A systematic review of economic evaluations assessing the cost-effectiveness of licensed drugs used for previously treated epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) negative advanced/metastatic non-small cell lung cancer

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Short title: Systematic review of economic evaluations of licensed drugs for previously treated advanced NSCLC

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Abstract

Background: Non-small cell lung cancer (NSCLC) is one of the most commonly diagnosed cancers. There are many published studies of cost-effectiveness analyses of licensed treatments, but no study has compared these studies or their approaches simultaneously.

Objective: To investigate the methodology used in published economic analyses of licensed interventions for previously treated advanced/metastatic NSCLC in patients without anaplastic lymphoma kinase or epidermal growth factor receptor expression.

Methods: A systematic review was performed, including a systematic search of key databases (e.g. MEDLINE, EMBASE, Web of Knowledge, Cost-effectiveness Registry) limited from 01 January 2001 to 26 July 2019.

Two reviewers independently screened, data extracted and quality appraised studies identified. The reporting quality of the studies was assessed by using the Consolidated Health Economic Evaluation Reporting Standards and the Philips' checklists.

Results: Thirty-one published records met the inclusion criteria which corresponded to 30 individual cost-effectiveness analyses. Analytical approaches included partitioned survival models (n=14), state-transition models (n=7) and retrospective analyses of new or published data (n=8). Model structure was generally consistent, with pre-progression, post-progression and death health states used most commonly. Other characteristics varied more widely, including the perspective of analysis, discounting, time horizon, usually to align with the country that the analysis was set in.

Conclusions: There are a wide range of approaches in the modelling of treatments for advanced NSCLC, however the model structures are consistent. There is variation in the exploration of sensitivity analyses, with considerable uncertainty remaining in most evaluations. Improved reporting is necessary to ensure transparency in future analyses.

Key points for decision makers

The structure of the models was consistent with little deviation from the pre-progression, post-progression and death health states.

The modelling of overall survival is routinely one of the most influential factors on the cost-effectiveness conclusions but is often associated with considerable uncertainty.

Studies should report with greater transparency their methods for extrapolating survival curves to reduce bias in cost-effectiveness analyses.

There is insufficient evidence to conclude which treatment is the most cost-effective and further research is necessary.

1. Introduction

Lung cancer is one of the most commonly diagnosed cancer and the leading cause of cancer-related deaths globally [1], with non-small lung cancer (NSCLC) accounting for 85 to 90% of all forms of lung cancer [2]. The development of targeted therapies and immunotherapies promises to fill some of the unmet need for the treatment of advanced/metastatic NSCLC. To date, 13 agents have a label indication for the treatment of advanced/metastatic NSCLC in patients after failure to first-line chemotherapy (docetaxel, pemetrexed, ramucirumab with docetaxel, erlotinib, nintedanib with docetaxel, afatinib, nivolumab, pembrolizumab, atezolizumab, crizotinib, ceretinib, gefitinib and osimertinib), four of which are targeted therapies for patients with anaplastic lymphoma kinase expression (ALK+) or epidermal growth factor receptor expression (EGFR+) disease. In the absence of head-to-head comparison studies between most of the licensed drugs for this specific population, we showed in a previous systematic review with network meta-analyses that the three recent immune checkpoints inhibitors namely, nivolumab, pembrolizumab and atezolizumab exhibited superior benefit/risk balance compared to other licensed drugs [3]. The same was found in a secondary analysis of trials using restricted-mean-survivals and parametric modelling to measure effectiveness [4].

However, due to the substantial costs of these drugs, their use is raising concerns because of the high economic impact these drugs are likely to have on health systems [5]. This advocates for the use of economic modelling to be conducted in order to comprehensively compare these licensed drugs on both the cost and effectiveness dimensions.

Prior to this comprehensive cost-effectiveness evaluation, we aimed to undertake a systematic review of existing economic evaluations relating to previously treated NSCLC drugs to synthesise existing evidence, specifically focusing on model-based economic analyses. This first stage is required because of the anticipated complexity of the cost-effectiveness modelling of NSCLC drugs. In this systematic review, we have summarised the modelling techniques, clinical inputs, resource use and costs, and outcome measures used in the analyses, and suggested key issues to consider in developing further cost-effectiveness models. Previous systematic reviews comparing the clinical-effectiveness of interventions for NSCLC have been published [3, 6], but our literature search did not identify any systematic reviews with a focus on cost-effectiveness evidence. This paper addresses this gap in the literature.

2. Methods

The protocol for this systematic review was registered on the PROSPERO international prospective register of systematic reviews [7].

2.1. *Search strategy*

A literature search of published economic evaluations was performed, following the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) guidelines [8]. Electronic databases (MEDLINE, EMBASE (Ovid), Cochrane Library (Wiley), , Science Citation Index (Web of Knowledge), Research Papers in Economics (RePEC) and the Cost-Effectiveness Analysis (CEA) Registry), and the National Institute of Health and Care Excellence (NICE) website were searched for relevant literature. We also performed citation searches and searched reference lists of relevant included studies, and any previously published systematic reviews. The search was limited to studies published in the English language from 1 January 2001 up to 26 July 2019. This start point was chosen because it corresponds to the year that docetaxel was appraised by NICE for NSCLC, docetaxel being the first agent that was labelled for this indication and was established as the standard of care in second-line therapy [9]. The search strategy combined NSCLC terminology with economic terms. A copy of the search terms is available in the supplementary information.

2.2. Study selection/Inclusion and exclusion criteria

All citations retrieved were screened independently by two reviewers (DG and PA) at title/abstract stage, of which potentially relevant records were further examined at full-texts. Any disagreements between the reviewers were resolved by consensus or recourse to a third reviewer (XA). We examined original papers, technology appraisal guidance, letters, editorials and meeting abstracts. Studies were considered to be relevant if the study examined at least one treatment with label indication for advanced/metastatic NSCLC as of January 2018 (docetaxel, pemetrexed, ramucirumab with docetaxel, erlotinib, nintedanib with docetaxel, afatinib, nivolumab, pembrolizumab, atezolizumab, best supportive care alone or in combination with a drug of interest. We excluded the four targeted therapies (crizotinib, ceretinib, gefitinib and osimertinib. To be included, studies should have used an economic analysis to compare treatments licensed for adults with advanced/metastatic NSCLC, and meeting the following characteristics:

- Non-squamous (adenocarcinoma, large cell), or squamous histology
- ALK expression either predominantly negative or 100% negative
- EGFR expression either predominantly negative or 100% negative
- Patients who experienced failure to prior first line chemotherapy (i.e., those receiving second line treatment and beyond)

We excluded studies that included people with ALK+ and/or EGFR+ expression, as according to current practices, these patients are routinely offered targeted therapies.

2.3. Data extraction & synthesis

Two reviewers (DG & PA) each extracted information from half of the studies and further cross-checked each other's extractions. Any disagreements were resolved by discussion or by recourse to a third reviewer (XA). Information was extracted on study details (title, author and year of study), baseline characteristics (population, intervention, comparator and outcomes), methods (study perspective, time horizon, discount rate, measure of effectiveness, units of currency, conversions, assumptions and analytical methods), results (study parameters, base-case and sensitivity analysis results), discussion (study findings, limitations of the models and generalisability), other (source of funding and conflicts of interests), overall comments and conclusions (author's and reviewer's). A template of the extraction form is provided in the supplementary information. Information extracted from the included studies were summarised and presented in Table 1. Due to the nature of economic analyses (different aims/objectives, study designs, populations, and methods) these findings from individual studies were compared narratively, and recommendations for future economic analyses are discussed.

2.4 Critical appraisal and quality assessment tools

The reporting quality of the studies was assessed against the Consolidated Health Economic Reporting Standards (CHEERS) [10] and the Philips' checklist [11], respectively. PA and DG critically appraised half of the final list of included studies, with XA independently verifying the accuracy of the information. Any differences were resolved by discussion or by a fourth assessor (HM).

3. Results

3.1 Search results

Details of the literature search and review process can be found in the PRISMA flow chart [12] in Figure 1. Following screening of the 837 identified records, 612 were screened at title and abstract and 54 were assessed at full text level, with 30 records included in the review, representing 30 separate studies.

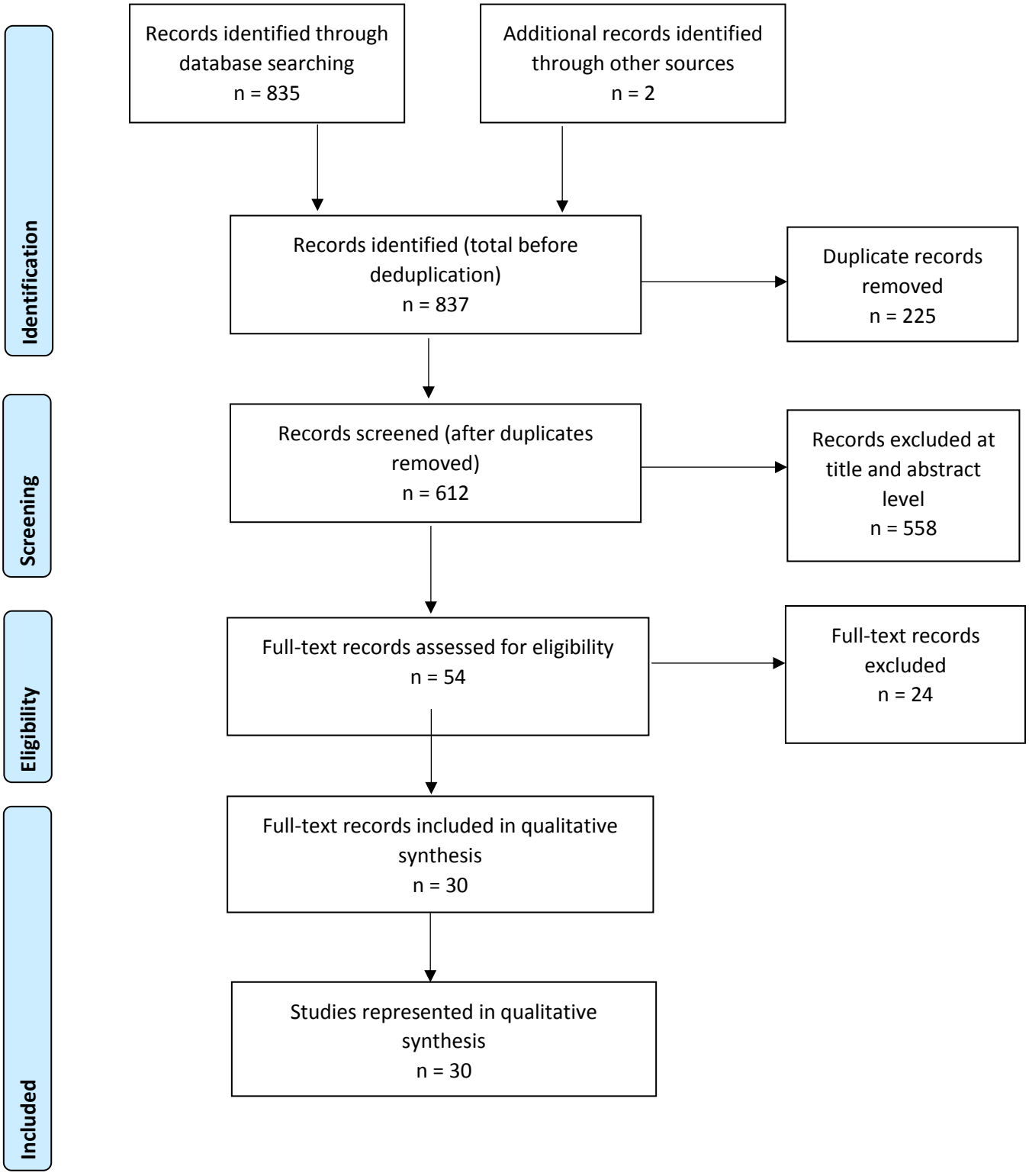
Identification
Screening
Eligibility
Included
Records identified through database searching
n = 835
Additional records identified through other sources
n = 2
Records identified (total before deduplication)
n = 837
Duplicate records removed
n = 225
Records screened (after duplicates removed)
n = 612
Records excluded at title and abstract level
n = 558
Full-text records assessed for eligibility
n = 54
Full-text records excluded
n = 24
Full-text records included in qualitative synthesis
n = 30
Studies represented in qualitative synthesis
n = 30

Table 1: Summary characteristics and results of included studies

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
Leighl et al., 2002, Canada [13]	Docetaxel (100mg/m^2 and 75mg/m^2) vs BSC	Patients with advanced NSCLC who had previously received one or more cisplatin-based chemotherapy, ECOG ≤ 2.	Retrospective CEA of a clinical trial, National Health Care System, No discounting was applied.	Data from 20 months of trial follow-up	Cost per LYG	CEA conducted retrospectively using trial data	None	ICER of docetaxel (combined) vs BSC = CAD$ 57,750/LY ICER of docetaxel (75mg/m^2) = CAD$ 31,780 /QALY	Survival is most influential parameter on cost-effectiveness results
Holmes et al., 2004, UK [14]	Docetaxel vs BSC	NSCLC patients who had received prior treatment with platinum containing chemotherapy The disease severity of patients is unclear.	Retrospective analysis of cost and survival data, NHS perspective, No discounting was applied.	2 years	Cost per LYG	CEA conducted retrospectively	Zero costs assumed for BSC arm.	ICER = £ 13,863/LY	Mean survival was most influential on cost/LY
NICE Technology Appraisal 124 - Pemetrexed Eli Lilly 2006, UK [15]	Pemetrexed vs docetaxel (also compared to BSC indirectly)	Adults with locally advanced or metastatic NSCLC and had relapsed after	Economic analysis from NHS/PSS perspective, with a 3.5% discount rate	3 years	Cost per LYG; Cost per QALY gained	CEA using a Markov model with four main health states: Stable, Response, Progressive or Death, 21 day cycle	Patients could only die from progressive health state, or via	Company ICER vs docetaxel: £ 7,097/LY and £ 18,672/QALY Company ICER vs BSC: £	Time horizon, drug costs and survival modelling were all influential

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
		previous chemotherapy					febrile neutropenia Patients remained on treatment for up to 6 cycles.	10,418/LY and £ 16,458/QALY ERG base case of £ 458,333/QALY vs docetaxel	
Araujo et al., 2008, Portugal [16]	Erlotinib vs docetaxel vs pemetrexed vs BSC	Patients with advanced or metastatic disease NSCLC (IIIA, IIIB, IV) who have failed at least one prior chemotherapy	Model-based economic analysis, NHS perspective, 5% discount rate	2 years	Cost per LYG; Cost per QALY gained	CEA using a partitioned survival model with three states (progression-free, post-progression and death), 1 month cycle	Equal efficiacy assumed for erlotinib, docextaxel and pemetrexed for PFS and OS.	Erlotinib dominated docetaxel and pemetrexed. ICER vs BSC was € 161,742/QALY and € 70,424/LY PSA results were € 161,356/QALY and € 71,152/LY	Choice of parametric curve was influential along with later line treatments.
Carlson et al., 2008, USA [17]	Erlotinib vs docetaxel vs pemetrexed	Patients with advanced (stage III—IV) NSCLC who failed at least one platinum-based chemotherapy	Model based economic analysis, US health system perspective,	2 years	Cost per QALY gained	Decision analytic model, with three health states (progression free, post-progression and death)	Equal efficiacy assumed for erlotinib, docextaxel and pemetrexed	Erlotinib dominated both docetaxel and pemetrexed. pemetrexed vs docetaxel ICER	Most influential on cost and QALYs were time spent in PFS state

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
			3% discount rate				for PFS and OS.	was US$ 1,743,369/QALY	
McLeod et al., 2009, UK [18]	Erlotinib vs docetaxel	Patients with locally advanced or metastatic (stage IIIB/IV) NSCLC	Model-based economic analysis, NHS and PSS, discount rate not reported.	Not reported	Cost per QALY gained	CEA using a Markov model with three health states (progression free, post-progression and death), cycle length unknown	Equivalent OS assumed	The company's results suggests that erlotinib dominated docetaxel, with a 0.68 probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained. However, under new assumptions by the ERG, the base-case ICER was approximately £ 52,000 per QALY. The ERG's PSA results showed that there was	Not reported

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
								a 0.44 probability of being cost-effective	
Lewis et al., 2010, UK [19]	Erlotinib vs docetaxel	Patients with previously treated stage IIIB/IV NSCLC	Model-based economic analysis, NHS and PSS, 3.5% discount rate	2 years	Cost per QALY gained	CEA using a Markov model with three health states (progression-free, progression and dead), 1 month cycle	Equivalent OS assumed	Erlotinib dominated docetaxel. Incremental costs were approximately -£ 200 and expected to yield 0.032 more QALYs. At a willingness-to-pay threshold of £ 30,000 per QALY, erlotinib had a 0.70 probability of being cost-effective	Reducing the cost of docetaxel administration, the cost of progression and utility score for PFS for docetaxel had the greatest impact to the results
Asukai et al., 2010, Spain [20]	Pemetrexed vs docetaxel	Patients with previously treated advanced-stage (stage III or IV) with	Model-based economic analysis, health care provider, 3% discount rate	3 years	Cost per LYG; Cost per QALY gained	CEA using a Markov model with three health states: stable, response and progression, 21 day cycle	Constant hazard rate assumed for OS	Pemetrexed compared to docetaxel resulted in an ICER of approximately	Overall survival appeared to be the main driver of the

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
		predominantly non-squamous histology and are eligible for second line treatment						€ 24,000 per QALY and € 17,200 per LY. Results from the PSA showed that pemetrexed had a 0.62 probability of being cost-effective than docetaxel at a willingness-to-pay threshold of € 30,000 per QALY.	economic model
Cromwell et al., 2011, Canada [21]	Erlotinib vs docetaxel	Patients with stage IIIb/IV advanced NSCLC receiving second-line treatment	Retrospective CEA, British Columbia health care, discount rate not applied.	31 months	Costs and LY	CEA conducted retrospectively	None	No ICER presented as only 1 day difference in mean OS and CAD$ 2,891 cost difference	Unclear
Vergnenegre et al., 2011, France [22]	Docetaxel (75mg/m2 as a one-hour intravenous infusion) vs BSC (pemetrexed)	Adults >18 years, with at least one measurable lesion, stage IIB or IV NSCLC,	Economic analysis alongside a randomised, prospective multicentre	2 year trial	Cost per QALY gained	CEA with 7 health states: responding on chemotherapy, with or without grade	None	Results showed that docetaxel dominated pemetrexed	Results from the one-way sensitivity analysis showed that changes to key

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
		ECOG score 0-2, and progressive disease after chemotherapy for metastatic disease	study, payer's perspective, discount rate not applied			3/4 AEs; stable, with or without grade 3/4 AE; progression, with or without grade 3/4 AE; and death, cycle length unknown			parameter did not have an impact on the results
Cromwell et al., 2012, Canada [23]	Erlotinib vs symptom management	Patients with previously treated stage IIIB/IV advanced NSCLC	Retrospective CEA, British Columbia health care, discount rate not applied	Not applicable	Cost per LYG	CEA conducted retrospectively	None	An estimated ICER of approximately CAD$ 36,800 per LYG. PSA results showed that at a willingness-to-pay-threshold of CAD$ 50,000, CAD$ 100,000 and CAD$ 200,000/LY, erlotinib is likely to be cost-effective in 58%, 79% and 95% of the simulations, respectively.	Sensitivity analysis showed that all parameters impacted the base-case ICER

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
Greenhalgh et al., 2015, UK [24]	Erlotinib vs docetaxel or best supportive care	People aged ≥ 18 years with an ECOG PS score between 0-3, with documented evidence of NSCLC.	Model-based economic analysis, NHS and PSS, 3.5% discount rate	Company: 6-year ERG: 5-year	Cost per QALY gained	CEA using a partitioned survival model with three health states (progression-free, progressed and dead); AG model includes four health states (advanced/metastatic NSCLC progressed after first-line chemo, progression-free after second-line chemotherapy, post progression and dead), 1 week cycle	Utility scores are not treatment specific	Company results: erlotinib compared to BSC has an ICER of approximately £ 51,000/QALY gained in EGFR unknown population. AG for EGFR negative population, concluded that docetaxel dominated erlotinib. AG ICER for erlotinib vs BSC was £ 54,687/QALY in EGFR unknown population.	Not reported by the company. AG stated that using alternative British National Formulae pricing for docetaxel was the most influential parameter
NICE Technology Appraisal 347 –Nintedanib,	Nintedanib vs docetaxel	People with locally advanced or metastatic NSCLC whose disease	Model-based economic analysis, NHS and PSS,	15 years	Cost per QALY gained	CEA using a partitioned survival model with three health states (progression-free,	None	Company results vs docetaxel: £ 46,580/QALY	Company reported that changes to the survival modelling

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
Boehringer Ingelheim, 2015, UK [25]		progressed following platinum-based treatment	3.5% discount rate			progressed and dead), 3 week cycle		ERG results: £ 56,804/QALY	were influential on ICER. ERG reported post-progression utility values were influential
Bosch et al., 2016, Spain [26]	Nintedanib plus docetaxel vs placebo plus docetaxel	Adults with locally advanced, metastatic or locally recurrent NSCLC, with adenocarcinoma histology after treatment with first-line chemotherapy	Economic analysis alongside a RCT, NHS, discount rate is not applied	Approx. 36 months	Cost per LYG	CEA of a trial.	None	PFS: Results showed that nintedanib + docetaxel compared to placebo + docetaxel has an ICER of approximately € 134,300/LY. Based on a 25% discount on the cost of nintedanib resulted in an ICER of approximately € 106,300/ LY	Not reported

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
								Adenocarcinoma OS: Results showed that nintedanib + docetaxel compared to placebo + docetaxel has an ICER of approximately € 40,900/LY. Based on a 25% discount on the cost of nintedanib resulted in an ICER of approximately € 32,400/LY	
Matter-Walstra et al., 2016, Switzerland [27]	Nivolumab vs docetaxel	Advanced Non-squamous NSCLC patients with failure to at least one prior therapy	Model based economic analysis, National Healthcare system, No discounting was applied	"lifelong"	Cost per QALY gained	CEA using a Markov model with three health states (progression-free, progression and dead) with monthly cycles, 1 month cycle	PFS and OS hazard rates were assumed constant over time. Treatment received until	ICER CHf 177,478/QALY	Of the investigated variables, utility scores of the health-states were the most influential on the ICER

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
							disease progression.		
Goeree et al., 2016, Canada [28]	Nivolumab vs docetaxel vs erlotinib	Patients with advanced squamous NSCLC who have been previously treated	Model based economic analysis, Public Healthcare System, 5% discount rate	10 years	Cost per QALY gained and cost per LYG.	CEA using a partitioned survival model and Markov model were used. Both had three health states (progression-free, post-progression and death), 4 week cycle	Utility values were not treatment specific. Treatment received until disease progression.	PSM results ICER vs docetaxel CAD$ 151,560/QALY ICER vs erlotinib CAD$ 140,601 Markov results: ICER vs docetaxel CAD$ 152,239/QALY ICER vs erlotinib CAD$ 141,838/QALY PSA ICERs Vs docetaxel CAD$ 158,154/QALY Vs erlotinib CAD$ 145,773/QALY	Utility values were most influential on ICER, of the investigated parameters

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
NICE Technology Appraisal 403 – Ramucirumab, Eli Lilly, 2016, UK [29]	Ramucirumab plus docetaxel vs docetaxel	Adults with locally advanced or metastatic NSCLC whose disease has progressed after platinum-based chemotherapy	Economic analysis from NHS/PSS perspective, with a 3.5% discount rate	15 years	Cost per QALY gained	CEA using a partitioned survival model with 3 states: pre-progression, post-progression and death, 21 day cycle	Treatment received until disease progression or unacceptable toxicities. Proportional hazards was assumed for OS.	Company base-case vs docetaxel: £ 194,919/QALY ERG ICER was £ 175,000/QALY	ICER was most sensitive to price of interventions, discount rate, the time on treatment and choice of parametric fit
Huang et al., 2017, USA [30]	Pembrolizumab 2mg/kg vs docetaxel	Adults (>18 years) with advanced NSCLC who experienced diseased progression following first-line treatment with a platinum-based therapy	Model-based economic analysis, third-party payer, 3% discount rate	20 years	Cost per LYG; Cost per QALY gained	CEA with partitioned-survival model with three health states, 1 week cycle	Equal OS hazard rate assumed for both treatments beyond 6.5 years.	Pembrolizumab is expected to cost approximately US$ 160,500 more than docetaxel and expected to yield 1.18 LYs equating to an ICER of approximately US$ 135,600 per LY	Sensitivity analysis showed that extrapolation of overall survival, time-on-treatment for pembrolizumab, and utilities for time greater or equal to 360 days from death had the

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
								Pembrolizumab is expected to yield 0.95 QALYs equating to an ICER of approximately US$ 168,600 per QALY	greatest impact to the ICER
Pignata et al., 2017, France [31]	Afatinib vs erlotinib	Squamous advanced NSCLC patients who experienced disease progression during or following treatment with platinum-based chemotherapy	Model based economic analysis, NHS, 4% discount rate	10 years	Cost per QALY gained	Partitioned survival analysis with three health states: pre-progression, post-progression and death, 1 month cycle	Treatment received until disease progression. Subsequent treatment not considered in model.	ICER € 30,277/QALY and € 18,568/LY	Changing the projected OS was the most influential factor on the ICER
NICE Technology Appraisal 428 - Pembrolizumab, Merck Sharp & Dohme, 2017, UK [32]	Pembrolizumab vs docetaxel vs nintedanib plus docetaxel	Previously treated adults with advanced NSCLC, following platinum-containing chemotherapy	Economic analysis from NHS/PSS perspective, with a 3.5% discount rate	20 years	Cost per QALY gained	Partitioned survival model with 3 states: pre-progression, post-progression and death, 1 week cycle	All treatment would not go beyond 2 years.	Company Base Case 1: ICER vs docetaxel = £ 43,351/QALY Company Base Case 1: ICER vs Nin+Doc = £ 34,997/QALY	ICER was very sensitive to duration of treatment effect, and method of OS extrapolation

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
								Company Base Case 2: ICER vs docetaxel = £ 49,048/QALY Company Base Case 2: ICER vs Nin+Doc = £ 23,424/QALY Revised submission Company Base Case ICER vs docetaxel = £ 49,063/QALY ERG preferred ICER is £ 61,954 /QALY	
NICE Technology Appraisal 483 – Nivolumab, Bristol Myers-Squibb, 2017, UK [33]	Nivolumab vs docetaxel	People with previously treated locally advanced or metastatic (stage IIIB or IV) squamous NSCLC	Economic analysis from NHS/PSS perspective, with a 3.5% discount rate	20 years	Cost per QALY gained	Partitioned survival model with 3 states: pre-progression, post-progression and death, 7 day cycle	Proportional hazards assumed for PFS by company. Treatment received until	Company base-case: ICER = £ 85,950/QALY ERG base-case: ICER = £ 132,989/QALY These ICERs do not include a PAS and are	ICER was sensitive to parametric fit, hazard ratio, body weight and discount rates

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
							disease progression.	from first company submission. FAD ICERs: Committee preferred: £ 50,014/QALY (including a PAS, and based on a later company submission)	
NICE Technology Appraisal 484 – Nivolumab, Bristol Myers-Squibb, 2017, UK [34]	Nivolumab vs docetaxel (also compared with nintedanib plus docetaxel)	Target: Adults with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy NICE recommendation: as above but their tumours must be PD-L1 positive	Economic analysis from NHS/PSS perspective, with a 3.5% discount rate	20 years	Cost per QALY gained	Partitioned survival model with 3 states: pre-progression, post-progression and death, 7 day cycle	After 18.4 years, all patients in PFS were assumed cured, and subject to background mortality. Subsequent treatment not considered in model.	Nivolumab vs Ddocetaxel: ICER = £ 103,589/QALY, inc costs = £ 75,452, inc QALY = 0.73 Nivolumab vs Nin+Doc: ICER = £ 126,861/QALY, inc costs = 62,598, inc QALY = 0.49 Unclear if these results include	ICER was most sensitive to choice of parametric fits, body weight and discount rates

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
								any discount on drug prices. ERG ICER vs Doc= £ 165,234/QALY FAD ICER: £ 49,160	
NICE Technology Appraisal 520 – Atezolizumab, Roche, 2018, UK [35]	Atezolizumab vs docetaxel vs nintedanib plus docetaxel	People with advanced or metastatic NSCLC who had previously been treated with chemotherapy	Economic analysis from NHS/PSS perspective, with a 3.5% discount rate	25 years	Cost per QALY gained	Partitioned survival model with three health states: on treatment, off treatment and dead, 3 week cycle	The company assumes that the treatment effect remains for the duration of the economic model. A cure fraction is applied for patients with stable disease.	Company base-case (list prices): vs Docetaxel ICER = £ 72,356/QALY vs Nin+Doc ICER = £ 56,100/QALY ERG preferred (list prices): Vs docetaxel ICER = £ 170,500/QALY Vs Nin+Doc ICER = £ 1,170,800/QALY	Cure fraction and choice of OS parametric curve were the most influential on the ICER
Aguiar et al., 2018, South America [36]	Nivolumab and pembrolizumab and	Patients with advanced NSCLC eligible for	Economic analysis from payers	5 years	Cost per LYG and Cost per	A model-based analysis but the	None	Nivo in squamous	No sensitivity analyses were reported

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
	atezolizumab vs docetaxel and platinum-based chemotherapy	second-line treatment in either Brazil, Argentina or Peru	perspective with no reported discount rate		QALY gained	model was not described in detail		disease patients: Brazil ICER = US$ 168,100 /QALY Arg ICER = US$ 224,000/QALY Peru ICER = US$ 170,400/QALY Nivo in non-squamous disease patients: Brazil ICER = US$ 217,600/QALY Arg ICER = US$ 297,100/QALY Peru ICER = US$ 221,000/QALY Pembro in PD-L1>1% patients: Brazil ICER = US$ 131,600/QALY	

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
								Arg ICER = US$ 218,300/QALY Peru ICER = US$ 131,100/QALY No results for atezolizumab were reported	
Guirgis, 2018, unclear setting [37]	Atezolizumab, nivolumab, pembrolizumab vs docetaxel	Patients with advanced second line NSCLC.	Unclear	1 year	Cost per LYG, relative value.	Crude retrospective study using external data.	Used median OS and prices published by parent companies.	ICER nivolumab vs doc in squamous = US$ 488,524/LYG ICER nivolumab vs doc in non-squamous = US$ 558,326/LYG ICER atezolizumb vs doc = US$ 618,244/LYG ICER pembrolizumab vs doc in PD-L1 >1% = US$ 1,490,729/LYG	No sensitivity analyses were performed.

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
Shafrin et al., 2018, Canada [38]	Nivolumab vs docetaxel	Patients with stage IIIB or IV squamous-cell NSCLC who had disease recurrence after one prior platinum-containing regimen	Economic analysis exploring different perspectives, with a 5% discount rate	10 years	Cost per QALY gained	Extension to existing partitioned survival model (see Goeree et al.) 1 week cycle	OS and PFS based on Goeree et al.	Traditional payer ICER = CAD$ 151,560/QALY Traditional societal ICER = CAD$ 141,344/QALY Broad societal ICER = CAD$ 80,645/QALY	Varying the value of a QALY and insurance value were the most influential on the net monetary benefit. Effects on ICER were not explored
Zhu et al., 2018, China [39]	Afatinib vs Erlotinib	Patients with advanced squamous lung cancer who progressed after at least four cycles of platinum containing chemotherapy	Economic analysis from Chinese healthcare system perspective, with a 5% discount rate.	10 years	Cost per QALY gained	Authors state it is a Markov model, but we believe it is a partitioned survival model from the description.	OS, PFS and utility data come from LUX-Lung 8 trial, without adaptation.	ICER = ¥ 109,429/QALY	Net monetary benefit estimates were sensitive to values of OS and PFS parameters, and to the cost of the post-progression health state. Effects on ICER were not explored

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
Gao et al., 2019, Australia [40]	Nivolumab vs docetaxel	Patients with advanced or metastatic squamous NSCLC who progressed on or after platinum-based chemotherapy.	Economic analysis from Australian healthcare system perspective with 3% discount rate	6 years	Cost per LYG and Cost per QALY gained	Used both a Markov model and a partitioned survival analysis, both with three health states: on treatment, off treatment and dead.	OS and PFS data are from Checkmate 017	ICER Partitioned survival = A$ 198,862/QALY ICER Markov = A$ 220,029/QALY	Choice of OS and PFS curve, cost of nivolumab and time horizon were all influential on ICER.
Merino Almazan et al., 2019, Spain [41]	Nivolumab vs docetaxel	Patients who experienced progression after first-line therapy for advanced or metastatic NSCLC and were treated with nivolumab between January 2016 and July 2017	Economic analysis of data from 15 hospitals in Spain	Maximum of 19 months of follow-up.	Cost per LYG	Retrospective analysis, no model.	Docetaxel performance was estimated by applying a hazard ratio of 0.73 for non-squamous patients and 0.59 for squamous patients. It is unclear how it was applied.	ICER = € 110,026/LYG	The ICER was sensitive to the value used for the hazard ratio. No other sensitivity analysis were conducted.
Ondhia et al., 2019, Canada [42]	Atezolizumab vs docetaxel vs nivolumab	Patients with advanced NSCLC who progressed after first-line	Cost utility analysis from Canadian healthcare	10 year	PFS and OS	Partitioned survival model with three health states: on treatment, off	Time varying hazard ratios were	ICER of atezolizumab vs docetaxel:	Time horizon, source of hazard ratio and treatment

Author, year, location	Intervention/ Comparator	Population/ Disease	Study characteristics (study design, perspective, setting, discounting)	Time Horizon	Outcomes	Analysis/model type	Key Assumptions	Main Findings	Most Influential Parameters
		platinum-doublet chemotherapy	perspective with 1.5% discount rate			treatment and dead.	obtained from a fractional polynomial network meta-analysis.	CAD$ 142,074/QALY. Atezolizumab dominated nivolumab.	duration were the most influential parameters.

Abbreviations and Acronym: AG, assessment group; Arg, Argentina; BSC, best supportive care; CAD, Canadian dollar; CEA, cost-effectiveness analysis; CHf, Swiss franc; Doc, Docetaxel; ECOG, Eastern Cooperative Oncology Group; ERG, evidence review group; FAD, final appraisal document; ICER, incremental cost-effectiveness ratio; inc, incremental; LY, Life-years; LYG, life-years gained; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; Nin, Nintedanib; Nivo, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PAS, patient access scheme; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; PFS, progression-free survival; PS, performance status; PSA, probabilistic sensitivity analysis; PSM, partitioned survival model; PSS, personal social services; QALY, quality adjusted life-years gained.

3.2 Summary of modelling techniques, clinical inputs, resource use and costs, and outcome measures

3.2.1 Structure

Eight studies did not use a formal economic model for their analysis, and used benefits observed from a clinical trial or registry data [13, 14, 21-23, 26, 37, 41]. The structure of the economic models in all other studies were clearly stated and were consistent, all reflecting the progressive nature of NSCLC. Most model-based studies used the same three health states (progression-free, post-progression and death) to distinguish between patient quality of life and associated costs, but two used alternative health states [15, 35]. The most commonly used models were partitioned-survival models [16, 24, 25, 28-36, 39, 40, 42] and Markov models [15, 18-20, 27, 28, 40]. Carlson et al. appeared to use a decision tree [17], whilst the type of model used was unclear for two studies [36, 38]. All studies but one [27] with model-based cost-effectiveness analyses clearly stated the time horizon, which ranged from 2 years [16-19] to 25 years [35]. The study that did not provide a specific time horizon did state that it used a 'lifetime' time horizon [27]. The choice of economic model was rarely well justified and it was often unclear why a study opted for their implemented approach. It is possible that the modelling approach may influence the outcome and so it is important to consider which approach is best suited to answer the question with the data available [43]. Goeree et al. and Gao et al. both compared Markov and partitioned survival approaches. The results from Goeree et al. were similar for both models, though for one treatment comparison the ICER did vary by CAD$ 1,200/QALY based only on the modelling approach [28]. The results of Gao et al. produced ICERs that differed by over A$ 20,000/QALY [40].

3.2.2 Data

The source of clinical and cost inputs was reported and adequate for all studies, except one [37] where the sources were not referenced. All studies which included medical resource use in their analysis clearly stated the source of resource use information used. The choices of outcome measure were clearly stated and always consistent with model structure (OS and PFS). All but two studies [37, 41] stated the perspective from which their economic analysis was conducted, with all other studies including costs from the perspective of the relevant healthcare system or funder. Ten studies reported also considered costs related to personal social services [15, 18, 19, 24, 25, 29, 32, 34, 35, 38].

3.2.3 Uncertainty and assumptions

Almost all studies explored potential sources of uncertainty in their analysis, with three studies not performing any sensitivity analyses [36, 37, 41]. Uncertainty was most commonly explored through one-way sensitivity analyses (OWSA) (n=23), probabilistic sensitivity analyses (PSA) (n=22), and

scenario analyses (n=21). Sixteen studies included all three approaches [18-20, 22-25, 27, 29-35, 40], however there was inconsistency over the parameters included in the sensitivity analyses.

The most influential factors observed in multiple studies were the survival related parameters, including hazard ratios, parametric curves and cure proportions, and utility values, however not all studies were exhaustive in their inclusion of variables within their sensitivity analyses. No study comprehensively addressed all potential sources of uncertainty.

The majority of assumptions were related to patient survival, assuming either equal survival or proportional hazard rates between different interventions. Additional assumptions made within studies were related to the utility values, treatment duration or the impact of later lines of treatment. Many studies did not report any assumptions made within their economic analysis. Only the technology appraisals presented analyses where the impacts of the main assumptions were assessed through the application of alternative assumptions.

3.2.4 Economic Results

Table 1 summarises the characteristics of included studies. Docetaxel was the most commonly considered intervention, with only three studies not including it as an intervention of interest or comparator [23, 31, 39]. The majority of studies reported results in terms of cost per QALY as well as cost per LYG, with six reporting results in terms of LYG alone [13, 14, 23, 26, 37, 41] and two only in terms of QALYs [38, 39]. One study did not present any form of cost-effectiveness ratio, due to the interventions being indistinguishable in their benefits [21].

The majority of studies were from Western Europe (UK=11 [14, 15, 18, 19, 24, 25, 29, 32-35], France=2 [22, 31], Spain=3 [20, 26, 41], Portugal=1 [16], Switzerland=1 [27]) with the remaining studies based in the Americas (Canada=7 [13, 17, 21, 23, 28, 38, 42], USA=2 [30, 37], South America=1 [36]), China (n=1) [39] and Australia (n=1) [40].
Most studies (n=19) were sponsored by pharmaceutical companies with 11 studies not declaring any pharmaceutical support [18, 21-24, 26, 27, 36, 37, 40, 41].

3.2.5 Patient Characteristics

All analyses focussed on the same general population (patients on second line or later treatment for previously treated metastatic or advanced NSCLC), however there was slight variation in the staging of patients with two studies including stage IIIA patients in addition to IIIB and IV stage patients [15, 16], and five studies not reporting on the disease stage of patients [14, 27, 36, 37, 41]. Aside from Carlson et al. [17], (stage III and IV) and technology appraisal 403 (stage IV only) [29], all other

studies considered stage IIIB and IV patients. Restrictions on ECOG performance status was also reported by 13 studies, with restrictions varying across 0 to 1 [29, 33, 34, 40, 42], 0 to 2 [13-15, 22, 39, 41], and 0 to 3 [19, 24]. Two analyses focussed on non-squamous disease [20, 34], six on squamous disease [28, 31, 33, 38-40], with the remaining studies not distinguishing between NSCLC subtypes. Nine studies presented results by subgroup, with the range of subgroups considered: ECOG score [15, 16], line of treatment [16], squamous/non-squamous disease [29, 36, 37], EGFR negative/unknown [24, 34], programmed death-ligand 1 (PD-L1) expression [27, 34, 36, 37] and adenocarcinoma [29, 32].

3.2.6 Survival

A range of approaches were used to modelling the clinical effectiveness of the interventions. Retrospective studies used the mean or median survival observed from their relevant source of data. Meanwhile the Markov models assumed a constant hazard to calculate the transition rates between its health-states. An increasingly popular approach was to use a partitioned survival model where the progression-free survival (PFS) and overall survival (OS) curves are modelled parametrically, either jointly to multiple trial arms, or independently. This provides the number of patients in the progression-free and death health states. The number of patients in the post-progression heath state is then calculated as the difference between the PFS and OS curves. For indirect comparisons, hazard ratios were estimated and applied to parametric models.

3.3 Quality assessment

We assessed the reporting quality of 30 studies using both the CHEERS and Philips checklists, summaries of which can be found in tables 2 and 3 respectively. The reporting quality was generally high, with the majority of items on both checklists fulfilled by over 85% of studies. All studies reported their characteristics such as setting, perspective, the comparators and measures of effectiveness. There were several key areas for improvement: inclusion of additional relevant comparators, presentation of justification when multiple sources of information were available, consideration of subgroups and other sources of heterogeneity and discussions of the generalisability of the findings. It was apparent that half-cycle corrections were not used in the majority of models, but given the short cycle length used, this was not thought to detract from the quality.

4. Discussion

This review demonstrated that there are a number of different approaches to performing an economic analysis within the scope of assessing therapeutic options for advanced/metastatic NSCLC. Whilst in the older studies economic evaluations of clinical trials were very popular, as computing power and awareness of modelling techniques increased, Markov models and partitioned survival models have become more common. This likely reflects better awareness of modelling approaches combined with superior treatments and healthcare which prolong patient survival. Whilst two-years of trial follow-up may have been sufficient to observe all survival events twenty years ago, with time horizons of over twenty years in the more recent articles, it is clear that some prediction and accompanying assumptions are necessary.

Whilst all of the studies provided a comparison to a suitable and relevant intervention, often the comparator was not recently licensed. Whilst this may be explained by the rapidly evolving nature of healthcare and interventions, there may also be a bias when selecting comparators to ensure new interventions look as good as possible [44]. It is important to compare to the current best treatments, to ensure patients receive the best care and that a healthcare system receives optimal value for money.

The complexity of the evaluations varied greatly, with some making assumptions such as equal efficacy between treatments with limited or no direct comparative evidence, whilst others creating *de novo* economic models.

Alongside the shift towards partitioned survival modelling is the consideration of quality of life, through quality-adjusted life years (QALYs), rather than length of life alone, life years (LYs). This reflects a change in attitude of decision makers that the quality of life of patients should be considered with the length of life, and that treatments which offer life extending benefits but with heavy side effects may not be in the interest of patients.

There was a general trend of increasing time horizon as studies became more recent, suggesting that improved healthcare is improving the life expectancy of NSCLC patients.

It was rare for studies that were not directly related to a technology appraisal to consider and explore sources of uncertainty within their economic evaluation. Those that did explore uncertainty performed either probabilistic sensitivity analyses, allowing for uncertainty around multiple factors feeding into the economic model, or explored scenario / one-way sensitivity analyses, using confidence intervals or other parameter values to capture uncertainty in individual parameters.

A challenge of this systematic review was how to extract information from the evaluations directly from a NICE technology appraisal, as there can often be multiple opinions from the company, the

ERG and even the committee themselves. Opinions too may change during an appraisal with the availability of more information. It was sometimes challenging for our review team to select the most useful information for inclusion in this review, and so we focused our extraction on the first available set of committee papers.

It is plausible that publication-based evaluations may also be hampered from mistakes in modelling or bias(es) that are not identified, without the level of critique that comes with a NICE technology appraisal. A further limitation is that we have not specifically captured the quality of the methodology within each paper, having focused on the reporting quality, nor completed a formal assessment of transferability of each study.

The geographical range of studies showed that the cost-effectiveness of treatments is an important factor in the decision making process in many countries around the world. The transferability of all the results is difficult to ascertain because what may be cost-effective in one setting is not necessarily cost-effective in another setting. Different countries have different healthcare priorities and budgets with which to accomplish them. Indeed, the relative cost-effectiveness of two interventions may vary between countries due to differences in administration, cost and availability of later line treatments, and discounts offered by the manufacturer on the interventions. Whilst aspects of the different studies may be generalisable to other settings, the different currencies, decision makers and funders make it difficult to transfer conclusions of cost-effectiveness.

It is difficult to draw conclusions over which treatment is the most cost-effective, not least because manufacturers often offer a discount on the list price for their interventions. These discounts are confidential, and so economic analyses published in journals are based on list prices, with only analyses from decision-making processes (such as NICE technology appraisal documentation) including the actual prices paid. Whilst this suggests that technology appraisals may be the more informative source of information, however, part of the cost-effectiveness results are often redacted. Whilst the ICER is usually available, detailed breakdowns of costs and benefits are withheld to prevent back-calculation of the discount.

Whilst all licensed interventions have had their cost-effectiveness assessed against at least one comparator, there has been no published work comparing them simultaneously. This review has highlighted an unmet area of research. In order to ensure health services receive best value-for-money, it is important to perform such an evaluation.

Both partitioned survival models and Markov models have their limitations. A Markov model can cope with any number of health states, and allow for transitions from any one state to any other.

However, these transition probabilities will often be modelled in a simple manner and assumed to be constant over time. It becomes harder to obtain reliable estimates for the transitions when modelling more health states.

Meanwhile, a partitioned survival model can more easily capture hazards which vary over time, utilizing a wide range of parametric survival curves, but requires the health states to be ordered with transition between them only allowed in one direction. Whilst this may be adequate at present for progressive diseases such as NSCLC, it is unclear whether they will always be suitable for capturing the benefits of future treatments. As demonstrated by Goeree et al. [28], the approaches can lead to almost identical results. It is likely that for the majority of interventions considered in this review, the decision to analyse using either a partitioned survival model or a Markov model is relatively inconsequential on the outcome. However, for more recent interventions, such as immunotherapies which claim to be very effective in certain patients, both approaches can fall short of accurately capturing the patient pathway, without adjustment. For example two of the most recent technology appraisals reported altering the basic partitioned survival framework to assume that certain patients were cured or at a reduced risk of a cancer related death [34, 35]. Further developments in the treatment for advanced NSCLC may require further adjustments to be made to the traditional modelling approaches, but we certain of the suitability of any adjustments without supporting data.

Whilst all aspects of a cost-effectiveness analysis should be scrutinised, survival extrapolations should be given extra attention given that they were highly influential to cost-effectiveness results in a number of studies. If an intervention was wrongfully demonstrated to be cost-effective, and became a benchmark for future treatments to be assessed against, this could result in more heavily stretched healthcare budgets. With model time horizons increasing alongside pressure from public and patients demands to get rapid access to treatments, survival extrapolations will only become more influential. In the NICE technology appraisals, it was common for the ERG to disagree with the company's survival related assumptions. It raises questions over the reliability of the extrapolations in other published studies, as it is unlikely that the peer-review process contained the same rigour as a NICE technology appraisal. A recent review of NICE technology appraisals showed that in only 7% of appraisals did the ERG agree with all the major survival-related assumptions [45]. This demonstrates the need for well-established guidelines to reduce the extent to which survival extrapolations are based on subjective assumptions. Methods detailing the selection of extrapolation approach should be clearly described, with all supporting material provided in appendices.

We recommend that an economic model should accurately capture all of the major phases of a patient's pathway. The framework, inputs and assumptions should be clearly stated and referenced.

Inputs should be relevant to the population and setting where possible. The potential effects of key areas of uncertainty should be explored through OWSAs, PSAs and scenario analyses. Supporting evidence related to decisions around influential assumptions, such as choice of survival extrapolation, should be presented as supplementary material to maximise transparency and reproducibility.

This approach could be used to undertake a cost-effectiveness comparing all currently licensed drugs used for EGFR and ALK negative advanced/metastatic NSCLC, and could be extended to other disease areas.

5. Conclusion

This review summarises the range of methods used in assessing the cost-effectiveness of licensed interventions for advanced/metastatic NSCLC. The structure of the models was generally consistent. The modelling of overall survival is routinely one of the most influential factors on the cost-effectiveness conclusions and often contains considerable uncertainty due to the short follow-up of the most recent studies used in the economic evaluations. Transparency over survival extrapolation approaches is critical to reduce bias in cost-effectiveness analyses.

Compliance with Ethical Guidelines

Funding

This project was funded by the University of Warwick Research Development Fund (Warwick Medical School, December 2017).

Conflict of interest: Daniel Gallacher: No conflicts
Peter Auguste: No conflicts
Pamela Royle: No conflicts
Hema Mistry: No conflicts
Xavier Armoiry: No conflicts

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Table 2: Summary of Results from CHEERS Checklist

Question	N(YES)/N(Applicable) [%]	Question	N(YES)/N(Applicable) [%]
Title	28/30 [93%]	Estimating resources and costs	29/30 [97%]
Abstract	22/23 [96%]	Currency, price date, and conversion	23/30 [77%]
Background/objectives	30/30 [100%]	Choice of model	19/22 [86%]
Target population and subgroups	30/30 [100%]	Assumptions	22/25 [88%]
Setting and location	30/30 [100%]	Analytical methods	26/29 [90%]
Study perspective	28/30 [93%]	Study parameters	27/30 [90%]
Comparators	30/30 [100%]	Incremental costs and outcomes	30/30 [100%]
Time horizon	23/26 [88%]	Characterising uncertainty	28/30 [93%]
Discount rate	19/25 [76%]	Characterising heterogeneity	7/30 [23%]
Choice of health outcomes	30/30 [100%]	Study findings, limitations, generaliseability and current knowledge	6/30 [20%]
Measurement of effectiveness	30/30 [100%]	Sources of funding	24/26 [92%]
Measurement and valuation of preference based outcomes	23/27 [85%]	Conflicts of interest	25/26 [96%]

Table 3: Summary of results of Phillips Checklist

Question	N(YES)/N(Applicable) [%]	Question	N(YES)/N(Applicable) [%]
Is there a clear statement of the decision problem?	30/30 [100%]	Where choices have been made between data sources are these justified appropriately?	8/18 [44%]
Is the objective of the model evaluation and model specified and consistent with the stated decision problem?	22/22 [100%]	Where expert opinion has been used are the methods described and justified?	10/17 [59%]
Is the primary decision maker specified?	15/30 [50%]	Is the choice of baseline data described and justified?	29/30 [97%]
Is the perspective of the model stated clearly?	22/22 [100%]	Are transition probabilities calculated appropriately?	16/21 [76%]
Are the model inputs consistent with the stated perspective?	21/22 [95%]	Has a half-cycle correction been applied to both costs and outcomes?	10/22 [45%]
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	20/22 [91%]	If not, has the omission been justified?	2/12 [17%]
Are the sources of the data used to develop the structure of the model specified?	20/22 [91%]	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	19/21 [90%]
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	21/22 [95%]	Are the costs incorporated into the model justified?	22/22 [100%]
Is there a clear definition of the options under evaluation?	30/30 [100%]	Has the source for all costs been described?	26/27 [96%]

Have all feasible and practical options been evaluated?	11/30 [37%]	Have discount rates been described and justified given the target decision maker?	21/22 [95%]
Is there justification for the exclusion of feasible options?	6/19 [32%]	Are the utilities incorporated into the model appropriate?	21/23 [91%]
Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	20/22 [91%]	Is the source of utility weights referenced?	19/23 [83%]
Is the time horizon of the model sufficient to reflect all important differences between the options?	20/22 [91%]	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	9/20 [45%]
Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	21/22 [95%]	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	22/26 [85%]
Is the cycle length defined and justified in terms of the natural history of disease?	20/22 [91%]	Has heterogeneity been dealt with by running the model separately for different sub-groups?	7/30 [23%]
Are the data identification methods transparent and appropriate given the objectives of the model?	22/22 [100%]	Have the results been compared with those of previous models and any differences in results explained?	14/30 [47%]