6506 ORAL

Predictive markers in patients with upper gastrointestinal cancers treated with erlotinib and bevacizumab in a multicenter phase II trial

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Background: As the number of targeted drugs increases, the prediction of response to therapy based on tumour biology is getting increasingly important. Several growth factors, their receptors, and components of the plasminogen activation system are important for tumour angiogenesis and the malignant phenotype of signaling via the epidermal growth factor receptor (EGFR) pathway.
Material and Methods: This prospective study evaluated the predictive value of soluble EGFR (sEGFR), soluble vascular endothelial growth factor receptor 2 (sVEGFR2), placental growth factor (PlGF), plasminogen activator inhibitor type 1 (PAI-1), and different forms of the urokinase type plasminogen activator receptor (uPAR) (intact, intact+cleaved, and domain I) in patients with advanced carcinomas of the upper GI tract in progression after chemotherapy. Patients were treated with drugs targeting angiogenesis (bevacizumab) and the EGFR pathway (erlotinib) in a multicenter phase II trial (ASCO GI 2009, abstract #170). Plasma was collected at baseline and weekly during the first 4 weeks. Plasma was analysed using validated quantitative immuno assays. Results of baseline samples and changes in plasma levels of the markers were correlated to PFS and clinical benefit (CB), defined as SD or PR.
Results: Baseline plasma was available in 77 out of 100 patients (median age 62 [25−78]) with carcinoma in esophagus (36%) (adeno [30%], squamous [6%]), stomach (12%), pancreas (33%), and biliary tract (19%). Three patients had PR, 28 SD, 22 PD, and 24 were not evaluable.
Plasma PlGF increased significantly during therapy with erlotinib and bevacizumab ($p < 0.0001$). This was not found for any of the other markers. High levels of uPAR domain I was significantly associated to shorter PFS (HR: 1.75 [95% CI: 1.2−2.5] $p = 0.003$). Patients with low levels of intact uPAR and intact+cleaved uPAR at baseline, had higher probability of CB (Intact uPAR OR: 3.0 [95% CI: 1.1−7.8], $p = 0.025$ and Intact+cleaved uPAR OR: 4.1 [95% CI: 1.5−11.4], $p = 0.007$). The remaining markers were not significantly associated with PFS or CB.
Conclusion: Plasma PlGF increased significantly during therapy, which could be a resistance mekanism to bevacizumab and suggests that anti PlGF-therapy could be interesting to investigate in patients progressing on the current therapy.
High levels of uPAR domain I were associated to shorter PFS. Low levels of intact and intact+cleaved uPAR predicted CB from therapy with erlotinib and bevacizumab.

Poster discussion presentations
(Tue, 22 Sep, 11:15−12:15)

Gastro-intestinal malignancies − Non-colorectal cancer

6507 POSTER DISCUSSION

Catumaxomab treatment in gastric-cancer patients with malignant ascites – subgroup-analysis of a pivotal trial

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Background: Malignant ascites is associated with poor prognosis and reduced quality of life. In February 2009 the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion recommending approval of catumaxomab for the intraperitoneal (i.p.) treatment of malignant ascites in EpCAM-positive carcinomas. Catumaxomab (anti-EpCAM x anti-CD3) is known to destroy tumor cells within ascites fluid by activating T cells and accessory cells. Results of the pivotal trial including two strata (ovarian-cancer and non-ovarian-cancer patients) were reported by Parsons et al. (ASCO 2008). We present the results of malignant ascites patients due to gastric-cancer, the largest subgroup of the non-ovarian-cancer stratum.
Material and Methods: A total of 66 gastric-cancer patients with symptomatic malignant ascites were treated with paracentesis plus catumaxomab (46 patients) versus paracentesis alone (control) (20 patients). Four i.p. infusions of catumaxomab were to be administered (over 6 hours in ascending doses: Day 0: 10 μg, Day 3: 20 μg, Day 7: 50 μg, Day 10: 150 μg). The primary endpoint of the study was puncture-free survival defined as time to puncture or death, whichever occurred first. Main secondary endpoints are time to next puncture, overall survival and safety parameters.
Results: For the primary endpoint puncture-free survival a median of 44 days for catumaxomab versus 15 days for control was observed ($p < 0.0001$, HR: 0.289 with 95% CI from 0.151 to 0.554). The secondary endpoint time to next puncture resulted in a median of 118 days versus 15 days ($p < 0.0001$, HR: 0.143 with 95% CI from 0.057 to 0.359). Although the study was not powered nor designed for overall survival the difference between treatment and control arm was significant (71 versus 44 days, $p = 0.0313$, HR: 0.469 with 95% CI from 0.232 to 0.915). The most frequent reported AEs were abdominal pain, potentially associated with the mode of application and symptoms associated with cytokine release, as important aspect of mode of action of catumaxomab e.g. pyrexia, nausea and vomiting. They were in general mild to moderate, limited to the treatment period and reversible.
Conclusions: I.p. catumaxomab is a new promising option for the treatment of patients suffering from malignant ascites due to gastric cancer. The positive efficacy results were demonstrated in a truly late stage patient population together with a predictable and manageable safety profile.

6508 POSTER DISCUSSION

A randomized phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in advanced gastric cancer (AGC): a preliminary safety results

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Background: Both CX and ECX have clearly demonstrated efficacy against AGC. The objective of the study is to evaluate the safety and activity of CX and ECX combination chemotherapy given as first-line therapy for AGC.
Methods: Patients with chemotherapy-naïve, histologically-confirmed, metastatic AGC were randomized to receive CX (cisplatin 75 mg/m^2 iv on day 1 and oral capecitabine 1000 mg/m^2 bid on days 1−14) or ECX (epirubicin 50 mg/m^2 on day 1 plus CX) every 3 weeks. The primary endpoint was progression-free survival (PFS).
Results: Of the 89 registered patients, 46 patients were treated with CX and 43 with ECX. As of Mar 2009, 45 patients experienced disease progression and therapy is ongoing in 18 patients. For both arms, 417 chemotherapy cycles were delivered (median, 5; range, 1−10). Treatment duration was similar for both arms (3.37 for CX v 2.82 months for ECX). Both CX and ECX were generally well tolerated. There was no relevant difference in the occurrence of overall grade 3/4 toxicities between the two arms (52.17% v 53.48%, respectively; $P = 0.901$). In the CX and ECX arms, 2.1% and 6.9% of patients, respectively, discontinued treatment because of toxicity. There were no significant differences in therapeutic efficacy between CX and ECX with respect to the response rate (40.4% vs. 24.3%; $P = 0.127$) and PFS (5.2 v 6.2 months; $P = 0.805$).
Conclusion: Both CX and ECX appear to be active as first-line chemotherapy for AGC, and the safety profiles are acceptable.