



ASCO Abstract Number: 3506

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## News Release

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May 15, 2014

### **Merck KGaA, Darmstadt, Germany, Announces New Retrospective Analysis Shows Significant Clinical Benefit in Overall Survival for Metastatic Colorectal Cancer Patients with RAS Wild-Type Tumors Receiving Erbitux plus FOLFIRI**

- **In a retrospective analysis of the Phase III CRYSTAL\* study, which assessed RAS tumor status, significant clinical benefit was observed in mCRC patients with RAS wild-type tumors receiving Erbitux plus FOLFIRI, compared with FOLFIRI alone**
- **No benefit was observed for patients with RAS mutations receiving Erbitux plus FOLFIRI for the treatment of mCRC, compared with FOLFIRI alone, which is in line with the EU label and recent scientific evidence**

Darmstadt, Germany, May 15, 2014 – Merck KGaA, Darmstadt, Germany, today announced new biomarker findings from a retrospective analysis of the completed Phase III study CRYSTAL that compared Erbitux® (cetuximab) plus FOLFIRI with FOLFIRI alone. The analysis involved a subgroup of patients with KRAS wild-type (exon 2) metastatic colorectal cancer (mCRC). A significant clinical improvement was observed in patients with RAS wild-type tumors when Erbitux was added to FOLFIRI in firstline mCRC.<sup>1</sup> The new data will be presented at the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting (May 30 - June 3) during the Gastrointestinal (Colorectal) session on June 2, 2014, from 10:00 to 10:12 am. The results of this analysis reinforce the company's commitment to improve patient care, and underpins the leading role of Merck KGaA, Darmstadt, Germany, in the highly innovative area of personalized cancer care.

#### Merck KGaA

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In this new analysis, 430 (65% of 666 patients) patient tumor samples with wild-type KRAS (exon 2) status were assessed for additional RAS mutations (defined as mutations in exons 3 or 4 of KRAS and/or exons 2, 3 or 4 of NRAS). Of these, 367 were RAS wild-type, while 63 presented a mutation. The analysis shows a 27.7% increase in response rate (RR), a 3.0-month increase in median progression-free survival (PFS), and an 8.2-month increase in median overall survival (OS) in mCRC patients with RAS wild-type tumors (n=367) receiving firstline Erbitux plus FOLFIRI, compared with patients receiving FOLFIRI alone (RR: 66.3% vs. 38.6%, respectively; odds ratio: 3.11; 95% confidence interval [CI]: 2.03–4.78; p<0.0001; PFS: median 11.4 months vs. 8.4 months, respectively; hazard ratio [HR]: 0.56; 95% CI: 0.41–0.76; p=0.0002; OS: median 28.4 months vs. 20.2 months, respectively; HR: 0.69; 95% CI: 0.54–0.88; p=0.0024).<sup>1</sup>

“The data from this analysis clearly demonstrate a clinical benefit from treating RAS wild-type metastatic colorectal cancer patients with Erbitux plus FOLFIRI, compared with FOLFIRI alone,” said Dr. Steven Hildemann, Global Chief Medical Officer and Head of Global Medical and Safety for the biopharmaceutical division of Merck KGaA, Darmstadt, Germany. “This CRYSTAL analysis contributes to our evolving understanding of this disease, and confirms that RAS biomarker testing is essential for patient-centric care and a truly personalized approach to metastatic colorectal cancer.”

“The new analysis from the CRYSTAL study is in line with the results seen from other studies with anti-epidermal growth factor receptor treatments in metastatic colorectal cancer patients with RAS wild-type tumors,” said Professor Fortunato Ciardiello, Professor of Medical Oncology at the Seconda Università degli Studi di Napoli in Naples, Italy, and lead author of the CRYSTAL RAS analysis. “Importantly, these results reinforce that RAS testing should be conducted at the point of diagnosis in order to support physicians in selecting the most appropriate firstline treatment for their mCRC patients.”

In the patient group with either KRAS exon 2 mutations identified in the initial KRAS analysis (n=397) or other RAS mutations (n=63) receiving Erbitux plus FOLFIRI (n=246) no benefit was observed, compared with FOLFIRI alone (n=214) (RR: 31.7% vs. 36.0%, respectively; odds ratio: 0.85; 95% CI: 0.58–1.25; p=0.40; PFS: median 7.4 months vs. 7.5



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months, respectively; HR: 1.10; 95% CI: 0.85–1.42; p=0.47; OS: median 16.4 months vs. 17.7 months, respectively; HR: 1.05; 95% CI: 0.86–1.28; p=0.64).<sup>1</sup> This subgroup analysis confirms the findings of OPUS and other studies which have shown that patients with RAS mutations do not benefit from anti-EGFR therapy.

Following an update to the Erbitux label that was approved by the European Commission in December 2013, Erbitux is now indicated for the treatment of patients with epidermal growth factor receptor-expressing RAS wild-type mCRC in combination with irinotecan-based chemotherapy, in firstline in combination with FOLFOX, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. Erbitux is contraindicated in combination with oxaliplatin-containing chemotherapy in patients with mutant RAS mCRC or for whom RAS mCRC status is unknown.<sup>2</sup>

### About CRYSTAL

CRYSTAL (Cetuximab combined with iRinotecan in first-line therapY for metaSTatic colorectAL cancer) was a randomized, Phase III study involving 1,198 chemo-naïve patients with EGFR-expressing mCRC in Stage IV, of whom 666 had confirmed KRAS wild-type (exon 2) tumors. The study showed that progression-free survival, overall survival time and response rate were significantly better in patients with KRAS wild-type mCRC who received Erbitux plus FOLFIRI, compared with FOLFIRI alone.<sup>3</sup>

### About Colorectal Cancer

Colorectal cancer (CRC) is the second most common cancer worldwide, with an estimated incidence of more than 1.36 million new cases annually.<sup>4</sup> An estimated 694,000 deaths from CRC occur worldwide every year, accounting for 8.5% of all cancer deaths and making it the fourth most common cause of death from cancer.<sup>4</sup> Almost 55% of CRC cases are diagnosed in developed regions of the world, and incidence and mortality rates are substantially higher in men than in women.<sup>4</sup>

\*CRYSTAL: **C**etuximab combined with **i**Rinotecan in first-line therap**Y** for meta**ST**atic colorect**AL** cancer



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### References

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For more information on Erbitux in colorectal and head & neck cancer, please visit:  
[www.globalcancernews.com](http://www.globalcancernews.com).

### About Erbitux

Erbitux<sup>®</sup> 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 over 90 countries for the treatment of colorectal cancer and for the treatment of squamous cell carcinoma of the head and neck (SCCHN).

Merck KGaA, Darmstadt, Germany, licensed the right to market Erbitux outside the US and Canada from ImClone LLC, a wholly-owned subsidiary of Eli Lilly and Company, in 1998. In Japan, ImClone, Bristol-Myers Squibb Company and Merck KGaA, Darmstadt, Germany, jointly develop and commercialize Erbitux. Merck KGaA, Darmstadt, Germany, has an ongoing commitment to the advancement of oncology treatment and is currently investigating novel therapies in highly targeted areas.

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### About Merck KGaA, Darmstadt, Germany

Merck KGaA of Darmstadt, Germany, is a leading company for innovative and top-quality high-tech products in the pharmaceutical and chemical sectors. Its subsidiaries in Canada and the United States operate under the umbrella brand EMD. Around 38,000 employees work in 66 countries to improve the quality of life for patients, to further the success of customers and to help meet global challenges. The company generated total revenues of € 11.1 billion in 2013 with its four divisions: Biopharmaceuticals, Consumer Health, Performance Materials and Life Science Tools. Merck KGaA of Darmstadt, Germany is the world's oldest pharmaceutical and chemical company – since 1668, the name has stood for innovation, business success and responsible entrepreneurship. Holding an approximately 70 percent interest, the founding family remains the majority owner of the company to this day.