

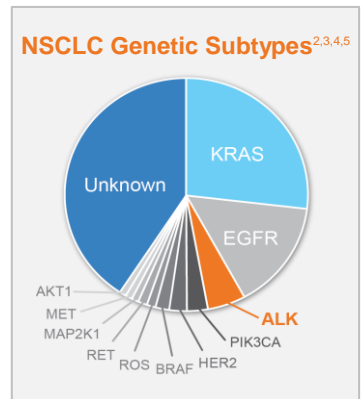
# About Zykadia™ (ceritinib) and ALK+ Non-Small Cell Lung Cancer

## What is Non-Small Cell Lung Cancer (NSCLC)?

Lung cancer is the leading cause of cancer death worldwide in both men and women<sup>1</sup>. In the U.S. alone an estimated 224,210 new cases of lung cancer are expected to be diagnosed in 2014, accounting for 13 percent of new cancers<sup>1</sup>. It is also expected that 159,260 Americans will die from lung cancer this year, accounting for 27 percent of all cancer deaths<sup>1</sup>.

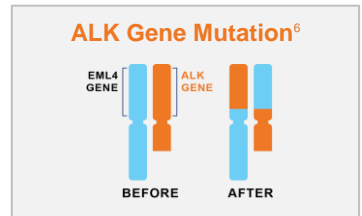
Lung cancer is typically diagnosed as either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)<sup>1</sup>. NSCLC is the most common type of lung cancer, accounting for 85-90% of all lung cancer cases, and is classified into three main subtypes based on histology or what it looks like under a microscope: adenocarcinoma, squamous cell carcinoma and large-cell carcinoma<sup>1</sup>. Adenocarcinoma represents the most common subtype of NSCLC and accounts for 40% of cases<sup>1</sup>.

In addition, NSCLC can also be characterized based on different underlying genetic abnormalities<sup>1</sup>. Researchers have identified over 12 unique mutations and biomarkers that are responsible for tumor growth including anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), human epidermal growth factor (HER) family of receptors, MET and ROS-1<sup>2,3,4,5</sup>.



## What is ALK+ NSCLC?

ALK is a gene that can fuse with other genes to form an abnormal "fusion protein" that promotes the development and growth of certain tumors in cancers including NSCLC<sup>6</sup>. Approximately 2-7% of patients with NSCLC have the ALK gene rearrangement<sup>7</sup>.



## How is ALK+ NSCLC Diagnosed?

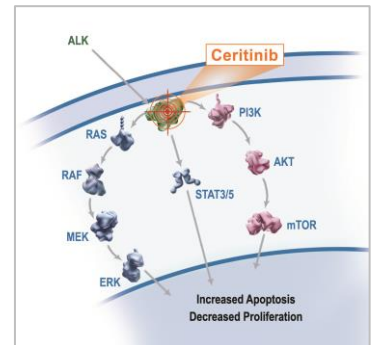
- To determine ALK status, doctors obtain a tumor sample via biopsy or surgery and send it to a specialized lab for molecular testing
- Molecular testing is a form of genetic testing that can be used to provide information about the genetic makeup of a patient's tumor and to further help classify their specific type of NSCLC<sup>8</sup>
- Oncologists and pathologists are encouraged to use molecular testing at the time of diagnosis on all patients with advanced NSCLC to further understand which biomarkers may be driving the cancer<sup>9</sup>
- Testing for biomarkers may help a physician choose the most appropriate therapy and help guide the selection of clinical trials for the patient<sup>9</sup>

## How is ALK+ NSCLC Treated?

Precision oncology has changed the diagnosis and treatment of ALK+ NSCLC. However, studies have shown that patients first treated with an ALK inhibitor may experience disease progression, where their cancer may continue to grow or spread, less than a year after starting therapy<sup>10</sup>. Therefore, more treatment options are needed for when progression occurs in these patients.

## About Zykadia (ceritinib)

- Outside of the U.S., Zykadia (ceritinib) is an investigational agent and has not been approved by regulatory authorities
- Zykadia is a selective, small-molecule inhibitor of ALK<sup>7,11</sup> and the first Novartis lung cancer treatment to be approved by the U.S. Food and Drug Administration (FDA)
- Zykadia is indicated for the treatment of patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib<sup>12</sup>
- 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.
- The FDA approval of Zykadia addresses an unmet medical need for patients with this type of lung cancer
- Zykadia is one of the first medicines to be approved following FDA Breakthrough Therapy designation, which it received due to the results observed in the pivotal trial and the serious and life-threatening nature of ALK+ NSCLC<sup>13</sup>



Zykadia inhibits ALK, disrupting the signaling cascade that leads to the growth and spread of cancer cells

Please see US indication and Important Safety Information on the next page



## About Zykadia

In the United States, Zykadia (ceritinib) is indicated for the treatment of patients with ALK+ metastatic NSCLC who have progressed on or are 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.

## Zykadia Important Safety Information

Diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients including severe cases in 14% of patients treated with Zykadia in Study 1. Dose modification due to diarrhea, nausea, vomiting, or abdominal pain occurred in 38% of patients. Patients should be monitored and managed using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as indicated. Based on the severity of the adverse drug reaction, withhold Zykadia with resumption at a reduced dose as described in Table 1 of the package insert.

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. Patients should be monitored with liver laboratory tests including ALT, aspartate aminotransferase (AST), and total bilirubin once a month and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Based on the severity of the adverse drug reaction, withhold Zykadia with resumption at a reduced dose, or permanently discontinue Zykadia as described in Table 1 of the package insert.

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with Zykadia. In Study 1, pneumonitis was reported in 4% of 255 patients treated with Zykadia. CTCAE Grade 3 or 4 ILD/pneumonitis was reported in 3% of patients, and fatal ILD/pneumonitis was reported in 1 patient (0.4%) in Study 1. One percent (1%) of patients discontinued Zykadia in Study 1 due to ILD/pneumonitis. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue Zykadia in patients diagnosed with treatment-related ILD/pneumonitis.

QTc interval prolongation occurs in patients treated with Zykadia. Three percent (3%) of 255 patients experienced a QTc interval increase over baseline greater than 60 msec in Study 1. Across the development program of Zykadia, one of 304 patients (less than 1%) treated with Zykadia doses ranging from 50 to 750 mg was 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 analysis suggested that Zykadia causes concentration-dependent increases in the QTc interval. When possible, avoid use of Zykadia in patients with congenital long QT syndrome. Conduct periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold Zykadia in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume Zykadia at a reduced dose as described in Table 1 of the package insert. Permanently discontinue Zykadia in patients who develop QTc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.

Hyperglycemia can occur in patients receiving Zykadia. In Study 1, CTCAE Grade 3-4 hyperglycemia, based on laboratory values, occurred in 13% of 255 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. Monitor serum glucose levels as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated. Based on the severity of the adverse drug reaction, withhold Zykadia until hyperglycemia is adequately controlled, then resume Zykadia at a reduced dose as described in Table 1 of the package insert. If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue Zykadia.

Bradycardia can occur in patients receiving Zykadia. In 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 patients. Bradycardia was reported as an adverse drug reaction in 3% of patients in Study 1. Avoid using Zykadia in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of Zykadia. Permanently discontinue Zykadia for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with a concomitant medication known to cause bradycardia or hypotension, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if the concomitant medication can be adjusted or discontinued, resume Zykadia at a reduced dose as described in Table 1 of the package insert upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring.

Based on its mechanism of action, Zykadia may 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. Advise women of reproductive potential of the potential hazard 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.



The most common adverse reactions (incidence of at least 25%) are diarrhea, nausea, vomiting, abdominal pain, fatigue, decreased appetite, and constipation. Key laboratory abnormalities (incidence of at least 25%) were decreased hemoglobin (84%), increased alanine transaminase (80%), increased aspartate transaminase (75%), increased creatinine (58%), increased glucose (49%), decreased phosphate (36%), and increased lipase (28%).

Avoid concurrent use of Zykadia with strong CYP3A inhibitors and strong CYP3A inducers. If concurrent use of a strong CYP3A inhibitor is unavoidable, reduce the dose of Zykadia by approximately one-third. Avoid concurrent use of Zykadia with CYP3A and CYP2C9 substrates with narrow therapeutic indices. Patients should not consume grapefruit and grapefruit juice during treatment with Zykadia. Patients should be instructed to take Zykadia on an empty stomach (i.e., do not take within 2 hours of a meal).

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<sup>1</sup> American Cancer Society. Lung Cancer – Non-Small Cell Detailed Guide 2014. Available at: <http://www.cancer.org/Cancer/LungCancer-Non-SmallCell/DetailedGuide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer>. Accessed February 14, 2014.

<sup>2</sup> Riess JW, Wakelee, HA. Metastatic Non-Small Cell Lung Cancer Management: Novel Targets and Recent Clinical Advances. *Clinical Advances in Hematology & Oncology*. 2012; 10: 226-224.

<sup>3</sup> Pao W, Girard N. New driver mutations in non-small-cell lung cancer. *Lancet Oncol*. 2011;12:175-180.

<sup>4</sup> Paik PK, Arcila ME, Fara M, et al. Clinical Characteristics of Patients With Lung Adenocarcinomas Harboring BRAF Mutations. *J Clin Oncol*. 2011;29:2046-2051.

<sup>5</sup> Takeuchi, K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nature*. 2012;378-381.

<sup>6</sup> Lin E, Li L, Guan Y, et al. Exon Array Profiling Detects EML4-ALK Fusion in Breast, Colorectal, and Non-Small Cell Lung Cancers. *Mol Cancer Res*. 2009;7(9):1466-1476.

<sup>7</sup> National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Non-Small Cell Lung Cancer. NCCN 2014 3:1-148.

<sup>8</sup> National Human Genome Research Institute. Frequently Asked Questions About Genetic Testing. National Human Genome Research Institute. <http://www.genome.gov/19516567#al-2>. Accessed February 4, 2014.

<sup>9</sup> Lindeman NI, Cagle PT, et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors. *Arch Pathol Lab Med*. 2013; 137: 828-1174.

<sup>10</sup> Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Sci Transl Med*. 2012;4(120):1-12.

<sup>11</sup> Mehra R, et al. First-in-Human Phase I Study of the ALK Inhibitor LDK378 in Advanced Solid Tumors. Abstract #3007. American Society of Clinical Oncology 2012 Annual Meeting, Chicago, IL.

<sup>12</sup> Zykadia™ (ceritinib) Prescribing Information. East Hanover, New Jersey, USA: Novartis Pharmaceuticals Corporation; April 2014.

<sup>13</sup> U.S. Food and Drug Administration. Frequently Asked Questions: Breakthrough Therapies. Available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCA/SignificantAmendmentstotheFDCA/FDASIA/ucm341027.htm>. Accessed April 2, 2013.

