Vectibix® and *RAS* Biomarker Information

This Physician Education Brochure explains the importance of determining RAS tumour status prior to prescribing Vectibix®

<u>Approved Vectibix® Indication</u>[1]

Vectibix® is indicated for the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer (mCRC):

- **in first-line in combination with FOLFOX or FOLFIRI**
- **in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan)**
- **as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens**

The combination of Vectibix® with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant RAS mCRC or for whom RAS mCRC status is unknown [1]

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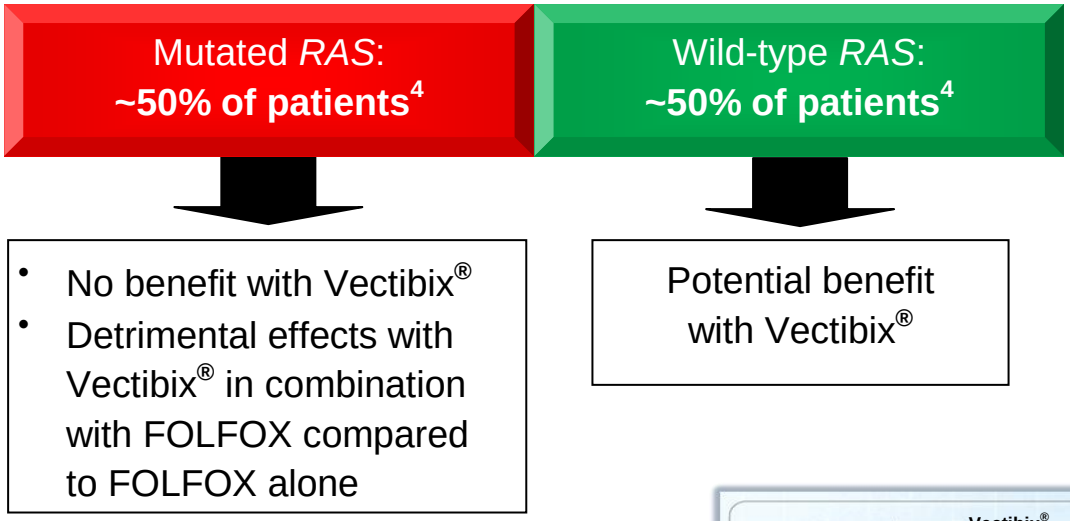
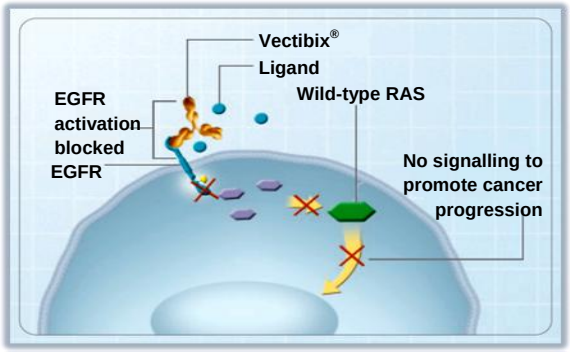
The importance of *RAS* as a predictive biomarker: selecting the patients who may benefit from Vectibix®

- The *RAS* genes (*KRAS* and *NRAS*) are found in two forms: mutated and wild-type (non-mutated)[1,2]
- Vectibix® in combination with FOLFOX chemotherapy has shown a detrimental effect on survival in patients whose tumours carry mutated *RAS* compared to FOLFOX alone[1,3,4]
- Vectibix® has no beneficial effect as a monotherapy and in combination with FOLFIRI in patients with mutant *RAS* tumours[1]
- Conversely, patients whose tumours carry wild-type *RAS* may benefit from Vectibix® [1,3,5,6]



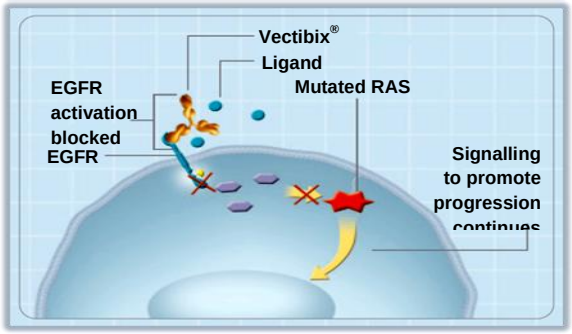
How Vectibix® works in patients with wild-type *RAS*

Vectibix® blocks the activation of EGFR. With wild-type *RAS*, Vectibix® treatment results in the inhibition of signalling that leads to proliferation, angiogenesis and metastasis.[1,8]



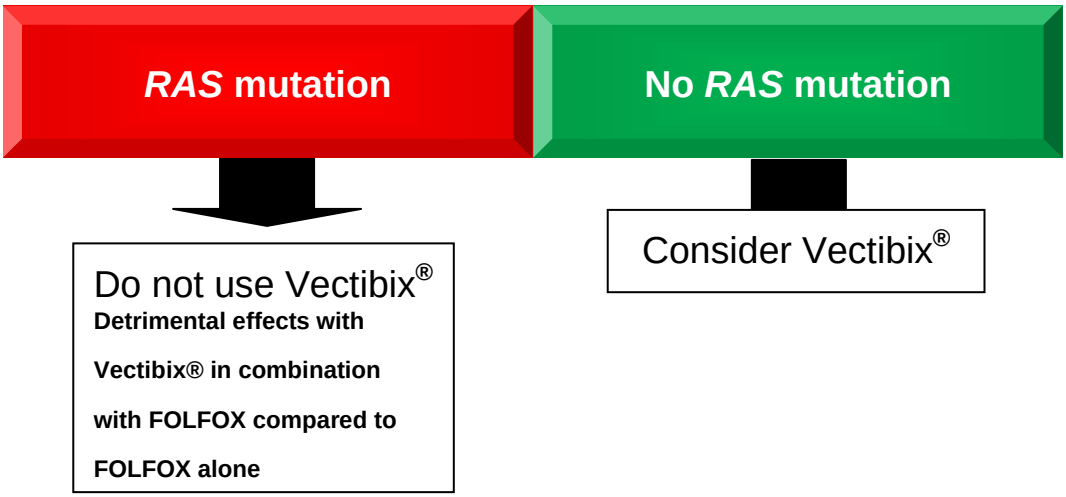
Vectibix in patients with mutated *RAS*

However, when *RAS* is mutated, Vectibix® has no effect, because either the *KRAS* or *NRAS* genes produce a dysfunctional protein. The dysfunctional protein remains activated, downstream of EGFR, transmitting signals even when EGFR is inhibited.[5,9,10]



The importance of testing for *RAS* status

- Using *RAS* mutation status as a biomarker can identify appropriate patients for Vectibix® treatment[3,5,6,10]
- Focusing treatment on patients with wild-type *RAS* will:
  - maximise response rates, disease control, progression-free survival (PFS), and overall survival (OS)[1,3,5,6]
  - avoid unnecessary harm in patients who do not benefit[3,6,11]



Detection of mutated *RAS* (*KRAS* [exons 2,3 and 4] and *NRAS* [exons 2,3 and 4] mutations) should be performed by an experienced laboratory using a validated test method. If Vectibix® is to be used in combination with FOLFOX, it is recommended that mutational status be determined by a laboratory that participates in a *RAS* External Quality Assurance program or that wild-type status be confirmed in a duplicate test.

For patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown, the combination of Vectibix® with oxaliplatin-based chemotherapy is contraindicated[1]. Phase III clinical data demonstrated a detrimental effect on PFS and OS in patients with mutant *RAS* status receiving Vectibix® with FOLFOX chemotherapy compared to FOLFOX alone[1,3,4]. Vectibix in combination of FOLFIRI chemotherapy has no benefit in patients whose tumours carry mutated *RAS*[1]. This further highlights the importance of establishing *RAS* tumour status prior to the administration of Vectibix® either as monotherapy, or with chemotherapy, in order to ensure that only patients with wild-type (non-mutated) *RAS* receive treatment.

The current Summary of Product Characteristics (SmPC) for Vectibix® is appended to this document. Should you have any questions or require additional information regarding the use of Vectibix®, please contact medical information on (national contact).

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions on www.medicinesauthority.gov.mt/adrportal

References: 1. Vectibix® Summary of Product Characteristics. **2.** Schubbert S, Shannon K, Bollag G. Hyperactive Ras in developmental disorders and cancer. Nature Rev Cancer. 2007;7(4):295-308. **3**. Douillard J-Y et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Eng J Med. 2013;369: 1023-34. **4.** Douillard J-Y, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697-4705. **5.** Benvenuti S, Sartore-Bianchi 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(6):2643-2648. **6.** Peeters M, Oliner K, Parker A, et al. Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase 3 study of metastatic colorectal cancer. Clin Cancer Res. 2013: Published Online First January 16, 2013 at: doi:10.1158/1078-0432.CCR-12-1913. **7.** Vaughn CP, ZoBell SD, Furtado LV, Baker CL, Samowitz WS. Frequency of *KRAS*, *BRAF*, and *NRAS* mutations in colorectal cancer. Genes Chromosome, and Cancer. 2011; wileyonlinelibrary.com. **8.** Baselga J. The EGFR as a target for anticancer therapy—focus on cetuximab. Eur J Cancer. 2001;37(suppl 4):S16-S22. **9.** Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol. 2007;25(22):3230-3237. **10.** Conlin A, Smith G, Carey FA, et al. The prognostic significance of K-ras, p53, and APC mutations in colorectal carcinoma. Gut. 2005;54(9):1283-1286. **11.** Lièvre A, Bachet J-B, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res. 2006;66(8):3992-3995.