

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009;360:563-72.

## Web Supplement

### Reasons for ineligibility

Second malignancy in the past 5 years (n=5), inadequate bone marrow or liver function (n=3), serious concomitant disease (n=3), previous intolerance of fluoropyrimidines (n=2), withdrawal of informed consent (n=2), no histological confirmation of colorectal cancer (n=1), use of therapeutic dose anticoagulant drugs (n=1), no measurable disease (n=1), and death before randomization (n=1).

### Treatment Details

The median number of treatment cycles was 10 (range 1-44) in the CapoxB group and 9 (range 1-44) in the CapoxB + cetuximab group (P=0.009). The mean number of cycles was 12.8 in the CapoxB group and 11.0 in the CapoxB + cetuximab group. The median time on treatment was 7 months (range 1-31) in the CapoxB group versus 6 months (range 1-33) in the CapoxB + cetuximab group (p<0.001). The median relative dose intensity was comparable in the two groups for all agents (capecitabine 84.7% vs. 84.0%, oxaliplatin 97.9% vs. 98.0%, bevacizumab 99.6% vs. 99.5% and cetuximab 92.2%).

## Toxicity Details

Diarrhea, any skin toxicity, and acneiform skin reactions occurred more frequently in the CapoxB + cetuximab group, and hypertension was more frequent in the CapoxB group. The incidence of other grade 3-4 adverse events did not significantly differ between the treatment groups. The incidence of grade 3 acneiform skin toxicity in the CapoxB + cetuximab group was 16% in women and 31% in men ( $P= 0.003$ ). Hypomagnesemia, which in 97% of cases was of grade 1-2 severity, occurred in 68 patients in the CapoxB group and 146 patients in the CapoxB + cetuximab group ( $p<0.001$ ). Six patients died of causes that were probably related to study treatment (4 in the CapoxB group and 2 in the CapoxB + cetuximab group): 3 patients in the CapoxB group and one in the CapoxB + cetuximab group died as a result of gastrointestinal perforation, one patient in the CapoxB group died of respiratory insufficiency with unknown cause, and one patient in the CapoxB + cetuximab group died with neutropenic fever. Central review of the files of 42 patients who died within 30 days after the last administration of study drugs and in whom progressive disease was not the only reported event revealed major protocol

violations in 19 patients. These concerned non-adherence to the study guidelines for dose reduction or discontinuation of study drugs.

### *KRAS* Mutations

The 7 most prevalent *KRAS* mutations in codon 12 (n=6) and 13 (n=1) (21) were assessed using a real-time PCR-based assay (DxS; Manchester, UK). To confirm the results obtained by assay, sequencing of exon 2 was performed in all samples. In case of discordant test results both assay and sequencing were repeated. Only samples with a concordant result using both sequencing and assay or, in case of initial discrepancy, in at least 3 out of 4 tests, were included in the analysis.