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Daiichi-Sankyo Plexxikon

Press Release

Daiichi Sankyo and Plexxikon Announce FDA Approval of Cobimetinib in Combination with Zelboraf® (vemurafenib) in Advanced Melanoma

- *Combination of cobimetinib and Zelboraf reduced risk of disease worsening or death by half compared to Zelboraf alone*
- *Daiichi Sankyo, Inc. to co-promote cobimetinib in combination with Zelboraf along with Genentech and Exelixis*
- *New co-promote agreement along with pipeline of innovative oncology compounds demonstrate Daiichi Sankyo's commitment to oncology*

Parsippany, NJ and Berkeley, CA – (November 10, 2015) – Daiichi Sankyo, Inc. and Plexxikon Inc., a member of the Daiichi Sankyo Group, today announced the U.S. Food and Drug Administration (FDA) approved cobimetinib, developed by Genentech, a member of the Roche Group, and Exelixis Inc., for the treatment of people with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma in combination with Zelboraf® (vemurafenib). Cobimetinib and Zelboraf are not used to treat melanoma with a normal BRAF gene. Cobimetinib in combination with Zelboraf will be co-promoted in the United States by Genentech, Daiichi Sankyo, Inc. and Exelixis. Cobimetinib will be available within two weeks.

"We are excited to bring a new dual pathway treatment option to patients with BRAF mutation-positive advanced melanoma," said Ken Keller, President, U.S. Commercial, Daiichi Sankyo, Inc. "We look forward to strengthening our existing relationship with Genentech with the ultimate goal of benefiting patients with advanced melanoma."

The FDA approval of cobimetinib is based on results from the Phase III coBRIM study, which showed cobimetinib plus Zelboraf reduced the risk of disease worsening or death (progression-free survival; PFS) by about half in people who received the combination (HR=0.56, 95 percent CI 0.45-0.70; $p<0.001$), with a median PFS of 12.3 months for cobimetinib plus Zelboraf compared to 7.2 months with Zelboraf alone. An interim analysis also showed the combination of cobimetinib and Zelboraf helped people live significantly longer (overall survival) than Zelboraf alone (HR=0.63, 95 percent CI 0.47-0.85; $p=0.0019$). The objective response rate (tumor shrinkage) was higher with cobimetinib plus Zelboraf compared to Zelboraf alone (70 vs. 50 percent; $p<0.001$), as was the complete response rate (complete tumor shrinkage, 16 vs. 10 percent).

Possible serious side effects with cobimetinib include risk of skin cancers, increased risk of bleeding, heart problems that can lead to inadequate pumping of the blood by the heart, rash, eye problems, abnormal liver test or liver injury, increased levels of an enzyme in the blood, and photosensitivity. The most common side effects of cobimetinib include diarrhea, sunburn or sun sensitivity, nausea, fever and vomiting. Cobimetinib can also cause changes in blood test results.

"This FDA approval underscores the importance of combining two different targeted medicines to help delay disease progression and help people live longer," said Gideon Bollag, PhD, Chief Executive Officer of Plexxikon.

About the coBRIM study

CoBRIM is an international, randomized, double-blind, placebo-controlled Phase III study evaluating the safety and efficacy of 60 mg once daily of cobimetinib plus 960 mg twice daily of Zelboraf compared to 960 mg twice daily of Zelboraf plus placebo. 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 randomized 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.

About Cobimetinib plus Zelboraf

Cobimetinib and Zelboraf are prescription medicines used in combination to treat melanoma that has spread to other parts of the body or cannot be removed by surgery, and that has a certain type of abnormal "BRAF" gene. Found in approximately half of melanomas, mutated BRAF causes abnormal signaling inside cancer cells leading to tumor growth. Zelboraf is designed to inhibit some mutated forms of BRAF and cobimetinib is designed to inhibit some forms of MEK. Both BRAF and MEK are proteins in a cell signaling pathway that help control cell growth and survival. When used in combination, cobimetinib and Zelboraf are thought to reduce cancer cell growth longer than with Zelboraf alone. A patient's healthcare provider will perform a test to make sure cobimetinib and Zelboraf are right for the patient. It is not known if cobimetinib and Zelboraf are safe and effective in children under 18 years of age.

About Zelboraf

Zelboraf was the first prescription treatment for patients with a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery, and has a certain type of abnormal BRAF gene as detected by an FDA-approved test. Zelboraf is now approved in more than 90 countries and has been used to treat more than 20,000 patients worldwide. Daiichi Sankyo, Inc. currently co-promotes Zelboraf with Genentech in the United States.

Zelboraf was discovered by scientists at Plexxikon in 2005 and co-developed under a 2006 license and collaboration agreement between Roche and Plexxikon. In 2011, Daiichi Sankyo acquired Plexxikon and upon FDA approval of Zelboraf in August 2011, co-promotion rights for Zelboraf were transferred to Daiichi Sankyo, Inc.

About Cobimetinib

Cobimetinib is a prescription medicine used with Zelboraf for the treatment of patients with a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery, and has a certain type of abnormal BRAF gene. Cobimetinib was discovered by Exelixis Inc. and was developed by Genentech. In April 2015, Genentech and Daiichi Sankyo, Inc. entered into a co-promotion agreement for cobimetinib in combination with Zelboraf.

About Advanced Melanoma

Melanoma is less common, but more aggressive and deadlier than other forms of skin cancer.[1,2] When melanoma is diagnosed early, it is generally a curable disease,[1] but most people with advanced melanoma have a poor prognosis.[2] The American Cancer Society estimates there will be nearly 74,000 new cases of melanoma and 10,000 melanoma deaths this year in the United States.[1]

In recent years, there have been significant advances in treatment for advanced 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.[1]

Cobimetinib Important Safety Information

Before taking cobimetinib, patients should tell their doctor if they:

- have any previous or current skin problems other than melanoma
- have any medical conditions and/or are on any medications that increase your risk of bleeding
- have any heart problems
- have any eye problems
- have any liver problems

- have any muscle problems
- have any other medical conditions
- are pregnant or plan to become pregnant. Cobimetinib can harm an unborn baby.
    - Patients who take cobimetinib should use effective methods of birth control during treatment, for at least two weeks after stopping cobimetinib, and for at least two months after stopping Zelboraf.
    - Patients should talk to their healthcare provider about birth control methods that may be right for them.
    - Patients should tell their healthcare provider right away if they become pregnant or think they are pregnant during treatment with cobimetinib.
- are breastfeeding or plan to breastfeed. It is not known if cobimetinib passes into breast milk, so patients should not breastfeed during treatment with cobimetinib and for two weeks after the final dose. Patients should talk to their healthcare provider about the best way to feed their baby during this time.

Patients should tell their healthcare provider about all the medicines they take, including prescription and over-the-counter medicines, vitamins and herbal supplements because some types of medicines will make cobimetinib more harmful or less effective. Patients should know the medicines they take and keep a list of them to show their healthcare provider and pharmacist when they get a new medicine.

Patients should avoid sunlight while taking cobimetinib. Cobimetinib can make patients‘ skin sensitive to sunlight and cause them to burn more easily and get severe sunburns. To help protect against sunburn:

- When patients go outside they should wear clothes that protect their skin, including their head, face, hands, arms and legs.
- Patients should use lip balm and a broad-spectrum sunscreen with SPF 30 or higher.

Cobimetinib may cause serious side effects, including:

- **Risk of skin cancers.** Cobimetinib may cause skin cancers (cutaneous squamous cell carcinoma, keratoacanthoma or basal cell carcinoma).

Patients must check their skin and tell their doctor right away about any skin changes, including:

- new wart

- skin sore or reddish bump that bleeds or does not heal
- change in size or color of a mole

A patient's healthcare provider should check their skin before they start taking cobimetinib and every two months while taking cobimetinib. A patient's healthcare provider may continue to check their skin for six months after they stop taking cobimetinib.

- **Increased risk of bleeding.** Cobimetinib may cause bleeding, including blood in the urine, rectal bleeding, unusual or excessive vaginal bleeding, bleeding of the gums and bleeding within the brain (cerebral hemorrhage). A patient should tell their healthcare provider right away if they experience any of these symptoms:
  - red or black stools that look like tar
  - blood in the urine
  - headache, dizziness or feeling weak
  - abdominal pain
  - unusual vaginal bleeding

- **Heart problems that can lead to inadequate pumping of the blood by the heart.** A patient's healthcare provider should perform tests before the patient starts taking cobimetinib and during a patient's treatment with cobimetinib to check the ability of the heart to pump blood. Signs and symptoms of a decrease in the amount of blood pumped include:
  - persistent coughing or wheezing
  - shortness of breath
  - swelling of their ankles and feet
  - tiredness
  - increased heart rate

- **Rash.** Patients should tell their healthcare provider right away if they experience any of these symptoms:
  - a rash that covers a large area of their body, blisters or peeling skin

- **Eye problems.** Patients should tell their healthcare provider right away if they experience any of these symptoms during treatment with cobimetinib:
  - blurred vision
  - distorted vision

- partly missing vision
- halos
- any other vision changes

Some of these eye problems may be a result of something called "serous retinopathy" (a build-up of fluid under the retina of the eye). A patient's healthcare provider should check their eyes if they notice any of the symptoms above.

- **Abnormal liver test or liver injury.** A patient's healthcare provider should perform blood tests before the start taking cobimetinib, and during treatment. A patient should tell their healthcare provider right away if you experience any of these symptoms:
  - yellowing of their skin or the white of their eyes
  - dark or brown (tea color) urine
  - nausea or vomiting
  - feeling tired or weak
  - loss of appetite

- **Increased levels of an enzyme in the blood.** Creatine phosphokinase (CPK) is an enzyme that is primarily found in the muscle, heart and brain. Treatment with cobimetinib may increase the level of this enzyme in your blood and be a sign of muscle damage. A patient's healthcare provider should perform a blood test before and during treatment. Increased blood levels of CPK can also be an indication of a serious condition caused by injury to the muscles (rhabdomyolysis). A patient should tell their healthcare provider right away if they experience any of these symptoms:
  - muscle aches
  - muscle spasms and weakness
  - dark, reddish urine

- **Photosensitivity.** A patient's skin may become more sensitive to sunlight while taking cobimetinib. A patient should tell their healthcare provider if they notice any of the following symptoms:
  - red, painful, itchy skin that is hot to touch
  - sun rash
  - skin irritation bumps or tiny papules
  - thicken, dry, wrinkled skin

The most common side effects of cobimetinib include:

- diarrhea
- sunburn or sun sensitivity
- nausea
- vomiting
- fever

A patient's healthcare provider will take blood tests while they are taking cobimetinib. The most common changes to blood tests include:

- increased blood levels of liver enzymes (GGT, ALT or AST)
- increased blood level of enzyme from muscle (creatine phosphokinase)
- decreased blood level of phosphate, sodium or potassium
- increased blood level of liver or bone enzyme (alkaline phosphatase)
- decreased blood level of a type of white blood cell (lymphocyte)

Patients should tell their healthcare provider if they have any side effect that bothers them or that does not go away.

These are not all the possible side effects of cobimetinib. For more information about side effects, patients should ask their healthcare provider or pharmacist. Patients should call their doctor for medical advice about side effects.

Patients should talk to their doctor for medical advice about side effects. Report side effects to FDA at (800) FDA-1088. Report side effects to Genentech at (888) 835-2555.

Please see accompanying full Cobimetinib Prescribing Information and Patient Information for additional important safety information.

Zelboraf Important Safety Information

Zelboraf can cause serious side effects, including risk of cancers. Zelboraf may cause a type of skin cancer called cutaneous squamous cell carcinoma (cuSCC). New melanoma lesions have occurred in people who take Zelboraf. Zelboraf may also cause another type of cancer called non-cutaneous squamous cell carcinoma (SCC). Patients must talk with their healthcare provider about their risk for these cancers.

Patients must check their skin and tell their doctor right away about any skin changes, including:

- A new wart
- A skin sore or reddish bump that bleeds or does not heal
- A change in size or color of a mole

A patient's doctor should check their skin before the patient starts taking Zelboraf, and every two months while the patient is taking Zelboraf, to look for any new skin cancers. Their doctor may continue to check the patient's skin for six months after the patient stops taking Zelboraf.

A patient's doctor should also check for cancers that may not occur on the skin. Patients should tell their doctor about any new symptoms they get while taking Zelboraf.

Before taking Zelboraf, patients should tell their doctor if they:

- Have any heart problems, including a condition called long QT syndrome
- Have liver or kidney problems
- Have had or are planning to receive radiation therapy
- Have been told they have low blood levels of potassium, calcium or magnesium
- Have any other medical conditions
- Are pregnant or plan to become pregnant. Zelboraf can harm an unborn baby.
    - Females who are able to become pregnant, and males who take Zelboraf, should use birth control during treatment and for at least two months after stopping Zelboraf.
    - Patients should talk to their doctor about birth control methods that may be right for them.
    - Patients should tell their doctor right away if they become pregnant during treatment with Zelboraf.
- **Are breastfeeding or plan to breastfeed.** A patient and their doctor should decide if the patient will take Zelboraf or breastfeed. Patients should not do both.

Patients should tell their doctor about all of the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Patients should avoid sunlight while they are taking Zelboraf. Zelboraf can make a patient's skin sensitive to sunlight. Patients may burn more easily and get severe sunburns. To help protect against sunburn:

- When a patient goes outside, they should wear clothes that protect their skin, including their head, face, hands, arms, and legs.

- Patients should use lip balm and a broad-spectrum sunscreen with SPF 30 or higher.

Possible Side Effects of Zelboraf

- **Allergic reactions can happen while taking Zelboraf, and can be severe.** Patients should stop taking Zelboraf and get medical help right away if they get any of these symptoms of an allergic reaction:
  - Rash or redness all over their body
  - Trouble breathing or swallowing
  - Swelling of the face, lips, or tongue
  - Throat tightness or hoarseness
  - Feel faint
  - Fast heartbeat

- **Severe skin reactions.** Patients should stop taking Zelboraf and call their doctor right away if they get a skin rash with any of the following symptoms, because they may have a severe skin reaction:
  - Blisters on their skin
  - Blisters or sores in their mouth
  - Peeling of their skin
  - Fever
  - Redness or swelling of their face, hands, or soles of their feet

- **Changes in the electrical activity of the heart called QT prolongation. QT prolongation can cause irregular heartbeats that can be life threatening.** A patient's doctor should do tests before a patient starts taking Zelboraf and during their treatment with Zelboraf to check the electrical activity of the heart. Patient should tell their doctor right away if they feel faint, lightheaded, dizzy or feel their heart beating irregularly or fast while taking Zelboraf. These may be symptoms related to QT prolongation.

- **Liver injury.** A patient's doctor should do blood tests to check their liver function before they start taking Zelboraf and during treatment. Patients should tell their doctor right away if they get any of these symptoms of a liver problem during treatment:
  - Yellowing of their skin or the white part of their eyes
  - Dark or brown (tea color) urine
  - Nausea or vomiting
  - Loss of appetite
  - Pain on the right side of their stomach

- **Eye problems.** Patients should tell their doctor right away if they get any of these symptoms during treatment with Zelboraf
  - Eye pain, swelling, or redness
  - Blurred vision or other vision changes

- **Worsening side effects from radiation treatment.** Patients should tell their healthcare provider if they have had or are planning to receive radiation therapy.

The most common side effects include:

- Joint pain
- Rash
- Hair loss
- Tiredness
- Sunburn or sun sensitivity
- Nausea
- Itching
- Warts

Patients should tell their doctor if they have any side effect that bothers them or does not go away. These are not all of the possible side effects of Zelboraf. For more information about side effects, patients should ask their doctor or pharmacist.

Patients may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. Patients may also report side effects to Genentech at (888) 835-2555.

Patients should read the full Prescribing Information and Medication Guide for additional important safety information.

About Daiichi Sankyo Oncology

In addition to co-promoting cobimetinib and Zelboraf with Genentech in the United States, Daiichi Sankyo is focused on the discovery and development of novel oncology agents with the goal of delivering first-in-class and best-in-class treatments that address unmet medical needs. The oncology pipeline of Daiichi Sankyo continues to grow and currently includes both small molecules and monoclonal antibodies with novel targets in both solid and hematological cancers.

Daiichi Sankyo currently has four compounds in phase 3 clinical development in the U.S. each with a unique mechanism of action with three focusing on rare or orphan indications. These investigational

compounds include quizartinib, an oral FLT3 inhibitor, for relapsed or refractory FLT3-ITD-positive acute myeloid leukemia (AML); pexidartinib (PLX3397), an oral CSF-1R inhibitor, for tenosynovial giant cell tumor (TGCT) being developed with Plexxikon, a member of the Daiichi Sankyo Group; tivantinib, an oral MET inhibitor, for second-line treatment of hepatocellular carcinoma in partnership with ArQule, Inc.; and patritrumab, a HER3 monoclonal antibody, for non-small cell lung cancer.

About Plexxikon

Plexxikon, a member of the Daiichi Sankyo Group since April 2011, is a leader in the structure-guided discovery and development of novel small molecule pharmaceuticals to treat human disease. The company's drug Zelboraf® (vemurafenib/PLX4032) was approved by the FDA in 2011, and is being co-promoted in the U.S. by Daiichi Sankyo Inc. and Genentech. Plexxikon is developing a portfolio of preclinical and clinical stage compounds to address significant unmet medical needs in oncology and other therapeutic areas. Plexxikon's Scaffold-Based Drug Discovery™ platform integrates multiple state-of-the-art technologies, including structural screening as a key component that provides a significant advantage over other drug discovery approaches.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address diversified, unmet medical needs of patients in both mature and emerging markets. With over 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 17,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to its strong portfolio of medicines for hypertension, dyslipidemia, bacterial infections, and thrombotic disorders, the Group's research and development is focused on bringing forth novel therapies in cardiovascular-metabolic diseases, pain management, and oncology, including biologics. For more information, please visit: www.daiichisankyo.com. Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit www.dsi.com.

Contact

Jennifer Brennan
Daiichi Sankyo, Inc.
jbrennan2@dsi.com
+1 973 944 2393 (office)
+1 201 709 9309 (mobile)

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[2] Finn L, et al. Therapy for metastatic melanoma: the past, present, and future. BMC Med. 2012;10:23.