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Update on galiximab: anti-CD80 monoclonal antibody

CD80 (B7.1) is a membrane-bound co-stimulatory molecule known for its role in regulating T-cell activity. Several studies suggest that it is also involved in the regulation of normal and malignant B-cells. CD80 is transiently expressed on the surface of activated B-cells, antigen-presenting cells, and T-cells, but is constitutively expressed on a variety of NHL's (e.g. follicular lymphoma (FL), Hodgkin's lymphoma, etc.). Galiximab is a chimeric ("primatized" = human IgG1 constant regions plus primate variable regions) anti-CD80 monoclonal antibody (mAb) with low immunogenicity. Cross-linking CD80 with anti-CD80 on lymphoma cells *in vitro* has been shown to induce antibody-dependent cellular cytotoxicity (ADCC), upregulate proapoptotic molecules, and inhibit cell proliferation.[1] Another possible mechanism of action may involve immunomodulatory effects on host effector cells affecting the tumor microenvironment. *In vivo*, galiximab delays tumor growth and prolongs survival in a human lymphoma SCID mouse model.[2] Based on its immunomodulatory properties, galiximab was initially studied at various doses/schedules as a treatment for plaque psoriasis. These early studies demonstrated that galiximab could be safely infused over one hour with an excellent safety profile (i.e. similar to placebo). A phase I/II dose-escalation, single-agent, multiple dose study by Czuczman *et al*.[3] demonstrated that 4 weekly infusions of galiximab were: well tolerated and had modest anti-tumor activity in relapsed/refractory FL. A phase I/II study of galiximab in combination with rituximab in relapsed/refractory FL by Leonard *et al*.[4] has also been published. In this study, the overall response rate (ORR) at a galiximab dose of 500 mg/m^2 was 66% :19% CR, 14% CRu, and 33% PR. Median PFS was 12.1 months. There appeared to be a trend for patients in lower FLIPI risk groups and rituximab-naïve patients to have better clinical outcome as measured by ORR and PFS. Based on these findings, an upfront, CALGB (50402) phase II trial of "prolonged" dosing of eight doses of combination galiximab plus rituximab was performed and preliminary data recently presented at the Lugano 2008 Lymphoma Meeting.[5] Primary objectives of CALGB 50402 were to determine the ORR and time-to-progression after upfront galiximab plus rituximab. Galiximab plus rituximab were given together weekly x 4; then every 2 months x 4 in patients with previously untreated CD20-positive FL patients: WHO grades 1-3a; bulky Stage II or Stage

III/IV; measurable disease; adequate hematologic, hepatic and renal function; signed IRB-approved informed consent. Sixty-two patients were registered; one patient withdrew consent prior to initiating therapy. Base-line characteristics of the 61 patients are: 61%M:39%F; median age = 57 years (range 22-85), with 48% of patients >60; 23% with an elevated LDH; FLIPI: good risk = 20.3%; intermediate-risk = 42%; high-risk =37%; histology = 44% grade 1; 46% grade 2; 10% grade 3a. An overall response rate of 69% (41% CR; 28% PR), with a 95% CI of (0.56, 0.80) was achieved. Median F/U time is 1.4 years (range 0.3 to 2 years) and the estimated 1-year DFS probability is 0.87 (0.75, 0.93). Treatment was very well tolerated, with only 13% experiencing grade 3 AEs. Of interest, a subset of patients are demonstrating "delayed" tumor responses. Also, there appears to be a correlation between responsiveness to galiximab plus rituximab therapy versus FLIPI score. Current galiximab trials include: an international phase III, randomized, double-blind study comparing rituximab + placebo vs. rituximab + galiximab in relapsed/refractory FL; a CALGB phase II monotherapy study in relapsed Hodgkin's lymphoma; an *in vivo* mechanism-of-action pilot study in FL to gain further insight into this exciting novel mAb with multiple mechanisms-of-action, including direct antitumor, as well as possible immunomodulatory effects. An update of available clinical data will be presented at this meeting.

References

1. Suvas S, Singh V, Sahdev S, et al. Distinct role of CD80 and CD86 in the regulation of the activation of B cell and B cell lymphoma. J Biol Chem 2002; 277:7766-75.
2. Hariharan K, Anderson D, Leigh B, et al. Therapeutic activity of IDEC-114 (anti-CD80) and rituximab (Rituxan®) in B-cell lymphoma. Blood 2001;98:608a (abstract 2549).
3. Czuczman MS, Thall A, Witzig TE, et al. Phase I/II study of galiximab, an anti-CD80 antibody, for relapsed or refractory follicular lymphoma. J Clin Oncol 2005; 23:4390-8.
4. Leonard JP, Friedberg JW, Younes A, et al. A phase I/II study of galiximab (an anti-CD80 monoclonal antibody) in combination with rituximab for relapsed or refractory, follicular lymphoma. Annals of Oncology 2007;18:1216-23.
5. Czuczman MS, Johnson JL, Jung SH, Cheson BD. A phase II trial of extended induction ogaliximab ([G] andit-CD80 monoclonal antibody) plus rituximab [R] in previously untreated follicular lymphoma (FL): Initial report of CALGB study 50402. 10th International Conference on Malignant Lymphoma. Lugano, Switzerland 2008.