CLINICAL DEVELOPMENT OF CATUMAXOMAB (REMOVAB) IN MALIGNANT ASCITES

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Introduction: Malignant ascites is a frequent late-stage manifestation of advanced intraabdominal malignancies, associated with a poor prognosis and poor survival. At present, there are no evidence-based guidelines for the evaluation and treatment of malignant ascites. Repeated paracentesis often plays an important palliative role in patients in whom chemotherapy fails. Rapid reaccumulation of fluid leads to a relatively short duration of symptom improvement and necessitates frequent drainage procedures. Since April 2009, catumaxomab (Removab) is the first drug worldwide with an approval (EU) for intraperitoneal (i.p.) treatment of malignant ascites.

Background: Catumaxomab is a trifunctional bispecific monoclonal antibody, characterized by the ability to bind three different cell types. It is targeting the epithelial cell-adhesion molecule (EpCAM) expressed on epithelial tissues/tumours and CD3, a component of the T cell receptor complex. In addition, the Fc region binds to accessory cells like macrophages, dentritic cells and natural killer cells. These bindings induce a simultaneous activation of different immune cells, mediated by co-receptors and cytokines. Subsequently, an anti-tumour immune response is initiated resulting in an effective destruction of tumour cells.

Purpose: EpCAM is expressed on the majority of ascites-causing epithelial tumours (e.g. ovarian-, pancreatic-, colon- or gastric-cancer). Due to the fact that the peritoneum is of mesothelial origin, the application of catumaxomab directly into the peritoneal cavity is tumour-specific in patients with malignant ascites. As a first phase I/II trial with ovarian cancer patients suffering from malignant ascites has shown promising efficacy results, a pivotal trial was performed.

Methods: This pivotal trial was a two-arm, randomized (2:1) open-label, phase II/III study. Patients were randomized to receive either paracentesis plus catumaxomab or paracentesis alone. Catumaxomab treatment consisted of 4 i.p. infusions (administered over 6 hours via a constant infusion pump system) at 10, 20, 50, and 150 µg; on day 0, 3, 7, and 10. The primary endpoint was puncture-free survival, defined as time to next therapeutic puncture or time to death, which ever occurred first. Main secondary endpoints were time to next therapeutic puncture, overall survival, ascites signs and symptoms. Main inclusion criteria were: Symptomatic ascites with a volume of >1l, EpCAM-positive tumour cells in the ascites fluid and at least one previous puncture within 5 weeks before screening. Patients had to be resistant to chemotherapy or chemotherapy was no longer feasible.

Results: Overall, 258 patients (129 ovarian and 129 non-ovarian cancer patients) were randomized. Median puncture-free survival resulted in clinically relevant prolongation of 46 days for catumaxomab versus 11 days for control ($p>0.0001$). Median puncture-free time was 77 versus 11 days for control ($p<0.0001$). Even though the study was neither designed nor powered for overall survival, it showed a positive trend for catumaxomab. Gastric cancer patients, the major subgroup of the non-ovarian cancer stratum, benefited even significantly from the catumaxomab therapy. The significant benefit of catumaxomab treatment was confirmed independently of the primary tumour or other prognostic factors like previous chemotherapies or presence of distant metastases. Significantly fewer patients had signs and symptoms of ascites in the catumaxomab arm versus paracentesis-only arm in both cancer groups (ovarian and non-ovarian cancer patients).

Catumaxomab was well tolerated with more than 80% of the patients receiving all four infusions. The observed safety profile was expected due to catumaxomab´s mode of action and consisted of cytokine release related symptoms like pyrexia, nausea or vomiting. The side effects were in most cases mild to moderate and fully reversible. The frequently reported event of abdominal pain could also be related to peritoneal irritation due to protocol-related procedures and/or underlying disease. Transient increases in liver enzymes and bilirubin, and transient decreases in lymphocyte count were observed but were rarely considered clinically significant and were reversible.

Conclusion: Catumaxomab administered as a sequence of four i.p. infusions of 10, 20, 50, and 150 μg; resulted in a clear clinical benefit in symptomatic malignant ascites due to epithelial tumours. The predictable and manageable safety profile underlines the positive benefit / risk ratio. Therefore, catumaxomab represents a new treatment option in this indication.