

## History and Development of Zykadia® (ceritinib)

- 1994** Researchers identify anaplastic lymphoma kinase (ALK) as the tyrosine kinase component of a novel fusion gene that results from a chromosomal translocation in anaplastic large-cell lymphoma (ALCL)<sup>1</sup>
- 2003** Researchers at Novartis begin efforts to develop targeted ALK inhibitors for ALCL
- 2007** The EML4-ALK translocation is identified in non-small cell lung cancer (NSCLC)<sup>2</sup>  
Selective ALK inhibitor activity is first demonstrated in animal models of ALCL<sup>3</sup>
- 2010** Novartis identifies ceritinib in animal models as a potent and specific inhibitor of ALK
- 2011** **January:** Ceritinib enters Phase I clinical trials and the first patient is treated  
**August:** The US Food and Drug Administration (FDA) approves the first therapy for ALK+ NSCLC (Xalkori®\* [crizotinib])  
**November:** First presented ceritinib data show durable responses in patients with an EML4-ALK xenograft with a crizotinib-resistant mutation (C1156Y)<sup>4</sup>
- 2012** **April:** Novartis demonstrates Proof of Concept for ceritinib showing that the compound is active in patients with ALK+ NSCLC  
**June:** Novartis presents Phase I data of ceritinib in advanced solid tumors showing preliminary responses in crizotinib-naïve and crizotinib-relapsed patients<sup>5</sup>  
**November:** Novartis initiates large Phase II studies in patients with ALK+NSCLC
- 2013** **March:** Ceritinib receives Breakthrough Therapy designation from the US FDA  
**June:** Phase I data demonstrate clinical response in 78 patients with ALK+ metastatic NSCLC who had progressed during or after crizotinib therapy or had not been previously treated with crizotinib<sup>6</sup>  
**June:** Novartis initiates large Phase III studies in patients with ALK+NSCLC  
**September:** Novartis initiates expanded treatment protocol for ceritinib in ALK+ NSCLC<sup>7</sup>  
**December:** Ceritinib regulatory application is submitted to the US FDA
- 2014** **Q1:** Novartis submits European Medicines Agency (EMA) regulatory application for ceritinib  
**March:** Ceritinib Phase I data published in *The New England Journal of Medicine* showed 66 patients with ALK+ NSCLC in the study experienced a clinical response<sup>8</sup>  
**April:** Zykadia is approved by the US FDA for the treatment of patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib<sup>9</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. This indication addresses an unmet medical need for patients.  
**June:** Updated Phase I data presented at the American Society of Clinical Oncology (ASCO) Annual Meeting show ceritinib demonstrated a high level of activity in 246 patients with ALK+ NSCLC, based on a 7-month median duration of follow-up<sup>10</sup>.

\*Xalkori® is a registered trademark of Pfizer Inc.



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**2015 February:** The Committee for Medicinal Products for Human Use (CHMP) of the EMA adopted a positive opinion for Zykadia, recommending marketing authorization for the drug in the European Union (EU) for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

**May:** Zykadia is approved by the European Commission for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib<sup>11</sup>.

*Outside of the U.S. and EU, Zykadia is approved in nine countries within North America, South America, Central America and Asia (as of May 2015).*

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### **About Zykadia**

Zykadia is an oral, selective inhibitor of anaplastic lymphoma kinase (ALK), a gene that can fuse with others to form an abnormal “fusion protein” that promotes the development and growth of certain tumors in cancers including non-small cell lung cancer (NSCLC). Zykadia is approved by the European Commission for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. Outside the European Union, Zykadia is approved for patients with ALK+ NSCLC in the United States and other countries within North America, South America, Central America and Asia. Additional regulatory reviews for Zykadia are underway worldwide.

### **Zykadia Important Safety Information**

Zykadia may cause serious side effects.

Zykadia may cause stomach upset and intestinal problems in most patients, including diarrhea, nausea, vomiting and stomach-area pain. These problems can be severe. Patients should follow their doctor's instructions about taking medicines to help these symptoms, and should call their doctor for advice if symptoms are severe or do not go away.

Zykadia may cause severe liver injury. Patients should have blood tests prior to the start of treatment with Zykadia, every two weeks for the first month of treatment and monthly thereafter, and should talk to their doctor right away if they experience any of the following symptoms: tiredness (fatigue), itchy skin, yellowing of the skin or the whites of the eyes, nausea or vomiting, decreased appetite, pain on the right side of the abdomen, urine turns dark or brown, or bleeding or bruising more easily than normal.

Zykadia may cause severe or life-threatening swelling (inflammation) of the lungs during treatment that can lead to death. Symptoms may be similar to those symptoms from lung cancer. Patients should tell their doctor right away about any new or worsening symptoms, including trouble breathing or shortness of breath, fever, cough, with or without mucous, or chest pain.

Zykadia may cause very slow, very fast, or abnormal heartbeats. Doctors should check their patient's heart during treatment with Zykadia. Patients should tell their doctor right away if they feel new chest pain or discomfort, dizziness or lightheadedness, faint, or have abnormal heartbeats, blue discoloration of lips, shortness of breath, swelling of lower limbs or skin, or if they start to take or have any changes in heart or blood pressure medicines.

Zykadia may cause high levels of glucose in the blood. People who have diabetes or glucose intolerance, or who take a corticosteroid medicine have an increased risk of high blood sugar with Zykadia. Patients should have glucose blood tests prior to the start of treatment with Zykadia and during treatment. Patients should follow their doctor's instructions about blood sugar monitoring and call their doctor right away with any symptoms of high blood sugar, including increased thirst and/or urinating often.



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Before patients take Zykadia, they should tell their doctor about all medical conditions, including liver problems; diabetes or high blood sugar; heart problems, including a condition called long QT syndrome; if they are pregnant, if they think they may be pregnant, or if they plan to become pregnant; are breastfeeding or plan to breastfeed.

Zykadia may harm unborn babies. Women who are able to become pregnant must use a highly effective method of birth control (contraception) during treatment with Zykadia and up to 3 months after stopping Zykadia. It is not known if Zykadia passes into breast milk. Patients and their doctor should decide whether to take Zykadia or breastfeed, but should not do both.

Patients should tell their doctor about medicines they take, including prescription medicines, over-the-counter medicines, vitamins and herbal supplements. If they take Zykadia while using oral contraceptives, the oral contraceptives may become ineffective.

The most common adverse reactions with an incidence of  $\geq 10\%$  were diarrhea, nausea, vomiting, tiredness (fatigue), liver laboratory test abnormalities (requires blood test monitoring), abdominal pain, decreased appetite, constipation, rash, kidney laboratory test abnormalities (requires blood test monitoring), heartburn and anemia. Grade 3-4 adverse reactions with an incidence of  $\geq 5\%$  were liver laboratory test abnormalities, tiredness (fatigue), diarrhea, nausea and hyperglycemia (requires blood test monitoring).

Patients should stop taking Zykadia and seek medical help immediately if they experience any of the following, which may be signs of an allergic reaction:

- Difficulty in breathing or swallowing
- Swelling of the face, lips, tongue or throat
- Severe itching of the skin, with a red rash or raised bumps

Patients should tell their doctor of any side effect that bothers them or does not go away. These are not all of the possible side effects of Zykadia. For more information, patients should ask their doctor or pharmacist.

Patients should take Zykadia exactly as their health care provider tells them. Patients should not change their dose or stop taking Zykadia unless their health care provider advises them to. Zykadia should be taken once a day on an empty stomach. Patients should not eat for at least 2 hours before and 2 hours after taking Zykadia. If a dose of Zykadia is missed, they should take it as soon as they remember. If their next dose is due within the next 12 hours, they should skip the missed dose and take the next dose at their regular time. They should not take a double dose to make up for a forgotten dose. Patients should not drink grapefruit juice or eat grapefruit during treatment with Zykadia, as it may make the amount of Zykadia in their blood increase to a harmful level. If patients have to vomit after swallowing Zykadia capsules, they should not take more capsules until their next scheduled dose.

*Please see full Prescribing Information for Zykadia.*

<sup>1</sup> Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL, Look AT. "Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma". *Science* 263: 1281-4 (1994).

<sup>2</sup> Soda M, Choi YL, Enomoto M, et al. "Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer". *Nature* 448 (7153): 561-6 (2007).

<sup>3</sup> Galkin AV, Melnick JS, Kim S, Hood TL, Li N, Li L, Xia G, Steensma R, Chopiuk G, Jiang J, Wan Y, Ding P, Liu Y, Sun F, Schultz PG, Gray NS, Warmuth M. "Identification of NVP-TAE684, a potent, selective, and efficacious inhibitor of NPM-ALK". *Proc Natl Acad Sci U S A*.104:270-5 (2007).

<sup>4</sup> Li N, Michellys PY, Kim S, et al. Activity of a potent and selective phase 1 ALK inhibitor LDK378 in naïve and crizotinib-resistant preclinical tumor models. Abstract #B232. 2011 AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, San Francisco, CA, USA.

<sup>5</sup> Mehra R, et al. Results of a First-in-Human Phase I Study of the ALK Inhibitor LDK378 in Advanced Solid Tumors. Abstract #3007. 2012 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA.

<sup>6</sup> Shaw A, et al. Clinical Activity of the ALK Inhibitor LDK378 in Advanced, ALK-positive NSCLC. Abstract #8010. 2013 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA.

<sup>7</sup> ClinicalTrials.gov. Expanded Treatment Protocol With LDK378 in ALK(+) NSCLC. Available at: <http://clinicaltrials.gov/ct2/show/NCT01947608>. Accessed March 17, 2014.

<sup>8</sup> Shaw A, et al. Ceritinib in ALK-Rearranged Non-Small-Cell Lung Cancer. *N Engl J Med*. 2014;370(13):1189-97.

<sup>9</sup> Zykadia™ (ceritinib) Prescribing Information. East Hanover, New Jersey, USA: Novartis Pharmaceuticals Corporation; April 2014.

<sup>10</sup> Kim, DW. Ceritinib in Advanced Anaplastic Lymphoma Kinase (ALK)-rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC) – Results of the ASCEND-1 Trial. Abstract #8003. 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA.

<sup>11</sup> Zykadia® (ceritinib) Summary of Product Characteristics. Basel, Switzerland: Novartis Pharma AG; 06-May-2015.

