Technology Brief

90Y Zevalin for the treatment of non-Hodgkin’s lymphoma (v1.0)

August 2011
NAME OF TECHNOLOGY  | Yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin) therapy

PURPOSE AND TARGET GROUP  | To treat patients with Non-Hodgkin’s lymphoma, in particular follicular lymphoma

STAGE OF DEVELOPMENT (IN AUSTRALIA)
- ☑ Experimental
- ☑ Established
- ☑ Established but changed indication or modification of technique
- ☑ Investigational
- ☑ Should be taken out of use
- ☑ Nearly established

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL
- ☑ Yes
- ☑ No
- ☑ Not applicable

INTERNATIONAL UTILISATION

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>LEVEL OF USE</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Trials underway or completed</td>
</tr>
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<td>Australia</td>
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<td>Canada</td>
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<td>Europe</td>
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<td>Japan</td>
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<td>United Kingdom</td>
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<td>United States</td>
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IMPACT SUMMARY
Zevalin® (Spectrum Pharmaceuticals), a combination product consisting of tiuxetan and radiolabelled ibritumomab, belongs to a group of cancer drugs known as monoclonal antibodies (MAbs). This radiolabelled MAb recognises and locks onto specific proteins found on the surface of cancer cells, providing assistance to the body’s immune system in identifying and destroying them. The radioactive substance attached to the antibody is Yttrium-90 (90Y) which produces radiation strong enough to destroy cancer cells.
**BACKGROUND**

Lymphoma describes a group of cancers affecting the lymphatic system. The lymphatic system comprises the thymus, bone marrow, spleen, lymph nodes, and a network of lymphatic vessels that connect the lymph nodes and carry lymphatic fluid around the body. The main function of the lymphatic system is to fight infection; this is achieved by collecting and filtering infectious/harmful substances in the lymph nodes, e.g. bacteria, viruses, damaged cells and cancer cells. Lymphatic fluid contains B and T lymphocytes that are directly responsible for identifying and destroying infection and disease (Balentine 2011):

- B lymphocytes are created and mature in the bone marrow. They produce antibodies that recognise and attach to antigens present on the cell surface of infectious organisms and abnormal cells (pathogens). These antibodies alert other cells of the immune system to destroy the pathogens.

- T lymphocytes are created in the bone marrow but mature in the thymus. When activated, T cells can kill pathogens directly. T cells also play a role in cell mediated immunity.

Both B and T lymphocytes have the ability to ‘remember’ pathogens and can provide a quicker and more effective immune response if the pathogen was to return to the body (Balentine 2011).

Lymphoma is a disease where either B or T lymphocytes grow in an uncontrolled manner, collect in lymphatic tissues and result in tumour development (Balentine 2011). Through the network of lymphatic vessels, cancer cells may travel from one affected node to the next, and sometimes to remote organs (Leukaemia Foundation 2008).

There are two main types of lymphoma, which are distinguishable from each other via microscopic examination (Leukaemia Foundation 2008):

- Hodgkin’s lymphoma which develops from a specific abnormal B lymphocyte lineage. There are five subtypes of Hodgkin’s lymphoma.

- All other lymphomas (non-Hodgkin’s lymphoma or NHL) which may derive from abnormal B or T lymphocytes. There are approximately 30 subtypes of NHL – these are similar in appearance but possess different functionality and respond to different therapies.

Follicular lymphoma is a common subtype of NHL. It arises from B lymphocytes, is slow growing (‘indolent’ or ‘low-grade’) and may remain unnoticed and undiagnosed for a long period of time. The subtlety of its symptoms often means that patients are only diagnosed once the condition is advanced (stage III or IV); however, this generally does not translate into an increased threat to life. Even though none of the treatments used to treat follicular lymphoma are curative many patients with advanced disease will survive 8 to 10 years (or more) with treatment (Mallick 2010).
The goal of treating NHL is complete remission. The most widely used first-line (primary) therapies are combinations of chemo- and radiation therapy. Biological therapy, or immunotherapy, is becoming increasingly popular in conjunction with or as an alternative to standard care. Immunotherapy takes advantage of the body’s natural immunity against pathogens and is considered an attractive treatment option because it is not associated with the same adverse effects (AEs) seen with standard therapies, e.g. fatigue, nausea/vomiting, hair loss) (American Cancer Society 2010). MAbs are the most widely used form of cancer immunotherapy. MAbs are developed to recognise a specific antigen found on the surface of the target cancer cell. Once the antibodies are given to a patient, they can then recruit other parts of the patient’s immune system to destroy the cancer cells.

Conjugated MAbs are those with a drug, toxin or radioactive substance attached and act as a ‘homing device’ to take these substances directly to the cancer cell so that damage to normal cells is reduced. MAbs with radioactive particles attached to them (such as Zevalin) are referred to as being radiolabeled, and therapy with this type of antibody is known as radio-immunotherapy (RIT) (American Cancer Society 2010).

Zevalin consists of the90Y radiolabelled monoclonal antibody ibritumomab bound to the chelator tiuxetan. It locks onto the CD20 protein present on the surface of B lymphocytes (malignant and normal), and releases radiation which damages or kills them. Both malignant and normal B lymphocytes are destroyed but the body can replace the healthy cells. Zevalin is given as a single treatment course consisting of two parts given approximately one week apart – first rituximab to reduce the number of normal B lymphocytes and then Zevalin (Spectrum Pharmaceuticals 2011).

**CLINICAL NEED AND BURDEN OF DISEASE**

In Australia, lymphomas are the most common form of haematological cancer and the fifth most common form of cancer (Leukaemia Foundation 2008). Data according to the Australian Institute of Health and Welfare (AIHW) found (AIHW 2010):

- NHL cancer cases in 2007: 4,025 (2,194 males; 1,831 females).
- Mean annual change in incidence, 2002 to 2006: -0.5% (-0.1% males; 1.3% females).
- Deaths due to NHL in 2007: 1,319 (733 males; 586 females).
- Mean change in mortality, 2003 to 2007: -5.3% (-5.2% males; -5.7% females).

Follicular lymphoma is a common form of NHL, accounting for approximately one third of all lymphomas. This disease almost always affects adults, with a slight preference for females and an average age of diagnosis of 60 years. The disease course typically
includes multiple relapses with the time between relapses shrinking (Morchhauser et al 2008).

AIHW data report the total number of patients with follicular lymphomas as 903 in 2005; males 483 (4.7 per 100,000) and females 420 (3.8 per 100,000), with an age-standardised incidence rate of 4.3 per 100,000 persons (AIHW 2008).

**DIFFUSION**

Zevalin is a radiolabelled product solution which is regulated as a prescription medicine. An application for a kit for the radiolabelling of ibritumomab tiuxetan with final radiopharmaceutical grade yttrium-90 for the treatment of non-Hodgkin’s lymphoma was lodged with the Therapeutic Goods Administration (TGA) in 2004, but was withdrawn before a decision was made. Zevalin is not registered for use in Australia.

Zevalin received regulatory approval by the United States Food and Drug Administration (FDA) in February 2002 for treatment of relapsed or refractory low-grade and follicular or transformed B-cell NHL (Cheson 2005) and rituximab-refractory follicular NHL (CenterWatch 2011). The product was approved for a similar patient population in Canada in May 2005 based on two multi-centre trials (n=197) (Health Canada 2005). Zevalin was approved for first-line consolidation use in Europe on April 28th 2008 (Hall 2009).

According to the distribution of clinical trials appearing in the peer-reviewed evidence base, use of Zevalin to treat follicular lymphoma appears mainly in the United States of America, Europe and the United Kingdom.

**COMPARATORS**

Treatment for follicular lymphoma is normally reserved for symptomatic patients. In asymptomatic patients, the agent has not shown a survival advantage but may lead to unnecessary morbidity; treatment is deferred until patients are symptomatic, reflecting the evidence base (Macmillan Cancer Support 2010).

Follicular lymphoma is traditionally treated with chemotherapy and radiation therapy (see below). Single or combined cytotoxic drugs may be administered, orally or intravenously, and the combination of other treatment modalities with chemotherapy is common (Macmillan Cancer Support 2010).

- Steroid therapy is usually used in conjunction with chemotherapy to help treat lymphoma and reduce AEs in patients undergoing treatment.

- Stem cell treatment is sometimes used and involves the transplant of a patient’s own (or donated) stem cells following chemotherapy to help restore normal blood cells, which allows a higher dose of chemotherapy to be used.
Radiotherapy uses high-energy rays to destroy cancer cells; it is often used as a first-line treatment when only one or two groups of lymph nodes in the same part of the body are affected.

MAb therapy* can be part of chemotherapy maintenance therapy; rituximab may be offered for up to two years after remission.

Expert clinical opinion states that there is now interest in adding Zevalin to chemotherapy prior to autologous stem cell transplantation in diffuse large B cell lymphomas, rather than just low grade follicular lymphomas (Personal communication, 15 July 2011). Although Zevalin is yet to receive TGA approval, the Australasian Leukaemia and Lymphoma Group are currently undertaking a trial to examine the effects of this treatment combination for this emerging indication.

Another comparator is Bexxar (Iodine-131 (131I) tositumomab) which is a similar agent to Zevalin but is labelled with 131I instead of 90Y. This product is also registered for use in the United States. An advantage of Bexxar over Zevalin is the ability to manufacture it in-house.

After initial therapy most patients will relapse, regardless of the regimen used. For these patients and those refractory to therapy, treatment options are limited. For this reason, researchers have been seeking a new agent that reduces tumour burden and conveys a prolonged, treatment-free period (Witzig et al 2002).

SAFETY AND EFFECTIVENESS ISSUES

Three randomised controlled trials (RCTs) were eligible for inclusion in this technology brief (Morschhauser et al 2008; Gordon et al 2004; Witzig et al 2002). Two of the publications report outcomes in the same patient population (Witzig et al 2002; Gordon et al 2004), with Gordon et al (2004) providing the longest follow up.

Study profiles

Morschhauser et al (2008) conducted an industry-sponsored, open-label, international, multicentre, randomised, Phase III trial to evaluate the safety and efficacy of consolidation treatment with 90Y ibritumomab tiuxetan (Zevalin) in patients with advanced-stage follicular lymphoma in first remission†. Between August 2001 and January 2005, 414 adult patients were enrolled from 77 centres in Europe and Canada. Included patients had stage III or IV disease and a World Health Organization (WHO) performance score‡ of 0 to 2. They had achieved complete response (CR)/complete

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*Traditionally involves rituximab in as regime like R-CVP (rituximab with cyclophosphamide, vincristine and prednisolone) and R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone).
†NCT00185393; see http://clinicaltrials.gov/ct2/show/NCT00185393?term=00185393&rank=1
‡WHO performance score: 0 – asymptomatic; 1 – symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature); 2 – symptomatic, < 50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities); 3 –
response unconfirmed (CRu) or partial response (PR) to first-line therapy, with the last dose delivered 6 to 12 weeks before study treatment. There were multiple exclusion criteria including prior radiation or myeloablative therapy. All patients received induction therapy, after which they were randomised to the Zevalin (n=208) or no treatment/control (n=206) group. In the Zevalin group, patients received two infusions of rituximab (250 mg/m²) 1 week apart, with the first dose administered alone and the second dose administered with Zevalin (14.5 MBq/kg). Zevalin was delivered as a slow intravenous push over 10 minutes.

Statistical calculations to determine the sample size required to detect a prolongation of progression free survival (PFS) by 50% and to obtain 80% power with a two-sided significance level of $\alpha = 0.05$ at the inception of the study were performed (350 patients were required). This later changed to 364 patients; however, this number of patients in each group was not achieved. Efficacy evaluations were based on an intention-to-treat (ITT) population and safety evaluations were based on the safety population. Patients in both groups were well balanced at baseline.

Gordon et al (2004) conducted a Phase III, open-label, prospective, multicentre RCT to evaluate the safety and efficacy of Zevalin versus rituximab (control) in patients with several types of lymphoma, 79% having relapsed or refractory low-grade, follicular or transformed NHL. A total of 143 adult patients from 27 institutions throughout the United States were eligible for inclusion. Patients had received a median of two prior NHL therapies (range, 1-6). These patients were stratified by histology type (non-follicular low-grade, follicular or transformed). Selection criteria included rituximab-naïve patients with disease $\geq 3$ cm (later amended to $\geq 2$ cm) via imaging, a pre-study WHO performance score of 0 to 2 and a life expectancy $\geq 3$ months. There were multiple exclusion criteria including prior external-beam radiation therapy to more than 25% of the bone marrow. All prior chemotherapy was required to have been completed at least 3 weeks before study treatment commenced.

Patients randomly assigned to the Zevalin group (n=73) received a regimen of rituximab 250 mg/m² intravenous on days 1 and 8, Indium 111 ibritumomab tiuxetan intravenous (over 10 minutes) on day 1 and Zevalin 0.4 mCi/kg intravenous (over 10 minutes) on day 8. Control patients received four once-weekly doses of rituximab 375 mg/m². The primary study end point was overall response rate (ORR) assessed by a blinded, independent panel, Lymphoma Expert’s Confirmation of Response (LEXCOR). Patients in both treatment groups were well matched at baseline.

symptomatic, > 50% in bed, but not bedbound (capable of limited self-care); 4 – bedbound (completely disabled; cannot carry out any self-care); 5 – death.
Safety

The most commonly reported grade 3 and 4 AEs reported in the Zevalin arm in the study by Morschhauser et al (2008) were haematologic toxicities (Table 1). The statistical significance of the grade 3 and 4 AE differences between study arms was not reported. Non-haematologic AEs reported in more than 10% of patients on Zevalin were primarily of grades 1 and 2 including fatigue (32.8%), nasopharyngitis (19.1%), nausea (18.1%), asthenia (14.2%), arthralgia (11.8%), cough (11.3%), headache (11.3%), diarrhoea (10.8%) and pyrexia (10.3%).

Table 1: Summary of Grade 3 or 4 AEs reported in Morschhauser et al (2008)

<table>
<thead>
<tr>
<th>AE</th>
<th>Zevalin (n=204)</th>
<th>Control (n=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 n (%)</td>
<td>Grade 4 n (%)</td>
</tr>
<tr>
<td>Haematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>123 (60.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>82 (40.2%)</td>
<td>54 (26.5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>120 (58.8%)</td>
<td>4 (2.0%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6 (2.9%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Non-haematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>48 (23.5%)</td>
<td>11 (5.4%)</td>
</tr>
<tr>
<td>Infection</td>
<td>14 (6.9%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (2.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

AE: adverse event

At median follow-up (3.5 years) a total of 11 patients had died; six patients in the Zevalin arm and five patients in the control arm. Cause of death in patients treated with Zevalin included neutropenic sepsis after subsequent chemotherapy (n=1), pancreatic carcinoma (n=1), acute myeloblastic leukaemia approximately 2 years after the start of treatment (n=1) and progressive disease (n=3). In the control arm, cause of death included sepsis (n=1) and progressive disease (n=4).

For the Gordon et al (2004) RCT, detailed safety data are reported in the earlier publication by Witzig et al (2002). A statistically similar overall incidence of non-haematologic AEs was reported (with probable, possible, or unknown association to treatment) between treatment groups (P = 0.36). Higher incidences of the following AEs
were noted in the Zevalin group compared with the control group, although the statistical significance of these differences was not reported (Table 2).

**Table 2:** Most frequent non-haematologic AEs reported in Witzig et al (2002)

<table>
<thead>
<tr>
<th>AE</th>
<th>Zevalin (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough (Grade 1 and 2)</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Nausea (Grade 1 and 2)</td>
<td>43</td>
<td>19</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11</td>
<td>3</td>
</tr>
</tbody>
</table>

AE: adverse event

During the initial follow-up period reported in Witzig et al (2002), five patients in the Zevalin group were hospitalised for infection (n=4) or febrile neutropenia (n=1) and one patient in the control group was hospitalised with gastroenteritis; all of these patients recovered. At longer-term follow-up, an additional patient in the Zevalin group developed acute myelogenous lymphoma (Gordon et al 2004). In Witzig et al (2002), 12 patients in the Zevalin group died of disease progression (seven of which received additional NHL therapy before death) compared with ten patients in the control group – eight with disease progression, one with neutropenic sepsis after subsequent chemotherapy and another with pancreatic cancer.

An additional safety concern is highlighted in a Biogen Idac “Dear Healthcare Professional” letter dated October 2005 (FDA 2005). Post-marketing experience revealed severe cutaneous or mucocutaneous reactions, some with fatal outcomes. Onset was variable, from several days to 3 to 4 months.

**Effectiveness**

Morschhauser et al (2008) reported a statistically significant improvement in the main study outcome, PFS, in the Zevalin treatment arm compared with the control treatment arm after a median observation period of 3.5 years (Table 3). The data were presented for all patients and for the subgroups of patients with PR and CR/CRu after first-line therapy. As the data show, patients in the Zevalin group experienced nearly 2 more years of PFS than did patients in the control (no additional treatment) arm; the authors attributed this to a possible role for Zevalin in elimination of minimal residual disease.
<table>
<thead>
<tr>
<th>Progression free survival (months)</th>
<th>Zevalin</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>36.5</td>
<td>13.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PR following first-line therapy</td>
<td>29.3</td>
<td>6.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CR/CRu following first-line therapy</td>
<td>53.9</td>
<td>29.5</td>
<td>0.0154</td>
</tr>
</tbody>
</table>

PFS: progression free survival; PR: partial response; CR/CRu: complete response/complete response unconfirmed.

There were also significantly more patients in the Zevalin treatment arm who had a PR treatment compared with the control arm (P < 0.001). Seventy-seven per cent (78/101) of PR patients in the Zevalin arm converted versus 17.5% (17/97) of patients in the control arm. The final CR/CRu rates were 87.4% and 53.3% for Zevalin versus control, respectively.

In the RCT by Witzig et al (2002), LEXCOR initially assessed response to treatment at 6, 9 and 12 months (Table 4). During this time a statistically significant increase in ORR was observed in the Zevalin group (80%) compared with the control group (56%) (P = 0.002). This significant difference was maintained at longer-term follow-up (73% versus 42%, respectively) (P = 0.013) (Gordon et al 2004).

At longer-term follow-up, as reported in Gordon et al (2004), 12 patients had ongoing CR or CRu. Ongoing response duration was 47.6 to 65.6 months in nine patients in the Zevalin group and 53.9 to 60.3 months in three patients in the control group. The duration of response in patients who achieved CR/CRu was longer in patients receiving Zevalin treatment for both the ITT population and the subset (79%) of patients who had follicular histology (however, the difference seen was only statistically significant in the follicular histology subgroup, 26.4 months versus 8.5 months, P = 0.055).
Table 4: LEXCOR assessment reported in Witzig et al (2002)

<table>
<thead>
<tr>
<th></th>
<th>Zevalin n/N (%)</th>
<th>Control n/N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>58/73 (80%)</td>
<td>39/70 (56%)</td>
<td>0.002</td>
</tr>
<tr>
<td>CR</td>
<td>22/73 (30%)</td>
<td>11/70 (16%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Complete CR / CRu</td>
<td>3/73 (4%)</td>
<td>3/70 (4%)</td>
<td>NR</td>
</tr>
<tr>
<td>PR</td>
<td>33/73 (45%)</td>
<td>25/70 (36%)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Durable response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>49/72 (68%)</td>
<td>37/70 (53%)</td>
<td>0.046</td>
</tr>
<tr>
<td>At 9 months</td>
<td>38/72 (53%)</td>
<td>28/69 (41%)</td>
<td>0.110</td>
</tr>
<tr>
<td>At 12 months</td>
<td>27/67 (40%)</td>
<td>21/67 (31%)</td>
<td>0.231</td>
</tr>
<tr>
<td><strong>Durable response follicular only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>40/54 (74%)</td>
<td>30/58 (52%)</td>
<td>0.019</td>
</tr>
<tr>
<td>At 9 months</td>
<td>32/54 (59%)</td>
<td>22/57 (39%)</td>
<td>0.037</td>
</tr>
<tr>
<td>At 12 months</td>
<td>24/51 (47%)</td>
<td>17/56 (30%)</td>
<td>0.111</td>
</tr>
</tbody>
</table>

LEXCOR: Lymphoma Expert’s Confirmation of Response; CR: complete response; CRu: complete response unconfirmed.

Time to tumour progression in the ITT population for all patients, those patients who achieved a clinical response (responders) and those who achieved CR/CRu are summarised in Table 5.

Table 5: Median time to tumour progression reported in Gordon et al (2004)

<table>
<thead>
<tr>
<th>Time to tumour progression</th>
<th>Zevalin (months)</th>
<th>Control (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>10.6 (range, 0.8-67.2+)</td>
<td>10.1 (range, 0.7-61.9+)</td>
</tr>
<tr>
<td>Responders</td>
<td>15 (range, 2.1-67.2+)</td>
<td>13.4 (range, 2.8-61.9+)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>24.7 (range, 5.6-67.2+)</td>
<td>13.2 (range, 6.8-61.9+)</td>
</tr>
</tbody>
</table>

CR/CRu: complete response/complete response unconfirmed.
+: plus sign indicates censored data.

Interestingly, in those patients with follicular histology, those treated with Zevalin had a significantly longer time to tumour progression compared with those in the control group (Table 6). The median time to next treatment for all patients and patients with follicular
histology also favoured those treated with Zevalin (Table 7); 81% (17/21) of patients who initially received rituximab alone responded to subsequent Zevalin treatment with response duration of 0.5 to 53.2 months.

**Table 6: Median time to tumour progression in patients with follicular histology reported in Gordon et al (2004)**

<table>
<thead>
<tr>
<th>Time to tumour progression</th>
<th>Zevalin (months)</th>
<th>Control (months)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>15 (range, 2.9-67.2+)</td>
<td>10.2 (range, 0.7-58.7+)</td>
<td>0.07</td>
</tr>
<tr>
<td>Responders</td>
<td>17.8 (range, 2.9-67.2+)</td>
<td>13.2 (range, 2.8-57.2+)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

+: plus sign indicates censored data

**Table 7: Median time to next treatment in all patients and those with follicular histology reported in Gordon et al (2004)**

<table>
<thead>
<tr>
<th>Time to tumour progression</th>
<th>Zevalin (months)</th>
<th>Control (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ITT patients</td>
<td>17.6 (range, 1.2-62.8+)</td>
<td>13.1 (range, 0.8-61.9+)</td>
</tr>
<tr>
<td>Patients with follicular lymphoma (79% of group)</td>
<td>21.1 (range, 3.5-58.7+)</td>
<td>13.8 (range, 1.6-58.7+)</td>
</tr>
</tbody>
</table>

ITT: intention-to-treat
+: plus sign indicates censored data

**COST IMPACT**

There were no cost analysis studies identified from the retrieved material, and the current cost of Zevalin in an Australian clinical setting could not be determined. A news article featured in the Business Courier in 2002 suggests the cost per Zevalin regimen may be as high as $30,000 per patient (Tortora 2002).

One study surveying the opinions of oncologists and haematologists in the United States regarding RIT for the treatment for NHL reported concerns regarding the cost of Zevalin treatment (Schaefer et al 2010). It was noted that the high price of Zevalin was of significant concern to clinicians who had not used the drug to treat their patients in the last 24 months. It was also reported that, in the United States, Medicare reimbursed hospitals approximately US$16,000 for each RIT treatment and the cost for combined chemo-immunotherapy with R-CHOP was approximately US$17,000, making the price for these second-line treatments comparable (Schaefer et al 2010). The reimbursement practice by Medicare for Zevalin was questioned, and hospitals administering the treatment were thought to lose about US$10,000 per treatment, leading to a decline in its use (Schaefer et al 2010).
In addition to the absence of TGA approval for the drug, expert clinical opinion suggests the dissemination of Zevalin in Australia has also been limited by its high cost (Personal communication, 15 July 2011).

**ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

There were no issues identified from the retrieved material.

**OTHER ISSUES**

The authors of Morschhauser et al (2008) disclosed a number of relationships, both compensated and uncompensated, that may have posed as a conflict of interest. These relationships included employment or leadership positions within Bayer Schering Pharma, as well as consultant or advisory roles within Bayer Schering Pharma, stock ownership and research funding. The study was industry-supported. Funding for the Gordon et al (2004) study was not reported but three of the eight study authors were employed by Biogen Idec Pharmaceuticals, makers of rituximab.

A fourth RCT was identified (Wiseman et al 2001) reporting outcomes in the same patient population as Witzig et al (2002) and Gordon et al (2004). The primary outcomes reported in this RCT were biodistribution and dosimetry; therefore, the study was not eligible for inclusion in the safety and effectiveness section of this technology brief.

**SUMMARY OF FINDINGS**

Based on the findings reported in the included RCTs, Zevalin appears to be at least as safe and effective as conventional rituximab treatment for NHL for the treatment of patients with relapsed or refractory low-grade and follicular NHL and rituximab-refractory follicular NHL.

Overall, PFS appeared to be significantly improved for patients receiving treatment with Zevalin compared with those receiving rituximab alone (Gordon et al 2004) or no further treatment (Morschhauser et al 2008). Long-term follow-up data provided in the RCT by Gordon et al (2004) confirmed a significant improvement in ORR was maintained in patients treated with Zevalin. Despite this, the occurrence of haematological AEs was generally higher in patients treated with Zevalin, as compared with controls. Non-haematological AEs occurred more consistently between the treatment groups, with one RCT reporting a non-statistically significant difference.

**HEALTHPACT ASSESSMENT**

Based on the high-level evidence in this brief, it would appear that Zevalin is a safe and effective treatment for non-Hodgkin’s lymphoma. HealthPACT have noted and will disseminate this information.
NUMBER OF STUDIES INCLUDED

Total number of studies  3
Total number of Level II studies  3

REFERENCES


**Sources of Further Information**


Winter JN, Inwards DJ, Spies S et al. Yttrium-90 ibritumomab tiuxetan doses calculated to deliver up to 15 Gy to critical organs may be safely combined with high-dose BEAM and autologous transplantation in relapsed or refractory B-cell non-Hodgkin's lymphoma. *Journal of Clinical Oncology* 2009; 27(10): 1653-1659.


**Search Criteria to be used**

(90Y Zevalin OR Zevalin OR Ibritumomab tiuxetan) OR (radiolabelled monoclonal antibodies OR radioimmunotherapy) AND (Non-Hodgkin’s lymphoma OR Follicular lymphoma)