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Cost Effectiveness of Nivolumab in Advanced Renal Cell Carcinoma

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Abstract

Background: In recent years, new drugs have been introduced for second-line treatment of advanced renal cell carcinoma (RCC). Nivolumab increases overall survival and is associated with less toxicity compared to everolimus in this setting according to the CheckMate 025 study. However, because of the high cost of nivolumab, there is a need to define its value by considering both efficacy and cost.
Objective: To estimate the cost effectiveness of nivolumab for second-line treatment of advanced RCC from the US payer perspective.
Design, setting, and participants: A Markov model was developed to compare the costs and effectiveness of nivolumab with those of everolimus and placebo in second-line treatment of advanced RCC. Health outcomes were measured in life-years (LYs) and quality-adjusted LYs (QALYs). Drug costs were based on 2016 Medicare reimbursement rates.
Outcome measurements and statistical analysis: Model robustness was assessed in univariable and probabilistic sensitivity analyses. We addressed the issue of the extensive duration of immunotherapy treatment among long-term survivors, which may or may not be approved by payers.
Results and limitations: The total mean cost per patient was $101 070 for nivolumab and $50 935 for everolimus. Nivolumab generated a gain of 0.24 LYs (0.34 QALYs) compared to everolimus. The incremental cost-effectiveness ratio (ICER) for nivolumab was $146 532/QALY versus everolimus and $226 197/QALY versus placebo. Limiting the maximal treatment duration of nivolumab to 2 yr reduced the ICER to $121 788/QALY versus everolimus. The analysis is limited by data availability and our assumptions.
Conclusions: Our analysis established that with a willingness-to-pay threshold of $100 000 to $150 000 per QALY, nivolumab is estimated to be cost-effective versus everolimus, but not cost-effective versus placebo.
Patient summary: We assessed the cost effectiveness of nivolumab in previously treated metastatic kidney cancer. In the USA, it would cost $146 532 to gain one quality-adjusted life-year with nivolumab versus everolimus, or $226 197 versus placebo. Nivolumab is considered cost-effective versus everolimus, but not versus placebo.

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1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of newly diagnosed cancer worldwide [1]. The survival of RCC patients has improved over time; however, the 5-yr survival rate for advanced disease is only 11% [2]. First-line treatment of advanced disease includes anti-angiogenesis therapy [3]. In recent years, new drugs have been introduced to the second-line setting and have provided hope for patients and their physicians. Approved treatments in the second-line setting include a number of different mechanisms for the anti-cancer effects, including tyrosine kinase inhibitors (sorafenib, axitinib, cabozantinib, levantinib), mTOR inhibitors (everolimus, temserolimus), and checkpoint inhibitors (nivolumab) [3]. Everolimus was approved for this setting because of superior disease-free survival (DFS) over placebo in the RECORD-1 trial [4]. The overall survival (OS) was similar between the groups, but may have been influenced by crossover in the trial design.

Nivolumab is an IgG4 antibody that causes immune checkpoint blockade by diminishing inhibitory signaling through the programmed death receptor-1 pathway [5]. Nivolumab was approved by the US Food and Drug Administration (FDA) in 2015 for this indication on the basis of the CheckMate 025 study [6]. This pivotal phase 3 study demonstrated a 5.4-mo improvement in median OS for nivolumab compared to everolimus (25.0 vs 19.6 mo). The toxicity profile was also improved, with patients typically suffering from asthenia and infrequently from immune-mediated side effects [7]. There is additional concern regarding the cost of nivolumab [8]. As cancer drug prices continue to rise, there is an increasing need to understand the economic value of the drug in terms of both cost and efficacy to guide coverage decisions by public and private payers. In 2015, the American Society of Clinical Oncology and the European Society of Medical Oncology issued value frameworks to tackle the issue of rising costs associated with cancer treatment.

A cost-effectiveness analysis (CEA) examines the amount of money required to extend life by 1 yr using a certain treatment. It also takes into account the quality of the life that is extended using a metric called a quality-adjusted life-year (QALY). This reflects the fact that extending the life of a person with advanced cancer might often not provide the same benefit as extending the life of a person in full health. Further details regarding CEAs are provided in Table 1.

The objective of this study was to estimate the cost effectiveness of nivolumab versus everolimus versus placebo for second-line treatment of advanced RCC from the US payer perspective.

2. Materials and methods

2.1. Model structure

The Markov model involved an initial decision on treatment with nivolumab or everolimus or placebo (Fig. 1). Patients then transitioned through different health states: stable/responsive (progression-free) disease; progressive disease; and death. Each model cycle represented 1 mo over a 10-yr time horizon. All patients started with stable, progression-free disease and either remained at that stage or transitioned to progressive disease or death. Once in the progressive stage, patients could remain in that stage or transition to death.

The primary outputs of the model included cost, life-years (LYs), and QALYs, which were used to calculate the incremental cost effectiveness ratio (ICER). The Markov model was implemented in TreeAgePro 2016 software (TreeAge, Williamstown, MA, USA), and statistical analyses were performed in Matlab 2016-B (MathWorks, Natick, MA, USA).

2.2. Mortality estimates

The overall mortality rate corresponded to the probability of transition to the death state, estimated as the cause-specific mortality from RCC and background mortality from other causes. The cause-specific mortalities for each treatment strategy were derived from the OS curves in the CheckMate 025 and RECORD-1 trials. For the nivolumab and everolimus arms, we used Plot Digitizer software (version 2.1; http://plotdigitizer.sourceforge.net) to extract the data points from each OS plot from the CheckMate 025 trial, and these data points were then used to fit parametric survival models.

We decided to incorporate a placebo arm into the model for a very specific reason. Traditionally, when cost-effectiveness models are developed, they should compare the new therapy to the previous standard of care (SOC). This strategy makes sense when the previous SOC became the standard as a result of proof that it was cost-effective, as occurs in the UK. However, the situation in the USA is different. Many expensive treatments have become the SOC without being proven to be cost-effective, and therefore create an expensive comparator arm, thus making the new treatment appear more cost-effective than it actually is [9]. The mortality estimate for the placebo arm was presumed to be similar to that for everolimus on the basis of the RECORD-1 trial. To

Table 1 – Explanation of health economic terms

Term	Explanation
Quality-adjusted life-year (QALY)	QALY expresses both the quality and quantity of life lived: 1 yr lived in perfect health is equal to 1 QALY; 1 yr lived in less than perfect health is equal to less than 1 QALY (perhaps 0.7 QALYs), depending on the actual quality of life measured using a variety of validated assessment tools
Incremental cost effectiveness ratio (ICER)	The final result of a cost-effectiveness analysis is the ICER, which is essentially the cost required to gain 1 QALY with a new treatment
Willingness to pay (WTP) threshold	WTP thresholds are used by some regulatory bodies, such as the National Institute for Health and Care Excellence (NICE), to decide whether a new treatment should be provided by the health care system. If the ICER is below this threshold, the treatment is considered good value and should be provided
Markov model	Markov models are used to model the effect of an intervention via probabilistic decision trees that demonstrate different courses of the disease and the total cost for a patient depending on the course. This is subsequently reproduced for a large cohort of theoretical patients to represent a large population of patients

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