Osimertinib (Tagrisso®) with pemetrexed and platinum-based chemotherapy for the first-line treatment of advanced non-small cell lung cancer (NSCLC)

General information

Drug description [1]

Osimertinib (Tagrisso®) is a third-generation epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor (TKI) that is selective for EGFR-TKI–sensitising and EGFR T790M resistance mutations.

Indication [2]

Osimertinib (Tagrisso®) is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Incidence [3]

In Austria, in 2022, 5,203 persons were newly diagnosed with cancer of the lung, bronchia and trachea. The age-standardised incidence rate was 68.0/100,000 in men and 45.8/100,000 in women.

Current treatment [4]

The Onkopedia treatment recommendation for the treatment of patients with stage IV NSCLC with Exon 19 deletion or L858R mutation is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [2]	FDA [5]
Approval status for this indication: On 30 May 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Tagrisso®. The CHMP adopted a new indication as follows: ❖ Tagrisso® is indicated in combination with **pemetrexed and platinum-based chemotherapy** for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. **Other indications**: Tagrisso® as monotherapy is indicated for: ❖ the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. ❖ the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. ❖ the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. ✓ **Accelerated assessment**[1]	**Approval status for this indication**: Tagrisso® is indicated in combination with pemetrexed and platinum-based chemotherapy, the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. **Other indications**: Tagrisso® is indicated for: ❖ adjuvant therapy after tumour resection in adult patients with NSCLC whose tumours have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. ❖ the first-line treatment of adult patients with metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. ❖ the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

Manufacturer

Tagrisso® is manufactured by AstraZeneca.

Costs [6]

[1] This medicine had an accelerated assessment, meaning that it is a medicine of major interest for public health, so its timeframe for review was 150 evaluation days rather than 210.

30 Tagrisso® film tablets 40 mg = € 5,083.50 (ex-factory price)

Warnings and precautions [7]

- **Assessment of EGFR mutation status**
  - When considering the use of Tagrisso® as adjuvant treatment after complete tumour resection in patients with NSCLC, it is important that the EGFR mutation positive status (exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations (L858R)) indicates treatment eligibility. A validated test should be performed in a clinical laboratory using tumour tissue DNA from biopsy or surgical specimen.
  - When considering the use of Tagrisso® as a treatment for locally advanced or metastatic NSCLC, it is important that the EGFR mutation positive status is determined. A validated test should be performed using either tumour DNA derived from a tissue sample or circulating tumour DNA obtained from a plasma sample.
  - Positive determination of EGFR mutation status (activating EGFR mutations for first-line treatment or T790M mutations following progression on or after EGFR TKI therapy) using either a tissue-based or plasma-based test indicates eligibility for treatment with Tagrisso®. However, if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test. Only robust, reliable and sensitive tests with demonstrated utility for the determination of EGFR mutation status should be used.
- **Interstitial lung disease (ILD)**
  - Severe, life-threatening or fatal ILD or ILD-like adverse reactions (e.g. pneumonitis) have been observed in patients treated with Tagrisso® in clinical studies. Most cases improved or resolved with interruption of treatment. Patients with a past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from clinical studies.
  - ILD or ILD-like adverse reactions were reported in 3.8% of the 1479 patients who received Tagrisso® in the ADAURA, FLAURA and AURA studies. Five fatal cases were reported in the locally advanced or metastatic setting. No fatal cases were reported in the adjuvant setting. The incidence of ILD was 11.3% in patients of Japanese ethnicity, 1.6% in patients of Asian ethnicity and 2.5% in non-Asian patients.
  - Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD is diagnosed, Tagrisso® should be discontinued and appropriate treatment initiated as necessary. Reintroduction of Tagrisso® should be considered only after careful consideration of the individual patient's benefits and risk.
- **Severe cutaneous adverse reactions**
  - Case reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with frequency categories of rare and not known, respectively, in association with Tagrisso® treatment. Before initiating treatment, patients should be advised of signs and symptoms of SJS and TEN. If signs and symptoms suggestive of SJS or TEN appear, Tagrisso® should be interrupted. Tagrisso® should be discontinued immediately if SJS or TEN are diagnosed.
- **QTc interval prolongation**
  - QTc interval prolongation occurs in patients treated with Tagrisso®. QTc interval prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. No arrhythmic events were reported in ADAURA, FLAURA or AURA studies. Patients with clinically important abnormalities in rhythm and conduction as measured by resting ECG (e.g. QTc interval greater than 470 msec) were excluded from these studies.
  - When possible, the use of osimertinib in patients with congenital long QT syndrome should be avoided. Periodic monitoring with ECGs and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Treatment should be withheld in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume Tagrisso® at a reduced dose as described in Table 1. Osimertinib should be permanently discontinued in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.
- **Changes in cardiac contractility**
  - Across clinical studies, left ventricular ejection fraction (LVEF) decreases greater than or equal to 10 percentage points and a drop to less than 50% occurred in 3.2% (40/1233) of patients treated with Tagrisso® who had baseline and at least one follow-up LVEF assessment. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered. In an adjuvant placebo-controlled study (ADAURA), 1.6% (5/312) of patients treated with TAGRISSO and 1.5% (5/331) of patients treated with placebo experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

- **Keratitis**
  - Keratitis was reported in 0.7% (n=10) of the 1479 patients treated with Tagrisso® in the ADAURA, FLAURA and AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.
- **Aplastic anaemia**
  - Rare cases of aplastic anaemia, including fatal events, have been reported in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, pallor, infection and fatigue. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anaemia.
- **Age and body weight**
  - Elderly patients (>65 years) or patients with low body weight (<50 kg) may be at increased risk of developing adverse events of Grade 3 or higher. Close monitoring is recommended in these patients.
- **Sodium**
  - This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

Study characteristics [1, 8-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
FLAURA-2 NCT04035486	557 (1:1)	**osimertinib** (80 mg once daily) with chemotherapy (**pemetrexed** 500 mg/m2 of BSA) + either **cisplatin** (75 mg/m2) **or carboplatin** (pharmacologically guided dose)	**osimertinib monotherapy** (80 mg once daily)	PFS investigator-assessed	19.5 months vs. 16.5 months	**ongoing**[2], international, open-label, phase 3 trial	EGFR	AstraZeneca	FLAURA-2 [1]

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline (n=279 vs. n=278)
❖ Male or female, ≥18 years; patients from Japan ≥20 years. ❖ Pathologically confirmed nonsquamous NSCLC. ❖ Newly diagnosed locally advanced (clinical stage IIIB, IIIC) or metastatic NSCLC (clinical stage IVA or IVB) or recurrent NSCLC (per Version 8 of the IASLC Staging Manual in Thoracic Oncology), not amenable to curative surgery or radiotherapy. ❖ The tumour harbours 1 of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, which may include T790M. ❖ Mandatory provision of a baseline plasma sample and an unstained, archival tumour tissue sample in a quantity	❖ Spinal cord compression; symptomatic and unstable brain metastases, except for those patients who have completed definitive therapy, are not on steroids, and have a stable neurological status for at least 2 weeks after completion of the definitive therapy and steroids. ❖ Past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD. ❖ Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection, including hepatitis B, hepatitis C and HIV. ❖ Any of the following cardiac criteria:	❖ Median age (range): 61 (26–83) vs. 62 (30–85) years ❖ Female sex: 62% vs. 61% ❖ Race or ethnic group: • Asian: 64% vs. 63% • White: 27% vs. 30% • American Indian or Alaska Native: 4% vs. 2% • Black: 1% vs. 1% • Other: 5% vs. 4% ❖ WHO performance-status score: • 0: 37% vs. 37% • 1: 62% vs. 63%

[2] The FLAURA-2 trial is currently ongoing; the estimated study completion date is 06/2026.
[3] For detailed in- and exclusion criteria, please see trial protocol.

sufficient to allow for central confirmation of the EGFR mutation status. ❖ Patients must have untreated advanced NSCLC not amenable to curative surgery or radiotherapy. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapy, investigational agents, are permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease. ❖ WHO PS of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks. ❖ Life expectancy >12 weeks at Day 1. ❖ At least 1 lesion, not previously irradiated that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis of ≥15 mm) with CT or MRI, and that is suitable for accurate repeated measurements. If only 1 measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and as long as it has not been biopsied within 14 days of the baseline tumour assessment scans. ❖ Female patients who are not abstinent and intend to be sexually active with a male partner must be using highly effective contraceptive measures, must not be breast feeding, and must have a negative pregnancy test prior to first dose of IP or must have evidence of non-child-bearing potential by fulfilling 1 of the following criteria at screening: • Post-menopausal, defined as more than 50 years of age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments. • Women under 50 years old would be considered as postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and have LH and FSH levels in the post-menopausal range for the institution	❖ Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value; ❖ Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG; ❖ Any factors that increase the risk of QTc prolongation or risk of arrhythmic events. ❖ Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: • Absolute neutrophil count below the LLN • Platelet count below the LLN • Haemoglobin <90 g/L • ALT >2.5 x the ULN if no demonstrable liver metastases or>5 x ULN in the presence of liver metastases • AST >2.5 x ULN if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases • Total bilirubin >1.5 x ULN if no liver metastases or >3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases • Creatinine clearance <60 mL/min calculated by Cockcroft and Gault equation. ❖ Any concurrent and/or other active malignancy that has required treatment within 2 years of first dose of IP. ❖ Any unresolved toxicities from prior systemic therapy greater than CTCAE Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2 prior platinum-therapy related neuropathy. ❖ Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib. ❖ Prior treatment with any systemic anti-cancer therapy for advanced NSCLC not amenable to curative surgery or radiation including chemotherapy, biologic therapy, immunotherapy, or any investigational drug. ❖ Prior treatment with an EGFR-TKI. ❖ Major surgery within 4 weeks of the first dose of IP. ❖ Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of IP. ❖ Current use of medications or herbal supplements known to be strong inducers of cytochrome P450 (CYP) 3A4 (at least 3 weeks prior). ❖ Participation in another clinical study with an investigational product during the 4 weeks prior to Day 1.	• 2: <1% vs. 0 ❖ Histologic characteristics: • Adenocarcinoma: 99% vs. 99% • Adenosquamous carcinoma: 1% vs. 0 • Other: 1% vs. 1% ❖ EGFR mutation at randomisation: • Exon 19 deletion: 61% vs. 60% • L858R mutation: 38% vs. 38% • Both exon 19 deletion and L858R mutation 3: 1% vs. <1% • Unknown: <1% vs. 1% ❖ Disease extent at trial entry: • Locally advanced: 5% vs. 3% • Metastatic: 95% vs. 97% ❖ CNS metastases • Yes: 42% vs. 40% • No: 58% vs. 60% ❖ Extrathoracic metastases: • Yes: 53% vs. 54% • No: 47% vs. 46% ❖ Liver metastases • Yes: 15% vs. 24% • No: 85% vs. 76% ❖ Bone and locomotor-system metastases • Yes: 47% vs. 51% • No: 53% vs. 49% ❖ Median baseline tumour size (range): 57 (10–284) vs. 57 (11–221) mm

• Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation. ❖ Male patients must be willing to use barrier contraception.	❖ Currently pregnant (confirmed with positive pregnancy test) or breast-feeding. ❖ History of hypersensitivity to active or inactive excipients of IP or drugs with a similar chemical structure or class to IP. ❖ Contraindication for pemetrexed and cisplatin/carboplatin according to local approved label. ❖ Prior allogeneic bone marrow transplant. ❖ Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.	

Efficacy (I vs. C)	**Safety** (I vs. C, n=276 vs. n=275)
<u>Analysis According to the Investigator</u> **Median PFS**: 25.5 months (95% CI, 24.7-NC) vs. 16.7 (95% CI, 14.1–21.3); HR for disease progression or death 0.62 (95%CI, 0.49–0.79) **PFS at 12 months**: 80% (95% CI, 74–84) vs. 66% (60–71) **PFS at 18 months:** 71% (95% CI, 65–76) vs. 49% (95%CI, 42–54) **PFS at 24 months**: 57% (95% CI, 50–63) vs. 41% (95%CI, 35–47) **Objective response:** 83% (95% CI, 78–87) vs. 76% (95%, 70–80) **Best objective response**: - CR: <1% vs. 1% - PR: 83% vs. 75% - Stable disease for ≥35 days: 12% vs. 18% - Disease progression: <1% vs. 3% - Death: 2% vs. 1% - Could not be evaluated: 2% vs. 2% **Disease control:** 95% (95% CI, 92–98) vs. 94% (95%CI, 90–96) **Median duration of response**: 24.0 months vs. 15.3 months **Continued response at 12 months**: 80% vs. 64% **Continued response at 18 months**: 69% vs. 44% **Continued response at 24 months**: 49% vs. 35% **<u>Analysis According to Central Review:</u>** **Median PFS**: 29.4 (95% CI, 25.1–NC) vs. 19.9 (95% CI, 16.6–25.3); HR for progression or death 0.62 (95% CI, 0.48–0.80) **PFS at 12 months**: 80% (95% CI, 75–84) vs. 67% (95% CI, 61–73) **PFS at 18 months:** 71% (95% CI, 65–76) vs. 54% (95% CI, 48–60) **PFS at 24 months**: 62% (95% CI, 55–68) vs. 47% (95% CI, 40–53) **Objective response:** 92% (95% CI, 88–95) vs. 83% (95% CI, 78–87) **Best objective response**: - CR: 1% vs. <1% - PR: 91% vs. 82% - Stable disease for ≥35 days: 4% vs. 10%	**AEs:** 100% vs. 97% **AEs of grade ≥3:** 64% vs. 27% **Hematologic toxic effects:** 71% vs. 24% **ILD or pneumonitis:** 3% vs. 4% **Cardiac effects:** 9% vs. 4% **Serious AEs:** 38% vs. 19% **AEs with an outcome of death that were considered by the investigator to be possibly causally related to trial treatment:** n=5 vs. n=1 **AEs leading to the discontinuation of osimertinib:** 11% vs. 6%

- Disease progression: 1% vs. 4%
- Death: 2% vs. 1%
- Could not be evaluated: 1% vs. 1%

Disease control: 95 (95% CI, 92–98) vs. 93 (95% CI, 90–96)
Median duration of response: 28.3 (95% CI, 23.7–NC) vs. 21.0 (95% CI, 17.8–NC)
Continued response at 12 months: 81% vs. 73%
Continued response at 18 months: 70% vs. 56%
Continued response at 24 months: 56% vs. 45%

OS: immature (data maturity, 27%)

Patient-reported outcomes

According to the trial protocol, the assessment of disease-related symptoms and health-related QoL is planned; to date, there are no results available.

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	>6 months	PFS: +8.8 months	0.62 (0.49–0.79)	HR≤0.65 AND gain ≥3 months	3	-	NA	-	3
Adapted	NC	2B	>6 months	PFS: +8.8 months	0.62 (0.49–0.79)	HR≤0.65 AND gain ≥3 months	3	+37% AEs of grade ≥3 +19% serious AEs +47% haematologic toxic effects	NA	-1	2

Risk of bias (RCT) [12]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no[4] high risk	unclear[5] unclear risk	yes[6] high risk	unclear

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
NCT04035486 / FLAURA-2	Please see above.	06/2026
NCT04181060	Randomised phase III study of combination osimertinib and bevacizumab vs. osimertinib alone as first-line treatment for patients with metastatic EGFR-mutant NSCLC.	12/2026
NCT04487080 / MARIPOSA	A phase 3, randomised study of amivantamab and lazertinib combination therapy vs. osimertinib vs. lazertinib as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC.	06/2027
NCT06350097/ TROPION-Lung14	A phase III, open-label, randomised study of osimertinib with or without datopotamab deruxtecan, as first-line treatment in participants with EGFR mutation-positive, locally advanced or metastatic NSCLC.	05/ 2032

[4] Open-label trial design.
[5] The FLAURA-2 trial is currently ongoing.
[6] The trial was designed by the sponsor in consultation with the investigators. The sponsor was responsible for data collection and analysis and had a role in the interpretation of the data. Medical writing assistance was funded by the sponsor in accordance with Good Publication Practice guidelines.

Available assessments

- NICE published a Technology appraisal guidance, "Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer" in October 2020 [14].
- No assessments were identified via ICER, CDA-AMC and G-BA.

Other aspects and conclusions

- In May 2024, the **CHMP adopted a new indication** for Tagrisso®, indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The FDA has also approved this indication.
- **FLAURA-2** (NCT04035486) is an **ongoing**, randomised, open-label phase 3 trial evaluating the efficacy and safety data for first-line osimertinib plus platinum–pemetrexed as compared with osimertinib monotherapy in patients with EGFR-mutated advanced NSCLC. Eligible patients were ≥18 years (or ≥20 years in Japan), had locally advanced or metastatic NSCLC, and had not previously received systemic
  treatment for advanced disease. Nonsquamous NSCLC had to be pathologically confirmed, with local or central confirmation of the EGFR exon 19 deletion or L858R mutation, either alone or in combination with other EGFR mutations.
- **Investigator-assessed PFS** was the primary endpoint of FLAURA-2; **median PFS** was 25.5 months (95% CI, 24.7-NC) vs. 16.7 (95% CI, 14.1–21.3); **HR for disease progression or death was 0.62** (95%CI, 0.49–0.79).
- According to the trial protocol, the assessment of disease-related symptoms and health-related QoL is planned; currently, **results are not available**.
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of **3 and 2**, respectively.
- Due to the **ongoing status** of the trial, the **risk of bias** was considered **unclear**. However, the risk is **increased** by the open-label trial design and the involvement of the sponsor throughout trial design, data collection and analysis.
- Besides FLAURA-2, three further trials assessing the efficacy and safety of osimertinib with either bevacizumab, lazertinib or datopotamab for the first-line treatment in participants with EGFR mutation-positive, locally advanced or metastatic NSCLC, were identified.
- The final analysis data and patient-reported outcomes of the FLAURA-2 trial are required to determine the future role of osimertinib combined with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

First published: 06/2024

Abbreviations: AE=adverse event, AJ=adjustment, BSA=body surface area, C=comparator, CDA-AMC=Canada's Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, ECG=electrocardiogram, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FSH=follicle-stimulating hormone, G-BA=Gemeinsamer Bundesausschuss, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, IASCL=International Association for the Study of Lung Cancer, ICER=Institute for Clinical and Economic Review, IDL=interstitial lung disease, Int.=intention, LH=luteinizing hormone, LLN=lower limit of normal, LVEF=left ventricular ejection fraction, MG=median gain, n=number of patients, NC=not calculable, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, SJS=Stevens-Johnson syndrome, ST=standard treatment, TEN=toxic epidermal necrolysis, TKI=tyrosine kinase inhibitor, ULN=upper limit of normal, WHO=World Health Organization

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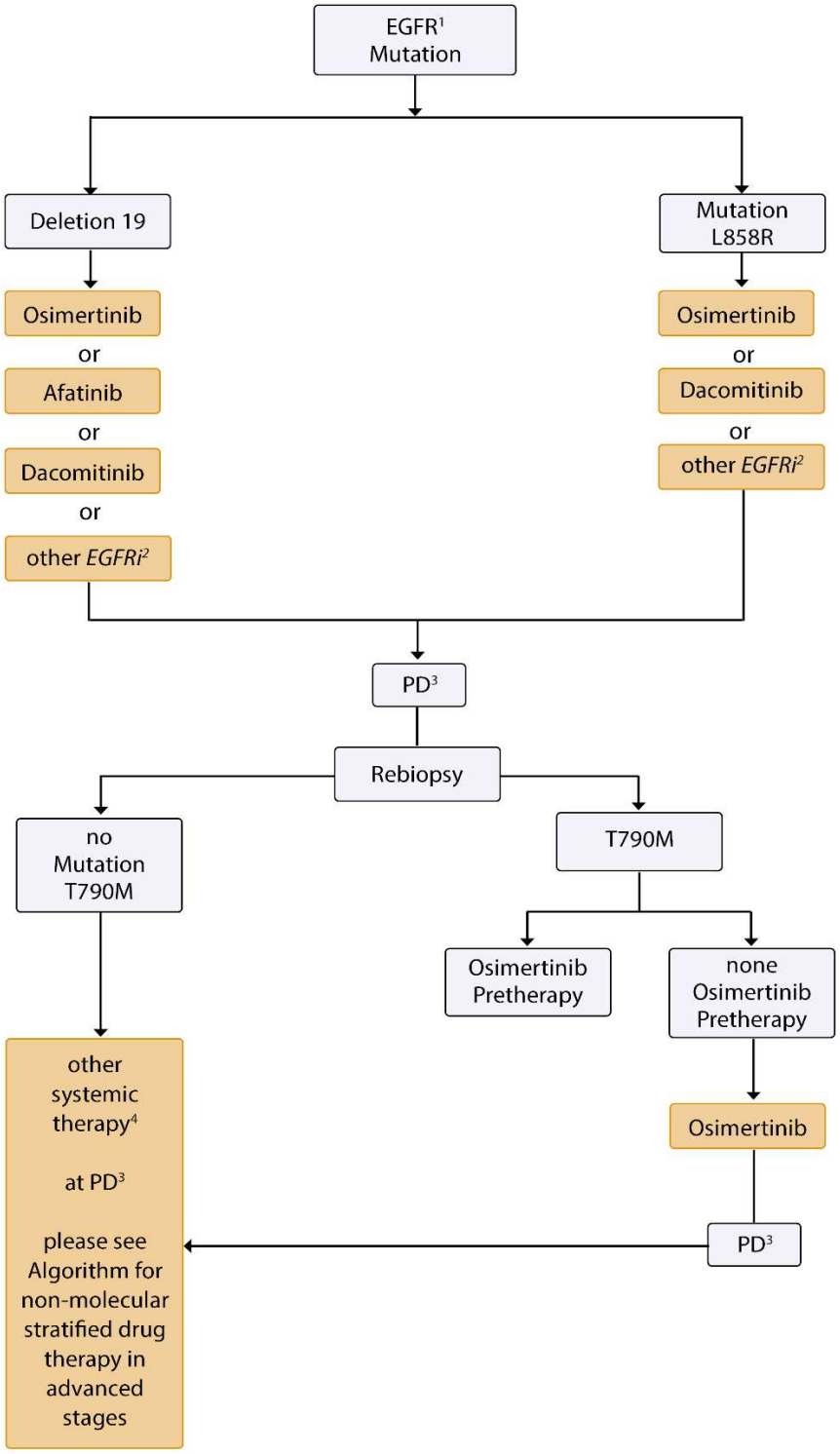
Appendix – Figure 1:



Legend:

[1]*EGFR - epidermal growth factor receptor gene;*
[2]*EGFR-TKI - afatinib, dacomitinib, erlotinib in combination with bevacizumab resp. ramucirumab, osimertinib;*
[3]*PD - progressive disease;*
[4]*In the pivotal IMpower 150 trial of carboplatin/paclitaxel/bevacizumab/atezolizumab, patients with ALK and EGFR mutations included.*