**Supplementary methods**

**Data analysis for the GSE39528 dataset:**

*Generation of gene lists.* Initialdata analysis was carried out using the R Statistical Package (version 3.2.1). The data used in this study was obtained from 566 Affymetrix U133 Plus 2.0 patient transcriptional profiles accessed through the NCBI GEO accession number GSE39582 ([1](#_ENREF_1)). Quality Control using the AffyQCReport and simpleaffy packages combined with batch correction using the SVA package reduced this cohort to 444 stage II/III profiles. The untreated batch-corrected *BRAF*MT stage II/III subset was composed of 31 tumours, of which 7 patients had a relapse-free-survival (RFS) of < 1 year (“poor prognostic subgroup”) and 24 patients had a RFS of > 2 years (“good prognostic subgroup”).

Partek Genomics Suite was subsequently used for downstream dataset analysis. A genelist was created of those genes that were upregulated and downregulated between poor prognostic and good prognostic *BRAF*MT CRC subgroups (1.3-fold cut-off; p < 0.05).

**Data analysis for the stage II E-MTAB-863 and E-MTAB-864 Almac datasets:**

*BRAF*MT *surrogate variable.* For the prediction of *BRAF*MT status a highly specific classification model was built and validated using publicly available data. The model consisted in two main steps: a feature selection step (based on recursive feature elimination with linear support vector machine) followed by a classification step (based on an ElasticNet classifier). For the performance estimation, the two steps were embedded into an external 5-fold stratified cross-validation loop. The same steps were used for building the final model which was then applied on the independent validation sets. The training set (the one used for the performance estimation as well) is described above (GSE39582 ([1](#_ENREF_1))). For the independent validation, two other small datasets were used: GSE35896 ([2](#_ENREF_2)) and GSE75315 ([3](#_ENREF_3)). The estimated area under the ROC curve (AUC) was 0.9987 (std.dev. 0.0017) for a precision of 0.9477 (std.dev. 0.0641) and a recall of 0.8819 (std.dev. 0.0938) corresponding to the default cut-off 0.5. On the validation sets, the precision of the predictor was 0.98 and 0.95, and the recall 0.98 and 0.95, respectively.

*Generation of gene lists.* Initialdata analysis was carried out using the R Statistical Package (version 3.2.1). This dataset was comprised of 359 untreated stage II CRC samples and, using the classifier described in the previous paragraph, we predicted 26 patients (7.24%) with *BRAF*MT tumours. In this study, high-risk patients were previously defined as those with metastatic cancer recurrence within 5 years of primary surgery ([4](#_ENREF_4)): 11 *BRAF*MT patients had a disease-free-survival (DFS) < 5 years (subgroup with poor outcome), whereas 15 *BRAF*MT patients had a DFS > 5 years (subgroup with good outcome). A differentially expressed gene list was generated (2-fold cut-off; p<0.05) between the good and poor *BRAF*MT subgroup using the LIMMA package.

**Nascent protein synthesis labelling**

Cells were seeded on coverslips in 24-well plates. Cells were cultured in 100μL/well of FCS/PBS (methionine-free) with 50μM Click-iT® HPG. Cells were fixed using 100μL/well 3.7% formaldehyde in PBS for 15min, followed by permeabilization using 100μL/well of 0.5% Triton® X-100/PBS for 20 min. 100μL/well Click-iT® reaction cocktail was added for 30min. DNA was stained using HCS NuclearMask™ Blue Stain. Detection of the incorporated amino acid was assessed using fluorescent microscope.

**REFERENCES**

1. Marisa L, de Reynies A, Duval A, Selves J, Gaub MP, Vescovo L, et al. Gene expression classification of colon cancer into molecular subtypes: characterization, validation, and prognostic value. PLoS medicine. 2013;10:e1001453.

2. Schlicker A, Beran G, Chresta CM, McWalter G, Pritchard A, Weston S, et al. Subtypes of primary colorectal tumors correlate with response to targeted treatment in colorectal cell lines. BMC medical genomics. 2012;5:66.

3. Barras D, Missiaglia E, Wirapati P, Sieber OM, Jorissen RN, Love C, et al. BRAF V600E Mutant Colorectal Cancer Subtypes Based on Gene Expression. Clin Cancer Res. 2017;23:104-15.

4. Kennedy RD, Bylesjo M, Kerr P, Davison T, Black JM, Kay EW, et al. Development and Independent Validation of a Prognostic Assay for Stage II Colon Cancer Using Formalin-Fixed Paraffin-Embedded Tissue. J Clin Oncol. 2011.