PCN214

COST-EFFECTIVENESS ANALYSIS OF NIVOLUMAB IN COMBINATION WITH IPILIMUMAB VERSUS SUNITINIB FOR THE FIRST-LINE TREATMENT OF INTERMEDIATE- TO POOR-RISK ADVANCED RENAL CELL CARCINOMA IN FRANCE

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Introduction

Renal cell carcinoma

- Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for around 80% of all kidney malignancies.[1] In France, the incidence of RCC was estimated to be 13,000 patients in 2018.[2]
- In the advanced setting of the disease, the International Metastatic RCC Database Consortium (IMDC) criteria are used as a prognostic model, and treatment decisions are based on this risk score (favourable, intermediate, poor).
- Around 82% of advanced RCC first-line (1L) patients have intermediate- to poor-risk disease.[3]
- In France, sunitinib (SUN) is prescribed the most of all recommended first-line RCC therapies (>60%).[4]
- Despite available first-line therapies, a high unmet medical need exists for a treatment that extends survival with improved quality of life relative to the standard of care, especially for patients with intermediate- to poor-risk disease.

Nivolumab + ipilimumab in advanced 1L RCC

- Nivolumab in combination with ipilimumab (NIVO+IPI) is the first immuno-oncology regimen to substantially increase overall survival (OS) for advanced 1L RCC patients versus the current standard of care, SUN, that is sustained over the long term, 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 [CI: 0.54-0.80], p<0.0001) and had a significantly higher objective response rate (42% versus 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]
  - The safety profile of NIVO+IPI was consistent with that in multiple tumor types; a lower incidence of grade 3 and 4 treatment-related adverse events (AEs) was observed with NIVO+IPI than with SUN (46% versus 63%).[6]

Objective

- To assess the cost-effectiveness and the cost-utility of NIVO+IPI compared with SUN in advanced 1L RCC in France.

Methods

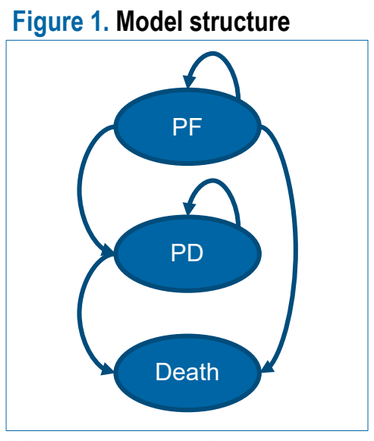
Model structure choices and population of analysis

- A partitioned survival model was developed to assess the cost-effectiveness of NIVO+IPI versus SUN, with three health states (progression-free disease [PF], progressed disease [PD] and death; Figure 1). Model choices and patient characteristics are presented in Table 1.

Table 1. Model choices and population of analysis

Setting	Base case value
Perspective	French all-payer, as per the French guidelines for health economic evaluations[8]
Time horizon	20 years
Cycle length	7 days, half-cycle correction applied
Discounting	4.0% for both costs and effects, as per the French guidelines for health economic evaluations[8]
Patient characteristics	Age (60.5 years) and gender (72.6% male) from CheckMate-214,[5] as these are similar for the French population. Weight (79.0 kg) from French patients of CheckMate-214

Figure 1. Model structure



PD progressed disease; PF progression-free

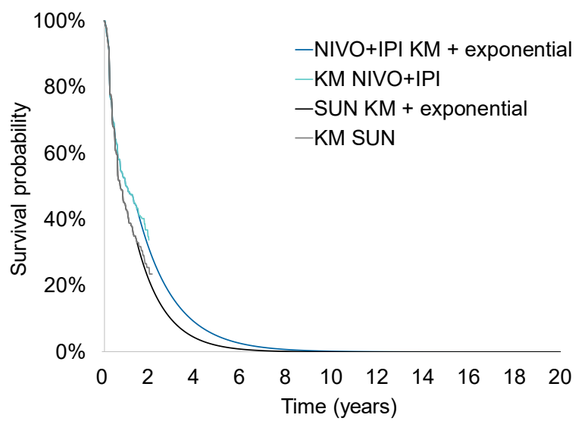
Survival extrapolations

- Efficacy measures for NIVO+IPI versus SUN were based on CheckMate-214:
  - Progression-free survival (PFS) was based on the August 2017 database lock (DBL),[5] as Independent Regulatory Review Committee-assessed PFS was not available for the August 2018 DBL.
  - OS was based on the August 2018 DBL with a minimum of 30 months follow-up.[6]
- Parametric extrapolations were fitted per guidelines from the NICE Decision Support Unit,[9] supplemented by criterion assessment for OS as described by Tremblay et al.[10]

PFS

- Independent models were fitted as the proportional hazards assumption was rejected due to multiple crossings of the log-cumulative hazards curves.
- While spline models provided the best statistical fit to CheckMate-214, they lacked clinical validity when compared to external data for SUN;[11,12] standard parametric models did not provide a good fit to the KM-curves as observed in the first 1.5 years of CheckMate-214.
- Therefore, a piecewise approach was implemented using Kaplan-Meier (KM) data up to 17 months, followed by an independent exponential extrapolation (Figure 2).
- The long-term PFS extrapolation of SUN was consistent with data available in the literature.[11,12]
- Scenario analyses explored alternative extrapolations post-17 months (Gamma and Weibull).

Figure 2. KM curves for PFS (August 2017 DBL) and extrapolation for NIVO+IPI versus SUN

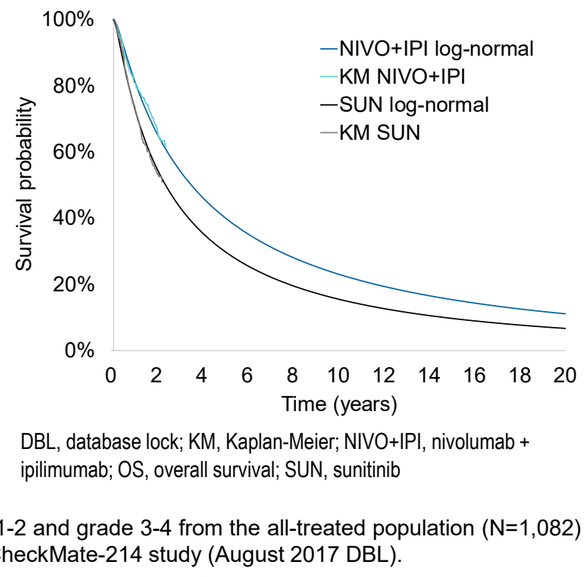


DBL, database lock; KM, Kaplan-Meier; NIVO+IPI, nivolumab + ipilimumab; PFS, progression-free survival; SUN, sunitinib

OS

- A single dependent model was fitted to both KM curves as the proportional hazards assumption could not be rejected; the log-normal and 1-knot normal spline provided the best statistical fit.
- Validation of the SUN OS extrapolation was not possible; data identified in a literature search only returned sources published prior to the introduction of subsequent treatments used in the SUN arm of CheckMate-214 (NIVO monotherapy and cabozantinib).
- Methodology by Tremblay et al.,[10] namely comparison of the marginal OS gain in the pre-extrapolation and extrapolated time periods, was then used and confirmed the appropriateness of the log-normal and 1-knot normal spline extrapolations.
- The base case analysis used a log-normal distribution for OS (Figure 3) and a scenario was conducted using a 1-knot normal spline distribution.

Figure 3. KM curves for OS (August 2018 DBL) and extrapolation for NIVO+IPI versus SUN



DBL, database lock; KM, Kaplan-Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; SUN, sunitinib

Adverse events

- AEs included in the model reflect all-cause AEs of grade 1-2 and grade 3-4 from the all-treated population (N=1,082) with an incidence ≥20% in either treatment arm from the CheckMate-214 study (August 2017 DBL).
- Overall, 38 AEs (19 grade 1-2 AEs and 19 grade 3-4 AEs) were considered in the model.

Health state utility values

- Health state utility values were derived from the EuroQol 5-dimension (EQ-5D-3L) questionnaires collected in the CheckMate-214 study using a mixed model for repeated measures and French utility tariffs (Table 2).[13]
- In the PF health state, utility values were treatment-specific, and no AE utility decrements were considered as these were assumed to be captured by the treatment-specific health state utilities.
- In the PD health state, utility values were not treatment-specific.

Table 2. Health state utilities

Health state	NIVO+IPI (N=425)	SUN (N=422)
PF utility (SE) (95% CI)	0.770 (0.011) (0.748; 0.793)	0.723 (0.012) (0.701; 0.746)
PD utility (SE) (95% CI)	0.689 (0.010) (0.670; 0.708)	

CI, confidence interval; NIVO+IPI, nivolumab + ipilimumab; PD, progressed disease; PF, progression-free; SE, standard error; SUN, sunitinib

Costs

- Drug acquisition costs considered the latest published price (Table 3).[14]
- All other costs were French-specific, derived from literature, and expressed in €2017 (Table 5); AE costs were derived from Mickisch et al.[15]
- A €36.75 round trip travel cost was applied to intravenous drug administrations, oncologist visits and management of grade 3-4 AEs; a €19.40 one-way travel cost was applied for terminal care.
- Total subsequent treatment costs were calculated based on the distribution of treatments per arm in CheckMate-214 (Table 4).
- In CheckMate-214, 49% of the patients received a subsequent systemic treatment, which was applied in the model.

Table 3. Drug acquisition costs

Treatment and dosing applied in the model	Cost per mg or box‖	Cost per 4 weeks
NIVO (10 mg/ml) induction phase*	€10.34	€3,302.16¶
NIVO (10 mg/ml) maintenance phase†		€4,962.36
IPI (5 mg/ml)‡	€58.61	€6,239.24¶
SUN§	€4,389.51	€2,926.45
Subsequent treatment after NIVO+IPI	NA	€2,494.31
Subsequent treatment after SUN	NA	€2,825.63

IPI, ipilimumab; NA, not applicable; NIVO, nivolumab; SUN, sunitinib
*Induction phase: 3 mg/kg every 3 weeks for the first four doses; †Maintenance phase: 240 mg/kg every two weeks or 480 mg every 4 weeks; ‡1 mg/kg, only for four 3-week cycles; §50 mg daily for 28 days in 6-week cycles. SUN's 4-weekly costs represent two-thirds of the total 28-day drug costs to reflect the intermittent treatment schedule; ‖Official Gazette price, VAT and dispensing fees included; ¶Drug wastage of 1.06% considered[16]

Table 4. Distribution of subsequent treatments (based on CheckMate-214 August 2017 DBL)

RCC treatment	NIVO	SUN	Axitinib	Cabozantinib	Everolimus	Pazopanib
NIVO+IPI (1L)	8%	51%	32%	15%	14%	33%
SUN (1L)	51%	15%	37%	10%	18%	8%

DBL, database lock; NIVO, nivolumab monotherapy; NIVO+IPI, nivolumab + ipilimumab; RCC, renal cell carcinoma; SUN, sunitinib

Table 5. Unit costs and resource use

Administration, healthcare visits, monitoring, tests and scans	Cost‖	4-weekly resource use NIVO+IPI	4-weekly resource use SUN
Intravenous drug administration	€427.48	1.33 (induction)* 2.00 (maintenance)†	NA
Visit to general practitioner	€30.95	0.33	0.33
Visit to oncologist	€35.59	NA	1.00
Full blood test NIVO+IPI (baseline)	€111.51	Only applied at treatment initiation	NA
Full blood test NIVO+IPI (on treatment)	€52.65	1.33	NA
Full blood test SUN	€51.03	NA	1.00*
Full blood test progressed disease	€48.33	1.00	1.00
CT scan	€112.32	0.33	0.33
Terminal care	€5,052.58	Only applied at moment of death	Only applied at moment of death

CT, computed tomography; NA, not applicable; NIVO+IPI, nivolumab + ipilimumab; SUN, sunitinib
‖VAT included; *These activities also apply at treatment initiation; †Intravenous drug administration periodicity differed by treatment phase: once every 3 weeks for NIVO+IPI for four doses during induction followed by once every 2 weeks for NIVO 240 mg flat dosing monotherapy in the maintenance phase. For 480 mg flat dosing in the maintenance phase, intravenous drug administration resource use was 1.00 per four weeks.

Outcomes

- 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 sensitivity analyses (based on 95% CIs for parameters when available, or varied ±20%) and probabilistic sensitivity analyses were conducted.
- In scenario analyses, maximum treatment duration (scenario 1: 96 weeks for NIVO+IPI, scenario 2: 24 months for all treatments), survival extrapolations and utility values (i.e. non-treatment specific + AE utility decrements) were varied.

Results

Base case

- NIVO+IPI was associated with an increase in discounted LYs compared with SUN (4.95 versus 3.87 LYs) over a 20-year time horizon.
- Accumulated discounted QALYs were substantially higher for NIVO+IPI compared with SUN (3.53 versus 2.71; Table 6).
- For both treatments, drug acquisition costs represented the highest cost category; although total discounted treatment costs were higher for NIVO+IPI, cost savings were realised for subsequent treatments and AEs (Table 6).
- At French list prices, the incremental results led to an ICER of €68,626 per LY gained for NIVO+IPI versus SUN; the ICUR was €89,793 per QALY gained (Table 6).

Table 6. Base case results (discounted)

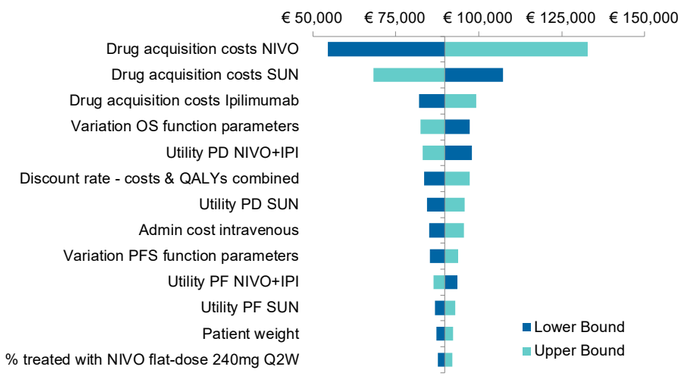
Setting	NIVO+IPI	SUN	Incremental (NIVO+IPI versus SUN)
Total costs	**€160,751**	**€86,596**	**€74,155**
Drug acquisition	€110,099	€45,772	
Drug administration	€13,409	€0	
Disease management	€14,246	€13,297	
Subsequent treatments	€21,946	€25,189	
Adverse events	€1,051	€2,338	
Total LYs	**4.95**	**3.87**	**1.08**
Total QALYs*	**3.53**	**2.71**	**0.83**
Progression-free	1.16	0.86	
Progressed disease	2.38	1.85	
ICER			**€68,626 / LY gained**
ICUR			**€89,793 / QALY gained**

ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LY, life year; NIVO+IPI, nivolumab + ipilimumab; QALY, quality-adjusted life year; SUN, sunitinib; *rounded values

Sensitivity analyses

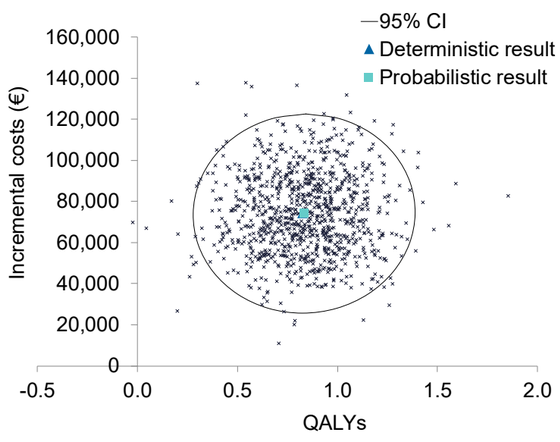
- Deterministic sensitivity analyses showed that uncertainty around the following parameters had the highest impact on the ICUR: drug acquisition costs for both treatments, discounting, variation of PFS and OS function parameters and health state utilities (Figure 4).
- Probabilistic sensitivity analyses showed a similar ICUR to the deterministic base case (mean €88,869 per QALY, -1.0%), confirming model robustness.
- Nearly all (99.9%) of the 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 versus SUN, Figure 5).
- The probability of NIVO+IPI to be cost-effective was 62% at a willingness-to-pay (WTP) of €100,000 per QALY gained (Figure 6).
- The scenario analyses revealed that most of the scenarios (e.g. applying non-treatment-specific utilities or applying different PFS and OS extrapolations) did not result in >10% deviation from the base case ICUR.
- However, assuming a maximum treatment duration for either NIVO+IPI (96 weeks) or both treatments (24 months) lowered the ICUR by 47% and 30%, respectively, due to lower incremental costs.

Figure 4. Tornado diagram: incremental cost-utility ratio



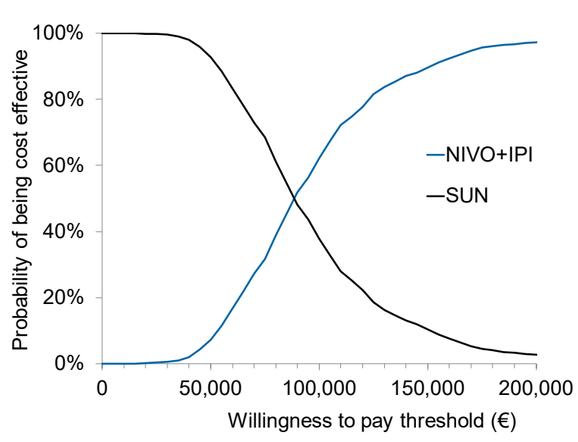
NIVO, nivolumab; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; Q2W, every two weeks; QALYs, quality-adjusted life years; SUN, sunitinib

Figure 5. Incremental scatterplot



CI, confidence interval; QALYs, quality-adjusted life years

Figure 6. Cost-effectiveness acceptability curves



NIVO+IPI, nivolumab + ipilimumab; SUN, sunitinib

Conclusions

- Based on the results of this robust health economic evaluation in a French context, NIVO+IPI presents a valuable alternative to the current standard of care in 1L RCC, leading to a substantially longer life expectancy (i.e. 1.08 LYs) and better quality survival (i.e. 0.83 QALYs) compared with SUN.
- Driven by an increased and sustained OS benefit, NIVO+IPI would be a cost-effective treatment when compared with sunitinib for 1L RCC patients in France at a WTP threshold of €100,000/QALY gained.

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