Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: Final results of PRODIGE 23 phase III trial, a UNICANCER GI trial

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Background: PRODIGE 23 investigated the role of neoadjuvant mFOLFIRINOX before preoperative (preop) chemoradiation (CRT), with TME-surgery and adjuvant chemotherapy (CT) in resectable locally advanced rectal cancer.

Methods: PRODIGE 23 is a phase III multicenter randomized clinical trial. Eligible pts had cT3 or cT4, M0 rectal adenocarcinomas <15 cm from the anal verge, age 18-75 years, and WHO PS ≤1. Randomization was stratified by center, T stage, N status, tumor location, and perirectal fat extramural extension. Primary endpoint was 3-yr disease-free survival (DFS). Main secondary endpoints were ypT0N0 rate, overall survival (OS) and metastasis-free survival (MFS). 460 pts were required to observe 136 events to show a gain in 3-year DFS from 75% to 85% (HR=0.56) with a 2-sided α=0.05 and 90% power. HR and 95% CI were estimated by a stratified Cox proportional hazard model. Arm A pts received preop CRT (50 Gy, 2 Gy/fraction [fr]; 25 fr + capecitabine), surgery, then adjuvant CT for 6 months (mos). Arm B pts received 6 cycles of mFOLFIRINOX (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m² D1, and 5-FU 2.4 g/m² over 46 h) every 14 days, followed by the same preop CRT, surgery and 3 mos of adjuvant CT. Adjuvant CT consisted of mFOLFOX6 or capecitabine, depending on the centre's choice for all pts. Imaging work-up, operative and pathology reports were centrally reviewed.

Results: (ITT) Between 6/2012 and 6/2017, 230 and 231 pts were randomly assigned in Arm A/B, respectively by 35 participating centers. Pts characteristics were well balanced. Neoadjuvant mFOLFIRINOX and CRT in both arms were well tolerated. Compliance to CRT and to adjuvant CT was not hampered by neoadjuvant CT. Surgical morbidity did not differ between the 2 arms. The ypT0N0 rate was 11.7 vs 27.5% in Arm A/B (p<0.001). Median follow-up was 46.5 mos. 136 DFS events was reported. 3-yr DFS was significantly increased in arm B (HR 0.69, 95% CI 0.49-0.97, p=0.034): 68.5% (CI: 61.9-74.2) vs 75.7% (CI: 69.4-80.8) in arm A/B. The subgroup analysis showed no evidence of heterogeneity of the effect size of treatment on DFS. 3-yr MFS was also significantly higher in arm B: 71.7 in arm A vs 78.8% (HR 0.64, CI 0.44-0.93, p<0.02) in arm B. 3-yr OS was 87.7 vs 90.8% (HR 0.65, CI 0.40-1.05, p=0.077) in arm A/B, with 54.2% of the pts with recurrence being alive.

Conclusions: Neoadjuvant mFOLFIRINOX plus CRT is safe, and significantly increased ypCR rate, DFS and MFS. OS data are not mature. Clinical trial information: NCT01804790