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Title

Comparison of mutational status in the EGFR pathway across four different platforms in the Fluoropyrimidine Oxaliplatin and Targeted Receptor Pre-Operative Therapy (FOxTROT) trial.

Abstract Text

The FOxTROT trial assessed the potential benefit of pre-operative chemotherapy in locally advanced colon cancer. RAS wild type patients were additionally randomised to receive an anti-EGFR antibody. The optimal method for RAS analysis is currently unclear. We aimed to look at the concordance in mutational calls across the EGFR pathway using four different platforms.

Cases of complete/near complete response were not tested (n=8). DNA was extracted from resected tumour blocks in the phase II group (n=142). The mutational status of KRAS (codons 12/13/59/61/117/146), NRAS (12/13/59/61), BRAF (600) and PIK3CA (542/545/546/1047) were tested using next generation sequencing (NGS) of direct PCR products. This was compared to three alternative platforms, each covering a variable number of amplicons: pyrosequencing (no KRAS117/146, NRAS & PIK3CA); Fluidigm Access Array NGS (no KRAS117 & NRAS117); and Affymetrix DNA microarrays (no KRAS59/117 & NRAS 13/59/117). Part funded by PathSoc.

Mutations were detected in 37% of samples for KRAS, 2% for NRAS, 16% for BRAF and 18% for PIK3CA using NGS of direct PCR products. Pyrosequencing showed excellent correlation for KRAS12 (97%), KRAS13 (99%), KRAS61 (100%) and BRAF (97%). Affymetrix chips showed excellent agreement for NRAS (100%) and KRAS 13 & 61 (99%), but slightly lower agreement for KRAS 12 (94%) and BRAF (95%). Fluidigm agreement ranged from 92% to 100%, however, due to technical difficulties the data were incomplete for a number of cases.

NGS of direct PCR products is currently our gold standard test for determining EGFR pathway mutational status prior to treatment with anti-EGFR monoclonal antibodies. Pyrosequencing and Affymetrix chips produced very similar results with generally excellent agreement. Cases with discrepancies are currently undergoing further exploration. Due to technical difficulties when using FFPE, Fluidigm Access Arrays frequently failed to produce a result and are considered suboptimal for routine mutational detection

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