

**Combining RNAscope and IHC results to Identify a C-MET Aberrant High-risk Colorectal Cancer Patient Subgroup with a High RNA and Low Protein Expression Profile**

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Colorectal cancer (CRC) is Europe-wide the second most common cause of cancer death and represents with several different phenotypes. c-MET overexpression is associated with poor outcome and c-MET inhibitors were suggested to be applicable to resistant tumours. Despite promising results in clinical phase 1 and 2 trials, phase 3 trials tend to be unsuccessful. A reason for the latter could be the lack of an officially regulated and well-established scoring system for c-MET.

The aim of this study was to analyse c-MET DNA amplification as well as to score RNA and protein levels, correlate these results, evaluate them statistically and identify the prognostic significance of aberrations. The present study includes 241 FFPE tissue microarrays (TMAs) of CRC patients that were stained during double-DNA in-situ hybridization (DDISH), RNAscope processing and immunohistochemistry (IHC). The samples were evaluated by digital pathology methods.

We show for the first time that a high-risk c-MET aberrant subgroup must be identified by a combination of RNA and protein evaluating methods. Furthermore, our results suggest that the high-risk patients (HR = 2.1, 95% CI = 1.2 - 3.67) that present with a 35 % lower 5-year survival, display a phenotype comprised of high RNA levels and low protein expression. This finding contrasts with earlier studies that correlate protein overexpression with poor prognosis but are in line with recent study findings from 2016.

It is crucial to identify the biological mechanism behind this phenotype to establish appropriate treatment options. Furthermore, we suggest to conduct a more detailed analysis concentrating on focal and invasive edge expression of c-MET.