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SYSTEMATIC REVIEW

Critical Examination of Modeling Approaches Used in Economic Evaluations of First-Line Treatments for Locally Advanced or Metastatic Non-Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Mutations: A Systematic Literature Review

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Abstract

Background Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, with up to 32% of patients with NSCLC harboring an epidermal growth factor receptor (EGFR) mutation. NSCLC harboring an EGFR mutation has a dedicated treatment pathway, with EGFR tyrosine kinase inhibitors and platinum-based chemotherapy often being the therapy of choice.

Objective The aim of this study was to systemically review and summarize economic models of first-line treatments used for locally advanced or metastatic NSCLC harboring EGFR mutations, as well as to identify areas for improvement for future models.

Methods Literature searches were conducted via Ovid in PubMed, MEDLINE, MEDLINE In-Process, Embase, Evidence-Based Medicine Reviews: Health Technology Assessment, Evidence-Based Medicine Reviews: National Health Service Economic Evaluation Database, and EconLit. An initial search was conducted on 19 December 2022 and updated on 11 April 2023. Studies were selected according to predefined criteria using the Population, Intervention, Comparator, Outcome and Study design (PICOS) framework.

Results Sixty-seven articles were included in the review, representing 59 unique studies. The majority of included models were cost-utility analyses ($n = 52$), with the remaining studies being cost-effectiveness analyses ($n = 4$) and a cost-minimization analysis ($n = 1$). Two studies incorporated both a cost-utility and cost-minimization analysis. Although the model structure across studies was consistently reported, justification for this choice was often lacking.

Conclusions Although the reporting of economic models in NSCLC harboring EGFR mutations is generally good, many of these studies lacked sufficient reporting of justification for structural choices, performing extensive sensitivity analyses and validation in economic evaluations. In resolving such gaps, the validity of future models can be increased to guide healthcare decision making in rare indications.

1 Background

Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers and 25% of cancer deaths [1]. Adenocarcinoma is the most common histological subtype of NSCLC, comprising approximately 40–50% of all cases [2–5]. The characterization of tumor subtype and the detection of actionable oncogenic driver mutations are the key features of adenocarcinoma treatment [6, 7]. Mutations in the epidermal growth factor receptor (*EGFR*) tyrosine kinase occur in approximately 11.9% [8] to 32.3% [9] of patients with NSCLC. Most *EGFR* mutations are associated with a dedicated treatment pathway, as defined by guidelines from the National Comprehensive Cancer Network and European Society for Medical Oncology, among others [10, 11]. In recent years, *EGFR* tyrosine kinase inhibitors (TKIs), such as dacomitinib, osimertinib, erlotinib, gefitinib, and afatinib, have been developed to treat patients with *EGFR*-positive NSCLCs that have demonstrated high efficacy in treating

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Key Points For Decision Makers

The cost effectiveness of treatments in first-line non-small cell lung cancer is well established, with all identified models including an epidermal growth factor receptor tyrosine kinase inhibitor as an intervention.

There is a lack of reporting for the justification of structural choice for the model.

Future models should provide justification for the structural choice made, and perform extensive sensitivity analyses and validation in economic evaluations to increase validity to guide healthcare decision making in rare indications.

patients with some forms of *EGFR* mutations in exons 18–21 [10, 12–14].

Decision-analytic models are a key component of economic evaluations used to inform policy makers, payers, and stakeholders on whether new treatments should be adopted and reimbursed [15]. The framework provided by decision-analytic models can place treatment options in context with one another, which is particularly valuable when assessing multiple emerging therapies [15]. The goal of this study was to assess the approach and structure of decision-analytic models used in previous economic evaluations for therapies indicated for *EGFR*-positive NSCLC to present the best practices for use in upcoming models for therapies to treat first-line *EGFR*-positive NSCLC. To accomplish this, a systematic literature review (SLR) was performed to identify published economic evaluations in adults with locally advanced (stage IIIB or IIIC) or metastatic (stage IV) NSCLC, with tumors harboring *EGFR* mutations, who had not previously received systemic treatment for locally advanced or metastatic disease. Previous publications have reviewed economic evaluations for targeted therapies in NSCLC; however, these have focused on the detail provided in models or the quality of reporting [16, 17].

This review aimed to (1) critically examine modeling approaches from published economic evaluations based on five components (conceptualization, model structure, uncertainty, model validation, and transparency) as recommended by Caro [18]; (2) explore variation across studies; and (3) discuss challenges and potential areas for improvement for decision-analytic models in front-line *EGFR*-positive NSCLC.

2 Methods

An SLR was conducted based on guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [19] and the Cochrane Handbook for Systematic Reviews of Interventions [20].

2.1 Literature Sources

Literature searches were first conducted on 19 December 2022 and updated on 11 April 2023 via Ovid in MEDLINE, MEDLINE In-Process, Embase, Evidence-Based Medicine Reviews: Health Technology Assessment (HTA), Evidence-Based Medicine Reviews: National Health Service Economic Evaluation Database, and EconLit. The bibliographies of relevant SLRs and meta-analyses published during the same timeframe that were identified through the database searches were also searched. Eight conferences of interest that featured oncology or health economics content were identified. Searches of these relevant proceedings were conducted to identify records from 2020 to the present, since most high-quality congress abstracts are published as full text within a 2-to 3-year timeframe. While full publications of economic evaluations are common, some remain unpublished and reported only in HTAs. Several HTA agencies commonly review the type of economic evaluations relevant to this study (i.e., cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, etc.), including the Canadian Agency for Drugs and Technologies in Health (CADTH) [21], the National Institute for Health and Care Excellence (NICE) [22], and Pharmaceutical Benefits Advisory Committee [23]. Eight HTA agencies [21–28] and the Institute for Clinical and Economic Review [29] were therefore searched for relevant economic evaluations published from 2020 to the present.

The Embase search strategies are provided in Online Resource Table 1 (update search) and Online Resource Table 2 (original search), and the full list of sources searched is provided in Online Resource Table 3.

2.2 Study Selection

The study selection criteria were predefined using the population, intervention, comparator, outcome, and study (PICOS) design framework, as outlined in Table 1. Two independent reviewers screened identified articles at both the title/abstract and full-text levels, and a third reviewer resolved any discrepancies. HTA submission dossiers were searched manually by one reviewer, and a second reviewer validated the search approach and results.

The target population comprised adults with locally advanced (stage IIIB or IIIC) or metastatic (stage IV)

NSCLC, with tumors harboring *EGFR* mutations, who had not previously received systemic treatment for locally advanced or metastatic disease.

Interventions were included if they were routinely used in clinical care, such as platinum-doublet chemotherapy, immunotherapy alone or in combination with other regimens, TKIs, and emerging therapies, including amivantamab. Interventions with curative intent (e.g., surgery and radiotherapy) were excluded, along with any systemic anticancer treatments not considered usual care. No restrictions were placed on included comparators.

Outcomes of interest included economic model conceptualization, structure, how uncertainty was assessed, validation, and transparency to align with the recommendations reported by Caro [18].

Literature databases and HTA submissions were searched for economic evaluations relevant to this study, including cost-benefit analyses, cost-utility analyses, cost-effectiveness analyses, cost-consequence analyses, and cost-minimization analyses. Publications that were categorized as SLRs or network meta-analyses (NMA) in the literature databases were also hand-searched to identify relevant economic evaluations. Budget impact analyses and cost analyses were excluded.

No geographical or timeframe restrictions were applied to the literature database searches; conference proceedings and SLRs/NMAs were included if they were published from 2020 onward. English-language publications from literature and conference proceedings and HTA submissions were included, along with non-English HTA submissions from the Institute for Quality and Efficiency in Health Care in Germany [27], French National Health Authority [26], Dutch National Health Care Institute [24], and the Dental and Pharmaceutical Benefits Agency in Sweden [25].

2.3 Data Extraction

Data were extracted into predefined data extraction sheets. The extracted data were related to key model elements: conceptualization, structure, uncertainty, validation, and transparency.

Records that used an identical model structure for the same treatment and country were considered to be related to the model's original publication. Only the record of a unique model with the earliest publication date was used when summarizing model designs and characteristics.

3 Results

At the title/abstract level, 721 records were screened in the original search and 43 records were screened during the update; 81 reports of the 721 records (78 from the original search and three from the update) were selected for full-text review. As part of the original search, four congress abstracts were identified through hand-searching and 82 reports from HTA bodies were reviewed for eligibility; no additional congress abstracts or HTA reports were identified as part of the update search. In total, 59 unique studies reporting on an economic evaluation (summarized in 67 reports) were selected for data extraction (see Fig. 1 for details on both the original and updated searches). Among the 67 reports, 33 were published as manuscripts in peer-reviewed journals, and six as conference abstracts [30–68], 20 were HTA submission documents [69–88], and eight were related reports [89–95]. The full list of the 67 reports is presented in Online Resource Table 4. Among the eight related reports, one was an abridged secondary publication [96] and seven were resubmission documents to an HTA body [89–95]; these eight reports were not included as part of summary analysis.

Study characteristics for the included economic evaluations are summarized in Table 2. The global distribution of identified economic evaluations is illustrated in Fig. 2.

3.1 Conceptualization

The model conceptualization is summarized in Table 3.

Eighteen studies explicitly described the intended audience [30–32, 39, 49, 50, 55–57, 59–61, 66, 84–88]. Among these studies, 13 categorized the audience as a medical/clinical decision maker [30–32, 39, 49, 50, 55–57, 59–61, 66] and five were NICE submission documents that specified the audience as '[NICE] consultees and commentators' [84–88]. The results of the economic evaluations were used to directly support decisions regarding reimbursement via HTA documents ($n = 20$) [69–88]. For the remainder, studies stated that the use was for policy/funding decisions ($n = 5$) [34, 35, 48, 56, 62], to promote the sustainability of limited healthcare resources ($n = 5$) [30–32, 60, 61], or to support treatment choices ($n = 7$) [39, 47, 50, 55, 57, 59, 65]. Twenty-two studies did not explicitly state the intended use of the economic evaluations [33, 36–38, 40–46, 49, 51–54, 58, 63, 64, 66–68].

Caro [18] calls for a description on whether models have a single- or multiple-application use. Fifty-seven studies evaluated treatment at a single point in the therapeutic pathway, and two studies evaluated treatment in first- and second-line settings [62, 68]. Multiple applications or whole disease modeling is described as valuable when, for example, upstream events in the treatment pathway are expected to have important downstream effects, or when simple cost-utility decisions fail to reflect the complexity of the decision-makers' objectives [97]. Given the intended use and objectives of the economic evaluations identified, i.e., to make decisions at a single point in the disease pathway (locally advanced [stage IIIB/IIIC]

Table 1 Population, interventions, comparisons, outcomes, and study design selection criteria

	Inclusion	Exclusion
Population	Target population: • Adults with locally advanced (stage IIIB/IIIC) or metastatic (stage IV) NSCLC with at least one patient harboring *EGFR* exon 20 insertion mutation, who have not previously received systemic treatment for locally advanced or metastatic disease Expanded population: • Adults with locally advanced (stage IIIB/IIIC) or metastatic (stage IV) NSCLC harboring *EGFR* mutations, who have not previously received systemic treatment for locally advanced or metastatic disease	• Early-stage, resectable/unresectable (I–IIIA) disease • Second-line treatment or greater NSCLC • NSCLC with any other targetable mutations (i.e., ROS1, ALK, etc.) • Any other population
Intervention	Treatment recommended by key international clinical guidelines (e.g., NCCN and ESMO), and/or licensed or routinely used in patient care: • Platinum-doublet chemotherapy IO monotherapy or in combination with other regimens, including platinum-based chemotherapy including, but not limited to, for example: • *PD-L1 <50% or >1% (any):* • Atezolizumab, bevacizumab, carboplatin, and paclitaxel • Pembrolizumab, pemetrexed, and platinum-based chemotherapy • Pembrolizumab • Nivolumab, ipilimumab, pemetrexed, and (carboplatin or cisplatin) • Atezolizumab, carboplatin, and albumin-bound paclitaxel • *PD-L1 >50%* • Atezolizumab, pemetrexed, and platinum-based chemotherapy • Pembrolizumab • Nivolumab, ipilimumab, pemetrexed, and (carboplatin or cisplatin) • Atezolizumab, carboplatin, and albumin-bound paclitaxel • Atezolizumab • Cemiplimab-rwlc TKIs, including, but not limited to, for example: • Osimertinib • Afatinib • Erlotinib ± ramucirumab/bevacizumab • Gefitinib • Dacomitinib Any technologies in development (target population only): • ABT-101 • Afatinib • Amivantamab • BLU-451 • Cetuximab • CLN-081 • EMB-01 • Furmonertinib • HS-10376 • JMT 101 • Lazertinib • Mobocertinib • ORIC-114 • Osimertinib • Poziotinib • Pyrotinib • DZD9008	• Treatments with curative intent (e.g., radiotherapy alone or in combination with pharmacotherapy, surgery) • Any other systemic anticancer treatments not considered usual care
Comparators	No restriction	NA Comparators
Outcomes	• Model conceptualization • Model structure • Uncertainty assessment • Validation • Transparency	Any other outcome
Study design	From the literature and HTA submissions: • Cost-benefit analyses • Cost-utility analyses • Cost-effectiveness analyses • Cost-consequence analyses • Cost-minimization analyses From the literature, to be hand-searched for relevant economic evaluations: SLRs/NMAs	• Cost analyses • Budget impact models

Table 1 (continued)

	Inclusion	Exclusion
Date of publication	No restrictions were applied for literature searches or HTA submissions Conference proceedings: since 2020	Conference proceedings and SLRs/NMAs published prior to 2020
Language	• English language for literature searches, conference proceedings, and HTA submissions • German, French, Dutch, and Swedish for HTA submissions to the German Federal Joint Committee, French National Health Authority, Dutch National Health Care Institute, and the Dental and Pharmaceutical Benefits Agency in Sweden, respectively	Other non-English language evaluations

ALK anaplastic lymphoma kinase, *EGFR* epidermal growth factor receptor, *ESMO* European Society for Medical Oncology, *HTA* health technology assessment, *IO* immuno-oncology, *NA* not applicable, *NCCN* National Comprehensive Cancer Network, *NMAs* network meta-analyses, *NSCLC* non-small cell lung cancer, *PD-L1* programmed death-ligand 1, *SLRs* systematic literature reviews, *TKIs* tyrosine kinase inhibitors

or metastatic [stage IV] NSCLC that have not previously received systemic treatment for locally advanced or metastatic disease), it was appropriate that only two of the economic evaluations considered multiple applications.

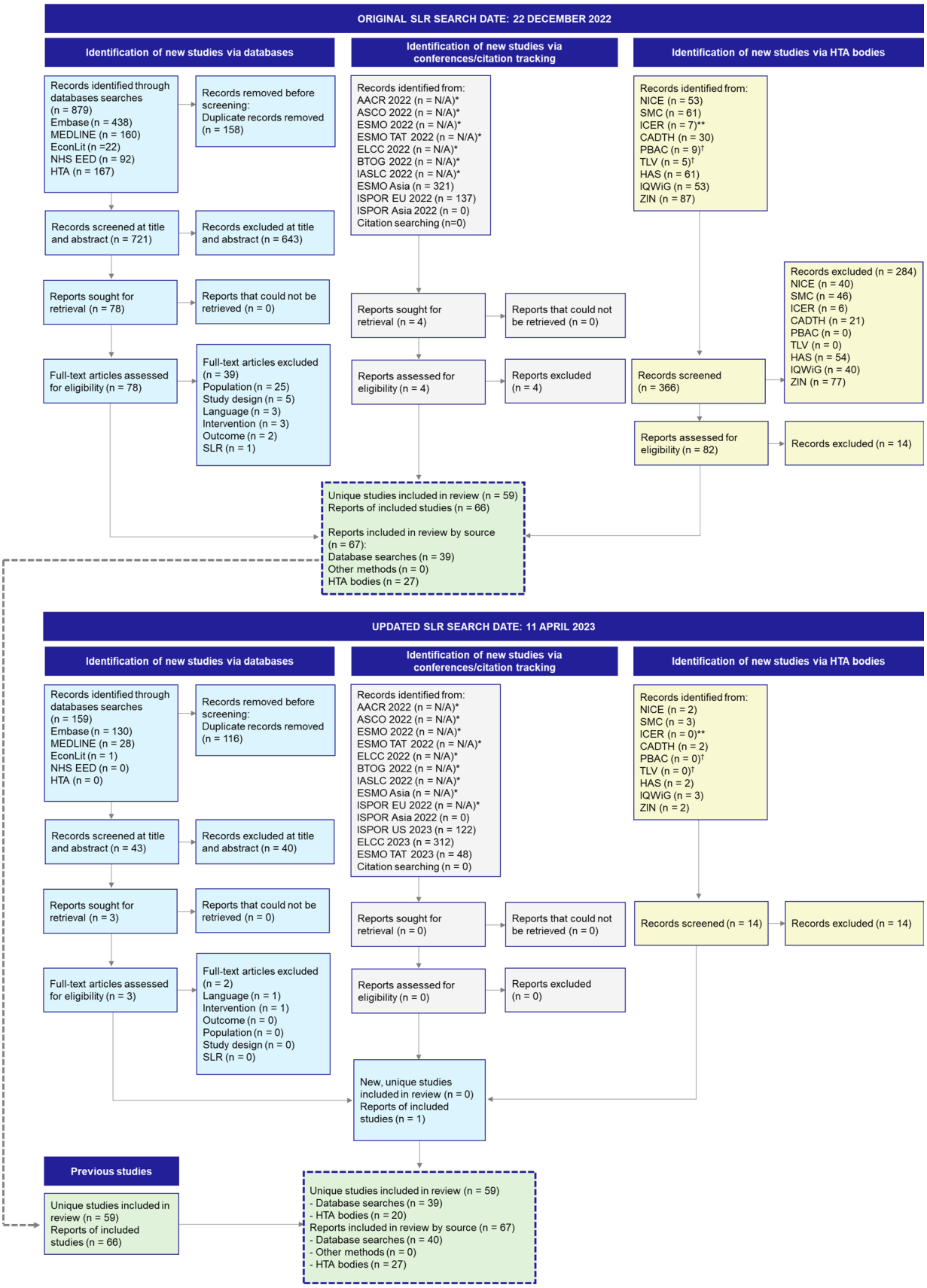
All 59 studies included an *EGFR* TKI as an intervention; this was considered appropriate given the focus of the identified studies in patients harboring an *EGFR* mutation. The most frequently evaluated interventions were osimertinib ($n = 18$) [30, 32, 34, 35, 38, 40, 44, 47, 50, 51, 55, 62, 68, 71, 73, 78, 83, 88], dacomitinib ($n = 14$) [31, 32, 40, 42, 43, 47, 52, 53, 63, 67, 72, 74, 82, 87], afatinib ($n = 17$) [32, 33, 36, 39, 40, 45, 46, 56, 57, 59, 65, 66, 69, 70, 77, 80, 86], gefitinib ($n = 12$) [33, 37, 40, 41, 49, 50, 54, 65, 69, 75, 81, 84], and erlotinib ($n = 12$) [32, 40, 50, 57, 58, 60, 64, 65, 69, 76, 79, 85]. Ramucirumab, an immunotherapy, was included in a combination treatment arm with erlotinib in one economic evaluation [48]; the rationale in the investigation of this treatment was to support policy decision toward its listing in China [48]. Twelve studies [32, 33, 40, 46, 47, 49, 50, 57, 62, 64, 65, 69] had a primary aim to evaluate multiple first-line treatments.

The most common comparators among the 59 studies reporting on an economic evaluation in locally advanced NSCLC patients harboring an *EGFR* mutation were *EGFR* TKIs ($n = 35$) [30–32, 34–36, 38, 41–45, 48, 51–55, 59, 61, 63, 67, 68, 71–74, 78, 80, 82, 83, 85–88], platinum-based chemotherapy ($n = 12$) [49, 56, 58, 60, 65, 66, 75–77, 79, 81, 84], or either *EGFR* TKIs or platinum-based chemotherapies evaluated in the same model ($n = 5$) [37, 39, 57, 62, 70]. Seven studies did not distinguish a reference comparator but evaluated multiple first-line treatments [33, 40, 46, 47, 50, 64, 69]. Among the 20 HTA submissions, the comparator of choice transitioned from platinum-based chemotherapy to a TKI, as TKIs became the standard of care—all new technologies submitted to a HTA agency after 2016 evaluated against a TKI only ($n = 9$) [71–74, 78, 82, 83, 87, 88] (Fig. 3). Twenty-eight studies did not state the rationale for the choice of comparator [30, 33, 35, 36, 38, 39, 41–43, 45, 46, 48, 52, 54, 56–63, 65–68, 72, 76]. In the remaining 31 studies, comparators were selected to reflect standard of care, which was defined as commonly used regimens or licensed treatment [31, 32, 34, 37, 40, 44, 47, 49–51, 53, 55, 64, 69–71, 73–75, 77–88]. Only one of these studies also included comparator regimens that were investigational in order to provide a comprehensive picture of possible treatment options [40]. The use of economic evaluations relying on 'commonly used' treatments to select comparator choices in a new mutation subgroup (i.e., patients harboring *EGFR* mutations) is reflective of the treatment paradigm shift from standard chemotherapy in an all-comer population, to new treatment options for *EGFR* TKIs in a new mutation subgroup. The use of investigational agents as comparators that do not reflect standard of care in the case of one study [40] has limited use in the context of clinical/policy decision making.

Most were cost-utility analyses ($n = 52$) [30–32, 34–44, 46–50, 52, 53, 55–79, 81–95], four were cost-effectiveness analyses [33, 45, 51, 54], one was a cost-minimization analysis [80], and two (both of which were HTA submissions) presented both a cost-utility and cost-minimization analysis depending on the comparator [76, 81]. The choice of model type was only reported in two studies that used a cost-minimization analysis, to justify that model type, given there were no statistically significant differences in efficacy and safety between treatment options [80, 81]. Among the cost-effectiveness analyses, incremental cost-effectiveness ratio by median survival time [45], life-years [54], and overall and progression-free survival [33, 51] were presented; however, no rationale was provided for why these outcomes were selected.

3.2 Model Structure

The model structures for each study are summarized in Table 4.


ORIGINAL SLR SEARCH DATE: 22 DECEMBER 2022
Identification of new studies via databases
Identification of new studies via conferences/citation tracking
Identification of new studies via HTA bodies
Records identified through databases searches (n = 879) Embase (n = 438) MEDLINE (n = 160) EconLit (n =22) NHS EED (n = 92) HTA (n = 167)
Records removed before screening: Duplicate records removed (n = 158)
Records identified from: AACR 2022 (n = N/A)* ASCO 2022 (n = N/A)* ESMO 2022 (n = N/A)* ESMO TAT 2022 (n = N/A)* ELCC 2022 (n = N/A)* BTOG 2022 (n = N/A)* IASLC 2022 (n = N/A)* ESMO Asia (n = 321) ISPOR EU 2022 (n = 137) ISPOR Asia 2022 (n = 0) Citation searching (n=0)
Records identified from: NICE (n = 53) SMC (n = 61) ICER (n = 7)** CADTH (n = 30) PBAC (n = 9)† TLV (n = 5)† HAS (n = 61) IQWiG (n = 53) ZIN (n = 87)
Records screened at title and abstract (n = 721)
Records excluded at title and abstract (n = 643)
Reports sought for retrieval (n = 78)
Reports that could not be retrieved (n = 0)
Reports sought for retrieval (n = 4)
Reports that could not be retrieved (n = 0)
Records excluded (n = 284) NICE (n = 40) SMC (n = 46) ICER (n = 6) CADTH (n = 21) PBAC (n = 0) TLV (n = 0) HAS (n = 54) IQWiG (n = 40) ZIN (n = 77)
Full-text articles assessed for eligibility (n = 78)
Full-text articles excluded (n = 39) Population (n = 25) Study design (n = 5) Language (n = 3) Intervention (n = 3) Outcome (n = 2) SLR (n = 1)
Reports assessed for eligibility (n = 4)
Reports excluded (n = 4)
Records screened (n = 366)
Reports assessed for eligibility (n = 82)
Records excluded (n = 14)
Unique studies included in review (n = 59) Reports of included studies (n = 66)
Reports included in review by source (n = 67): Database searches (n = 39) Other methods (n = 0) HTA bodies (n = 27)
UPDATED SLR SEARCH DATE: 11 APRIL 2023
Identification of new studies via databases
Identification of new studies via conferences/citation tracking
Identification of new studies via HTA bodies
Records identified through databases searches (n = 159) Embase (n = 130) MEDLINE (n = 28) EconLit (n = 1) NHS EED (n = 0) HTA (n = 0)
Records removed before screening: Duplicate records removed (n = 116)
Records identified from: AACR 2022 (n = N/A)* ASCO 2022 (n = N/A)* ESMO 2022 (n = N/A)* ESMO TAT 2022 (n = N/A)* ELCC 2022 (n = N/A)* BTOG 2022 (n = N/A)* IASLC 2022 (n = N/A)* ESMO Asia (n = N/A)* ISPOR EU 2022 (n = N/A)* ISPOR Asia 2022 (n = 0) ISPOR US 2023 (n = 122) ELCC 2023 (n = 312) ESMO TAT 2023 (n = 48) Citation searching (n = 0)
Records identified from: NICE (n = 2) SMC (n = 3) ICER (n = 0)** CADTH (n = 2) PBAC (n = 0)† TLV (n = 0)† HAS (n = 2) IQWiG (n = 3) ZIN (n = 2)
Records screened at title and abstract (n = 43)
Records excluded at title and abstract (n = 40)
Reports sought for retrieval (n = 3)
Reports that could not be retrieved (n = 0)
Reports sought for retrieval (n = 0)
Reports that could not be retrieved (n = 0)
Records screened (n = 14)
Records excluded (n = 14)
Full-text articles assessed for eligibility (n = 3)
Full-text articles excluded (n = 2) Language (n = 1) Intervention (n = 1) Outcome (n = 0) Population (n = 0) Study design (n = 0) SLR (n = 0)
Reports assessed for eligibility (n = 0)
Reports excluded (n = 0)
New, unique studies included in review (n = 0) Reports of included studies (n = 1)
Previous studies
Unique studies included in review (n = 59) Reports of included studies (n = 66)
Unique studies included in review (n = 59) - Database searches (n = 39) - HTA bodies (n = 20) Reports included in review by source (n = 67) - Database searches (n = 40) - Other methods (n = 0) - HTA bodies (n = 27)

◂**Fig. 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. *These conferences were searched as part of the original SLR. **Not an HTA body. †Search by intervention (brand and generic name) since it is not possible to search by indication. *AACR* American Association for Cancer Research, *ASCO* American Society of Clinical Oncology, *BTOG* British Thoracic Oncology Group, *CADTH* Canadian Agency for Drugs and Technologies in Health, *ELCC* European Lung Cancer Congress, *ESMO* European Society for Medical Oncology, *EU* European Union, *HAS* French National Health Authority (Haute Autorité de Santé), *HTA* health technology assessment, *IASLC* International Association for the Study of Lung Cancer, *ICER* Institute for Clinical and Economic Review, *IQWiG* Federal Joint Committee (Gemeinsamer Bundesausschuss/Institute for Quality and Efficiency in Health Care), *ISPOR* The Professional Society for Health Economics and Outcomes Research, *NHS EED* National Health Service Economic Evaluations Database, *NICE* National Institute for Health and Care Excellence, *PBAC* Pharmaceutical Benefits Advisory Committee, *SLR* systematic literature review, *SMC* Scottish Medicines Consortium, *TAT* targeted anticancer therapies, *TLV* Dental and Pharmaceutical Benefits Agency (Tandvårds-och läkemedelsförmånsverket), *ZIN* National Health Care Institute (Zorginstituut Nederland)

Fifty-six of the 59 studies were deterministic [30–44, 46–50, 52, 53, 55–88] and three studies did not report structure type [45, 51, 54]. A similar number of studies used a Markov model ($n = 20$) [30, 33, 38, 40, 41, 47, 50, 57–62, 65, 68, 71, 75, 77, 81, 84] or a partitioned survival model ($n = 22$) [31, 32, 34, 36, 42–44, 46, 52, 53, 56, 67, 69, 70, 72, 73, 78, 82, 83, 86–88]. For the remaining studies, seven used a decision tree and Markov model ($n = 7$) [35, 39, 48, 49, 55, 63, 66], six of which depicted a schematic decision tree, followed by the Markov state transition model [35, 39, 49, 55, 66]. Other model structures included semi-Markov ($n = 2$ [79, 85]) or decision tree only ($n = 1$ [37]). The remaining seven economic evaluations did not clearly specify the model structure [45, 51, 54, 64, 74, 76, 80]. There was a gap in justification of the model structure chosen; 52 studies did not provide a rationale [30–43, 45–52, 54–66, 68–83, 85]. Of the seven studies that reported a rationale, six used a partitioned survival model and cited ease in construction/direct use of summary data from published Kaplan–Meier curves and representativeness of the trial data (progression-free survival and overall survival) [44, 88]; representativeness of the disease pathway (e.g., the chronic/metastatic nature of the disease, and treatment goal to avoid disease progression and prolong life) [44, 67, 87, 88]; and due to its use in other published economic evaluations in NSCLC and/or oncology more broadly [53, 86]. The other study that reported a rationale was a Markov model and provided justification for the structure as it was previously used to inform decision problems in lung cancer and reflected the natural progression of the disease [84]. For the studies that used a decision tree only and semi-Markov, no rationale was provided to confirm suitability of the structured used [37, 79, 85].

Of the studies that adopted a decision tree and semi-Markov model, two studies utilized the decision tree to present two strategies in regard to *EGFR* testing/screening [49, 66]. In both studies, patients who did not undergo *EGFR* testing were assigned to receive platinum-based chemotherapy, regardless of *EGFR* mutation status. Patients who underwent testing and tested positive for an *EGFR* mutation would receive an *EGFR* TKI, while those testing negative would receive platinum-based chemotherapy [49, 66]. Other studies that also adopted a decision tree used it as a basis for assigning different interventions to patients [35, 39, 48, 55, 63].

The majority of the 59 studies ($n = 46$) [30–37, 39–41, 44, 46–50, 52, 53, 55–61, 63, 65–70, 72–74, 76–79, 82, 83, 85–88] employed a three-health state model consisting of progression-free, progressive disease, and death. An additional three studies used a four-health state model including response, stable disease, disease progression and death (two of which were HTA submissions for gefitinib to NICE [84] and the Scottish Medicines Consortium [SMC] [81], and one for osimertinib for the CADTH [71]). In addition, two studies [38, 62] used a six-health state model as described in Table 4. Lastly, eight studies did not specify the number or description of the health states [42, 43, 45, 51, 54, 64, 75, 80]. Of the studies that used a four- or six-health state model, rationale was only provided in the HTA submission for gefitinib, which used health states to model the natural progression of advanced NSCLC [84].

Nearly half ($n = 28$) of the 59 studies used a 1-month cycle length (or 28/30 days) [30–32, 36, 39, 41, 44, 45, 47, 50, 53, 55–58, 63, 65, 71–73, 77, 78, 82–85, 87, 88], followed by 3 weeks (or 21 days) [$n = 10$] [35, 49, 59–62, 66, 67, 79, 84], 1 week ($n = 4$) [34, 38, 40, 69], and 2 weeks ($n = 1$) [48]. Sixteen economic evaluations did not report the cycle length [33, 37, 42, 43, 45, 51, 52, 54, 64, 68, 70, 74–76, 80, 81]. Rationale for choice of cycle length was not typically reported. However, the main justification noted included alignment with treatment schedules, as well as being long enough to reasonably detect meaningful differences in the interventions being compared.

Sixteen studies applied a half-cycle correction in the model [31, 32, 34, 38, 41, 48, 55, 56, 58, 73, 77, 84–88]; however, the method utilized was only stated in HTA submissions for dacomitinib [87] and osimertinib [88], in which the number of patients at the start and end of each cycle was averaged for costs and outcomes.

Time horizons modeled were 1 year ($n = 2$) [51, 80], 4 years ($n = 1$) [58], 5 years ($n = 10$) [44, 46, 56, 66, 70, 75–77, 79, 84], 7 years ($n = 1$) [72], 10 years ($n = 20$) [34–36, 38, 39, 49, 50, 55, 57, 59–63, 65, 67, 72, 78, 85, 86], 15 years ($n = 8$) [30–32, 42, 43, 53, 82, 87], and 20 years ($n = 4$) [68, 73, 83, 88]. Two studies each used two time horizons (5 and 10 years [47]; 3 and 5 years [33]), and six economic evaluations modeled a lifetime horizon but did not specify the number of years [40, 41, 48, 52,

Table 2 Study characteristics

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Shu et al., 2022 [55]	Chinese healthcare system	China; National Natural Science Foundation of China	Advanced or metastatic NSCLC *EGFR*m (ex19del and/or L858R); 1L	Osimertinib	Erlotinib or gefitinib (standard EGFR-TKI)	CUA	Costs, QALYs, ICER, INMB, INHB
Guan et al., 2022 [40]	UK NHS and the Chinese healthcare system	UK and China; National Natural Science Foundation of China	Advanced NSCLC *EGFR*m (mutation type NR); 1L	• Osimertinib • Dacomitinib • Afatinib • Erlotinib • Gefitinib • Icotinib • Afatinib + cetuximab • Erlotinib + bevacizumab • Gefitinib + PbCT • Gefitinib + PbCT • PfCT	NR	CUA	LYs, QALYs, costs, ICER, sequential ICER
Aguilar-Serra et al., 2022 [32]	Spanish National Health System	Spain; NR	Stage IIIB/IV NSCLC *EGFR*m (mutation type NR); 1L	• Erlotinib • Afatinib • Dacomitinib • Osimertinib	Gefitinib	CUA	Costs, LYs, QALYs, ICER
Wang et al., 2022 [61]	Chinese health system	China; NR	Stage IIIB/IV NSCLC or *EGFR* mutation recurrence (mutation type NR); 1L	Gefitinib + chemotherapy	Gefitinib	CUA	Costs, QALYs, ICER
Khoo and Gao, 2021 [44]	Australian healthcare system	Australia; NR	Advanced NSCLC *EGFR*-mutated; 1L	Osimertinib	Erlotinib or gefitinib (standard *EGFR*-TKI)	CUA	Costs, LYs, QALYs, ICER
You et al., 2021 [65]	Hong Kong public healthcare provider	Hong Kong; NR	Stage IIIB/IV NSCLC *EGFR*m (mutation type NR); 1L	• Afatinib • Erlotinib • Gefitinib	Cisplatin-pemetrexed	CUA	Costs, QALYs, ICER
Li et al., 2021 [47]	Chinese healthcare system	China; Nation Key Research and Development Program of China	Advanced NSCLC *EGFR*m (mutation type NR); 1L	• Dacomitinib • Osimertinib • *EGFR*-TKI • Bevacizumab + erlotinib • Gefitinib + carboplatin + pemetrexed • Pemetrexed + carboplatin, gefitinib	• Gefitinib • *EGFR*-TKI • Erlotinib • Carboplatin-pemetrexed	CUA	Costs, QALY, ICER, ACER

Table 2 (continued)

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Xu et al., 2021 [63]	Healthcare payer in the US and China	US and China; National Natural Science Foundation of China, China Medical Board, and the Joint Project between Southeast University and Nanjing Medical University	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Dacomitinib	Gefitinib	CUA	Costs, QALYs, ICER
Zhang et al., 2021 [67]	US payer	US; NR	Stage IIIB/IV NSCLC *EGFR*m (mutation type NR); 1L	Dacomitinib	Gefitinib	CUA	Costs, LYs, QALYs, ICER
Nilsson et al., 2021 [53]	Healthcare provider	Sweden; Pfizer	Locally advanced or metastatic NSCLC *EGFR*m (mutation type NR); 1L	Dacomitinib	• Afatinib • Osimertinib	CUA	Costs, LYs, PFLYs, QALYs, ICER
Luo et al., 2021 [50]	Chinese medical system	China; NR	Advanced NSCLC *EGFR*m (mutation type NR); 1L	• Gefitinib • Afatinib • Erlotinib • Osimertinib	NR	CUA	Costs, LYs, QALYs, ICER
Aguilar-Serra et al., 2021 [31]	Spanish National Health System	Spain; NR	Advanced NSCLC *EGFR*m (ex19del and/or L858R); 1L	Dacomitinib	Gefitinib	CUA	Costs, QALYs, ICER
Liu et al., 2020 [48]	Chinese healthcare system	China; The Natural Science Foundation of Hunan Province (grant 2019JJ50864); the project of scientific research plan of health and Health Commission of Hunan Province in 2019 (grant B2019156)	Metastatic NSCLC *EGFR*m (mutation type NR); 1L	Ramucirumab + erlotinib	Intravenous placebo + erlotinib	CUA	Costs, LYs, QALYs, ICER
Aziz et al., 2020 [34]	Singapore healthcare system	Singapore; NR	Locally advanced or metastatic NSCLC *EGFR*m; 1L	Osimertinib	Erlotinib or gefitinib (standard *EGFR*-TKI)	CUA	Costs, LYs, QALYs, ICER
Arrieta et al., 2020 [33]	NR	Mexico; NR	Advanced NSCLC *EGFR*m (mutation type NR); 1L	• Afatinib • Erlotinib • Gefitinib	NR	CEA	Costs, PFS, OS, ICER

Table 2 (continued)

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Lasalvia et al., 2021 [46]	Colombian third-party payer	Colombia; Boehringer Ingelheim Colombia	Locally advanced or metastatic NSCLC *EGFR*m (ex19del and/or L858R); 1L	• Treatment sequences: • Afatinib to CT/osimertinib • 1G TKI to CT/osimertinib • Osimertinib to CT • 1G TKI: erlotinib + bevacizumab to • CT: carboplatin + pemetrexed or cisplatin + pemetrexed	NR	CUA	Costs, QALYs, ICER, INMB
Yang et al., 2020 [64]	Payer	Taiwan; Ministry of Science and Technology and National Cheng Kung University Hospital	Advanced NSCLC *EGFR*m (ex19del, L858R and other); 1L	Erlotinib	• Afatinib • Gefitinib	CUA	Costs, QALY, QALE, ICER
Wu et al., 2019 [62]	Public payer	US and China; none	Advanced NSCLC *EGFR*m (ex19del and/or L858R); 1L (and 1L followed by 2L)	1L osimertinib followed by pemetrexed + cisplatin chemotherapy when 1L osimertinib failed	• Comparator 1: 1L gefitinib or erlotinib followed by osimertinib for those with a positive T790 M mutation test or pemetrexed + cisplatin chemotherapy for those with a negative mutation test or when 1L osimertinib failed (referred to as 2L osimertinib strategy) • Comparator 2: gefitinib or erlotinib followed by pemetrexed + cisplatin chemotherapy when 1L gefitinib or erlotinib failed (referred to as SoC)	CUA	Costs, QALYs, ICER

Table 2 (continued)

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Cai et al., 2019 [35]	Chinese healthcare system	China; none	Locally advanced or metastatic NSCLC *EGFR*m (ex19del and/or L858R); 1L	Osimertinib	• 1L gefitinib/erlotinib and 2L osimertinib if T790M mutation-positive after failure of therapy (GE-T790M) • 1L and 2L gefitinib/erlotinib after failure of therapy (GE-chemotherapy)	CUA	Costs, QALYs, ICERs
Wang et al., 2018 [59]	Chinese healthcare	China; none	Locally advanced or metastatic NSCLC *EGFR*m (ex19del and/or L858R); 1L	Afatinib	Gefitinib	CUA	Costs, QALYs, ICER
Gu et al., 2019 [39]	Chinese healthcare system	China; Boehringer Ingelheim and the Fourth Round of the Three-year Action Plan on Public Health Discipline and Talent Program (Evidence-based Public Health and Health Economics, No. 15GWZK0901) from the Shanghai Health and Family Planning Commission	Advanced NSCLC patients with *EGFR*m (type of *EGFR* mutation NR); 1L	Afatinib	• 4-cycle chemotherapy based on pemetrexed + cisplatin • Gefitinib • Erlotinib	CUA	Costs, LYs, QALYs, ICER
You et al., 2019 [66]	Chinese payer	China; none	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Afatinib	Gemcitabine + cisplatin	CUA	Costs, QALYs, ICER
Aguilar-Serra et al., 2019 [30]	Spanish national health system	Spain; none	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Osimertinib	Erlotinib or gefitinib (standard *EGFR*-TKI)	CUA	Costs, QALYs, ICER
Ezeife et al., 2018 [38]	Public payer	Ontario, Canada; none	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Osimertinib	Gefitinib or afatinib (SoC)	CUA	Costs, LYs, QALYs, ICER
Tan et al., 2018 [56]	Healthcare payer	Singapore; none	Locally advanced or metastatic NSCLC *EGFR*m (mutation type NR); 1L	Afatinib	Pemetrexed + cisplatin	CUA	Costs, PFLYs, LYs, QALYs, ICER

Table 2 (continued)

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Kimura et al., 2018 [45]	Payers	Japan; none	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Afatinib	• Gefitinib • Erlotinib	CEA	Costs, MST, ICER
Chouaid et al., 2017 [36]	NR	France; NR	Advanced NSCLC *EGFR*m (ex19del and/or L858R); 1L	Afatinib	Gefitinib	CUA	Costs, QALYs, ICER
Lu et al., 2016 [49]	Chinese healthcare system	China; none	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Icotinib and gefitinib	Pemetrexed-containing chemotherapy	CUA	Costs, QALYs, ICER
Vergnenegre et al., 2016 [58]	Healthcare	France, Spain, Italy; none	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Erlotinib	Platinum-based doublet chemotherapy	CUA	Costs, QALYs, ICER
Ting et al, 2015 [57]	NR	US; none	Stage IIIB/IV NSCLC *EGFR*m (mutation type NR); 1L	• Erlotinib • Afatinib	• (Erlotinib vs.) • cisplatin-carboplatin • gemcitabine • (Afatinib vs.) • cisplatin-pemetrexed	CUA	Costs, QALYs, ICER
Wang et al., 2013 [60]	Chinese healthcare system	China; China National Natural Science Funds	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Erlotinib	Carboplatin-gemcitabine	CUA	Costs, LYs, QALYs, ICER
de Lima Lopes et al., 2012 [37]	NR	Asia; AstraZeneca	Advanced NSCLC *EGFR*m (mutation type NR); 1L	1L treatment with gefitinib followed by 2L chemotherapy	1L treatment with chemotherapy and 2L treatment with gefitinib	CUA	Costs, QALYs, ICER
Rungtivasuwan and Eiamprapaporn, 2022 [54]	NR	Thailand; none	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Gefitinib	• Original erlotinib • Generic erlotinib	CEA	LYs, ICER
Jin et al., 2021 [42]	Social	China; none	Locally advanced or metastatic NSCLC with *EGFR*m (exon 21 and L858R); 1L	Dacomitinib	• Gefitinib • Erlotinib • Icotinib • Afatinib • Osimertinib	CUA	Costs, LY, QALYs, ICER
Zhou and Jiang, 2020 [68]	NR	China; NR	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Osimertinib	Gefitinib	CUA	Costs, QALYs, ICER
Miguel et al., 2020 [52]	Payers	Portugal; NR	Locally advanced or metastatic NSCLC with *EGFR*m; 1L	Dacomitinib	Gefitinib	CUA	Costs, LYs, QALYs, ICER

Table 2 (continued)

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Machín et al., 2020 [51]	NR	Spain; none	Advanced NSCLC *EGFR*m (mutation type NR); 1L	Osimertinib	• Erlotinib • Gefitinib • Afatinib	CEA	Costs, PFS, ICER
Jin et al., 2020 [43]	Social	China; NR	Locally advanced or metastatic NSCLC with *EGFR*m (mutation type NR); 1L	Dacomitinib	• Gefitinib • Erlotinib • Icotinib • Afatinib • Osimertinib	CUA	Costs, LYs, QALY, ICER
Holleman et al., 2020 [41]	Social perspective	Netherlands; none	Stage IIIB/IV NSCLC *EGFR*m (ex19del and/or L858R); 1L	Gefitinib	• Erlotinib • Afatinib • Osimertinib	CUA	Costs, LYs, QALYs, ICERs
Osimertinib NICE submission, 2020 [88]	NHS/PSS	England and Wales; AstraZeneca	Locally advanced or metastatic NSCLC *EGFR*m (ex19del and/or L858R); 1L	Osimertinib	• Erlotinib • Gefitinib • Afatinib	CUA	Costs, LYs, QALYs, ICER
Dacomitinib NICE submission, 2019 [87]	NHS/PSS	England and Wales; Pfizer	Locally advanced or metastatic NSCLC *EGFR*m (exon 19 deletion and L858R); 1L	Dacomitinib	• Afatinib • Erlotinib • Gefitinib	CUA	Costs, LYs, QALYs, ICER
Afatinib NICE submission, 2014 [86]	NHS/PSS	England and Wales; Boehringer Ingelheim	Locally advanced or metastatic NSCLC *EGFR*m not previously treated with an *EGFR*-TKI; 1L	Afatinib	• Erlotinib • Gefitinib	CUA	Costs, LYs, QALYs, ICER
Erlotinib NICE submission, 2012 [85]	NHS/PSS	England and Wales; Roche	Advanced or metastatic NSCLC *EGFR*m; 1L	Erlotinib	Gefitinib	CUA	Costs, LYs, QALYs, ICER
Gefitinib NICE submission, 2010 [84]	NHS/PSS	England and Wales; AstraZeneca	Locally advanced or metastatic NSCLC *EGFR*m not previously treated with an *EGFR*-TKI; 1L	Gefitinib	• Gemcitabine + carboplatin • Paclitaxel + carboplatin (baseline comparator) • Vinorelbine + cisplatin • Gemcitabine + cisplatin	CUA	Costs, LYs, QALYs, ICER
Osimertinib SMC submission, 2022 [83]	NHS Scotland	Scotland; AstraZeneca	Locally advanced or metastatic NSCLC *EGFR*m; 1L	Osimertinib	• Afatinib • Erlotinib	CUA	ICER per QALY

Table 2 (continued)

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Dacomitinib SMC submission, 2019 [82]	NHS Scotland	Scotland; Pfizer	Locally advanced or metastatic NSCLC and *EGFR*m; 1L	Dacomitinib	• Gefitinib • Afatinib • Erlotinib	CUA	ICER per QALY
Gefitinib SMC submission, 2010 [original] [81]; [resubmission] [94]	NHS Scotland	Scotland; AstraZeneca	Locally advanced or metastatic NSCLC with *EGFR*m (activating mutations of *EGFR*-TKI); 1L	Gefitinib	Original submission: • Main comparator: • gemcitabine/carboplatin • Additional comparators: • gemcitabine/cisplatin; paclitaxel/carboplatin; vinorelbine/cisplatin; • pemetrexed/cisplatin Resubmission: • Afatinib • Erlotinib	CUA; CMA	Cost differences; ICER per QALY
Afatinib SMC submission (2014) [80]	NHS Scotland	Scotland; Boehringer Ingelheim	Locally advanced or metastatic NSCLC with *EGFR*m not previously treated with an *EGFR*-TKI; 1L	Afatinib	Erlotinib	CMA	Cost differences
Erlotinib SMC submission, 2012 [79]	NHS Scotland	Scotland; Roche	Locally advanced or metastatic NSCLC with *EGFR*m; 1L	Erlotinib	Platinum-based doublet regimens (combination of gemcitabine, vinorelbine, docetaxel, paclitaxel or pemetrexed with cisplatin or carboplatin)	CUA	ICER per QALY
Osimertinib PBAC submission [original, 2019] [78]; [resubmission, 2020] [93]	Clinical	Australia; AstraZeneca	Locally advanced or metastatic NSCLC with *EGFR*m; 1L	Osimertinib	• Erlotinib • Gefitinib	CUA	Costs, LYs, QALYs, ICER

Table 2 (continued)

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Afatinib PBAC submission [original, 2013] [77]; [resubmission, 2015] [92]	Clinical	Australia; Boehringer Ingelheim	• Original submission: Locally advanced or metastatic NSCLC patients with *EGFR*m; 1L • Resubmission: Locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified NSCLC with *EGFR* exon 19 deletions	Afatinib	• Original submission: cisplatin/pemetrexed, cisplatin/gemcitabine • Resubmission: erlotinib, gefitinib	CUA	Costs, LYs, QALYs, ICER
Erlotinib PBAC submission [original, 2012] [76]; [resubmission, 2013] [90]	Clinical	Australia; Roche	Locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified NSCLC with EGFRm; 1L	Erlotinib	• Original submission: platinum-based doublet chemotherapy • Resubmission: platinum-based doublet chemotherapy (carboplatin and gemcitabine), gefitinib	CUA; CMA	ICER per QALY
Gefitinib PBAC submission [original, 2010] [75]; [first resubmission, 2012] [89]; [second resubmission, 2013] [91]	Clinical	Australia; AstraZeneca	• Original submission: Locally advanced or metastatic NSCLC (stage IIIb/IV) with *EGFR*m (type of *EGFR*m+ NR) 1L • First resubmission: Locally advanced or metastatic NSCLC with *EGFR*m (exon 19 deletions, exon 21 L858R or *EGFR*m in tumor material); 1L • Second resubmission: Locally advanced or metastatic NSCLC with *EGFR*m (exon 19 deletions, exon 21 L858R or *EGFR*m in tumor material); 1L	Gefitinib	• Original submission: carboplatin and gemcitabine • carboplatin and paclitaxel • First and second resubmission: carboplatin and paclitaxel	CUA	ICER per QALY

Table 2 (continued)

Study, year	Perspective	Country; sponsor	Population	Interventions	Comparators	Type of economic analysis	Model outcomes
Dacomitinib TLV submission, 2019 [74]	NR	Sweden; Pfizer	1L treatment of locally advanced or metastatic *EGFR*m NSCLC; 1L	Dacomitinib	• Gefitinib • Afatinib	CUA	ICER per QALY
Osimertinib ZIN submission [original, 2018]; [73]; [resubmission, 2020] [95]	Societal	Netherlands; AstraZeneca	Locally advanced or metastatic NCSLC without prior systemic therapy with activating *EGFR* mutation; 1L	Osimertinib	• Original submission: erlotinib, gefitinib, afatinib • Resubmission: standard EGFR TKIs	CUA	Costs, LYs, QALYs, ICER
Dacomitinib CADTH submission, 2019 [72]	Canadian public payer	Canada; Pfizer	1L treatment of locally advanced or metastatic NSCLC with *EGFR*-activating mutations; 1L	Dacomitinib	• Gefitinib • Afatinib • Erlotinib • Osimertinib (scenario analysis only)	CUA	Costs, QALYs, ICER
Osimertinib CADTH submission, 2019 [71]	Publicly funded healthcare payer	Canada; AstraZeneca	1L treatment of locally advanced or metastatic NSCLC whose tumors have *EGFR* mutations; 1L	Osimertinib	• Gefitinib • Afatinib	CUA	Costs, QALYs, ICER
Afatinib CADTH submission, 2014 [70]	NR	Canada; Boehringer Ingelheim	1L treatment of *EGFR*m+, advanced NSCLC; 1L	Afatinib	• Pemetrexed/cisplatin • Gefitinib	CUA	Costs, QALYs, ICER
Institute for Clinical and Economic Review report, 2016 [69]	Health system	US; (1) Boehringer Ingelheim (2) AstraZeneca (3) Genentech	*EGFR*+ advanced NSCLC; 1L	• Afatinib • Gefitinib • Erlotinib	Cisplatin and pemetrexed	CUA	Costs, LYs, QALYs, ICER

1L first-line, *2L* second-line, *ACER* average cost-effectiveness ratio, *CADTH* Canadian Agency for Drugs and Technologies in Health, *CEA* cost-effectiveness analysis, *CMA* cost-minimization analysis, *CT* chemotherapy, *CUA* cost-utility analysis, *EGFR*, epidermal growth factor receptor, *EGFRm* epidermal growth factor receptor mutation, *ICER* incremental cost-effectiveness ratio, *INHB* incremental net health benefit, *INMB* incremental net monetary benefit, *LYs* life-year, *m+* mutation-positive, *MST* median survival time, *NHS* National Health Service, *NICE* National Institute for Health and Care Excellence, *NR* not reported, *NSCLC* non-small cell lung cancer, *OS* overall survival, *PBAC* Pharmaceutical Benefits Advisory Committee, *PbCT* pemetrexed-based chemotherapy, *PfCT* pemetrexed-free chemotherapy, *PFLYs* progression-free life-year, *PFS* progression-free survival, *PSS* Personal Social Services, *QALE* quality-adjusted life expectancy, *QALYs* quality-adjusted life-years, *SMC* Scottish Medicines Consortium, *SoC* standard of care, *TKI* tyrosine kinase inhibitor, *TLV* Dental and Pharmaceutical Benefits Agency, *ZIN* Zorginstituut Nederland

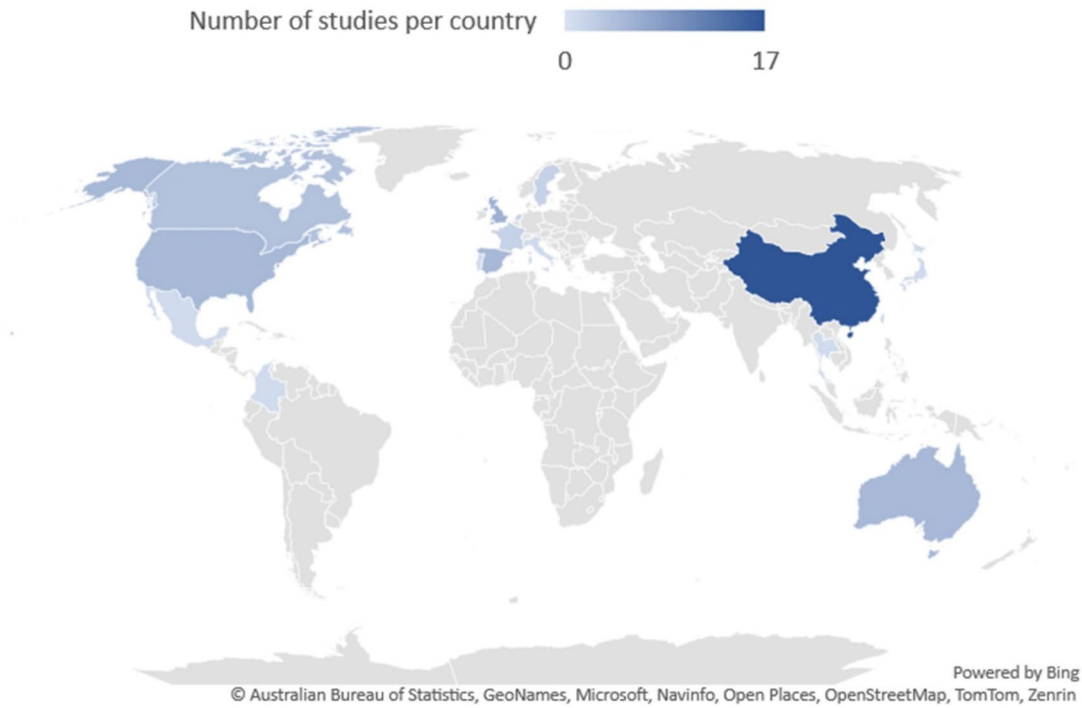


Fig. 2 World map of economic evaluations in patients with non-small cell lung cancer harboring epidermal growth factor receptor mutations

64, 69]. The remaining studies did not report any details on the time horizon ($n = 5$) [37, 45, 54, 74, 79]. Among the studies that used a lifetime horizon and specified the length of years, the range was between 5 and 20 years. Justification for the time horizon was infrequently reported, but usually aligned with the maximum life expectancy and/or nature of NSCLC, and was sufficiently long enough to capture all meaningful differences (which generally aligns with methods set out by HTA guidelines [e.g., NICE]) [98].

The most frequently reported cost discount rate was 3%, which was used for economic evaluations for China [47, 48, 55, 59, 60], Hong Kong [67], multiple European countries (France, Italy, and Spain) [58], Singapore [34, 56], Spain [30–32], Sweden [53], Taiwan [64], United States (US) [57, 67, 69] and the US and China [62, 63]. Other cost discount rates included 1.5% for Canada and The Netherlands [38, 71], 3.5% for the UK [40, 84–88], 4% France [36] and Netherlands [41, 73], and 5% for Australia, China, Colombia, Mexico, and Portugal [33, 39, 40, 42–44, 46, 49, 50, 52, 61–63, 66, 68, 77, 92]. A 0% discount rate was used in one economic evaluation for Asia [37], and discount rate was not reported in five studies [45, 51, 54, 70, 72, 74–83]. In two studies based in The Netherlands [41, 95], a 5% discount rate was applied for costs, but 1.5% for outcomes, in accordance with Dutch guidelines. In one study [50] in which a discount rate (5%) was only applied to costs, it was unclear if outcomes were also discounted; no justification was provided. Generally, however, studies applied the same discount rate for both costs and outcomes in accordance with local HTA guidelines.

Utilities were generally sourced from literature (secondary sources included longitudinal cohort studies and other cost-effectiveness models) or trial data and were applied to health states, although this is inferred. In three studies [47, 57, 84], utilities were applied for the delivery of treatment (oral vs. intravenous). Disutilities were also sourced from published literature and were typically applied as a utility decrement (utility values adjusted). Disutilities were explicitly not included in the base-case analysis of two studies, one in which the stated rationale was to avoid double-counting [87] and the other that stated treatment-specific utility values would have accounted for this already [63]. No rationale was provided in the remaining two studies [44, 55]. No studies reported on applying age-related disutilities.

3.3 Uncertainty

Sensitivity analyses, including probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OWSA), were described in 47 of the 59 economic evaluations [30–36, 38–44, 46–50, 52, 53, 55, 56, 58–69, 71–73, 77, 78, 82–88]. The most common parameters tested in the PSA and OWSA were costs, efficacy inputs such as hazard ratios, utility, disutility, as well as routine care frequency, treatment durations, and discount rates. Justifications provided on the upper/

Table 3 Conceptualization

Study, year	Objective	Audience	Intended use	Model type	Application
Shu et al., 2022 [55]	To evaluate the economics of osimertinib versus first-generation *EGFR*-TKIs (gefitinib or erlotinib) as 1L treatment of untreated *EGFR*m advanced NSCLC based on the FLAURA trial results from the perspective of the Chinese healthcare system	Medical decision makers	To support treatment decisions	Deterministic	Single-use
Guan et al., 2022 [40]	To comprehensively analyze the cost effectiveness of the 12 1L treatments including 6 *EGFR*-TKIs (osimertinib, dacomitinib, afatinib, erlotinib, gefitinib, icotinib), 4 combination treatments (afatinib plus cetuximab, erlotinib plus bevacizumab, gefitinib plus pemetrexed-based chemotherapy, and gefitinib plus pemetrexed) pemetrexed-based chemotherapy, and pemetrexed-free chemotherapy, for patients with advanced *EGFR*m NSCLC	NR	NR	Deterministic	Single-use
Aguilar-Serra et al., 2022 [32]	To evaluate the cost-effectiveness of 1L treatments such as erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib, for patients diagnosed with stage IIIB/IV NSCLC harboring *EGFR* mutations, in the context of Spain	Medical decision makers	To promote sustainability of healthcare systems	Deterministic	Single-use
Wang et al., 2022 [61]	To examine the cost effectiveness of maintenance combination therapy versus monotherapy in NSCLC from a Chinese health system perspective	Medical decision makers	To promote sustainability of healthcare systems	Deterministic	Single-use
Khoo and Gao, 2021 [44]	To assess the cost effectiveness of osimertinib versus standard *EGFR*-TKIs, gefitinib or erlotinib, as 1L treatment for patients with *EGFR* mutation-positive advanced NSCLC in Australia from a healthcare system perspective	NR	NR	Deterministic	Single-use
You et al., 2021 [65]	To compare the *EGFR* mutation-guided target therapy versus empirical chemotherapy for 1L treatment of advanced NSCLC in the public healthcare setting of Hong Kong	NR	To support treatment decisions	Deterministic	Single-use

Table 3 (continued)

Study, year	Objective	Audience	Intended use	Model type	Application
Li et al., 2021 [47]	To conduct a cost-effectiveness analysis that measures different treatment schemes via multiple dimensions from the perspective of the Chinese health system, aiming to provide guidance for treatment decisions in clinical practice	NR	To support treatment decisions	Deterministic	Single-use
Xu et al., 2021 [63]	This study investigated the cost effectiveness of dacomitinib and gefitinib for the 1L treatment of advanced *EGFR*m+ NSCLC patients in the US and China	NR	NR	Deterministic	Single-use
Zhang et al., 2021 [67]	To evaluate the economics of dacomitinib and gefitinib in the 1L treatments for *EGFR*-positive advanced or metastatic NSCLC from a US payer perspective	NR	NR	Deterministic	Single-use
Nilsson et al., 2021 [53]	To evaluate the cost effectiveness of dacomitinib in the 1L treatment of *EGFR*m NSCLC in Sweden, compared with afatinib and osimertinib	NR	NR	Deterministic	Single-use
Luo et al., 2021 [50]	To evaluate the cost effectiveness of four TKIs, gefitinib, erlotinib, afatinib, and osimertinib (except for dacomitinib because of its unavailability in China) from the perspective of the Chinese medical systems	Medical decision makers	To support treatment decisions	Deterministic	Single-use
Aguilar-Serra et al., 2021 [31]	To assess the cost effectiveness of 1L treatment with dacomitinib compared with gefitinib in patients newly diagnosed with advanced NSCLC *EGFR*-positive in the context of Spain	Medical decision makers	To promote sustainability of healthcare systems	Deterministic	Single-use
Liu et al., 2020 [48]	To compare ramucirumab plus erlotinib with placebo plus erlotinib, from the perspective of Chinese healthcare	NR	To support policy/funding decisions	Deterministic	Single-use
Aziz et al., 2020 [34]	To evaluate the cost effectiveness of osimertinib compared with standard *EGFR* TKIs (erlotinib or gefitinib) for 1L treatment of locally advanced or metastatic *EGFR*-mutant NSCLC patients in Singapore	NR	To support policy/funding decisions	Deterministic	Single-use

Table 3 (continued)

Study, year	Objective	Audience	Intended use	Model type	Application
Arrieta et al., 2020 [33]	To retrospectively evaluate the cost effectiveness of three different TKIs (afatinib, erlotinib, and gefitinib) in patients with *EGFR*m NSCLC from a single tertiary-care medical center located at a developing country	NR	NR	Deterministic	Single-use
Lasalvia et al., 2021 [46]	To evaluate the cost effectiveness of afatinib as a 1L treatment in patients diagnosed with locally advanced or metastatic NSCLC with mutations of the *EGFR*	NR	NR	Deterministic	Single-use
Yang et al., 2020 [64]	Using real-world data of a tertiary hospital in Taiwan, this study attempted to directly compare the effectiveness and cost effectiveness of three 1L *EGFR*-TKIs	NR	NR	Deterministic	Single-use
Wu et al., 2019 [62]	To compare the cost effectiveness of three treatment strategies (standard chemotherapy using first-generation *EGFR*-TKI (gefitinib or erlotinib), 1L or 2L use of osimertinib, for patients newly diagnosed with advanced NSCLC with confirmed *EGFR* mutation	NR	To support policy/funding decisions	Deterministic	Multiple
Cai et al., 2019 [35]	To evaluate the cost effectiveness of osimertinib compared with gefitinib/erlotinib in the treatment of Chinese 1L and sequential therapy for advanced or metastatic *EGFR*m+ NSCLC	NR	To support policy/funding decisions	Deterministic	Single-use
Wang et al., 2018 [59]	To evaluate the economic benefits of afatinib vs. gefitinib	Medical decision makers	To support treatment decisions	Deterministic	Single-use
Gu et al., 2019 [39]	To compare the cost effectiveness of afatinib with traditional chemotherapy and other *EGFR*-TKIs (gefitinib and erlotinib) for 1L treatment of advanced NSCLC from the perspective of the Chinese health care system	Medical decision makers	To support treatment decisions	Deterministic	Single-use

Table 3 (continued)

Study, year	Objective	Audience	Intended use	Model type	Application
You et al., 2019 [66]	To develop a decision-analytic model and use it to evaluate the cost-effectiveness analysis of *EGFR* mutation testing followed by targeted individualized 1L afatinib treatment compared with no test and treatment with conventional chemotherapy from the perspective of Chinese payers	Medical decision makers; patients	NR	Deterministic	Single-use
Aguilar-Serra et al., 2019 [30]	To evaluate the ICER of osimertinib versus standard *EGFR*-TKIs (erlotinib and gefitinib) in order to determine which is the most efficient drug in 1L	Medical decision makers	To promote sustainability of healthcare systems	Deterministic	Single-use
Ezeife et al., 2018 [38]	To evaluate the cost-effectiveness analysis of osimertinib compared with standard of care *EGFR*-TKIs in patients with previously untreated *EGFR*m advanced NSCLC in the province of Ontario, Canada.	NR	NR	Deterministic	Single-use
Tan et al., 2018 [56]	To evaluate the cost effectiveness of afatinib vs. pemetrexed-cisplatin for 1L treatment of locally advanced or metastatic *EGFR* mutation-positive NSCLC to inform local drug subsidy decisions in Singapore	Medical decision makers	To support policy/funding decisions	Deterministic	Single-use
Kimura et al., 2018 [45]	To evaluate the economic superiority of afatinib to gefitinib and erlotinib as treatments for patients with advanced *EGFR*m+ NSCLC	NR	NR	NR	Single-use
Chouaid et al., 2017 [36]	To assess afatinib and gefitinib costs, with evaluation of the entire *EGFR*m+ population outcomes and those of each subgroup (del19 or L858R)	NR	NR	Deterministic	Single-use
Lu et al., 2016 [49]	To compare the economic outcomes of gene-guided 1L icotinib and gefitinib treatment with those of pemetrexed-containing chemotherapy for advanced NSCLC in the Chinese health care setting	Medical decision makers	NR	Deterministic	Single-use

Table 3 (continued)

Study, year	Objective	Audience	Intended use	Model type	Application
Vergnenegre et al., 2016 [58]	To conduct an economic analysis of 1L targeted therapy vs. 1L chemotherapy in patients with *EGFR*m NSCLC on the basis of individual data from the European erlotinib versus chemotherapy (EURTAC) trial over the entire treatment sequence until death or censorship	NR	NR	Deterministic	Single-use
Ting et al, 2015 [57]	To compare the cost effectiveness of erlotinib, afatinib, and cisplatin-pemetrexed for 1L treatment of advanced *EGFR*m+ NSCLC for the US	Medical decision makers	To support treatment decisions	Deterministic	Single-use
Wang et al., 2013 [60]	To evaluate the cost effectiveness of carboplatin-gemcitabine chemotherapy compared with erlotinib monotherapy as a 1L therapy for patients with *EGFR*m+ NSCLC	Medical decision makers	To promote sustainability of healthcare systems	Deterministic	Single-use
de Lima Lopes et al., 2012 [37]	To determine the cost effectiveness of *EGFR* mutation testing and 1L treatment with gefitinib followed by 2L chemotherapy for patients who have activating *EGFR* mutations, and chemotherapy followed by BSC for those who do not	NR	NR	Deterministic	Single-use
Rungtivasuwan and Eiamprapaporn, 2022 [54]	To determine the efficacy and cost effectiveness of each *EGFR*-TKI	NR	NR	NR	Single-use
Jin et al., 2021 [42]	To evaluate the cost effectiveness of dacomitinib vs. other TKI comparators (gefitinib, erlotinib, icotinib, afatinib and osimertinib) for locally advanced or metastatic non-small cell lung cancer with *EGFR* exon 21 L858R substitution mutation from the social perspective in China	NR	NR	Deterministic	Single-use
Zhou and Jiang, 2020 [68]	To evaluate the cost effectiveness of osimertinib as 1L and 2L therapy for EGFRm+ advanced NSCLC in China	NR	NR	Deterministic	Multiple
Miguel et al., 2020 [52]	To evaluate the cost effectiveness of dacomitinib vs. gefitinib for the 1L treatment of locally advanced or metastatic NSCLC with *EGFR*-activating mutations in Portugal	NR	NR	Deterministic	Single-use

Table 3 (continued)

Study, year	Objective	Audience	Intended use	Model type	Application
Machín et al., 2020 [51]	To evaluate the cost effectiveness of osimertinib in patients with mutated *EFGR* NSCLC compared with other TKIs	NR	NR	NR	Single-use
Jin et al., 2020 [43]	To evaluate the cost effectiveness of dacomitinib vs. other TKI comparators (gefitinib, erlotinib, icotinib, afatinib and osimertinib) for locally advanced or metastatic NSCLC with *EGFR*-activating mutations from the social perspective of China	NR	NR	Deterministic	Single-use
Holleman et al., 2020 [41]	To assess the cost effectiveness of 1L gefitinib, erlotinib, afatinib, and osimertinib in patients with stage IIIB/IV NSCLC harboring *EGFR* mutations (exon 19 deletion or exon 21 L858R mutation) in The Netherlands from a Dutch societal perspective	NR	NR	Deterministic	Single-use
Osimertinib NICE submission, 2020 [88]	To assess the cost and benefit of osimertinib compared with erlotinib, gefitinib or afatinib in patients with previously untreated NSCLC with *EGFR* mutations	Consultees and commentators	To support reimbursement decisions	Deterministic	Single-use
Dacomitinib NICE submission, 2019 [87]	To assess the cost and benefit of dacomitinib compared with erlotinib, gefitinib or afatinib in patients with previously untreated NSCLC with *EGFR* mutations	Consultees and commentators	To support reimbursement decisions	Deterministic	Single-use
Afatinib NICE submission, 2014 [86]	To assess the cost and benefit of afatinib compared with erlotinib and gefitinib in patients with previously untreated NSCLC with *EGFR* mutations	Consultees and commentators	To support reimbursement decisions	Deterministic	Single-use
Erlotinib NICE submission, 2012 [85]	To assess the cost and benefit of erlotinib compared with gefitinib in patients with previously untreated NSCLC with *EGFR* mutations	Consultees and commentators	To support reimbursement decisions	Deterministic	Single-use
Gefitinib NICE submission, 2010 [84]	To assess the cost and benefit of gefitinib compared with gemcitabine and carboplatin, paclitaxel and carboplatin, vinorelbine and cisplatin, and gemcitabine and cisplatin in patients with previously untreated NSCLC with *EGFR* mutations	Consultees and commentators	To support reimbursement decisions	Deterministic	Single-use

Table 3 (continued)

Study, year	Objective	Audience	Intended use	Model type	Application
Osimertinib SMC submission, 2022 [83]	To assess the cost and benefit of osimertinib compared with erlotinib or afatinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Dacomitinib SMC submission, 2019 [82]	To assess the cost and benefit of dacomitinib compared with gefitinib, afatinib and erlotinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Gefitinib SMC submission, 2010 [original] [81]; [resubmission] [94]	• Original submission: To assess the cost and benefit of gefitinib compared with gemcitabine/carboplatin, gemcitabine/cisplatin, paclitaxel/carboplatin, vinorelbine/cisplatin, pemetrexed/cisplatin in patients with previously untreated NSCLC with *EGFR* mutations • Resubmission: To assess the cost of gefitinib compared with afatinib and erlotinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Afatinib SMC submission (2014) [80]	To assess the cost of afatinib compared with erlotinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Erlotinib SMC submission, 2012 [79]	To assess the cost and benefit of erlotinib compared with pemetrexed/cisplatin in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Osimertinib PBAC submission [original, 2019] [78]; [resubmission, 2020] [93]	To assess the cost and benefit of osimertinib compared with erlotinib or gefitinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Afatinib PBAC submission [original, 2013] [77]; [resubmission, 2015] [92]	To assess the cost and benefit of afatinib compared with platinum-based doublet chemotherapy and no *EGFR* gene mutation testing in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use

Table 3 (continued)

Study, year	Objective	Audience	Intended use	Model type	Application
Erlotinib PBAC submission [original, 2012] [76]; [resubmission, 2013] [90]	To assess the cost and benefit of erlotinib compared with platinum-based doublet chemotherapy and no *EGFR* gene mutation testing in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Gefitinib PBAC submission [original, 2010] [75]; [first resubmission, 2012]; [89] [second resubmission, 2013] [91]	To assess the cost and benefit of gefitinib compared with carboplatin + paclitaxel in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Dacomitinib TLV submission, 2019 [74]	To assess the cost and benefit of dacomitinib compared with erlotinib and gefitinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Osimertinib ZIN submission [original, 2018] [73]; [resubmission, 2020] [95]	To assess the cost and benefit of osimertinib compared with afatinib and gefitinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Dacomitinib CADTH submission, 2019 [72]	To assess the cost and benefit of dacomitinib compared with gefitinib, afatinib and erlotinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Osimertinib CADTH submission, 2019 [71]	To assess the cost and benefit of osimertinib compared with gefitinib or afatinib in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Afatinib CADTH submission, 2014 [70]	To assess the cost and benefit of single-agent therapy with afatinib compared with an appropriate comparator in patients with previously untreated NSCLC with *EGFR* mutations	NR	To support reimbursement decisions	Deterministic	Single-use
Institute for Clinical and Economic Review report, 2016 [69]	NR	NR	To support reimbursement decisions	Deterministic	Single-use

1L first-line, *2L* second-line, *BSC* best supportive care, *CADTH* Canadian Agency for Drugs and Technologies in Health, *EGFR*, epidermal growth factor receptor; *EGFR*m epidermal growth factor receptor mutation, *ICER* incremental cost-effectiveness ratio, *m+* mutation-positive, *NICE* National Institute for Health and Care Excellence, *NR* not reported, *NSCLC* non-small cell lung cancer, *PBAC* Pharmaceutical Benefits Advisory Committee, *SMC* Scottish Medicines Consortium, *TKIs* tyrosine kinase inhibitors, *TLV* Dental and Pharmaceutical Benefits Agency, *ZIN* Zorginstituut Nederland

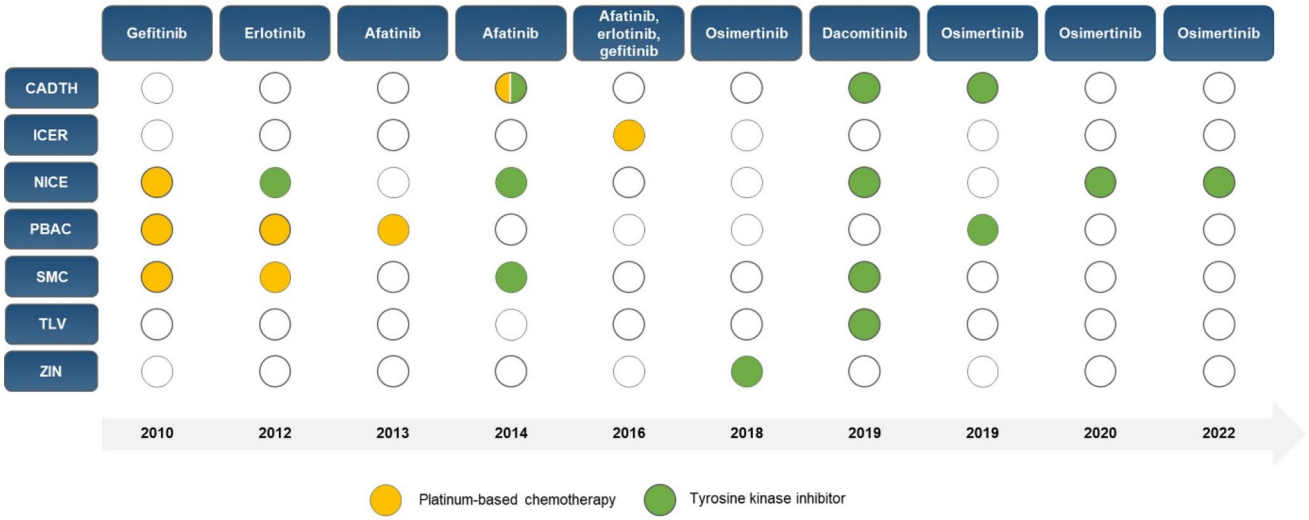


Fig. 3 Evolving comparator landscape among health technology assessment and/or value Assessments. *CADTH* Canadian Agency for Drugs and Technologies in Health, *ICER* Institute for Clinical and Economic Review, *NICE* National Institute for Health and Care Excellence, *PBAC* Pharmaceutical Benefits Advisory Committee, *SMC* Scottish Medicines Consortium, *TLV* Dental and Pharmaceutical Benefits Agency (Tandvårds-och läkemedelsförmånsverket), *ZIN* National Health Care Institute (Zorginstituut Nederland)

lower bounds used in the deterministic sensitivity analyses were based on 95% confidence intervals identified in the literature, or, in the absence of data from the literature, the variables used in the model were commonly changed (i.e., by more than one economic evaluation) by plus or minus 20% [30, 41, 50, 55, 60], 25% [34, 41, 44, 56, 73, 83, 88], or 50% of the mean (i.e., base-case value of the parameter being varied) [34, 40, 44, 53, 73, 86].

Scenario analyses were described in 25 of the 59 studies [34, 36, 37, 40, 41, 44, 46, 49, 53, 55, 56, 66, 69, 71–73, 77, 78, 82–88]. As depicted in Fig. 4, the most common parameters tested were the overall survival and progression-free survival parametric distributions modeling ($n = 10$) [34, 41, 44, 56, 73, 78, 83, 85, 87, 88]; health state utility values and disutility values associated with adverse events ($n = 9$) [34, 40, 44, 53, 73, 82, 84, 86, 87]; drug costs ($n = 8$) [34, 40, 48, 56, 66, 73, 78, 88]; subsequent treatment assumptions such as those receiving subsequent treatment and the distribution/regimens assumed in the subsequent line of therapy ($n = 7$) [40, 41, 78, 83, 86–88]; time horizon ($n = 7$) [44, 72, 73, 78, 82, 84, 88]; and rebate/patient access scheme for the intervention and comparators ($n = 4$) [30, 41, 50, 55, 60]. Only five studies (all HTA submissions) presented additional analyses where assumptions around treatment waning and relative treatment effect were explored [69, 71, 83–85]. The remaining parameters were each represented in three or fewer studies.

3.4 Model Validation

The distribution of validation across the models is depicted in Fig. 5.

Four types of validation methods were identified, including internal validation, external validation, cross validity and face validity. Thirty-two of the 59 studies reported at least one validation method [30, 32, 34, 38, 39, 41, 44, 45, 48, 49, 53, 55, 57–63, 65–67, 69, 70, 73, 78, 83–88]. Approximately one-quarter ($n = 15$) of the studies were cross-validated with other published cost-effectiveness models in the same indication, where the estimated quality-adjusted life-years, life-years, and incremental cost-effectiveness ratio were compared [30, 32, 34, 38, 39, 41, 44, 49, 53, 55, 58, 59, 62, 65, 66]. External validity was used in 16 studies, as extrapolated progression-free survival and/or overall survival curves were compared with trial data or real-world data [44, 48, 53, 55, 57, 60–63, 73, 83–88]. Face validity was used in nine studies, by means of clinical or health economics experts [53, 69, 70, 73, 78, 84, 85, 87, 88]. Ten studies reported to have undergone an internal validation, where model calculations, mathematical equations, and data sources were checked for consistency and accuracy [38, 53, 63, 67, 73, 84–88]. As shown in Fig. 5, 16 studies reported using a single validation method [30, 32, 34, 39, 41, 45, 48, 49, 57–61, 65–67], six studies used two methods [38, 44, 55, 62, 63, 86], five studies used three methods [69, 70, 78], and one study used four types of validation [53].

Table 4 Model structure

Study, year	Model approach	Model type	Health states	Structure justification	Time horizon	Discount rate	Cycle length
Shu et al., 2022 [55]	Decision tree and three health-state Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	Lifetime (10 years)	3.0%	1 month
Guan et al., 2022 [40]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	Lifetime (years not specified)	UK: 3.5% China: 5%	1 week
Aguilar-Serra et al., 2022 [32]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	15 years	3.0%	28 days
Wang et al., 2022 [61]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	5.0%	3 weeks
Khoo and Gao, 2021 [44]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	The main advantage of the PSM approach is the ease in constructing the model using summary data from the published KM charts. As the KM charts with summary data of PFS and OS for FLAURA were published, PSM was utilized in this study	5 years	5.0%	1 month (30 days)
You et al., 2021 [65]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	3.0%	1 month
Li et al., 2021 [47]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	5 and 10 years	3.0%	28 days and 21 days
Xu et al., 2021 [63]	Decision tree and Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	US: 3% China: 5%	28 days
Zhang et al., 2021 [67]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	According to the disease development process and published pharmacoeconomic model of NSCLC	10 years	3.0%	3 weeks

Table 4 (continued)

Study, year	Model approach	Model type	Health states	Structure justification	Time horizon	Discount rate	Cycle length
Nilsson et al., 2021 [53]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	Standard model structure in oncology; follows best modeling practices described by ISPOR and NICE DSU	Lifetime (15 years)	3.0%	28 days
Luo et al., 2021 [50]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	5.0% (costs only)	1 month
Aguilar-Serra et al., 2021 [31]	PSM	Probabilistic	1. Stable disease 2. Progressive disease 3. Death	NR	15 years	3.0%	28 days (4 weeks)
Liu et al., 2020 [48]	Decision tree and Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	Lifetime (years not specified)	3.0%	2 weeks
Aziz et al., 2020 [34]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	3.0%	1 week
Arrieta et al., 2020 [33]	Markov modeling	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	3 and 5 years	5.0%	NR
Lasalvia et al., 2021 [46]	PSM	Probabilistic	1. Stable disease in 1L 2. Progression to 2L 3. BSC and death	NR	5 years	5.0%	1 month
Yang et al., 2020 [64]	NR	Probabilistic	NR	NR	Lifetime (years not specified)	3.0%	NR
Wu et al., 2019 [62]	Markov model	Probabilistic	First model: 1. 1L progression-free without CNS metastases 2. 1L progression-free with CNS metastases 3. 2L progression-free without CNS metastases 4. 2L progression-free with CNS metastases 5. Progressed survival 6. Death Second model: 1. 1L progression-free 2. 2L progression-free 3. Progressed disease 4. Death	NR	10 years	US: 3% China: 5%	21 days

Table 4 (continued)

Study, year	Model approach	Model type	Health states	Structure justification	Time horizon	Discount rate	Cycle length
Cai et al., 2019 [35]	Decision tree and Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	NR	21 days
Wang et al., 2018 [59]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	3.0%	21 days
Gu et al., 2019 [39]	Decision tree and Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	5.0%	1 month
You et al., 2019 [66]	Decision tree and Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	5 years	5.0%	3 weeks
Aguilar-Serra et al., 2019 [30]	Markov model	Probabilistic	1. Stable disease 2. Progressive disease 3. Death	NR	15 years	3.0%	28 days
Ezeife et al., 2018 [38]	Markov model	Probabilistic	1. Progression free on 1L osimertinib 2. Post progression on 2L platinum doublet chemotherapy 3. Post progression on 3L docetaxel 4. Post progression on 4L immunotherapy 5. Post-progression on BSC 6. Death	NR	10 years	1.5%	1 week
Tan et al., 2018 [56]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	5 years	3.0%	1 month
Kimura et al., 2018 [45]	NR	NR	NR	NR	NR	NR	NR
Chouaid et al., 2017 [36]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	4.0%	1 month
Lu et al., 2016 [49]	Decision tree and Markov model	Probabilistic	1. Progression-free 2. Survival after progression 3. Death	NR	10 years	5.0%	21 days
Vergnenegre et al., 2016 [58]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	4 years	3.0%	1 month

Table 4 (continued)

Study, year	Model approach	Model type	Health states	Structure justification	Time horizon	Discount rate	Cycle length
Ting et al, 2015 [57]	Markov model	Probabilistic	1. Stage IIIB/IV disease 2. Progressed disease 3. Death	NR	Lifetime (10 years)	3.0%	1 month
Wang et al., 2013 [60]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	3.0%	3 weeks
de Lima Lopes et al., 2012 [37]	Decision-analytic model	Deterministic	1. Time in treatment state under chemotherapy 2. Time in treatment state under gefitinib	NR	NR	0.0%	NR
Rungtivasuwan and Eiamprapaporn, 2022 [54]	NR	NR	NR	NR	NR	NR	NR
Jin et al., 2021 [42]	PSM	Probabilistic	NR	NR	15 years	5.0%	NR
Zhou and Jiang, 2020 [68]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	20 years	5.0%	NR
Miguel et al., 2020 [52]	PSM	Probabilistic	1. Progression-free 2. Post progression 3. Death	NR	Lifetime (years not specified)	5.0%	NR
Machín et al., 2020 [51]	NR	NR	NR	NR	1 year	NR	NR
Jin et al., 2020 [43]	PSM	Probabilistic	NR	NR	Lifetime (15 years)	5.0%	NR
Holleman et al., 2020 [41]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	Lifetime (years not specified)	4.0%	30 days
Osimertinib NICE submission, 2020 [88]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	The PSM approach allows for direct modeling of PFS and OS (respectively, primary and secondary endpoints in FLAURA) based on trial observed events	Lifetime (20 years)	3.5%	30 days

Table 4 (continued)

Study, year	Model approach	Model type	Health states	Structure justification	Time horizon	Discount rate	Cycle length
Dacomitinib NICE submission, 2019 [87]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	Captures the chronic nature of the condition and two of the key objectives of treatment in NSCLC, namely avoiding disease progression and prolonging life. Commonly used in previous oncology NICE appraisals, including NSCLC	Lifetime (15 years)	3.5%	28 days
Afatinib NICE submission, 2014 [86]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	Both the model structure and health states are characteristic of modeling in metastatic oncology and have been used in previous HTA submissions	Lifetime (10 years)	3.5%	1 month
Erlotinib NICE submission, 2012 [85]	Semi-Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	3.5%	1 month
Gefitinib NICE submission, 2010 [84]	Markov model	Probabilistic	1. Treatment response 2. Stable disease 3. Disease progression 4. Death	The structure is similar to those previously used to inform decision problems related to the treatment of lung cancer. In the model, patients making one-way transitions from the progression-free health states to disease progression and ultimately death, which reflects the natural progression of aNSCLC	Lifetime (5 years)	3.5%	21 days
Osimertinib SMC submission, 2022 [83]	Markov model	Probabilistic	1. Progression-free 2. Progressed 3. Death	NR	Lifetime (20 years)	NR	30 days
Dacomitinib SMC submission, 2019 [82]	Partitioned survival model	Probabilistic	1. Progression-free survival 2. Post-progression survival 3. Death	NR	15 years	NR	28 days

Table 4 (continued)

Study, year	Model approach	Model type	Health states	Structure justification	Time horizon	Discount rate	Cycle length
Gefitinib SMC submission, 2010 [original] [81]; [resubmission] [94]	Markov model	Probabilistic	1. Response 2. Stable disease 3. Progressive disease 4. Death	NR	1 year	NR	NR
Afatinib SMC submission (2014) [80]	NR	Probabilistic	NR	NR	NR	NR	NR
Erlotinib SMC submission, 2012 [79]	Semi-Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	5 years	NR	21 days
Osimertinib PBAC submission [original, 2019] [78]; [resubmission, 2020] [93]	PSM (i.e. area under the curve)	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	10 years	NR	30 days
Afatinib PBAC submission [original, 2013] [77]; [resubmission, 2015] [92]	Markov model	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	5 years	5.0%	1 month
Erlotinib PBAC submission [original, 2012] [76]; [resubmission, 2013] [90]	NR	• Probabilistic	• Original submission: 1. Progression-free 2. Progressive disease 3. Death • Resubmission: 1. Unprogressed 2. Progressed 3. Death	NR	5 years	NR	NR
Gefitinib PBAC submission [original, 2010] [75]; [first resubmission, 2012] [89]; [second resubmission, 2013] [91]	Markov model	Probabilistic	NR	NR	5 years	NR	NR
Dacomitinib TLV submission, 2019 [74]	NR	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	NR	NR	NR
Osimertinib ZIN submission [original, 2018] [73]; [resubmission, 2020] [95]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	Lifetime (20 years)	4.0%	30 days
Dacomitinib CADTH submission, 2019 [72]	PSM	Probabilistic	1. Progression-free 2. Post-progressive 3. Death	NR	15 years	NR	28 days

Table 4 (continued)

Study, year	Model approach	Model type	Health states	Structure justification	Time horizon	Discount rate	Cycle length
Osimertinib CADTH submission, 2019 [71]	Markov model	Probabilistic	1. Progression-free (1L) 2. Progression-free (2L) 3. Progressed disease 4. Death	NR	10 years	1.5%	30 days
Afatinib CADTH submission, 2014 [70]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	5 years	NR	NR
Institute for Clinical and Economic Review report, 2016 [69]	PSM	Probabilistic	1. Progression-free 2. Progressive disease 3. Death	NR	Lifetime (years not specified)	3.0%	1 week

1L first-line, *2L* second-line, *3L* third-line, *4L* fourth line, *aNSCLC* advanced non-small cell lung cancer, *BSC* best supportive care, *CADTH* Canadian Agency for Drugs and Technologies in Health, *CNS* central nervous system, *DSU* Decision Support Unit, *HTA* health technology assessment, *ISPOR* The Professional Society for Health Economics and Outcomes Research, *KM* Kaplan–Meier, *NICE* National Institute for Health and Care Excellence, *NR* not reported, *NSCLC* non-small cell lung cancer, *OS* overall survival, *PBAC* Pharmaceutical Benefits Advisory Committee, *PFS* progression-free survival, *PSM* partitioned survival model, *SMC* Scottish Medicines Consortium, *TLV* Dental and Pharmaceutical Benefits Agency, *ZIN* Zorginstituut Nederland

3.5 Transparency

A summary of the transparency elements from included economic evaluations is provided in Table 5.

As depicted in Fig. 6, 24 of the economic evaluations were sponsored by the manufacturer of the intervention [37, 39, 46, 53, 69–88] (among these, 19 were identified from HTA documents [70–88]) and 24 did not state the sponsor [30–35, 38, 41, 42, 44, 45, 49–51, 54, 56–59, 61, 62, 65–67]. For the remaining economic evaluations, seven were sponsored by non-industry organizations (such as National Natural Science Foundation of China, and University Hospital in China) [40, 47, 48, 55, 60, 63, 64], and four did not report details on sponsorship [36, 43, 52, 68]. A non-technical summary was provided in 31 economic evaluations [30–41, 44, 46, 48, 50, 53, 55–62, 64–67, 71, 72], of which all documentation was freely available. Full technical documentation was available in 26 economic evaluations [30, 31, 35–41, 44, 45, 47, 48, 50, 58, 59, 63, 65–67, 69, 73, 85–88]. No models were available to review and use/replicate. TreeAge Pro® software (Williamstown, MA, USA) was used in 14 models [35, 37, 38, 44, 47, 50, 55, 57, 59, 61, 65–68], followed by Microsoft Excel® (Redmond, WA, USA) in 12 models [31, 34, 53, 56, 63, 69, 73, 84–88], and R was utilized in four models [33, 41, 60, 62]. The remainder ($n = 28$) did not report the type of software used [30, 32, 36, 39, 40, 42, 43, 46, 48, 49, 51, 52, 54, 58, 64, 70–72, 74–83].

In half of the 59 studies, sufficient documentation detailing the model structure, assumptions, and model inputs as well as data sources used were presented. Studies that did not provide adequate documentation were mainly congress abstracts and HTA submissions from agencies other than NICE, such as SMC and CADTH, or NICE submissions that were published more than a decade ago.

4 Discussion

Decision-analytic models are an integral component of the economic evaluation of new health technologies, providing a common framework to contextualize the comparative clinical and economic consequences of treatments, and inform healthcare reimbursement decision making [15]. The current study critically examined the approach and structure of economic evaluations used in previous published studies for therapies in untreated locally advanced or metastatic NSCLC harboring an *EGFR* mutation. This examination was conducted in five areas as recommended by Caro [18]—conceptualization, model structure, uncertainty, model validation, and transparency.

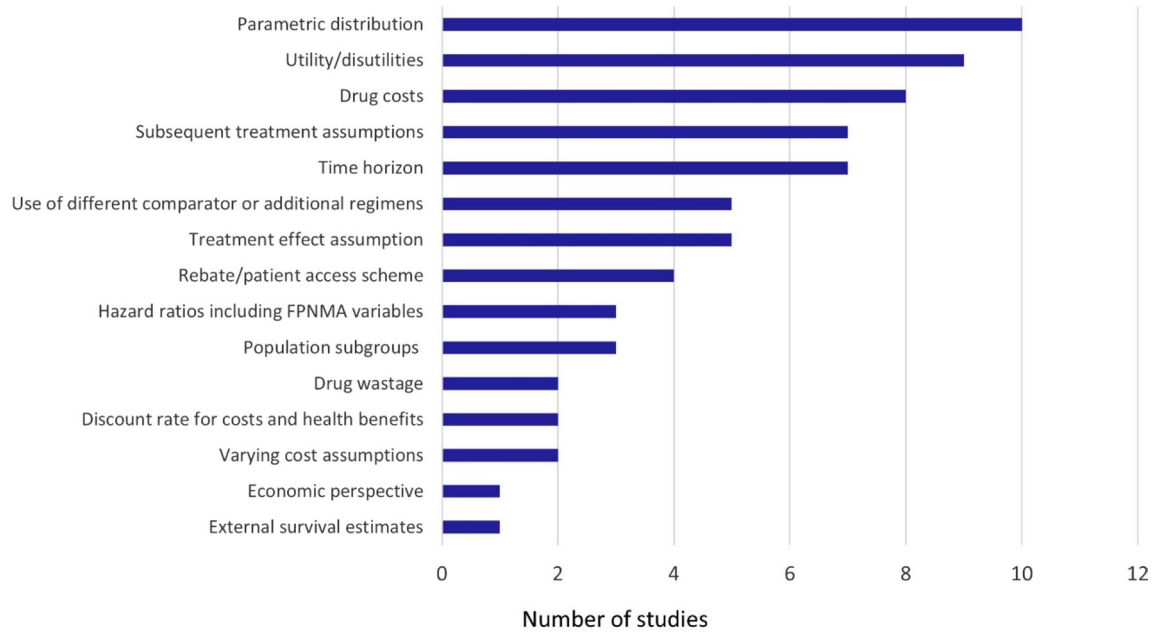
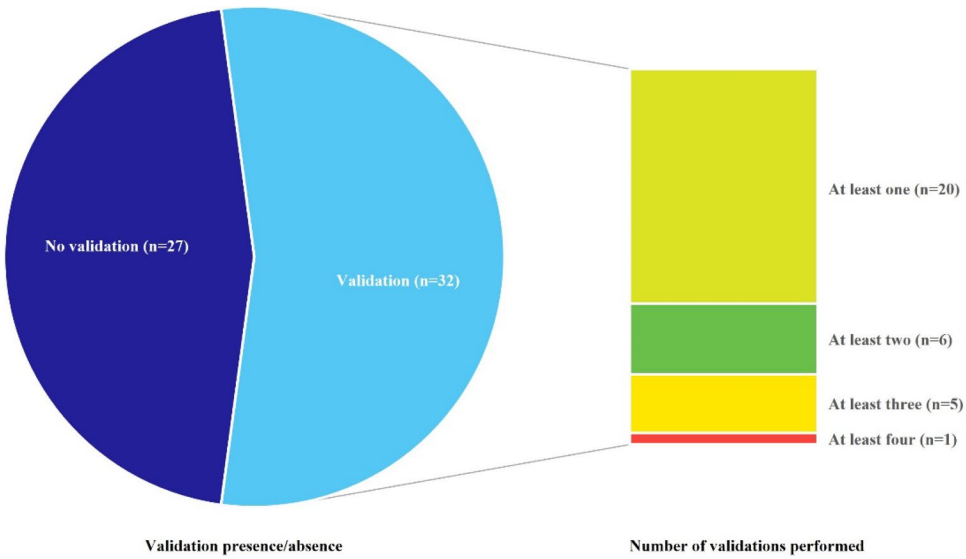


Fig. 4 Uncertainty parameters tested in scenario analysis. External survival estimates refers to the use of an external clinical trial to estimate the survival probability of patients in the chemotherapy arm. *FPNMA* fractional polynomial network meta-analysis

Fig. 5 Model validation



4.1 Conceptualization

Researchers should outline basic details regarding the conceptualization of their models, including the decision problem, target audience, model type and its rationale. Caro [18] also recommends stating whether models have a single- or multiple-application use. Not surprisingly, the majority of identified models were built for a single application, which aligns with the decision at a single point in the disease pathway for the population of interest. Almost 90% of the models were cost-utility analyses, which allow for the consideration of measuring how well treatments may impact clinical outcomes and patient's quality of life [99, 100]. This is also the standard established by many HTA and value assessment agencies and methods task forces [99, 100].

Table 5 Transparency

Study, year	Sponsor type	Plain-language summary availability	Technical documentation availability	Model available to review and use/replicate	Software
Shu et al., 2022 [55]	Non-industry	Yes	No	No	TreeAge Pro R
Guan et al., 2022 [40]	Non-industry	Yes	Yes	No	NR
Aguilar-Serra et al., 2022 [32]	None	Yes	No	No	NR
Wang et al., 2022 [61]	None	Yes	No	No	TreeAge Pro
Khoo and Gao, 2021 [44]	None	Yes	Yes	No	TreeAge Pro
You et al., 2021 [65]	None	Yes	Yes	No	TreeAge Pro
Li et al., 2021 [47]	Non-industry	No	Yes	No	TreeAge Pro
Xu et al., 2021 [63]	Non-industry	No	Yes	No	Microsoft Excel
Zhang et al., 2021 [67]	None	Yes	Yes	No	TreeAge Pro
Nilsson et al., 2021 [53]	Industry	Yes	No	No	Microsoft Excel
Luo et al., 2021 [50]	None	Yes	Yes	No	TreeAge Pro
Aguilar-Serra et al., 2021 [31]	None	Yes	Yes	No	Microsoft Excel
Liu et al., 2020 [48]	Non-industry	Yes	Yes	No	NR
Aziz et al., 2020 [34]	None	Yes	No	No	Microsoft Excel
Arrieta et al., 2020 [33]	None	Yes	No	No	R
Lasalvia et al., 2021 [46]	Industry	Yes	No	No	NR
Yang et al., 2020 [64]	Non-industry	Yes	No	No	NR
Wu et al., 2019 [62]	None	Yes	No	No	R
Cai et al., 2019 [35]	None	Yes	Yes	No	TreeAge Pro
Wang et al., 2018 [59]	None	Yes	Yes	No	TreeAge Pro
Gu et al., 2019 [39]	Industry	Yes	Yes	No	NR
You et al., 2019 [66]	None	Yes	Yes	No	TreeAge Pro
Aguilar-Serra et al., 2019 [30]	None	Yes	Yes	No	NR
Ezeife et al., 2018 [38]	None	Yes	Yes	No	TreeAge Pro
Tan et al., 2018 [56]	None	Yes	No	No	Microsoft Excel
Kimura et al., 2018 [45]	None	No	Yes	No	R EZR
Chouaid et al., 2017 [36]	NR	Yes	Yes	No	NR
Lu et al., 2016 [49]	None	No	No	No	NR
Vergnenegre et al., 2016 [58]	None	Yes	Yes	No	NR
Ting et al, 2015 [57]	None	Yes	No	No	TreeAge Pro
Wang et al., 2013 [60]	Non-industry	Yes	No	No	R
de Lima Lopes et al., 2012 [37]	Industry	Yes	Yes	No	TreeAge Pro
Rungtivasuwan and Eiamprapaporn, 2022 [54]	None	No	No	No	NR
Jin et al., 2021 [42]	None	No	No	No	NR
Zhou and Jiang, 2020 [68]	NR	No	No	No	TreeAge Pro
Miguel et al., 2020 [52]	NR	No	No	No	NR
Machín et al., 2020 [51]	None	No	No	No	NR
Jin et al., 2020 [43]	NR	No	No	No	NR
Holleman et al., 2020 [41]	None	Yes	Yes	No	R
Osimertinib NICE submission, 2020 [88]	Industry	No	Yes	No	Microsoft Excel
Dacomitinib NICE submission, 2019 [87]	Industry	No	Yes	No	Microsoft Excel
Afatinib NICE submission, 2014 [86]	Industry	No	Yes	No	Microsoft Excel
Erlotinib NICE submission, 2012 [85]	Industry	No	Yes	No	Microsoft Excel
Gefitinib NICE submission, 2010 [84]	Industry	No	No	No	Microsoft Excel
Osimertinib SMC submission, 2022 [83]	Industry	No	No	No	NR
Dacomitinib SMC submission, 2019 [82]	Industry	No	No	No	NR

Table 5 (continued)

Study, year	Sponsor type	Plain-language summary availability	Technical documentation availability	Model available to review and use/replicate	Software
Gefitinib SMC submission, 2010 [original] [81]; [resubmission] [94]	Industry	No	No	No	NR
Afatinib SMC submission (2014) [80]	Industry	No	No	No	NR
Erlotinib SMC submission, 2012 [79]	Industry	No	No	No	NR
Osimertinib PBAC submission [original, 2019] [78]; [resubmission, 2020] [93]	Industry	No	No	No	NR
Afatinib PBAC submission [original, 2013] [77]; [resubmission, 2015] [92]	Industry	No	No	No	NR
Erlotinib PBAC submission [original, 2012] [76]; [resubmission, 2013] [90]	Industry	No	No	No	NR
Gefitinib PBAC submission [original, 2010] [75]; [first resubmission, 2012] [89]; [second resubmission, 2013] [91]	Industry	No	No	No	NR
Dacomitinib TLV submission, 2019 [74]	Industry	No	No	No	NR
Osimertinib ZIN submission [original, 2018] [73]; [resubmission, 2020] [95]	Industry	No	Yes	No	Microsoft Excel
Dacomitinib CADTH submission, 2019 [72]	Industry	Yes	No	No	NR
Osimertinib CADTH submission, 2019 [71]	Industry	Yes	No	No	NR
Afatinib CADTH submission, 2014 [70]	Industry	No	No	No	NR
Institute for Clinical and Economic Review report, 2016 [69]	Industry	No	Yes	No	Microsoft Excel

CADTH Canadian Agency for Drugs and Technologies in Health, *NICE* National Institute for Health and Care Excellence, *NR* not reported, *PBAC* Pharmaceutical Benefits Advisory Committee, *SMC* Scottish Medicines Consortium, *TLV* Dental and Pharmaceutical Benefits Agency, *ZIN* Zorginstituut Nederland

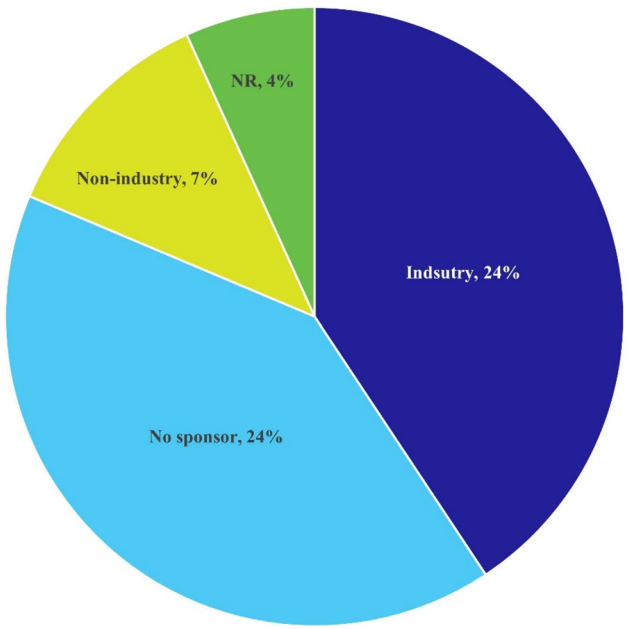


Fig. 6. Reported sponsors. NR, not reported

4.2 Model Structure

Although descriptions regarding model structure were consistently reported across the studies, justification for these choices were lacking in many studies. For example, rationales were infrequently reported for the choice of number of health states, time horizon, cycle length, and model type. Markov models and partitioned survival models each were used in more than one-half of the studies, with the others employing decision tree, semi-Markov, or a combination of approaches. Decision tree models are particularly well suited for modeling simple scenarios occurring over a short time horizon, limiting their suitability to adequately model the continuous changes in health-related quality of life and costs associated with oncology treatments over a longer time horizon. These limitations arise due to the inherent characteristics of decision tree models, which may impact their suitability and accuracy in capturing complex cost-effectiveness dynamics [101, 102]. In locally advanced (stage IIIB or IIIC) or metastatic (stage IV) NSCLC, with tumors harboring *EGFR* mutations, the use of a partitioned survival model or Markov model may be considered appropriate due to the common use of these structures in existing studies and the progressive nature of the disease. Partitioned survival models also have the advantage of the direct use

of endpoints measured in the clinical trial. While partition survival models do capture subsequent treatment costs, it is important to acknowledge their limitation in reflecting the impact of subsequent treatment on overall survival from a health outcome perspective. Other approaches offer additional advantages. For example, semi-Markov and Markov models are able to capture subsequent disease progressions across multiple stages or lines of treatments (i.e., transition from first-line progressed disease to second-line progressed disease, etc.). This may be more representative of real-world clinical practice, allowing for an accurate depiction of disease progression, especially given that drugs such as amivantamab could be available at later lines of therapy. None of the studies identified in this review reported the utilization of discrete event simulation (DES) models. DES models might offer enhanced flexibility in implementing complex models, resulting in a simpler structure compared with Markov models that require a large number of health states. However, it is important to note that these models are mainly used in the presence of baseline heterogeneity, continuous disease markers, time-varying event rates, and the need to assess the impact of prior events on subsequent event rates. In addition, a DES model might often require patient-level data, time, and expertise from both the reviewers and analysts [103]. As for modeling NSCLC harboring *EGFR* mutations, it has been demonstrated that more straightforward models such as Markov models or partition survival models are adequate for accurately assessing the cost and health benefits of treating patients with NSCLC harboring *EGFR* mutations. However, due to the potential significant heterogeneity in clinical and physiological manifestations of NSCLC, which can have an impact on outcomes, it becomes crucial to take into account and explain the influence of these heterogeneous groups on the reported differences in effects, and to select the appropriate model structure based on the decision problem.

In general, the appropriateness of the chosen cycle length can be guided by clinical judgment and available clinical trial data. In populations with NSCLC harboring *EGFR* mutations, cycle length should be determined based on the administration schedule of the treatment regimens considered in the economic evaluation, varying from a 1-week to a monthly cycle length. In the majority of the studies, the application of half-cycle correction was not reported; however, the application of a half-cycle correction is recommended, adjusting for potential bias in estimating costs and health outcomes by accounting for the timing of the transitions between health states. The selection of an appropriate time horizon for modeling NSCLC, harboring *EGFR* mutation, should consider the natural history of the disease and be long enough to capture all the relevant economic and health consequences of the interventions of interest (which may require extrapolation of clinical outcomes observed in clinical trials). Since NSCLC is a chronic disease, a lifetime time horizon may be necessary. Lastly, it is recommended that the choice of discount rates for costs and benefits aligns with the guidelines or recommendations from relevant HTA agencies or decision-making bodies, with widely used annual discount rates ranging from 1.5 to 5%.

4.3 Uncertainty

Sensitivity analysis is a fundamental element in economic evaluations, serving as a tool to assess the reliability and robustness of the presented results by evaluating the impact of varying key inputs and assumptions on key model outputs. Approximately 80% of the models incorporated sensitivity analyses, with common parameters including costs, efficacy inputs (e.g., hazard ratios) and utilities/disutilities. Parameters were also varied in scenario analyses, but less frequently (approximately 42% of studies).

4.4 Model Validation and Transparency

Validation and transparency are both crucial, interrelated steps when developing cost-effectiveness models [104], and Caro [18] recommends seeking independent face validity and documentation of all testing, comparison, and resolutions. Model validation involves assessing the accuracy and reliability of the model results. This ensures that the model accurately represents the expected costs and health benefit of the modeled patient population with robust and reliable conclusions and predictions. Model transparency, on the other hand, refers to clear and explicit documentation of the model structure, assumptions, data sources and calculations. This enables other researchers in the field to not only understand but also replicate the analyses [104].

Model validation is performed through various steps. These include internal validity: model calculations, mathematical equations, and data sources are checked for consistency and accuracy; external validity: model results are compared with reported data, including clinical trials and real-world data; cross validity: model results are compared with other published cost-effectiveness studies in the same indication; face validity: an external clinical and/or health economic expert assess(es) the model structure, assumptions, and predications; predictive validity: the model results are compared with prospectively observed events [104].

Current published models generally failed to properly validate the results and assumptions in the cost-effectiveness models. For example, cross-validation with other published cost-effectiveness models in the same indication was used in one-quarter ($n = 15$) of the studies, and nine other studies used face validity. Slightly more than half of the models reported using at least one type of validation method (internal validation, external validation, cross validity, and face validity), and of these, half used a single method. There are

no clear guidelines on the required number of validations for a model to be classified as robust and high-quality evidence. However, employing at least two to three levels of validation is recommended to enhance the reliability and robustness of the cost-effectiveness analysis used to inform decision making. With additional levels of validation, the analysis becomes more reliable and less susceptible to uncertainties or variations in the input parameters. Robustness ensures that the results of the cost-effectiveness analysis are more dependable and can withstand scrutiny, providing more confidence in the findings for decision makers. Starting with an internal validity that follows published quality check guidelines is an important step in the model development to ensure the accuracy of model calculations and overall model inputs and to identify any potential errors or biases. Following the technical validation step, model results and assumptions should be validated at least through external validation with real-world data or clinical trial data, or a through a face validity involving clinical experts. While we acknowledge the limitation of the external validation and cross-validation due to paucity of the data, researchers are encouraged to compare model results with other published studies in a similar indication or perhaps in a different line of therapy, or in the wider patient population within the same indication to ensure the model is accurately projecting the patients' outcomes.

4.5 Limitations

The SLR provides a comprehensive review of literature published up to April 2023. It is possible that new decision-analytic models have been published since this date. Given the lack of economic evaluations in locally advanced (stage IIIB or IIIC) or metastatic (stage IV) NSCLC, with tumors harboring *EGFR* mutations, that had not previously received systemic treatment, regular monitoring and surveillance of new literature published in this rare indication can help to enhance the understanding of the most appropriate modeling approaches. In addition, although a broad range of HTA and non-HTA agencies were hand searched, the SLR did not include a critical review of economic evaluations from agencies outside these organizations, unless the models were published in manuscripts in peer-reviewed journals accessible via electronic databases and conference abstracts available via key scientific congresses.

5 Conclusions

Although almost two-thirds of the cost-effectiveness studies identified were published in recent years (2019–2022), many lacked sufficient reporting on the justification for structural choice, validation, and the incorporation of sufficient sensitivity analyses. Future models should aim to provide rigorous justifications of structural choices, extensive sensitivity analyses, and multi-level validation in economic evaluations while carefully considering various factors such as data sources and demographic heterogeneity to ensure the validity of model results and enhance the accuracy of the presented model. This critical review of existing decision-analytic models highlights how increased transparency and collaboration with multiple stakeholders (clinicians and payers) can help to strengthen the validity of economic evaluations to guide healthcare decision making. As the treatment landscape for NSCLC with *EGFR* mutations evolves, the need to replicate and refine the decision-analytic models in these indications will be required.

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Declarations

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Conflict of interest Angie Raad, Maria Rizzo and Katherine Appiah are full-time employees of Cytel. Isabella Kearns is a full-time employee of Takeda UK Ltd, and Luis Hernandez is a full-time employee of Takeda Pharmaceuticals America, Inc. This article reflects the views and opinions of the authors and not necessarily those of the organizations to which individuals are affiliated.

Data availability statement The authors declare that all the data supporting the findings of this study (i.e., the information extracted from the studies included in this review) are available within the article and the Online Resource.

Author contributions All authors contributed to the study design, literature search, and writing, review and approval of the manuscript.

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