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NCCN Guidelines Panel: Non-Hodgkin's Lymphomas

On behalf of Spectrum Pharmaceuticals Inc., I respectfully request the NCCN Guideline Panel for Non-Hodgkin's Lymphomas (NHL) review the enclosed data in consideration of incorporating ibritumomab tiuxetan (ZEVALIN®) into the current treatment guidelines for diffuse large B-cell lymphoma (DLBCL).

Specific Changes: Request to include ibritumomab tiuxetan as an option for first-line consolidation in the treatment of DLBCL.

FDA Clearance: Ibritumomab tiuxetan (ZEVALIN®) is a CD20-directed radiotherapeutic antibody administered as part of the Zevalin therapeutic regimen indicated for the treatment of patients with relapsed or refractory, low-grade or follicular B–cell NHL, and previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy. The therapeutic regimen includes rituximab and Yttrium-90 (Y-90) ZEVALIN®.

Rationale: The only current treatment option listed for first-line consolidation of DLBCL is CHOP±R followed by auto-transplant which is not a feasible option for all patients. Ibritumomab tiuxetan is already indicated for use in certain sub-types of NHL including as consolidation therapy following response to front-line treatment for follicular lymphoma and has further demonstrated efficacy and tolerability in multiple formal studies as first-line consolidation following CHOP-based chemotherapy in DLBCL.[1-7]

The following articles are submitted in support of this proposed change:

1. Yang DH, Kim WS, Kim SJ, *et al*. Pilot trial of yttrium-90 ibritumomab tiuxetan consolidation following rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone chemotherapy in patients with limited-stage, bulky diffuse large B-cell lymphoma. *Leukemia and Lymphoma*. 2012; 53: 807-11.
   - A prospective, multicenter pilot trial was conducted to evaluate ibritumomab tiuxetan consolidation therapy following 6 cycles of R-CHOP chemotherapy in patients with limited-stage, bulky DLBCL (N=21). Overall response rate (ORR) following consolidation treatment was 80.9% with 28.8 month median follow-up. Three year overall and progression-free survival (PFS) rates were 85.0±8% and 75.0±9.7%, respectively. Grade ≥3 adverse events were mainly hematologic toxicities, such as thrombocytopenia (35%) and neutropenia (60%).

2. Zinzani PI, Rossi G, Franceschetti S, *et al*. Phase II trial of short-course R-CHOP followed by 90Y-ibritumomab tiuxetan in previously untreated high-risk elderly diffuse large B-cell lymphoma patients. *Clinical Cancer Research* 2010; 16:3998-4004.
   - In a single-arm, non-randomized phase 2 trial, 55 high-risk elderly patients with previously untreated DLBCL were treated with 4 cycles of R-CHOP chemotherapy followed by ibritumomab tiuxetan consolidation. ORR to the entire treatment regimen was 80% (73% CR + 7% PR). With a median follow-up of 18 months, 2-year PFS was estimated to be 85% with an overall survival (OS) of 86%. Adverse events following ibritumomab tiuxetan administration were primarily hematologic and transient; no patient discontinued treatment because of an adverse event. Grade ≥3 thrombocytopenia and neutropenia occurred in 19 patients (39.5%) and 23 patients (48%), respectively.

3. Zinzani PL, Tani M, Fanti S, *et al*. A phase II trial of CHOP chemotherapy followed by yttrium 90 (90Y) ibritumomab tiuxetan (Zevalin) for previously untreated elderly diffuse large B-cell lymphoma patients. *Annals of Oncology*. 2008; 19:769-73.
   - A single-arm phase 2 trial was conducted to evaluate CHOP chemotherapy followed by consolidation with ibritumomab tiuxetan in elderly patients with previously untreated DLBCL (N=20). ORR for the entire treatment regimen was 100% (95% CR + 5% PR). With a median follow-up of 15 months, 2-year PFS was estimated to be 75% with an OS of 95%. Adverse events included grade ≥3 hematologic toxicity in 12/20 patients; the most common grade ≥3 toxic effects were neutropenia (n=12) & thrombocytopenia (n=7).

4. Hamlin PA, Rodriguez MA, Noy A, *et al*. Final results of a phase II study of sequential R-CHOP and yttrium-90 ibritumomab (RIT) for elderly high risk patients with untreated diffuse large B-cell lymphoma (DLBCL). *Blood*. 2010 116: Abstract 1793.
   - In a phase 2, open-label study, investigators evaluated the safety and efficacy of R-CHOP followed by consolidation with the ZEVALIN therapeutic regimen as first-line treatment of elderly patients with DLBCL (N=65). For the 44 patients treated with Ibritumomab tiuxetan consolidation, ORR was 88% and CR/CRu was 86% with 7 patients (16%) upgrading response post RIT. With a median follow-up of 42 months, Median OS and PFS were not reached. Authors conclude efficacy and tolerability results were favorable compared to historic controls.

5. Karmali R, Manson A, Buescel K, *et al*. Phase II study of 2-weekly CHOP + rituximab followed by yttrium-90 ibritumomab tiuxetan (Zevalin) in patients with previously untreated diffuse large B-cell lymphoma (DLBCL): Final analysis. *Blood*. 2010 116: Abstract 3947.
   - A phase 2 clinical trial was conducted to evaluate induction with R-CHOP-14 followed by ibritumomab tiuxetan consolidation in patients with previously untreated DLBCL (N=20). Following ibritumomab tiuxetan consolidation, 3 patients converted from PR to CR, maintaining an ORR of 100% (n=20) with an improved CR of 90% and a PR of 10%. At a median follow-up of 42.4 months, median PFS and OS were not reached. The most common grade ≥3 toxicity observed was neutropenia in 8 patients.

6. Peyrade F, Lepeu G, Gal J, *et al*. Phase II study of short CHOP-rituximab combination with early consolidation with ibritumomab-tiuxetan-Y90 (IT-Y90) in non-pretreated patients age 65 to 80 with CD20+ diffuse large B-cell lymphoma (DLBCL). *Journal of Clinical Oncology* 2012; 30 (suppl.; abstract 6633).
   - In an international, open-label, phase 2 study, patients with DLBCL received 3 cycles of R-CHOP-14 and, in cases of complete response, ibritumomab tiuxetan (N=30). Following ibritumomab tiuxetan consolidation and a median follow-up time of 29.5 months, the estimated 3-year PFS was 90% and the estimated 3-year OS was 100%. Among patients treated with ibritumomab tiuxetan, only 3 relapses were recorded. The authors concluded this regimen was a safe and effective treatment option.

7. Witzig TE, Hong F, Micallef IN *et al*. A phase II trial of R-CHOP followed by Zevalin radioimmunotherapy for patients with previously untreated stages I and II CD20+ diffuse large cell non-Hodgkin lymphoma: An Eastern Cooperative Oncology Group Study (E3402). *Blood* 2012 120: Abstract 2687.
   - A phase 2 trial was conducted to evaluate response to R-CHOP followed by ibritumomab tiuxetan in patients with early stage DLBCL (N=62). Of 48 patients who received radioimmunotherapy, 87% were in CR/CRu and 89% were in functional CR. At 4 years, 88% of patients remained progression free and 98% remained alive.

Sincerely,

Dennis Kim, MD, MPH