PCN170

Cost-effectiveness of nivolumab in combination with ipilimumab compared to sunitinib in the first-line treatment of advanced or metastatic intermediate- or poor-risk renal cell carcinoma in Italy

Di Rienzo P[1], Zarrelli L[2], Mennini FS[3], Marcellusi A[3], Bini C[3], Malcolm B[4], May JR[4], Gooden KM[5], Van de Wetering G[6], Smith van Carroll LE[7]

[1]Bristol Myers Squibb, Roma, Italy at the time the study was conducted, [2]Bristol Myers Squibb, Rome, Italy, [3]Faculty of Economics, Centre for Economic and International Studies (CEIS)-Economic Evaluation and HTA (EEHTA), University of Rome Tor Vergata, Rome, Italy, [4]Bristol-Myers Squibb, Uxbridge, UK, [5]Bristol-Myers Squibb, Lawrenceville, NJ, USA, [6]Pharmerit International, Rotterdam, Netherlands, [7]Pharmerit International, York, UK

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 11,947 patients were diagnosed with RCC in Italy 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) than was SUN (46% versus 63%).[5]

Objective

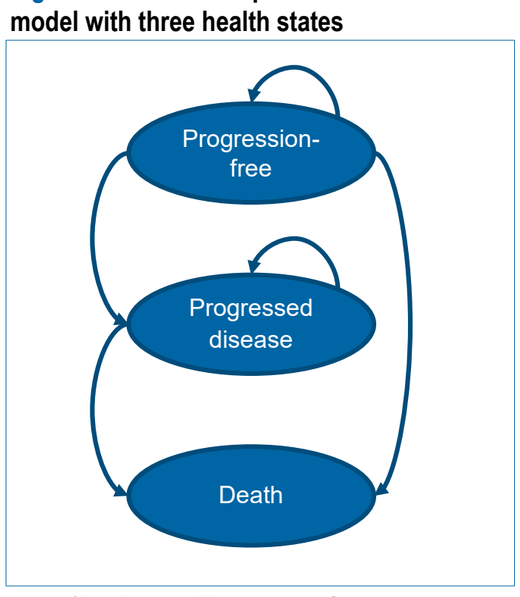
- To assess the cost-effectiveness of NIVO+IPI compared with SUN in 1L RCC patients from a healthcare system perspective in Italy.

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).

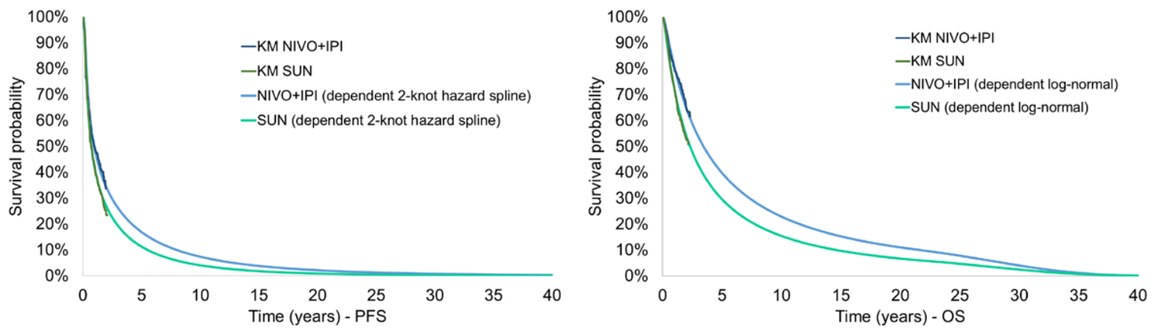
Figure 1. Structure of partitioned survival model with three health states



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

Table 1. Base case settings

Setting		Base case value
Perspective		Italian healthcare system
Time horizon		Lifetime (40 years)
Cycle length		7 days, half-cycle correction applied
Discounting		3.0% for costs and effects, in line with Italian guidelines[11]
Patient characteristics (age, gender, weight)		Based on the CheckMate-214 trial
Extrapolations	***PFS***	Dependent 2-knot hazard spline
	TTD	Independent log-logistic
	OS	Dependent log-normal
Endpoint for estimates	***Costs***	TTD
	Utilities	PFS
Health state utilities	***PF***	0.879 for NIVO+IPI; 0.858 for SUN
	PD	0.855 for NIVO+IPI; 0.834 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

Inputs, settings & outcomes

- Costs for drug acquisition, drug administration, AEs, monitoring and subsequent therapies were obtained from the published literature,[9] DRG tariffs and AIFA (Table 3).
- Resource use was based on CheckMate-214 and Italian clinical expert input.
- Grade 3-4 AEs with an incidence ≥1% for NIVO+IPI and SUN from CheckMate-214 were included.
- Treatment-specific health state utility values for PF and PD states were derived from CheckMate-214 using the EuroQol 5-dimensions 3-level (EQ-5D-3L) questionnaire using Italian tariffs.[10]
- Quality-adjusted life years (QALY) losses due to AEs were also included.
- Duration of subsequent treatment was based on CheckMate-214.

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

	1L treatment received	
Subsequent treatment	**NIVO + IPI**	**SUN**
NIVO monotherapy	0%	28.70%
SUN	25.90%	10.10%
Axitinib	15.50%	20.20%
Cabozantinib	7.80%	5.90%
Everolimus	6.30%	10.50%
Sorafenib	2.30%	1.00%

NIVO + IPI = nivolumab + ipilimumab; SUN = sunitinib

Table 3. Unit costs and resource use per four weeks in the model

Health state		Use per treatment arm in progression-free state		Progressed disease
Healthcare resource	**Costs**	**NIVO+IPI**	**SUN**	**Active treatment/BSC**
General practitioner	€ 20.66	1	1	1
Oncologist	€ 20.66	2	1	1
Full blood test	€ 38.47	2	1	1
Computed tomography scan	€ 134.37	0.32	0.32	0.32
Terminal care	€ 1,193.00	One-off end of life cost		

BSC = best supportive care; NIVO + IPI = nivolumab + ipilimumab; SUN = sunitinib

- Model outcomes included total costs, life years (LYs), QALYs, the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) to assess the cost-effectiveness of NIVO+IPI versus SUN.
- Deterministic and probabilistic sensitivity analyses were conducted to confirm robustness of the model structure and assumptions.
- Furthermore, two scenarios were conducted, investigating the required price reduction on NIVO+IPI to reach an ICUR of €30,000/QALY and €20,000/QALY.

Results

Base case

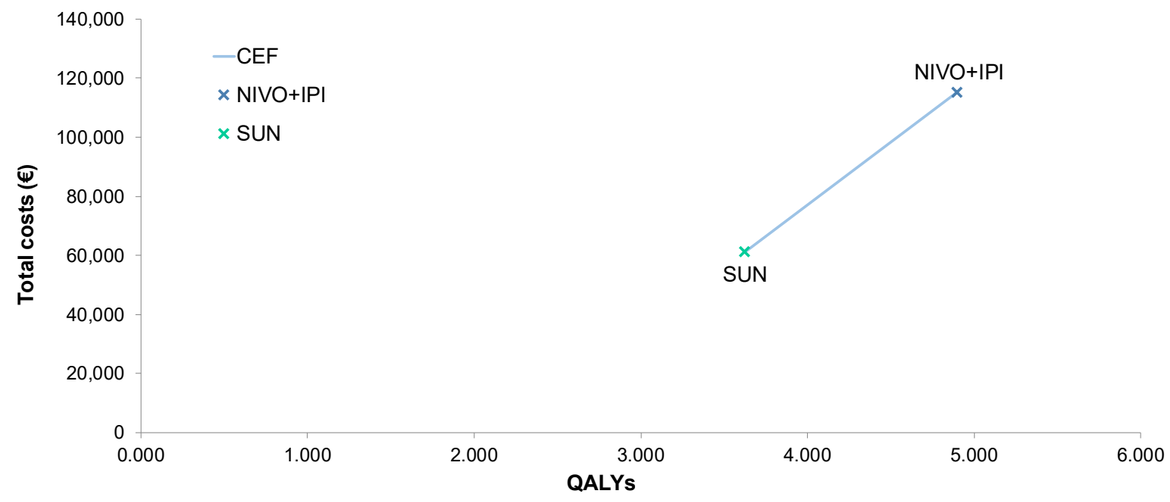
- Incremental survival was substantially higher for NIVO+IPI, with a 1.34 LY difference (Total LYs: 5.66 versus 4.32, respectively) compared with SUN over a lifetime horizon (40 years), driven by the superior OS for NIVO+IPI seen in CheckMate-214.
- Treatment with NIVO+IPI was associated with greater total QALYs compared with SUN (Total QALYs: 4.89 versus 3.63, respectively; incremental QALYs: 1.26).
- While total treatment costs were higher for NIVO+IPI, cost savings were observed in terms of subsequent treatment, AEs and terminal care (Table 4).
- The resulting ICER was € 40,143/LY gained, while the ICUR was € 42,521/QALY gained for NIVO+IPI versus SUN (Table 4); both treatments are represented on the efficiency frontier (Figure 3).

Table 4. Base case results (costs and QALYs discounted)

	NIVO+IPI	SUN	Incremental (NIVO+IPI versus SUN)
Costs	**€ 115,095**	**€ 61,226**	**€ 53,869**
With the following cost savings:			
Subsequent costs	€ 13,779	€ 29,591	-€ 15,812
AEs	€ 523	€ 690	-€ 167
Terminal care	€ 992	€ 1,040	-€ 48
LYs	**5.66**	**4.32**	**1.34**
Pre-progression	2.57	1.90	0.67
Post-progression	3.09	2.42	0.67
QALYs	**4.89**	**3.63**	**1.27**
Pre-progression	2.26	1.63	0.63
Post-progression	2.64	2.02	0.63
Disutilities due to AEs	-0.01	-0.02	0.01
ICER (cost/LY gained)			**€ 40,143/LY**
ICUR (cost/QALY gained)			**€ 42,521/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

Figure 3. Efficiency frontier

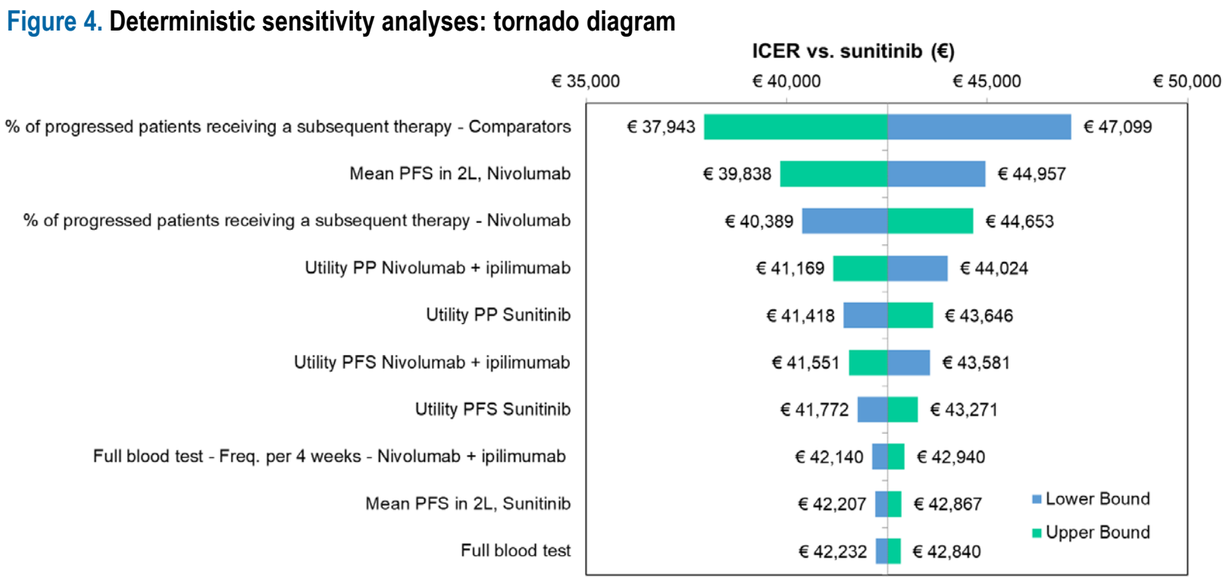


CEF = cost-efficiency frontier; NIVO + IPI = nivolumab + ipilimumab; QALYs = quality-adjusted life years; SUN = sunitinib

Sensitivity analyses

- Deterministic sensitivity analyses showed that the most influential parameters included the proportion of patients that received subsequent treatment, mean PFS for subsequent treatment of nivolumab and post-progression utilities (Figure 4).
- Probabilistic sensitivity analyses showed similar ICERs and ICURs as the deterministic case, confirming model robustness. The probability of NIVO+IPI being cost-effective was 86% at a willingness-to-pay threshold of € 60,000 per QALY.
- Price reductions of 9.91% and 30.06% for NIVO+IPI would be required to reach ICURs of € 30,000/QALY and € 20,000/QALY, respectively.

Figure 4. Deterministic sensitivity analyses: tornado diagram



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

Discussion

- The results of this pharmacoeconomic evaluation are of direct relevance to the Italian payer, as inputs were based on Italian expert data, Italian publications or data from the CheckMate-214 trial.
- The analysis shows that NIVO+IPI presents a valuable alternative to the current standard of care (SUN) for 1L RCC in Italy, leading to a substantially longer life expectancy (1.34 life 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, AE costs, and terminal care 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, ESMO and Italian AIOM guidelines,[12,13,14] which is important given the increasing 1L RCC burden in industrialised countries.
- The absence of relevant and accessible real-world Italian data to validate the long-term extrapolations is a limitation of this work.

Conclusions

- NIVO+IPI improves treatment options for Italian 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 should be considered a cost-effective and valuable treatment option in Italy at an ICUR of € 42,521 per QALY gained versus SUN.

References

1. Ljungberg, B. et al. (2015). EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol, 67, 913-924
2. World Health Organisation. (2018). The Global Cancer Observatory - Population fact sheets - Italy. [Available from: gco.iarc.fr/today/data/factsheets/populations/380-italy-fact-sheets.pdf]
3. Heng D. Y. et al. (2009). Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol, 27, 5794-5799
4. National Cancer Intelligence Network. (2014). Kidney cancer: survival report (Urological cancers SSCRG).
5. Motzer, R. J. et al. (2018). Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. New England Journal of Medicine, 378, 1277-1290
6. Motzer, R. J. et al. (2019). Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol, 20, 1370-1385
7. Cella, D. et al. (2019). Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. Lancet Oncol, 20, 297-310
8. Woods, B, et al. (2017). NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. [Available from http://www.nicedsu.org.uk]
9. Lazzaro, C, et al. (2013). An Italian cost-effectiveness analysis of paclitaxel albumin (nab-paclitaxel) versus conventional paclitaxel for metastatic breast cancer patients: the COSTANza study, Clinicoecon Outcomes Res, 5, 125-35
10. Scalone, L. et al. (2013). Italian Population-Based Values of EQ-5D Health States. Value in Health, 16, 814-822
11. Capri, S. et al. (2001). Guidelines for economic evaluations in Italy: recommendations from the Italian group of pharmacoeconomic studies. Drug information Journal, 35, 189-201

Acknowledgments

- Bristol-Myers Squibb (Princeton, NJ) and ONO Pharmaceutical Company Ltd. (Osaka, Japan)
- This study was supported by Bristol-Myers Squibb
- All authors contributed to and approved the presentation; medical writing and editorial assistance was provided by Laura Smith van Carroll, MMSc, of Pharmerit International, funded by Bristol-Myers Squibb

Presented at ISPOR Europe 2019; November 2–6, 2019; Copenhagen, Denmark

Email: Jessica.May@bms.com