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Clinical activity of PAT-SM6 monoclonal antibody in advanced and extramedullary Multiple Myeloma – results from a phase I study and a single patient treatment use

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Introduction: PAT-SM6 is a monoclonal IgM antibody, developed for the treatment of patients with various tumor types including multiple my-

eloma. PAT-SM6 specifically targets a cancer-specific isoform of the heat shock protein member "glucose regulated protein 78 (GRP78)" which is expressed on the surface of multiple myeloma (MM) cells. Antibody treatment leads to the induction of apoptosis and complement activation. Moreover, PAT-SM6 significantly reduced M protein levels and tumor cells in a murine model of MM (5T33). We therefore conducted a Phase 1 study with single-agent PAT-SM6 in relapsed-refractory MM patients in order to determine safety and preliminary efficacy. In addition we treated a patient with refractory extramedullary myeloma with PAT-SM6 in combination with lenalidomide and bortezomib on the basis of a single-patient treatment use.

Methods: Single-center, dose escalating Phase I study. Twelve heavily pretreated MM patients received 4 intravenous doses of PAT-SM6 at 0.3, 1, 3, or 6 mg/kg dose in a two-week cycle. Safety and response assessment was performed up to day 40. In addition, a 61-year-old patient with asecretory MM and extramedullary involvement received three doses of PAT-SM6 (10mg/kg) together with lenalidomide (25mg d1–15) and bortezomib (1.3mg/m2 d1, 4, and 8). Response was determined by PET-CT scans.

Results: In both settings PAT-SM6 treatment was very well tolerated with only a mild and transient leucopenia as a possible treatment-related side-effect. Objective responses (≥PR) were not seen in this trial, but four out of twelve patients experienced disease stabilization (SD), which was maintained in two patients for more than 120 days. Interestingly, in the group of patients with SD an increase of CD8+ T-cells and NK cells could be observed, indicating a possible clinical relevant cross-talk between PAT-SM6 and the cellular immunity. PAT-SM6 in combination with lenalidomide and bortezomib led to a rapid response in a single case of asecretory extramedullary MM that had occurred during lenalidomide and bortezomib treatment. After one course of therapy, EMD lesions fully disappeared and also intramedullary manifestations were significantly decreasing in PET-CT scans. Remission was not durable.

Conclusion: Targeting GRP78 with monoclonal antibodies provides a promising approach for resistant disease in MM. Combinations of PAT-SM6 with novel agents will be studied in future trials, which will be initiated soon.

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