Application for the inclusion of osimertinib in the WHO Model List of Essential Medicines for the 1st line treatment of EGFR mutated locally advanced or metastatic non-small cell lung cancer (NSCLC).

- **List of Contributors**:

  George Pentheroudakis, MD PhD on behalf of the European Society for Medical Oncology (ESMO)

- **Name of the focal point in WHO supporting the application**

  Lorenzo Moja, Technical Officer, Department of Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland

  Andrè Ilbawi, Technical Officer, Department of Universal Health Coverage, Non-Communicable Diseases, World Health Organization, Geneva, Switzerland

- **Name of the organisation supporting the application**

  European Society for Medical Oncology (ESMO)

- **International Non-proprietary Name (INN, generic name) of the medicine**

  Osimertinib (INN Name), ATC Code (L01XE35) - Last updated:
  2019-12-16

Background

This medicine belongs to the Tyrosine Kinase Receptor Inhibitor (TKI) class, which comprises small molecules directed against the ATP binding site of the Epidermal Growth Factor Receptor (EGFR). This drug class serves to treat locally advanced or metastatic non-small cell lung carcinoma (NSCLC) harbouring EGFR sensitising mutations, in the non-curative setting.

This application aims to address the priority for EGFR mutated, metastatic NSCLC, where there is a compelling public health interest and where the role of TKIs is definite, for indications with no controversies and debates ongoing, for which a valuable role in cancer treatment has been established and widely agreed upon by the oncology experts and scientific societies.

1. Formulation proposed for inclusion, including adult and paediatric (if appropriate) (1,2)

Osimertinib is a 3rd generation, oral TKI targeting and irreversibly binding the cysteine-797 residue in the ATP binding site via covalent bond formation. There are two pharmaceutical forms available, as 80mg or 40mg film-coated tablet, as mesylate.

- Generics availability: Patent will expire by 2035, however a recent generic version is available in Bangladesh under the generic name Tagrix.
- Posology and Pharmaceutical Form:

  For adults: the recommended treatment schedule is 80 mg daily (1 tablet) until disease progression or unacceptable toxicity. Osimertinib can be taken with or without food, and omeprazole does not seem to impact on osimertinib pharmacokinetics (1).

  According to the US Food and Drug Administration (FDA) label, patients who have difficulty to swallow might follow the following instructions: “Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until the tablet is dispersed into small pieces (tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.”

  “If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).”

  For children and adolescents under 18 years: There is no study effectiveness or safety (2, 3).

2. International availability - sources, if possible, manufacturers and trade names

Osimertinib (Trade name: Tagrisso; Manufacturer: Astra Zeneca) (2, 3)

3. Whether listing is requested as an individual medicine or as an example of a therapeutic group?

Individual medicine.

4. Treatment details (requirements for diagnosis, treatment and monitoring).

Osimertinib (Tagrisso) is indicated as monotherapy until disease progression or unacceptable toxicity according to the pivotal clinical trials. Such indication has been adopted by the European Medicine Agency (EMA), and FDA in the following scenarios:

a. Frontline treatment for metastatic NSCLC with EGFR sensitizing éxon 19 and L858R mutations, detected by validated molecular test;
b. T790M EGFR resistance mutation-bearing NSCLC that progressed to 1st or 2nd generation EGFR TKI directed therapy, also detected by validated molecular test (2-4).

For WHO Essential Medicines List (EML) submission purpose, we considered the indication of osimertinib given its high score (grade 4), according to the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) version 1.1 in the non-curative setting, and a meaningful progression free survival benefit (PFS gain) of 8.7months, hazard ratio (HR) 0.46 (0.37-057), overall survival (OS) gain of 6.8 months - mature data is available and published in 2020 (5, 6).

Considering the WHO EML recommended threshold for cancer medicines analysis, this submission follows the proposed and prioritises the osimertinib recommendation only for untreated locally advanced, metastatic NSCLC with EGFR sensitizing éxon 19 and L858R mutations.

4.1 Frontline metastatic NSCLC, EGFR sensitizing mutation:

The use of osimertinib treatment has been tested in randomised, double-blind, prospective, phase III clinical trials. The FLAURA trial compared osimertinib with the 1st generation EGFR TKI, gefitinib or erlotinib, which are the standard of care treatment for EGFR mutated patients and are endorsed by the WHO EML 2019. Osimertinib was given orally as an 80 mg tablet, once daily, until disease progression or unacceptable toxicity for WHO Performance Status 0 and 1, patients with untreated locally advanced / metastatic NSCLC, whose tumour hosts EGFR-TKI-sensitizing mutations (éxon 19 deletion and L858R mutation)(4).

Osimertinib treatment is solely given to patients whose tumours exhibit EGFR-TKI sensitizing mutations detected by validated molecular tests according to regulatory agencies (2, 3).

The evidence for EGFR mutation comes from a clinical trial that found that EGFR mutation predicts patients' outcomes benefit when treated with EGFR-TKI gefitinib rather than standard platinum-doublet chemotherapy (HR for progression or death, 0.48; 95% CI, 0.36 to 0.64; P<0.001). Conversely, the patients with EGFR non-mutated tumours exhibit worse outcomes (hazard ratio for progression or death when treated with gefitinib, 2.85; 95% CI, 2.05 to 3.98; P<0.001)(7). Therefore, not immunohistochemistry for detecting EFGR protein expression, but mutational analysis is the preferred method to assess the EGFR gene mutational status(8).

The need for molecular testing is also a requirement for osimertinib treatment according to the Third WHO Model List of Essential in Vitro Diagnostics, 2021, (ICD11 code: 2A20.0Z) and the Medical Oncology Societies treatment guidelines (9). Of note, the ESMO Scale for Clinically Actionability of molecular tests (ESCAT) confers a "Tier A" score for EGFR molecular testing directed to NSCLC for this submission". In other words, this specific indication follows the highest ESCAT Tier, reinforcing that the molecular test result supports the medicine's prescription according to the ESCAT best level of evidence, identifying the patient population with marked benefit from the therapeutic (10).

Medical Oncology Societies recommend to request EGFR testing for all non-squamous NSCLC advanced/recurrent disease [I, A], and selected squamous tumors (non-smokers or second hand smokers) should strongly be considered for testing [IV, B]. A wide coverage of mutations in exons 18–21 encouraged, including those associated with resistance to EGFR TKI. However, when material or resources are limited, the most common activating target mutations (Exon19del, L858R) should be determined [I, A]. Any methodology employed should be validated by an external quality assurance program [V, A] (11).

EGFR assessment validated molecular tests can be performed on different platforms like NGS (Next-Generation Sequencing), Real-Time Polymerase Chain Reaction (RT-PCR), and SANGER.

DNA direct sequencing of éxon 18 to 21, where availability, expertise, quality of specimen in terms of tumour cell enrichment, and costs influence the method of choice (8,11). In addition, the choice of the testing method should take into consideration, strongly influenced by specimen tumour enrichment (%) requirement. In other words, the tumour cell percentage requirement for analysis will also influence the sensitivity of each method, as for example, SANGER sequencing (25%), SANGER with LNA/PNA 0.1 to 2%, NGS 1 to 10%. Fragment Allele-Specific PCR 5%(12).

FDA provides a list of approved companion diagnostics devices, which is "in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product". The list is online and publicly available at www.fda.gov for both tissue and plasma samples (accessed on 13 Nov 2020)(13).

Considering the feasibility and complexity of molecular diagnosis, EGFR tests follow standard patterns defined by international pathologist guidelines and target sensitizing mutations, the same required for 1st generation NSCLC EGFR-TKI already included in the WHO EML 2019 (14). Therefore, the aforementioned molecular diagnosis demands the same high-skilled workforce, and capacity building as proposed for gefitinib and erlotinib.

FDA List of Companion Tests of Approved Companion Devices (updated in 11/09/2020) includes: EGFR Companion Tests FDA Approved, Cobas EGFR Mutation Test v2 , Foundation One CDx, Guardant360® CD, FoundationOne® Liquid CDx, not to mention the Nucleic Acid Based Tests as non-companion test, which also include THERASCREEN EGFR RGQ PCR KIT, Oncomine Dx Target Test and the Cobas EGFR MUTATION TEST v2. (13).

Lastly, Medical Oncology Society guidelines (i.e., ESMO, NCCN), regulatory, and Health Technology Assessment (HTA) agencies recognise and endorse the diagnosis, treatment duration, and posology expressed above (2, 3, 8, 15, 16).

5. Information supporting the public health relevance.

Lung cancer is the most commonly diagnosed and the first cause of death for cancer worldwide, estimating 2 million new cases and 1.7 related deaths in 2018, according to Global Cancer Observatory 2018 (17). Lung cancer is a highly lethal malignancy, with an economic impact estimated at around $8 billion in productivity lost in the BRICS countries (18). Moreover, in the absence of wide coverage of an effective screening programme in place on a global scale, lung cancer diagnoses occur in advanced stages (i.e., III and IV, TNM 8th) in more than 60% of cases, with highly regional variability (18-20) .Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide.

Over 80% of the lung cancers are classified as non-small cell (NSCLC), and nearly 70% are diagnosed at late stages as locally advanced or metastatic.

Oncogene driver directed therapies, also known as targeted therapies or personalised medicine, have reshaped the therapeutic landscape for patients with molecularly druggable NSCLC (e.g., epidermal growth factor receptor [EGFR] mutations, anaplastic lymphoma kinase [ALK] rearrangements, ROS1 rearrangements, BRAF mutations, HER2 mutations or amplifications, NTRK1-3 fusions) in the metastatic setting. This landmark improvement is not only a result of the mutation overall prevalence but also due to meaningful clinical benefit and better toxicity profile of the targeted TKIs, when compared to previous standard chemotherapy regimens.

Targetable approved medicines comprise nearly 50% of NSCLC, where EGFR mutation is the most prevalent drugable abnormality. A meta-a-analysis and systematic reviews found an overall EGFR mutation prevalence of approximately 30%, yet EGFR prevalence varies according to the world region, risk factors' and population phenotype. For instance, the Asian-Pacific region has the highest prevalence (47%), followed by South America (36%), North America (22%), Africa (21%), Europe (15%), and Oceania (12%). The aforementioned prevalence is expected to influence the outcomes of cohorts exposed to the TKI-EGFR therapies and should be taken into account for National Cancer Control (NCCP) investment cases, as the prevalence will ultimately determine their budget impact (21-23).

Osimertinib target population does not differ from the existing EGFR-TKI inhibitors, erlotinib and gefitinib, in terms of targetable EGFR mutation profile. This constitutes helpful information when planning the workforce or capacity-building needs.

Conversely, the 3rd generation EGFR TKI, osimertinib, adopted for a molecularly defined NSCLC population, produces a meaningful clinical benefit (OS gain of 6.8 months) linked to better toxicity profile and strongly translate into improvement for cancer treatment on a major scale due to the magnitude of the target population. For instance, NSCLC represents the leading cause of death among cancer, frequently diagnosed as metastatic disease, where the EGFR mutation is the most frequent oncogene driver mutation (30% of cases).

6. Review of benefits: summary of evidence of comparative effectiveness.

The data are provided by the ESMO Clinical Practice Guidelines (12) for the management of advanced lung cancer and implemented with the use of other clinical guidelines, where available, and a manual research of databases (Medline, Scopus, Ovid, Google Scholar) and the relevant abstracts manually retrieved from the medical oncology conferences (ESMO, ASCO, ESMO Asia, ELCC, WLCC). The ESMO Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (13). The relevant literature has been selected by the expert authors, reporting the levels of evidence (I-V) and the grades of recommendations (A-E), adapting the Infectious Diseases Society of America-United States Public Health Service Grading System. ESMO-MCBS v1.1 is used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016, with 4 or 5 and A, B considered as valuable scores to suggest priority medicines in advanced and curative setting, respectively (6).

7. First-line treatment of EGFR mutated metastatic NSCLC as described in Sep 2020 last update of ESMO Clinical Practice Guideline on NSCLC (12)

7.1A Frontline treatment with osimertinib in EGFR sensitizing mutation

EGFR TKIs are the standard of care for first-line treatment of metastatic NSCLC whose tumours harbour EGFR éxon18-21 sensitizing mutations. In this regard, éxon 19 deletion and éxon 21 L858R insertion mutation comprise the most frequent sites, 90%. Notably, one key turning point for thoracic malignancies modern precision oncology relies not only on 1st generation EGFR-TKI development and approval in 2003, but also the finding that EGFR mutational status diagnosis predicts the patients' clinical benefit, as discussed above.

Such historical data reinforces the imperative need for a timely, quality, and reliable molecular pathology assessment and guarantees the target therapy feasibility. Therefore, the critical role of validated companion diagnostic tests to translate the expected clinical trial outcomes to real-world populational benefit has been expressly described in TKI labelling forms.

Randomised clinical trials (RCT) that explored the role of EGFR TKI for advanced NSCLC showed meaningful PFS benefit and a better toxicity profile for patients with lung cancer. A systematic review with meta-analysis that evaluated 8 RCT, 82 cohort studies, and 17.621 patients, found no statistically significant OS difference in the first-line setting among 1st generation (gefitinib, erlotinib), and 2nd generation (afatinib) EGFR TKI. With respect to PFS, Afatinib showed no significant difference when compared to erlotinib. With respect to the geftinib, the result favour afatinib in the observational study (>18 versus 11.4 months), but not in the RCT (11.0 versus 10.9 months) (24). Thus, the physicians' choice relies mostly on posology, toxicity profile, personal experience, availability, and affordability.

The FLAURA trial, a phase 3, double-blind, prospective clinical trial, compared the 3rd generation EGFR TKI, osimertinib, with the standard 1st generation TKI (gefitinib and erlotinib) for EGFR mutated NSCLC metastatic patients. The study randomized 556 patients in a 1:1 ratio to receive osimertinib, as mesylate, 80 mg once daily, or the standard (gefitinib at a dose 250 mg once daily or erlotinib at a dose of 150 mg once daily) until disease progression, unacceptable toxicity or consent withdrawal.

In terms of efficacy, significant improvement for PFS, the primary endpoint, favoured the osimertinib arm, (mPFS 18.9 versus 10.2 months; HR 0.46, 95% CI 0.37–0.57, P<0.0001). Moreover, the study revealed a meaningful clinical benefit for median OS in favour of osimertinib (mOs 38.6 months (95% CI 34.5–41.8) in the osimertinib group and 31.8 months (95% CI 26.6–36.0) in the 1st generation TKI arm (HR 0.80, 95% CI 0.64–1.00, P=0.046), a 6.8 month gain for OS after a 35.8 and 27.0 months follow up in the osimertinib and comparator arm, respectively

Importantly, osimertinib also revealed a statistically and clinically meaningful PFS benefit for patients with Central Nervous System (CNS) metastasis, a common site of progression and a frequent cause of Quality of Life (QOL) deterioration (mPFS 15.2 versus 9.6 months, HR 0.47, 95% CI 0.30–0.74, P=0.0009).

Concerning safety, toxicity profile and QOL, a PRO analysis of FLAURA Trial patients revealed similar outcomes for both arms for the domains analysed (25, 26). According to FLAURA data, grade 3 or higher adverse event rates were 34% in the osimertinib group and 45% in the comparator group, thus improving the toxicity profile. Considering the FLAURA trial results, with mature data recently published, both NCCN and ESMO updated their NSCLC Guidelines, and describe osimertinib as "the preferred" option in first-line for NSCLC patients with sensitizing EGFR mutations" [I, A; ESMO-MCBS v1.1 score 4]. Therefore, osimertinib is now considered the standard of treatment due to the efficacy and toxicity profile when no feasibility, cost, or affordability constraints limit the access.

In other comparative effectiveness regimens that were recently evaluated and approved by regulatory agencies, the majority failed to translate into OS improvement in the same target population, as follows:

- Ramucirumab in combination with erlotinib compared with erlotinib and placebo [I, B; ESMO-MCBS v1.1 score 3]
- Erlotinib and bevacizumab - NEJ026 Trial [[I, A; ESMO-MCBS v1.1 score 3](27).

The marginal added benefit of these alternative options was less than the benefits observed with osimertinib.

A recently published systematic review with meta-analysis confirms the trend to improve overall response rate (ORR), OS and PFS (HR<1 and p< 0.05) (28).

Considering the public health relevance of elderly populations in treatment for NCSLC, a network meta-analysis that examined 10 RCTs and more than 3700 patients also validates the osimertinib OS benefit for both elderly and non-elderly populations with EFGR sensitive mutations (29).

Considering central nervous system progression as a source of special concern due to its frequency and associated morbidity and mortality in metastatic NSCLC patients, a pre specified analysis was conducted in 128 patients from FLAURA trial. The compelling results show a 2.5 higher CNS ORR (66% vs 43%), and a lower CNS progression rate of 20% vs 39% favoring osimertinib, as compared to the 1st line TKI (30).

Table 1. The ESMO-MCBS score for EGFR-TKI for NSCLC – 1st line metastatic setting

Tested agent	Control arm	Treatment setting	Primary outcome	PFS Control	PFS Gain	PFS HR	OS Control	OS Gain	OS HR	QoL	Toxicity	ESMO-MCBS v1.1	Ref
Osimertinib	Gefitinib or erlotinib	Advanced NSCLC, previously untreated EGFR mutated (exon 19 deletion or L858R)	PFS	10.2 months	8.7 months	0.46 (0.37-0.57)	31.8 months	6.8 months	0.80 (0.64-1.00)	Similar between arms	Improved toxicity profile	4	4,5,25

Table 2. Toxicities of Interest comparison between osimertinib and comparator arm (gefitinib or erlotinib). Adapted from FLAUTA TRIAL results.

	Osimertinib (N = 279)				Comparator EGFR-TKI (N = 277)			
Adverse Event	Any Grade n(%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Diarrhoea	167 (60)	119 (43)	41 (15)	7 (3)	162 (58)	118 (43)	35 (13)	7 (3)
Rash or acne	164 (59)	132 (47)	29 (10)	3 (1)	219 (79)	111 (40)	88 (32)	20 (7)
Dry skin	106 (38)	89 (32)	16 (6)	1 (<1)	102 (37)	78 (28)	21 (8)	3 (1)
Stomatitis	82 (29)	66 (24)	14 (5)	1 (<1)	60 (22)	51 (18)	8 (3)	1 (<1)
Fatigue	45 (16)	25 (9)	17 (6)	3 (1)	35 (13)	23 (8)	10 (4)	2 (1)
Prolonged QT interval	28 (10)	12 (4)	12 (4)	4 (1)	12 (4)	7 (3)	3 (1)	2 (1)
Increase in aspartate aminotransferase	28 (10)	19 (7)	7 (3)	2 (1)	69 (25)	39 (14)	18 (6)	12 (4)

8. Summary of available data on comparative cost and cost-effectiveness of the medicine

Cost-effectiveness analyses for the proposed submission scenario have been performed and published for countries with different income levels, and healthcare systems, such as Brazil, United Kingdom and United States of America (31).

A study published at JAMA evaluated the cost-effectiveness ratio for osimertinib in Brazil and USA following the WHO cost-effectiveness threshold of three times the Gross Domestic Product (GDP) per capita in each country. The primary endpoint was the cost of Quality Years Gained (QALY) - ICER (Incremental Cost-Effectiveness Ratio). The study assessed frontline metastatic EGFR mutated NSCLC treatment with osimertinib vs 1st and 2nd generation TKI, a comparison similar to the pivotal study that showed OS gain, which supports this submission.

A comprehensive model analysed the medicine acquisition' cost and the costs related to supportive care in adverse events and medicines prescribed after progression. Additionally, the authors conducted a sensitivity analysis to increase the results strength.

According to the authors, incremental 0.594 QALY gain estimates were defined, assuming the FLAURA trial clinical benefit. Also, as a secondary endpoint, the study revealed incremental life-years gained of 1.01.

Considering the comparative evaluation, the incremental cost per 1 life-year saved in USA and Brazil was respectively, $133,472 vs $95,646 for erlotinib, $136,180 vs $106,532 for gefitinib, and $129,552 vs $103,366 for afatinib. Likewise, the osimertinib ICER per QALY comparison with 1st and 2nd generation TKI in United States was $226,527 (vs erlotinib), $231 123 (vs gefitinib) $219 874 (vs afatinib), and $162 329 (vs erlotinib), $180,804 (gefitinib), and $175,432 (vs afatinib) in Brazil.

The sensitive analysis informs that the major determinant for Incremental QALY was OS (IC 95%, 0.106 to 1.02), depending on the OS range. Discounts were the second most influent

Lastly, the authors conclude that “at current costs and considering the willing to-pay thresholds, we found that osimertinib is unlikely to be cost-effective for EGFR-mutated first-line therapy”.

Additionally, a systematic review designed to review the economic evaluations for 1st and 2nd line Tyrosine Kinase Inhibitors confirms that osimertinib remains not cost-effective when compared to other TKIs, regardless of distinct thresholds, designs or settings.

Conversely, it is important to recognise that the National Institute for Health and Care Excellence (NICE) in England, recently adopted osimertinib as standard of care for untreated locally advanced/metastatic NSCLC EGFR mutated patients after a commercial agreement with the manufacturer aiming to improve the cost-effectiveness ratio. The NICE Appraisal Consultation Document, dated April 2019, initially did not recommend osimertinib and formally stated that the medicine did not meet the criteria to be included in the Cancer Drugs Fund - the original reference price on the website stands for £5,770 f/pack containing 80 mg of osimertinib, as mesylate. Even though the discount size is not public, the negotiation with the manufacturer, AstraZeneca, made osimertinib available into the National Health System (NHS) and has been included in the NICE NSCLC Treatment Guidelines (32).

9. Overview

Considering the prevalence of advanced NSCLC, and EGFR mutation as the most frequent oncogene driver targetable aberration, this application offers the opportunity to impact the clinically significant OS gain derived from osimertinib, as compared to existing standard treatments for the target population. Notably, the OS gain of 6.8 months and ESMO-MSCBS 4, high score for non-curative intent medicines, along with the magnitude of the target population, elicited ESMO to consider osimertinib eligible for the WHO EML application submission in the specific setting – untreated metastatic advanced, EGFR mutated NSCLC.

Acknowledging feasibility, there is a need for high skilled molecular pathology and capacity building, yet this submission is not expected to increase the demand for workforce and capacity building beyond the already

required for the 1st generation EGFR TKI, and previously adopted by the WHO EML, namely erlotinib and gefitinib. In fact, the inclusion of osimertinib in the EML would rationalise the withdrawal from the list of first generation EGFR TKIs (erlotinib, gefitinib) in view of their inferior efficacy in the first line setting compared to osimertinib and the absence of efficacy after resistance to osimertinib.

Lessons learned from NICE regarding the process for medicines 'adoption, and negotiation are opportunities to improve the cost-effectiveness ratio, reduce budget impact, design the proper investment case, and ultimately make osimertinib affordable and available without financial toxicity.

References

1. Vishwanathan K, Dickinson PA, Bui K, Weilert DK, So K, Thomas K, et al. Abstract B153: Effect of food and gastric pH modifiers on the pharmacokinetics of AZD9291. Molecular Cancer Therapeutics. 2015;14(12 Supplement 2):B153.

2. US Food and Drug Administration (FDA) https://www.fda.gov/ (Accessed 12 Nov 2022).

3. European Medicines Agency. https://www.ema.europa.eu/ (Accessed 12 Nov 2022). [Available from: https://www.ema.europa.eu/

4. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(2):113-25.

5. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. New England Journal of Medicine. 2019;382(1):41-50.

6. Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol. 2017;28(10):2340-66.

7. Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saijo N, et al. Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. New England Journal of Medicine. 2009;361(10):947-57.

8. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer. 2020.

9. D. Planchard SP, K. Kerr, S. Novello, E. F. Smit, C. Faivre-Finn, and cols. ESMO Clinical Practice Living Guidelines – Metastatic Non-Small-Cell Lung Cancer. Ann Oncol 2018;29:iv192–iv237.

10. Mateo J, Chakravarty D, Dienstmann R, Jezdic S, Gonzalez-Perez A, Lopez-Bigas N, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol. 2018;29(9):1895-902.

11. Kerr KM, Bubendorf L, Edelman MJ, Marchetti A, Mok T, Novello S, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. Annals of Oncology. 2014;25(9):1681-90.

12. Oxnard GR, Arcila ME, Chmielecki J, Ladanyi M, Miller VA, Pao W. New Strategies in Overcoming Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Lung Cancer. Clinical Cancer Research. 2011;17(17):5530-7.

13. US Food and Drug Administration (FDA). List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). 2020.

14. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, The International Association for the Study of Lung Cancer, and The Association for Molecular Pathology. Journal of Thoracic Oncology. 2018;13(3):323-58.

15. Australian Government Department of Health. Pharmaceutical Benefit Scheme (PBS). https://www.pbs.gov.au/info/about-the-pbs (accessed 10 December 2022).

16. National Institute for Health and Care Excelence (NICE) https://www.nice.org.uk (accessed 12 Nov 2022).

17. International Agency fir Research on Cancer (IARC). Global Cancer Observatory. 2020. https://gco.iarc.fr/ (accessed 10 December 2022)

18. Pearce A, Sharp L, Hanly P, Barchuk A, Bray F, de Camargo Cancela M, et al. Productivity losses due to premature mortality from cancer in Brazil, Russia, India, China, and South Africa (BRICS): A population-based comparison. Cancer Epidemiol. 2018;53:27-34.

19. Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax. 2013;68(6):551-64.

20. Gaafar R. SC17.05 Lung Cancer in Africa: Challenges and Perspectives. Journal of Thoracic Oncology. 2017;12(1):S115-S6.

21. Werutsky G, Debiasi M, Sampaio FH, Nunes Filho PR, Mathias C, Zukin M, et al. P1.08: Updated Analysis of Global Epidemiology of EGFR Mutation in Advanced Non-Small Cell Lung Cancer: Track: Prevention, Early Detection, Epidemiology and Tobacco Control. Journal of Thoracic Oncology. 2016;11(10):S184-S5.

22. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016;7(48):78985-93.

23. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res. 2015;5(9):2892-911.

24. Yang Z, Hackshaw A, Feng Q, Fu X, Zhang Y, Mao C, Tang J. Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: A meta-analysis. Int J Cancer. 2017 Jun 15;140(12):2805-2819. doi: 10.1002/ijc.30691. Epub 2017 Mar 27. PMID: 28295308.

25. Leighl NB, Karaseva N, Nakagawa K, Cho B-C, Gray JE, Hovey T, et al. Patient-reported outcomes from FLAURA: Osimertinib versus erlotinib or gefitinib in patients with EGFR-mutated advanced non-small-cell lung cancer. European Journal of Cancer. 2020;125:49-57.

26. National Institute of Cancer. Common Terminology Criteria for adverse events (CTCAE). NIH Publ 0– 71.

27. Maemondo M, Fukuhara T, Saito H, Furuya N, Watanabe K, Sugawara S, et al. NEJ026: Final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harboring activating EGFR-mutations. Journal of Clinical Oncology. 2020;38(15_suppl):9506.

28. Li L, Huang Q, Sun J, et al. Efficacy and safety of osimertinib for patients with EGFR-mutated NSCLC: a systematic review and meta-analysis of randomized controlled studies [published online ahead of print, 2022 Oct 14]. Acta Oncol. 2022;1-7. doi:10.1080/0284186X.2022.2132116

29. Xu Z, Liu C, Zhu Y, et al. Efficacy of first-line treatments in the elderly and non-elderly patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: a network meta-analysis. BMC Cancer. 2022;22(1):514. Published 2022 May 7. doi:10.1186/s12885-022-09592-3

30. Reungwetwattana T, Nakagawa K, Cho BCet al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018 Aug 28:JCO2018783118. doi: 10.1200/JCO.2018.78.3118. Epub ahead of print. PMID: 30153097. https://ascopubs.org/doi/full/10.1200/JCO.2018.78.3118

31. Aguiar PN, Jr., Haaland B, Park W, San Tan P, Del Giglio A, de Lima Lopes G, Jr. Cost-effectiveness of Osimertinib in the First-Line Treatment of Patients With EGFR-Mutated Advanced Non-Small Cell Lung Cancer. JAMA Oncol. 2018;4(8):1080-4.

32. National Institute For Health And Care Excellence (NICE). Appraisal consultation document. Osimertinib for untreated EGFR mutation- positive non-small-cell lung cancer. 2019.