Cost-Effectiveness Analysis of Neoadjuvant Nivolumab plus Platinum-based Chemotherapy (PDC) in Resectable Non-Small Cell Lung Cancer (NSCLC) in France : a Situation of Dominance

Casabianca P[1], Carette J[2], Chouaid C[3], Harris M[4], Chartier M[1], Sun A[4], White B[4], Leleu H[2], Lucherini S[5], Cotte FE[1]

[1] Bristol Myers Squibb, Rueil-Malmaison, France, [2] Public Health Expertise, Paris, France, [3] CHI Créteil, France, [4] Evidera PPD, [5] Bristol Myers Squibb, Uxbridge, UK

Background

Lung cancer

A total of 52,777 new cases of lung cancer were recorded in France in 2023 with men predominating (63%).[1] It is associated with a poor prognosis leading to the death of 33,100 patients in France in 2018. Non-small cell lung cancer (NSCLC) accounts for the majority (85%) of all lung cancer cases, and approximately half of patients with NSCLC are diagnosed with local or locally advanced stage I-III disease (40%).[2] The treatment strategy of these patients is based on the complete resection that can be associated with a neoadjuvant treatment with platinum-based chemotherapy (PDC) and/or with an adjuvant treatment with PDC and/or radiotherapy depending on the pre- and post-surgical evaluation.[3-5] Despite the benefits of surgical resection with neoadjuvant and/or adjuvant treatment, some patients with early-stage NSCLC experience recurrence and death.

CheckMate-816

CheckMate-816 is an open-label, phase 3 trial where patients with stage IB to IIIA resectable NSCLC (7th TNM classification) were randomly assigned to receive nivolumab plus PDC or PDC alone, followed by resection.[6] Patients were stratified at inclusion according to their status of programmed death ligand 1 (PD-L1) expression (<1 or ≥ 1%). The primary endpoints were event-free survival (EFS) and pathological complete response (0% viable tumour in resected lung and lymph nodes), both evaluated by blinded independent review. Overall survival was a key secondary endpoint.

Context

On June 26, 2023, nivolumab received marketing authorization in European Union in combination with PDC as neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%. An early access authorisation has been granted in September 2023 in France for nivolumab in combination with PDC as neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%, and without known Epithelial Growth Factor Receptor (EGFR) mutation or Anaplastic Lymphoma Kinase (ALK) translocation.

Methods

Population and comparators

A cost-effectiveness analysis compared clinical and economic outcomes of nivolumab plus PDC versus PDC alone as neoadjuvant treatment in the approved population in France. Patients could receive nivolumab (360 mg every three weeks for three weeks) and/or PDC before surgery and any additional adjuvant treatment. Patient characteristics and clinical inputs were derived from the CheckMate-816 clinical trial.

Model structure

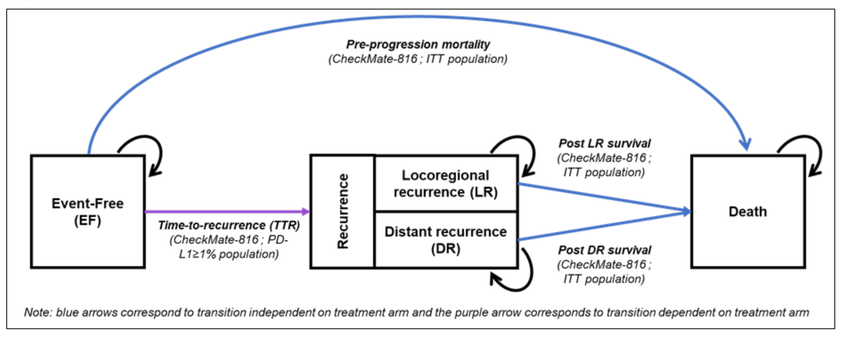
A semi-Markov model with four health-states: event-free (EF), locoregional-recurrence (LR), distant-recurrence (DR), and death was developed (Figure 1). This structure allowed to model the distribution of the types of recurrences (locoregional or distant) using the CheckMate-816 results and accounting for their survival, costs and quality of life outcomes.

Transitions from the EF to post-recurrence health states were informed by treatment-specific time-to-recurrence (TTR) estimates from CheckMate-816. Progressing patients were distributed into the LR or DR health states in accordance with the distributions observed in CheckMate-816. Mortality in EF health-state and post LR and DR survivals were treatment-independent, and the age-and-sex-matched general population mortality was also taken into account to cap these estimates.

According to the patient selection in CheckMate-816 and stratification on the PD-L1 expression (≥1% or <1%) and modelling assumptions, TTR results in patients expressing PD-L1≥1% in CheckMate-816 were used to estimate the risk of recurrence in patients treated with neoadjuvant nivolumab plus PDC or PDC alone. Otherwise, the pooled clinical results in the ITT population were used to estimate pre- and post-recurrence survival in both treatment arms, due to the low number of events recorded in the PD-L1≥1% population.

A 20-year time horizon was chosen due to the median age at resection (64 years) of patients in the simulated population, the natural history of the disease and to limit uncertainty. Costs and outcomes were discounted by 2.5% per year.

Figure 1. Semi-Markov model structure (4 health-states)



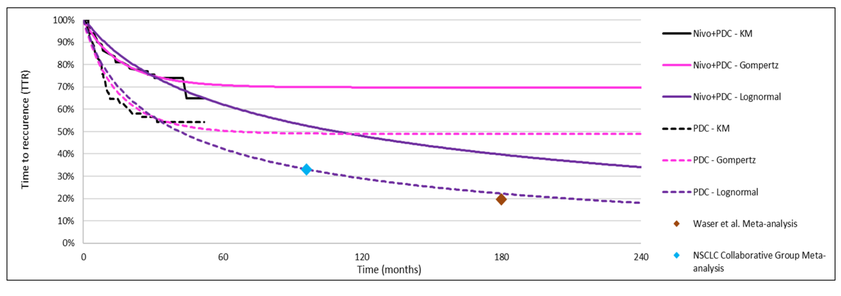
TTR and survival in EF health-state

Schoenfeld residuals, cumulative hazard plot, and log-log survival plot tests suggested that both proportional hazard of recurrence between nivolumab plus PDC and PDC alone, and accelerated failure time assumptions hold. Therefore, the use of jointly fitted distributions with treatment arm as predictor of the risk of recurrence was selected based on Akaike and Bayesian Information Criteria (AIC and BIC), visual inspection and long-term plausibility using literature.

In both arms, Lognormal (basecase) and Gompertz (pseudo-cure scenario) distributions offered the best fit, the former being more pessimistic, whereas Gompertz distributions plateaued from 5 years, consistent with the notion that patients who have not recurred after 5 years in the neoadjuvant context may have limited to no chance of recurrence (Figure 2). Two meta-analyses confirmed the plausibility of the Lognormal distribution in the basecase analysis.[7,8] The distribution of the first recurrence was determined by the pooled results in the PD-L1≥1% population in CheckMate-816. In the analysis, 61% of LR and 39% of DR were considered in both arms.

Parametric distributions were fitted to CheckMate-816 pre-recurrence survival data and selected based on AIC and BIC and visual inspection. In both arms, Generalized Gamma (basecase) offered the best fit.

Figure 2. Log-normal (basecase) and Gompertz (cure scenario) distributions for TTR - Nivolumab plus PDC and PDC alone arms



Survival in LR and DR health-states

Parametric distributions were fitted to CheckMate-816 post-LR and DR survival data and selected based on AIC and BIC, visual inspection, and long-term plausibility using literature. In both arms, Lognormal (basecase) distributions offered the best fit for post-LR and DR survival extrapolation. In absence of staging measurement at progression in CheckMate-816, it was assumed that patients with LR had NSCLC stage IIIA-IIIB and patients with DR had NSCLC stage IV. The results of a meta-analysis and results of KN-189 and KN-407 trials confirmed the plausibility of the Lognormal distribution in the basecase analysis.[9-13]

Adverse events

Grade ≥1 all causes AEs with an incidence of ≥5% in CheckMate-816 were included in the analysis. According to their severity, it was considered they had an impact on costs, and grade ≥3 AEs had an impact on both costs and quality of life.

Utilities and costs

Survival in each health-state was associated with utilities derived from the EQ-5D-3L results of CheckMate-816 in ITT population estimated by mixed model for repeated measures and valued according to the preferences of the French general population to assess the impact of disease progression on patients' health-related quality of life (Table 1). Disutilities related to grade ≥3 AEs were estimated from the literature.

Table 1. French utility values derived from CheckMate-816 EQ-5D-3L results by health-state

Health-state (n observations)	Utility (CI95%) - ITT population (n=358)
Event-Free (2 783)	0.878 (0.862-0.894)
Post-recurrence - Locoregional (254) - Distant (121)	 0.809 (0.783-0.836) 0.695 (0.661-0.729)

A collective perspective restricted to health system excluding indirect costs valued based on production costs was adopted. Costs of treatment acquisition and administration, disease monitoring, management of all causes grade 1-4 AEs, subsequent treatments, transportation, and end-of-life care were considered. Cost of surgery was estimated based on a study from French hospital claims database (BRONTES study).[14]

Subsequent treatment distribution for patients with LR and DR was estimated based on CheckMate-816 results in ITT population, distinguishing treatment arms and the type of recurrence (Table 2). It was assumed that the neoadjuvant treatment had no impact on the subsequent strategy (surgery, radiotherapy and/or systemic treatment) which is driven by the nature of first recurrence (LR of DR) and decided by clinicians. However, among the systemic treatment options, and as observed in CheckMate-816, the neoadjuvant treatment with nivolumab leads to a reduction in the use of immunotherapies (pembrolizumab, durvalumab) in case of recurrence in favour of the use of tyrosine kinase inhibitor (TKI) treatments (afatinib, crizotinib, gefitinib, lorlatinib, osimertinib, brigatinib) or PDC protocols. All costs were updated to €2023.

Table 2. Subsequent treatment regimen distribution after recurrence from CheckMate-816

Subsequent treatment distribution	Nivolumab plus PDC	PDC alone
Locoregional recurrence (LR)		
Radiotherapy	26.3%	26.3%
Surgery	1.1%	1.1%
Systemic treatment Immunotherapy +/- chemotherapy TKI Chemotherapy alone	62.1% 37.5% 4.2% 58.3%	62.1% 51.4% 25.7% 22.9%
Distant recurrence (DR)		
Radiotherapy	43.1%	43.1%
Metastasis surgery	15.5%	15.5%
Systemic treatment Immunotherapy +/- chemotherapy TKI Chemotherapy alone	58.6% 25.0% 37.5% 37.5%	58.6% 73.1% 7.7% 19.2%

The robustness of results was assessed by deterministic and probabilistic sensitivity analyses (DSA and PSA) as well as through different scenario analyses.

Results

Basecase analysis

At 20 years, the average discounted survival of the modelled population was 8.95 years, corresponding to 7.38 QALY in the intervention arm. Nivolumab plus PDC was associated with an incremental survival gain of 1.58 years (+22%) and 1.37 QALY (+23%). The total treatment and follow-up cost of patients in the PDC arm was €53,185 (Table 3). Neoadjuvant treatment with nivolumab plus PDC was associated with cost savings of €4,167. This is explained by the fact that patients treated with neoadjuvant nivolumab plus PDC progressed more slowly than those who received PDC only, thus incurring fewer post-recurrence costs. These cost savings also offset the limited treatment costs with nivolumab (maximum of 3 administrations).

Thus, neoadjuvant treatment with nivolumab plus PDC dominates the treatment strategy with PDC alone.

Table 3. Disaggregated discounted outcomes and costs in the basecase analysis

Outcomes	Nivolumab plus PDC	PDC alone	Difference
Survival			
Event-free	7.25	5.04	2.21 (+44%)
Post-recurrence	1.70	2.33	-0.63 (-27%)
Locoregional	1.24	1.70	-0.46 (-27%)
Distant	0.46	0.63	-0.17 (-27%)
Total Life years	**8.95**	**7.36**	**1.58 (+22%)**
QALY			
Event-free	6.12	4.27	1.85 (+43%)
Post-recurrence	1.26	1.73	-0.48 (-27%)
Locoregional	0.95	1.31	-0.36 (-27%)
Distant	0.31	0.42	-0.11 (-26%)
Total QALY	**7.38**	**6.00**	**1.37 (+23%)**
Costs (€2023)	**Nivolumab plus PDC**	**PDC alone**	**Difference**
Neoadjuvant treatment	13,788	2,544	11,245 (+442%)
Disease management in EF including surgery and adjuvant treatment	13,671	14,252	-581 (-4%)
Disease management in LR including subsequent treatments	8,630	16,907	-8,277 (-49%)
Disease management in DR including subsequent treatments	4,990	9,594	-4,604 (-48%)
AE management	4,769	6,262	-1,492 (-24%)
End of life	3,170	3,627	-457 (-13%)
Total cost	**49,018**	**53,185**	**- 4,167 (-8%)**

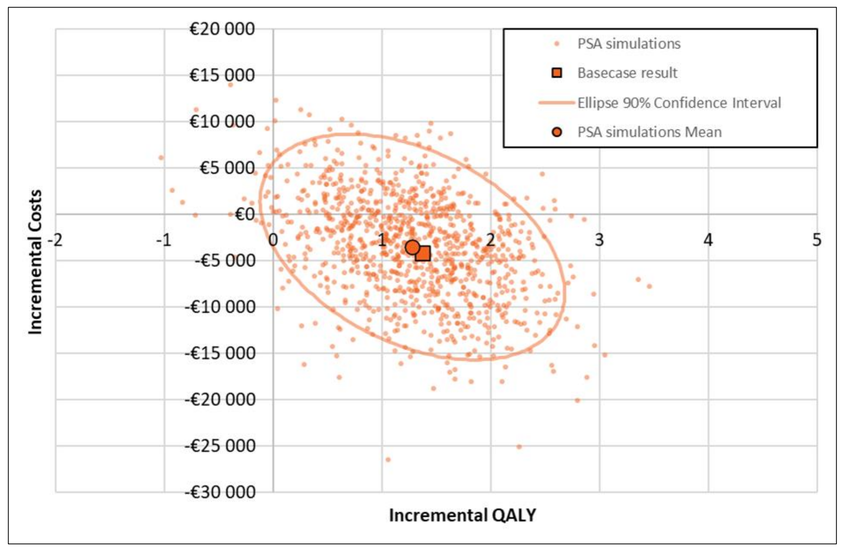
Sensitivity Analyses

DSA and PSA confirmed the robustness of the basecase analysis.

DSA led to an incremental benefit in QALYs between +0.75 and +1.60 and cost savings between €1,082 and €7,252 in favour of the neoadjuvant strategy with nivolumab plus PDC compared with the strategy with PDC alone. The most sensitive parameters were the subsequent treatment costs, the occurrence of surgery and the extrapolation of pre-recurrence survival by the Generalized Gamma function.

PSA over 1,000 simulations confirmed the results and the dominance of the neoadjuvant strategy with nivolumab plus PDC with 76% probability of nivolumab being dominant. Nivolumab has 80% probability being cost-effective at a willingness-to-pay threshold of €750/QALY. In most cases (98%), nivolumab plus PDC leads to incremental QALY in comparison with PDC alone and the simulations in the top right-hand quadrant (22%) are explained by the uncertainty surrounding the subsequent treatment costs (Figure 2).

Figure 2. Incremental cost-effectiveness plane



Scenario Analyses

Alternative assumptions had moderate impact and did not change the dominance of the neoadjuvant nivolumab plus PDC strategy (Table 4).

Increasing the time horizon of the analysis to 30 years enhances the incremental QALY benefits in favour of nivolumab plus PDC in comparison with PDC alone (+16.6% QALY vs. the basecase).

The pseudo-cure assumption using a Gompertz distribution to extrapolate TTR had a moderate impact on the results, as those tend to increase life-years and QALY (+7,2% vs. the basecase) due to the fact that patients whose disease has not progressed in the first 5 years have a near zero risk of progression beyond that. It is associated with lower incremental cost savings (-43% vs. the basecase) because the absence of recurrence beyond 5 years in the PDC arm limits the cumulative costs of subsequent post-recurrence treatments.

Using the full CheckMate-816 results in the PD-L1≥1% population to estimate pre- and post-recurrence survival of patients in both treatment arms led to a minor change in incremental QALY and cost savings vs. the basecase (+5.4% and +6.0%, respectively). This scenario reinforces confidence in the results, even when using a low number of events recorded in the PD-L1≥1% population.

The progressive or direct reduction of the nivolumab treatment effect led to decrease the incremental QALY vs. the basecase (-5.3% and -25.1%, respectively). It is associated with lower incremental cost savings vs. the basecase (-14.4% and -43.1%, respectively) because the progression of patients treated with neoadjuvant nivolumab + PDC is faster.

Alternative assumptions on the distribution of the first recurrence (LR or DR) in comparison to the distribution in the basecase (61% of LR and 39% of DR) had a limited impact on the results. Otherwise, the total restriction to immunotherapy in post-recurrence subsequent treatments for patients previously treated with nivolumab in the neoadjuvant setting considerably increases the incremental cost savings (+74,2% vs. the basecase).

Only one extreme scenario assuming equivalent subsequent treatment distribution for both arms yielded a non-dominant result with an ICER of €1,542/QALY.

Table 4. Scenario analyses results

Scenario	Incremental Costs (variation vs. basecase in %)	Incremental QALY (variation vs. basecase in %)	ICER
10-year time-horizon	-3,952 € (+5.2%)	0.75 (-45.3%)	Dominant
30-year time-horizon	-3,930 € (+5.7%)	1.60 (+16.6%)	Dominant
Modelling of TTR with Gompertz distribution (pseudo-cure assumption)	-2,375 € (+43.0%)	1.47 (+7.2%)	Dominant
Nivolumab effect waning from 45 months to 20 years	-3,565 € (+14.4%)	1.30 (-5.3%)	Dominant
Use of full CheckMate-816 results in the PD-L1≥1% population	-4,415 € (-6.0%)	1.45 (+5.4%)	Dominant
Nivolumab effect waning immediately at 45 months	-2,373 € (+43.1%)	1.03 (-25.1%)	Dominant
Distribution of the first recurrence: 80% LR & 20% DR	-4,397 € (-5.5%)	1.31 (-4.2%)	Dominant
Distribution of the first recurrence: 40% LR & 60% DR	-3,814 € (+8.5%)	1.44 (+4.7%)	Dominant
Subsequent treatments: total restriction to immunotherapy in patients treated by nivolumab	-7,259 € (-74.2%)	1.37 (0%)	Dominant
Subsequent treatments: equivalent distribution in both arms	+2,117 € (+150.8%)	1.37 (0%)	1,542 €/QALY

Conclusions

Neoadjuvant nivolumab plus chemotherapy for resectable NSCLC is the first oncology strategy with cost-effective dominant result validated by the French National Health Authority (HAS). This outcome is explained by the short treatment duration (maximum 3 administrations), delayed/avoided subsequent treatments, and because patients are kept in early stage with slowing risk of progression associated with relatively high utility scores.

Early treatment with immunotherapies is a current trend in many cancers and is associated with attractive cost-effectiveness results (less than €50,000/QALY). Our study demonstrates the significant clinical and economic value of nivolumab in the neoadjuvant treatment of resectable NSCLC in patients with tumours expressing PD-L1≥1%.

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Email: paul.casabianca@bms.com