**Supplementary Figure S1.** Forest plots of progression-free survival by subgroups within the intention-to-treat population.

*Abbreviations*. HR: Hazard ratio. ECOG: Easter Cooperative Oncology Group. PFS: progression-free survival.

**Supplementary Figure S2.** Forest plots of overall survival by patient subgroups within the intention-to-treat population.

*Abbreviations.* HR: Hazard ratio. ECOG: Easter Cooperative Oncology Group. PFS: progression-free survival. OS: overall survival.

**Supplementary Figure S3.** The waterfall plots of the best percentage change in the tumor burden from baseline evaluation in patients treated with CAPTEM (A) and FOLFIRI (B).

*Abbreviations.* PD: progressive disease. PR: partial response. SD: stable-disease. CR: complete response

**Supplementary Figure S4.** Compliance to quality of life questionnaires (number of patients completing baseline assessments and the assessments at designated time points). Panel A: EORTC QLQ-C30. Panel B: FACT-C.

*Abbreviations.* PD: progressive disease.

**Supplementary Figure S5.** Mean changes from baseline by study arm in European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 global quality of life and functional scales.

*Abbreviations.*PD: progressive disease.

**Supplementary Figure S6.** Mean changes from baseline by study arm in European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 symptom items.

*Abbreviations.* PD: progressive disease

**Supplementary Figure S7.** Mean changes from baseline by study arm in Functional Assessment of Cancer Therapy-Colorectal [FACT-C].

*Abbreviations.* PD: progressive disease. FACT-G: Functional Assessment of Cancer Therapy-General. FACT-C: Functional Assessment of Cancer Therapy-Colorectal.

**Supplementary Figure S8.** The waterfall plots of the best percentage change in the tumor burden from baseline evaluation in patients treated with CAPTEM (left panels) and FOLFIRI (right panels) according to MGMT IHC expression and MGMT % methylation by Methyl-BEAMing.

*Abbreviations.* IHC: immunohistochemistry. MB: methyl-BEAMing.