Erlotinib

**Expert Committee recommendation**

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of the tyrosine kinase inhibitors afatinib, erlotinib and gefitinib. The Committee noted that afatinib, erlotinib and gefitinib were all scored as 4/5 on the ESMO-MCBS v1.1 for this indication. The Expert Committee recommended the addition of erlotinib with a square box to the complementary list of the EML for first-line treatment of EGFR mutation-positive advanced non-small cell lung cancer. Afatinib and gefitinib should be considered as therapeutically equivalent alternatives. The Committee noted that these medicines are associated with relevant survival benefits for patients, acceptable toxicity and improvements in quality of life compared to chemotherapy. The Committee also noted that since these medicines were considered for inclusion on the EML in 2015, generic versions of these medicines are more widely available, as are quality-assured diagnostic molecular tests for EGFR mutations.

**Background**

The application requested the addition of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) to the complementary list of the EML for first-line treatment of EGFR mutation positive, non-small cell lung cancer. EGFR TKIs have been considered and rejected for inclusion on the EML on two previous occasions in 2015 and 2017. In each case, the Expert Committee acknowledged that individual patients with a drug-sensitive EGFR mutation may derive benefit from TKI therapy, which has been associated with similar efficacy and more favourable tolerability compared to cytotoxic chemotherapy. However, the requirements to screen patients for suitability for treatment must be taken into account by health systems (1, 2). Cytotoxic chemotherapy
Lung cancer is the most commonly diagnosed cancer globally, and the leading cause of cancer death, with estimated 2 million new cases and 1.7 related deaths in 2018. The economic impact of lung cancer has been estimated at around US$ 8 billion in lost productivity in the BRICS countries (Brazil, Russia, India, China and South Africa) (3). Moreover, in the absence of wide coverage of effective screening programmes on a global scale, lung cancer diagnoses occur in advanced stage in more than 60% of cases, with highly regional variability (4, 5). The mutational pattern of NSCLC varies across the different regions, with a higher prevalence in Asia Pacific (up to 76% of patients) and the lowest registered in Oceania (12%). Africa, Europe and North America registered the same rate of EGFR-mutated NSCLC, at around 20% (6–8). Non-squamous NSCLC has been linked to gene mutations in EGFR. This disease, given its incidence, comprises a high burden and leads to a high mortality. However, with advances in cancer gene-directed treatment, the outcome of the disease has improved. The response rate doubled as compared to chemotherapy, the progression free survival (PFS) doubled and the median survival time increased to nearly three years if patients receive both the targeted medicines and chemotherapy together (the median survival time for patient receiving chemotherapy only is approximately 10 months, in historical series).
The OS probabilities at 30 months were 56.2% and 46.3% with dacomitinib and gefitinib, respectively.

### Harms

The toxicity profile of EGFR-TKIs is generally clinically manageable, with 6% of toxicity-related treatment discontinuation reported in one pooled analysis (27, 28). The use of EGFR-TKI was favoured over chemotherapy in quality of life (QoL) analyses, reporting a longer time to clinical deterioration and maintained overall QoL (29–31). For afatinib, an extensive investigation of patient-reported symptoms and health-related QoL benefits have been reported, showing that afatinib delayed the time to deterioration for cough (HR 0.60, 95%CI 0.41 to 0.87; p=0.007) and dyspnoea (HR 0.68, 95%CI 0.50 to 0.93; p=0.015), with more patients on afatinib (64%) versus chemotherapy (50%) experiencing improvements in dyspnoea scores (p=0.010), the cardinal symptom for lung cancer patients (32). For erlotinib, a secondary analysis from the OPTIMAL (CTONG-0802) Phase III clinical trial, showed that patients receiving erlotinib experienced clinically relevant improvements in QoL compared with the chemotherapy group, across different scales to assess general outcome and lung-specific subscales (33). Data for gefitinib are still consistent with the findings for the other two EGFR-TKIs: time to deterioration in physical and life well-being favoured gefitinib over chemotherapy (HR of time to deterioration, 0.34, 95%CI 0.23 to 0.50; p<0.0001 and HR 0.43, 95%CI 0.28 to 0.65; p<0.0001, respectively) (29).

### Cost / cost effectiveness

A cost-effectiveness analysis performed by the Institute for Clinical and Economic Review showed that the use of each of the first-line EGFR-TKI regimens resulted in a 0.84 life-year gain in survival relative to chemotherapy. Quality-adjusted life-years (QALYs) gained versus chemotherapy were also very similar, ranging from 0.60 for gefitinib to 0.62 for afatinib and erlotinib. Incremental costs versus chemotherapy were lower for gefitinib (approximately US$ 66 000) than for the other EGFR-TKIs, as a function of a shorter duration of time spent in the progression-free state (and a consequently shorter duration of treatment). Cost-effectiveness estimates were similar across the EGFR-TKIs, ranging from approximately US$ 110 000 to US$ 150 000 per QALY gained (34). In another cost-effectiveness analysis, two different strategies were compared: the ‘EGFR testing strategy’, in which EGFR mutation testing was performed before treatment and patients with EGFR mutations received gefitinib while those without mutations received standard chemotherapy, to the ‘notesting strategy,’ in which genetic testing was not conducted and all patients were treated with standard chemotherapy. The authors concluded that the combination use of gefitinib and EGFR testing can be considered a cost-effective first-line therapy compared to chemotherapy such as carboplatin-paclitaxel for the treatment for NSCLC in Japan (35). Technology appraisal guidance issued by National Institute for Health and Care Excellence (NICE) for first-line EGFR-TKIs gefitinib, erlotinib and afatinib state that these medicines are recommended treatment options people with locally advanced or metastatic EGFR mutation-positive NSCLC if the manufacturers provide the drugs at agreed fixed or discounted prices (36–38).

### WHO guidelines

None available.

### Availability

Originator brands of afatinib, erlotinib and gefitinib are manufactured by Boehringer Ingelheim, Roche and AstraZeneca, respectively. Generic brands are becoming available.

### Other considerations

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of EGFR TKIs on the EML, stating that there is sufficient evidence that these medicines are equivalent or superior to existing listed medicines, based on updated meta-analysis and real-world data, particularly in middle-income countries. Based on the results of the LUX-Lung 3 study (14, 32), afatinib received a score of 4 on the ESMO-Magnitude of Clinical Benefit Scale (MCBS, v1.1) for first-line use in metastatic EGFR+ NSCLC (39). Based on the results of the OPTIMAL (40) and EURTAC (13) studies, erlotinib received a score of 4 on the ESMO-MCBS v1.1 for use in metastatic EGFR+ NSCLC (39). Based on the results of the IPASS study (10, 41), gefitinib received a score of 4 on the ESMO-MCBS v1.1 for first-line use in metastatic EGFR+ NSCLC (39).


