any variations between populations. Results reported in economic analyses are vulnerable to conflicts of interest.52 However, the funding source for our study (the National Institutes of Health) was neutral, thus limiting any potential conflicts. We note that alternative first-line chemotherapy regimens in practice include carboplatin-paclitaxel and cisplatin-docetaxel, both with similar levels of efficacy.5,9 As the platinum-doublet regimen was used in both arms of our model, any differences in costs would not affect the model results or value of necitumumab. We extrapolated utility data from an alternative study,21 as is common practice in modeling studies.25,26 However, our sensitivity analyses will account for any possible variations in actual utility.

The American Society of Clinical Oncology has proposed raising the bar for establishing the level of meaningful benefit in clinical trials.16 In this study, we demonstrate how adjustments in the HR in the SQUIRE trial14 would affect the cost-effectiveness of necitumumab. This analysis provides important data to guide the development of future clinical trials in advanced lung cancer to increase the value of newly approved agents. Given the lack of any alternative biologic agent to combine with chemotherapy, clinicians may incorporate necitumumab as part of the first-line standard of care.

Conclusions

The process for drug development is lengthy. It begins with laboratory studies in cell lines and mouse models. Phase I studies evaluate safety in humans. Phase 2 and 3 studies evaluate efficacy prior to potential approval. Postmarketing surveillance evaluates long-term adverse effects of a drug. But there is a crucial step in the process that is missing—an evaluation of cost and value. Cost-effectiveness analyses can help to establish drug prices that reflect the benefit they convey to patients and the health care system. Our study provides a value-based cost for necitumumab, and in doing so has implications for the global cost of this drug. This study also provides a framework for establishing a value-based cost of any new cancer drug entering the US marketplace. We are hopeful that this study and the recent attention on value in oncology set the stage for multiparty discussions to find solutions to the current pricing problem of cancer drugs. There is a desperate need to find appropriate prices for new treatments while maintaining incentives to drive game-changing innovations.


44. Kupferschmidt K. Germany moves to lower drug prices. CMAJ. 2011;183(2):E77-E78.


