Ofatumumab (Arzerra) for refractory follicular lymphoma – third line in combination with bendamustine

LAY SUMMARY

Follicular lymphoma is the most common type of indolent (slow growing) non-Hodgkin lymphoma. Non-Hodgkin lymphoma is a type of blood cancer. People with follicular lymphoma often have large painless lymph nodes in the neck, armpits, stomach or groin. They may often suffer from fatigue, shortness of breath, night sweats and weight loss. Some patients may develop more aggressive forms of the disease.

Ofatumumab is a new drug for the treatment of follicular lymphoma and is delivered straight into a vein. It sticks to cancer cells, making it easier for the body to destroy them. If licensed in the UK, ofatumumab with chemotherapy may be an option for patients whose disease has returned after initially responding to treatment.

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TARGET GROUP

- Follicular lymphoma: refractory to rituximab – third line; in combination with bendamustine.

TECHNOLOGY

DESCRIPTION

Ofatumumab (Arzerra; GSK 1841157; HuMax-CD20) is a fully human, high affinity monoclonal antibody targeted against the CD20 cell surface antigen of B-cell membranes. It is intended to be used as add on therapy for the treatment of follicular lymphoma that is refractory to rituximab. Ofatumumab is administered by intravenous (IV) infusion at 1,000mg on day 1 of every 21 day cycle when given with bendamustine (for the first 8 cycles), and then every 28 days as monotherapy for a total of 12 doses.

Ofatumumab is currently licensed in the EU (but not recommended by NICE) for the treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab. Ofatumumab is also licensed for previously untreated CLL in combination with chlorambucil or bendamustine in patients that are not eligible for fludarabine based therapies. Some of the recognised very common adverse effects associated with ofatumumab include lower respiratory tract infection, neutropenia, anaemia, nausea, pyrexia and rash.

Ofatumumab is in the following phases of clinical trials for the stated indications:

Phase III
- B-cell lymphoma.
- Non-Hodgkin’s lymphoma (follicular lymphoma, second line).

Phase II
- B-cell, marginal zone lymphoma
- Multiple sclerosis, relapsing-remitting.
- Waldenstrom’s macroglobulinaemia.

INNOVATION and/or ADVANTAGES

If licensed, ofatumumab will offer an additional treatment option for this patient group who are refractory to standard rituximab therapy.

DEVELOPER

Novartis Oncology.

AVAILABILITY, LAUNCH OR MARKETING

Ofatumumab is a designated orphan drug in the EU and USA.

It is currently in a phase III clinical trial.
Follicular lymphoma is the most common indolent lymphoma and the second most common form of non-Hodgkin lymphoma (NHL), accounting for 19% of all lymphomas in England. The incidence of follicular lymphoma, as with all NHL, is rising, although the absolute incidence varies between geographical regions and ethnic groups, being lower in Asian and sub-Saharan African countries than in North America and European countries, which is thought likely to be due to a combination of both genetic and environmental factors.

The genetic hallmark of follicular lymphoma is the translocation t(14;18)(q32;q21), which results in the constitutive overexpression of the BCL-2 protein, impairing the normal germinal centre apoptotic programme. Tumour cells are malignant counterparts of normal germinal centre B-cells. Together with a heterogeneous group of cells (including macrophages, follicular dendritic cells, fibroblasts, endothelial cells and T lymphocytes) follicular lymphoma cells form a disease-specific microenvironment allowing a dynamic and bidirectional feedback process between cancer cells and the complex network of reactive cells.

Almost all cases of follicular lymphoma carry additional genetic alterations such as gains, losses or mutations of genes such as MLL2, EPHA7, TNFRSF14, BCL6, CREBBP, EZH2 amongst many others. However, the impact of these alterations on the pathogenesis of follicular lymphoma is not completely understood.

Follicular lymphoma is usually characterised by an indolent course, and many patients remain asymptomatic despite extensive disease. Only around 10-15% of follicular lymphomas are detected at an early stage, with the vast majority of patients being diagnosed at the advanced stages III and IV. The initial symptoms of follicular lymphoma include painless swelling in one or more lymph nodes, particularly in the cervical, axillary, inguinal and femoral regions. The progression of follicular lymphoma varies, depending upon the speed of the tumour’s growth and the involvement of other organs. Advanced stage III-IV follicular lymphoma eventually becomes resistant to chemotherapy and may transform into a more aggressive form of NHL, such as diffuse large B-cell lymphoma (DLBCL).

This topic is relevant to:

Follicular lymphoma is characterised by a relapsing and remitting clinical course over several years, with a successful response to treatment becoming more difficult to achieve and of shorter duration with each relapse. In the early 1990s, median survival was expected to be
8-10 years. However, in the past decade, longer median survival has been reported; survival at 20 years has been reported to be as high as 44%\(^9\). The crude incidence of follicular lymphoma in the UK is 3.2 per 100,000 per year\(^4\). The median age of diagnosis is between 55 and 60 years\(^5\) and 91% of cases occur in patients over the age of 45\(^4\).

In England, there were 2,011 new cases of follicular lymphoma (ICD-10 C82) recorded in 2014\(^10\). Ninety percent of patients with follicular lymphoma have stage III or IV disease, and approximately 13% of these patients relapse each year\(^11\). In 2014-15, there were 22,327 admissions for follicular lymphoma (ICD-10 C82) in England, resulting in 14,035 bed-days and 22,892 finished consultant episodes\(^12\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in progress. Leukaemia (chronic lymphocytic) – idelalisib (ofatumumab) (ID817). Expected date of issue to be confirmed.

**Other Guidance**

- European Society for Medical Oncology. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2014\(^14\).
- European Society for Medical Oncology. ESMO Consensus Guidelines: Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukaemia (CLL). 2013\(^15\).
CURRENT TREATMENT OPTIONS

Due to the indolent nature of follicular lymphoma, asymptomatic and/or low-tumour-burden patients may be actively observed under a “watch and wait” approach. NICE guidance recommends rituximab for first line treatment of relapsed/refractory follicular lymphoma. The introduction of rituximab has markedly improved outcomes for patients with follicular lymphoma, and was the first drug to show an improvement in overall survival in in many years. Current treatment strategies include:

- Monoclonal CD20 antibodies — rituximab, alone or in combination with chemotherapy (such as chlorambucil) for patients that present with advanced-stage disease.
- Radioimmunotherapy — rituximab maintenance or consolidation with radioimmunotherapy after first-line therapy has shown clear benefit for progression-free survival and potentially for overall survival.
- Radiation for limited-stage patients.
- High dose chemotherapy — CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or FCR (fludarabine, cyclophosphamide and rituximab); for patients that require an aggressive treatment approach.
- Autologous or allogeneic stem cell transplantation is reserved for patients with more resistant disease and good performance status.
- Pixantrone may be used if the follicular lymphoma has transformed to DLBCL.

Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>COMPLEMENT A+B, NCT01077518, 110918; ofatumumab with bendamustine vs bendamustine; phase III.</th>
<th>NCT01294579, 114612; ofatumumab with bendamustine; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Novartis.</td>
<td>Novartis.</td>
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<tr>
<td>Status</td>
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<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry⁷, manufacturer.</td>
<td>Trial registry¹⁸.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>USA.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Non-randomised, single-arm.</td>
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<tr>
<td>Participants</td>
<td>n=346 (planned); aged ≥18 yrs; indolent lymphoma, including grades 1-3a follicular, small lymphocytic, lymphoplasmacytic, and marginal zone lymphoma; stages III-IV, or bulky disease (i.e. as any single mass &gt;5 cm in any direction); disease that is stable or unresponsive during or within 6 mths of treatment with rituximab or a rituximab-containing regimen; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; no grade 3b follicular lymphoma or evidence of transformation to aggressive lymphoma; no previous allogeneic or autologous stem cell transplant, fludarabine therapy, or</td>
<td>n=53 (planned); aged ≥18 yrs; indolent lymphoma, including grades 1-3a follicular, small lymphocytic, lymphoplasmacytic, and marginal zone lymphoma; rituximab-sensitive disease, defined as a PR or CR to the last rituximab-containing therapy lasting at least 6 mths following completion of therapy; relapse or disease progression following response to prior rituximab-based therapy; ECOG 0-2; no CLL or grade 3b follicular lymphoma or evidence of transformation to aggressive lymphoma; no previous allogeneic or autologous stem cell transplant, or radioimmunotherapy in the past 6 mths;</td>
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radioimmunotherapy in the past 12 mths; no previous external beam radiation therapy; no high dose steroids ≥60mg prednisone/day (or equivalent) within 3 mths of randomisation; no more than 10mg prednisone (or equivalent) daily at the time of randomisation; no prior bendamustine treatment within 1 yr that did not result in a complete remission (CR) or partial remission (PR) for at least 6 mths; no treatment with anti-CD20 monoclonal antibody within 3 mths of randomisation.

| Schedule | Randomised to IV ofatumumab in combination with bendamustine or bendamustine alone. In the combination arm, up to 8 cycles of bendamustine at 90mg/m² are administered on days 1 and 2 of each 21 day cycle with ofatumumab at 1,000mg administered on day 1 of each cycle for as long patients are receiving bendamustine. Thereafter, ofatumumab is continued once every 28 days until a total 12 doses are completed. In the bendamustine only arm, patients administered chemotherapy at 120mg/m² on days 1 and 2, of a 21 day cycle for up to 8 cycles. | Patients received ofatumumab IV 1,000mg on day 1 of each cycle (cycles 1-6) for the induction phase, thereafter 1,000mg every 2 mths for 2 yrs; in combination with bendamustine 90mg/m² IV on day 1 (after ofatumumab IV) and day 2 of each cycle (cycles 1-6). |

| Follow-up | Active treatment for 12 cycles (40 wks), follow-up for up to 68 mths. | Active treatment up to 2 yrs, follow-up for up to 261 wks. |

| Primary outcome/s | Progression-free survival (PFS). | CR. |

| Secondary outcome/s | Overall response rate (ORR); overall survival; time to and duration of response; clinical benefit; changes in patient reported outcome measures; pharmacokinetics; safety and tolerability. | ORR; conversion of PR to CR; PFS; safety and tolerability; pharmacokinetics. |

| Expected reporting date | Study completion date reported as July 2023. | Study completion date reported as Aug 2021. |

**ESTIMATED COST and IMPACT**

**COST**

Ofatumumab is already marketed in the UK for the treatment of CLL; a 1,000mg/50ml vial costs £1,820\(^\text{19}\). Drug cost per patient per treatment course, assuming a total cumulative 12,000mg dose, would be £21,840. Five vials of 25mg bendamustine powder for concentration for infusion costs £347.26; or £1,379.04 for 100mg vials in packs of 5\(^\text{19}\). Drug cost per patient per year, assuming a body surface area of 1.88m² and an average treatment course of 8 cycles (at 90mg/m²), would be £4,484.38.
 Horizon Scanning Research & Intelligence Centre

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
- 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
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other
- None identified

Other Issues

- Clinical uncertainty or other research question identified
- None identified

REFERENCES


