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Cost Effectiveness of Nivolumab for Patients With Advanced, Previously-Treated Renal Cell Carcinoma in Scotland

PCN155

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Introduction

In previously-treated patients with advanced renal cell carcinoma (RCC), nivolumab (OPDIVO®, a programmed death-1 [PD-1] checkpoint inhibitor) was the first treatment to demonstrate a significant overall survival (OS) benefit in the Phase III randomised controlled trial (RCT) CheckMate 025.

In CheckMate 025 (data cut-off June 2015, minimum follow-up 14 months), nivolumab demonstrated a superior OS benefit compared with everolimus (HR: 0.73 [98.5% CI: 0.57, 0.93]).[1] Plimack *et al.* later reported 2-year OS rates of 52% with nivolumab and 42% with everolimus.[2] A summary of the OS rates observed in clinical trials for nivolumab in previously-treated patients with advanced RCC is presented in Table 1.

The improved OS observed for nivolumab-treated patients in CheckMate 025 is expected to translate into long-term OS benefits for a substantial proportion of patients. There is evidence supportive of an OS plateau in longer-term Phase I and II studies of nivolumab in previously-treated patients with advanced RCC,[3, 4] and across other tumour types.[6, 7]

This combination evidence has led clinicians in the UK to expect that some patients with advanced, previously-treated RCC will achieve long-term OS benefits comparable to the general population if treated with nivolumab.[8]

Table 1. OS rates in advanced, previously-treated RCC with nivolumab monotherapy

Study	Time (years)			
	2	3	4	5
CA209-003 (Phase I)	48%[3]	44%[3]	38%[4]	34%[4]
CA209-010 (Phase II)	42%–53%*[5]	33%–40%*[5]	29%[4]	NA
CheckMate 025 (Phase III)	52%[2]	NA	NA	NA

Key: NA, not available; OS, overall survival; RCC, renal cell carcinoma
Note: *Dependent on dose

Objectives

This study aimed to assess the cost effectiveness of nivolumab versus everolimus or axitinib as monotherapies for the treatment of advanced, previously-treated RCC from a Scottish National Health Service (NHS) perspective.

Methods

A previously-reviewed *de novo* state-transition model was adapted to the NHS Scotland perspective.[9] The model is based on the key clinical outcomes of disease progression and death. It is informed by CheckMate 025 data and published literature, with modelling assumptions clinically and economically validated for the NHS Scotland setting. The base case assumes efficacy and utility equivalence between everolimus (mTORi class) and axitinib (VEGFR-TKI class).

To extrapolate progression-free survival (PFS), a restricted cubic spline model using the odds functional form with 2 internal knots was fitted to reflect the change in hazards observed in CheckMate 025 PFS data. To extrapolate OS, a range of parametric survival models were fitted using the six parametric model forms recommended for consideration in the NICE DSU TSD 14 (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma).[10] Of these parametric models, the generalised gamma curves were found to provide the best relative statistical fit to the observed data via Akaike and Bayesian information criteria. For long-term survival, the expected immunomodulatory effect of nivolumab on OS was characterised by assuming 50% of patients in the nivolumab arm who survived to 5 years would have the same mortality rate as the age-matched general population as captured by ONS Life Tables for Scotland from this point onwards.[11]

To incorporate patient health-related quality of life (HRQL), EQ-5D data were taken from CheckMate 025. The UK EQ-5D tariff was used to value patient questionnaire responses. A mixed model equation was fitted to the CheckMate 025 EQ-5D data, including fixed covariates for progression status and treatment arm; a variable interacting treatment arm with progression status; and a random effect for subject.

Utility estimates used in the base-case model are 0.80 and 0.76 for progression-free patients, and 0.73 and 0.70 for progressed patients, for nivolumab and everolimus, respectively. The base-case model assumes utility equivalence between everolimus and axitinib.

Nivolumab is associated with an increased utility for both health states, which may be due to higher response rates, its immunotherapeutic mechanism of action and tolerable safety profile.

Costs used within the model reflect those incurred by NHS Scotland and social work services, and were taken from reference sources specific to the Scottish setting such as the Monthly Index of Medical Specialities (MIMS) and NHS reference costs.[12,13] Costs are described as comprising four components: treatment acquisition and administration, disease management, adverse event resolution and miscellaneous (which include the costs of subsequent treatment and end-of-life care).

Results

Table 2 presents the base-case results and pairwise analyses of incremental results, using treatment list prices as of December 2016. Nivolumab is shown to be a highly effective therapy versus axitinib and everolimus, with a predicted survival benefit of 2.09 life years (1.15 quality-adjusted life years [QALYs]).[9]

Table 2. Base-case results, pairwise analysis, nivolumab versus comparator, using list prices

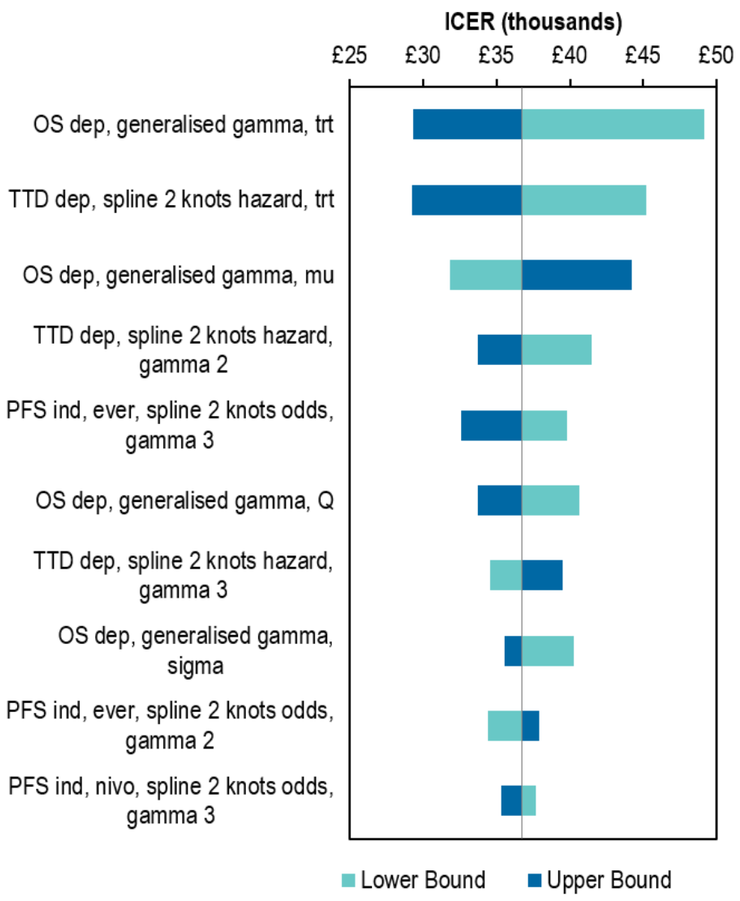
	Total			Incremental (nivo vs)			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Nivo	£92,475	2.84	4.64				
Axit	£50,300	1.69	2.55	£42,175	1.15	2.09	£36,685
Ever	£39,429	1.69	2.55	£53,045	1.15	2.09	£46,140

Key: axit, axitinib; ever, everolimus; ICER, incremental cost-effectiveness ratio; LY, life year; nivo, nivolumab; QALY, quality-adjusted life year

To test the sensitivity of base-case results of the primary comparison between nivolumab and axitinib to parameter uncertainty, comprehensive one-way and probabilistic sensitivity analyses (OWSA and PSA, respectively) were run.

While the OWSA results (Figure 1) show the base-case findings to be most sensitive to parameter uncertainty around OS and time-to-discontinuation model parameters, the ICER for nivolumab versus axitinib remained below £50,000 across all parameters tested, further illustrating the cost-effectiveness of nivolumab as a novel, end-of-life treatment option.

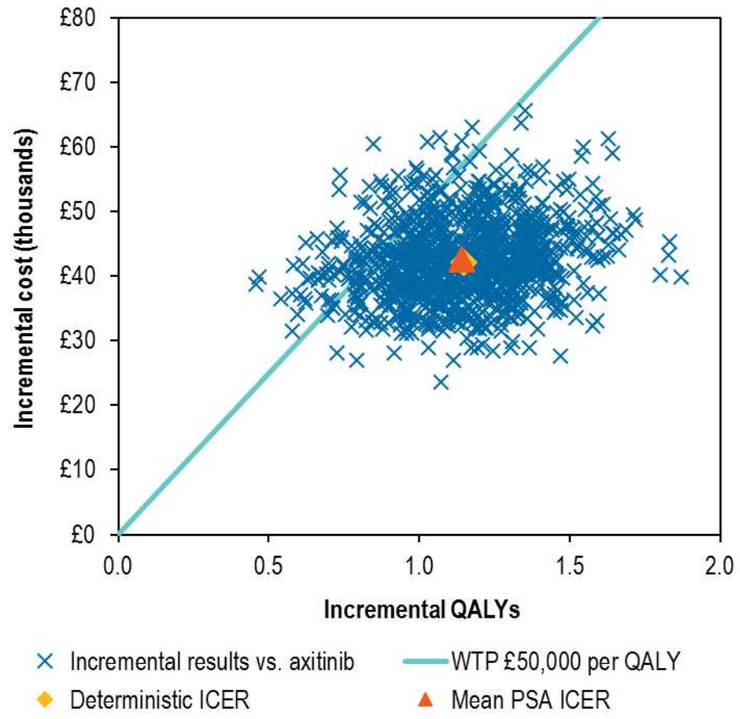
Figure 1. OWSA tornado diagram of 10 most influential parameters, nivolumab versus axitinib, list prices



Key: dep, dependent; ever, everolimus; ICER, incremental cost-effectiveness ratio; ind, independent; nivo, nivolumab; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TTD, time to discontinuation

PSA results indicate an 89% probability that nivolumab is a cost-effective alternative to axitinib at a willingness-to-pay threshold of £50,000 per QALY gained (Figure 2).

Figure 2. PSA scatterplot, nivolumab versus axitinib, list prices



Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay

Conclusions

The results show nivolumab to be a highly effective and cost-effective end-of-life treatment option for patients with advanced, previously-treated RCC in Scotland. In May 2017, the SMC recommended nivolumab for use in routine clinical practice, with a patient access scheme discount agreed. Therefore, nivolumab is now recommended for the treatment of patients with advanced, previously-treated RCC across the UK. As the first licensed PD-1 checkpoint inhibitor in RCC, nivolumab represents a notable advancement in current treatment options and is considered a step change in the management of this life-limiting condition.

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