Antisense Pharma presents data in oral presentation at ASCO 2011

Antisense Pharma’s trabedersen showed excellent safety profile and first signals of encouraging efficacy in solid tumors

TGF-β2 inhibitor trabedersen achieves Proof of Concept for systemic intravenous (i.v.) application as monotherapy

Regensburg/Chicago, 7th June 2011. At the international cancer congress ASCO 2011 in Chicago, USA, the biopharmaceutical company Antisense Pharma presented today current data from its ongoing clinical Phase I/I trial with intravenous monotherapy of trabedersen (AP 12009) for the treatment of patients with advanced pancreatic cancer (PanCa), malignant melanoma (MM), and colorectal carcinoma (CRC). During the oral presentation session ‘Developmental Therapeutics – Clinical Pharmacology and Immunotherapy’ Helmut Oettlé, MD, PhD, Charité Medical Faculty of the Humboldt University of Berlin, coordinating investigator pointed out trabedersen’s encouraging safety and efficacy data: “These data suggest that trabedersen is safe and very well tolerated in systemic application – and quality of life is already a crucial factor in validation of new anti cancer drugs.”

PanCa patients treated 2nd-line with trabedersen (N=15) reached a median overall survival (mOS) of 6.9 months which is comparable to approved 2nd-line treatment for PanCa patients in the USA and Europe, – in comparison to best available chemotherapy. “Since there is no showed an encouraging survival benefit: their mOS was 13.4 months – in comparison to best available chemotherapy. “Since there is no approved 2nd-line treatment for PanCa patients in the USA and Europe, we are confident that our innovative immunostimulatory medication trabedersen will help to prolong survival in advanced pancreatic cancer patients.” adds Hubert Heinrichs, MD, PhD, Chief Medical Officer at Antisense Pharma. “Based on this very encouraging data we are currently preparing an international randomized, active-controlled Phase II/III study as 2nd-line treatment in PanCa patients – scheduled to start in 2012.”

Phase I/II study design: trabedersen monotherapy for the treatment of patients with advanced pancreatic cancer, malignant melanoma, and colorectal carcinoma

AP 12009-P001 is an open-label, multicenter, Phase I/II dose escalation trial to evaluate safety and tolerability of i.v. administration of trabedersen in 61 patients with advanced solid tumors known to overproduce TGF-β2, who were either not or no longer amenable to established forms of therapies. The enrollment and treatment of patients is completed. The evaluation of patients and collection of data is ongoing. Final analysis (database lock) is planned in 2011.

AP 12009-P001: Treatment schedule and dose finding

Primary objective of this multicenter Phase I/II study was the determination of the maximum tolerated dose (MTD) as well as the dose limiting toxicity (DLT) of two core cycles and up to 8 extension cycles of trabedersen administered every other week. Secondary objectives include safety and tolerability, pharmacokinetic profile and potential antitumor activity of intravenous trabedersen treatment.

Initially 33 adult patients with advanced pancreatic carcinoma (PanCa, stage III/IV, N=23), malignant melanoma (MM, stage III/IV, N=5), or colorectal carcinoma (CRC, stage III/IV, N=5) have been enrolled into the dose-escalation part of the study. Patients were treated in cohorts with i.v. trabedersen monotherapy as 2nd- to 6th-line therapy with escalating doses in 2 treatment schedules (1st schedule: 7d on, 7d off; 2nd schedule: 4d on, 10d off; up to 10 cycles). After completion of dose-escalation, further patients (PanCa, n=14 / MM, n=14) were enrolled in the Phase II part of the study and treated with a dose of 140 mg/m^2/d in the 4d on, 10d off schedule.

The dose escalation followed a classical cohort design with at least 3 and up to 6 patients per cohort receiving trabedersen. The starting dose was chosen based on the Lowest Observed Adverse Effect Level (LOAEL) determined in monkeys as the most relevant species. LOAEL was found to be equivalent to 48 mg/m^2/d in human adults and therefore, the starting dose was set at 40 mg/m^2/d (equivalent to approx. 1 mg/kg b.w./day). The Data and Safety Monitoring Board (DSMB) regularly reviewed available safety and efficacy data before each dose escalation step. Toxicity was assessed based on National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2). A DLT was defined as an at least possibly related, medically important event, of NCI-CTC grade 3 or 4, a worsening by ≥ 2 grades from baseline for renal or hepatic toxicities, a worsening by ≥ 3 grades from baseline for other laboratory parameters, or other toxicities considered dose-limiting by the investigator. If more than 2 patients of a cohort had DLTs, the next lower dose was defined as MTD. Dose-escalation had to be stopped if MTD was reached.

Conclusion: Safety, dosage and efficacy of trabedersen in solid tumors

A total of 61 patients have been treated: PanCa (n=37), MM (n=19, follow up for 7 MM patients is ongoing), and CRC (n=5). Trabedersen showed excellent safety and encouraging survival results. The only identified expected adverse reaction was non-serious and transient thrombocytopenia. Within the 1st schedule, MTD was established at a dose of 160 mg/m^2/d. In the 2nd schedule (4d on, 10d off) dose escalation was stopped prior to reaching a MTD. In this schedule, a well tolerated and efficacious dose (140 mg/m^2/d) was identified. The median overall survival of all PanCa patients treated 2nd-line (independent of dose and schedule, n=15), was 6.9 months (95% CI: 2.9, 13.4), while the mOS of all PanCa Patients treated 2nd-line with 140 mg/m^2/d (n=9) was 13.4 months (95% CI: 2.2, 39.7). One PanCa patient had a long-lasting complete response of liver metastases and is still alive after 61 months (status Oct 2010). Further promising efficacy data were also observed in stage IV melanoma patients with a mOS of 13.8 months (N=5; status May 2011). The evaluation of 14 melanoma patients treated with the 140 mg/m^2/d dose is ongoing.
Inhibition of TGF-β2 via trabedersen – a novel immunotherapeutic approach in cancer treatments

"Treatment of cancer remains one of the biggest challenges in medical care. Involving the body’s own immune system to fight tumor cells is an intelligent approach and will probably become the future of innovative targeted therapies", says Dr. Oettle. The antisense oligonucleotide trabedersen specifically inhibits the synthesis of the protein transforming growth factor beta 2 (TGF-β2) – one of the strongest immunosuppressors produced by many advanced tumors. “Treatment with trabedersen downregulates the synthesis of TGF-β2 and de-masks tumor cells by breaking down the immunosuppressing shield. This process may lead to an immuno-modulatory effect”, explains Karl-Hermann Schlingensiepen, MD PhD, Chief Executive Officer at Antisense Pharma. This mode-of-action hypothesis is supported by results from high-grade glioma patients treated with trabedersen in a randomized, active controlled Phase IIb study: Trabedersen was administered into a single tumor lesion – even if the patients had shown multiple lesions. Several of these patients showed a partial or complete response of all tumor lesions – even if further tumors were located on the contralateral hemisphere of the brain and a direct effect of trabedersen was unlikely. “We assume that this response is caused by activated immune cells”, resumes Dr. Schlingensiepen. “Immune cells are able to penetrate the entire tumor tissue and are capable to attack tumor cells at any place in the body.” The immuno-modulating and survival enhancing effects of the TGF-β2-inhibitor trabedersen needs to be confirmed in further studies. Therefore Antisense Pharma is currently preparing an international randomized, active-controlled Phase II/III study as 2nd-line treatment of advanced PanCA patients.

Additional Information

About Antisense Pharma GmbH
Antisense Pharma is a biopharmaceutical company located in Regensburg, Germany. The company focuses on targeted therapies for malignant tumors and is dedicated to discovering and developing drugs based on antisense technology for worldwide commercialization. The medications specifically block the synthesis of key cancer proteins. Antisense Pharma has clinical trials running that involve patients with brain tumors, advanced pancreatic carcinoma, malignant melanoma and colorectal carcinoma. Therapies for other indications are under preclinical development. The company has been honored with the German Founder’s Award and the Bavarian Innovation Award and received the Innovation Prize TOP 100.

Trabedersen (AP 12009) and TGF-β2
Trabedersen is a first-in-class gene silencing antisense compound – a phosphorothioate oligodeoxynucleotide – designed to selectively downregulate the production of transforming growth factor-beta 2 (TGF-β2) at the translational level. TGF-β2 plays a pivotal role as a multimodal cytokine by regulating key mechanisms of tumor progression. Immunosupression, invasion and metastasis, proliferation and angiogenesis are simultaneously promoted by TGF-β2 in a variety of malignant tumors. Therefore Trabedersen is a targeted multimodal therapy and one of the very promising immunotherapeutic approaches in the oncological field. Besides in high grade glioma, trabedersen is also being investigated in other aggressive cancers which over-express TGF-β2: Trabedersen is being systemically administered intravenously (i.v.) in adult patients with advanced pancreatic carcinoma, malignant melanoma, or advanced colorectal carcinoma in a Phase I/II study.

REFERENCES
1. Literature-Data: CONKO 3 study, Pelzer et. al JCO, 2008
2. American Joint Committee on Cancer, AJCC 2002; corresponds to AJCC 1997 stage IVA or IVB

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