Osimertinib (Tagrisso®) as monotherapy for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC)

General information

Drug description [1]	Indication [2]
Osimertinib is a third-generation oral EGFR tyrosine kinase inhibitor (EGFR-TKI).	Osimertinib as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

Current treatment [3]

- Patients with NSCLC are offered the following chemotherapy drugs, in combination with cisplatin or carboplatin:
  - Vinorelbine
  - Gemcitabine
  - Paclitaxel
  - Docetaxel
  - Etoposide
- Pemetrexed

Regulatory status

EMA [2]

Approval status for this indication: On 22 April 2021, 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® 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.

Other indications: Tagrisso® as monotherapy is indicated for:

- 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.

✓ **Medicine under additional monitoring**
✓ **Accelerated assessment**[1]

FDA [4]

Approval status for this indication: On 18 December 2020, the FDA approved osimertinib (Tagrisso®) for adjuvant therapy after tumour resection in patients with 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:

- 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.

Costs

30 Tagrisso® tablets 80 mg = € 6,000.00 [5]
ADAURA trial patients (osimertinib group) received oral osimertinib at a dose of 80 mg once daily; the median duration of total treatment exposure was 22.5 months in the osimertinib group [1].

Assessment of EGFR mutation status [6]

- 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 a biopsy or surgical specimen.
- When considering the use of Tagrisso® as a treatment for locally advanced or metastatic NSCLC, the EGFR mutation positive status must be determined. A validated test should be performed using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.

[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.

- ❖ 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.

Warnings and precautions [4]

- ❖ **Interstitial lung disease (ILD)/pneumonitis:**
  - Occurred in 3.7% of patients.
  - Permanently discontinue Tagrisso® in patients diagnosed with ILD/Pneumonitis.
- ❖ **QTc interval prolongation:**
  - Monitor electrocardiograms and electrolytes in patients who have a history or predisposition for QTc prolongation, or those who are taking medications that are known to prolong the QTc interval.
  - Withhold then restart at a reduced dose or permanently discontinue Tagrisso®.
- ❖ **Cardiomyopathy:**
  - Occurred in 3% of patients.
  - Conduct cardiac monitoring, including left ventricular ejection fraction assessment in patients with cardiac risk factors.
- ❖ **Keratitis:**
  - Promptly refer patients with signs and symptoms of keratitis to an ophthalmologist for evaluation.
- ❖ **Erythema Multiforme and Stevens-Johnson Syndrome:**
  - Withhold Tagrisso® if erythema multiforme major or Stevens-Johnson syndrome is suspected and permanently discontinue if confirmed.
- ❖ **Cutaneous vasculitis:**
  - Withhold Tagrisso® if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation.
  - If no other aetiology can be identified, consider permanent discontinuation based on severity.
- ❖ **Embryo-foetal toxicity**:
  - Tagrisso® can cause foetal harm.
  - Advise females of the potential risk to the foetus and to use effective contraception during treatment with Tagrisso® and for 6 weeks after final dose.
  - Advise males to use effective contraception for 4 months, after the last dose of Tagrisso®.

Study characteristics [1, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ADAURA NCT02511106	682	oral osimertinib (at a dose of 80 mg once daily)	placebo	DFS among patients with stage II to IIIA disease[2]	International, randomized, double-blind, placebo-controlled phase 3 trial	EGFR	AstraZeneca	[1]

Efficacy (I vs. C)[3]

OS data: immature

Disease-free survival:

Patients with **stage II to IIIA disease** who were alive and disease-free at 24 months: 90% (95% CI, 84-93) vs. 44% (95% CI, 37-51) (overall HR for disease recurrence or death, 0.17; 99.06% CI, 0.11-0.26; p<0.001).

Safety (I vs. C)

Grade ≥3 AEs: n=68/337 (20%) vs. n=46/343 (13%)

SAEs: n=54/337 (16%) vs. n=42/343 (12%)

[2] according to investigator assessment
[3] Interim analysis data

Patients (**overall population**) who were alive and disease-free at 24 months: 89% (95% CI, 85-92) vs. 52% (95% CI, 46-58) (overall HR, 0.20; 99.12% CI, 0.14-0.30; p<0.001).
Median disease-free survival: not reached (95% CI, could not be calculated) vs. 27.5 months (95% CI, 22.0-35.0)
Patients with **stage IB disease** who were alive and disease-free at 24 months: 88% vs. 71% (overall, 0.39; 95% CI, 0.18-0.76)
Patients with **stage II disease** who were alive and disease-free at 24 months: 91% vs. 56% (overall HR, 0.17; 95% CI, 0.08-0.31)
Patients with **stage IIIA disease** who were alive and disease-free at 24 months: 88% vs. 32% (overall HR, 0.12; 95% CI, 0.07 to 0.20).
Patients who received **adjuvant chemotherapy** and were alive and disease-free at 24 months: 89% vs. 49% (overall HR, 0.16; 95% CI, 0.10-0.26)
Patients who did **not receive adjuvant chemotherapy** and were alive and disease-free at 24 months: 89% vs. 58% (overall HR, 0.23; 95% CI, 0.13-0.40)
Distant recurrence (either distant only or with locoregional recurrence): 4% vs. 28%
Recurrence of CNS-related disease or death: 2% vs. 11%
Recurrence in the CNS: 1% vs. 10%
Patients who were alive **without CNS-related disease** at 24 months: 98% vs. 85% (overall HR for CNS disease recurrence or death 0.18; 95% CI, 0.10-0.33).
Median CNS disease-free survival: not reached vs. 48.2 months

Patient-Reported Outcomes [6]:

- HRQL in ADAURA was assessed using the Short Form (36) Health Survey version 2 (SF-36v2) questionnaire.
- SF-36v2 was administered at 12 weeks, 24 weeks and then every 24 weeks relative to randomisation until treatment completion or discontinuation.
- Overall, HRQL was maintained in both arms up to 30 months, with at least 70% of patients in the stage II-IIIA population not experiencing a clinically meaningful deterioration in the physical component of the SF-36 or death (70% vs 76% for Tagrisso® vs. placebo), or in the mental component of the SF-36 or death (70% vs 71% for Tagrisso® vs. placebo).

Fatal AEs: n=0/337 (0%) vs. n=1/343 (0.3%)

Discontinuation[4]: n=37/337 (11%) vs. n=10/343 (3%)

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	Curative	1	-	DFS: +37%	0.20 (0.14-0.30)	Improvements in DFS alone (PE) (HR<0.65) in studies without mature survival data	A	-	-	-	A
Adapted	Curative	1	-	DFS: +37%	0.20 (0.14-0.30)	Improvements in DFS alone (PE) (HR<0.65) in studies without mature survival data	A	-	-	-	A

Risk of bias (study level) [11]

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	yes	yes	unclear[5]	yes[6]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, ctDNA=circulating tumour DNA, DFS=disease-free survival, DNA=deoxyribonucleic acid, 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, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ILD=interstitial lung disease, Int.=intention, n=number, MG=median gain, n=number of patients, NSCLC=non-small cell lung cancer, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TKI=tyrosine kinase inhibitor

[4] Discontinuation due to AE(s)
[5] Interim analysis data reported; ADAURA trial is ongoing until 01/2023.
[6] The trial was funded by the sponsor and was designed by the investigators and the sponsor. The sponsor was responsible for collection and analysis of the data and had a role in data interpretation. The first draft of the manuscript was written by the first, second, and last authors, with medical-writing support funded by the sponsor and conducted in accordance with Good Publication Practice guidelines.

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