מרץ 2018

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון: Zykadia 150mg, Hard gelatin capsules

זיקאדיה 150 מ"ג, כמוסות ג'לטין קשות

ברצוננו להודיעכם על הרחבת התוויה של התכשיר הנדון ועל עדכונים נוספים בעלונים לרופא לצרכן.

התכשיר רשום בישראל להתוויה הבאה:

ZYKADIA is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive.

המרכיב הפעיל: CERITINIB

עדכון ההתוויה ושינויים מהותיים בעלונים לרופא ולצרכן מפורטים בעמודים הבאים.

העלונים בגרסתם המלאה נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום.

בברכה,

ילנה גיטלין
רוקחת ממונה

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NOVARTIS

עדכונים בעלון לרופא:

(מידע שהתווסף מודגש בקו תחתון, מידע שנמחק – מסומן ~~בקו חוצה~~. החמרות מודגשות בצהוב)

פרק 1- INDICATIONS AND USAGE:

ZYKADIA is indicated for the treatment of patients with ~~anaplastic lymphoma kinase (ALK)-positive~~ metastatic non- small cell lung cancer (NSCLC) whose tumors ~~have progressed on or~~ are anaplastic lymphoma kinase (ALK)-positive .
~~intolerant to crizotinib~~.

~~This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established.~~
~~Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.~~

פרק 2- DOSAGE AND ADMINISTRATION:

2.1 Patient Selection

Select patients for treatment of metastatic NSCLC with ZYKADIA based on the presence of ALK positivity in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14.1)]*.

2.2 Dosing and Administration

The recommended dose of ZYKADIA is 750 mg orally once daily until disease progression or unacceptable toxicity. ~~Administer~~ Take ZYKADIA ~~on an empty stomach (i.e., do not administer within~~at least 1 hour before or at least ~~of~~ after a meal~~)~~ *[see Clinical Pharmacology (12.3)]*.

~~A recommended dose has not been determined for patients with moderate to severe hepatic impairment *[see Use in Specific Populations (8.6)].*~~

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2.3 Dose Modifications for Adverse Reactions

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~~Approximately 58% of patients initiating treatment at the recommended dose required at least one dose reduction and the median time to first dose reduction was 7 weeks.~~

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Table 1: ZYKADIA Dose Reduction Increments

Dose Reduction Schedule	Dose Level
Starting dose	750 mg taken orally once daily
First dose reduction	600 mg taken orally once daily
Second dose reduction	450 mg taken orally once daily
Third dose reduction	300 mg taken orally once daily

.....

פרק 5- WARNINGS AND PRECAUTIONS:

5.1 Severe or Persistent Gastrointestinal Toxicity

Severe gastrointestinal toxicity occurred in patients treated with ZYKADIA. Diarrhea, nausea, vomiting, or abdominal pain occurred in ~~96~~95% of ~~255~~ 925 patients including severe cases (Grade 3 or 4) in 14% of patients treated with ZYKADIA ~~in Study 1~~ across clinical studies. Dose ~~modification~~ interruptions or reductions due to diarrhea, nausea, vomiting, or abdominal pain occurred in ~~38~~36% of patients and led to treatment discontinuation in 1.6% of patients.

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5.2 Hepatotoxicity

Drug-induced hepatotoxicity occurred in patients treated with ZYKADIA. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in ~~27% of 255 patients in Study 1. One patient (0.4%) required permanent discontinuation due to elevated transaminases, and jaundice~~ 28% and elevations in aspartate aminotransferase (AST) greater than 5 times ULN occurred in 16% of 925 patients across clinical studies. Concurrent elevations in ALT greater than 3 times the ULN and total bilirubin greater than 2 times the ULN, with ~~normal~~ alkaline phosphatase less than 2 times the ULN~~,~~ occurred in ~~less than 1~~0.3% of patients ~~in~~ across clinical studies. Approximately 1.0% of patients required permanent discontinuation due to hepatotoxicity.

....

5.3 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal ILD/pneumonitis ~~can~~ occurred in patients treated with ZYKADIA. ~~In Study 1~~Across clinical studies, ILD/~~,~~ pneumonitis was reported in 2.4% of ~~255~~ 925 patients treated with ZYKADIA across clinical studies. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 or 4 ILD/pneumonitis was reported in 1.3% of patients, ~~and~~ with fatal ~~ILD/pneumonitis~~events ~~was~~ reported in ~~1 patient (0.4%) in Study 1~~0.2% of patients. Ten patients (1.1%) ~~One percent (1%) of patients~~ discontinued ZYKADIA across clinical studies~~in Study 1~~ due to ILD/pneumonitis.

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5.4 QT Interval Prolongation

QTc interval prolongation, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade torsade de pointes) or sudden death, occurred in patients treated with ZYKADIA. in Across clinical studies, trials. Three percent (3%) 6% of 255 919 patients with at least one post-baseline ECG assessment experienced a QTc interval increase over baseline of greater than 60 msec in Study 1. Approximately Across the development program of ZYKADIA, one 1.3% of 304 patients (less than 1%) taking ZYKADIAtreated with ZYKADIA doses ranging from 50 to 750 mg was were found to have a QTc greater than 500 msec. and 3% of patients had an increase from baseline QTc greater than 60 msec. A pharmacokinetic/pharmacodynamic analysis suggested that ZYKADIA causes concentration-dependent increases in the QTc interval. Across clinical studies, 0.2% of patients discontinued ceritinib due to QTc prolongation.

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5.5 Hyperglycemia

Hyperglycemia can occur occurred in patients receiving ZYKADIA. In Study 1Across clinical studies, CTCAE Grade 3– or 4 hyperglycemia, based on laboratory values, occurred in 13% of 255 925 patients. There was a 6-fold increase in the risk of CTCAE Grade 3–4 hyperglycemia in patients with diabetes or glucose intolerance and a 2-fold increase in patients taking corticosteroids.

....

5.6 Bradycardia

Bradycardia can occur occurred in patients receiving ZYKADIA. Across clinical studiesIn Study 1, sinus bradycardia, defined as a heart rate of less than 50 beats per minute, was noted as a new finding in 1% of 255 925 patients. Bradycardia was reported as an adverse drug reaction in 31% of patients in Study 1. No patient required discontinuation and 0.1% required interruption with subsequent dose reduction for bradycardia.

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5.7 Pancreatitis

Pancreatitis occurred in patients receiving ZYKADIA. Pancreatitis, including one fatality, has been reportedoccurred in less than 1% of patients receiving ZYKADIA in clinical trialsstudies. CTCAE Grade 3 or 4 elevations of lipase and/or elevations of amylase occurred in 157% of patients receiving ZYKADIA across clinical studies, while CTCAE Grade 3 or 4 elevations of lipase occurred in 14% of patients.in Study 1.

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5.8 Embryofetal Toxicity

Based on its mechanism of action and findings in animal studies, ZYKADIA may can cause fetal harm when administered to a pregnant woman. In animal studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose of 750 mg daily caused increases in skeletal anomalies in rats and rabbits. Apprise Advise pregnant women of of reproductive potential of the potential hazard risk to a fetus *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for at least 26 months weeks following completion of therapy. Based on the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ZYKADIA and for 3 months following completion of therapy *[see Use in Specific Populations (8.71, 8.3) and Nonclinical Toxicology (13.1)]*.

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פרק 6- ADVERSE REACTIONS:

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6.1 Clinical Trials Experience

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The data in the Warnings and Precautions section reflect exposure to ZYKADIA 750 mg once daily in 925 patients with ALK-positive NSCLC across seven clinical studies, including ASCEND-4 and ASCEND-1, described below, a randomized active-controlled study, two single arm studies, and two dose-escalation studies. The majority of patients enrolled in these studies had received prior treatment with chemotherapy and/or crizotinib for NSCLC. Among these 925 patients the most common adverse reactions (greater than or equal to 25% incidence) were diarrhea, nausea, fatigue, vomiting, abdominal pain, decreased appetite, and weight loss. Approximately 62% of patients initiating treatment at the recommended dose required at least one dose reduction and the median time to first dose reduction was 7 weeks.

Previously Untreated ALK-Positive Metastatic NSCLC

The safety evaluation of ZYKADIA is based on ASCEND-4, an open-label, randomized, active-controlled multicenter study of 376 previously untreated ALK-positive NSCLC patients. Patients received ZYKADIA 750 mg daily (N=189) or chemotherapy plus maintenance chemotherapy (N=187). Chemotherapy regimens were pemetrexed (500 mg/m^2) plus investigator's choice of cisplatin (75 mg/m^2) or carboplatin (AUC of 5 - 6 mg*min/mL) administered every 21 days. Patients who completed 4 cycles of chemotherapy without progressive disease received pemetrexed (500 mg/m^2) as single-agent maintenance therapy every 21 days.

The demographic characteristics of the study population were 57% female, median age 54 years (range: 22 to 81 years); 22% of patients were 65 years older, 54% White, 42% Asian, 2% Black, and 2% other races. Patients were enrolled in Europe (53%), Asia Pacific (42%), and South America (5%) regions. The majority of patients had adenocarcinoma (97%), never smoked (61%) and 32% had brain metastasis at screening. The median duration of exposure to ZYKADIA was 18 months.

Serious adverse reactions were reported in 72 patients (38%) treated with ZYKADIA. The most frequent serious adverse reactions were pneumonia (4%), pleural effusion (4%), vomiting (4%), nausea (3%), dyspnea (3%), hyperglycemia (3%), AST increased (2%), lung infection (2%), and pericardial effusion (2%). Among patients treated with ZYKADIA, dose interruptions due to adverse reactions occurred in 77%, dose reductions were required in 66%, and adverse reactions that led to discontinuation of therapy occurred in 12% of patients. The most frequent adverse reactions, reported in at least 10% of patients treated with ZYKADIA, that led to dose interruptions or reductions were: ALT increased (48%), AST increased (34%), vomiting (15%), blood creatinine increased (14%), GGT increased (13%), diarrhea (13%), and nausea (13%). The most frequent adverse reactions that led to discontinuation of ZYKADIA in 1% or more of patients in ASCEND-4 were blood creatinine increased (2.1%), amylase increased (1.1%), and lipase increased (1.1%). The following fatal adverse reactions occurred in 4 patients treated with ZYKADIA: myocardial infarction, respiratory tract infection, pneumonitis, and unknown cause.

Tables 3 and 4 summarize adverse reactions and laboratory abnormalities, respectively, in ASCEND-4.

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Table 3: Adverse Reactions (>10% for All NCI CTCAE* Grades or ≥2% for Grades 3-4) of Patients in ASCEND-4

	ZYKADIA N=189		Chemotherapy N=175[a]	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Gastrointestinal				
Diarrhea	85	4.8	11	1.1
Nausea	69	2.6	55	5
Vomiting	67	5	36	6
Abdominal pain[b]	40	3.7	13	0
Constipation	20	0	22	0
Esophageal disorder[c]	15	0.5	8	0.6
General				
Fatigue[d]	45	7	49	6
Non-cardiac chest pain	21	1.1	10	0.6
Back pain	19	1.6	18	2.3
Pain in extremity	13	0	7	0
Musculoskeletal pain	11	0.5	6	0.6

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	ZYKADIA N=189		Chemotherapy N=175[a]	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Pruritus	11	0.5	5	0
Pyrexia	19	0	14	1.1
Metabolism And Nutrition				
Decreased appetite	34	1.1	32	1.1
Weight loss	24	3.7	15	0.6
Respiratory				
Cough	25	0	17	0
Neurologic				
Headache	19	0.5	13	1.1
Dizziness	12	1.1	10	0.6
Skin				
Rash[e]	21	1.1	8	0.6
Cardiac				
Prolonged QT Interval	12	2.6	1.1	0.6
Pericarditis[f]	4.2	1.6	2.3	1.1

*National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)
[a] Twelve patients randomized to chemotherapy did not receive study drug.
[b] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)
[c] Esophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia)
[d] Fatigue (fatigue and asthenia)
[e] Rash (rash, dermatitis acneiform, rash maculo-papular)
[f] Pericarditis (pericardial effusion and pericarditis)

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ZYKADIA included: vision disorder (4%; comprised of vision impairment, blurred vision, photopsia, accommodation disorder, presbyopia, reduced visual acuity, or vitreous floaters), bradycardia (4%), ILD/pneumonitis (2%), hepatotoxicity (2%) and renal failure (2%).

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Table 4: Laboratory Abnormalities Occurring in >10% (All NCI CTCAE Grades) of Patients in ASCEND-4

	ZYKADIA N=189		Chemotherapy N=175[a]	
	All Grades	Grade 3–4	All Grades	Grade 3–4
	%	%	%	%
Hematology				
Anemia	67	4.2	84	11
Neutropenia	27	2.1	58	20
Thrombocytopenia	16	1.0	38	4.6
Chemistry				
Increased alanine transaminase (ALT)	91	34	65	3.4
Increased aspartate transaminase (AST)	86	21	58	2.3
Increased gamma-glutamyl transpeptidase (GGT)	84	49	67	10
Increased alkaline phosphatase	81	12	47	1.7
Increased creatinine	77	4.2	37	0.6
Hyperglycemia	53	10	67	10
Increased amylase	37	8	43	4.5
Decreased phosphate	38	3.7	27	4.0
Increased bilirubin (total)	15	0.5	6	0.6
Increased lipase[b]	13	6	7	0.6

[a] Twelve patients randomized to chemotherapy did not receive study drug.

[b] In the ZYKADIA arm, no patients had baseline lipase laboratory assessments, 112 had post-baseline assessments. In the chemotherapy arm, one patient had baseline lipase laboratory assessments but no post-baseline assessment; 49 patients had post-baseline assessments.

פרק 8- USE IN SPECIFIC POPULATIONS:

8.1 Pregnancy

~~**Category D**~~

Risk Summary

Based on animal studies and its mechanism of action, ZYKADIA ~~may~~ can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. The limited available data on the use of ZYKADIA in pregnant women are insufficient to inform a risk. Administration ~~. In animal studies, administration~~ of ceritinib to rats and rabbits during the period of organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits~~. If this drug is used during pregnancy~~ *[see Data]*. Advise ~~, or if the patient becomes~~ a pregnant woman ~~while taking this drug, apprise the patient~~ of the

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potential ~~hazard~~ risk to a fetus.

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8.2 Lactation

Risk Summary

There are no data regarding the presence of ~~It is not known whether~~ ceritinib or its metabolites ~~are present~~ in human milk, the effects of ceritinib on the breastfed infant, or its effects on milk production. ~~.~~ Because ~~many drugs are present in human milk and because~~ of the potential for serious adverse reactions including gastrointestinal toxicity, hepatotoxicity, pneumonitis, bradycardia and pancreatitis, ~~in nursing infants from ceritinib~~, advise a woman not to breastfeed during treatment with ZYKADIA and for 2 weeks following completion of therapy.

~~mothers to discontinue nursing.~~

8.3 Females and Males of Reproductive Potential

Contraception

Females

ZYKADIA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for 6 months following completion of therapy.

Males

Based on the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ZYKADIA and for 3 months following completion of therapy *[see Nonclinical Toxicology (13.1)]*.

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8.5 Geriatric Use

~~Clinical~~ Of the 925 patients in clinical studies of ZYKADIA, 18% were 65 years or older, while 5% were 75 years or older. No overall differences in safety or effectiveness were observed between these ~~did not include sufficient numbers of~~ subjects ~~aged 65 years and older to determine whether they respond differently from~~ and younger subjects. ~~Of the 255 patients in Study 1 who received ZYKADIA at the recommended dose, 40 (16%) were 65 years or older~~.

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:CLINICAL PHARMACOLOGY -12 פרק

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12.2 Pharmacodynamics

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in ~~an open-label, dose-escalation, and expansion study. A total of 304~~ 925 -patients ~~were~~ treated with

ZYKADIA ~~doses ranging from 50 to~~ 750 mg ~~with 255~~once daily. Twelve of 925 patients ~~treated with ZYKADIA 750 mg. One of 304 patients (less than~~ (1.3%) ~~was~~ were found to have a QTc greater than 500 msec and ~~10~~ 58 patients (~~3~~6%) had an increase from baseline QTc greater than 60 msec. ~~A~~ In ASCEND-4, a central tendency analysis of the QTc data at average steady-state concentrations demonstrated that the upper bound of the 2-sided 90% CI for QTc was ~~16~~ 15.3 msec at ZYKADIA 750 mg once daily. A pharmacokinetic / pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation *[see Warnings and Precautions (5.4)]*.

Based on central review of ECG data, ~~2~~ 10 of ~~304~~ 925 patients (~~0.7~~1.1%) had bradycardia defined as less than 50 beats per minute. ~~Bradycardia was reported as an adverse drug reaction in 3% of patients in Study 1.~~

12.3 Pharmacokinetics

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Specific Populations

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Hepatic Impairment: As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in patients with hepatic impairment has not been conducted. Ceritinib exposures were similar between patients with mild hepatic impairment and patients with normal hepatic function based ~~Based~~ on a population pharmacokinetic analysis of ~~48~~ 140 patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST) and ~~254~~ 832 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN)~~, ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function~~. The pharmacokinetics of ceritinib has not been studied in patients with moderate to severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

Renal Impairment: A pharmacokinetic trial in patients with renal impairment has not been conducted as ceritinib elimination via the kidney is low (1.3% of a single oral administered dose). Ceritinib exposures were similar between patients with mild to moderate renal impairment and patients with normal renal function based~~Based~~ on a population pharmacokinetic analysis of ~~97~~ 345 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), ~~22~~ 82 patients with moderate renal impairment (CLcr 30 to less than 60 mL/min) and ~~183~~ 546 patients with normal renal function (greater than or equal to 90 mL/min)~~), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function, suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment~~. Patients with severe renal impairment (CLcr less than 30 mL/min) were not included in the clinical trial.

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פרק 14- CLINICAL STUDIES:

14.1 Previously Untreated ALK-Positive Metastatic NSCLC

The efficacy of ZYKADIA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ASCEND-4, NCT01828099). Patients were required to have WHO performance status 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx Assay. Neurologically stable patients with central nervous system (CNS) metastases that did not require increasing doses of steroids to manage CNS symptoms were permitted to enroll. Patients with uncontrolled diabetes mellitus; a history of interstitial lung disease or interstitial pneumonitis; or a history of pancreatitis or increased amylase or lipase that was due to pancreatic disease were not eligible.

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The major efficacy outcome measure was progression-free survival (PFS) as determined by blinded independent review committee (BIRC) according to RECIST v1.1. Additional efficacy outcome measures were overall survival (OS), overall response rate (ORR) and duration of response (DOR) determined by BIRC, overall intracranial response rate (OIRR), duration of intracranial response (DOIR) determined by BIRC neuro-radiologist, and patient reported outcomes.

Patients were randomized 1:1 to receive ZYKADIA 750 mg orally daily or chemotherapy plus maintenance chemotherapy. Randomization was stratified by World Health Organization (WHO) performance status, prior adjuvant/neoadjuvant chemotherapy and presence or absence of brain metastasis. Patients randomized to chemotherapy received pemetrexed (500 mg/m^2) and investigator's choice of cisplatin (75 mg/m^2) or carboplatin (AUC of 5 - 6 mg*min/mL) administered on day 1 of each 21-day cycle for a maximum of 4 cycles followed by pemetrexed (500 mg/m^2) every 21 days. Treatment in both arms was continued until disease progression or unacceptable toxicity.

A total of 376 patients were randomized, ZYKADIA (n=189) or chemotherapy (n=187). The demographic characteristics of the study population were 57% female, median age 54 years (range: 22 to 81 years); 22% of patients were 65 years older; and 54% White, 42% Asian, 2% Black, and 2% other races. The majority of patients had adenocarcinoma (97%) and never smoked (61%). CNS metastases were present in 32% (n=121) of patients. Approximately half (n=55) had measurable CNS metastases as determined by BIRC neuro-radiologist and 71% (n=39) of these patients received no prior intracranial radiotherapy. Of those randomized to chemotherapy, 43% received ZYKADIA as the next antineoplastic therapy after platinum-based chemotherapy.

Efficacy results from ASCEND-4 are summarized in Table 7 and Figure 1.

Table 7: Efficacy Results by BIRC Assessment in ASCEND-4

	ZYKADIA (N=189)	**Chemotherapy (N=187)**
Progression-Free Survival		
Number of events (%)	89 (47%)	113 (60%)
Progressive disease (%)	79 (42%)	105 (56%)
Death (%)	10 (5%)	8 (4%)
Median PFS in months (95% CI)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)
Hazard ratio (95% CI)[a]	0.55 (0.42, 0.73)	
P-value[b]	<0.0001	
Overall Response Rate		
Overall response rate, % (95% CI)[c]	73 (66, 79)	27 (21, 34)
Complete response, %	1	0
Partial response, %	72	27
Duration of response		
Number of responders	n=137	n=50
Median in months (95% CI)	23.9 (16.6, NE)	11.1 (7.8, 16.4)

BIRC: Blinded Independent Review Committee; **CI:** Confidence Interval; **NE:** Not Estimable

[a] Cox proportional hazards model stratified by brain metastases (absence vs. presence), WHO performance status (0 vs. ≥ 1), and prior adjuvant chemotherapy (absence vs. presence).

[b] Log-rank test stratified by brain metastases (absence vs. presence), WHO performance status (0 vs. ≥ 1), and prior adjuvant chemotherapy (absence vs. presence).

[c] Clopper and Pearson exact binomial 95% confidence interval.

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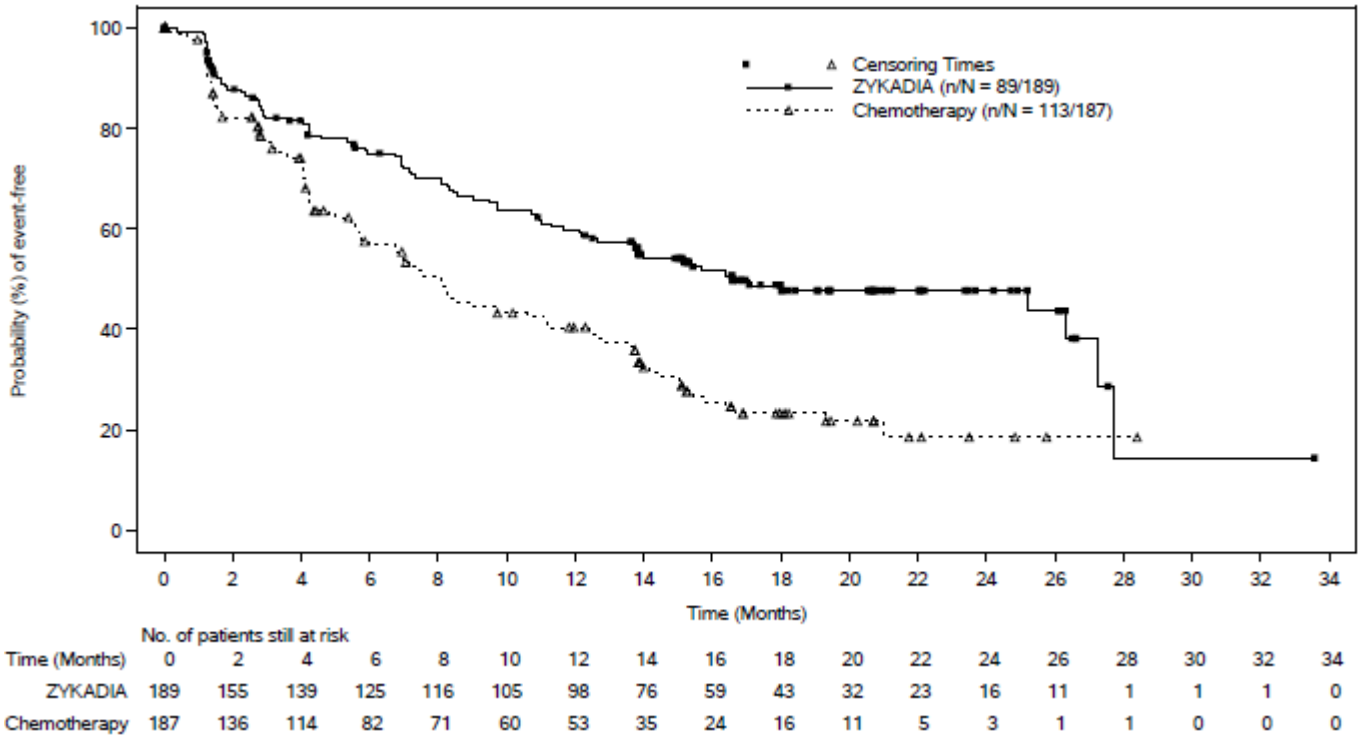
There was no significant difference in OS in a pre-specified interim analysis conducted at 42% of the events required for the final analysis.

Figure 1: Kaplan-Meier Plot of Progression-Free Survival as Assessed by BIRC by Treatment Arm in ASCEND-4



Antitumor activity of ZYKADIA in the brain was assessed in patients with measurable disease as determined by the BIRC neuro-radiologist at baseline (N=55) according to RECIST 1.1.

Table 8: BIRC Assessed CNS Responses in Patients with Measurable CNS Lesions in ASCEND-4

	ZYKADIA	**Chemotherapy**
Intracranial Tumor Response Assessment	N=28	N=27
Overall intracranial response rate, % (95% CI)[a]	57% (37, 76)	22% (9, 42)
Complete response, %	7%	7%
Partial response, %	50%	15%
Duration of Intracranial Response		
Number of responders	n=16	n=6
Median in months (95% CI)	16.6 (8.1, NE)	NE (1.5, NE)
[a]Clopper and Pearson exact binomial 95% confidence interval **BIRC:** Blinded Independent Review Committee; **CI:** Confidence Interval; **NE:** Not Estimable		

Exploratory analyses of patient-reported outcome measures suggested a delay in time to development of or worsening of shortness of breath in patients treated with ZYKADIA as compared to chemotherapy. The patient-reported delay in onset or worsening of shortness of breath may be an overestimation, because patients were not blinded to treatment assignment.

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פרק 17- PATIENT COUNSELING INFORMATION:

Advise the patient to read the patient leaflet (Patient Information).

- Inform patients that diarrhea, nausea, vomiting, and abdominal pain are the most commonly reported adverse reactions in patients treated with ZYKADIA. Inform patients of supportive care options such as anti-emetic and anti- diarrheal medications. Advise patients to contact their healthcare provider for severe or persistent gastrointestinal symptoms. Inform patients that if vomiting occurs during the course of treatment, they should not take an additional dose, but should continue with the next scheduled dose of ZYKADIA *[see Warnings and Precautions (5.1)]*.
- Inform patients of the signs and symptoms of hepatotoxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.2)]*.
- Inform patients of the risks of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.3)]*.
- Inform patients of the risks of QTc interval prolongation and bradycardia. Advise patients to contact their healthcare provider immediately to report new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, and changes in or new use of heart or blood pressure medications *[see Warnings and Precautions (5.4, 5.6)]*.
- Inform patients of the signs and symptoms of hyperglycemia. Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperglycemia *[see Warnings and Precautions (5.5)]*.
- Inform patients of the signs and symptoms of pancreatitis and the need to monitor lipase and amylase levels prior to the start of treatment and periodically thereafter as clinically indicated *[see Warnings and Precautions (5.7)]*.
- Advise females to inform their healthcare provider if they are pregnant. Inform females of reproductive potential of the risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for at least 2 weeks following completion of therapy *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.7)]*.
- Advise females not to breastfeed during treatment with ZYKADIA *[see Use in Specific Populations (8.32)]*.
- Inform patients not to consume grapefruit and grapefruit juice during treatment with ZYKADIA *[see Drug Interactions (7.1)]*.
- Take ZYKADIA on an empty stomach (i.e., do not take within 2 hours of a meal) *[see Dosage and Administration (2.1)]*.

Advise patients to make up a missed dose of ZYKADIA unless the next dose is due within 12 hours *[see Dosage and Administration (2.1)]*.

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עדכונים בעלון לצרכן:

(מידע שהתווסף מודגש בקו תחתון, מידע שנמחק – מסומן ~~בקו חוצה~~, החמרות מודגשות בצהוב)

פרק 1- למה מיועדת התרופה?

זיקאדיה הינה תרופת מרשם המשמשת לטיפול באנשים עם סרטן ריאות מסוג non-small cell lung cancer (NSCLC) שנגרם על ידי פגם בגן הנקרא Anaplastic Lymphoma Kinase (ALK), ושהתפשט לאיברים אחרים בגוף, ~~ואשר נטלו את התרופה crizotinib, אך ה- NSCLC שלהם החמיר או שלא יכלו לסבול את הטיפול ב-crizotinib.~~

פרק 2- לפני שימוש בתרופה:

....

! לפני שאתה לוקח את זיקאדיה, יידע את הרופא המטפל שלך על כל הבעיות הרפואיות שלך, כולל אם

....

-יש לך בעיות בריאות או בעיות נשימה

....

-את בהריון או מתכננת להיכנס להריון. זיקאדיה עלולה להזיק לעובר שלך. נשים העשויות להיכנס להריון צריכות להשתמש בשיטה יעילה למניעת הריון במהלך הטיפול בזיקאדיה ~~ולפחות שבועיים~~ ולמשך 6 חודשים לאחר הפסקת הטיפול בזיקאדיה. שוחחי עם הרופא המטפל לגבי אמצעי מניעה שעשויים להיות מתאימים לך. ספרי לרופא מיד אם נכנסת להריון או את חושבת שאת עשויה להיות בהריון.

- גברים עם בנות זוג שעשויות להיכנס להריון צריכים להשתמש בקונדומים במהלך הטיפול בזיקאדיה ולמשך 3 חודשים לאחר סיום הטיפול בזיקאדיה

-את מניקה או מתכננת להניק. לא ידוע אם זיקאדיה עוברת לחלב האם שלך. ~~אל תניקי אם את לוקחת~~ אין להניק במהלך הטיפול בזיקאדיה ולמשך שבועיים לאחר סיום הטיפול בזיקאדיה.

! שימוש בתרופה ומזון -

-יש ליטול זיקאדיה ~~על קיבה ריקה, אין לאכול במשך שעתיים~~ לפחות שעה לפני ~~ולא במשך שעתיים~~ או לפחות שעתיים לאחר ~~נטילת זיקאדיה~~הארוחה.

! הריון והנקה

זיקאדיה עלולה להזיק לעובר שלך. נשים ~~המסוגלות~~ העשויות להיכנס להריון צריכות להשתמש בשיטה יעילה למניעת הריון במהלך טיפול בזיקאדיה ו~~לפחות שבועיים~~ 6 חודשים לאחר הפסקת הטיפול בזיקאדיה. שוחחי עם הרופא המטפל לגבי אמצעי מניעה שעשויים להיות מתאימים לך.ספרי לרופא מיד אם נכנסת להריון או את חושבת שאת עשויה להיות בהריון.

גברים לבנות זוג שעשויות להיכנס להריון צריכים להשתמש בקונדומים במהלך הטיפול בזיקאדיה ובמשך 3 חודשים לאחר סיום הטיפול בזיקאדיה

לא ידוע אם זיקאדיה עוברת לחלב אם. אין להניק במהלך הטיפול בזיקאדיה ובמשך שבועיים לאחר סיום הטיפול בזיקאדיה.

~~אל תניקי אם את לוקחת זיקאדיה~~

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פרק 3 – כיצד תשתמש בתרופה ?:

.....
יש לקחת את זיקאדיה ~~על קיבה ריקה. אין לאכול במשך שעתיים~~ לפחות שעה לפני ~~נטילת זיקאידה ושעתיים~~ או לפחות שעתיים אחרי ~~נטילת זיקאדיה~~ הארוחה..
.....

פרק 4- תופעות לוואי:

המידע הבא הועבר מראשית העלון לסעיף "תופעות לוואי":

זיקאדיה עלולה לגרום לתופעות לוואי חמורות, שכוללות:
בעיות קיבה ומעיים (מערכת העיכול) זיקאדיה גורמת לבעיות קיבה ומעיים אצל רוב האנשים, כולל שלשול, בחילות, הקאות וכאב באיזור הבטן. בעיות אלה לעתים עלולות להיות חמורות. עליך למלא אחר הוראות הרופא המטפל לגבי נטילת תרופות שיעזרו לתסמינים אלה. פנה לרופא לצורך יעוץ אם יש לך תסמינים חמורים או כאלה שלא חולפים.

בעיות כבד זיקאדיה עלולה לגרום לפגיעה בכבד. הרופא המטפל צריך לערוך לך בדיקות דם לפחות פעם בחודש על מנת לבדוק את הכבד שלך במהלך הטיפול בזיקאדיה. **יש ליידע את הרופא מיד** אם:

- אתה מרגיש עייף
- עורך או הלבן בעיניים מצהיבים
- יש לך ירידה בתאבון
- השתן שלך הופך לכהה או חום (בצבע של תה)
- יש לך גרד בעור
- יש לך בחילות או הקאות
- יש לך כאבים בצד ימין באיזור של הבטן
- אתה מדמם או נפצע בקלות רבה יותר מהרגיל

בעיות בריאות (דלקת ריאות - פנאומוניטיס) זיקאדיה עלולה לגרום לדלקת חמורה או מסכנת חיים של הריאות במהלך הטיפול שעלולה להוביל למוות. התסמינים יכולים להיות דומים לתסמינים של מחלת סרטן הריאות. **יידע את הרופא המטפל שלך מיד** אם יש לך תסמינים חדשים או אם תסמינים כלשהם מחמירים, כולל:

- קשיי נשימה או קוצר נשימה
- חום
- שיעול עם או ללא ליחה
- כאב בחזה

בעיות לב זיקאדיה עלולה לגרום לפעימות לב מאוד איטיות, מאוד מהירות או לא תקינות. הרופא המטפל שלך עשוי לבדוק את הלב שלך במהלך הטיפול בזיקאדיה. יידע את הרופא מיד אם אתה מרגיש כאב חדש בחזה או אי נוחות, סחרחורת או תחושת סחרור, אם אתה על סף עילפון או יש לך פעימות לב לא תקינות. יידע את הרופא שלך אם אתה מתחיל ליטול או שינו לך תרופות ללב או ללחץ דם.

....

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- ~~**תוצאות בדיקות מעבדה שאינן תקינות.** יתכן ויהיו לך תוצאות לא תקינות בבדיקות מעבדה, כולל עליה ברמות ליפאז ו/או עמילאז (אנזימי לבלב). הרופא המטפל שלך צריך לערוך בדיקות דם כדי לבדוק את רמות הליפאז והעמילאז שלך לפני שאתה מתחיל את הטיפול בזיקאדיה ובהתאם לצורך במהלך הטיפול שלך.~~

תופעות ~~ה~~לוואי נוספות ~~השכיחות ביותר~~ של זיקאדיה הינן:

- ~~בעיות קיבה ומעיים (מערכת עיכול). ראה **"מידע חיוני שיש לדעת על זיקאדיה"**.~~
- ~~אי נוחות בבטן לאחר ארוחה, קשיי עיכול, צרבת, קושי בבליעה.~~
- ~~עייפות, ירידה בתאבון ועצירות.~~

תופעות לוואי שכיחות מאוד (עלולות להופיע ביותר מ-1 מתוך 10 משתמשים):
עצירות, צרבת (סימן לבעיה אפשרית בוושט), עייפות, כאב בחזה שאינו ממקור לבבי, כאב גב, כאב בגפיים, כאב בשרירים ו/או עצמות, גרד, חום, ירידה תאבון, ירידה במשקל, שיעול, כאב ראש, סחרחורת, פריחה, אנמיה (ירידה במספר תאי דם אדומים), נויטרופניה (ירידה במספר תאי דם לבנים), טרומבוציטופניה (ירידה במספר טסיות הדם), תוצאות לא תקינות של תפקודי כבד בבדיקות הדם (עליה ברמות האנזימים מסוג אלנין אמינוטרנספראז (ALT) ו/או אספרטאט אמינוטרנספראז (AST) ו/או גמא גלוטאמילטרנספראז(GGT) ו/או באלקלין פוספטאז, רמות גבוהות של בילירובין), תוצאות לא תקינות של תפקודי כליות בבדיקות הדם (רמה גבוהה של קריאטינין), רמה נמוכה של פוספאט בדם, רמות גבוהות של עמילאז וליפאז בדם (אנזימי לבלב)

תופעות לוואי שכיחות (עלולות להופיע ב-1-10 משתמשים מתוך 100):
הפרעות בראיה, ירידה משמעותית בזרם השתן (סימן לבעיה בכליות), התייבשות, פרכוסים.

....

העלונים לרופא ולצרכן כוללים שינויי עריכה / שינויים נוספים שאינם החמרות.

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