Nivolumab for follicular non-Hodgkin lymphoma — third line

LAY SUMMARY

Lymphoma is a cancer of the lymphatic system, which is part of the immune system. It contains cells called lymphocytes that fight infections. Follicular lymphoma is the second most common type of non-Hodgkin lymphoma. It often progresses slowly, with patients showing no symptoms for many years.

Nivolumab is a new antibody drug for the treatment of follicular lymphoma that is delivered straight into the bloodstream via a drip. Some studies have suggested that this drug may be helpful for people with follicular lymphoma whose disease has returned after previous treatments have stopped working.

If nivolumab is licensed for use in the UK, it could be a new treatment option for follicular lymphoma that may improve survival.

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TARGET GROUP

• Non-Hodgkin lymphoma: follicular; relapsed or refractory – third or subsequent line.

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo; anti-PD-1 monoclonal antibody - Medarex/Ono; BMS936558; MDX1106; ONO4538) is a fully human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). PD-1 is expressed on the surface of activated lymphocytes and acts as part of an immune checkpoint pathway. PD-1 blockade by nivolumab may activate T-cell responses and promote an anti-tumour immune response. In phase II clinical trials, subjects with relapsed or refractory follicular non-Hodgkin lymphoma were administered nivolumab 3mg/kg intravenously (IV) once every 2 weeks, until disease progression or unacceptable toxicity.

Nivolumab (Opdivo) is licensed in the EU as monotherapy for the treatment of advanced, unresectable or metastatic melanoma in adults (first and second line therapy). Nivolumab (Nivolumab BMS) is also licensed for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (second line therapy). Commonly (>10%) reported adverse events include: decreased appetite, nausea, fatigue, increased AST, increased ALT, increased alkaline phosphatase, increased creatinine, decreased lymphocytes, decreased platelet count, decreased haemoglobin, hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia and hyponatraemia.

Nivolumab is also currently in late phase clinical trials in the EU for:
• Glioblastoma; phase III.
• Head and neck cancer; phase III.
• Renal cancer; phase III.
• Diffuse large B-cell lymphoma; phase II.
• Hodgkin lymphoma; phase II.
• Bladder cancer; phase II.

INNOVATION and/or ADVANTAGES

If licensed, nivolumab will offer an additional treatment option for patients with relapsed or refractory follicular non-Hodgkin lymphoma; a group who currently have few effective therapies available.

DEVELOPER

Bristol-Myers Squibb.

AVAILABILITY, LAUNCH OR MARKETING

Nivolumab is a designated orphan drug in the USA and is currently in phase II clinical trials.
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\(^3\). 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\(^4,5,6\).

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\(^7,8\). 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\(^7,8\). 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\(^8\).

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\(^8,9\). The initial symptoms of follicular lymphoma include painless swelling in one or more lymph nodes, particularly in the cervical, axillary, inguinal and femoral regions\(^4\). 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)\(^4,9\).

This topic is relevant to:
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%\textsuperscript{9}. The crude incidence of follicular lymphoma in the UK is 3.2 per 100,000 per year\textsuperscript{3}. The median age of diagnosis is between 60 and 65 years\textsuperscript{10} and 92\% of cases occur in patients over the age of 45\textsuperscript{3}.

In England, there were 2,011 new cases of follicular lymphoma (ICD-10 C82) recorded in 2012\textsuperscript{11}. 90\% of patients with follicular lymphoma have stage III or IV disease, and approximately 13\% of these patients relapse each year\textsuperscript{12}. In 2013-14, there were 22,015 admissions for follicular lymphoma (ICD-10 C82) in England, resulting in 14,046 bed-days and 22,551 finished consultant episodes\textsuperscript{13}. In 2010, NICE estimated 11,412 patients in England had follicular lymphoma, of whom 10,271 were estimated to have stage III-IV disease, and 1,326 patients were thought to relapse in any one year\textsuperscript{14}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**Other Guidance**

- European Society for Medical Oncology. ESMO Consensus Guidelines: Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukaemia (CLL). 2013\textsuperscript{16}.
- European Society for Medical Oncology. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2011\textsuperscript{17}.
- British Committee for Standards in Haematology. Best practice in lymphoma diagnosis and reporting. 2010\textsuperscript{18}.
- British Committee for Standards in Haematology. Best practice in lymphoma diagnosis and reporting – specific disease appendix. 2010\textsuperscript{19}.
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\textsuperscript{17}. 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 follicular lymphoma in many years\textsuperscript{7}. Current treatment strategies include\textsuperscript{7,17,20}:

- 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.
- Pixantrone may be used if the follicular lymphoma has transformed to DLBCL.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02038946, CA209-140, EudraCT 2013-003645-42; nivolumab; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Bristol-Myers Squibb.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trials registry\textsuperscript{1}, manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada, Australia and Singapore.</td>
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<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
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<tr>
<td>Participants</td>
<td>n=90 (planned); over 18 years old. Relapsed or refractory follicular lymphoma with ≥2 prior lines of treatment (must include CD20 antibody and/or alkylating agent); grade 1, 2 or 3a follicular lymphoma without pathological evidence of transformation; ECOG\textsuperscript{a} performance status of 0 or 1; no central nervous system lymphoma; no history of interstitial lung disease; no autoimmune disease; no prior allogeneic stem cell transplant; prior autologous stem cell transplant must be &gt;12 weeks prior to first dose of study drug.</td>
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<tr>
<td>Schedule</td>
<td>Participants receive nivolumab 3mg/kg IV every 2 weeks until disease progression or discontinuation due to toxicity.</td>
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<td>Follow-up</td>
<td>Participants will be followed-up until death or the conclusion of the study.</td>
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<tr>
<td>Primary outcome</td>
<td>Overall response rate (ORR) as determined by Immune-Related Response Criteria (IRRC) according to revised IWG Criteria for non-Hodgkin lymphoma.</td>
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<td>Secondary outcomes</td>
<td>Duration of response, complete remission (CR) and duration of CR, partial remission (PR) and duration of PR, and progression-free survival; all based on IRRC assessments; ORR based on investigator assessments.</td>
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<tr>
<td>Expected reporting date</td>
<td>Estimated study completion date reported as July 2017.</td>
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\textsuperscript{a} Eastern Cooperative Oncology Group.
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ESTIMATED COST and IMPACT

COST

The company state a 4ml vial (10mg/ml) of nivolumab costs £439. Dosing at 3mg/kg would cost £2,634 per patient per dose b.

IMPACT - SPECULATIVE

Impact on Patients and Carers

☑ Reduced mortality/increased length of survival
☐ Other
☐ Reduced symptoms or disability
☐ No impact identified

Impact on Health and Social Care Services

☐ Increased use of existing services
☐ Re-organisation of existing services
☐ Other
☐ Decreased use of existing services
☐ Need for new services
☐ None identified

Impact on Costs and Other Resource Use

☐ Increased drug treatment costs
☐ Other increase in costs
☑ Other: uncertain unit cost compared to existing alternative therapies.
☐ Reduced drug treatment costs
☐ Other reduction in costs
☐ None identified

Other Issues

☐ Clinical uncertainty or other research question identified
☑ None identified

REFERENCES

2 electronic Medicines Compendium. OPDIVO 10 mg/mL concentrate for solution for infusion. https://www.medicines.org.uk/emc/medicine/30476

b Average adult bodyweight 77.3kg (Health survey for England, 2013). Assumes wastage.