# A Biomarker for Metastatic Colorectal Cancer and Treatment Goals

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The incidence of colorectal cancer (CRC) is rapidly increasing world-wide including in Indonesia and controversy not with standing, making it as the second most common malignancy (GLOBOCAN 2012). As with other cancers – more importantly with its adenoma-carcinoma sequence being one of the first to be elucidated by Vogelstein[1] – its treatment and prognosis are determined by disease staging and molecular profile. Yet, identifying those for whom chemotherapy is indicated is still a challenge due to its histopathological heterogeneity; with special emphasis on stage II disease, for example, having a five-year survival that ranges from 87.5% for IIA to 58.4% in stage IIC. It is in such situation that predictive and prognostic markers are constantly being investigated.

As one of the leading causes of cancer death in developed countries, much interest has grown in research in the development of biomarkers to improve the diagnostic process and to predict efficacy of chemotherapy.[2] Only a few biomarkers are qualified as such, and the paucity of data has resulted in under- and overtreatment when relying only on the current TNM system. At present, only mutant KRAS, mutant BRAF, Microsatellite Instability (MSI) and the Oncotype DX® ColonCancer Assay are used in clinical practice. MSI and mutant KRAS are the established markers to date.[3] But as the world is shifting towards personalized medicine (or "precision therapy" as is more frequently called), much work remains to be done.

Which brings us to the topic of BRAF in this edition of Acta Medica Indonesiana. Identified in several cancers such as melanoma, thyroid cancer, glioma, lung cancer, sarcoma, breast and colorectal aner, it is part of the Ras-Raf-MEK-ERK pathway, having important functions in cell division, differentiation, migration, apoptosis and protein secretion.[4]

The V600E mutation is found in 80% of all BRAF mutations in the abovementioned cancers, with enhanced kinase activities for B-Raf resulting in constitutive activation of the downstream signaling pathway, leading to increased cell proliferation and survival.

Current research reveals that 9-14% of colorectal cancer patients have the BRAF V600E mutation, the mutation of which increased the risk of mortality two-fold. Combined with microsatellite instability assays, BRAF mutation showed that microsatellite stable and the BRAF mutation are independent adverse factors for patient survival, as the BRAF mutation in colorectal cancer rendered the tumor resistant to anti-EGFR therapy and wild-type BRAF is required for response to drugs such as panitumumab or cetuximab. Thus, BRAF genotype could be used to select eligible patients for the treatment with these drugs.

However, although testing for K-ras mutations is recommended in metastatic colorectal cancer to determine whether an anti-EDFR drug such as cetuximab, should be used only if the tumor is negative for KRAS (wild-type); yet 30-40% will not respond. Thus, additional biomarkers will have to be used, and the BRAF V600E mutation is one of these markers for which early evidence showed improvement in the stratification of K-ras negative mCRC patients,[5] and acknowledging the ethnic and populations among countries – thus the paper reporting among Indonesians –, the work of Hernowo is in the right direction, and future research is anticipated to elucidate the behavior of this cancer among Indonesians.

## REFERENCES

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