Identifying and Quantifying Elements of Value for Nivolumab and Ipilimumab in First-Line Metastatic Non-Small Cell Lung Cancer

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Introduction

- Cost-effectiveness analyses (CEA) are commonly used by health technology appraisal (HTA) agencies to inform reimbursement decisions for new therapies.
  - A new therapy's efficacy, safety profile and associated costs are compared to those of the current standard of care (SoC) to estimate its cost-effectiveness relative to country-specific willingness-to-pay (WTP) thresholds.
  - CEA are often performed adopting a payer's perspective and, consequently, are limited to the inclusion of direct costs and quality-adjusted survival.
  - Few HTA agencies recommend expanding the CEA to a societal perspective, requiring the inclusion of productivity losses and additional indirect costs.
  - Neither the traditional payer's perspective nor the traditional societal perspective account for any additional elements of value that treatments may generate (e.g., caregiver burden, insurance value, option value, or value of hope).
- In 2018, the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) Special Task Force identified twelve potential elements of value that could be considered for HTA CEA.[1]
  - Limited evidence is currently available on the impact that novel value elements could have on cost-effectiveness estimates and on HTA final recommendations.

Objective

- The objective of this study was to assess the impact of novel value elements on payer's perspective and societal perspective cost-effectiveness results associated with nivolumab plus ipilimumab (N+I) as first-line strategy for patients with metastatic non-small cell lung cancer (mNSCLC) compared with platinum doublet chemotherapy (PDC).
- Following the approach adopted in a previous Canadian CEA for second-line mNSCLC[2], this study estimated the net monetary benefit (NMB) associated with N+I in the United Kingdom (UK); the NMB was calculated for three different perspectives: traditional payer's, traditional societal and broad societal.
  - The NMB was calculated as the difference between incremental benefits (expressed in monetary terms using a UK WTP threshold of £50,000/quality-adjusted life-year [QALY] gain) and incremental costs.
    - A positive NMB indicates that, at the specified WTP threshold, the new intervention (i.e. N+I) provides acceptable value for money, while a negative NMB indicates that the new intervention's costs exceed its benefits.

Methods

Traditional payer's perspective

- The first perspective used, the traditional payer's perspective, included direct medical costs to the UK payer, the National Health Service (NHS), and benefits for the patient covered by that payer.
- The CEA for the traditional payer's perspective was mostly informed by a previous CEA for N+I versus PDC for first-line mNSCLC in the United States (US) – *Berling et al. (2022)*.[3]
  - A three-health state partitioned survival model (PSM) with progression-free (PF), progressed disease (PD) and death health states was developed by *Berling et al.*[3] to estimate the cost-effectiveness of N+I compared with PDC over a lifetime horizon of 25 years.
  - For this UK CEA, the most recent 5-year database lock from the CheckMate 227 Part 1 trial, external data and long-term registry data were used to inform long-term progression-free survival (PFS) and overall survival (OS).
    - CheckMate 227 Part 1 is an open-label, randomized, Phase III trial evaluating first-line nivolumab-based regimens for mNSCLC.[4]
  - Grade 3–5 treatment-related adverse events (AEs) experienced by at least 5% of patients in any arms of the CheckMate 227 Part 1 trial were included in the analysis.
  - CheckMate 227 Part 1 EQ-5D-3L results were used to derive UK-specific utility estimates based on the time-to-death approach.
  - CheckMate 227 Part 1 duration of therapy was used to estimate N+I and PDC treatment-related costs (i.e., drug acquisition, administration and monitoring costs).
  - UK-specific unit costs for drug acquisition, administration, monitoring, disease management, end-of-life, AE management and subsequent treatments were used for this UK CEA.

Traditional societal perspective

- The traditional payer's perspective CEA was expanded to a traditional societal perspective CEA by including indirect costs associated with patients' productivity losses.
- To reflect the patients' productivity losses in first-line mNSCLC, a targeted literature review (TLR) was performed to identify estimates of cost burden for patients with mNSCLC.
  - A European study conducted among patients with first-line mNSCLC and their caregivers informed patients' hours of missed work due to absenteeism and presenteeism.[5]
  - UK published sources informed the average hourly wage (£16.79) and the average age of retirement (64.55 years).[6]

Broad societal perspective

- A TLR was performed to identify: (I) novel value elements relevant to the first-line mNSCLC setting and (II) associated quantitative measures.
  - Consistent with the previous Canadian CEA for second-line mNSCLC[2], the novel value elements incorporated in broad societal perspective CEA were: (I) caregiver burden, (II) insurance value, (III) option value and (IV) value of hope.

Broad societal perspective - Caregiver Burden

- Similar to the traditional payer's perspective, the broad societal perspective included indirect costs associated with caregivers' productivity losses (**Table 1**).

Table 1. Caregiver burden associated with N+I in first-line mNSCLC

Novel value element	Inputs and sources
Caregivers' productivity losses	A TLR was performed to estimate productivity losses for caregivers' in mNSCLC; a European study[5] and UK published sources[6] informed: • caregivers' hours of missed work due to absenteeism/ presenteeism, caregivers' average age[5] • UK average hourly wage and average age of retirement[6]

mNSCLC, metastatic non-small cell lung cancer; N+I, nivolumab plus ipilimumab; TLR, targeted literature review; UK, United Kingdom.

Broad societal perspective - Insurance Value

- The insurance value is described in the ISPOR Special Task Force[1] as the additional value a new treatment provides to healthy individuals as it reduces the "physical risk" of getting sick and the "financial risk" of spending money on medical care.
- The broad societal perspective included the insurance value associated with N+I in first-line mNSCLC (**Table 2**).

Table 2. Insurance value associated with N+I in first-line mNSCLC

Novel value element	Inputs and sources
Insurance value	The insurance value of N+I in the mNSCLC population was informed by a preference survey administered to two cohorts of US adults: healthy individuals and individuals diagnosed with lung cancer[7] • The value to the healthy relative to the sick was 89.8%[7]

mNSCLC, metastatic non-small cell lung cancer; N+I, nivolumab plus ipilimumab; US, United States.

Broad societal perspective - Option Value

- The option value is described in the ISPOR Special Task Force[1] as the additional value a new treatment provides to patients as it offers the option to benefit from future medical innovations.
- The broad societal perspective included the option value associated with N+I in first-line mNSCLC (**Table 3**).

Table 3. Option value associated with N+I in first-line mNSCLC

Novel value element	Inputs and sources
Option value	The model developed by Snider et al. (2017)[8] was replicated: • Step 1: estimate pre-N+I first-line mNSCLC OS curve from SEER[9] • Step 2: estimate forecast survival improvement by applying lung cancer-specific mortality rate decrease[10] to the curve from step 1 • Step 3: estimate N+I survival by applying HR_{OS} between N+I and PDC (CheckMate 227 Part 1) to curves from step 1 (N+I OS without further innovation)) and step 2 (N+I OS with further innovation) • Step 4: difference between curves estimated in step 3 provided the option value for N+I in first-line mNSCLC (3.6% of PDC average survival)

HR, hazard ratio; mNSCLC, metastatic non-small cell lung cancer; N+I, nivolumab plus ipilimumab; OS, overall survival; PDC, platinum doublet chemotherapy; SEER, Surveillance, Epidemiology and End Results.

Broad societal perspective - Value of Hope

- The value of hope is described in the ISPOR Special Task Force[1] as the additional value a new treatment might provide to patients that are willing to exchange some expected survival for a small chance of much longer survival (tail of the curve).
- CheckMate 227 Part 1 trial has demonstrated a decrease in the mortality hazard rates associated with N+I (long-term durable survival gain versus PDC).
  - N+I in mNSCLC demonstrated a decrease in mortality hazard rates: OS rates for the subgroup of patients with PD-L1 expression ≥1% were 33%, 28% and 24% at 3, 4 and 5 years, respectively.[4]
- The value of hope of N+I was informed by a discrete-choice experiment (DCE) performed by *Hauber et al. (2020)* on US patients with mNSCLC and oncologist.[11]
  - The DCE was designed to elicit trade-offs patients and oncologists are willing to make among second-line NSCLC treatment attributes ("expected survival" and "long-term survival") by observing choice patterns.
  - Attributes and attribute levels used in the DCE were based on the results of two Phase III clinical trials in second-line mNSCLC.[12]
  - The results from the DCE provided preference weight estimates used to calculate the importance of each attribute relative to other attributes.
    - The study found that patients with mNSCLC considered increases in the probability of "long-term survival" as more important than increases in "expected survival".
- To adapt the DCE performed by *Hauber et al.*[11] to the first-line mNSCLC setting, the results from CheckMate 227 Part 1[4] were used to update the attribute levels.
  - It was estimated that N+I value of hope (i.e., patients' preference for improvements in "long-term survival" relative to "expected survival") correspond to 0.14 QALYs in addition to the baseline incremental QALYs (traditional payer's perspective CEA where patients' preferences are not considered).

Results

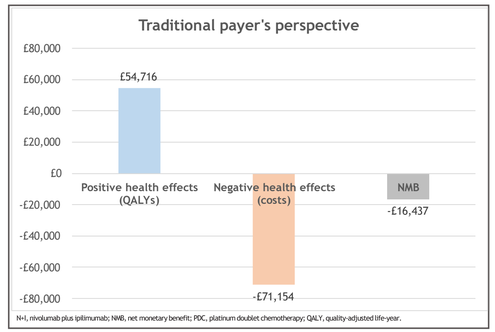
- In the traditional payer's perspective CEA, N+I was associated with higher costs and provided more QALYs compared with PDC (**Table 4**).
  - The incremental costs of N+I versus PDC were £71,154, while the incremental QALYs were 1.09.
    - The incremental costs were mainly driven by higher treatment acquisition costs (+£74,504) and higher disease management costs (+£3,439).
  - Assuming a UK WTP threshold of £50,000/QALY gain, 1.09 incremental QALYs would be valued at £54,716 under the traditional payer's perspective.
  - Combining costs and benefits, the NMB for N+I versus PDC was -£16,437 at a WTP threshold of £50,000/QALY gain (**Figure 1**).
    - A negative NMB indicated that N+I associated costs exceeded its benefits when performing the analysis under the traditional payer's perspective.
- In the traditional societal perspective CEA, N+I was associated with higher costs and provided more QALYs compared with PDC (**Table 4**).
  - The incremental costs of N+I versus PDC were £71,190, while the incremental QALYs of N+I versus PDC remained 1.09.
    - There was a marginal difference in incremental costs between the traditional payer's perspective and the traditional societal perspective.
  - Combining costs and benefits, the NMB for N+I versus PDC was -£16,474 at a WTP threshold of £50,000/QALY gain (**Figure 2**).
- In the broad societal perspective CEA, N+I was associated with higher costs and provided more QALYs compared with PDC (**Table 4**).
  - The incremental costs of N+I versus PDC were £73,690, while the incremental QALYs of N+I versus PDC increased by 118%, from 1.09 to 2.38.
    - The inclusion of value of hope increased the baseline incremental QALYs by 0.14 (+13% versus baseline); by adding option value, the incremental QALYs increased further by 0.05 (+17% versus baseline); and the inclusion of insurance value further increased the incremental QALYs by 1.10 (+118% versus baseline).
    - More than 50% of gain in QALYs estimate (1.29) originated from the inclusion of novel value elements.
  - Combining costs and benefits, the NMB for N+I versus PDC was +£45,517 at a WTP threshold of £50,000/QALY gain (**Figure 3**).
- The benefits improvement associated with N+I estimated expanding the CEA from a traditional payer's perspective to a broad societal perspective considerably outweighed the small increase in costs.

Table 4. Results of CEA analysis for N+I versus PDC in first-line mNSCLC adopting a broad societal perspective

Component	Traditional payer's[a]	Traditional societal	Broad societal
Incremental benefit[b]	**£54,716**	**£54,716**	**£119,207**
Incremental QALYs	1.09	1.09	1.09
Incremental QALYs with added VH (A)	NA	NA	1.23 (+13%)
Incremental QALYs [=(A)x(1+OV)]	NA	NA	1.28 (+17%)
Incremental QALYs [=(A)x(1+OV+IV)]	NA	NA	2.38 (+118%)
Incremental costs	**£71,154**	**£71,190**	**£73,690**
Disease management costs	£3,439	£3,439	£3,439
Treatment acquisition costs	£74,564	£74,564	£74,564
Treatment administration and monitoring costs	£2,175	£2,175	£2,175
Adverse events costs	-£581	-£581	-£581
Subsequent treatment costs	-£8,321	-£8,321	-£8,321
Other direct costs	-£122	-£122	-£122
Productivity loss costs	NA	£36	£36
Caregiver burden costs	NA	NA	£2,500
NMB (at UK WTP of £50,000/QALY gain)	**-£16,437**	**-£16,474**	**+£45,517**
ICUR	£65,021	£65,054	£30,908

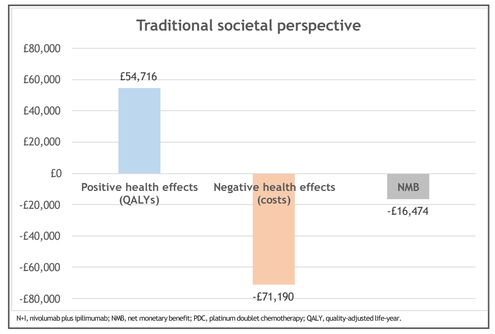
[a]Analysis originally performed by *Berling et al. (2022)*.[3]
[b]Total incremental QALYs x value of a QALY of £50,000.
CEA, cost-effectiveness analysis; ICUR, incremental cost-utility ratio; IV, insurance value; mNSCLC, metastatic non-small cell lung cancer; N+I, nivolumab plus ipilimumab; NA, not applicable; NMB, net monetary benefit; OP, option value; OV, option value; PDC, platinum doublet chemotherapy; QALY, quality-adjusted life-year; UK, United Kingdom; VH, value of hope; WTP, willingness-to-pay.

Figure 1. N+I versus PDC NMB - traditional payer's perspective



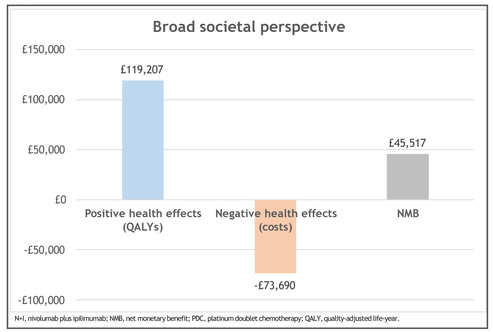
N+I, nivolumab plus ipilimumab; NMB, net monetary benefit; PDC, platinum doublet chemotherapy; QALY, quality-adjusted life-year.

Figure 2. N+I versus PDC NMB - traditional societal perspective



N+I, nivolumab plus ipilimumab; NMB, net monetary benefit; PDC, platinum doublet chemotherapy; QALY, quality-adjusted life-year.

Figure 3. N+I versus PDC NMB - broad societal perspective



N+I, nivolumab plus ipilimumab; NMB, net monetary benefit; PDC, platinum doublet chemotherapy; QALY, quality-adjusted life-year.

- This study estimated the significant impact that novel value elements can have on first-line mNSCLC CEA results when expanding the traditional payer's perspective to a broad societal perspective.

Conclusions

- Adopting a broad societal perspective significantly improved the cost-effectiveness estimates for N+I in first-line mNSCLC.
  - More than 50% of gain in QALYs estimate originated from adopting a broad societal perspective and inclusion of novel value elements.
- When adopting CEA to inform reimbursement decisions, HTA agencies should consider expanding the analysis from a traditional payer's perspective to a broad societal perspective.
  - This would allow the inclusion of additional elements of value considered important by patients.
- Further research should be conducted to identify and quantify additional condition-specific novel value elements.

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