Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) as perioperative treatment of resectable gastric or gastro-esophageal junction adenocarcinoma: The multicenter, randomized phase 3 FLOT4 trial (German Gastric Group at AIO)

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Background: The MAGIC trial established perioperative (periop) epirubicin, cisplatin, and 5-FU (ECF) as a standard treatment for patients (pts) with operable esophagogastric cancer, but survival continues to remain poor. FLOT4 is a multicenter, randomized, investigator-initiated, phase 3 trial. It compares the docetaxel-based triplet FLOT with the anthracycline-based triplet ECF/ECX as a periop. treatment for pts with resectable gastric or GEJ adenocarcinoma.

Methods: Eligible pts of stage ≥T2 and/or cN+ were randomized to either 3 preoperative and 3 post-operative 3-week cycles of ECF/ECX (epirubicin 50 mg/m², cisplatin 60 mg/m², both d1, and 5-FU 200 mg/m² as continuous infusion or capecitabine 1250 mg/m² orally d1-21) or 4 pre-operative and 4 post-operative 2-week cycles of FLOT (docetaxel 50 mg/m², oxaliplatin 85 mg/m², leucovorin 200 mg/m², and 5-FU 2600 mg/m² as 24-hour infusion, all d1). The primary endpoint was overall survival (OS). Funded by Deutsche Krebshilfe.

Results: Between Aug 2010 and Feb 2015, 716 pts (360 ECF/ECX; 356 FLOT) were randomly allocated. Baseline characteristics were well balanced. 91% and 44% of pts with ECF/ECX and 90% and 51% with FLOT completed pre-operative and post-operative cycles, respectively. Median follow-up was 43 mon. FLOT increased the rate of complete marginal free (R0) resection (ECF/ECX 77%, FLOT 48%; p = 0.011) and improved OS (mOS, 35 mon with ECF/ECX vs. 50 mon with FLOT; HR 0.77 [0.63 - 0.94]; p = 0.012), and PFS (mPFS, 18 mon with ECF/ECX vs. 30 mon with FLOT; HR 0.75 [0.62 - 0.91]; p = 0.004). 3y OS rate was 48% with ECF/ECX and 57% with FLOT. Downsizing also favored FLOT with tumors < = pT1 being at 15% with ECF/ECX and 25% with FLOT (p = 0.001). Periop. complications were 50% with ECF/ECX and 51% with FLOT. 30- and 90-day mortality was 3% and 8% with ECF/ECX and 2% and 5% with FLOT.

Conclusions: Periop FLOT improved outcome in patients with resectable gastric and GEJ cancer compared to periop ECF/ECX and is new standard therapy in this setting.