Ibrutinib for relapsed or refractory mantle cell lymphoma

SUMMARY

Ibrutinib is intended to be used as therapy for the treatment of relapsed or refractory mantle cell lymphoma (MCL) and acts by irreversibly inhibiting Bruton’s Tyrosine Kinase (BTK), resulting in the inhibition of B-cell proliferation and survival. If licensed, it would offer an additional treatment option for patients with relapsed or refractory mantle cell lymphoma.

MCL is a rare, aggressive type of non-Hodgkin lymphoma (NHL). It comprises 5-10% of newly diagnosed cases of NHL with approximately 500 new cases diagnosed each year in the UK. The peak age of diagnosis is 65 or over and approximately 75% of patients present with advanced-stage disease. Although MCL often responds to initial treatment, most patients will relapse after a short remission period. The median overall survival time for MCL is shorter than that seen in other lymphomas, at approximately 3-5 years. Approximately 30% of patients have complete response to current treatments.

MCL is usually treated with combination chemotherapy and rituximab, or stem cell transplant. However, as there is no standard of care for relapsed MCL, treatment will depend upon patient age, performance status, bone marrow reserve and initial therapy. Ibrutinib is currently in a phase III clinical trial comparing its effect on progression free survival against treatment with temsirolimus. This trial is expected to complete in 2014.
TARGET GROUP

- Mantle cell lymphoma (MCL): relapsed or refractory.

TECHNOLOGY

DESCRIPTION

Ibrutinib (PCI-32765) covalently binds to, and irreversibly inhibits, Bruton’s Tyrosine Kinase (BTK), resulting in the inhibition of B-cell proliferation and survival as well as inhibition of B-cell migration and homing. Ibrutinib is intended to be used as treatment for patients with relapsed or refractory mantle cell lymphoma (MCL). In phase III clinical trials, ibrutinib is administered orally at 560mg once daily as monotherapy\(^1\).

Ibrutinib is also in phase III trials for chronic lymphocytic leukaemia (as monotherapy in newly diagnosed elderly patients and as both combination and monotherapy in patients with relapsed or refractory disease), mantle-cell lymphoma (combination in newly diagnosed patients), diffuse large B-cell lymphoma (combination for newly diagnosed non-GCB type patients and relapsed refractory), follicular lymphoma (combination, relapsed setting) and in phase II trials for diffuse large B-cell lymphoma (monotherapy, second or subsequent line), multiple myeloma (monotherapy or in combination, relapsed and/or refractory) and Waldenstrom’s macroglobulinemia.

INNOVATION and/or ADVANTAGES

If licensed, ibrutinib will offer an additional treatment option, as oral therapy, for patients with relapsed or refractory mantle cell lymphoma.

DEVELOPER

Janssen and Pharmacyclics.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

MCL is a rare, aggressive type of non-Hodgkin lymphoma (NHL). It is a cancer of the lymphatic system affecting B-cells. Although MCL begins in the mantle zone of lymph nodes (the outer ring of lymphocytes), lymphoma cells can accumulate, enter the lymphatic system and bloodstream, and spread to other lymph nodes or tissues such as the spleen, liver, bone marrow, or gastrointestinal tract\(^2,3\). MCL appears as a low grade lymphoma but may behave like a high grade lymphoma and is often widespread when diagnosed. The most common symptom is one or more painless swellings in the neck, axilla or groin. Other general symptoms of NHL include heavy sweating at night, fever and weight loss. MCL that has spread to the gastrointestinal tract may also cause symptoms such as diarrhoea and nausea\(^4,5\).
**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to: Improving Outcomes: A Strategy for Cancer (2011).

**CLINICAL NEED and BURDEN OF DISEASE**

MCL comprises 5-10% of newly diagnosed cases of NHL with approximately 500 new cases diagnosed each year in the UK\(^4,8\). The peak age of diagnosis is 65 or over. Patients are predominantly male (ratio M/F: 4:1) and approximately 75% of patients present with advanced-stage disease\(^7,8\). Although MCL often responds to initial treatment, most patients will relapse after a short remission period\(^9,10\). The median overall survival time for MCL is shorter than that seen in other lymphomas, at approximately 3-5 years\(^7\). Approximately 30% of patients have complete response to current treatments\(^7\). Two-hundred and thirty six deaths from MCL were registered in England and Wales during 2011 (ICD-10 C83.1)\(^11\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma (ID609). Suspended Feb 2013\(^12\).
- NICE technology appraisal in development. Lymphoma (non-Hodgkin’s) bendamustine (with rituximab) (ID434). Expected July 2014\(^13\).
- NICE technology appraisal in development. Lymphoma (non-Hodgkin’s, relapsed, refractory) pixantrone (monotherapy) (ID414). Last updated July 2013\(^14\).
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV non-Hodgkin’s lymphoma: review of technology appraisal guidance 37 (TA137). February 2008\(^15\).
- NICE cancer service guidance. Healthcare services for haematological cancer (CSGHO). October 2003\(^17\).

**Other Guidance**

- British Committee for Standards in Haematology. Guidelines for the investigation and management of mantle cell lymphoma. September 2012\(^18\).
- British Committee for Standards in Haematology. Royal College of Pathologists. Best practice in lymphoma diagnosis and reporting; specific disease appendix. April 2012\(^19\).

**EXISTING COMPARATORS and TREATMENTS**

MCL is usually treated with combination chemotherapy or stem cell transplant. However, as there is no standard of care for relapsed MCL, treatment will depend upon patient age, performance status, bone marrow reserve and initial therapy\(^18\).

For the first line treatment of MCL in younger patients (generally under 65), high-dose cytarabine (Ara-C) and rituximab containing regimens, followed by autologous stem cell
transplant (ASCT) is considered the standard of care\textsuperscript{18, a}. For older patients or those not suitable for intensive chemotherapy and ASCT, chemotherapy in combination with rituximab is recommended\textsuperscript{18}. Chemotherapy options include\textsuperscript{18, 20}:

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) – most commonly used combination in the UK\textsuperscript{21, b}.
- FCR (fludarabine, cyclophosphamide, and rituximab).
- R-CVP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone).
- R-bendamustine
- R-chlorambucil
- Other fludarabine containing regimens.

For patients with relapsed MCL, there is no gold standard treatment. The following options may be considered\textsuperscript{18}:

- Rituximab
- Bortezomib.
- Temsirolimus.
- Combination chemotherapy.
- Allogeneic stem cell transplantation in younger, fit patients.

Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) is not widely used in the UK as it is considered too toxic for most patients\textsuperscript{22} and is not recommended by guidelines for use at relapse due to high induction mortality\textsuperscript{18}. Also, guidelines do not recommend the use of flavopiridol and enzastaurin for relapsed patients due to inadequate response rates\textsuperscript{18}.

**Efficacy and Safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01833039, PCI-32765MCL4001, CR101862; ibrutinib; phase IV.</td>
<td>Janssen Biotech, Inc.</td>
<td>Ongoing.</td>
<td>Trial registry\textsuperscript{22}.</td>
<td>USA and Puerto Rico.</td>
<td>Uncontrolled, single arm.</td>
<td>n=250 (planned); aged ≥18 years; MCL; progression following prior therapy.</td>
<td>Ibrutinib, 560mg oral once daily.</td>
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<tr>
<td>NCT01646021, 2012-000601-74, PCI-32765MCL3001, CR100848; ibrutinib vs temsirolimus; phase III.</td>
<td>Janssen Research and Development, LLC.</td>
<td>Ongoing.</td>
<td>Trial registry\textsuperscript{1}.</td>
<td>EU (incl UK), Canada and other countries.</td>
<td>Randomised, active-controlled.</td>
<td>n=280 (planned); aged ≥18 years; MCL; received at least 1 prior rituximab-containing chemotherapy regimen; relapse or disease progression following last treatment.</td>
<td>Randomised to ibrutinib 560mg oral once daily continuously in 21 day cycles; or temsirolimus 175mg IV on days 1, 8, and 15.</td>
</tr>
<tr>
<td>NCT01804686, 2012-004225-24, PCI-32765CAN3001, CR100955; ibrutinib; phase IIIb extension.</td>
<td>Janssen Research and Development, LLC.</td>
<td>Ongoing.</td>
<td>Trial registry\textsuperscript{23}.</td>
<td>EU (incl UK) and USA.</td>
<td>Uncontrolled, single arm.</td>
<td>n=200 (planned); aged ≥18 years; currently in a ibrutinib clinical study considered completed; ≥6 months of treatment with ibrutinib.</td>
<td>Ibrutinib 560mg, 420mg, 280mg, or 140mg (according to current dosing regimen in parent trial), oral, once daily.</td>
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</tbody>
</table>

\textsuperscript{a} Expert personal communication.
<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Active treatment will continue until disease progression or unacceptable toxicity, then 9 months follow up.</th>
<th>Active treatment until disease progression or unacceptable toxicity. Follow up until disease progression, death or clinical cut-off.</th>
<th>Ibrutinib is administered until disease progression or unacceptable toxicity. Active treatment period 3 years maximum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome/s</td>
<td>Treatment emergent adverse experiences (AEs).</td>
<td>Progression free survival (PFS).</td>
<td>AEs.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>-</td>
<td>Overall response rate (ORR); overall survival (OS); 1-year survival rate; duration of response; time-to-next treatment; AEs; pharmacokinetics; Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) scale score; EuroQol (EQ-5D-5L) index score; medical resource utilisation; biomarkers that alter B-cell receptor signalling or activate alternative signalling pathways; resistance biomarkers from bone marrow.</td>
<td>Change in disease status.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as May 2014.</td>
<td>Primary completion date reported as Aug 2014.</td>
<td>Estimated primary completion date reported as Jan 2016.</td>
</tr>
<tr>
<td>Trial</td>
<td>NCT01599949, 2012-000711-88, PCI-32765MCL2001, CR100847; ibrutinib; phase II.</td>
<td>NCT01236391, PCYC-1104-CA, PCI-32765; ibrutinib; phase II.</td>
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<tr>
<td>Sponsor</td>
<td>Janssen Research and Development, LLC.</td>
<td>Pharmacyclics.</td>
<td></td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry&lt;sup&gt;24&lt;/sup&gt;.</td>
<td>Trial registry&lt;sup&gt;25&lt;/sup&gt;, publication&lt;sup&gt;26&lt;/sup&gt;.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Israel, Puerto Rico and Russia.</td>
<td>EU (incl UK) and USA.</td>
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<tr>
<td>Participants</td>
<td>n=120 (planned); aged ≥18 years; MCL; received ≥1 prior rituximab-containing regimen (but no more than 5 prior regimens); received ≥2 cycles of bortezomib therapy; disease progression during or after bortezomib therapy.</td>
<td>n=111; aged ≥18 years; MCL; relapsed or refractory; failed to achieve at least partial response with, or had disease progression following the most recent treatment; ≥1 but ≤5 prior treatment regimens; failed prior bortezomib regimen or bortezomib naive.</td>
<td></td>
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<tr>
<td>Schedule</td>
<td>Ibrutinib 560mg oral once daily.</td>
<td>Ibrutinib 560mg oral once daily.</td>
<td></td>
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<tr>
<td>Follow-up</td>
<td>Active treatment until disease progression, unacceptable toxicity, or study end; follow up 2 years.</td>
<td>Active treatment until disease progression or unacceptable toxicity. Follow up until disease progression or start of another anti-cancer treatment.</td>
<td></td>
</tr>
</tbody>
</table>
Primary outcome/s | ORR. | ORR.
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Secondary outcome/s | OS; PFS; Lym sub-scale; EQ-5D-5L index; pharmacokinetics; AEs; ORR. | Duration of response; time to response; OS; PFS; AEs; pharmacokinetics; EORTC QLQ-30.
Key results | - | Response rate, 68%; complete response rate, 21%; partial response rate, 47% (prior treatment with bortezomib reportedly had no effect on response rate); estimated median response duration, 17.5 months; estimated median PFS, 13.9 months; median OS was not reached; estimated OS rate was 58% at 18 months.
Adverse effects (AEs) | - | Most AEs observed were grade 1/2, without attribution to the study drug. The most common treatment-related, non-haematologic AEs were diarrhoea (50%), fatigue (41%), and nausea (31%). The most common grade ≥3 infection was pneumonia in 6% of patients. Grade 3 or higher haematological events included neutropenia (16% of patients), thrombocytopenia (11%), and anaemia (10%).
Expected reporting date | Primary completion date reported as Sep 2013. | -

ESTIMATED COST and IMPACT

COST

The cost of ibrutinib is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: No impact identified

Impact on 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

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other: uncertain unit cost compared to existing treatments.
- None identified
Other Issues

☐ Clinical uncertainty or other research question  ☐ None identified

REFERENCES


