Predictive biomarkers help to determine the likelihood that an individual responds to a particular treatment. RAS proteins are either validated or potential biomarkers for predicting the efficacy of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies in colorectal cancer (CRC).1

The RAS family of proteins are encoded by three closely related genes: KRAS, NRAS and HRAS.1 RAS proteins, specifically KRAS and NRAS, play an important role in the EGFR signaling pathway – a complex signaling cascade that is involved in the development and progression of cancer.4 (See the ‘Erbitux and the Epidermal Growth Factor Receptor’ fact sheet for further information.) Data from clinical trials have demonstrated that RAS wild-type proteins (defined as having no activating mutations in codons 2, 3 or 4 of KRAS and/or NRAS), in particular, are predictive biomarkers of sensitivity to anti-EGFR therapy in metastatic CRC (mCRC).

RAS and the EGFR signaling pathway

The RAS proteins regulate other proteins downstream in the EGFR signaling pathway that are associated with tumor survival, angiogenesis, proliferation and metastasis.2,3 Different types of RAS genes are found in tumors. These either code for ‘normal’, non-mutated RAS proteins known as RAS wild-type, or for mutated proteins known as RAS mutant (defined as having activating mutations in exons 2, 3 or 4 of KRAS and/or NRAS).

- In RAS wild-type tumors, the EGFR pathway is normal and the RAS proteins are only temporarily activated in response to certain stimuli, such as EGFR signaling.
- In RAS mutant tumors, the RAS proteins are permanently ‘switched on’ whether or not they are activated by upstream EGFR-mediated signaling. As a result, the downstream effects that lead to tumor growth and spread continue unregulated.
- In mCRC, approximately 50% of patients have an EGFR pathway carrying the normal RAS wild-type genes, with the remaining 50% having mutant versions of another of the RAS genes.4

RAS wild-type genes are associated with an increased likelihood of response to anti-EGFR therapy.3-7 In mCRC patients with mutated genes, due to the RAS proteins (KRAS and NRAS) being always ‘switched on’, downstream signaling – and thus the resulting cancer growth and proliferation – occurs even when the signaling is blocked by an anti-EGFR therapy, such as Erbitux® (cetuximab). Hence, testing a tumor’s RAS status (wild-type versus mutant) may help identify those patients with mCRC who are most likely to benefit from treatment with an anti-EGFR therapy, such as Erbitux.

Erbitux and RAS

Erbitux is a monoclonal antibody – a type of targeted therapy used in the treatment of certain cancers. Like the antibodies circulating as part of the immune system, Erbitux identifies and locks onto a specific target – in this case, EGFR. Erbitux may kill tumor cells by stimulating antibody-dependent cellular cytotoxicity (ADCC), whereby it recruits the body’s immune system to attack and kill cancer cells.8,9 Preclinical data for Erbitux provided further evidence that supports a mode of action that includes marked ADCC activity.10

Since 2008, results from various studies have indicated that patients with mCRC with a normal EGFR pathway carrying the KRAS wild-type (exon 2) gene (a member of the RAS family) may benefit from Erbitux.11-19 In 2013, additional data were made available from a retrospective analysis of the completed Phase II study OPUS (OxaliPlatin and cetUXimab in firSt-line treatment of mCRC), confirming that Erbitux may benefit patients carrying RAS wild-type genes, with significantly higher response rates (RR) and longer progression-free survival (PFS).5 The data also showed that Erbitux had no benefit in patients carrying RAS mutant genes.5

These data have led to the approval of an update to the Erbitux label for the treatment of patients with EGFR-expressing, RAS wild-type mCRC.

- Erbitux is now indicated for the treatment of patients with EGFR-expressing, RAS wild type mCRC in combination with irinotecan-based chemotherapy, in 1st line 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 for patients with mutant RAS mCRC or for whom RAS mCRC status is unknown.
RAS identified as a biomarker in Erbitux studies

In a retrospective analysis of the OPUS study, it was confirmed that Erbitux has a positive benefit-risk profile as an addition to FOLFOX-4 in mCRC patients with RAS wild-type tumors as a 1st line therapy. In the RAS wild-type population:

- Patients treated with Erbitux plus chemotherapy had a significantly higher RR than patients treated with chemotherapy only (61.1% vs. 30.4%, respectively; odds ratio [OR]: 3.46; p=0.008).5
- Patients treated with Erbitux plus chemotherapy had a numerically longer median PFS than patients treated with chemotherapy only (12.0 months vs. 5.8 months, respectively; hazard ratio [HR]: 0.43; p=0.018).5
- Median overall survival (OS) in patients treated with Erbitux plus chemotherapy was 20.7 months, compared with 17.8 months in patients treated with chemotherapy only (HR: 0.83; p=0.51).5

Patients with mCRC, whose tumors are RAS mutant, are unlikely to benefit from the addition of Erbitux to FOLFOX-4.

What this could mean for patients with metastatic colorectal cancer

Until recently, the potential significance of mutations in the RAS family of proteins in clinical practice had not been evaluated in pivotal clinical studies.

The results from the Erbitux OPUS study show that RAS tumor status is likely to help identify those patients who are most likely to benefit from Erbitux as a 1st line treatment.5

Identifying patients with RAS wild-type tumors suitable for Erbitux therapy is an important step towards tailoring treatment in mCRC. Based on the recent European Commission approval of the label change, mCRC patients need to be tested for RAS mutations before Erbitux is prescribed.

References