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## Anti-CD80 monoclonal antibody: galiximab

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In recent years, the major approach to cancer therapy is rapidly moving away from the standard use of myelosuppressive combination chemotherapy regimens towards the testing and incorporation of more *targeted* therapies (e.g. monoclonal antibodies [mAbs], proteasome inhibition, anti-sense oligonucleotides, etc.). In general, these *targeted* therapies are associated with improved anti-tumor activity with significantly less non-specific toxicities. Nowhere is this evolution to more specific, less toxic therapy more apparent than in the field of non-Hodgkin's lymphoma (NHL). Although rituximab has demonstrated significant activity as a single agent against relapsed/refractory indolent B-cell lymphomas, many patients do not have objective responses (i.e. PR/CR) and many responders progress at one year or less and subsequently demonstrate variable degrees of rituximab resistance.<sup>1,2</sup> The evolution of other mAbs directed against tumor cell surface targets to be used alone or in combination with other agents (i.e. drugs, mAbs, etc.) is needed. One such novel mAb is galiximab, an anti-CD80 mAb. Recently, a Phase I/II monotherapy trial<sup>3</sup> and separate Phase II combination trial with rituximab in previously treated follicular B-cell lymphoma patients have been completed.

CD80 (also known as B7.1) is a costimulatory molecule known for its role in regulating T-cell activity<sup>4,5</sup> and a possible role in regulating normal and malignant B-cells as well.<sup>6</sup> Surface CD80 is transiently expressed on activated B-cells, T-cells, and dendritic cells, but constitutively expressed on a variety of lymphomas, including follicular lymphoma.<sup>7</sup> *In vitro* research demonstrated that cross-linking surface CD80 on lymphoma cells with anti-CD80 antibodies leads to: upregulation of proapoptotic molecules, anti-proliferation, and induction of anti-dependent cellular cytotoxicity (ADCC) and suggests that it may play a potential role in the treatment of B-cell NHL.<sup>6</sup>

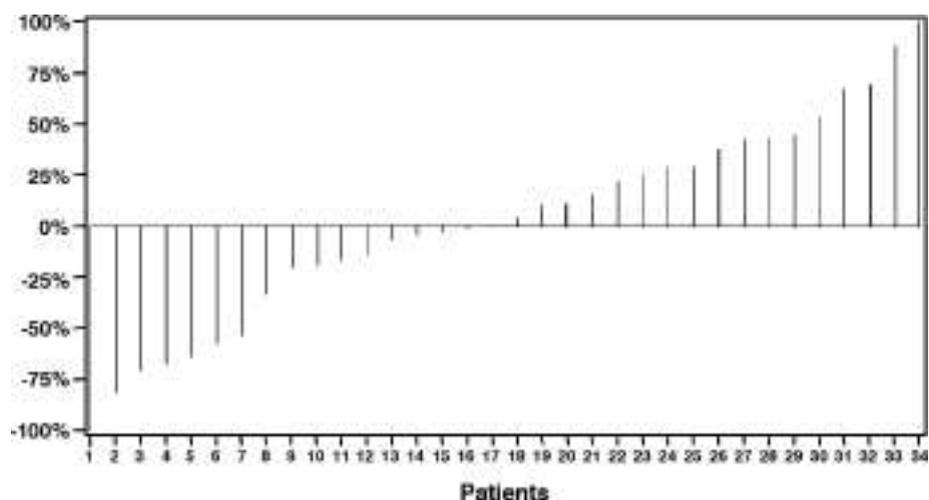
Galiximab is a chimeric (human IgG1 constant regions with primate [cynomolo-

gous macaque] variable regions), or in this case, *primatized* anti-CD80 mAb (produced by Biogen Idec Inc, San Diego, CA) with predicted low immunogenicity in humans. No adverse reactions were seen in primates receiving galiximab, even at doses greater than 1,000 mg/m<sup>2</sup>. Because of its immunomodulatory properties, galiximab was evaluated as a potential novel therapy for psoriasis. Galiximab demonstrated a favorable safety profile in 242 patients receiving it as part of multiple-dose psoriasis studies. In particular: (1) its safety profile was similar to placebo, (2) no T-cell or B-cell depletion was seen, and (3) no patient developed anti-galiximab antibodies.

Recently, an open-label, multicenter, phase I/II monotherapy trial of galiximab in relapsed/refractory follicular lymphoma has been published.<sup>3</sup> Patients received outpatient intravenous (IV) administration of galiximab at dose levels of 125, 250, 375, or 500 mg/m<sup>2</sup> over one hour once weekly times 4 weeks. A total of 37 patients were treated on this study. Characteristics of patients were as follows: median age = 56.5 (42 to 86 years old); 53% female; 47% male; 92% White; 8% Hispanic; 89% Stage III/IV; median of 5.1 years from diagnosis; and median of 2 prior lymphoma treatment regimens. A favorable safety profile and no dose-limiting toxicities (DLT) were noted in treated patients. The most common related adverse events (AEs) experienced were grade 1 or 2 (fatigue, nausea, head-ache) with only 1 case of grade 3 axillary pain and 2 cases of grade 3 deep venous thrombosis. Cytopenias were rare with only one (3%) of 37 patients experiencing cytopenias which were considered unrelated to galiximab, but related to study disease.

Mean serum half-life of galiximab was between 13 to 24 days. Tumor reductions were seen in 49% of patients (see Figure 1).

An overall objective response rate of 11% (4 of 37 patients) was demonstrated. Two CRs and one PR was seen among 21 patients treatment at the 375 mg/m<sup>2</sup> level and one PR was seen in the 10 patients



**Figure 1. Maximum percent change in SPD of indicator lesions for patients evaluable for response. Each bar represents one patient. Lesion measurements were not available for 1 patient; patient refused CT scans. SPD = Sum of the product of the perpendicular diameters. [From: *J Clin Oncol* 23:4390-8, 2005].**

treated at the 500 mg/m<sup>2</sup> level.

Of note, the time to response was delayed (i.e. months 3, 6, 9, and 12) for the four responders. Maximum reduction in tumor burden in 2 of 3 responders occurred at 9 and 12 months when galiximab serum concentrations were near or below the lower limit of detection suggesting a possible cellular-mediated mechanism of anti-tumor activity different from the more typical mAb-associated ADCC or complement-dependent cytotoxicity (CDC). Event-free survival for responders: 11.2, 24.3+, 26.5, and 31 months.

Because of galiximab's excellent safety profile and, in addition to ADCC, potentially a unique mechanism-of-action which differs from other current agents used to treat NHL, it is an attractive agent to integrate into current anti-lymphoma therapies. In addition, pre-

clinical human B-lymphoma murine tumor models demonstrate augmented *in vivo* anti-tumor activity and a prolongation in survival in animals receiving combination therapy (i.e. galiximab plus rituximab) compared to those receiving mAb monotherapy (i.e. rituximab or galiximab) alone.

Based on these pre-clinical and favorable clinical phase I/II monotherapy results, a phase I/II study of galiximab plus rituximab was undertaken in patients with relapsed/refractory follicular lymphoma. Preliminary results from this Phase I/II galiximab plus rituximab trial are favorable. Results from this combination trial, along with the proposed schedule for a future CALGB upfront follicular lymphoma clinical trial will be presented at the *New Drugs in Hematology* meeting in Bologna in September, 2005.

## References

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