COST-EFFECTIVENESS ANALYSIS OF NIVOLUMAB IN COMBINATION WITH IPILIMUMAB FOR THE FIRST-LINE TREATMENT OF ADVANCED/METASTATIC RENAL CELL CARCINOMA IN GREECE

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Diamantogiannis F[1], Viktoratos P[1], May JR[2], Malcolm B[2], Van de Wetering G[3], Ignacio T[3]

[1]Bristol-Myers Squibb, Athens, Greece; [2]Bristol-Myers Squibb, London, United Kingdom; [3]Pharmerit International, Rotterdam, the Netherlands

Introduction

Renal cell carcinoma

- Renal cell carcinoma (RCC) forms in cells in the lining of small tubules in the kidney that filter blood and remove waste products, and is the most common type of kidney cancer, accounting for almost 90% of all kidney malignancies[1]
- Approximately 75% of the diagnosed patients have intermediate- or poor-risk disease and, as a result, have worse outcomes than those with favourable-risk[2,3]
- An estimated 2,097 patients were diagnosed with RCC in Greece in 2018[4]
- In Greece, the majority of these patients receive systemic first-line treatment with sunitinib (SUN), while alternative options include pazopanib (PAZO), the combination of bevacizumab and interferon (BEV+IFN), temsirolimus (TEM), and most recently cabozantinib (CABO)
- However, despite available therapies, life expectancy for patients with metastatic RCC is short, with a 5-year survival rate of only 10-15%[5]

Nivolumab + ipilimumab

- Nivolumab in combination with ipilimumab (NIVO+IPI) is the first immuno-oncology combination to provide a substantial and sustained increase in overall survival (OS) for 1st line (1L) RCC patients versus the current standard of care, SUN, as demonstrated in the phase 3 randomised controlled CheckMate-214 study with a minimum of 30 months follow-up (NCT02231749)[6]
  - NIVO+IPI significantly reduced the risk of death by 34% (hazard ratio for death versus SUN: 0.66 (95% confidence interval [CI: 0.54-0.80], p<0.0001) and had a significantly higher objective response rate (42% versus 29%, p<0.001) compared with SUN, with 11% CR versus 1%, respectively[6]
  - NIVO+IPI was also associated with sustained improvement in health-related quality of life, with fewer symptoms for patients versus SUN[7]
  - NIVO+IPI was associated with a lower incidence of grade 3 and 4 treatment-related adverse events (AEs) than was observed with SUN (46% versus 63%)[6]

Objective

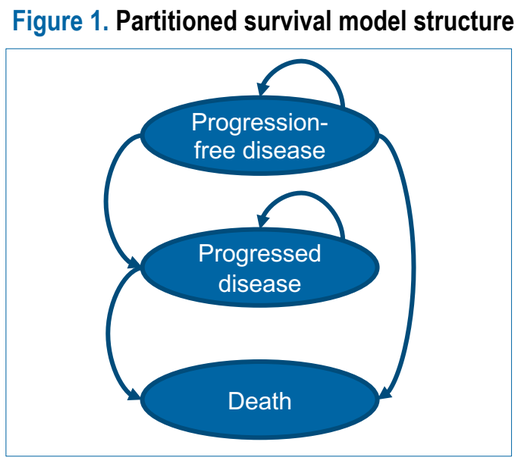
- To assess the cost-effectiveness of NIVO+IPI versus other systemic treatments in patients with previously untreated, advanced or metastatic renal cell carcinoma, from a Greek healthcare payer perspective

Methods

Model structure

- A partitioned survival model was developed to assess the cost-effectiveness of NIVO+IPI versus all relevant comparators in the Greek setting (SUN, PAZO, BEV+IFN, TEM, CABO)
- The model (Figure 1) comprises three health states (progression-free disease [PF], progressed disease [PD], and death); to better estimate costs, treatment-related costs were based on the duration of treatment as seen in CheckMate-214
  - This was done as patients in either arm of Checkmate-214 could discontinue therapy before or after disease progression

Figure 1. Partitioned survival model structure



Efficacy & survival

- Efficacy measures for NIVO+IPI versus SUN were based on the August 2017 data cut from the Checkmate-214 study, which has a minimum follow-up of 18 months[8]
- The efficacy of other comparators versus SUN was based on the results of a network meta-analysis (Table 1)
- Guidance from the National Institute for Health and Care Excellence (NICE) was followed to extrapolate NIVO+IPI's and SUN's progression-free survival (PFS), time to treatment discontinuation (TTD) and OS outcomes using dependent and independent parametric survival models, as well as spline models[9]
- The base case extrapolations (Table 2 and Figures 2 & 3) were determined according to statistical fit of extrapolated curves (Akaike and Bayesian information criterion), visual inspection, comparing median survival between the Kaplan-Meier (KM) curves and extrapolated curves (for OS, this was only done for SUN as median had not been reached for NIVO+IPI), and clinical plausibility

Table 1. Hazard ratios versus sunitinib

Treatment	PFS hazard ratio versus SUN (95% CI)	OS hazard ratio versus SUN (95% CI)
Pazopanib	1.18 (0.59-2.32)	0.88 (0.70-1.11)
Bevacizumab + interferon	1.49 (0.85-2.59)	1.14 (0.81-1.60)
Temsirolimus	1.68 (1.03-2.74)	0.98 (0.70-1.37)
Cabozantinib	0.48 (0.31-0.74)	0.80 (0.53-1.21)

CI, confidence interval; PFS, progression-free survival; OS, overall survival; SUN, sunitinib

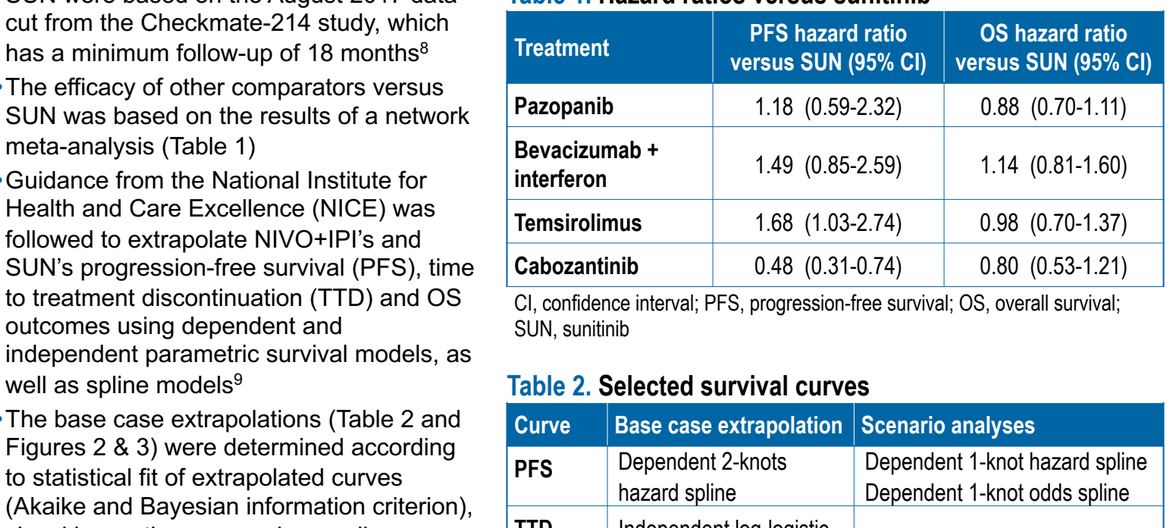
Table 2. Selected survival curves

Curve	Base case extrapolation	Scenario analyses
PFS	Dependent 2-knots hazard spline	Dependent 1-knot hazard spline Dependent 1-knot odds spline
TTD	Independent log-logistic	-
OS	Dependent log-normal	Dependent 1-knot normal spline Dependent 1-knot odds spline

PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

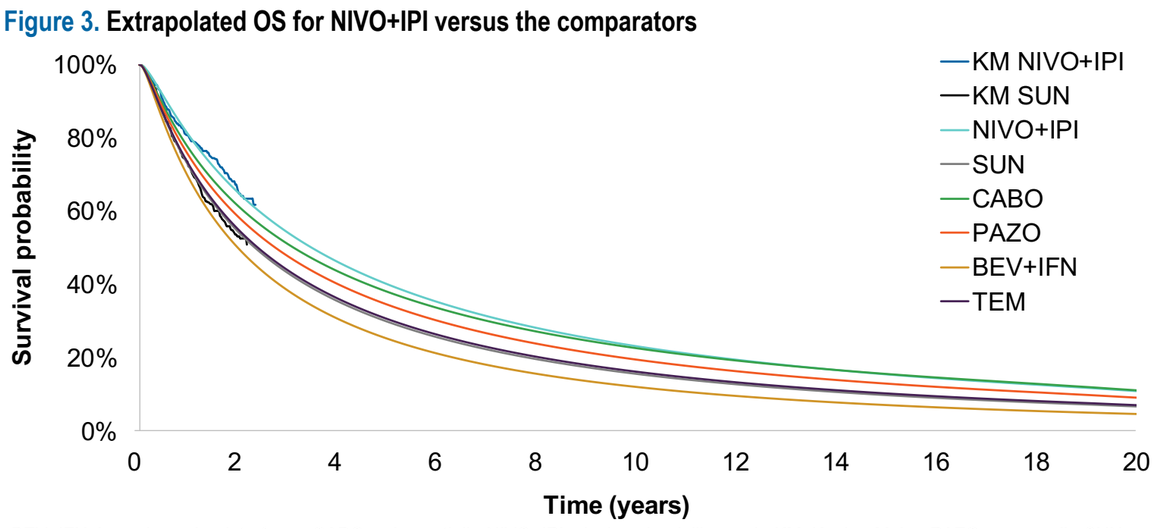
- TTD was used to inform time on treatment for NIVO+IPI and SUN, whereas PFS was used for other comparators due to lack of data in the literature

Figure 2. Extrapolated PFS for NIVO+IPI versus the comparators



BEV+IFN, bevacizumab + interferon; CABO, cabozantinib; NIVO+IPI, nivolumab + ipilimumab; KM, Kaplan-Meier; PAZO, pazopanib; SUN, sunitinib; TEM, temsirolimus;

Figure 3. Extrapolated OS for NIVO+IPI versus the comparators



BEV+IFN, bevacizumab + interferon; CABO, cabozantinib; NIVO+IPI, nivolumab + ipilimumab; KM, Kaplan-Meier; PAZO, pazopanib; SUN, sunitinib; TEM, temsirolimus;

Inputs, settings & outcomes

- Costs for drug acquisition, administration, grade 3-4 adverse events (AEs), monitoring, subsequent therapies, and terminal care were sourced from published prices, literature reviews, and Greek clinical expert input
- Treatment-specific resource use was based on Greek clinical expert input
- The incidence of AEs was derived from the CheckMate-214 study[8]
- Treatment-specific health state utility values were derived from the EuroQol 5-dimension (EQ-5D) questionnaire conducted in the CheckMate-214 study, using United Kingdom tariffs (Table 3)
- Quality-adjusted life year (QALY) losses due to AEs were not considered as these were assumed to be captured by the treatment-specific health state utilities

Table 3. Health state utilities

	PF	PD
NIVO+IPI	0.819	0.786
Other comparators	0.776	0.753

NIVO+IPI, nivolumab + ipilimumab; PF, progression free disease; PD, progressed disease

- An annual discount of 3.5% was applied to costs, in line with NICE guidelines[10]
- The model adopted a healthcare payer perspective, over a 20-year time horizon with a weekly cycle length
- Model outcomes included total costs, life years (LYs), quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs) and incremental cost-utility ratios (ICURs) to assess the cost-effectiveness of NIVO+IPI versus the comparators, as well as to represent all interventions on an efficiency frontier
- In addition to the base case analysis, deterministic sensitivity analyses, probabilistic sensitivity analyses and scenario analyses were conducted to assess robustness of the model structure and results

Results

Base case

- Over a time horizon of 20 years, treatment with NIVO+IPI was associated with substantially greater survival (incremental LYs: 0.758 to 2.153, depending on the comparator) and accrued quality-adjusted life years (incremental QALYs: 0.833 to 1.895, depending on the comparator) versus its comparators
- Total costs were highest for CABO, followed by NIVO+IPI. NIVO+IPI reduced subsequent treatment costs versus comparators
- The incremental results (Table 4) led to pairwise ICERs for NIVO+IPI ranging from €9,701 per LY gained (versus BEV+IFN) to €29,709 per LY gained (versus SUN), and ICURs ranging from €11,025 per QALY gained (versus BEV+IFN) to €32,209 per QALY gained (versus SUN); CABO was dominated by NIVO+IPI

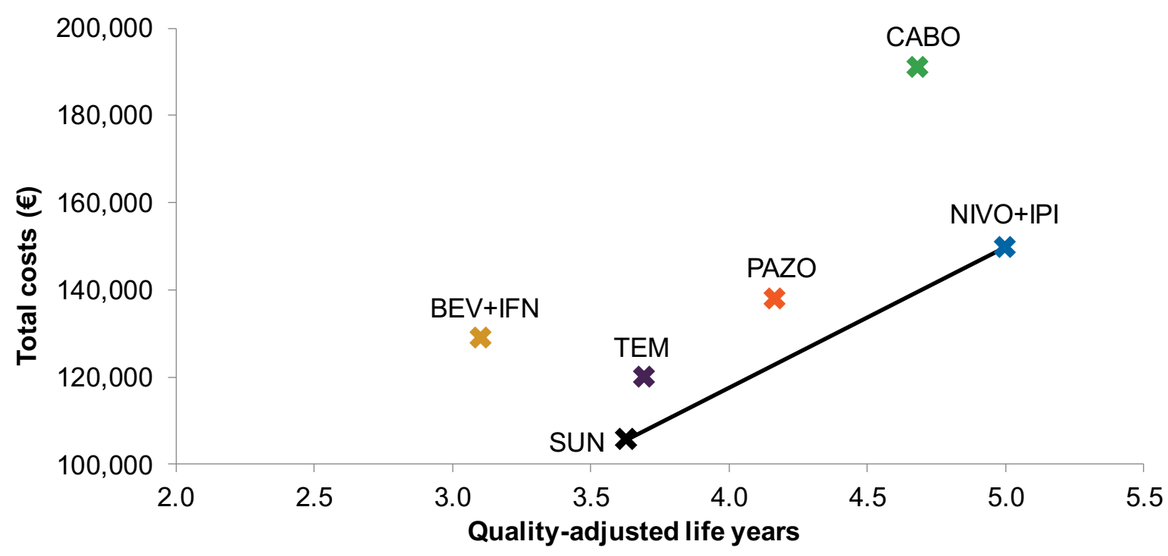
Table 4. Base case results (costs discounted)

Incremental outcomes (NIVO+IPI versus comparator)	SUN	PAZO	BEV+IFN	TEM	CABO
Incremental costs	€ 44,108	€ 11,926	€ 20,890	€ 29,758	-€ 41,345
Incremental life years	1.485	0.758	2.153	1.366	0.193
Incremental QALYs	1.369	0.833	1.895	1.306	0.316
ICER (€/LY) versus comparator	€ 29,709	€ 15,740	€ 9,701	€ 21,789	Dominant
ICUR (€/QALY) versus comparator	€ 32,209	€ 14,323	€ 11,025	€ 22,785	Dominant

BEV+IFN, bevacizumab + interferon; CABO, cabozantinib; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LY, life year; NIVO+IPI, nivolumab + ipilimumab; PAZO, pazopanib; SUN, sunitinib; TEM, temsirolimus; QALY, quality-adjusted life year

- The efficiency frontier consisted of SUN and NIVO+IPI (Figure 4)
  - As TEM and PAZO were associated with a higher ICUR versus SUN compared with NIVO+IPI, these treatments were extendedly dominated
  - As BEV+IFN and CABO were associated with higher costs and lower QALYs versus SUN and NIVO+IPI, respectively; these treatments were strongly dominated

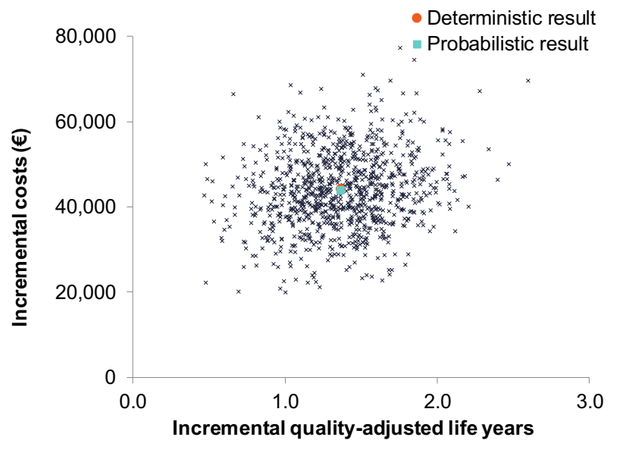
Figure 4. Efficiency frontier



Sensitivity analyses

- Deterministic sensitivity analyses showed that the uncertainty around the following parameters had most impact on the results: PFS and OS hazard ratios of NIVO+IPI versus its comparators, the proportion of patients that received a subsequent treatment (87% in the base case [11]), and health state utilities
- Probabilistic sensitivity analyses showed similar ICERs and ICURs as the deterministic base case, confirming the robustness of the model
- In the comparison versus SUN, all 1,000 probabilistic iterations were in the North-East quadrant on the incremental scatterplot (i.e. indicating more QALYs and LYs at higher costs for NIVO+IPI; Figure 5)
- NIVO+IPI was the most cost-effective treatment strategy from a willingness-to-pay threshold of €31,000 per QALY (Figure 6)

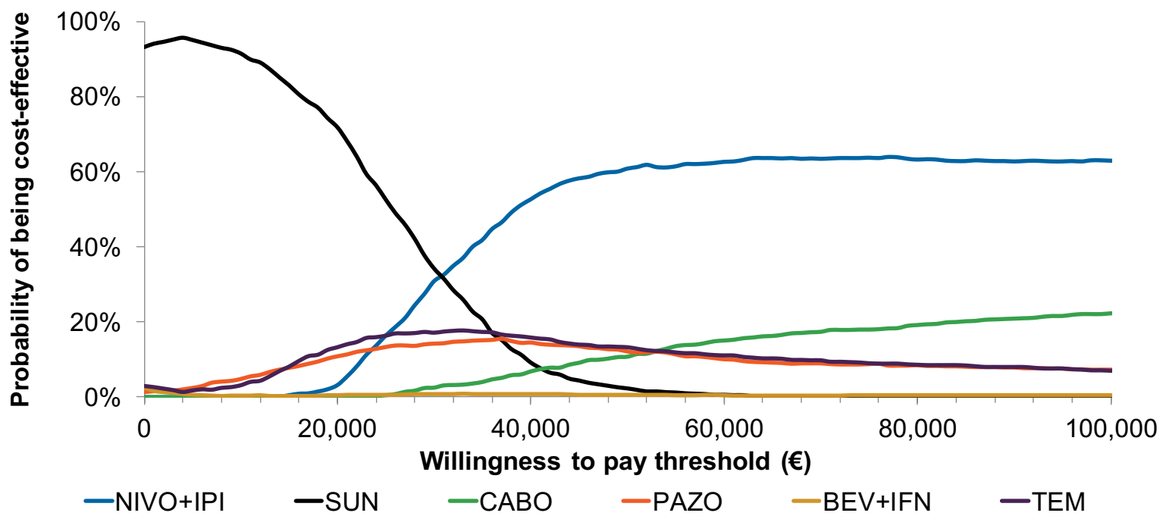
Figure 5. Incremental scatterplot of NIVO+IPI versus SUN



NIVO+IPI, nivolumab + ipilimumab; SUN, sunitinib
* Only the probabilistic mean is visible as it overlaps the deterministic mean

- The scenario analyses revealed that most of the scenarios did not result in a considerable deviation (>10%) from the base case ICUR. The most influential parameters were the time horizon, PFS and OS parameterisations and drug acquisition costs

Figure 6. Cost-effectiveness acceptability curve



BEV+IFN, bevacizumab + interferon; CABO, cabozantinib; NIVO+IPI, nivolumab + ipilimumab; PAZO, pazopanib; SUN, sunitinib; TEM, temsirolimus

Discussion

- The results of this pharmacoeconomic evaluation are of direct relevance to the Greek payer, as inputs were either based on Greek data or data from the CheckMate-214 trial. The model structure was developed according to NICE and local guidance, and sensitivity analyses showed that model outcomes were stable
- NIVO+IPI appears to be a valuable alternative to the current standard of care for 1L RCC in Greece, leading to a substantially longer life expectancy versus its comparators
- NIVO+IPI was associated with fewer AEs, which resulted in more accrued QALYs with fewer symptoms compared to SUN

Conclusions

- Over a lifetime horizon, the combination of NIVO+IPI is associated with a longer survival and more accrued QALYs compared to the other comparators
- Given the high unmet need of intermediate-poor prognosis patients in 1L RCC, NIVO+IPI could be considered a valuable and cost-effective treatment with ICURs ranging from €11,025 per QALY gained (versus BEV+IFN) to €32,209 per QALY gained (versus SUN), which is a value below twice the gross domestic product per capita in Greece

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- All authors contributed to and approved the presentation

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Email: fotios.diamantogiannis@bms.com