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Circulating tumor (ct) DNA-guided anti-EGFR rechallenge strategy in metastatic colorectal cancer (mCRC): Final results of the phase II randomized CITRIC trial

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Background

Rechallenge with anti-EGFR agents is a promising strategy in mCRC to prolong the continuum of care of RAS/BRAF wild-type (wt) mCRC patients (pts). ctDNA profiling before rechallenge enables molecular selection by excluding molecular alterations of acquired resistance.

Methods

CITRIC trial is a multicentre, randomized, phase II trial that enrolled RAS wt mCRC, with benefit from 1L anti-EGFR containing regimen, a second anti-EGFR-free line, and RAS, BRAF and EGFR ectodomain (ECD) wt in ctDNA at molecular screening before 3L. ctDNA was analysed using the Oncomine™ Colon cfDNA Assay. Pts were randomized 1:1 to cetuximab (CET) + irinotecan (IRI) (Arm A) vs investigator's choice (IC) excluding anti-EGFR agents (Arm B). Primary endpoint was ORR per RECIST v1.1; secondary endpoints: DCR, PFS, OS, and safety; exploratory endpoint: extended ctDNA analysis with MSK ACCESS.

Results

Between August 15 2020 and February 5 2024, 114 pts were molecularly screened by ctDNA. RAS/BRAF/EGFR-ECD mutations were detected in 28 pts (25%). 58 pts were randomized to CET+IRI (N=31) or IC (N=27). IC included FTD TPI + bevacizumab (BEV) (N=7); FTD TPI (N=8); fluoropyrimidine +/- BEV (N=11); regorafenib (N=1). Pts characteristics were balanced between arms. Efficacy endpoints are shown in the table. Adverse events occurred with the expected frequency and grade in both treatment arms. Adhoc analysis by treatment arms showed statistically significant higher DCR (77% vs 57% vs 40%; p<0.05) and PFS (4.8m vs 3m vs 2.2m; p=0.02) with CET+IRI vs FTD TPI + BEV vs other. ctDNA hyperselection discriminated for PFS in pts treated with CET+IRI (negative 4.9m vs positive 2.8m), but not in IC arm (p=0.01).Table: LBA33

	Cetuximab + irinotecan Arm A; N=31	Investigator's choice Arm B; N=27	
Overall response rate, No (%) 95% CI	3 (10) 2.7-23.7	1 (3.7) 0.2-16.4	p=0.6
Disease control rate, No (%) 95% CI	24 (77) 61.7-88.9	12 (44) 28.1-61.8	p=0.01

	Cetuximab + irinotecan Arm A; N=31	Investigator's choice Arm B; N=27	
mPFS, months	4.8	2.7	HR, 0.6; 95%CI, 0.35-1.03 p=0.06
mOS, months	11.4	7.4	HR, 0.8; 95% CI, 0.44-1.57 p=0.6

Crossover rates after trial treatment discontinuation were 82.3% in Arm A (14/17) and 68.8% in Arm B (11/16); data cutoff: July 18, 2025; median follow up: 8.7 months.

Conclusions

In ctDNA molecularly selected pts, rechallenge with CET+IRI demonstrated clinically meaningful increase in efficacy compared to IC. Hyperselection panel helps refining treatment selection and may be considered in future rechallenge strategies.

Clinical trial identification

EudraCT: 2020-000443-31.

Legal entity responsible for the study

Associacio per la Recerca Oncologica (APRO).

Funding

Merck.

Disclosure

C. Montagut: Financial Interests, Personal, Advisory Board: Merck Serono, Roche, Takeda; Financial Interests, Personal, Invited Speaker: Merck Serono, Pierre Fabre, Guardant Health, Amgen, Pfizer, MSD; Financial Interests, Institutional, Invited Speaker: MSD; Financial Interests, Institutional, Royalties: Biocartis; Financial Interests, Institutional, Coordinating PI: Merck-Serono; Non-Financial Interests, Member: TTD (Grupo Tratamiento Tumores Digestivos). J. Vidal: Financial Interests, Personal, Advisory Board: Amgen, BMS, Merck, Pierre Fabre; Financial Interests, Personal, Invited Speaker: Amgen, Merck, Novartis, Pierre Fabre. F. Salvà Ballabrera: Financial Interests, Personal, Advisory Board: Amgen; Financial Interests, Personal, Invited Speaker: Sanofi, Merck, Servier, Roche, Terumo company, MSD, Takeda. V. Alonso-Orduna: Financial Interests, Personal, Advisory Board: Amgen; Financial Interests, Personal, Invited Speaker: Merck, Novartis, Servier. R. Garcia-Carbonero: Financial Interests, Personal, Advisory Board: AAA, Amgen, Astellas, Bayer, BMS, Boehringer, Esteve, GSK, Hutchmed, Ipsen, MSD, Novartis-AAA, PharmaMar, Pierre Fabre, Sanofi, Servier, Takeda; Financial Interests, Institutional, Research Grant: BMS, MSD, Pfizer; Non-Financial Interests, Leadership Role, Global PI of investigator-initiated clinical trials (AXINET, NICENEC, PEMBROLA): BMS, MSD, Pfizer; Non-Financial Interests, Leadership Role, Chair: European Neuroendocrine Tumor Society (ENETS); Non-Financial Interests, Leadership Role, Past president, Member of the Executive Committee: Grupo Español de Tumores Neuroendocrinos (GETNE); Other, Honoraria received by spouse for advisory board or invited speaker roles: ABBIE, AstraZeneca, Bayer, Boehringer, Bms, Genomica , Lilly, MSD, Merck, Novartis, Pfizer, Pharma Mar, Roche, Sanofi, Servier, Takeda. N. Tarazona Llaveró: Financial Interests, Personal, Advisory Board: Merck, Guardant Health, Grifols; Financial Interests, Personal, Invited Speaker: Merck, Pfizer, Servier, Amgen; Financial Interests, Institutional, Funding: Natera Inc, Guardant Health; Non-Financial Interests, Member: SEOM Committee. M.J. Safont Aguilera: Financial Interests, Personal, Advisory Board: Amgen, Servier, Bristol Myers Squibb International, Takeda Pharmaceuticals; Financial Interests, Personal, Invited Speaker: Merck, Servier, Pierre Fabre. F. Rivera Herrero: Financial Interests, Personal, Invited Speaker: Roche, MSD, BMS, Servier, Astellas, Amgen, Merck; Financial Interests, Personal, Advisory Board: MSD, BMS, Servier, Astellas, Amgen, Astra-Zeneca, BeiGene; Financial Interests, Institutional, Local PI: Astra-Zeneca, MSD, Novartis, Seagen, OBT, Inspirna. L. Layos Romero: Financial Interests, Personal, Invited Speaker: Terumo, AstraZeneca; Other, Other, Support for attending meetings and educational events: Servier, AstraZeneca, Roche, Incyte, Merck. M.J. Ortiz Morales: Financial Interests, Institutional, Invited Speaker: Servier. J. Alcaide-Garcia: Financial Interests, Personal, Other, Congress support.: MSD, Amgen; Financial Interests, Personal, Invited Speaker: Amgen, Servier, Merck; Financial Interests, Personal, Other, Congress support: Merck. D. Paez: Financial Interests, Personal, Invited Speaker: MSD, Novartis, BMS; Financial Interests, Personal, Advisory Board: Amgen, Esteve, Ipsen; Financial Interests, Personal and Institutional, Research Grant: Merck. J. Hernandez Yague: Financial Interests, Personal, Advisory Board, Advisory board: Merck Serono; Financial Interests, Personal, Advisory Board, Expert testimony: Amgen; Other, ESMO congress registration: MSD. R. Alvarez Gallego: Financial Interests, Personal, Advisory Board: AstraZeneca; Financial Interests, Personal, Invited Speaker: Merck, Servier; Financial Interests, Institutional, Research Grant: Servier, BMS. R. Vera: Financial Interests, Personal, Advisory Board: Roche, Amgen, Sanofi; Financial Interests, Personal, Invited Speaker: Merck, Lilly, Bayer, Eisai, Servier, MSD. B. Bellosillo Paricio: Financial Interests, Personal, Advisory Board: Menarini, Johnson and Johnson, Incyte, AstraZeneca, MSD; Financial Interests, Personal, Invited Speaker: AstraZeneca, Novartis, Merck Serono, Roche, Thermofisher, Pfizer, BMS, MSD; Financial Interests, Institutional, Funding: AstraZeneca; Financial Interests, Institutional, Research Grant: Roche. C. Santos Vivas: Financial Interests, Personal, Advisory Board: Amgen; Financial Interests, Personal, Invited Speaker: Amgen, Takeda Pharmaceuticals; Other, Other, Travel grant: Merck, MSD, Amgen, Takeda Pharmaceuticals. All other authors have declared no conflicts of interest.

