4004 **Oral Abstract Session**

Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol). (NCT01726452).

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Background: The optimum combination curative approach to locally advanced adenocarcinoma of the esophagus and esophago-gastric junction (AEG) is unknown. A key question is whether neoadjuvant multimodal therapy, specifically CROSS (carboplatin/paclitaxel, 41.4Gy radiation therapy), is superior to optimum peri-operative chemotherapeutic regimens including modified MAGIC (epirubicin, cisplatin (oxaliplatin), 5-FU (capecitabine)) and more latterly FLOT (docetaxel, 5-FU, leucovorin, oxaliplatin). Neo-AEGIS was designed as the first randomised controlled trial to address this question. **Methods:** 377 patients with $cT_{2\text{-}3}N_{0\text{-}3}M_0$ AEG were randomly assigned to CROSS or peri-operative chemotherapy (ECF/ECX/EOF/EOX pre-2018, FLOT option 2019/20) at 24 sites (Ireland, UK, Denmark, France, Sweden). The primary outcome was overall survival. The initial power calculation was based on CROSS superiority of 10%. This was modified after the first futility analysis (70 events) to a non-inferiority margin of 5%. Secondary end points included toxicity, pathologic measures of response, and postoperative complications as per the Esophageal Complications Consensus Group (ECCG) definitions and Clavien-Dindo severity grade. **Results:** Of 362 evaluable patients, 178 CROSS, 184 MAGIC/FLOT (157/27), 90% were male, median (range) age 64 (35-83), 84% were cT3, and 58% cN1. At a median (range) follow up of 24.5 (1-92) months, at the second futility analysis (60% of planned events), there were 143 deaths, 70 CROSS and 73 MAGIC/FLOT arm, with 3-year estimated survival probability of 56% (95% CI 47,64) and 57% (95% CI 48,65), respectively [(HR 1.02 (95%CI. 0.74-1.42))]. Based on the absence of futility evidenced in this data the DSMB recommended closure of recruitment in December 2020. **Conclusions:** This RCT reveals no evidence that peri-operative chemotherapy is unacceptably inferior to multimodal therapy, notwithstanding greater proxy markers of local tumour response in the CROSS arm. Oncologic and operative outcomes were consistent with optimum modern benchmarks. These data strongly suggest non-inferiority and support equipoise in decision making in modern practice. Clinical trial information: NCT01726452. Research Sponsor: Health Research Board Ireland, Cancer Research UK (C49462/A18483), Irish Cancer Society, Oesophageal Cancer Fund Ireland.

	Arm A (Magic/FLOT)	Arm B CROSS
R0 (negative margins)	82%	95%
ypN0	44.5%	60.1%
Tumor regression grade 1 & 2	12.1%	41.7%
Pathologic complete response	5%	16%
Neutropenia (Gr 3/4)	14.1%	2.8%
Neutropenic sepsis	2.7%	0.6%
Postoperative in-hospital deaths	3%	3%
Postoperative Pneumonia/ARDS	20%/0.6%	16%/4.3%
Anastomotic Leak	12%	11.7%
Clavien-Dindo > III<V	23.6%	22%

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