Media Release

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FDA approves Roche's Alecensa (alectinib) as first-line treatment for people with specific type of lung cancer

- **Approval based on phase III results that showed Alecensa extended the average time that people lived without their disease worsening compared to crizotinib**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the US Food and Drug Administration (FDA) approved the supplemental New Drug Application (sNDA) for Alecensa® (alectinib) for the treatment of people with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test. The approval is based on results from the phase III ALEX study, which showed Alecensa significantly reduced the risk of disease worsening or death (progression-free survival, PFS) by 47% (HR=0.53, 95% CI: 0.38, 0.73, p<0.0001) compared to crizotinib as assessed by independent review committee (IRC). Median PFS was 25.7 months (95% CI: 19.9, not estimable) for people who received Alecensa compared with 10.4 months (95% CI: 7.7, 14.6) for people who received crizotinib. The safety profile of Alecensa was consistent with that observed in previous studies. The study also showed that Alecensa significantly reduced the risk of the cancer spreading to or growing in the brain or central nervous system (CNS) compared to crizotinib by 84% (HR=0.16, 95% CI: 0.10, 0.28, p<0.0001). This was based on a time to CNS progression analysis in which there was a lower risk of progression in the CNS as the first site of disease progression for people who received Alecensa (12%) compared to people who received crizotinib (45%).[1]

"Our goal is to develop medicines that have the potential to significantly improve upon the standard of care," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "In our pivotal study, Alecensa significantly extended the time that people lived without their disease worsening compared to crizotinib and also showed a marked reduction in the risk of their cancer spreading to the brain."

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Alecensa received Breakthrough Therapy Designation from the FDA in September 2016 for the treatment of adults with advanced ALK-positive NSCLC who have not received prior treatment with an ALK inhibitor. Breakthrough Therapy Designation is designed to expedite the development and review of medicines intended to treat serious or life-threatening diseases and to help ensure people have access to them through FDA approval as soon as possible. Results from the phase III ALEX study were simultaneously presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting and published in *The New England Journal of Medicine*. Subsequently, Alecensa was recommended in the National Comprehensive Cancer Network (NCCN) guidelines as a treatment option for first-line ALK-positive metastatic NSCLC (*Category 1, Preferred*).[2]

In addition to today's approval, the FDA also converted Alecensa's initial accelerated approval in December 2015 for the treatment of people with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib (second-line) to a full approval.

About the ALEX study[1]

ALEX (NCT02075840/B028984) is an open-label, randomised, active-controlled, multicentre, phase III study evaluating the efficacy and safety of Alecensa versus crizotinib in people with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease and whose tumours were characterised as ALK-positive by the VENTANA ALK (D5F3) CDx Assay, a immunohistochemistry (IHC) test developed by Roche Tissue Diagnostics. People were randomised (1:1) to receive either Alecensa or crizotinib. The major efficacy outcome measure of the ALEX study is PFS according to RECIST v1.1 as determined by investigator assessment. Additional efficacy outcome measures include: PFS as determined by IRC, time to CNS progression by IRC based on RECIST v1.1, objective response rate (ORR) and duration of response (DOR), and overall survival (OS). Additional exploratory outcome measures were CNS-ORR and CNS-DOR by IRC in people with measurable CNS metastases at baseline. The multicentre study was conducted in 303 people across 161 sites in 31 countries. OS data are currently considered immature with only about a quarter of events being reported.

Results include:

Summary of ALEX Study Key Efficacy Endpoints per IRC Assessment		
	Alecensa n=152	**Crizotinib** n=151
Progression-Free Survival (PFS)		
Number of Events (%)	63 (41%)	92 (61%)
Progressive Disease (%)	51 (34%)	82 (54%)
Death (%)	12 (8%)	10 (7%)
Median in months (95% CI) PFS	25.7 (19.9, NE)	10.4 (7.7, 14.6)
Hazard Ration (HR) (95% CI)[a]	0.53 (0.38, 0.73)	
P-value[b]	p<0.0001	
Overall Response Rate (ORR)		
ORR, % (95% CI)[c]	79% (72, 85)	72% (64, 79)
P-value[d]	0.1652	
Complete Response	13%	6%
Partial Response	66%	66%
Duration of Response (DOR)		
Number of Responders	n=120	n=109
Response Duration ≥ 6 months	82%	57%
Response Duration ≥ 12 months	64%	36%
Response Duration ≥ 18 months	37%	14%

[a, b, d] Stratified by race (Asian vs. non-Asian) and CNS metastases at baseline (yes v. no) for Cox model, log-rank test and Cochran Mantel-Haenszel test, respectively.

[c] Clopper and Pearson exact binomial 95% confidence interval.

CNS: central nervous system, ORR: overall response rate, IRC: independent review committee, CI: confidence interval, NE: not estimable

IRC-Assessed CNS Responses in Patients with Measurable CNS Lesions at Baseline		
	Alecensa	Crizotinib
CNS Tumour Response Assessment	n=21	n=22
CNS ORR, % (95% CI) [a]	81% (58, 95)	50% (28, 72)
Complete Response	38%	5%
Duration of CNS Response		
Number of Responders	17	11
CNS Response Duration ≥ 12 months	59%	36%

[a] Clopper and Pearson exact binomial 95% confidence interval.
IRC: independent review committee; CI: confidence interval; NE: not estimable

Grade ≥ 3 adverse reactions were reported for 41% of patients treated with Alecensa. The most common Grade 3-4 adverse reactions (≥3%) were evidence of kidney dysfunction (increased creatinine; 4.1%), evidence of liver dysfunction (hyperbilirubinemia; 5%), low levels of sodium (hyponatremia; 6%), increased liver enzymes (aspartate transaminase; 6%, and alanine transaminase; 6%), and decreased red blood cells (anaemia; 7%). Serious adverse reactions reported in ≥2% of patients treated with Alecensa were lung infection (pneumonia; 4.6%) and renal impairment (3.9%).

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.[3] It is almost always found in people with a specific type of NSCLC called adenocarcinoma.[3]

Alecensa is currently approved in the United States, Europe, Kuwait, Israel, Hong Kong, Canada, South Korea, Switzerland, India, Australia, Singapore, Taiwan, Liechtenstein, Thailand, United Arab Emirates, Saudi Arabia, Argentina and Turkey for the treatment of people with advanced (metastatic) ALK-positive NSCLC whose disease has worsened after, or who could not tolerate treatment with, crizotinib and in Japan for people with ALK-positive NSCLC.

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 2016 employed more than 94,000 people worldwide. In 2016, Roche invested CHF 9.9 billion in R&D and posted sales of CHF 50.6 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] Food and Drug Administration. Alecensa Prescribing Information.
[2] NCCN Guidelines. Non-small cell lung cancer. Version 7. 2017.
[3] Gridelli C, et al. ALK inhibitors in the treatment of advanced NSCLC. Cancer Treatment Reviews. 2014;40:300-306.