Osimertinib

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

ATC codes: L01EB04

Indication	Other specified malignant neoplasms of bronchus or lung ICD11 code: 2C75.Y
INN	Osimertinib
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid: 40 mg (as mesylate) ; 80 mg (as mesylate)
EML status history	Application rejected in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer
Wikipedia	Osimertinib
DrugBank	Osimertinib

Expert Committee recommendation

The Expert Committee acknowledged the treatment of lung cancer to be complex and recognized the need to provide the best available care within the context of both non-small-cell lung cancer and small-cell lung cancers. Over the past decade, the treatment outcomes for advanced non-small-cell lung cancer have improved with new treatment models involving targeted therapy based on the molecular and biological characteristics of the cancer. For EGFR mutation-positive non-small-cell lung cancer, the Committee recalled its recommendations in 2019 to include erlotinib, gefitinib and afatinib as therapeutic alternatives for this indication. These medicines are associated with improved quality of life and longer overall survival compared with cytotoxic chemotherapy in patients with the EGFR driver mutation. The Expert Committee noted that the application to list osimertinib was based on the results of a single randomized control trial (FLAURA), in which osimertinib was compared to physician's choice of erlotinib or gefitinib. Interim trial results showed that osimertinib extended overall survival compared with the two first-generation EGFR tyrosine kinase inhibitors. However, the Committee considered that overall survival data, while promising, were still immature and therefore confidence that osimertinib prolongs survival compared with erlotinib and gefitinib is limited. The Expert Committee also noted that the current price of osimertinib is very high, and several analyses have concluded it is not cost-effective. Meanwhile, first- and second-generation tyrosine kinase inhibitors, including those currently included on the EML, are available as generic products and are more likely to be affordable, accessible treatment options for patients and health systems. The Committee considered the option of including osimertinib as an additional therapeutic alternative to the EGFR tyrosine kinase inhibitors already included on the EML, thereby allowing selection of osimertinib at the country level. However, given the difference in current prices, the Committee decided against this option due to the risk of considerable additional expenditure at the

country level. Therefore, the Expert Committee did not recommend the inclusion of osimertinib on the EML at this time. However, the Committee considered that the current evidence for osimertinib was promising and requested that an application with updated survival data be submitted for consideration at the next Expert Committee meeting. Without committing a future Expert Committee to a favourable recommendation to include osimertinib on the EML, the Committee recommended that osimertinib be flagged to the Medicines Patent Pool as a candidate for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this medicine in low- and middle-income countries.

Background

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor. It has not been previously considered for inclusion on the EML. In 2019, the Expert Committee recommended the addition of the first-generation EGFR tyrosine kinase inhibitor erlotinib to the EML for the treatment of EGFR mutation-positive non-small-cell lung cancer. Listing was recommended with a square box specifying gefitinib and the second-generation tyrosine kinase inhibitor afatinib as therapeutic alternatives. The Committee noted that these medicines were associated with relevant survival benefits for patients, acceptable toxicity and improvements in quality of life compared with chemotherapy. The Committee also noted the availability of generics and quality-assured diagnostic molecular tests for EGFR mutations (1). Epidermal growth factor receptor is a transmembrane protein with kinase implicated in cell division, angiogenesis and apoptosis. Mutations in the EGFR gene (so-called driver mutations), of which many types exist but most concern deletions in exon 19 or substitutions of leucine for arginine (L858R) in exon 21, can contribute to uncontrolled cell proliferation. EGFR mutations (without prior exposure to tyrosine kinase inhibitors) are observed in about one in three patients with non-small-cell lung cancer (see the following section on public health relevance). First- and second-generation tyrosine kinase inhibitors are often associated with a pronounced initial response in patients with driver mutations but acquisition of secondary resistance to tyrosine kinase inhibitors and disease progression after several months of treatment are frequently observed. This acquired resistance is most frequently due to a mutation that substitutes methionine for threonine at amino acid position 790 (T790M). Osimertinib retains inhibitory activity in the presence of the T790M mutation.

Public health relevance

Lung cancer is the leading cause of cancer death worldwide, with an estimated 1.7 million related deaths in 2018 (2). Lung cancer is a highly lethal malignancy, with an economic impact estimated at around US$ 8 billion in lost productivity in the BRICS countries (Brazil, Russia, India, China, and South Africa). Moreover, in the absence of wide coverage of an effective screening programme in place globally, lung cancer diagnoses occur in advanced stages in more than 60% of cases, with large regional variation (3–5). Over 80% of lung cancers are classified as non-small-cell lung cancer (6). Targeted therapies have redefined treatment for patients with genomic alterations in driver oncogenes (e.g. EGFR mutations, anaplastic lymphoma kinase rearrangements, ROS1 rearrangements, BRAF mutations, human epidermal growth factor receptor 2 (HER2) mutations or amplifications and neurotrophic tyrosine kinase (NTRK) 1–3 fusions) to guide the selection of treatments. However, these therapies are ineffective in most patients with non-small-cell lung cancer who have tumours that lack such genetic alterations. Gene-targeted therapies are now estimated to benefit less than 10% of patients with non-small-cell lung cancer, but this proportion might increase rapidly over time (7). A meta-analysis and systematic reviews found an overall prevalence of EGFR mutation of about 30%, although this varies by world region, risk factors and population phenotype. For instance, the Asian–Pacific region has the highest prevalence of EGFR mutation (47%), followed by South America (36%), North America (22%), Africa (21%), Europe (15%) and Oceania (12%) (8–10).

Benefits

The phase III FLAURA trial was a double-blind, prospective clinical trial that compared osimertinib with standard first-generation tyrosine kinase inhibitors (gefitinib and erlotinib) for first-line treatment of EGFR-mutated locally advanced or metastatic non-small-cell lung cancer (11,12). The study randomized 556 participants in a 1:1 ratio to receive osimertinib 80 mg once daily, or standard treatment (gefitinib 250 mg once daily or erlotinib 150 mg once daily) until disease progression, unacceptable toxicity or consent withdrawal. At the time of primary analysis (data cut-off 12 June 2017) for the primary endpoint of progression-free survival, osimertinib was associated with a statistically significant improvement compared with standard treatment (median progression-free survival 18.9 months versus 10.2 months; hazard ratio (HR) for disease progression or death 0.46, 95% confidence interval (CI) 0.37 to 0.57). Osimertinib also demonstrated a significant progression-free survival benefit for

participants with central nervous system metastasis, a common site of progression of non-small-cell lung cancer and frequently responsible for deterioration in quality of life (median progression-free survival 15.2 months versus 9.6 months; HR for disease progression or death 0.47, 95% CI 0.30 to 0.74) (11). A final analysis (data cut-off 25 June 2019) was performed for the secondary endpoint of overall survival with a median duration of follow-up for overall survival of 35.8 months in the osimertinib group and 27.0 months in the comparator group (12). Median overall survival favoured the osimertinib group over the standard treatment group (median overall survival 38.6 months versus 31.8 months (HR 0.80, 95% CI 0.64 to 1.00), a 6.8-month survival gain in absolute terms (12). At 36 months, 54% of participants in the osimertinib group were alive compared with 44% in the comparator group.

Harms

From the final analysis of the FLAURA trial (12), adverse events of grade 3 or higher were reported in 42% and 47% of participants in the osimertinib group and standard treatment group, respectively. The most commonly reported adverse events possibly related to osimertinib treatment (investigator assessed) were diarrhoea (50%), paronychia (30%), dry skin (31%), stomatitis (25%) and dermatitis acneiform (25%). Serious adverse events were reported in 27% of the participants in each treatment arm. Decreased ejection fraction was reported in a greater proportion of participants in the osimertinib group than the standard treatment group (5% versus 2%). Similarly, QT prolongation was also reported in a greater proportion of participants in the osimertinib group than the standard treatment group (10% versus 4%). Compared with the primary analysis, there were no new reports of interstitial lung disease or pneumonitis, which were both reported in 2% and 1% of participants in the osimertinib and standard treatment groups, respectively (11,12). In the osimertinib and standard treatment groups, dose interruptions occurred in 43% and 41% of participants, dose reductions in 5% and 4% and permanent discontinuation of treatment due to adverse events in 15% and 18%, respectively (12).

Cost / cost effectiveness

A cost–effectiveness analysis was conducted of osimertinib compared with first- and second-generation EGFR tyrosine kinase inhibitors for first-line treatment of advanced EGFR-mutated non-small-cell lung cancer using direct costs from United States and Brazilian payer perspectives and a 10-year time horizon based on results from the FLAURA trial (13). In the base case, for the United States, the incremental costs per quality-adjusted life year (QALY) for osimertinib compared with erlotinib, gefitinib and afatinib were more than US$ 200 000 for each comparison. For Brazil, the incremental costs per QALY for osimertinib compared with erlotinib, gefitinib and afatinib were more than US$ 160 000 for each comparison. Applying a cost–effectiveness threshold of three times the gross domestic product per capita for each country, the authors concluded that osimertinib was not a cost-effective intervention at current prices in either country. In October 2020, the National Institute for Health and Care Excellence of the United Kingdom of Great Britain and Northern Ireland recommended coverage under the National Health System for osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer, after confidential commercial arrangements with the manufacturer were negotiated resulting in lower price and cost–effectiveness estimates within the acceptable range for use of National Health System resources (14).

WHO guidelines

WHO guidelines for treatment of non-small-cell lung cancer are not available.

Availability

Osimertinib (trade name Tagrisso, Astra Zeneca) has regulatory approval in 40 countries including the United States, Japan and in Europe for frontline treatment of EGFR-mutated non-small-cell lung cancer. It has primary patent protection until 2032.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of osimertinib on the EML at this time. The Working Group noted that earlier tyrosine kinase inhibitors currently listed on the EML for EGFR-mutated non-small-cell lung cancer are available as generics and are more likely to be affordable, accessible treatment options for patients and health systems. The Working Group noted that osimertinib has a demonstrated meaningful overall survival benefit compared with first-generation tyrosine kinase inhibitors and meets the criteria of the European Society for Medical Oncology's magnitude of clinical benefit scale

(ESMO-MCBS) v1.1 score. However, the current price of osimertinib is prohibitively high for both patients and health systems, and it has not been found to be cost-effective at current prices in some analyses. The Working Group also noted the requirement for accompanying diagnostic testing, which has variable and limited availability in low- and middle-income settings. Osimertinib treatment is only given to patients whose tumours exhibit EGFR-tyrosine kinase inhibitor sensitizing mutations detected by molecular tests validated by regulatory agencies. The need for molecular testing is also a requirement for osimertinib treatment according to existing treatment guidelines of medical oncology societies (15). The EGFR gene mutation test was added to the WHO Model List of Essential In-Vitro Diagnostics in 2020 (16). The European Society for Medical Oncology clinical practice guidelines for metastatic non-small-cell lung cancer recommend osimertinib as the preferred option for first-line treatment of non-small-cell lung cancer patients with sensitizing EGFR mutations (ESMO-MCBS v1.1 score: 4) (17). Current National Comprehensive Cancer Network (NCCN) guidelines for NSCLC also recommend osimertinib as preferred first-line therapy for EGFR mutation positive NSCLC (category 1, high-level evidence) (15). Comments were received from the WHO Department of Noncommunicable Diseases. The technical department acknowledged that evidence suggests that osimertinib offers clinical value when compared with the first-generation tyrosine kinase inhibitors gefitinib and erlotinib in terms of overall survival gain and a more favourable toxicity profile. However, the technical department noted concerns about the accessibility of first-generation tyrosine kinase inhibitors already included on the 21st WHO EML. Furthermore, first-generation tyrosine kinase inhibitors (for which generics products are available) may also be more cost-effective and have less effect on health system budgets due to their lower price. The technical department concluded that these factors may argue against consideration of osimertinib for inclusion on the EML at this time. Finally, the technical department advised that future evaluation of osimertinib should take into account evolving data and the broader context of accessibility and prioritization.

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