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News Release

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Merck Serono: Phase III Erbitux data published in *NEJM* confirm enhanced efficacy in mCRC Patients in the 1st-line setting

- **Erbitux in combination with standard chemotherapy should be considered as a new standard of care for patients with untreated, KRAS wild-type mCRC**

Darmstadt, March 27 – Data published in today's *New England Journal of Medicine* (*NEJM*), from the Phase III CRYSTAL^a trial confirm, the enhanced efficacy of Erbitux[®] (cetuximab) in combination with standard irinotecan-based chemotherapy (FOLFIRI) in metastatic colorectal cancer (mCRC) patients compared to chemotherapy alone.¹ Patients with KRAS wild-type tumors receiving Erbitux benefited from significantly increased tumor response rates of up to 59% [p=0.0025] and a 32% decrease in the risk of disease progression compared to patients receiving FOLFIRI alone [Hazard Ratio (HR)=0.68; p=0.02].^{1,2}

“These results are an important advance in the 1st-line treatment of mCRC and clearly demonstrate the benefit of selecting the appropriate treatment for patients, based on the KRAS status of their tumor, before treatment begins,” commented Professor Eric Van Cutsem, lead investigator of the CRYSTAL study and Professor of Medicine and Digestive Oncology from the University Hospital Gasthuisberg in Leuven, Belgium. “The response rates are particularly exciting – by shrinking tumors we can relieve patients from discomfort or symptoms or, in other cases, shrink tumors sufficiently to allow them to be surgically removed, which provides the potential for cure. These findings suggest Erbitux should be considered an important new option in this setting.”

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CRYSTAL was a multi-center, Phase III, randomized, controlled trial involving 1,198 patients that investigated the efficacy and safety of Erbitux in combination with FOLFIRI vs. FOLFIRI alone in the 1st-line treatment of patients with mCRC.¹ KRAS mutation status was included within the analysis and tumor samples from 540 patients were analyzed. The KRAS-evaluable population was found to be representative of the overall study population and 64.4% of these patients tested KRAS wild-type.¹ In these patients, the addition of Erbitux to FOLFIRI led to the following:¹⁻³

- Significant increase in tumor response rate – up to 59% compared to 43% for those receiving FOLFIRI alone [p=0.0025]
- Decrease of 32% in the risk of disease progression [HR=0.68; p=0.02]
- Trend towards prolonged survival, with patients receiving Erbitux showing a median overall survival of 24.9 months compared to 21.0 months in those receiving FOLFIRI alone [HR=0.84; p=0.22]

The safety profile of Erbitux in the CRYSTAL study was in line with that expected with the agents used in the trial. The adverse events reported to be significantly more frequent in the Erbitux arm – Grade 3/4 diarrhea, skin reactions and infusion-related reactions – were all deemed to be manageable.¹

“These impressive results from CRYSTAL, demonstrating high response rates of nearly 60% in KRAS wild-type patients, clearly support the use of Erbitux in the 1st-line setting,” noted Dr. Wolfgang Wein, Executive Vice President, Oncology, Merck Serono. “This is a landmark trial supporting the introduction of biomarkers for tailored therapy in patients with mCRC.”

The efficacy of Erbitux in combination with standard oxaliplatin-based chemotherapy (e.g. FOLFOX-4) as 1st-line mCRC therapy has also been established as evidenced by data from the OPUS^b study recently published in the *Journal of Clinical Oncology*.⁴ The results of the CRYSTAL and OPUS trials supported the recently approved license extension of Erbitux in Europe, which is now approved for use in combination with chemotherapy in all lines of treatment of patients with EGFR-expressing, KRAS wild-

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type mCRC, and also as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

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 and 5-year survival rates for patients with mCRC can be 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.

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 76 countries. It has been approved for the treatment of colorectal cancer in 75 countries and for the treatment of squamous cell carcinoma of the head and neck (SCCHN) in 71 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.

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- 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 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 jointly develop and commercialize Erbitux. Merck 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 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 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 obtained the exclusive worldwide licensing rights from Oncothyreon Inc., Bellevue, Washington, USA.

In addition, Merck 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, a global pharmaceutical and chemical group. Headquartered in Geneva, Switzerland, Merck Serono discovers, develops, manufactures and markets innovative small molecules and biopharmaceuticals to help patients with unmet medical needs. Its North American business operates in the United States and Canada as EMD Serono.

Merck Serono has leading brands serving patients with cancer (Erbitux®), multiple sclerosis (Rebif®), infertility (Gonal-f®), endocrine and cardiometabolic disorders (Glucophage®, Concor®, Saizen®, Serostim®), as well as psoriasis (Raptiva®).

With an annual R&D investment 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.

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

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