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ANALYSIS OF PROGRESSION FREE SURVIVAL IN THE NEW EPOC STUDY IN AN ALL RAS WILD-TYPE POPULATION


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Aim: The New EPOC study randomised KRAS exon 2 wild-type (WT) patients with resectable or suboptimally resectable colorectal liver metastases (CRLM) to receive chemotherapy with or without cetuximab before and after liver resection. KRAS status was determined using pyrosequencing in codons 12, 13 and 61. The trial demonstrated a detriment in progression free survival (PFS) from 20.5 to 14.1 months with the addition of cetuximab to chemotherapy (HR 1.48 95%CI 1.04-2.12 p = 0.03).

Methods: Samples of tumour from the primary colorectal and liver resections were obtained. Patients were further analysed using MiSeq for KRAS (codon 12, 13, 61, 117 and 146), NRAS (12, 13, 61, 117 and 146), PIK3CA (547 and 1047) and EGFR S492R. Survival analyses were completed using the Kaplan-Meier method and the log-rank test.

Results: To date 140 samples of primary tumour and 103 samples of CRLM have been analysed. Paired samples of primary tumour and CRLM were analysed for 61 patients. Further mutations were found in samples from 12 patients in the initial “KRAS WT” group, 8 KRAS (4 in codons previously analysed by pyrosequencing) and 4 NRAS. 3 mutations identified in CRLM were not in the matching primary. Analysis of the all RAS WT primary tumour population (chemo alone arm n = 53, chemo plus cetuximab arm n = 72) demonstrated a detriment in median PFS of 20 months to 15 months respectively (HR 1.4 95%CI 0.82-2.4 p = 0.22). 7 tumours were found to be BRAF mutated in all patients sequenced.

Conclusions: In this study the addition of cetuximab to chemotherapy and surgery for operable CRLM in KRAS wild-type patients resulted in an inferior PFS. More stringent selection of an all RAS WT cohort did not alter the detriment observed. BRAF mutation is uncommon and likely reflects the selection of a relatively good prognosis cohort. Differences in mutational status between primary and metastasis were infrequent and could reflect either a treatment effect or clonal outgrowth. Initial pyrosequencing failed to detect <1% of mutations subsequently detected and most new mutations were discovered in previously un-interrogated sequences.

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