International Session 4: ‘How can we maximize the effect of chemotherapy in gastric cancer?’

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The inclusion of new targeted drugs into treatment strategies of advanced or metastatic esophagogastric cancers (AGC) shows great promise, particularly with validated predictive biomarkers. The majority of agents already tested or in current phase III trials are targeting the epidermal growth factor receptor family (EGFR1/HER2) or angiogenesis inhibitors. Against HER2, only trastuzumab (T) combined with first-line chemotherapy significantly improved overall survival (OS) in patients with HER2-overexpressing (HER+) tumors (ToGA). Despite first positive signals, the dual tyrosine kinase inhibitor (TKI) of HER2 and EGFR1 lapatinib did not reach primary endpoints in HER2+ tumors in first- and second-line trials in Europe (LoGIC) or Asia (TYTAN), respectively. As T plus docetaxel plus a second HER2 antibody pertuzumab (P) demonstrated significant better OS versus T/docetaxel in metastatic breast cancer, a similar study (JACOB) evaluates efficacy and safety of P/T/CTX in HER2+ AGC patients. While EGFR1 antibody combinations improved outcome in metastatic KRAS wild-type colorectal cancer or squamous-cell cancer of head and neck, cetuximab provided no benefit to first-line chemotherapy in unselected patients (EXPAND) and panitumumab combined with EOC was associated with worse OS (REAL3). Even if rare, predominantly exclusive overexpression of EGFR signalling may be favoured for targeting in these subgroups. Regarding tumor angiogenesis, chemotherapy with bevacizumab did not reach better OS despite higher response rate and PFS (AVAGAST). In second line ( REGARD), Ramucirumab was recently well established as the first oral TKI of VEGFR-2 with comparable benefits to second-line chemotherapy and with a good tolerability profile. Results of paclitaxel +/- Ramucirumab (RAINBOW) are awaited. After positive results for Rilotumumab and data for MetMab, 2 trials in high c-Met expressing tumors addressing hepatocyte growth factor (HGF) and c-Met inhibition are ongoing (RILOMET-1; MetGastric). As fibroblast growth factor receptor FGF2 gene amplification may occur particularly in diffuse AGC, FGFR inhibitors such as AZD4547 (SHINE) or Cediranib are in early trials. Finally, the oral PARP inhibitor olaparib plus paclitaxel showed OS benefit in a randomized phase II as a new combination strategy (ASCO 2013).