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IROCAS: A randomized phase III trial of adjuvant treatment intensification with mFOLFIRINOX versus mFOLFOX6 in high-risk stage III (T4 and/or N2) colon cancer

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Background

Patients (pts) with high-risk stage III colon cancer have poor outcomes, with a 3-year disease-free survival (DFS) of approximately 65%, highlighting an unmet need. The IDEA collaboration established 6 months of oxaliplatin-containing doublet chemotherapy as the standard in this subgroup. These findings provide a strong rationale for evaluating intensified adjuvant strategies such as mFOLFIRINOX in high-risk pts.

Methods

From May 2017 to June 2023, in this academic phase III trial (PRODIGE for France, CCTG for Canada and GONO for Italy), 795 pts with R0-resected pT4 and/or N2 colon adenocarcinoma were randomized 1:1 to mFOLFIRINOX (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m², and 5-FU 2.4 g/m² over 46 h) or mFOLFOX6 (oxaliplatin 85 mg/m², leucovorin 400 mg/m², 5-FU bolus 400 mg/m² followed by 5-FU 2.4 g/m² over 46 h) every 2 weeks for 12 cycles. Pts were followed for 5 years after completion of adjuvant chemotherapy. The primary endpoint was 3-year DFS, analysed in the intent-to-treat population.

Results

Overall, 398 pts were allocated to mFOLFIRINOX and 397 to mFOLFOX6. Median age was 59 (19–75); 39.7% were female, 52.8% had pT4 disease, 72.2% pN2 disease, and 25.3% both pT4 and pN2. At a median follow-up of 55 months (IQR, 42.6–65.9), 284 DFS events had occurred, 146 with mFOLFIRINOX and 138 with mFOLFOX6. Three-year DFS was 65.6% versus 66.3% (HR 1.07, 95% CI 0.84–1.36; p=0.61) and 3-year Overall Survival (OS) was 91.2% versus 86.7% (HR 0.85, 95% CI 0.61–1.21; p=0.37) for mFOLFIRINOX versus mFOLFOX6. OS data remain immature. No statistically significant treatment-by-subgroup interaction was observed across prespecified subgroups. Grade ≥3 adverse events occurred in 62.2% versus 62.1%. Grade ≥3 diarrhea (15.6% vs 3.8%) and fatigue (7.3% vs 1.8%) were more frequent with mFOLFIRINOX, whereas grade ≥3 neutropenia was less frequent (18.0% vs 23.9%); G-CSF use was 37.8% versus 19.1%.

Conclusions

Among the high-risk stage III colon cancer, adjuvant chemotherapy intensification with mFOLFIRINOX did not improve DFS compared with mFOLFOX6. These findings highlight the need for novel adjuvant strategies beyond empirical intensification based on TNM stage alone.

Clinical trial identification

NCT02967289.

Legal entity responsible for the study

UNICANCER Group.

Funding

PHRC-K (Programme Hospitalier de Recherche Clinique en Cancérologie), France.

Disclosure

J. Bennouna: Financial Interests, Personal, Advisory Board: XENOTHERA, MSD, AstraZeneca, Pfizer, Bristol-Myers Squibb, Servier; Financial Interests, Personal, Invited Speaker: Daiichi Sankyo, MSD, AstraZeneca, Bristol-Myers Squibb, Servier, Johnson and Johnson, Bristol-Myers Squibb International; Financial Interests, Institutional, Coordinating PI: AstraZeneca; Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Institutional, Local PI: Amgen, Sanofi, Daiichi Sankyo, MSD, Bristol-Myers Squibb; Financial Interests, Institutional, Funding: GSK; Non-Financial Interests, Member: Institut Francophone de Cancérologie Thoracique, GERCOR. T. André: Financial Interests, Personal, Advisory Board, Advosiry Board on February 12, 2021: Astellas pharma; Financial Interests, Personal, Advisory Board, Advisory Board on February 2021: Kaleido Biosciences; Financial Interests, Personal, Invited Speaker, and advisory board 2021: Amgen; Financial Interests, Personal, Invited Speaker, Ivited speaker in a symposuim december 2020: AstraZeneca; Financial Interests, Personal, Advisory Board, and consultant fees and consultant contract 2021 and 2022: Bristol-Myers Squibb; Financial Interests, Personal, Advisory Board, Advisory board in Janaury 2020: Clovis; Financial Interests, Personal, Advisory Board, Advisory board in january 2020: Gritstone Oncology; Financial Interests, Personal, Advisory Board, Advisory board 2020: Haliodx; Financial Interests, Personal, Advisory Board, and consultant fees/consultant contract and invited speaker: MSD Oncology; Financial Interests, Personal, Invited Speaker, and other: Pierre Fabre; Financial Interests, Personal, Invited Speaker, in an symposuim in 2020: Roche; Financial Interests, Personal, Invited Speaker, in a meeting in 2019: Ventana; Financial Interests, Personal, Invited Speaker, In a educational meeting in 2019: Sanofi; Financial Interests, Personal, Advisory Board, in a symposuim in 2020: Servier; Financial Interests, Personal, Advisory Board, Consultant with personnal fees and invited speaker: Servier; Financial Interests, Personal, Advisory Board, in 2019: GSK; Financial Interests, Personal, Invited Speaker, in 2020 and 2021: GSK; Financial Interests, Personal, Invited Speaker, Virtual symposuimLecture: 1 MSI-H CRC: Implementation of Immunotherapy in clinical practice (30 minutes) – (this will be pre-recorded)Q&A – Live Q&A – (10 minutes) (on July 2, 2021): MSD Oncology; Financial Interests, Personal, Invited Speaker, June 2022: Sanofi; Financial Interests, Personal, Advisory Board, Contract 2021, 2022, 2023: Merck & Co., Inc; Financial Interests, Personal, Advisory Board, Contrat 2019, 2020, 2021, 2022: BMS; Financial Interests, Personal, Advisory Board, Contract 2021: Gritstone Oncologie; Financial Interests, Personal, Invited Speaker, June 2022 and June 2023 during ESMO GI meeting: Seagen; Financial Interests, Personal, Writing Engagement, Contract of consulting 2021 and 2022 and 2023: MSD Oncology; Financial Interests, Personal, Advisory Board, September 2022: GSK, Seagen; Financial Interests, Personal, Writing Engagement, Contract of consulting 2022 and 2023: GSK; Financial Interests, Personal, Writing Engagement, Contract of consulting 2022: Nordic Pharma; Financial Interests, Personal, Invited Speaker, October 2022: Merck Serono; Financial Interests, Personal, Other, Educationnal in 2022: Roche; Financial Interests, Personal, Other, Contract of consulting 2020, 2021, 2022,2023: Servier; Financial Interests, Personal, Advisory Board, Gilead Sciences Global GI Advisory Board on January 18, 2023: Aptitude Health, Gilead; Financial Interests, Personal, Other, Consultant like member of the SGNTUC-029 Steering Committee (the “Steering Committee”) Services related to the Company’s Study titled “An Open-label Randomized Phase 3 Study of Tucatinib in Combination with Trastuzumab and mFOLFOX6 versus mFOLFOX6 given with or without either Cetuximab or Bevacizumab as First-line Treatment for Subjects with HER2+ Metastatic Colorectal Cancer” (collectively, the “Services”).Including teleconferences and board preparation before the board (6h)Participation of the Board on September 2022 in Paris, September 10, 2022 MOUNTAINEER-03 Steering Committee Meeting during ESMO: Seagen; Financial Interests, Personal, Other, Consultant like member of the to be a member of the Colorectal Program Scientific Advisory Committee (SAC). In charges for reviewing V940 Pembro on Engagezone (as per your contract in ref).and also an inrtview about Pembrolizumab for MSI/dMMR Metastaic colo-rectal 2023: MSD Oncology; Financial Interests, Personal, Advisory Board, but also formation for the Takeda team, and consultant for TakedaContract between 1 sept 2023 and 15 october 2024: Takeda; Financial Interests, Personal, Advisory Board, Board Meeting (October 19, 2023): AbbVie; Financial Interests, Personal, Invited Speaker, Emerging Role of Biomarkers in Gastrointestinal Cancers Webcast Engagement reference : Wenibar: MSD; Financial Interests, Personal, Invited Speaker, Preparation and resентация at the Seagen ESMO GI 2023 Scientific Exchange HER2 as an emerging target for the treatment of mCRC in the context MOUNTAINEER03: Seagen; Financial Interests, Personal, Advisory Board, Fruquitinib: Takeda; Financial Interests, Personal, Invited Speaker, Oral speaker in a Symposuim 2 and 3 February 2024, GI ancer MSI: MSD; Financial Interests, Personal, Invited Speaker, Management of CRC 2024: Aptitude Health; Financial Interests, Personal, Invited Speaker, symposuim JFHOD GI CancerPARIS15 03-2024: Servier; Financial Interests, Personal, Advisory Board, Advisory board on fruquitinib 2024: Takeda Pharmaceuticals; Financial Interests, Personal, Invited Speaker, Symposuim 2024: BMS, Bristol-Myers Squibb International; Financial Interests, Personal, Advisory Board, Advisory board 2024: Bristol-Myers Squibb International; Financial Interests, Personal, Invited Speaker, Symposuim concening MSI CRC2024: MSD; Financial Interests, Personal, Advisory Board, in London 2024: GSK; Financial Interests, Personal, Advisory Board, Consultant with contract 2024: Nimbus, BMS; Financial Interests, Personal, Advisory Board, Consultat with contract 2024: MSD; Financial Interests, Personal, Advisory Board, consultant with contract: MSD; Financial Interests, Personal, Advisory Board, ASCO GI 2025: Aptitude Health; Financial Interests, Personal, Invited Speaker, Cancers CCRm dMMR/MSI visioconf with l’Australia on15/may2025: MSD; Financial Interests, Personal, Other, consultant contract 2025: Medicenna; Financial Interests, Personal, Invited Speaker, Speaker for Bristol-Myers Squibb AB, Hemvärnsgatan 9, 171 54 Solna, Sweden (“BMS”), at of the presentation of the new 1L CRC dMMR/MSI-H Landscape in 2 Webinars on April 2, 2025 and May 23, 2025 in Virtual: BMS; Financial Interests, Personal, Other, Consultant contract 2025: BMS; Financial Interests, Personal, Other, consultantContract 2025: MSD; Financial Interests, Personal, Advisory Board, and consultant contract 2025: Nimbus; Financial Interests, Personal, Advisory Board, Advosiboard in ESMO 2025 This

meeting will be held in person in Berlin, Germany on (Fri) October 17, 2025 from 9-11 AM local time.: Sanofi Aventis; Financial Interests, Personal, Advisory Board, advisory Board on ESMO in Berlin October 16, 2025: AbbVie; Financial Interests, Personal, Other, Consultant 2025 and advisory Board: GSK; Financial Interests, Personal, Advisory Board, Advisory Board nov 19, 2025: Biocartis; Financial Interests, Personal, Invited Speaker, BMS Belgium at Speaker tour mCRC from November 19th to 21st, 2025 at different sites: BMS; Financial Interests, Institutional, Local PI, a randomized, open-label, phase 2 study of botensilimab (AGEN1181) as monotherapy and in combination with balstilimab (AGEN2034) or investigator's choice standard of care (regorafenib or trifluridine and tipiracil) for the treatment of refractory metastatic colorectal cancer: Agenus; Financial Interests, Institutional, Coordinating PI, SPOTLIGHT study: Astellas; Financial Interests, Institutional, Coordinating PI, BMS CA209-8HW, BMS CA209-142, BMS CA209-577, 8HW: BMS; Financial Interests, Institutional, Local PI, Study with trazituzumab derxtec in mCRC C study: Daichi; Financial Interests, Institutional, Coordinating PI, PI Garnet study: GSK; Financial Interests, Institutional, Coordinating PI, Keynote 164 and 171 and 811 and C08: MSD; Financial Interests, Personal, Steering Committee Member, MOUNTAINEER and MOUNTAINEER-03 study (PI for France) 2022, 2023: Seagen; Financial Interests, Personal, Steering Committee Member, and international PI (trial chair Solstice study): Servier; Financial Interests, Personal, Steering Committee Member, MOUNTAINEER and MOUNTAINEER-03 study (PI for France) 2024 and 2025: Pfizer; Financial Interests, Institutional, Local PI, Local PI for study: Evaluation of efficacy and safety of GSK5764227 (alone and in combination) in participants with previously treated advanced unresectable or metastatic gastrointestinal solid tumors: GSK; Financial Interests, Institutional, Coordinating PI, Protocol Title: A Phase 2, Multicenter, Multi Arm, Study to Evaluate Pembrolizumab (MK-3475) or MK-1308A (Co-formulated quavonlimab (MK-1308)/pembrolizumab) in Participants with Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Cancer: (MK-1308A-008): MSD; Non-Financial Interests, Principal Investigator, DEWI trial: Watch-and-wait strategy to initiate Dostarlimab-based Immunotherapy in localized deficient mismatch repair (dMMR) and/or microsatellite instability high (MSI-H) oEso-gastric junction and gastric adenocarcinoma: A two-cohort open-label GERCOR phase II study DEWI G-123: Gercor; Non-Financial Interests, Member of Board of Directors, President since october 2022: ARCAD Foundation; Non-Financial Interests, Principal Investigator, Dostarlimab en traitement de première ligne chez des patients atteints d'un cancer localement avancé ou métastatique dMMR/MSI (non colorectal/non endométrial): essai randomisé de phase 2 avec « Crossover » dans le bras standard à la progression.: INI Cancer et INCA 5 institut National du cancer en France); Other, Other, DMC Meeting by Teleconference o2023 and 2024 and 2025 5member of steering committee of A randomized Phase 2 Study of ompenacilid versus placebo in combination with FOLFIRI plus bevacizumab in patients with previously treated RAS mutant advanced or metastatic colorectal cancer (RGX-202-002): Inspira. E. Mitry: Financial Interests, Personal, Advisory Board: MSD, Tarian, GSK, Novocure; Financial Interests, Personal, Invited Speaker: Pierre Fabre. S. Gill: Financial Interests, Personal, Advisory Board: Roche Canada, Eisai, Pfizer, Bristol-Myers Squibb, Ipsen Canada, AstraZeneca, Takeda; Financial Interests, Personal, Invited Speaker: Amgen; Non-Financial Interests, Leadership Role, Past-President: Canadian association of medical oncologists; Non-Financial Interests, Project Lead, Chair, GI Disease Site Committee: Canadian Clinical Trials Group. T.R. Asmis: Financial Interests, Personal, Advisory Board: Pfizer, Merck, AstraZeneca, Bristol-Myers Squibb International, Novartis, Eisai. S. Hiret: Financial Interests, Institutional, Advisory Board: BMS, Takeda, AstraZeneca, Sanofi, Roche; Financial Interests, Institutional, Other, support for attending meeting: Novartis; Financial Interests, Institutional, Other, support for WCLC CONGRESS: PharmaMar. P. Artru: Financial Interests, Personal, Advisory Board: AstraZeneca, MSD, Roche, Servier, Pierre Fabre, BMS, Merck Serono, Takeda; Financial Interests, Personal, Invited Speaker: Amgen. O. Bouche: Financial Interests, Personal, Advisory Board: Amgen, Merck, Deciphera, Astellas, Takeda; Financial Interests, Personal, Invited Speaker: Servier, Pierre Fabre, BMS, MSD. Y. Toucheffeu: Financial Interests, Personal, Invited Speaker: BMS, Pierre Fabre, Roche, AstraZeneca, Amgen, Merck Serono, Takeda. P. Kavan: Non-Financial Interests, Other, travel expense coverage to attend CCTG meeting: CCTG; Non-Financial Interests, Institutional, Other, remuneration for patient enrollment on the study: CCTG. C. Cremolini: Financial Interests, Personal, Advisory Board: Roche, MSD, Amgen, Pierre Fabre, Nordic Pharma, Takeda, Lilly, AstraZeneca, Revolution Medicine, Rottapharm, AbbVie, Merck Serono, GSK, Bicara Therapeutics, Johnson and Johnson; Financial Interests, Personal, Invited Speaker: Bayer, Servier, Merck Serono, AbbVie, Pierre Fabre; Financial Interests, Personal, Other, Independent Data Monitoring Committee for a clinical trial: BMS; Financial Interests, Institutional, Coordinating PI: Roche, Bayer, Servier, Merck, tempus, Takeda, Nordic Pharma; Financial Interests, Institutional, Local PI: Seagen, Hutchinson, GSK, Amgen, Pfizer, Revolution Medicine, Johnson and Johnson, Merck. J. Taieb: Financial Interests, Personal, Advisory Board: MSD, Astellas, Merck, Servier, Pierre Fabre, Amgen, BMS, Novartis, Pfizer, Sanofi, Rottapharm, Takeda, Takeda, Boehringer; Financial Interests, Personal, Invited Speaker: Amgen, Merck, MSD, Novartis, Servier, Pierre Fabre, Natera; Financial Interests, Personal, Invited Speaker, symposia: Astellas; Financial Interests, Personal, Other, steering committee of clinical trial: Novartis; Financial Interests, Personal, Invited Speaker, esmo sympo 2025: Takeda Pharmaceuticals; Non-Financial Interests, Leadership Role, President of the scientific committee of the ARCAD foundation until end 2022: ARCAD Foundation; Non-Financial Interests, Leadership Role, Chair of the ARCAD pancreas research group: ARCAD Foundation; Non-Financial Interests, Leadership Role, Member of the administrative council, the scientific committee, the executive board and responsible for the international relationships/partnership for FFCD in the prodige intergroup: Federation Francophone de Cancerologie Digestive (FFCD); Non-Financial Interests, Other, steering committee of clinical trials: Pfizer, Servier. All other authors have declared no conflicts of interest.