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Ramucirumab: an update

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In the last ten years different clinic applications of angiogenesis research have been developed in patients (pts) with gastric cancer (GC). The addition of bevacizumab, which inhibits vascular endothelial growth factor A(VEGF-A), in combination with chemotherapy as first-line therapy failed to increase overall survival (OS) (1). Recently ramucirumab, a monoclonal antibody that binds to the extracellular domain of VEGF receptor-2 (VEGFR-2), was shown to be the first antiangiogenetic drug that prolongs survival in pts with advanced GC or esophagogastric junction (AEG). In particular, the large Phase III REGARD trial evaluated ramucirumab versus BSC in preteated pts. The median OS of pts treated with ramucirumab was 5.2 months compared to 3.8 months on placebo (2). Following the successful completion of the REGARD trial, two additional trials have been conducted. The RAINBOW trial was a large phase III randomized, placebo-controlled trial in refractory GC patients, evaluating the efficacy of combination of ramucirumab and paclitaxel versus only paclitaxel. The primary endpoint of the study (OS) was met reporting a statistically significant benefit in OS in pts treated with combination (3). A subgroup analysis shows that, Asian population did not received similar benefit on OS compared to non-Asian pts; the reasons for a discrepant outcome are not completely known. It is noteworthy that Asian pts have a relatively less aggressive disease biology and have often received more than third and fourth therapies that useless the survival advantage (4). Recently pharmacokinetic (PK) data from REGARD and RAINBOW PK sample collected were analyzed according exposure efficacy and safety analysis. The results document that an improvement in efficacy was observed in increasing levels of ramucirumab exposure, these results remain significant even after adjusting for imbalances in baseline factors (5). The second randomized study evaluated ramucirumab and FOLFOX as first line for pts with advanced esophageal cancer: it did not show any benefits on PFS and OS compared to only FOLFOX (6). A possible reason for these negative results is at first that biology of esophageal cancer is different from GC. On the other hand, platinum would not be the best chemotherapeutic backbone to which antiangiogenic therapy should be associated. Moreover there is evidence about the antiangiogenic activity of paclitaxel that can explain a potential synergy with ramucirumab (7). The REACH trial evaluated the safety and efficacy of ramucirumab in pts with advanced HCC following first-line therapy with sorafenib (8). Additional analyses were conducted to evaluate the relationship between baseline AFP and ramucirumab treatment effects. The results show that baseline AFP is identified as a potential marker for selecting pts who may benefit from ramucirumab (9). The RAISE trial evaluated the efficacy and safety of adding ramucirumab to the standard second-line treatment FOLFIRI. This trial met its primary endpoint and demonstrated a statistically significant improvement in OS for ramucirumab and FOLFIRI vs only FOLFIRI. Moreover ramucirumab in combination with FOLFIRI was well tolerated in patients with mCRC (10). In conclusion ramucirumb (Cyramza) is the first EMA-approved therapy for advanced GC after prior chemotherapy. Future investigation will address the potential role of this drug in the first-line setting for advanced GC and for early-stage disease.

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