

Basel, 30 May 2015

## **Updated data showed Roche's investigational combination of cobimetinib and Zelboraf (vemurafenib) helps people with advanced melanoma live for a year without their disease worsening**

- Phase III coBRIM study demonstrated a median progression-free survival of 12.3 months with cobimetinib plus Zelboraf
- Additional data from Phase Ib BRIM7 study showed 61 percent of people who had not been previously treated with a BRAF inhibitor were alive after two years
- U.S. FDA is expected to make a decision on Roche's new drug application for cobimetinib in combination with Zelboraf by August 2015, and a marketing authorization application is under review by the EMA

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced follow-up data from two studies of the investigational MEK inhibitor cobimetinib in combination with Zelboraf<sup>®</sup> (vemurafenib). Updated data from the pivotal coBRIM Phase III study showed the combination helped people with previously untreated BRAF V600 mutation-positive advanced melanoma live a median of one year (12.3 months) without their disease worsening or death (progression-free survival; PFS) compared to 7.2 months with Zelboraf alone (hazard ratio [HR]=0.58, 95 percent confidence interval [CI] 0.46-0.72).<sup>1</sup>

"The combination of cobimetinib and Zelboraf extended the time people lived without their disease getting worse to a year," said Sandra Horning, M.D., Chief Medical Officer and Head of Global Product Development. "These results are exciting because they underscore the importance of combining medicines that target the signals, which cause about half of all melanomas to grow."

The updated results from coBRIM also demonstrated higher response rates with cobimetinib and Zelboraf compared to Zelboraf alone. The objective response rate (ORR) with the combination was 70 percent (16 percent complete response [CR], 54 percent partial response [PR]) compared to 50 percent (11 percent CR, 40 percent PR) in the Zelboraf arm.<sup>1</sup> With further follow-up, the complete response rate increased from 10

percent to 16 percent with the combination as some patients who had a partial response achieved a complete response after more than one year of treatment. The safety profile of cobimetinib and Zelboraf was consistent with safety data previously reported. The most common adverse events in the combination arm were diarrhea, rash, nausea, fever, sun sensitivity, liver lab abnormalities, elevated creatine phosphokinase (CPK, an enzyme released by muscles) and vomiting.

Follow-up data from the Phase Ib BRIM7 study showed cobimetinib plus Zelboraf helped people who had not been previously treated with a BRAF inhibitor live a median of more than two years (28.5 months). In addition, extended follow-up showed 61 percent of patients who had not been previously treated with a BRAF inhibitor were alive after two years.<sup>2</sup> The safety profile was consistent with the previous analyses. The incidence of serous retinopathy, cardiomyopathy and cutaneous squamous cell carcinoma were similar to those previously reported.

The coBRIM and BRIM7 data will be presented during the 51<sup>st</sup> Annual Meeting of the American Society of Clinical Oncology (ASCO) meeting in Chicago held from 29 May – 2 June. CoBRIM data will be presented in an oral session presentation today by Dr. James Larkin, FRCP, The Royal Marsden Hospital, London, UK (Abstract #9006, 30 May, 3:15-3:27 pm CDT). The BRIM7 data will be presented in a poster presentation by Dr. Anna Pavlick, New York University Medical Center (Abstract #9020, 1 June, 1:15-4:45 pm CDT).

The cobimetinib new drug application for BRAF V600 mutation-positive advanced melanoma was granted priority review by the U.S. Food and Drug Administration and a decision is expected by August 2015. The European Medicines Agency is expected to make a decision on Roche's marketing authorization application for cobimetinib before the end of 2015.

### **About the coBRIM study**

CoBRIM is an international, randomised, double-blind, placebo-controlled Phase III study evaluating the safety and efficacy of 60 mg once daily of cobimetinib in combination with 960 mg twice daily of Zelboraf, compared to 960 mg twice daily of Zelboraf alone. In the study, 495 patients with BRAF V600 mutation-positive unresectable locally advanced or metastatic melanoma (detected by the cobas® 4800 BRAF Mutation Test) and previously untreated for advanced disease, were randomised to receive Zelboraf every day on a 28-day cycle plus either cobimetinib or placebo on days 1-21. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. Investigator-assessed PFS is the primary endpoint. Secondary endpoints include PFS by independent review committee, objective response rate,

overall survival, duration of response and other safety, pharmacokinetic and quality of life measures.<sup>3</sup>

The most common adverse events reported in patients taking cobimetinib in combination with Zelboraf ( $\geq 20\%$ ) were diarrhea, rash, nausea, fever, sun sensitivity, liver lab abnormalities, elevated creatine phosphokinase (CPK, an enzyme released by muscles) and vomiting. Serous retinopathy (collection of fluid under the retina) was observed at a higher frequency in the combination arm (26 vs. 3 percent) with most of these events either Grade 1 or 2, asymptomatic, and temporary in nature. Some adverse events, including cutaneous squamous cell carcinomas and keratoacanthomas, were reported less frequently in the combination arm.

#### **About the BRIM7 study**

BRIM7 is a Phase Ib study of 129 patients evaluating the safety and tolerability of cobimetinib in combination with Zelboraf in people with BRAF V600 mutation-positive unresectable or metastatic melanoma who had either not been previously treated with a BRAF inhibitor or had shown disease progression following treatment with a BRAF inhibitor. The primary endpoint of the BRIM7 study focused on safety, tolerability, and the identification of an optimal dose. The secondary outcome measures focused on efficacy. Patients in the dose-escalation stage of the study received cobimetinib 60, 80 or 100 mg once daily given on a schedule of 14 days on/14 days off; 21 days on/7 days off; or continuously for 28 days, and Zelboraf 720 or 960 mg twice daily continuously. Following the dose-escalation stage, two dose levels were selected for further investigation: cobimetinib 60 mg once daily for 21 days on/7 days off and Zelboraf (720 mg or 960 mg twice daily).<sup>4</sup>

The most common adverse events were mild to moderate in severity, and the overall frequency of adverse events with an extended median follow-up of up to 21 months have remained consistent without new safety signals.

#### **About the cobimetinib and Zelboraf combination**

Cobimetinib is designed to selectively block the activity of MEK,<sup>5</sup> one of a series of proteins inside cells that make up a signalling pathway that helps regulate cell division and survival.<sup>6</sup> Cobimetinib binds to MEK while Zelboraf binds to mutant BRAF, another protein on the pathway, to interrupt abnormal signalling that can cause tumours to grow.<sup>7,8</sup>

### **About cobimetinib**

Cobimetinib (GDC-0973, XL518) was discovered by Exelixis Inc. and is being developed in collaboration with Exelixis. Cobimetinib is also being investigated in combination with several investigational medicines, including an immunotherapy, in several tumour types such as non-small cell lung cancer and colorectal cancer.

### **About Zelboraf**

Zelboraf was the first prescription treatment for patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by a validated test, such as Roche's cobas 4800 BRAF Mutation Test. Zelboraf is not indicated for use in patients with wild-type BRAF melanoma.<sup>9</sup> It is now approved in more than 90 countries and has been used to treat more than 11,000 patients worldwide. Zelboraf was co-developed under a 2006 license and collaboration agreement between Roche and Plexxikon, now a member of the Daiichi Sankyo Group.

### **About melanoma**

Melanoma is less common, but more aggressive and deadlier than other forms of skin cancer.<sup>10,11</sup> BRAF is mutated in approximately half of melanomas.<sup>12</sup> When melanoma is diagnosed early, it is generally a curable disease,<sup>13,14</sup> but most people with advanced melanoma have a poor prognosis.<sup>11</sup> More than 232,000 people worldwide are currently diagnosed with melanoma each year<sup>15</sup> and more than 55,000 people worldwide die every year from melanoma skin cancers.<sup>15</sup> In recent years, there have been significant advances in treatment for metastatic melanoma and people with the disease have more options. However, it continues to be a serious health issue with a high unmet need and a steadily increasing incidence over the past 30 years.<sup>16</sup>

### **About Roche in skin cancer**

Roche has been studying new treatments for skin cancer for nearly 20 years. In the last five years, we have brought two new medicines to people with potentially disfiguring or deadly skin cancers. Our two first-in-class approved medicines, Erivedge and Zelboraf, have significantly improved treatment options for advanced stages of the most common and most serious skin cancers. Zelboraf was the first targeted oral medicine to be approved with a companion diagnostic. Erivedge is the first hedgehog pathway inhibitor and first medicine ever approved for advanced forms of the most common skin cancer, basal cell carcinoma. Roche is continuing to study Zelboraf, Erivedge and cobimetinib as monotherapies and in combination with other investigational medicines, such as cancer immunotherapies, in several cancer types and diseases.

## **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, immunology, infectious diseases, ophthalmology and neuroscience. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Roche's personalised healthcare strategy aims at providing medicines and diagnostics that enable tangible improvements in the health, quality of life and survival of patients. Founded in 1896, Roche has been making important contributions to global health for more than a century. Twenty-eight medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and chemotherapy.

In 2014, the Roche Group employed 88,500 people worldwide, invested 8.9 billion Swiss francs in R&D and posted sales of 47.5 billion Swiss francs. 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 [roche.com](http://roche.com).

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## **Additional information**

- Roche in Oncology: [www.roche.com/media/media\\_backgrounduer/media\\_oncology.htm](http://www.roche.com/media/media_backgrounduer/media_oncology.htm)

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