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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 Peru

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Introduction

- Lung cancer is the leading cause of cancer mortality worldwide, accounting for 18% of all cancer-related deaths[1,2]
- Non-small cell lung cancer (NSCLC) is the most common type of lung cancer.[2] Patients with NSCLC often present with advanced disease,[1-3] which is associated with a 5-year survival rate of just 9%[4]
- Recently, however, immunotherapy-based therapies 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]
  - NIVO + IPI is recommended as a 1L treatment option for metastatic NSCLC by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[14] and American Society of Clinical Oncology (ASCO) living guideline[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]
- NSCLC patients in Peru have access to various immunotherapies including NIVO + IPI, but thus far only pembrolizumab plus carboplatin and paclitaxel (PEMBRO + PLAT + TAX) has been appraised and recommended by the local HTA agency RENETSA as first-line treatment option for patients with metastatic, squamous, EGFR- and ALK-unmutated NSCLC[17]

Objective

- The objective of this study was to evaluate the cost-effectiveness of NIVO + IPI versus PDC and other immunotherapies used as first-line treatment for stage IV or recurrent NSCLC in Peru from a third-party payer perspective
- The analysis was based on a previously published partitioned-survival model using efficacy, safety, and utility data from the Phase III CheckMate 227 Part 1 trial with 49.4-month minimum follow-up for OS[18]

Methods

- This cost-effectiveness analysis (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
  - For the treatment regimens relevant to the Peruvian setting, four 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 relevant 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)*				
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)

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 for 1L treatment of stage IV or recurrent NSCLC[18]
- It comprised 3 mutually exclusive health states: progression free (PF), progressed disease (PD), and death
- 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 other combination regimens by histology (squamous or non-squamous) in patients across the tumour PD-L1 spectrum (**Table 1**)
- 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
- A 20-year time horizon was used in the base case analysis.
- 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[18]
- 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 and ATEZO + BEVA + PLAT + TAX; 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]
- To ensure clinical plausibility, the OS and PFS curves were adjusted for general population mortality (based on local life tables) 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)

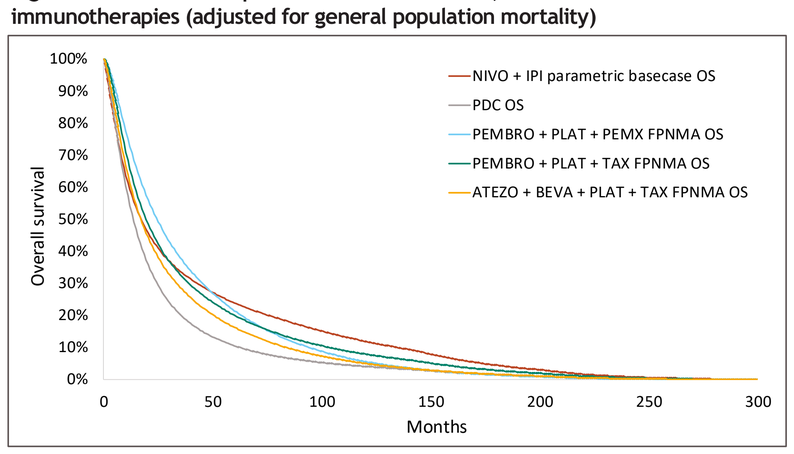
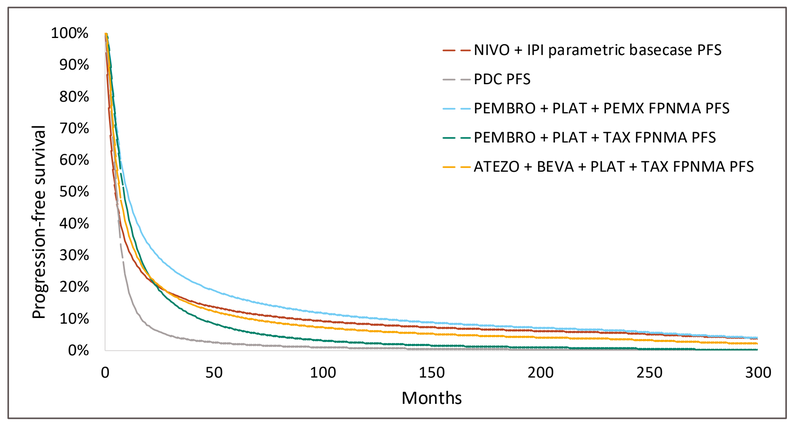


Figure 2. Selected extrapolated PFS curves for PDC, NIVO + IPI and other immunotherapies (unadjusted for corresponding OS curves)



Safety data

- Grade 3–5 treatment-related adverse events (TRAEs), as reported for the respective clinical studies, were included in the analysis.[3,18] 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 these TRAEs

Health-related quality of life: utilities

- Non-treatment-specific time-to-death (TTD) utilities derived from EQ-5D-3L data collected in CheckMate 227 were used in the base case analysis[18] **(Table 2)**
- In the absence of an EQ-5D-3L-value set for Peru, the model used utility values derived with the relevant Argentinian value set as a proxy

Table 2. Time-to-death utilities

Time to death	Mean (overall)	SE (95% CI)
>52 weeks	0.838	0.005 (0.828, 0.847)
27-52 weeks	0.790	0.006 (0.780, 0.802)
5-26 weeks	0.711	0.006 (0.700, 0.722)
≤4 weeks	0.574	0.011 (0.553, 0.596)

CI, confidence interval; SE, standard error

Perspective and costs

- The analysis was conducted from a third-party Peruvian payer perspective and costs were expressed in 2024 Peruvian Sols (PEN)
- 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**
- Information on subsequent therapies was collected from publications[24-26] 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), and 47.8% (ATEZO + BEVA + PLAT + TAX).

Table 3. Model cost inputs

Parameter	Costs, PEN
Disease management, PF (Q4W)[20]	645.31
Disease management, PD (Q4W)[20]	1232.73
End-of-life care	85.00
Drug acquisition costs (per dose)[21]	
NIVO	12,206.38
IPI	20,083.40
PDC	358.61
PEMBRO + PLAT + PEMX	22,247.08
PEMBRO + PLAT + TAX	33,154.91
ATEZO + BEVA + PLAT + TAX	31,667.44
Drug administration costs (per administration)[22]	
NIVO (Q2W) + IPI (Q6W)	101.25
PDC (Q3W)	101.25
PEMBRO + PLAT + PEMX (Q3W)	101.25
PEMBRO + PLAT + TAX (Q3W)	283.30
ATEZO + BEVA + PLAT + TAX (Q3W)	101.25
Drug monitoring costs (per 4 weeks)[20]	
NIVO + IPI	219.00
PDC	179.81
PEMBRO + PLAT + PEMX	215.81
PEMBRO + PLAT + TAX	215.81
ATEZO + BEVA + PLAT + TAX	204.81
Treatment-related adverse event costs[23]	
NIVO + IPI	602,00
PDC	10,249.61
PEMBRO + PLAT + PEMX	19,381.83
PEMBRO + PLAT + TAX	21,305.65
ATEZO + BEVA + PLAT + TAX	16,407.56

Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks

Results

Base case analysis

- Results of the base case analysis are shown in **Table 4**
- The total cost of NIVO + IPI was PEN 359,065, and the number of LYs and QALYs was 3.17 and 2.57, 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 lower costs (ie, dominant) versus PEMBRO + PLAT + TAX
  - Higher LYs/QALYs and lower costs (ie, dominant) versus ATEZO + BEVA + PLAT + TAX
- Disaggregated and total cost outcomes for all comparators are presented in **Table 5**

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

Treatment	Total cost, PEN[a]	LYs[a]	QALYs[a]	ICER,[b] PEN
NIVO + IPI *(both histologies; all tumour PD-L1 expression levels)*	359,065	3.17	2.57	-
PDC *(both histologies; all tumour PD-L1 expression levels)*	86,759	2.04	1.54	264,116
PEMBRO + PLAT + PEMX *(non-squamous)*	500,610	3.01	2.26	Dominant
PEMBRO + PLAT + TAX *(squamous)*	476,063	2.92	2.18	Dominant
ATEZO + BEVA + PLAT + TAX *(non-squamous)*	538,480	2.50	1.87	Dominant

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

Table 5. Disaggregated and total cost outcomes for all comparators (PEN)

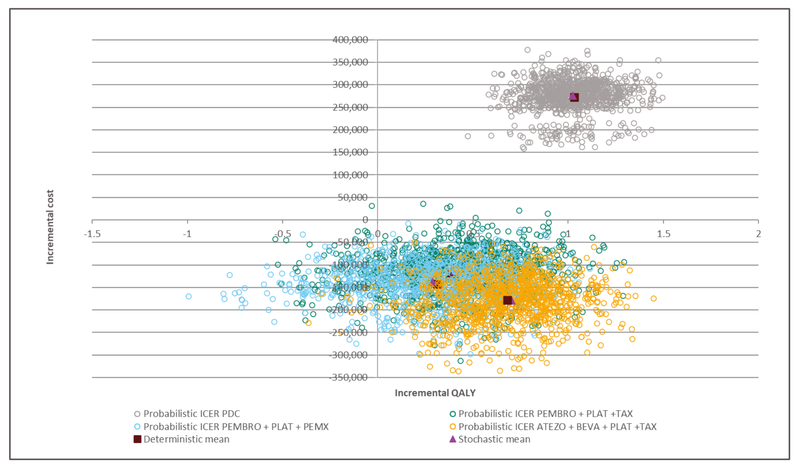
Treatment	Acquisition	Administration	Monitoring	Disease mgmt	TRAE mgmt	Subsequent Tx	Total
NIVO + IPI	312,492	1,635	1,749	36,390	602	6,198	359,065
PDC	2,218	733	955	26,875	10,250	45,729	86,759
PEMBRO + PLAT + PEMX	410,897	1,877	4,882	31,142	19,382	32,430	500,610
PEMBRO + PLAT + TAX	405,569	1,988	2,622	35,410	21,306	9,168	476,063
ATEZO + BEVA + PLAT + TAX	476,250	2,491	4,570	27,053	16,408	11,709	538,480

Costs are values discounted at 3% annually
Mgmt, management; TRAE, treatment-related adverse events; Tx, therapies

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



Conclusion

- 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 Peru
- 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 total costs
- NIVO + IPI is a cost-effective option when compared to other immunotherapy regimens currently available in Peru

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