



BRAF Testing Fact Sheet

WHAT IS BRAF?

BRAF is a gene that codes for a protein involved in the Epidermal Growth Factor Receptor (EGFR) signalling cascade which is important in cell proliferation, angiogenesis, cell migration, cell survival and cell adhesion.

In normal cells, this signalling pathway is not activated unless growth factor is bound to the Epidermal Growth Factor Receptor (EGFR). When BRAF is activated by mutation, it leads to uncontrolled cell growth and division, resulting in cancer.

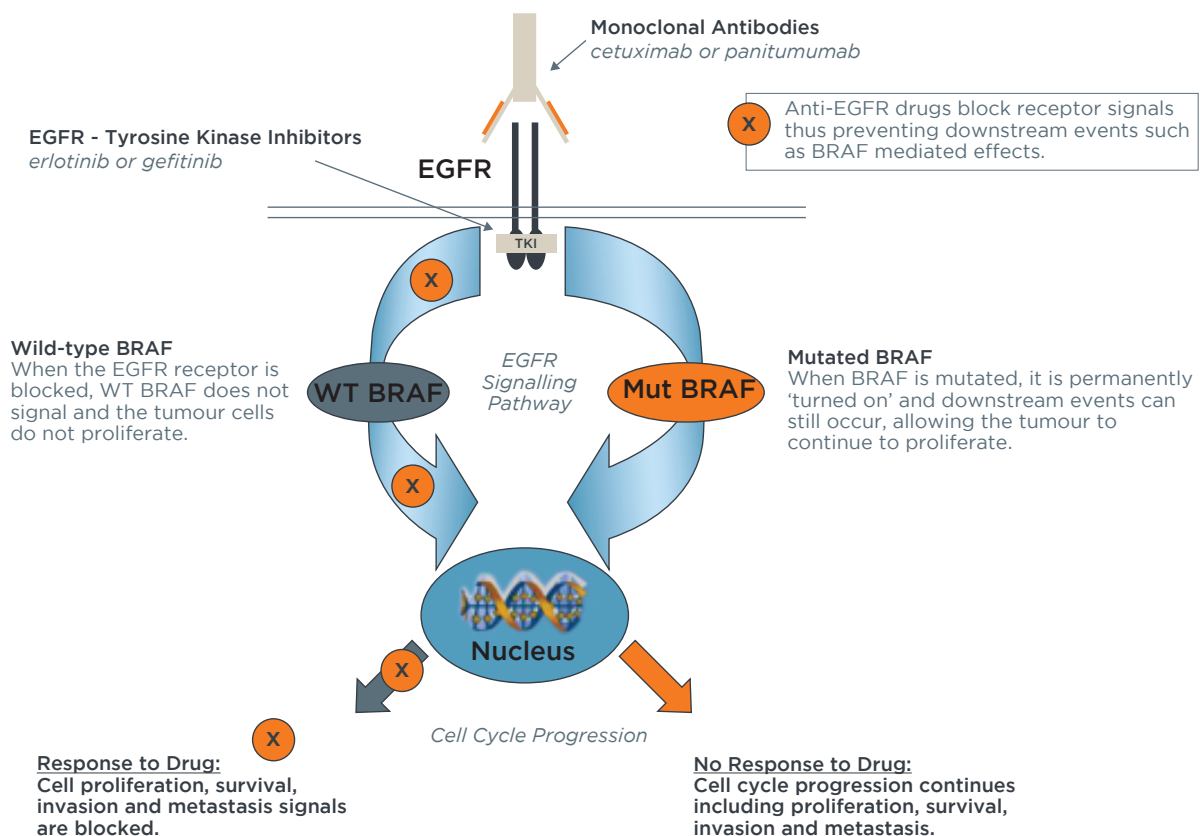
BRAF MUTATIONS IN COLORECTAL CANCER

BRAF mutations are detected in about 10% of colorectal cancers and are associated with a poor prognosis and a lack of response to anti-Epidermal Growth Factor Receptor (anti-EGFR) therapy.¹ The most common activating mutation is V600E and it results in 10 times more BRAF activity than its normal counterpart.¹ This results in fuelling the runaway growth of cancer cells. BRAF V600E constitutes about 90% of all activating BRAF mutations.

TARGETED THERAPIES

The EGFR gene is over-expressed in colorectal cancer and anti-EGFR treatments such as Vectibix® (Panitumumab) or Erbitux® (Cetuximab) bind to EGFR and inhibit the growth and survival of cells expressing EGFR. They competitively inhibit the binding of ligands to EGFR, which in turn prevents signal transduction leading to reduced cell growth and apoptosis. The effect of the BRAF mutation is to lock the BRAF gene product permanently in the 'on' position. It can be seen from the diagram that as BRAF is downstream of EGFR, inhibiting EGFR will have little effect on tumours where growth is being driven by BRAF gene mutations.

BRAF MUTATIONS AND ANTI-EGFR THERAPY



BENEFIT OF TESTING FOR BOTH KRAS AND BRAF

KRAS is a gene that codes for a protein involved in the Epidermal Growth Factor Receptor (EGFR) signalling cascade. KRAS mutations are identified in 30-40% of colorectal carcinomas and studies have shown that patients with mutated KRAS do not respond to anti-EGFR treatment. BRAF mutations account for another 10% of the non-responsive patients. BRAF and KRAS mutations are mutually exclusive and therefore are not found in the same tumours. However, when BRAF testing is performed on patients whose tumours are demonstrated to be wild-type (normal) KRAS, approximately 50% of patients who will be non-responsive to anti-EGFR treatment are identified.² Healthscope Advanced Pathology offers testing for both KRAS and BRAF mutations.

BRAF AND MELANOMA

As reviewed by Garnett et al³ the highest incidence of BRAF mutations is found in malignant melanoma (27-70%). This has led to the development of melanoma therapies that specifically inhibit the mutant BRAF. One of the drugs in development, currently called PLX4032 (R7204), is already in Phase II and Phase III trials.⁴ Early stages of clinical testing suggest that it may help shrink advanced melanoma tumours with BRAF V600E mutations.⁵ Another recent clinical study indicates that BRAF V600K mutations may be present in 10% of all melanoma patients and that these patients may also benefit from PLX4032 (R7204).⁶

CLINICAL SIGNIFICANCE OF BRAF MUTATIONS

- BRAF mutations may be present in 10% of colorectal cancer patients who fail to respond to anti-EGFR therapy. Testing for BRAF mutations can provide important information to the clinician regarding potential candidates for Vectibix® (Panitumumab) or Erbitux® (Cetuximab).
- The high frequency of BRAF mutations in melanoma and the relative lack of effective therapies for advanced stages of the disease suggest that inhibition of BRAF activity may be an important new strategy for the treatment of metastatic melanoma.

BRAF TESTING AT HEALTHSCOPE ADVANCED PATHOLOGY

- Formalin-fixed paraffin embedded tumour sample or seven unstained slides and one H & E stained section are required for mutation analysis.
- All the logistics in getting the tumour block to our laboratory for analysis is handled by Healthscope Advanced Pathology staff.
- Each sample undergoes a pathologist review to ensure that tumour cells are present and a macrodissection to enrich for tumour cells that are then used for analysis.
- BRAF V600E, V600K and V600R mutations are identified by our assay.
- Results are available within 5-7 working days from sample receipt in the laboratory.
- Currently this test is not Medicare rebated, but we are optimistic about reimbursement as the market becomes more aware of the value of such testing.

REFERENCES

1. Sharma S.G. et al. (2010) BRAF Mutation Testing in Colorectal Cancer. Archives of Pathology & Laboratory Medicine 134(8): 1225-1228.
2. Di Nicolantonio F. et al (2008) Wild-type BRAF is Required for Response to Panitumumab or Cetuximab in Metastatic Colorectal Cancer. J Clin Oncol 26: 5705-5712.
3. Garnett MJ and Marais R. Guilty as Charged: B-RAF is a Human Oncogene. Cancer Cell, 2004; 6: 313-319.
4. Plexikon Announces First Patient Dosed in Phase 3 Trial of PLX4032 (RG7204) for Metastatic Melanoma. [Online] (Updated 08 January 2010). Available at: <http://www.plexikon.xom.au/view.cfm/74/Pres-Releases> [Accessed August 31 2010].
5. Flaherty K.T. et al (2010) Inhibition of Mutated, Activated BRAF in Metastatic Melanoma. NEJM 363: 809-819.
6. Rubenstein J.C. et al (2010) Incidence of the V600K Mutation Among Melanoma Patients with BRAF Mutations, and Potential Therapeutic Response to the Specific BRAF Inhibitor PLX4032.

Providing services since 1936, Healthscope Pathology operates throughout Australia, New Zealand, Singapore and Malaysia.

Healthscope Pathology has purpose built, state-of-the-art service and molecular research laboratories which ensure the highest standard of testing.



focused on you

healthscopepathology.com.au

HAP-1142-BRAF-001 (10/10)
Clinical Laboratories Pty Ltd ABN 62 006 823 089