Sequential Versus Combination Therapy of Metastatic Colorectal Cancer Using Fluoropyrimidines, Irinotecan, and Bevacizumab: A Randomized, Controlled Study

Background & Purpose	Background: • In untreated metastatic colorectal cancer (mCRC) use of fluoropyrimidines (FP), irinotecan (Iri) and oxaliplatin were not associated with disadvantage in overall survival (OS) vs. other initial treatment combinations in the pre-antibody era • Bevacizumab (Bev), a vascular endothelial growth factor antibody shows use as a component to combination therapy, with proven prolongation of progression-free survival (PFS) • FP and Bev have demonstrated safety and efficacy in elderly patients • Comparable efficacy seen in combinations of fluorouracil (FU), Iri and leucovorin (FOLFIRI) + Bev, or the combination chemotherapy capecitabine and Iri (CAPIRI) + Bev Purpose: • To determine if initial treatment of a sequential escalation strategy of FP plus Bev, followed by the addition of Iri at first progression (Arm A) versus upfront use of a three drug regimen (FP + Iri + Bev) (Arm B) showed non-inferiority in patients with untreated metastatic colorectal cancer
Study Design	• 1:1 Multicenter (82 centers in Germany), randomized controlled phase III trial • Between December 21, 2010 – April 6, 2016
Methods	Inclusion Criteria: • ≥18 years; Eastern Cooperative Oncology Group (ECOG) status of 0 to 1; stage IV, histologically confirmed colorectal cancer; adequate organ function and unresectable disease (or patients wish not to undergo surgery), and one or more measureable tumor lesion(s) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 Exclusion Criteria: • Prior chemotherapy for mCRC, adjuvant therapy within 6 months before enrollment, cardiac insufficiency greater than New York Heart Association (NYHA) grade II or cardiac ischemic event within 6 months before study start, and major bleeding event within 6 months before study start and untreated brain metastases Primary Outcome: • Non-inferiority of the time to failure of the strategy (TFS) • Evaluation of symptomatic toxicities included to the hierarchically structured primary end point Secondary Outcomes: • PFS (time from randomization to disease progression, use of new anticancer drug, or death) • OS (time from randomization to death) • Overall response rate (according to RECIST 1.1) • Evaluation of efficacy according to molecular subgroups Drug Regimens: • Arm A: (initial FP + Bev): Either (capecitabine PO 1250mg/m^2 BID on days 1-14, plus Bev IV 7.5mg/kg body weight on day 1, repeated every 3 weeks); OR FU-based (IV on day 1: racemic folinic acid with 400 mg/m^2, FU bolus of 400 mg/m^2, FU over 46 hours 2,400 mg/m^2 and 5mg/kg body weight of Bev, repeated every 2 weeks) regimens were administered. After first progression, treatment was continued with CAPIRI + Bev (oral capecitabine 800 mg/m^2 twice daily, days 1-14, IV Iri 200mg/m^2 on day 1 plus Bev at a dose of 7.5 mg/kg body weight infused on day 1, repeated every 3 weeks) or biweekly FOLFIRI + Bev with Iri at a dose of 180 mg/m^2 in addition to the FU regimen described above • Arm B: CAPIRI or FOLFIRI + Bev (FP + Iri + Bev) as described. In arm B, de-escalation of Iri (in the case of at least stable disease for > 6 months) and consecutive re-escalation to the full—after progression while on de-escalated treatment—was allowed
Size	421 Patients: 212 assigned to arm A and 209 to arm B 274 (88.8%) of 421 tumors available for testing of RAS and BRAF mutations
Power	• Difference in an early end point in TFS is considered meaningful if the relative benefit is greater than 20%, corresponding to hazard ratio (HR) of less than 0.8 • Aimed to exclude relative disadvantage by sequential treatment of 20% corresponding to a limit for non-inferiority of 8 months (Δ = 2 months) • Non-inferiority shown at a significance level of 5% if the lower limit of the 90% CI (HR) is 0.8 or more

	• Initial design required 506 events for TFS, but after interim analysis at 5 years, several factors resulted in reduction to a power of 70% needing 378 events
Results	• Median follow-up 36 months (range, 0.8 to 60.7 months) • Escalation of sequential treatment (Arm A) seen in 80 (37.7%) of patients • 63.2% of patients received Iri at some point in Arm A vs. 100% in Arm B • Median TFS in Arm A was 9.6 months (90% CI, 8.6 to 10.6 months) and 9.9 months (90% CI, 8.8 to 10.6 months) in Arm B • HR for TFS was 0.86 (90% CI, 0.73 to 1.02), which exceeded the non-inferiority margin of 0.8 • Adjusted by stratification factors HR analysis for TFS was 0.88, (90% CI, 0.72 to 1.08) • Subgroups indicated benefit from upfront combination therapy in patients with RAS/BRAF wild-type tumors (HR, 0.61; 90% CI, 0.46 to 0.82; p = 0.005), but not in patients with RAS mutant factors (HR, 1.09; 90% CI, 0.81 to 1.46; p = 0.58) • Cox proportional hazards regression model analysis of TFS for interaction of RAS mutational status and study arm was statistically significant with p = 0.03 • Median OS was not statistically different (HR, 0.84; 0.95% CI, 0.66 to 1.06; p = 0.14) • Toxicity score of grade 2-5 events per treatment cycle significantly favored arm A vs. arm B (arithmetic mean, 0.6; standard deviation, 0.7 vs. arithmetic mean, 0.7; standard deviation, 0.7; p = 0.03) Authors Conclusions: • The non-inferiority of Arm A vs. Arm B could not be demonstrated • Frequency of adverse events did not seem to be substantially different between study arms • If only grade ≥ 2 events are considered advantage to Arm A • Patients sufficiently fit to receive Iri in Arm A, but given median treatment duration of 7.4 months, many patients seemingly discontinued therapy without progression • Patients with RAS/BRAF wild-type tumors outcome was superior in Arm B across all efficacy end points, also explaining why non-inferiority was not demonstrated in the full population • RAS status was clearly superior in RAS/BRAF wild-type tumors, whereas sequential escalation chemotherapy seems to provide comparable results n RAS mutant tumors
Conclusions	• Continue use of upfront three drug regimen of FP + Iri + Bev in current treatment • Authors utilized appropriate clinical outcomes in the setting of mCRC • Difference with age, sex, site of primary tumor and ECOG status between the two groups, but unclear how that effects results • Potential for the results to have been different if no prior adjuvant chemotherapy, alkaline phosphate <300U/L, and males were excluded from trial • Would have found it interesting to examine health related quality of life (HRQoL) as a secondary outcome in this trial • Would have preferred consistency across the board in Bev dosing of 5mg/kg body weight per guidelines • Studies breaking down use of CAPIRI or FOLFIRI in this setting are essential as CAPIRI currently demonstrates no utility per NCCN guidelines • Further studies, examining RAS status with larger sample size and a defined effect size might serve clinical utility in the setting of mCRC
Comments	Strengths: • Multicenter • Non-inferiority study • Primary and secondary outcomes Weaknesses: • Reduced sample size and power • More elderly population • >75% resected primary tumors • Many not candidates for secondary resection • Site of primary tumor • Largely male population • CAPIRI • Bev dosing • Limited feasibility of sequential escalation
Reference	Modest et al. Sequential Versus Combination Therapy of Metastatic Colorectal Cancer Using Fluoropyrimidines, Irinotecan, and Bevacizumab: A Randomized, Controlled Study – XELAVIRI (AI0 KRK0110). Journal of Clinical Oncology. 37(1); 22-32.

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