Novartis receives EU approval for first-line use of Zykadia® in ALK-positive advanced non-small cell lung cancer (NSCLC)

- In ALK-positive advanced NSCLC patients, Zykadia demonstrated superior median progression-free survival (PFS) compared to SOC chemotherapy with maintenance1

- Zykadia benefit was also seen in patients with brain metastases1

- Approximately 3-7% of all patients with NSCLC have an ALK gene rearrangement2

Basel, June 29, 2017 – Novartis today announced the European Commission approved expanding the use of Zykadia® (ceritinib) to include the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive. Approval follows a positive opinion granted in May by the Committee for Medicinal Products for Human Use (CHMP), and is applicable to all 28 European Union member states plus Iceland, Liechtenstein, and Norway.

The first-line approval of Zykadia is based on results from an open-label, randomized, multicenter, global, Phase III trial, ASCEND-4. The study met its primary endpoint, demonstrating a 45% reduction in the risk of disease progression in the Zykadia arm, compared to the chemotherapy arm (hazard ratio [HR] = 0.55 [95% confidence interval (CI): 0.42, 0.73; one-sided p value <0.0001])1. Patients treated with first-line Zykadia had a median progression-free survival (PFS) of 16.6 months (95% CI: 12.6, 27.2), compared to 8.1 months (95% CI: 5.8, 11.1) for patients treated with standard first-line pemetrexed-platinum chemotherapy with pemetrexed maintenance1.

Overall intracranial response rate (OIRR) in patients with measurable brain metastases at baseline and at least one post-baseline assessment was 72.7% (95% CI: 49.8, 89.3; n = 22) for patients treated with Zykadia, versus 27.3% (95% CI: 10.7, 50.2; n = 22) for patients treated with chemotherapy1. The whole body overall response rate (ORR) was 72.5% (95% CI: 65.5, 78.7; n = 189) in patients treated with Zykadia1.

Further, patients without brain metastases at screening receiving Zykadia experienced a median PFS of 26.3 months (95% CI: 15.4, 27.7), compared with 8.3 months (95% CI: 6.0, 13.7) among patients treated with chemotherapy (HR = 0.48 [95% CI: 0.33, 0.69])1. Among patients with brain metastases at screening, the median PFS was 10.7 months (95% CI: 8.1, 16.4) in the Zykadia group, versus 6.7 months (95% CI: 4.1, 10.6) in the chemotherapy group (HR = 0.70 [95% CI: 0.44, 1.12])1.

“Today’s EC approval of Zykadia as a first-line treatment of ALK+ non-small cell lung cancer is an important step forward for patients with this type of serious disease,” said Bruno Strigini, CEO, Novartis Oncology. “Our commitment to innovation in lung cancer will continue and we look forward to providing additional advancements for patients as the incidence of the disease grows around the world.”
In May, US Food and Drug Administration (FDA) approved the expanded use of Zykadia to include the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive, as detected by an FDA-approved test.

**Novartis Commitment to Lung Cancer**

Worldwide, lung cancer causes more deaths than colon, breast and prostate cancer combined, and an estimated 1.8 million new cases of lung cancer are diagnosed each year.\(^3\)\(^4\)

Over the past decade, Novartis Oncology’s research has supported the evolution of treatment approaches for patients living with mutation-driven types of lung cancer. The company continues its commitment to the global lung cancer community through ongoing studies, as well as the exploration of investigational compounds that target genomic biomarkers in NSCLC.

**About ASCEND-4**

ASCEND-4 is a Phase III randomized, open-label, multicenter, global clinical trial to evaluate the safety and efficacy of Zykadia compared to standard chemotherapy, including maintenance, in adult patients with Stage IIIIB or IV ALK-positive advanced NSCLC who received no prior therapy for their advanced disease. Patients received Zykadia orally at 750 mg/daily or standard pemetrexed-based platinum doublet chemotherapy (pemetrexed 500 mg/m\(^2\) plus cisplatin 75 mg/m\(^2\) or carboplatin AUC 5-6) for four cycles followed by pemetrexed maintenance.

Of 376 patients, 189 (59 with brain metastases) were randomized to Zykadia and 187 (62 with brain metastases) to chemotherapy\(^1\). Approximately 59.5% of patients with measurable brain metastases at baseline did not have prior radiation therapy, the current standard of treatment for baseline brain metastases\(^1\). One hundred and five (105) patients out of the 145 patients (72.4%) that discontinued treatment in the chemotherapy arm received subsequent ALK inhibitor as first antineoplastic therapy. Of these patients 81 received Zykadia\(^1\).

The most common adverse reactions in ASCEND-4 (incidence ≥25% all grades) were diarrhea (85%), nausea (69%), vomiting (67%), fatigue (45%), abdominal pain (40%), decreased appetite (34%) and cough (25%). Grade 3/4 adverse reactions (incidence ≥2%) were fatigue (7%), vomiting (5%), diarrhea (4.8%), abdominal pain (3.7%), weight loss (3.7%), nausea (2.6%) and prolonged QT interval (2.6%). The most common laboratory abnormalities in ASCEND-4 (incidence ≥25% all grades) were increased ALT/AST (91%/86%), increased GGT (84%), increased alkaline phosphatase (81%), creatinine increase (77%), anemia (67%), hyperglycemia (53%), decreased phosphate (38%), increased amylase (37%) and neutropenia (27%). Grade 3/4 laboratory abnormalities (incidence ≥2%) were increased GGT (49%), ALT/AST (34%/21%), increased alkaline phosphatase (12%), hyperglycemia (10%), increased amylase (8%), increased lipase (6%), creatinine increase (4.2%), anemia (4.2%), decreased phosphate (3.7%) and neutropenia (2.1%).

**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 currently approved in over 70 countries worldwide. Please visit [https://www.novartisoncology.com/news/product-portfolio/zykadia](https://www.novartisoncology.com/news/product-portfolio/zykadia) for additional information.

**Zykadia Important Safety Information**

Zykadia may cause stomach upset and intestinal problems in most patients, including diarrhea, nausea, vomiting and stomach-area pain. These problems can be severe. Zykadia may also cause severe liver injury, abnormal heartbeats (slow, fast, or irregular), severe or
life-threatening swelling (inflammation) of the lungs that can lead to death, pancreatitis, and high levels of pancreatic enzymes or glucose (sugar) in blood.

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. Patients and their healthcare provider should decide whether to take Zykadia or breastfeed, but should not do both.

Some side effects can be serious and patients should call your healthcare provider immediately if experiencing changes in your heartbeat (fast, slow, or irregular), lightheadedness, fainting, dizziness, pain in the chest, cough, difficult or painful breathing, wheezing, pain in chest when inhaling, fever, yellow skin and eyes, nausea, loss of appetite, dark urine, and severe upper stomach pain.

Before taking Zykadia, patients should tell their healthcare provider 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. Patients should also tell their healthcare provider about all medicines they take. 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.

Patients should have blood tests before starting treatment with Zykadia to check their liver, pancreas, and the level of sugar in blood. While taking Zykadia, blood tests to check the liver should be performed monthly, while pancreas and the level of sugar in blood should be performed regularly.

The most common adverse reactions with an incidence of ≥10% diarrhea, nausea, vomiting, liver laboratory test abnormalities, fatigue, abdominal pain, decreased appetite, weight decreased, constipation, blood creatinine increased, rash, anemia, and esophageal disorder. Grade 3-4 adverse reactions with an incidence of ≥5% were liver laboratory test abnormalities, fatigue, vomiting, hyperglycemia, nausea, diarrhea.

Please see full Prescribing Information for Zykadia.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "continuing," "must," "continue," "hope," "commitment," "continues," "ongoing," "exploration," "investigational," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Zykadia, or regarding 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 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, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; 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 and reimbursement pressures; safety, quality or 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, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are sold in approximately 155 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 and @NovartisCancer at http://twitter.com/novartiscancer.

For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

References
1. Zykadia® (ceritinib) Summary of Product Characteristics.

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