

BOA15

Association of topoisomerase-1 (Topo1) with the efficacy of chemotherapy in a randomized trial for advanced colorectal cancer patients (FOCUS)

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Background: We have assessed potential predictive markers of the efficacy of irinotecan and oxaliplatin in advanced CRC patients randomized to fluorouracil (FU), FU+irinotecan (Ir) or FU+oxaliplatin (Ox).

Methods: Pathology specimens were retrieved from 1281 patient in the FOCUS trial. Normal and tumor DNA were extracted and tissue microarrays were made for immunohistochemistry (IHC). The following factors were assessed for effect on failure-free survival (FFS) with first-line therapy: IHC for MLH1, MSH2, P53, Topo1, ERCC1, MGMT, and COX2; DNA polymorphisms in GSTP1 (105Val), ABCB1 (C3435T), XRCC1 (Q399R), ERCC2 (K751Q), and UGT1A1*28.

Results: For the primary endpoint of FFS we observed significant heterogeneity (interaction) of treatment effect in relation to Topo1 staining intensity ($p=0.03$) among 823 assessable patients. 488 patients (59%) had moderate or high Topo1 expression; these patients derived highly significant benefit from 1st-line chemotherapy with either Ir or Ox (HR 0.5 (moderate) and 0.4 (high) for both Ir and Ox). In contrast, the 334 (41%) patients with low Topo1 IHC expression showed no significant benefit from the addition of either Ir or Ox compared with FU alone (HR 0.9 and 0.8 respectively). When patients receiving FU alone are considered separately, low Topo1 expression was associated with significantly better FFS (HR 0.7 (0.6-0.9)). The other 11 molecular markers showed no significant interactions with treatment received (p values for interaction all > 0.1).

Conclusions: We have identified Topo1 expression as a potential predictive marker for chemotherapy efficacy. If verified in an independent dataset, this information could be used to individualise patient treatment.