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Bongers, M.L.; Coupé, V.M.H.; Jansma, E.P.; Smit, E.F.; Uyl-de Groot, C.A.

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Cost Effectiveness of Treatment with New Agents in Advanced Non-Small-Cell Lung Cancer

A Systematic Review

Mathilda L. Bongers,[1] *Veerle M.H. Coupé,*[1] *Elise P. Jansma,*[2] *Egbert F. Smit*[3] and *Carin A. Uyl-de Groot*[1,4]

1 Department of Epidemiology and Biostatistics, VU Medical Centre, Amsterdam, the Netherlands
2 VU Amsterdam University Library, Medical Library, Amsterdam, the Netherlands
3 Department of Pulmonary Diseases, VU Medical Centre, Amsterdam, the Netherlands
4 Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, the Netherlands

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Abstract

In past decades, studies focusing on new chemotherapeutic agents for patients with inoperable non-small-cell lung cancer have reported only modest gains in survival. These health gains are achieved at considerable cost, but economic evidence is lacking on superiority of one agent in terms of cost effectiveness. The objective of this systematic review was to assess fully published cost-effectiveness studies comparing the new agents docetaxel, paclitaxel, vinorelbine, gemcitabine and pemetrexed, and the targeted therapies erlotinib and gefitinib with one another.

We performed systematic searches in the bibliographic databases PubMed, EMBASE and Health Economic Evaluations (HEED) [via the Cochrane

Library] for fully published studies from the past 10 years. Studies were screened by two independent reviewers according to *a priori* inclusion criteria. The methodological quality of the included studies was evaluated by two independent reviewers using standardized assessment tools.

A total of 222 potential studies were identified; 11 studies and six reviews were included. The methodological quality of the full economic evaluations was fairly good. Transparency in costs and resource use, details on statistical tests and sensitivity analysis were points for improvement. In first-line treatment, gemcitabine+cisplatin was cost effective compared with other platinum-based regimens (paclitaxel, docetaxel and vinorelbine). In one study, pemetrexed+cisplatin was cost effective compared with gemcitabine+cisplatin in patients with non-squamous-cell carcinoma. In second-line treatment, docetaxel was cost effective compared with best supportive care; erlotinib was cost effective compared with placebo; and docetaxel and pemetrexed were dominated by erlotinib.

We found indications of superiority in terms of cost effectiveness for gemcitabine+cisplatin in a first-line setting, and for erlotinib in a second-line setting.

Key points for decision makers

- Due to the small number of studies, heterogeneity between studies and lack of a clear and consistent definition of best supportive care (BSC) in each study, strong conclusions cannot be drawn
- The estimates of key parameters, model assumptions and calculations in modelling studies were often poorly reported
- However, there was reasonable consensus between studies that gemcitabine+cisplatin is a cost-effective option for first-line treatment of non-small-cell lung cancer, although pemetrexed+cisplatin appears more cost effective for non-squamous-cell carcinoma
- In second-line treatment, docetaxel appears to be cost effective compared with BSC, while erlotinib may be a cost-effective alternative compared with docetaxel

Lung cancer is the most common cause of cancer-related death in the Western world.[1] Approximately 85% of all lung cancer cases are of the subtype non-small-cell lung cancer (NSCLC).[2] Many patients with NSCLC are diagnosed in an advanced stage (IIIB or IV), for which surgical resection is not recommended. These patients are treated with radiotherapy and/or (combinations of) chemotherapeutic agents.[2,3]

In past decades, research into chemotherapeutic treatments for patients with inoperable NSCLC has led to only modest gains in survival. Nevertheless, trials have generally supported the use of two chemotherapeutic drugs rather than one in terms of response rates, survival and quality of life (QOL). A recent systematic review[4] of the literature concerning the effectiveness in terms of response rates, survival, progression-free survival (PFS) and QOL of new drugs such as docetaxel, gemcitabine, paclitaxel, pemetrexed and vinorelbine, also known as third-generation agents, concluded that no single one among these new drugs was clearly superior over the others when used in combination with a platinum agent.

The modest improvements in the care of advanced NSCLC patients are achieved at considerable cost.[5] Therefore, the economic evaluation of new chemotherapeutic drugs has become

important for health policy makers who are charged with allocating limited funds to various healthcare programmes. The evidence with respect to cost effectiveness requires updating, especially because of the intensive research efforts in the last decade to improve treatment outcomes for NSCLC patients. Reviews available in the literature up until now mainly focused on third-generation agents compared with best supportive care (BSC) or with second-generation agents, which are older agents such as vindesine and mitomysin. Because second-generation drugs are no longer recommended, we chose to include in this review only studies comparing the third-generation agents docetaxel, gemcitabine, paclitaxel, pemetrexed and vinorelbine with each other or with BSC. Moreover, we included cost-effectiveness analyses (CEAs) focusing on the new targeted therapies erlotinib and gefitinib, as recently these drugs have shown positive results in phase III trials and are approved as second-line therapy and maintenance therapy (erlotinib) and as all-line therapy (gefitinib).

1. Literature Review

1.1 Search Strategy

We performed systematic searches in the bibliographic databases PubMed, EMBASE and Health Economic Evaluations (HEED) [via the Cochrane Library] for papers published between January 2001 and October 2010. Search terms included controlled medical subject heading (MeSH) terms in PubMed and Emtree in EMBASE, as well as free-text terms. We used free-text terms only in the HEED database. Search terms expressing non-small-cell lung carcinoma were used in combination with search terms representing expensive chemotherapies and terms for cost effectiveness. The search strategy is presented in table S1 in the Supplemental Digital Content (SDC), http://links.adisonline.com/PCZ/A132.

1.2 Selection Phase

To identify relevant studies, two independent reviewers (MLB and EPJ) screened the studies resulting from the search strategy, based on title and abstract. Studies were considered eligible if they met the following inclusion criteria:

- evaluated the agents of interest as one of the main topics in a full economic evaluation, more specifically in a CEA or cost-utility analysis (CUA);
- reported on at least one of the following outcomes: costs and QOL, or costs and survival;
- were full-text articles written in either Dutch or English.

Studies were excluded for the following reasons:

- included new agents, but the primary objective of the study was to evaluate a non-eligible agent or therapy (except for BSC or placebo);
- included a new agent but the only other comparator arm was a non-eligible agent;
- solely focused on the cost effectiveness of the treatment of metastases instead of primary tumours.

The results of the screenings by both reviewers were compared, and any disagreements were discussed. If disagreement remained, a third reviewer (VMHC) was consulted in order to reach a consensus. The references of the selected articles were searched for relevant publications.

1.3 Data Assessment

The full text of each of the selected studies was obtained for further review. Two reviewers (MLB and VMHC) independently evaluated the methodological quality of the full economic evaluations using the *British Medical Journal* (BMJ) 35-item checklist for authors and peer reviewers of economic submissions.[6] Again, the results were compared and disagreements were discussed in order to reach consensus. The objective of a critical appraisal is to assess whether the included studies describe methods, assumptions, models and potential biases in a way that is transparent and supported by the evidence, in order to enable appraisal by any critical reader. Although no checklist has been formally validated, the BMJ checklist by Drummond and Jefferson[6] is recommended for Cochrane reviews.[7]

As the BMJ checklist by Drummond and Jefferson[6] does not provide for the assessment of modelling studies, we supplemented the evaluation

of methodological quality with a framework proposed by Philips et al.[8] This framework consists of three dimensions of quality: structure, data and consistency, which are each subdivided into several questions for critical appraisal, such as the rationale for model structure, justification of identification of data and the extent to which consistency of the results with other models is discussed.

1.4 Search Results

The literature search generated a total of 368 references: 113 in PubMed, 188 in EMBASE and 67 in HEED from the Cochrane Library. After removing 146 duplicates that were included in more than one database, 222 papers remained. Of these 222 papers, 30 met the inclusion criteria, of which seven were conference abstracts only, two were not available in full text in time after two requests, one was only available in Portuguese, two were reports describing a manufacturer's economic evaluation, and one was a comment on another included study. The flow chart of the search and selection process is presented in figure 1.

Among the 17 remaining studies, six were reviews, six were CEAs and five were CUAs. We present an overview of the reviews, followed by a summary of the CEAs and CUAs by type of treatment: first-line treatment (four studies), maintenance therapy (one study) and second-line treatment (six studies).

2. Quality of the Evidence

The results of the assessment of the methodological quality for first- and second-line treat-

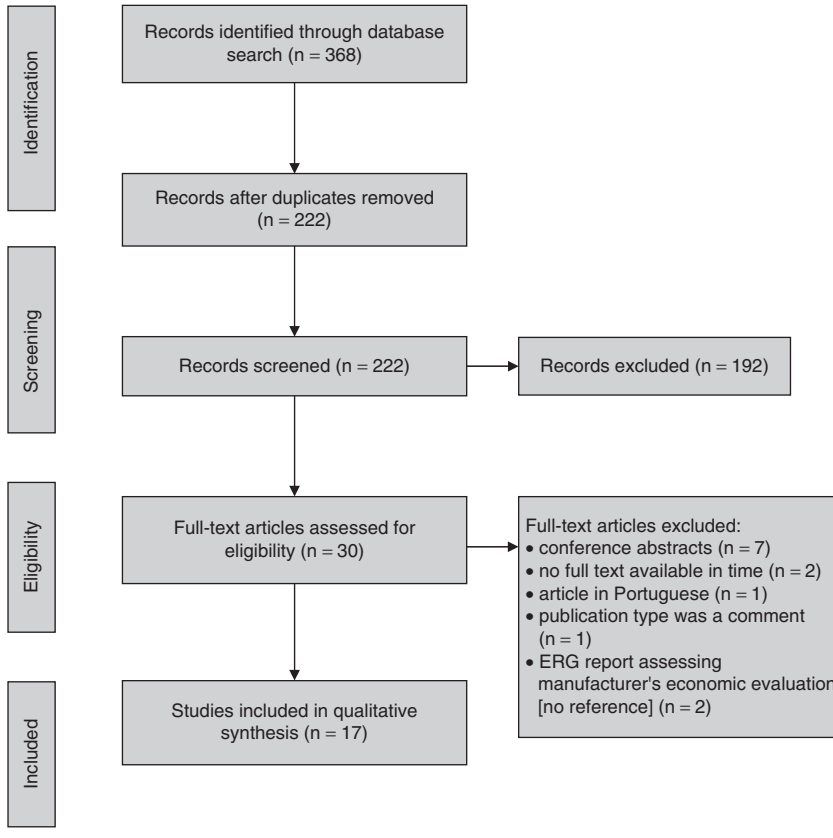

Fig. 1. Flowchart of the search and selection procedure for cost-effectiveness analyses. **ERG** = Evidence Review Group.

ment and maintenance therapy, as well as the assessment of the modelling studies, are presented in tables S2, S3 and S4 in the SDC. A few items were consistently under-reported, such as 'are the ranges over which the variables were varied for sensitivity analysis justified?',[9-16] 'were details of statistical tests and confidence intervals of stochastic data reported?'[10-16] and 'were quantities of resource use reported separately from their unit costs?'.[12,13,16-18]

3. Summary of the Evidence from Reviews Published between 2001 and 2010

The six reviews identified by our search strategy are summarized in table I and discussed below. Three reviews[20-22] assessed the literature with respect to any treatment for NSCLC. As these reviews were quite broad in the range of included treatments, no strong conclusions regarding specific chemotherapeutic agents were drawn. In general, it was suggested that therapies for NSCLC were cost effective or even cost saving compared with BSC, but that additional (cost-utility) studies were warranted. The review conducted by Clegg et al.[19] in 2001 evaluated the cost effectiveness of third-generation agents docetaxel, gemcitabine, paclitaxel and vinorelbine compared with BSC, and found all of these agents to extend life at reasonable cost (£6249–15 283 per life-year gained [LYG]).

The two remaining reviews[23,24] recently evaluated the cost effectiveness of erlotinib.

Lyseng-Williamson[24] included ten CEAs evaluating erlotinib after the failure of at least one chemotherapy regimen; three of these were fully published studies. Overall, in eight studies, erlotinib dominated docetaxel (erlotinib was cheaper and more effective). Of five studies comparing erlotinib with pemetrexed, three concluded that erlotinib dominated pemetrexed, and the two remaining studies reported erlotinib to be cost saving compared with pemetrexed (erlotinib was cheaper and equally effective). The author concluded that, in patients with advanced NSCLC, second- or third-line therapy with erlotinib was clinically effective in improving survival, and the available pharmacoeconomic data supported the use of erlotinib as a cost-saving treatment compared with docetaxel and pemetrexed.

In 2009, Carlson[23] reviewed eight CEAs of erlotinib, five of which were also included by Lyseng-Williamson.[24] Similarly to Lyseng-Williamson, the author concluded that erlotinib provided equivalent or additional effectiveness compared with BSC and pemetrexed. The main difference between erlotinib and the alternative treatments docetaxel and pemetrexed appeared to be the convenience and cost savings associated with oral versus intravenous administration, as well as the favourable toxicity profile of erlotinib. Both reviews included (conference) abstracts as well as peer-reviewed full publications.

4. First-Line Treatment

All of the studies focusing on first-line treatment included gemcitabine in one of the treatment arms, either in combination with cisplatin (three studies[12,14,18]) or in combination with docetaxel (one study[25]). Table II provides an overview of all studies for first-line treatment. In table III, the reported costs and benefits in the three studies with a gemcitabine+cisplatin arm[12,14,18] are presented in detail. Table S5 in the SDC presents the included clinical and cost inputs for all first-line treatment studies.

Neymark et al.[18] conducted a study in the Netherlands, comparing paclitaxel+cisplatin with gemcitabine+cisplatin and with gemcitabine+paclitaxel. For both comparisons, the results were presented on a cost-effectiveness plane, showing the joint distribution of 5000 bootstrap replicates of differences in costs and survival time in years. The authors found a 72% probability that gemcitabine+cisplatin improves survival and reduces costs compared with paclitaxel+cisplatin. The difference in costs was explained by the chemotherapy costs, paclitaxel being a more expensive drug than gemcitabine (€8654 vs €5234 per patient [year 2002 values]). Comparing paclitaxel+cisplatin with gemcitabine+paclitaxel resulted in a probability of 82% that gemcitabine+paclitaxel would reduce mean survival while increasing costs. The authors concluded that gemcitabine+paclitaxel is clearly dominated by

Table I. Overview of identified reviews[a]

Study, drug(s) of interest	Search strategy	Authors' conclusion	Remarks	References included in present review
Clegg et al.[19] DOC, PAC, VIN, GEM	*Databases*: 11 databases including MEDLINE, EMBASE and The Cochrane Library *Inclusion/exclusion criteria*: Tx includes DOC, PAC, VIN and GEM, used alone or in combination with other drugs, for NSCLC and SCLC. Studies on tx of lung metastases, on the use of drugs as adjuvant therapy before surgery, or on drugs in combination with radiotherapy were not included *Number of included studies*: 16	VIN has been reported to deliver cost savings or low incremental cost vs BSC. GEM and PAC have also led to small but arguably acceptable incremental costs over BSC. However, there have been no direct comparisons of efficacy in phase III trials between the drugs. Studies evaluating DOC mostly see it as second-line therapy	Inclusion criteria were not specifically aimed at full economic evaluations. CMAs were also included and there were no restrictions to types of comparator arms. Many studies compared the drugs with second-generation drugs. Although the conclusions were based on comparisons with BSC, only 4 studies actually compared the drug(s) with a BSC arm	None
Dranitsaris et al.[20] Chemotherapy for NSCLC	Not reported	New and expensive chemotherapy drugs can be cost effective vs BSC. This finding emphasizes the need for well designed CEAs of chemotherapy alternatives, rather than a simple concern for the unit cost of a new drug or a comparison with BSC only	This review considered the literature on four third-generation agents vs BSC or second-generation agents. Although the tx strategies are compared with each other in a table, there is no transparency in the costs and health gains accompanied with each strategy. A proper search strategy is lacking	None
Carlson et al.[21] Several drugs used in the tx of NSCLC	*Databases*: PubMed, EMBASE, BIOSIS Previews, HREA, NICE, CADTH *Inclusion criteria*: Original publications of economic evaluations in English from peer-reviewed journals of antineoplastic agents for the tx of NSCLC with an abstract *Number of included studies*: 20	In general, the studies favoured tx with chemotherapy over BSC and CIS over CAR. However, the identified studies varied in disease stage, line of tx and comparator arms. The results of this review reflect the large number of tx strategies available in the tx of NSCLC	The scope of the study (all tx, all types of economic evaluations) is too broad for result interpretation. This review is more an overview of available studies. Therefore, no overall conclusions with respect to the content of the studies could be drawn	Leighl et al.[15] Neymark et al.[18] Holmes et al.[11] Lees et al.[14] 16 studies did not meet our inclusion criteria for reasons outlined in footnotes[b,c,d]
Chouaid et al.[22] Not specified	*Databases*: MEDLINE, CRD, HEED *Exclusion criteria*: Economic analyses on SCLC and other aspects of NSCLC management (e.g. smoking cessation, screening, diagnosis and staging procedures) and on the impact of supportive medications *Number of included studies*: 13	Third-generation agents used in the first-line advanced NSCLC setting can be administered with acceptable incremental cost effectiveness. In the second-line setting, new agents (targeted therapies) have been shown to have acceptable cost effectiveness	Although this review subdivided the identified studies to the disease stages, heterogeneity in tx remained. Therefore, it does not generate stronger evidence regarding cost-effective tx decisions, nor a comparison of agents in terms of cost effectiveness	Lees et al.[14] Neymark et al.[18] Leighl et al.[15] Holmes et al.[11] Lewis et al.[16] 9 studies did not meet our inclusion criteria for reasons outlined in footnotes[b,c,d]
Carlson[23] ERL	*Databases*: Not reported *Inclusion/exclusion criteria*: Not reported *Number of included studies*: Not reported, but 8 studies on ERL were discussed	ERL vs DOC and PEM, provides equivalent to slightly improved outcomes with variability in the incremental costs depending on the health system in which the analysis was performed	The authors discussed two full publications of their own research group and six abstracts. The general conclusion derived from these additional abstracts was that they tended to agree with the results of the authors' prior publications. No proper search strategy was reported	Carlson et al.[10] Carlson et al.[21] 7 studies did not meet our inclusion criteria for reasons outlined in footnotes[e,f]

Continued next page

Table I. Contd

Study, drug(s) of interest	Search strategy	Authors' conclusion	Remarks	References included in present review
Lyseng-Williamson[24] ERL	*Databases:* Not reported *Inclusion/exclusion criteria:* Not reported *Number of included studies:* 10	In advanced NSCLC, second- or third-line therapy with ERL is clinically effective in improving survival. ERL is also considered a cost-saving tx vs DOC or PEM in this pt population	This review included mainly abstracts, only three studies were full publications. CMAs were also included, but were discussed separately. All fully published modelling studies were assessed via a checklist for pharmacoeconomic analyses	Carlson et al.[10] Lewis et al.[16] 8 studies did not meet our inclusion criteria for reasons outlined in footnotes[b,e,f]

a For the purpose of this review, only the sections evaluating CEAs or CUAs of tx for stage III/IV NSCLC pts were considered, although some reviews were less specific with respect to this topic (i.e. evaluating economic impact, clinical and cost effectiveness, or all stages of NSCLC).

b Study was a study other than a CEA or CUA (e.g. CMA, review).

c Comparator arms were other than third-generation agents, targeted agents, BSC or placebo.

d Study was published before January 2000.

e Study was only published as an abstract/conference poster.

f Other.

BSC = best supportive care; **CADTH** = Canadian Agency for Drugs and Technologies in Health; **CAR** = carboplatin; **CEA** = cost-effectiveness analysis; **CIS** = cisplatin; **CMA** = cost-minimization analysis; **CRD** = Centre for Research and Dissemination; **CUA** = cost-utility analysis; **DOC** = docetaxel; **ERL** = erlotinib; **GEM** = gemcitabine; **HEED** = Health Economic Evaluations Database; **HREA** = Harvard Review of Economic Analyses; **NICE** = National Institute for Health and Clinical Excellence; **NSCLC** = non-small-cell lung cancer; **PAC** = paclitaxel; **PEM** = pemetrexed; **pt(s)** = patient(s); **SCLC** = small-cell lung cancer; **tx** = treatment(s); **VIN** = vinorelbine.

paclitaxel+cisplatin, which in turn is dominated by gemcitabine+cisplatin.

The second study considering the gemcitabine+cisplatin regimen was the UK cost-effectiveness study by Lees et al.[14] The authors compared gemcitabine+cisplatin with paclitaxel+cisplatin, paclitaxel+carboplatin, docetaxel+cisplatin and vinorelbine+cisplatin. Overall survival was similar for the treatment arms containing either docetaxel or paclitaxel, but median survival time was increased for gemcitabine+cisplatin compared with vinorelbine+cisplatin (42 weeks vs 35 weeks; survival times of other arms were not reported). PFS was reported for all regimens. Compared with all other regimens, gemcitabine+cisplatin resulted in incremental progression-free life-years ranging from 0.083 to 0.135 (see table III). Main cost drivers in this study were the costs of chemotherapy and its administration. The authors concluded that the gemcitabine+cisplatin regimen provided value for money relative to other novel regimens. The authors did not report any incremental cost-effectiveness ratios (ICERs), nor any incremental analysis of the treatment regimens.

Klein et al.[12] assessed the cost effectiveness of pemetrexed+cisplatin compared with gemcitabine+cisplatin in a general stage IIIB/IV population in the US, as well as in patients with non-squamous cell carcinoma. In this latter subgroup, they found an ICER of $US83 537 per LYG for pemetrexed+cisplatin compared with gemcitabine+cisplatin (year 2002 values), based on incremental costs of $US4509 and incremental life-years of 0.054. The CUA resulted in an ICER of $US132 829 per QALY gained, based on $US4509 incremental costs and 0.0339 incremental QALYs. In the total group (non-squamous- and squamous-cell carcinoma), the incremental costs for pemetrexed were higher than in the non-squamous group, and LYG and QALYs were lower, resulting in higher ICERs ($US104 577 per LYG; $US179 597 per QALY). In the US, the value of $US50 000 per QALY gained is frequently quoted as being the threshold for cost effectiveness, but a range of $US109 000–297 000 is more likely to be consistent with societal preferences.[30] In this regard, Klein et al.[12] considered pemetrexed+cisplatin to be cost effective compared with gemcitabine+

Table II. Overview of included studies for first-line treatment

Study	Study characteristics	Treatment: administration (frequency × dose [mg/m^2] per cycle)	Data input	Reported outcomes[a]	Authors' conclusion and reviewers' remarks
Neymark et al.[18]	CEA of a multicentre trial[26] *Perspective*: Dutch health insurance system *Time horizon*: 3 y *Discounting*: None *Population*: Stage IIIB/IV NSCLC pts (mainly Dutch)	PAC+CIS: IV 3 h (1×175+1×80) GEM+CIS: IV <1 h (2×1250+1×80) GEM+PAC: IV 3 h (2×1250+1×175)	*Clinical data*: Head-to-head trial data: mean survival, by restricted mean analysis (AUC) *Resource use*: Trial case reports (drugs) and trial protocol (medical services) *Costs*: Costs of clinical stay, transfusions and radiotherapy from the national reimbursement tariffs by CTG valid for 2002; for costs of hospitalization, a charge-to-cost ratio was based on CTG tariff of day clinic stay; cost of drugs from Dutch Pharmaceutical Compass	*Mean survival time (y)*: PAC+CIS: 0.94 GEM+CIS: 0.98 GEM+PAC: 0.80 *Total costs (€)*: PAC+CIS: 16 662 GEM+CIS: 13 944 GEM+PAC: 17 377	*Conclusion*: The probability that GEM+CIS improves outcome and at the same time reduces costs is 72% vs PAC+CIS. GEM+PAC is not likely to improve survival (6%) or reduce costs (12%) vs PAC+CIS *Remarks*: As their total costs are an underestimation, the authors do not present an ICER but a cost-effectiveness plane. National tariffs were used instead of costs, resource use for drugs was based on trial reports from different hospitals, and trial protocols were used regarding the medical resources
Lees et al.[14]	CEA based on two trials[27,28] *Perspective*: UK healthcare system *Time horizon*: Randomization until death *Discounting*: None *Population*: Advanced stage IIIB/IV NSCLC. The trial with GEM vs DOC and PAC arms had mainly stage IV pts	GEM+CIS: NR (2×1250+1×100) PAC+CIS: IV 24 h (1×175+1×75) PAC+CAR: IV 3 h (1×225+1×AUC dose) DOC+CIS: NR (1×75+1×75) VIN+CIS: NR (NR)	*Clinical data*: Two head-to-head trials: survival, time to progression *Resource use*: Trial data for chemotherapy and administration; hospitalization was based on incidence of adverse effects *Costs*: Chemotherapy costs from BNF; hospital costs from UK national schedule of reference costs; administration and health professionals costs from UK-based source of unit costs in healthcare (all y 2000 values)	Reference = GEM+CIS *Incremental PFS (LY)*: PAC+CIS: −0.083 PAC+CAR: −0.075 DOC+CIS: −0.100 VIN+CIS: −0.135 *Incremental costs (£)*: PAC+CIS: 3 506 PAC+CAR: 2 907 DOC+CIS: 242 VIN+CIS: 571	*Conclusion*: From the UK healthcare perspective, GEM+CIS represents a cost-effective tx for NSCLC vs novel therapies *Remarks*: Hospitalization costs may be underestimated as not all relevant AEs were included. All tx were administered in an outpatient setting, except for PAC+CIS. Data regarding the resource use of radiotherapy, transfusions and concomitant medications were not available and, therefore, these costs were assumed equal. In the trial with the VIN+CIS arm, all costs except for chemotherapy and administration were assumed to be equal
Klein et al.[12]	Model-based CEA and CUA *Perspective*: US payer *Time horizon*: 2 y *Discounting*: No discounting but 3–5% varied in sensitivity analysis *Population*: Chemotherapy-naive pts, stage IIIB/IV NSCLC, with non-squamous pts as subgroup of primary interest	PEM+CIS: NR (1×500+1×75) GEM+CIS: NR (2×1250+1×75)	*Clinical data*: Head-to-head trial data for survival, PFS and response rates *Resource use/costs*: Chemotherapy costs from max. reimbursement assuming average doses; costs of administration and monitoring from claims database of the y 2002	PEM vs GEM (ICERs [$US]) Non-squamous: 83 537 per LYG; 132 829 per QALY All: 104 577 per LYG; 179 597 per QALY	*Conclusion*: Considering a $US100 000 threshold value for LYG, PEM+CIS is a cost-effective option vs GEM+CIS in a non-squamous population *Remarks*: It is not clear whether costs of hospitalization were included. Costs associated with serious AEs and second-line tx were considered equal in both tx arms, which is unlikely to be true in daily clinical practice. This may have biased the results against PEM+CIS

Continued next page

Table II. Contd

Study	Study characteristics	Treatment: administration (frequency × dose [mg/m²] per cycle)	Data input	Reported outcomes[a]	Authors' conclusion and reviewers' remarks
Maniadakis et al.[25]	CEA of a trial[29] *Perspective*: Greek national healthcare system *Time horizon*: Randomization until death *Discounting*: None *Population*: Advanced/metastatic stage IIIB/IV NSCLC pts	DOC: NR (1×100) DOC+GEM: NR (1×100+2×2000)	*Clinical data*: Head-to-head trial data for survival, PFS, response rates and response duration *Resource use/costs*: Head-to-head trial data on resource use was combined with unit costs (2005) of (pre)medication, administration, radiotherapy and hospitalization from Greek national sources and hospitals database	Reference = DOC *Incremental mean survival (mo)*: DOC+GEM: 1.94 *Incremental costs (€)*: DOC+GEM: 1542	*Conclusion*: In the Greek national health system setting, DOC+GEM is a cost-effective tx for NSCLC, with a ratio of about €9500 per LYG, in relation to monotherapy with DOC alone *Remarks*: Although all costs seem to be included, the differences between tx arms were not explained in terms of resource use

a Conversion rate as at 13 December 2010: €1 = $US1.32 = £0.84.

AE = adverse event; **AUC** = area under the curve; **BNF** = British National Formulary; **CAR** = carboplatin; **CEA** = cost-effectiveness analysis; **CIS** = cisplatin; **CTG** = College Tarieven Gezondheidszorg; **CUA** = cost-utility analysis; **DOC** = docetaxel; **GEM** = gemcitabine; **ICER** = incremental cost-effectiveness ratio; **IV** = intravenous; **LYG** = life-years gained; **max.** = maximum; **NR** = not reported; **NSCLC** = non-small-cell lung cancer; **PAC** = paclitaxel; **PEM** = pemetrexed; **PFS** = progression-free survival; **pt(s)** = patient(s); **tx** = treatment(s); **VIN** = vinorelbine.

cisplatin, regardless of histological subtype. Although the authors included all relevant costs from a healthcare payer perspective, the costs for adverse events within both treatment arms were considered equal. This assumption may have biased the ICERs against pemetrexed+cisplatin, as the original trial[31] reported a higher incidence of serious adverse events in the gemcitabine arm. A sensitivity analysis was conducted to address this assumption, resulting in an ICER of $US39 000–44 000 per LYG, corresponding with a 45–55% decrease in adverse events for pemetrexed.

Maniadakis et al.[25] compared gemcitabine+docetaxel with docetaxel alone in Greece and reported an ICER of €9538 per LYG (year 2005 values), which is far below international thresholds used to accept implementation and reimbursement of new treatments. They concluded that gemcitabine+docetaxel is a cost-effective treatment option in the Greek healthcare setting, compared with docetaxel monotherapy.

To summarize, in two studies,[14,18] gemcitabine+cisplatin was a cost-effective treatment option compared with paclitaxel+cisplatin and, in one study,[14] compared with paclitaxel+carboplatin, docetaxel+cisplatin and vinorelbine+cisplatin. However, pemetrexed+cisplatin was cost effective compared with gemcitabine+cisplatin, especially in the subgroup of patients with non-squamous-cell carcinoma.[12]

5. Maintenance Therapy

One US study[13] was available for maintenance therapy. The primary objective was to estimate the cost effectiveness of maintenance therapy with pemetrexed compared with observation, each in addition to BSC, in patients with advanced NSCLC who have completed, without progression, at least four cycles of first-line platinum chemotherapy. The median overall survival for patients treated with pemetrexed compared with observation was 15.5 months versus 10.3 months, respectively, in patients with non-squamous-cell histology, and 13.4 months versus 10.6 months, respectively, in the total study population. Additionally, patients treated with pemetrexed had a longer PFS compared with observation (non-squamous:

Table III. Detailed overview of results of the studies of first-line treatment that have gemcitabine+cisplatin (GEM+CIS) as one of the treatment arms

Study, comparator	Costs			Survival (y)		
	GEM+CIS arm	comparator arm	incremental costs	GEM+CIS arm	comparator arm	incremental survival
Klein et al.[12]				Median survival		
PEM+CIS	$US61 008	$US65 517	–$US4509	0.87	0.98	–0.054[a]
Neymark et al.[18]				Mean survival		
PAC+CIS	€13 944	€16 662	–€2718	0.98	0.94	0.04
PAC+GEM	€13 944	€17 377	–€3433	0.98	0.80	0.18
Lees et al.[14]				Progression-free survival		
PAC+CIS	£5537	£9043	–£3506	0.375	0.292	0.083
PAC+CAR	£5537	£8444	–£2907	0.375	0.300	0.075
DOC+CIS	£5537	£5779	–£242	0.375	0.275	0.100
VIN+CIS[b]	£4477	£5048	–£571	0.808	0.673	0.135

a Incremental survival resulting from running the model. Median survival of both arms presented here was directly taken from the trial and cannot be subtracted to obtain incremental survival.

b The results for VIN+CIS vs GEM+CIS were obtained from another trial.

CAR = carboplatin; **DOC** = docetaxel; **PAC** = paclitaxel; **PEM** = pemetrexed; **VIN** = vinorelbine.

2.6 months; total: 1.7 months). Major drivers of cost differences were drug costs, as well as costs for serious adverse events. The incremental cost per LYG was $US122 371 for pemetrexed compared with observation in the non-squamous population and $US205 597 in the total study population (year 2009 values). The authors concluded that histology is important in targeting the appropriate patients for pemetrexed maintenance therapy.

6. Second-Line Treatment

Five of six studies focusing on second-line treatment included docetaxel in one of the treatment arms, either as a comparator or as the reference agent. Table IV presents an overview of the studies. An overview of the included costs and benefits for all treatment arms of the six studies is presented in table S6 in the SDC. The total and incremental costs, as well as survival estimates, for the five studies with a docetaxel arm are presented in table V.

Holmes et al.[11] and Leighl et al.[15] compared docetaxel 75 mg with BSC. Both studies considered survival and resource use based on the same trial, TAX 317,[32] although they used different methods to estimate the key parameters in their analyses. The cost effectiveness of docetaxel versus BSC was found to be $Can31 776 per LYG in Canada (year 1999 values)[15] and £13 863 per LYG in the UK (year 2000/2001 values),[11] and both studies concluded that docetaxel is cost effective from a healthcare system perspective. The main cause of the difference in ICERs was related to costs for hospitalization and for adverse events, which were not included in Holmes et al.,[11] whereas they were included by Leighl et al.[15]

Asukai et al.[17] performed a CUA comparing pemetrexed with docetaxel. QOL estimates were based on utility values, which were obtained from a study of 100 participants. They found that, compared with docetaxel, pemetrexed was associated with higher chemotherapy costs and lower costs for adverse events. Median survival and PFS were both higher in the pemetrexed arm (9.3 vs 8.0 months and 3.1 vs 3.0 months, respectively). Based on the mean values of survival and PFS in both arms, this resulted in an ICER of €17 225 per LYG and €23 967 per QALY gained for pemetrexed compared with docetaxel (year 2007 values). The lower number of reported adverse events in the pemetrexed arm contributed favourably to the health-related QOL of patients treated with pemetrexed. Given the Spanish threshold of €30 000 per QALY gained, pemetrexed was considered cost effective in comparison with docetaxel in Spain.

Table IV. Overview of included studies for second-line treatment

Study	Study characteristics	Treatment: administration (frequency × dose [mg/m^2] per cycle)	Data input	Reported outcomes[a]	Authors' conclusion and reviewers' remarks
Leighl et al.[15]	CEA of a trial, TAX 317[32] *Perspective*: Canadian healthcare system *Time horizon*: Randomization until death *Discounting*: No discounting *Population*: Stage IIIB/IV NSCLC pts with WHO performance status ≤ 2, previously treated with platinum-based therapy	BSC: NR (NR × 75) DOC: IV 1 h (1 × 75)	*Clinical data*: Mean survival from head-to-head trial data *Resource use*: Trial and hospital records *Costs*: Costs of chemotherapy, administration, palliative care, radiation therapy and toxicity were taken from trial and hospital records (1999). Costs of hospitalization and clinical visits were calculated by hotel approximation method	*DOC vs BSC ($Can)* Incremental. costs: 10 804 Incremental LY: 0.34 ICER per LYG: 31 776	*Conclusion*: The clinical benefits of second-line chemotherapy seem similar in magnitude to those derived from first-line therapy, but the costs of second-line are higher. The ICER is below an acceptable range for health interventions in Canada ($Can53 000–251 000) *Remarks*: Pts in the DOC arm were more likely to be admitted to the acute care setting or a palliative care facility
Holmes et al.[11]	CEA of a trial, TAX 317[32] *Perspective*: UK NHS *Time horizon*: 2 y *Discounting*: No discounting *Population*: Stage IIIB/IV NSCLC pts with WHO performance status ≤ 2, previously treated with platinum-based therapy	BSC: NR (NR × 75) DOC: IV 1 h (1 × 75)	*Clinical data*: Mean survival from head-to-head trial data, by AUC curve analysis *Resource use*: Trial data *Costs*: Source for chemotherapy costs was NR Administration costs were based on a study on unit costs and resource use in healthcare. Toxicity costs (included in sensitivity analysis only) were based on a study on colorectal cancer, all in y 2000/2001	*DOC vs BSC (£)* Incremental costs: 4 432 Incremental LY: 0.32 ICER per LYG: 13 863	*Conclusion*: DOC 75 mg/m^2 in 3-weekly cycles is a cost-effective second-line tx for pre-treated NSCLC pts, from the perspective of the NHS, in terms of survival gains made for a reasonable increase in costs *Remarks*: There is uncertainty about chemotherapy costs, and only therapeutic and palliative interventions were considered. In addition, cost estimates were not separately presented from resource use and only incremental costs were reported, which make this study poor in its transparency
Asukai et al.[17]	Model-based CEA and CUA, 2 trials[31,33] *Perspective*: Spanish healthcare system *Time horizon*: 3 y *Discounting*: 3% for both costs and benefits *Population*: stage IIIB/IV NSCLC pts with predominantly non-squamous population, previously treated with chemotherapy	PEM: IV <2 h (1 × 500) DOC: IV <2 h (1 × 75)	*Clinical data*: Model input variables were survival, PFS and tumour response, based on head-to-head trial data *Resource use*: Head-to-head trial data for chemotherapy and administration. Hospitalization was based on AEs *Costs*: Chemotherapy costs from summary of product information; hospital costs from healthcare databases; costs of AEs, BSC and palliative care were opinion-based. Y of value NR	*PEM vs DOC (€)* Incremental costs: 2334 Incremental LYG: 0.14 Incremental QALYs: 0.10 ICER per LYG: 17 225 ICER per QALY: 23 967	*Conclusion*: In the Spanish healthcare setting, PEM for second-line tx of pts with NSCLC other than predominantly squamous cell histology is indicated as a cost-effective tx option vs the standard DOC, based on its superior overall survival benefit and toxicity profile *Remarks*: Costs of AEs, BSC and palliative care were based on expert opinion surveys of five Spanish clinicians. It was assumed that survival would follow an exponential distribution, although this is very unlikely, as this distribution assumes constant hazards

Continued next page

Table IV. Contd

Study	Study characteristics	Treatment: administration (frequency × dose [mg/m^2] per cycle)	Data input	Reported outcomes[a]	Authors' conclusion and reviewers' remarks
Carlson et al.[10]	Model-based CEA and CUA, 4 trials: BR.21,[34] TAX 317,[32] TAX 320,[35] Hanna et al.[33] *Perspective*: US payer *Time horizon*: 2 y *Discounting*: Costs and effects were discounted at 3% *Population*: Stage III/IV NSCLC pts, who failed at least one platinum-based tx	DOC: IV 1 h (NR × 150) PEM: IV 1 h (NR × 880) ERL: oral (NR × 150)	*Clinical data*: Survival and PFS from the four trials, utilities based on EQ-5D from a study *Resource use*: AEs and drugs were from the pivotal trials and the prescribing information *Costs*: Drug costs were from the wholesale acquisition costs from the First Data Bank I online database of 2007. Costs of disease progression were based on a study. Administration and AEs were based on CMS physicians' fee schedule and the acute inpatient prospective payment system	*PEM vs DOC ($US)* Incremental costs: 4 655 Incremental QALYs: 0 *ERL vs PEM* Incremental costs: –6782 Incremental QALYs: 0.01 *ERL vs DOC* Incremental costs: –2127 Incremental QALYs: 0.01	*Conclusion*: ERL is less costly in the tx of refractory NSCLC in the US vs alternative tx, and potentially leads to a slight improvement in QALYs *Remarks*: Survival and PFS were assumed equal in all arms. QALYs were assumed to be equal in DOC and PEM arms, but not for ERL. These assumptions may not reflect clinical practice. It was not clear how PFS and QALYs were calculated. The four trials differed in their population, in terms of prior tx and WHO performance status. No costs for prognostic testing of an EGFR marker were considered
Lewis et al.[16]	Model-based CEA and CUA, 2 trials: BR.21[34] TAX317[32] *Perspective*: NHS *Time horizon*: 2 y *Discounting*: Costs and probably also effects were discounted at 3.5% *Population*: Stage IIIB–IV NSCLC pts, previously treated with one or more chemotherapy regimens	DOC: IV NR (1 × 75) ERL: oral (daily × 150)	*Clinical data*: Mean survival based on trial data; tx duration was used as PFS surrogate; utilities based on EQ-5D from a study *Resource use*: Based on panel of five lung cancer physicians *Costs*: Drug costs were provided by NHS reference cost sources. Other costs were derived from the same source or from figures provided by the Personal Social Services Unit. Y 2004–8 values	*ERL vs DOC (£)* Incremental costs: –226 Incremental QALYs: 0.032 ICER per QALY: –7 106	*Conclusion*: The authors concluded ERL to be cost effective vs DOC, although the CEA plane showed that incremental costs and effects are equally distributed among the four quadrants *Remarks*: Survival is assumed to be equal, which probably biases the results against ERL. PFS data were not available for DOC, so in both arms mean tx duration was used as a proxy instead. No costs for prognostic testing of an EGFR marker were considered
Bradbury et al.[9]	CEA of a trial, BR.21[34] *Perspective*: Canadian public healthcare system *Time horizon*: NR *Discounting*: No discounting *Population*: Pts with previously treated, advanced NSCLC	ERL: oral (daily × 150) Placebo: oral (daily × 150)	*Clinical data*: Mean overall survival from trial data *Resource use*: Hospitalization, AEs, tests, OP visits and all therapies were obtained from the trial database. *Costs*: Drug costs were obtained from PPS Pharma publication; hospitalization from a national database; costs of other drugs were modelled based on Canadian practice; sources of costs for radiotherapy and for OP visits were NR. Y 2007 values	*ERL vs placebo ($Can)* Incremental costs: 12 303 Incremental LY: 0.13 ICER per LYG: 94 638	*Conclusion*: From a Canadian perspective, ERL is at the upper boundary of moderate cost effectiveness. Specific subgroups (never-smokers, high EGFR gene copy number, adenocarcinoma histology and EGFR protein expression) were associated with lower ICERs *Remarks*: This is the first study to evaluate the cost effectiveness of ERL in subgroups in which better response may be expected. No costs for prognostic testing of an EGFR marker were considered

a Conversion rate as at 13 December 2010: €1 = $US1.32 = £0.84.

AE = adverse event(s); **AUC** = area under the curve; **BSC** = best supportive care; **CEA** = cost-effectiveness analysis; **CMS** = Center for Medicare and Medicaid Services; **CUA** = cost-utility analysis; **DOC** = docetaxel; **EGFR** = epidermal growth factor receptor; **ERL** = erlotinib; **ICER** = incremental cost-effectiveness ratio; **IV** = intravenous; **LY(G)** = life-years (gained); **NR** = not reported; **NSCLC** = non-small-cell lung cancer; **OP** = outpatient; **PEM** = pemetrexed; **PFS** = progression free survival; **pt(s)** = patient(s); **tx** = treatment(s).

Table V. Detailed overview of results of the studies of second-line treatment that have docetaxel (DOC) as one of the treatment arms

Study, comparator	Costs			Survival (y)		
	DOC arm	comparator arm	incremental costs	DOC arm	comparator arm	incremental survival
Leighl et al.[15]				Mean survival		
BSC	$Can17 739	$Can6 935	$Can10 804	0.79	0.45	0.34
Holmes et al.[11]				Incremental survival		
BSC	£4 432	£0	£4432	0.32	0.00	0.32
Asukai et al.[17]				Mean survival		
PEM	€32 343	€34 677	–€2334	0.89	1.03	–0.14
Carlson et al.[10]				Overall survival		
PEM	$US39 104	$US43 759	–$US4655	0.75	0.75	0.00
ERL	$US39 104	$US36 977	$US2127	0.75	0.75	0.00
Lewis et al.[16]				QALYs		
ERL	£13 956	£13 370	£226	0.206	0.238	0.032

BSC = best supportive care; **ERL** = erlotinib; **PEM** = pemetrexed.

Carlson et al.[10] evaluated costs and effectiveness of docetaxel, pemetrexed and erlotinib from a US payer perspective. Overall survival was assumed to be equal in all treatment arms, as was PFS. When QALYs were used as the health outcome measure, erlotinib provided an incremental QALY gain of 0.01 compared with docetaxel and pemetrexed, due to less severe adverse events and the oral administration of erlotinib versus the intravenous administration of pemetrexed and docetaxel. In the CUA, erlotinib dominated both docetaxel and pemetrexed.

Lewis et al.[16] also compared erlotinib with docetaxel in a CUA, but from a UK NHS perspective. The survival was derived from Kaplan-Meier curves of the same trials as the studies by Carlson et al.,[10] Holmes et al.[11] and Leighl et al.[15] (BR.21 for erlotinib,[34] and TAX 317 for docetaxel[32]). The BR.21 trial included more patients with a poor performance status (WHO performance status of 3) than the TAX 317 trial. Whereas Carlson et al.[10] adjusted for this potential bias, Lewis et al.[16] did not. In addition, Lewis et al.[16] assumed PFS to be equal to the mean treatment duration (3.33 months in docetaxel arm and 4.11 months in erlotinib arm), while Carlson et al.[10] did not report how PFS was estimated (4 months in both arms). With the exception of the costs associated with disease progression, Lewis et al.[16] reported similar cost estimates as Carlson et al.[10] Lewis et al.[16] found erlotinib to dominate docetaxel, although the incremental costs and incremental effects were very small. The cost-effectiveness plane showed an equal distribution of incremental costs and effects among the four quadrants.

Bradbury et al.[9] evaluated the cost effectiveness of erlotinib piggybacked alongside the actual BR.21 trial, from a Canadian public healthcare system perspective. As such, data on resource utilization and costs were available and taken directly from the trial. The ICER of erlotinib was $Can94 638 per LYG versus placebo (year 2007 values). In addition to their principal analyses, Bradbury et al.[9] evaluated the cost effectiveness of erlotinib for subgroups characterized by molecular features that are expected to be related to response to erlotinib. The greatest change in the ICER compared with the total group was found in the subgroup of patients with a high epidermal growth factor receptor (EGFR)-gene copy number and in the subgroup of never-smokers (ICER $Can33 353 and $Can39 487 per LYG, respectively).

To summarize, docetaxel seems a cost-effective treatment option when compared with BSC. The adverse events associated with docetaxel were febrile neutropenia and neutropenia, which are both related to hospitalization and, therefore, were the main drivers of costs for docetaxel.[10,15,17] One study[11] did not take adverse events into account. Pemetrexed was a more expensive drug

than docetaxel, with less adverse events, in two independent studies,[10,17] although each was performed in a different country. In one of these studies,[17] pemetrexed was cost effective compared with docetaxel but was dominated by erlotinib. Erlotinib was cost effective compared with docetaxel in a UK study[16] and borderline cost effective compared with BSC in a Canadian study.[9] The Canadian study found lower ICERs in never-smokers and in a subgroup of patients with a high gene copy number.

7. Sensitivity Analyses

Overall, univariate sensitivity analyses showed assumptions on survival time, and PFS had a major impact on the outcomes.[9-11,13,15,17] However, none of the varied cost and effectiveness drivers led to alternative conclusions (i.e. dominated became dominant treatment), indicating robust results.

Carlson et al.[10] assumed equal survival and PFS of docetaxel, pemetrexed and erlotinib. The sensitivity analyses in the study by Carlson et al.[10] showed that length of time in the progressive-disease state has a huge influence on total costs, as well as QALYs. As such, different assumptions for PFS difference between the treatment arms will influence the ICER. The sensitivity analyses by Lewis et al.[16] assessed alternative scenarios, such as equivalent overall survival and PFS, equivalent treatment duration, equivalent utility scores for PFS and the omission of adverse events utilities, instead of the trial-based outcomes. Erlotinib remained the dominant treatment. Additionally, cost and effectiveness drivers were varied across 'plausible ranges' of −20% and +20% or −50% and +50%, but no rationale behind the selection of drivers, nor behind the 20% or 50% ranges, was given.

8. Discussion

The available literature comparing the chemotherapeutic drugs docetaxel, gemcitabine, paclitaxel, pemetrexed, vinorelbine and erlotinib with respect to health effect, costs and cost effectiveness was presented and discussed.

In our systematic review, we summarized the findings of six reviews[19-24] that were published between 2001 and 2010, and critically appraised 11 CEAs and CUAs published in that same period.[9-18,25] The reviews provided little evidence on our central research question, which concerned the comparison of third-generation drugs with one another. In two reviews,[10,16] however, erlotinib was compared with docetaxel and/or pemetrexed. The included evidence suggested that erlotinib is cost saving compared with the two alternative treatments, due to equal or better survival, its oral administration and its favourable toxicity profile. None of the six reviews that we included were conducted according to the guidelines for systematic reviews.[7,36] Of six reviews, three did not report a search strategy nor any inclusion criteria,[18,22,23] and only one review assessed the quality of the identified studies.[23] In addition, all reviews included abstracts, which made the obtained information less transparent.

The evidence generated by the 11 fully published CEAs and CUAs can be summarized as follows. In two studies on first-line treatment,[14,18] gemcitabine+cisplatin was cost effective compared with paclitaxel+cisplatin. In addition, gemcitabine+cisplatin was cost effective compared with paclitaxel+carboplatin, docetaxel+cisplatin and vinorelbine+cisplatin.[14] However, pemetrexed+cisplatin was more cost effective than gemcitabine+cisplatin in the subgroup of patients with non-squamous-cell carcinoma.[12] In second-line treatment, docetaxel was cost effective compared with BSC in two studies.[11,15] The evidence on pemetrexed was contradictory: it was a cost-effective option compared with docetaxel in one study[17] but not in another.[10] Erlotinib was cost effective compared with placebo,[9] docetaxel[10,16] and pemetrexed.[10]

Although there were no CEAs on gefitinib compared with another new agent or BSC, the IPASS trial (Iressa Pan-Asia Study) showed a better response rate and PFS in patients with a EGFR gene mutation in the first-line setting.[37] Moreover, Chouaid et al.[38] evaluated the economic impact of gefitinib in a third-line treatment setting in a model-based study, and found the costs to be acceptable from a healthcare payer perspective.

As this study was a costing study, it was not included in our review.

A combination therapy of a third-generation agent and a platinum agent is recommended as first-line treatment in patients with stage IV NSCLC in US, UK and Dutch guidelines.[2,3,39] These recommendations are based on clinical effectiveness rather than cost effectiveness. In terms of clinical effectiveness, no preference for any particular agent is indicated in these guidelines. The current review provides the opportunity to include cost-effectiveness arguments in decision making concerning optimal chemotherapeutic treatment in advanced NSCLC. Unfortunately, we found no single third-generation drug to unequivocally dominate other agents, and the number of studies available to adequately compare the agents with one another was low. Individual CEAs may have influenced local treatment uptake of particular agents, but this is difficult to establish because patient registries showing actual clinical use are lacking.

None of the included studies used a societal perspective for their analyses, although this is recommended in economic evaluations.[36] For advanced NSCLC, however, the improvement in disease-free survival can be expected to have no effect on patient-related loss-of-productivity costs. On the other hand, there may be loss-of-productivity costs for family and caregivers, and other direct costs, such as travel costs associated with intravenous administration, which may also be incurred by the patient and their family or caregivers. In the US, it has been estimated that death from lung cancer will account for 27% of the total costs of productivity loss due to cancer in the coming 10 years.[40]

In most of the CUAs included in this review, QALYs were based on generic EQ-5D studies and, in one CUA,[17] QALYs were based on the standard gamble approach. Although the QALY – a generic measure of health benefit – is recommended by NICE, the NHS and other health authorities, its use for certain medical conditions is questionable. Three main limitations of using QALYs in cancer were stressed in a review by Garau et al.[41] First, concerning QALYs based on the EQ-5D, lack of sensitivity has been found in measuring changes in the health states of cancer patients. Second, the methodology for valuing health states assumes that individuals are willing to trade a constant proportion of their life expectancy to obtain a proportional improvement in health benefit, regardless of their life expectancy. It has been suggested that for cancer patients – especially NSCLC patients, who have a short life expectancy – this assumption (based on a 10-year framework) may not reflect their trade-off preferences. Third, a growing body of evidence indicates that patients tend to value a given health state more highly than non-patients. In addition to these limitations, in a meta-analysis of utility values for lung cancer, the identity of the responder (patient vs non-patient) was found to have a significant impact on the utility value.[42] It is clear that the methods currently being used to assess health benefit are far from perfect when evaluating healthcare technologies for a terminal stage of disease, such as advanced NSCLC. The gained utilities as an outcome measure in the CUAs included in the present review were based on generic EQ-5D studies and, therefore, in view of these methodological limitations, they should be interpreted cautiously.

In general, comparing the results of CEAs is difficult because of differences in country, perspective and year of publication.[36,43] There is a wide range of factors that limit the generalizability of results over time and between health systems and healthcare settings, including the context-dependency of resource use, different decision contexts and budget constraints.[44] The CEAs included in the present study differed, for example, in study design (trial based vs model based), time horizon, treatment dosage and infusion time. Model-based studies were difficult to compare because of different assumptions regarding model structure and different calculations of parameter values. The studies by Carlson et al.[10] and Lewis et al.[16] were both modelling studies based on the same two trials. Carlson et al.[10] assumed PFS to be equal in all treatment arms, whereas Lewis et al.[16] used the trial data for PFS. The trial data showed a longer PFS for erlotinib than for docetaxel.[32,34] As such, the results in the study by Carlson et al.[10] are probably biased against

erlotinib. The studies by Leighl et al.[15] and Holmes et al.[11] were also based on the same trial. Holmes et al.[11] did not include costs of toxicity treatment, while Leighl et al.[15] did. Although both studies concluded that docetaxel was cost effective compared with BSC, the incremental costs for docetaxel were higher in the study by Leighl et al.[15] Similarly, the incremental survival for docetaxel differed in the two studies due to different methods of calculating survival.

A related issue is that none of the included studies defined BSC, suggesting potential variations between trials in the type of supportive care. This lack of clarity has been discussed previously.[45] It complicates the interpretation of cost-effectiveness results for new agents compared with BSC within studies, and threatens the validity of comparisons between studies with a BSC reference arm.

8.1 Quality of the Evidence

The methodological quality assessment showed that the quality of the studies was acceptable, although a few items were consistently under-reported. In addition, some shortcomings could not be assessed with the checklist by Drummond and Jefferson.[6] For example, there is no question that addresses the inclusion of all relevant cost items. We found that none of the studies clearly described whether costs for palliative care or terminal care were included. With respect to the quality of the modelling studies, we found estimates of the key parameters, model assumptions or calculations to be poorly reported. Preferably, economic evaluations would be more explanatory in their intents and methods. More detailed and transparent model descriptions would possibly permit better comparisons between studies and, as such, systematic reviews of economic evaluations could generate stronger evidence for policy makers.[44]

8.2 Strengths and Limitations

Although we searched three relevant databases, we may have missed studies. We have tried to minimize this risk by scanning the reference lists of all included studies. Studies were limited to those in the English or Dutch languages, which may have precluded relevant studies published in different languages. Additionally, publication bias may have occurred, as industry-funded studies with unfavourable findings may not have been published.

For the purpose of this review, we specifically restricted ourselves to economic evaluations conducting CUAs and/or CEAs. Moreover, we restricted our selection to studies that compared the five third-generation drugs and the targeted drugs erlotinib and gefitinib with one another or BSC. This inclusion criterion greatly reduced the number of initially selected studies. Although this resulted in a relatively small number of included studies, our strategy corresponds to our aim of discovering whether any of the third-generation agents is superior in terms of cost effectiveness. Furthermore, it should be noted that the included studies mainly concerned gemcitabine and docetaxel. Other agents, such as vinorelbine and gefitinib, were under-represented or absent in this review. Only one study[14] included vinorelbine as a comparator arm for gemcitabine.

9. Conclusions

Due to the lack of transparency concerning BSC, the small number of studies included in this review and the aforementioned heterogeneity between studies, strong conclusions cannot be drawn. Nevertheless, there is reasonable consensus between the studies with respect to the direction of differences in cost and health effects for a number of drug comparisons. As such, we conclude that, in first-line treatment, gemcitabine+cisplatin seems a cost-effective treatment option, although pemetrexed+cisplatin performs better in a non-squamous population. In second-line treatment, docetaxel is a cost-effective option compared with BSC. Erlotinib may be a cost-effective alternative to docetaxel.

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Correspondence: *Mathilda L. Bongers*, MSc, PK Z 161, PO Box 7057, 1007 MB Amsterdam, the Netherlands.
E-mail: ml.bongers@vumc.nl