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Merck Serono: Overall Survival in First-Line NSCLC Reaches 15 Months With Erbitux

- **New data from pivotal FLEX study reveal that patients treated with Erbitux who develop early skin rash show median overall survival of 15 months (p<0.001)**
- **FLEX data reconfirm the value of adding Erbitux to platinum-based chemotherapy in the first-line treatment of patients with NSCLC**

Geneva, Switzerland, November 13, 2008 – Data presented today at the 2008 Chicago Multidisciplinary Symposium in Thoracic Oncology show that patients with non-small cell lung cancer (NSCLC) who were given Erbitux[®] (cetuximab) in addition to a standard first-line platinum-based chemotherapy lived significantly longer than those who received chemotherapy alone.¹ This effect was more pronounced in patients treated with Erbitux who developed early acne-like rash, resulting in median overall survival of 15 months.¹

In the overall population of FLEX^a, the addition of Erbitux to chemotherapy prolonged median overall survival from 10.1 to 11.3 months (Hazard Ratio HR=0.87, p=0.04). The new analysis demonstrated that overall survival for patients receiving Erbitux, who experienced any grade of rash (acne-like rash) within three weeks of treatment initiation, was 15.0 months compared to 8.8 months in those patients who developed no rash (HR=0.63, p<0.001).¹ Therefore, development of such a skin rash is associated with a better outcome for patients treated with Erbitux in combination with chemotherapy. It appears to be an important indicator for longer survival.

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“As physicians, we have been waiting for the best part of a decade for a novel treatment that would yield a significant increase in the key endpoint in NSCLC – overall survival – and now FLEX will give us a new option, Erbitux, to use with our patients,” said Dr. Ulrich Gatzemeier of the Hospital Grosshansdorf, Germany, one of the lead FLEX trial investigators. “In addition, patients who develop the early skin rash can take comfort from the fact that it appears to be a clear signal that the drug is working.”

The FLEX trial was a multinational, randomized, Phase III study which involved a total of 1,125 patients with stage IIIB and IV NSCLC, representing all histological subtypes and ECOG performance status 0-2. Overall, patients randomized to the Erbitux treatment arm survived for additional 1.2 months compared to those receiving chemotherapy alone (11.3 vs. 10.1 months; Hazard Ratio HR=0.87, p=0.04). Response rate and time to treatment failure were also significantly improved (p=0.01 and 0.02 respectively).¹ Erbitux was well tolerated in this trial, with expected and manageable side effects including the development of skin rash, which was only observed as grade 1-3. The FLEX trial formed the basis of the submission for the use of Erbitux in the first-line treatment of NSCLC to the European Medicines Agency (EMA) in September 2008.

In a pre-planned analysis, the relation of early-onset skin rash (i.e. within three weeks of treatment initiation) and efficacy of Erbitux was evaluated. The new data demonstrate a particularly high median overall survival of 15.0 months (95% CI 12.8-16.4 months) in those FLEX patients who showed any grade of rash (grade 1-3; 56%; n=290), whereas overall survival was 8.8 months (95% CI 7.6-11.1 months) in patients who developed no rash (n=228). This difference was reflected in a Hazard Ratio of 0.63 (95% CI 0.52-0.77, p<0.001).¹ Patients' characteristics in both groups were similar.

“A 15 month survival in patients with early skin rash achieved in a clinical trial that included an overall population with 94% being stage IV and 17% with an ECOG performance status 2 marks an outstanding signal of efficacy and opens the door to

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new treatment strategies in NSCLC,” said Wolfgang Wein, Executive Vice President, Oncology, Merck Serono, a division of Merck KGaA.

About non-small cell lung cancer

More men – approximately 975,000 worldwide – die of lung cancer than of any other tumor type. After breast cancer, it is also a leading cause of mortality from cancer in women (approximately 376,000 deaths reported globally).^{2,3} NSCLC accounts for around 80% of all cases of lung cancer,⁴ and the growth of approximately one-third of these tumors will have advanced to the point where surgical resection is no longer possible.⁵ Lung cancer patients have a poor prognosis, with only around 10% of patients surviving for five years. This survival rate compares unfavorably with the rates regularly now being achieved with other tumor types such as melanoma (81%) or breast cancer (75%).⁶

^a **FLEX:** First-line in Lung cancer with ErbituX

References

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4. D'Addario G & Felip E. Ann Oncol 2008;19 Suppl 2:ii39-40.
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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 75 countries. It has been approved for the treatment of colorectal cancer in 74 countries so far: Argentina, Australia, Belarus, Canada, Chile, China, Colombia, Costa Rica, Croatia, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Iceland, India, Indonesia, Israel, Japan, Kazakhstan, Kuwait, Lebanon, Liechtenstein, Malaysia, Mexico, Moldova, New Zealand, Nicaragua, Norway, Oman, Panama, Peru, the Philippines, Qatar, Russia, Serbia, Singapore, South Africa, South Korea, Switzerland, Taiwan, Thailand, Ukraine, Uruguay, the US, and Venezuela for use in combination with irinotecan in patients with EGFR-expressing mCRC who have failed prior irinotecan therapy. In the European Union, the license was updated in July 2008 for the treatment of patients with epidermal growth factor receptor (EGFR) expressing, KRAS wild-type mCRC (metastatic colorectal cancer) 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. Apart from the European Union label, Erbitux is also approved for single-agent use in: Argentina, Australia, Canada, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Iceland, Japan, Lebanon, Liechtenstein, Mexico, Moldova, New Zealand, Nicaragua, Norway, Panama, Peru, the Philippines, Russia, Singapore, Thailand, the US, and Venezuela.

In addition, Erbitux in combination with radiotherapy has been approved for the treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN) in 69 countries: Argentina, Australia, Belarus, Brazil, Canada, Chile, Colombia, Costa Rica, Croatia, El Salvador, the European Union, Guatemala, Hong Kong, Iceland, India, Indonesia, Israel, Kazakhstan, Kuwait, Lebanon, Liechtenstein, Malaysia, Mexico, Moldova, New Zealand, Nicaragua, Norway, Oman, Panama, Peru, the Philippines, Qatar, Russia, Serbia, Singapore, South Africa, South Korea, Switzerland, Taiwan, Ukraine, Uruguay, the US, and Venezuela. In Argentina, Chile, Costa Rica, El Salvador, Guatemala, Hong Kong, Israel, Lebanon, Mexico, Moldova, Nicaragua, Peru, the Philippines, Russia, and the US, Erbitux is also approved as monotherapy in patients with recurrent and/or metastatic SCCHN who failed prior chemotherapy.

Merck licensed the right to market Erbitux outside the US and Canada from ImClone Systems Incorporated of New York in 1998. In Japan, ImClone Systems Incorporated, 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.

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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®, Euthyrox®, Saizen®, Serostim®), as well as psoriasis (Raptiva®).

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 € 7.1 billion in 2007, a history that began in 1668, and a future shaped by 32,458 employees in 59 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.net or www.merck.de