

## Appendix A Evidence Table

Summary Evidence Table for Evaluating Effectiveness of Zevalin®

Author/Year	Objectives	Study Design	Major Inclusion Criteria	Major Exclusion Criteria	Key Baseline Characteristics	Results																											
Witzig/2002, Corresponding to FDA Study 106-04	To compare the efficacy of Zevalin® therapy in relapsed or refractory, low-grade or follicular NHL with that of Rituxan monotherapy.	Randomized controlled trial with masking of the primary endpoint for the review committee. 73 subjects assigned to Zevalin® and 70 to Rituxan, enrolled from 27 centers.	(1) Histologically confirmed, relapsed or refractory low-grade or follicular NHL or transformed from low-grade to intermediate-grade histology, requiring treatment due to increased tumor size, symptoms and/or symptomatic masses. (2) At least 18 years old. (3) Expected survival at least 3 months. (4) CD20+ antigen expression.	The following prior therapies: Myeloablation with autologous bone marrow transplantation or peripheral blood stem cell (PBSC) rescue; Radioimmunotherapy; Anti-CD20 therapy, including IDEC-Y2B8 and Rituxan; External beam radiation therapy; or G-CSF or GM-CSF within past 2 weeks.	<table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">Zevalin® n=73</th> <th style="text-align: center;">Rituxan n=70</th> </tr> </thead> <tbody> <tr> <td>&lt;65</td> <td style="text-align: center;">48</td> <td style="text-align: center;">46</td> </tr> <tr> <td>65-75</td> <td style="text-align: center;">17</td> <td style="text-align: center;">20</td> </tr> <tr> <td>&gt;75</td> <td style="text-align: center;">8</td> <td style="text-align: center;">4</td> </tr> <tr> <td>Follicular</td> <td style="text-align: center;">55</td> <td style="text-align: center;">58</td> </tr> <tr> <td>Non-follic.</td> <td style="text-align: center;">9</td> <td></td> </tr> <tr> <td>Transform.</td> <td style="text-align: center;">9</td> <td style="text-align: center;">8</td> </tr> <tr> <td>Stage I/II</td> <td style="text-align: center;">8</td> <td style="text-align: center;">6</td> </tr> <tr> <td>Stage III/IV</td> <td style="text-align: center;">65</td> <td style="text-align: center;">64</td> </tr> </tbody> </table>		Zevalin® n=73	Rituxan n=70	<65	48	46	65-75	17	20	>75	8	4	Follicular	55	58	Non-follic.	9		Transform.	9	8	Stage I/II	8	6	Stage III/IV	65	64	(1) Zevalin® therapy has a superior overall response rate (73% vs. 47%, $p=0.002$ ) in patients with relapsed or refractory, low-grade, follicular B-cell NHL, using study protocol defined criteria. (2) Zevalin® group time to progression (all subjects) and duration of response (responders only) were not statistically different from the Rituxan group.
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FDA and IDEC Briefing Materials, Corresponding to FDA Study 106-06	(1) Determine the efficacy of Zevalin® therapy in relapsed or refractory follicular NHL subjects whose disease was refractory to previous treatment with Rituxan. (2) Determine the overall response rate (ORR) to Zevalin® therapy in follicular NHL patients.	Open-label, single-arm, 17-center study with 57 subjects, 54 of whom with follicular NHL.	Follicular NHL subjects who were previously treated with Rituxan 375 mg/m <sup>2</sup> times four and whose most recent treatment did not result in a partial response (PR) or complete response (CR), as documented by baseline and post-treatment CT scans and who now have disease progression, or who had progression of disease within 6 months of first Rituxan infusion (could have been in Rituxan arm of 106-04, without PR or CR, and needing therapy).	Similar to Witzig/106-04 above.	<p>Mean age 54.4 (34-73)</p> <p>51% F, 49% M</p> <p>7% Stage I/II, 90% Stage III/IV and 3% Unknown</p> <p>54 follicular NHL subjects, 2 non-follicular NHL subjects and 1 transformed NHL subject.</p>	(1) Zevalin® therapy has clinical activity in patients with relapsed or refractory follicular B-cell lymphoma who are also refractory to Rituxan therapy. (2) The overall response rate to Zevalin® was 58%, using an independent (LEXCOR) panel with protocol-defined criteria. (3) Time to progression for all subjects was 6.8 months. (4) Duration of response (complete and partial) was 7.7 months.																											
Wiseman/2002	Assess the efficacy of	Phase II open-label,	Similar entry profile to	Similar to Witzig/106-04	Median age 61 (29-85)	Overall response rate =																											

	Zevalin® in mildly thrombocytopenic patients with advanced relapsed or refractory low-grade, follicular or transformed NHL.	single-arm, 12-center study with 30 subjects.	Witzig/106-04 above, and requiring platelet count between 100-149.	above.	40% F, 60% M  2 small lymphocytic lymphomas, 25 follicular lymphomas and 3 transformed lymphomas.	83% based upon International Workshop criteria, and 67% using study protocol defined criteria.
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Summary Evidence Table for Evaluating Effectiveness of Bexxar®

Author/Year	Objectives	Study Design	Major Inclusion Criteria	Major Exclusion Criteria	Key Baseline Characteristics	Results
Kaminski/2001	1) To establish the efficacy and safety of a single course of Bexxar® in patients meeting a strict chem.-refractory definition 2) to compare efficacy outcomes of the last chemo regimen with the efficacy outcomes after Bexxar®.	Phase 3, nonblinded, single Bexxar® dose, multicenter study using an “internal control” (i.e., each patient served as their own control using a paired analysis). 60 subjects were studied.  Primary endpoint: number of subjects with a longer duration of response (defined as >30 days difference) after chemo regimen v. after Bexxar®.  Assessment performed by a masked panel comprised of 2 independent teams consisting of 1 radiologist and 1 oncologist.	Adults with low-grade or transformed low-grade CD20-positive B-cell lymphoma who received at least 2 prior protocol-specified chemo regimens and did not respond or had a relapse within 6 months of completion of the last regimen.  90 subjects entered the study.	Exposure to unlabeled or radiolabeled monoclonal antibodies (i.e., Rituxan®- naive).	Median age 60 (38-82)  63% male  60% Low-grade 38% transformed low-grade 2% intermediate grade, mantle cell  Median duration of response to last chemo- 3.4 months (1.7-6.9)	# subjects with longer duration of response to prior chemo regimen- 11  # subjects with longer duration of response to Bexxar® - 32 (p< 0.001 v. longer duration after prior chemo group)  # subjects with equivalent duration of response between prior chemo and Bexxar® (defined as ≤30 day difference)- 17