Media Release

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Roche announces vemurafenib improved survival in people with metastatic melanoma who have BRAF V600 mutations

Roche's Personalised Healthcare approach demonstrated through vemurafenib and its investigational companion diagnostic, Roche's cobas 4800 BRAF V600 Mutation Test

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that a Phase III study (BRIM3) showed vemurafenib (RG7204, PLX4032) significantly improved overall survival (OS) in people with previously untreated BRAF V600 mutation-positive metastatic melanoma, compared to chemotherapy. In the study, the risk of death was reduced by 63 percent for people who received vemurafenib compared to those who received chemotherapy (hazard ratio [HR]=0.37, $p<0.0001$). In addition, vemurafenib significantly reduced the risk of the disease getting worse (progression-free survival, or PFS, a co-primary endpoint), by 74 percent compared to chemotherapy (HR=0.26, $p<0.0001$). The safety profile of vemurafenib was consistent with previous clinical studies.

"We are greatly encouraged by the results of BRIM3, which showed that vemurafenib not only extended life and reduced the risk of disease worsening, but also led to significant tumour shrinkage, an important result for this devastating cancer," said Hal Barron M.D., Chief Medical Officer and head, Global Product Development. "We will continue to work closely with regulatory authorities to seek approval for vemurafenib and its companion diagnostic test to provide patients with BRAF-mutated metastatic melanoma a personalised option as soon as possible."

Vemurafenib, a "BRAF-inhibitor," is a personalised investigational medicine designed to specifically inhibit the activity of the mutant BRAF protein that is found in approximately half of all cases of melanoma, the deadliest and most aggressive form of skin cancer. People were enrolled into the study based on BRAF mutation status as determined by the cobas 4800 BRAF V600 Mutation Test, an investigational diagnostic from Roche.

F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
Group Communications Roche Group Media Relations
Tel. +41 61 688 88 88 Fax +41 61 688 27 75 www.roche.com

"The joint development of the investigational cobas BRAF test and vemurafenib exemplify how our personalised healthcare approach is one step closer to becoming a reality for patients," said Paul Brown, Head of Roche Molecular Systems. "In BRIM3 our investigational test enabled rapid and accurate identification of eligible patients with metastatic melanoma."

The results are being featured in a press briefing titled, "Trials That Set New Standards of Care," at 10:00 a.m. on June 5th, 2011 at the Annual Meeting of the American Society of Clinical Oncology (ASCO), and will be presented by Paul Chapman, M.D., Memorial Sloan Kettering Cancer Center in New York, principal investigator of the pivotal BRIM3 study, in the ASCO plenary session (Abstract #LBA4, June 5, 2011 3:15 – 3:30 p.m. CDT, Hall B1). Data will also be published today in the online edition of the *New England Journal of Medicine.*

Additional data from the BRIM3 analysis showed:

- The response rate (those who experienced tumour shrinkage) in the group of patients who received vemurafenib (48.4 percent) was nearly nine times higher than in the group who received chemotherapy (5.5 percent, $p<0.0001$).
- After six months, 84 percent of patients who received vemurafenib were alive compared to 64 percent who received chemotherapy.
- The improvement in OS, PFS and tumour shrinkage with vemurafenib was seen in patients regardless of age, gender, or disease risk factor.
- In January 2011, an independent data monitoring board reviewed data from a planned interim analysis of BRIM3 and recommended the release of study results due to compelling efficacy. The board also recommended that patients in the chemotherapy arm be permitted to crossover or receive vemurafenib instead of chemotherapy.
- The median length of time patients lived (median OS) cannot be reliably estimated at this time because of the small number of patients in long-term follow-up. Median OS estimates when BRIM3 met this co-primary endpoint in January 2011 were 9.2 months in patients receiving vemurafenib and 7.8 months in those receiving chemotherapy; an additional two months of follow-up showed an estimated median OS of 10.5 months for patients receiving vemurafenib, while the median OS estimate for patients receiving chemotherapy remained at 7.8 months.
- The most common Grade 3 or higher adverse events were keratoacanthomas, rash, joint pain, sensitivity to the sun and fatigue. Squamous cell carcinoma (cSCC, a common type of skin cancer) was reported in

12 percent of patients. In cases of cSCC, the lesions were removed and the patients continued with treatment.

Vemurafenib has been granted priority review by the United States (U.S.) Food and Drug Administration (FDA). Roche recently announced the submission of new drug applications for vemurafenib in the United States (U.S.) and European Union (E.U.). While Roche seeks regulatory approval of vemurafenib, a global Expanded Access Programme (EAP) is available for people with previously treated or untreated BRAF V600 mutation-positive metastatic melanoma.

About BRIM3

BRIM3 (Study NO25026) is a global, randomised, open-label, controlled, multicentre, Phase III study that compared vemurafenib to dacarbazine chemotherapy, a current standard of care, in 675 patients with previously untreated BRAF V600 mutation-positive, unresected locally advanced or metastatic melanoma. Co-primary endpoints were OS and PFS. Secondary endpoints included response rate, response duration and safety profile.

Other vemurafenib data at ASCO

Updated results from a single-arm Phase II study (BRIM2) of vemurafenib in previously treated BRAF V600 mutation-positive metastatic melanoma will also be presented in an oral session by Antoni Ribas, M.D., UCLA Jonsson Comprehensive Cancer Center (Abstract 8509). Additionally, results are being presented from an analysis of patients enrolled in a single-arm study that is exploring the use of vemurafenib in tumours that have spread to the brain (brain metastases) in people with BRAF V600 mutation-positive metastatic melanoma (Abstract 8548).

About BRIM2

BRIM2 (Study NP22657) is a global, single-arm, multicentre, open-label Phase II study that enrolled 132 patients with previously treated BRAF V600 mutation-positive metastatic melanoma. Unlike BRIM3, BRIM2 enrolled people who have previously received a treatment for metastatic melanoma. The primary endpoint of the study was best overall response rate and the updated data showed that 53 percent of patients had tumour shrinkage (median duration of response = 6.7 months). People who participated in BRIM2 also lived a median of 6.7 months without their disease getting worse (median PFS). Median OS has not yet been reached after a median follow-up of 10 months.

The safety profile of vemurafenib in BRIM2 was generally consistent with that previously reported in clinical studies of vemurafenib. Grade 3 cSCC was reported in 26 percent of patients. In cases of cSCC, the lesions were removed and the patients continued with treatment. The most common adverse events of any severity were joint pain, rash, sensitivity to the sun, and fatigue.

About the vemurafenib brain metastases safety study

The vemurafenib brain metastases safety study is a single-arm study enrolling 20 patients with BRAF V600 mutation-positive metastatic melanoma with brain metastases. Preliminary data from patients enrolled in the study to date suggested that vemurafenib may have activity in brain metastases. The safety profile of vemurafenib was generally consistent with that observed in other clinical trials.

Roche is planning to initiate a global, multicentre Phase II study exploring the efficacy and safety profile of vemurafenib in people with BRAF V600 mutation-positive metastatic melanoma that has spread to the brain.

About metastatic melanoma and BRAF

When melanoma is caught early, it is generally a curable disease. However, when it spreads to other parts of the body, it is the deadliest and most aggressive form of skin cancer. A person with metastatic melanoma typically has on average a short life expectancy that is measured in months. Less than one in four people are expected to be alive one year after a diagnosis and every year there are an estimated 40,000 deaths worldwide from the disease.

The BRAF protein is a key component of the RAS-RAF pathway involved in normal cell growth and survival. Mutations that lock the BRAF protein in an active state may cause excessive signalling in the pathway, leading to uncontrolled cell growth and survival. These mutations are thought to occur in an estimated half of all cases of melanoma and eight percent of solid tumours.

About vemurafenib

Vemurafenib is an investigational, oral, small molecule that is designed to selectively inhibit a cancer-driving mutated form of the BRAF protein. Vemurafenib is being co-developed under a 2006 license and collaboration agreement between Roche and Plexxikon, a member of the Daiichi Sankyo Group.

Roche is pursuing a broad development programme with vemurafenib that includes combinations with other medicines (both approved and investigational, from Roche and other companies), as well as studies in other

tumour types. While Roche seeks approval of vemurafenib, vemurafenib is available to eligible patients with BRAF V600 mutation-positive metastatic melanoma through a global patient access programme. More information about this program or other vemurafenib studies is available at www.clinicaltrials.gov (in the U.S.) or the Roche Clinical Trials Registry at www.roche-trials.com (in the EU).

About the cobas 4800 BRAF V600 Mutation Test

The cobas 4800 BRAF V600 Mutation Test is an investigational, polymerase chain reaction-based companion diagnostic being developed by Roche to identify people whose tumours carry the BRAF V600 mutation. Roche submitted a Premarket Approval Application (PMA) for the cobas 4800 BRAF V600 Mutation Test in the U.S. The test will also be registered in Europe.

About Roche

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company with truly differentiated medicines in oncology, virology, inflammation, metabolism and CNS. Roche is also the world leader in in-vitro diagnostics, tissue-based cancer diagnostics and a pioneer in diabetes management. Roche's personalised healthcare strategy aims at providing medicines and diagnostic tools that enable tangible improvements in the health, quality of life and survival of patients. In 2010, Roche had over 80'000 employees worldwide and invested over 9 billion Swiss francs in R&D. The Group posted sales of 47.5 billion Swiss francs. Genentech, United States, is a wholly owned member of the Roche Group. Roche has a majority stake in Chugai Pharmaceutical, Japan. For more information: www.roche.com.

Roche Group Media Relations

Phone: +41 -61 688 8888 / e-mail: basel.mediaoffice@roche.com

- Alexander Klauser (Head)
- Silvia Dobry
- Daniel Grotzky
- Claudia Schmitt