Legend to Supplementary Figures

Supplementary Figure S1. Copy number increase of *MDM2* gene at progression after vemurafenib+panitumumab.

In panel **A** and **B**: analyses performed on archival surgical specimen and on post-progression liver rebiopsy, respectively. Dual color bright field in situ hybridization (ISH) for *MDM2* gene (black dots) and CEP12 (chromosome twelve α-centromeric, red dots). In baseline tumor tissue, the signals corresponding to the MDM2 and CEP12 probes ranged from 2 to 5 (mean values of 3.5 and 3.3 for MDM2 and CEP12, respectively), with a gene-to-chromosome ratio of just over 1, indicating absence of gene amplification. However, in a small fraction of cells (5%) within the pre-treatment sample the *MDM2* gene copy number was ≥5. In the post-progression tumor biopsy, MDM2 copy number varied from 3 to 16 (mean 7.2) while CEP12 ranged from 1 to 8 (mean 3.4). At least 75% cells in the post-treatment liver biopsy were found to carry ≥5 *MDM2* gene copy number and the gene-to-chromosome ratio was >2. Original magnification X20.

Supplementary Figure S2. A-D. Representative examples of colorectal carcinomas bearing BRAF mutations and *MET* gene copy number gain.

A Hematoxylin & Eosin staining of a poorly differentiated colon carcinoma. **B** Dual color bright field ISH for *MET* gene (black dots) and CEP7 (red dots) of case in panel A. Tumor cells contain *MET* gene copy number (ranging from 2 to 7; mean: 4.2) and Chromosome 7 signals (ranging from 2 to 5; mean: 3.4). Interestingly, 38% of neoplastic cells featured ≥ 5 *MET* gene copy number. **C** Hematoxylin & Eosin staining of a pancreatic lesion from an intestinal adenocarcinoma. **D** Single color bright field ISH for *MET* gene (black dots) of case in panel C. Tumor cells contain *MET* gene copy number (ranging from 4 to 11; mean: 5.4). Up to 77% of tumor cells contained ≥ 5 *MET* gene copy number. Arrows indicate neoplastic cells with high *MET* gene copy number.

Supplementary Figure S3. Untreated WiDr parental cells exhibit similar levels of activated RAS-GTP protein compared to their MET-amplified resistant derivatives treated with encorafenib+cetuximab+alpelisib (E+C+A). Whole-cell extracts were subjected to pull-down of active KRAS-GTP using the GST-RAF1 Ras-binding domain. Lysate of SW480 colorectal cancer cells carrying a *KRAS* G12V mutation is loaded as a positive control.