Non-small cell lung cancer – EML

The application sought the addition of vinorelbine, cisplatin, gemcitabine, erlotinib and gefitinib to the core list of the Essential Medicines List and the endorsement of etoposide, carboplatin and paclitaxel (currently included on the complementary list) for the treatment of non-small cell lung cancer.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

In 2013, there were approximately 1.8 million incident lung cancer cases diagnosed worldwide and approximately 1.6 million deaths from the disease *(1)*. Lung cancer had the second highest absolute incidence globally after breast cancer, and in 93 countries was the leading cause of death from malignant disease, accounting for one fifth of the total global burden of disability-adjusted life years from cancer. Men were more likely to develop lung cancer than women, with 1 in 18 men and 1 in 51 women being diagnosed between birth and age 79 years *(1)*. Non-small cell lung cancer (NSCLC) is the most common form of the disease, accounting for 85–90% of all lung cancers *(2)*.

Most patients with NSCLC present with advanced stage disease – stage IV in particular – and half of all patients treated initially for potentially curable early-stage disease will experience recurrences with metastatic disease *(3)*. Patients with stage IV disease are never curable, and chemotherapy, targeted therapy and radiation can only extend survival and palliate symptoms. Although NSCLC is generally regarded as a disease of the elderly, a third of cases are diagnosed in patients under 65 years of age *(3)*.

Platinum-based doublet chemotherapy as adjuvant therapy is the standard treatment for patients with resectable stage II or III disease. Neoadjuvant and/or concurrent platinum-based doublet chemotherapy with radiotherapy is standard treatment for patients with unresectable stage III disease. Platinum-based doublet chemotherapy is also the standard first-line treatment for patients with advanced (stage IV) disease.

Where molecular diagnostics and targeted therapies are available, patients with activating mutations of epidermal growth factor receptor (EGFR) may benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs – erlotinib, gefitinib, afatinib), which have been shown to improve progression-free survival in patients with advanced disease, while being associated with greater tolerability than standard chemotherapy.

Public health relevance

According to GLOBOCAN, lung cancer has been the most common cancer globally for several decades; estimated worldwide incidence in 2012 was 1 824 701 (12.9% of all cancers), with an age-standardized rate (ASR) of 23.1 per 100 000 (4). Of the 1.8 million new cases in 2012, 58% occurred in less-developed regions. ASR incidence rates in 2012 were highest in central and eastern Europe (53.5 per 100 000) and in eastern Asia (50.4 per 100 000) and were

25% higher for men than for women (205 and 165 per 100 000 respectively). GLOBOCAN estimated the global mortality rate in 2012 to be 1 589 925 with an ASR of 19.7 per 100 000.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Histopathological diagnosis from surgical sample, core- or fine-needle biopsies or cytology cell blocks from pleural effusion is essential. Adequate tissue must be obtained to permit the needed testing outlined here to be performed.

Immunohistochemistry (IHC) helps to subtype NSCLC: squamous cells are generally TTF1-negative and p40- and p63-positive, while adenocarcinomas are generally TTF1-positive and p40- and p63-negative (5, 6). Molecular testing is crucial for first-line treatment with molecular targeted therapy. This includes EGFR gene mutation analysis by Sanger sequencing or amplification refractory mutation system and anaplastic lymphoma kinase (ALK) gene rearrangement by break-apart fluorescent-in-situ hybridization or IHC (7). Laboratories should use a validated mutation platform and participate in an external quality assurance programme.

Testing

Contrast-enhanced computerized tomography (CT) scan of the chest and upper abdomen, blood counts and blood chemistries for renal and hepatic function are required. CT scan or magnetic resonance imaging of brain or bone should be offered to patients with clinical symptoms suggestive of brain or bone metastases.

Administration and care of patients

Intravenous infusion capacity and regular patient access to acute clinical care are essential. Medications can be delivered in outpatient facilities. Antiemetics should accompany administration of all chemotherapy and intravenous hydration is essential before cisplatin. Clinical staff should be competent in identifying and managing soft tissue extravasation reactions from vinca alkaloids, and severe allergic reactions during taxane or carboplatin administration.

CT scans are required to assess response to treatment. Access to laboratory facilities for monitoring adverse effects is also required. Clinicians should be proficient in recognizing and addressing the potential side-effects of chemotherapy, and broad-spectrum antibiotics and transfusion facilities must be available to manage life-threatening events such as bone marrow suppression and neutropenic fever. Social well-being is inevitably affected by the diagnosis and treatment of NSCLC, and the financial burden of treatment may be particularly heavy for patients with metastatic NSCLC as many drugs are still on patent. Psychological and social support professionals are best integrated into multidisciplinary teams to care for patients with NSCLC.

Overview of regimens

The following includes basic information on administration and dosing for the proposed standard regimen options; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens – by stage of disease

- **Adjuvant chemotherapy for stage II and III NSCLC (every 21 days, 4 cycles)**

  – vinorelbine 25–30 mg/m^2 IV infusion on days 1 and 8
  – cisplatin 75–100 mg/m^2 IV infusion on day 1
  or

  – etoposide 50 mg/m^2 IV infusion on days 1–5
  – cisplatin 50 mg/m^2 IV infusion on days 1 and 8
  or

  – gemcitabine 1250 mg/m^2 IV infusion on days 1 and 8
  – cisplatin 75 mg/m^2 IV infusion on day 1
  or

  – paclitaxel 200 mg/m^2 IV infusion on day 1
  – carboplatin AUC 6 IV infusion on day 1

- **Concurrent chemotherapy/radiotherapy regimen for stage III unresectable NSCLC**

  If performance status good, age <70 and adequate renal function:

  – etoposide 50 mg/m^2 IV infusion on days 1–5 and 29–33
  – cisplatin 50 mg/m^2 IV infusion on days 1, 8, 29 and 36
  concurrent with thoracic RT

  or

  – paclitaxel 45–50 mg/m^2 IV infusion weekly
  – carboplatin AUC 2 IV infusion weekly
  concurrent with thoracic RT

  followed by:

  – paclitaxel 200 mg/m^2 IV infusion on day1
  – carboplatin AUC 6 IV infusion on day 1
  two cycles, starting 2–4 weeks after completion of radiation therapy

  If age >70, or fair performance status, or CrCl 50–60:

  – cisplatin 40 mg/m^2 IV infusion on first day of each treatment week of thoracic RT

Standard regimens – first-line chemotherapy for metastatic NSCLC

The regimens detailed below are for patients with no detectable targeted mutation or in whom mutation analysis could not be done. They have similar outcomes in relation to NSCLC survival. Toxicities vary among regimens but are not greatly different overall. Regimen choice can be based on drug availability and cost. Platinum agents improve survival only in patients without prior platinum exposure in the first-line setting *(8).*

- paclitaxel 90 mg/m^2 IV infusion on days 1, 8 and 15
- carboplatin AUC 6 IV infusion on day 1

every 21 days for 4–6 cycles

or

- paclitaxel 200 mg/m^2 IV infusion on day 1
- carboplatin AUC 6 IV infusion on day 1

every 21 days for 4–6 cycles

or

- gemcitabine 1000 mg/m^2 IV infusion on days 1, 8 and 15
- cisplatin 75 mg/m^2 IV infusion on day 1

every 28 days for 4–6 cycles

or

- gemcitabine 1000 mg/m^2 IV infusion on days 1 and 8
- cisplatin 75 mg/m^2 IV infusion on day 1

every 21 days for 4–6 cycles

or

- gemcitabine 1000 mg/m^2 IV infusion on days 1 and 8
- carboplatin AUC 5 IV infusion on day 1

every 21 days for 4–6 cycles

Standard regimens – TKI for metastatic NSCLC with activating EGFR mutations

- erlotinib 150 mg/day orally

or

- gefitinib 250 mg/day orally

Review of benefits and harms

Benefits

Surgery and adjuvant chemotherapy are important contributors to cure for early-stage disease. Combined modality treatment preserves a chance of long-term survival for patients with unresectable stage III disease.

A significant improvement in overall survival has been confirmed by several systematic reviews of randomized controlled studies assessing modern cisplatin-based chemotherapies. A first meta-analysis showed an absolute 5-year survival improvement of 5.4% (hazard ratio (HR) 0.89; 95% CI: 0.82–0.96) after adjuvant chemotherapy *(9)*. Heterogeneity of chemotherapy effect among trials was limited (I^2 = 6%). The effect of cisplatin and vinorelbine was marginally better than that of other chemotherapy combinations: vinorelbine (HR 0.80; 95% CI: 0.70–0.91), etoposide or vinca alkaloid (HR 0.92; 95% CI: 0.80–1.07), or other (HR 0.97; 95% CI: 0.84–1.13); test for interaction, *P* = 0.11. With the exception of cisplatin plus vinorelbine, the effect of chemotherapy was independent of whether patients received two- or three-drug regimens. The benefit varied with stage (test for trend, *P* = 0.04; for stage IA, HR 1.40; 95% CI: 0.95–2.06; for stage IB, HR 0.93; 95% CI: 0.78–1.10; for stage II, HR 0.83; 95% CI: 0.73–0.95; and for stage III, HR 0.83; 95% CI: 0.72–0.94). A second meta-analysis showed an absolute improvement of 4% (95% CI: 3–6) at 5 years associated with adjuvant chemotherapy, with the main survival benefit being in stage II and III disease *(10)*. After surgery, studies have shown that doublet chemotherapy produces a relevant extension of life for patients, with survival extending to up to 10–12 months.

A systematic review confirmed the benefit for survival of platinum-based regimens compared with non-platinum chemotherapy in advanced NSCLC *(11)*. Platinum-based chemotherapy was associated with a reduction in the risk of death at 1 year (odds ratio (OR) 0.88; 95% CI: 0.78–0.99; *P* = 0.044) compared with non-platinum chemotherapy, but also with an increased risk of grade 3–4 gastrointestinal and haematological toxicity. Another systematic review investigated whether chemotherapy given in addition to supportive care could prolong survival in advanced NSCLC *(12)*. Trials in the meta-analysis included patients who were unsuitable for surgery or radical radiation therapy who had received either chemotherapy and supportive care or supportive care alone. Survival analyses were based on 2533 deaths and 2714 patients from 16 trials. Chemotherapy was associated with a highly statistically significant benefit for survival (HR 0.77; 95% CI: 0.71–0.83). This benefit translated to an absolute improvement of 9% at 12 months increasing survival from 20% to 29% or an absolute increase in median survival of 1.5 months (from 4.5 months to 6 months).

In an indirect comparison, the effects of preoperative and postoperative chemotherapy on survival rates were compared in patients with operable NSCLC *(13)*. Both adjuvant and preoperative (neoadjuvant) chemotherapy had similar effects on overall survival. The relative HR of postoperative to preoperative administration on survival was 0.99 (95% CI: 0.81–1.21; *P* = 0.91), a statistically non-significant difference. In clinical practice,

adjuvant chemotherapy has become the standard of care as it represents a more pragmatic and feasible approach *(14)*. First-line platinum-based doublets commonly use docetaxel, etoposide, gemcitabine, paclitaxel and vinorelbine.

The majority of patients with stage IV NSCLC will inevitably progress after first-line or maintenance treatment. For elderly or frail patients, single-agent vinorelbine or low-dose weekly carboplatin and paclitaxel are treatment options, although doublet chemotherapy is generally preferred.

In the supportive setting, platinum-based chemotherapy does not adversely affect quality of life *(15)*. Side-effects of chemotherapy (e.g. fatigue, reduced functioning) are likely to be balanced by the palliative effect on symptoms such as pain. When platinum-based regimens in association with gemcitabine or vinorelbine were compared with a regimen of gemcitabine plus vinorelbine, quality-of-life scores were similar in the two arms of the trial. More haematological toxicity, renal toxicity and ototoxicity were seen in the platinum arm, but there was more hepatic toxicity in the gemcitabine-based arm *(16)*.

Where molecular diagnostics and targeted therapies are available, tumours could be subjected to molecular analysis, in particular EGFR gene mutation status and ALK gene rearrangement. Gefitinib and erlotinib have been shown to be effective in patients with mutations in the EGFR kinase region and were proposed for inclusion on the EML for these patients as first-line therapy. Fewer data were available to support use of afatinib, which was therefore not proposed for EML inclusion at this time.

In the 10–15% of NSCLC with EGFR-activating mutations (defined as in-frame deletions in exon 19 and L858R substitution in exon 21), EGFR-TKIs (erlotinib, gefitinib, afatinib) achieve tumour response rates of 70–80% and progression-free survival (PFS) of 10–14 months *(17-23)*. Several systematic reviews of randomized controlled trials compared TKI monotherapy with platinum-based doublet chemotherapy in first-line treatment of advanced or metastatic NSCLC *(24-26)*. Meta-analyses showed an improved efficacy of TKIs on overall response rates and PFS. However, the advantages for surrogate outcomes did not translate into a difference for mortality. OS data were similar for TKIs and chemotherapy (1-year: OR 1.04; 95% CI: 0.79–1.36, $P = 0.79$; 2-year: OR 0.95; 95% CI 0.76–1.17, $P = 0.62$) *(26)*. A second meta-analysis provided overlapping results, with similar benefit for OS among patients who first received TKI or chemotherapy (HR 0.98; 95% CI: 0.87–1.10, fixed-effect model) *(24)*.

TKIs have a different toxicity profile from that of chemotherapy *(17-23)*. Rash (relative risk (RR) 6.29; 95% CI: 4.05–9.77), diarrhoea (RR 3.51; 95% CI: 2.15–5.75), stomatitis (RR 3.57; 95% CI: 1.81–7.04), and interstitial lung disease (RR 6.07; 95% CI: 1.66–22.2) were significantly more frequent after TKIs. Fatigue (RR 0.38; 95% CI 0.32–0.45), nausea/vomiting (RR 0.19; 95% CI: 0.11–0.32), and haematological disorders, including thrombocytopenia (RR 0.18; 95 % CI: 0.09–0.35), anaemia (RR 0.22; 95% CI: 0.15–0.33), and grade 3–4 neutropenia (RR 0.06; 95% CI: 0.04–0.08) were significantly more frequent after chemotherapy *(24)*. Indirect comparisons showed that EGFR-TKIs have similar efficacy but they might differ within class in terms of toxicities *(26, 27)*.

For patients with ALK gene rearrangements, first-line crizotinib has been associated with a tumour response rate of 71% and PFS of 11.9 months *(28)*. Patients with driver oncogenes who failed to receive a targeted therapy previously may be treated with EGFR-TKIs or crizotinib as salvage therapy *(29, 30)*. When compared with chemotherapy, there are improvements in quality of life and PFS, but no significant improvements in OS among patients given crizotinib *(31, 32)*. Since there is, as yet, no clear evidence of an effect to extend OS, crizotinib was not proposed for inclusion in the EML at this time.

Harms and toxicity considerations

Because of the multitude of couplet options available for treatment of NSCLC, chemotherapeutic-specific harms and toxicities for this briefing are described below by drug or drug class rather than by regimen.

Platinum agents

Platinum agents, including cisplatin and carboplatin, cause myelosuppression with dose-limiting thrombocytopenia, and can also cause ototoxicity and asthenia. Nausea and vomiting occur in almost all patients treated with cisplatin and carboplatin and is often severe, necessitating the use of antiemetic medications. Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Intravenous hydration both before and after administration of cisplatin is necessary to reduce the incidence of renal toxicity *(33)*. Notably, carboplatin causes less nephrotoxicity, ototoxicity, and nausea and vomiting in this patient population but more frequent severe thrombocytopenia *(34)*.

Paclitaxel

Paclitaxel is associated with high incidences of neutropenia, which is frequently severe (grade 3–4) *(35)*. Paclitaxel can cause hypersensitivity reactions in up to 30% of patients and premedication is required to reduce this risk. Most infusion reactions are mild and easily managed *(36)*. Paclitaxel causes universal alopecia and many patients experience peripheral neuropathy; both of which are reversible.

Gemcitabine

Gemcitabine frequently causes myelosuppression with dose-limiting thrombocytopenia and leukopenia and associated risk of infection. Gemcitabine is also associated with increased hepatic transaminases, which may lead to more severe hepatotoxicity in up to 10% of patients. Many patients experience oedema and dyspnoea *(37)*.

Vinorelbine

Vinorelbine often causes severe neutropenia and granulocytopenia, which increase patients' risk of infection. Like other vinca alkaloids, vinorelbine also frequently causes constipation. It is a strong vesicant and care must be taken to avoid extravasation and associated tissue damage *(38)*.

Etoposide

The most frequent dose-limiting toxicity for etoposide is myelosuppression, primarily leukopenia, which can be grade 3–4 in >10% of patients. A small percentage (up to 2%) of patients receiving intravenous etoposide experience hypersensitivity reactions, which may include angioedema, bronchospasm and/or chest discomfort. Etoposide also causes reversible alopecia in up to 60% of patients *(39)*. The use of etoposide has been associated with a small but increased risk of secondary cancers.

EGFR tyrosine kinase inhibitors

EGFR tyrosine kinase inhibitors are well tolerated by many patients. Agents have similar toxicity profiles, although the incidence of toxicity depends on the drug. Diarrhoea is common, occurring in more than 60% of patients treated with EGFR-TKIs. Rarely, more severe gastrointestinal toxicity, including perforation, can occur, particularly with erlotinib. All agents are associated with characteristic dermatological toxicity and rash, and they may also cause hepatic toxicity and increased hepatic transaminases. Although the incidence is small, hepatic failure and hepatorenal syndrome have been reported in patients treated with erlotinib *(40-42)*.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee endorsed etoposide, carboplatin and paclitaxel (already included on the complementary list) for use in the treatment of non-small cell lung cancer. The Committee also recommended the addition of vinorelbine, gemcitabine and cisplatin to the complementary list for this indication. The Committee noted that cisplatin is the preferred platinum agent for use in adjuvant treatment and as a radio-sensitizer.

The Committee noted that combination chemotherapy with the regimens described in the application has been associated with modest improvements in overall survival and improved quality of life during extended survival.

The Committee did not recommend addition of the TKIs gefitinib and erlotinib to the complementary list of the EML for the treatment of non-small cell lung cancer. The Committee acknowledged that, while individual patients with a drug-sensitive EGFR mutation may derive a substantial extension of life, the average increase in progression-free survival was modest (3–4 months). The Committee considered that substantial infrastructure would be required to establish routine and reliable molecular testing for EGFR mutations in NSCLC. The Committee considered it was neither practical nor cost–effective to establish molecular testing, and therefore the use of tyrosine kinase inhibitors as essential medicines for this disease could not be supported at this time. Afatinib and crizotinib were not proposed for inclusion by applicants or recommended by the Expert Committee.

1. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The Global Burden of Cancer 2013. JAMA Oncol. 2015;1(4):505-27.
2. Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. Int J Cancer. 2005;117(2):294-9.
3. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62(4):220-41.
4. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [Available from: http://globocan.iarc.fr.
5. Bishop JA, Teruya-Feldstein J, Westra WH, Pelosi G, Travis WD, Rekhtman N. p40 (DeltaNp63) is superior to p63 for the diagnosis of pulmonary squamous cell carcinoma. Mod Pathol. 2012;25(3):405-15.
6. King JE, Thatcher N, Pickering CA, Hasleton PS. Sensitivity and specificity of immunohistochemical markers used in the diagnosis of epithelioid mesothelioma: a detailed systematic analysis using published data. Histopathology. 2006;48(3):223-32.
7. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Arch Pathol Lab Med. 2013;137(6):828-60.
8. Di Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, Wachters FM, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2009;27(11):1836-43.
9. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552-9.
10. Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, Le Chevalier T, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375(9722):1267-77.
11. Pujol JL, Barlesi F, Daures JP. Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. Lung Cancer. 2006;51(3):335-45.
12. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol. 2008;26(28):4617-25.
13. Lim E, Harris G, Patel A, Adachi I, Edmonds L, Song F. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. J Thorac Oncol. 2009;4(11):1380-8.
14. Reck M, Heigener DF, Mok T, Soria JC, Rabe KF. Management of non-small-cell lung cancer: recent developments. Lancet. 2013;382(9893):709-19.

15. Spiro SG, Rudd RM, Souhami RL, Brown J, Fairlamb DJ, Gower NH, et al. Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. Thorax. 2004;59(10):828-36.
16. Gridelli C, Gallo C, Shepherd FA, Illiano A, Piantedosi F, Robbiati SF, et al. Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer: a phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2003;21(16):3025-34.
17. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-57.
18. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380-8.
19. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11(2):121-8.
20. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-46.
21. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213-22.
22. Yang JC-H, Sequist LV, Schuler MH, Mok T, Yamamoto N, O'Byrne KJ, et al. Overall survival (OS) in patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring common (Del19/L858R) epidermal growth factor receptor mutations (EGFR mut): Pooled analysis of two large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy (CT). ASCO Meeting Abstracts. 2014;32(15_suppl):8004.
23. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735-42.
24. Guetz GD, Landre T, Uzzan B, Chouahnia K, Nicolas P, Morere JF. Is There a Survival Benefit of First-Line Epidermal Growth Factor Receptor Tyrosine-Kinase Inhibitor Monotherapy Versus Chemotherapy in Patients with Advanced Non-Small-Cell Lung Cancer?: A Meta-Analysis. Target Oncol. 2015.
25. Lee CK, Brown C, Gralla RJ, Hirsh V, Thongprasert S, Tsai CM, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst. 2013;105(9):595-605.
26. Liang W, Wu X, Fang W, Zhao Y, Yang Y, Hu Z, et al. Network meta-analysis of erlotinib, gefitinib, afatinib and icotinib in patients with advanced non-small-cell lung cancer harboring EGFR mutations. PLoS One. 2014;9(2):e85245.
27. Haspinger ER, Agustoni F, Torri V, Gelsomino F, Platania M, Zilembo N, et al. Is there evidence for different effects among EGFR-TKIs? Systematic review and meta-analysis

of EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy as first-line treatment for patients harboring EGFR mutations. Crit Rev Oncol Hematol. 2015;94(2):213-27.
28. Mok T, Kim D-W, Wu Y-L, Solomon BJ, Nakagawa K, Mekhail T, et al. First-line crizotinib versus pemetrexed-cisplatin or pemetrexed-carboplatin in patients (pts) with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC): results of a phase III study (PROFILE 1014). ASCO Meeting Abstracts. 2014;32(15_suppl):8002.
29. Okano Y, Ando M, Asami K, Fukuda M, Nakagawa H, Ibata H, et al. Randomized phase III trial of erlotinib (E) versus docetaxel (D) as second- or third-line therapy in patients with advanced non-small cell lung cancer (NSCLC) who have wild-type or mutant epidermal growth factor receptor (EGFR): Docetaxel and Erlotinib Lung Cancer Trial (DELTA). ASCO Meeting Abstracts. 2013;31(15_suppl):8006.
30. Shaw AT, Yeap BY, Solomon BJ, Riely GJ, Gainor J, Engelman JA, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol. 2011;12(11):1004-12.
31. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-94.
32. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167-77.
33. Portilla D, Safar AM, Shannon ML, Penson RT. Cisplatin nephrotoxicity. In: UpToDate [website]. Waltham, MA: UpToDate; 2013.
34. Lilenbaum R. Systemic therapy for the initial management of advanced non-small cell lung cancer without a driver mutation. In: UpToDate [website]. Waltham, MA: UpToDate; 2014.
35. Paclitaxel. DrugPoints Summary. Micromedex 2.0. Greenwood Village, CO: Truven Health Analytics, Inc.; 2012-2015.
36. Castells M, Matulonis U. Infusion reactions to systemic chemotherapy. In: UpToDate [website]. Waltham, MA: UpToDate; 2014.
37. Gemcitabine. DrugPoints Summary. Micromedex 2.0. Greenwood Village, CO: Truven Health Analytics, Inc.; 2012-2015.
38. Vinorelbine. DrugPoints Summary. Micromedex 2.0. Greenwood Village, CO: Truven Health Analytics Inc.; 2012-2015.
39. Etoposide. DrugPoints Summary. Micromedex 2.0. Greenwood Village, CO: Truven Health Analytics, Inc.; 2012-2015.
40. Lilenbaum R. Systemic therapy for advanced non-small cell lung cancer with an activating mutation in the epidermal growth factor receptor. In: UpToDate [website]. Waltham, MA: UpToDate; 2014.
41. Afatinib. DrugPoints Summary. Micromedex 2.0. Greenwood Village, CO: Truven Health Analytics, Inc.; 2012-2015.
42. Erlotinib. DrugPoints Summary. Micromedex 2.0. Greenwood Village, CO: Truven Health Analytics, Inc.; 2012-2015.