

3



5

6

7

80

10

11

12

14

15

17

18

19

20

21

22

23 **Table 2. ALECENSA Dose Modifications for Adverse Reactions**

Criteria ^a	ALECENSA Dose Modification
ALT or AST elevation of greater than 5 times upper limit of normal (ULN) <u>with</u> total bilirubin less than or equal to 2 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 3 times ULN, then resume at reduced dose as per Table 1.
ALT or AST elevation greater than 3 times ULN <u>with</u> total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	Permanently discontinue ALECENSA.
Total bilirubin elevation of greater than 3 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 1.5 times ULN, then resume at reduced dose as per Table 1.
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue ALECENSA.
Symptomatic bradycardia	Withhold ALECENSA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume ALECENSA at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume ALECENSA at reduced dose (see Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia ^b (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ALECENSA if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume ALECENSA at reduced dose (see Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently discontinue ALECENSA in case of recurrence.
CPK elevation greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.
CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose as per Table 1.

24 ^a ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal; ILD = interstitial lung
25 disease; CPK = blood creatine phosphokinase

26 ^b Heart rate less than 60 beats per minute (bpm)

27

28 **3 DOSAGE FORMS AND STRENGTHS**

29 150 mg hard capsules, white, with “ALE” printed in black ink on the cap and “150 mg” printed in black ink on
30 the body.

31

32

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Elevations of AST greater than 5 times the upper limit of normal (ULN) occurred in 3.6% of patients, and elevations of ALT greater than 5 times the ULN occurred in 4.8% of patients. Elevations of bilirubin greater than 3 times the ULN occurred in 2.8% of patients. The majority (73% of the patients with hepatic transaminase elevations and 49% of the patients with bilirubin elevations) of these events occurred during the first 2 months of treatment. Four patients discontinued ALECENSA for Grade 3-4 AST and/or ALT elevations, and 3 patients discontinued ALECENSA for Grade 3 bilirubin elevations. Two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy.

Monitor liver function tests including ALT, AST, and total bilirubin every 2 weeks during the first 2 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase and bilirubin elevations. Based on the severity of the adverse drug reaction, withhold ALECENSA and resume at a reduced dose, or permanently discontinue ALECENSA as described in Table 2 [*see Dosage and Administration (2.2)*].

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

Severe ILD (Grade 3) occurred in one (0.4%) of 253 patients exposed to ALECENSA in clinical trials.

Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough and fever).

Immediately withhold ALECENSA treatment in patients diagnosed with ILD/pneumonitis and permanently discontinue ALECENSA if no other potential causes of ILD/pneumonitis have been identified [*see Dosage and Administration (2.2) and Adverse Reactions (6)*].

5.3 Bradycardia

Symptomatic bradycardia can occur with ALECENSA. Cases of bradycardia (7.5%) have been reported in patients treated with ALECENSA. Twenty percent of 221 patients treated with ALECENSA for whom serial ECGs were available had heart rates of less than 50 beats per minute (bpm).

Monitor heart rate and blood pressure regularly. Dose modification is not required in cases of asymptomatic bradycardia. In cases of symptomatic bradycardia that is not life-threatening, withhold ALECENSA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above and evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If attributable to a concomitant medication, resume ALECENSA at a reduced dose (see Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently discontinue ALECENSA in case of recurrence. Permanently discontinue ALECENSA in cases of life-threatening bradycardia if no contributing concomitant medication is identified [*see Dosage and Administration (2.2)*].

5.4 Severe Myalgia and Creatine Phosphokinase (CPK) Elevation

Myalgia or musculoskeletal pain occurred in 29% of patients in Study 1 and Study 2. The incidence of Grade 3 myalgia/musculoskeletal pain was 1.2%. Dose modifications for myalgia/musculoskeletal pain were required in 0.8% of patients.

Elevations of CPK occurred in 43% of 218 patients with CPK laboratory data available in Study 1 and Study 2. The incidence of Grade 3 elevations of CPK was 4.6%. Median time to Grade 3 CPK elevation was 14 days (interquartile range 13-14 days). Dose modifications for elevation of CPK occurred in 5.0% of patients.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every two weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, withhold ALECENSA, then resume or reduce dose [see Dosage and Administration (2.2)].

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to pregnant women. Administration of alectinib to pregnant rats and rabbits during the period of organogenesis resulted in embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7-times those observed in humans with alectinib 600 mg twice daily. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 1 week following the final dose [see Use in Specific Populations (8.1 and 8.3) and Clinical Pharmacology (12.1)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hepatotoxicity [see Warnings and Precautions (5.1)]
- Interstitial Lung Disease (ILD)/Pneumonitis [see Warnings and Precautions (5.2)]
- Bradycardia [see Warnings and Precautions (5.3)]
- Severe Myalgia and Creatine Phosphokinase (CPK) Elevation [see Warnings and Precautions (5.4)]
- Embryo-Fetal Toxicity [see Warnings and Precautions (5.5)]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ALECENSA was evaluated in 253 patients with ALK-positive non-small cell lung cancer (NSCLC) treated with ALECENSA 600 mg orally twice daily in two clinical trials, Studies 1 and 2. The median duration of exposure to ALECENSA was 9.3 months. One hundred sixty-nine patients (67%) were exposed to ALECENSA for more than 6 months, and 100 patients (40%) for more than one year. The population characteristics were: median age 53 years, age less than 65 (86%), female (55%), White (74%), Asian (18%), NSCLC adenocarcinoma histology (96%), never or former smoker (98%), ECOG Performance Status (PS) 0 or 1 (91%), and prior chemotherapy treatment (78%).

Serious adverse reactions occurred in 19% of patients; the most frequently reported serious adverse reactions were pulmonary embolism (1.2%), dyspnea (1.2%), and hyperbilirubinemia (1.2%). Fatal adverse reactions occurred in 2.8% of patients and included hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%), pulmonary embolism (0.4%), and endocarditis (0.4%). Permanent discontinuation of ALECENSA for adverse reactions occurred in 6% of patients. The most frequent adverse reactions that led to permanent discontinuation were hyperbilirubinemia (1.6%), increased ALT levels (1.6%), and increased AST levels (1.2%). Overall, 23%

of patients initiating treatment at the recommended dose required at least one dose reduction. The median time to first dose reduction was 48 days. The most frequent adverse reactions that led to dose reductions or interruptions were elevations in bilirubin (6%), CPK (4.3%), ALT (4.0%), and AST (2.8%), and vomiting (2.8%).

Table 3 summarizes adverse reactions in Studies 1 and 2.

Table 3. Adverse Reactions in $\geq 10\%$ (All Grades) or $\geq 2\%$ (Grade 3-4) of Patients in Studies 1 and 2

Adverse Reactions	ALECENSA N=253	
	All Grades (%)	Grades 3-4 (%)*
Fatigue ^a	41	1.2
Constipation	34	0
Edema ^b	30	0.8
Myalgia ^c	29	1.2
Cough	19	0
Rash ^d	18	0.4
Nausea	18	0
Headache	17	0.8
Diarrhea	16	1.2
Dyspnea	16	3.6 ^e
Back pain	12	0
Vomiting	12	0.4
Increased weight	11	0.4
Vision disorder ^f	10	0

* Per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

^a Includes fatigue and asthenia.

^b Includes peripheral edema, edema, generalized edema, eyelid edema, and periorbital edema.

^c Includes myalgia and musculoskeletal pain.

^d Includes rash, maculopapular rash, acneiform dermatitis, erythema, generalized rash, papular rash, pruritic rash, and macular rash.

^e Includes one Grade 5 event

^f Includes blurred vision, vitreous floaters, visual impairment, reduced visual acuity, asthenopia, and diplopia.

Additional safety information from clinical trial experience

Photosensitivity occurred in 9.9% of patients exposed to ALECENSA in Studies 1 and 2. Patients were advised to avoid sun exposure and to use broad-spectrum sunscreen. The incidence of Grade 2 photosensitivity was 0.4%; the remaining events were Grade 1 in severity.

Table 4 summarizes laboratory abnormalities of ALECENSA in Studies 1 and 2.

Table 4. Laboratory Abnormalities Occurring in >20% of Patients in Studies 1 and 2

Parameter	Alectinib N=250	
	All Grades (%)	Grades 3-4 (%)*
Chemistry		
Increased AST	51	3.6
Increased Alkaline Phosphatase	47	1.2
Increased CPK ^a	43	4.6
Hyperbilirubinemia	39	2.4
Hyperglycemia ^b	36	2.0
Increased ALT	34	4.8
Hypocalcemia	32	0.4
Hypokalemia	29	4.0
Increased Creatinine ^c	28	0
Hypophosphatemia	21	2.8
Hyponatremia	20	2.0
Hematology		
Anemia	56	2.0
Lymphopenia ^d	22	4.6

* Per CTCAE version 4.0

^a n=218 for CPK (with baseline values missing for 91 of these patients).

^b n=152 for fasting blood glucose (with baseline values missing for 5 of these patients).

^c Only patients with creatinine increases based on ULN definition.

^d n=217 for lymphocytes (with baseline values missing for 5 of these patients).

7 DRUG INTERACTIONS

No pharmacokinetic interactions with alectinib requiring dosage adjustment have been identified [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. There are no available data on ALECENSA use in pregnant women.

Administration of alectinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7-times those observed in humans treated with alectinib at 600 mg twice daily [see *Data*]. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a preliminary rabbit embryo-fetal study, administration of alectinib by oral gavage during the period of organogenesis resulted in abortion or complete embryo-fetal mortality at a maternally toxic dose of 27 mg/kg/day (approximately 2.9-fold the estimated area under the curve (AUC_{0-24h,ss}) in humans treated with alectinib 600 mg BID) in three of six pregnant rabbits. The remaining three pregnant rabbits in this group had few live fetuses, decreased fetal and placental weights, and retroesophageal subclavian artery. In a rat preliminary embryo-fetal development study, administration of alectinib during organogenesis resulted in complete litter loss in all pregnant rats at 27 mg/kg/day (approximately 4.5-fold the estimated AUC_{0-24h,ss} in humans treated with alectinib 600 mg BID). Doses greater than or equal to 9 mg/kg/day (approximately 2.7-fold the estimated human AUC_{0-24h,ss} in humans treated with alectinib 600 mg BID), resulted in maternal toxicity as well as developmental toxicities including decreased fetal weight, dilated ureter, thymic cord, small ventricle and thin ventricle wall, and reduced number of sacral and caudal vertebrae.

8.2 Lactation

Risk Summary

There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breast-fed infant, or its effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants from alectinib, advise a lactating woman not to breastfeed during treatment with ALECENSA and for 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ALECENSA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 1 week after the final dose [see *Use in Specific Populations* (8.1)].

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with ALECENSA and for 3 months following the final dose [see *Non Clinical Toxicology* (13.1)].

8.4 Pediatric Use

The safety and effectiveness of ALECENSA in pediatric patients have not been established.

Animal Data

Juvenile animal studies have not been conducted using alectinib. In general toxicology studies, treatment of rats with doses of alectinib resulting in exposures greater than or equal to approximately 4.5 times those in humans treated with alectinib at 600 mg twice daily resulted in changes in the growing teeth and bones. Findings in teeth included discoloration and changes in tooth size along with histopathological disarrangement of the ameloblast and odontoblast layers. There were also decreases in the trabecular bone and increased osteoclast activity in the femur and sternum.

8.5 Geriatric Use

Clinical studies of ALECENSA did not include sufficient number of subjects aged 65 and older to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. The safety of ALECENSA in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease has not been studied [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

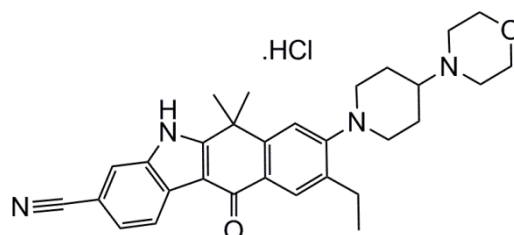
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal (ULN) and aspartate transaminase (AST) greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST). The safety of ALECENSA in patients with moderate or severe hepatic impairment has not been studied [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

No experience with overdose is available. There is no specific antidote for overdose with ALECENSA. Alectinib and its major active metabolite M4 are > 99% bound to plasma proteins; therefore, hemodialysis is likely to be ineffective in the treatment of overdose.

11 DESCRIPTION

ALECENSA (alectinib) is a kinase inhibitor for oral administration. The molecular formula for alectinib is $C_{30}H_{34}N_4O_2 \cdot HCl$. The molecular weight is 482.62 g/mol (free base form) and 519.08 g/mol (hydrochloride salt). Alectinib is described chemically as 9-ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6, 11-dihydro-5H-benzo[*b*]carbazole-3-carbonitrile hydrochloride. The chemical structure of alectinib is shown below:



Alectinib HCl is a white to yellow white powder or powder with lumps with a pKa of 7.05 (base).

ALECENSA is supplied as hard capsules containing 150 mg of alectinib (equivalent to 161.33 mg alectinib HCl) and the following inactive ingredients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, and carboxymethylcellulose calcium. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, corn starch, and carnauba wax. The printing ink contains red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, and glyceryl monooleate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET. In nonclinical studies, alectinib inhibited ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations. The major active metabolite of alectinib, M4, showed similar in vitro potency and activity.

Alectinib and M4 demonstrated in vitro and in vivo activity against multiple mutant forms of the ALK enzyme, including some mutations identified in NSCLC tumors in patients who have progressed on crizotinib.

In mouse models implanted with tumors carrying ALK fusions, administration of alectinib resulted in antitumor activity and prolonged survival, including in mouse models implanted intracranially with ALK-driven tumor cell lines.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The ability of alectinib to prolong the QT interval was assessed in 221 patients administered ALECENSA 600 mg twice daily in clinical studies. ALECENSA did not prolong the QTc (QT corrected for heart rate) interval to any clinically relevant extent. One patient had a maximum post-baseline QTcF value of greater than 500 msec and one patient had a maximum QTcF change from baseline of greater than 60 msec.

12.3 Pharmacokinetics

The pharmacokinetics of alectinib and its major active metabolite M4 have been characterized in patients with ALK-positive NSCLC and healthy subjects.

In patients with ALK-positive NSCLC, the geometric mean (coefficient of variation %) steady-state maximal concentration ($C_{\max,ss}$) for alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%) with peak to trough concentration ratio of 1.2. The geometric mean steady-state area under the curve from 0 to 12 hours ($AUC_{0-12h,ss}$) for alectinib was 7,430 ng*h/mL (46%) and for M4 was 2,810 ng*h/mL (46%). Alectinib exposure is dose proportional across the dose range of 460 mg to 900 mg (i.e., 0.75 to 1.5 times the approved recommended dosage) under fed conditions. Alectinib and M4 reached steady-state concentrations by day 7. The geometric mean accumulation was approximately 6-fold for both alectinib and M4.

Absorption

Alectinib reached maximal concentrations at 4 hours following administration of ALECENSA 600 mg twice daily under fed conditions in patients with ALK-positive NSCLC.

The absolute bioavailability of alectinib was 37% (90% CI: 34%, 40%) under fed conditions.

A high-fat, high-calorie meal increased the combined exposure (AUC_{0-inf}) of alectinib plus M4 by 3.1-fold (90% CI: 2.7, 3.6) following oral administration of a single 600 mg dose of ALECENSA.

Distribution

The apparent volume of distribution is 4,016 L for alectinib and 10,093 L for M4.

Alectinib and M4 are bound to human plasma proteins greater than 99%, independent of drug concentration.

Alectinib concentrations in the cerebrospinal fluid in patients with ALK-positive NSCLC approximate estimated alectinib free concentrations in the plasma.

In vitro studies suggest that alectinib is not a substrate of P-glycoprotein (P-gp), but M4 is a substrate of P-gp. Alectinib and M4 are not substrates of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1, or OATP1B3.

Elimination

The apparent clearance (CL/F) is 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life is 33 hours for alectinib and 31 hours for M4 in patients with ALK-positive NSCLC.

Metabolism

Alectinib is metabolized by CYP3A4 to its major active metabolite M4. The geometric mean metabolite/parent exposure ratio at steady-state is 0.40. M4 is subsequently metabolized by CYP3A4. Alectinib and M4 were the main circulating moieties in plasma, constituting 76% of the total radioactivity.

Excretion

Ninety-eight percent of the radioactivity was excreted in feces following oral administration of a single radiolabeled dose of alectinib under fed conditions. Eighty-four percent of the dose was excreted in the feces as unchanged alectinib and 6% of the dose was excreted as M4. Excretion of radioactivity in urine was less than 0.5% of administered radiolabeled dose of alectinib.

Specific Populations

Age, body weight, mild hepatic impairment, mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min), race (White, Asian, and Other), and sex had no clinically meaningful effect on the systemic exposure of alectinib and M4. The pharmacokinetics of alectinib has not been studied in patients with severe renal impairment, end-stage renal disease or moderate to severe hepatic impairment [see *Use in Specific Populations* (8.6, 8.7)].

Drug Interactions

Effect of Other Drugs on Alectinib

No clinically meaningful effect on the combined exposure of alectinib plus M4 was observed in clinical studies following co-administration of ALECENSA with a strong CYP3A inhibitor (posaconazole), a strong CYP3A inducer (rifampin), or an acid-reducing agent (esomeprazole).

Effect of Alectinib on Other Drugs

No clinically meaningful effect on the exposure of midazolam (sensitive CYP3A substrate) or repaglinide (sensitive CYP2C8 substrate) is expected following co-administration with ALECENSA.

In vitro studies suggest that alectinib and M4 do not inhibit CYP1A2, 2B6, 2C9, 2C19 or 2D6.

In vitro studies suggest that alectinib and M4 inhibit P-gp and BCRP. Alectinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 transport activity in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with alectinib have not been conducted.

Alectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay, but was positive with an increased number of micronuclei in a rat bone marrow micronucleus test. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes.

No studies in animals have been performed to evaluate the effect of alectinib on fertility. No adverse effects on male and female reproductive organs were observed in general toxicology studies conducted in rats and monkeys.

14 CLINICAL STUDIES

The safety and efficacy of ALECENSA were established in two single-arm, multicenter clinical trials (Studies 1 and 2). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib, with documented ALK positive NSCLC based on an FDA-approved test, and ECOG PS of 0-2 were enrolled in both studies. Eligibility criteria permitted enrollment of patients with prior chemotherapy and prior CNS radiotherapy provided that CNS metastases were stable for at least two weeks. All patients received ALECENSA 600 mg orally twice daily. The major efficacy outcome measure in both studies was objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) as evaluated per Independent Review Committee (IRC). Additional outcome measures as evaluated by the IRC included duration of response (DOR), CNS ORR, and CNS DOR.

Study 1 was conducted in North America and enrolled 87 patients. Baseline demographic and disease characteristics in Study 1 were median age 54 years old (range 29 to 79, 18% 65 and over), 84% White and 8% Asian, 55% female, 35% ECOG PS 0 and 55% ECOG PS 1, 100% never or former smokers, 99% Stage IV, 94% adenocarcinoma, and 74% prior chemotherapy. The most common sites of extra-thoracic metastasis included 60% CNS (of whom 65% had received CNS radiation), 43% lymph nodes, 36% bone, and 34% liver.

Study 2 was conducted internationally and enrolled 138 patients. Baseline demographic and disease characteristics in Study 2 were median age 52 years old (range 22 to 79, 10% 65 and over), 67% White and 26% Asian, 56% female, 32% ECOG PS 0 and 59% ECOG PS 1, 98% never or former smokers, 99% Stage IV, 96% adenocarcinoma, and 80% prior chemotherapy. The most common sites of extra-thoracic metastasis included 61% CNS (of whom 73% had received CNS radiation), 51% bone, 38% lymph nodes, and 30% liver.

Efficacy results from Studies 1 and 2 in all treated patients are summarized in Table 5. The median duration of follow-up on Study 1 was 4.8 months for both IRC and Investigator assessments and on Study 2, 10.9 months for IRC assessment and 7.0 months for Investigator assessment. All responses were partial responses.

Table 5: Efficacy Results in Studies 1 and 2

Efficacy Parameter	Study 1 (N=87)		Study 2 (N=138)	
	IRC* Assessment	Investigator Assessment	IRC* Assessment	Investigator Assessment
Objective Response Rate (95% CI)	38% (28; 49)	46% (35; 57)	44% (36; 53)	48% (39; 57)
Number of Responders	33	40	61	66
Duration of Response, median in months (95% CI)	7.5 (4.9, Not Estimable)	NE (4.9, Not Estimable)	11.2 (9.6, Not Estimable)	7.8 (7.4, 9.2)

* 18 patients in Study 1 and 16 patients in Study 2 did not have measurable disease at baseline as per IRC assessment and were classified as non-responders in the IRC analysis.

An assessment of ORR and duration of response for CNS metastases in the subgroup of 51 patients in Studies 1 and 2 with baseline measurable lesions in the CNS according to RECIST v1.1 are summarized in Table 6. Thirty-five (69%) patients with measurable CNS lesions had received prior brain radiation, including 25 (49%) who completed radiation treatment at least 6 months before starting treatment with ALECENSA. Responses were observed irrespective of prior brain radiation status.

Table 6: CNS Objective Response in Patients with Measurable CNS Lesions in Studies 1 and 2

Efficacy Parameter	N=51
CNS Objective Response Rate (95% CI)	61% (46, 74)
Complete Response	18%
Partial Response	43%
CNS Duration of Response, median in months (95% CI)	9.1 (5.8, not evaluable)

16 HOW SUPPLIED/STORAGE AND HANDLING

white to yellowish white, size 1 capsules with “ALE” printed in black ink on the cap and “150 mg” printed in black ink on the body, available in:

240 capsules per bottle:

Storage and stability: Do not store above 30°C (86°F). Store in the original container to protect from light and moisture.

Shelf life after first opening: 12 months

17. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079.

18. MARKETING AUTHORISATION NUMBER(S): 34552

19. MANUFACTURER

Hoffmann-La Roche ltd, Basel, Switzerland

<i>Medicine: keep out of reach of children</i>
--