C. Assaf

Skin Cancer Center Charité, Department of Dermatology and Allergy Charité Universitätsmedizin-Berlin, Germany

Zanolimumab (HuMax-CD4®), a fully human monoclonal antibody in clinical development for cutaneous T-cell lymphoma

Zanolimumab (HuMax-CD4®; Genmab, Copenhaven, Denmark) is a monoclonal human anti-CD4 antibody and specifically targets T-helper cells as well as $CD4^+$ CTCL tumor cells and at a lower level monocytes and macrophages. Due to the interference with the interaction of the CD4 antigen and the major histocompatibility complex class II-molecule (MHC-II) this antibody is decreasing T-cell activation. In 2 phase II multicenter, prospective, open-label clinical trials the efficiency and safety of this anti-CD4 antibody was determined in relapsed early and advanced staged CTCL patients. 38 patients with MF and 9 patients with SS were treated intravenously with zanolimumab at a dosage of 280 mg or 560 mg for early stage patients and with 280 mg or 980 mg for advanced stage patients. Overall responses could be seen in both patient groups. 13 cases of MF and 2 cases of SS showed a response. In the group of MF 56% within the high-dose levels showed an objective response compared to 15% with a dosage of 280 mg. The response rate within the SS was 20% for the patients who were treated with the higher dose and 25% for the low dose. The median duration of response for the high-dose levels was 81 weeks in the group of MF. The duration of response for the two responding patients with SS was 61 weeks (980 mg) and 8 weeks (280 mg). These two studies with zanolimumab give an appreciable efficacy in patients with CTCL and a high response rate as well as partially durable responses. A phase III pivotal trial, in patients with MF (stage IB-IVB) or SS who are refractory or intolerant to bexarotene and one other standard therapy is now running for registration. After the safety dose-escalation part I (n=21), the part II of the study is currently running as an open label single arm mono-therapy study where Zanolimumab is administered i.v at a dose of 14 mg/kg, once weekly for 12 weeks.

A. Hagenbeek

Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands

Monoclonal antibodies (novel): humax-CD20, ofatumumab

Ofatumumab, the first fully human anti-CD20 monoclonal antibody, targets a novel epitope of the CD20 molecule on B-cells and releases only very slowly from the target compared with rituximab. The antibody is generated via transgenic mouse and hybridoma technology. Compared with rituximab, ofatumumab has similar ADCC, but stronger CDC, even to lymphoma cells with a low CD20 antigen density and a high number of CD55 and CD59 complement inhibitory molecules present in the cell membrane. In addition, ofatumumab kills fresh B-CLL cells resistant to rituximab. In the cynomolgus monkey model, the ofatumumab-depletion of B-cells from peripheral blood and lymph nodes lasted longer than the depletion induced by rituximab.

Given the above, ofatumumab has the potential to treat B-cell malignancies with low CD20 expression, such as B-CLL and rituximab-refractory follicular lymphoma.

Indeed, in a multicenter dose-escalating study including 33 patients with relapsed or refractory CLL (Binet stage B: 67%; median number of previous treatments: 3). The response rate in the cohort receiving the highest doses (first infusion 500 mg, followed by 3 infusions of 2000 mg each, given at weekly intervals), a response rate of 50% (13/26) was achieved (Coiffier *et al.*, 2008). No complete remissions were observed. Most patients showed more than 50% decrease in lymph node size from week 4, which was sustained until week 15. The median percentage reduction from baseline of malignant $CD5^+$ $CD19^+$ B-cells in the peripheral blood was 97%, which lasted until week 24. Infections were experienced by 17/33 patients (51%), 88% of these were of grade 1/2. One event of interstitial pneumonia was fatal.

In relapsed/refractory follicular lymphoma, 4 dose groups of 10 patients each received 4 weekly infusions of 300, 500, 700 or 1000 mg. Patients had a median of 2 prior FL therapies. No safety concerns or maximum tolerated dose were identified. Treatment caused immediate and profound B-cell depletion lasting up to 1 year and 65% of patients reverted to a negative bcl2 status. Clinical response rates range from 20-63%, without a clear-cut dose-response relationship. Median time to progression for all patients/responders was 8.8/32.6 months and median duration of response was 29.9 months (Hagenbeek *et al*., 2008).

Based on these promising data, several new ofatumumab trials were launched, e.g. in CLL addressing the efficacy in patients