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ctDNA-guided adjuvant chemotherapy de-escalation in stage III colon cancer: Primary analysis of the ctDNA-negative cohort from the randomized AGITG DYNAMIC-III trial (Intergroup study of AGITG and CCTG)

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Background

Adjuvant chemotherapy (ACT) benefit is uncertain for any individual patient (pt). Post-surgery circulating tumour DNA (ctDNA) testing could support risk-adjusted treatment selection. The DYNAMIC-III study explored ACT de-escalation or escalation, informed by post-surgery ctDNA results.

Methods

In this multicentre, randomised, phase II/III trial, pts with stage III colon cancer underwent tumour-informed ctDNA testing 5-6 weeks post-surgery and were randomised (1:1) to ctDNA-guided or standard management. Clinicians pre-specified standard ACT. In the ctDNA-guided arm, ctDNA-negative results prompted ACT de-escalation: from 6 to 3 months of fluoropyrimidine (FP) or observation, from 3 months of doublet to single-agent FP, or from 6 months of doublet to 3 months doublet or single-agent FP. The primary endpoint was 3-year recurrence-free survival (RFS). A sample size of 750 provided 80% power with a one-sided 97.5% CI to demonstrate non-inferiority (NI) with a NI margin of 7.5%.

Results

Of 968 evaluable pts, 702 (72.5%) were ctDNA-negative; 353 assigned to ctDNA-guided and 349 to standard management. Median follow-up was 45 months. 319 (90.4%) pts received ctDNA-guided per-protocol de-escalation. Treatment de-escalation reduced oxaliplatin-based chemotherapy use versus standard management (34.8% vs 88.6%, P < 0.001) and lowered grade 3+ adverse events of special interest (6.2% vs 10.6%, P = 0.037) and treatment-related hospitalisation (8.5% vs 13.2%, P = 0.048). However, non-inferiority of ctDNA-guided de-escalation was not confirmed (3-year RFS, 85.3% vs 88.1%; difference = -2.8%; 97.5% lower CI = -8.0%). Pre-planned subgroup analysis suggested de-escalation may be non-inferior in clinical low-risk (T1-3N1) tumours (3-year RFS, 91.0% vs. 93.2%; difference = -2.2%; 97.5% lower CI = -7.2%).

Conclusions

Stage III colon cancer pts with negative post-surgery ctDNA had low recurrence risk. ctDNA-guided de-escalation is feasible, substantially reduces oxaliplatin exposure and adverse events, with outcomes approaching standard management, especially for clinical low-risk tumours.

Clinical trial identification

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Legal entity responsible for the study

Australasian GastroIntestinal Trials Group (AGITG).

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Disclosure

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