NOVARTIS AG
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FORM 6-K

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MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG

Novartis gains FDA approval for Zykadia , first therapy for patients with ALK+ NSCLC previously treated with the ALK inhibitor crizotinib

- *Zykadia (ceritinib) demonstrated an overall response rate of 54.6% in patients with ALK+ metastatic NSCLC who have no other treatment option(1)*

- *Median duration of response to Zykadia was 7.4 months; patients in study started treatment with metastases, including brain (60%), liver (42%) and bone (42%)(1)*

- *ALK+ NSCLC is driven by a rearrangement of the ALK gene, which is responsible for cancer cell growth in 2-7% of patients with NSCLC(2)*

- *Approval follows FDA Breakthrough Therapy designation; regulatory application submitted in the EU and filings underway with other health authorities worldwide*

Basel, April 29, 2014 Novartis announced today that the US Food and Drug Administration (FDA) has approved Zykadia (ceritinib, previously known as LDK378) for the treatment of patients with anaplastic lymphoma kinase-positive (ALK+) metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib(1). The approval of Zykadia addresses an unmet medical need for patients with this type of lung cancer who have progressed on prior therapy.

Zykadia represents an important treatment option for ALK+ NSCLC patients who relapse after starting initial therapy with crizotinib, said lead investigator Alice T. Shaw, MD, PhD, Massachusetts General Hospital Cancer Center, Boston. This approval will affect the way we manage and monitor patients with this type of lung cancer, as we will now be able to offer them the opportunity for continued treatment response with a new ALK inhibitor.

Lung cancer is the leading cause of cancer death worldwide. The most common type of lung cancer is NSCLC, accounting for 85-90% of all cases(3). Of those, 2-7% are driven by a rearrangement of the ALK gene, which increases the growth of cancer cells and can be identified by a

molecular test of the cancer tumor(2). Despite significant treatment advances for patients with ALK+ NSCLC, disease progression is often inevitable and more options are needed.

The approval of Zykadia is based on a pivotal trial that included 163 patients with metastatic ALK+ NSCLC who progressed on or were intolerant to treatment with crizotinib. The most common sites of metastases in the patient population studied were brain (60%), liver (42%) and bone (42%)(1).

Among previously-treated patients, Zykadia achieved an overall response rate (ORR) of 54.6% [95% CI, 47-62%] and a median duration of response (DOR) of 7.4 months [95% CI, 5.4-10.1 months](1). The most common adverse reactions (incidence of at least 25%) were diarrhea, nausea, elevated transaminases, vomiting, abdominal pain, fatigue, decreased appetite and constipation (1).

The approval of Zykadia less than three and a half years after the first patient entered our clinical trial exemplifies what is possible with a highly focused approach to drug development and strong collaboration, said Alessandro Riva, MD, President, Novartis Oncology ad interim and Global Head, Oncology Development and Medical Affairs. The dedication of clinical investigators, patients, the FDA and others has enabled us to bring this medicine to patients in need as swiftly as possible.

Zykadia is an oral, selective inhibitor of ALK, an important therapeutic target in lung cancer. ALK is a gene that can fuse with other genes to form an aberrant fusion protein that promotes the development and growth of cancer cells(4),(5). Zykadia is one of the first medicines to be approved following FDA Breakthrough Therapy designation, which was received in March 2013 due to the significance of results observed in the pivotal trial and the serious and life-threatening nature of ALK+ NSCLC. Additional regulatory submissions for Zykadia are underway worldwide, with an application currently filed in the European Union.

About the pivotal trial and Zykadia clinical trial program

The efficacy of Zykadia was established in a multicenter, single-arm, open-label clinical trial. A total of 163 patients with metastatic ALK+ NSCLC who progressed on or were intolerant to treatment with crizotinib were enrolled and treated at a Zykadia dose of 750 mg once daily. The major efficacy outcome measure was ORR according to RECIST v1.0 as evaluated by both investigators and a Blinded Independent Central Review Committee (BIRC). DOR was an additional outcome measure(1).

The study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastasis included brain (60%), liver (42%) and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients(1).

Zykadia achieved an ORR of 54.6% [95% CI, 47-62%] and a median DOR of 7.4 months [95% CI, 5.4-10.1 months] based on investigator assessment. The analysis by the BIRC assessment was similar to the analysis by the investigator assessment with an ORR of 43.6% [95% CI, 36-52%] and a median DOR of 7.1 months [95% CI, 5.6-NE months](1).

This study is part of the ongoing Novartis clinical trial program in this patient population. Several major studies evaluating treatment with ceritinib are being conducted in more than 300 study centers across more than 30 countries. Two Phase II single-arm clinical trials in previously-treated and treatment-naïve ALK+ NSCLC patients, (www.clinicaltrials.gov identifiers NCT01685060 and NCT01685138), are fully enrolled and ongoing. In addition, two Phase III clinical trials comparing ceritinib with chemotherapy in treatment-naïve and in previously-treated patients, (www.clinicaltrials.gov identifiers NCT01828099 and NCT01828112), are ongoing and actively recruiting patients worldwide(6),(7),(8),(9).

About Zykadia

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. Apprise 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 (86%), nausea (80%), vomiting (60%), abdominal pain (54%), fatigue (52%), decreased appetite (34%), and constipation (29%). 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).

Please see full Prescribing Information for Zykadia.

Outside of the US, Zykadia (LDK378) is an investigational agent and has not been approved by regulatory authorities.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as Breakthrough Therapy, underway, will, offer, opportunity, inevitable, possible, can, ongoing, being conducted, may, or similar terms, or by express or implied discussions regarding additional marketing authorizations for Zykadia, potential new indications or labeling for Zykadia, or potential future revenues from Zykadia. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Zykadia will be approved for sale in any market where it has been submitted, or that it will be submitted or approved for sale in any additional markets, or at any particular time. Neither can there be any guarantee that Zykadia will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Zykadia will be commercially successful in the future. In particular, management s expectations regarding Zykadia could be affected by, among other things,

unexpected regulatory actions or delays or government regulation generally; the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; the company s ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected manufacturing issues, and other risks and factors referred to in Novartis AG s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care, cost-saving generic pharmaceuticals, preventive vaccines, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2013, the Group achieved net sales of USD 57.9 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 135,000 full-time-equivalent associates and sell products in more than 150 countries around the world. For more information, please visit http://www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis.

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Accessed on October 11, 2013.

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SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Novartis AG

Date:	April 29, 2014	By:	/s/ MALCOLM B. CHEETHAM
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