יולי 2021

רופא/ה נכבד/ה

רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלון התכשיר :</u>

<u>TAGRISSO 40mg film-coated tablets</u>

<u>TAGRISSO 80mg film-coated tablets</u>

הרכב:

TAGRISSO 40 mg tablets

Each tablet contains osimertinib 40mg (equivalent to 47.7mg of osimertinib mesylate)

TAGRISSO 80 mg tablets

Each tablet contains osimertinib 80mg (equivalent to 95.4mg of osimertinib mesylate)

התוויה:

TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations.

Tagrisso as monotherapy is indicated for:

- the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.
- the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **יולי 2021.**

העדכון העיקרי בעלון לרופא הוא:

4.4 Special warnings and 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 using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.

~~Only robust, reliable and sensitive tests with demonstrated utility for the determination of EGFR mutation status of tumour derived DNA (from a tissue or a plasma sample) 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.

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

Interstitial lung disease (ILD)

~~Interstitial Lung Disease (~~ILD~~)~~ or ILD-like adverse reactions ~~(e.g. pneumonitis)~~ were reported in 3.7% ~~and were fatal in 03%~~ of the 1479 patients who received TAGRISSO in the ADAURA, FLAURA and AURA studies.~~, clinical 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.~~4~~9% in patients of Japanese ethnicity, 1.~~8~~6% in patients of Asian ethnicity and 2.~~8~~5% in non-Asian patients. (See Section 4.8).

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 ~~Of the 1479 patients treated with TAGRISSO in clinical trials, 0.8% were found to have a QTc > 500 msec, and 3.1% of patients had an increase from baseline QTc > 60 msec No QTc related arrhythmias were reported~~ (see section 4.8).

Changes in cardiac contractility

Across clinical trials, 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 trial (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%.~~cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.~~

~~A decline in left ventricular ejection fraction (LVEF) ≥10 percentage points from baseline and to less than 50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (5/325) of patients treated with TAGRISSO experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.~~

~~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~~.

4.8 Undesirable effects

Summary of the safety profile

Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (~~49~~47%), ~~and~~ rash (~~47~~45%), paronychia (33%), dry skin (32%), and stomatitis (24%). Grade 3 and Grade 4 adverse reactions ~~-~~across ~~both~~ the studies were ~~9.7~~10% and 0.~~9~~1%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in ~~2.1~~3.4% of the patients. Discontinuation due to adverse reactions was 4.~~3~~8%.

Tabulated list of adverse reactions

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]
Metabolism and nutrition disorders	Decreased appetite	Very common (19%)	1.1%
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common (5%)	0
	Interstitial lung disease[c]	Common (3.~~9~~7%)[d]	1.~~5~~1%
Gastrointestinal disorders	Diarrhoea	Very common (~~49~~47%)	1.~~2~~4%
	Stomatitis[e]	Very common (~~20~~24%)	0.~~2~~5%
Eye disorders	~~Keratitis[e]~~Keratitis[f]	Uncommon (0.7%)	0.1%
Skin and subcutaneous tissue disorders	~~Rash[f]~~Rash[g]	Very common (~~47~~45%)	0.~~9~~7%
	Paronychia[h] ~~Dry skin[g]~~	Very common (33%)	0.~~1~~4%
	Dry skin[i] ~~Paronychia[h]~~	Very common (~~31~~32%)	0.~~3~~1%
	~~Pruritus[i]~~Pruritus[j]	Very common (17%)	0.1%
	Alopecia	Common (4.6%)	0
	Urticaria	Common (1.9%)	0.1%
	Palmar-plantar erythrodysaesthesia	Common (1.7%)	0

	syndrome		
	Erythema multiforme[j]multiforme[k]	Uncommon (0.35%)	0%
	Stevens-Johnson syndrome[k]Cutaneous Vasculitis[l]	Uncommon (0.3%)Rare (0.02%)	0
	Stevens-Johnson Syndrome[m] Cutaneous Vasculitis[l]	Rare (0.02%)Uncommon (0.26%) 0	
Investigations	QTc interval prolongation[m]prolongation[n]	Uncommon (0.98%)	
(findings based on test results presented as CTCAE grade shifts)	Leucocytes decreased[o] Platelet count decreased [n]	Very common (5465%)	1.62%
	Lymphocytes decreased [o] Leucocytes decreased[n]	Very common (6862%)	1.56.1%
	Platelet count decreased [o] Lymphocytes decreased [n]	Very common (6753%)	7.21.2%
	Neutrophils decreased [no]	Very common (3533%)	4.13.2%
	Blood creatinine increased[o]	Common (9%)	0

[a]Data is pooled cumulative 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 summarized.

[b]National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

[c]Includes cases reported within the clustered terms: Iinterstitial lung disease and pneumonitis.

[d]5 CTCAE grade 5 events (fatal) were reported.

[e]Includes: mouth ulceration, stomatitis.cases reported within the clustered terms:

[f] Includes: corneal epithelium defect, corneal erosion, Kkeratitis, punctate keratitis, corneal erosion, corneal epithelium defect.

[f]Includes [g]Includescases reported within the clustered terms for rash AEs: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular,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.

[g]Includes [h]Includescases reported within the clustered terms: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychiaDry skin, skin fissures, xerosis, eczema, xeroderma.

[h]Includes cases reported within the clustered terms: Nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[i]Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.

[j]Includes cases reported within the clustered terms: eyelid pruritus, pruritus, pruritus generalised, eyelid pruritus.

[j]Four [k]Five of the 1142 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).

[k]One [l]Estimated frequency. The upper limit of the 95% CI for the point estimate is 3/1142 (0.3%)event was reported in a post-marketing study, and the frequency has been derived from the FLAURA and AURA studies and the post-marketing study (N=4720).

[l]Estimated [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).frequency. The upper limit of the 95% CI for the point estimate is 3/1142 (0.26%).

[m]Represents [n]Represents the incidence of patients who had a QTcF prolongation >500msec.

[n]Represents [o]Represents the incidence of laboratory findings, not of reported adverse events.

Clinically relevant adverse reactions in AURA3 in <10% of patients receiving TAGRISSO were epistaxis (5%), interstitial lung disease (3.9%), alopecia (3.6%), palmar-plantar erythrodysaesthesia syndrome (1.8%), QTc interval prolongation (1.4%), keratitis (1.1%), and erythema multiform (0.7%). QTc interval prolongation represents the incidence of patients who had a QTcF prolongation >500msec.

Clinically relevant laboratory abnormalities in AURA3 that occurred in <20% of patients receiving TAGRISSO included increased blood creatinine (7%).

Clinically relevant adverse reactions in FLAURA in <10% of patients receiving TAGRISSO were alopecia (7%), epistaxis (6%), interstitial lung disease (3.9%), palmar-plantar erythrodysaesthesia syndrome (1.4%), QTc interval prolongation (1.1%), and keratitis (0.4%). QTc interval prolongation represents the incidence of patients who had a QTcF prolongation >500msec.

Clinically relevant laboratory abnormalities in FLAURA that occurred in <20% of patients receiving TAGRISSO was increased blood creatinine (9%).

~~Safety findings in the single-arm Phase 2 AURAex and AURA2 studies were generally consistent with those observed in the AURA3 TAGRISSO arm. No additional or unexpected toxicity has been observed and adverse events have been aligned in type, severity and frequency.~~

Description of selected adverse reactions

Interstitial lung disease (ILD)

In the ADAURA, FLAURA and AURA studies, the incidence of ILD was ~~10.4~~11% in patients of Japanese ethnicity, 1.~~8~~6% in patients of non-Japanese Asian ethnicity and 2.~~8~~5% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was ~~85~~ 84 days (see section 4.4).

QTc interval prolongation

Of the ~~1142~~ 1479 patients in ADAURA, FLAURA and AURA studies treated with TAGRISSO 80 mg, 0.~~9~~8% of patients (n=~~10~~12) were found to have a QTc greater than 500 msec, and 3.~~6~~1% of patients (n=~~41~~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 ~~49~~47% of patients of which ~~39~~38% were Grade 1 events, ~~8.0~~7.9% Grade 2 and 1.~~2~~4% were Grade 3; no Grade 4 or 5 events were reported. Dose reduction was required in 0.~~2~~3% of patients and dose interruption in ~~1.4~~2%. ~~One~~ Four event~~s~~ (0.~~1~~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.

~~**Adjuvant Treatment of EGFR Mutation-Positive NSCLC**~~

~~The safety of TAGRISSO was evaluated in ADAURA, a randomized, double-blind, placebo-controlled trial for the adjuvant treatment of patients with EGFR exon 19 deletions or exon 21 L858R mutation positive NSCLC who had complete tumor resection, with or without prior~~

adjuvant chemotherapy. At time of DFS analysis, the median duration of exposure to TAGRISSO was 22.5 months.

Serious adverse reactions were reported in 16% of patients treated with TAGRISSO. The most common serious adverse reaction (≥1%) was pneumonia (1.5%). Adverse reactions leading to dose reductions occurred in 9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were diarrhea (4.5%), stomatitis (3.9%), nail toxicity (1.8%) and rash (1.8%). Adverse reactions leading to permanent discontinuation occurred in 11% of patients treated with TAGRISSO. The most frequent adverse reactions leading to discontinuation of TAGRISSO were interstitial lung disease (2.7%), and rash (1.2%). Table 3 and 4 summarize common adverse reactions and laboratory abnormalities which occurred in ADAURA.

Table 3. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in ADAURA

Adverse Reaction	TAGRISSO (N=337)		PLACEBO (N=343)	
	All Grades (%)	Grade 3 or higher† (%)	All Grades (%)	Grade 3 or higher† (%)
Gastrointestinal Disorders				
Diarrhea*	47	2.4	20	0.3
Stomatitis‡	32	1.8	7	0
Abdominal Pain**	12	0.3	7	0
Skin Disorders				
Rash§	40	0.6	19	0
Nail toxicity¶	37	0.9	3.8	0
Dry skin§§	29	0.3	7	0
Pruritus#	19	0	9	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough‖	19	0	19	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain ††	18	0.3	25	0.3
Infection and Infestation Disorders				
Nasopharyngitis	14	0	10	0
Upper respiratory tract infection	13	0.6	10	0

Adverse Reaction	TAGRISSO (N=337)		PLACEBO (N=343)	
	All Grades (%)	Grade 3 or higher† (%)	All Grades (%)	Grade 3 or higher† (%)
Urinary Tract Infection¶¶	10	0.3	7	0
General Disorders and Administration Site Conditions				
Fatigue§	13	0.6	9	0.3
Nervous System Disorders				
Dizziness ##	10	0	9	0
Metabolism and Nutrition Disorders				
Decreased appetite	13	0.6	3.8	0

~~- NCI CTCAE v4.0.~~

~~†All events were grade 3.~~

~~*Includes diarrhea, colitis, enterocolitis, enteritis.~~

~~‡Includes aphthous ulcer, cheilitis, gingival ulceration, glossitis, tongue ulceration, stomatitis and mouth ulceration.~~

~~**Includes abdominal discomfort, abdominal pain, abdominal lower pain, abdominal upper pain, epigastric discomfort, hepatic pain.~~

~~§Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative generalized, drug eruption, eczema, eczema asteatotic, lichen planus, skin erosion, pustule.~~

~~¶Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.~~

~~§§Includes dry skin, skin fissures, xerosis, eczema, xeroderma.~~

~~#Includes pruritus, pruritus generalized, eyelid pruritus.~~

~~þIncludes cough, productive cough, upper-airway cough syndrome~~

~~††Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.~~

~~¶¶Includes cystitis, urinary tract infection, and urinary tract infection bacterial.~~

~~- Includes asthenia, fatigue~~

~~##Includes dizziness, vertigo, and vertigo positional.~~

~~Clinically relevant adverse reactions in ADAURA in <10% of patients receiving TAGRISSO were alopecia (6%), epistaxis (6%), interstitial lung disease (3%), palmar-plantar erythrodysaesthesia syndrome (1.8%), keratitis (0.6%), QTc interval prolongation (0.6%), and erythema multiform (0.3%). QTc interval prolongation represents the incidence of patients who had a QTcF prolongation >500msec.~~

~~Table 4. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in ADAURA~~

Laboratory Abnormality*,†	TAGRISSO (N=337)		PLACEBO (N=343)	
	All Grades (%)	Grade 3 or Grade 4 (%)	All Grades (%)	Grade 3 or Grade 4 (%)
Hematology				
Leukopenia	54	0	25	0
Thrombocytopenia	47	0	7	0.3
Lymphopenia	44	3.4	14	0.9
Anemia	30	0	12	0.3
Neutropenia	26	0.6	10	0.3
Chemistry				
Hyperglycemia	25	2.3	30	0.9
Hypermagnesemia	24	1.3	14	1.5
Hyponatremia	20	1.8	16	1.5

~~*NCI CTCAE v4.0~~

~~†Based on the number of patients with available follow-up laboratory data~~

~~Laboratory abnormalities in ADAURA that occurred in <20% of patients receiving TAGRISSO was increased blood creatinine (10%).~~

Elderly

In ADAURA, FLAURA and AURA3 (N=1479), 43% of patients were 65 years of age and older and ~~13~~12% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (~~14.3~~16% versus ~~8.4~~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 (~~10.5~~13% versus ~~7.1~~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 (~~52~~46% versus ~~35~~31%) and QTc prolongation (~~14~~12% versus ~~4~~5%) than patients with higher body weight (≥50 kg).

Clinical efficacy and safety

Adjuvant Treatment of ~~Early-Stage~~ EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC), with or without prior adjuvant chemotherapy – ADAURA

The efficacy and safety of TAGRISSO ~~was demonstrated in a randomized, double-blind, placebo-controlled trial (ADAURA [NCT02511106])~~ for the adjuvant treatment of patients with EGFR ~~exon 19 deletions or exon 21 L858R~~ mutation-positive (Ex19del or L858R) NSCLC who have had complete tumor 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), ~~predominantly non-squamous histology and EGFR exon 19 deletions or exon 21 L858R mutations~~ identified ~~prospectively from tumor tissue in a central laboratory~~ 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 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). At the time of the data cut-off, 205 (61%) patients were still on active treatment; of the 73 (11%) patients who had the opportunity to complete the 3-year treatment period, 40 (12%) were in the osimertinib arm and 33 (10%) in the placebo arm.

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 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).

ADAURA demonstrated a statistically significant reduction in the risk of disease recurrence or death for patients treated with TAGRISSO compared to patients treated with placebo in the stage II-IIIA population. Similar results were observed in the stage IB-IIIA population. Overall survival (OS) data were not mature at the time of DFS analysis. Efficacy results from ADAURA by investigator assessment are summarised in Table 3.~~Patients with clinically significant uncontrolled cardiac disease, prior history of ILD/pneumonitis, or who received treatment with any EGFR kinase inhibitor were not eligible for the study.~~

~~Patients were randomized (1:1) to receive TAGRISSO 80 mg orally once daily or placebo following recovery from surgery and standard adjuvant chemotherapy if given. Patients who did not receive adjuvant chemotherapy were randomized within 10 weeks and patients who received adjuvant chemotherapy were randomized within 26 weeks following surgery.~~

~~Randomization was stratified by mutation type (exon 19 deletions or exon 21 L858R mutations),~~

~~race (Asian or non-Asian) and pTNM staging (IB or II or IIIA) according to AJCC 7th edition. Treatment was given for 3 years or until disease recurrence, or unacceptable toxicity. The major efficacy outcome measure was disease-free survival (DFS, defined as reduction in the risk of disease recurrence or death) in patients with stage II – IIIA NSCLC determined by investigator assessment. Additional efficacy outcome measures included DFS in the overall population (patients with stage IB – IIIA NSCLC), and overall survival (OS) in patients with stage II – IIIA NSCLC and in the overall population.~~

~~A total of 682 patients were randomized to TAGRISSO (n=339) or placebo (n=343). The median age was 63 years (range 30-86 years); 70% were female; 64% were Asian and 72% were never smokers. Baseline WHO performance status was 0 (64%) or 1 (36%); 31% had stage IB, 35% II, and 34% IIIA. With regard to EGFR mutation status, 55% were exon 19 deletions and 45% were exon 21 L858R mutations. The majority (60%) of patients received adjuvant chemotherapy prior to randomization (27% IB; 70% II, 79% IIIA). ADAURA demonstrated a statistically significant and clinically meaningful difference in DFS for patients treated with TAGRISSO compared to patients treated with placebo. Overall survival (OS) data were not mature at the time of the DFS analysis with 27% of the 94 deaths required for the final analysis of OS in patients with stage II-IIIA disease. Efficacy results from ADAURA are summarized in Table 5 and Figure1, respectively.~~

Table ~~5~~3. Efficacy Results from ADAURA~~in Stage II-IIIA Patients~~ by Investigator Assessment

	STAGE II-IIIA POPULATION		STAGE IB-IIIA POPULATION	
Efficacy Parameter	**TAGRISSO (N=233)**	**PLACEBO (N=237)**	**TAGRISSO (N=339)**	**PLACEBO (N=343)**
DFS events (%)	26 (11)	130 (55)	37 (11)	159 (46)
Recurrent disease (%)	26 (11)	129 (54)	37 (11)	157 (46)
Deaths (%)	0	1 (0.4)	0	2 (0.6)
Median DFS, months (95% CI)	NR (38.8, NE)	19.6 (16.6, 24.5)	NR (NE, NE)	27.5 (22.0, 35.0)
Hazard ratio (95% CI)[†‡§]	0.17 (0.12, 0.23)		0.20 (0.15, 0.27)	
p-value[‡,‖]	<0.0001		<0.0001	

	Stage II-IIIA population		Stage IB-IIIA population	
Efficacy Parameter	TAGRISSO (N=233)	Placebo (N=237)	TAGRISSO (N=339)	Placebo (N=343)
Disease-Free Survival				
Number of events (%)	26 (11)	130 (55)	37 (11)	159 (46)
Recurrent disease (%)	26 (11)	129 (54)	37 (11)	157 (46)
Deaths (%)	0	1 (0.4)	0	2 (0.6)
Median, months (95% CI)	NC (38.8, NC)	19.6 (16.6, 24.5)	NC (NC, NC)	27.5 (22.0, 35.0)
HR (99.06% CI); P-value	0.17 (0.11, 0.26); <0.0001[a]		0.20 (0.14, 0.30); <0.0001[b]	
DFS rate at 12 months (%) (95% CI)	97 (94, 99)	61 (54, 67)	97 (95, 99)	69 (63, 73)
DFS rate at 24 months (%) (95% CI)	90 (84, 93)	44 (37, 51)	89 (85, 92)	52 (46, 58)
DFS rate at 36 months (%) (95% CI)[c, d]	78 (65, 87)	28 (19, 38)	79 (69, 86)	40 (32, 48)

HR=Hazard Ratio; CI=Confidence Interval; NC=Not Calculable

DFS results based on investigator assessment

A HR< 1 favours TAGRISSO

Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO, 14.9 months for patients receiving placebo (stage II-IIIA population) and 16.6 months for patients receiving placebo (stage IB-IIIA population).

[a] Adjusted for an interim analysis (33% maturity) a p-value < 0.0094 was required to achieve statistical significance.

[b] Adjusted for an interim analysis (29% maturity) a p-value <0.0088 was required to achieve statistical significance.

[c] The number of patients at risk at 36 months was 18 patients in the osimertinib arm and 9 patients in the placebo arm (stage II-IIIA population).

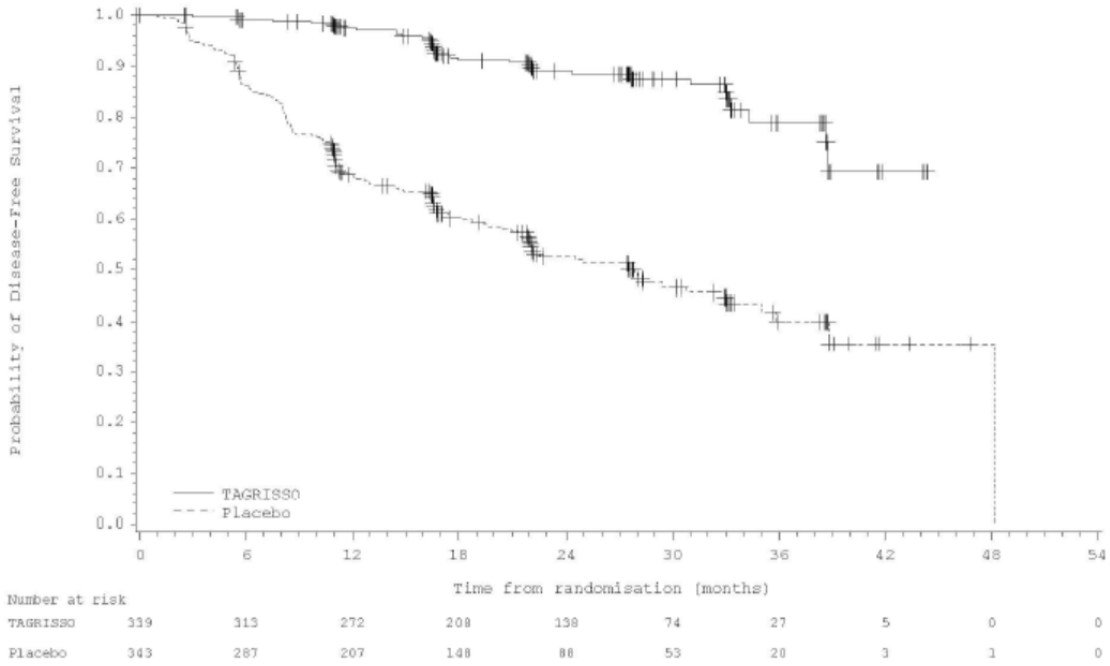
[d] The number of patients at risk at 36 months was 27 patients in the osimertinib arm and 20 patients in the placebo arm (stage IB-IIIA population).~~CI=Confidence Interval; NE=Not Estimable; NR=Not Reached~~

~~‡Stratified by race (Asian vs non-Asian), mutation status (Ex19del vs L858R), and pTNM staging~~

~~§Pike estimator~~

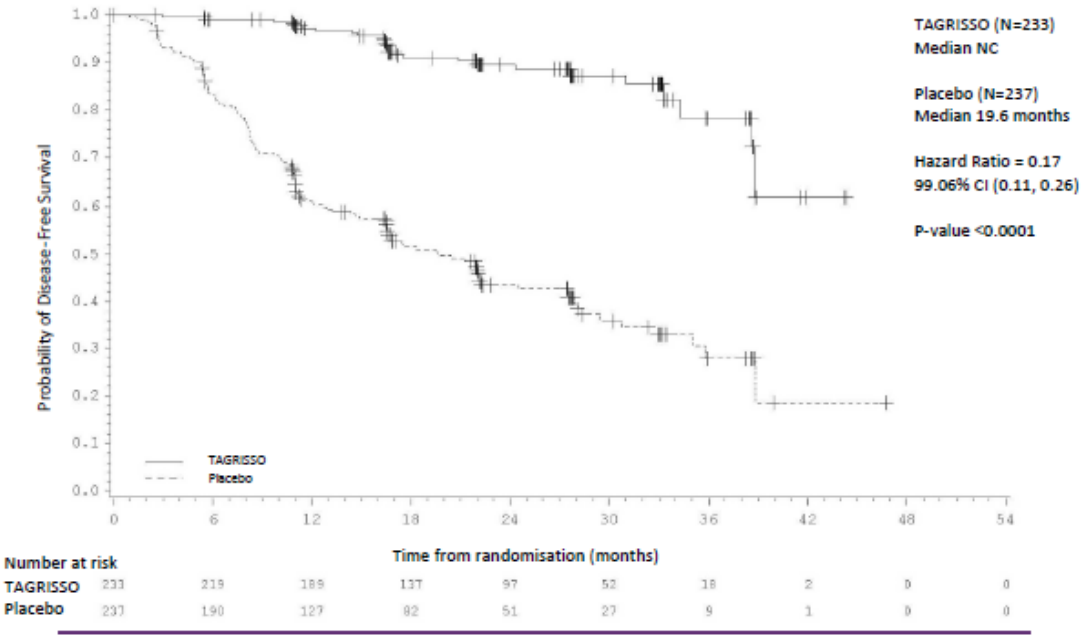
~~‖Stratified log-rank test~~

Figure 1. Kaplan-Meier curve of disease-free survival in stage II-IIIA patients ~~(overall population)~~ by Investigator Assessment ~~in ADAURA~~



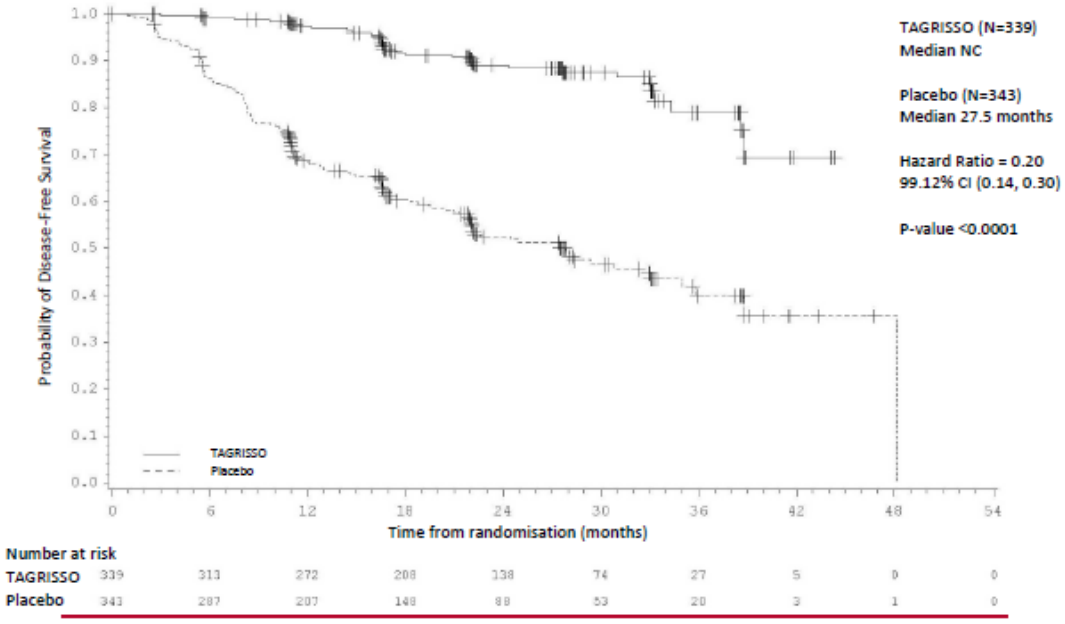
Number at risk										
TAGRISSO	339	313	272	209	138	74	27	5	0	0
Placebo	343	287	207	148	88	53	20	3	1	0

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



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

Figure 2. Kaplan-Meier curve of Disease-Free Survival in stage IB-IIIA (overall population) patients by investigator assessment



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

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).

An exploratory analysis of CNS DFS (time to CNS recurrence or death) for patients on TAGRISSO compared to patients on placebo showed a HR of 0.18 (95% CI: 0.10, 0.33; p <0.0001) for the overall population (stage IB-IIIA).

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, HRQL was maintained in both arms up to 30 months, with at least 70% of patients in the stage II-IIIA population not experiencing a clinically meaningful deterioration in the physical component of the SF-36 or death (70% vs 76% for TAGRISSO vs placebo), or in the mental component of the SF-36 or death (70% vs 71% for TAGRISSO vs placebo).~~In an exploratory analysis of site(s) of relapse, the proportion of patients with CNS involvement at the time of disease recurrence was 5 patients (1.5%) on the TAGRISSO arm and 34 patients (10%) on the placebo arm.~~

~~Effects of osimertinib on P-gp and BCRP~~

Based on *in vitro* studies~~,~~ osimertinib is a substrate of P-gp and BCRP~~,~~ but at clinical doses, clinically relevant interactions are ~~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 and P-gp. (See section 4.5).

Special populations

Renal impairment

In a clinical trial, 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, ~~A pharmacokinetic study in patients with renal impairment has not been conducted. Based~~ based on a population pharmacokinetic 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. ~~Severe renal impairment may influence the elimination of hepatically eliminated medicinal products.~~ Patients with CLcr less than or equal to ~~15~~10 mL/min were not included in the clinical trials

5.3 Preclinical safety data

~~Carcinogenesis and mutagenesis~~

Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays. Osimertinib showed no carcinogenic potential when administered orally to Tg rasH2 transgenic mice for 26 weeks~~Osimertinib showed no carcinogenic potential when administered orally to rasH2 transgenic mice for 26 Weeks. Osimertinib did not cause genetic damage in in vitro and in vivo assays~~.

העדכון העיקרי בעלון לצרכן הוא:

ספר לרופא מיד כאשר אתה משתמש בתרופה זו אם:

- יש לך פעימות לב מהירות או לא סדירות, סחרחורת, תחושת סחרור, חוסר נוחות בחזה, קוצר נשימה ועילפון.
- אם אתה מפתח עיניים דומעות, רגישות לאור, כאבי עיניים, עיניים אדומות או שינויים בראייה.

4. תופעות לוואי

תופעות לוואי המחייבות התייחסות מיוחדת:

- ~~נגעים דמויי מטרה, שהנם תגובות עוריות בצורת טבעת (סימנים המעידים על אדמנת רב צורתית - Erythema multiforme). תופעת לוואי זו אינה שכיחה (משפיעה על עד 1 מתוך 100 משתמשים~~).

תופעות לוואי אחרות:

תופעות לוואי שכיחות מאוד (משפיעות על יותר ממשתמש אחד מעשרה):

- דלקת של הריריות בחלל הפה או היווצרות כיבים בפה (סטומטיטיס).
- איבוד תיאבון.

תופעות לוואי שכיחות (משפיעות על עד ממשתמש אחד מעשרה):

- חרלת (אורטיקריה) – כתמים מגרדים, מורמים על פני העור, עשויים להיות ורודים או אדומים ועגולים בצורתם. יש ליידע את הרופא אם אתה מבחין בתופעת לוואי זו.

תופעות לוואי שאינן שכיחות (תופעות שמופיעות בעד 1 מתוך 100):

- נגעים בצורתם מטרה, שהינם תגובות עוריות המופיעות בצורת טבעת (עלול להעיד על אדמנת רב-צורתית Erythema multiforme)

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בכבוד רב,

אורה סטוליק
רוקחת ממונה
אסטרהזניקה (ישראל) בע"מ

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