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Lung Cancer

How Affordable are Targeted Therapies in Non-Small Cell Lung Cancer?

Linda E. Coate, MB, MRCPI
*Natasha B. Leighl, MD, MMSc, FRCP (C)**

Address
**Division of Medical Oncology, Princess Margaret Hospital, Room 5-105, 610 University Avenue, Toronto, ON M5G 2M9, Canada.*
E-mail: natasha.leighl@uhn.on.ca

Opinion statement

As the treatment of non-small cell lung cancer (NSCLC) evolves to include more targeted therapies, costs of treatment have increased significantly. Advances in NSCLC treatment include longer survival duration, and in some cases, better progression-free survival and quality of life, and the potential for decreased toxicity. Through pharmacoeconomic analyses, payors seek to value the improvements in outcomes from novel therapies, and relate these improvements to their costs. In NSCLC, three categories of novel agents have been introduced into clinical practice: (1) agents targeting the epidermal growth factor receptor (EGFR); (2) agents targeting the vascular endothelial growth factor (VEGF) and (3) novel chemotherapy agents, specifically pemetrexed. Here we review published economic analyses for these agents in lung cancer, and their potential impact on treatment decisions.

Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related death in the industrialized world [1]. Recently, molecularly targeted agents have taken their place in disease treatment paradigms. The survival improvement seen with the addition of these molecularly targeted agents is modest. By contrast, the cost of these agents is substantial. In 2009, the sales of oncology drugs in the United States, excluding hormonal therapies and vaccines, reached $18.5 billion USD, an increase of approximately 11% compared with the year prior [2]. This has led to closer scrutiny of the incremental costs of these agents and how they relate to patient benefit.

Search strategy

- Medline, Pub Med and Google Scholar were searched using the following terms: non-small cell lung cancer; pharmacoeconomic analysis; cost-effectiveness analysis; epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR); pharmacoeconomic analysis in lung cancer: erlotinib, gefitinib, cetuximab, bevacizumab and pemetrexed. Abstracts from ASCO

annual meetings were also searched using the same terms. Fourteen articles were identified, and five abstracts. Only manuscripts in the English language were considered.

Current treatment paradigms in advanced non-small cell lung cancer

First-line therapy

- While first-line therapy with a platinum-based combination remains the standard for many good performance status patients, the addition of selected novel agents may further improve outcomes. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been shown to improve median survival by 2 months, and 1 year survival by 7%, when added to paclitaxel/carboplatin compared to chemotherapy alone in patients with advanced non-squamous NSCLC [3]. In the subset of patients with adenocarcinoma, post hoc analysis revealed a median survival improvement of 4 months with the addition of bevacizumab [4]. Response rate and progression-free survival were also improved with the new agent. However, a confirmatory trial of bevacizumab in combination with gemcitabine/cisplatin did not demonstrate a survival benefit, although response and progression-free survival were improved [5]. In certain jurisdictions, bevacizumab with a platinum doublet has emerged as a standard treatment for eligible non-squamous patients. Another monoclonal antibody, cetuximab, targeting the epidermal growth factor receptor (EGFR), may also improve outcomes when added to first-line platinum doublet chemotherapy. One phase III trial of vinorelbine/cisplatin with or without cetuximab demonstrated a median survival improvement of 1 month, and an increase in 1-year survival of 5% [6]. Response rates were improved although progression-free survival was not. In another phase III trial using cetuximab/paclitaxel/carboplatin, response rates and progression-free survival were improved, but not survival [7]. While this represents a potential treatment option in first-line, it has not been widely adopted because of the modest survival increment and additional toxicity of cetuximab.
- The introduction of pemetrexed into the platinum doublet may also improve outcomes for patients with non-squamous NSCLC. A randomized trial of pemetrexed/cisplatin vs gemcitabine/cisplatin demonstrated similar outcomes in unselected NSCLC in terms of response, progression-free and overall survival [8]. But a pre-planned analysis of outcomes by histology revealed a median 1 month survival improvement with pemetrexed/cisplatin in non-squamous NSCLC patients, with similar response rates and progression-free survival compared with gemcitabine/cisplatin. Patients with squamous histology appeared to derive greater survival benefit from gemcitabine/cisplatin, allowing further refinements in the selection of first-line therapy that may improve outcomes.
- Finally, for patients with activating EGFR mutations, first-line treatment with EGFR tyrosine kinase inhibitors (TKI) may provide better response rates, progression-free survival, symptom control and quality of life scores, than first-line platinum-based chemotherapy [9, 10]. While it does not introduce a new line of therapy for these patients, who would otherwise receive EGFR TKI treatment after chemotherapy, it optimizes the sequence of treatment in this subgroup of NSCLC patients.

Subsequent or maintenance therapy

- While more than 4 to 6 cycles of platinum-based chemotherapy is not felt to improve patient outcomes significantly [11], switching to non-cross-resistant therapy or maintaining at least one agent from first-line (*eg*, bevacizumab, cetuximab or single agent chemotherapy), may yield better outcomes. Early initiation of pemetrexed has demonstrated a major improvement in median survival of 5 months in non-squamous NSCLC patients after first-line platinum-based chemotherapy (not including pemetrexed), who have stable or better disease [12]. Early initiation of erlotinib may also improve survival, although only modestly [13]. In patients with stable or responding disease after first-line platinum doublet therapy, erlotinib improved median survival by 1 month over placebo in the overall study population. In subset analyses, patients with wild-type EGFR had a similar magnitude of benefit from erlotinib as the overall study population, while those activating mutations had significantly longer progression-free survival but no significant survival improvement, likely because of subsequent EGFR TKI therapy.

Second- and third-line therapy

- Systemic chemotherapy has been shown to modestly improve survival and delay symptom deterioration [14, 15]. Docetaxel and pemetrexed are standard options, and pemetrexed has emerged as the preferred option in non-squamous patients with a more favourable toxicity profile [8]. Gefitinib has been shown to have similar outcomes in one comparative trial with docetaxel, with less toxicity and better quality of life scores in unselected patients [16]. After chemotherapy failure, second- or third-line erlotinib has been shown to improve survival and quality of life in a placebo-controlled trial in unselected advanced NSCLC patients [17].

Personalized therapy

- While the benefits in unselected NSCLC patients are modest, there are trends to suggest that molecular and clinical selection may identify subgroups with greater benefit from treatment. This has shifted the focus of drug development in lung cancer to early identification of biomarkers of response. For example, a recently developed multi-targeted kinase inhibitor, crizotinib, demonstrated dramatic and prolonged responses in advanced lung adenocarcinoma patients, whose tumours contained the EML4-ALK fusion gene [18]. This gene rearrangement has been identified in approximately 4% of adenocarcinoma patients, who tend to be younger, never or light smokers, without activating EGFR mutations [19]. As drug development in cancer is shifting towards personalized medicine based on molecular features, policy makers must ensure that they maximize patient outcomes where possible, in a system of constrained resources and competing alternatives. It is increasingly important to assess the modest clinical benefits derived from new agents, with their substantial incremental cost. Also where treatment can be tailored to

maximize outcomes, cost and budget impact analyses of new therapies must incorporate the costs of personalized medicine. For example, the cost of molecular diagnostics is rarely considered as part of an overall treatment strategy, although this is now being explored by several groups.

Pharmacoeconomic analysis

- There are different ways to evaluate the economic impact of novel therapies. Cost-analysis, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis and budget-impact analysis all are examples. Cost analysis deals only with costs and represents a partial form of economic appraisal. CEA evaluates the consequences of an intervention measured in natural units, *ie*, cost per life-year gained. Cost-utility analysis evaluates the consequences of an intervention adjusted by health state preference score, or utility measure. The quality- adjusted life-year (QALY) is the unit of measurement most commonly used. Cost-benefit analysis attempts to value the consequences of an intervention in monetary terms. Budget impact analysis (BIA) is used to predict the potential financial impact of introducing a new intervention.
- The incremental cost-effectiveness ratio (ICER) expresses the incremental cost of one treatment over another, divided by the incremental benefit from that treatment. A threshold value is often set by policy makers, to assist in deciding whether or not to adopt or fund a new therapy. Additional factors are important, such as budget impact, available therapeutic alternatives, size of the population affected, the magnitude of treatment benefit and other societal considerations.

Pharmacoeconomics and lung cancer

- As one of the most common cancers in North America, lung cancer generates a large economic burden [20]. These include direct medical costs of care, such as surgery, radiation and systemic therapy, hospitalization, physician and nursing costs and supportive care. Indirect costs are also important, but infrequently measured. These include potential societal costs, such as lost productivity of patients and caregivers.
- There have been many studies of cost effectiveness of chemotherapy in lung cancer, but fewer addressing newer targeted therapies [21–23]. In particular, there have been few if any economic analyses incorporating the impact of molecular profiling and molecular selection of patients for treatments and associated costs.

Agents targeting the epidermal growth factor receptor pathway

Cetuximab plus chemotherapy first-line

- Cetuximab, a monoclonal antibody which attaches to the extracellular domain of the EGFR, added to vinorelbine/cisplatin chemotherapy, demonstrated an overall median survival benefit of 1.2 months in a large, randomized trial including over 1000 patients [6]. Fojo and Grady [24] have estimated that 18 weeks of cetuximab treatment for NSCLC would cost $80,000, translating to an ICER of $800,000 USD per life-year gained (LYG).

EGFR tyrosine kinase inhibitors in second- and third-line

Gefitinib

- Gefitinib has been studied in all stages of NSCLC over the past decade. Currently, it is indicated as an option for first-line systemic therapy in patients with EGFR activating mutations, but has also been demonstrated to have non-inferior efficacy to chemotherapy in the second-line setting.
- An economic model was developed by Astra Zeneca Mexico, using discrete event simulation to cost two strategies [25]. The first strategy tested NSCLC cancer patients for EGFR mutations, prescribing gefitinib first-line if positive, and chemotherapy if negative. The second strategy did not use routine testing, and all patients received first-line chemotherapy. Outcomes were based on the pivotal I-PASS trial [9]. The cost of mutation testing was estimated at $415 USD, and the mutation rate was estimated at 13%. Cost per patient using EGFR mutation testing was estimated at $14,833 USD; the cost without testing was estimated at $14,177, an incremental $646 USD. The incremental benefit of the mutation testing strategy with gefitinib use in mutation positive patients was estimated as an additional 0.46 months of progression-free survival over the non-testing strategy. Thus, an incremental cost of $1,432 USD per progression-free month was estimated. However, it is important to remember that progression-free survival as an independent outcome is difficult to value in economic analyses of palliative cancer therapy, particularly in lung cancer. A more meaningful analysis would have derived the incremental quality-adjusted survival benefit between the two strategies. Also, a more in-depth analysis of mutation testing would be important, as advanced lung cancer patients are often diagnosed using fine needle aspiration, which may not yield sufficient tissue for molecular testing. Thus, downstream costs of repeat biopsy and potential complications must also be built into the cost of testing.
- INTEREST (IRESSA in Non-small cell lung cancer Trial Evaluating Response and Survival against Taxotere) was a randomized non-inferiority trial that compared gefitinib to docetaxel second-line [26]. Gefitinib demonstrated non-inferior progression-free and overall survival, but had a better toxicity profile and greater quality of life improvement than docetaxel chemotherapy. In a cost consequence analysis of this trial, Horgan *et al.* [27] found that gefitinib was associated with higher treatment costs than docetaxel, largely related to higher drug costs (75% and 47% of total in each arm, respectively).
- French investigators analysed the direct cost of third-line gefitinib therapy in advanced NSCLC patients in a compassionate-use programme in six public hospitals during 2004 [28]. The mean duration of gefitinib treatment was 4.6 ± 5.8 months (range 1–29 months); the median survival was 4 months, and the 1- and 2-year survival rates were 12.3% and 4.7%, respectively. The mean total medical costs were €39,708–20,279, and gefitinib drug cost represented 10.7% of the total.

Erlotinib

- Erlotinib is currently approved for second- or third-line therapy after chemotherapy failure in advanced NSCLC patients, who are otherwise unselected. In a Canadian study [29], 100 subjects, 50 with advanced NSCLC and 50 healthy controls, were interviewed about their willingness to pay for EGFR TKI therapy. Both the groups were willing to pay $100 (CAD), significantly less than the actual cost of erlotinib, which is approximately $3000 (CAN) per month [30]. One of the key determinants of willingness to pay in the lung cancer patients was their financial ability to pay.
- A number of studies are based on analyses of the pivotal placebo-controlled trial of erlotinib [17]. A retrospective cost of care analysis performed from the United States (U.S.) healthcare payor perspective [31] has been conducted, using claims from private insurers, Medicare and Medicaid. Among approved second-line therapies, patients prescribed erlotinib had the lowest monthly cost per patient (US $2,929), while those who received docetaxel or pemetrexed had higher costs, $6,276 and $4,461, respectively.
- The U.S. budget impact model was developed, to include costs of treating NSCLC patients, including treatment costs, and management of adverse events. A formulary with or without erlotinib was costed [32]. Total costs of treating advanced NSCLC patients including with erlotinib were US $382,418, and US $380,968 without erlotinib use in the program. The difference in budget impact was $1450, (90% confidence interval $61,376 to $29,855 USD), which translated into less than one cent incremental cost per member per month. The conclusions drawn were that the direct treatment cost of erlotinib (when used instead of cytotoxic chemotherapy) is offset by reductions in the associated costs relating to standard, cytotoxic chemotherapy, such as infusion costs and treatment of adverse events.
- A recent systematic review [33] examined data from 18 cost studies of erlotinib in advanced NSCLC. In modelled analyses of the cost utility of erlotinib relative to the second-line docetaxel or pemetrexed, or supportive care in the second- and/or third-line treatment of NSCLC. This review included cost analyses (cost per QALY) of erlotinib relative to second-line chemotherapy or supportive care, and permitted inclusion of data presented in abstract form. All analyses were conducted from a healthcare payor perspective in a variety of countries. Second-line erlotinib in patients with NSCLC was predicted to have a cost advantage with regard to the cost per QALY or life year gained (LYG) relative to second-line docetaxel and/or pemetrexed. Drug acquisition costs were higher with erlotinib than with docetaxel in most but not all analyses. In contrast, total direct medical costs were lower with erlotinib than with docetaxel in all analyses because of the higher costs of treating adverse events and of drug administration associated with docetaxel. Erlotinib was also predicted to be dominant or cost-saving relative to pemetrexed, assuming similar effects on overall survival and health-related quality of life (HR-QOL). In this case, drug acquisition costs were higher with pemetrexed than with erlotinib. In the case of erlotinib vs best supportive care, the incremental increase in direct costs associated with erlotinib is partially offset by an improvement in overall survival. It is important to recall that many of these analyses relied on assumptions or predictions of efficacy, rather than on randomized data.

- There is a growing focus on using molecular biomarkers to select patients most likely to benefit from novel targeted therapies. A cost-effectiveness study of erlotinib has been performed by the NCIC Clinical Trials Group (CTG), based on the NCIC CTG randomized placebo-controlled study of erlotinib after chemotherapy failure, including subset analyses of cost-effectiveness by clinical and molecular predictors of erlotinib benefit [34]. The ICER from this study was $94,638 per LYG in 2009 CAD for all patients. Patients who were never-smokers, or had tumours with high EGFR gene copy number, had CE ratios of $39,487 and $33,353, respectively, which are highly cost-effective. Interestingly, patients with activating EGFR mutations, who derive dramatic responses from EGFR TKI therapy, had a higher ICER, $138,168. This is because these patients are more likely to stay on treatment for a longer duration, resulting in greater cost.
- The cost of pharmacogenetic testing has not been factored into most analyses, and has a clear budget impact if adopted in routine clinical practice. Currently, testing a tumour specimen for EGFR mutation costs approximately $400 to $500 USD [Dr. S. Kamel-Reid, University Health Network, 15 July 2010, personal communication; 25]. This estimate does not take into account the potential need to rebiopsy a patient's tumour depending on the quality and volume of the initial diagnostic sample, and may include another procedure and the cost of potential complications. There are a number of unvalidated biomarker tests also commercially available. Although some of these are currently funded through third party payors, most patients undergoing these tests pay out of pocket.

Agents targeting the vascular endothelial growth factor receptor pathway

Bevacizumab

- Bevacizumab is currently approved for use with first-line platinum-based chemotherapy, and then bevacizumab as a single agent until disease progression, in patients with non-squamous NSCLC. The incremental cost effectiveness of adding bevacizumab to carboplatin plus paclitaxel was calculated based on the pivotal ECOG4599 randomized trial, using 2005 Medicare reimbursement costs [35]. With a median overall survival increase of 2.3 months, the cost per life-year gained with bevacizumab was $345,762 USD. With a price reduction of bevacizumab of 74%, thie ICER would reach $US 100,000 per LYG. A Canadian study estimated a cost of $47,250 per patient treated with bevacizumab relative to conventional therapy [36]. With substantial incremental costs, some payors have declined to adopt this as part of national funding programs, *eg*, the National Health System in the United Kingdom (U.K.). While some subsets may benefit preferentially, such as those with adenocarcinoma who may have a median survival improvement of 4 months with bevacizumab compared to chemotherapy alone, the high cost of drug acquisition still remains a significant challenge to widespread adoption. However, other countries such as the United States would accept this range of expenditure for modest benefit.

Pemetrexed

- While chemotherapy is not currently considered as molecular targeted therapy, pemetrexed is a novel and costly chemotherapy agent of emerging importance in NSCLC. It is a multi-targeted antifolate, and while a predictive biomarker for benefit has not been identified, a putative biomarker may be thymidylate synthase levels in tumour tissue. It is most active in non-squamous NSCLC, specifically adenocarcinoma. Current indications include first-line doublet therapy with pemetrexed/cisplatin, maintenance therapy after a first-line doublet, and second-line therapy, all in non-squamous NSCLC.
- In the first-line setting, the National Institute for Health and Clinical Excellence (NICE) has appraised the clinical and cost-effectiveness of pemetrexed within its licensed indication for the treatment of first-line NSCLC. The final determination was published in 2009, and recommended pemetrexed in combination with cisplatin as an option for first-line treatment of NSCLC if the histology of the tumour has been confirmed to be adenocarcinoma or large-cell carcinoma [37]. The key evidence for the clinical effectiveness was based on one phase III non-inferiority randomized controlled trial (JMBD trial) [8]. This study compared pemetrexed plus cisplatin with gemcitabine plus cisplatin and included over 1700 patients. For patients who had non-squamous NSCLC, median overall survival with pemetrexed plus cisplatin was 11 months vs 10.1 months with gemcitabine plus cisplatin. The manufacturer of pemetrexed, Eli Lilly, did an indirect comparison of pemetrexed plus cisplatin with gemcitabine plus carboplatin and with docetaxel plus cisplatin using data from two phase 2 open-label randomised trials. In this analysis, pemetrexed plus cisplatin was associated with fewer adverse events than any of the alternative therapies examined and this was found to be highly valued by patients [38]. However, the indirect comparison used by the manufacturer was not found by the committee to be methodologically robust. A modified Markov model suggested ICERs of between £17000(UK) and £25000 per QALY gained for pemetrexed plus cisplatin compared with gemcitabine plus cisplatin in patients with non-squamous NSCLC, and pemetrexed/cisplatin was deemed cost-effective by NICE [39].
- A study performed from the US payor perspective compared the 2-year impact of cisplatin and pemetrexed to three other first-line regimens using modelling. In the subset of patients with nonsquamous histology, the ICER was $83,537 for cisplatin/pemetrexed compared to cisplatin/gemcitabine, and $178,613 for cisplatin/pemetrexed compared to carboplatin/paclitaxel. The incremental cost per life-year gained for carboplatin/paclitaxel/bevacizumab compared to cisplatin/pemetrexed was more than $300,000 in the model.
- In the second-line setting, a Spanish study compared docetaxel and pemetrexed using a Markov model in patients with non-squamous histology [40]. Mean survival in the model was estimated at 1.03 years for the pemetrexed arm and 0.89 years in the docetaxel arm; QALYs were 0.52 compared to 0.42; lifetime costs per patients were € 34,677 and € 32,343 for pemetrexed and docetaxel, respectively. This finding was largely driven by projected toxicity costs in the docetaxel arm, despite higher drug acquisition costs on the pemetrexed arm. As with any model, one must be cautious about assumptions that may not be supported by clinical trial data. For example, the number of days in hospital was similar in both arms of the study, raising the potential for

missing hospitalization costs in the pemetrexed arm. Incremental cost-effectiveness ratios were € 23,967 per QALY and € 17,225 per LYG for pemetrexed and docetaxel, and authors concluded pemetrexed was a cost-effective second-line treatment option for patients with a predominantly non-squamous histology in NSCLC.

Discussion

- While progress in lung cancer continues in modest increments, the cost of novel therapies has escalated dramatically. A study of American medical oncologists suggests an implied cost effectiveness threshold of over $300,000 USD/QALY [41]. While different countries are able to afford different thresholds for adopting novel therapies, the historical standard of $50,000 USD per QALY, based on the cost effectiveness of dialysis from the 1970s, is outdated. Modern day dialysis is associated with a cost effectiveness ratio of approximately $130,000 USD per QALY [24], and is in the range of cost effectiveness of some, but not all, new targeted therapies in lung cancer.
- How to value improvements in outcome remains challenging. Better efficacy, in particular improved survival, remains clinically important. But therapeutic improvements enabling better quality of life and symptom control, greater convenience with less toxic therapy and oral treatment administration, are also major contributors to advances in lung cancer therapy. These outcomes, however, are more challenging to value against alternatives, and to factor into the cost-effectiveness ratio, even when using quality-adjusted survival as the main outcome. In addition, the cost to society of the burden of lung cancer, including loss of productivity among patients and caregivers, is important and rarely accounted for in economic analyses of lung cancer therapy. For example, Yabroff *et al*. estimated that during their last year of life, lung cancer patients averaged an additional 27 days in the hospital, and 488 hours receiving treatment, compared to control subjects without a cancer diagnosis [29].
- While lung cancer may not be a unique case among chronic illnesses, it is clear that improved outcomes in this disease are urgently needed. Modest improvements, for the most part at substantial cost, are being demonstrated in advanced disease. With molecular and patient selection, the benefits seen in selected populations may be magnified. With selection of those most likely to benefit, cost effectiveness should also be enhanced, although this is not always the case, as seen with EGFR TKI therapy after chemotherapy failure in patients with activating mutations [34]. A recent editorial in the Journal of the National Cancer Institute [24] questioned what we as a society counts as a benefit, the extent to which cost should factor in deliberations and who should be involved in deciding which drugs get funded. The conclusion of this editorial was that there is an urgent and shared responsibility of the oncology community, the FDA and the payers to at least examine the evidence more closely, and set it against cost. There is also a clear responsibility for pharmaceutical companies to assist in setting more reasonable costs for novel therapeutics.
- While we struggle to relate the benefits of novel lung cancer therapies to their incremental costs, it is important for trialists and cooperative groups to consider the prospective collection of high quality economic data alongside practice-changing trials. While some groups, such as the NCIC Clinical Trials Group, are moving towards this, all groups must recognize that economic endpoints are of increasing importance in valuing and adopting new therapies in lung cancer.

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References and Recommended Reading

1. Jemal A, Siegel R, Ward E, *et al.*: **Cancer statistics, 2008.** *CA Cancer J Clin* 2008, **58:**71–96.
2. Aggarwal S: **Targeted cancer therapies.** *Nat Rev Drug Discov* 2010, **9:**427–428.
3. Sandler A, Gray R, Perry MC, *et al.*: **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006, **355:**2542–2550.
4. Herbst RS, Sandler ATreatment Outcomes by Tumor Histology in Eastern Cooperative Group (ECOG) Study E4599 of Bevacizumab (BV) with Paclitaxel/Carboplatin (PC) for Advanced Non-small Cell Lung Cancer (NSCLC).: **Non-small cell lung cancer and antiangiogenic therapy: what can be expected of bevacizumab?** *J Thorac Oncol* 20083:S283.
5. Reck M, von Pawel J, Zatloukal P, *et al.*: **Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil.** *J Clin Oncol* 2009, **27:**1227–1234.
6. Pirker R, Pereira JR, Szczesna A, *et al.*: **Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial.** *Lancet* 2009, **373:**1525–1531.
7. Lynch TJ, Patel T, Dreisbach L, *et al.*: **Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099.** *J Clin Oncol* 2010, **28:**911–917.
8. Scagliotti GV, Parikh P, von Pawel J, *et al.*: **Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.** *J Clin Oncol* 2008, **26:**3543–3551.
9. Mok TS, Wu YL, Thongprasert S, *et al.*: **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med* 2009, **361:**947–957.
10. Maemondo M, Inoue A, Kobayashi K, *et al.*: **Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR.** *N Engl J Med* 2010, **362:**2380–2388.
11. Soon YY, Stockler MR, Askie LM, *et al.*: **Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials.** *J Clin Oncol* 2009, **27:**3277–3283.
12. Ciuleanu T, Brodowicz T, Zielinski C, *et al.*: **Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study.** *Lancet* 2009, **374:**1432–1440.
13. Cappuzzo F, Ciuleanu T, Stelmakh L, *et al.*: **SATURN: A double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC.** *J Clin Oncol* 2009, **27:**8001.
14. Shepherd FA, Dancey J, Ramlau R, *et al.*: **Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy.** *J Clin Oncol* 2000, **18:**2095–2103.
15. Hanna N, Shepherd FA, Fossella FV, *et al.*: **Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.** *J Clin Oncol* 2004, **22:**1589–1597.
16. Douillard JY, Shepherd FA, Hirsh V, *et al.*: **Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial.** *J Clin Oncol* 2010, **28:**744–752.
17. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, *et al.*: **Erlotinib in previously treated non-small-cell lung cancer.** *N Engl J Med* 2005, **353:**123–132.
18. Bang Y, Kwak EL, Shaw AT, *et al.*: **Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC).** *J Clin Oncol* 2010, **28:**3.
19. Shaw AT, Costa D, Mino-Kenudson M, *et al.*: **Clinicopathologic features of EML4-ALK mutant lung cancer.** *J Clin Oncol* 2009, **27:**11021.
20. Molinier L, Combescure C, Chouaid C, *et al.*: **Cost of lung cancer: a methodological review.** *Pharmacoeconomics* 2006, **24:**651–659.
21. Holmes J, Dunlop D, Hemmett L, *et al.*: **A cost-effectiveness analysis of docetaxel in the second-line treatment of non-small cell lung cancer.** *Pharmacoeconomics* 2004, **22:**581–589.
22. Neymark N, Lianes P, Smit EF, *et al.*: **Economic evaluation of three two-drug chemotherapy regimens in advanced non-small-cell lung cancer.** *Pharmacoeconomics* 2005, **23:**1155–1166.
23. Szczepura A: **Healthcare outcomes: gemcitabine cost-effectiveness in the treatment of non-small cell lung cancer.** *Lung Cancer* 2002, **38(2):**S21–S28.
24. Fojo T, Grady C: **How much is life worth: cetuximab, non-small cell lung cancer, and the $440 billion question.** *J Natl Cancer Inst* 2009, **101:**1044–1048.
25. Arrieta O AP, López RJ, Polanco AC: Cost-effectiveness analysis of EGFR mutation testing patients with advanced non small-cell lung cancer treated with gefitinib or carboplatin-paclitaxel. ISPOR 15th Annual International Meeting Atlanta, GA, USA May, 2010.
26. Kim ES, Hirsh V, Mok T, *et al.*: **Gefitinib versus docetaxel in previously treated non-small-cell lung**

cancer (INTEREST): a randomised phase III trial. *Lancet* 2008, **372:**1809–1818.

27. Horgan AM, Shepherd FA, Bradbury PA, *et al.*: **Preliminary cost-consequence analysis of the INTEREST trial, a randomized trial of docetaxel versus gefitinib as 2nd line therapy in advanced non-small cell lung cancer.** *J Clin Oncol* 2008, **26:**8110.
28. Chouaid C, Monnet I, Robinet G, *et al.*: **Economic impact of gefitinib for refractory non-small-cell lung cancer: a Markov model-based analysis.** *Curr Med Res Opin* 2007, **23:**1509–1515.
29. Leighl NB, Tsao WS, Zawisza DL, *et al.*: **A willingness-to-pay study of oral epidermal growth factor tyrosine kinase inhibitors in advanced non-small cell lung cancer.** *Lung Cancer* 2006, **51:**115–121.
30. van Zandwijk N: **Epidermal growth factor tyrosine kinase inhibitors (EGFR TKIs) and economics.** *Lung Cancer* 2006, **51:**137–138.
31. Ramsey SD, Martins RG, Blough DK, *et al.*: **Second-line and third-line chemotherapy for lung cancer: use and cost.** *Am J Manag Care* 2008, **14:**297–306.
32. Ramsey SD, Clarke L, Kamath TV, *et al.*: **Evaluation of erlotinib in advanced non-small cell lung cancer: impact on the budget of a U.S. health insurance plan.** *J Manag Care Pharm* 2006, **12:**472–478.
33. Lyseng-Williamson KA: **Erlotinib: a pharmacoeconomic review of its use in advanced non-small cell lung cancer.** *Pharmacoeconomics* 2010, **28:**75–92.
34. Bradbury PA, Tu D, Seymour L, *et al.*: **Economic analysis: randomized placebo-controlled clinical trial of erlotinib in advanced non-small cell lung cancer.** *J Natl Cancer Inst* 2010, **102:**298–306.
35. Grusenmeyer PA, Gralla RJ: **Examining the cost and cost-effectiveness of adding bevacizumab to carboplatin and paclitaxel in advanced non-small cell lung cancer.** *J Clin Oncol* 2006, **24:**6057.
36. Drucker A, Virik K, Skedgel C, *et al.*: **The cost burden of trastuzumab and bevacizumab monoclonal antibody therapy in solid tumors: can we afford it?** *J Clin Oncol* 2006, **24:**6044.
37. Fleeman N, Bagust A, McLeod C, *et al.*: **Pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer.** *Health Technol Assess* 2010, **14(Suppl 1):**47–53.
38. Vrouchou P, Kandaswamy P, George E, *et al.*: **Pemetrexed approved for the first-line treatment of non-small-cell lung cancer: summary of the NICE appraisal.** *Lancet Oncol* 2009, **10:**1031–1032.
39. NICE: Pemetrexed for the first-line treatment of non-small cell lung cancer. Final Appraisal Determination. August, 2009. http://www.nice.org.uk/nicemedia/pdfFADPemetrexedLungCancer.pdf, 2009.
40. Asukai Y, Valladares A, Camps C, *et al.*: **Cost-effectiveness analysis of pemetrexed versus docetaxel in the second-line treatment of non-small cell lung cancer in Spain: results for the non-squamous histology population.** *BMC Cancer* 2010, **10:**26.
41. Nadler E, Eckert B, Neumann PJ: **Do oncologists believe new cancer drugs offer good value?** *Oncologist* 2006, **11:**90–95.