P – 206 Intensive first line FIr-C/FOx-C association of triplet chemotherapy plus cetuximab in RAS wild-type metastatic colorectal cancer patients: Preliminary phase II data and individual limiting toxicity syndromes prediction by pharmacogenomic biomarkers

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Introduction: Intensive triplet chemotherapy/bevacizumab significantly increased MCRC outcome. Phase II study investigated safety/activity of FIr-C/FOx-C triplet/cetuximab (CET) in first line RAS wild-type and prediction of individual limiting toxicity syndromes by pharmacogenomic biomarkers.

Methods: Simon two-step design: p0 70%, p1 85%, power 80%, α 5%, β 20%; projected objective response rate (ORR) I step 14/19. FIr-C/FOx-C: 5-fluorouracil (5-FU) 12h-timed-flat-infusion 900 mg/m2 days (d)1-2,8-9,15-16,22-23; alternating irinotecan (CPT-11) 160 mg/m2 d1,15, oxaliplatin 80 mg/m2 d8,22; CET loading 400 then 250 mg/m2 d1,8,15,22; every 28d. Toxicity, individual limiting toxicity syndromes (LTS) evaluated, compared by chi-square test; activity/efficacy by log-rank. 5-FU/CPT-11 pharmacogenomic biomarkers, 5-FU degradation rate (5-FUDR), SNPs ABCB1, CYP3A4, DYPD, UGT1A1 evaluated in patients with LTS and at recommended dose.

Results: Enrolled: 29 patients 80%; G3-4 toxicities: diarrhea 23%, asthenia 15%, vomiting 8%, hypertransaminasemy 8%; LTS 19 patients (65.5%), 83% yE. LTS prevalently multiple (ms) vs single site (59 vs 7% p 0.006). Reduced FUDR 56%, SNPs CYP3A4 22%, UGT1A1 71%, >2 positive pharmacogenomics biomarkers 78% prevalently in patients with gastrointestinal LTS.

Conclusion: Intensive first-line FIr-C/FOx-C at recommended doses is tolerable, highly effective in RAS wild-type. Reduced FUDR, CYP3A4, UGT1A1 SNPs may predict individual LTS-ms to select fit patients. Prospective studies personalized by toxicity biomarkers will confirm efficacy.