Investor News

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Bayer, Bristol-Myers Squibb and Ono Pharmaceutical enter into a clinical collaboration agreement to investigate Stivarga® (regorafenib) and Opdivo® (nivolumab) as combination therapy in patients with colorectal cancer

- Combination of regorafenib and nivolumab vs. regorafenib alone to be evaluated in patients with micro-satellite stable metastatic colorectal cancer
- Companies plan indication-seeking trial

Leverkusen, Germany, July 18, 2019 – Bayer, Bristol-Myers Squibb Company (NYSE: BMY) and Ono Pharmaceutical Co.,Ltd. ("Ono") announced today that the three companies have entered into a clinical collaboration agreement to evaluate the combination of Bayer's multikinase inhibitor, Stivarga® (regorafenib) and Bristol-Myers Squibb's / Ono's anti-PD-1 immune checkpoint inhibitor, Opdivo® (nivolumab) in patients with micro-satellite stable metastatic colorectal cancer (MSS mCRC), the most common form of mCRC.

Regorafenib as monotherapy has demonstrated an overall survival benefit versus placebo in the pivotal Phase III CORRECT study and has shown activity irrespective of micro-satellite status in a retrospective analysis from this study, though with limited responses observed. Despite progress in the treatment of CRC including the advance of effective immuno-oncology
(I-O) treatments for certain subsets of CRC, around 95% of mCRC patients have MSS tumors, for which I-O monotherapy treatment approaches have shown limited activity. Thus, the need for additional treatment options including combination approaches remains high. Encouraging early data have been seen with the combination of regorafenib and nivolumab. In a Phase 1b investigator sponsored trial from Japan called REGONIVO (NCT03406871, EPOC1603), the combination of regorafenib and nivolumab has shown promising preliminary efficacy results. The detailed data of the study were presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.

“The data seen in REGONIVO warrant further exploration of the combination of regorafenib and nivolumab in patients with colorectal cancer. Regorafenib has proven its efficacy and positive safety profile as a third-line monotherapy and we are excited to enter into a clinical collaboration to evaluate this combination with the hope to deliver an additional therapeutic benefit to patients,” said Scott Z. Fields, M.D., Senior Vice President and Head of Oncology Development at Bayer's Pharmaceuticals Division.

“We continue to invest in innovative approaches to maximize the potential of our pipeline, and interrogate new combinations to help more patients with cancers typically not responsive to I-O therapy,” said Fouad Namouni, M.D., Head of development, oncology, Bristol-Myers Squibb. “We are looking forward to a strong collaboration to investigate nivolumab with regorafenib, with the goal of serving more patients who have cancer.”

“We have been actively engaged in the development of nivolumab including combination therapies with other agents. We are excited to initiate the clinical collaboration with Bayer and Bristol-Myers Squibb to investigate this combination therapy as a new treatment option for patients with colorectal cancer and other types of cancer,” said Kiyoaki Idemitsu, Corporate Officer, Executive Director, Clinical Development, Ono.

Further terms of the clinical collaboration were not disclosed.

About Colorectal Cancer

Colorectal Cancer (CRC) is the third most common cancer worldwide, with 1.8 million cases occurring every year, and the second leading cause of cancer-related death with 1 in 10 cancer-related deaths coming from CRC every year. The five-year survival estimate for CRC on average is 55% but is highly variable dependent on the stage of the disease (from 74% for patients with Stage I disease to only 6% for Stage IV patients). Several forms of genomic instability are known to drive the development of CRC. 15% of the CRC patients have microsatellite instability (MSI) while the other 85% have a so called micro-satellite stable (MSS) status. The identification of MSS status is clinically important as studies have revealed that MSI tumors have a better stage-adjusted survival compared with MSS tumors. MSS tumors have been referred to as “cold” tumors. These tumors often exist in an environment that suppresses the immune system. Research continues to study ways to effectively treat MSS tumors.

About Stivarga® (regorafenib)
Regorafenib is an oral multi-kinase inhibitor that potently blocks multiple protein kinases involved in tumor angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF), metastasis (VEGFR3, PDGFR, FGFR) and tumor immunity (CSF1R).

Regorafenib is approved under the brand name Stivarga® in more than 90 countries worldwide, including the U.S., countries of the EU, China and Japan for the treatment of metastatic colorectal cancer (mCRC). The product is also approved in over 80 countries, including the U.S., countries of the EU, China and Japan, for the treatment of metastatic gastrointestinal stromal tumors (GIST) as well as the second-line treatment of hepatocellular carcinoma (HCC).

In the EU, Stivarga is indicated as monotherapy for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy, as well as for the treatment of adult patients with unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib, and for the treatment of adult patients with HCC who have been previously treated with sorafenib.

Regorafenib is a compound developed by Bayer. In 2011, Bayer entered into an agreement with Onyx, now an Amgen subsidiary, under which Onyx receives a royalty on all global net sales of regorafenib in oncology.

About Oncology at Bayer
Bayer is committed to delivering science for a better life by advancing a portfolio of innovative treatments. The oncology franchise at Bayer includes five marketed products and several other assets in various stages of clinical development. Together, these products reflect the company’s approach to research, which prioritizes targets and pathways with the potential to impact the way that cancer is treated.

About Bayer
Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to benefit people by supporting efforts to overcome the major challenges presented by a growing and aging global

population. At the same time, the Group aims to increase its earning power and create value through innovation and growth. Bayer is committed to the principles of sustainable development, and the Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2018, the Group employed around 117,000 people and had sales of 39.6 billion euros. Capital expenditures amounted to 2.6 billion euros, R&D expenses to 5.2 billion euros. For more information, go to www.bayer.com.

About Opdivo® (nivolumab)

Opdivo is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to uniquely harness the body's own immune system to help restore anti-tumor immune response. By harnessing the body's own immune system to fight cancer, *Opdivo* has become an important treatment option across multiple cancers.

Opdivo's development program includes a broad range of clinical trials across all phases, including Phase 3, in a variety of tumor types. To date, the *Opdivo* clinical development program has enrolled more than 25,000 patients. The *Opdivo* trials have contributed to gaining a deeper understanding of the potential role of biomarkers in patient care, particularly regarding how patients may benefit from *Opdivo* across the continuum of PD-L1 expression.

In July 2014, *Opdivo* was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. *Opdivo* is currently approved in more than 65 countries, including the United States, the European Union, Japan and China. In October 2015, the Company's *Opdivo* and *Yervoy* combination regimen was the first Immuno-Oncology combination to receive regulatory approval for the treatment of metastatic melanoma and is currently approved in more than 50 countries, including the United States and the European Union.

About Bristol-Myers Squibb: Advancing Oncology Research

At Bristol-Myers Squibb, patients are at the center of everything we do. The focus of our research is to increase quality, long-term survival for patients and make cure a possibility. Through a unique multidisciplinary approach powered by translational science, we harness our deep scientific experience in oncology and Immuno-Oncology (I-O) research to identify novel treatments tailored to individual patient needs. Our researchers are developing a diverse, purposefully built pipeline designed to target different immune system pathways and address the complex and specific interactions between the tumor,

its microenvironment and the immune system. We source innovation internally, and in collaboration with academia, government, advocacy groups and biotechnology companies, to help make the promise of transformational medicines, like I-O, a reality for patients.

About the Bristol-Myers Squibb and Ono Pharmaceutical Collaboration
In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Bristol-Myers Squibb expanded its territorial rights to develop and commercialize Opdivo globally, except in Japan, South Korea and Taiwan, where Ono had retained all rights to the compound at the time. On July 23, 2014, Ono and Bristol-Myers Squibb further expanded the companies' strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

About Bristol-Myers Squibb
Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

About Ono Pharmaceutical Co., Ltd.
Ono Pharmaceutical Co., Ltd., headquartered in Osaka, is an R&D-oriented pharmaceutical company committed to creating innovative medicines in specific areas. It focuses primarily on the oncology and diabetes areas. For further information, please visit the company's website at www.ono.co.jp/eng.

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Forward-Looking Statements
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