Regulatory and Valuation Challenges of Immune Checkpoint Inhibitors in Lung Cancer

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Regelgeving en waardering uitdagingen van immuuncheckpoint remmers bij longkanker

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General Introduction

Lung cancer care

In 2017, the United States (US) Food and Drug Administration (FDA) granted the first site-agnostic approval of pembrolizumab, a monoclonal antibody used in cancer immunotherapy, regardless of the tissue of origin or the site of the tumor. [1] After this pivotal approval, innovative therapies became more quickly available to a broader range of cancers. In parallel, clinical trials have evolved towards a more adaptive design with added flexibility for investigators and patients. [2] While traditional clinical trials constituted very distinct and separate stages, these stages have been evolving into a seamless continuum with the potential to positively impact costs, time to approval decisions, and probability of success.

Innovation in drug research and development translated into tangible improvements in clinical outcomes for most patients with cancer. However, lung cancer, one of the most common types of cancer, with approximately 2.2 million diagnoses worldwide in 2020, is the leading cause of global cancer-related mortality, resulting in 1.80 million deaths annually. [3] Despite the broader histological classification of lung cancer into small-cell and non-small cell (NSCLC) subtypes, an in-depth taxonomy may comprise more precise molecular markers. NSCLC accounts for most of the cases, about 85–90% of lung cancers. [4] Since 2004, the introduction of small molecule tyrosine kinase inhibitors and monoclonal antibodies directed against genetic aberrations have transformed the treatment landscape of NSCLC. The mutations of Epidermal Growth Factor Receptor (EGFR), translocations of Anaplastic Lymphoma Kinase (ALK), and Kirsten rat sarcoma viral oncogene homolog, c-ros oncogene, v-Raf murine sarcoma viral oncogene homolog B, Ret proto-oncogene, c-MET, neurotrophic tyrosine receptor kinase are some molecular targets in NSCLC that were shown to confer sensitivity to innovative therapies. [5] More recently, it has been demonstrated that NSCLC patients express programmed cell death ligand-1 (PD-L1) on tumor cells or immune cells infiltrating the tumor. [6] PD-L1 and its receptor, PD-1, comprise a critical pathway that downregulates immune activity. [6] Complete and durable responses can be achieved by exposing tumor cells to the immune system by utilizing patients' immune cells. The immune system can keep itself from attacking normal cells. To start an immune response, the 'checkpoint' molecules must be turned on/off. Immune checkpoint blockade allows the immune system to generate an antitumor response. [7] The regulatory approval of the first immune checkpoint inhibitor (ICI) in 2015 [8,9] opened a new era for patient subgroups with pretreated advanced NSCLC. It was discovered that tumor cells could escape the immune system via a 'checkpoint' on the T cell.

Immunotherapy targeting T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 or ligand 1 (PD-1/PD-L1) have been part of the clinical care of NSCLC patients. [10] Clinical interest in immunotherapy is high, primarily due to the potential for durable responses, with thousands of trials investigating anti-PD-1/anti-PD-L1 therapies alone. [11] However, it is shown that a subset of patients treated with immune checkpoint inhibitors (ICIs) respond to these agents. [12,13] A subgroup of patients who respond may then progress to have a refractory disease. [14] Primary and acquired resistance to immunotherapy is multifaceted and necessitates different approaches, including combination regimens. Although much attention has been paid to intrinsic tumor factors such as PD-L1 expression, [15] mutational burden, [16] and deficiencies in antigen presentation, [10] the problem of immunotherapy resistance is more complex because these tumors exist in a dynamic microenvironment.

Specifically, in the first-line treatment of advanced NSCLC, platinum-based doublet chemotherapy was historically the standard treatment for patients with recurrent or metastatic NSCLC, whose tumors do not harbor EGFR mutations or ALK translocations. In 2019, pembrolizumab monotherapy for patients with a PD-L1 expression ≥1% was approved as the standard first-line therapy for advanced NSCLC without treatable driver mutations. [5] Also, nivolumab and ipilimumab are monoclonal antibodies that bind to PD-1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4) to restore T-cell activity against tumor cells. In 2019, the CheckMate 227 Phase 3 trial had favorable outcomes on the progression-free and overall survival with dual checkpoint inhibition, anti-CTLA-4 and PD-1, in recurrent or metastatic NSCLC. [17] The CheckMate 227 trial results showed that nivolumab in combination with ipilimumab was associated with improved survival in pre-specified subgroups, including PD-L1 ≥ 1% and PD-L1 < 1%. [17] In 2021, the CheckMate 9LA Phase 3 trial stratified patients by PD-L1 ≥ 1% and < 1% and showed that nivolumab in combination with ipilimumab plus two cycles of chemotherapy provided positive improvements in progression-free and overall survival, compared with four cycles of chemotherapy. [18] Consequently, the FDA approved nivolumab in combination with ipilimumab for patients with PD-L1 ≥ 1% [19], and the National Comprehensive Cancer Network panel extended their use for patients with PD-L1 < 1%. [5] Nivolumab combined with ipilimumab plus two cycles of chemotherapy was also approved for patients regardless of PD-L1 expression levels. [20] These monoclonal antibodies have been approved for several indications in previously treated patients with recurrent or metastatic NSCLC.

Regulatory Landscape of Immune Checkpoint Inhibitors

The regulatory authorization process for oncology drugs, including ICIs, is continuously streamlined. [21] Regulatory decisions on ICIs are often based on enhanced efficacy and acceptable toxicity profiles, investigated in randomized, open-label clinical trials. [22] Despite continuing efforts and harmonized practices that have helped decrease the regulatory burden and delays in decision-making processes, there remain differences among regulatory agencies. Moreover, there might be a concern that regulation hampers drug development and slows patients' access to innovation because of costs incurred by manufacturers to meet regulatory requirements that may be excessive and duplicative. [21] For example, the high treatment costs of NSCLC are associated, in part, with the significant research and development costs. Streamlining the regulatory processes comprising safety, efficacy, patient outcomes, and resources will be crucial to facilitate innovative drug approval pathways and containing costs. These processes are vital for the approval of ICIs, particularly in NSCLC, where there has been significant progress in understanding tumor biology, immunology, and molecular targets. [21]

Drug discovery and development advances have increased harmonization and alignment between regulatory authorities. For example, the FDA and the European Medicines Agency (EMA) decisions are frequently compared and contrasted regarding review requirements and time to technology approvals or refusals. These agencies adopted specific guidelines to align requirements to ensure safe, effective, high-quality drugs. [23] Under the auspices of their confidentiality agreements, the FDA and the EMA have established various mediums (called 'clusters') for information sharing and collaboration on drug development and regulation. [24] These clusters bring together technical experts that share information on plans for manufacturing or clinical site inspections, oncology products, pharmacogenomics, biostatistics, rare diseases, vaccines, and others. [24] Although discussions on basics in regulatory science are a bedrock to facilitate alignment on high standards and methods, the FDA and the EMA decide on regulatory authorization for ICIs using their respective legal and regulatory frameworks. Therefore, improved regulatory environments in North America and Europe and alignment of practices can guide resource allocation, facilitate innovation in cancer care, and ultimately optimize patient care. [21]

Valuation of Immune Checkpoint Inhibitors

Although ICIs have brought meaningful benefits in NSCLC care and transformed the treatment landscape, following their regulatory approvals, economic value assessment of ICIs may pose additional challenges to the health systems. Health technology assessment (HTA) is often used as a supportive process for the value assessment of ICIs. HTA comprises multidisciplinary strategies that use methods to determine the value of each medical technology throughout its lifecycle. The purpose is to inform decision-making and promote an equitable, efficient, high-quality health system. The overall economic value may vary based on perspectives, comparators, stakeholders, and decision context.

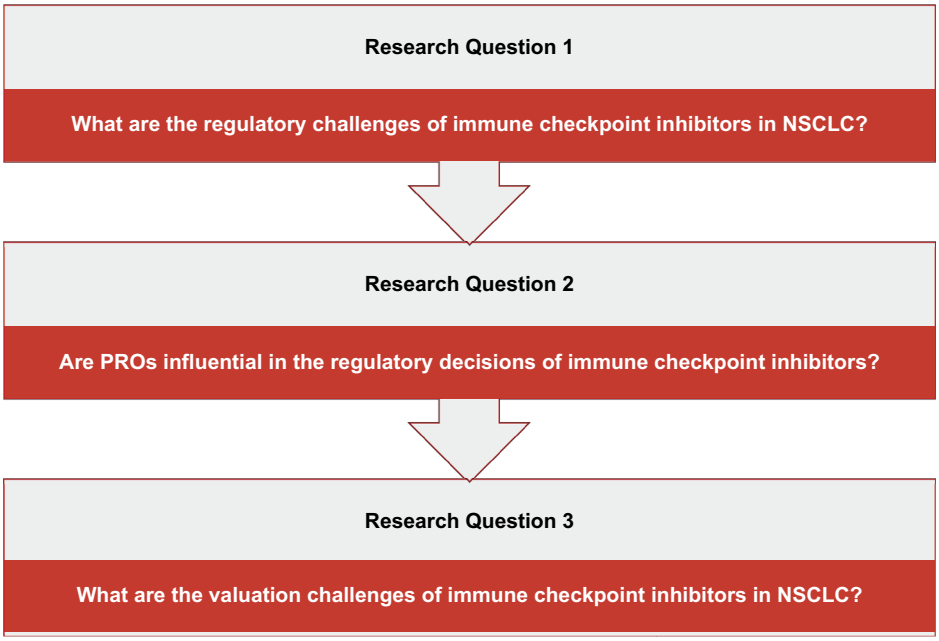
The economic aspect of HTA is clear: high-value ICIs are expected to be added to the health system to maximize health benefits. However, whether this perspective should dominate depends on the healthcare resources in each jurisdiction. If treatment is cost-effective but not affordable, then the (implicit or explicit) 'threshold' used to judge cost-effectiveness is expected to reflect the scale and value of the opportunity costs. [26] It is also imperative that the assessment of the health expected to be forgone elsewhere in the healthcare system due to additional costs displacing other activities is evidence-based. [26] Although the cost-effectiveness of ICIs is a critical decision criterion, additional value dimensions could provide further insights. [27] For instance, choosing treatments with promising clinical profiles is essential, especially when patients prefer to accept an increased short-term risk of death for a slight chance of long-term benefit. However, it is necessary to determine how these additional value dimensions should be incorporated into HTA and the subsequent decision-making processes. Therefore, there is a considerable need to increase transparency about all relevant value criteria for healthcare resource allocation decisions.

Specifically for combination ICIs, the application of HTA becomes more complex. Although treatment combinations are evaluated as single technologies, they have multiple constituents, and each should be priced independently. Novel methods are needed to determine how to attribute value for combination ICIs. These methods may help facilitate dialogue among researchers and stakeholders, including HTA agencies, manufacturers, payers, policymakers, and others, who are expected to work together to ensure that new health technologies are available and accessible to all patients.

Research Outline

This research explores the application of health technology assessment in the field of NSCLC to address the *regulatory and valuation challenges of ICIs*. Three key research questions are depicted in **Figure 1**.

Figure 1. Research questions explored to address the regulatory and valuation challenges of ICIs in NSCLC.



NSCLC: Non-Small Cell Lung Cancer, PROs: Patient Reported Outcomes

To explore these key research questions:

- **Chapter 2** compares regulatory approvals of immune checkpoint inhibitors for NSCLC in Europe and the United States.
- **Chapter 3** analyzes the most recent evidence on patient-reported outcomes in the registrational clinical trials of nivolumab in advanced NSCLC.
- **Chapter 4** systematically addresses the methodological quality of cost-effectiveness analyses for first-line nivolumab combined with ipilimumab for treating advanced NSCLC.
- **Chapter 5** reviews the value attribution frameworks for combination therapies to explore the potential valuation of constituent parts of combination immune checkpoint inhibitors in NSCLC.

- **Chapter 6** explores additional dimensions of value with a particular focus on 'hope' to help capture patients' risk preferences in NSCLC.
- **Chapter 7** focuses on the discussion of the research findings, limitations, and future implications.
- **Chapter 8** summarizes key research highlights.

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Immune Checkpoint Inhibitors for the Treatment of Non-Small Cell Lung Cancer: A Comparison of the Regulatory Approvals in Europe and the United States

Zaim R, Redekop WK, Uyl-de Groot CA.

Immune checkpoint inhibitors for the treatment of non-small cell lung cancer: A comparison of the regulatory approvals in Europe and the United States. J Cancer Policy 2022 Jun 30;33:100346. doi:10.1016/j.jcpo.2022.100346.

Abstract

Regulatory authorization of oncology drugs, including immune checkpoint inhibitors (ICIs), is often based on improved outcomes and acceptable toxicity that result from randomized, open-label clinical trials. Regulatory decisions of the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) are frequently compared and contrasted. This comparison is usually based on review requirements and time to regulatory decisions. The EMA, the FDA, and Clinicaltrials.gov databases were reviewed from January 1, 2015, until December 31, 2021, to analyze regulatory approvals for ICIs in treating non-small cell lung cancer (NSCLC). The focus of this analysis was ICI's approval duration. In addition, regulatory considerations of patient-reported outcomes (PROs) for the two agencies were explored. The findings show similarities in the regulatory pathways and methods used for ICI approvals. The indications that stood out in outcome divergence were observed in the first-line indications for untreated NSCLC patients. The approval decisions for ICIs were quicker when the US FDA was compared with the EMA. Both regulatory agencies recognize the value of PROs as necessary patient-centered endpoints.

Policy statement: Several regulatory structures in the US and Europe help accelerate the regulatory approval processes. The accelerated access programs did not influence the preponderance of outcome differences in approvals. Increased harmonization and collaboration are encouraged among these agencies in measuring and validating PROs in future drug evaluations.

Introduction

Advancements in drug development have increased the need for harmonization and collaboration between regulatory authorities. Regulatory approval decisions of the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) are often compared and contrasted. This comparison is usually based on review requirements and time to regulatory decisions. These two agencies have adopted the guidelines of "the International-Council-for-Harmonisation-of-Technical-Requirements-for-Pharmaceuticals-for-Human-Use" to ensure safe, effective, and high-quality drugs [1]. Under their confidentiality agreements, the US FDA and the EMA have established various mediums (called 'clusters') for information sharing and collaboration about drug development and regulation [2]. These clusters bring together technical experts that share information on plans for manufacturing or clinical site inspections, oncology products, pharmacogenomics, biostatistics, rare diseases, vaccines, and others [2]. Although discussions on basics in regulatory science are a bedrock to facilitate alignment on high standards and methods, the US FDA and the EMA make the regulatory authorization decisions for oncology drugs within their respective legal and regulatory frameworks.

The process of regulatory authorization of oncology drugs, including immune-checkpoint inhibitors, is continuously streamlined by the US FDA and the EMA. The immune-checkpoint blockade is an effective therapeutic strategy that harnesses the immune system to generate an antitumor response [3]. These agencies' regulatory decisions regarding ICIs are often based on improved outcomes and acceptable toxicity profiles investigated in randomized, open-label clinical trials [4]. Despite continuing efforts and harmonized practices that have helped decrease the regulatory burden and delays in decision-making processes, there remain significant differences between these two agencies.

Improved regulatory environments in the US and Europe and efforts to align practices can guide resource allocation, facilitate advancements in cancer care, and ultimately optimize patient care. For example, high treatment costs of non-small cell lung cancer (NSCLC) are associated, in part, with the significant research and development costs. To contain development costs and facilitate novel drug approvals, the alignment of the regulatory environment becomes critical, where drug efficacy, safety, and patient outcomes are carefully assessed. This streamlined process is expected for the approval of immune-checkpoint inhibitors, particularly in NSCLC, where there has been significant progress in understanding tumor biology, immunology, and molecular targets. Therefore, in this policy analysis, the aim was to analyze the differences in regulatory approvals between the US FDA and the EMA for immune-checkpoint inhibi-

tors in the treatment of NSCLC from the year 2015 until 2021 by focusing on the time to approval duration of immune-checkpoint inhibitors, and considerations of patient-reported outcomes (PROs) in regulatory decisions by each agency.

Regulatory approvals of immune-checkpoint inhibitors in NSCLC

From January 2015 until December 2021, the US FDA approved 17 immune-checkpoint inhibitor indications, whereas the EMA approved 13 for NSCLC. (see **Table 1**) Among the US FDA-approved indications, 11 were indicated for front-line NSCLC patients without prior treatment history. The remaining six indications were approved for previously treated NSCLC patients for second and third-line treatments. Eight EMA-approved indications were indicated for the first-line patients with no prior treatment history, and the remaining five were approved for previously treated patients. **Table 1** lists immune checkpoint inhibitor (including target and histology), clinical trial, approval date by each regulatory agency, type of each approval (regular or accelerated), line of treatment, and PRO measurement.

Figures 1 and **2** show approved immune-checkpoint inhibitor indications in the treatment of NSCLC, from 2015 until the end of 2021, for the US FDA and the EMA, respectively. **Figures 1** and **2** depict each regulatory agency's approval decision dates (month, year).

Figure 3 shows discordant-concordant approval outcomes of immune checkpoint inhibitors for NSCLC when two regulatory agencies are compared. Discordant outcomes were defined as approvals for which the US FDA and the EMA had different regulatory conclusions, namely; one agency approved the immune-checkpoint inhibitor while the other did not approve it, or one agency approved the immune-checkpoint inhibitor whereas the application was withdrawn (by the manufacturer) from the other agency. Concordant outcomes were defined as approvals for which both the US FDA and the EMA had the same regulatory conclusion, namely, both agencies approved the drug indication; both agencies did not approve the drug indication; the drug application was withdrawn (by the manufacturer) from both agencies before a decision; or the drug application was not approved by one agency and withdrawn at the other agency.

Figure 4 shows differences (Δ in additional days) in approvals of immune checkpoint inhibitors by the US FDA and the EMA. In eleven of the directly compared thirteen indications (85 %), the US FDA was quicker to reach an approval decision when compared to the EMA. The indications that stood out regarding outcome divergence were mainly first-line immune checkpoint inhibitors for untreated NSCLC patients. The accelerated access programs did not influence the preponderance of outcome differences in approvals in this setting.

Table 1. Regulatory approvals of immune-checkpoint inhibitors in non-small cell lung cancer [2015–2021]

Immune Checkpoint Inhibitor [target or target expression level, histology]	Clinical Trial(s) [Number]	The US FDA Approval	Approval Type	The EMA Approval	Treatment Line	PROs
Nivolumab [PD-1/ regardless of PD-L1 expression, squamous]	CheckMate 017 [NCT01642004] CheckMate 063 [NCT01721759]	March 4, 2015	Regular Approval	September 24, 2015	Second-line	✓
Nivolumab [PD-1/ regardless of PD-L1 expression, non-squamous]	CheckMate 057 [NCT01673867]	October 9, 2015	Regular Approval	February 25, 2016	Second-line	✓
Pembrolizumab [PD-L1 TPS ≥1%, squamous or non-squamous]	KEYNOTE 001 [NCT01295827] KEYNOTE 010 [NCT01905657]	October 2, 2015	Accelerated Approval	June 23, 2016	Second-line	✓
Pembrolizumab [PD-L1 TPS ≥50%, squamous or non-squamous]	KEYNOTE 024 [NCT02142738]	October 24, 2016	Regular Approval	December 15, 2016	First-line	✓
Atezolizumab [regardless of PD-L1 expression, squamous or non-squamous]	Poplar [NCT01903993] OAK [NCT02008227]	October 18, 2016	Regular Approval	July 20, 2017	Second-line	✓
Pembrolizumab combination (Pemetrexed + Carboplatin) [PD-L1 TPS≥1%, non-squamous]	KEYNOTE 021 [NCT02039674][6]	May 10, 2017	Accelerated Approval	**Application Withdrawn**	First-line	-
Durvalumab [PD-1/ PD-L1, TPS≥1%, squamous or non-squamous]	PACIFIC [NCT02125461]	February 16, 2018	Regular Approval	July 26, 2018	Third-line	✓
Pembrolizumab combination (Pemetrexed + Carboplatin/Cisplatin) [regardless of PD-L1 expression, non-squamous]	KEYNOTE 189 [NCT02578680]	August 20, 2018	Regular Approval	July 26, 2018	First-line	✓
Pembrolizumab combination (Paclitaxel or Nab-Paclitaxel) [regardless of PD-L1 expression, squamous]	KEYNOTE 407 [NCT02775435]	October 30, 2018	Regular Approval	January 31, 2019	First-line	✓
Atezolizumab combination (Bevacizumab, Carboplatin, Paclitaxel) [regardless of PD-L1 expression, non-squamous]	IMpower 150 [NCT02366143]	December 6, 2018	Regular Approval	January 31, 2019	First-line	✓
Pembrolizumab [PD-L1 TPS ≥1%, squamous or non-squamous]	KEYNOTE 042 [NCT02220894][^]	April 11, 2019	Regular Approval	**Not Approved**	First-line	-

Table 1. Regulatory approvals of immune-checkpoint inhibitors in non-small cell lung cancer [2015–2021] (*continued*)

Immune Checkpoint Inhibitor [target or target expression level, histology]	Clinical Trial(s) [Number]	The US FDA Approval	Approval Type	The EMA Approval	Treatment Line	PROs
Atezolizumab combination (Carboplatin/Nab-Paclitaxel) [regardless of PD-L1 expression, non-squamous]	IMpower 130 [NCT02367781]	December 3, 2019	Regular Approval	July 25, 2019	First-line	✓
Nivolumab + Ipilimumab combination [PD1, CTLA-4, PD-L1 TPS ≥1%, squamous or non-squamous]	CheckMate 227 [NCT02477826]#	May 15, 2020	Regular Approval	**Application Withdrawn**	First-line	✓
Atezolizumab [PDL1, TC≥ 50% or IC ≥ 10%, squamous or non-squamous]	IMpower 110 [NCT02409342]	May 18, 2020	Regular Approval	March 25, 2021	First-line	✓
Nivolumab + Ipilimumab combination (2 cycles of platinum doublet) [PD1, CTLA-4, regardless of PD-L1 expression, squamous or non-squamous]	CheckMate 9LA [NCT03215706]	May 26, 2020	Regular Approval	November 6, 2020	First-line	✓
Cemiplimab [PD-L1, TPS ≥50%, squamous or non-squamous]	EMPOWER-Lung1 [NCT03088540]	February 22, 2021	Regular Approval	May 24, 2021	First-line	✓
Atezolizumab [PD-L1, TC≥1%, non-squamous]	IMpower 010 [NCT02486718]	October 15, 2021	Regular Approval	**No Information**	Third-line	-

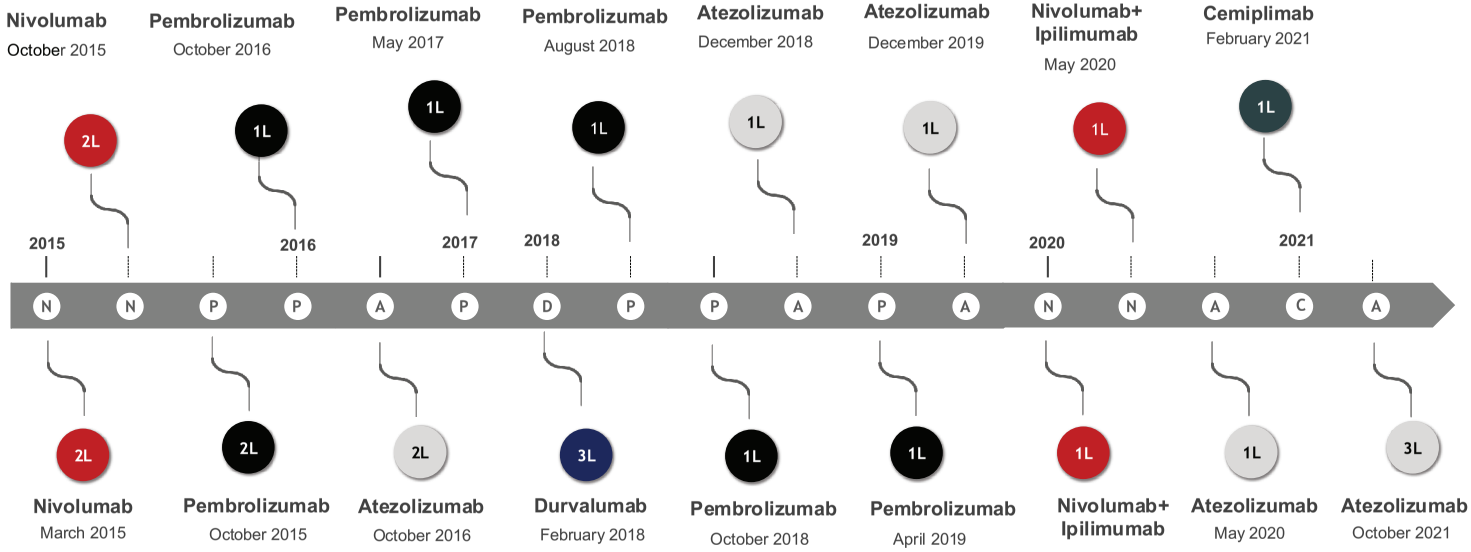
Abbreviations: NSCLC: Non-Small Cell Lung Cancer, US: United States, FDA: Food and Drug Administration, EMA: European Medicines Agency, PRO: Patient Reported Outcomes, NCT: National Clinical Trial, PD1:Programmed cell death protein 1, PD-L1: Programmed death ligand 1, CTLA-4: Cytotoxic T lymphocyte-associated antigen 4, TPS: Tumor Proportion Score, TC: PD-L1 stained Tumor Cells, IC: PD-L1 stained tumor-infiltrating Immune Cells.

Table 1 Legend: §NCT02039674: The manufacturer withdrew this application based on the CHMP's concern that the available data did not allow firm conclusions on the effectiveness and safety of pembrolizumab in this trial. Additional data from ongoing studies were needed to assess the benefit-risk balance.

#NCT02477826: The manufacturer withdrew this application based on the CHMP's central concern that the available data did not allow firm conclusions on the benefit-risk balance for nivolumab and ipilimumab. In addition, the CHMP had concerns about the trial, that it had changed substantially several times, and that there were concerns about how the manufacturer handled the data, with inconsistencies in the study results for different groups of patients. The manufacturers informed the CHMP that these two withdrawn indications had no consequences for patients included in clinical trials. In addition, there were no consequences for using these drugs in their previously authorized indications.

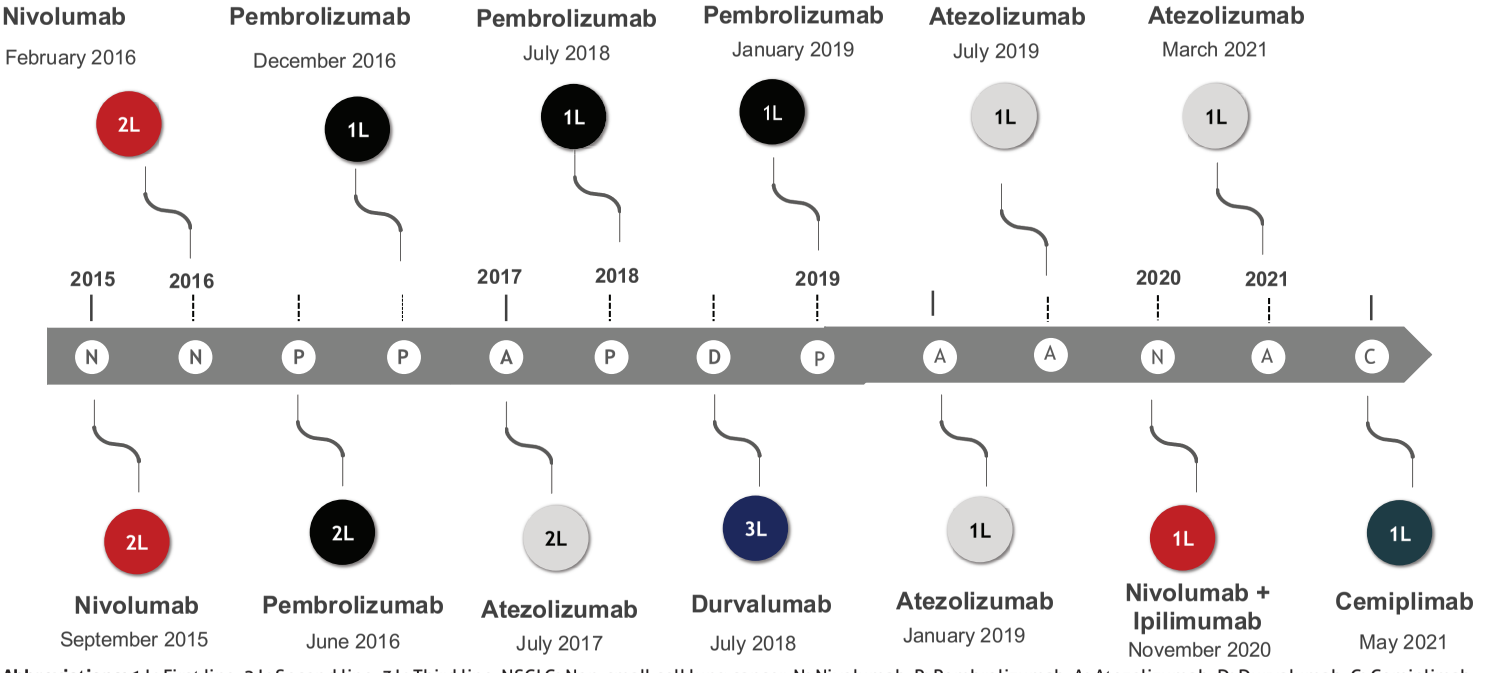
^NCT02220894: The EMA rejected this indication because the overall benefit-risk ratio of pembrolizumab monotherapy was deemed negative for patients with a PD-L1 TPS 1-49 %. When lower levels of PD-L1 were considered separately, the results were inconclusive. The study data from this application was included in the general product information.

Figure 1: Approvals of immune-checkpoint inhibitors by the US Food and Drug Administration for non-small cell lung cancer.



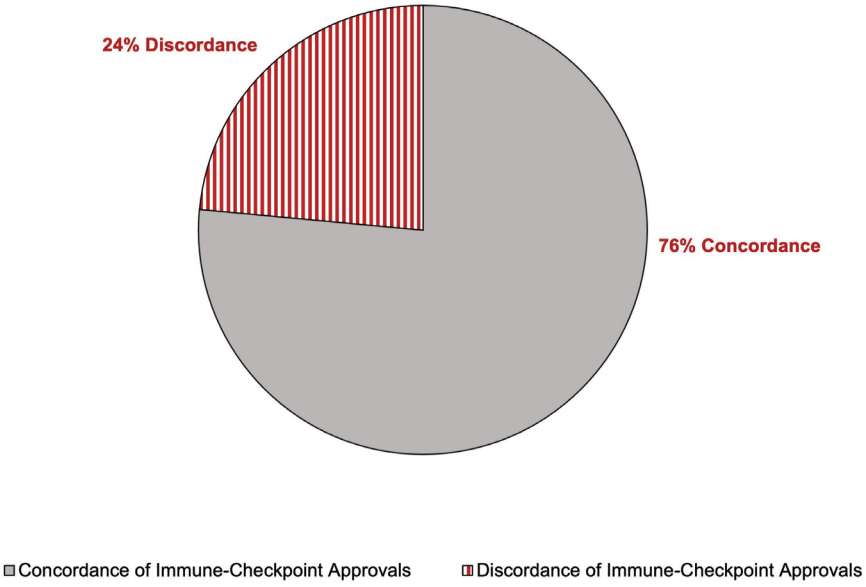
Abbreviations: 1 L: First line, 2 L: Second line, 3 L: Third line, NSCLC: Non-small cell lung cancer, N: Nivolumab, P: Pembrolizumab, A: Atezolizumab, D: Durvalumab, C: Cemiplimab.

Figure 2: Approvals of immune-checkpoint inhibitors by the European Medicines Agency for non-small cell lung cancer.



Abbreviations: 1 L: First line, 2 L: Second line, 3 L: Third line, NSCLC: Non-small cell lung cancer, N: Nivolumab, P: Pembrolizumab, A: Atezolizumab, D: Durvalumab, C: Cemiplimab.

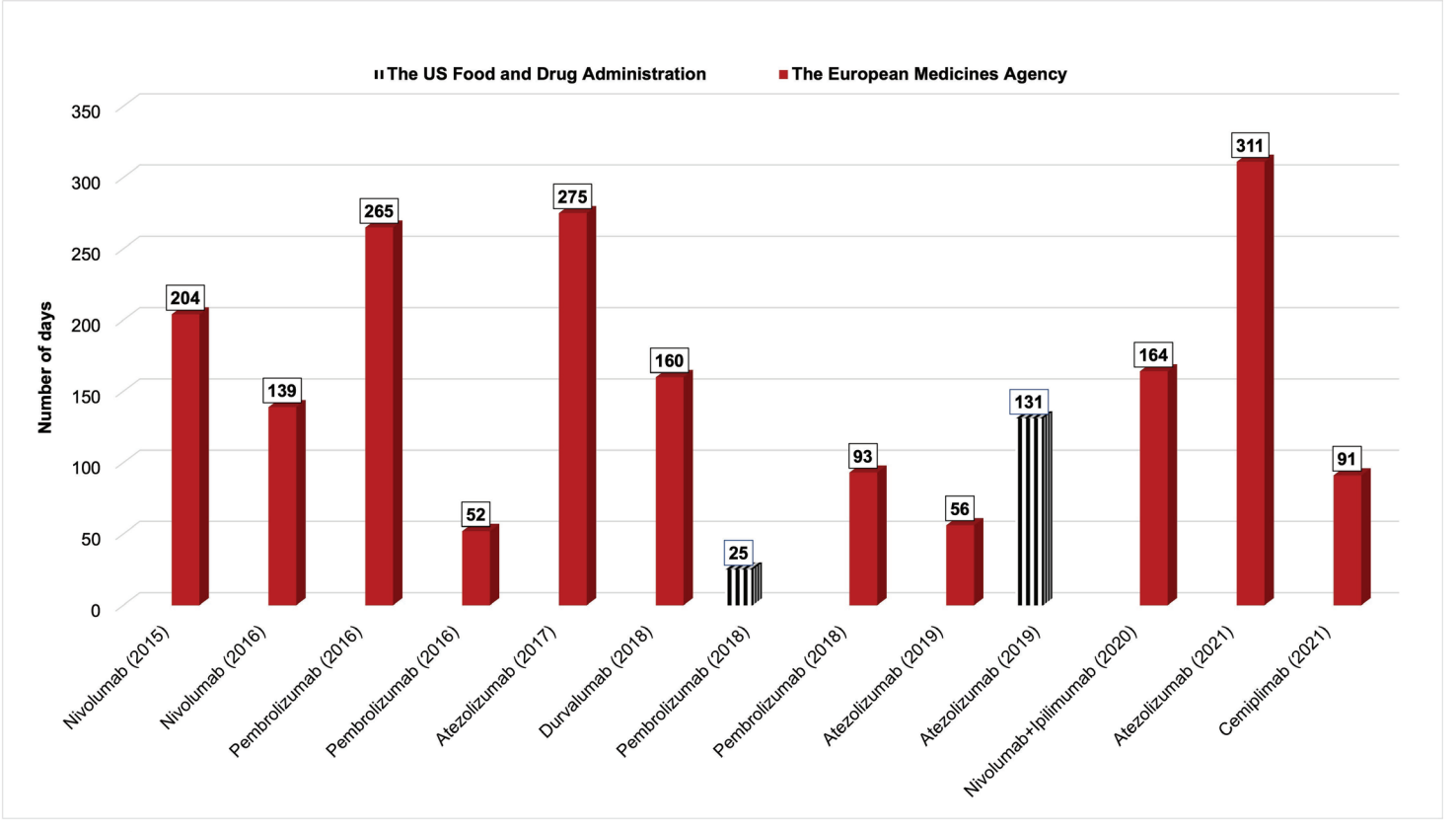
Figure 3: Discordant and concordant approval outcomes of immune-checkpoint inhibitors in non-small cell lung cancer when the US Food and Drug Administration decisions are compared with the European Medicines Agency [2015–2021].



Regulatory requirements for patient-reported outcomes

For this analysis, PROs were included in the clinical trials and considered in 15 indications by the US FDA and the EMA. Both regulatory agencies recognize the value of PROs as critical patient-centered endpoints when determining the efficacy of immunotherapies and considering them for approval. The EMA began drafting recommendations for using PROs in 2004, which were adopted in 2005 and 2016 [5]. The US FDA followed these efforts with a draft guidance published in 2006 and then updated it in 2009 [6]. Although these efforts highlight the importance of PROs for drug approvals, these two agencies are divergent in their approaches. From the perspective of the EMA, the agency's primary concern is to acknowledge the importance of improvements in health-related quality of life (HRQOL) [7]. The EMA's PRO practices center on multiple domains for generalized assessment of HRQOL, while the US FDA focuses on symptom-specific measures. In addition, the EMA incorporates the HRQOL data from the clinical trials; however, there is no mention of this endpoint in the US FDA assessments. The US FDA is explicit in its requirements for developing and using PROs as an outcome in clinical trials [8]. This trend toward more specific requirements indicates that the US FDA favors symptom-specific assessments over global HRQOL assessments.

Figure 4. Differences in time to approvals of immune-checkpoint inhibitors by the European Medicines Agency and the Food and Drug Administration (Δ in additional days).



Δ: change or difference in additional days

Moreover, the US FDA usually considers PROs as a secondary or exploratory endpoint instead of including them as a primary endpoint. Although both agencies acknowledge the role and value of these PRO measures in bringing the patients' perspective into the drug evaluation process, the approach of the US FDA on PRO development and validation is more stringent when compared to the EMA. Increased harmonization and collaboration on the PRO instrument development, measurement, and validation are needed to improve the efficiency of future regulatory decisions.

Discussion

Regulation may hamper drug development and slow patients' access to innovation because of the costs incurred by the drug manufacturers to meet regulatory requirements that may be excessive and duplicative. Differences in regulatory approvals were analyzed between the US FDA and the EMA for ICIs in treating NSCLC, from 2015 until 2021, based on time to approval durations and considerations of PROs in decisions by each agency. The indications that stood out regarding outcome divergence were mainly first-line options for treatment naïve patients. The expedited development and access programs did not influence the preponderance of outcome differences in approvals. Two clinical trials (NCT01905657, NCT02039674) underwent the accelerated approval process by the US FDA. Accelerated approvals advanced by the US FDA and the EMA are among the reform efforts manufacturers frequently take advantage of when using surrogate endpoints to demonstrate efficacy within a shorter period.

Several European regulatory structures aim to accelerate the regulatory approval processes. Accelerated assessment, similar to the priority review process in the US, requires manufacturers to demonstrate that their drugs are of significant interest to public health, particularly from the therapeutic innovation viewpoint, filling a market gap. The priority medicines scheme or designation provides enhanced support for developing drugs that target an unmet medical need. Similar to the fast-track review process in the US, this scheme enhances interaction and early dialogue between regulators and manufacturers of promising drugs. Early clinical data are required to demonstrate eligibility. Like the FDA's accelerated approval program, conditional marketing authorization allows for early drug approval in an unmet medical need for serious, debilitating, or life-threatening diseases, emergencies, or orphan indications. After conditional approval, a comprehensive data package must be submitted to the EMA to adapt the temporary authorization to a standard one, which lasts for five years and can be renewed.

Despite similarities in the regulatory pathways and assessments used for immune-checkpoint inhibitor approvals, there were differences between these two agencies when the time to approval duration or marketing authorization was considered. This study showed that the US FDA approved immune-checkpoint inhibitors in NSCLC quicker than the EMA. However, the preponderance of outcome differences in approvals was not influenced by the expedited drug development and access programs in this setting. While the US FDA scientifically evaluates new drugs or products and then issues marketing authorization decisions, the EMA's "Committee-for-Medicinal-Products-for-Human-Use" (CHMP) only focuses on a scientific evaluation. The EMA provides recommendations to the European Commission (EC) after the CHMP evaluation process. Decoupling the scientific approval process and the marketing authorization has ramifications on additional patient access delays.

Moreover, differences between the US and Europe may arise because each EU member state follows specific regulations to determine which drugs will have marketing authorization in each jurisdiction. Outside the member states, a manufacturer in the United Kingdom (UK) can apply for drug marketing authorization through the Medicines and Healthcare Products Regulatory Agency (MHRA) or the EMA. If the EMA approves it, then it must be approved by the MHRA to be marketed in the UK. In addition, the National Institute for Health and Care Excellence must evaluate each drug for cost-effectiveness and affordability to determine whether the National Health Service could purchase the approved indication [9], [10].

The European Commission invited the European Network for Health Technology Assessment (EUnetHTA) 21 consortium and the EMA to optimize further and shorten patients' access to new drugs in Europe to work on a joint plan [11]. This plan focuses on preparing the application of the Regulation on HTA (EU) 2021/228 in January 2025, after a three-year implementation period [12]. This work plan promotes close collaboration between Europe's EMA and Health Technology Assessment (HTA) agencies. Priority areas in the EMA-EUnetHTA 21 work plan include joint consultation for evidence generation, patient-relevant data to support decision-making, and methodology development to engage patients and healthcare professionals [11]. This joint scientific consultation initiative with EunetHTA 21 replaced the former parallel scientific advice practices by the EMA and HTA agencies, where drug manufacturers had to contact each member state HTA agency individually. This new initiative provides opportunities for drug developers to discuss their plans for (long-term) evidence generation throughout the life cycle of a drug, together with the regulators and HTA bodies. It further aims to facilitate information exchange between the regulatory assessors and HTA agencies on products of mutual interest. Earlier engagement between regulators and the HTA

agencies would facilitate the timely uptake of innovation in health systems for the benefit of patients across Europe.

Concerning PROs, the 21st Century Cures Act outlines ways to incorporate patients' experiences into drug development and regulatory review processes [13]. The importance of collecting appropriate PROs is reflected in the updated US FDA and the EMA drug approval guidelines [5], [6]. There is evidence that monitoring treatment side effects in real-time can improve outcomes for patients with cancer, including a potential benefit in survival rates [14]. Previous research showed that PRO data captured during treatment could increase accuracy in assessing patients' experience of symptomatic side effects compared with physician reports because physicians may underreport the frequency or severity of side effects [15]. NSCLC is classified as a high tumor mutational burden cancer [16]. During or after immunotherapy, patients may experience immune-related adverse events (irAEs) and commonly reported treatment-related side effects [16]. Although patients' assessments of the incidence and consequences of these irAEs are necessary, existing cancer-specific PRO instruments [17], [18] were not designed to capture irAEs, and may not fully reflect the benefits or toxicity profiles of immunotherapies. Clinical guidelines that promote transparent and accurate reporting of PROs to facilitate interpretation of these complex data and their limitations are further compounded by factors, such as the unblinded nature of the NSCLC clinical trials [19], [20]. Furthermore, PROs are increasingly included in health technology assessments and have important ramifications on patient access, drug reimbursement, and pricing [4].

All in all, improved alignment of drug regulatory practices can result in efficient allocation of resources. These efforts can also provide more streamlined and predictable practices for assessing clinical efficacy, safety outcomes, and PRO measurements. While significant steps have been taken to harmonize and align regulatory approval practices, differences in outcomes have consequences for patients' timely access to NSCLC immunotherapies. Adhering to mutually agreed approval structures and processes could lower barriers to drug development and eliminate redundant efforts that may affect both the availability of safe and effective drugs to patients and the sustainability of the healthcare systems in North America, Europe, and beyond.

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3

Analysis of Patient-Reported Outcomes Included in the Registrational Clinical Trials of Nivolumab for Advanced Non-Small Cell Lung Cancer

Zaim R, Redekop WK, Uyl-de Groot CA.

Analysis of patient reported outcomes included in the registrational clinical trials of nivolumab in advanced non-small cell lung cancer. Translational Oncology 2022 Jun;20:101418.doi:10.1016/j.tranon.2022.101418.

Abstract

Stakeholders increasingly use patient-reported outcomes (PROs) to guide clinical decisions. In addition, PROs are included in the assessments of health technologies to aid in drug reimbursement, access, and pricing decisions. This study reviewed PROs reported in the Food and Drug Administration-approved indications of nivolumab clinical trials in advanced NSCLC. The PRO data collected in the CheckMate 017 (NCT01642004), CheckMate 057 (NCT01673867), CheckMate 227 (NCT02477826), and CheckMate 9LA (NCT03215706) registrational clinical trials were analyzed. In these trials, nivolumab alleviated symptom burden and improved the health status of patients. However, immune-related adverse event measurements, PRO evaluation times between patient groups, participation of patients, and long-term PRO data impede accurate analysis and validation.

Introduction

Immune checkpoint blockade is an effective therapeutic strategy that harnesses the immune system to generate an antitumor response. [1] Nivolumab, a programmed cell death receptor-1 (PD-1) blocking antibody, prolongs survival alone or in combination with ipilimumab, a cytotoxic T lymphocyte antigen-4 (CTLA-4) receptor, in the treatment of metastatic or recurrent non-small cell lung cancer (NSCLC). [2–6] The US Food and Drug Administration (FDA) approved nivolumab for three NSCLC indications: [2]

i. In the first-line setting, adult patients with metastatic NSCLC and Programmed Cell Death Ligand-1 (PD-L1) (≥1%) measured by an FDA-approved test [7], combined with ipilimumab without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) aberrations.
ii. In the first-line setting, adult patients with metastatic NSCLC or recurrent disease without EGFR or ALK aberrations, combined with ipilimumab and two cycles of platinum-doublet chemotherapy.
iii. Metastatic NSCLC patients experienced progression treated with platinum-based chemotherapy. Patients with EGFR mutations or ALK translocations should have progressed on an FDA-approved therapy before receiving nivolumab.

The FDA approved these three nivolumab indications with improved efficacy and acceptable toxicity based on randomized, open-label, phase III clinical trials. [3–6] The 21st Century Cures Act [8] outlines ways for the FDA to incorporate patients' experiences into drug development and review processes through its patient-focused technology development program. [9] Monitoring treatment side effects in real time can potentially improve outcomes for cancer patients and their survival rates. [10] PROs collected during treatment could be better proxies when assessing symptomatic side effects directly compared to clinician reports to avoid underreporting the frequency or severity of patients' side effects. [11] NSCLC is a type of cancer classified as a high tumor mutational burden (TMB). [12] Patients may experience immune-related adverse events (irAEs) during or after immunotherapy in addition to the commonly reported AEs. [12] These irAEs have consequences; however, the (lung) cancer-specific PRO instruments [13,14] were not designed to capture irAEs and toxicity profiles. Transparency and reporting accuracy of PROs are promoted in the guidelines to improve the accurate interpretation of data and address various limitations of the NSCLC clinical trials, including unblinded trials. [15,16]

Exploring the benefits, costs, safety, and other value dimensions of technologies based on value frameworks can help quantify the net value of NSCLC therapies using formulary prioritization, cost-effectiveness, and affordability evaluations. For ex-

ample, the value frameworks used by England's National Institute for Health and Care Excellence and the Institute for Clinical and Economic Review use quality-adjusted life years when providing recommendations. [17–19] Similarly, the European Society for Medical Oncology enables optional weighting of efficacy outcomes based on health-related quality of life (HRQoL). [20] Therefore, PROs are increasingly included in value assessments, impacting patient access, drug reimbursement, and pricing. Collecting appropriate PROs is also reflected in the updated FDA and European Medicines Agency (EMA) drug approval processes. [21,22] This study analyzed PRO data reported in nivolumab's registrational clinical trials for patients with metastatic or recurrent NSCLC. In addition, it assessed whether PROs were captured rigorously using appropriate, reliable, and validated instruments.

Extraction of PRO data

The registrational clinical trials of nivolumab were reviewed in the US FDA databases and Clinicaltrials.gov, from January 1, 2012, until January 1, 2022. Published studies reporting these PROs were searched using PubMed as well. (See *Supplementary Appendix*) The findings were summarized descriptively. The following data were presented in tabular format: clinical trial number, approval date by the US FDA, publication author and year, trial phase, treatment(s), comparator(s), number of patients available for analysis, PRO instruments used in the trial, PRO assessment frequency, PRO completion rates, and PRO follow-up after treatment discontinuation.

Analysis of PRO data

The PRO data have been considered either exploratory or secondary endpoints in the included nivolumab trials. A generic HRQoL measure, the EuroQoL five dimensions (EQ-5D) 3-level version, [23,24] and a tumor-specific measure, the Lung Cancer Symptom Scale (LCSS), were explored. [14] LCSS comprises the average symptom burden index ([ASBI]; with six symptoms: anorexia, fatigue, cough, dyspnea, hemoptysis, and pain) and the 3-item global index ([3-IGI]; with symptom distress, interference with activities, and HRQoL). The EQ-5D comprises the utility index [UI] and visual analog scale [VAS]. The EQ-5D descriptive index responses were mapped into UI, ranging from death (0) to full health (1). The health states worse than death were made possible (<0) with utility weights for the United Kingdom (UK) population. At the time of this analysis, population norms for the UK for EQ-5D VAS were 82.8 and EQ-5D UI 0.86 [26]. The published estimates for UK patients were 68 and 0.67 for EQ-5D VAS and EQ-5D UI, respectively. [27] Additional details of the PRO instruments are listed in **Table 1**. In the published studies, PROs were analyzed using descriptive statistics in each treatment group, comparing scores during treatment to baseline and between treatment groups at specific time points. Longitudinal changes from baseline

within and between groups were assessed using mixed-effects models for repeated measures (MMRM). Time to deterioration or improvement in HRQoL, defined based on clinically meaningful change, was determined using the Kaplan-Meier method. A clinically meaningful change represents treatment benefits or harms sufficient to modify clinical management. These are also interpreted relative to the minimally important difference (MID), "the smallest difference patients perceive as beneficial or detrimental, and is established by extensive anchor-based or distribution-based quantitative analyses". [27–30] A MID was defined as a within-patient score difference between baseline and a given time point of 10 points for the LCSS [ASBI] and 30 points for the LCSS [3-IGI]. [14] A MID was defined as a score difference of 0.08 points for the EQ-5D [UI] and 7 points for the EQ-5D [VAS]. [27]

Table 1. PRO instruments used in the registrational clinical trials of nivolumab for metastatic or recurrent NSCLC

	CheckMate 9LA [31]	CheckMate 227 [32]	CheckMate 057 [33]	CheckMate 017 [34]
Trial Number	NCT03215706	NCT02477826	NCT01673867	NCT01642004
Trial Phase	Phase III trial, randomized, open-label	Phase III trial, randomized, open-label	Phase III trial, randomized, open-label	Phase III trial, randomized, open-label
The US FDA approval date	May 26, 2020	May 15, 2020	October 9, 2015	March 4, 2015
Publication Author, Year	Abstract only; Reck M et al. 2020	Reck M, et al. 2021	Reck M, et al. 2018	Reck M, et al. 2018
Patients	Treatment naive, stage IV or recurrent NSCLC, and no known sensitizing EGFR/ ALK alterations	Treatment naïve, advanced NSCLC with ≥1% PD-L1, and high TMB (≥10 mutations per megabase)	Non-squamous advanced NSCLC patients with disease progression during or after platinum doublet chemotherapy	Squamous advanced NSCLC patients with disease progression during or after one platinum doublet chemotherapy
Treatment(s)	Nivolumab (360 mg Q3W) + Ipilimumab (1 mg/kg Q6W) + 2 cycles of chemotherapy *(N = 361)*	Nivolumab (3 mg/kg Q2W) + Ipilimumab (1 mg/ kg Q6W), *(N = 396)*	Nivolumab (3 mg/kg Q2W), *(N = 292)*	Nivolumab (3 mg/kg Q2W), *(N = 135)*
Comparator(s)	Four cycles of chemotherapy *(N = 358)*	Nivolumab monotherapy, or Platinum doublet chemotherapy*, *(N = 397)*	Docetaxel (75 mg/ m^2 Q3W), *(N = 290)*	Docetaxel (75 mg/m^2 Q3W), *(N = 137)*

Table 1. PRO instruments used in the registrational clinical trials of nivolumab for metastatic or recurrent NSCLC (*continued*)

	CheckMate 9LA [31]	CheckMate 227 [32]	CheckMate 057 [33]	CheckMate 017 [34]
PRO Instruments	LCSS [ASBI] and LCSS [3-IGI], EQ-5D-3L [UI] and EQ-5D-3L [VAS]	LCSS [ASBI] and LCSS [3-IGI], EQ-5D-3L [UI] and EQ-5D-3L [VAS]	LCSS [ASBI] and LCSS [3-IGI], EQ-5D-3L [UI] and EQ-5D-3L [VAS]	LCSS [ASBI] and LCSS [3-IGI], EQ-5D-3L [UI] and EQ-5D-3L [VAS]
PRO Trial Endpoint	Exploratory	Exploratory	The proportion of pts with disease-related symptom improvement at 12 wk on the LCSS [ASBI] was a secondary endpoint. Overall health status, measured by the EQ-5D-3L was an exploratory endpoint.	The proportion of pts with disease-related symptom improvement at 12 wk on the LCSS [ASBI] (a ≥10-point) was a secondary endpoint. Overall health status, measured by EQ-5D-3L was an exploratory endpoint.
PRO Assessment Frequency	Not reported in the abstract	#For the first six mo of treatment, LCSS and EQ-5D assessments were completed Q2W) for nivolumab plus ipilimumab and Q3W for chemotherapy; beyond six mo, these were completed Q6W for both groups while patients were receiving treatment.	Baseline, the first day of every other cycle (i.e., every four wk) of nivolumab or every cycle (i.e., every three wk) of docetaxel for the first six mo on treatment before any clinical activities occurred, and subsequently, every 6 wk during therapy and at two follow-up visits after treatment discontinuation; EQ-5D assessments continued every three mo for 12 mo and then every six mo after that.	Baseline on the first day of every other cycle (i.e., every 4 wk) of nivolumab or every cycle (i.e., every 3 wk) of docetaxel for the first six mo on treatment before any clinical activities occurred, and subsequently, every 6 wk during therapy and at two follow-up visits after treatment discontinuation; EQ-5D assessments continued every three mo for 12 mo and then every Six mo after that.

Table 1. PRO instruments used in the registrational clinical trials of nivolumab for metastatic or recurrent NSCLC (*continued*)

	CheckMate 9LA [31]	CheckMate 227 [32]	CheckMate 057 [33]	CheckMate 017 [34]
PRO Completion Rate	> 80% across groups for most on-treatment assessment points for ≥ 10 pts (up to wk 90 for Nivolumab + Ipilimumab + chemotherapy and wk 78 for chemotherapy)	> 80%	The LCSS completion rates at baseline were 82.2% for nivolumab and 76.6% for docetaxel. The EQ-5D completion rates were 83.6% for nivolumab and 80.0% for docetaxel, respectively. At baseline and one or more post-baseline visits, the rates were: 70.5% (LCSS) and 71.2% (EQ-5D) for nivolumab, 69.7% (LCSS) and 73.1% (EQ-5D) for docetaxel.	The LCSS completion rates at baseline were 77.8% for nivolumab and 76.6% for docetaxel. At baseline and one or more post-baseline visits, the rates were: 68.9% for nivolumab and 62.8% for docetaxel. In both treatment groups, EQ-5D completion rates were >70% up to wk 12.
PRO Follow-up After Treatment Discontinuation	Not reported in the abstract	LCSS and EQ-5D-3L were completed at two follow-up[§] visits after treatment discontinuation. Only EQ-5D-3L continued every three mo for 12 mo and then every six mo after that, at survival.†	LCSS and EQ-5D-3L were completed at two follow-up[§] visits after treatment discontinuation. Only EQ-5D-3L continued every three mo for 12 mo and then every six mo after that, at survival.†	LCSS and EQ-5D-3L were completed at two follow-up[§] visits after treatment discontinuation. Only EQ-5D-3L continued every three mo for 12 mo and then every six mo after that, at survival.†

Table 1 legend [°]Chemotherapy was dependent on tumor histology and administered every three weeks and up to four cycles with optional pemetrexed maintenance therapy in non-squamous NSCLC patients. Immunotherapy continued until disease progression, unacceptable toxicity, or for two years. [#] Common time points to both treatment groups were at 6-week intervals. LCSS and EQ-5D were administered at follow-up visits 1 and 2. EQ-5D was also administered at survival follow-up visits (every three mo for the first year and then every six mo). [§]Follow-up visit 1 occurred 35 (±7) days from the last dose or at treatment discontinuation (±7 days) if the date of discontinuation was greater than 42 days from the last dose; follow-up visit two occurred 80 (±7) days from the follow-up visit one. †Survival follow-up visits occurred approximately every three months (±7 days) from follow-up visit 2. PRO: Patient Reported Outcome; NSCLC: Non-small Cell Lung Cancer; LCSS: Lung Cancer Symptom Scale; ASBI: Average Symptom Burden Index; 3-IGI: 3-Item Global Index; EQ5D-3L: EuroQoL 5-dimensional instrument-3 Level; UI: Utility Index; VAS: Visual analog scale; TMB: Tumor Mutational Burden; PD-L1: Programmed Cell Death-Ligand 1; EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase; QW: every week, mo: month; w: week; d: day; kg: kilogram; m^2: meter square; pts: patients.

Registrational clinical trials of nivolumab for treatment naïve NSCLC patients

In the CheckMate 9LA trial, [6] PROs were considered exploratory endpoints. Disease-related symptoms were evaluated using the LCSS ASBI and 3-IGI; HRQoL was assessed using EQ-5D-3L UI and VAS. The analyses included mean changes from baseline, MMRM of longitudinal changes, and TTD. PRO completion rates were > 80% across groups for most on-treatment assessment times in which there were ≥ 10 patients (up to week 90 for nivolumab plus ipilimumab plus chemotherapy and week 78 for chemotherapy). [31] PRO follow-up after treatment discontinuation was not reported in the study abstract. LCSS ASBI and 3-IGI improvements were reported in both treatment arms, although the MID was not reached. Mean EQ-5D-3L VAS scores reached the UK population norms after about thirty weeks. The MMRM analyses showed improvements across groups in overall LCSS ASBI when patients were sufficient (until week 78). [31] In the trial that compared nivolumab and ipilimumab plus chemotherapy with chemotherapy, delayed time to deterioration and decreased risk were reported. Time from randomization until definitive deterioration (with assessments that met/exceeded the deterioration threshold) were as follows: HR (95% CI); EQ-5D-3L UI 0.72 (0.57–0.90), EQ-5D-3L VAS 0.73 (0.58–0.93), LCSS ASBI 0.66 (0.47–0.92), and LCSS 3-IGI 0.66 (0.50–0.88). [31] NSCLC patients treated with nivolumab and ipilimumab plus chemotherapy (2 cycles) maintained quality of life compared to chemotherapy (4 cycles). However, the available information was obtained from the published abstract with limited interpretability during this analysis. This patient group experienced a decreased risk of deterioration in HRQoL and symptoms compared to the chemotherapy patients.

In the CheckMate 227 trial, [5] PROs were assessed as exploratory endpoints. Disease-related symptoms were evaluated using the LCSS ASBI and 3-IGI, and HRQoL using EQ-5D-3L UI and VAS. Patients with high TMB (≥10 mutations/megabase) were considered in the PRO analysis. [32,35] In the first six months, PROs were evaluated each cycle (Q2W, nivolumab plus ipilimumab; Q3W, chemotherapy). After that, the PROs were evaluated every six weeks during treatment and at the first and second follow-up visits. During follow-up, EQ-5D-3L was used as the sole assessment. The longitudinal changes from baseline were evaluated using MMRMs and TTD analyses. For (most) on-treatment assessments, PRO completion rates were >80%. [32,35]. The mean baseline scores for nivolumab plus ipilimumab and chemotherapy were as follows: HR (95% CI) LCSS ASBI, 27.7 (24.6-30.8) and 24.8 (22.2-27.5); LCSS 3-IGI, 195.8 (183.0-208.6) and 197.6 (185.4-209.8); fatigue, 35.8 (31.2-40.4) and 36.0 (31.5-40.5); dyspnea, 28.8 (23.9-33.8) and 24.8 (20.4-29.1). [32,35] Differences in mean changes from baseline in LCSS 3-IGI favored For nivolumab plus ipilimumab,

differences in mean changes measured using LCSS 3-IGI were favored compared to chemotherapy. These differences were higher than the MID for the overall score (mean change 27.5 versus -5.1; difference 32.6) and higher than or approaching the MID for individual items. The EQ-5D VAS and EQ-5D UI mean differences from baseline favored nivolumab plus ipilimumab compared to chemotherapy. The mean scores for these measures approached the general population scores in the UK. [32,35] The magnitude of the difference was small for EQ-5D VAS in the CheckMate 227 trial. However, for the EQ-5D UI, differences were clinically meaningful (i.e., in the least squares mean change of 0.091). TTD by LCSS ASBI and LCSS 3-IGI were delayed when patients received nivolumab plus ipilimumab. The HRs for nivolumab plus ipilimumab compared to chemotherapy were (95% CI) 0.40 (0.26-0.63) and 0.56 (0.38-0.82), respectively. [32,35] Conversely, patients without significant deterioration or improvement in the first year were only 10% better with the immunotherapy combination. [32,35] The findings for EQ-5D VAS and UI were (95% CI) 0.62 (0.42-0.92) and 0.50 (0.34-0.73), respectively. [32,35] After treatment discontinuation (i.e., follow-up visits one and two), the mean changes from baseline assessed using all instruments were negligible in both treatment groups. Nivolumab plus ipilimumab delayed symptom deterioration and improved HRQoL compared to chemotherapy in the CheckMate 227 trial in patients with 1% or greater PD-L1 levels.

Registrational clinical trials of nivolumab for previously treated NSCLC patients

Disease-related symptom improvements at 12 weeks measured by the LCSS was a secondary endpoint in the CheckMate 057. [3] Overall health status, measured by the EQ-5D UI and VAS, was an exploratory endpoint. PROs were evaluated each cycle for the first six months, every six weeks after that during treatment, and at follow-up visits 1 and 2. Only EQ-5D-3L was assessed during survival follow-up. The baseline questionnaire completion rates for nivolumab compared to docetaxel were EQ-5D: 84% vs. 80%; LCSS: 82% vs. 77%. [33] At week 12, the results were similar (EQ-5D; nivolumab:77%, docetaxel: 80% and LCSS; nivolumab: 77% docetaxel: 76%). [33] The differences in mean changes from baseline for the LCSS ASBI and 3-IGI were -5.8 (95% CI)(-8.5 to -3.0) and 20.3 (95% CI) (9.6-31.0), respectively. [33] The EQ-5D UI and VAS findings were 0.034 (-0.009 to 0.076) and 5.9 (2.2-9.7), respectively. [33] TTD analyses for the LCSS ASBI and 3-IGI were (95% CI) 0.65 (0.49-0.85) and 0.63 (0.48-0.82), respectively. [33] The EQ-5D UI and VAS findings were 0.90 (0.69-1.17) and 0.76 (0.59-0.98). [33] Mean baseline LCSS ASBI scores were similar for both groups. At 12 weeks, disease-related symptom improvement was (95% CI) 17.8% (13.6-22.7) for nivolumab and 19.7% (15.2-24.7) for docetaxel, respectively. [33] At weeks 12, 24, 30, and 42, LCSS ASBI scores were improved in the nivolumab group and worsened

in the docetaxel group. Nivolumab improved disease-related symptoms and overall health status compared to docetaxel in the CheckMate 057 trial for non-squamous patients.

In the CheckMate 017 trial, [4] disease-related symptom improvement at 12 weeks using the LCSS was a secondary endpoint. Overall health status, measured by the EQ-5D UI and VAS, was an exploratory endpoint. PROs were evaluated each cycle for the first six months, every six weeks after that during treatment, and at follow-up visits 1 and 2. Only EQ-5D-3L was assessed during survival follow-up. The differences in mean changes (95% CI) for the LCSS ASBI and 3-IGI were -5.6 (95% CI; -10.5 to -0.6) and 22.2 (2.5 - 41.8), respectively. [34] The EQ-5D UI and VAS findings were 0.027 (-0.047 to 0.100) and 7.2 (0.6 to 13.8), respectively. [34] TTD analyses for the LCSS ASBI and 3-IGI were (95% CI) 0.67 (95% CI; 0.43–1.03) and 0.57 (0.38–0.85). [34] The EQ-5D UI and VAS findings were 0.55 (95% CI; 0.36–0.84) and 0.59 (0.40–0.87). [34] At the start of week 42, the mean EQ-5D UI scores were more favorable for the nivolumab patients than the US general population (0.87). [36] On the contrary, docetaxel patients had comparable scores with the norms of the lung cancer population (0.67). [27] At weeks 48 and 60, mean VAS scores of nivolumab patients were higher than the US general population norm (80.05). [36] In contrast, patients receiving docetaxel had similar scores to those of a lung cancer population (68). [27] Estimated changes from baseline in the LCSS ASBI and 3-IGI scores worsened in both groups after treatment discontinuation (i.e., first and second follow-up visits). For the ASBI, the estimated changes (range 5.5–9.5) were less than the MID and significant in the docetaxel group only. [34] For the 3-IGI, a substantial worsening was observed in the nivolumab group (follow-up visit one only) and the docetaxel group (both follow-up visits), higher than the MID in the docetaxel group. After treatment discontinuation, no significant between-treatment group differences were observed with either instrument. Nivolumab alleviated symptom burden and improved health status in the CheckMate 017 trial compared with docetaxel for squamous patients.

Discussion

In the included registrational clinical trials, nivolumab provided clinical benefits, stabilized or improved HRQoL, and alleviated symptom burden. For advanced NSCLC, symptom burden alleviation and HRQoL improvements are vital. On the contrary, accurate PRO studies that evaluate registrational clinical trials are scarce. The CheckMate 9LA, CheckMate 227, CheckMate 057, and CheckMate 017 registrational clinical trials suggest that nivolumab is favorable. However, these results should be interpreted

cautiously, particularly for the CheckMate 9LA registrational trial. At the time of this analysis, a detailed PRO assessment of the CheckMate 9LA trial was not publicly available. Like nivolumab, ipilimumab's mechanism of action depends on generating a T cell-mediated immune antitumor response. Although irAEs are commonly observed in immunotherapy-treated patients (i.e., with anti-CTLA-4 antibody), the instruments included in the PRO measurement of the CheckMate 9LA and CheckMate 227 trials did not have the capabilities to assess irAEs. Although clinical outcomes of nivolumab plus ipilimumab were compared with nivolumab alone in the CheckMate 227 trial, PRO analyses did not include this critical comparison for additional insights. Assessing a correlation (or lack thereof) between PRO benefits and progression-free or overall survival would have been informative. [37] There have been several concerns about PRO assessments in randomized clinical trials, [38,39] including reporting bias when measuring PROs in open-label trials; however, some of these concerns have been challenged. [40,41] Some patients may have increased expectations about nivolumab, and having an open-label study design may lead to complete questionnaires or a favorable ranking of nivolumab. [33] In contrast, patient exclusions due to therapy discontinuation could explain the differences among patient groups. Discontinuing patients could signal an inferior quality of life. [3] PROs were considered exploratory endpoints in the nivolumab trials without a hypothesis or a rationale for the expected benefit. In addition, the included PRO measurement tools were only partially justified. It is expected that cancer-specific measurement tools have yet to be developed and validated to evaluate PROs in immunotherapy-treated patients and those experiencing irAEs. This expectation has led to the Functional Assessment of Cancer Therapy-Immune Checkpoint Modulator. [42] In some PRO assessments, the outcomes for immunotherapy-treated patients (combination drugs and chemotherapy) overlap over several weeks. In addition, immunotherapy offers sustained clinical benefits for some patients in the long term. Therefore, applying methods to estimate proportional hazards may not adequately show delayed benefits due to immunotherapy. Instead, milestone survival analysis has been proposed to estimate the long-term benefits of immunotherapy. [43,44] Similarly, a differential approach might be necessary to accurately quantify PRO data changes when patients are treated with immunotherapy. An accurate PRO evaluation could provide a comprehensive evaluation of therapies and facilitate the application of better measurement tools in clinical practice. In a meta-analysis, Wang et al. [12] showed that irAEs could predict the efficacy of ICIs in patients with lung cancer. A total of 34 records were examined. [12] The occurrence of irAEs was significantly associated with higher ORR {risk ratio (RR): 2.43, 95% confidence interval (CI) [2.06–2.88]}, and improved OS {hazard ratio (HR): 0.51, 95% CI [0.43–0.61]}, and PFS (HR: 0.50, 95% CI [0.44–0.57]) in patients treated with ICIs. [12] OS was significantly longer in patients with dermatological (OS: HR: 0.53, 95%CI

[0.42–0.65]), endocrine (OS: HR: 0.55, 95%CI [0.45–0.67]), and gastrointestinal (OS: HR: 0.58, 95%CI [0.42–0.80]) irAEs. [12] However, hepatobiliary, pulmonary, and high-grade (≥3) irAEs were not correlated with increased OS and PFS. [12] Wang et al. concluded that the occurrence of irAEs in these patients, particularly dermatological, endocrine, and gastrointestinal irAEs, helps to predict enhanced ICIs efficacy.

A meta-analysis by Boutros et al. [45] compared PRO measures between ICIs (or ICIs in combination with chemotherapy) to chemotherapy in advanced solid tumors. ICIs were associated with higher QoL and delayed clinical deterioration compared to chemotherapy in various solid tumors. Time from baseline to first deterioration was the primary endpoint. Other endpoints were defined as the time from baseline to the first clinically significant deterioration in PROs and the changes in PROs from baseline to follow-up between ICI and chemotherapy groups. [45] Seventeen randomized trials of ICIs were compared to chemotherapy. The findings demonstrated that ICIs delayed clinical deterioration compared to standard chemotherapy in Global Health Status EORTC QLQ-C30 ([HR] 0.81; 95% [CI], 0.74–0.89), including EQ-5D UI (HR 0.65; 95% CI, 0.52–0.82) and VAS (HR 0.70; 95% CI, 0.61–0.80). [45] The mean difference between the ICI-treated and the chemotherapy-treated groups was 5.82 (95% CI, 4.11–7.53) in favor of ICIs. [45] When EQ-5D was considered, the mean change differences favored treatment with ICIs in both UI and VAS, 0.05 (95% CI, 0.03–0.07) and 5.41 (95% CI, 3.39–7.43), respectively. [45]

Gonzalez et al. [46] performed a similar meta-analysis. For global QOL, the authors used the EORTC QLQ-C30 global health status score and the EQ-5D VAS. The co-primary endpoints were "change in global QOL among patients treated with ICIs" and "difference in change from baseline in global QOL" in ICI-treated patients compared to non-ICI treatment. [46] In this meta-analysis, twenty-six studies were included. Patients who received ICIs had no change in global QOL and improved QOL versus those treated with non-ICI treatments. There was no statistical significance on the overall QOL from baseline until follow-up (mean: 1.13, 95% CI:-0.54 to 2.81). [46] Patients receiving ICIs reported better overall QOL improvements than non-ICI treatments (mean: 3.44, 95% CI: 2.00 to 4.89). [46] There was no statistically significant change across all ICI-treated patients in physical functioning from baseline until follow-up (mean: 0.46, 95% CI: -0.79 to 1.71). [46]

PROs are considered objective measures because PROs rely solely on patients' responses instead of subjective assessments provided by health professionals. [47,48] It is possible that baseline PROs could emerge as a stratification factor and could be used in addition to performance status. [37] Additionally, it has been shown that

worsening PRO scores may correlate with progression. [47,49] Therefore, more work is encouraged on the quality of the data captured during follow-up (i.e., posttreatment discontinuation) in clinical trials. [50] The follow-up data on PROs have been relevant for many countries when analyzing the comparative effectiveness of new interventions for technology assessments, drug reimbursement decisions, and market access. For example, the German Institute for Quality and Efficiency in Health Care expects drug manufacturers to report PRO data collected after disease progression. [51] Although PRO data collected after posttreatment discontinuation are informative, the FDA's Oncology Center of Excellence primarily uses PROs to address safety or tolerability issues during treatment. [52] After treatment discontinuation, the timing and frequency of PRO assessments remain critical considerations for meaningful data interpretation.[53] Moreover, during cancer clinical trials, the assessment of PROs is generally tied to clinical visits for convenience, despite the possibility that these clinical visit schedules may not be useful. PRO assessment schedules during treatment compared to follow-up ones may vary between assessments. This variation could make data interpretation and analysis difficult, leading to potential under- or overestimating outcomes.

The FDA issued a draft guidance and outlined core PRO measures for cancer clinical trials in June 2021. [54] This guidance focuses on patients' symptoms, AEs, and physical function. It is specific to registrational cancer trials that aim to demonstrate survival effects, tumor response, or progression delays. The FDA recommends a separate analysis of disease-related symptoms, adverse events, side effects, and physical and role functions. [54] For instance, this guidance suggests using disease symptom scales, including the NSCLC Symptom Assessment Questionnaire. [54] It also indicates that "when disease symptoms are heterogeneous in type and incidence, for advanced cancers, this may include pain, anorexia, and fatigue, to be measured individually or with other disease-related symptoms." Although the PRO–CTCAE (PRO-Common Terminology Criteria for AEs) may not be sufficiently comprehensive in its current form to incorporate all irAEs, the FDA recommends using it for AEs. [54]

The 21st Century Cures Act has helped to bolster the inclusion of PROs in clinical trials since 2015. [8] Despite this act, studies on registrational cancer trials have shown wide variation in how PRO measures are captured and analyzed. A multiple myeloma trial submitted to the FDA showed substantial heterogeneity in PRO collection methods, patient population definitions, measures completion, and clinically meaningful change. [55] Forty PRO instruments were used across 17 clinical trials. [55] The time points of the PRO assessments were variable and limited. It was also shown that the registrational trials had varying definitions of baseline. For instance,

seven trials defined baseline as "cycle one, day one". In contrast, two trials described baseline as "being on or before cycle one, day one", and eight trials defined baseline as "being the screening phase or before randomization". The trials also used different definitions of PRO instrument completions. For example, one trial focused on completing all questions, two trials half of the questions, and 14 trials defined it as "completing enough items to calculate the score in any domain." [55] Trials also varied whether they included intent-to-treat or safety populations in their analysis. In another study, the FDA researchers explored PRO use after treatment discontinuation in prostate, breast, pancreatic, and hepatocellular carcinoma. [53] The findings indicated variations in PRO completion rates and duration of follow-up for therapies approved by the FDA between January 2010 and January 2019. [53] Based on the 54 trials, PRO data were collected for at least one follow-up assessment in 46%. [53] The follow-up schedules varied, ranging from 30 days and six months posttreatment. [53] Also, mean PRO completion rates at the first follow-up varied depending on the cancer type, with >70% completion rates in breast cancer and nearly 55% in prostate cancer. PRO completion rates at the first follow-up assessment were unavailable for hepatocellular or pancreatic cancer trials. [53] The researchers concluded that "the follow-up phase of PRO assessments has not been given the same attention as on-treatment assessments."

Conclusion

Nivolumab alleviated symptom burden and improved the health status of patients in the registrational clinical trials of advanced NSCLC. However, immune-related adverse event measurements, PRO evaluation times among patient groups, participation of patients at specified times, and long-term data pose a compounded challenge to accurately analyze and validate the clinical trial findings.

Supplementary Table 1: Search Syntax

Category	Search terms
Population	"non-small cell cancer" AND (advanced OR metastatic OR recurrent) AND ("PD-1" OR "PD-L1" OR "CTLA-4" OR "programmed cell death" OR "cytotoxic T lymphocytes")
Intervention	AND ("phase 3" OR "phase III") AND (nivolumab OR ipilimumab)
Comparison	N/A (no restriction)
Outcome	AND (QoL OR pro OR prom OR "quality of life" OR "patient-reported outcome" OR "patient-reported outcomes" OR "health-related quality of life")

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Cost-Effectiveness of First Line Nivolumab-Ipilimumab Combination Therapy for Advanced Non-Small Cell Lung Cancer: A Systematic Review and Methodological Quality Assessment

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Cost-effectiveness of first line nivolumab-ipilimumab combination therapy for advanced non-small cell lung cancer. A systematic review and methodological quality assessment. Frontiers in Health Services 2023 Mar 13;3:1034256. doi:10.3389/frhs.2023.1034256.

Abstract

To assess the methodological quality of cost-effectiveness analyses (CEA) of nivolumab in combination with ipilimumab, a systematic literature review was conducted in the first-line treatment of patients with recurrent or metastatic non-small cell lung cancer (NSCLC), whose tumors express programmed death ligand-1, with no epidermal growth factor receptor or anaplastic lymphoma kinase genomic tumor aberrations. PubMed, Embase and the Cost-Effectiveness Analysis Registry were searched per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The Philips checklist and the Consensus Health Economic Criteria (CHEC) checklist were used to assess the quality of the methodology. One hundred seventy-one records were identified. Seven studies met the inclusion criteria. Cost-effectiveness analyses differed substantially due to the applied modeling methods, sources of costs, health state utilities, and key assumptions. Quality assessment of the included studies highlighted shortcomings in data identification, uncertainty assessment, and methods transparency. This systematic review and methodology assessment revealed that the methods of estimation of long-term outcomes, quantification of health state utility values, estimation of drug costs, the accuracy of data sources, and their credibility have important implications on the cost-effectiveness outcomes. The included studies fulfilled only some criteria reported in the Philips and the CHEC checklists. To compound the economic consequences of these limited CEAs, ipilimumab's drug action as a combination therapy poses significant uncertainty. Further research is encouraged to address the economic implications of these combination agents in future CEAs and the clinical uncertainties of ipilimumab for NSCLC in future trials.

Introduction

Platinum-based doublet chemotherapy was historically the standard first-line treatment for patients with recurrent or metastatic non-small cell lung cancer (NSCLC), whose tumors lack Epidermal Growth Factor Receptor or Anaplastic Lymphoma Kinase aberrations. More recently, pembrolizumab monotherapy for patients with a high level of tumor programmed cell death ligand- 1 (PD-L1) expression ≥1% became the standard first-line therapy for advanced NSCLC without treatable driver mutations. (1–3) Nivolumab and ipilimumab are monoclonal antibodies that bind to programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) receptors, respectively, to restore T-cell activity against tumor cells. In 2019, the CheckMate 227 Phase 3 trial showed improved progression-free and overall survival with this dual checkpoint inhibition in recurrent or metastatic NSCLC. (4) The CheckMate 227 trial results indicated that nivolumab plus ipilimumab improved survival in PD-L1 ≥ 1% and PD-L1 < 1% subgroups. (4) In 2021, the CheckMate 9LA Phase 3 trial, stratified patients by PD-L1 ≥ 1% and < 1%, showed that nivolumab in combination with ipilimumab plus two cycles of chemotherapy improved progression-free and overall survival, compared with four cycles of chemotherapy. (5) The United States (US) Food and Drug Administration (FDA) approved nivolumab plus ipilimumab for patients with PD-L1 ≥ 1%, (6) and the National Comprehensive Cancer Network panel extended their use for PD-L1 < 1% patients. (7) The US FDA also approved Nivolumab plus ipilimumab with two cycles of chemotherapy in patients regardless of PD-L1 expression levels.(8)

Although several studies have shown single-agent immune checkpoint inhibitors with or without chemotherapy to be cost-effective, (9–13) double-agent immunotherapy combinations may not be cost-effective, given their high price tags. To assess the economic value of nivolumab in combination with ipilimumab, a systematic literature review of model-based cost-effectiveness analyses (CEA) was conducted in the first-line recurrent or metastatic NSCLC. To evaluate the methodological quality of the published CEAs, the Philips checklist (14) and the Consensus Health Economic Criteria (CHEC) checklist (15) were used to critically review the applied methods and modeling efforts in this setting.

Methods

Search strategy

A systematic literature review was conducted per the PRISMA guidelines. (16) Searches in PubMed, Embase, and the Cost-Effectiveness Analysis (CEA) Registry database were

conducted. The searches were built using the Population Intervention Comparison Outcome (PICO) framework (*Supplementary Table 1a, 1b, and 1c*). Each search was limited to English-language studies of human subjects. No date restrictions were applied. The search strategies in PubMed, Embase, and the CEA Registry database *are included in Supplementary* ***Table 1.*** Manual reference checks supplemented database searches. All searches were finalized on January 5, 2022.

Study selection

Studies accepted at the title-abstract screening stage were retrieved in full text for review. Two reviewers screened all studies and resolved any issues of discrepancy through consensus or consultation with a third reviewer. Studies were included if they fulfilled the eligibility criteria. Articles' selection, inclusion, and exclusion processes were recorded in Rayyan (https://www.rayyan.ai/cite) and Microsoft Excel. This method provides transparency regarding all selection steps and assures reproducibility. Additional details of the eligibility criteria are listed in **Table 1**.

Data extraction

An evidence table (**Table 2**) is created according to the PICO framework to extract data on the study author, year, country, population, clinical trial, PD-L1 expression, intervention, comparator, time horizon, study perspective, incremental outcomes (QALYs and costs), incremental cost-effectiveness ratio (ICER), as well as the author's stated conclusions.

Quality assessment

The included studies' quality assessment was performed using the Philips checklist (14) and the Consensus Health Economic Criteria (CHEC) checklist. (15) One reviewer assessed the quality of the methodology for each study, and a second reviewer validated the findings. Any discrepancy issues were resolved through consensus or consultation with a third reviewer.

Results

PRISMA flow diagram (**Figure 1**) shows the details of all (N=171) identified records. After duplicates (N=33) were removed, 138 records were screened, and 130 were excluded based on title and abstract. Eight studies were then selected for full-text screening. Seven studies met the inclusion criteria and underwent data extraction. The reason for excluding one study is listed in the *Supplementary Appendix* (*Supplementary Table 3*). **Table 3** shows the quality assessment results based on the CHEC

checklist. **Table 4** shows the quality assessment results found on the Philips checklist. A schematic representation of the outcomes and differences between these checklists is presented in the *Supplementary Appendix* (*Supplementary Figures 1 and 2*).

Table 1: Study inclusion and exclusion criteria

Item	Inclusion	Exclusion
Period publication	No restriction	-
Country of study	Worldwide	-
Study design/type	Cost-effectiveness analysis Cost-utility analysis	Resource use, patient-reported outcomes
Study population	First-line (treatment naïve) metastatic or advanced NSCLC without treatable driver mutations	Any other population
Study intervention	Nivolumab Ipilimumab	All other study interventions
Study comparison	Chemotherapy	No comparator
Study outcomes	Quality-adjusted life years Incremental Cost Effectiveness Ratio	-

Abbreviation: NSCLC: Non-small cell lung cancer

Included CEAs and study characteristics

In the first-line treatment of advanced NSCLC, the cost-effectiveness of nivolumab-ipilimumab or nivolumab-ipilimumab plus two cycles of chemotherapy was compared with standard chemotherapy. According to the PICO framework (see **Table 2**), in the CEAs (17–22) that sourced the CheckMate 227 clinical trial *(Population)*, "nivolumab (three mg/kg every two weeks) plus ipilimumab (one mg/kg every six weeks)" (*Interventions*) was compared with platinum-doublet chemotherapy every three weeks for up to four cycles *(Comparator)*. (4) In the CEAs (21,23) that sourced the CheckMate 9LA clinical trial *(Population)*, nivolumab (360 mg every three weeks) and ipilimumab (1 mg/kg every six weeks) were combined with histology-based, platinum doublet chemotherapy (every three weeks for two cycles) (*Interventions*), and were compared with chemotherapy alone (every three weeks for four cycles) *(Comparator)*. (5) Study outcomes in all CEAs were expressed in incremental costs, QALYs, and ICERs (see **Table 2** for details on the included study *Outcomes* and conclusions).

Model type and health states: Markov models were developed to extrapolate study outcomes. Transition probabilities were derived from the CheckMate 227 and the CheckMate 9LA clinical trials. The methods developed by Hoyle and Henley (24) were used in studies to recreate patient data from published Kaplan-Meier Survival Curves for CEA models. In all CEAs, health states comprised stable disease (progression-free), progressed disease, and death.

Model cycle and time horizon: Variable model cycle lengths were adapted, including intervals of one week, (17) 3 weeks, (23) 6 weeks, (18–21), and one month. (22) Similarly, time horizons varied among the CEAs, including ten years, (17,19,22) 20 years, (18), and lifetime. (20,21,23)

Estimation of long-term outcomes showed variability among the included CEA studies due to: (i) variation in the extraction of data points of survival curves from the CheckMate 227 and the CheckMate 9LA trials, (ii) calibration of the probability of progressive disease to death at each model cycle (i.e., intervals of one week, (17) 3 weeks, (23) 6 weeks, (18–21) and one month, (22) to fit the overall survival curve, (iii) variation in statistical techniques in fitting and extrapolating survival functions. Age-specific mortality from other causes was estimated based on the US life tables. (25)

Costs and their sources: All CEAs included the United States (US) healthcare, payer or societal perspectives, and expressed costs in US dollars (*years ranging from 2018 to 2021*). In one study (18), the authors did not specify a year for the included costs. In another study (17), the rationale for the cost year of 2018 was not included. In this study, (17) the authors indicated that the vial prices of nivolumab-ipilimumab were discounted by 17%, based on a previously published study (26), and the cost of chemotherapy was $24,437 per patient regardless of histology. (27) In the same study (17), the cost of maintenance chemotherapy was $5,887 for non-squamous NSCLC. (27) All remaining sources for drug prices were obtained from the US Medicare and Medicaid Services (25), literature, and publicly available sources. (28) Medical consumer price indices (29) were used to express costs in US dollars.

Utility values and their sources: Health state utility estimates were based on the literature (30–33) for six CEAs. (17,19–23) In one study (18), treatment-specific utilities (0.784 combination therapy and 0.693 chemotherapy) were collected in the CheckMate 227 trial. (34)

Cost-effectiveness thresholds: For the US setting, two studies used a willingness-to-pay threshold (WTP) of $100,000 per QALY, (17,22) four studies used a WTP of $150,000 per QALY, (18,19,21,23) and one study included both thresholds. (20) In addition, one study included the perspective of the Chinese healthcare system and used a WTP of $27,351 per QALY. (17)

Cost-effectiveness results: The ICERs (cost/QALY gained) reported in the included studies which are *not deemed cost-effective* were as follows: $401,700 (healthcare perspective) (22), $434,400 (societal perspective) [23], $551, 900 (received treat-

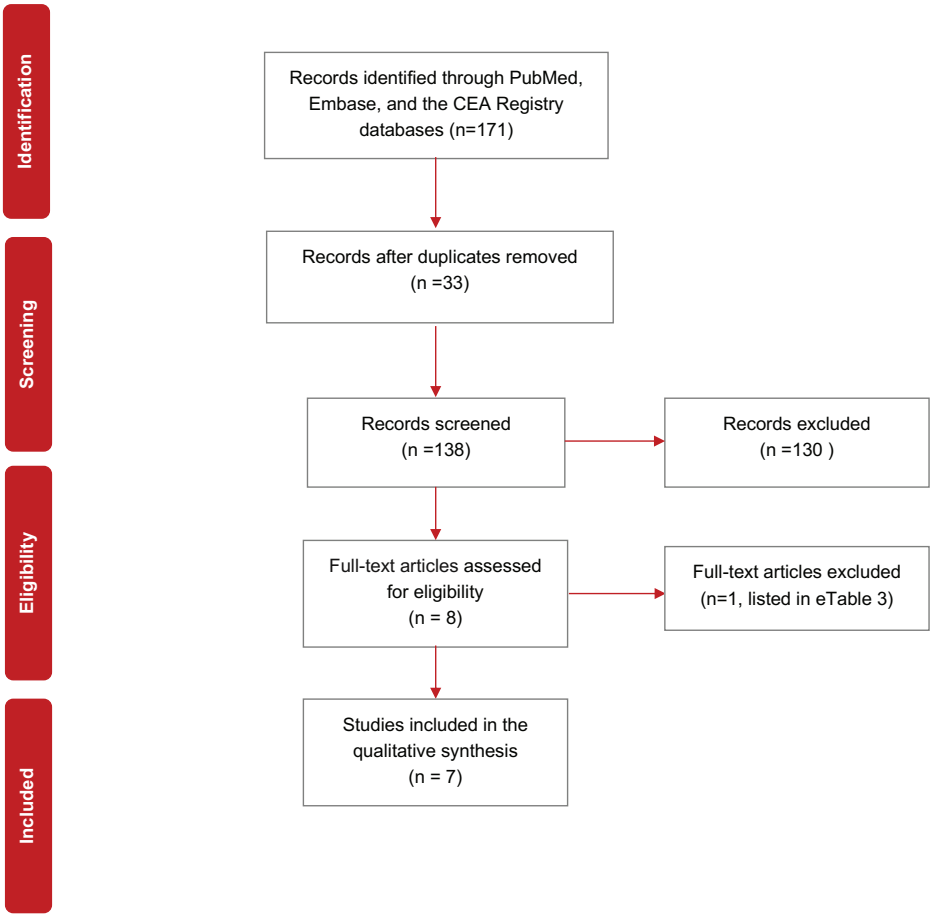
ment up to 24 months). (22) In patients with PD-L1 <1%, the ICER was $172,589 per QALY gained. (18) In China, the ICER of nivolumab-ipilimumab was $59,773 per QALY gained at a WTP threshold of $27,351 per QALY. (17) One study (19) showed that in patients with PD-L1 ≥1 and PD-L1 <1, the ICERs were $180,307 and $143,434 per QALY gained, respectively. (19) One study (23) reported that the ICER was $202,275 per QALY gained. (23) Another study (21) showed that the ICER of nivolumab-ipilimumab combination therapy was $239,072 per QALY compared to chemotherapy. The ICER of nivolumab-ipilimumab plus chemotherapy compared to nivolumab-ipilimumab was $838,198 per QALY gained. (21)

The ICERs reported in the included studies which are *deemed cost-effective* were as follows: In one study (18) for patients with PD-L1 expression levels ≥50% and ≥1% or a high Tumor Mutational Burden (TMB), the ICERs were $107,404 and $133,732 per QALY gained, respectively. (18) In another study, (17) the ICER was $75,871 per QALY gained (for the US setting). However, the credibility of the data sources in this study (17) is questionable and poses a challenge in comparing study outcomes accurately. The abovementioned study's outcomes (17) should be interpreted cautiously for the US setting. Another study (20) reported that the ICER was $104,238 per QALY gained (regardless of the PD-L1 expression level). (20)

Sensitivity and subgroup analyses: For patients with PD-L1 levels <1%, ≥1%, and ≥50%, the ICERs were $332,100, $440,100, and $375,700 per QALY gained, respectively. (22) The most influential model inputs were drug acquisition costs, duration of combination immunotherapy, patients' body weight, and survival hazard ratio. In one study (18), the analysis of patients with a high TMB resulted in an ICER of $69,182 per QALY gained compared with chemotherapy. In this study, (18) patients with PD-L1 <1%, nivolumab-ipilimumab combination therapy could be deemed cost-effective if the cost of nivolumab was discounted by 21% or the cost of ipilimumab were to be discounted by 24%. (18) Another study (19) reported from the US perspective that the ICERs were $143,434, $196,507, and $212,111 per QALY gained in patients with PD-L1 <1, ≥1, and ≥50%, respectively. (19) The authors in this study calculated that the cost of nivolumab should be discounted by 20% to have an ICER below the WTP threshold. (19) In one study, (20) the authors showed that when patients' weight increased to 140 kg or the overall survival hazard ratio increased to 0.84, the ICER exceeded the WTP threshold of $150,000 per QALY. (20) Finally, one study (23) showed that patients with Eastern Cooperative Oncology Group score of 0 and central nervous system metastases favored nivolumab-ipilimumab plus chemotherapy, with more than a 50% probability of being cost-effective compared with chemotherapy. (23) However, the cost-effectiveness probability was extremely low for subgroups of

patients with unfavorable HR of overall survival, such as those older than 75 years, with squamous NSCLC, and liver metastases. (23) In this study, when the cost of nivolumab was reduced by at least 28%, nivolumab-ipilimumab plus chemotherapy was cost-effective compared with chemotherapy alone at a threshold of $150,000 per QALY. (23)

Figure 1. PRISMA flow chart of the systematic review on the cost-effectiveness of first-line nivolumab in advanced non-small cell lung cancer



CEA: Cost-effectiveness analysis

Table 2. Evidence table of the included cost-effectiveness studies

Cost-effectiveness studies of nivolumab-ipilimumab for the first-line treatment of advanced NSCLC										
Author, Year, Country	Population, Clinical Trial	PD-L1 Test	Intervention	Comparator	Time Horizon	Study Perspective	Incremental Outcomes		Incremental Cost-Effectiveness Ratio (ICER)	Conclusions of the study authors
							△Costs (US dollars)	△QALY	△Costs/△QALY gained	
Courtney et al., 2021, (22) United States	First-line advanced NSCLC, Checkmate 227	PD-L1≥ 50%, PD-L1≥ 1%, PD-L1< 1%	Nivo (3 mg/kg Q2W) + Ipi (1 mg/kg Q6W)	Chemo	Ten years	US Healthcare and Societal Perspectives	$201, 900	0.50	Healthcare: $401,700 per QALY gained. Societal: $434400 per QALY gained	Nivo+Ipi combination therapy was not cost-effective compared with chemo as first-line treatment for patients with advanced NSCLC
Hao et al., 2021, (17) United States & China	First-line advanced NSCLC, Checkmate 227	PD-L1< 1%	Nivo (3 mg/kg Q2W) + Ipi (1 mg/kg Q6W)	Chemo	Ten years	US Payer (Medicare & Medicaid) Perspective and Chinese Healthcare Perspective	US: $95,617, China: $66,178	US: 1.26, China: 1.1	US: $75,871 per QALY gained, China: $59,773 per QALY gained	Nivo+Ipi was a cost-effective option compared with chemo in the US. However, it was not cost-effective in China.
Hu et al., 2020, (18) United States	First-line advanced NSCLC, Checkmate 227	PD-L1≥ 50%, PD-L1≥ 1%, PD-L1< 1%	Nivo (3 mg/kg Q2W) + Ipi (1 mg/kg Q6W)	Chemo	20 years	US Payer (Medicare & Medicaid) Perspective	PD-L1≥ 50%: $124,181, PD-L1≥ 1%: $70,951, PD-L1< 1%: $144,093	PD-L1≥ 50%: 1.15, PD-L1≥ 1% : 0.53, PD-L1< 1%: 0.84	PD-L1≥ 50%: $107,404 per QALY gained, PD-L1≥ 1%: $133,732 per QALY gained, PD-L1< 1%: $172, 589 per QALY gained	Nivo+Ipi was a better cost-effective strategy than chemo in patients with PD-L1 ≥ 50% and ≥ 1% or a high TMB, but not in patients with a PD-L1 < 1%, at a WTP of $150K per QALY gained.

Table 2. Evidence table of the included cost-effectiveness studies (*continued*)

Cost-effectiveness studies of nivolumab-ipilimumab for the first-line treatment of advanced NSCLC										
Author, Year, Country	**Population, Clinical Trial**	**PD-L1 Test**	**Intervention**	**Comparator**	**Time Horizon**	**Study Perspective**	**Incremental Outcomes**		**Incremental Cost-Effectiveness Ratio (ICER)**	**Conclusions of the study authors**
							△Costs (US dollars)	**△QALY**	**△Costs/△QALY gained**	
Li et al., 2020, (19) United States	First-line advanced NSCLC, Checkmate 227	PD-L1≥ 1%, PD-L1< 1%	Nivo (3 mg/kg Q2W) + Ipi (1 mg/kg Q6W)	Chemo	Ten years	US Payer (Medicare & Medicaid) Perspective	PD-L1 <1% $128,250, PD-L1 ≥ 1% $128,984	PD-L1 <1% 0.894, PD-L1 ≥ 1% 0.715	PD-L1 <1% $143,434, PD-L1 ≥ 1% $180,307 per QALY gained	Nivo+Ipi is cost-effective only in patients with PD-L1 <1% in the first-line setting but not cost-effective for PD-L1 ≥ 1% or all populations.
Peng et al., 2021, (23) United States	First-line advanced NSCLC, Checkmate 9LA	Not reported	Nivo (360 mg Q3W) + Ipi (1 mg/kg Q6W) + 2 cycles of chemotherapy	Chemo	Lifetime Horizon	US Payer (Medicare & Medicaid) Perspective	$161,993	0.8	$202,275 per QALY gained	Nivo+Ipi combined with two cycles of chemo was not deemed cost-effective as a first-line treatment at the WTP of 150K per QALY gained.
Wan et al., 2021, (20) United States	First-line advanced NSCLC, CheckMate 227	PD-L1≥ 50%, PD-L1≥ 1%, PD-L1< 1%	Nivo (3 mg/kg Q2W) + Ipi (1 mg/kg Q6W)	Chemo	Lifetime Horizon	US Payer (Medicare & Medicaid) Perspective	$66,218	0.62	$104,238 per QALY gained	Nivo+Ipi was cost-effective compared with chemo at a WTP threshold between 100K and 150K per QALY gained.

Table 2. Evidence table of the included cost-effectiveness studies (*continued*)

Cost-effectiveness studies of nivolumab-ipilimumab for the first-line treatment of advanced NSCLC										
Author, Year, Country	**Population, Clinical Trial**	**PD-L1 Test**	**Intervention**	**Comparator**	**Time Horizon**	**Study Perspective**	**Incremental Outcomes**		**Incremental Cost-Effectiveness Ratio (ICER)**	**Conclusions of the study authors**
							△Costs (US dollars)	**△QALY**	**△Costs/△QALY gained**	
Yang et al., 2021, (21) United States	First-line advanced NSCLC, CheckMate 227, and CheckMate 9LA	PD-L1≥ 1%, PD-L1< 1%	Nivo(3 mg/kg Q2W) + Ipi (1 mg/kg Q6W) and Nivo (360 mg Q3W) + Ipi (1 mg/kg Q6W) + 2 cycles of chemo	Chemo	Lifetime Horizon	US Healthcare Perspective	Nivo+Ipi $110,333 Nivo+ Ipi+Chemo: $217,820	Nivo+Ipi: 0.46, Nivo+Ipi+ Chemo: 0.59	Nivo+Ipi: $239,072 per QALY gained Nivo +Ipi+Chemo $838,198 per QALY gained	Nivo+Ipi or Nivo+ Ipi plus chemo was not cost-effective regardless of PD-L1 expression levels.

Abbreviations NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand-1; Nivo: Nivolumab; Ipi: Ipilimumab; Chemo: Chemotherapy; QALY: Quality-adjusted life years; US: United States; QnW: every n weeks; mg/kg: milligram per kilogram; WTP: willingness-to-pay; TMB: Tumor mutational burden; △Costs/△QALY: Incremental costs per incremental quality-adjusted life years.

Chemotherapy in the CheckMate 227 trial: platinum-doublet chemotherapy (every three weeks for up to four cycles). Chemotherapy in the CheckMate 9LA trial: carboplatin plus paclitaxel for patients with squamous histology or carboplatin plus pemetrexed or cisplatin plus pemetrexed for patients with non-squamous histology.

Methodological quality assessment of the included cost-effectiveness studies

Table 3 shows methodological quality assessment results based on the CHEC checklist. The CHEC checklist consists of 19 questions. (15) The quality outcomes of each study were based on whether insufficient or missing information was identified in the article or other published materials. The assessment criteria were fulfilled if the study authors paid sufficient attention to the listed checklist items. **Table 4** shows the quality assessment results based on the Philips checklist. This checklist comprises 20 quality dimensions according to model structure, data, and consistency. (14) Similar assessment criteria were employed, and the quality outcomes of each study based on the Philips checklist are presented in **Table 4**. For a visual representation of the quality assessment study findings and differences among these checklists, see the *Supplementary Appendix* (*Supplementary Figures 1 and 2*).

Table 3: Quality assessment results based on the CHEC checklist

CHEC Checklist	Questions (1-19)																		
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Courtney et al., (22)	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	NA
Hao et al. (17)	Y	Y	Y	Y	P	Y	P	P	P	Y	P	P	Y	Y	Y	Y	Y	Y	NA
Hu et al., (18)	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
Li et al., (19)	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	P	P	Y	Y	Y	Y	Y	Y	NA
Peng et al., (23)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y	Y	Y	Y	NA
Wan et al., (20)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y	Y	P	Y	NA
Yang et al., (21)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA

Abbreviations: Y; item completely fulfilled, P; item partially fulfilled, N; item not fulfilled, N/A; item not applicable **Item Checklist**: 1; Study population, 2; Competing alternatives, 3; Research question, 4; Study design, 5; Time horizon, 6; Perspective, 7; Costs identified, 8; Costs measured, 9; Costs valued, 10; Outcomes identified, 11; Outcomes measured, 12; Outcomes valued, 13; Incremental analysis, 14; Costs outcomes discounted, 15; Sensitivity analysis, 16; Conclusions, 17; Generalizability of results, 18; Conflict of interest, 19; Ethical distributional issues

Based on the CHEC checklist, time horizon and health outcome measurement (**Table 3**) were items that were 'partially fulfilled' by Courtney et al. (22). In studies reported by Hu et al. (18), Hao et al. (17), Li et al. (19), Wan et al. (20), and Peng et al. (23), a combination of 'partially fulfilled' and "not reported" checklist items affected the quality of each study. Using this checklist, the CEA that scored the highest methodological quality was published by Yang et al. (21).

Based on the Philips checklist, time horizon, cycle length, health utilities, and external consistency (**Table 4**) were items that were 'partially fulfilled' by Courtney et al. (22). In studies reported by Hu et al. (18), Hao et al. (17), Li et al. (19), Wan et al. (20), and Peng et al. (23), a combination of 'partially fulfilled' and "not reported" checklist

Table 4: Quality assessment results based on the Philips checklist

Philips Checklist: dimensions of quality																				
Study	**Structure (S)**									**Data (D)**									**Consistency (C)**	
	S1	S2	S3	S4	S5	S6	S7	S8	S9	D1	D2a	D2b	D2c	D3	D4a	D4b	D4c	D4d	C1	C2
Courtney et al., (22)	Y	Y	Y	Y	Y	Y	P	Y	P	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	P
Hao et al. (17)	Y	Y	Y	Y	Y	Y	P	Y	P	P	P	Y	P	P	Y	Y	Y	Y	P	N
Hu et al., (18)	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	P	N	Y
Li et al., (19)	Y	Y	Y	Y	Y	Y	P	Y	Y	P	P	Y	P	P	Y	Y	P	Y	N	P
Peng et al., (23)	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	P	P	P	P	Y	Y	Y	Y	Y	N
Wan et al., (20)	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	P	P	Y	Y	Y	P	P	P	N
Yang et al., (21)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

Abbreviations: Y; item completely fulfilled, P; item partially fulfilled, N; item not fulfilled, N/A; item not applicable **Item Checklist**: S1; Statement of decision problem/objective, S2; Justification of modelling approach, S3; Statement of scope/perspective, S4; Structural assumptions, S5; Strategies/comparators, S6; Model type, S7; Time horizon, S8; Disease states/pathways, S9; Cycle length, D1; Data Identification, D2; Pre-model data analysis, D2a; Baseline data, D2b; Treatment effects, D2c; Quality-of-life weights (utilities), D3; Data incorporation, D4; Assessment of uncertainty, D4a; methodological, D4b; structural, D4c; heterogeneity, D4d; parameter, C1; Internal consistency, C2; External consistency

items affected the quality of each study. According to the Philips checklist, the CEA that scored the highest methodological quality was published by Yang et al. (21).

Overall, this assessment highlighted shortcomings in data identification and methods of transparency. Quantification of health state utility values, estimation of drug costs, the accuracy of data sources, and their credibility have important quality implications on the cost-effectiveness outcomes. The included studies did not fulfill the criteria reported in the Philips and the CHEC checklists. Although the conclusions of the four CEAs indicated that nivolumab-ipilimumab combination therapy had favorable cost-effectiveness (i.e., 4 out of 7 studies), the quality assessment of these studies revealed several uncertainties and limitations of each study. From a clinical perspective, ipilimumab has not been approved as a single agent (monotherapy) in treating NSCLC, and its mechanism of action (i.e., synergy or additivity), combined with nivolumab, is not fully understood in this setting. (35) To compound the economic consequences presented in these limited CEAs, ipilimumab's drug action as a combination therapy poses significant uncertainty and requires further clinical investigation. (35) We encourage further research to address the economic consequences of these combination agents in future CEAs and the clinical uncertainties of ipilimumab for NSCLC in future trials.

Discussion

Nivolumab-ipilimumab combination therapy has a high price tag and the potential to be used for a range of indications, also in combination with other agents. This systematic review showed that the methods of estimating long-term outcomes, quantifying the health state utility, estimating drug costs, the accuracy of data sources, and their credibility have important implications on the ICERs. The included studies did not fulfill the requirements presented in the Philips and CHEC checklists. Quality assessment of the included studies highlighted shortcomings in data identification, uncertainty assessment, and methods transparency domains.

The estimation of long-term immunotherapy outcomes has important implications. Given that the CEA model inputs were sourced from the clinical trials, the durability of response and potentially long-term survival after immunotherapy are crucial factors for these economic analyses. Currently, the minimum effective dose of immunotherapy remains unknown, as does the optimal duration of treatment. A better understanding of optimal drug dosage and treatment duration may influence the overall costs of immunotherapy. To theoretically address the long-term estimation of

outcomes, CEAs are encouraged to vary nivolumab-ipilimumab dosing and treatment duration in their sensitivity analyses.

Assessing the cost-effectiveness of immunotherapy drugs depends on the relative efficacy of treatments observed in the clinical trials and the model structure and assumptions. Good practice recommendations were developed for fitting curves to observe progression-free and overall survival. (36,37) Although stochastic uncertainty (i.e., model parameters and assumptions) is usually assessed in CEA models, structural uncertainty (i.e., alternative modeling approaches) is rarely considered. It is common practice to acknowledge potential limitations in the model structure. However, identified studies in this review need more clarity about methods to characterize the uncertainty surrounding alternative structural assumptions and their contribution to decision uncertainty. Given that alternative modeling techniques (i.e., cure models, spline-based models) may complement standard methods, future CEAs may incorporate structural uncertainty by considering alternative modeling approaches concurrently.

Although patient-reported outcomes (PROs) were collected in the CheckMate 227 and the CheckMate 9LA trials, six CEA models were developed based on health utility estimates from previously published studies. (30–33) Similarly, utility decrements of AEs were sourced from the publicly available literature. Cancers with a high TMB, such as NSCLC, are associated with higher immune-related AEs (irAEs) during immunotherapy treatment. These cancers are often associated with a higher risk of irAEs than cancers with a low TMB. Although irAEs are rare, the cost of treatment in such cases is relatively high. Therefore, the benefits of nivolumab-ipilimumab combination therapy could be over- or underestimated in the included models. The inclusion of irAEs in future economic models of NSCLC is encouraged.

TMB is an emerging biomarker for immunotherapy in lung cancer. (38–42) The CheckMate 568 trial showed that the TMB of more than ten mutations per megabase could be used as a practical cutoff value for selecting responders. (43) Similarly, the analysis of Hellmann et al. showed that the first-line treatment with nivolumab-ipilimumab provided clinical benefits for patients with NSCLC with a high TMB (≥10 mutations per megabase), regardless of their tumor PD-L1 expression levels. (44) Although nivolumab-ipilimumab provided better absolute survival for patients with a high TMB in the CheckMate 227 trial, the clinical benefits were similar to those of chemotherapy in patients regardless of their TMB. Therefore, it is necessary to understand the implications of TMB as a biomarker and then re-analyze clinical and cost-effectiveness findings accordingly.

This study is the first systematic review focused on the methodological quality of CEAs explicitly conducted for the front-line nivolumab-ipilimumab combination. Previously published systematic reviews of CEAs focusing on immunotherapy in the advanced NSCLC (45–47) did not assess the quality of the study methodology based on either the Philips checklist or the CHEC checklist. One study (45) used the Consolidated Health Economic Evaluation Reporting Standards checklist. (48) However, this checklist is not designed for the quality assessment of the CEA study methodology.

All in all, efficient allocation of existing resources is essential for health systems to meet the evolving needs of populations and sustainability efforts. From this analysis, the quality assessment of the included CEAs highlighted shortcomings in various domains of the included checklists. To improve methodological study quality, the authors of future CEAs are encouraged to consider the inclusion of a quality assessment checklist (e.g., the CHEC or Philips checklist) in their studies and follow its guidance to report their analyses. The application of high-quality knowledge that stems from scientific evidence and economic modeling can aid in achieving sustainable health systems worldwide. Improving the methodological quality of the future CEAs would be a vital step toward this achievement.

Supplementary Appendix

Table 1: Search strategy

a. Search strategy: PubMed (MEDLINE)

Population	("non-small-cell lung cancer"[Mesh] OR NSCLC*[tiab])
Intervention	("Nivolumab"[Mesh] OR PD1*[tiab] OR checkpoint*[tiab]) AND ("Ipilimumab"[Mesh] OR CTLA-4*[tiab]) AND (first line*[tiab] OR front line*[tiab] OR treatment naïve*[tiab])
Comparator	No search string
Outcomes	No search string
Limits	*Study design:* ("cost-effectiveness analysis"[Mesh] OR "economic"[Mesh] OR "economic evaluation"[tiab] OR economic value*[tiab])
Limits	*Publication period:* No restrictions
	Language: No restrictions

b. Search strategy: EMBASE

Population	('non-small cell lung cancer'/exp OR NSCLC*:ti,ab)
Intervention	('Nivolumab'/exp OR checkpoint*:ti,ab OR PD1*:ti,ab) AND ('Ipilimumab'/exp OR CTLA-4*:ti,ab) AND (first line:ti,ab OR front line:ti,ab OR treatment naive:ti,ab)
Comparator	No search string
Outcomes	No search string
Limits	*Study design:* ('cost effectiveness /exp OR 'cost utility'/exp OR 'economic'/exp OR 'economic evaluation'/de OR (economic NEAR/3 value*):ti,ab)
Limits	*Publication period:* No restrictions
	Language: No restrictions

c. Search strategy: The Cost-Effectiveness Analysis Registry

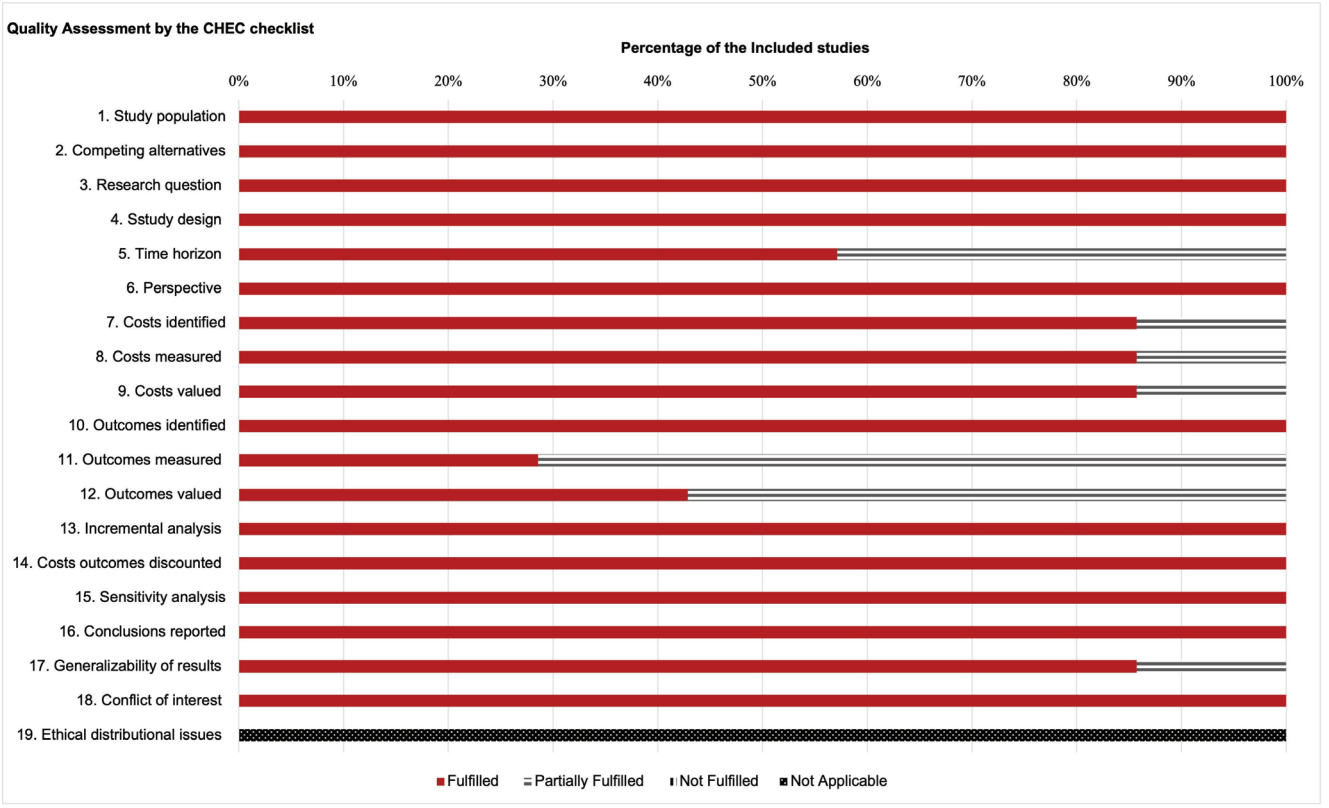
Database	The CEA registry [http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx]
Population	(non-small cell lung cancer) OR (NSCLC)
Intervention	(Nivolumab) OR (Ipilimumab) AND (first line)
Comparator	No search string
Outcomes	No search string
Limits	No limits

Abbreviations CEA: Cost effectiveness analysis, NSCLC: non-small cell lung cancer

Table 2: Excluded full-text studies

Reference	Reason for exclusion
Teng MM, Chen SY, Yang B, et al. Determining the optimal PD-1/PD-L1 inhibitors for the first-line treatment of non-small-cell lung cancer with high-level PD-L1 expression in China. Cancer Med. 2021;10(18):6344-6353. doi:10.1002/cam4.4191.	Clinical data for nivolumab were sourced from the CheckMate 026 clinical trial, instead of the CheckMate 227 and/or CheckMate 9LA trials. The US FDA did not approved first-line nivolumab based on the CheckMate 026 trial.

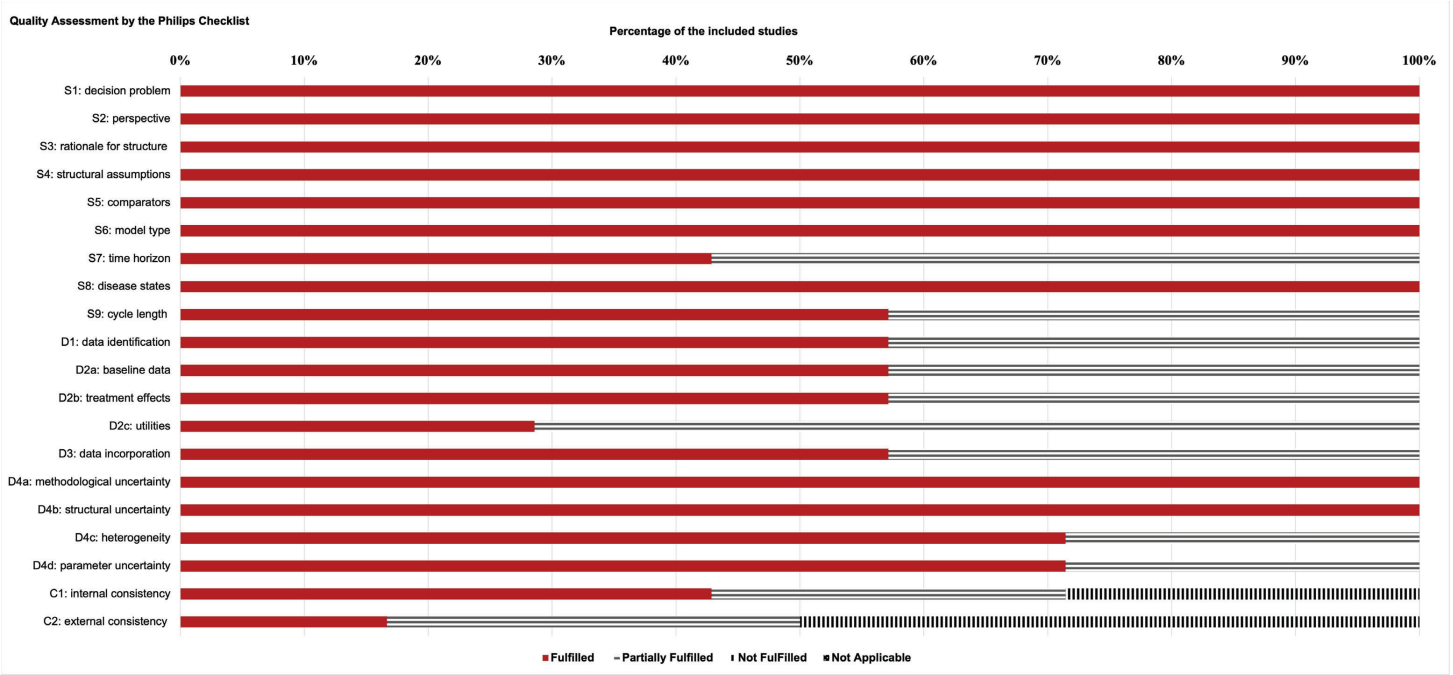
Figure 1. Quality assessment of the study methodology by the CHEC checklist



F; item completely fulfilled, P; item partially fulfilled, N; item not fulfilled, N/A; item not applicable

Item Checklist: 1; Study population, 2; Competing alternatives, 3; Research question, 4; Study design, 5; Time horizon, 6; Perspective, 7; Costs identified, 8; Costs measured, 9; Costs valued, 10; Outcomes identified, 11; Outcomes measured, 12; Outcomes valued, 13; Incremental analysis, 14; Costs outcomes discounted, 15; Sensitivity analysis, 16; Conclusions, 17; Generalizability of results, 18; Conflict of interest, 19; Ethical distributional issues

Figure 2. Quality assessment of the study methodology by the Philips checklist



F; item completely fulfilled, P; item partially fulfilled, N; item not fulfilled, N/A; item not applicable

Item Checklist: S1; Statement of decision problem/objective, S2; Justification of modelling approach, S3; Statement of scope/perspective, S4; Structural assumptions, S5; Strategies/comparators, S6; Model type, S7; Time horizon, S8; Disease states/pathways, S9; Cycle length, D1; Data Identification, D2; Pre-model data analysis, D2a; Baseline data, D2b; Treatment effects, D2c; Quality-of-life weights (utilities), D3; Data incorporation, D4; Assessment of uncertainty, D4a; methodological, D4b; structural, D4c; heterogeneity, D4d; parameter, C1; Internal consistency, C2; External consistency

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Attribution of Value for Combination Immune Checkpoint Inhibitors in Advanced Non-Small Cell Lung Cancer

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Attribution of value for combination immune checkpoint inhibitors in advanced non-small cell lung cancer. J Cancer Policy 2023 Mar;35:100382. doi:10.1016/j.jcpo.2022.100382.

Abstract

Immune checkpoint inhibitors (ICIs) are combined with other treatments to help provide clinically meaningful benefits for non-small cell lung cancer (NSCLC) patients. ICIs could provide such clinically meaningful benefits via distinct mechanisms of action. Valuation of ICIs, when combined with other treatments, may pose specific challenges. To explore value attribution challenges of ICIs in approved combination indications in NSCLC, the databases of the FDA and Clinicaltrials.gov were searched. Health technology assessment databases, PubMed and grey literature were also reviewed to identify publicly available methods. The FDA approved eight ICI indications for combination use in NSCLC by June 1, 2022. Improved clinical outcomes observed in combination ICI treatments do not indicate whether additivity or synergy exists.

Policy statement: The mechanism of action of ICIs pose significant uncertainty. Additional clinical research is needed to address whether additivity or synergy exists. Further research is encouraged to develop value attribution methods for combination ICIs in NSCLC.

Introduction

Immunotherapy has revolutionized the treatment of cancer. Immune checkpoint inhibitors (ICI) targeting programmed cell death protein 1/ligand 1 (PD-1/PD-L1), as well as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), have been included in the clinical care of cancer patients, such as non-small cell lung cancer (NSCLC). [1] Thousands of trials are underway to explore the clinical efficacy and safety of these ICIs. [2] The approaches to treat many cancers comprise administering several drugs with distinct yet complementary mechanisms of action in combination or close sequence to lower drug resistance. [3] ICIs combined with other ICI or different drugs aim to provide clinically meaningful outcomes for cancer patients. [4,5] ICIs could provide clinical benefits through distinct mechanisms of action. For example, when combination ICIs work through independent drug action, the clinical benefit can be attributed to one of the drugs in the combination; and the superiority over monotherapy can be attributed to the increasing odds that the combination may comprise an effective drug. [6] This type of mechanism contrasts with synergy, where immunotherapy could improve the clinical activity of other constituents in the combination, and additivity, where the clinical improvements are the sum of multiple drug combinations. [6]

Increasingly, combination ICIs are used in clinical trials and daily practice; however, the societal challenges these drugs pose with such high prices lead to payment hurdles in several healthcare systems. [7] Combination ICIs face challenges when value is attributed to different indications. The complex steps of value attribution for combination immunotherapy are evident in NSCLC. From a valuation perspective, payers or health technology assessment (HTA) agencies infrequently report that the expected incremental benefits of a new ICI, when added to an existing drug combination, outweigh treatment costs. [8] Standard HTA approaches to evaluate whether incremental cost-effectiveness of an ICI is acceptable given a willingness to pay threshold (WTP) may sometimes generate results counterintuitive to societal preferences. [9–12] To attribute value for combination ICIs, it should be possible to adjust the price of both constituents of a combination regimen and reflect their value. [13] Given that the constituent drugs are not developed solely for a particular indication, this approach would be applicable when indication-based prices or payment models were permitted.

Nonetheless, a fundamental problem of unrealized benefits of ICIs is the need for a new solution to price and pay for them as combination regimens. Previous research contributed to the debate about possible approaches to address the value attribution problem in combination drugs. [8,13,14] This study focused on the value attribution

of ICIs when combined with existing drugs in NSCLC to explore the question: Do ICI combinations improve clinical outcomes through independent drug action - rather than additivity or synergy? Furthermore, how should the economic value be attributed to the combination ICIs' constituent parts?

Identification of combination ICIs and valuation methods

To identify approved indications of ICIs in NSCLC when used in combination, Clinicaltrials.gov, and the US Food and Drug Administration databases were reviewed between January 1, 2012, and June 1, 2022. PubMed, HTA databases and grey literature were searched separately to identify published methods for valuing combination (cancer) drugs. The searches were built using the Population Intervention Comparison Outcome (PICO) framework. (see *Supplementary Appendix*) The findings were summarized descriptively. In addition, clinical trial number, combination ICI(s) target or target expression level, histology, approval by the FDA, treatment line or setting, ICI dose, and schedule were presented in a tabular format.

The clinical landscape of combination ICIs in NSCLC

As of June 1, 2022, the FDA approved eight combination ICI indications in NSCLC. These indications include: **(1)** "*Pembrolizumab* plus pemetrexed and carboplatin for untreated metastatic non-squamous NSCLC"; [15] **(2)** "*Pembrolizumab* plus pemetrexed combined with platinum chemotherapy for untreated patients without aberrations of Epidermal Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK) in metastatic, non-squamous NSCLC"; [16] **(3) "***Pembrolizumab* plus carboplatin combined with either paclitaxel or nab-paclitaxel in untreated metastatic squamous NSCLC"; [17] **(4)** "*Atezolizumab* plus bevacizumab, paclitaxel, and carboplatin in front-line metastatic non-squamous NSCLC, without EGFR or ALK aberrations"; [18] **(5)** "Atezolizumab plus paclitaxel and carboplatin for untreated metastatic non-squamous NSCLC, without EGFR or ALK aberrations"; [19] **(6)** "Nivolumab plus ipilimumab in front-line metastatic NSCLC with PD-L1(≥1%), using an FDA-approved test, without EGFR or ALK aberrations"; [20] **(7)** "Nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy in metastatic or recurrent NSCLC for the first-line treatment, without EGFR or ALK aberrations"; [21] **(8)** "Nivolumab plus platinum-doublet chemotherapy in NSCLC for the neoadjuvant setting". [22] **Table 1** shows details of all combination ICIs in NSCLC approved by the FDA.

Table 1. The US Food and Drug Administration approved combination immune checkpoint inhibitors to treat non-small cell lung cancer [2017-2022]

Clinical Trial(s) [Number]	Combination Immune Checkpoint Inhibitor [target or target expression level, histology]	FDA Approval	Treatment Line	Dose and Schedule
KEYNOTE 021 [NCT02039674]	**Pembrolizumab combination (Pemetrexed + Carboplatin)** [PD-L1 TPS≥1%, non-squamous]	May 10, 2017	First-line	200 mg as an intravenous infusion every three weeks until progression, unacceptable toxicity, or up to 24 months without progression
KEYNOTE 189 [NCT02578680]	**Pembrolizumab combination (Pemetrexed + Carboplatin/Cisplatin)** [regardless of PD-L1 expression, non-squamous]	August 20, 2018	First-line	200 mg intravenous infusion, 30 minutes every three weeks
KEYNOTE 407 [NCT02775435]	**Pembrolizumab combination (Paclitaxel or Nab-Paclitaxel)** [regardless of PD-L1 expression, squamous]	October 30, 2018	First-line	200 mg intravenously every three weeks before chemotherapy, when given on the same day, until disease progression, unacceptable toxicity, or 24 months after initiation.
IMpower 150 [NCT02366143]	**Atezolizumab combination (Bevacizumab, Carboplatin, Paclitaxel)** [regardless of PD-L1 expression, non-squamous]	December 6, 2018	First-line	1200 mg intravenously over 60 minutes every three weeks
IMpower 130 [NCT02367781]	**Atezolizumab combination (Carboplatin/Nab-Paclitaxel)** [regardless of PD-L1 expression, non-squamous]	December 3, 2019	First-line	1200 mg as an intravenous infusion every three weeks before chemotherapy, given on the same day
CheckMate 227 [NCT02477826]	**Nivolumab + Ipilimumab combination** [PD1, CTLA-4, PD-L1 TPS ≥1%, squamous or non-squamous]	May 15, 2020	First-line	Nivolumab 3 mg/kg every two weeks Ipilimumab one mg/kg every six weeks until progression, unacceptable toxicity, or up to 2 years in patients without disease progression

Table 1. The US Food and Drug Administration approved combination immune checkpoint inhibitors to treat non-small cell lung cancer [2017-2022] (*continued*)

Clinical Trial(s) [Number]	Combination Immune Checkpoint Inhibitor [target or target expression level, histology]	FDA Approval	Treatment Line	Dose and Schedule
CheckMate 9LA [NCT03215706]	**Nivolumab + Ipilimumab combination (two cycles of platinum doublet)** [PD1, CTLA-4, regardless of PD-L1 expression, squamous or non-squamous]	May 26, 2020	First-line	Nivolumab 360 mg every three weeks, Ipilimumab 1 mg/kg every six weeks, and two cycles of platinum-doublet chemotherapy continued until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.
CheckMate 816 [NCT02998528]	**Nivolumab* combination (+ platinum-doublet chemotherapy)** [PD1, regardless of PD-L1 expression, squamous or non-squamous]	March 4, 2022	Early-stage, Neoadjuvant setting	Nivolumab 360 mg with platinum-doublet chemotherapy on the same day every three weeks for three cycles

*Nivolumab platinum-doublet chemotherapy combination represents the first FDA approval of neoadjuvant therapy for early-stage NSCLC.
Table 1 Abbreviations: NSCLC: Non-Small Cell Lung Cancer, US: United States, FDA: Food and Drug Administration, NCT: National Clinical Trial, PD1:Programmed cell death protein 1, PD-L1: Programmed death ligand 1, CTLA-4: Cytotoxic T lymphocyte-associated antigen 4, TPS: Tumor Proportion Score, TC: PD-L1 stained Tumor Cells, IC: PD-L1 stained tumor-infiltrating Immune Cells.

The case of atezolizumab combination therapy in NSCLC

Combinations ICIs may provide clinically meaningful benefits to patients, measured by population-averaged outcomes, without requiring pharmacologic additivity or synergy. The contribution of each drug as a monotherapy and their respective contributions to the combination regimen is essential. **Figure 1** shows a schematic representation of the combination therapy constituents, comprised of backbone therapy, add-on therapy, and (potential) additional drugs. To determine whether independent drug action is possible in ICIs, Palmer et al. [6] developed a predictive model based on retrospective analysis of 13 clinical trials of combination ICIs representing eight cancer types. Particularly for NSCLC, Palmer et al. focused on atezolizumab plus bevacizumab, paclitaxel, and carboplatin for front-line metastatic non-squamous NSCLC without EGFR or ALK aberrations. [6]

The IMpower150 clinical trial investigated front-line bevacizumab, carboplatin, and paclitaxel, with or without the PD-L1 inhibitor atezolizumab [23]. In this trial, progression-free survival (PFS) in the ICI combination group "surpassed the expectation

Figure 1. Constituent parts of combination immune checkpoint inhibitors

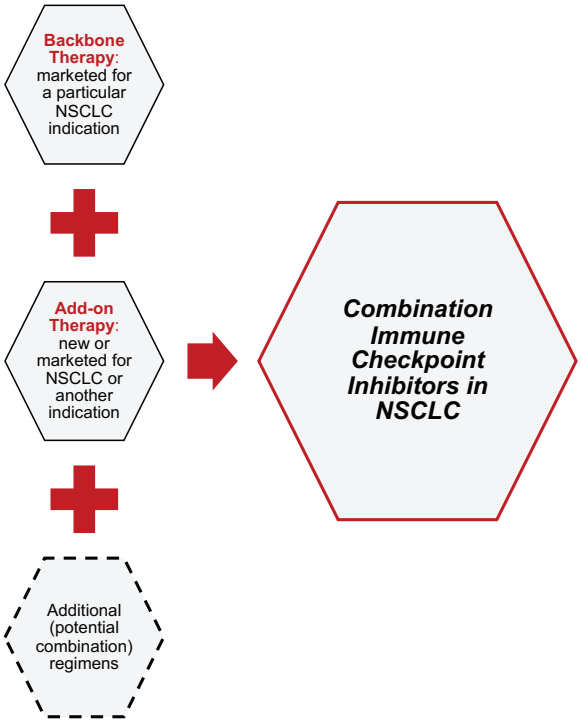

Figure 1. Legend A schematic representation of the constituents of a combination immune checkpoint inhibitor, including a backbone therapy, an add-on therapy, and (potential) additional drugs.

of independence with a hazard ratio of 0.84" (P 0.01, n=356; median PFS surpassed expectation by nine days). [23] The IMpower150 trial did not evaluate atezolizumab as monotherapy. Moreover, data were obtained from the OAK trial for atezolizumab monotherapy in non-squamous NSCLC, with no PD-L1 preselection. [24] However, the OAK trial enrolled second or third-line patients. To compound this issue, the BIRCH trial investigated atezolizumab in NSCLC (72% non-squamous, all tumors ≥5% PD-L1 positive) [25] and reported that atezolizumab was more active as first-line than in second- or third-line.

Palmer et al. used a predictive model to quantify atezolizumab combination therapy with the expected PFS distribution to address whether an independent mechanism of action exists. [6] This model was compared to the clinical trial results. The hypothesis was that if the actual PFS observed in the clinical trial was similar to the predicted outcomes, the combination worked through independent action. The combination worked through synergy or additivity if the actual PFS was better than the prediction. [6] Clinically observed differences were measured in atezolizumab activity by the line

of therapy [25] to construct a synthetic arm for atezolizumab in treatment-naive non-squamous NSCLC. [26] The authors reported that IMpower150 closely matched the independent drug action (hazard ratio:1.04, P: 0.46, N:356). Palmer et al. concluded that: "atezolizumab is less active at second-line than first-line therapy and independent drug action could explain the benefit of adding atezolizumab to combination chemotherapy ."[6] In the BIRCH trial, the measured differences in atezolizumab activity per line of therapy support this conclusion. [25] Although these findings are based on a predictive model using a retrospective study design, a more precise assessment of independence in such cases is unlikely. Such an assessment would be considered unethical if first-line therapy from eligible patients were to be withheld.

Attribution of value for the constituent parts of combination ICIs

Combination regimens have features that pose a challenge when assessing economic value under existing frameworks. However, value demonstration has been particularly challenging for combination ICIs, given their complex mechanisms of action. Valuation challenges of combination therapies were previously addressed in a report published by the NICE Decision Support Unit (DSU), which highlighted cases where combination drugs were not deemed cost-effective when add-on therapy was provided for free. [10] The DSU report showed that "even if the price of the add-on therapy is set to zero, the prolonged treatment duration of backbone therapy increases the total costs in the combination therapy." [10] In addition, the report indicated that "if a combination regimen extends the time spent in a post-progression state, patients may require additional care, and hence incur more costs."[10,11] Therefore, clinically beneficial combination regimens could not be deemed cost-effective even when a novel add-on therapy is provided for free. [10,11] Valuation frameworks that focused explicitly on cancer treatments (i.e., American Society of Clinical Oncology, National Comprehensive Cancer Network, European Society for Medical Oncology, Memorial Sloan Kettering Cancer Center's Drug Pricing Lab) did not e specific methods to address the valuation challenges of combination regimens. [27–30]

More recently, international experts in HTA outlined the main challenges and potentials for valuing combination cancer therapies. [12,13] These experts indicated that when existing monotherapies are combined, their value is not proportional to their combined costs. It would then be appropriate to re-assess and negotiate constituent drug prices. [12,13] When new add-on drugs are combined with an existing backbone drug, the cost of the backbone therapy should be re-assessed in its new use. [12,13] The latter finding raises implementation issues and legal challenges, primarily when different manufacturers develop constituent therapies. **Figure 2** depicts a schematic diagram of potential methods for valuing and paying combination ICIs.

Figure 2. Valuing and paying for combination ICIs

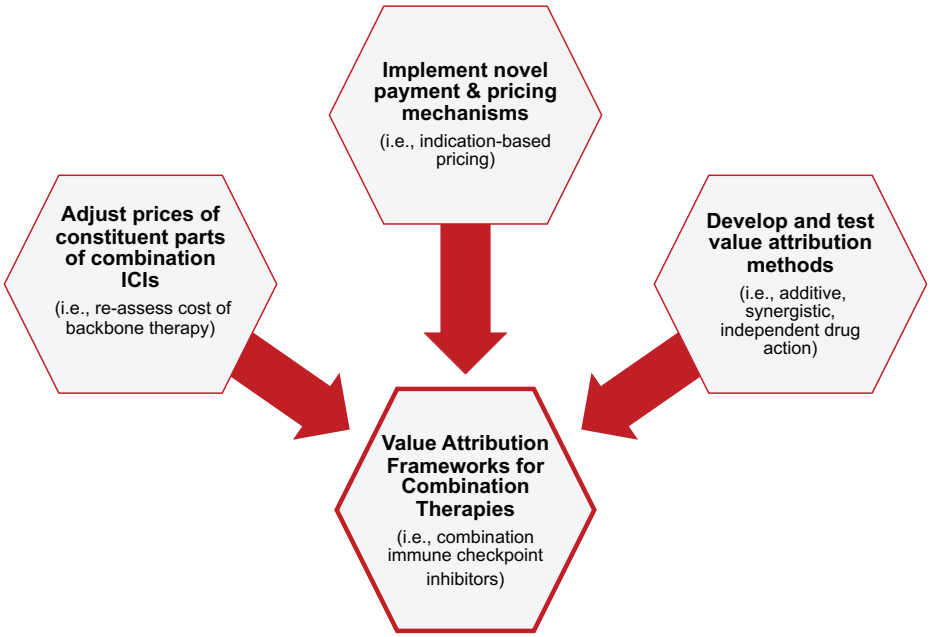

Figure 2. Legend A schematic representation of potentials methods to be considered for valuing and paying for combination immune checkpoint inhibitors

Briggs et al. proposed a conceptual value attribution framework for combination regimens in 2021. [8] This conceptual framework depicts methods for determining how to attribute value to each therapy component. [8] This framework does not depend on price and focuses solely on valuing health benefits such as QALY, a metric used in cost-effectiveness analysis. [8] Various case examples demonstrate that proposed solutions could be based on publicly available evidence for treatment combinations, including ICIs. However, the underlying assumption in this framework was that the mechanism of drug action for the components would be additive, sub-additive, or synergistic. This finding contrasts with the results of Palmer et al. [6]

Briggs et al. also discussed potential methods for ICI combination therapies that are characterized using distinct features of the problem: "perfect/imperfect information about the monotherapy effect of component therapies (individual effects are known/unknown)" and "balanced/unbalanced market power between their manufacturers (unbalanced: one manufacturer already has market access and a new entrant seeks to add to this 'backbone' therapy)." [8] The authors used the term "imperfect" information to define scenarios where the "independent benefit of one or more of the component therapies is unknown for the indication under consideration." Imperfect information scenarios typically arise when a novel add-on is combined with an existing backbone

therapy. [8] In contrast, the authors used the term "perfect" information to define scenarios where the "independent benefit of every component benefit is known for the indication for which the combination therapy is being assessed." [8] Perfect information scenarios typically arise when combination therapy comprises two existing treatments appraised and approved independently. [8] Briggs et al. introduced the term "imbalanced market power" to define scenarios where "the manufacturer of one component therapy has control over pricing decisions compared to the manufacturer of another component therapy." [8] Market power could be imbalanced when a "novel add-on is combined with an existing backbone therapy that has already been appraised and approved." [8] Additionally, there can be a market power imbalance when "one of the component therapies holds a larger share of the market, either in the indication for which the combination is being appraised or across multiple indications." [8] The authors used the term 'balanced market power' to define scenarios where none of the component therapy manufacturers has more control over pricing decisions than others. [8] Market power can be balanced in cases where a combination therapy consists of two or more existing therapies that have already been appraised and approved, and there is no large discrepancy in their respective market shares. [8] The authors then proposed potential solutions to these four scenarios.

It is important to note that this framework does not depend on price and focuses on health consequences (i.e., QALY). Together, this 'net-QALY' represents the "value of a new treatment in health terms and can be monetized using threshold WTP for a QALY." [8] This monetized value of the net-health consequences can then be considered the maximum (differential) price the health system would be willing to pay for a combination treatment. Thus, this framework avoids the complications of judging whether the current price is 'fair' without depending on confidential patient access schemes. [8]

Similarly, in 2021, researchers at the Office of Health Economics in the UK published a report on the conceptual valuation of combination therapies. [14] The authors focused on the "additive scale" and the "relative change in treatment duration when compared with an increase in overall survival." [14] This second conceptual framework shows that the value attribution approaches are only comparable if an implicit assumption about "additive scale" is made. [14] This assumption is, again, in contrast to the finding that combination therapies may work through an independent mechanism of action. [6] Nevertheless, further considerations are needed when evaluating and selecting clinical evidence. These considerations may introduce layers of complexity that need to be addressed. Therefore, the challenges these potential valuation methods might face in different health systems and HTA jurisdictions should be explored.

The case of ipilimumab therapy in NSCLC

Ipilimumab plus nivolumab is approved in front-line NSCLC based on the CheckMate 227 [NCT02477826] and the CheckMate 9LA [NCT03215706] trials with or without (i.e., for PD-L1 ≥ 1%) platinum doublet chemotherapy. [31,32] Although ipilimumab's drug action as a single-agent was investigated in NSCLC trials (i.e., CA184-041 trial [NCT00527735]), [33]), its single-agent activity is not fully understood or demonstrated. Regulatory agencies have not approved ipilimumab as a single-agent treatment in NSCLC. Valuation studies focusing on the cost-effectiveness of nivolumab-ipilimumab combination therapy, based on the CheckMate 227 and CheckMate 9LA clinical trials, reported substantial costs (i.e., mainly attributable to drug acquisition costs). [34–40] In the CheckMate 227-based cost-effectiveness analyses, additional nivolumab and ipilimumab cost outcomes ranged from US$ 66,218 [34] to US$ 201,900. [35] Similarly, in the CheckMate 9LA-based cost-effectiveness analyses, additional nivolumab and ipilimumab cost outcomes ranged from US$ 161,993 [37] to US$ 217,820. [40] Given these substantial economic consequences, ipilimumab's drug action (as a combination therapy) requires further (clinical) investigation due to current uncertainties to address if synergy or additivity exists.

Indication-based pricing for combination ICIs

Indication-based pricing (IBP) can allow differential prices for the same treatment when used in different indications. [41] In combination ICIs, IBP is relevant when used in multiple indications and has different uses within the same indication. ICIs may have other uses within the same indication, either as a monotherapy or an add-on as part of a combination. If differential or IBP prices are permitted depending on distinctive uses, there will be greater flexibility in determining acceptable costs for combination ICIs. However, the feasibility of differential drug pricing depends on the local market construct. [14] Although there are various approaches to pricing combination drugs based on their indications, such as weighted average (blended), differential discounts, different brand names for further indications, and outcome-based payment models, in some healthcare markets, IBP is not permitted. [42] For example, if a backbone therapy is approved for multiple indications, and the market does not allow any price or discount variation by indication, the manufacturer(s) may have little incentive to amend prices. [8] The manufacturer of the add-on therapy has the option to set a lower price and captures limited value from the combination therapy. [41,43]. "When the backbone therapy is an established therapy, and the add-on is a new market entrant, many novel combination therapies may fail to demonstrate cost-effectiveness." [8] In such cases, cost-effectiveness analysis methods could reduce patient access to clinically meaningful combination ICIs. [43]

Alternatively, the lack of price flexibility means that the prices agreed upon for the combination ICIs automatically apply to all other indications of the constituents when sold as monotherapy or within different combinations. [44] Allowing IBP for combination therapies will, as a result, be critical to "avoid any breach of competition law when agreeing on the component prices for the combination." [44]

Nonetheless, IBP could be challenging in practice since it requires information on volumes of usage by indication or assumptions of predicted utilization based on epidemiological data. It may be complex for many health systems to identify IBP use, as there should be minimal opportunities for arbitrage. [41] Although there are several challenges in making IBP work in practice, this pricing method has the potential to be both advantageous and attainable for combination ICIs in treating many cancers, including NSCLC.

Discussion

Immunotherapy has revolutionized treatment for many cancers, including NSCLC. Combining ICIs either with each other or with other cancer drugs has improved responses and resulted in the approval of various combination ICIs in NSCLC. However, the underlying drug mechanism for combination therapies compared with single-agent ICIs still needs to be well studied. [6] The clinical success of ICI combinations has been widely interpreted as evidence of interaction-based mechanisms, but clinical trials and predictive models do not always support such hypotheses. The superiority of combination ICIs compared to monotherapy for specific indications does not indicate whether synergy or additivity exists. [6] When component therapies are developed to be used with existing treatments, such therapies may have yet to be evaluated independently outside of early-phase safety and dose escalation trials. [8] This situation poses a challenge as the monotherapy effect of component therapies remains uncertain.

Palmer et al. reported that combination ICIs, including atezolizumab, may improve outcomes due to independent rather than synergistic or additive drug action. [6] In the IMpower150 clinical trial [NCT02366143], front-line metastatic NSCLC patients treated with atezolizumab plus chemotherapy and bevacizumab had longer PFS than would be expected by independent drug action, suggesting a synergistic or additive effect. However, Palmer et al. found that the "PFS of patients in the clinical trials was comparable or shorter than the predicted outcomes." This finding could suggest that "the overall clinical benefits were due to independent drug action rather than synergy

or additivity." [6] As reported previously, improved benefits that can be predicted from monotherapy have ramifications when designing future trials. [45–47] However, it remains to be seen to what extent the findings of Palmer et al. in NSCLC and various advanced solid tumors will be transferable to other neoplasms such as hematologic malignancies, where drug additivity appears to be critical, [48] or to adjuvant therapies for early-stage cancers".

These findings indicate that ICI combinations were clinically effective through a different mechanism of action. The main limitation of Palmer et al. is that it was a retrospective analysis involving imputed data. [6]

From a valuation standpoint, progress may depend upon finding ways of aligning monotherapy drug prices with the value attributable to combination ICIs, which could differ from the value in another combination. [49] In recent years, potential value attribution methods have been suggested [8,14]. Additional work will be needed to improve these proposed methods, validate them, and theoretically work on new ones.

In the identified conceptual frameworks, it was suggested that the limitations in monotherapy data "tilt the scales" in favor of synergy. [8] This phenomenon may apply to the first-line nivolumab-ipilimumab combination therapy, where no proven single-agent ipilimumab activity exists. For example, some trials did not include an ICI monotherapy arm, requiring data from another trial in a comparable patient population. In these cases, study authors matched the line of therapy and dosing to the greatest extent possible. Specifically, for the KEYNOTE-407 clinical trial [NCT02775435] in squamous NSCLC, monotherapy data were not available for pembrolizumab but for nivolumab from the CheckMate-017 clinical trial [NCT01642004]. [50] A meta-analysis of 1,887 patients with NSCLC observed no significant difference in PFS or overall survival between pembrolizumab and nivolumab. [51] Therefore, the authors used nivolumab as a non-inferior comparator for pembrolizumab. This approach could potentially "tilt the scales" in favor of synergy.

A distinct but important issue related to value attribution is the issue of the feasibility of negotiating a combined price for ICIs. It is essential to recognize how manufacturers, who may be competitors in different indications, can share information compliantly without breaching competition law. [44] Although competition law differs per jurisdiction, it does not (often) permit competing manufacturers to discuss prices with each other. The manufacturer of an add-on therapy must devise a pricing strategy without knowing the pricing strategy of the manufacturer of the backbone therapy. [52] Flexibility in pricing the backbone therapy will depend on its current stage in the

product life cycle and patent status or duration. If a backbone therapy has many years left under patent with a significant market share, its manufacturer may have little incentive to reduce its price. [53,54]

When different manufacturers develop combination ICIs, some form of IBP would be considered. This approach, in turn, requires reaching an agreement on the value and price of each specific use. Previous studies exploring the methods of value attribution indicated that the problem arises when the 'backbone' drug is priced at the limit (i.e., WTP threshold) of what a payer is prepared to pay, given the outcomes delivered. [8] One feasible way forward to address the challenges of combination ICIs is adjusting the price of both constituents of a combination to reflect the value they each offer when used in that specific combination.

To conclude, it is vital that various stakeholders, including HTA bodies, manufacturers, policymakers, and payers, are involved in developing value attribution frameworks. Novel methods should allow value attribution for possible configurations of (multiple) combination drugs and healthcare systems that use different measures to assess value (e.g., for QALY or non-QALY-based systems). A structured approach should be used to tackle these challenges of combination ICIs and address the issues systematically. Increased stakeholder involvement at the regulatory, academic, industry, government, and research levels may help leverage resources to advance future work.

Lastly, it is essential that various stakeholders, including HTA bodies, manufacturers, policymakers, and payers, are involved in the development of value attribution frameworks. Novel methods should allow value attribution for possible configurations of (multiple) combination drugs and healthcare systems that use different health measures to assess value (e.g., for QALY or non-QALY-based systems). A structured approach should be used to tackle other challenges of combination ICIs and address these issues systematically. Increased stakeholder involvement at the regulatory, academic, industry, government, and research levels may help leverage resources to advance valuation frameworks.

Supplementary Table 1: Search Syntax

Category	Search terms
Population	"cancer" AND (early OR adjuvant OR advanced OR metastatic OR recurrent) AND ("immune therapy" OR "immunotherapy" OR "immune checkpoint inhibitor")
Intervention	AND (combination) AND (combined) OR (plus) OR (add-on)
Comparison	N/A (no restriction)
Outcome	AND (value OR quantitative OR methods OR methodology OR "value assessment" OR "value frameworks" OR "value attribution")

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Incorporating Risk Preferences of Patients in the Valuation of Immune Checkpoint Inhibitors for Non-Small Cell Lung Cancer

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Incorporating risk preferences of patients in the valuation of immune checkpoint inhibitors for non-small cell lung cancer. Frontiers in Oncology 2023 Mar 8;13:1027659. doi:10.3389/fonc.2023.1027659.

Abstract

Immunotherapy offers a unique mechanism of action compared to traditional treatments, arising from additional value dimensions that may not be captured in standard health technology assessments. Cancer patients may expect immunotherapy provides durable, long-term survival gains. Moreover, some patients may be willing to take a 'risk' to undergo immunotherapy to achieve better survival outcomes. Quantitative methods that explored patients' risk preferences in their non-small cell lung cancer (NSCLC) treatment choices were searched in PubMed (MEDLINE), from January 1, 2015, until July 1, 2022. A value dimension ('hope') based on patients' risk-seeking preferences is addressed explicitly for evaluating immune checkpoint inhibitors in NSCLC. The findings indicate that quantitative methods that empirically measure patients' risk preferences or 'hope' are emerging. Value assessments should comprise survival improvements for the mean or median patient and consider methods reflecting durable, long-term survival gains for risk-seeking patients. However, the published evidence for incorporating 'hope' based on patients' stated preferences for uncertain treatment profiles is not strong. More research could strengthen this evidence base. Further research is encouraged in developing and validating quantification methods to incorporate 'hope' and risk preferences of patients treated with immunotherapy for NSCLC and beyond.

Introduction

Immunotherapy is an important breakthrough in the treatment of cancer. Immune checkpoint blockade is an effective therapeutic strategy that harnesses the immune system to generate an antitumor response. [1,2] Immune checkpoint inhibitors (ICIs) targeting Programmed cell Death protein 1/ligand 1 (PD-1/PD-L1) and Cytotoxic T Lymphocyte-Associated protein 4 (CTLA-4) have been integrated into the standard of care for patients with various cancers, including non-small cell lung cancer (NSCLC). [2] Thousands of clinical trials are underway to explore the clinical efficacy and safety of these ICIs. [3] Clinical trial guidelines promote transparent and accurate reporting of patient-reported outcomes (PROs) to facilitate the interpretation and limitations of complex patient data. [4,5] Also, there is evidence that monitoring treatment side effects in real-time can improve outcomes for patients with cancer, including a potential benefit in survival rates. [2,6] However, patients may express their preferences for innovative, durable therapies (e.g., immune checkpoint inhibitors) with uncertain levels of benefit, with a likelihood of a good outcome. [7] Moreover, some patients (i.e., risk-seeking patients) may be willing to take additional risks (at the end of life situations) to increase the probability of a survival outcome. This preference could be attributed to the evidence that although individuals are generally risk averse, they become risk-seeking in cases where they face inferior prospects. [8–10]

Recently, there have been theoretical research efforts to consider additional dimensions of benefit, including patients' risk preferences in their treatment choices. [11] Value assessment frameworks quantifying clinical and economic outcomes of health technologies are often used to quantify the net value of NSCLC therapies. [12] For example, the value frameworks of the NICE (National Institute for Health and Care Excellence in England) and the ICER (Institute for Clinical and Economic Review in Boston, Massachusetts) include average health-related quality of life (HRQoL) as a key measure of health benefit. [13–15] Similarly, the European Society for Medical Oncology value framework enables optional weighting of treatment outcomes based on HRQoL. [16] Moreover, the value framework of the American Society of Clinical Oncology (ASCO) recognizes the value of additional survival gains as part of their evaluation process. [17]

As a health benefit measure, quality-adjusted life year (QALY) assumes that marginal utility equals average utility in both "quality of life and life year" and that the utility is linear, not concave, or equivalently that patients are risk-neutral. [9] Introducing risk preferences may provide a way to incorporate variability in health benefits that have yet to be included in standard value assessments. To address the potential impact

of incorporating patients' risk-seeking preferences in value assessment frameworks, the evidence on quantitative methods were reviewed. The potential incorporation of patients' risk-seeking preferences in the valuation of ICIs for NSCLC was explored. A consideration of 'hope' as a value dimension based on patients' risk-seeking preferences is specifically addressed.

Identification of valuation methods on patients' risk preferences

Quantitative methods in PubMed (MEDLINE) were searched that explored the risk preferences of patients in their cancer treatment choices from January 1, 2015, until July 1, 2022. (see *Supplementary Table 1*). A value dimension ('hope') based on patients' risk-seeking preferences is addressed explicitly for the valuation of ICIs in NSCLC. Study findings were summarized descriptively.

Consideration of risk preferences in standard value assessment

Standard value assessment foundations and methods were explored specifically for patients' risk preferences and their treatment choices. Although the traditional value assessment frameworks provide a helpful starting point, some limitations may occur without broader value considerations. These limitations could lead to suboptimal resource allocation decisions, such as distorted signals to innovators and imprecise evaluation of durable medical technologies (i.e., ICIs). [11] The standard value assessments may have strengths when using the 'incremental cost-effectiveness ratio' methodology, however, several limitations do exist. In the standard value assessments, average health benefits and costs are included in the valuation of technologies. However, patient preferences and clinical practice may differ from such average outcomes. While HTA agencies use several criteria to make coverage decisions, institutions such as the NICE in the United Kingdom focus on cost-effectiveness and affordability as key determinants of their appraisal decisions. [21] Although healthcare budgets are limited to public funds in such jurisdictions, there is a strong desire to reimburse innovative cancer therapies with some uncertainty, as demonstrated by the Cancer Drug Fund of the National Health Services in England. [18] Similarly, Canada has a distinct review process for reimbursement of oncology drugs. The pan-Canadian Oncology Drug Review is responsible for the assessment of cancer treatments. [19] However, the methods used by these agencies do not explicitly capture patients' risk preferences or incorporate 'hope' for risk-seeking patients.

'Hope' for risk-seeking patients

The consideration of 'hope' as a value dimension based on patients' risk-seeking preferences is becoming evident for evaluating therapies in NSCLC. However, we found that several definitions may include 'hope' in valuing health technologies in the

context of risk. **Figure 1** shows multiple definitions of 'hope' identified in this context. Regardless of its nomenclature, the value of choosing among treatments with different clinical profiles, especially when some patients are willing to risk a small chance of durable survival benefit or a potential cure, creates conditions for further research.

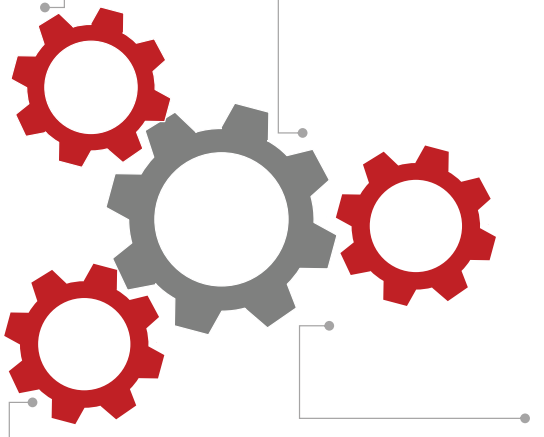
Valuation of risk preferences in patients treated with ICIs for NSCLC

To explore the risk preferences of patients for durable overall survival benefits, Shafrin et al. 2017 prospectively surveyed lung and melanoma cancer patients and their physicians. [20] For this study, however, we solely described methods and findings about lung cancer. The authors specifically compared physicians' view of a chance of durable survival (at the tail of the survival curve), independent of average survival, to that of the patients. The survey results determined "how patients and their physicians value therapies that offer a likelihood of durable survival outcomes ."[20] "Durable survival treatments were calibrated based on survival outcomes (i.e., 66 months of follow-up) from the pivotal trials of nivolumab investigated in patients with advanced NSCLC". [21] The primary endpoint was "the proportion of respondents who selected a therapy with a variable survival profile (with some patients experiencing long-term durable survival and others experiencing shorter survival), compared to a therapy with a fixed survival duration." [20] Fixed survival was hypothetical, where "all patients were assumed to live for a specified period before their death." [20] Parameter estimation by sequential testing ("PEST") was applied to "calculate to estimate the duration of survival that would make patients or physicians indifferent between fixed survival and therapy with durable survival." [20] "PEST is an adaptive elicitation technique that determines the stimulus value for each new question using responses to the previous question." [20,22] In the study, patients and physicians continued to receive questions until an indifference point was reached or until ten questions were answered. [20]

Overall, the analysis comprised 84 lung cancer patients and 96 physicians. [20] There were two primary endpoints: "1) whether the respondent preferred a durable survival therapy compared with a fixed survival therapy"; and "2) the indifference point in terms of survival between a durable survival therapy and a fixed survival therapy." [20] For lung cancer, "65.5% of patients preferred the therapy with a variable survival profile, compared with 40.8% of physicians (Δ=24.7%; P<0.001)." [20] "Patients' indifference point indicated that therapies with a variable survival profile were preferred unless the treatment with fixed survival had 11.6 months longer mean survival". [20] "Physicians were prescribing treatments with a fixed survival if the treatment had 1.0 months shorter survival than the uncertain survival profile". [20] Shafrin et al. assumed a constant relative risk aversion utility function based on

Figure 1. Definitions of 'hope' for risk-seeking patients

- 'Hope revolves around the risk that a treatment may or may not work for a particular patient'
- 'Hope is defined by how risk attitudes and anticipation of future events might influence preferences.'
- 'Hope is the value of choosing among treatments with different clinical profiles, especially when patients prefer to accept an increased short-term risk of death for a small chance of long-term benefit or a potential cure.'
- 'Hope is the value of having the choice among treatments with a different balance and timing of risks and benefits.'
- 'Hope is the difference between expected incremental QALYs (based on the mean benefit) and the certainty equivalent.'



- 'Many severely ill patients may wish to select a treatment that provides lower overall QALYs on average (e.g., due to an increased risk of early death from a risky treatment) if that treatment offers a greater chance for an extended or durable survival.'
- 'Many severely ill patients may be willing to trade-off some survival (e.g., undertaking a risky procedure) for a chance of a cure, even if only for a small probability of that much longer expected survival.'
- 'Hope is considered by patients with a life-threatening condition that some treatments might be found to offer a glimmer of a chance of benefit, even if that chance is very small.'
- 'There are situations where patients may be willing to take risks that do not focus solely on maximizing expected QALYs.'

QALY: Quality adjusted life year

the Kaplan-Meier curve estimations' risk preference distributions. [23] T-tests were performed to compare the indifference point with the certainty equivalent. Patients' indifference point among lung cancer therapies with durable and fixed survival was "41.6 months (i.e., 11.6 months greater than the average survival at 30 months)". [20] In contrast, the physicians' indifference point was 29 months. [20] The overall "indifference point was 12.6 months greater ($P < 0.001$) for patients compared to the physicians." [20] Applying a constant relative risk aversion (RRA) utility function, the authors estimated that "patients are risk-seeking (RRA = +0.39 for NSCLC; $P < 0.001$), and physicians are risk neutral for lung cancer treatments (RRA = –0.03; $P = 0.523$)." [20] "The patient's utility function was $u(x) = x^{1.39}$ and the physician's utility function was $u(x) = x^{0.97}$." [20]

Shafrin et al. showed that "lung cancer patients were willing to give up 38.7% of an average survival for a likelihood of durable survival". [20] The patient preferences reported in this study are consistent with the prospect theory, which predicts that people may be risk-seeking in the circumstances starting below their reference point. [24,25] However, it should be noted that discordant preferences do not necessarily mean that "physicians override their patients' desires ."[26] Some patients may prefer that their physicians make treatment decisions on their behalf. [27] Nonetheless, physicians' decisions may not always align with patients' interests. [28] Therefore, it is essential to conduct additional research to understand 'when, why, and how' physicians may implicitly or explicitly substitute their perspectives on patients' behalf.

Shafrin et al. 2018 examined whether incorporating additional value considerations influenced the cost-effectiveness estimates. [26] Previous research suggested that broader societal benefits could be considered in value assessments. [29,30] For example, assessments could include patients' treatment preferences that offer durable survival benefits instead of average outcomes. [20,31] Building upon a previously published cost-effectiveness analysis, [32] Shafrin et al. studied patients in Canada with advanced squamous NSCLC treated with second-line nivolumab. The authors used the net monetary benefit framework [33] to estimate cost-effectiveness. [34] The authors conducted their analyses from three perspectives, namely the "traditional payer," "traditional societal," and "broad societal" perspectives. [34] The traditional payer perspective was built based on a model developed in Canada by Goeree et al. [32] Goeree et al. extrapolated progression-free survival (PFS) and overall survival (OS) Kaplan Meier curves from the CheckMate 017 Phase 3 clinical trial. [35] Goeree et al. estimated the proportion of patients in "progression-free, progressed disease and death" health states for ten years. [32] The CheckMate 017 trial investigated the clinical and safety outcomes of "nivolumab (3 mg/kg every two weeks) compared to

docetaxel (75 mg/m^2 every three weeks) for previously treated patients with advanced squamous NSCLC". [35] The results of this trial showed "significant improvements in median OS and PFS for nivolumab patients compared to docetaxel patients (OS: 9.2 vs. 6.0 months, HR: 0.59; PFS: 3.5 months vs. 2.8 months, HR: 0.62)." [35] Goeree et al. reported that based on the CheckMate 017 clinical trial results, the incremental cost-effectiveness ratio (ICER) was " Canadian dollars (CA)$151,560 per QALY gained." [32]

To explore a broader societal perspective, Shafrin et al. quantified 'hope' in addition to caregiver burden, insurance value, and option value of the nivolumab treatment in patients with advanced NSCLC. For this review, however, the findings on the valuation of 'hope' or patients' risk preferences were descriptively summarized. The Checkmate 017 clinical trial showed that the "two-year overall survival for nivolumab was 24%, and reduced to 16% at five years". [35] To quantify 'hope' [31], the authors first measured the difference in the expected survival between nivolumab and docetaxel using the Kaplan-Meier curve obtained from Goeree et al. [32]. Subsequently, they estimated the "certainty equivalent between the two treatments using a utility function based on the previously reported risk aversion estimates for NSCLC patients." [20] The authors assumed that the difference between the expected survival difference and this estimated certainty equivalent provides a valuation method to quantify 'hope.' Using this method, Shafrin et al. estimated an "additional QALY gain of 0.039, beyond the baseline estimate of 0.66 QALYs" [32] at an additional cost of CA$ 5,850. [26] The ICERs for nivolumab compared to docetaxel were "$151,560, $141,344, and CA$80,645 per QALY gained from the traditional payer, traditional societal, and broader societal perspectives, respectively." [26]

Similarly, the American researchers at the Innovation and Value Initiative (IVI) developed a patient-centered value assessment, which incorporated 'hope' into a cost-effectiveness model for advanced NSCLC. [36] This model's treatment regimens for the study population comprised ICIs for the progressed disease after second-line therapy. From a clinical perspective, this model requires an update based on the modifications in the latest NSCLC guidelines. From an economic perspective, in the IVI's four-state model, patients were assumed to begin first-line (1L) treatment in stable disease (S1) and can either experience disease progression and consequently transition to second-line (2L) treatment (P1/S2) or death (D). [36] With 2L treatment, patients can experience disease progression (P2) or death (D). At P2, patients begin 2L+ treatment (including ICIs) and remain in this state until death. [36] IVI's NSCLC model specifically focused on the quantification of 'hope' to address patients' risk attitudes when "treatments with equivalent expected health benefits differ in their overall benefit distributions ."[36] This assumption was valid when a benefit distribu-

tion had a longer-term survival for some patients. The authors of this study quantified 'hope' as the "difference between expected incremental QALYs (average health benefit) and the certainty equivalent." [36] The certainty equivalent was "the number of QALYs that a patient needs to obtain to be indifferent between the comparator and comparative treatment strategy, with an alternative distribution of survival outcomes." [20,36] This definition was again based on the Shafrin et al. study, which showed that "patients place a high value on treatments with a higher probability of durable overall survival benefits." [20]

Although these NSCLC case studies illustrate potential methods to quantify patients' risk preferences or 'hope' when treated with an ICI, several methodological and practical issues require careful consideration. Standard value assessments, including cost-effectiveness analyses, assume risk neutrality. [37] Ignoring risk preferences may underestimate or overestimate the value of interventions for different indications. [9,10] The consideration of two competing interventions with the same average survival, one with greater uncertainty, would be deemed comparable in a conventional or standard cost-effectiveness assessment. For some patients, however, this uncertainty may indicate that they have a treatment preference. As quantified by Shafrin et al. [20], the certainty equivalent may comprise health benefits (i.e., QALYs) that a patient may be indifferent among ICIs or the alternative treatment strategy. Estimations of 'hope' indicate that the distribution of health benefits should be characterized by their variance and skewness. Some risk-seeking patients, including those with NSCLC, may prefer the treatment option with durable survival with a higher risk of dying earlier. [31] In the Shafrin et al. case study [26], data limitations were specific to nivolumab or NSCLC to measure broader societal benefits. Even if such data were available, it might only be possible for the studies to address some indications during value assessments. [26] Moreover, after clinical trial results are published, there is significant uncertainty related to the long-term benefits of ICIs, owing to most immunotherapy clinical trials' relatively short follow-up period. Therefore, payers and the HTA agencies may under or overestimate treatment value, extrapolate value estimates from different studies, indications, and conditions, or consider alternative assumptions. Nonetheless, these case studies illustrate that quantifying patients' risk preferences, referred to as 'hope,' is a research area requiring further investigation and validation in NSCLC patients, specifically those treated with an ICI.

Valuation of patients' risk preferences beyond immunotherapy in NSCLC

Studies included in this review also highlighted potential ways to characterize patients' risk preferences ("hope") beyond NSCLC. Valuation of patients' risk prefer-

ences or 'hope' in the assessments of health technologies has yet to gain traction, partly due to reliance on established practices and the lack of motivation to improve existing frameworks. [38] An alternative viewpoint is that using standard value assessment methods is sufficient because "cost-effectiveness estimates are only an input to, and not a substitute for, a deliberative decision-making process that allows additional value elements to be contextualized into the process without the need for formal quantification." [39] Regardless of the viewpoints, patients' risk preferences, their relative importance for some indications, valuation methods, and potential quantification methods remain areas for further research. In this section, we highlight key studies that provide distinct methods to help quantify 'hope' and incorporate patients' risk preferences beyond the treatment of NSCLC.

Lakdawalla et al. estimated patients' risk preferences in melanoma, breast cancer, and other solid tumor patients. [31] The authors recommended incorporating 'hope" into the valuation of end-of-life treatments or considering a higher cost-effectiveness threshold for treatments at the end of life. The authors surveyed patients' preferences on two treatment choices; "one offering a modest length of survival, and the other offering a 50% chance of a substantially longer survival, but also a 50% chance of no additional survival." [31]

If patients care about long-term survival prospects, not just average survival, this study suggests the need to incorporate the valuation of risk preferences as a unique consideration in the HTA. Arguably, a two-step approach could be considered. [40] First-step may comprise a standard cost-effectiveness assessment based on average clinical survival and other health benefits (i.e., QALY) estimates. Second-step may include other value considerations, both qualitatively and quantitatively. [40] This viewpoint assumes patients acknowledge and act on their own (risk) preferences. Lakdawalla et al. highlighted that value should incorporate the "perspective of the patient," and value assessment frameworks should consider this perspective.

Lakdawalla and Phelps [10] examined additional value elements, including 'hope,' using a "generalized risk-adjusted cost-effectiveness (GRACE) model, which assumes that patients are utility maximizers in their choices about their treatment choices." [9,10,41] Building on the study by Garber and Phelps [37] and Lakdawalla et al. [41], this study authors incorporated patients' risk preferences in treatment choices. Patients with "severe impairments and prospects of continued poor health, or those facing shorter life expectancy, were shown to have a higher willingness to pay for durable health gains." [41] Some patients may be willing to take the risk for a treatment that has a likelihood of 'cure' or 'hope.' [31] The GRACE model suggested that

"patients are not indifferent to the length of life or quality of life, which could indicate that marginal utility does not equal average utility." [41] The study authors indicated that "willingness to pay per QALY thresholds may need adjustments for value assessments." [41] However, this finding may significantly affect the 'incentives' for future innovation developers and investments. [38]

Another method to quantify 'hope' was presented using a discrete choice experiment (DCE). [42] Using a DCE for 200 patients with cancer or a history of cancer, Reed et al. [42] reported that "patients valued treatments with 5% and 10% chances of 10-year survival, independent of expected survival, although the findings did not hold in all scenarios." [42] First, a pilot DCE was designed, and "participants were asked to assume that they had recently been diagnosed with cancer that had begun to metastasize." [42] Participants then had to consider choices "when expected survival was three years, with a given chance of 10-year survival, or a case with certain 3-year survival outcome (i.e., 10-year survival was zero)." [42] After piloting the DCE using general participants, cancer patients were asked to complete the online DCE survey. The study authors found that the "estimated value of 'hope' for a 5% chance of survival was on average about $6,000, and 10% for $12,500." [42] "With a life expectancy of 5 years, when a 20% chance of 10-year survival corresponds to 80% of an average 3.8 years, participants' choices were consistent with expectations according to utility theory and risk neutrality." [42] However, when the choices had a "scenario with a life expectancy of 2 years, where a 20% chance of 10-year survival implies an 80% chance of a 1-month survival, patients rarely chose this option." [42] The study authors highlighted that there was heterogeneity in patients' preferences across attributes. For example; "a latent class analysis, designed to identify groups with similar preferences, found four distinct groups of participants differing in terms of their sensitivity to costs and preferences for treatments enabling durable survival." [42] All in all, Reed et al. highlighted that the quantification of 'hope' is essential; however, there are uncertainties about how much 'hope' may be worth and how to quantify heterogeneous preferences. Reed et al. concluded that researchers and policymakers should assess heterogeneous patterns of risk preferences and carefully consider them for resource allocation and reimbursement decisions. [42]

All in all, these studies highlighted in Section 3.3 do not specifically focus on immunotherapy or NSCLC. Given the unique characteristics of immunotherapy, such as the "tail of the curve survival potential," future studies that will present methods to quantify "hope" specifically for the valuation of ICIs are encouraged.

Discussion

Immunotherapy offers a unique mechanism of action compared to traditional treatments, arising from additional value dimensions that may not be captured in standard HTA methods. The focus of this study was on the patients' risk-seeking preferences because some cancer patients may prefer treatments that have a likelihood of durable survival. Based on the available evidence, our review revealed that economic value assessment methods should not only be based on survival improvement for the mean or median patient but also on the quantification of risk preferences for durable overall survival gains. Although ICIs have distinctive characteristics that may increase the relevance of considerations of additional value dimensions, a significant issue that should be considered against the inclusion of 'hope' relates to equity concerns. Higher spending on certain ICIs or other durable medical technologies that get extra importance based on 'hope' or patients' stated preferences may have consequences (i.e., opportunity costs) inside and outside the health systems.

This study showed that the quantitative methods that aim to measure 'hope' empirically are emerging. Some viewpoints support and refute the inclusion of 'hope' alongside standard measures of health gain. [7] The evidence on the quantification methods for 'hope' based on patients' stated preferences for uncertain treatments is not strong, and future research could strengthen this evidence base. One complexity is that the value of having access to therapies with different clinical profiles can diverge across patients and indications. Therefore, any attempt to add an empirical weighting for 'hope' at the population level may be premature.

In the United Kingdom, NICE includes additional criteria in assessing health technologies, in the end-of-life context, as a modifier when considering its cost-effectiveness threshold. [43] The intention is not to raise the threshold per se but to provide further weight to QALYs achieved at the end-of-life (under certain circumstances) by focusing on the expected gain rather than any element of 'hope.' The Professional Society for Health Economics and Outcomes Research Task Force (ISPOR) researchers, who studied the US Value Assessment Frameworks, identified eight elements of value and suggested considering additional value dimensions, including 'hope.' [11] However, this ISPOR Task Force report recognizes, as did the Second Panel on Cost-Effectiveness recommendations, that these additional value dimensions are subject to further research. The methods for empirically integrating them into value frameworks still need to be validated. [44,45] There are also intrinsic equity concerns about "incorporating additional dimensions of value, without considering the opportunity costs and potential health losses that might be foregone." In its value assessment framework covering

2020 to 2023, ICER stated that it would consider broader value elements such as option value, hope, and scientific spillovers in the '*other benefits or disadvantages*' and '*contextual considerations*' sections of ICER evidence reports. [14] However, such considerations do not influence cost-effectiveness results or value-based prices.

Others have stated that "value elements, such as hope and fear, could legitimately affect individual decision-making but are fraught with difficulties in measurement as they relate to subjective experience and could be manipulated by the context." [39] Arguably, standard value assessments using the QALY also face measurement challenges because the utility measurement can reflect subjective experiences. [38] Value elements such as 'hope' has the potential to be measured quantitatively using skewness in the outcome distribution. [38] Improved measurement methods of value elements allow modifiers to be applied quantitatively in the future, although challenges remain. [38]

All in all, this review suggests the need for further research to develop and validate reliable methods for the quantification of 'hope' and valuing risk preferences for patients treated with immunotherapy in NSCLC. The proliferation of empirical studies is promising; however, additional methods of development efforts are needed. If 'hope' were incorporated into the valuation of ICIs, the HTA evaluation would then need to depart from the traditional focus on average outcomes and include the notion that (some) patients may care about the distribution of durable benefits, not just the average.

Supplementary Table 1: Search Syntax

Category	Search terms
Population	"non-small cell cancer" AND (advanced OR metastatic OR recurrent) AND ("PD-1" OR "PD-L1" OR "CTLA-4" OR "programmed cell death" OR "cytotoxic T lymphocytes" OR "nivolumab OR ipilimumab" OR "immunotherapy" OR "immune checkpoint inhibitor")
Intervention	AND (risk or stated) AND (preferences) OR (hope)
Comparison	N/A (no restriction)
Outcome	AND (quantitative OR methods OR methodology OR "value assessment" OR "value frameworks" OR "patient preferences" OR "value of hope")

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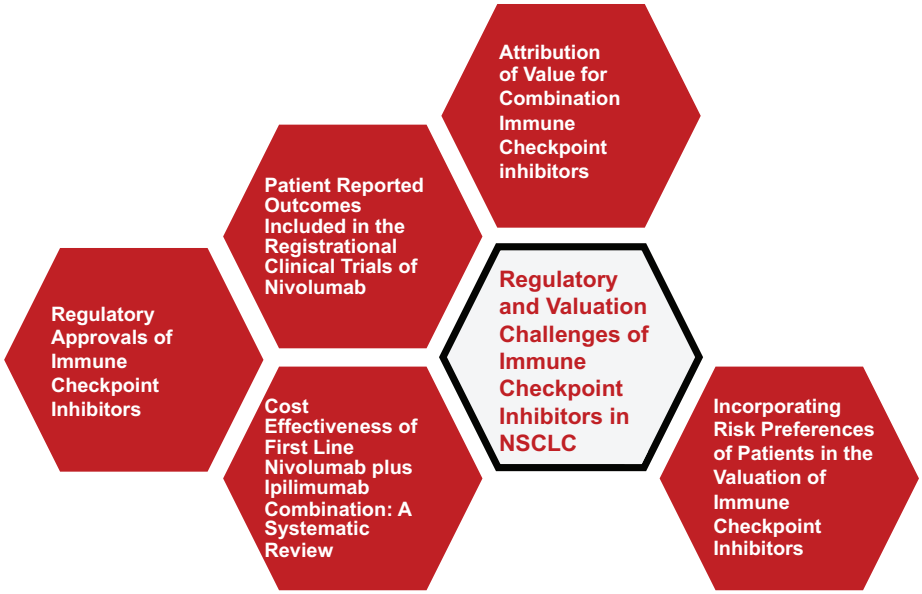
7

General Discussion

This chapter aims to highlight the research findings of the regulatory and valuation challenges of immune checkpoint inhibitors (ICIs) and serve as a foundation to spur dialogue among researchers and stakeholders, including physicians, drug manufacturers, regulators, lawmakers, health technology assessment (HTA) agencies, and policymakers. A schematic representation of the research chapters included in the general discussion is depicted in Figure 1. This chapter discusses key challenges that impede regulatory decisions and analysis of patient-reported outcomes collected in the non-small cell lung cancer (NSCLC) clinical trials of ICIs. It also highlights challenges that impede the accurate valuation of ICIs for NSCLC. This chapter concludes with implications for future research.

Figure 1. Schematic representation of research chapters on the regulatory and valuation challenges of ICIs in non-small cell lung cancer (NSCLC).



• Regulatory challenges of immune checkpoint inhibitors in NSCLC

High treatment costs of NSCLC are often associated with significant research and development costs. It is crucial to align and streamline the regulatory landscape, including drug efficacy, safety, patient outcomes, and resources, to facilitate innovative technology approvals and reduce costs. **Chapter 2** compared the differences in regulatory approvals between the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for ICIs in the treatment of NSCLC from 2015 to 2021,

focusing on the time to approval durations of ICIs. [1] Patient-reported outcomes (PROs) were analyzed at the time of regulatory decisions by each agency. The FDA was quicker to reach approval decisions when compared with the EMA [i.e., in eleven of the compared thirteen indications (85%)]. [1] The indications that stood out regarding outcome divergence were mainly first-line ICIs for untreated NSCLC patients. Only two clinical indications (NCT01905657, NCT02039674) underwent the accelerated approval process by the FDA. [1]

- *Harmonized practices have helped to decrease the regulatory burden and delays in decision-making processes; however, there are differences in regulatory approvals between the FDA and the EMA.*
- *The expedited development and access programs did not influence the preponderance of approval decisions between the FDA and the EMA for ICIs in NSCLC.*
- *Improved alignment of regulatory practices can guide efficient resource allocation, facilitate advancements in cancer treatments, and ultimately optimize patient care.*

The FDA both scientifically evaluates new drugs or products and issues marketing authorization decisions, while the scope of the EMA's Committee for Medicinal Products for Human Use (CHMP) is limited only to scientific evaluation. [1,2] Based on the CHMP assessment, the EMA makes recommendations to the European Commission (EC) for marketing approval of each drug. When the scientific approval process and the marketing authorization are decoupled, delays may occur in patients' access to new drugs. Moreover, differences between North America and Europe may arise because each EU member state follows specific regulations to determine which drugs will have marketing authorization in each jurisdiction.

The European Commission initiated the EMA and the European Network for HTA (EUnetHTA) 21 consortium to work on a joint plan to optimize patients' access duration for new drugs in Europe. [3,4] This plan focuses on preparing the "*application of the Regulation on HTA (EU) 2021/228 in January 2025*" [3,4], which aims to promote close collaboration between Europe's EMA and HTA agencies. It is expected to replace the former parallel scientific advice practices by the EMA and HTA agencies, where drug manufacturers have had to contact each member state's HTA agency individually. This new initiative allows drug developers to discuss their plans for (long-term) evidence generation throughout the lifecycle of medical technology (e.g., ICI) by involving the regulators and HTA agencies. Further, this plan aims to facilitate information exchange between the regulatory assessors and HTA agencies on technologies of mutual interest. Consequently, earlier engagement between regulators and the HTA agencies is

expected to facilitate the timely uptake of medical technologies, including ICIs, to benefit patients across Europe.

• Patient-reported outcomes collected in the immune checkpoint trials for NSCLC

NSCLC is classified as a high tumor mutational burden cancer. [5] Patients may experience immune-related adverse events (irAEs) during or after immunotherapy and commonly reported treatment-related side effects. [5] Although patients' assessments of the incidence and consequences of these irAEs are vital, existing cancer-specific PRO instruments [6,7] were not designed to capture irAEs, and they may not fully reflect the benefits or toxicity profiles of immunotherapies. The FDA and the EMA both recognize the value of PROs as necessary patient-centered endpoints. PROs are also included in value assessments, impacting patient access, drug reimbursement, and pricing decisions. [8]

In **Chapter 2**, PROs were included in the ICI clinical trials and considered in 15 indications by the FDA and the EMA. [1] Both regulatory agencies well recognize the value of PROs as critical patient-centered endpoints when determining the efficacy of immunotherapy and approval. The EMA began drafting recommendations for using PROs in 2004, which were adopted in 2005 and 2016. [9] The FDA followed these efforts with a draft guidance published in 2006 and then updated it in 2009. [10] Although these efforts highlight the importance of PROs for drug approvals, these two agencies can diverge in their approaches. From the perspective of the EMA, the agency's primary concern is to assess the degree of improvement that a drug will provide in patients' health-related quality of life (HRQOL). [11] The PRO guidance from the EMA centers on multiple domains for generalized assessment of HRQOL, while the FDA focuses on symptom-specific measures. In addition, the EMA incorporates the HRQOL data from the clinical trials. The FDA is explicit in its requirements for developing and using PROs as an outcome in clinical trials. [12] The FDA often considers PROs a secondary or exploratory trial endpoint. The HRQoL data are not usually included in the FDA assessments of ICIs.

Chapter 3 analyzed PROs reported in the CheckMate 9LA (NCT03215706), CheckMate 227 (NCT02477826), CheckMate 057 (NCT01673867), and CheckMate 017 (NCT01642004) registrational clinical trials. [8] The central research question asks whether PROs were collected rigorously using appropriate, reliable, and validated instruments. The findings suggest that PRO analysis for the CheckMate 9LA trial should

be interpreted cautiously. [8] Like nivolumab, ipilimumab's mechanism of action depends on generating a T cell-mediated immune antitumor response. Although irAEs are commonly observed in immunotherapy-treated patients (i.e., with anti-CTLA-4 antibody), the instruments included in the PRO measurement of the CheckMate 9LA and CheckMate 227 trials did not have the capabilities to assess irAEs. [8] In the CheckMate 227 trial, clinical outcomes of nivolumab plus ipilimumab were compared with nivolumab alone. However, published PRO analyses in the included trials did not consider this critical comparison for further insights. It would have been informative to assess whether a correlation (or lack thereof) was observed between PRO benefits and progression-free or overall survival. [13] PROs were considered exploratory endpoints in the nivolumab trials without a hypothesis or a rationale for the expected benefit. In addition, the included PRO measurement tools were only partially justified. In these clinical trials, there was a paucity of information regarding the quality of the PRO data collected from patients during follow-up (i.e., after treatment discontinuation). [14] In some jurisdictions, the follow-up PRO data is critical for analyzing the comparative effectiveness of new therapies as part of the HTA processes and determining drug reimbursement and patient access. [15]

Key challenges that impede accurate analysis and validation of PROs in the immune checkpoint trials for NSCLC

- *The incapability of the included PRO instruments to measure immune-related adverse events*
- *Differences between treatment groups in the timing of PRO evaluation*
- *Incomplete patient participation (i.e., data collection) at all time points*
- *Limited patient participation in the later time points*
- *Interpretation of the longitudinal data*

Increased harmonization and collaboration among the regulatory agencies are encouraged on the PRO measurement and validation to improve ICIs' regulatory decision processes in the future.

• Valuation challenges of immune checkpoint inhibitors in NSCLC

Value assessment frameworks encompassing benefits, toxicity, and costs of medical technologies can be used to quantify the net value of ICIs for NSCLC. Although several studies have shown single-agent ICIs with or without chemotherapy to be cost-effective, [16–20] double-agent immunotherapy combinations may not often be

deemed cost-effective, given their high price tags. In **Chapter 4**, a systematic literature review of model-based cost-effectiveness analyses (CEA) was conducted to assess the economic value of nivolumab in combination with ipilimumab in the first-line treatment setting. [21] The quality assessment of the included CEAs was performed using the Philips checklist [22] and the Consensus Health Economic Criteria (CHEC) checklist. [23] One hundred seventy-one records were identified, and seven studies met the inclusion criteria. [21] Quality assessment of the included studies highlighted shortcomings in data identification, uncertainty assessment, and methods transparency. The included studies did not fulfill all requirements reported in the Philips and the CHEC checklists. [21] CEAs differed substantially due to the estimation methods of long-term outcomes, drug acquisition costs, quantification of health state utility values, the accuracy of data sources, and their credibility. Although the conclusions of the four CEAs indicated that nivolumab-ipilimumab combination therapy could be deemed cost-effective (i.e., four out of seven studies), the quality assessment of these studies revealed several uncertainties and limitations for each study. [21] For ICIs in NSCLC, the estimation of long-term outcomes has important implications. Considering that the CEA model inputs were sourced from the clinical trials with a limited follow-up, the durability of response and long-term survival after immunotherapy remains crucial. Currently, the minimum effective dose of immunotherapy remains unknown, as does the optimal duration of each treatment. [21] A better understanding of optimal drug dosage and treatment duration may change the overall treatment costs of immunotherapy. To accurately analyze the long-term estimation of outcomes, the authors of the CEAs should vary nivolumab-ipilimumab dosing and treatment duration in their future assessments. [21] To compound the valuation challenges presented in these limited CEAs, ipilimumab's clinical drug action as a combination therapy poses significant uncertainty. [24] Further research is encouraged to address the valuation challenges of ICI combination agents in future CEAs, and the clinical uncertainties of ipilimumab for NSCLC in future trials.

Key challenges that impede accurate valuation of immune checkpoint inhibitors for NSCLC

- *The minimum effective dose of immunotherapy remains unknown, as does the optimal duration of each ICI treatment.*
- *The superiority of combination ICI therapies compared to monotherapy in some NSCLC indications does not indicate whether synergy or additivity exists.*
- *Ipilimumab's drug action as a combination therapy poses significant uncertainty in NSCLC.*
- *Quantitative valuation methods reflecting durable, long-term survival gains are needed to measure patients' risk preferences and hope.*

Chapter 5 focused on the valuation of ICIs when used in combination with existing treatments for NSCLC by addressing the following questions: "*Do ICI combinations improve clinical outcomes through independent drug action - rather than additivity or synergy? How should the economic value be attributed to the combination ICIs' constituent parts?*" [24] Combination ICI treatments face challenges in the recognition of value by indication. There are distinct mechanisms of action that an ICI may provide clinically meaningful benefits. For example, when combination ICIs work through independent drug action, the observed benefit is attributed to only one of the drugs in the combination; and the advantage over monotherapy may increase the odds that the combination treatment comprises a drug that is effective for some patients. [25] This type of mechanism contrasts with synergy, where immunotherapy could improve the clinical activity of other constituents in the combination, and additivity, where the clinical improvements are the sum of multiple drug combinations. [25] Palmer et al. reported that combination atezolizumab therapy could improve outcomes due to independent rather than synergistic or additive drug action. [25] In the identified value attribution frameworks, it was suggested that the limitations in monotherapy data for some indications "tilt the scales" in favor of synergy. [26] This phenomenon may apply to the first-line nivolumab-ipilimumab combination therapy, where no proven single-agent ipilimumab activity exists. To address the challenges of combination ICIs, one possible method could involve adjusting the prices of both constituents of a combination to reflect the value they each offer. When different manufacturers produce ICIs, indication-based pricing (IBP) would be considered. [27] IBP, in turn, requires reaching an agreement on the value and price of each specific use and indication. [28] Nevertheless, a structured approach should be used to tackle the critical challenges of combination ICIs, and address issues systematically. Increased stakeholder involvement may help leverage resources to advance value attribution frameworks in the future.

Chapter 6 explored incorporating patients' risk preferences in the valuation of ICIs for NSCLC. [29] A value dimension (called 'hope') based on patients' risk-seeking preferences is specifically addressed to evaluate ICIs in NSCLC. The findings indicate that quantitative methods that empirically measure patients' risk preferences or 'hope' are emerging. [29] Value assessments should consider methods reflecting durable, long-term survival gains for risk-seeking patients. The published evidence for incorporating 'hope' based on patients' stated preferences for uncertain treatment profiles is not strong, and future research could strengthen this evidence base. [29] Although ICIs have distinctive characteristics that may increase the relevance of considerations of additional value dimensions, a significant issue that should be considered against the inclusion of 'hope' relates to equity concerns. For example, higher spending on

certain ICIs or other durable medical technologies that get priority based on 'hope' or patients' stated preferences may lead to inequalities in access to health care. The proliferation of empirical studies in this area is promising; however, additional methods of development efforts are needed. If 'hope' were incorporated into the valuation of ICIs, the HTA evaluation would then need to depart from the traditional focus on average outcomes and include the perspective that (some) patients may care about the distribution of durable benefits, not just the average. Further research is encouraged on developing and validating quantification methods to incorporate 'hope' and risk preferences of patients treated with immunotherapy for NSCLC and beyond.

Concluding Remarks

From a regulatory perspective: Improved alignment of drug regulatory practices can result in the efficient allocation of resources. These efforts can also provide more streamlined and predictable practices for assessing clinical efficacy, safety outcomes, and PRO measurements. While significant steps have been taken to harmonize and align regulatory approval practices, existing differences in outcomes have consequences for patients' timely access to NSCLC immunotherapies. Increased harmonization and collaboration on the PRO measurement and validation are encouraged among the regulatory agencies to improve the efficiency of regulatory decisions for ICIs. Adhering to mutually agreed regulatory approval structures and processes could lower barriers to drug development and eliminate redundant efforts that affect patients' access to safe and effective drugs. Researchers and stakeholders are encouraged to consider potential solutions and future research ideas to improve patient care by supporting innovative technologies without financially stifling the healthcare systems in Europe, North America, and beyond.

From a valuation perspective: The efficient allocation of existing resources is essential for health systems to meet the evolving needs of populations and sustainability efforts. To improve the quality of the valuation studies, the authors of future CEAs are encouraged to consider including a methodological quality assessment checklist (e.g., the CHEC or Philips checklist) in their studies and follow its guidance. To theoretically address the long-term estimation of (combination) ICI outcomes beyond clinical trials, the authors of the CEAs should vary nivolumab-ipilimumab dosing and treatment duration in their assessments. Given the valuation challenges of combination ICIs, their mechanism of action poses significant uncertainty and requires further clinical investigation to address whether synergy or additivity exists. Although conceptual value attribution methods have been suggested, additional work will be needed to improve these proposed methodologies, validate them and potentially add new ones. Further research is encouraged on developing value attribution methods for combination therapies and quantifying durable, long-term survival gains for risk-seeking patients in the future.

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8

Summary
Summary in Dutch Language (Samenvatting)

Summary

Advances in innovative drug development translated into tangible improvements in clinical outcomes for patients with non-small cell lung cancer (NSCLC). Immunotherapy, specifically immune checkpoint inhibitors (ICIs), has transformed the standard of care for NSCLC patients. Although ICIs have brought meaningful opportunities in NSCLC care and transformed the treatment landscape, their regulatory decisions and economic value assessments may pose additional challenges. In this doctoral research, regulatory and valuation challenges of ICIs in NSCLC were addressed to help support the future use of ICIs within the healthcare systems in Europe, North America, and beyond.

Chapter 1 introduced research questions on the regulatory and valuation challenges of ICIs in NSCLC. Advances in innovative drug development increased the need for harmonization and collaboration between the regulatory authorities. To better understand the regulatory environments in Europe and North America and efforts to align practices, regulatory practices can guide resource allocation, facilitate innovation in cancer research, and ultimately optimize patient care. Although ICIs have brought meaningful treatment opportunities in NSCLC care, several challenges remain. Chapters 2 through 7 explore the application of health technology assessment in the field of NSCLC to study potential regulatory and valuation challenges of ICIs and address their future implications.

Chapter 2 reviewed regulatory approvals of ICIs for NSCLC in Europe and the United States. Regulatory approval decisions of the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) are frequently compared and contrasted. The comparison is often based on drug review requirements and their time to approval or refusal decisions. The focus was on each ICI's time to approval duration and the considerations of patient-reported outcomes (PROs) by each regulatory agency. Despite similarities in the regulatory pathways and methods used for ICI approvals, NSCLC indications that stood out in outcome divergence were mainly first-line inhibitors for treatment naïve patients. The FDA was quicker to reach approval decisions when compared with the EMA. The FDA and EMA both recognize the value of PROs as necessary patient-centered endpoints. Although several regulatory structures in Europe and North America aim to leverage the latest clinical trial evidence and speed up the regulatory approval processes, in this study, the preponderance of outcome differences in approvals was not influenced by the expedited drug development and access programs. Increased harmonization and collaboration on the PRO measurement and validation are encouraged among these agencies to improve the efficiency of regulatory decisions in the future.

Chapter 3 analyzed PROs used in the registrational clinical trials of nivolumab, a programmed cell death-1 inhibitor, in advanced NSCLC. PROs included in the FDA-approved indications of nivolumab clinical trials were reviewed. The PRO data reported in four registrational clinical trials: CheckMate 017 (NCT01642004), CheckMate 057 (NCT01673867), CheckMate 9LA (NCT03215706) and CheckMate 227 (NCT02477826) were analyzed. It was concluded that nivolumab alleviated symptom burden and improved the health status of patients in this setting. However, the incapability of the included PRO instruments to measure immune-related AEs, differences in the timing of PRO evaluation between treatment groups, incomplete patient participation at all time points, limited patient participation in the later time points, and interpretation of the longitudinal data were posing a compounded challenge to analyze and validate the findings of these clinical trials accurately.

Chapter 4 systematically assessed the methodological quality of the cost-effectiveness studies of nivolumab in combination with ipilimumab in the first-line treatment setting. A systematic literature review was conducted in treatment-naive patients with recurrent or metastatic NSCLC, whose tumors expressed programmed death ligand-1 without any epidermal growth factor receptor and anaplastic lymphoma kinase genomic tumor aberrations. The Philips and Consensus Health Economic Criteria (CHEC) checklists were used to assess the quality of the methodology of the included cost-effectiveness studies. One hundred seventy-one records were identified. Seven studies met the inclusion criteria. Cost-effectiveness analyses differed substantially due to the applied modeling methods, sources of costs, health state utilities, and key model assumptions. Quality assessment of the included studies highlighted shortcomings in data identification, uncertainty assessment, and methods transparency. Nivolumab plus ipilimumab can be used for a range of clinical indications, also in combination with other agents. However, the findings of the systematic review revealed that methods of estimating long-term outcomes, quantifying the health state utility, estimating drug costs, the accuracy of data sources, and credibility have implications on the cost-effectiveness outcomes. The included studies fulfilled only some of the items reported in the Philips and the CHEC checklists.

Chapter 5 explored the attribution of value for ICIs combined with other treatments that aim to provide clinically meaningful outcomes for NSCLC patients. There are distinct mechanisms of action that an ICI may provide for such clinically meaningful benefits. The focus of this study was on the valuation of ICIs when used in combination with existing treatments in NSCLC. Key questions of this study were: Do ICI combinations improve clinical outcomes through independent drug action - rather than additivity or synergy? How should the economic value be attributed to the combination

ICIs' constituent parts? The search databases of the FDA and Clinicaltrials.gov were reviewed to identify combination ICIs in NSCLC. For valuation methods, a separate search was conducted in PubMed, health technology assessment databases, and grey literature to identify methods, particularly in combination (cancer) treatments. At the time of this analysis, the FDA approved eight combination ICI indications for NSCLC. These therapies' underlying mechanisms for improved clinical benefits still need to be well studied. The superiority of combination ICIs to monotherapy in multiple indications does not indicate whether synergy or additivity is involved or necessary. Further research is encouraged on methods of value attribution frameworks for combination therapies to quantify their added health benefits and economic value in the future.

Chapter 6 focused on patients' risk preferences or 'hope' as an additional value dimension. Immunotherapy offers a unique mechanism of action compared to traditional treatments, arising from additional value dimensions that may not be captured in standard HTA. Quantitative methods exploring patients' risk preferences in their cancer treatment choices were reviewed. It was reported that quantitative methods that empirically measure patients' risk preferences or 'hope' are emerging. Based on the available evidence, patient-centered care and value frameworks should be based on survival improvements for the mean or median patient and consider valuation methods incorporating durable, long-term overall survival gains. However, the evidence for incorporating 'hope' based on patients' stated preferences for uncertain treatment profiles is not strong, and future research could strengthen this evidence base. Further research is encouraged to develop and validate reliable methods for the quantification of 'hope' and to value risk preferences in patients with NSCLC and other cancers to illustrate how these estimates can be used in the deliberative processes integral to value assessments.

Chapter 7 highlighted the identified challenges and future perspectives of this doctoral research. From a regulatory perspective, adhering to mutually agreed approval structures and processes could lower barriers to drug development and eliminate redundant efforts affecting safe and effective ICIs to patients. Increased harmonization and collaboration on the PRO instrument development, measurement, and validation are needed to improve the efficiency of regulatory decisions. Also, PRO instruments are expected to capture immune-related adverse events in the future, given that they are increasingly included in HTA and have ramifications on patient access, drug reimbursement, and pricing. Quality assessment of the cost-effectiveness studies highlighted shortcomings in various domains. Applying high-quality methods from scientific evidence and economic modeling can aid in achieving sustainable healthcare systems. Improving the methodological quality of the cost-effectiveness

studies will be a significant step in the right direction toward this achievement. Combination ICIs are increasingly used to achieve better health outcomes. The superiority of combination ICIs to monotherapy in multiple indications does not indicate whether synergy or additivity is involved or necessary. From a valuation perspective, it is vital to advance the objective of researching and developing methods of value attribution for combination therapies and to support efforts to ensure that patients have access to clinically meaningful combination ICIs as rapidly as possible. Lastly, quantitative methods that empirically measure patients' risk preferences or 'hope' are emerging. However, the evidence for incorporating 'hope' based on patients' stated preferences for uncertain treatment profiles is not strong, and future research could strengthen this evidence base. Further research is encouraged to develop and validate reliable methods for the quantification of 'hope' and to value risk preferences in cancer patients.

To conclude, this doctoral research highlighted the need to continue the dialogue among stakeholders, including researchers, physicians, drug manufacturers, regulators, lawmakers, HTA agencies, and policymakers, to work on ICIs' regulatory and valuation challenges in NSCLC. It also highlighted that novel methods are needed to determine how to attribute the benefits of combination ICIs by supporting future innovation without financially stifling the healthcare systems in Europe, North America, and beyond.

Summary in Dutch Language

(Samenvatting)

Vooruitgang in de ontwikkeling van innovatieve geneesmiddelen vertaalde zich in tastbare verbeteringen in klinische resultaten voor patiënten met niet-kleincellige longkanker (NSCLC). Immunotherapie, met name Immuun checkpoint-remmers (ICI's), heeft de zorgstandaard voor NSCLC-patiënten getransformeerd. Hoewel ICI's betekenisvolle kansen hebben geboden in de NSCLC-zorg en het behandelingslandschap hebben veranderd, kunnen hun regelgevingsbeslissingen en economische waardebeoordelingen voor extra uitdagingen zorgen. In dit doctoraatsonderzoek werden uitdagingen op het gebied van regelgeving en waardering van ICI's in NSCLC aangepakt om het toekomstige gebruik van ICI's binnen de gezondheidszorgsystemen in Europa, Noord-Amerika en daarbuiten te helpen ondersteunen.

Hoofdstuk 1 introduceerde onderzoeksvragen over de uitdagingen op het gebied van regelgeving en waardering van ICI's in NSCLC. Vooruitgang in de ontwikkeling van innovatieve geneesmiddelen verhoogde de behoefte aan harmonisatie en samenwerking tussen de regelgevende instanties. Om de regelgevingsomgevingen in Europa en Noord-Amerika en inspanningen om praktijken op elkaar af te stemmen beter te begrijpen, kunnen regelgevingspraktijken de toewijzing van middelen sturen, innovatie in kankeronderzoek vergemakkelijken en uiteindelijk de patiëntenzorg optimaliseren. Hoewel ICI's zinvolle behandelingsmogelijkheden hebben gebracht in de NSCLC-zorg, blijven er een aantal uitdagingen. Hoofdstukken 2 tot en met 7 onderzoeken de toepassing van de beoordeling van gezondheidstechnologie op het gebied van NSCLC om mogelijke regelgevings- en waarderingsuitdagingen van ICI's te bestuderen en hun toekomstige implicaties aan te pakken.

Hoofdstuk 2 de wettelijke goedkeuringen van ICI's voor NSCLC in Europa en de Verenigde Staten beoordeeld. Regelgevende goedkeuringsbesluiten van de Food and Drug Administration (FDA) en het Europees Geneesmiddelenbureau (EMA) worden vaak met elkaar vergeleken en gecontrasteerd. De vergelijking is vaak gebaseerd op vereisten voor geneesmiddelenbeoordeling en hun tijd tot goedkeuring of weigering. We hebben ons gericht op de duur van elke ICI tot goedkeuring en de overwegingen van door de patiënt gerapporteerde uitkomsten (PRO's) door elke regelgevende instantie. Ondanks overeenkomsten in de regulatoire trajecten en methoden die worden gebruikt voor ICI-goedkeuringen, waren NSCLC-indicaties die opvielen in uitkomstafwijking voornamelijk eerstelijnsremmers voor behandelingsnaïeve patiënten. De FDA kwam sneller tot goedkeuringsbesluiten in vergelijking met de EMA. De FDA en EMA erkennen beide de waarde van PRO's als noodzakelijke pati-

entgerichte eindpunten. Hoewel verschillende regelgevende structuren in Europa en Noord-Amerika erop gericht zijn gebruik te maken van de meest recente bewijzen van klinische onderzoeken en de wettelijke goedkeuringsprocessen te versnellen, werd in deze studie het overwicht van uitkomstverschillen in goedkeuringen niet beïnvloed door de versnelde ontwikkeling van geneesmiddelen en programma's voor toegang. Meer harmonisatie en samenwerking op het gebied van de PRO-meting en -validatie worden door deze agentschappen aangemoedigd om de efficiëntie van regelgevende beslissingen in de toekomst te verbeteren.

Hoofdstuk 3 analyseerde PRO's die werden gebruikt in de registratie-klinische onderzoeken van nivolumab, een geprogrammeerde celdood-1-remmer, bij gevorderde NSCLC. We hebben PRO's beoordeeld die zijn opgenomen in de door de FDA goedgekeurde indicaties van klinische onderzoeken met nivolumab. We analyseerden de PRO-gegevens die werden gerapporteerd in vier klinische registratieonderzoeken: CheckMate 017 (NCT01642004), CheckMate 057 (NCT01673867), CheckMate 9LA (NCT03215706) en CheckMate 227 (NCT02477826). We concludeerden dat nivolumab de symptoomlast verlichtte en de gezondheidstoestand van patiënten in deze setting verbeterde. Het onvermogen van de meegeleverde PRO-instrumenten om immuungerelateerde AE's te meten, verschillen in de timing van PRO-evaluatie tussen behandelingsgroepen, onvolledige patiëntenparticipatie op alle tijdstippen, beperkte patiëntenparticipatie op de latere tijdstippen en interpretatie van de longitudinale gegevens vormden een nog grotere uitdaging om de bevindingen van deze klinische onderzoeken nauwkeurig te analyseren en te valideren.

Hoofdstuk 4 systematisch de methodologische kwaliteit beoordeeld van de kosteneffectiviteitsstudies van nivolumab in combinatie met ipilimumab in de eerstelijnsbehandeling. We hebben een systematisch literatuuronderzoek uitgevoerd bij niet eerder behandelde patiënten met recidiverende of gemetastaseerde NSCLC, van wie de tumoren geprogrammeerde dood ligand-1 tot expressie brachten zonder enige epidermale groeifactorreceptor en genomische tumorafwijkingen van anaplastisch lymfoomkinase. De checklists van Philips en Consensus Health Economic Criteria (CHEC) werden gebruikt om de kwaliteit van de methodologie van de opgenomen kosteneffectiviteitsonderzoeken te beoordelen. Honderd eenenzeventig records werden geïdentificeerd. Zeven studies voldeden aan de inclusiecriteria. Kosteneffectiviteitsanalyses verschilden aanzienlijk vanwege de toegepaste modelleringsmethoden, bronnen van kosten, hulpprogramma's voor de gezondheidstoestand en belangrijke modelaannames. Kwaliteitsbeoordeling van de opgenomen onderzoeken bracht tekortkomingen aan het licht op het gebied van gegevensidentificatie, onzekerheidsbeoordeling en transparantie van methoden. Nivolumab plus ipilimumab

kan voor uiteenlopende klinische indicaties worden gebruikt, ook in combinatie met andere middelen. Uit onze systematische review bleek echter dat methoden voor het schatten van langetermijnresultaten, het kwantificeren van het nut van de gezondheidstoestand, het schatten van medicijnkosten, de nauwkeurigheid van gegevensbronnen en geloofwaardigheid belangrijke implicaties hebben voor de kosteneffectiviteitsresultaten. De geïncludeerde onderzoeken voldeden slechts aan enkele van de items die vermeld staan in de checklists van Philips en CHEC.

Hoofdstuk 5 onderzocht de toekenning van waarde voor ICI's in combinatie met andere behandelingen die gericht zijn op het bieden van klinisch betekenisvolle resultaten voor NSCLC-patiënten. Er zijn verschillende werkingsmechanismen die een ICI kan bieden voor dergelijke klinisch relevante voordelen. We hebben ons gericht op de waardering van ICI's bij gebruik in combinatie met bestaande behandelingen bij NSCLC door de volgende vragen te beantwoorden: (1) verbeteren gecombineerde ICI's de klinische resultaten als gevolg van onafhankelijke in plaats van synergetische of additieve medicijnwerking; en (2) hoe moeten we waarde toekennen aan de samenstellende delen van gecombineerde ICI's? Om deze vragen te beantwoorden, hebben we databases van de FDA en Clinicaltrials.gov beoordeeld om goedgekeurde indicaties van combinatie-ICI's bij NSCLC te identificeren. Voor waarderingsmethoden is apart gezocht in PubMed, health technology assessment databases en grijze literatuur om gepubliceerde waardebepalings- of attributiemethoden te identificeren, specifiek in combinatie (kanker)behandelingen. Ten tijde van onze analyses keurde de FDA acht gecombineerde ICI-indicaties voor NSCLC goed. De onderliggende mechanismen van deze therapieën voor verbeterde klinische voordelen moeten nog goed worden bestudeerd. De superioriteit van combinatie-ICI's ten opzichte van monotherapie bij meerdere indicaties geeft niet aan of synergie of additiviteit een rol speelt of noodzakelijk is. We moedigen verder onderzoek aan naar methoden voor waardetoekenningskaders voor combinatietherapieën om hun toegevoegde gezondheidsvoordelen en economische waarde in de toekomst te kwantificeren.

Hoofdstuk 6 gericht op de risicovoorkeuren van patiënten of 'hoop' als een toegevoegde waardedimensie. Immunotherapie biedt een uniek werkingsmechanisme in vergelijking met traditionele behandelingen, voortkomend uit aanvullende waardedimensies die mogelijk niet zijn vastgelegd in standaard HTA. We hebben kwantitatieve methoden beoordeeld die de risicovoorkeuren van patiënten onderzoeken bij hun keuzes voor de behandeling van kanker. We meldden dat kwantitatieve methoden in opkomst zijn die empirisch de risicovoorkeuren of 'hoop' van patiënten meten. Op basis van het beschikbare bewijsmateriaal zouden patiëntgerichte zorg en waardekaders niet alleen gebaseerd moeten zijn op overlevingsverbeteringen voor de gemiddelde

of mediane patiënt, maar zouden ook waarderingsmethoden moeten worden overwogen die duurzame winsten op het gebied van algehele overleving op de lange termijn omvatten. Het bewijs voor het opnemen van 'hoop' op basis van de door patiënten aangegeven voorkeuren voor onzekere behandelingsprofielen is echter niet sterk, en toekomstig onderzoek zou deze bewijsbasis kunnen versterken. We moedigen meer werk aan om betrouwbare methoden te ontwikkelen en te valideren voor de kwantificering van 'hoop' en om risicovoorkeuren te waarderen bij patiënten met NSCLC en andere kankers om te illustreren hoe deze schattingen kunnen worden gebruikt in de deliberatieve processen die een integraal onderdeel zijn van waardebeoordelingen.

Hoofdstuk 7 benadrukte de geïdentificeerde uitdagingen en toekomstperspectieven van dit doctoraatsonderzoek. Vanuit een regelgevend perspectief zou het naleven van onderling overeengekomen goedkeuringsstructuren en -processen de belemmeringen voor de ontwikkeling van geneesmiddelen kunnen verlagen en overbodige inspanningen die van invloed zijn op veilige en effectieve ICI's voor patiënten, kunnen elimineren. Meer harmonisatie en samenwerking bij de ontwikkeling, meting en validatie van het PRO-instrument zijn nodig om de efficiëntie van regelgevende beslissingen te verbeteren. Ook wordt verwacht dat PRO-instrumenten in de toekomst immuungerelateerde bijwerkingen kunnen opvangen, aangezien ze steeds vaker worden opgenomen in HTA en gevolgen hebben voor de toegang van patiënten, de terugbetaling van geneesmiddelen en de prijsstelling. De kwaliteitsbeoordeling van de kosteneffectiviteitsstudies bracht tekortkomingen op verschillende domeinen aan het licht. Het toepassen van hoogwaardige methoden op basis van wetenschappelijk bewijs en economische modellen kan helpen bij het bereiken van duurzame gezondheidszorgstelsels. Het verbeteren van de methodologische kwaliteit van de kosteneffectiviteitsstudies zal een belangrijke stap in de goede richting zijn om dit te bereiken. Combinatie-ICI's worden steeds vaker gebruikt om betere gezondheidsresultaten te bereiken. De superioriteit van combinatie-ICI's ten opzichte van monotherapie bij meerdere indicaties geeft niet aan of synergie of additiviteit een rol speelt of noodzakelijk is. Vanuit een waarderingsperspectief is het van vitaal belang om de doelstelling van het onderzoeken en ontwikkelen van methoden voor waardetoekenning voor combinatietherapieën te bevorderen en inspanningen te ondersteunen om ervoor te zorgen dat patiënten zo snel mogelijk toegang hebben tot klinisch relevante combinatie-ICI's. Ten slotte zijn er kwantitatieve methoden in opkomst die empirisch de risicovoorkeuren of 'hoop' van patiënten meten. Het bewijs voor het opnemen van 'hoop' op basis van de door patiënten aangegeven voorkeuren voor onzekere behandelingsprofielen is echter niet sterk, en toekomstig onderzoek zou deze bewijsbasis kunnen versterken. We moedigen meer werk aan om betrouwbare methoden te

ontwikkelen en te valideren voor het kwantificeren van 'hoop' en om risicovoorkeuren bij kankerpatiënten te waarderen.

Dit doctoraatsonderzoek benadrukte de noodzaak om de dialoog tussen belanghebbenden voort te zetten, waaronder onderzoekers, artsen, geneesmiddelenfabrikanten, regelgevers, wetgevers, HTA-agentschappen en beleidsmakers, om te werken aan de regelgevings- en waarderingsuitdagingen van ICI's in NSCLC. Het benadrukte ook dat er nieuwe methoden nodig zijn om te bepalen hoe de voordelen van gecombineerde ICI's kunnen worden toegeschreven door toekomstige innovatie te ondersteunen zonder de gezondheidszorgstelsels in Europa, Noord-Amerika en daarbuiten financieel te verstikken.

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List of Publications
Ph.D. Portfolio
About the Author

List of Publications

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Zaim R, Redekop WK, Uyl-de Groot CA. Incorporating risk preferences of patients in the valuation of immune checkpoint inhibitors for non-small cell lung cancer. *Frontiers in Oncology 2023* Mar 8;13:1027659. *doi:10.3389/fonc.2023.1027659.*

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Wolff R, Al M, **Zaim R**, Lang S, Leunis A, Noake C, Ryder S, Worthy G, Stirk L, Armstrong N, Riemsma R, Severens JL, Kleijnen J. Naloxegol for treating opioid-induced constipation: A Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd, the ***United Kingdom***.

Uyl-de Groot CA, Al MJ, **Zaim R**. Nivolumab bij gevorderd plaveiselcelcarcinoom van de long. Kosteneffectiviteit en op waarde gebaseerde prijsbenchmarks, the ***Netherlands***.

Taimr P, **Zaim R**, de Knegt R, Dwarkasing R, Hansen BE, IJzermans I, Uyl-de Groot CA, Janssen HLA. Characterization of Focal Liver Lesions by Contrast-Enhanced Ultrasound in the Netherlands: Clinical and Economic Evaluation, the ***Netherlands***.

International Conference Publications

•Annual ISPOR Congress, Boston, Massachusetts, the United States.
Zaim R, Shaw JA. Building a lifecycle ethics framework for the assessment of artificial intelligence technologies in health: A scoping review of reviews.

•Annual European ISPOR Congress [virtual], Milan, Italy.
Zaim R, Redekop WK, Uyl-De Groot CA. How should value be attributed to the constituent parts of combination immunotherapy in non-small cell lung cancer?

•Annual European ISPOR Congress, Vienna, Austria.
Holleman MS, **Zaim R**, Uyl-De Groot CA. Cost-utility analysis of first-line gefitinib, erlotinib, and afatinib in patients with non-small cell lung cancer harboring EGFR mutations.

•Annual European ISPOR Congress, Vienna, Austria.
Holleman MS, **Zaim R**, Uyl-De Groot CA. Gefitinib, erlotinib, or afatinib for EGFR mutated NSCLC patients? A meta-analysis and indirect comparison on the efficacy of first-line tyrosine kinase inhibitors.

•Annual European ISPOR Congress, Milan, Italy.
Zaim R, van der Putten L, de Groot S, van Tinteren H, Boers M, Comans E, van der Laan B, Janssen L, Takes R, van den Brekel M, Oyen W, Valdés-Olmos R, Hobbelink M, Wedman J, Leemans C, Hoekstra O, de Bree R, Uyl-de Groot CA. Recurrent Laryngeal Carcinoma PET Study (RELAPS): A cost analysis of $^{(18F)}$ FDG PET in patients with suspected recurrent laryngeal cancer previously treated with radiotherapy.

•Annual European ISPOR Congress, Milan, Italy.
Maan R, **Zaim R**, van der Meer AJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Manns MP, Zeuzem S, Hansen BE, Janssen HLA, Veldt BJ, de Knegt RJ, Uyl-de Groot CA. Real-world medical costs of antiviral therapy among patients with chronic HCV infection and advanced hepatic fibrosis.

•The Liver Meeting, AASLD, San Francisco, the United States.
Maan R, **Zaim R**, van der Meer AJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Manns MP, Zeuzem S, Hansen BE, Janssen HLA, Veldt BJ, de Knegt RJ, Uyl-de Groot CA. Real-world medical costs of antiviral therapy among patients with chronic HCV infection and advanced hepatic fibrosis.

•Annual European ISPOR Congress, Amsterdam, the Netherlands.
Zaim R, Tran L, Groen HM, Uyl-de Groot CA. De novo quantification of genotype-directed therapy with afatinib in metastatic lung cancer.

•World Conference on Lung Cancer, Sydney, Australia.
Zaim R, Tran L, Dingemans AMC, Herder JG, Lammers E, Postmus PE, Uyl-de Groot CA. Retrospective Longitudinal Chart Review of Patients with Advanced Non-Small Cell Lung Cancer: A Quantification of Disease Burden.

•World Conference on Lung Cancer, Sydney, Australia.
Zaim R, Thunnissen E, Dingemans EMC, Postmus PE, Uyl-de Groot CA. Molecular Screening in Advanced Non-Small Cell Lung Cancer: A Systematic Review of Cost-Effectiveness Analyses for First-Line Therapy.

•ECCO-ESMO-ESTRO Congress, Amsterdam, the Netherlands.
Zaim R, Redekop WK, Valezquez ER, Hoebers F, Lambin P, Uyl-de Groot CA. Tailoring Treatment Based on Risk of Relapse in Advanced Laryngeal Squamous Cell Carcinoma.

•ESMO Congress, Vienna, Austria.
Zaim R, Redekop WK, van Dongen GAMS, de Bree R, Uyl-de Groot CA. Molecular Therapeutics in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: A systematic review of cost-effectiveness analyses.

•Annual European ISPOR Congress, Berlin, Germany.
Zaim R, Redekop WK, de Bree R, van Dongen GAMS, Hoekstra OC, Uyl-de Groot CA. Positron Emission Tomography in Head and Neck Squamous Cell Carcinoma: A systematic review of cost-effectiveness analyses.

•CTMM Annual Meeting, Utrecht, the Netherlands.
Zaim R, Redekop WK, de Bree R, van Dongen GAMS, Hoekstra OC, Uyl-de Groot CA. Positron Emission Tomography in Head and Neck Squamous Cell Carcinoma: A systematic review of cost-effectiveness analyses.

•Annual European ISPOR Congress, Madrid, Spain.
Zaim R, Gaultney JG, Redekop WK, Uyl-de Groot CA. Potential benefits of introducing a companion diagnostic in advanced non-small cell lung cancer.

•Annual European ISPOR Congress, Madrid, Spain.
Zaim R, Taimr P, de Knegt RJ, Redekop WK, Uyl-de Groot CA. Characterization of focal liver lesions by contrast-enhanced ultrasound in the Netherlands: An economic evaluation.

•The Liver Meeting, AASLD, San Francisco, the United States.
Taimr P, **Zaim R**, de Knegt RJ, de Man RA, Uyl-de Groot CA, Janssen HL. Characterization of focal liver lesions by contrast-enhanced ultrasound in the Netherlands: Clinical and economic evaluation.

Ph.D. Portfolio

COURSES AND WORKSHOPS	ECTS
Regression Analysis, NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands.	0.7
Biostatistics, NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands.	0.7
Diagnostics Research, NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands.	0.7
Advanced Modeling Methods for Economic Evaluations, University of Scotland, Glasgow, Scotland.	0.6
Network Meta-Analysis in Relative Effectiveness Research, ISPOR short course.	0.2
Discrete Event Simulation for Economic Analyses, ISPOR short course.	0.2
Meta Analyses and Systematic Literature Review, ISPOR short course.	0.2
Drug Discovery, Drug Development, and Regulation, CERSI, Stanford University & the University of California San Francisco, the United States.	2.7
Markov Model: Concepts, Assumptions and Calculations, ISPOR short course.	0.2
Modelling Healthcare Costs Part 1, ISPOR short course.	0.2
Modelling Healthcare Costs Part 2, ISPOR short course.	0.2
Innovation Leadership & Global Health, Massachusetts Institute of Technology, Cambridge, Massachusetts, the United States.	2.7
Klaar in vier jaar, Erasmus University, Rotterdam, the Netherlands.	1.0
Dutch Language Course (A1+A2), Erasmus University, Rotterdam, the Netherlands.	2.0
Academic Integrity, Master class, Erasmus University, Rotterdam, the Netherlands.	0.4
Head and Neck Cancer, VU University Medical Center, Amsterdam, the Netherlands.	0.6

CONFERENCES & SYMPOSIA	ECTS
ISPOR Annual European Congress, Milan, Italy. [virtual]	1.0
ISPOR Annual European Congress, Milan, Italy.	1.0
ISPOR Annual European Congress, Amsterdam, the Netherlands.	1.0
ISPOR Annual European Congress, Berlin, Germany.	1.0
ISPOR Annual European Congress, Madrid, Spain.	1.0
Lowlands Health Economics Study Group Conference, the Netherlands.	1.0
European Society of Medical Oncology (ESMO) Congress, Vienna, Austria.	1.0
ECCO - ESMO - ESTRO Congress, Amsterdam, the Netherlands.	1.0
Perspectives in Lung Cancer, European Congress, Amsterdam, the Netherlands.	0.4
Perspectives in Lung Cancer, European Congress, Amsterdam, the Netherlands.	0.4
Center for Translational Molecular Medicine Annual Meeting, Utrecht, the Netherlands.	0.4
Center for Translational Molecular Medicine Annual Meeting, Utrecht, the Netherlands.	0.4
International Congress on Targeted Anticancer Therapies, Amsterdam, the Netherlands.	0.4

OTHER ACTIVITIES	ECTS
Reviewer for scientific publications and conference abstracts, Erasmus University, Rotterdam, the Netherlands.	0.7
Workgroup trainer Pharmaceutical Pricing and Market Access (Master class), Erasmus University, Rotterdam, the Netherlands.	1.6
Workgroup trainer Health Technology Assessment (Master class), Erasmus University, Rotterdam, the Netherlands.	0.4
Workgroup trainer Health Economics NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands.	0.4
Master thesis evaluator and/or co-supervisor, Erasmus University, Rotterdam, the Netherlands.	10.5
Total ECTS	**36.9**

About the Author

Remziye Zaim holds Bachelor of Science and Master of Science degrees (with honors) in life sciences with a specialization in cancer genetics from the State University of New York in the United States of America (USA). Throughout her studies in New York, Remziye received various merit scholarships, including a Fulbright fellowship, which the Cyprus-America Scholarship Program and the Fulbright Program jointly awarded. Upon graduation, she received a research grant from the Swiss Federal Institute of Technology and completed her postgraduate training in Switzerland.

Remziye holds a Master of Science degree in health economics, policy, and law, funded by the European Commission, from Erasmus University Rotterdam in the Netherlands. At the Erasmus School of Health Policy and Management, she worked on health technology assessment (HTA) projects, critiqued and contributed to conference abstracts, and (co)authored scientific reports and peer-reviewed publications. She participated in international conferences, co-supervised Master's thesis students, and taught graduate-level courses. Key highlights of her HTA contributions were; (i) participation in the Evidence Review Groups for England's National Institute for Health and Care Excellence (NICE) to assess medical technologies within the Highly-Specialized Technology Program, the Single Technology Appraisal and Diagnostic Assessment Programs, and (ii) assessment of the first immune checkpoint inhibitor in advanced lung cancer for the Netherlands Healthcare Institute. Her doctoral research focused on immune checkpoint inhibitors' regulatory and valuation challenges in lung cancer.

Remziye received a 12-month fellowship and worked at the Institute for Clinical and Economic Review (ICER) in Boston, Massachusetts, USA. At the ICER, she oversaw value assessments of medical technologies. She researched additional value dimensions for potentially curative treatments, including cell and gene therapies. After this fellowship, she joined the Institute for Medical Technology Assessment at Erasmus University in the Netherlands. She worked in various teams to evaluate technologies for the NICE, the Federal Office of Public Health in Switzerland, and the pharmaceutical industry.

To complement her HTA experiences, Remziye completed an entrepreneurial training program in innovation leadership and global health at the Massachusetts Institute of Technology in Cambridge, Massachusetts, USA. Consequently, she earned a Master of Business Administration degree (with high honors) at Boston University, Questrom School of Business, in Boston, Massachusetts, USA. Remziye continues to pursue her academic career in North America.