COST-EFFECTIVENESS ANALYSIS OF FIRST-LINE SYSTEMATIC TREATMENTS IN ADVANCED RENAL CELL CARCINOMA IN FRANCE

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Introduction

Renal cell carcinoma (RCC)

- RCC, the most common type of kidney cancer, accounts for approximately 85% of all kidney malignancies. It is the 7th most common cancer worldwide in men, and the 10th most common cancer worldwide in women.[1]
- In France, it is estimated that nearly 33% of patients with RCC have advanced or metastatic RCC (aRCC) disease at diagnosis.[2]
- In recent years, standard of care in France for first-line (1L) treatment of aRCC has evolved from tyrosine kinase inhibitor (TKI) monotherapy, such as sunitinib (SUN) and pazopanib (PAZ), to immuno-oncology (IO) combination therapies, including the dual IO combination nivolumab+ipilimumab (NIVO+IPI) and IO+TKI therapy: pembrolizumab+axitinib (PEM+AXI).
- IO+TKI therapies have demonstrated clinical benefit vs SUN[3-5], and SUN has shown non-inferiority vs PAZ.[6]

Nivolumab+cabozantinib (NIVO+CABO)

- NIVO+CABO was granted European Medicines Agency approval for the 1L treatment of adults with aRCC on April 13, 2021.[7]
- In comparison with SUN, results from the recent CheckMate 9ER (CM 9ER, NCT03141177) trial (September 2020 database lock) showed that NIVO+CABO significantly improved both progression-free survival (PFS) and overall survival (OS).[8] Although, NIVO+CABO was associated with adverse effects; NIVO+CABO has shown statistically significant health-related quality of life (HRQoL) benefits over SUN.[5,9]
  - The median PFS per blinded independent review committee was 17.0 months (95% confidence interval [CI]: 12.6-19.4 months) for NIVO+CABO and 8.3 months (95% CI: 6.9-9.7 months) for SUN, with a corresponding hazard ratio (HR) of 0.52 (95% CI: 0.43-0.64).
  - The median OS was not reached for NIVO+CABO, the median OS for SUN was 29.5 months (95% CI: 28.4 months - not estimable) with a corresponding HR of 0.66 (95% CI: 0.50-0.87).

Objective

- To assess the incremental cost-effectiveness and cost-utility ratios of NIVO+CABO compared with relevant comparators utilized in France: (i) SUN, (ii) NIVO+IPI, (iii) PEM+AXI and (iv) PAZ in 1L aRCC for an intention-to-treat population (ITT) from an all-payer perspective.

Methods

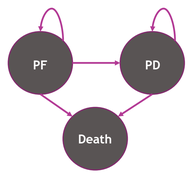
Model structure and population of interest

- A partitioned survival model was developed comprising of three distinct health states: progression-free (PF), progressed disease (PD), and death as the absorbing state.
- The base case analysis included all patients irrespective of baseline RCC risk status to reflect the full 1L aRCC treatment landscape in France.
- The analysis was performed in line with French Haute Autorité de Santé recommendations.[10]
- Time on treatment was defined by PFS to inform drug-related costs. 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[10]
Time horizon	15 years
Cycle length	7 days, half-cycle correction applied
Discounting	2.5% for both costs and health outcomes[10]
Patient characteristics	Age (60.9 years), gender (73.9% male) and weight (81.6 kg) based on the CM-9ER trial

Figure 1. Model structure



Key: PF, progression-free; PD, progressed disease

Treatment safety and efficacy

- Available evidence on safety and efficacy for studies other than CM 9ER were collected from all pivotal trials identified via a systematic literature review (June 2020)[11], considering the most recent database lock. Efficacy data for NIVO+IPI was based on 4-year trial follow-up; the longest of all treatments included in this analysis.
- Grade 1-2 and 3-4 adverse events were included in the model.
- To determine the comparative effectiveness of 1L aRCC treatments, a multi-dimensional treatment effect network meta-analysis (NMA) was implemented within in a Bayesian framework to account for time-varying HRs.[12]
- Two orders of fractional polynomial (FP) models were considered for inclusion: first-order, and second-order. The power level for each order was chosen from the following set: -2, -1, -0.5, 0, 0.5, 1, 2, 3.[12]
- Based on clinical plausibility, external validity and the model with the lowest deviance information criterion, the best-fitting fractional polynomials were:
  - Base case: PFS – 2nd order FP model with p1 = -1, p2 = -2; OS – 1st order FP model with p1 = -1
  - Scenario: PFS – 2nd order FP model with p1 = -2, p2 = -2; OS – 1st order FP model with p1 = -2
- The relative benefit of NIVO+CABO over SUN is informed through the FP analysis using data from the CM 9ER trial.
- As SUN was a common comparator for all included studies, it was used as the anchor treatment.
- Time-varying HRs obtained from the FP analysis were applied relative to the SUN arm and the resulting 15-year survival extrapolations are shown in Figure 2 and Figure 3.

Figure 2. Extrapolated PFS curves

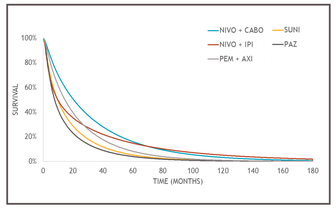
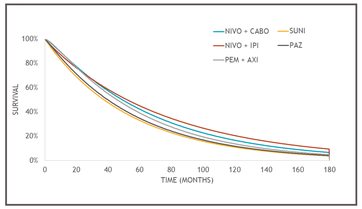


Figure 3. Extrapolated OS curves



Costs and utilities

- Health state utility values were derived from the EuroQol 5-dimension (EQ-5D-3L) questionnaires collected in the CM 9ER study using a mixed model for repeated measures and French utility tariffs (Table 2). Adverse events were associated with a cost and a disutility and were applied only in the first cycle. An additional disutility was applied for therapies administered by intravenous (IV) injection.
- Drug acquisition costs were obtained from the Base des Médicaments et Informations Tarifaires (11/02/2021),[13] and treatment dosing was based on each treatment's pivotal trial and the SmPC. All possible formulations for each drug were considered in the model and only the formulation with the lowest cost per administration was then used in the economic analysis (Table 3).
- In France, two flat doses of NIVO are used in clinical practice, 240mg once every two weeks and 480mg once every four weeks. This flexibility was considered in the model by implementing a 50/50 split between the two doses.
- All costs were French-specific, derived from literature, and expressed in Euros (€) for the year 2020 (Table 4). A one-off monitoring cost of €213.66 was applied for each treatment whereas administering an IV treatment costed €533.23. There was a dispensing fee of €1.02 per package associated with administering orals. Cost related to oncologist visits, computed tomography (CT) scan and biologic tests were inclusive of transport costs (departure and return). A one-off cost of €4,543 for terminal care (including cost of departure transport only) was applied to all patients who transitioned to the death state.

Table 2. Health state utilities

Health state	Utility value
PF (SE) [95% CI]	0.735 (0.010) [0.716,0.755]
PD (SE) [95% CI]	0.701 (0.011) [0.679,0.723]

Key: PF, progression-free; PD, progressed disease; SE, standard error; CI, confidence interval

Table 3. Drug acquisition costs

Int.	Drug	Dosing, dose, admin frequency	Cost/ pack	Cost/4 wks[b]
NIVO+ CABO	NIVO[a]	IV, Flat, 240mg/480mg, QW2/Q4W	€2,481	€4,942
	CABO	Oral, Flat, 40mg, QD	€4,841	€4,519
SUN	SUN	Oral, Flat, 50mg, QD4W;OFF-2W	€4,391	€2,928
NIVO+ IPI	NIVO ind.	IV, WB, 3mg/kg, Q3W for 4 cycles	€2,481	€3,410
	IPI	IV, WB, 1mg/kg, Q3W for 4 cycles	€2,930	€6,443
	NIVO	IV, Flat, 240mg/480mg, Q2W/Q4W	€2,481	€4,962
PAZ	PAZ	Oral, Flat, 800mg, QD	€1,303	€2,401
PEM+ AXI	PEM	IV, Flat, 200mg, Q3W	€2,647	€7,059
	AXI	Oral, Flat, 5mg, BID	€3,228	€3,228

[a]50% of patients on 240mg, Q2W and 50% of patients on 480mg, Q4W
[b]including dispensing fee

Key: BID, twice a day; ind, induction; Int, intervention; OFF-2W, Off two weeks QD4W, once daily for 4 weeks; Q2W, once every two weeks; Q3W, once every three weeks; Q4W, once every four weeks; wks, weeks

Table 4. Resource use frequency and unit costs per week (7 days)

Resource	PF #	PD #	Unit Cost
GP visit	0.08	0.08	€33.12
Oncol. visit + tp	0.25	0.25	€142.93
CT Scan + tp	0.08	0.08	€217.91
Biol. tests + tp	0.25	0.05	€156.69

Key; #, number; Biol., biological; CT, computerised tomography; GP, general practitioner; Oncol., Oncologist; PF, progression-free; PD, progressed disease; tp, transport

Outcomes

- Model outcomes included total costs, life years (LYs), quality-adjusted life-years (QALYs), incremental cost-effectiveness ratio (ICER), and incremental cost-utility ratio (ICUR).
- In addition to the base case analysis, deterministic sensitivity analyses (DSA) (based on 95% CIs for parameters when available or varied by ±20% around the base case values) and probabilistic sensitivity analyses (PSA) were conducted.
- To test the robustness of the base case results, scenario analyses with respect to time horizon, treatment waning and survival extrapolation (alternative FP models) were explored.

Results

- The cost-effectiveness frontier was only comprised of two treatments: PAZ and NIVO+IPI (Figure 4).
- PAZ had the lowest total costs (Table 5), and NIVO+IPI generated the highest QALYs followed by NIVO+CABO (Table 6).
- The ICUR for NIVO+IPI vs PAZ was estimated to be €219,344/QALY (Table 6).

Table 5. Base case results - total and disaggregated costs (discounted)

Int.	PAZ	SUN	NIVO+IPI	PEM+AXI	NIVO+CABO
Total costs	€105,119	€126,452	€245,964	€256,471	€309,756
Drug acquisition	€37,840	€59,625	€152,173	€188,014	€236,176
Drug admin.	€0	€0	€22,063	€11,137	€14,100
Disease mgt.	€20,438	€19,615	€25,246	€22,418	€23,854
One-off monit.	€213.66	€213.66	€213.66	€213.66	€213.66
Subseq. costs	€39,894	€39,693	€41,254	€28,698	€29,474
Adverse events	€2,603	€3,157	€995	€1,905	€1,886
Terminal care	€4,130	€4,148	€4,020	€4,085	€4,053

Key: admin., administration; Int, intervention; mgt., management; Subseq., subsequent; monit., monitoring

Figure 4. Cost-effectiveness frontier

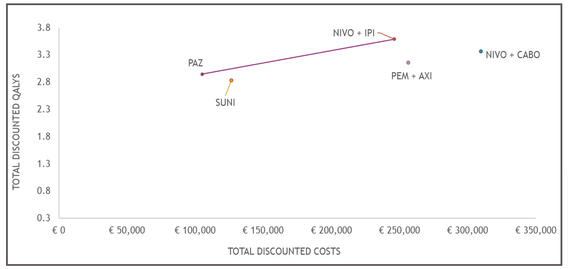


Figure 5. One-way sensitivity analysis of ICURs for NIVO+IPI vs PAZ

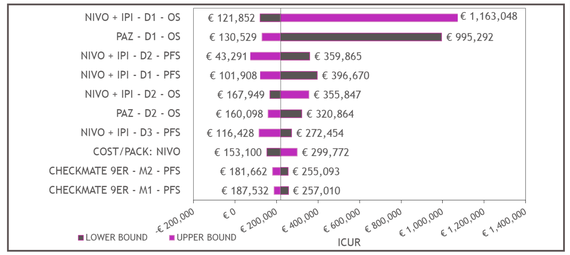


Table 6. Base case results (discounted)

Int.	Total costs	Total LYs	Total QALYs	Δ costs	Δ LYs	Δ QALYs	ICER (€/LY)	ICUR (€/QALY)
PAZ	€105,119	4.52	2.95	-	-	-	On frontier	On frontier
SUN	€126,452	4.34	2.83	€21,333	-0.19	-0.12	Str. dominated by PAZ	Str. dominated by PAZ
NIVO+ IPI	€245,964	5.69	3.59	€140,845	1.17	0.64	€120,383	€219,344
PEM+ AXI	€256,471	4.98	3.16	€10,507	-0.71	-0.43	Str. dominated by NIVO+IPI	Str. dominated by NIVO+IPI
NIVO+ CABO	€309,756	5.33	3.37	€63,792	-0.36	-0.22	Str. dominated by NIVO+IPI	Str. dominated by NIVO+IPI

Key: Int, intervention; LY, life-year; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ration, ICUR, incremental cost-utility ratio; Str. strictly

Sensitivity analysis

- DSA showed that uncertainty around the parameters of the fitted FP models had the highest impact on the ICURs. In particular, FP parameters for NIVO+IPI and PAZ in the OS analyses, and FP parameters for NIVO+IPI in the PFS analyses were most influential on ICURs (Figure 5).
- PSA showed a consistent result to the deterministic base case; for most of the simulations, PAZ had the lowest total costs and NIVO+IPI had the highest total QALYs; however, there was a substantial amount of uncertainty in the simulations in terms of both total costs and total QALYs for NIVO+CABO, NIVO+IPI, and PEM+AXI with a high degree of overlap (Figure 6).
- PAZ had the highest probability of being cost-effective until a willingness-to-pay threshold of ~€243k, after which NIVO+IPI had the highest probability of being cost-effective (Figure 7).
- The base case results were robust to alternative scenarios as PAZ and NIVO+IPI remained the only two treatments on the efficiency frontier where NIVO+CABO and PEM+AXI were dominated by NIVO+IPI. However, using an alternative FP model for OS brought NIVO+CABO to the frontier with an ICER of €18,243,384 while keeping PEM+AXI dominated.

Figure 6. Scatter plot - cost-effectiveness plane for all treatments

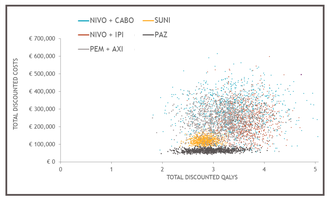
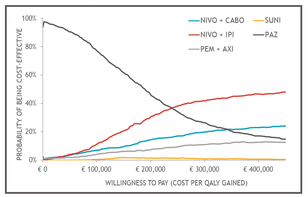


Figure 7. Cost-effectiveness acceptability curves



Conclusions

- Over a 15-year time horizon, NIVO+IPI generated the highest LYs and was predicted to have the highest OS and PFS, followed by NIVO+CABO, PEM+AXI, PAZ, and SUN.
- NIVO+IPI resulted in the highest QALY gains among all 1L treatments and resulted in lower costs than both PEM+AXI and NIVO+CABO.
- A limitation of this study is that this analysis reflects an ITT population, although NIVO+IPI is not licenced for use in the favourable-risk population.

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