מאי 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 **ינואר 2021.**

העדכון העיקרי בעלון לרופא הוא:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<u>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.</u>

4.2 Posology and method of administration

<u>Select patients with resectable tumors for the adjuvant treatment of NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimens.
Treat patients in the adjuvant setting until disease recurrence, or unacceptable toxicity, or for up to 3 years.
Treat patients with metastatic lung cancer until disease progression or unacceptable toxicity.</u>

Posology

The recommended dose is 80 mg osimertinib once a day until disease progression or unacceptable toxicity.

Select patients with resectable tumors for the adjuvant treatment of NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimens

Treat patients in the adjuvant setting until disease recurrence, or unacceptable toxicity, or for up to 3 years

Treat patients with metastatic lung cancer until disease progression or unacceptable toxicity.

4.4 Special warnings and precautions for use

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.

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.

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 3.29% (35/908) of 1233 patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment~~.

Across clinical trials, 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%.

4.8 Undesirable effects

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%).

Description of selected adverse reactions

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~~s~~ 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

ββNCI 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.
JIncludes 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.
βIncludes 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%).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical efficacy and safety

Adjuvant Treatment of Early-Stage EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

The efficacy 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 NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy. Eligible patients with resectable tumors (stage IB – IIIA according to American Joint Commission on Cancer [AJCC] 7th edition) were required to have 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. 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).

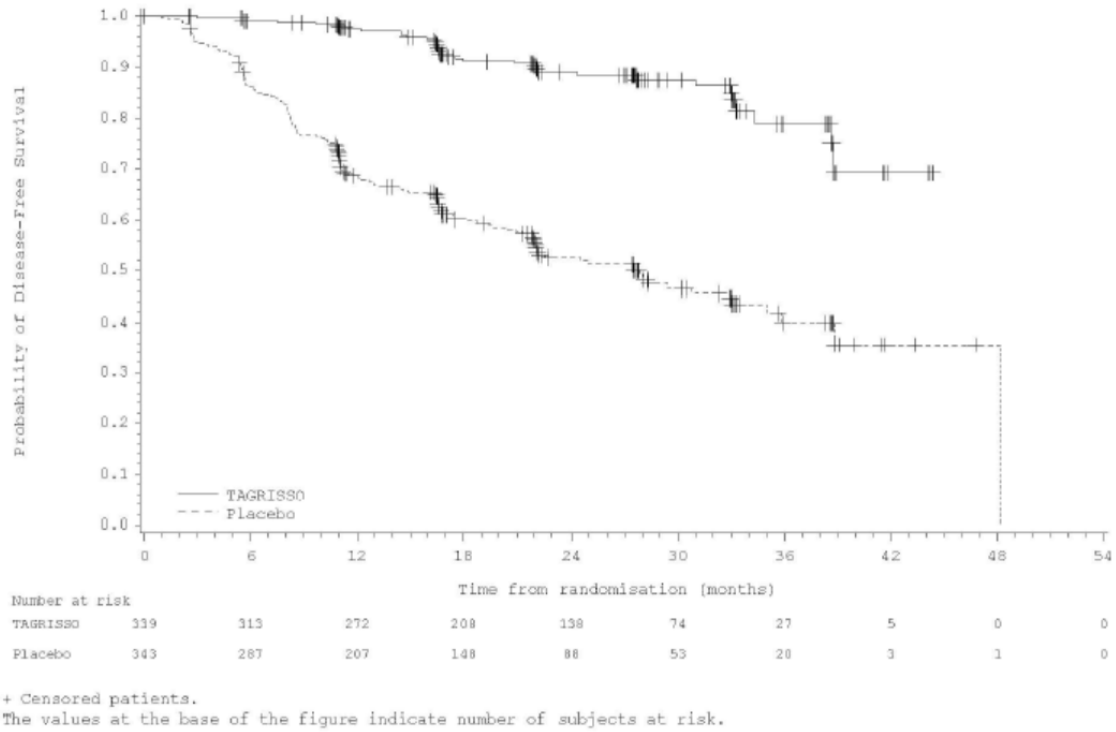
~~).~~ ADAURA demonstrated a statistically significant and clinically meaningful difference in DFS for patients treated with TAGRISSO compared to patients treated with placebo. Overall survival (OS) data were not mature at the time of the DFS analysis with 27% of the 94 deaths required for the final analysis of OS in patients with stage II-IIIA disease. Efficacy results from ADAURA are summarized in Table 5 and Figure1, respectively.

Table 5. Efficacy Results 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	

DFS results based on investigator assessment
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 (overall population) by Investigator Assessment in ADAURA



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.

5.3 Preclinical safety data

Carcinogenesis and mutagenesis

~~Carcinogenicity studies have not been performed with osimertinib.~~ 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:

1. מהי טאגריסו ולמה היא מיועדת?

טאגריסו מיועדת כטיפול משלים לאחר כריתת גידול במטופלים מבוגרים עם סרטן ריאה מסוג תאים שאינם קטנים (NSCLC), בו הגידול נושא מוטציה ב EGFR מסוג חוסר באקסון 19 (exon19 deletion) או מוטציית L858 באקסון

4. תופעות לוואי

תופעות לוואי המחייבות התייחסות מיוחדת:

יש לפנות מיידית לרופא אם אתה מבחין באחת מתופעות הלוואי החמורות הבאות:

- שינויים בפעילות החשמלית של הלב (הארכת מקטע QT) כגון פעימות לב מהירות או לא סדירות, סחרחורת, תחושת סחרור, חוסר נוחות בחזה, קוצר נשימה והתעלפות.

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

- עלייה בקריאטינין בדם (חומר המיוצר בגוף ומפונה על ידי הכליות).
- דימום מהאף
- דילול שיער
- תסמונת כף היד והרגל (Hand-foot syndrome) – תופעה זו עלולה לכלול אדמומיות, נפיחות או תחושת עקצוץ או בעירה עם סדקים של העור בכפות הידיים ו/או בכפות הרגליים. ניתן בדרך כלל לטפל בתופעות אלה על ידי קרמים ותחליבי לחות.

תוספות לעלון מסומנות בקו תחתון וטקסט שנמחק מסומן בקו חוצה.

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

אסטרהזניקה (ישראל) בע"מ, עתירי ידע 1, כפר סבא
טלפון 0732226099 פקס 09-7406527