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PREOPERATIVE CHEMORADIOTHERAPY AND POSTOPERATIVE CHEMOTHERAPY WITH 5-FLUOROURACIL AND OXALIPLATIN VERSUS 5-FLUOROURACIL ALONE IN LOCALLY ADVANCED RECTAL CANCER: RESULTS OF THE GERMAN CAO/ARO/AIO-04 RANDOMIZED PHASE III TRIAL

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Introduction: The German CAO/ARO/AIO-94 trial established preoperative chemoradiotherapy (CRT) with 5-FU, total mesorectal excision (TME) surgery, and postoperative chemotherapy with 5-FU as standard treatment for locally advanced rectal cancer. The goal of the next generation CAO/ARO/AIO-04 trial was the integrating of more effective systemic treatment into combined modality treatment (CMT). First results of secondary endpoints (acute toxicity, treatment compliance, early efficacy data) have already been published (Rödel C. et al., Lancet Oncol 2012). Here we present the primary endpoint of this trial, disease-free survival (DFS) at 3 years.

Methods: This was a multi-centre, open-label, randomised, phase III study in patients with histologically proven adenocarcinoma of the rectum with clinically staged T3-4 or any node-positive disease. Patients were randomised into two arms: 1) standard 5-FU-CMT according to our CAO/ARO/AIO-94 trial (preoperative 50.4 Gy plus infusional 5-FU 1000 mg/m^2 days 1-5 and 29-33, followed by TME-surgery and four cycles of bolus 5-FU 500 mg/m^2 for 5 days, repeated day 29), and 2) preoperative 50.4 Gy plus infusional 5-FU (250 mg/m^2 days 1-14 and 22-35), oxaliplatin (50 mg/m^2 days 1, 8, 22, and 29), followed by TME-surgery and eight cycles of adjuvant chemotherapy with oxaliplatin (100 mg/m^2 day 1), leucovorin (400 mg/m^2 day 1) and infusional 5-FU (2,400 mg/m^2 day 1-2), repeated day 15. The primary endpoint was DFS at 3 years defined as the interval from randomization to incomplete surgical resection (R2), locoregional or metastatic recurrence or death, whichever occurred first. Assuming that the 3y-DFS of 75% in arm 1 could be improved to 82% in arm 2, about 1200 patients were necessary to achieve a power of 80% at 5% significance level (two-sided) with the log-rank test.

Results: A total of 637 patients were randomized to arm 1 and 628 to arm 2. After a median follow-up time of 50 months (80% interquantile range, 25 - 64 months), 198 patients in arm 1 had a DFS-related event, as compared with 159 patients in arm 2 (HR 0.79, 95% confidence interval 0.64 to 0.98, P = 0.03 by the mixed effects Cox model). The rate of DFS at three years was 71.2% (95% confidence interval, 67.6% to 74.9%) in arm 1 and 75.9% (95% confidence interval, 72.4% to 79.5%) in arm 2 (P = 0.03 by the exact stratified log-rank test). Grade 3-4 late overall treatment-related toxicity occurred in 23% in arm 1 and 26% in arm 2 (P = 0.14). The incidence of grade 3-4 sensory neuropathy in the oxaliplatin containing arm was 7% during treatment, decreasing to 3% at one year of follow-up.

Conclusion: Adding oxaliplatin to 5-FU-based neoadjuvant CRT and adjuvant chemotherapy in locally advanced rectal cancer significantly improves disease-free survival.