
Proceedings Paper:
Westwood, AC, Hemmings, GJ, Bottomley, D et al. (7 more authors) (2018) Comparison of Mismatch Repair Protein Expression Between Biopsies and Resections in Advanced Colon Cancer from the Phase II Group of the Fluoropyrimidine Oxaliplatin and Targeted Receptor Pre-Operative Therapy (FOxTROT) Trial. In: Journal of Pathology. Maastricht Pathology 2018. 11th Joint Meeting of the British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland, 19-22 Jun 2018, Maastricht. Wiley , S26-S26.

https://doi.org/10.1002/path.5165

Maastricht Pathology 2018

Maastricht Exhibition and Congress Centre
The Netherlands
19 – 22 June 2018

Abstract Submission Details

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Title

Comparison of mismatch repair protein expression between biopsies and resections in advanced colon cancer from the phase II group of the Fluoropyrimidine Oxaliplatin and Targeted Receptor Pre-Operative Therapy (FOxTROT) trial

Abstract Text

Colorectal cancer is diagnosed in around 41,000 people a year in the UK. Approximately 15% develop following a defect in the mismatch repair (MMR) pathway. FOxTROT is a novel trial assessing the potential benefit of pre-operative chemotherapy in locally advanced colon cancer. We aimed to compare MMR status between biopsy and resection tissue from the phase II component of the FOxTROT trial and identify possible changes following chemotherapy.

Cases of complete/near complete response were not tested (n=8). Resection material for 131 cases in tissue microarrays (3 tumour cores per case) was stained using immunohistochemistry for MLH1, PMS2, MSH2 and MSH6. 100 cases had matched biopsy material. Slides were digitally scanned and scored as either positive or negative by two independent pathologists. In cases with poor staining or discordant scoring, repeat staining was performed on whole tissue sections. Part funded by PathSoc.

99 cases showed proficient MMR with the remainder (24%) showing deficiency. Of the deficient cases, the majority showed loss of MLH1/PMS2 (n=25) with loss of MSH2/MSH6 in 2 cases, isolated PMS2 loss in 2 cases and isolated MSH6 loss in 1 case. 1 case showed additional clonal negativity of its non-paired protein. The remaining 2 cases showed unusual patterns of loss of one or more proteins. Of the 25 cases with MLH1/PMS2 loss, 15 were associated with a BRAF codon 600 mutation and 10 were wild type. There was agreement in MMR status between the biopsy and resection in 98% of cases (n=98). The two discordant cases showed unusual patterns of sub-clonal protein loss not entirely consistent across the biopsy and resection.

There was a very good correlation in MMR protein expression status between the biopsy and resection in the FOxTROT trial. The two discrepant cases are currently undergoing further investigation. There is no evidence that pre-operative chemotherapy induces a change in MMR status unlike the loss of MSH6 described following radiotherapy.

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