

Y.H Kim

Stanford Cancer Center,
Stanford, CA, USA

Zanolimumab (Humax-CD4), a fully human monoclonal antibody with significant clinical responses in cutaneous T-cell lymphoma



Zanolimumab (HuMax-CD4, Genmab, Copenhagen, Denmark) is a fully human monoclonal anti-CD4 antibody that targets the CD4 molecule on malignant T-cells in cutaneous T-cell lymphoma. Zanolimumab inhibits CD4⁺ T cells by combining signaling inhibition with antibody dependent cellular cytotoxicity (ADCC). T cell activation is inhibited by a fast dual mechanism in which the antibody abrogates signaling via the T cell receptor and, in addition, down regulates T cell activation by transmission of direct inhibitory signals. Zanolimumab induces killing of CD4⁺ T cells via ADCC by NK cells to which memory type (CD45RO⁺ CD4⁺) T cells are more sensitive than naïve (CD45RA CD4⁺) cells [Rider *et al.* Cancer Res 2007;67:9945-53] This latter observation may be of particular relevance for the treatment of cutaneous t-cell lymphoma (CTCL) which typically comprise CD45RO memory-type cells.

In phase II multicenter, prospective, open-label clinical trials (Hx-CD4-007 & -008), the clinical efficacy and safety of zanolimumab in CD4⁺ CTCL was demonstrated in previously-treated patients stratified into early vs. advanced stages. Total of 47 patients with CD4⁺ CTCL (38 mycosis fungoides [MF], 9

Sezary syndrome [SS]) were enrolled. Zanolimumab was administered as weekly infusions for total 17 treatments. Twenty-five patients were of early stage disease (23 IB, 2 IIA) and 22 were with advanced stage disease (7 IIB, 5 III, 9 IVA, 1 IVB). The early stage patients received either 280 or 560 mg dose and those with advanced disease were treated with 280 mg or 980 mg weekly doses. Overall, objective responses were observed in both patient groups with 13 patients with MF and 2 with SS showing responses. In the high-dose groups (560 and 980 mg), an overall response rate (ORR) of 56% was obtained with a median response duration of 81 wks. The ORR within the SS was 20% for patients treated with high-dose and 25% in those treated with low-dose. Among responders, time to response ranged from 2 to 12 wks. In patients with MF at the high-dose levels, the median time to response was 8 wks, and 9 of 10 responses were achieved within 8 wks. The adverse events reported most frequently included eczematous dermatitis, pruritus, fatigue, flu-like symptoms and low grade infections. Although zanolimumab resulted in profound depletion of circulating CD4⁺ T-cells, the incidence of drug related significant infections were minimal and mostly man-

ageable. These results of the phase II studies showed promising clinical efficacy and acceptable safety profile and supported further development of this fully human anti-CD4 antibody [Kim *et al.* *Blood* 2007; 109:4655-62].

Based on the phase II data, a phase III pivotal trial (Hx-CD4-110) in patients with MF (stage IB-IVB) and SS who were refractory or intolerant to oral bexarotene and one other

standard therapy was initiated. The pivotal trial started with a safety-dose escalation part with a total of 21 patients enrolled in dose groups of 4, 8, or 14 mg/kg. The ORR was greatest in the 14 mg/kg dose group at 67%, 8 mg/kg at 16% and no responses in the 4 mg/kg group. Data from the dose escalation part of the study showed an acceptable safety profile. Thus, the stage 2 part began enrollment.