Everolimus (Afinitor) for diffuse large B-cell lymphoma – maintenance therapy

LAY SUMMARY

Lymphoma is a cancer of the lymphatic system, which is part of the immune system. The lymphatic system contains cells called lymphocytes that fight infections. Diffuse large B-cell lymphoma is the most common type of lymphoma. It can occur at any age but is more common in those over 65 years of age.

Everolimus is a new drug for diffuse large B-cell lymphoma taken as a tablet once a day. Some studies have suggested everolimus may be helpful in preventing the cancer from coming back in people whose first treatment with chemotherapy has worked.

If everolimus is licensed for use in the UK, it could be a new treatment option for diffuse large B-cell lymphoma that may reduce symptoms of the disease and improve survival.

NIHR HSRIC ID: 12096
TARGET GROUP

- Diffuse large B-cell lymphoma – maintenance therapy following complete remission to first line rituximab chemotherapy.

TECHNOLOGY

DESCRIPTION

Everolimus (Afinitor; Certican; Votubia; RAD-001) is an orally active immunosuppressant analogue of sirolimus, a macrolide antibiotic produced by *Streptomyces hygroscopicus*. These compounds are also known as mammalian Target of Rapamycin (mTOR) inhibitors. The protein mTOR functions as a regulator of tumour cell division, blood vessel growth and cell metabolism. Everolimus is administered orally at 10mg once daily for 12 months.

Everolimus (as Afinitor) is licensed in the EU for the treatment of hormone receptor-positive advanced breast cancer, neuroendocrine tumours of pancreatic origin, and renal cell carcinoma. Everolimus (as Certican) is licensed in the EU for the prophylactic treatment of organ rejection in adult patients following heart, kidney, and liver transplantation. Everolimus (as Votubia) is licensed in the EU for the treatment of renal angiomyolipoma, and subependymal giant cell astrocytoma associated with tuberous sclerosis complex. Very common (>10%) reported adverse events include anaemia, decreased appetite, hyperglycaemia, hypercholesterolaemia, dysgeusia, headache, pneumonitis, epistaxis, stomatitis, diarrhoea, nausea, rash, pruritus, fatigue, asthenia, and peripheral oedema.

Everolimus is currently in phase II clinical trials for the treatment of soft tissue sarcoma, endometrial cancer, breast cancer (combination therapy), thyroid cancer, and glioma (in children).

INNOVATION and/or ADVANTAGES

If licensed, everolimus will offer an additional oral treatment option for patients with diffuse large B-cell lymphoma who would benefit from maintenance therapy.

DEVELOPER

Novartis Oncology.

AVAILABILITY, LAUNCH OR MARKETING

Everolimus is a designated orphan drug in the USA.

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 13% of all haematological malignancies. It is the most common form of non-Hodgkin lymphoma.
Horizon Scanning Research & Intelligence Centre

(NHL), and is estimated to account for almost half (48%) of all NHL cases diagnosed in the UK. DLBCL behaves in an aggressive fashion and typically presents as a nodal or extranodal mass with fast tumour growth associated with systemic symptoms, such as sweats, fatigue and fever. In about 40% of cases, DLBCL presents in areas outside lymph nodes, such as the digestive tract, skin, bone, thyroid, and testes. The causes of NHL in general, and DLBCL specifically, are unclear, however identified potential risk factors include immunosuppression, ultraviolet radiation, pesticides, hair dyes, and diet. A subset of DLBCL, including immunoblastic and primary central nervous system (CNS) disease, is highly associated with the Epstein-Barr virus.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

The crude incidence of DLBCL in the EU is estimated at 3-4 per 100,000 per year. The crude incidence of DLBCL in the UK is 8.5 per 100,000 per year; incidence increases with age from 2.5 per 100,000 per year in those aged 35-39 years to 32 per 100,000 per year in those aged 70-74 years.

In England, there were 4,532 cases of DLBCL (ICD-10 C83.3) recorded in 2013. In 2014, there were 679 deaths from DLBCL registered in England and Wales (ICD-10 C83.3). In 2014-15, there were 33,123 admissions for DLBCL (ICD-10 C83.3) in England, resulting in 79,925 bed days and 36,392 finished consultant episodes. Research suggests that more than 30% of patients with DLBCL who initially respond to therapy will ultimately relapse.

Expert opinion suggests that patients with stage III-IV DLBCL are at high risk of relapse and there is a clinical need to reduce this and improve survival in this population.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

*a Expert personal communication.


Other Guidance

- European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015


- British Committee for Standards in Haematology. Best practice in lymphoma diagnosis and reporting. 2010

- British Committee for Standards in Haematology. Best practice in lymphoma diagnosis and reporting – specific disease appendix. 2010

CURRENT TREATMENT OPTIONS

First-line treatment regimens for patients with DLBCL are based on individual International Prognostic Index (IPI) scores and age. DLBCLs have a high cure rate with both initial and conventional dose salvage chemotherapy, with around 50% of patients responding to primary therapy with chemotherapy and rituximab type regimens. However, long-term survival is low in patients with high IPI risk scores and these individuals have a greater tendency to relapse following treatment.

Treatments options include:

- In patients <61 years who are high and high-intermediate-risk – six to eight cycles of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy combined with eight doses of rituximab given every 21 days (R-CHOP21) is the most commonly used treatment. CHOP chemotherapy with rituximab given every 14 days (R-CHOP14) is also an option for such patients.

- In patients aged 60 to 80 years – eight cycles of R-CHOP21 is the current standard treatment. Six cycles R-CHOP14 with two additional cycles of rituximab is also an option for this patient group.

- In patients older than 80 years – six cycles of rituximab combined with attenuated CHOP chemotherapy (R-miniCHOP21) is recommended. Expert opinion suggests that R-miniCHOP21 is also appropriate for people who are suitable for anthracyclines but not fit for full dose therapy, usually because of poor performance score or comorbidity. For patients with cardiac dysfunction or otherwise unfit, doxorubicin may be substituted with etoposide or liposomal doxorubicin (or omitted) from the beginning of treatment or after the first few cycles. A pre-chemotherapy phase, where a single injection of vincristine and seven days of oral prednisolone is administered, may be utilised in order to reduce toxicity in elderly patients. Expert opinion states that the use of a non-anthracycline containing regimen is appropriate for patients of any age who are not fit for anthracyclines. In the UK, gemcitabine is usually substituted for doxorubicin. R-CVP therapy (rituximab, cyclophosphamide, vincristine, and prednisolone) where doxorubicin is omitted without substitution is only suitable for the very elderly or frail.

b Expert personal communication.
Expert opinion states that most clinicians in the UK are currently using six cycles of R-CHOP21 for all patients with DLBCL who are fit for anthracycline-based therapy. Some will give an additional two cycles of rituximab for those over the age of 60 years\(^c\). Some clinicians do prefer to treat patients with high risk DLBCL by alternating between two chemotherapy combinations; rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate (R-CODOX-M), and rituximab, etoposide, ifosfamide, and cytarabine (R-IVAC)\(^c\).

Relapse is most likely to happen within two years of the end of the first treatment\(^17\). Approximately 30% of patients with a high-risk IPI develop refractory disease (progressing during first line therapy or relapsing within one year)\(^14\). In relapsed or refractory disease, some patients with generally good health who respond to salvage chemotherapy may be offered stem cell transplantation (SCT) after high-dose chemotherapy\(^17\). Allogeneic SCT also offers a potential cure for relapsed DLBCL, but carries a higher risk than autologous SCT\(^17\).

CNS prophylaxis (intrathecal or IV high-dose methotrexate) is recommended for certain groups of patients at risk of the lymphoma spreading to CNS\(^17\).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00790036, CRAD001N2301, 2008-000498-40; everolimus vs placebo; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Novartis Pharmaceuticals.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry(^18).</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=741 (planned); aged 18 yrs and older; previously confirmed stage III-IV diffuse large B-cell lymphoma; achieved complete remission following first line rituximab chemotherapy; received a minimum of five and maximum of eight rituximab chemotherapy cycles; no ongoing radiation therapy; no previously received treatment with systemic mTOR inhibitor; no evidence of current CNS involvement; no transformed follicular lymphoma.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to everolimus 10mg oral once daily for 12 mths; or placebo oral once daily for 12 mths.</td>
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<td>Follow-up</td>
<td>Active treatment for 12 mths, follow-up 5 yrs.</td>
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<td>Primary outcome</td>
<td>Disease-free survival.</td>
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<td>Secondary outcomes</td>
<td>Overall survival, lymphoma-specific survival, safety profile. No quality of life outcome measures.</td>
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<td>Expected reporting date</td>
<td>Study completion date reported as Jan 2019.</td>
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### ESTIMATED COST and IMPACT

#### COST

Everolimus (as Afinitor) is already marketed in the UK for the treatment of hormone receptor-positive advanced breast cancer, neuroendocrine tumours of pancreatic origin, and renal cell

\(^c\) Expert personal communication.
carcinoma; a pack of 30 x 10mg tablets costs £2,673, and treatment with 10mg daily for 12 months would cost £32,521.50\(^1\).

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- ☑ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other.
- ☐ No impact identified

**Impact on Health and Social Care Services**
- ☑ Increased use of existing services: *expert opinion states that maintenance therapy with everolimus will increase the toxicity of therapy which will also impact on service delivery\(^d\).*
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other.
- ☐ None identified

**Impact on Costs and Other Resource Use**
- ☑ Increased drug treatment costs: *expert opinion states that maintenance therapy with everolimus will increase the cost of treatment and follow-up\(^d\).*
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs.
- ☐ Other reduction in costs..
- ☐ Other.
- ☐ None identified

**Other Issues**
- ☑ Clinical uncertainty or other research question identified: *expert opinion states that there will be residual uncertainty about the role of maintenance everolimus in people with high IPI but early stage disease, as these patients were not included in the trial. There will also be new uncertainty about the role of maintenance everolimus in the future if RCHOP is routinely delivered in combination with biological agents such as bortezomib, lenalidomide or ibrutinib (all are currently being investigated in clinical trials and may become the new standard of care if trials are positive)*\(^d\).
- ☐ None identified

**REFERENCES**


\(^d\) Expert personal communication.

4 UpToDate. Patient information: Diffuse large B-cell lymphoma in adults. 


