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HER2 gene copy number status may influence clinical efficacy to anti-EGFR monoclonal antibodies in metastatic colorectal cancer patients

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Background: In metastatic colorectal cancer (mCRC), *KRAS* is the only validated biomarker used to select patients for administration of epidermal growth factor receptor (EGFR)-targeted therapies. To identify additional predictive markers, we investigated the importance of HER2, the primary EGFR dimerisation partner, in this particular disease.

Methods: We evaluated the *HER2* gene status by fluorescence *in situ* hybridisation (FISH) in 170 *KRAS* wild-type mCRC patients treated with cetuximab or panitumumab.

Results: Depending on *HER2* gene copy number status, patients showed three distinct cytogenetic profiles: 4% of patients had *HER2* gene amplification (R:*HER2*/CEP17 $\geqslant 2$) in all neoplastic cells (*HER2*-all-A), 61% of patients had *HER2* gain due to polysomy or to gene amplification in minor clones (*HER2*-FISH + *), and 35% of patients had no or slight *HER2* gain (*HER2*-FISH −). These subgroups were significantly correlated with different clinical behaviours, in terms of response rate (RR; $P = 0.0006$), progression-free survival (PFS; $P < 0.0001$) and overall survival (OS; $P < 0.0001$). Patients with *HER2*-all-A profile experienced the worst outcome, patients with *HER2*-FISH − profile showed an intermediate behaviour and patients with *HER2*-FISH + * profile were related to the highest survival probability (median PFS in months: 2.5 *vs* 3.9 *vs* 7.6, respectively; median OS in months: 4.2 *vs* 9.7 *vs* 13, respectively).

Conclusion: *HER2* gene copy number status may influence the clinical response to anti-EGFR-targeted therapy in mCRC patients.