Non-Hodgkin’s lymphoma (NHL) is a heterogeneous group of lymphoid malignancies that most commonly occur in individuals over the age of 60 years. Aggressive (high-grade) subtypes progress rapidly but are potentially curable, whereas indolent (low-grade) subtypes grow more slowly but usually relapse after conventional treatment. The introduction of immunotherapy and its combination with chemotherapy greatly improved remission rates compared with chemotherapy alone in NHL; more recently, the combination of immunotherapy plus yttrium-90 (90Y) or iodine-131 (131I) radiation has shown much greater efficacy than immunotherapy alone and may improve overall survival (OS).

The greatest challenge in NHL is keeping patients in remission once they have responded to therapy. Conventional chemotherapy for indolent lymphoma has a high response rate, but relapses will occur. Although patients may respond to salvage therapy, the duration of remissions decreases progressively. High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) has been shown to increase progression-free survival (PFS) with a two-year probability of 70%; however, the curative potential in these patients is unclear.

**Rationale for Using Yttrium-90-Ibritumomab Tiuxetan in Autologous Stem Cell Transplantation**

NHL is inherently radiosensitive, providing a rationale for using radiation to treat lymphomas, and the targeted delivery of radiation directly to tumour sites is better tolerated and more efficient than total body irradiation (TBI). The principles of radiolabelled immunotherapy, which allows targeted delivery of a therapeutic dose of radiation not only to the surface of tumour cells at multiple sites but also to neighbouring deeper sites, have been reviewed extensively in recent publications. The only radiolabelled immunon conjugates currently approved for the treatment of NHL are 90Y–ibritumomab tiuxetan (Zevalin®), GlaxoSmithKline, US; only approved in the US), both of which are directed against the CD20 cell surface antigen, 90Y–ibritumomab tiuxetan comprises the anti-CD20 monoclonal antibody ibritumomab, conjugated via the tiuxetan chelator to the pure beta-emitting radioisotope 90Y. It is currently approved for the treatment of adult patients with rituximab-refractory CD20-positive follicular B cell-NHL, and is the only therapy approved for use after rituximab failure. Adverse events with 90Y–ibritumomab tiuxetan are predictable and manageable, with the primary toxicity being transient reversible haematotoxicity, as expected.

No preparative regimens prior to ASCT have been shown to be clearly superior and none has ever been tested in a randomised study. Fractionated TBI has been used in the past, especially in indolent lymphoid malignancies, with encouraging results, but is not recommended for patients above 60 years of age or for those treated with previous radiotherapy.

Therefore, radiolabelled immunotherapeutic agents such as 90Y–ibritumomab tiuxetan are likely to play an increasingly significant role in ASCT by increasing the efficacy of the conditioning regimen and reducing the relapse risk. Owing to its good tolerability profile, the use of 90Y–ibritumomab tiuxetan at high doses as the sole conditioning agent in place of HDC is also showing promise, and may allow transplantation in patients who cannot tolerate the more aggressive conditioning regimens, such as the elderly or those with co-morbidities (especially cardiovascular disease). The dose-limiting toxicity of radiolabelled immunotherapy is haematotoxicity, which can be circumvented by ASCT and may allow further dose escalation.

**Standard-dose Yttrium-90-Ibritumomab Tiuxetan Associated with BEAM Chemotherapy plus Autologous Stem Cell Transplantation**

Experience has been gained in several phase II studies with the combination of Zevalin with other conditioning regimens before auto- or allograft transplantation. The Groupe d’Etude des Lymphomes de l’Adulte (GELA) in France investigated the Z-BEAM conditioning regimen prior to ASTC in patients with relapsing low-grade NHL. The radiolabelled immunotherapy 90Y–ibritumomab tiuxetan (Zevalin) is effective in B-cell lymphoma and delivers targeted radiation without TBI toxicity. To take advantage of this antilymphoma effect, a conventional dose of 90Y–ibritumomab tiuxetan 15MBq/kg (maximum total dose 1,200MBq) was given without dosimetry on day -14 before ASCT and combined with a standard-dose BEAM regimen starting at day -7.

The goal of this phase II study was to evaluate the efficacy and toxicity of Z-BAEM. Patients <65 years of age with CD20+ low-grade B-cell lymphoma in first or second relapses, or not achieving complete
remission after first-line treatment, were included in the trial. They had to be chemosensitive to prior salvage therapy, have had no more than three lines of treatment and be eligible for ASCT. The primary end-point was to detect a two-year event-free survival (EFS) rate of at least 80%. Haematological reconstitution was evaluated after transplant and during the first year of follow-up. Between March 2005 and August 2006, 77 patients were included. Patient characteristics at last salvage chemotherapy inclusion were: 68 follicular lymphoma, six marginal zone lymphoma (MZ), four mantle cell lymphoma (MCL), one mantle-cell plus two transformed histology after pathological review; median age 53 years (range 31–64); follicular lymphoma (FL) grade I–III, Z-BEAM Two-year OS 88%; Z-BEAM Two-year OS and PFS were 88.9 and 69.8%, respectively. There was a median follow-up of 18.4 months and the estimated two-year OS and PFS were 88.9 and 69.8%, respectively.

Median delay between first-line therapy and ASCT was 31 months and median delay between last salvage and ASCT was 4.4 months. Response rates before ASCT were ASCT complete response (CR) and partial response (PR) 22% and stable 1%. As first-line treatment, patients received mostly cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), associated in 29 cases with rituximab. Twenty-nine patients received a second-line chemotherapy with rituximab in 22 cases prior to last salvage chemotherapy; 49 patients after first-line treatment received directly after relapse another line of chemotherapy before ASCT. Overall, among the 77 patients, last salvage chemotherapy regimen included rituximab in 74, and ASCT was performed in 75. The haematological reconstitution after Z-BEAM followed by ASCT in 75 patients was: time to neutrophils >1 g/l 12 days (9–35) and time to platelets >20 g/l 12 days (range three to 42).

Median number of platelet transfusions was four; median number of red blood cell transfusions was two. Grade 3–4 toxicities were infection (83%), mucositis (47%) and pulmonary (4%). Safety data indicated 35 serious adverse events in 24 patients; these did not appear to significantly differ from those usually seen after ASCT is performed. No cases of toxic death were observed. At weeks 12 and 42 after ASCT, median haemoglobin levels were 11.6 g/dl and 11.3 g/dl, respectively. Median platelet counts were 111 g/l and 148 g/l and leukocyte counts were 3.48 g/l and 4.80 g/l, respectively. After transplant, 91% of the patients were in CR or CRu. Only five adverse events were reported. After a minimum follow-up of one year for all patients, estimated event-free survival (EFS) was 93%. Z-BEAM is a safe conditioning regimen that can be used for B-cell lymphoma. Longer follow-up is necessary to evaluate long-term toxicity and efficacy.

The Z-BEAM regimen is used in other types of lymphoma, for example in those patients who are ineligible for TBI due to older age or prior radiotherapy. The group of City of Hope was a pioneer in their domain and reported their experience of a study of 41 patients with a median age of 60 years. Disease histology were diffuse large B-cell (n = 20), mantle-cell (n = 13), follicular (n = 6) and transformed (n = 4) lymphoma. There was a median follow-up of 18.4 months and the estimated two-year OS and PFS were 88.9 and 69.8%, respectively.

Shimoni and others 8,9 have investigated the inclusion of standard-dose 90Y–ibritumomab tiuxetan in the conditioning regimen prior to ASCT in refractory, aggressive NHL expected to have poor outcome with standard conditioning (see Table 2). Presence of active disease was determined using positron emission tomography (PET) and computed tomography (CT) scanning. Overall, 11 patients had primary refractory disease, 12 had...
2. Weigert O, Illidge T, Hiddemann W, Dreyling M, Haematological Cancer

5. Gisselbrecht C, Bethge W, Duarte RF, et al., Current status and high-dose therapy and improved outcomes in patients with refractory lymphoma. Escalating-dose 90Y–ibritumomab tiuxetan (0.3–1.2mCi/kg) plus high-dose BEAM was investigated in a phase I trial of relapsed or refractory CD20-positive NHL.11 Based on dosimetry results, patient-specific doses of 90Y–ibritumomab tiuxetan calculated to deliver escalating radiation doses (300–2,100Gy) to critical organs (liver, lung or kidney) were administered. The median age of the patients was 54 years (range 25–72 years) and most had received three or more treatment regimens, including rituximab. The toxicity profile of the 90Y–ibritumomab tiuxetan-containing conditioning regimen was similar to that seen with high-dose BEAM alone. The most common grade III or IV toxicities were infection, fever, stomatitis, nausea, vomiting, diarrhoea, haemorrhage and oedema. Engraftment was rapid and three-year OS and PFS rates were good.

Tolerability
These preliminary data indicate that 90Y–ibritumomab tiuxetan at standard- and high-escalating-dose was well tolerated as a component of transplant-conditioning regimens. Toxicity profiles were similar to those seen with other high-dose regimens such as TBI, etoposide and cyclophosphamide, with no additional toxicity and no adverse events or allergic reactions specifically attributed to 90Y–ibritumomab tiuxetan. Adverse events observed following 90Y–ibritumomab tiuxetan plus HDC and transplant were as expected and included skin rashes, nausea/vomiting, mucositis, infection and cardiac, pulmonary and hepatic toxicity. In studies where 90Y–ibritumomab tiuxetan was the sole myeloablative agent, adverse events were as expected for monotherapy (neutropenia, infections) and were relatively mild. The most frequent, severe complications normally seen with conventional HDC conditioning were not observed. Tolerability findings were similar in 131I–tositumomab studies; abnormal levels of thyroid-stimulating hormone were also frequently observed following 131I–tositumomab-based conditioning.

Conventional chemotherapy for NHL is associated with an increased risk of myelodysplastic syndrome. This usually develops within 10 years of treatment exposure. Analysis estimated the risk of myelodysplastic syndrome or acute myeloid leukaemia in NHL patients receiving high-dose chemotherapy and ASCT to be between 5 and 10%. Clinical data for 90Y–ibritumomab tiuxetan in 746 patients reported 17 myelodysplastic syndromes, with an annualised rate of 0.7% from the time of treatment, indicating that there is no increase in risk compared with conventional chemotherapy.12

Current and Future Directions for Yttrium-90-Ibritumomab Tiuxetan in Autologous Stem Cell Transplantation
There is still a substantial need to further improve conditioning regimens in SCT through a safe treatment modality. The high relapse rates observed after ASCT suggest that most conditioning regimens are inadequate and more effective options are needed. Radiolabelled immunotherapy, in particular 90Y–ibritumomab tiuxetan, has shown great promise as part of conditioning regimens both as high-dose monotherapy and at standard- and escalated-dose alongside HDC, and appears to offer an effective and well-tolerated alternative to TBI.

Future research to evaluate the role of 90Y–ibritumomab tiuxetan alone with peripheral blood SC support should take a stepwise approach, focusing initially on phase II studies in patients with different histological NHL subtypes. Clear eligibility criteria should be included to define a homogenous population of lymphoma patients and those with a poor prognosis. Research also needs to be carried out with 90Y–ibritumomab tiuxetan as first-line therapy and following relapse. Subsequently, these results can be compared with a standard regimen in historical controls before making the decision to move on to randomised studies in poor-prognosis NHL patients.
When first-line chemoimmunotherapy fails ...

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**Adverse reactions may be reported to GPV.CaseProcessing@bayerhealthcare.com**

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**Name of the medicinal product:** Zevalin® 1 mg/10ml, kit for radiopharmaceutical preparation for infusion. Qualitative and quantitative composition: Ibritumomab tiuxetan (produced by a genetically engineered Chinese Hamster Ovary (CHO) cell line containing the human CD20 antigen) conjugated to the radiolabelling agent Y90DOTA, 1 mg per ml. One vial contains 2.92 mg of Ibritumomab tiuxetan in a total volume of 10ml. **Therapeutic indications:** The 90Y-radiolabelled Zevalin® is indicated for the treatment of adult patients with fludarabine-refractory (20-22) follicular B-cell non-Hodgkin’s lymphoma (FL). **Contraindications:** Hypersensitivity to Ibritumomab tiuxetan or to any component of the formulation or to any of the excipients. Pregnancy and lactation. **Undesirable effects:** The radiodose resulting from therapeutic exposure may result in secondary malignancies and in development of hypersensitivity reactions. It is necessary to ensure that the use of this radiopharmaceutical does not harm the patient. The majority of patients may be expected to experience adverse reactions. The frequency of adverse reactions reported below is very common >10%, common 1 to <10%, uncommon <1 to <10%, very rare <0.1% to <1%. Because of clinical trial data irrespective of causality.

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**Undesirable effects:**

**Tumour pain. Nervous system disorders, common:** Dizziness (except vertigo), headache, paresthesia, tremor, syncope. **Musculoskeletal, connective tissue and bone disorders, common:** Arthralgia, back pain, myalgia, neck pain. **Neoplasms (benign and malignant), common:** Anorexia. **Metabolism and nutrition disorders, common:** Hyperglycaemia. **Mucocutaneous reactions, including Stevens-Johnson Syndrome with fatal outcome, have rarely been reported in association with the Zevalin® therapeutic regimen, which includes ibritumomab tiuxetan and radiolabelled Zevalin®. Long-term animal studies on the effect on fertility and reproductive function have not been performed. Due to the nature of the compound, patients who have developed HAMA may have allergic or hypersensitivity reactions when treated with Zevalin® or other murine-derived proteins. Severe infusion reactions may occur during or following infusions.** Patients who have developed HAMA may have allergic or hypersensitivity reactions when treated with Zevalin® or other murine-derived proteins. Severe infusion reactions may occur during or following infusions, which may be associated with shock, cardiac arrest, hypotension, pulmonary oedema, oedema, chills, hypotension, angioedema, urticaria, flushing, hypoxia, respiratory distress syndrome, and anaphylactic reaction—related reactions due to Zevalin® are less common and less severe. Anaphylaxis and other hypersensitivity reactions have been reported in less than 1% of patients following the intravenous administration of proteins to patients. **Medicinal products for the treatment of hypersensitivity reactions, e.g. adrenaline, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of Zevalin®.** **Special warnings and special precautions for use:** Ibritumomab tiuxetan should be used by qualified personnel with the appropriate aseptic precautions. Anaphylactic reactions and hypersensitivity. Anaphylactic and other hypersensitivity reactions have been reported in less than 1% of patients following the intravenous administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g. adrenaline, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of Zevalin®. **Adverse effects:** Adverse effects may be reported to GPV.CaseProcessing@bayerhealthcare.com.