Cost-effectiveness analysis of nivolumab plus ipilimumab versus other first-line therapies for patients with stage IV or recurrent non-small cell lung cancer in the United States

EE203

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Introduction

- Lung cancer is the leading cause of cancer mortality worldwide, accounting for 18% of all cancer-related deaths[1]
- Non-small cell lung cancer (NSCLC) is the most common type of lung cancer.[2] Patients with NSCLC often present with advanced disease,[3] which is associated with a 5-year survival rate of just 9%[4]
- Recently, however, immunotherapy-based treatments have begun to change the treatment landscape for NSCLC[3]
- Nivolumab (NIVO) and ipilimumab (IPI) are immunotherapy agents with distinct but complementary mechanisms of action.[5] In combination, NIVO + IPI-based regimens have improved long-term survival outcomes versus comparators for patients with a variety of advanced solid tumours[6-8]
- In the randomised, phase 3 CheckMate 227 Part 1 trial, first-line (1L) therapy with NIVO + IPI demonstrated long-term, durable overall survival (OS) benefit when compared with platinum-doublet chemotherapy (PDC) in patients with advanced NSCLC, regardless of tumour programmed death ligand 1 (PD-L1) expression level and tumour histology[9-11]
  - NIVO + IPI is approved in the United States (US) as a chemotherapy-free 1L treatment for adults with metastatic NSCLC (without *EGFR*/*ALK* tumour aberrations) expressing tumour PD-L1 ≥ 1%,[12] and in some countries as 1L treatment regardless of tumour PD-L1 expression[13,14]
  - NIVO + IPI is also recommended as a 1L treatment option for metastatic NSCLC by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®),[15] regardless of tumour PD-L1 expression, and by the European Society for Medical Oncology (ESMO) guidelines for patients with tumour PD-L1 expression ≥ 1%[16]

Objective

- A recent cost-effectiveness analysis (CEA), undertaken from a third-party payer perspective in the US, showed that NIVO + IPI is cost-effective as 1L treatment for stage IV or recurrent NSCLC when compared with PDC[17]
- As other immunotherapy regimens are also relevant treatment options for specific subgroups of patients with advanced NSCLC, we conducted an additional analysis to assess the cost-effectiveness of NIVO + IPI versus PDC and other immunotherapies currently available as 1L treatment options for stage IV or recurrent NSCLC in the US, from a third-party payer perspective. Here, we report the results of this analysis

Methods

- This CEA was supported by results from a recently published indirect treatment comparison (ITC) in patients with advanced NSCLC, which suggested a significant long-term survival benefit with NIVO + IPI versus immunotherapies + chemotherapy in tumour PD-L1-expressing all-comer populations and a trend towards long-term benefit in patients with tumour PD-L1 expression ≥ 1%[3]
- This ITC was conducted using the following approach[3]:
  - A systematic literature review was conducted to identify randomised controlled trials (RCTs) in adults treated with 1L therapies for locally advanced, advanced, or recurrent NSCLC with at least 3 years of patient follow-up
  - Six of the identified RCTs were eligible for quantitative evidence synthesis (**Table 1**)
  - Quantitative analysis of OS and progression-free survival (PFS) was performed using fractional polynomial network meta-analysis (FPNMA)
    - FPNMA was used instead of Bucher ITC because the proportional hazards assumption was violated[3]
    - The FPNMA was used to estimate time-varying hazard ratios (HRs) of OS and PFS

Table 1. Model populations and comparators for NIVO + IPI, as derived from the recent ITC[3]

Trial	Treatment	Histology	Tumour PD-L1 expression	Follow-up
Comparator: chemotherapy *(Stage IV or recurrent NSCLC; previously untreated for advanced disease)*				
CheckMate 227 Part 1	PDC **(n = 583)**	All	All	Minimum: 4 years Median: 54.8 months (Range: 49.4-65.8 months)
Comparator: immunotherapy-based regimens *(Stage IIIB to stage IV or recurrent; 1L treatment with immunotherapy[a])*				
KEYNOTE-189	PEMBRO + PLAT + PEMX **(n = 410)**	Non-squamous	All	Minimum: 4 years Median: 46.3 months (Range: 41.8-54.1 months)
KEYNOTE-407	PEMBRO + PLAT + TAX **(n = 278)**	Squamous	All	Minimum: 3 years Median: 14.3 months (Range: 0.1-31.3 months)
IMpower150	ATEZO + BEVA + PLAT + TAX **(n = 359)**	Non-squamous	All	Final OS analysis Median: approx. 40.0 months (Minimum: 32.4 months)
KEYNOTE-024	PEMBRO **(n = 154)**	All	≥ 50%	Minimum: 5 years Median: 59.9 months (Range: 55.1-68.4 months)
KEYNOTE-042	PEMBRO **(n = 637)**	All	≥ 1% (≥ 50%, n = 299)[18]	Minimum: 3 years Median: 46.9 months (Range: 35.8-62.1 months)

[a]Approved for 1L treatment by the US Food and Drug Administration (FDA) or European Medicines Agency.
ATEZO, atezolizumab; BEVA, bevacizumab; PEMBRO, pembrolizumab; PEMX, pemetrexed; PLAT, platinum (cisplatin or carboplatin); TAX, paclitaxel.

Model framework

- A partitioned-survival model was developed to evaluate the cost-effectiveness of NIVO + IPI versus PDC and other immunotherapy-based regimens approved by the FDA for 1L treatment of stage IV or recurrent NSCLC[17]
- This model used the recently published ITC results.[3] Therefore, all clinical data informing the model were current at the time of the FPNMA and were used for quantitative evidence synthesis in the ITC
  - Consistent with evidence from the FPNMA,[3] NIVO + IPI was compared to PEMBRO monotherapy in patients with tumour PD-L1 expression ≥ 50% and against other combination regimens by histology in patients across the tumour PD-L1 spectrum
- The model comprised 3 mutually exclusive health states: progression free (PF), progressed disease (PD), and death
- Fitted parametric and spline-based distributions for PFS and OS derived from the CheckMate 227 Part 1 trial and the FPNMA were used directly to inform time spent in the PF and PD health states
- Treatment costs and treatment outcomes were calculated by combining occupancy in the PF and PD health states with costs, resource use, and measures of health effects associated with those states
- Weekly model cycles were used for the first 28 weeks, followed by 4-week cycles. Half-cycle correction was applied
- Key model outcomes included incremental cost-effective ratios (ICERs) calculated as cost per life-year (LY) gained and cost per quality-adjusted LY (QALY) gained

Survival analyses

- Survival (OS and PFS) curves were extrapolated to a 20-year time horizon (**Figure 1**, **Figure 2**)
- For NIVO + IPI and PDC treatments, 4-year OS and PFS data from the phase 3 CheckMate 227 Part 1 trial[10] were extrapolated using parametric distributions (exponential, Weibull, Gompertz, gamma, generalized gamma, log normal, log logistic) and spline-based models (1- and 2-knot configurations across 3 link functions: normal, hazards, and odds)
- Curve selections were based on statistical goodness of fit and validated with data from external sources, as per the approach explained by Berling et al[17]
- Survival distributions selected for the base case OS were 2-knot splines on hazards for the NIVO + IPI arm and log logistic for the PDC arm; for PFS, 1-knot spline on odds for NIVO + IPI and 2-knot splines on hazards for PDC were selected
- For other immunotherapy-based regimens (PEMBRO + PLAT + PEMX, PEMBRO + PLAT + TAX, ATEZO + BEVA + PLAT + TAX, and PEMBRO monotherapy; see **Table 1** for more details), time-to-event data were extrapolated to 20 years using the published time-varying HRs of OS and PFS estimated by Bayesian FPNMA[3]
- When needed, the OS and PFS curves were adjusted for general population mortality and corresponding OS, respectively (**Figure 1**, **Figure 2**)

Figure 1. Selected extrapolated OS curves for PDC, NIVO + IPI, and other immunotherapies (adjusted for general population mortality)

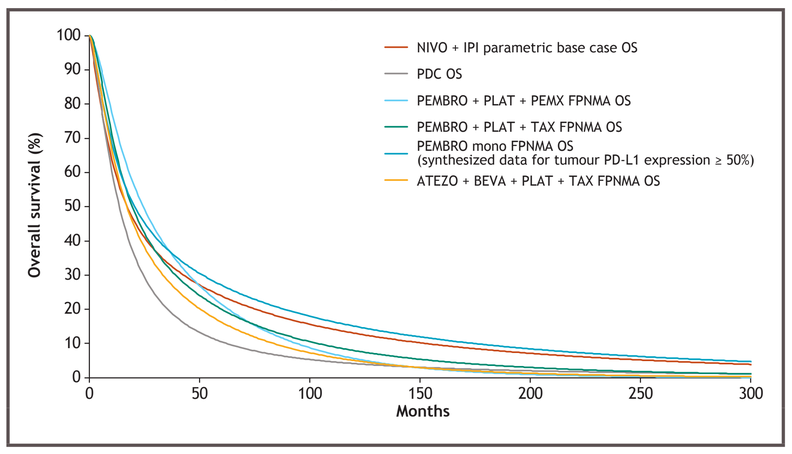
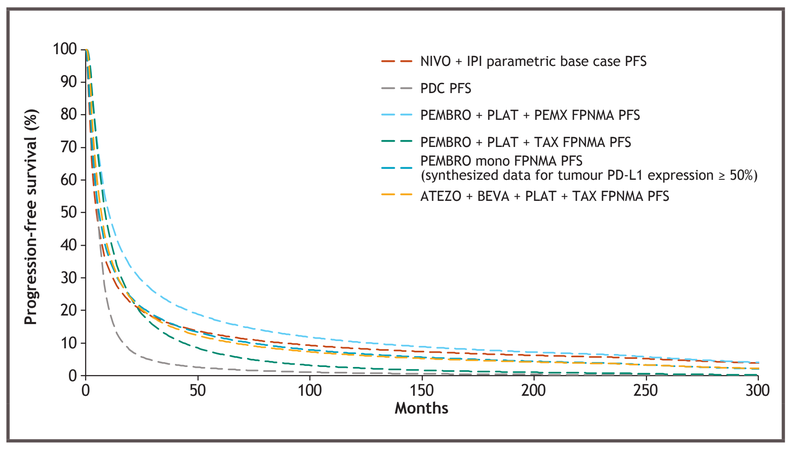


Figure 2. Selected extrapolated PFS curves for PDC, NIVO + IPI, and other immunotherapies (unadjusted for corresponding OS curves)



Safety data

- Grade 3-5 treatment-related adverse events (TRAEs), as reported for the respective clinical studies, were included in the analysis.[3,17] Grades 3-5 TRAEs are most likely to require active treatment and therefore most likely to require healthcare resource utilization and incur costs
- One-off utility decrements and management costs were applied in the first model cycle to account for adverse events (AEs)

Health-related quality of life: utilities

- Non-treatment-specific time-to-death (TTD) utilities, derived from EuroQol-5D-3L data collected in CheckMate 227 with a US value set, were used in the base case analysis[17] (**Table 2**)

Table 2. Time-to-death utilities

Time to death	Mean (overall)	SE (95% CI)
> 52 weeks	0.837	0.005 (0.828-0.846)
27-52 weeks	0.794	0.005 (0.788-0.804)
5-26 weeks	0.715	0.005 (0.705-0.726)
≤ 4 weeks	0.578	0.010 (0.557-0.598)

CI, confidence interval; SE, standard error.

Perspective and costs

- The analysis was conducted from a third-party payer perspective in the US (both public and private healthcare providers) following the approach reported in Berling et al in 2022[17]
- US-specific costs were included in the model, inflated to 2023 dollars (US$) as needed by the medical care consumer price index (CPI) using the average index across all months
  - These included costs for drug acquisition, drug administration, patient monitoring; disease management (PF and PD health state costs); end-of-life care; management of AEs; and subsequent treatments
- An annual discount rate of 3% was applied to both costs and outcomes
- Duration of treatment (DoT) Kaplan-Meier curves obtained from CheckMate 227 patient-level data were used to estimate treatment costs for NIVO + IPI and PDC
- PFS was used as a proxy to inform treatment duration for other immunotherapies
  - This is a reasonable assumption because patients are generally treated until progression, and PFS versus DoT curves were generally very similar for the few immunotherapy studies that reported both
- A treatment-stopping rule was applied at 24 months to all immunotherapies and to PEMX maintenance therapy in the PEMBRO + PLAT + PEMX regimen
- Key cost inputs are presented in **Table 3**

Table 3. Model cost inputs

Parameter	Costs, $
Disease management costs, PF (Q4W)[19]	514.37
Disease management costs, PD (Q4W)[19]	1558.53
End-of-life care costs[20,a]	16,408.99
Drug acquisition costs (per dose)[21]	
NIVO	6594.77
IPI	16,402.34
PDC	5353.64
PEMBRO + PLAT + PEMX	18,235.49
PEMBRO + PLAT + TAX	14,821.41
ATEZO + BEVA + PLAT + TAX	19,676.85
PEMBRO	10,897.12
Drug administration costs (per administration)[19]	
NIVO (Q2W) + IPI (Q6W)	197.22
PDC (Q3W)	208.06
PEMBRO + PLAT + PEMX (Q3W)	276.52
PEMBRO + PLAT + TAX (Q3W)	401.96
ATEZO + BEVA + PLAT + TAX (Q3W)	384.28
PEMBRO (Q3W)	132.16
Drug monitoring costs (per 4 weeks)[19,22]	
NIVO + IPI	180.43
PDC	124.78
PEMBRO + PLAT + PEMX	144.86
PEMBRO + PLAT + TAX	144.86
ATEZO + BEVA + PLAT + TAX	145.25
PEMBRO	134.53
Treatment-related AE costs[23,b]	
NIVO + IPI	161.38
PDC	4246.71
PEMBRO + PLAT + PEMX	5354.87
PEMBRO + PLAT + TAX	6736.35
ATEZO + BEVA + PLAT + TAX	5219.71
PEMBRO	111.05

[a]Inflated from 2009 values.
[b]Inflated from 2016 values.
Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks.

- Information on subsequent therapies was collected from publications[24-27] related to the respective trials. The proportions of patients who received subsequent therapy were 39.1% (NIVO + IPI), 55.1% (PDC), 55.3% (PEMBRO + PLAT + PEMX), 39.2% (PEMBRO + PLAT + TAX), 47.8% (ATEZO + BEVA + PLAT + TAX), and 50.0% (PEMBRO)

Results

Base case analysis

- Results of the base case analysis are shown in **Table 4**
- The total cost of NIVO + IPI was $269,122, and the number of LYs and QALYs was 3.40 and 2.77, respectively
- Treatment with NIVO + IPI was associated with:
  - Higher LYs/QALYs and higher costs versus PDC
  - Higher LYs/QALYs and lower costs (ie, dominant) versus PEMBRO + PLAT + PEMX
  - Higher LYs/QALYs and higher costs versus PEMBRO + PLAT + TAX
  - Higher LYs/QALYs and lower costs (ie, dominant) versus ATEZO + BEVA + PLAT + TAX
  - Lower LYs/QALYs and higher costs (ie, dominated) versus PEMBRO in patients with tumour PD-L1 expression ≥ 50%

Table 4. Base case results for NIVO + IPI versus PDC and immunotherapies

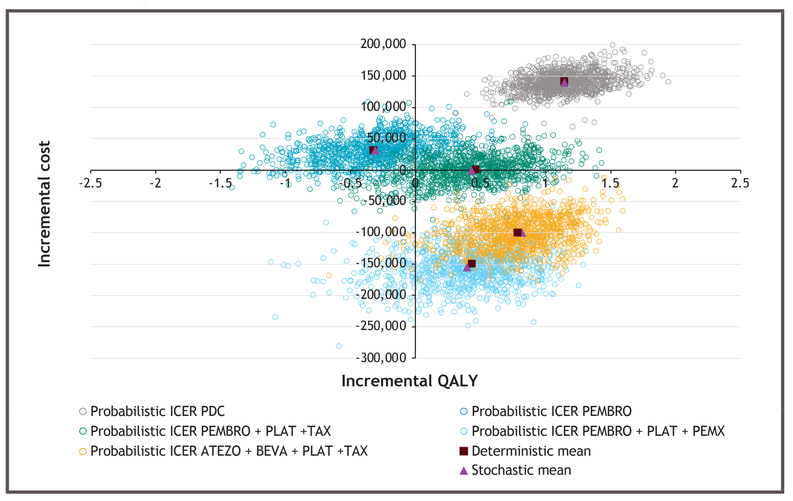
Treatment	Total cost, $	LYs[a]	QALYs[a]	ICER,[b] $
NIVO + IPI *(both histologies; all tumour PD-L1 expression levels)*	269,122	3.40	2.77	–
PDC *(both histologies; all tumour PD-L1 expression levels)*	127,007	2.09	1.63	124,306
PEMBRO + PLAT + PEMX *(non-squamous)*	418,595	3.01	2.34	Dominant
PEMBRO + PLAT + TAX *(squamous)*	268,678	2.97	2.31	957
ATEZO + BEVA + PLAT + TAX *(non-squamous)*	368,679	2.51	1.96	Dominant
PEMBRO *(both histologies; tumour PD-L1 expression ≥ 50%)*	237,313	3.78	3.10	Dominated

[a]QALYs and LYs are values discounted at 3% annually.
[b]ICERs for NIVO + IPI vs comparators.

Sensitivity analyses

- Results of probabilistic sensitivity analyses were consistent with the base case findings (**Figure 3**)

Figure 3. Cost-effectiveness plane for NIVO + IPI versus PDC and immunotherapies



Conclusions

- This cost-effectiveness analysis is the first to incorporate published FPNMA results comparing NIVO + IPI against other immunotherapies used as 1L treatment for metastatic NSCLC in the US
- The LY and QALY outputs from the model are consistent with results from the published FPNMA,[3] suggesting a trend towards clinical benefit with NIVO + IPI versus other immunotherapies + chemotherapy, for lower or equivalent total costs
- NIVO + IPI is a cost-effective option when compared to PDC and most other immunotherapy regimens currently available in the US, apart from the comparison to PEMBRO monotherapy in patients with tumours with high PD-L1 (≥ 50%) expression

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