

KRAS

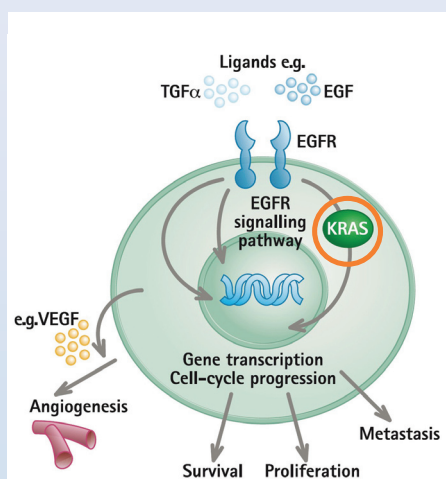
FACT SHEET EMBARGOED UNTIL 1 JUNE 2008, 11.00 A.M. CENTRAL DAYLIGHT TIME CDT

What is KRAS?

- KRAS is a gene that codes for a protein that plays an important role in the epidermal growth factor receptor (EGFR) pathway – a complex signaling cascade that is involved in the development and progression of cancer (see Erbitux® & The Epidermal Growth Factor Receptor fact sheet).¹

KRAS and the EGFR pathway

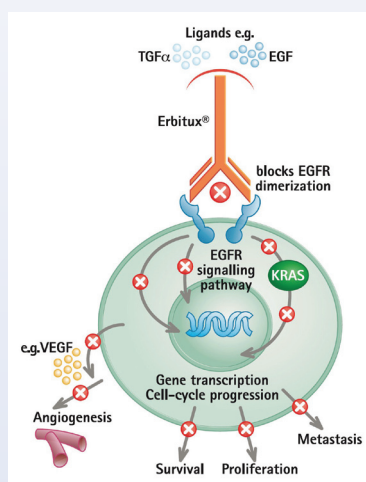
- The KRAS protein regulates other proteins, downstream in the EGFR signaling pathway, that are associated with tumor survival, angiogenesis, proliferation and metastasis.²
- There are different types of the KRAS gene found in tumors, which either code for a "normal", non-mutated KRAS protein known as *wild-type* KRAS, or an abnormal, mutated protein known as *mutant* KRAS. The KRAS "status" (wild-type versus mutant) may be indicative of prognosis and predictive of response to certain drugs.
- In tumors with wild-type KRAS, the protein is only temporarily activated in response to certain stimuli such as EGFR signaling. This tight regulation warrants a close control of downstream effects.
- In tumors with the mutated version of the KRAS gene, the KRAS protein is permanently "turned on" even without being activated by the upstream EGFR-mediated signaling. As a result the downstream effects that lead to tumor growth and spread continue unregulated.



EGFR pathway in a tumor cell (KRAS circled in orange)

KRAS status in EGFR-expressing tumors

- In colorectal cancer (CRC), up to 65% of patients have the wild-type KRAS; the remaining 35% have the mutant version of the gene.^{3,4}
- In non-small cell lung cancer (NSCLC), 80–90% of patients have KRAS wild-type tumors.^{5,6,7}
- In squamous cell carcinoma of the head and neck (SCCHN), almost 95% of patients have KRAS wild-type tumors.⁸



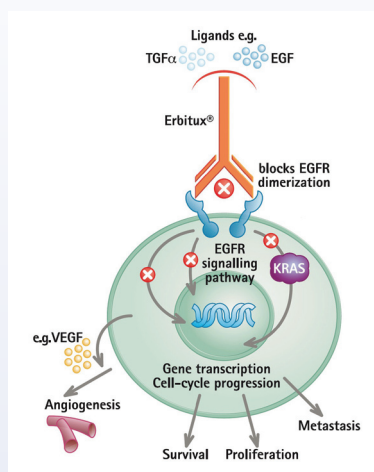
Erbitux inhibits the EGFR pathway and blocks the downstream effects – cell survival and proliferation, angiogenesis and metastasis

Erbitux® and KRAS

- Erbitux (cetuximab) works by blocking EGFR signaling and inhibiting downstream intracellular signals. Erbitux may also kill tumor cells by stimulating an antibody-dependent cellular cytotoxicity (ADCC) reaction, where it recruits the body's immune system to attack and kill cancer cells.⁹
- In the last two years first results from various studies indicated that CRC patients with the wild-type KRAS protein have an enhanced response to Erbitux and a higher overall survival rate than those with the mutant KRAS.^{3,10-13}
- It has been hypothesized that, in patients with mutant KRAS, because the protein is permanently "turned on" – even when Erbitux is blocking the upstream signaling – the drug's inhibition of the downstream effects is less efficient and the tumor may continue to grow, proliferate and spread.
- However, given that Erbitux may also work via ADCC, it may have some beneficial effect even in patients with mutant KRAS, as ADCC seems to be unaffected by KRAS status.

KRAS

FACT SHEET EMBARGOED UNTIL 1 JUNE 2008, 11.00 A.M. CENTRAL DAYLIGHT TIME CDT



With the mutated KRAS protein permanently "turned on" the downstream effects are less efficiently inhibited by Erbbitux blocking the EGFR compared to KRAS wild-type tumors and the tumor continues to grow

KRAS as a biomarker

- There has recently been heightened interest in the relevance of biomarkers in oncology, including the role of KRAS as a biomarker in CRC and other EGFR-associated cancers.
- Because the KRAS protein is always "turned on" in patients with the mutated gene, the downstream signaling, and thus the resulting cancer growth and proliferation, occurs even when the signaling is blocked by an anti-EGFR therapy such as Erbbitux.
- Testing a tumor for its KRAS status (wild-type versus mutant) helps to identify those patients who will benefit most from treatment with Erbbitux.
- Due to the low incidence of mutant KRAS in SCCHN, KRAS is unlikely to be a relevant predictive biomarker for treatment selection in this cancer type.⁸

KRAS in Erbbitux trials

- Erbbitux data examining the importance of the KRAS mutation status in the 1st-line treatment of mCRC have shown a remarkably increased efficacy of Erbbitux in patients with KRAS wild-type tumors:
 - A study presented at the Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology 2008 showed a response rate (RR) of 55% for Erbbitux + FOLFIRI in the patient population with KRAS wild-type tumors compared with 32% for those patients with mutated KRAS. The relative risk of progression in the KRAS wild-type group was reduced by 53% compared to the KRAS mutant group.¹¹

- In the randomized, controlled Phase III CRYSTAL^a study, the KRAS wild type population showed a relative increase in response of 37% to Erbbitux + FOLFIRI compared to FOLFIRI alone (RR: 59% versus 43% respectively, $p = 0.003$).³
- The CRYSTAL study also showed a 32% decreased risk for progression (Hazard Ratio (HR) = 0.68) in patients with KRAS wild-type tumors treated with Erbbitux + FOLFIRI compared to FOLFIRI alone.³
- The randomized, controlled Phase II trial OPUS^b study demonstrated a relative increase in response of 65% to Erbbitux + FOLFOX compared to FOLFOX alone in patients with KRAS wild-type tumors (RR: 61% vs. 37% respectively, $p = 0.011$).⁴
- In addition the OPUS study showed a 43% decreased risk for progression (Hazard Ratio (HR) = 0.57) in patients treated with Erbbitux + FOLFOX compared to FOLFOX alone in the KRAS wild-type population.⁴

- These data confirm the consistent efficacy of Erbbitux with both oxaliplatin- and irinotecan-based chemotherapies in the 1st-line treatment of mCRC.
- Findings from various retrospective studies also demonstrate a more pronounced efficacy of Erbbitux (as a monotherapy or in combination) in pretreated patients with metastatic CRC (mCRC) who have wild-type KRAS tumors:
 - A recently published study in the *Journal of Clinical Oncology* showed a median progression-free survival (PFS) following treatment with Erbbitux of 31 weeks versus 10 weeks ($p=0.0001$) in patients with KRAS wild-type tumors versus the ones with mutant tumors, respectively.¹²
 - A second study published in *Annals of Oncology* demonstrated an improved median overall survival (OS) of 43 weeks versus 27 weeks ($p=0.020$) in patients treated with Erbbitux, with KRAS wild-type tumors versus mutant tumors, respectively. In addition, the study found that patients with wild-type KRAS tumors experienced greater decreases in tumor size than patients with a mutant KRAS tumor. This group of patients also experienced significantly better OS compared to those without decreases in tumor size (median OS: 75 weeks versus 31 weeks, $p=0.00000012$).¹³

What could this mean for CRC patients?

- CRC patients may soon be able to undergo a test to determine the KRAS status of their tumor. This will enable their medical team to select the most appropriate treatment from the beginning and thus improve their overall long term outcomes.
 - o Those mCRC patients with wild-type KRAS tumors may benefit from a response rate of over 60% and a decreased risk for progression of over 40% when treated with Erbitux in the 1st-line. It is known from different trials that high response rates are desirable as they correlate with increased resection rates and thereby provide an increased likelihood of a cure.¹⁴
 - o As ADCC seems to be unaffected by KRAS status, patients with mutant KRAS tumors may still benefit from Erbitux. Alternative treatment strategies that are not affected by KRAS mutations may also be appropriate for patients with mutant KRAS tumors.

Testing for KRAS

- The KRAS test is performed on a sample of tumor tissue.
- The tumor tissue is sent to a laboratory for analysis of the KRAS mutation status.
- The process helps to enable the most effective treatment to be selected for each individual patient.

Recently the CHMP recommended the use of Erbitux in the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type 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.

^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

1. Salomon DS, Brandt R, Ciardiello F, et al. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol* 1995;19:183-232.
2. Benvenuti S, Sartore-Bianche A, Di Nicolantonio F, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. *Cancer Res* 2007;67:2643-2648.
3. Van Cutsem, E. et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. ASCO 2008 Abstract No: 2
4. Bokemeyer, C et al. KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: The OPUS experience ASCO 2008 Abstract No: 4000
5. Motoi N, Szoke J, Riely GJ, et al. Lung Adenocarcinoma: Modification of the 2004 WHO Mixed Subtype to Include the Major Histologic Subtype Suggests Correlations Between Papillary and Micropapillary Adenocarcinoma Subtypes, EGFR Mutations and Gene Expression Analysis. *Am J Surg Pathol* 2008;Apr 3[Epub].
6. Young Tae K, Tae-you K, Dong Soon, L, et al. Molecular changes of epidermal growth factor receptor (EGFR) and KRAS and their impact on the clinical outcomes in surgically resected adenocarcinoma of the lung. *Lung Cancer* 2008;59(1):111-8.
7. Suzuki M, Shigematsu H, Lizasa T, et al. Exclusive mutation in epidermal growth factor receptor gene, HER-2, and KRAS, and synchronous methylation of nonsmall cell lung cancer. *Cancer* 2008;106(10):2200-7.
8. Weber A, Langhanki L, Sommerer F, et al. Mutations of the BRAF gene in squamous cell carcinoma of the head and neck. *Oncogene* 2003;22:4757-59.
9. Kimura H, Sakai K, Arai T, et al. Antibody-dependent cellular cytotoxicity of cetuximab against tumor cells with wild-type or mutant epidermal growth factor receptor. *Cancer Sci* 2007;98:1275-80.
10. Lieve A, Bachet JB, Le Corre, D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006;66:3992-3995.
11. Taberero J, Cervantes A, Macarulla T, et al. Correlation of efficacy to KRAS status (wt vs. mut) in patients (pts) with metastatic colorectal cancer (mCRC), treated with weekly (q1w) and q2w schedules of cetuximab combined with FOLFIRI. ASCO GI 2008 Abstract No: 435
12. Lieve A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with Cetuximab. *J Clin Onc* 2008;26(3):374-379.
13. De Roock W, Piessevaux H, De Schutter J, et al. KRAS mutation status and early radiological response predict survival in colorectal cancer treated with Cetuximab. *Ann Oncol* 2008;19:508-15
14. Folprecht G, et al. Neoadjuvant treatment of colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2008;16(8):1311-9

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 (Glucofage®, 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

About Merck KGaA

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 31,681 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.

FACT SHEET EMBARGOED UNTIL 1 JUNE 2008, 11.00 A.M. CENTRAL DAYLIGHT TIME CDT