



News Release

January 24, 2010

ASCO-GI: Overall Survival With Erbitux Is Significantly Improved in Patients With KRAS Wild-Type Tumors in CRYSTAL

- **New data indicate Erbitux treatment effect does not vary by BRAF mutation status**
- **KRAS remains the standard marker for personalized treatment with Erbitux in mCRC**

Orlando, FL, USA/Geneva, Switzerland, January 24, 2010 – Merck Serono, a division of Merck KGaA, Darmstadt, Germany, today announced that Erbitux[®] (cetuximab) provided an improvement in overall survival (OS) when added to the standard 1st-line FOLFIRI chemotherapy regimen for metastatic colorectal cancer (mCRC) patients with KRAS wild-type tumors in the CRYSTAL study.¹ In addition, the final results from this study included an analysis of the predictive value of BRAF status on Erbitux efficacy – one of the first to be based on a large subgroup (n=59) of a prospective, randomized study in the 1st-line setting. The analysis indicates that patients with KRAS wild-type tumors bearing a BRAF mutation also benefit from Erbitux treatment;¹ therefore, KRAS remains the only validated, clinically predictive marker of responsiveness to this drug.² These study results were presented at the American Society of Clinical Oncology's 2010 Gastrointestinal Cancers Symposium (ASCO-GI) in Orlando.

"It is clear that overall survival is a critically important outcome in metastatic colorectal cancer, so it is extremely rewarding to achieve this result in patients with KRAS wild-type tumors," commented Professor Claus-Henning Köhne, Head of the Department of Oncology and Hematology, Klinikum Oldenburg, Germany, who presented the results of a pooled analysis of the CRYSTAL and OPUS trials today. "The analysis indicating

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that BRAF is not predictive for Erbitux efficacy is also of interest, as it confirms the current role of KRAS as the only clinically predictive biomarker for Erbitux.”

Final CRYSTAL data¹

In patients with KRAS wild-type tumors (n=666) receiving Erbitux plus FOLFIRI:

- Median OS was 23.5 months compared to 20.0 months in those receiving chemotherapy alone (Hazard Ratio [HR] 0.796; p=0.0093)
- The risk of disease progression was reduced by 30.4% (HR 0.696; p=0.0012)
- The likelihood of achieving a tumor response doubled overall (Odds Ratio [OR] 2.0693; ORR 57.3% vs. 39.7%; p<0.0001)

In patients with KRAS/BRAF wild-type tumors (n=566):

- The addition of Erbitux to FOLFIRI led to significant improvements in ORR (61.0% vs. 42.6%; p<0.0001) and PFS (10.9 vs. 8.8 months; p=0.0016)

CRYSTAL/OPUS pooled analysis³

This analysis was designed to evaluate OS, PFS and ORR in the combined CRYSTAL and OPUS populations of patients with KRAS wild-type tumors (n=845). The analysis showed that for the combined study population:

- The risk of death was reduced by 19% (HR 0.81; p=0.0062) for patients receiving Erbitux plus chemotherapy compared with those receiving chemotherapy alone
- The risk of disease progression was reduced by 34% (HR 0.66; p<0.0001) for patients receiving Erbitux plus chemotherapy compared with those receiving chemotherapy alone
- The likelihood of achieving a response in patients receiving combination treatment increased more than two-fold compared to those receiving only chemotherapy (OR 2.16; ORR 57.3% vs. 38.5%; p<0.0001)

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Updated OPUS data⁴

Updated results from the OPUS study showed that in patients with KRAS wild-type tumors (n=82) treated with Erbitux and chemotherapy (FOLFOX4):

- Median OS was 22.8 months compared with 18.5 months in the chemotherapy-alone arm (HR 0.855; p=0.3854)
- The risk of disease progression was reduced by 43.3% (HR 0.567; p=0.0064)
- The likelihood of achieving a tumor response doubled overall (OR 2.5512; ORR 57.3% vs. 34.0%; p=0.0027)

“Merck Serono is a leader in advancing personalized medicine through continued research and development into the area of predictive biomarkers for metastatic colorectal cancer,” added Dr. Oliver Kisker, Senior Vice-President, Global Clinical Development Unit Oncology, Merck Serono. “The identification of the KRAS biomarker has revolutionized the treatment of this disease, allowing patients to receive the most suitable treatment for their disease and resulting in improved outcomes.”

Colorectal cancer

More than 370,000 people develop colorectal cancer in Europe every year, accounting for 13% of the total cancer burden and around 200,000 deaths.⁵ Approximately 25% of patients present with metastatic disease.⁶ Five-year survival rates for patients with mCRC are as low as 5%.⁷

^a**CRYSTAL:** Cetuximab combined with irinotecan in first line therapy for metastatic colorectal cancer

^b**OPUS:** Oxaliplatin and cetuximab in first-line treatment of mCRC

References

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For more information on Erbitux in colorectal, head & neck and non-small cell lung cancer, please visit: www.globalcancernews.com.

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About Erbitux

Erbitux[®] is a first-in-class and highly active IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR). As a monoclonal antibody, the mode of action of Erbitux is distinct from standard non-selective chemotherapy treatments in that it specifically targets and binds to the EGFR. This binding inhibits the activation of the receptor and the subsequent signal-transduction pathway, which results in reducing both the invasion of normal tissues by tumor cells and the spread of tumors to new sites. It is also believed to inhibit the ability of tumor cells to repair the damage caused by chemotherapy and radiotherapy and to inhibit the formation of new blood vessels inside tumors, which appears to lead to an overall suppression of tumor growth.

The most commonly reported side effect with Erbitux is an acne-like skin rash that seems to be correlated with a good response to therapy. In approximately 5% of patients, hypersensitivity reactions may occur during treatment with Erbitux; about half of these reactions are severe.

Erbitux has already obtained market authorization in 77 countries. It has been approved for the treatment of colorectal cancer in 77 countries and for the treatment of squamous cell carcinoma of the head and neck (SCCHN) in 72 countries:

- December 2003 (Switzerland), February 2004 (USA), June 2004 (EU) and followed by other countries: for use in combination with irinotecan in patients with EGFR-expressing mCRC (metastatic colorectal cancer) who have failed prior irinotecan therapy. In addition, Erbitux is also approved for single-agent use in further countries.
- April 2006 (EU) and followed by other countries: for use in combination with radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN). In further countries, Erbitux is also approved as monotherapy in patients with recurrent and/or metastatic SCCHN who failed prior chemotherapy.
- July 2008 (EU): license was updated for the treatment of patients with epidermal growth factor receptor (EGFR) expressing, KRAS wild-type mCRC in combination with chemotherapy and as a single agent in patients who have failed oxaliplatin-and irinotecan-based therapy and who are intolerant to irinotecan.
- July 2008 (Japan): for use in combination with irinotecan in patients with EGFR-expressing mCRC who have failed prior irinotecan therapy
- In November 2008 (EU): license was updated for the use in combination with platinum-based chemotherapy in patients with recurrent and/or metastatic SCCHN

Merck Serono licensed the right to market Erbitux outside the US and Canada from ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, in 1998. In Japan, ImClone Systems, Bristol-Myers Squibb Company and Merck Serono jointly develop and commercialize Erbitux. Merck Serono has an ongoing commitment to the advancement of oncology treatment and is currently investigating novel therapies in highly targeted areas, such as the use of Erbitux in colorectal cancer, squamous cell carcinoma of the head and neck and non-small cell lung cancer. Merck Serono has also acquired the rights for the cancer treatment UFT[®] (tegafur-uracil) – an oral chemotherapy administered with folinic acid (FA) for the first-line treatment of metastatic colorectal cancer.

Merck Serono is also investigating among other cancer treatments the use of Stimuvax[®] (formerly referred to as BLP25 Liposome Vaccine) in the treatment of non-small cell lung cancer. The vaccine was granted fast-track status in September 2004 by the FDA. Merck Serono obtained the exclusive worldwide licensing rights from Oncocyte Inc., Seattle, Washington, USA.

In addition, Merck Serono is developing cilengitide, which is the first in a new class of investigational anti-cancer therapies called integrin inhibitors to reach Phase III of development; it is currently being investigated for the treatment of glioblastoma, SCCHN and NSCLC. Integrin inhibitors are thought to work by targeting the tumor and its vasculature.

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About Merck Serono

Merck Serono is the division for innovative prescription pharmaceuticals of Merck KGaA, Darmstadt, Germany, a global pharmaceutical and chemical company. Headquartered in Geneva, Switzerland, Merck Serono discovers, develops, manufactures and markets innovative small molecules and biopharmaceuticals to help patients with unmet medical needs. In the United States and Canada, EMD Serono operates through separately incorporated affiliates.

Merck Serono has leading brands serving patients with cancer (Erbix[®], cetuximab), multiple sclerosis (Rebif[®], interferon beta-1a), infertility (Gonal-f[®], follitropin alpha), endocrine and metabolic disorders (Saizen[®] and Serostim[®], somatropin), (Kuvan[®], sapropterin dihydrochloride) as well as cardiometabolic diseases (Glucophage[®], metformin), (Concor[®], bisoprolol), (Euthyrox[®], levothyroxine). Not all products are available in all markets.

With an annual R&D expenditure of around € 1bn, Merck Serono is committed to growing its business in specialist-focused therapeutic areas including neurodegenerative diseases, oncology, fertility and endocrinology, as well as new areas potentially arising out of research and development in autoimmune and inflammatory diseases.

About Merck

Merck is a global pharmaceutical and chemical company with total revenues of € 7.6 billion in 2008, a history that began in 1668, and a future shaped by approximately 33,000 employees in 60 countries. Its success is characterized by innovations from entrepreneurial employees. Merck's operating activities come under the umbrella of Merck KGaA, in which the Merck family holds an approximately 70% interest and free shareholders own the remaining approximately 30%. In 1917 the U.S. subsidiary Merck & Co. was expropriated and has been an independent company ever since.

For more information, please visit www.merckserono.com or www.merck.de