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Cost-effectiveness analysis of nivolumab + ipilimumab versus sunitinib in the first-line treatment of advanced or metastatic intermediate- or poor-risk renal cell carcinoma in Spain

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Introduction

Renal cell carcinoma

- Renal cell carcinoma (RCC) forms in cells in the lining of small tubules in the kidney that filter blood. RCC is the most common type of kidney cancer, accounting for 80-90% of all kidney malignancies.[1]
- An estimated 8,075 patients were diagnosed with RCC in Spain in 2018,[2] of which approximately 77% have intermediate- or poor-risk disease, and as a result, have worse outcomes than those with favourable-risk.[3]
- Despite available first-line RCC (1L RCC) therapies, life expectancy for patients with metastatic RCC is short, with a 5-year survival rate of only 10-15%,[4] indicating a high unmet need for a new treatment option.

Nivolumab + ipilimumab

- Nivolumab in combination with ipilimumab (NIVO+IPI) in the 1L RCC setting provides a substantial and sustained increase in overall survival (OS) versus the current standard of care, sunitinib (SUN), as demonstrated in the phase 3 randomised controlled CheckMate-214 study with a minimum of 30 months follow-up (NCT02231749).[5,6]
  - NIVO+IPI significantly reduced the risk of death by 34% (hazard ratio for death vs SUN: 0.66 [95% confidence interval: 0.54-0.80, p<0.0001]) and had a significantly higher objective response rate compared with SUN (42% vs. 29%; p<0.0001), with 11% complete responses (vs 1% with SUN).[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) was observed with NIVO+IPI than with SUN (46% versus 63%).

Objective

- To assess the cost-effectiveness of NIVO+IPI compared with SUN in 1L RCC patients from the healthcare payer perspective in Spain.

Methods

Population & model structure

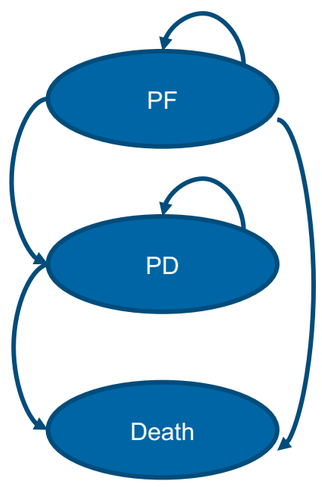
- A partitioned survival model with three health states was developed to assess the cost-effectiveness of NIVO+IPI versus SUN (progression-free disease [PF], progressed disease [PD], and death; Figure 1).
- The model also considers time to treatment discontinuation (TTD) to better estimate drug-related costs as patients in either arm of CheckMate-214 could discontinue therapy before or after disease progression (Table 1).

Table 1. Base case settings

Setting		Base case value
Perspective		Spanish healthcare system
Time horizon		Lifetime (40 years)
Cycle length		7 days, half-cycle correction applied
Discounting		3.0% for costs and effects based on Spanish guidelines[13]
Patient characteristics		Based on the CheckMate-214 trial
Extrapolation choices	*PFS*	Independent 2-knot odds spline
	TTD	Independent log-logistic
	OS	Dependent log-normal
Endpoint for estimates	*Costs*	TTD
	Utilities	TTD
Health state utilities	*PF*	0.854 for NIVO+IPI; 0.815 for SUN
	PD	0.829 for NIVO+IPI; 0.789 for SUN
Subsequent treatment		Distribution (Table 2) and mean duration of subsequent treatment from CheckMate-214

NIVO + IPI = nivolumab + ipilimumab; OS = overall survival; PD = progressed disease; PF = progression free; PFS = progression-free survival; SUN = sunitinib; TTD = time to treatment discontinuation

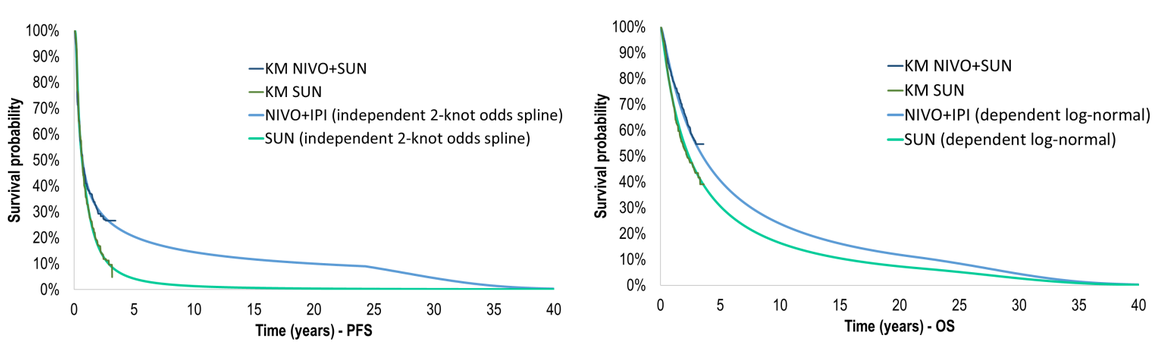
Figure 1. Model structure



Survival extrapolation

- Efficacy measures for NIVO+IPI versus SUN (progression-free survival [PFS] per investigator, TTD, and OS) were based on the August 2018 data cut from CheckMate-214 (minimum follow-up: 30 months).
- Guidance from the National Institute for Health and Care Excellence was followed to extrapolate outcomes using standard parametric and spline models.[8]
- The base case extrapolations (Table 1 and Figure 2) were determined according to statistical fit of extrapolated curves (Akaike and Bayesian information criterion), visual inspection, comparing median survival between the KM curves and extrapolated curves (SUN only for OS as median had not been reached for NIVO+IPI), and clinical plausibility.

Figure 2. Extrapolated PFS (left) and OS (right) for NIVO+IPI versus SUN



KM = Kaplan-Meier; NIVO+IPI = nivolumab + ipilimumab; OS = overall survival; PFS = progression-free survival; SUN = sunitinib

Inputs, settings & outcomes

- The maximum treatment duration for all model arms was 5 years, based on recommendations from a Dutch expert working group for immune-oncology therapy. The clinical experts indicated that it is unlikely for a patient to remain on the same treatment for more than 5 years.[9]
- Costs (Tables 3 and 4) were obtained from several sources:
  - Costs for AEs and drug acquisition were obtained from Isla[10] and CGCOF[11], respectively.
  - A discount was applied to all drug acquisition costs based on the Royal Decree-Law 08/2010; additionally, a confidential discount was applied to NIVO+IPI.
  - Costs for drug administration, monitoring, terminal care and subsequent therapies were obtained from ESALUD.[12]
- Resource use (Tables 3 and 4) was based on CheckMate-214 and clinical expert input.
- Grade 3-4 AEs with an incidence ≥20% for NIVO+IPI and SUN from CheckMate-214 were included.
- Treatment-specific health state utility values were derived from the EuroQol 5-dimensions 3-level (EQ-5D-3L) questionnaire conducted in the CheckMate-214 trial, using Spanish tariffs
- QALY losses due to AEs were not considered as these were assumed to be captured by the treatment-specific health state utilities.
- Model outcomes included total costs, life years (LYs), quality-adjusted life-years (QALYs), the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) to assess the cost-effectiveness of NIVO+IPI versus SUN.
- In addition to the base case analysis, deterministic and probabilistic sensitivity analyses were conducted.

Table 2. Distribution of subsequent treatments by 1L treatment received

	1L treatment received	
Subsequent treatment	NIVO + IPI, %	SUN, %
NIVO monotherapy	10	58
SUN	48	17
Axitinib	35	37
Cabozantinib	23	16
Everolimus	17	19
Pazopanib	36	10
Sorafenib	6	2

NIVO = nivolumab; NIVO + IPI = nivolumab + ipilimumab; SUN = sunitinib

Table 3. Unit costs and resource use per four weeks: terminal care

Terminal care	Costs (€)	One-off at end of life	
		Pts (%)	Res. use
Palliative care admission	650,56	30	7.00
Previous hospital admission	711,71	3	7.00
Home hospitalization	290,91	40	1.00
Previous hospital admission	711,71	4	7.00

BSC = best supportive care; NIVO + IPI = nivolumab + ipilimumab; Pts = patients; Res. = resource; SUN = sunitinib

Table 4. Unit costs and resource use: healthcare visits, monitoring tests and scans

Health state		Trt. initiation		Progression-free				Progressed disease			
				NIVO + IPI		SUN		Active Trt.		BSC	
Healthcare resource	Costs (€)	Pts (%)	Res. use	Pts (%)	Freq/ 4 wks	Pts (%)	Freq/ 4 wks	Pts (%)	Freq/ 4 wks	Pts (%)	Freq/ 4 wks
GP	24,50	50	2.00	25	1.00	25	1.00	25	1.00	100	1.00
Oncologist	87,50	100	2.00	100	1.00	100	1.00	100	1.00	50	1.00
Nurse	28,26	50	1.00	25	1.00	25	1.00	25	1.00	100	1.00
Hospital pharmacist	87,50	50	1.00	50	1.00	50	1.00	100	1.00	100	1.00
Emergency visit	76,80	0	0.00	7	1.00	7	1.00	0	0.00	0	0.00
Blood count	4,05	0	0.00	100	1.00	100	1.00	100	1.00	0	0.00
Complete met. panel	187,11	50	2.00	100	1.00	100	1.00	100	1.00	0	0.00
CT scan	248,18	50	2.00	33	1.00	33	1.00	33	1.00	0	0.00
Bone scintigraphy	235,11	0	0.00	3	1.00	3	1.00	0	0.00	0	0.00
Echocardiogram	86,67	75	1.00	0	0.00	0	0.00	0	0.00	0	0.00

BSC = best supportive care; CT = Computed tomography; Freq / 4wks = frequency per 4 weeks; GP = general practitioner; met. = metabolic; NIVO + IPI = nivolumab + ipilimumab; PTS = patients; Res. = resource; SUN = sunitinib; trt = treatment

Results

Base case

- Incremental survival was substantially higher for NIVO+IPI, with a 1.33 LY difference (total LYs: 5.81 versus 4.48, respectively) compared with SUN over a lifetime horizon (40 years), driven by the superior OS for NIVO+IPI seen in CheckMate-214.
- Treatment with NIVO+IPI was associated with greater total QALYs compared to SUN (total QALYs: 4.86 versus 3.54, respectively).
- While total treatment costs were higher for NIVO+IPI, cost savings were observed in terms of subsequent treatment and AEs (table 5).
- The resulting ICER was €28,886/LY gained, while the ICUR was €29,146/QALY gained for NIVO+IPI versus SUN (Table 5).

Table 5. Base case results (costs and QALYs discounted)

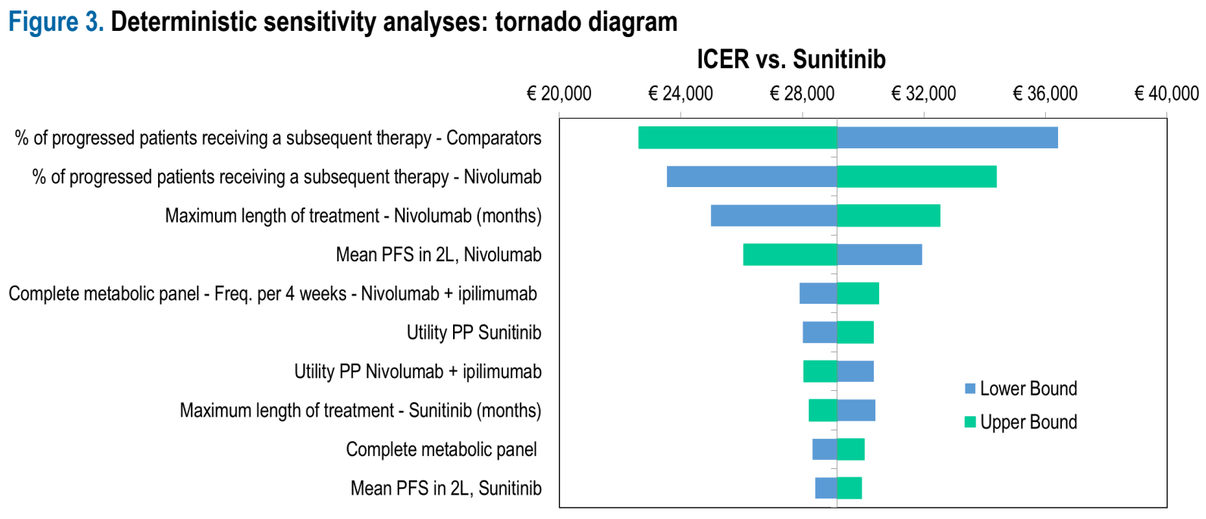
	NIVO+IPI	SUN	Incremental (NIVO+IPI versus SUN)
Costs	**€ 142,450**	**€ 104,450**	**€ 38,365**
With the following cost savings:			
Subsequent treatment costs	€ 36,585	€ 46,596	- € 10,011
AEs	€ 94	€ 326	- € 73
Terminal care	€ 1,515	€ 1,587	- € 233
LYs	**5.81**	**4.48**	**1.33**
Pre-progression	2.04	1.13	- 0.88
Post-progression	3.77	3.32	- 0.45
QALYs	**4.86**	**3.54**	**1.32**
Pre-progression	1.74	0.94	0.79
Post-progression	3.13	2.62	0.51
Disutilities due to AEs	-0.01	-0.02	- 0.01
ICER (cost/LY gained)			**€ 28,886/LY**
ICUR (cost/QALY gained)			**€ 29,146/QALY**

AE = adverse event; LY = life year; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; NIVO+IPI = nivolumab + ipilimumab; SUN = sunitinib

Sensitivity analyses

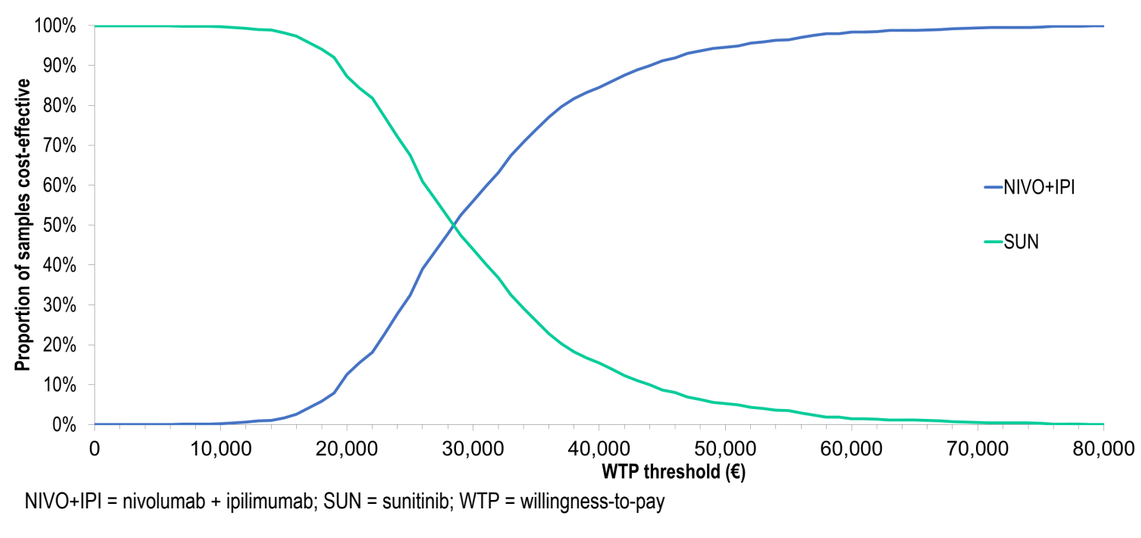
- Deterministic sensitivity analyses showed that the most influential parameters included: the proportion of patients that received subsequent treatment and maximum length of treatment (figure 4).
- Probabilistic sensitivity analyses showed similar ICERs and ICURs as the deterministic case, confirming the robustness of the model. The probability of NIVO+IPI being cost-effective was 98% at a willingness to pay threshold of € 60,000 per QALY (figure 5).

Figure 3. Deterministic sensitivity analyses: tornado diagram



PFS = progression-free survival; 2L = second-line; PP = post-progression

Figure 4. Cost-effectiveness acceptability curve



NIVO+IPI = nivolumab + ipilimumab; SUN = sunitinib; WTP = willingness-to-pay

Discussion

- The results of this pharmacoeconomic evaluation are of direct relevance to the Spanish payer, as inputs were based on Spanish expert data, Spanish publications, and data from the CheckMate-214 trial.
- NIVO+IPI presents a valuable alternative to the current standard of care (SUN) for 1L RCC in Spain, leading to a substantially longer life expectancy (1.33 years).
- NIVO+IPI was associated with fewer AEs and a better quality of life compared with SUN.
- Similarly, NIVO+IPI is cost-saving in terms of subsequent treatment and AE costs, compared with SUN.
- The sensitivity analyses confirmed the robustness of the deterministic results.
- Moreover, the combination of NIVO+IPI has already been mentioned as the preferred first-line treatment option in the EAU and ESMO guidelines, which is important given the increasing 1L RCC burden in industrialised countries.
- Once Spanish real-world evidence for the treatment of previously untreated 1L RCC patients with NIVO+IPI becomes available, the results presented in this analysis should be revisited to validated long term survival extrapolations.

Conclusions

- NIVO+IPI improves treatment options for Spanish patients with previously untreated 1L RCC.
- The combination of NIVO+IPI is associated with longer, better quality survival compared with SUN.
- Given the high unmet need in 1L RCC, NIVO+IPI could be considered a valuable alternative at an ICUR of € 29,146 per QALY gained versus SUN.

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