PCN140

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

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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. It is the most common type of kidney cancer, accounting for 80-90% of all kidney malignancies.[1]
- Approximately 77% of the diagnosed patients have intermediate- or poor-risk disease and, as a result, have worse outcomes than those with favourable-risk.[2,3]
- In Switzerland, the majority of these patients receive systemic first-line treatment with sunitinib.
- Despite available therapies, life expectancy for patients with advanced or 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 plus ipilimumab

- Nivolumab in combination with ipilimumab (NIVO+IPI) in the 1L RCC setting provided a substantial and sustained increase in overall survival (OS) versus the current standard of care, sunitinib (SUN), as demonstrated in the phase 3 randomized 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 (42% vs. 29%, p=0.0001) compared 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 observed with SUN (46% versus 63%).[5]

Objective

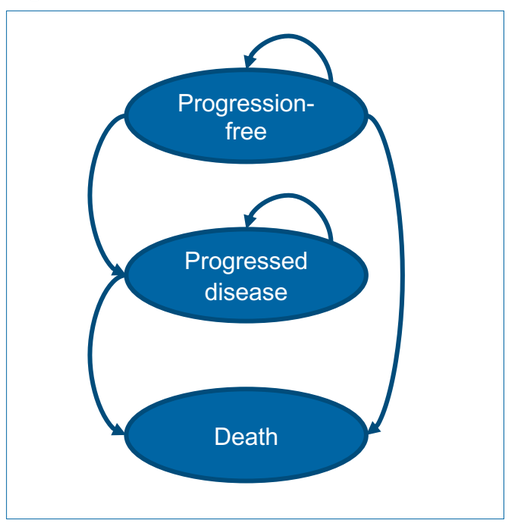
- To assess the cost-effectiveness of NIVO+IPI compared with SUN in 1L RCC patients from a healthcare system perspective in Switzerland.

Methods

Population & model structure

- The population of interest comprised patients with intermediate to poor diagnosis.
- Patient characteristics were based on the CheckMate 214 trial (average age, male/female distribution)[5] and Bundesamt für Gesundheit data (average weight).[8]
- A partitioned survival model was developed (Figure 1), comprising three health states (progression-free disease [PF], progressed disease [PD] and death).
- The model also considers time to treatment discontinuation (TTD) as patients in either arm of Checkmate 214 could discontinue therapy before or after disease progression.

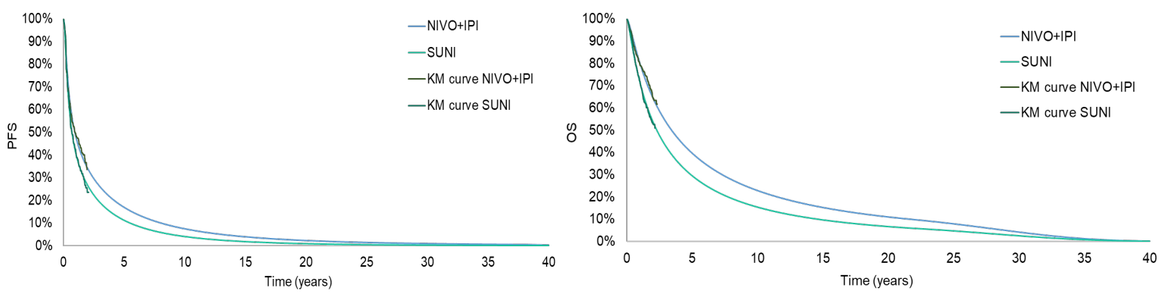
Figure 1. Partitioned survival model structure



Efficacy & Survival

- Efficacy measures for NIVO+IPI versus SUN (progression-free survival; PFS per investigator, TTD, and OS) were based on the September 2017 data cut from CheckMate-214 (minimum follow-up: 18 months).[5]
- Guidance from the National Institute for Health and Care Excellence was followed to extrapolate outcomes using standard parametric and spline models.[9]
- The base case extrapolations (Figure 2 and Table 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 analyses have been performed from a Swiss healthcare perspective, accounting for all direct costs to the healthcare system.
- Drug acquisition costs were obtained from the price list published by the Swiss Federal Office of Public Health (Positive Drug List 2018).[10]
- The maximum treatment duration for all model arms was 5 years, as treatment after this time period was considered unlikely.[11]
- Unit costs for drug administration and disease management were derived from Tarmed Browser 1.09[12] and the Quick Analysis List 2018.[13]
- Disease management resource use (outpatient visits, monitoring tests & scans and terminal care) was based on clinical expert input. (Mischo A, personal communication, April 10th, 2018).

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

	1L treatment received	
Subsequent treatment	**NIVO + IPI**	**SUN**
NIVO monotherapy	8%	51%
SUN	51%	15%
Pazopanib	33%	8%
Axitinib	32%	37%
Cabozantinib	15%	10%
Everolimus	14%	18%
Sorafenib	5%	2%

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

- Duration and distributions of subsequent treatment was based on CheckMate-214 and literature (Tables 1 and 2).
- Grade 3-4 adverse events (AEs) with an incidence ≥20% for NIVO+IPI and SUN from CheckMate-214 were included.[5] AE costs were derived from the Swiss DRG 2018.
- Treatment-specific health state utility values were derived from the EuroQol 5-dimension (EQ-5D-3L) questionnaire using French tariffs[14], as currently no Swiss-specific value set is available.
- Quality-adjusted life year (QALY) losses due to AEs were also included.
- An annual discount of 3% was applied to costs and utilities, based on guidance of the World Health Organization (WHO).[15]
- The model's time horizon was 40 years, which is equal to a lifetime horizon (less than 1% of patients alive).
- The cycle length was 7 days, with a half-cycle correction applied to increase model accuracy.

Table 2. Base case settings

Source / Setting		Base case value
Time horizon		40 years (lifetime)
Cycle length		7 days, half-cycle correction applied
Discounting		3% for costs; 3% for effects
Patient characteristics (age, gender, weight)		Based on the CheckMate 214 RCT (average age, male/female distribution) and Bundesamt für Gesundheit data (average weight)
Survival extrapolation	**PFS**	Dependent 2-knots hazard spline
	TTD	Independent log-logistic
	OS	Dependent log-normal
Health state utilities	**PF**	0.810 for NIVO+IPI; 0.758 for SUN
	PD	0.759 for NIVO+IPI; 0.724 for SUN
Subsequent treatment		Subsequent treatment distribution is informed by the CheckMate 214 RCT (Table 1). Subsequent treatment duration was derived from the CheckMate 025 RCT[16] and Sandmeier et al. (2018)[17] publication.
Resource use		Based on expert opinion
Unit costs	**Drug acquisition costs**	Derived from positive drug List 2018, published by the Swiss Federal Office of Public Health
	Drug administration & disease management costs	Derived from Tarmed Browser 1.09 & Quick Analysis List 2018
	AE costs	Derived from Swiss DRG 2018

AE: adverse event; NIVO+IPI: nivolumab + ipilimumab; OS: overall survival; PD: progressed disease ; PF, progression free; PFS: progression-free survival; RCT, randomized controlled trial; TTD: time to treatment discontinuation

- 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.
- In addition to the base case analysis, deterministic sensitivity analyses, probabilistic sensitivity analyses and scenario analyses were conducted to confirm robustness of the model structure and assumptions.

Acknowledgments

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- All authors contributed to and approved the presentation.

Results

Base case

- Incremental survival was substantially higher for NIVO+IPI, with a 1.35 LY difference (Total LYs: 5.67 versus 4.32, respectively) compared to SUN over a lifetime horizon (40 years; Table 3).
- Treatment with NIVO+IPI was associated with greater total QALYs compared to SUN (Total QALYs: 4.41 versus 3.14, respectively), resulting in an incremental QALYs gain of 1.27.
- Though total treatment costs were higher for NIVO+IPI; cost savings were observed in terms of subsequent treatment, AEs and terminal care.
- The corresponding ICER and ICUR amounted to CHF 72,621/LY and CHF 77,313/QALY, respectively.

Table 3. Base case results (costs and effects discounted)

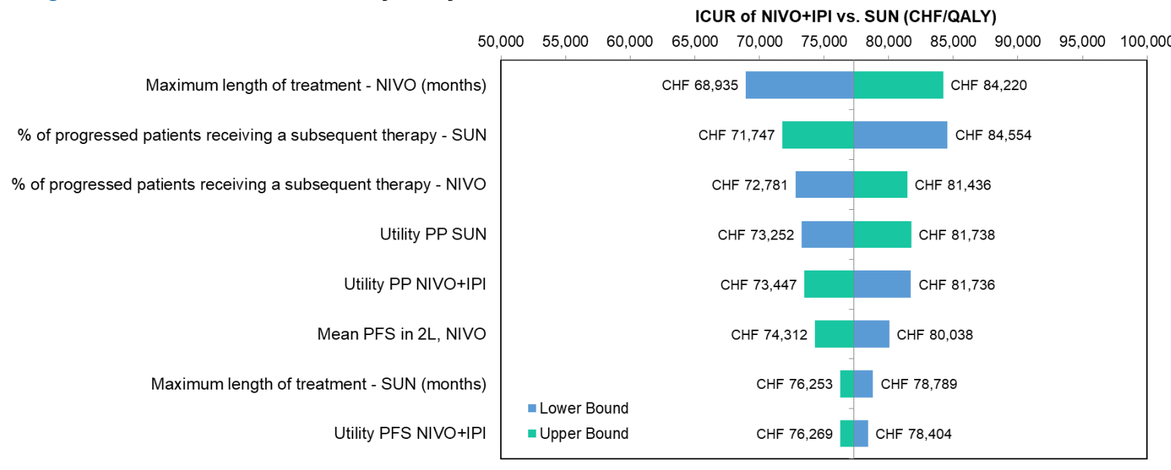
Setting	NIVO+IPI	SUN
Total costs	**CHF 216,148**	**CHF 118,428**
Drug acquisition	CHF 144,047	CHF 45,092
Drug administration	CHF 1,879	CHF 0
Treatment initiation	CHF 186	CHF 186
Disease management (PF)	CHF 16,128	CHF 8,540
Disease management (PD)	CHF 22,031	CHF 16,926
Subsequent treatment costs	CHF 28,053	CHF 41,881
Terminal care	CHF 917	CHF 961
AEs	CHF 2,906	CHF 4,841
Total QALYs	**4.407**	**3.143**
Pre-progression	1.803	0.842
Post-progression	2.613	2.326
Disability due to AEs	-0.009	-0.025
Total LYs	**5.669**	**4.323**
Pre-progression	2.226	1.111
Post-progression	3.443	3.213
Pairwise ICER versus comparator	-	**CHF 72,621**
Pairwise ICUR versus comparator	-	**CHF 77,313**

AE: adverse event; CHF: Swiss francs; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; LYs: life years; NIVO+IPI: nivolumab + ipilimumab; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life year; SUN: sunitinib

Sensitivity analyses

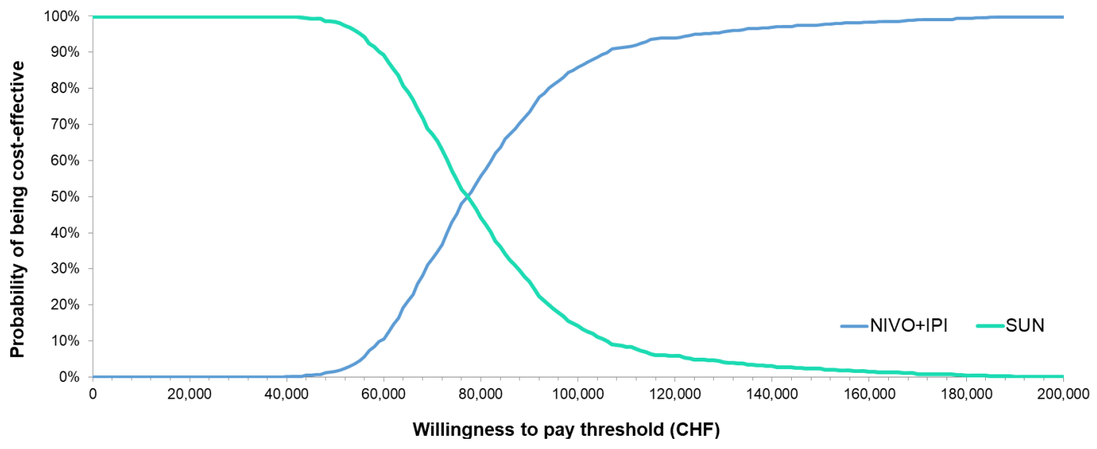
- Deterministic sensitivity analyses showed that the parameters with the largest uncertainty included the maximum length of treatment of nivolumab, the proportion of patients that received a subsequent treatment and health state utilities in the post-progression phase (Figure 3); none of the parameters tested resulted in an ICUR that exceeded the WTP treshold of CHF 100,000.
- The PSA confirmed robustness of the model results, with NIVO+IPI having an 86% probability of being cost-effective at a willingness-to-pay threshold of CHF 100,000 (Figure 4).
- The scenario analyses revealed that the most influential parameters were shortening the time horizon to 10 years (53% increase in ICUR from base case) and assuming no maximum treatment duration (74% increase in ICUR from base case). Using alternative PFS, OS and TTD distributions, assuming a German tariff for utilities (instead of a French tariff) and assuming alternative subsequent treatment distributions (based on expert opinion instead of CheckMate 214) all had little effect on the ICUR (less than 5% deviant from base case).

Figure 3. Deterministic sensitivity analysis



2L: second line; CHF: Swiss francs; NIVO: nivolumab; NIVO+IPI: nivolumab + ipilimumab; PFS: progression-free survival; PP: post-progression; SUN: sunitinib

Figure 4. Cost-effectiveness acceptability curve



CHF: Swiss francs; NIVO: nivolumab; NIVO+IPI: nivolumab + ipilimumab; SUN: sunitinib

Discussion

- NIVO+IPI was approved by Swissmedic for the treatment of patients with previously untreated advanced renal cell carcinoma intermediary/poor risk profile on July 26th, 2018.
- In this study, OS was based on the 18-month database lock of CheckMate-214, which resulted in the selection of a dependent log-normal curve for extrapolation. Recently published lifetime OS data of the 37-month database lock confirms the choice of a log-normal curve for OS and confirms the robustness of the lifetime OS estimates of the 18-month database lock.[18-19]
- NIVO+IPI leads to a substantially longer incremental life expectancy (1.35 LYs) compared with SUN. Also, NIVO+IPI is associated with fewer AEs and a better quality of life compared to SUN.
- The sensitivity analyses confirmed the robustness of the deterministic results.

Conclusions

- Driven by an increased and sustained OS benefit, NIVO+IPI results in an ICUR of CHF 77,313/QALY when compared with sunitinib for 1L RCC patients in Switzerland.
- The combination of NIVO+IPI is associated with longer, better quality survival compared to SUN.
- NIVO+IPI provides a valuable and cost-effective treatment option for this disease area with high unmet need for Swiss patients.

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