Health economic evaluation incorporating mixture cure survival analysis of nivolumab plus ipilimumab for previously untreated metastatic NSCLC

EE513

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Background

- The immune checkpoint inhibitor (ICI) combination of nivolumab plus ipilimumab (NIVO + IPI) has demonstrated a significant overall survival benefit vs platinum doublet chemotherapy (Chemo) amongst patients with previously untreated metastatic non-small cell lung cancer (NSCLC) in the CheckMate 227 study[1]
- CheckMate 227 is an ongoing multinational, randomised, open-label Phase 3 trial of NIVO + IPI vs Chemo.[1] Independent primary outcomes from this trial were overall survival (OS) in patients with programmed-death ligand 1 (PD-L1) ≥1% and progression-free survival (PFS) in patients with tumour mutational burden (TMB) ≥10 mut/Mb. Simultaneously, patient-reported outcomes were collected to inform health status as assessed by the EQ-5D index were collected to for an exploratory objective
- Compelling evidence has shown that dual ICI treatments offer long-term survival to a substantial proportion of patients,[2-5] suggesting that patients may be partitioned into a group experiencing more rapid progression, and one experiencing long-term survival
- The results of cost-effectiveness analysis of treatments in metastatic NSCLC can be highly sensitive to the difference in mean survival duration between treatments, which may in turn be sensitive to the approach taken to extrapolative survival modelling from trial data
- Mixture-cure models (MCM) allow for easily interpretable marginal hazard function and alternative rate of benefit accrual for those in 'long-term response' (LTR)

Objectives

- To evaluate the cost-effectiveness of NIVO + IPI vs Chemo in previously untreated metastatic NSCLC incorporating survival estimates from MCMs informed by the 3-year database lock (DBL) of CheckMate 227

Methods

Core assumptions are shown in Table 1

Table 1. Summary of Core Assumptions

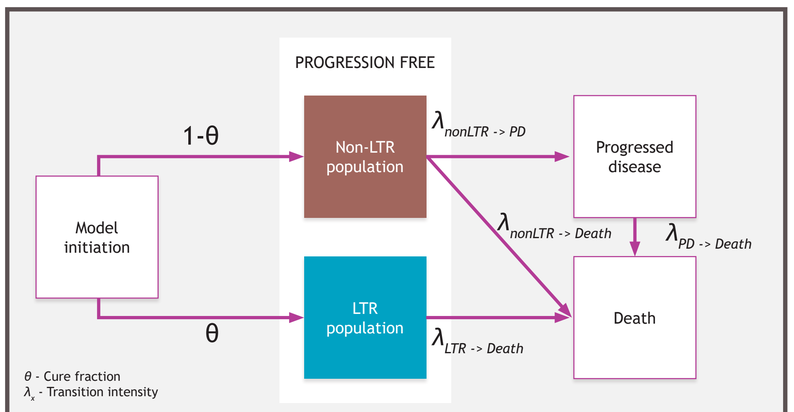
Feature	Cost-Effectiveness Model Summary
Perspective	US 3rd party payer perspective
Model type	Semi Markov model
Health states	Pre-progression (non-LTR), post-progression (non-LTR), long-term responders (LTR), death
Cycle length	3-Weekly
Time horizon	Lifetime (until 99% of patients have died)
Comparators	Nivolumab plus ipilimumab vs platinum doublet chemotherapy
Population	Consistent with CheckMate 227 ITT population
Resource use	Treatment costs (including administration), health state costs, adverse event, terminal care
Health state utility	Derived from CheckMate 227 ITT EQ-5D-3L
Discount rates	3% costs and 3% effects consistent with ICER reference case

ICER: incremental cost-effectiveness ratio; ITT, intention to treat; LTR: long-term responders ('LTR' fraction).

Model Structure

- Semi Markov mixture-cure approach (**Figure 1**)
  - Patients move through health states over time based on transition probabilities estimated from CM 227 progression-free survival (PFS) and overall survival (OS) data
  - Mixture cure survival analysis estimated the proportion of patients who are long-term responders (LTR), also referred to as the 'cured' proportion in mixture cure analysis

Figure 1. Model Structure



LTR, long-term responders; PD, progressed disease.

Survival Analysis: PFS and OS

- Mixture cure survival analysis undertaken to explore long-term survival trends
  - Assumes trial population is a mixture of two groups:
    - Long term responders to treatment (LTR)
    - Remainder of population (non-LTR)
  - The risk of death in the 'LTR' population assumed to incur general population mortality hazard
  - The risk of death for the non-LTR population assumed to be a mix of background mortality and excess disease mortality modelled from trial data using parametrically defined hazard
  - The survival for a treated population with a cure fraction is the weighted average of the survival among the 'LTR' and 'non-LTR' patients
  - Results of the survival analyses were compared to a previously published composite survival curve[1]

Cost-effectiveness Analysis Implementation: Survival (PFS and OS)

- Base case analysis
  - Mixture cure model: Lognormal distributions:
- Scenario analysis
  - Alternative survival models, including piecewise Kaplan-Meier/parametric models, and assumption of constant hazard ratio of Chemo vs NIVO + IPI

Health-related quality of life (Table 2) and time-to-death utilities (Table 3) were derived from published CEA[6]

Resource use

- Estimates as per previously published CM 227 informed CEA for consistency.[6] US Health care payer perspective with costs in USD indexed to 2021 using the medical care consumer price index (CPI), incorporating direct costs of care inclusive of:
  - Drug acquisition, administration and monitoring
  - Management of treatment related adverse events
  - Subsequent treatment costs (post-discontinuation 1st line treatment)
  - Disease management (PF and PD health states)
  - End-of-life care
  - Time on treatment data based on observed CM 227 data (within-trial)
- Details provided in online supplementary materials

Treatment-related adverse events

- Estimates as per previously published CM 227 informed CEA for consistency.[6] Details provided in online supplementary materials

Sensitivity and scenario analysis

- Sensitivity to parameter uncertainty was tested in probabilistic sensitivity analysis (PSA). Further scenarios investigating sensitivity to groups of model inputs were undertaken in one-way sensitivity analysis, including the use of utilities from the CheckMate 9LA study in which patients were treated with NIVO + IPI + two cycles of chemo vs four cycles of chemo alone. Details are given in online supplementary material

Table 2. Utility estimates from CM 227

	CheckMate 227[6]			CheckMate 9LA[7]
	Pooled mean utility	Treatment-specific utility		Pooled mean utility*
		NIVO + IPI	Chemo	
Health state				
Progression-free	0.795	0.793	0.796	0.797
Progressive disease	0.746	0.752	0.739	0.738
Long-term responsive	0.816[8]	0.816[8]	0.816[8]	0.816[8]

*Used in one-way sensitivity analysis. Treatment ratio of health state utility values from CheckMate 227 used to scale CheckMate 9LA utilities to treatment specific values. Age adjustment performed per US population norms.[8] Chemo: platinum doublet chemotherapy; IPI: ipilimumab; NIVO: nivolumab.

Table 3. Time-to-death utility estimates from CheckMate 227 (Sensitivity analysis)

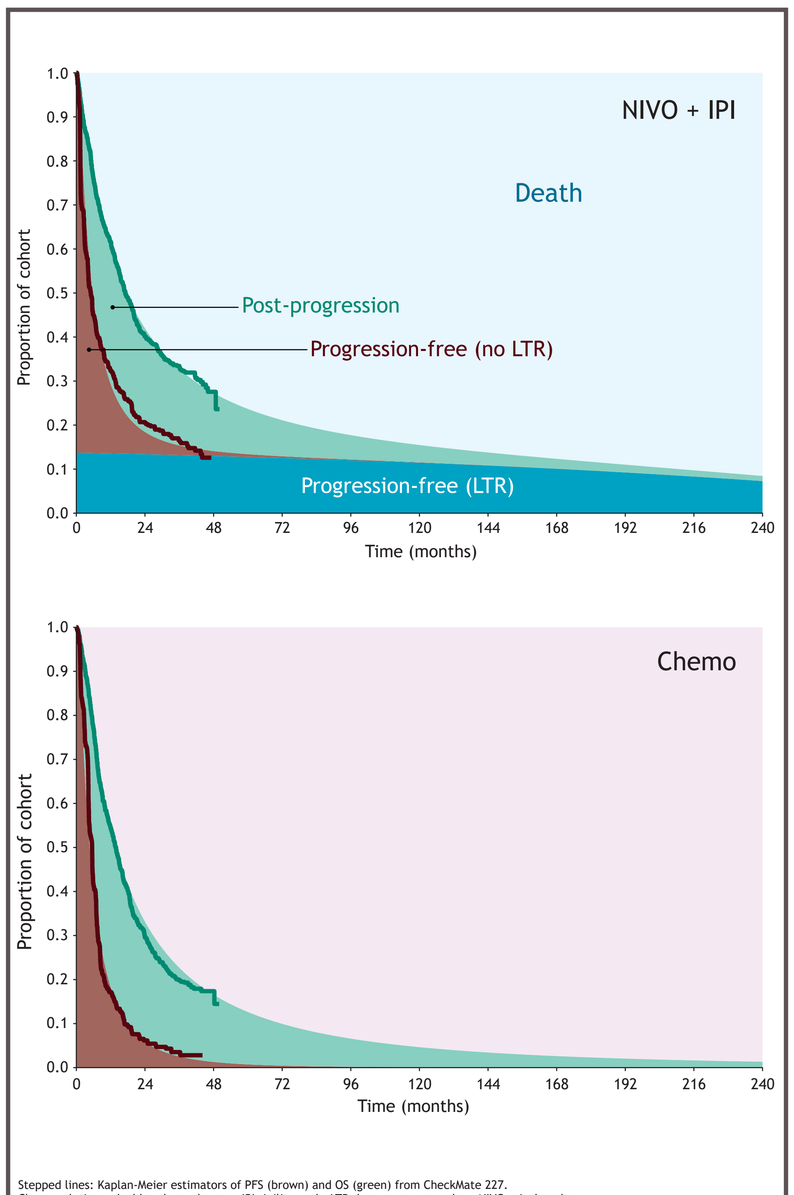
Time-to-death (weeks)	Utility*
0-4	0.577
4-26	0.715
26-52	0.794
52+	0.838

* Mixed model (repeated measures per patient) regression on CM 227. Time-to-death utilities adapted to 3-week cycle length. Source: Berling M et al., 2021[6]
CM 227: CheckMate 227.

Results

- The base case survival models gave plausible goodness-of-fit compared with the trial data (**Figure 2**) and plausible extrapolation vs external data (**Table 4**)
- Base-case cost-effectiveness analysis (**Table 5**) indicated that, based on the mixture cure lognormal distribution, NIVO + IPI was associated with a cost per additional QALY of $93,982
- LTR state occupancy was predicted to be substantial for NIVO + IPI and negligible for Chemo (**Table 6**). NIVO + IPI had lower average time in pre-progression state, as fewer patients were in this state, and lower time in post-progression as fewer patients modelled as progressing
- The limits of the 95% confidence interval based on probabilistic sensitivity analysis (PSA) were $129,705-$157,079 for incremental costs and 0.86-2.04 for incremental QALYs, indicating results were robust in PSA analyses (**Figure 3**)
- Results were sensitive to the distribution assumed for patients without LTR in the mixture cure approach and whether an OS or PFS endpoint was used to predict the LTR fraction. These scenarios resulted in differing estimates of the LTR fraction; larger LTR fractions were associated with lower ICERs. Results were also sensitive to utility values and drug acquisition costs (**Figure 4**)

Figure 2. Model state occupancy - base case



Stepped lines: Kaplan-Meier estimators of PFS (brown) and OS (green) from CheckMate 227.
Chemo: platinum doublet chemotherapy; IPI: ipilimumab; LTR: long-term responders; NIVO: nivolumab; PFS, progression-free survival; OS, overall survival.

Table 4. Overall survival for NIVO + IPI: historical conditional survival construction vs model prediction

Model	Year 5	Year 10	Year 15
Constructed OS	25.6%	13.1%	8.1%
Log Normal/LTR + LT	23.9%	14.1%	9.6%

Details in online supplementary material.
IPI: ipilimumab; LT: life table mortality; LTR: long-term responders; NIVO: nivolumab; OS: overall survival.

Table 5. Base case cost-effectiveness results

	NIVO + IPI	Chemo	Δ	ICER
Total life years	3.970	2.275	1.695	–
Total QALYs	3.142	1.708	1.434	–
Total Costs, $	245,023	110,241	134,792	93,982

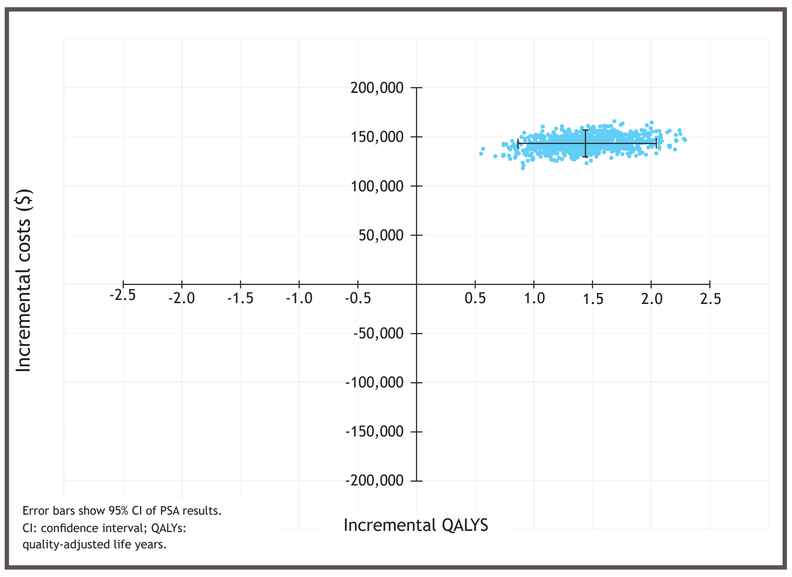
Chemo: platinum doublet chemotherapy; ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; NIVO: nivolumab; QALYs: quality-adjusted life years.

Table 6. Model predicted outcomes disaggregated by health states

	NIVO + IPI	Chemo
Pre-progression (Excluding LTR)		
Life years	0.5682	0.6588
QALYS	0.4527	0.5268
Costs, $	183,755	50,474
Post-progression		
Life years	1.3941	1.6162
QALYS	1.0469	1.1927
Costs, $	46,323	59,767
Long-term response		
Life years	2.0077	0.0000
QALYS	1.6426	0.0000
Costs, $	14,945	0

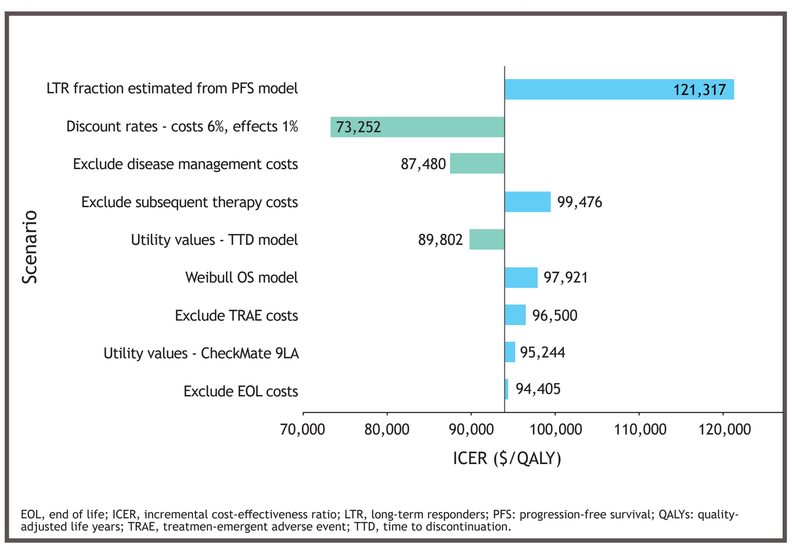
Chemo: platinum doublet chemotherapy; IPI: ipilimumab; NIVO: nivolumab; LTR: long-term responders; QALYs: quality-adjusted life years.

Figure 3. Probabilistic sensitivity analysis (PSA) - cost-effectiveness plane



Error bars show 95% CI of PSA results.
CI: confidence interval; QALYs: quality-adjusted life years.

Figure 4. One-way sensitivity analysis: Tornado Diagram



EOL, end of life; ICER, incremental cost-effectiveness ratio; LTR, long-term responders; PFS: progression-free survival; QALYs: quality-adjusted life years; TRAE, treatmen-emergent adverse event; TTD, time to discontinuation.

Discussion

- Model uses lognormal models for uncured fraction, which predict a lower LTR fraction than other models with similar goodness of fit (e.g. Weibull) models. The lognormal was selected after cross-validation of survival predictions to an early analysis of 5-year data from CM 227. Results informed by the 3-year DBL are presented for comparison of modelling assumptions to other estimates from this DBL
- Using MCM approach, incremental LYs and QALYS were estimated higher than previously published spline-based approach, which predicted incremental LYs: 1.54; QALYS: 1.33; ICER: $106,553
- Given evidence of an LTR, a mixture-cure approach may capture important trends in the observed risk of death and avoid underestimating the benefit of an effective therapy
- Estimating the LTR fraction from PFS rather than OS implies a lower LTR fraction in many ICI trials. Long-term validation of the best outcome for accurately predicting LTR fraction for ICIs would reduce uncertainty in cost-effectiveness estimation

Conclusions

- NIVO + IPI is a cost-effective treatment vs Chemo under a range of survival modelling assumptions. In developing a novel MCM CEM framework for previously untreated NSCLC, this study has demonstrated the importance of accounting for mixtures of survival distributions when establishing the value for money of NIVO + IPI for healthcare decision makers

References

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Disclosures

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