A cost-effectiveness analysis of adjuvant nivolumab for patients with resected esophageal cancer or gastroesophageal junction cancer in France

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Background

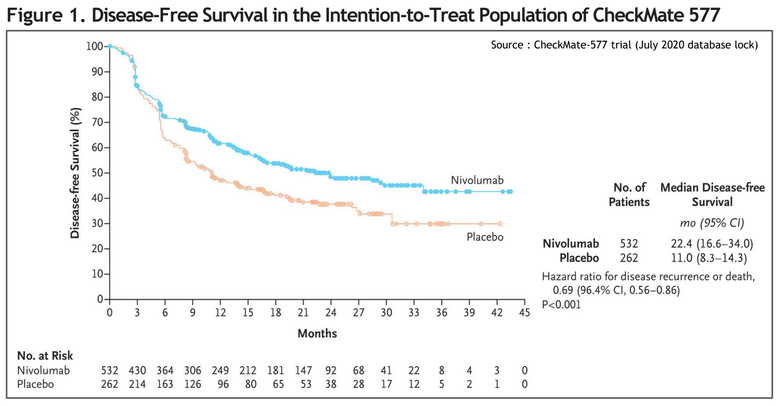
Esophagal and GastroEsophagal Junction Cancer

- Esophagal Cancer (EC) is the third most frequent gastro-intestinal cancers in France after colorectal and gastric cancer with around 5,500 incident cases in 2018.1 Squamous cell carcinoma represent the majority of EC with around 60%, mostly localised in the middle and upper part of the oesophagus, whereas adenocarcinoma typically affect the lower part.[1 - 5]
- GastroEsophagal Junction Cancer (GEJC) represents a third of gastric carcinoma, with around 2,000 incident annual cases.[1, 6]
- Due to the rapid evolution of the disease and low specificity of its symptoms, most patients are diagnosed at a locally-advanced (32%) or metastatic (30%) stage.[7] Advanced EC or GEJC are associated with poor prognosis with around 50% of patients surviving at one year.[8]
- French treatment guidelines[8] for resectable EC or GEJC depend on tumor histology and stage:
  - Surgery in patients with local disease, alone (T1-T2), or with neoadjuvant chemoradiotherapy (CRT) or chemotherapy (CT) alone (T3),
  - For EC or GEJC with T1-T3 lymph node infiltration or >T3, exclusive CRT or CT, followed by salvage surgery in case of recurrence or tumor persistence or neoadjuvant CRT/CT followed by tumor resection are recommended, with the additional option of peri-operative CT in adenocarcinoma.
- Although most patients present residual pathological disease and present a high risk of recurrence following resection, disease surveillance was the current standard of care after neoadjuvant CRT on the date of submission of the dossier (August 2021). [5, 8]

CheckMate 577

- CheckMate 577 pivotal trial is a global, randomized, double-blind, placebo-controlled phase 3 study to evaluate nivolumab at a dose of 240 mg every 2 weeks for 16 weeks, followed by 480 mg every 4 weeks, as adjuvant therapy in patients with EC or GEJC with a maximum treatment duration of 1 year.[9]
- 794 adults with completely resected (R0) stage II or III EC or GEJC who had received neoadjuvant CRT and had residual pathological disease were included and randomized between nivolumab and placebo in a 2:1 ratio. The primary endpoint was disease-free survival (DFS).
- CheckMate 577 demonstrated nivolumab superiority over placebo with:
  - A significant risk reduction of disease recurrence or death (HR=0.69, CI95%, 0.56 to 0.86, p=0,0003),
  - A 11.4 month-improvement in terms of median DFS (22.4 vs. 11 months; July 2020 database lock, 6.2 months minimum follow-up)
- DFS favored nivolumab across all stratification criteria (PD-L1 status, pathologic lymph node status and histology) and other prespecified subgroups.

Figure 1. Disease-Free Survival in the Intention-to-Treat Population of CheckMate 577



- On July 28th of 2021, nivolumab was granted marketing authorization as monotherapy for the adjuvant treatment of EC or GEJC who have residual pathologic disease following prior neoadjuvant CRT.
- Our objective was to determine the cost-effectiveness of adjuvant nivolumab versus current clinical practice (surveillance) in patients with EC or GEJC who have residual disease after neoadjuvant CRT followed by complete resection in France in view of an efficiency submission to the French Commission for Economic Evaluations and Public Health (CEESP).

Methods

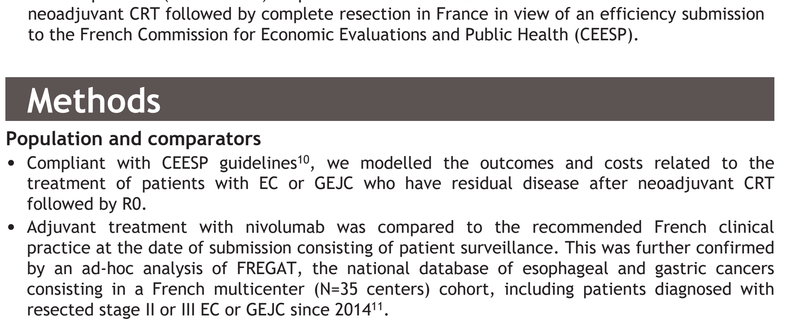
Population and comparators

- Compliant with CEESP guidelines[10], we modelled the outcomes and costs related to the treatment of patients with EC or GEJC who have residual disease after neoadjuvant CRT followed by R0.
- Adjuvant treatment with nivolumab was compared to the recommended French clinical practice at the date of submission consisting of patient surveillance. This was further confirmed by an ad-hoc analysis of FREGAT, the national database of esophageal and gastric cancers consisting in a French multicenter (N=35 centers) cohort, including patients diagnosed with resected stage II or III EC or GEJC since 2014[11].
  - Of 382 patients with resected locally advanced EC or GEJC who received neoadjuvant CRT and included between 2014 and 2019 identified, 362 (95%) did not receive active treatment,
  - Similarly, among 242 of these patients who matched CheckMate 577 inclusion criteria, 232 (94%) received no treatment after tumor resection.

Model structure

- A simplified semi-Markov model with four states: disease-free (DF), locoregional-recurrence (LR), distant-recurrence (DR), and death was applied (Figure 2). The 4-health state (HS) structure allowed to model the distribution of the types of recurrences (loco-regional, distant) based on CheckMate 577 results and to account for their specific survival, costs and outcomes.
- Indeed, the lack of mature overall survival (OS) data from the trial implied the use of an external source (IKNL registry[12]) to inform OS.
- Patients entered the model in the DF HS. Time-dependent DF to recurrence transition was informed by a parametric extrapolation of the treatment-specific time-to-recurrence (TTR, derived from CheckMate 577 mortality-censored DFS), applying the time-dependent distribution between locoregional and distant-recurrence observed in the trial.
- Patients could also die without recurrence based on the age-and-sex matched general population mortality, adjusted to CheckMate 577 pre-recurrence mortality levels by applying an age-adjusted HR (HR = 3,46 [2,53-4,74]). It was assumed that treatment did not affect this transition.
- Patients with LR and DR were associated with recurrence-specific mortality from the IKNL registry, regardless of the adjuvant treatment received.
- A 15-year time horizon simulated population-matched patients included in the trial. Costs and outcomes were discounted 2.5% per year.

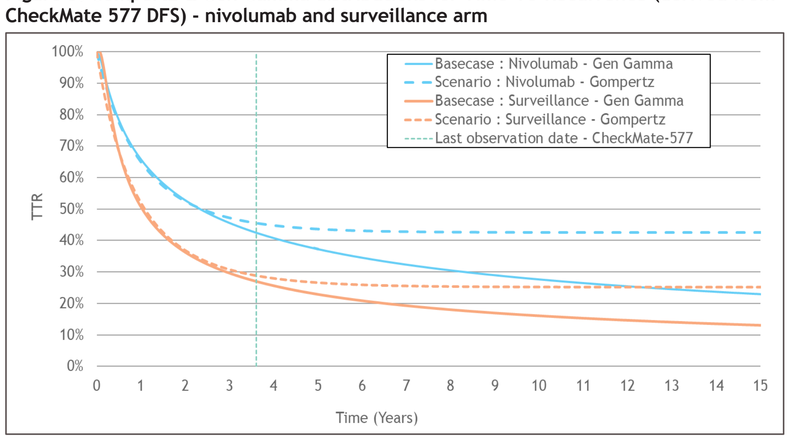
Figure 2. Simplified 4 health-state semi-markov model structure



Survival in Disease-Free health-state

- Schoenfeld residuals, cumulative hazard plot, and Log-log survival plot confirmed that hazards of recurrence between nivolumab and surveillance were not proportional.
- Thus, unrestricted parametric distributions were fitted independently to CheckMate 577 TTR data and selected based on Aikake and Bayesian Information Criteria (AIC and BIC), visual inspection and external validity using literature.
  - In both arms, Gompertz and Generalized Gamma distributions offered the best fit, the latter being more pessimistic, whereas Gompertz distributions produced plateaus starting at around 6 years, aligned with the notion that patients who have not progressed after 5 years in the adjuvant context may be cured.
  - Nevertheless, in the absence of robust data formally confirming this, the Generalized Gamma distribution was favored in the basecase analysis (Figure 3).
- Furthermore, given the uncertainty surrounding nivolumab's efficacy in the long term, the risk of recurrence in the nivolumab arm was progressively increased to reach the same level as in the surveillance arm at the end of the simulation, starting at 5 years.

Figure 3. Gompertz & Gen Gamma distributions for Time-To-Recurrence (derived from CheckMate 577 DFS) - nivolumab and surveillance arm



Survival in LR & DR HS

- Constant probabilities of death in the LR and DR HS were obtained from an ad-hoc analysis of 718 Dutch adult patients with EC or GEJC who matched CheckMate 577 inclusion criteria and were included in the IKNL Dutch cancer registry after initiating a treatment in 2015 and 2016. Constant hazards were fitted to recurrence-specific mortality data of respectively 332 and 27 patients with distant and loco-regional recurrence.
- IKNL was favored over FREGAT to inform the recurrence-specific mortality due to the limited number of patients (N=13) with locoregional recurrences identified in the *ad-hoc* analysis. Other potentially appropriate sources were discarded for the same reason. [13, 14]

Utilities and costs

- Survival in each HS was associated with utilities derived from the EQ-5D-3L results of CheckMate 577 valued according to the preferences of the French general population (Table 1) to characterize the impact of disease progression on patients' health-related quality of life. In the absence of significant utility differences between nivolumab and surveillance, the utilities in the ITT population were preferred in the basecase analysis.

Table 1. French utility values derived from CheckMate-577 EQ-5D-3L results by health-state and population

Health-state (n)	Utility (SE)		
	Intention-to-Treat	Nivolumab	Surveillance
Disease-Free (784)	0,837 (0,006)	0,833 (0,007)	0,846 (0,011)
Post-recurrence			
Locoregional (88)	0,757 (0,025)	0,747 (0,034)	0,771 (0,039)
Distant (198)	0,726 (0,017)	0,726 (0,023)	0,727 (0,027)
Any (286)	0,742 (0,015)	NR	NR

- HS occupancy, recurrences and deaths were associated with medical resource use estimated based on existing guidelines and informed assumptions. Unit costs were valued from a "healthcare system" perspective.
- Treatment acquisition and administration, disease monitoring, management of adverse events (AE) related to nivolumab, cost of subsequent treatments, transportation and end-of-life care were considered. Subsequent treatment distribution for patients with recurrence was modelled based on the results of CheckMate 577, distinguishing treatment arms and type of recurrence (Table 2). All costs were updated to 2021€.

Table 2. Subsequent treatment distribution after recurrence from CheckMate 577

	Nivolumab		Surveillance	
	Locoregional	Distant	Locoregional	Distant
Proportion of patients receiving treatment after recurrence	70%		74%	
Chemotherapy				
5FU + Cisplatin	10%	9%	7%	6%
Capecitabin + oxaliplatin	8%	7%	11%	10%
FOLFOX	67%	61%	69%	61%
Radiotherapy	43%	21%	42%	35%
Surgery	21%	16%	12%	21%

Exploration of uncertainty

- Robustness of results was evaluated with deterministic and probabilistic sensitivity analyses (DSA and PSA) and scenario analyses, including:
  - 10-year and 20-year time-horizons
  - Modelling of TTR using a Gompertz function that reflects a pseudo-cure assumption after 6 years (Figure 3),
  - Modelling using a simpler 3 HS structure (no distinction between types of recurrence) based on the aggregated post-recurrence survival from IKNL,
  - Modelling using a simpler 3 HS structure, allowing the use of FREGAT data to model post-recurrence survival and subsequent treatment distribution,
  - Absence of treatment effect waning after 5 years.

Results

Basecase analysis

- At 15 years, the average discounted survival of patients with EC or GEJC who had a residual disease after neoadjuvant CRT followed by R0 in France was 3.56 years, corresponding to 2.88 QALY in the surveillance arm (Table 3). Nivolumab was associated with an incremental survival gain of 1.19 years (+34%) and 0.98 QALY (+34%).

Table 3. Disagregated discounted outcomes in the basecase analysis

	Nivolumab	Surveillance	Incremental
Survival (LY)			
Disease-Free	4.16	2.88	1.28 (44.4%)
Post-recurrence	0.59	0.68	-0.09 (-13.1%)
Locoregional	0.18	0.20	-0.03 (-13.1%)
Distant	0.41	0.48	-0.06 (-13.1%)
Total	**4.75**	**3.56**	**1.19 (33.5%)**
QALY			
Disease-Free	3.43	2.38	1.05 (43.9%)
Post-recurrence	0.43	0.50	-0.07 (-13.1%)
Locoregional	0.13	0.15	-0.02 (-13.1%)
Distant	0.30	0.35	-0.05 (-13.1%)
Total	**3.86**	**2.88**	**0.98 (34.1%)**

- The total treatment and follow-up cost of patients in the surveillance arm was €17,771€ (Table 4). Nivolumab was associated with an incremental cost of €48,634.

Table 4. Disagregated discounted costs in the basecase analysis

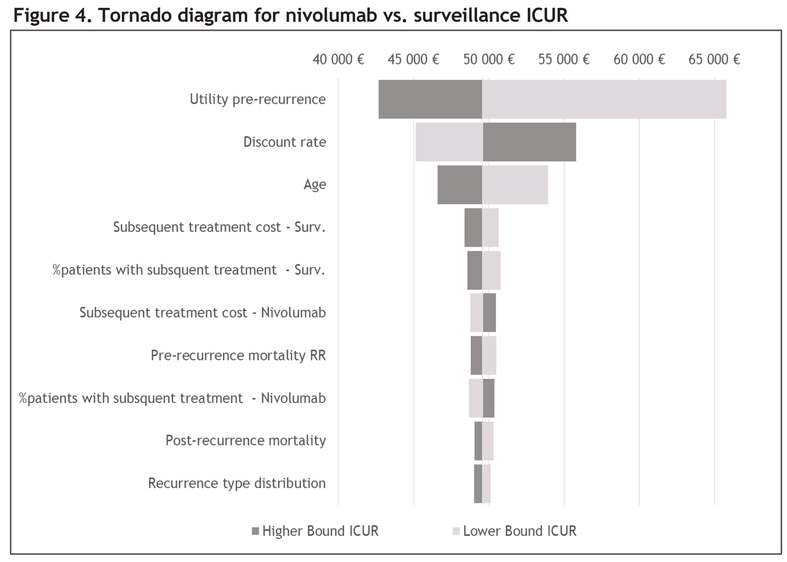
Costs (2021€)	Nivolumab	Surveillance	Incremental
Treatments	47,495	0	47,495
AE management	349	0	349
Disease follow-up			
Disease-Free	8,404	6,202	2,201
Post-recurrence	1,578	1,206	372
Subsequent treatments	4,309	5,720	-1,411
End of life	4,271	4,624	-371
Total cost	**66,405**	**17,771**	**48,634**

- Additional costs, survival and QALY associated with nivolumab resulted in an incremental cost-effectiveness ratio (ICER) of €40,797/LY and an incremental cost-utility ration (ICUR) of €49,572/QALY.

Sensitivity Analyses

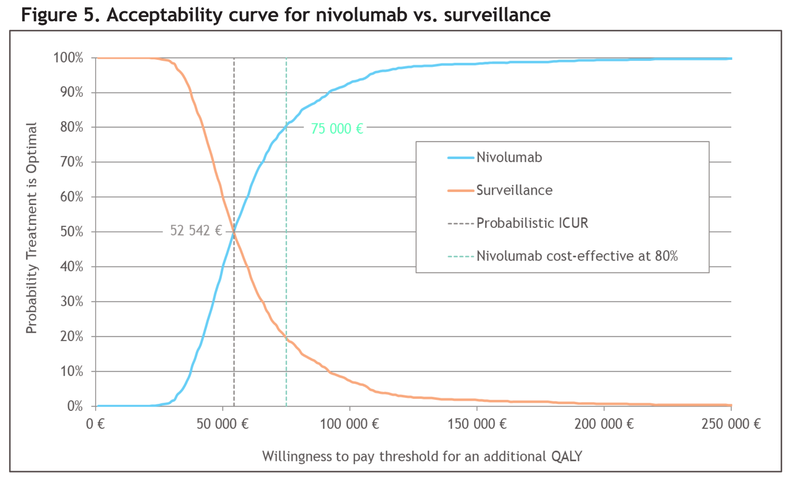
- DSA and PSA confirmed the robustness of this result. ICUR were consistently below €65,780 across all DSA (Figure 4) and were most sensitive to:
  - Utility value in DF HS, where patients treated with nivolumab generated additional QALYs over surveillance,
  - Discount rate, due to the relatively long time-horizon,
  - Average age at the beginning of the simulation and pre-recurrence mortality RR, both determinants of the additional outcomes associated with the longer DFS of nivolumab,
  - Proportion of patients receiving a subsequent (post-recurrence) treatment and its costs in surveillance and nivolumab arms.

Figure 4. Tornado diagram for nivolumab vs. surveillance ICUR



- PSA confirmed base-case ICUR (€52,542/QALY vs. €49,572/QALY) with 80% probability of nivolumab being cost-effective at a willingness-to-pay threshold of €75,000/QALY (Figure 5).

Figure 5. Acceptability curve for nivolumab vs. surveillance



Scenario analyses

- Alternative assumptions had limited impact: a maximum 26% ICUR increase at 10-year time horizon; 21% ICUR decrease with a TTR Gompertz extrapolation simulating pseudo-cure after 6 years; and negligeable impact of using a 3 HS semi-Markov structure (−0.1%).
- Additionally, recourse to FREGAT post-recurrence survival in the 3 HS structure showed a +7,0% ICUR increase, driven by the better post-recurrence survival vs. IKNL observed in the French database.

Table 5. Scenario analyses results

Scenario	ICUR €/QALY	ICUR Variation vs. Basecase €/QALY (%)
10-year time-horizon	62,509	+12,937 (+26.1)
20-year time-horizon	43,946	-5,625 (-11.3)
Modelling of Time-to-Recurrence with Gompertz distribution	39,082	-10,490 (-21.2)
3 health-state model structure	49,513	-59 (-0.1)
3 health-state model structure with FREGAT post-recurrence survival	53,018	+3,446 (+7.0)
No treatment effect waning after 5 years	46,836	-2,736 (-5,5)

Conclusions

- CEESP accepted this cost-effectiveness analysis methodology, only criticizing the choice of a constant post-recurrence mortality hazard. However, implementing time-dependent probabilities of death in the post-recurrence survival state would have required a considerable increase in model complexity through the addition of tunnel states tracking post-recurrence duration and would not have had a significant impact on results.
- Compared with previously evaluated and accepted efficiency analysis for immune-checkpoint inhibitors in a metastatic setting, ICUR appears particularly low because of capped treatment duration for nivolumab (1-year stopping rule), longer pre-recurrence survival associated with quality of life-benefits and poor prognosis in the post-recurrence health-state.
- In view of these results and their robustness, nivolumab is a cost-effective option for the adjuvant treatment for patient with EC or GEJC who have residual disease after neoadjuvant CRT followed by R0 in France.

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