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# Comparison of outcomes in clinical trials of locally advanced dMMR colon cancer: FOxTROT and NICHE-2

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## Background

In the NICHE-2 single-arm study, neoadjuvant nivolumab/ipilimumab showed remarkable efficacy in locally advanced dMMR colon cancers (CC), both in pathological response and long-term outcomes. However, concerns about overtreatment of a good prognosis population selected by radiologic staging persist and standard of care remains surgery followed by adjuvant chemotherapy (chemo). The FOxTROT trial tested perioperative chemo (NAC) vs upfront surgery with adjuvant chemo in a similarly selected dMMR population. We compared 3-year disease-free survival (DFS) between NICHE-2 and FOxTROT.

## Methods

Matching-adjusted indirect comparison (MAIC) was used to compare individual patient data from NICHE-2 to aggregated data from FOxTROT. NICHE-2 pts meeting FOxTROT eligibility criteria (cT3-4, N0-2, non-metastatic dMMR CC) were included. All dMMR pts from FOxTROT (NAC + surgery) were analyzed. MAIC adjusted NICHE-2 data for key prognostic factors (primary: age; sensitivity: gender, baseline T/N-stage). Weighted Kaplan-Meier curves were generated and compared using log rank test.

## Results

FOxTROT included 185 dMMR pts (117 NAC, 68 surgery); NICHE-2 included 94 pts with cT3-4 tumors. NICHE-2 pts were younger (mean 58 vs 63), more often female (62% vs 47%) and had more cT4 tumors (77% vs 35%), with similar cN+ rates (75% vs 80%). Pathologic response was 98% in NICHE-2 vs 7% in FOxTROT. The 3-year DFS was 80% (95% CI 73–85%) in FOxTROT (NAC + surgery) vs 100% (95% CI 100–100%) in NICHE-2 (log rank p <0.001). No difference was seen between FOxTROT arms (p=0.9). In FOxTROT, 3-year DFS was 70% (95% CI 58-80%) for cT4 tumors (n=65) and 84% (95% CI 76-90%) for cT3 tumors (n=120), while DFS for both cT3 (n=22) and cT4 (n=72) tumors was 100% in NICHE-2.

## Conclusions

Using MAIC, we show a statistically significant and clinically meaningful difference in 3-year DFS favoring neoadjuvant nivo/ipi over chemo in pts with locally advanced dMMR CC. Importantly, similarly selected dMMR pts had a significant recurrence rate despite chemo, challenging the view that these tumors have a good prognosis. No recurrences occurred in NICHE-2 despite a high proportion of cT4 tumors. These findings support neoadjuvant nivo/ipi for pts with radiologically staged locally advanced dMMR CC.

## Clinical trial identification

FOxTROT: NCT00647530; NICHE-2: NCT03026140.

## Legal entity responsible for the study

FOxTROT: University of Birmingham; NICHE-2: NKI - Netherlands Cancer Institute.

## Funding

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## Disclosure

J. Seligmann: Financial Interests, Personal, Other, Travel: Bristol Myers Squibb; Financial Interests, Personal, Other, CME activities: GI Connect; Financial Interests, Personal, Invited Speaker: Merck Serono, Pierre Fabre, Servier, tacked, GSK; Financial Interests, Personal,

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