Expanding the HTA Cost-Effectiveness Analyses for CheckMate 9LA: Nivolumab plus Ipilimumab plus 2 Cycles of Chemotherapy as a First-Line Strategy for Advanced Non-Small Cell Lung Cancer

HTA14

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Objectives

- The evidence required by health technology appraisal (HTA) agencies to assess the cost-effectiveness of new therapies is often limited to costs and benefits specific to the healthcare sector.
  - Therefore, these HTA cost-effectiveness analyses (CEAs) are often performed under a (traditional) payer's perspective.
    - Costs and benefits included in a payer's perspective CEA typically include drug costs, disease management, management of adverse events, and impact on quality of life of patients receiving care.
- In 2018, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force identified twelve potential elements of value that could be considered for HTA CEAs.[1]
  - These elements include: productivity, adherence-improving factors, reduction in uncertainty, fear/risk of contagion, severity of disease, equity, scientific spill overs, insurance value, real option value, and value of hope.
- Several HTA agencies recommend expanding the CEA from a (traditional) payer's perspective to a (traditional) societal perspective by including productivity losses and additional indirect costs.
- However, the inclusion of additional elements of value meaningful to patients is generally excluded by HTAs.
- The objective of this study was to evaluate the impact of including novel value elements in a United States (US) HTA-compliant CEA developed for CheckMate 9LA (*Polyzoi et al. 2022*).[2]
  - This US CEA assessed the cost-effectiveness of nivolumab plus ipilimumab plus 2 cycles of platinum doublet chemotherapy (NIVO + IPI + Chemo) versus 4 cycles of chemo as first-line strategy for patients with metastatic non-small cell lung cancer (mNSCLC) under a traditional payer's perspective.
- In line with a previous study assessing the impact of including novel value elements in a Canadian CEA for second-line mNSCLC[3], this study estimated the net monetary benefit (NMB) associated with NIVO + IPI + Chemo in the US; three different perspectives were explored: traditional payer's, traditional societal and broad societal.
  - The NMB was calculated as the difference between incremental benefits (expressed in monetary terms using a US willingness-to-pay [WTP] threshold of $150,000/quality-adjusted life-year [QALY] gain[4]) and incremental costs.
  - Previous reports indicate that WTP in the US may be higher than the assumed threshold of $150,000, especially for metastatic cancers[5-8]

Methods

Traditional payer's perspective

- The evidence included in this (traditional) payer's perspective CEA was limited to direct medical costs to the payer and health benefits for the patient, in line with common HTA requirements for CEAs.
- This traditional payer's perspective CEA was informed by a previous study for NIVO + IPI + Chemo versus Chemo for first-line mNSCLC in the US – Polyzoi et al. (2022).[2]
  - A three-health state partitioned survival model with progression-free, progressed disease, and death health states was developed to estimate the cost-effectiveness of NIVO + IPI + Chemo compared with chemo over a lifetime horizon of 25 years.
  - For this study, the CheckMate 9LA 2-year database lock and the more mature CheckMate 227 Part 1 data were used to extrapolate progression-free survival and overall survival over a lifetime horizon.
    - CheckMate 9LA is an open-label, randomized, Phase 3 trial evaluating first-line NIVO + IPI + Chemo for mNSCLC.[9]
    - CheckMate 227 Part 1 is an open-label, randomized, Phase III trial evaluating first-line nivolumab-based regimens for mNSCLC.[10]
  - Grade 3-5 treatment-related adverse events (AEs) experienced by at least 5% of patients in any arms of the CheckMate 9LA trial were included in the analysis.
  - CheckMate 9LA EQ-5D-3L results were used to derive US-specific, treatment-specific progression-based utility estimates.
  - CheckMate 9LA duration of therapy was used to estimate NIVO + IPI + Chemo and Chemo treatment related costs (i.e., drug acquisition, administration and monitoring costs).
  - US-specific unit costs for drug acquisition, administration, monitoring, disease management, end-of-life, AE management and subsequent treatments were used.

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.[11]
  - US published sources informed the average hourly wage and the average age of retirement.[12]

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[3], 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 NIVO + IPI + Chemo 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[11] and US published sources[12] informed: • caregivers' hours of missed work due to absenteeism/ presenteeism, caregivers' average age[11] • US average hourly wage and average age of retirement[12]

mNSCLC, metastatic non-small cell lung cancer; NIVO + IPI + Chemo, nivolumab plus ipilimumab plus platinum doublet chemotherapy; TLR, targeted literature review; US, United States.

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 NIVO + IPI + Chemo in first-line mNSCLC (**Table 2**).

Table 2. Insurance value associated with NIVO + IPI + Chemo in first-line mNSCLC

Novel value element	Inputs and sources
Insurance value	The insurance value of NIVO + IPI + Chemo 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[13] • The value to the healthy relative to the sick was 89.8%[13]

mNSCLC, metastatic non-small cell lung cancer; NIVO + IPI + Chemo , nivolumab plus ipilimumab plus platinum doublet chemotherapy; 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 NIVO + IPI + Chemo in first-line mNSCLC (**Table 3**).

Table 3. Option value associated with NIVO + IPI + Chemo in first-line mNSCLC

Novel value element	Inputs and sources
Option value	The model developed by Snider et al. (2017)[14] was replicated: • Step 1: estimate pre-NIVO + IPI + Chemo first-line mNSCLC OS curve from RWD[15] • Step 2: estimate forecast survival improvement by applying lung US cancer-specific mortality rate decrease[16] to the curve from step 1 • Step 3: estimate NIVO + IPI + Chemo survival by applying HR_{OS} between NIVO + IPI + Chemo and Chemo (CheckMate 9LA) to curves from step 1 (NIVO + IPI + Chemo OS without further innovation) and step 2 (NIVO + IPI + Chemo OS with further innovation) • Step 4: difference between curves estimated in step 3 provided the option value for NIVO + IPI + Chemo (6.3% of Chemo average survival)

HR, hazard ratio; mNSCLC, metastatic non-small cell lung cancer; NIVO + IPI + Chemo , nivolumab plus ipilimumab plus platinum doublet chemotherapy; OS, overall survival; chemo, platinum doublet chemotherapy; RWD, real-world data; US, United States.

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).
- The value of hope of NIVO + IPI + Chemo was informed by a discrete-choice experiment (DCE) performed by Hauber et al. (2020) on US patients with second-line mNSCLC and medical oncologists.[17]
  - The DCE results were adapted to the first-line setting (CheckMate 9LA).
    - It was estimated that NIVO + IPI + Chemo value of hope (i.e., patients' preference for improvements in "long-term survival" relative to "expected survival") correspond to 0.16 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, the incremental costs of NIVO + IPI + Chemo versus Chemo were $190,281, while the incremental QALYs were 1.23 (**Table 4**).
  - The incremental costs were mainly driven by higher treatment acquisition costs (+$193,632) and higher disease management costs (+$13,804).
  - At an assumed WTP threshold of $150,000/QALY gain, 1.23 incremental QALYs would be valued at $184,049 under the traditional payer's perspective.
  - The NMB for NIVO + IPI + Chemo versus Chemo was -$6,232 at a WTP threshold of $150,000/QALY gain under a traditional payer's perspective (**Figure 1**).
    - A negative NMB indicated that NIVO + IPI + Chemo associated costs exceeded its benefits when performing the analysis under the traditional payer's perspective.
- In the traditional societal perspective CEA, the incremental costs of NIVO + IPI + Chemo versus Chemo were $190,625, while the incremental QALYs of NIVO + IPI + Chemo versus Chemo remained unchanged at 1.23 (**Table 4**).
  - The NMB for NIVO + IPI + Chemo versus Chemo was -$6,576 under a traditional societal perspective (**Figure 2**).
- In the broad societal perspective CEA, the incremental costs of NIVO + IPI + Chemo versus Chemo slightly increased from $190,625 to $196,488, while the incremental QALYs of NIVO + IPI + Chemo versus Chemo increased by 122%, from 1.23 to 2.72 (**Table 4**).
  - The NMB for NIVO + IPI + Chemo versus Chemo was +$211,267 under a broad societal perspective (**Figure 3**).
  - As summarized in **Table 4** and in **Figure 4**:
    - The value of hope increased the baseline incremental QALYs by 0.16, corresponding to 13% of the baseline incremental QALYs.
    - The option value increased the incremental QALYs further by 0.08; value of hope and option value combined increased the baseline incremental QALYs by 20%.
    - The insurance value increased the incremental QALYs further by 1.25; value of hope, option value, and insurance value combined increased the baseline incremental QALYs by 122%.

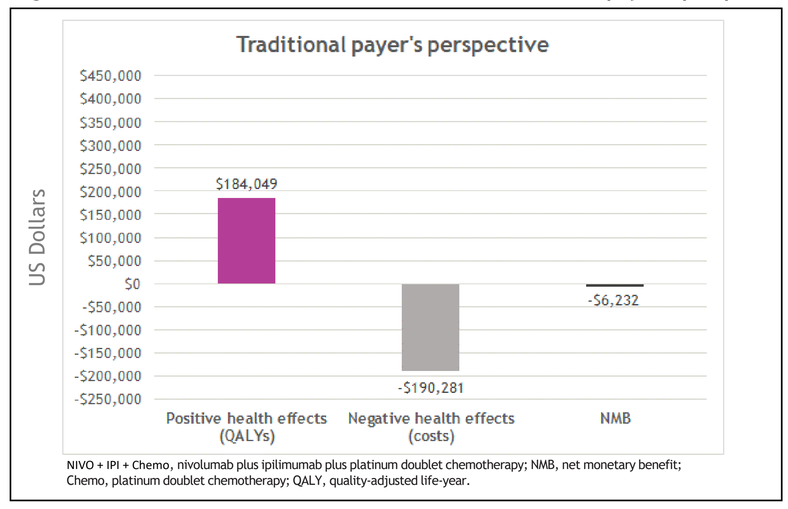
Table 4. Results of CEA analysis for NIVO + IPI + Chemo versus Chemo in first-line mNSCLC adopting a broad societal perspective

Component	Traditional payer's[a]	Traditional societal	Broad societal
Incremental benefit[b]			
Incremental QALYs	**$184,049**	**$184,049**	**$407,755**
Incremental QALYs with added VH (A)	1.23	1.23	1.23
Incremental QALYs [=(A)x(1+OV)]	NA	NA	1.39 (+13%)
Incremental QALYs [=(A)x(1+OV+IV)]	NA	NA	1.47 (+20%)
	NA	NA	2.72 (+122%)
Incremental costs			
Disease management costs	**$190,281**	**$190,625**	**$196,488**
Treatment acquisition costs	$13,804	$13,804	$13,804
Treatment administration and monitoring costs	$193,632	$193,632	$193,632
Adverse events costs	$2,219	$2,219	$2,219
Subsequent treatment costs	-$815	-$815	-$815
Productivity loss costs	-$18,558	-$18,558	-$18,558
Caregiver burden costs	NA	$344	$344
	NA	NA	$5,863
NMB (at US WTP of $150,000/QALY gain)	**-$6,232**	**-$6,576**	**+$211,267**
ICUR	$155,079	$155,360	$72,282

[a]Analysis originally performed by *Polyzoi et al. (2022)*.[2]
[b]Total incremental QALYs x value of a QALY of $150,000.
CEA, cost-effectiveness analysis; ICUR, incremental cost-utility ratio; IV, insurance value; mNSCLC, metastatic non-small cell lung cancer; NIVO + IPI + Chemo, nivolumab plus ipilimumab plus platinum doublet chemotherapy; NA, not applicable; NMB, net monetary benefit; OV, option value; Chemo, platinum doublet chemotherapy; QALY, quality-adjusted life-year; US, United States; VH, value of hope; WTP, willingness-to-pay.

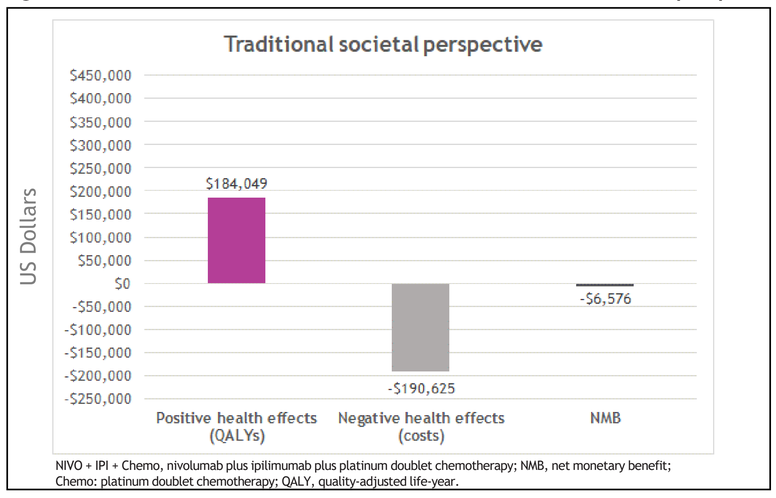
- The results presented for this this study should be viewed in the context of an assumed WTP threshold of $150,000 per QALY, which could be considered a conservative estimate of WTP for interventions for metastatic cancer in the US.[5-8]
- The benefits improvement associated with NIVO + IPI + Chemo estimated expanding the CEA from a traditional payer's perspective to a broad societal perspective considerably outweighed the small increase in costs.
- This study demonstrated that the QALY measures traditionally used by HTAs may not fully capture the benefits of NIVO + IPI + Chemo in first-line mNSCLC.
  - Therefore, novel value elements should be considered by HTA authorities.

Figure 1. NIVO + IPI + Chemo versus Chemo NMB - traditional payer's perspective



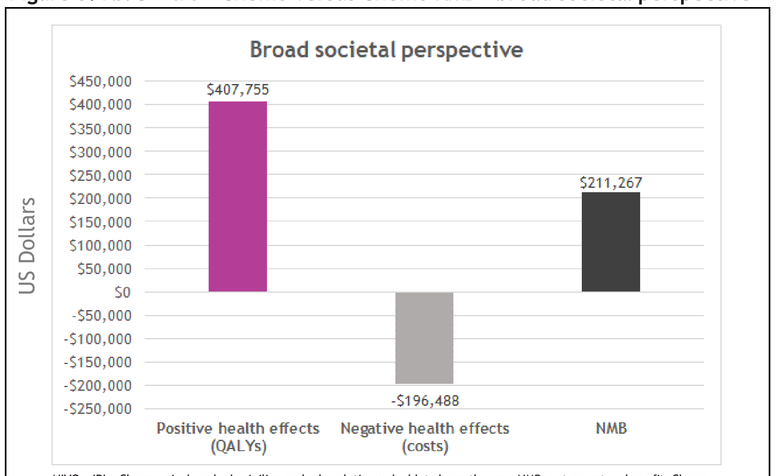
NIVO + IPI + Chemo, nivolumab plus ipilimumab plus platinum doublet chemotherapy; NMB, net monetary benefit; Chemo, platinum doublet chemotherapy; QALY, quality-adjusted life-year.

Figure 2. NIVO + IPI + Chemo versus Chemo NMB - traditional societal perspective



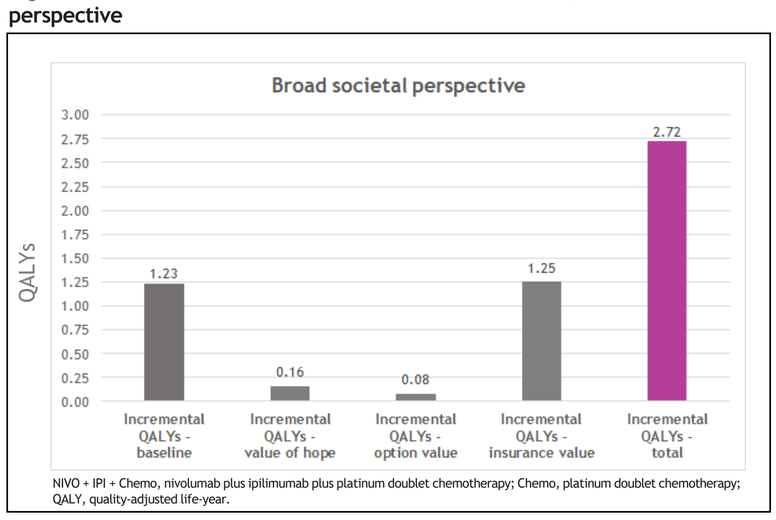
NIVO + IPI + Chemo, nivolumab plus ipilimumab plus platinum doublet chemotherapy; NMB, net monetary benefit; Chemo: platinum doublet chemotherapy; QALY, quality-adjusted life-year.

Figure 3. NIVO + IPI + Chemo versus Chemo NMB - broad societal perspective



NIVO + IPI + Chemo, nivolumab plus ipilimumab plus platinum doublet chemotherapy; NMB, net monetary benefit; Chemo, platinum doublet chemotherapy; QALY, quality-adjusted life-year.

Figure 4. NIVO + IPI + Chemo versus Chemo incremental QALYs - broad societal perspective



NIVO + IPI + Chemo, nivolumab plus ipilimumab plus platinum doublet chemotherapy; Chemo, platinum doublet chemotherapy; QALY, quality-adjusted life-year.

Conclusions

- The cost-effectiveness results for NIVO + IPI + Chemo in first-line mNSCLC were significantly improved by expanding the CEA from a traditional payer's to a broad societal perspective.
  - 55% of gain in incremental QALYs (NIVO + IPI + Chemo versus Chemo) originated from including novel value elements under a broad societal perspective (value of hope, option value, and insurance value).
- HTA-compliant CEAs for NIVO + IPI + Chemo in first-line mNSCLC have previously demonstrated acceptable value for money in the US. [2]
  - This study showed that novel value elements provide a more complete value assessment and should therefore be considered by HTAs.
- Further research should be conducted to identify and accurately quantify novel value elements.

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