Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC Trial

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**Background**

- HER2 amplification is common in upper GI tract adenocarcinomas including gastric, gastro-esophageal and esophageal cancer.
- Inhibition of HER2 signaling improves clinical outcomes.
- Trastuzamab (Herceptin), a monoclonal antibody against HER2 was recently approved for the use of advanced gastric or gastro-esophageal cancer in combination with chemotherapy based on promising phase III clinical results (Bang, YJ et al, Lancet, 2010).
- Lapatanib ditosylate is a dual anti-EGFR and anti-HER2 tyrosine kinase inhibitor.
- Lapatanib is currently approved for HER2 positive breast cancer and has shown both preclinical efficacy and modest clinical efficacy in small single agent exploratory studies of HER2+ upper GI tract adenocarcinomas.
- The authors performed a phase III, randomized, double blind trial evaluating the efficacy and safety of lapatinib in combination with capecitabine and oxaliplatin as the first-line treatment of advanced or metastatic HER2+ upper GI tract adenocarcinomas.

**Materials and Methods**

- All patients had pathologically confirmed adenocarcinoma.
- All subjects had overexpression or amplification of HER2 (IHC2+ and FISH amplified, or IHC 3+, or FISH, CISH, or SISH amplified).
- Subjects were randomized 1:1 to capecitabine and oxaliplatin every 3 weeks (oxaliplatin 130mg/m2 day 1; capecitabine 850mg/m2/BID days 1 — 14), and daily lapatinib (1250mg) or placebo.
- The primary efficacy population comprised all subjects whose tumors were confirmed to be FISH amplified by a central laboratory.
- The primary endpoint was overall survival (OS) of the primary efficacy population.
- Secondary endpoints included progression free survival (PFS), overall response rate (ORR) and safety, quality of life (QOL) and molecular/pharmacogenetic analysis.

**Materials and Methods**

- A total of 545 patients from 186 centers in 22 countries were randomized from 2008-2012, and 487 patients had HER2+ centrally confirmed.
- The pretreatment characteristics were well balanced between the 2 arms with a median age of 60 years and 40% of patients enrolled were from Asia.
- The primary endpoint of this study was not reached with a hazard ratio (HR) for OS of 0.91 (95% CI 0.73, 1.12, p=0.35)
A pre-specified subgroup analyses showed significant improvements with the addition of lapatinib in Asian patients with median survival increase of 10.9 to 16.5 months (HR=0.68), and those under 60 years with a median survival increase of 9 to 12.9 months (HR=0.69).

The HR for uncensored PFS was 0.86 (95% CI 0.71 - 1.04, p=0.10), with median PFS of 6.0 vs. 5.4 months.

The analysis of PFS censored by the time of subsequent anticancer therapy as per protocol showed a HR of 0.82 (95% CI 0.68, 1.00, p=0.04).

The ORR was 53% in the lapatinib arm and 40% in the control arm.

Toxicity profiles were similar between the two arms except for increased overall diarrhea, and skin toxicity and grade 3+ diarrhea (12 vs. 3%) in the lapatinib arm.

**Author's Conclusions**

- Although well tolerated, the addition of lapatinib to capecitabine and oxaliplatin did not improve overall survival in patients with HER2+ advanced or metastatic upper GI tract malignancies.
- Subgroup analysis did reveal that Asian patients and those younger then 60 years might benefit from the addition of lapatinib.
- Further clinical and molecular analysis from this trial will help to better define which patients may stand to benefit the most from lapatinib.

**Clinical Implications**

- HER2 is commonly expressed in many gastric, gastro-esophageal and esophageal adenocarcinomas and is a potentially important therapeutic target.
- The use of the monoclonal antibody trastuzumab against HER2 has shown clinical efficacy in these patients.
- The authors present a randomized trial evaluating the utility of lapatinib in addition to standard chemotherapy for the treatment of HER2+ gastric, gastro-esophageal and esophageal malignancies.
- Unfortunately, the trial failed to meet its primary endpoint and there was no OS benefit.
- However, there was a significant survival benefit in both Asian and young patients.
- Future research needs to explore how to best predict which patients will respond to lapatinib and how best to combine lapatinib with chemotherapy.
- The ongoing molecular analysis of this trial will hopefully provide more of these answers.
- As we learn more about HER2 targeted cancers in upper GI malignancies these therapies can eventually be introduced in the adjuvant or neoadjuvant setting.