Proposed packaging material		
Code	Tagrisso 40 mg & 80 mg – PIL-01.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: MU-133412-161664	
Code of previous version	N/A	
Changes	Aplastic Anaemia and ODIN Change	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: EU SmPC 1. ODIN Change (Doc ID-004809669 v40) 2. Aplastic Anaemia (Doc ID-004788452 v7.0) ☒GRL approval: N/A
Name & Date	DK (9 December 2022)	

Leaflet Informasi Pasien
TAGRISSO 40 mg tablet salut selaput
TAGRISSO 80 mg tablet salut selaput
Osimertinib

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi hal-hal penting untuk Anda.

- Simpanlah leaflet ini. Anda mungkin perlu membacanya di kemudian hari
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakanlah dokter, apoteker, atau perawat Anda
- Obat ini diresepkan khusus hanya untuk Anda. Jangan berikan pada orang lain. Obat ini dapat membahayakan mereka walaupun tanda-tanda penyakit yang mereka miliki sama dengan anda.
- Jika Anda mengalami efek samping, beritahu dokter, apoteker, ataupun perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi terdapat pada leaflet ini. Lihat bagian 4.

Leaflet ini berisi informasi mengenai:

1. TAGRISSO dan kegunaannya

TAGRISSO mengandung zat aktif osimertinib yang merupakan obat antikanker golongan penghambat protein kinase. TAGRISSO digunakan untuk pengobatan pada orang dewasa yang menderita kanker paru yang disebut 'non-small cell lung cancer.' Ketika tumor telah terjadi mutasi didalam gen yang disebut EGFR (epidermal growth factor receptor). TAGRISSO digunakan saat kanker semakin memburuk. TAGRISSO digunakan jika :

- Telah melakukan pengangkatan total kanker, sebagai pengobatan pasca operasi (adjuvan) anda
- Anda telah melakukan uji positif untuk 'penghapusan ekson 19' dan atau 'substitusi mutasi ekson

21 (L858R)' sebagai perawatan awal pada kanker anda,
- Kanker anda sudah stadium lanjut dan memburuk setelah menerima obat EGFR Tyrosine Kinase Inhibitor (TKI) dan Anda memiliki hasil tes positif terhadap 'mutasi T790M' – Baca"Cara kerja TAGRISSO"

Cara kerja TAGRISSO
- Suatu tes telah menunjukkan bahwa kanker anda terkait pada suatu perubahan tertentu pada gen EGFR yang disebut 'T790M.' yang dikenal sebagai mutasi T790M.
- Karena mutasi T790M ini, obat yang bekerja dengan menghambat EGFR tidak lagi memberikan hasil.
- TAGRISSO berefek pada T790M dan dapat membantu memperlambat atau menghentikan pertumbuhan kanker paru Anda. TAGRISSO juga membantu mengecilkan tumor, dan mencegah tumor datang kembali setelah pengangkatan dengan operasi.
- Jika Anda menerima TAGRISSO setelah pengangkatan total kanker Anda itu berarti kanker Anda mengandung kelainan pada gen EGFR, 'penghapusan ekson 19' atau 'mutasi substitusi ekson 21'.

Jika Anda mempunyai pertanyaan mengenai bagaimana obat ini bekerja dan mengapa obat ini diresepkan untuk anda, tanyalah dokter anda.

2. Hal yang perlu diketahui sebelum menggunakan TAGRISSO.

Jangan gunakan TAGRISSO, jika:
- Anda alergi (hipersensitif) terhadap osimertinib atau bahan lain yang terkandung dalam obat ini (baca bagian 6).
- Anda menggunakan St. John's wort (*Hypericum perforatum*).

Jika Anda tidak yakin, beritahu dokter, apoteker ataupun perawat Anda sebelum menggunakan TAGRISSO.

Peringatan dan perhatian
Beritahu dokter, apoteker ataupun perawat Anda, Jika:
- Anda mengalami peradangan di paru-paru Anda (suatu penyakit yang disebut Penyakit Paru interstisial).
- Anda memiliki riwayat penyakit jantung – dokter Anda mungkin ingin memantau penggunaan obat dengan seksama.
- Anda mengalami peradangan pada penglihatan Anda dengan tanda-tanda penglihatan kabur, menjadi peka terhadap cahaya, dan mata memerah (lensa kontak bisa menjadi faktor penyebab utama).

Jika Anda mengalami salah satu hal di atas (atau jika Anda tidak yakin), beritau dokter, apoteker, ataupun perawat Anda sebelum menggunakan obat ini.

Segera Beritahu dokter Anda jika:
- Jika secara tiba-tiba Anda mengalami kesulitan bernapas disertai batuk atau demam. Baca "efek samping serius" pada bagian 4 untuk informasi lebih lanjut.
- Anda mengalami pengelupasan kulit yang parah.
- Anda mengalami detak jantung yang cepat atau tidak teratur, pusing, kepala terasa ringan, rasa tidak nyaman di dada, sesak napas, dan pingsan.
- Anda memiliki mata berair, sensitif terhadap cahaya, nyeri pada mata, mata merah atau adanya perubahan pada penglihatan.
  Lihat 'Efek samping yang serius' pada bagian 4 untuk informasi lebih lanjut.
- Anda mengalami demam berkelanjutan, lebam, atau mudah mengalami pendarahan, rasa lelah yang meningkat, kulit pucat dan infeksi. Lihat 'Efek samping yang serius' pada bagian 4 untuk informasi lebih lanjut.

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Anak-anak dan remaja
Belum dilakukan studi TAGRISSO untuk penggunaan pada anak-anak dan remaja. Jangan berikan obat ini pada anak-anak atau remaja di bawah usia 18 tahun.

Obat-obatan lain dan TAGRISSO
Beritau dokter Anda jika Anda sedang menggunakan atau mungkin menggunakan obat-obatan lain termasuk obat herbal, dan obat yang Anda beli tanpa resep dokter. Hal ini karena TAGRISSO dapat mempengaruhi kerja beberapa obat lainnya dan obat lain juga dapat mempengaruhi cara kerja TAGRISSO.

Beritahu dengan dokter Anda sebelum menggunakan TAGRISSO, jika Anda sedang menggunakan obat-obatan berikut:

Obat-obatan berikut yang dapat menurunkan kerja TAGRISSO :
- Fenitoin, Karbamazepin atau fenobarbital—digunakan untuk terapi kejang
- Rifabutin atau rifampisin— digunakan untuk terapi tuberkulosis
- St. John's wort (*Hypericum perforatum*) – obat herbal untuk depresi

TAGRISSO dapat mempengaruhi kerja dan/atau meningkatkan efek samping dari obat-obatan berikut :
- Warfarin – digunakan untuk pembekuan darah
- Fenitoin and S-mefenitoin – digunakan untuk pengobatan kejang
- Alfentanil, fentanil dan antinyeri lainnya yang digunakan untuk operasi
- Rosuvastatin – digunakan untuk menurunkan kolesterol
- Pil hormon kontrasepsi – digunakan untuk mencegah kehamilan
- Bosentan – digunakan untuk tekanan darah tinggi pada paru-paru
- Efaviren dan etravirine – digunakan untuk mengobati infeksi HIV/AIDS.
- Modafinil – digunakan untuk mengobati kelainan tidur
- Aliskiren – digunakan untuk mengobati tekanan darah tinggi
- Digoksin – digunakan untuk mengobati detak jantung yang tidak teratur atau masalah jantung lainnya.
- Dabigatran – digunakan untuk mencegah pembekuan darah

Jika Anda menggunakan salah satu obat di atas, beritau dokter anda sebelum menggunakan TAGRISSO.
Dokter Anda akan mendiskusikan pengobatan yang sesuai untuk Anda.

Kehamilan—Informasi untuk pasien wanita
- Jika Anda hamil, atau Anda merasa Anda hamil, atau berencana untuk hamil, mintalah saran dari dokter Anda sebelum menggunakan obat ini. Jika Anda hamil selama pengobatan, segera beritau dengan dokter Anda. Dokter Anda akan memutuskan apakah pengobatan yang Anda lakukan dengan TAGRISSO akan dilanjutkan atau tidak.
- Anda sebaiknya tidak hamil selama menggunakan obat ini. jika Anda hamil, Anda harus menggunakan kontrasepsi yang efektif. Baca pada bagian 'Kontrasepsi' di bawah.
- Jika Anda berencana hamil setelah menggunakan dosis terakhir obat ini, mintalah saran pada dokter Anda, karena sedikit obat masih dapat tertinggal didalam tubuh Anda. (baca saran pada bagian kontrasepsi di bawah).

Kehamilan—Informasi untuk pasien pria
Jika pasangan Anda hamil ketika selama menggunakan obat ini, segera beritahu dokter Anda.

Kontrasepsi—Informasi untuk pasien wanita dan pria

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Anda harus menggunakan kontrasepsi yang efektif selama pengobatan dengan obat ini.
- TAGRISSO dapat mempengaruhi kerja kontrasepsi hormon oral. Diskusikan dengan dokter Anda untuk metode kontrasepsi yang paling sesuai.
- TAGRISSO dapat melewati air mani sehingga penting bagi pasien pria untuk menggunakan kontrasepsi juga.

Anda juga harus melakukan hal berikut setelah menyelesaikan terapi dengan TAGRISSO:
- **Wanita** – tetap menggunakan kontrasepsi hingga 6 bulan setelahnya.
- **Pria** – tetap menggunakan kontrasepsi hingga 4 bulan setelahnya.

Menyusui
Jangan menyusui selama menggunakan obat ini karena belum diketahui apakah obat ini berisiko terhadap bayi Anda.

Mengemudi dan menjalankan mesin
Tidak ada studi tentang efek pada kemampuan untuk mengemudi ataupun menjalankan mesin yang telah dilakukan. Jika pasien mengalami gejala yang mempengaruhi kemampuan Anda untuk berkonsentrasi dan bereaksi, disarankan Anda untuk tidak mengemudi atau menjalankan mesin sampai efek mereda.

3. Cara penggunaan TAGRISSO

Selalu gunakan obat ini sesuai dengan petunjuk dari dokter Anda. Periksa kembali dengan dokter atau apoteker Anda jika Anda tidak yakin.

Berapa banyak yang digunakan
- Dosis yang direkomendasikan adalah satu tablet 80 mg per hari.
- Jika diperlukan, dokter Anda dapat menurunkan dosis Anda hingga satu tablet 40 mg per hari.

Bagaimana cara menggunakannya
- Masukkan TAGRISSO ke mulut Anda, telan tablet secara utuh dengan air. Jangan dihancurkan, dibagi, ataupun dikunyah.
- Minumlah TAGRISSO setiap hari pada waktu yang sama.
- Anda dapat meminum obat ini dengan atau tanpa makanan.

Jika Anda memiliki masalah dalam menelan tablet, Anda dapat mencampurnya dalam air:
- Masukkan tablet ke dalam gelas.
- Tambahkan 50 mL (sekitar dua pertiga dari gelas penuh) air (non-soda) – jangan gunakan cairan lainnya.
- Aduk air tersebut hingga tablet hancur menjadi pecahan kecil - tablet tidak akan larut secara merata.
- Langsung minum seluruh air dalam gelas.
- Untuk memastikan Anda meminum semua obat dalam larutan di gelas, bilas gelas hingga bersih dengan 50 mL air, lalu minum.

Jika Anda menggunakan TAGRISSO lebih dari yang seharusnya
Jika Anda menggunakan lebih dari dosis normal, segera hubungi dokter Anda atau pergilah ke rumah sakit terdekat.

Jika Anda lupa menggunakan TAGRISSO
Jika Anda lupa menggunakan dosis, segera minum dosis yang terlupa saat Anda ingat. Namun, jika jadwal dosis berikutnya tidak sampai 12 jam, abaikan dosis yang terlupa tersebut. Minumlah dosis selanjutnya sesuai dengan yang telah dijadwalkan.

Jika Anda berhenti menggunakan TAGRISSO
Jangan langsung berhenti menggunakan obat ini, bicarakan dulu dengan dokter Anda sebelum memutuskan berhenti menggunakannya. Penting untuk menggunakan obat ini setiap hari selama yang diresepkan oleh dokter Anda untuk Anda.

Jika Anda memiliki pertanyaan lebih lanjut mengenai pemakaian obat ini, tanyakanlah pada dokter, apoteker, ataupun perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti obat lainnya, Obat ini dapat menimbulkan efek samping, walaupun tidak setiap orang dapat mengalaminya.

Efek samping serius
Segera hubungi dokter Anda jika Anda menyadari terjadi efek samping serius sebagai berikut:
- Kesulitan bernapas secara tiba-tiba disertai batuk atau demam—ini dapat menjadi tanda peradangan pada paru-paru (suatu kondisi yang disebut 'Penyakit paru intertisial') dan pada beberapa kasus dapat menjadi fatal. Dokter Anda dapat menghentikan konsumsi TAGRISSO jika Anda mengalami efek samping ini. Efek samping ini umum terjadi: dapat terjadi pada 1 dari 10 pasien.
- *Steven-Johnson syndrome* yang dapat muncul sebagai makula kemerahan seperti target atau bercak melingkar, sering disertai dengan lepuh pada tubuh, kulit mengelupas, luka pada mulut, tenggorokan, hidung, alat kelamin dan mata, diawali dengan demam dan gejala mirip flu. Efek samping ini jarang terjadi: dapat mempengaruhi hingga 1 dari 1000 orang.
- Perubahan aktivitas elektris di jantung (perpanjangan QTc) seperti detak jantung cepat atau tidak teratur, pusing, kepala terasa ringan, rasa tidak nyaman di dada, sesak napas, dan pingsan. Efek samping ini jarang terjadi: dapat mempengaruhi hingga 1 dari 100 orang.
- Lesi target, yaitu reaksi kulit yang terlihat seperti cincin (sugestif dari Erythema multiforme). Efek samping ini jarang terjadi: dapat mempengaruhi hingga 1 dari 100 orang
- Kelainan darah yang disebut anemia aplastik yaitu saat sumsum tulang belakang berhenti memproduksi sel darah baru. Hal ini dapat ditandai dengan demam berkelanjutan, lebam atau lebih mudah mengalami pendarahan, dan rasa lelah yang meningkat, serta menurunnya kemampuan untuk melawan infeksi. Efek samping ini sangat jarang: dapat terjadi pada 1 dari 1000 orang
- Kondisi dimana jantung tidak mampu memompa darah yang cukup dalam satu detak sebagaimana mestinya sehingga menyebabkan kesulitan bernapas, kelelahan dan pembengkakan pergelangan kaki (sebagai tanda dari gagal jantung atau menurunnya fraksi ejeksi ventrikel kiri)

Segera beritahu dokter Anda jika Anda menyadari efek samping serius di atas.

Efek samping lain
Efek samping yang sangat umum terjadi (dapat terjadi pada lebih dari 1, dari 10 pasien)
- Diare – dapat terjadi lalu berhenti selama pengobatan. Hubungi dokter Anda jika diare tidak berhenti atau menjadi lebih parah.
- Masalah pada kulit dan kuku, dapat berupa gatal, kulit kering, ruam, kemerahan di sekitar kuku jari. Ini lebih banyak terjadi pada kulit yang terpapar sinar matahari. Menggunakan pelembab secara rutin pada kulit dan kuku dapat membantu mengurangi efek ini. Beritahu dokter Anda jika masalah pada kulit dan kuku Anda memburuk.
- Stomatitis – peradangan pada lapisan dalam mulut.
- Penurunan yang tidak normal pada jumlah sel darah putih (leukosit, limfosit, dan neutrofil).
- Penurunan jumlah platelet dalam darah.

Efek samping yang umum terjadi (dapat terjadi pada 1 dari 10 pasien)
- Mimisan – (epistaxis)
- Penipisan rambut – biasanya terjadi dengan ringan

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- Hives (urtikaria) - gatal, bercak menonjol di mana saja pada kulit, yang mungkin berwarna merah muda atau merah dan berbentuk bulat. Beritahu dokter Anda jika Anda melihat efek samping ini.
- Sindrom tangan-kaki – dapat termasuk kemerahan, bengkak, kesemutan atau sensasi terbakar dengan retakan pada kulit di telapak tangan dan / atau telapak kaki. Jenis efek ini biasanya dapat diobati dengan krim dan losion.
- Peningkatan senyawa di dalam darah yang disebut dengan keratinin (dihasilkan oleh tubuh anda dan dikeluarkan melalui ginjal).

Efek samping yang jarang terjadi (dapat terjadi pada 1 dari 100 pasien)
- Lesi bertarget, yaitu reaksi kulit yang tampak seperti cincin (menunjukkan Eritema multiforme).
- Peradangan pada pembuluh darah di kulit. Hal ini dapat berupa memar atau kemerahan pada kulit yang tidak memudar warnanya ketika ditekan (*non-blanching*)

Pelaporan efek samping

Jika Anda mengalami efek samping, hubungi dokter, apoteker, atau perawat Anda, termasuk efek samping yang tidak tertera pada leaflet ini.
Anda juga dapat melaporkan efek samping secara langsung dengan menghubungi PT. AstraZeneca Indonesia melalui nomor telepon +62 21 2997 9000.
Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi mengenai keamanan obat ini.

5. Cara Penyimpanan TAGRISSO

- Jauhkan obat ini dari jangkauan anak-anak
- Jangan menggunakan obat ini setelah tanggal kadaluarsa yang tercantum pada blister dan karton.
- Tanggal kadaluarsa mengacu pada hari terakhir dari bulan itu.
- Obat ini tidak memerlukan kondisi penyimpanan khusus, simpanlah pada suhu dibawah 30^{o}C
- Jangan menggunakan obat jika kemasan rusak atau penyok.

Jangan buang obat yang tersisa melalui pembuangan rumah tangga. Hubungi apoteker Anda bagaimana cara membuang obat yang sudah tidak dikonsumsi lagi. Ini akan membantu menjaga lingkungan.

6. Isi kemasan dan informasi lainnya

TAGRISSO mengandung:
- Zat aktif osimertinib (dalam bentuk mesilat). Setiap tablet salut selaput 40 mg mengandung 40 mg osimertinib. Setiap tablet salut selaput 80 mg mengandung 80 mg osimertinib.
- Bahan lainnya adalah mannitol, mikrokristalin selulosa, hidroksipropil selulosa, natrium stearil fumarat, polivinil alcohol, titanium dioxide, makrogol 3350, talk, *yellow iron oxide, red iron oxide, black iron oxide.*

Isi kemasan

TAGRISSO 40 mg: berwarna krem, salut selaput, bundar, cembung ganda, ditandai dengan “AZ” dan “40” pada satu sisi dan polos pada sisi lainnya.

TAGRISSO 80 mg : berwarna krem, salut selaput, oval, cembung ganda, ditandai dengan “AZ” dan “80” pada satu sisi, dan polos pada sisi lainnya.

TAGRISSO dikemas dalam karton berisi 1 blister, masing-masing 10 tablet salut selaput dan 3 blister,

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masing-masing 10 tablet salut selaput.

HARUS DENGAN RESEP DOKTER

Diproduksi dan rilis oleh:
AstraZeneca AB Gärtunavägen
SE-151 85 Södertälje
Swedia

Diimpor oleh:
PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

Informasi lebih lanjut dapat menghubungi:
PT AstraZeneca Indonesia
Perkantoran Hijau Arkadia Tower F, 3rd floor
Jl. T.B. Simatupang Kav. 88, Jakarta – 12520
Tel: +62 21 299 79 000

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TAGRISSO

Osimertinib

Film-coated Tablet

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 80 mg film-coated tablets
TAGRISSO 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 80 mg tablet contains a dose of 80 mg osimertinib (as mesylate).
Each 40 mg tablet contains a dose of 40 mg osimertinib (as mesylate).

Excipient with known effect
Each 80 mg tablet contains 0.6 mg sodium
Each 40 mg tablet contains 0.3 mg sodium

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The TAGRISSO 80 mg tablet is a beige, 7.25 x 14.5 mm, oval, biconvex tablet, debossed with “AZ” and “80” on one side and plain on the reverse.

The TAGRISSO 40 mg tablet is a beige, 9 mm, round, biconvex tablet, debossed with “AZ” and “40” on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAGRISSO (osimertinib) is indicated for:

- the adjuvant treatment after complete tumour resection (stage IB, II, or resectable IIIA) in adult patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
- the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
- the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

4.2 Posology and method of administration

Treatment with TAGRISSO should be initiated by a physician experienced in the use of anticancer therapies.

When considering the use of TAGRISSO, EGFR mutation status (in tumour specimens for adjuvant treatment and tumour or plasma specimens for locally advanced or metastatic setting) should be determined using a validated test method (see section 4.4) for:

- exon 19 deletions or exon 21 (L858R) substitution mutations (for adjuvant therapy and first-line treatment)
- T790M mutations (following progression on or after EGFR TKI therapy).

Posology

The recommended dose of TAGRISSO is 80 mg osimertinib once a day.

Patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied.

Patients with locally advanced or metastatic lung cancer should receive treatment until disease progression or unacceptable toxicity.

Missed dose

If a dose of TAGRISSO is missed, make up the dose unless the next dose is due within 12 hours.

TAGRISSO can be taken with or without food at the same time each day.

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of TAGRISSO should be reduced to 40 mg taken once daily.

Dose reduction guidelines for adverse reactions toxicities are provided in Table 1.

Table 1. Recommended dose modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary[b]	ILD/Pneumonitis	Permanently discontinue TAGRISSO (see section 4.4)
Cardiac[b]	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue TAGRISSO
Cutaneous[b]	Stevens-Johnson Syndrome	Permanently discontinue TAGRISSO
Blood and lymphatic system[b]	Aplastic anaemia	Permanently discontinue TAGRISSO
Other	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of TAGRISSO for up to 3 weeks	TAGRISSO may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue TAGRISSO

[a] Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
[b] Refer to Section 4.4 Special warnings and special precautions for use for further details.

ECGs : Electrocardiograms; QTc : QT interval corrected for heart rate

Special patient populations

No dose adjustment is required due to patient age, body weight, gender, ethnicity and smoking status (see section 5.2).

Hepatic impairment

Based on clinical studies, no dose adjustment are necessary in patients with mild hepatic impairment (Child Pugh A) or moderate hepatic impairment (Child Pugh B). Similarly, based on population pharmacokinetic (PK) analysis, no dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1.0 to 1.5x ULN and any AST) or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST).[i] The appropriate dose of TAGRISSO has not been established in patients with severe hepatic impairment. The using in patients with moderate or severe hepatic impairment is not recommended (see section 5.2).

Renal impairment

Based on clinical studies and population pharmacokinetic analysis, no dose adjustment are necessary in patients with mild, moderate, or severe renal impairment. The safety and efficacy of this medicinal product has not been established in patients with end-stage renal disease [creatinine clearance (CLcr) less than 15 mL/min, calculated by the Cockcroft and Gault equation], or on dialysis. Caution should be exercised when treating patients with severe and end-stage renal impairment (see section 5.2).

Paediatric population

The safety and efficacy of TAGRISSO in children or adolescents aged less than 18 years have not been established. No data are available.

Elderly (>65 years)

Population PK analysis indicated that age did not have an impact on the exposure of osimertinib and hence, osimertinib can be used in adults without regard to age.

Method of administration

This medicinal product is for oral use. The tablet should be swallowed whole with water. The tablet should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, it may first be dispersed in 50 mL of non-carbonated water. The tablet should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added.

If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15 mL for the initial dispersion and 15 mL for the residue rinses. The resulting 30 mL of liquid should be administered as per the nasogastric tube manufacturer's instructions with appropriate water flushes. The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
St. John's wort should not be used together with TAGRISSO (see section 4.5).

4.4 Special warnings and special precautions for use

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 in a clinical laboratory using either tumour tissue DNA or circulating tumour DNA (ctDNA) obtained from a plasma sample.

Only robust, reliable and sensitive test(s) with demonstrated utility for the determination of EGFR mutation status should be used.

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.

Interstitial lung disease (ILD)

ILD or ILD-like adverse reactions (e.g. pneumonitis) were reported in 3.9% and were fatal in 0.4% (n=5) of the 1142 patients who received TAGRISSO in FLAURA and AURA studies.

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 3.7% of the 1479 patients who received TAGRISSO in 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 10.9% in patients of Japanese ethnicity, 1.6% in patients of Asian ethnicity and 2.5% in non-Asian patients (see section 4.8).

Withhold TAGRISSO and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g. dyspnoea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed.

Severe, life-threatening or fatal Interstitial Lung Disease (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.

Stevens-Johnson syndrome (SJS)

Case reports of SJS have been reported rarely in association with TAGRISSO treatment. Before initiating treatment, patients should be advised of signs and symptoms of SJS. If signs and symptoms suggestive of SJS appear, TAGRISSO should be interrupted or discontinued immediately.

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 (see section 4.8). Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 msec) were excluded from these studies (see section 4.8).

When possible, avoid use of TAGRISSO in patients with congenital long QT syndrome (see section 4.8). Consider periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold TAGRISSO 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. Permanently discontinue TAGRISSO 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 (see section 4.2, Dose and method of administration).Contact lens use may also be a risk factor for keratitis and ulceration.

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 (see section 4.2).

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 (see section 4.8).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Strong CYP3A4 inducers can decrease the exposure of osimertinib. Osimertinib may increase the exposure of breast cancer resistant protein (BCRP) and P-glycoprotein (P-gp) substrates.

Active substances that may increase osimertinib plasma concentrations

In vitro studies have demonstrated that the Phase I metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. In a clinical pharmacokinetic study in patients, TAGRISSO co-administered with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure of osimertinib (area under the curve (AUC) increased by 24% (90% CI 15, 35) and C_{max} decreased -20% (90% CI -27, -13). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib.

Active substances that may decrease osimertinib plasma concentrations

In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced by 78% when co-administered with rifampicin (600 mg daily for 21 days). Similarly, the exposure to metabolite AZ5104 decreased by 82% for the AUC and 78% for Cmax. It is recommended that

concomitant use of strong CYP3A inducers (e.g. Phenytoin, rifampicin and carbamazepine) with TAGRISSO should be avoided. Moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil) may also decrease osimertinib exposure and should be used with caution, or avoided when possible. There are no clinical data available to recommend a dose adjustment of TAGRISSO. Concomitant use of St. John's Wort is contraindicated (see section 4.3).

Effect of gastric acid reducing active substances on osimertinib

In a clinical pharmacokinetic study, co-administration of omeprazole did not result in clinically relevant changes in osimertinib exposures. Gastric pH modifying agents can be concomitantly used with TAGRISSO without any restrictions.

Active substances whose plasma concentrations may be altered by TAGRISSO

Based on *in vitro* studies, osimertinib is a competitive inhibitor of BCRP transporter.

In a clinical PK study, co-administration of TAGRISSO with rosuvastatin (sensitive BCRP substrate) increased the AUC and C_{max} of rosuvastatin by 35% (90% CI 15, 57) and 72% (90% CI 46, 103), respectively. Patients taking concomitant medicinal products with disposition dependent upon BCRP and with narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO (see section 5.2).

In a clinical PK study, co-administration of TAGRISSO with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and C_{max} of simvastatin, -9% (90% CI -23, 8) and -23% (90% CI -37, -6) respectively. These changes are small and not likely to be of clinical significance. Clinical PK interactions with CYP3A4 substrates are unlikely.

In clinical PK study, co-administration of TAGRISSO with fexofenadine (PXR/P-gp substrate) increased the AUC and Cmax of fexofenadine by 56% (90% CI 35, 79) and 76% (90% CI 49, 108) after a single dose and 27% (90% CI 11, 46) and 25% (90% CI 6, 48) at steady state, respectively. Patients taking concomitant medications with disposition dependent upon P-gp and with narrow therapeutic index (e.g. digoxin, dabigatran, aliskiren) should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO (see section 5.2).

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving TAGRISSO. Patients should be advised to use effective contraception for the following periods after completion of treatment with TAGRISSO: at least 6 weeks for females and 4 months for males. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

Pregnancy

There are no or limited amount of data from the use of TAGRISSO in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on its mechanism of action and preclinical data, TAGRISSO may cause foetal harm when administered to a pregnant woman. Administration of osimertinib to pregnant rats was associated with embryolethality, reduced foetal growth and neonatal death at exposures similar to what is expected in humans (see section 5.3). TAGRISSO is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether osimertinib/metabolites are excreted in human milk. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death. There is insufficient information on the excretion of osimertinib/metabolites in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with TAGRISSO.

Fertility

There are no data on the effect of TAGRISSO on human fertility. Results from animal studies have shown that TAGRISSO has effects on male and female reproductive organs and could impair fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. If patients experience symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

Overall summary of the safety profile

Studies in EGFR mutation positive NSCLC patients

The data described below reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive non-small cell lung cancer. These patients received TAGRISSO at a dose of 80 mg daily in three randomised Phase 3 studies (ADAURA, adjuvant; FLAURA, first line and AURA3, second line only), two single-arm studies (AURAex and AURA2, second line or later) and one Phase 1 study (AURA1, first-line or greater) (see section 5.1).

Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (47%), rash (45%), paronychia (33%), dry skin (32%), and stomatitis (24%). Grade 3 and Grade 4 adverse reactions across both studies were 10% and 0.1%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in 3.4% of the patients. Discontinuation due to adverse reactions was 4.8%.

Patients with a 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. 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. Patients were evaluated for LVEF at screening and every 12 weeks thereafter.

Tabulated list of adverse reactions

Adverse reactions have been assigned to the frequency categories in Table 2 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the 1479 EGFR mutation positive patients who received TAGRISSO at a dose of 80 mg daily in the ADAURA, FLAURA, AURA3, AURAex, AURA2 and AURA1 studies.

Adverse reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the CIOMS III convention and is defined as: very common (≥1/10); common (>1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 2. Adverse reactions reported in ADAURA, FLAURA and AURA studies[a]

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (all CTCAE grades)[b]	Frequency of CTCAE grade 3 or higher [b]
Blood and lymphatic system disorders	Aplastic anaemia	Rare (0.07%)	0.07%
Metabolism and nutrition disorders	Decreased appetite	Very common (19%)	1.1%
Eye disorders	Keratitis[c]	Uncommon (0.7%)	0.1%
Cardiac disorders	Cardiac failure	Uncommon (0.3%)	0.1%
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common (5%)	0
	Interstitial lung disease[d]	Common (3.7%)[e]	1.1%
Gastrointestinal disorders	Diarrhoea	Very common (47%)	1.4%
	Stomatitis[f]	Very common (24%)	0.5%
Skin and subcutaneous tissue disorders	Rash[g]	Very common (45%)	0.7%
	Paronychia[h]	Very common (33%)	0.4%
	Dry skin[i]	Very common (32%)	0.1%
	Pruritus[j]	Very common (17%)	0.1%
	Alopecia	Common (4.6%)	0
	Urticaria	Common (1.9%)	0.1%
	Palmar-plantar erythrodysaesthesia syndrome	Common (1.7%)	0
	Erythema multiforme[k]	Uncommon (0.3%)	0
	Cutaneous vasculitis[l]	Uncommon (0.3%)	0
	Stevens-Johnson syndrome[m]	Rare (0.02%)	
Investigations	QTc interval prolongation[n]	Uncommon (0.8%)	
	Blood creatine phosphokinase increased	Common (1.6%)	0.3%

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (all CTCAE grades)[b]	Frequency of CTCAE grade 3 or higher [b]
	Left ventricular ejection fraction decreased[o,p]	Common (3.2%)	
(Findings based on test results presented as CTCAE grade shifts)	Leucocytes decreased[o]	Very common (65%)	1.2%
	Lympocytes decreased[o]	Very common (62%)	6%
	Platelet count decreased[o]	Very common (53%)	1.2%
	Neutrophils decreased[o]	Very common (33%)	3.2%
	Blood creatinine increased[o]	Common (9%)	0
Musculoskeletal and connective tissue disorders	Myositis	Rare (0.07%)	

[a] Data is pooled from ADAURA, FLAURA and AURA (AURA3, AURAex, AURA 2 and AURA1) studies; only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarised.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[c] Includes: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect
[d] Includes Interstitial lung disease, pneumonitis.
[e] 5 CTCAE grade 5 events (fatal) were reported.
[f] Includes: Stomatitis, mouth ulceration
[g] Includes: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion, pustule.
[h] Includes: Nail bed disorder, nail bed inflammation, nail bed infection, nail discolouration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[i] Includes: Dry skin, skin fissures, xerosis, eczema, xeroderma.
[j] Includes: pruritus, pruritus generalised, eyelid pruritus.
[k] Five of the 1479 patients in the ADAURA, AURA and FLAURA studies reported erythema multiforme. Post-marketing reports of erythema multiforme have also been received, including 7 reports from a post-marketing surveillance study (N=3578).
[l] Estimated frequency. The upper limit of the 95% CI for the point estimate is 3/1142 (0.3%).
[m] One event was reported in a post-marketing study, and the frequency has been derived from the ADAURA, FLAURA and AURA studies and the post-marketing study (N=5057).
[n] Represents the incidence of patients who had a QTcF prolongation >500 msec.
[o] Represents the incidence of laboratory findings, not of reported adverse events.
[p] Represents decreases greater than or equal to 10 percentage points and a drop to less than 50%.

Description of selected adverse reactions

Interstitial lung disease (ILD)
In the ADAURA, FLAURA and AURA studies, the incidence of ILD was 11% in patients of Japanese ethnicity, 1.6% in patients of non-Japanese Asian ethnicity and 2.5% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 84 days (see section 4.4).

QTc interval prolongation
Of the 1479 patients in ADAURA, FLAURA and AURA studies treated with TAGRISSO 80 mg, 0.8% of patients (n=12) were found to have a QTc greater than 500 msec, and 3.1% of patients (n=46) had an increase from baseline QTc greater than 60 msec. A pharmacokinetic/ pharmacodynamic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmias were reported in the ADAURA, FLAURA or AURA studies (see sections 4.4 and 5.1).

Gastrointestinal effects

In the ADAURA, FLAURA and AURA studies, diarrhoea was reported in 47% of patients of which 38% were Grade 1 events, 7.9% Grade 2 and 1.4% were Grade 3; no Grade 4 or 5 events were reported. Dose reduction was required in 0.3% of patients and dose interruption in 2%. Four events (0.3%) led to discontinuation. In ADAURA, FLAURA and AURA3 the median time to onset was 22 days, 19 days and 22 days, respectively, and the median duration of the Grade 2 events was 11 days, 19 days and 6 days, respectively.

Haematological events

Early reductions in the median laboratory counts of leukocytes, lymphocytes, neutrophils and platelets have been observed in patients treated with TAGRISSO, which stabilised over time and then remained above the lower limit of normal. Adverse events of leukopenia, lymphopenia, neutropenia and thrombocytopenia have been reported, most of which were mild or moderate in severity and did not lead to dose interruptions. Rare cases of aplastic anaemia, including fatal events, have been reported in association with osimertinib treatment. Osimertinib should be discontinued in patients with confirmed aplastic anaemia (see section 4.2 and 4.4).

Special populations

Elderly

In ADAURA, FLAURA and AURA3 (N=1479), 43% of patients were 65 years of age and older, and 12% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had reported adverse reactions that led to study dose modifications (interruptions or reductions) (16% versus 9%). The types of adverse events reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (13% versus 8%). No overall differences in efficacy were observed between these subjects and younger subjects. A consistent pattern in safety and efficacy results was observed in the analysis of AURA Phase 2 studies.

Low body weight

Patients receiving TAGRISSO 80 mg with low body weight (<50 kg) reported higher frequencies of Grade ≥3 adverse events (46% versus 31%) and QTc prolongation (12% versus 5%) than patients with higher body weight (≥50 kg).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan (e-meso.pom.go.id)

4.9 Overdose

In TAGRISSO clinical studies a limited number of patients were treated with daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with TAGRISSO daily doses of 160 mg and 240 mg experienced an increase in the frequency and severity of a number of typical EGFR-induced AEs (primarily diarrhoea and skin rash) compared to the 80 mg dose.

All cases were isolated incidents of patients taking an additional daily dose of TAGRISSO in error, without any resulting clinical consequences.

There is no specific treatment in the event of TAGRISSO overdose. Physicians should follow general supportive measures and should treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01EB04.

Mechanism of action

TAGRISSO is a Tyrosine Kinase Inhibitor (TKI). It is an oral potent and selective irreversible inhibitor of EGFRs harboring sensitising mutations (EGFRm) and TKI-resistance mutation T790M.

Pharmacodynamic effects

In vitro studies have demonstrated that TAGRISSO has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising mutant and T790M mutant NSCLC cell lines (apparent IC_{50}s from 6 nM to 54 nM against phospho-EGFR). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines (apparent IC_{50}s 480 nM to 1.9 µM against phospho-EGFR). *In vivo* oral administration of TAGRISSO lead to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

Based on an analysis of dose-exposure response relationships over the dose range of 20 mg (0.25 times the recommended dose) to 240 mg (3 times the recommended dose), no apparent efficacy (Objective Response Rate (ORR), Duration of Response (DoR) and Progression-Free Survival (PFS)) relationship for osimertinib was identified. Over the same dose range, increased exposure led to increased probability of adverse reactions, specifically rash, diarrhoea and ILD.

Cardiac electrophysiology

The QTc interval prolongation potential of TAGRISSO was assessed in 210 patients who received osimertinib 80 mg daily in AURA2. Serial ECGs were collected following a single dose and at steady state to evaluate the effect of TAGRISSO on QTc intervals. A pharmacokinetic/pharmacodynamic analysis with TAGRISSO predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

Clinical efficacy and safety

Adjuvant treatment of EGFR mutation positive NSCLC, with or without prior adjuvant chemotherapy – ADAURA

The efficacy and safety of TAGRISSO for the adjuvant treatment of patients with EGFR mutation-positive (Ex19del or L858R) NSCLC who have had complete tumour resection with or without prior adjuvant chemotherapy was demonstrated in a randomised, double-blind, placebo-controlled study (ADAURA).

Eligible patients with resectable tumors stage IB – IIIA (according to American Joint Commission on Cancer [AJCC] 7th edition) were required to have EGFR mutations (Ex19del or L858R), identified by the cobas EGFR Mutation Test performed prospectively using biopsy or surgical specimen in a central laboratory.

Patients with resectable tumours (except for stage IA), were required to have EGFR mutations (Ex19del or L858R), identified by the cobas EGFR Mutation Test performed prospectively using biopsy or surgical specimen in a central laboratory.

Patients were randomised 1:1 to receive TAGRISSO (n=339, 80 mg orally once daily) or placebo (n=343) following recovery from surgery and standard adjuvant chemotherapy where given. Patients not receiving adjuvant chemotherapy were randomised within 10 weeks and patients receiving adjuvant chemotherapy within 26 weeks following surgery. Randomisation was stratified by EGFR mutation type (Ex19del or L858R), ethnicity (Asian or non-Asian) and staging based on percutaneous transthoracic needle biopsy (pTNM) (IB or II or IIIA) according to AJCC 7th edition. Treatment was given until disease recurrence, unacceptable toxicity, or for 3 years.

The major efficacy outcome measure was disease-free survival (DFS) by investigator assessment. in the stage II-IIIA population. DFS by investigator assessment in the stage IB-IIIA population (overall population) was an additional efficacy outcome measure. Other Additional efficacy outcome measures included DFS rate, overall survival (OS), OS rate, and time to deterioration in health-related quality of life (HRQoL) SF-36.

The baseline demographic and disease characteristics of the overall study population were: median age 63 years (range 30-86 years), ≥75 years old (11%), female (70%), Asian (64%), never smokers (72%), World Health Organization (WHO) performance status of 0 (64%) or 1 (36%), stage IB (31%), stage II (34%), and IIIA (35%). With regards to EGFR mutation status 55% were exon 19 deletions and 45% were exon 21 L858R substitution mutations; 9 patients (1%) also had a concurrent de novo T790M mutation. The majority (60%) of patients received adjuvant chemotherapy prior to randomization (26% IB; 71% IIA; 73% IIB; 80% IIIA).

An analysis of DFS for both the stage II-IIIA population and the overall population (IB-IIIA) was conducted. ADAURA demonstrated a statistically significant and clinically meaningful reduction in the risk of disease recurrence or death for patients treated with TAGRISSO compared to patients treated with placebo. Patients with stage II-IIIA disease treated with TAGRISSO compared to placebo, achieved 83% reduction in the risk of disease recurrence or death (median DFS not calculable (NC) for TAGRISSO and 19.6 months for placebo (HR=0.17, 99.06% CI: 0.11, 0.26; P<0.0001). The overall population (IB-IIIA) treated with TAGRISSO compared to placebo demonstrated 80% reduction in the risk of disease recurrence or death (median NC and 27.5 months, respectively, HR=0.20, 99.12% CI: 0.14, 0.30; P<0.0001).

There were 37 patients who had disease recurrence on TAGRISSO. The most commonly reported sites of recurrence were: lung (19 patients); lymph nodes (10 patients) and central nervous system CNS (5 patients). There were 157 patients who had disease recurrence on placebo. The most commonly reported sites were: lung (61 patients); lymph nodes (48 patients) and CNS (34 patients).

Efficacy results from ADAURA by investigator assessment are summarized in Table 3 and Table 4, and the Kaplan-Meier curve for DFS in stage II-IIIA patients and in the overall population (IB-IIIA) is shown in Figure 1 and Figure 2, respectively. Overall survival (OS) data were not mature at the time

of DFS analysis, however a preliminary numerical trend which did not reach statistical significance in favour of TAGRISSO was observed at this time.

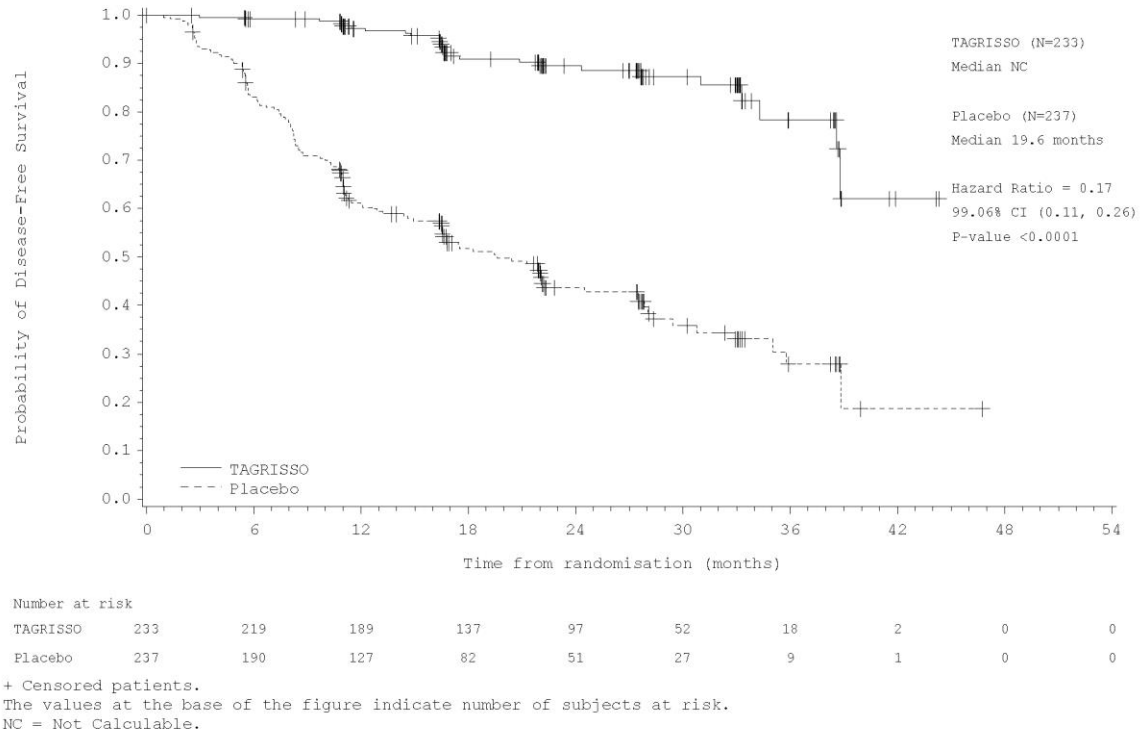
Table 3. Efficacy Results in Stage II-IIIA Patients by Investigator Assessment

Efficacy parameter	**TAGRISSO (N=233)**	**Placebo (N=237)**
Disease-free survival		
Number of events (%)	26 (11.2)	130 (54.9)
Recurrent disease (%)	26 (11.2)	129 (54.4)
Deaths (%)	0	1 (0.4)
Median, months (95% CI)	NC (38.8, NC)	19.6 (16.6, 24.5)
HR (99.06% CI); P-value[a]	0.17 (0.11, 0.26); <0.0001	
DFS rate at 12 months (%) (95% CI)	97.2 (93.9, 98.7)	60.8 (54.1, 66.8)
DFS rate at 24 months (%) (95% CI)	89.5 (84.0, 93.2)	43.6 (36.5, 50.6)
DFS rate at 36 months (%) (95% CI)[b]	78.3 (64.5, 87.3)	27.9 (18.9, 37.6)

HR=Hazard Ratio; CI=Confidence Interval; NC=Not Calculable
DFS results based on RECIST investigator assessment

A HR< 1 favours TAGRISSO
Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO and 14.9 months for patients receiving placebo.
[a] Adjusted for an interim analysis (33% maturity) a p-value < 0.0094 was required to achieve statistical significance.
[b] The number of patients at risk at 36 months was 18patients in the osimertinib arm, and 9 patients in the placebo arm.

Figure 1. Kaplan-Meier curve of disease-free survival (Stage II-IIIA Patients) by Investigator Assessment



+ Censored patients.
The values at the base of the figure indicate number of subjects at risk.
NC = Not Calculable.

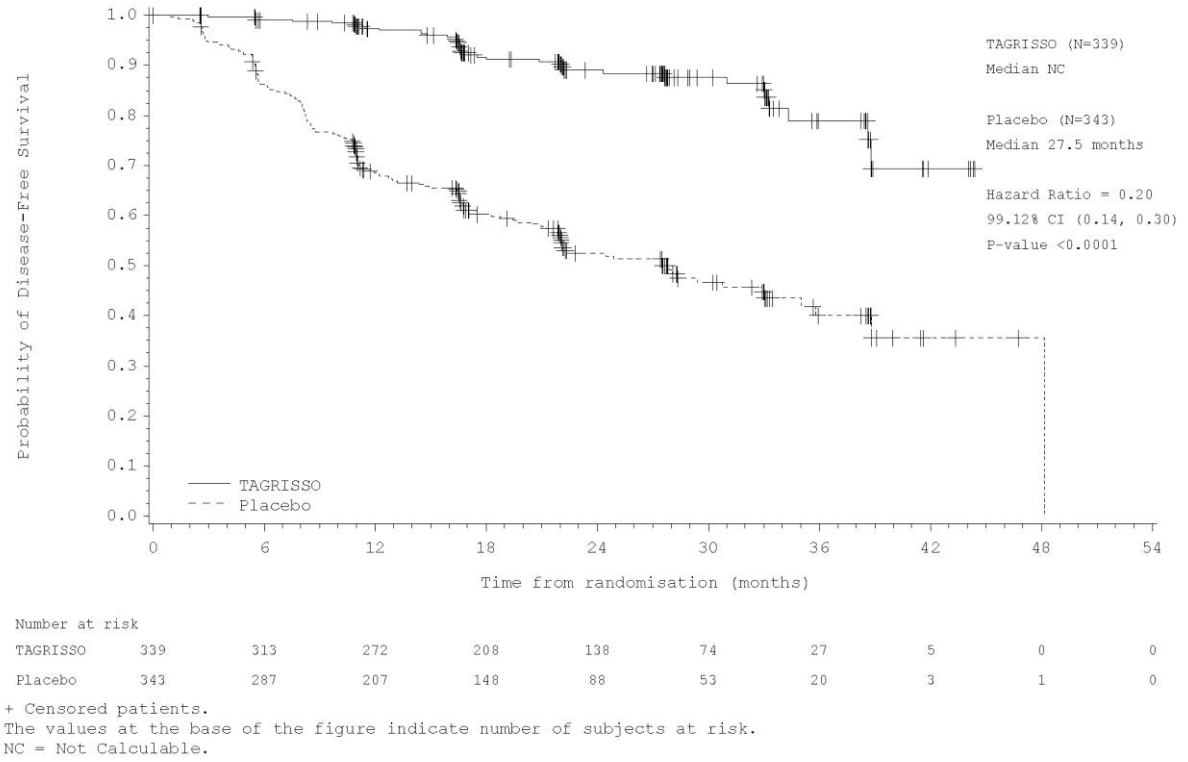
Table 4. Efficacy Results in Overall (IB-IIIA) Patients by Investigator Assessment

Efficacy Parameter	**TAGRISSO (N=339)**	**Placebo (N=343)**
Disease-free survival		
Number of events (%)	37 (10.9)	159 (46.4)
Recurrent disease (%)	37 (10.9)	157 (45.8)
Deaths (%)	0	2 (0.6)
Median, months (95% CI)	NC (NC, NC)	27.5 (22.0, 35.0)

Efficacy Parameter	TAGRISSO (N=339)	Placebo (N=343)
HR (99.12% CI); P-value[a]	0.20 (0.14, 0.30); <0.0001	
DFS rate at 12 months (%) (95% CI)	97.4 (94.9, 98.7)	68.5 (63.2, 73.2)
DFS rate at 24 months (%) (95% CI)	89.1 (84.5, 92.4)	52.4 (46.4, 58.1)
DFS rate at 36 months (%) (95% CI)[b]	78.9 (68.7, 86.1)	40.0 (32.1, 47.8)

HR=Hazard Ratio; CI=Confidence Interval; NC=Not Calculable
DFS results based on RECIST investigator assessment
A HR <1 favours TAGRISSO
Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO and 16.6 months for patients receiving placebo.
[a] Adjusted for an interim analysis (29% maturity) a p-value <0.0088 was required to achieve statistical significance.
[b] The number of patients at risk at 36 months was 27 patients in the osimertinib arm, and 20 patients in the placebo arm.

Figure 2. Kaplan-Meier curve of disease-free survival (overall population) by Investigator Assessment



The DFS benefit of TAGRISSO compared to placebo was consistent across all predefined subgroups analysed, including ethnicity, age, gender, and EGFR mutation type (Ex19Del or L858R).

A clinically meaningful improvement in an exploratory analysis of CNS DFS (time to CNS recurrence or death) for patients on TAGRISSO compared to patients on placebo was observed with a HR of 0.18 (95% CI: 0.10, 0.33; p <0.0001) for the overall population, indicating a 82% reduction in the risk of CNS disease recurrence or death in the TAGRISSO arm compared to placebo.

Patient reported outcomes

Health-related quality of life (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, HRQoL was maintained in both arms, with more than 75% of patients in the stage II-IIIA population not experiencing a clinically meaningful deterioration in the physical component of the SF-36 or death (75.1% vs 83.5% for TAGRISSO vs placebo), or in the mental component of the SF-36 or death (77.7% vs 78.1% for TAGRISSO vs placebo). A trend of shorter time to deterioration (TTD) for the physical component of SF-36 or death was observed in the TAGRISSO arm (HR=1.43, 95% CI: 0.96, 2.13), with a median TTD that was not reached in either arm. There was no difference between the arms in the TTD for the mental component of SF-36 or death (HR=0.90, 95% CI: 0.61, 1.33), with a median TTD of 39.0 months (95% CI: NC, NC) in the TAGRISSO arm and not reached in the placebo arm.

Previously untreated EGFR mutation positive locally advanced or metastatic NSCLC – FLAURA

The efficacy and safety of TAGRISSO for the treatment of patients with EGFR mutation positive locally advanced or metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomised, double-blind, active-controlled study (FLAURA). Patient tumour tissue samples were required to have one of the two common EGFR mutations known to be associated with EGFR TKI sensitivity (Ex19del or L858R), as identified by local or central testing.

Patients were randomised 1:1 to receive either TAGRISSO (n=279, 80 mg orally once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily). Randomisation was stratified by EGFR mutation type (Ex19del or L858R) and ethnicity (Asian or non-Asian). Patients received study therapy until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. For patients receiving EGFR TKI comparator, post-progression crossover to open-label TAGRISSO was permitted provided tumour samples tested positive for the T790M mutation.

The primary efficacy end-point was progression-free survival (PFS) as assessed by investigator. Additional efficacy end-points included overall survival (OS), objective response rate (ORR), duration of response (DoR), second PFS after start of first subsequent therapy (PFS2), time to first subsequent therapy or death (TFST) and time from randomisation to second progression on subsequent treatment or death (TSST) as assessed by investigator. CNS PFS, CNS ORR and CNS DoR as assessed by BICR, and patient reported outcomes (PRO) were also assessed.

The baseline demographic and disease characteristics of the overall study population were: median age 64 years (range 26-93 years), ≥75 years old (14%), female (63%), White (36%), Asian (62%), never smokers (64%). All patients had a World Health Organization (WHO) performance status of 0 or 1. Thirty-six percent (36%) of patients had metastatic bone disease and 35% of patients had extra-thoracic visceral metastases. Twenty one percent (21%) of patients had CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases).

TAGRISSO demonstrated a clinically meaningful and highly statistically significant improvement in PFS compared to EGFR TKI comparator (median 18.9 months and 10.2 months, respectively, HR=0.46, 95% CI: 0.37, 0.57; P<0.0001). Efficacy results from FLAURA by investigator assessment are summarised in Table 5, and the Kaplan-Meier curve for PFS is shown in Figure 1. At the time of

the interim analysis of overall survival (25% maturity), a HR of 0.63 favoured TAGRISSO (95% CI: 0.45, 0.88; P = 0.0068), which did not reach formal statistical significance. A greater proportion of patients treated with TAGRISSO were alive at 12 months and 18 months (89% and 83%, respectively) compared to patients treated with EGFR TKI comparator (83% and 71%, respectively).

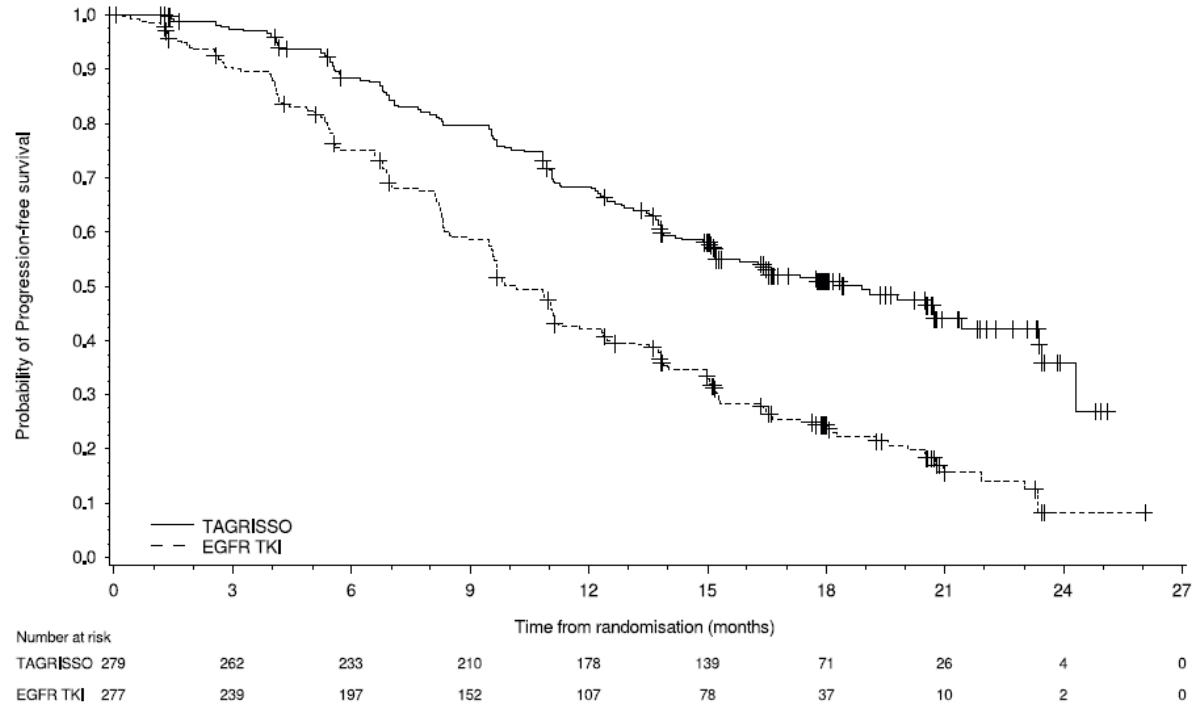
Table 5. Efficacy results from FLAURA by investigator assessment

Efficacy parameter	**TAGRISSO (N=279)**	**EGFR TKI comparator (gefitinib or erlotinib) (N=277)**
Progression-free survival		
Number of events (62% maturity)	136 (49)	206 (74)
Median, months (95% CI)	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)
HR (95% CI); P-value	0.46 (0.37, 0.57); P<0.0001	
Overall survival		
Number of deaths, (56% maturity)	155 (56)	166 (60)
Median OS in months (95% CI)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
HR (95% CI); P-value	0.799 (0.641, 0.997); P=0.0462	
Objective response rate[1]		
Number of responses (n), Response Rate % (95% CI)	223 80 (75, 85)	210 76 (70, 81)
Odds ratio (95% CI); P-value	1.3 (0.9, 1.9); P=0.2421	
Duration of Response (DoR)[1]		

Efficacy parameter	TAGRISSO (N=279)	EGFR TKI comparator (gefitinib or erlotinib) (N=277)
Median, months (95% CI)	17.2 (13.8, 22.0)	8.5 (7.3, 9.8)
Second PFS after start of first subsequent therapy (PFS2)		
Number of patients with second progression (%)	73 (26)	106 (38)
Median PFS2, months (95% CI)	NC (23.7, NC)	20.0 (18.2, NC)
HR (95% CI); P-value	0.58 (0.44, 0.78); P=0.0004	
Time from randomisation to first subsequent treatment or death (TFST)		
Number of patients who had first subsequent treatment or died (%)	115 (41)	175 (63)
Median TFST, months (95% CI)	23.5 (22.0, NC)	13.8 (12.3, 15.7)
HR (95% CI); P-value	0.51 (0.40, 0.64); P<0.0001	
Time from randomisation to second subsequent treatment or death (TSST)		
Number of patients who had second subsequent treatment or died (%)	74 (27)	110 (40)
Median TSST, months (95% CI)	NC (NC, NC)	25.9 (20.0, NC)
HR (95% CI); P-value	0.60 (0.45, 0.80); P=0.0005	

HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable, NS=Not Statistically Significant
All efficacy results based on RECIST investigator assessment
Based on unconfirmed response
Median follow-up time was 15.0 months for patients receiving TAGRISSO and 9.7 months for patients receiving EGFR TKI comparator
A HR< 1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO
† Based on an interim analysis with 25% maturity a P-value < 0.0015 was required to achieve statistical significance
[1] ORR results by Blinded Independent Central Review (BICR) were consistent with those reported via investigator assessment; ORR by BICR assessment was 78% (95% CI:73, 83) on TAGRISSO and 70% (95% CI:65, 76) on EGFR TKI comparator.

Figure 3. Kaplan-Meier curves of progression-free survival as assessed by investigator in FLAURA



+ Censored patients.

The PFS benefit of TAGRISSO compared to EGFR TKI comparator was consistent across all predefined subgroups analysed, including ethnicity, age, gender, smoking history, CNS metastases status at study entry and EGFR mutation type (Exon 19 deletion or L858R).

Patients randomised to TAGRISSO as first-line treatment also had clinically meaningful improvements in PFS2, TFST and TSST compared to patients randomised to EGFR TKI comparator. The analysis of these post-progression end–points demonstrated that PFS benefit was largely preserved through subsequent lines of therapy.

In patients with locally advanced EGFRm NSCLC not amenable to curative surgery or radiotherapy, the objective response rate was 93% (95% CI 66, 100) for patients receiving TAGRISSO (n=14) and 60% (95% CI 32, 84) for patients receiving EGFR TKI comparator (n=15).

CNS metastases efficacy data in FLAURA study

Patients with CNS metastases not requiring steroids and with stable neurologic status for at least two weeks after completion of the definitive therapy and steroids were eligible to be randomised in the FLAURA study. Of 556 patients, 200 patients had available baseline brain scans. A BICR assessment of these scans resulted in a subgroup of 128/556 (23%) patients with CNS metastases and these data are summarised in Table 6. EGFR mutation type (Ex19del or L858R) and ethnicity (Asian or non-Asian) was generally balanced within this analysis between the treatment arms. CNS efficacy by RECIST v1.1 in FLAURA demonstrated a nominal statistically significant improvement in CNS PFS (HR=0.48, 95% CI 0.26, 0.86; P=0.014).

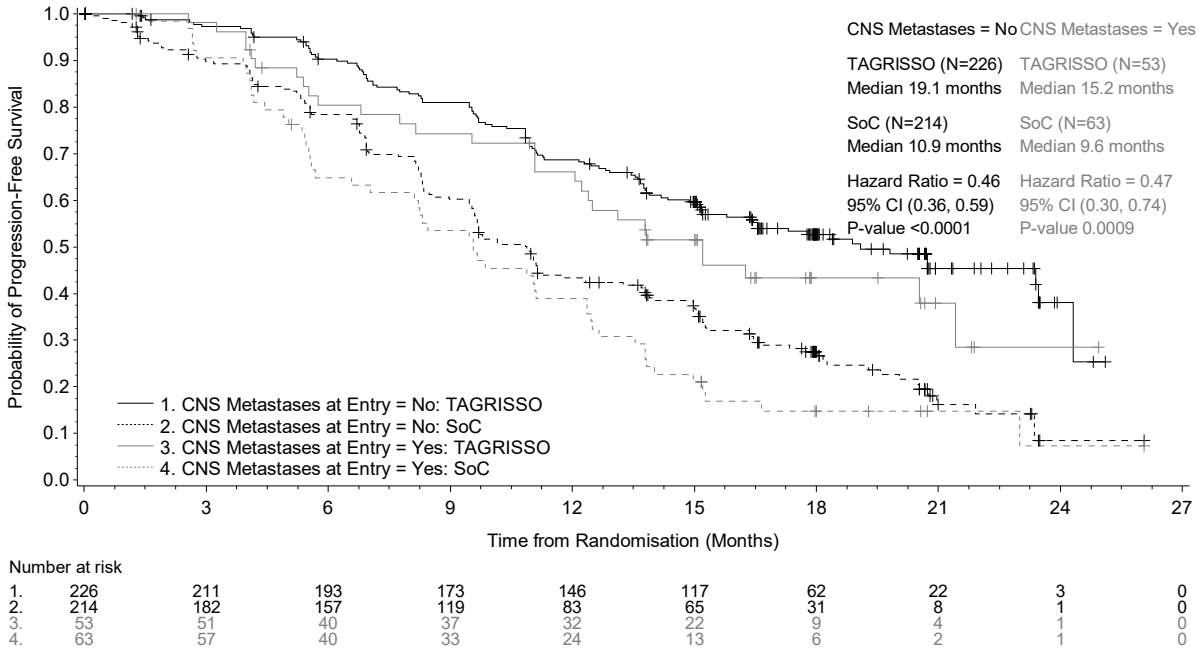
Table 6. CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in FLAURA

Efficacy parameter	TAGRISSO N=61	EGFR TKI comparator (gefitinib or erlotinib) N=67
CNS progression-free survival[1]		
Number of events (%)	18 (30)	30 (45)
Median, months (95% CI)	NC (16.5, NC)	13.9 (8.3, NC)
HR (95% CI); P-value	0.48 (0.26, 0.86); P=0.014†	
CNS progression free and alive at 6 months (%) (95% CI)	87 (74, 94)	71 (57, 81)
CNS progression free and alive at 12 months (%) (95% CI)	77 (62, 86)	56 (42, 68)
CNS Objective Response Rate[1]		
CNS response rate % (n) (95% CI)	66 (40) (52,77)	43 (29) (31,56)
Odds ratio (95% CI); P-value	2.5 (1.2, 5.2); P=0.011	
CNS Duration of Response[1]		
Median, Months (95% CI)	NC (12, NC)	14 (7, 19)
Patients remaining in response at 6 months (%) (95% CI)	86 (70, 94)	76 (55, 89)
Patients remaining in response at 12 months (%) (95% CI)	65 (46, 79)	67 (43, 82)

HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable
A HR< 1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO
[1] CNS PFS, ORR and DoR determined by RECIST v1.1by CNS BICR (CNS measurable and non-measurable lesions at baseline by BICR) n=61 for TAGRISSO and n=67 for EGFR TKI comparator; responses are unconfirmed
† Nominally statistically significant

A pre-specified PFS subgroup based on CNS metastases status (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) at study entry was performed in FLAURA and is shown in Figure 4. Irrespective of CNS lesion status at study entry, patients in the TAGRISSO arm demonstrated an efficacy benefit over those in the EGFR TKI comparator arm.

Figure 4. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in FLAURA



Number at risk

1.	226	211	193	173	146	117	62	22	3	0
2.	214	182	157	119	83	65	31	8	1	0
3.	53	51	40	37	32	22	9	4	1	0
4.	63	57	40	33	24	13	6	2	1	0

+ Censored patients.
The values at the base of the figure indicate number of subjects at risk.

Irrespective of CNS lesion status at study entry, based on investigator assessment, there were fewer patients with new CNS lesions in the TAGRISSO arm compared to the EGFR TKI comparator arm (TAGRISSO, 11/279 [3.9%] compared to EGFR TKI comparator, 34/277 [12.3%]). In the subset of patients without CNS lesions at baseline, there were a lower number of new CNS lesions in the TAGRISSO arm compared to the EGFR TKI comparator arm (7/226 [3.1%] vs. 15/214 [7.0]%, respectively).

Patient reported outcomes

Patient-reported symptoms and health-related quality of life (HRQL) were electronically collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 was initially administered once a week for the first 6 weeks, then every 3 weeks before and after progression. The C30 was assessed every 6 weeks before and after progression. At baseline, no differences in patient reported symptoms, function or HRQL were observed between TAGRISSO and EGFR TKI comparator (gefitinib or erlotinib) arms. Compliance over the first 9 months was generally high (≥70%) and similar in both arms.

Key lung cancer symptoms analysis

Data collected from baseline up to month 9 showed similar improvements in TAGRISSO and EGFR TKI comparator groups for the five pre-specified primary PRO symptoms (cough, dyspnoea, chest pain, fatigue, and appetite loss) with improvement in cough reaching the established clinically relevant cutoff. Up to month 9 there were no clinically meaningful differences in patient-reported symptoms between TAGRISSO and EGFR TKI comparator groups (as assessed by a difference of ≥ 10 points). Data are presented in Table 7.

Table 7. Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with EGFR TKI comparator (gefitinib or erlotinib)

	Cough	Dyspnea	Chest Pain	Appetite loss	Fatigue

Arms	TAGRISSO	gefitinib or erlotinib	TAGRISSO	gefitinib or erlotinib	TAGRISSO	gefitinib or erlotinib	TAGRISSO	gefitinib or erlotinib	TAGRISSO	gefitinib or erlotinib
N	248	252	248	252	248	252	252	247	252	247
Adj Mean	-10.97	-11.65	-4.04	-4.14	-6.62	-6.41	-6.15	-5.64	-5.48	-4.72
Estimated Difference (95%CI)	0.68 (-1.87, 3.24)		0.10 (-2.16, 2.35)		-0.21 (-2.51, 2.08)		-0.50 (-3.73, 2.73)		-0.77 (-3.59, 2.05)	

HRQL and physical functioning improvement analysis

Both groups reported similar improvements in most functioning domains and global health status/HRQL, indicating that patients overall health status improved. Up to month 9, there were no clinically meaningful differences between the TAGRISSO and EGFR TKI comparator groups in functioning or HRQL.

Pretreated T790M positive NSCLC patients - AURA3

The efficacy and safety of TAGRISSO for the treatment of patients with locally advanced or metastatic T790M NSCLC whose disease has progressed on or after EGFR TKI therapy, was demonstrated in a randomised, open label, active-controlled Phase 3 study (AURA3). All patients were required to have EGFR T790M mutation positive NSCLC identified by the cobas EGFR mutation test performed in a central laboratory prior to randomisation. The T790M mutation status was also assessed using ctDNA extracted from a plasma sample taken during screening. The primary efficacy outcome was progression-free survival (PFS) as assessed by investigator. Additional efficacy outcome measures included Objective Response Rate (ORR), Duration of Response (DoR), Disease Control Rate (DCR) and Overall Survival (OS) as assessed by investigator.

Patients were randomised in a 2:1 (TAGRISSO: platinum-based doublet chemotherapy) ratio to receive TAGRISSO (n=279) or platinum-based doublet chemotherapy (n=140). Randomisation was stratified by ethnicity (Asian and non-Asian). Patients in the TAGRISSO arm received TAGRISSO 80 mg orally once daily until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Chemotherapy consisted of pemetrexed 500 mg/m^2 with carboplatin AUC5 or pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2 on day 1 of every 21 day cycle for up to 6 cycles. Patients whose disease had not progressed after four cycles of platinum-based chemotherapy could receive pemetrexed maintenance therapy (pemetrexed 500 mg/m^2 on day 1 of every 21 day cycle). Subjects on the chemotherapy arm who had objective radiological progression (by the investigator and confirmed by independent central imaging review) were given the opportunity to begin treatment with TAGRISSO.

The baseline demographic and disease characteristics of the overall study population were: median age 62 years, 15% of patients were ≥ 75 years old, female (64%), white (32%), Asian (65%). Sixty-eight percent (68%) of patients were never smokers, 100% of patients had a World Health Organization (WHO) performance status of 0 or 1. Fifty-four percent (54%) of patients had extra-thoracic visceral metastases, including 34% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) and 23% with liver metastases. Forty-two percent (42%) of patients had metastatic bone disease.

AURA3 demonstrated a statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy. Efficacy results from AURA3 by investigator assessment are summarised in Table 8, and the Kaplan-Meier curve for PFS is shown in Figure 5. No statistically

significant difference was observed between the treatment arms at the final OS analysis.

Table 8. Efficacy results from AURA3 by investigator assessment

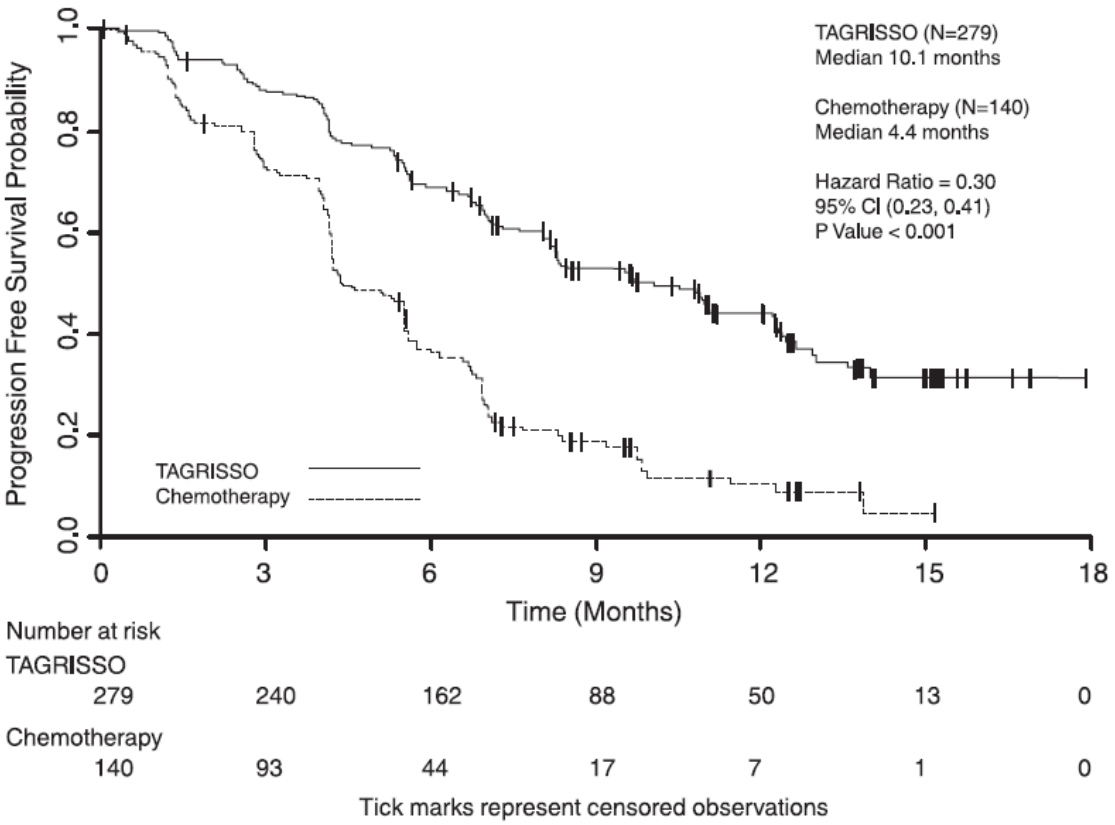
Efficacy parameter	**TAGRISSO (N=279)**	**Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=140)**
Progression-free survival		
Number of events (% maturity)	140 (50)	110 (79)
Median, months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
HR (95% CI) ; P-value	0.30 (0.23,0.41); P< 0.001	
Overall survival (OS)[1]		
Number of deaths (% maturity)	188 (67.4)	93 (66.4)
Median OS, months (95% CI)	26.8 (23.5, 31.5)	22.5 (20.2, 28.8)
HR (95.56% CI); P-value	0.87 (0.67, 1.13); P=0.277	
Objective response rate[2]		
Number of responses, response Rate (95% CI)	197 71% (65, 76)	44 31% (24, 40)
Odds ratio (95% CI); P-value	5.4 (3.5, 8.5); P <0.001	
Duration of response (DoR)[2]		
Median, months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)
Disease Control Rate[3]		
Number of patients with disease control, Response rate (95% CI)	260 93% (90, 96)	104 74% (66, 81)
Odds ratio (95% CI); P-value	4.8 (2.6, 8.8); P< 0.001	

HR=Hazard Ratio; CI=confidence interval; NC=non-calculable; OS=Overall Survival
All efficacy results based on RECIST investigator assessment
[1]The final analysis of OS was performed at 67% maturity. The CI for the HR has been adjusted for previous interim analyses. The OS analysis was not adjusted for the potentially confounding effects of crossover (99 [71%] patients on the chemotherapy arm received subsequent osimertinib treatment).
[2] ORR and DoR results by investigator assessment were consistent with those reported via Blinded Independent Central Review (BICR); ORR by BICR assessment was 64.9% [95% CI: 59.0, 70.5] on osimertinib and 34.3% [95% CI: 26.5, 42.8]

on chemotherapy; DoR by BICR assessment was 11.2 months (95% CI: 8.3, NC) on osimertinib and 3.1 months (95% CI: 2.9, 4.3) on chemotherapy

[3] Full analysis set

Figure 5. Kaplan-Meier Curves of progression-free survival as assessed by investigator in AURA3



A sensitivity analysis of PFS was conducted by a Blinded Independent Central Review (BICR) and showed a median PFS of 11.0 months with TAGRISSO compared with 4.2 months with chemotherapy. This analysis demonstrated a consistent treatment effect (HR 0.28; 95% CI: 0.20, 0.38) with that observed by investigator assessment.

Clinically meaningful improvements in PFS with HRs less than 0.50 in favour of patients receiving TAGRISSO compared to those receiving chemotherapy were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history, CNS metastases status at study entry, EGFR mutation (Exon 19 deletion and L858R), and duration of first-line therapy with an EGFR TKI.

CNS metastases efficacy data in AURA3 study

Patients with asymptomatic, stable brain metastases not requiring steroids for at least 4 weeks prior to the start of study treatment were eligible to be randomised in the study. A BICR assessment of CNS efficacy by RECIST v1.1 in the subgroup of 116/419 (28%) patients identified to have CNS metastases on a baseline brain scan are summarized in Table 9. CNS responses were observed irrespective of prior brain radiation status.

Table 9. CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3

Efficacy parameter	TAGRISSO	Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin)
CNS objective response rate[1]		
CNS response rate % (n/N) (95% CI)	70% (21/30) (51, 85)	31% (5/16) (11, 59)
Odds ratio (95% CI); P-value	5.1 (1.4, 21); P=0.015	
CNS duration of response[2]		
Median, Months (95% CI)	8.9 (4.3, NC)	5.7 (NC, NC)
CNS disease control rate		
CNS disease control rate	87% (65/75) (77, 93)	68% (28/41) (52, 82)
Odds ratio (95% CI); P-value	3 (1.2, 7.9); P=0.021	
CNS progression-free survival[3]	N=75	N=41
Number of events (% maturity)	19 (25)	16 (39)
Median, months (95% CI)	11.7 (10, NC)	5.6 (4.2, 9.7)
HR (95% CI); P value	0.32 (0.15, 0.69); P=0.004	

[1] CNS Objective Response Rate and Duration of Response determined by RECIST v1.1 by CNS BICR in the evaluable for response population (CNS measurable lesions at baseline by BICR) n=30 for TAGRISSO and n=16 for Chemotherapy

[2] Based on patients in the evaluable for response population with response only; DoR defined as the time from the date of first documented response (complete response or partial response, or stable disease ≥6 weeks)

[3] CNS Progression Free Survival determined by RECIST v1.1by CNS BICR in the full analysis set population (CNS measurable and non-measurable lesions at baseline by BICR) n=75 for TAGRISSO and n=41 for Chemotherapy

NC=non-calculable

A HR< 1 favours TAGRISSO

A pre-specified PFS subgroup analysis based on CNS metastases status at study entry was performed in AURA3 and is shown in Figure 6 and Table 10.

Figure 6. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in AURA3

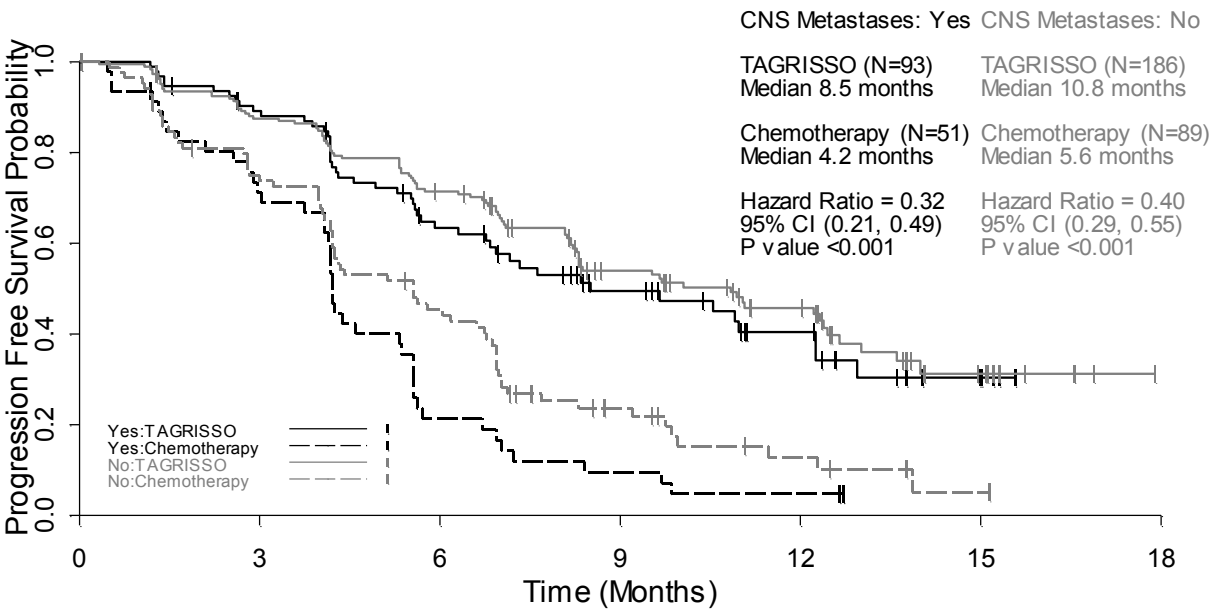


Table 10. PFS by CNS metastases at study entry based on investigator assessment (full analysis set) in AURA3

CNS metastases status	Yes		No	
	TAGRISSON =93	ChemotherapyN =51	TAGRISSON =186	Chemotherapy N=89
Number of events (maturity %)	48 (52)	42 (82)	92 (50)	68 (76)
Median, Months (95% CI)	8.5 (6.8, 12.3)	4.2 (4.1, 5.4)	10.8 (8.3, 12.5)	5.6 (4.2, 6.8)
HR (95% CI); P-value	0.32 (0.21, 0.49); P<0.001		0.40 (0.29, 0.55); P<0.001	

All efficacy results based on RECIST v1.1 investigator assessment
A HR< 1 favours TAGRISSO

AURA3 demonstrated an improvement in PFS for patients receiving TAGRISSO compared to those receiving chemotherapy irrespective of CNS metastases status at study entry.

TAGRISSO decreased the appearance of new CNS metastases (4.7%) as compared with chemotherapy (14.3%) according to RECIST v1.1 by investigator assessment.

Patient reported outcomes

Patient-reported symptoms and health-related quality of life (HRQL) were electronically collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 was initially administered once a week for the first 6 weeks, then every 3 weeks before and after progression. The C30 was assessed every 6 weeks before and after progression.

Key lung cancer symptoms analysis

TAGRISSO improved patient-reported lung cancer symptoms compared to chemotherapy by demonstrating a statistically significant difference in mean change from baseline versus chemotherapy during the overall time period from randomisation until 6 months for 5 pre-specified primary PRO symptoms (appetite loss, cough, chest pain, dyspnoea, and fatigue) as shown in Table 11.

Table 11. Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with chemotherapy

	Appetite Loss		**Cough**		**Chest Pain**		**Dyspnoea**		**Fatigue**	
Arms	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)
N	239	97	228	113	228	113	228	113	239	97
Adj Mean	-5.51	2.73	-12.22	-6.69	-5.15	0.22	-5.61	1.48	-5.68	4.71
Estimated Difference (95%CI)	-8.24 (-12.88, 3.60)		-5.53 (-8.89, -2.17)		-5.36 (-8.20, -2.53)		-7.09 (-9.86, -4.33)		-10.39 (-14.55, -6.23)	
p-value	p <0.001		p=0.001		p<0.001		p<0.001		p<0.001	

Adjusted mean and estimated differences obtained from a Mixed Model Repeated Measures (MMRM) analysis. The model included patient, treatment, visit, treatment-by-visit interaction, baseline symptom score, and baseline symptom score-by-visit interaction and used an unstructured covariance matrix.

HRQL and physical functioning improvement analysis

Patients on TAGRISSO had significantly greater chances of achieving a clinically meaningful improvement of greater than or equal to 10 points on the global health status and physical functioning of the EORTC-C30 questionnaire compared with chemotherapy during the study period Odds Ratio (OR) global health status: 2.11, (95% CI 1.24, 3.67, p=0.007); OR physical functioning 2.79 (95% CI 1.50, 5.46, p=0.002).

<u>Pretreated T790M positive NSCLC patients - AURAex and AURA2</u>

Two single-arm, open-label clinical studies, AURAex (Phase 2 Extension cohort, (n=201)) and AURA2 (n=210) were conducted in patients with EGFR T790M mutation positive lung cancer who have progressed on one or more prior systemic therapies, including an EGFR TKI. All patients were required to have EGFR T790M mutation positive NSCLC identified by the cobas EGFR mutation test performed in a central laboratory prior to dosing. T790M mutation status was also assessed retrospectively using ctDNA extracted from a plasma sample taken during screening. All patients received TAGRISSO at a dose of 80 mg once daily. The primary efficacy outcome measure of these two studies was objective response rate (ORR) according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Secondary efficacy outcome measures included Duration of Response (DoR) and Progression -Free Survival (PFS).

Baseline characteristics of the overall study population (AURAex and AURA2) were as follows: median age 63 years, 13% of patients were ≥75 years old, female (68%), White (36%), Asian (60%). All patients received at least one prior line of therapy. 31% (N=129) had received 1 prior line of therapy (EGFR TKI treatment only, second-line, chemotherapy naïve), 69% (N=282) had received 2 or more prior lines. Seventy-two percent (72%) of patients were never smokers, 100% of patients had a World Health Organization (WHO) performance status of 0 or 1. Fifty-nine percent (59%) of patients had extra-thoracic visceral metastasis including 39% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery and/or prior radiotherapy to CNS metastases) and 29% with liver metastases. Forty-seven percent (47%) of patients had metastatic bone disease. The median duration of follow up for PFS was 12.6 months.

In the 411 pre-treated EGFR T790M mutation positive patients, the ORR by BICR in the evaluable for response population was 66% (95% CI: 61, 71). In patients with a confirmed response by BICR, the median DoR was 12.5 months (95% CI: 11.1, NE). The median PFS by BICR was 11.0 months 95% CI (9.6, 12.4).

Objective response rates by BICR above 50% were observed in all predefined subgroups analysed, including line of therapy, race, age and region. The ORR by BICR in AURAex was 62% (95% CI: 55, 68) and 70% (95% CI: 63, 77) in AURA2.

Among the patients in the evaluable for response population with objective responses, 85% (223/262) had documentation of response at the time of the first scan (6 weeks); 94% (247/262) had documentation of response at the time of the second scan (12 weeks).

CNS metastases efficacy data in Phase 2 studies (AURAex and AURA2)

A BICR assessment of CNS efficacy by RECIST v1.1 was performed in a subgroup of 50 (out of 411) patients identified to have measurable CNS metastases on a baseline brain scan. A CNS ORR of 54% (27/50 patients; 95% CI: 39.3, 68.2) was observed with 12% being complete responses.

5.2 Pharmacokinetic properties

Osimertinib pharmacokinetic parameters have been characterized in healthy subjects and NSCLC patients. Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14.3 L/h, apparent volume of distribution is 918 L and terminal half-life of approximately 44 hours. The AUC and C_{max} increased dose proportionally over 20 to 240 mg dose range. Administration of TAGRISSO once daily results in approximately 3-fold accumulation with steady-state exposures achieved by 15 days of dosing. At steady state, circulating plasma concentrations are typically maintained within a 1.6 fold range over the 24-hour dosing interval.

Absorption

Following oral administration of TAGRISSO, peak plasma concentrations of osimertinib was achieved with a median (min-max) T_{max} of 6 (3-24) hours, with several peaks observed over the first 24 hours in some patients. The absolute bioavailability of TAGRISSO is 70% (90% CI 67, 73. Based on a clinical pharmacokinetic study in patients at 80 mg, food does not alter osimertinib bioavailability to a clinically meaningful extent. (AUC increase 6% (90% CI -5, 19) and C_{max} decrease -7% (90% CI -19, 6)). In healthy volunteers administered an 80 mg tablet where gastric pH was elevated by dosing of omeprazole for 5 days, osimertinib exposure was not affected (AUC and C_{max} increase by 7% and 2%, respectively) with the 90% CI for exposure ratio contained within the 80-125% limit.

Distribution

Population estimated mean volume of distribution at steady state (V_{ss}/F) of osimertinib is 918L indicating extensive distribution into tissue. *In vitro*, plasma protein binding of osimertinib is 94.7% (5.3% free). Osimertinib has also been demonstrated to bind covalently to rat and human plasma

proteins, human serum albumin and rat and human hepatocytes.

Biotransformation

In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4, and CYP3A5. Based on *in vitro* studies, 2 pharmacologically active metabolites (AZ7550 and AZ5104) have subsequently been identified in the plasma of preclinical species and in humans after oral dosing with TAGRISSO; AZ7550 showed a similar pharmacological profile to TAGRISSO while AZ5104 showed greater potency across both mutant and wild-type EGFR. Both metabolites appeared slowly in plasma after administration of TAGRISSO to patients, with a median (min-max) T_{max} of 24 (4-72) and 24 (6-72) hours, respectively. In human plasma, parent osimertinib accounted for 0.8%, with the 2 metabolites contributing 0.08% and 0.07% of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10% each of the exposure of osimertinib at steady state.

The main metabolic pathway of osimertinib was oxidation and dealkylation. At least 12 components were observed in the pooled urine and faecal samples in humans with 5 components accounting for >1% of the dose of which unchanged osimertinib, AZ5104 and AZ7550, accounted for approximately 1.9, 6.6 and 2.7% of the dose while a cysteinyl adduct (M21), and an unknown metabolite (M25) accounted for 1.5% and 1.9% of the dose, respectively.

Based on *in vitro* studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. Based on in vitro studies, osimertinib is not an inhibitor of UGT1A1 and UGT2B7 at clinically relevant concentrations hepatically. Intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown.

Elimination

Following a single oral dose of 20 mg, 67.8% of the dose was recovered in faeces (1.2% as parent) while 14.2% of the administered dose (0.8% as parent) was found in urine by 84 days of sample collection. Unchanged osimertinib accounted for approximately 2% of the elimination with 0.8% in urine and 1.2% in faeces.

Interactions with transport proteins

In vitro studies have shown that osimertinib is not a substrate of OATP1B1 and OATP1B3.

In vitro, osimertinib does not inhibit P-glycoprotein, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, OCT2 and MATE2K at clinically relevant concentrations.

Effects of osimertinib on P-gp and BCRP

Based on *in vitro* studies, osimertinib is a substrate of P-glycoprotein and breast cancer resistant protein (BCRP), but is unlikely to result in clinically relevant drug interactions with active substances by osimertinib at the clinical doses. Based on *in vitro* data, osimertinib is an inhibitor of BCRP. (See section 4.5).

Special populations

In a population based PK analysis (n=1367), no clinically significant relationships were identified between predicted steady-state exposure (AUC_{ss}) and patient's age (range: 25 to 91 years), gender (65% female), ethnicity (including White, Asian, Japanese, Chinese and non-Asian-non-White patients), line of therapy and smoking status (n=34 current smokers, n=419 former smokers). Population PK analysis indicated that body weight was a significant covariate with a less than 20% change in osimertinib AUC_{ss} expected across a body weight range of 88 kg to 43 kg respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median body weight of 61 kg. Taking the

extremes of body weight into consideration, from <43 kg to >88 kg, AZ5104 metabolite ratios ranged from 11.8% to 9.6% while for AZ7550 it ranged from 12.8% to 8.1%, respectively. Based on population PK analysis, serum albumin was identified as a significant covariate with a <30% change in osimertinib AUC_{ss} expected across the albumin range of 29 to 46 g/L respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median baseline albumin of 39 g/L. These exposure changes due to body weight or baseline albumin differences are not considered clinically relevant.

Hepatic impairment

Osimertinib is eliminated mainly via the liver. In clinical study, patients with mild hepatic impairment (Child Pugh A. n = 7) or moderate hepatic impairment (Child Pugh B. n = 5) had no increase in exposure compared to patients with normal hepatic function (n = 10) after a single 80 mg dose of TAGRISSO. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. The hepatic impairment marker serum albumin showed an effect on the PK of osimertinib. Clinical studies that were conducted excluded patients with AST or ALT >2.5x upper limit of normal (ULN), or if due to underlying malignancy, >5.0x ULN or with total bilirubin >1.5x ULN. Based on a pharmacokinetic analysis of 134 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1.0 to 1.5x ULN and any AST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5 times to 3.0 times ULN and any AST) and 1216 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN), osimertinib exposures were similar. There are no data available on patients with severe hepatic impairment (see section 4.2).

Renal impairment

In a clinical study, patients with severe renal impairment (CLcr 15 to less than 30 mL/min; n=7) compared to patients with normal renal function (CLcr greater than or equal to 90 mL/min; n=8) after a single 80 mg oral dose of TAGRISSO showed a 1.85-fold increase in AUC (90% CI; 0.94, 3.64) and a 1.19-fold increase in Cmax (90% CI: 0.69, 2.07). Furthermore, based on a population PK analysis of 593 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 254 patients with moderate renal impairment (CLcr 30 to less than 60 mL/min), 5 patients with severe renal impairment (CLcr 15 to less than 30 mL/min) and 502 patients with normal renal function (greater than or equal to 90 mL/min), osimertinib exposures were similar. Patients with CLcr less than or equal to 10 mL/min were not included in the clinical studies.

Patients with brain metastases

PET images following administration of microdoses of [^{11}C]osimertinib in EGFR mutation positive NSCLC patients with brain metastases (n=4) and healthy volunteers (n=7) demonstrated that the brain to plasma ratio (Kp) was similar and that [^{11}C]osimertinib crossed the blood brain barrier rapidly and was homogeneously distributed across all regions of the brain in both patients and healthy volunteers.

5.3 Preclinical safety data

The main findings observed in repeat dose toxicity studies in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including tongue), skin, and male and female reproductive tracts with secondary changes in spleen. These findings occurred at plasma concentrations that were below those seen in patients at the 80 mg therapeutic dose. The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing with the exception of partial recovery for some of the corneal changes.

Lens fibre degeneration was found in the 104-week carcinogenicity rat study at exposures 0.2-times the human AUC, at the recommended clinical dose of 80 mg once a day. Lens opacities were first

noted from week 52 of this study and showed a gradual increase in incidence and severity with increased duration of dosing. The clinical relevance of this finding cannot be ruled out.

Osimertinib penetrated the intact blood-brain barrier of the cynomolgus monkey (intravenous dosing), rat and mouse (oral administration).

Non-clinical data indicate that osimertinib and its metabolite (AZ5104) inhibit the h-ERG channel, and QTc prolonging effect cannot be excluded.

Carcinogenesis and mutagenesis
Osimertinib showed no carcinogenic potential when administered orally to Tg rasH2 transgenic mice for 26 weeks. Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays.
An increased incidence of proliferative vascular lesions (angiomatous hyperplasia and haemangioma) in the mesenteric lymph node was observed in the rat 104-week carcinogenicity study at exposures 0.2-times the AUC at the recommended clinical dose of 80 mg once daily, and is unlikely to be relevant for humans.

Reproductive toxicity
Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for ≥1 month and there was a reduction in male fertility in rats following exposure to osimertinib for 3 months. These findings were seen at clinically relevant plasma concentrations. Pathology findings in the testes seen following 1 month dosing were reversible in rats; however, a definitive statement on reversibility of these lesions in dogs cannot be made.

A female fertility study has not been conducted. In repeat dose toxicity studies, an increased incidence of anoestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to osimertinib for ≥1 month at clinically relevant plasma concentrations. Findings in the ovaries seen following 1 month dosing were reversible.

In a modified embryofoetal development study in the rat, osimertinib caused embryolethality when administered to pregnant rats prior to embryonic implantation. These effects were seen at a maternally tolerated dose of 20 mg/kg where exposure was equivalent to the human exposure at the recommended dose of 80 mg daily (based on total AUC). Exposure at doses of 20 mg/kg and above during organogenesis caused reduced foetal weights but no adverse effects on external or visceral foetal morphology. When osimertinib was administered to pregnant female rats throughout gestation and then through early lactation, there was demonstrable exposure to osimertinib and its metabolites in suckling pups plus a reduction in pup survival and poor pup growth (at doses of 20 mg/kg and above).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The names of excipients may vary according to region.

Tablet core:
Mannitol
Microcrystalline cellulose
Low-substituted hydroxpropyl cellulose
Sodium stearyl fumarate

Tablet coating:
Polyvinyl alcohol
Titanium dioxide

Macrogol 3350
Talc
Yellow iron oxide
Red iron oxide
Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Al/Al perforated unit dose blisters.

6.6 Instructions for use, handling and disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PACK SIZE

40 mg: Box, 1 blisters @ 10 film-coated tablets, Reg No: DKI1751303317A1
80 mg: Box, 1 blisters @ 10 film-coated tablets, Reg No: DKI1751303317B1

40 mg: Box, 3 blisters @ 10 film-coated tablets, Reg No: DKI1751303317A1
80 mg: Box, 3 blisters @ 10 film-coated tablets, Reg No: DKI1751303317B1

HARUS DENGAN RESEP DOKTER

Manufactured & released by:
AstraZeneca AB Gärtunavägen
SE-151 85 Södertälje
SWEDEN

Imported by:
PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

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