

China National Drug Administration grants rapid approval of Roche's Alecensa (alectinib) as a treatment for ALK-positive lung cancer

- **Approval follows priority review of Alecensa in China, just eight and nine months after EMA and FDA approvals, respectively**
- **Supporting data showed Alecensa significantly reduced the risk of disease progression or death by more than half compared to crizotinib**
- **Lung cancer incidence rates in China have continued to rise, with NSCLC the most common form of the disease**

Basel, 20 August 2018 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the China National Drug Administration (CNDA) has granted marketing authorisation for Alecensa® (alectinib) as a monotherapy treatment for patients with anaplastic lymphoma kinase (ALK)-positive, advanced non-small cell lung cancer (NSCLC). The approval follows priority review of Alecensa in China and has been granted just eight and nine months after European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approvals, respectively.

“Today’s approval marks a new era for ALK-positive lung cancer patients in China, who now have a treatment option that offers a meaningful, sustained benefit compared with the previous standard of care,” said Sandra Horning, MD, Roche’s Chief Medical Officer and Head of Global Product Development. “It also represents a significant regulatory shift, with the approval received under unprecedented timelines. We are proud to be at the forefront of healthcare innovation in China by helping to bring Alecensa to patients as quickly as possible.”

The approval is based on primary analyses from the pivotal global phase III ALEX study, assessing Alecensa versus crizotinib in the first-line treatment of people with ALK-positive metastatic (advanced) NSCLC, the pharmacokinetics results in Asian patients from the phase III ALESIA study, also investigating Alecensa compared to crizotinib in the first-line setting, and two phase II studies assessing Alecensa in patients who have progressed on or are intolerant to crizotinib.

In updated analyses of the phase III ALEX study presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, the primary endpoint of investigator assessed progression-free survival (PFS) was more than tripled in people who received Alecensa compared to those who received crizotinib (34.8 months [95% CI: 17.7 months-NE) versus 10.9 months [95% CI 9.1-12.9 months]) as assessed by the investigator.^[1]

Further supporting the use of Alecensa in this setting, the phase III ALESIA study, which met its primary endpoint and showed that Alecensa as an initial (first-line) treatment significantly reduced the risk of disease worsening or death (PFS) compared to crizotinib in Asian patients with ALK-positive NSCLC, will be submitted to the CNDA to complete a post-approval agreement.^[2] This is the third phase III study to show

that Alecensa was superior as an initial treatment compared to crizotinib in this type of lung cancer.^[2] Full results from the ALESIA study will be presented at an upcoming medical meeting.

Unlike in western countries, lung cancer incidence rates have continued to rise in China, and the disease is the most commonly diagnosed cancer type and the leading cause of cancer-related deaths.^[3] NSCLC is the most common form of lung cancer, with ALK-positive NSCLC, a distinct form, commonly affecting younger people (median age 52), and those with a light or non-smoking history.^[3,4] Approximately 5% of NSCLC cancer cases are ALK-positive, with around 75,000 people diagnosed with ALK-positive NSCLC every year.^[5-7]

Alecensa is now approved in over 57 countries around the world as an initial (first-line) treatment for ALK-positive advanced NSCLC, including the US, Europe and Japan. It was approved by the FDA and the EMA in November and December 2017, respectively.

About the ALEX study^[8]

ALEX (NCT02075840/B028984) is a randomised, multicentre, open-label, phase III study evaluating the efficacy and safety of Alecensa versus crizotinib in treatment-naïve people with ALK-positive NSCLC whose tumours were characterised as ALK-positive by the VENTANA ALK (D5F3) CDx Assay, a companion immunohistochemistry (IHC) test developed by Roche Tissue Diagnostics. People were randomised (1:1) to receive either Alecensa or crizotinib. The primary endpoint of the ALEX study was PFS as assessed by the investigator, and secondary endpoints included: Independent Review Committee (IRC)-assessed PFS, time to CNS progression, objective response rate (ORR), duration of response (DOR) and overall survival (OS). The multicentre study was conducted in 303 people across 161 sites in 31 countries. OS data are currently considered immature with only about a third of events being reported.

Primary data from the ALEX study were presented at the 2017 ASCO Annual Meeting, and were published in the *New England Journal of Medicine*, with key results showing:^[9,10]

- Alecensa reduced the risk of disease worsening or death (PFS) by 53% compared to crizotinib (HR=0.47, 95% CI: 0.34-0.65, p<0.0001).
- Investigator-reported median PFS (the primary endpoint) was not yet reached in the Alecensa arm (95% CI: 17.7-not reached) versus 11.1 months (95% CI: 9.1-13.1 months) in the crizotinib arm.
- IRC-reported median PFS (a secondary endpoint) was 25.7 months (95% CI: 19.9-not reached) in the Alecensa arm versus 10.4 months (95% CI: 7.7-14.6 months) in the crizotinib arm (HR=0.50, 95% CI: 0.36-0.70; p<0.0001).
- Alecensa reduced the risk of progression in the CNS by 84% (HR=0.16, 95% CI: 0.10-0.28; p<0.0001).
- The 12-month cumulative rate of CNS progression for people with or without existing CNS metastases at baseline was 9.4% (95% CI: 5.4-14.7%) for people treated with Alecensa and 41.4% (95% CI: 33.2-49.4%) for people treated with crizotinib.
- Overall survival (OS) data were considered immature with only about a quarter of events being reported.
- Grade 3-5 adverse events (AEs) were less frequent in the Alecensa arm (41%) compared to the crizotinib arm (50%). In the Alecensa arm, the most common Grade 3-5 AEs (≥5%) were increased liver enzymes (alanine transferase and aspartate transferase; 5%) and decreased red blood cells (anaemia; 5%). AEs

leading to discontinuation (11% vs. 13%), dose reduction (16% vs. 21%) and dose interruption (19% vs. 25%) were all lower in the Alecensa arm compared to the crizotinib arm. Follow-up results from the ALEX study analysis were presented at the 2018 ASCO Annual Meeting, and showed:^[1]

- After a further 10 months of follow-up, Alecensa reduced the risk of disease progression or death (PFS) by 57% compared to crizotinib (HR=0.43, 95% CI: 0.32–0.58). Median follow-up was 27.8 months versus 22.8 months for Alecensa-treated patients and crizotinib-treated patients, respectively.
- Investigator-reported median PFS (the primary endpoint) was 34.8 months in the Alecensa arm (95% CI: 17.7–NE) versus 10.9 months (95% CI: 9.1–12.9 months) in the crizotinib arm.
- ORR for people treated with Alecensa was 82.9% (95% CI: 75.95–88.51) compared to 75.5% (95% CI: 67.84–82.12) for people treated with crizotinib, as assessed by the investigator.
- Alecensa demonstrated superior efficacy compared to crizotinib regardless of the presence or absence of CNS metastases at baseline. Investigator-assessed median PFS for people without CNS metastases at baseline was 34.8 months with Alecensa (95% CI: 22.4–NE) versus 14.7 months (95% CI: 10.8–20.3) with crizotinib (HR=0.47, 95% CI: 0.32–0.71). Investigator-reported median PFS for people with CNS metastases at baseline was 27.7 months in the Alecensa arm (95% CI: 9.2–NE) versus 7.4 months (95% CI: 6.6–9.6) in the crizotinib arm (HR=0.35, 95% CI: 0.22–0.56).
- Improvements were observed in the time between first response to treatment and disease worsening (DOR): 33.3 months with Alecensa versus 11.1 months with crizotinib.
- Grade 3-5 AEs were less frequent in the Alecensa arm (44.7%) compared to the crizotinib arm (51.0%). The most common Grade 3-4 AEs were increased liver enzymes (aspartate transaminase; 5.5%, and alanine transaminase; 4.6%) and increased muscle enzymes (creatine phosphokinase; 3.3%). Serious adverse reactions reported in $\geq 2\%$ of people treated with Alecensa were acute kidney injury (2.6%) and decreased red blood cells (anaemia; 2.0%).
- AEs leading to dose reduction (16.4% vs. 20.5%) and dose interruption (22.4% vs. 25.2%) were lower in the Alecensa arm compared with the crizotinib arm. AEs leading to discontinuation were equal in both arms (13.2%).

About the ALESIA study^[11]

ALESIA (NCT02838420) is a randomised, multicentre, open-label phase III study evaluating the efficacy and safety of Alecensa versus crizotinib, and the pharmacokinetics of Alecensa in Asian patients with treatment-naive ALK-positive advanced NSCLC. Patients were randomised (2:1) to receive either Alecensa or crizotinib. The primary endpoint of the ALESIA study is PFS as assessed by the investigator using the RECIST v1.1 criteria. Secondary endpoints include: IRC-assessed PFS, ORR, DOR, time to CNS progression, OS, health-related quality of life (HRQoL) and safety. The multicentre study was conducted in 187 patients across 27 sites in three countries.

About Alecensa

Alecensa (RG7853/AF-802/RO5424802/CH5424802) is a highly selective, CNS active, oral medicine created at Chugai Kamakura Research Laboratories and is being developed for people with NSCLC whose tumours are identified as ALK-positive. ALK-positive NSCLC is often found in younger people who have a light or non-smoking history.^[4] It is almost always found in people with a specific type of NSCLC called

adenocarcinoma.^[4] Alecensa is now approved in over 57 countries as an initial (first-line) treatment for ALK-positive, metastatic NSCLC, including in the United States, Europe, Japan, China, Turkey, Cuba, Peru, Thailand, Australia, the Dominican Republic, India, Israel, Paraguay, Switzerland, Bolivia, Serbia, South Korea, Singapore and Argentina. In addition, Alecensa is approved in the US, Europe, Japan, Kuwait, Israel, Hong Kong, Canada, South Korea, Switzerland, India, Bolivia, Australia, Singapore, Taiwan, Thailand, Liechtenstein, Argentina, United Arab Emirates, Saudi Arabia, Peru, New Zealand, Cuba, the Dominican Republic, Qatar, Oman, Serbia, Paraguay, Turkey and China for the treatment of people with advanced (metastatic) ALK-positive NSCLC whose disease has worsened after, or who could not tolerate treatment with, crizotinib.

About Roche in lung cancer

Lung cancer is a major area of focus and investment for Roche, and we are committed to developing new approaches, medicines and tests that can help people with this deadly disease. Our goal is to provide an effective treatment option for every person diagnosed with lung cancer. We currently have four approved medicines to treat certain kinds of lung cancer and more than ten medicines being developed to target the most common genetic drivers of lung cancer or to boost the immune system to combat the disease.

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. Thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Roche has been recognised as the Group Leader in sustainability within the Pharmaceuticals, Biotechnology & Life Sciences Industry nine years in a row by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2017 employed about 94,000 people worldwide. In 2017, Roche invested CHF 10.4 billion in R&D and posted sales of CHF 53.3 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

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References

- [1] Camidge R et al. Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced ALK+ NSCLC. Presented at: ASCO Annual Meeting; 2018 Jun 3; Chicago, IL, USA. Abstract #9043.
- [2] F-Hoffmann La Roche. Data on file.
- [3] Zhou C. Lung cancer molecular epidemiology in China: recent trends. *Translational Lung Cancer Research*. 2014;3(5): 270–279.
- [4] Gridelli C, et al. ALK inhibitors in the treatment of advanced NSCLC. *Cancer Treatment Reviews*. 2014;40:300–306.
- [5] Dearden S, et al. Mutation incidence and coincidence in non-small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). *Ann Oncol*. 2013;24:2371–2376.
- [6] GLOBOCAN. Lung Cancer [Internet; cited 2018 July]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
- [7] American Cancer Society. What Is Non-Small Cell Lung Cancer? [Internet; cited 2018 August 15]. Available from: <https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html>.
- [8] ClinicalTrials.gov. A study comparing alectinib with crizotinib in treatment-naïve anaplastic lymphoma kinase-positive advanced non-small cell lung cancer participants (ALEX) [Internet; cited 2018 August 15]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02075840>.
- [9] Shaw AT, et al. Alectinib versus crizotinib in treatment-naïve advanced ALK-positive non-small cell lung cancer (NSCLC): Primary results of the global phase III ALEX study. Presented at: ASCO Annual Meeting; 2017 Jun 2-6; Chicago, IL, USA. Abstract #LBA9008.
- [10] Peters S et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *New England Journal of Medicine*. 2017;377:829–838.
- [11] ClinicalTrials.gov. A Study to Evaluate and Compare the Efficacy and Safety of Alectinib Versus Crizotinib and to Evaluate the Pharmacokinetics of Alectinib in Asian Participants With Treatment-Naïve Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) [Internet; cited 2018 August 15]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02838420>.

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