Nature Reviews Clinical Oncology | Published online 5 Jul 2016; doi:10.1038/nrclinonc.2016.107

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COLORECTAL CANCER

CpG island methylation indicates inferior survival outcomes

> more extensive methylation… is associated with significantly reduced overall survival

Altered CpG-island methylator phenotypes (CIMPs) have been observed in patients with many different types of cancer, although the clinical significance of these widely observed alterations remains unclear. Now, researchers have shown that more extensive methylation of up to eight different CIMP-specific promotor regions is associated with significantly reduced overall survival compared with no methylation of these same promotor regions in patients with stage IV metastatic colorectal cancer (CRC).

Lead author Sae-Won Han explains: "limited information is available on whether CIMP status has any prognostic significance in stage IV CRCs". Thus, the methylation status of primary CRC tumour samples from 153 patients who predominantly received fluoropyrimidine and oxaliplatin-based chemotherapy was examined using the MethyLight PCR-based assay.

The investigators found that patients with CIMP-negative tumours had a significantly longer median overall survival duration compared with that of patients with CIMP-low (featuring methylation of 1–4 promoters) and CIMP-high (methylation of ≥5 promotors) tumours. The authors highlight the importance of these results in the context of previous findings: "Thanks to other excellent previous works, such as those of the colorectal cancer subtype consortium, we are getting insights that the MSI, immune subtype, or BRAF-mutant CRC behave differently once they recur" adding that "CIMP does not affect recurrence in stage III CRC but, similar to BRAF and MSI status, the biology is aggressive in stage IV, based on this data".

Commenting upon future directions for research in this area, the authors highlight the importance of potential interactions of CIMP status with treatment: "a recent study has shown a trend towards increased survival in CIMP-high patients treated with irinotecan plus fluorouracil and leucovorin compared with similar patients treated with fluorouracil and leucovorin." Indeed, CIMP status has also been shown to affect responses to anti-EGFR therapy. These data reveal a need for further investigations into the relationship between CIMP status, prognosis and the optimal treatment approach.

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ORIGINAL ARTICLE Cha, Y. *et al.* Adverse prognostic impact of the CpG island methylator phenotype in metastatic colorectal cancer. *Br. J. Cancer* http://dx.doi.org/10.1038/bjc.2016.176 (2016)

FURTHER READING Lee, M. S. *et al.* Association of CpG island methylator phenotype and EREG/AREG methylation and expression in colorectal cancer. *Br. J. Cancer* **114**, 1352–1361 (2016)