

BLA #125019 ZEVALIN™ Kit
Questions for the Committee.

In two clinical trials, ZEVALIN™ therapy was associated with durable objective tumor responses as well as a high proportion of serious and life-threatening hematologic toxicity of prolonged duration. ZEVALIN™ is a combination product, consisting of both RITUXAN (an approved product) and radiolabeled ibritumomab. Approval for this product requires demonstration that both components contribute to benefit. Therefore, there should be a determination that ZEVALIN™ provides benefits beyond those provided by RITUXAN alone.

1. In the setting of treating chemotherapy and RITUXAN refractory patients:
 - a. Do the data support a determination that the clinical benefits associated with ZEVALIN™ extend beyond those that could have been realized by retreatment with RITUXAN?
 - b. Do the benefits associated with ZEVALIN use (clinically significant tumor shrinkage) considered together with the toxicity (hematologic and other) support a determination that ZEVALIN is safe and effective in this setting?
2. In patients who have not failed RITUXAN:
 - a. Has ZEVALIN™ been demonstrated to provide benefits beyond those attributable to RITUXAN alone?
 - b. Is the net clinical benefit of ZEVALIN™, as compared with RITUXAN [higher overall response rate, absence of a clear difference on time-to-progression or overall survival, and higher toxicity], sufficient to recommend approval for this patient population?
3. In the randomized, active-controlled study, 106-04, a small number of subjects with low grade, non-follicular NHL or CD20+ NHL that had undergone transformation to a more aggressive histology were enrolled. The clinical behavior and level of CD20 expression in low-grade, non-follicular lymphoma and low-grade lymphoma that has undergone transformation may be sufficiently different from that observed in low-grade follicular NHL to preclude extrapolation of the clinical results. The data obtained in these subgroups across other studies have not been as rigorously confirmed for histologic diagnosis or documentation of tumor response and duration.

The following table summarizes the response outcomes in 106-04 by subgroup:

Histology Type	Response	ZEVALIN™ Resp/Total (%)	RITUXAN Resp/Total (%)
Follicular	ORR	42/55 (76)	27/58 (47)
	CR	11/55 (20)	5/58 (9)
IWF A	ORR	6/9 (67)	3/8 (38)
	CR	1/9 (11)	1/8 (13)
Transformed	ORR	5/9 (56)	3/4 (75)
	CR	1/9 (11)	2/4 (50)

- a. RITUXAN is approved for the treatment of chemotherapy-refractory low-grade, non-follicular NHL (IWF A). Although the data for ZEVALIN™ in this group are quite limited, the overall response rate was higher and duration of response similar for the 9 patients who received ZEVALIN™ as compared to the 8 patients who received RITUXAN, a similar pattern to that observed in the follicular subgroup. Please discuss whether the data are sufficient to determine that ZEVALIN™ has benefits beyond those of RITUXAN and that there is net clinical benefit of ZEVALIN™ for patients with chemotherapy-refractory low-grade, non-follicular NHL. In particular, does this subpopulation require independent data or do the data from patients with follicular disease together the limited numbers of patients with IWF A, support a determination of regarding IWF A? If the data are insufficient, please discuss the design of additional studies that would be acceptable if the sponsor wishes to pursue this claim.

 - b. RITUXAN is not approved for the treatment of CD20+ low-grade NHL with transformation. The CD20+, transformed B-cell NHL subset [in ZEVALIN study 106-04] included subjects with transformation to diffuse small cleaved cell (IWF E), diffuse mixed cell (IWF F), or diffuse large cell (IWF G) histology at study entry. The overall response rate, the complete response rate, and the duration of response were lower in 9 ZEVALIN™-treated patients with low-grade lymphoma that had undergone transformation as compared to the 4 subjects who received RITUXAN. Please discuss whether the data are sufficient to determine that the data are sufficient to determine that ZEVALIN™ has benefits beyond those of RITUXAN and that ZEVALIN™ offers net clinical benefit for patients with chemotherapy-refractory CD20, low-grade NHL with transformation. If the data are insufficient, please discuss the design of additional studies that would be acceptable if the sponsor wishes to pursue this claim.
4. The initial step (step 1-administration of RITUXAN and ¹¹¹In-labeled ibritumomab) is an essential component of the ZEVALIN™ therapy. There are no data on the safety

and effectiveness of ZEVALIN™ using only one dose of RITUXAN (elimination of step 1) and an inadequate safety database in patients who received RITUXAN alone without radiolabeled material in step 1. Based on experience observed with other murine monoclonal antibodies, the safety profile and efficacy of administration of ZEVALIN™ in patients who have a pre-existing anti-murine antibody immune response is highly likely to be different from that observed in clinical studies. No other screening test, e.g., HAMA, has been adequately evaluated to identify patients at increased risk of altered biodistribution.

In addition, assessment of biodistribution aids in identification of normal tissues that would be exposed to unusually high doses of radiation due to alteration of clearance for mechanical reasons (ureteral obstruction) or based on proximity to tumor masses and may provide information on radiation dosimetry to assist in assessing cumulative doses for future planned radiotherapy.

The Agency seeks advice on additional post-marketing studies to better assess the utility of using ¹¹¹In-labeled ibritumomab for determination of biodistribution, as a component of Step 1, in optimizing the safety and effectiveness of ZEVALIN™.

What types of studies and other data should be collected to determine the safety and effectiveness of deletion of the biodistribution assessment while retaining the first dose of RITUXAN?

5. Low grade NHL is rare in the pediatric population. The Biological Response Modifiers Advisory Committee and the pediatric subcommittee to the ODAC have advised that studies in pediatric patients should not be required under the Pediatric Rule because the disease (follicular NHL) does not occur with sufficient frequency in children. The Agency seeks the Committee's advice regarding the waiver of studies in pediatric patients.