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Omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) versus placebo after resection of colorectal cancer liver metastases (EMT2): A multicentre, double-blind, randomised phase 3 trial

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Background

Pre-clinical and human observational studies suggest that the omega (*n*)-3 polyunsaturated fatty acid (PUFA) EPA has anti-colorectal cancer (CRC) activity. A phase 2 randomised trial of pre-operative EPA in patients undergoing CRC liver metastasis (CRLM) surgery showed possible benefit for the exploratory endpoint overall survival (OS). Therefore, we tested the hypothesis that EPA treatment, started before surgery and continued post-operatively, improves CRC outcomes after CRLM surgery.

Methods

Participants (aged ≥ 18 yrs, undergoing CRLM resection with curative intent) were randomly assigned (1:1) by means of minimisation (use of neo-adjuvant chemotherapy, presence of extra-hepatic metastasis, time between randomisation and surgery [<2 weeks, ≥ 2 weeks], aspirin use, and recruitment centre) to receive either 4 g pure EPA ethyl ester (Vascepa®) or mineral oil placebo capsules, starting at least one day before surgery for a minimum two years and maximum four years, even if CRC progression occurred. The primary endpoint was progression-free survival (PFS). The key secondary endpoint was OS. Efficacy and quality of life (QoL) analyses were performed on the intention-to-treat population.

Results

418 individuals (median age 64 yrs [IQR 56-70]; 61.5% male; 83.5% ASA grade ≤ 2) were randomly assigned to EPA or placebo (n=209 each). Median PFS was 12.9 (95% CI 10.4-16.3) months in the placebo group vs 13.5 (11.8-17.9) months in the EPA group (hazard ratio [HR] 0.89 [95% CI 0.70-1.13]; P=0.33). Five-year OS in the placebo arm was 45.1% (95% CI 33.7-55.9) compared with 62.0% (95% CI 52.7-70.0) in the EPA arm (HR [95% CI] in EPA users compared with placebo 0.68 [0.48-0.96]; P=0.030). In the safety population (n=411), there was no excess of total adverse events, bleeding or atrial fibrillation in the EPA arm *versus* the placebo group. QoL measures were similar in the treatment groups.

Conclusions

High-dose *n*-3 PUFA EPA did not alter subsequent CRC progression, but it reduced risk of death by approximately 30%, compared with placebo in patients with CRLM after resection surgery. EPA was safe and well-tolerated in patients with advanced CRC, with no detriment to QoL.

Clinical trial identification

Current protocol v10.0 dated 03 March 2026 (EudraCT 2016-000628-24; NCT03428477).

Legal entity responsible for the study

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Disclosure

M.A. Hull: Financial Interests, Personal, Speaker, Consultant, Advisor: SLA Pharma; Financial Interests, Institutional, Advisory Board: Curileum. R.P. Jones: Financial Interests, Personal, Advisory Role: BioNTech, Merck, Moderna. D.A. Cairns: Financial Interests, Institutional, Funding: GSK, Merck Serono, Pierre Fabre Foundation. All other authors have declared no conflicts of interest.

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