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. In the U.S. alone an estimated 221,200 new cases of lung cancer are expected to be diagnosed in 2015, accounting for 13 percent of new cancers. It is also expected that 158,040 Americans will die from lung cancer this year, accounting for 27 percent of all cancer deaths.

Lung cancer is typically diagnosed as either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). 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. Adenocarcinoma represents the most common subtype of NSCLC and accounts for 40% of cases.

In addition, NSCLC can also be characterized based on different underlying genetic abnormalities. 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.

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. Approximately 2-7% of patients with NSCLC have the ALK gene rearrangement. What 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
• 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
• Testing for biomarkers may help a physician choose the most appropriate therapy and help guide the selection of clinical trials for the patient

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. For patients with ALK+ NSCLC, the most common sites of disease progression (or metastasis) include brain, liver and bone. Brain metastases in particular can affect up to 50 percent of patients with ALK+ NSCLC. Therefore, more treatment options are needed for when progression occurs in these patients.

About Zykadia (ceritinib)
• Zykadia (ceritinib) is a selective, small-molecule inhibitor of ALK and the first Novartis lung cancer treatment to be approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).
• 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).
• Zykadia addresses an unmet medical need for patients with ALK+ NSCLC who have received previous treatment with an ALK inhibitor.
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.

Before patients take Zykadia, they should tell their doctor about all medical conditions, including liver or kidney 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 ≥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 ≥1% were: tiredness (fatigue) (7%); abdominal pain, increased appetite, vomiting, diarrhea (3%); rash, 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 (2%); facial swelling (1%).

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.

Novartis Pharma AG
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Please see full Prescribing Information for Zykadia.

11 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