Background:
The FIRE-3 trial compared 1st-line therapy of FOLFIRI plus either cetuximab or bevacizumab in 582 KRAS exon 2 wildtype (wt) mCRC patients. The subgroup of extended RAS wt patients consisted of 400 patients. The AADx molecular assay has previously been shown to identify a prognosis angiogenic subgroup across multiple cancer types including ovarian and lung cancer. Both, bevacizumab (through inhibition of VEGF–activation) and cetuximab (through inhibition of EGFR-signaling) are expected to have anti-angiogenic effects in colorectal cancer. The predictive role of AADx in FOLFIRI plus bevacizumab or cetuximab treated in colorectal cancer patients remains unclear.

Methods:
Transcriptional profiling of 501 formalin fixed embedded pre-treatment samples from the ITT population was performed using the Almac Diagnostic XioTM array. Patients were classified by the AADx assay as ANGIO ON or ANGIO OFF based on a predefined score. ORRs were compared using Fischer’s exact test. Progression-free survival (PFS) and Overall survival (OS) times were compared using Kaplan-Meier estimation and log-rank tests. Hazard ratios (HR) were estimated according to the Cox proportional hazard model.

Results:

- Almac has developed the angiogenic diagnostic (AADx) gene expression assay in ovarian cancer that:
  - identifies angiogenic molecular subtypes
  - is defined by activation/repression of genes associated with angiogenic processes
  - demonstrates prognostic performance in ovarian, colorectal and lung cancers
  - predicts response to bevacizumab in ovarian cancer
- Angiogenesis active v. AADx negative v. ANGIO ON (C1 and C3): Angiogenesis biology switched compared to ANGIO OFF (C2): Angiogenesis biology switched off in the patient tumour

Conclusions:
The data suggests that the AADx assay interacts with RAS mutation and may define RAS wt mCRC patients that respond differently to cetuximab or bevacizumab in combination with FOLFIRI. One potential explanation of the data is that Cetuximab is a more effective treatment for the poor prognosis ANGIO ON subtype.