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ZEVALIN® (IBRITUMOMAB TIUXETAN) RADIOIMMUNOTHERAPY HIGH RESPONSE RATES SHOWN WHEN USED AS CONSOLIDATION THERAPY IN CERTAIN TYPES OF NON-HODGKINS LYMPHOMA

On February 19, 2002, **Zevalin®** (ibritumomab tiuxetan) became the first commercially available radioimmunotherapy. Zevalin, a radiolabeled monoclonal antibody, is an innovative treatment option for patients with certain types of B-cell non-Hodgkins lymphoma who have failed to adequately respond to other cancer therapies. Radioimmunotherapy (RIT) combines the targeting power of monoclonal antibodies with the cell-damaging ability of localized radiation, creating an excellent modality in the treatment of Non-Hodgkin's lymphoma (NHL), which is intrinsically a radiation-sensitive malignancy. The Zevalin therapeutic regiment is indicated in the US for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including patients with rituximab (Rituxan) refractory follicular NHL. Extensive clinical studies have confirmed high response rates and durable responses in such patients. When given at 0.4mCi/Kg (maximum dose 32 mCi), Zevalin is safe and effective. Zevalin, developed and marketed in the United States by Biogen Idec (Cambidge, MA), is given as part of a regimen that takes 7 to 9 days to complete, with no requirement for patient hospitalization, isolation or shielding.

Radioimmunotherapies are manufactured by linking monoclonal antibodies, which are engineered in a laboratory to recognize and attach to substances on the surface of certain cells, to radioactive isotopes. Zevalin is linked with the radioactive isotope yttrium-90 (Y-90). The Zevalin therapeutic regimen consists of a low-dose infusion of Rituxan preceding indium-111 Zevalin, followed by 7 to 9 days later by a second low-dose infusion of Rituxan prior to Y-90 Zevalin. Zevalin binds to malignant and normal B-cells and the energy released from the Y-90 kills target cells, spreading to other nearby cancer cells, as well as some normal cells. Unlabeled pretreatment with Rituxan improves biodistribution, clears the majority of B-cells, and increases the specificity by which the Zevalin antibody binds to target cells, thus reducing the toxicity of Zevalin. This form of pretargeted RI could produce higher response rates than with Zevalin alone, and prove efficacious in more resistant forms of lymphoma. While RIT was once considered the pure domain of nuclear medicine physicians, more than 55 percent of all doses delivered in the US are being delivered by radiation oncologists, and this number continues to grow.

Once considered a rare disease, NHL is now the fifth most common cancer in the United States. While there is currently no cure for advanced stage indolent lymphoma, RIT can potentially increase survival by producing remission in patients when used either as a sole modality or in conjunction with other treatments. David A. Diamond, MD, Radiation Oncologist, Florida Hospital Cancer Institute, (Orlando, FL) has been strongly encouraged by the early clinical trials of up-front consolidative RIT. “Patients with recurrent disease appear to tolerate RIT very well, and early data suggests that this targeted therapy may have much broader applicability beyond the current FDA indication, which is for relapsed or refractory follicular/transformed lymphoma and mantle zone lymphoma. I am particularly

impressed by the efficacy demonstrated in studies of sequenced brief chemotherapy followed by RIT as primary treatment of advanced indolent lymphoma." As clinical trials have shown, Zevalin has become an important option in the treatment of indolent lymphoma in a broad range of patients. Data from the Eastern Cooperative Oncology Group Study (1499) presented at the 2006 ASCO Annual Meeting showed that previously untreated patients with stage II-IV mantle cell lymphoma (MCL) experienced a significant improvement in response rates with administration of Zevalin following R-CHOP (*1*). MCL has been shown to have a continuous relapse pattern with current treatments. This study was designed to evaluate response and toxicity, with a primary endpoint of time-to-treatment failure (TTF). After four cycles of R-CHOP, 7 of the 50 evaluable patients in the study (14 percent) achieved a complete response (CR/CRu) and 29 (58 percent) achieved a partial response. Following treatment with Zevalin, responses improved in 15 of 37 patients. Twelve of the patients with a partial response exhibited a complete response after Zevalin, 2 patients with stable disease exhibited a partial response, and one patient moved from stable disease to a complete response. The final response rate following Zevalin administration was 84 percent, with a complete response rate of 45 percent, more than triple the rate following R-CHOP alone. Further follow-up is needed to determine TTF (*1*).

Roger Macklis, MD, Professor of Medicine in the Department of Radiation Oncology, Cleveland Clinic Lerner College of Medicine, is involved in an ongoing trial utilizing an initial brief course of external beam radiation to reduce bulky disease in lymphoma patients scheduled for Zevalin treatment, but who have shown progression after conventional chemotherapy. "We know that for Zevalin, one negative sign in terms of the likelihood of patients doing well is bulky disease." The database showed that patients with bulky disease, with bulk being defined as 5 cm or greater of contiguous disease, did less well both in terms of the likelihood of reaching complete and durable response. The study was designed to demonstrate that if the bulk of disease could be reduced using focal external beam radiation (treating only up to 3 bulky sites), then patients would have an improved likelihood of reaching complete and lasting response. Dr. Macklis explains: "The study is in progress now, with 8 patients enrolled, and follow-up is relatively short for every patient. So far we have been very impressed that the great majority of these patients has shown a complete response or near complete response even in the previously bulky areas, and so far none has shown any progression."

Today, Zevalin is being investigated in multiple clinical trials at major medical centers in the United States and in a variety of treatment strategies, including combinations with front-line and salvage chemotherapy regimens and as part of autologous and allogeneic stem cell transplantation in both indolent and aggressive lymphomas.

About Biogen Idec

Biogen Idec creates new standards of care in oncology, neurology and immunology. As a global leader in the development, manufacturing, and commercialization of novel therapies, Biogen Idec transforms scientific discoveries into advances in human healthcare.

For more information about Biogen Idec or Zevalin, call 1-877-433-4332; contact a Biogen Idec representative at ASTRO, booth #719; or visit the company's Web site at www.biogenidec.com.

References:

1. Smith, *et al*. Phase II study of rituximab + CHOP followed by 90Y-ibritumomab tiuxetan in patients with previously untreated mantle cell lymphoma: An Eastern Cooperative Oncology Group Study (E1499). *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 7503.