Ibrutinib (Imbruvica) with rituximab for Waldenström’s macroglobulinaemia – untreated or previously treated patients

NIHR HSRIC ID: 10945

Lay summary

Ibrutinib is a new drug to treat Waldenström's macroglobulinaemia, which is a rare type of slow growing cancer called non-Hodgkin lymphoma. It develops when a type of white blood cells, called plasma cells, become abnormal and grow out of control. Ibrutinib is taken as a tablet in combination with a chemotherapy drug called rituximab. Some studies have suggested this combination may offer a useful additional treatment option for patients with Waldenström's macroglobulinaemia.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Waldenström’s macroglobulinaemia: relapsed or refractory – untreated or previously treated; in combination with rituximab.

TECHNOLOGY

DESCRIPTION

Ibrutinib (Imbruvica; PCI 32765) is an orally-active, small molecule, selective irreversible Bruton’s tyrosine kinase (Btk) inhibitor. Survival and progression of mature B-cell malignancies depend on signals from the B-cell antigen receptor, and Btk is a critical signalling kinase in this pathway. Ibrutinib irreversibly binds to Btk thus inhibiting B-cell proliferation and survival through specific active-site occupancy. In the phase III clinical trial, participants in the main experimental treatment arm received ibrutinib 420mg orally each day in combination with rituximab 375mg/m² intravenously (IV) weekly for 4 weeks.

Ibrutinib is licensed in the EU for the treatment of adult patients with:

- Waldenström’s macroglobulinaemia (monotherapy for patients who have received at least one prior therapy or as first line treatment for patients in whom chemoinmunotherapy is unsuitable).
- Relapsed or refractory mantle cell lymphoma.
- Chronic lymphocytic leukaemia (first line).
- Chronic lymphocytic leukaemia (monotherapy or in combination with bendamustine and rituximab for patients who have received at least one prior therapy).

Very common (≥10%) reported adverse events include pneumonia, upper respiratory tract, skin and urinary tract infections, sinusitis, neutropenia, thrombocytopenia, anaemia, dizziness, headache, haemorrhage, epistaxis, bruising, petechiae, diarrhoea, vomiting, stomatitis, nausea, constipation, rash, arthralgia, musculoskeletal pain, pyrexia and peripheral oedema.

Ibrutinib is also in phase III development for non-Hodgkin’s lymphoma (NHL) and pancreatic cancer. It is in phase II development for hairy cell leukaemia, follicular lymphoma, mantle cell lymphoma, breast cancer, acute myeloid leukaemia, central nervous system lymphoma, and mucosa-associated lymphoid tissue lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, ibrutinib with rituximab will provide an additional treatment option for patients with Waldenström’s macroglobulinaemia.

DEVELOPER

Janssen-Cilag Ltd and Pharmacyclics.

AVAILABILITY, LAUNCH OR MARKETING

Ibrutinib is a designated orphan drug in the EU and already has Marketing Authorisation in the UK for treating adult patients with Waldenström’s macroglobulinaemia who have
received at least one prior therapy, or as first line treatment for patients in whom chemo-immunotherapy is unsuitable.

Ibrutinib in combination with rituximab for Waldenström’s macroglobulinaemia is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Waldenström’s macroglobulinaemia (WM) is a chronic lymphoproliferative disorder characterised by aberrant production of monoclonal immunoglobulin (IgM) in the setting of histological evidence of lymphoid malignancy, most commonly lymphoplasmacytic lymphoma\(^6\). WM is a low grade (slow growing) form of NHL. Low grade or ‘indolent lymphomas’ make up less than 2% of lymphomas. They usually affect people over the age of 65 years and are slightly more common in men than women. In WM, high levels of IgM increase blood viscosity\(^8\), and WM was originally described as a clinical syndrome related to symptoms caused by hyperviscosity\(^7\). The understanding of WM has evolved with the recognition that patients with WM present along a continuum. The diagnosis of WM requires unequivocal evidence of bone marrow infiltration by the tumour together with an IgM monoclonal protein\(^8\). WM patients may be asymptomatic, they may present with symptoms related to effects of tumour infiltration (e.g. cytopenias, organomegaly), and/or they may present with features attributable to the monoclonal protein (e.g. cold agglutinins, autoimmune haemolytic anaemia, or peripheral neuropathy)\(^5\).

CLINICAL NEED and BURDEN OF DISEASE

WM is relatively rare, with an age standardised incidence rate of 0.55 per 100,000 per year in the UK\(^8\); over 400 patients may be diagnosed each year in the UK\(^9\). The incidence appears to be higher in those from White ethnic groups. WM is typically a disease of the elderly with a median age at presentation of over 70 years\(^10\). Published reports suggest a median survival of approximately 5 years from the time of diagnosis\(^11\). Young patients with WM (<50 years) have a longer median survival (13-14.8 years) and need special consideration if longevity is to be secured\(^12,a\). In rare instances, WM progresses to multiple myeloma\(^13\).

In 2014-15, there were 5,329 admissions due to WM (ICD10 C88.0) in England resulting in 2,580 bed days and 5,455 finished consultant episodes\(^14\). In 2014, there were 264 newly diagnosed cases of WM registered in England\(^15\) and 76 deaths from WM were registered in England and Wales during 2014\(^16\).

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


\(^a\) Expert personal communication.
**NHS England Policies and Guidance**

This topic is relevant to:


**Other Guidance**

- European Society for Medical Oncology. Waldenström’s macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2013\(^\text{17}\).

**CURRENT TREATMENT OPTIONS**

There is no single accepted treatment for WM. The British Committee for Standards in Haematology guidelines recommend treatment with a combination regimen including rituximab and either cladribine, bendamustine, dexamethasone (plus cyclophosphamide) or fludarabine (with or without cyclophosphamide)\(^\text{10}\). Chlorambucil monotherapy is also recommended for those people who cannot tolerate other more intensive treatments. Choice of treatment depends on a variety of clinical factors, including grade of disease, kidney function, co-morbidities and whether a person is suitable for stem cell transplantation. Patients treated with existing regimens generally achieve a partial response which lasts for a time before the disease relapses\(^\text{18}\). Patients should receive therapy only if they have symptoms or signs related to WM and/or specific laboratory abnormalities; therapy should not be based solely on the serum monoclonal protein level\(^\text{19}\).

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02165397; ibrutinib vs placebo, both in combination with rituximab alone, or ibrutinib alone; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Pharmacynics.</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(^3).</td>
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<tr>
<td>Location</td>
<td>EU (including 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=180 (planned); aged ≥18 years; untreated or previously treated for WM; centrally confirmed clinicopathological diagnosis of WM; measureable disease defined as serum monoclonal IgM &gt;0.5 g/dL; symptomatic disease meeting ≥1 of the recommendations from the Second International Workshop on Waldenström macroglobulinemia for requiring treatment; haematological and biochemical values within protocol-defined limits; Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.</td>
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Schedule

Randomised to ibrutinib 420mg (3 x 140mg) administered orally once daily in combination with rituximab 375mg/m² IV weekly for 4 weeks, followed by a second 4 weekly rituximab course after a 3 month interval; or placebo (3 capsules) administered orally once daily in combination with rituximab 375mg/m² IV weekly for 4 weeks, followed by a second 4 weekly rituximab course after a 3 month interval; or ibrutinib 420mg (3 x 140mg) administered orally once daily continuously (non-randomised substudy).

Follow-up

Active treatment until evidence of progressive disease or no longer tolerated by the subject.

Primary outcome/s

Progression Free Survival (PFS) assessed by independent review committee for up to 3 years after last subject is randomised.

Secondary outcome/s

Overall Response Rate (ORR); time to next treatment; Overall Survival (OS); haematological improvement measured by haemoglobin; safety.

Expected reporting date

Study completion date reported as January 2019.

ESTIMATED COST and IMPACT

COST

Ibrutinib is already marketed in the UK for the treatment of chronic lymphocytic leukaemia, mantle-cell lymphoma, and WM. The cost at list price of a pack of 90 x 140mg ibrutinib tablets is £4,59920. Rituximab is not currently licensed for the treatment of WM; however it is licensed for several other haematological malignancies. The cost of 2 vials of rituximab (100mg/10ml) is £349.2520.

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 - the use of this agent in the WM setting is not expected to cause additional resource requirements as the drug is simply dispensed by the pharmacy for oral consumption. No special training of NHS staff is required, and no additional resources requirements are anticipatedb.

b Expert personal communication.
Other Issues

☐ Clinical uncertainty or other research question  ☒ None identified

REFERENCES