Mogamulizumab for relapsed or refractory cutaneous T-cell lymphoma – second and subsequent lines

LAY SUMMARY

Cutaneous T-cell lymphoma is a rare form of non-Hodgkin lymphoma, a cancer affecting one type of white blood cell. At the beginning, lymphoma can be difficult to diagnose, but as the lymph nodes get bigger, a painless swelling in the neck, armpit or groin is sometimes noticed as well as raised, rash-like, itchy patches or lumps on the skin. By the time they are diagnosed, the lymphoma has often spread widely around the body. The main treatment is chemotherapy but as this disease mainly affects older people, not all patients are well enough to manage this, and the disease often returns after treatment.

Mogamulizumab is a new drug for the treatment of cutaneous T-cell lymphoma that is injected into the bloodstream weekly or fortnightly. It is being studied at the moment to see how well it works and whether it is safe to use. If it is licensed for use in the UK, it would be a new treatment option that could improve the life expectancy of patients whose lymphoma has returned after their first treatment has stopped working.

NIHR HSRIC ID: 9717
TARGET GROUP

- Cutaneous T-cell lymphoma (CTCL): relapsed or refractory – second and subsequent lines; following skin directed therapy and one systemic agent\(^a\).

TECHNOLOGY

DESCRIPTION

Mogamulizumab (Poteligeo; AMG 761; KW 0761) is a first-in-class humanised anti-CC chemokine receptor type 4 (CCR4) monoclonal antibody that directly targets and inhibits T cells expressing CCR4 and also demonstrates enhanced antibody-dependent cell-mediated cytotoxic (ADCC) activity to CCR4 expressing cells\(^1,2\). The inhibition of CCR4 expressing T-regulatory cells has indirect anti-tumour effects. Mogamulizumab is administered by intravenous (IV) infusion once a week for four weeks and then at least every two weeks thereafter until disease progression\(^a\). In a phase III clinical trial, mogamulizumab is administered at 1mg/kg\(^3\).

Mogamulizumab does not currently have Marketing Authorisation in the EU for any indication. Mogamulizumab is in phase II clinical trials for relapsing/refractory adult T cell leukaemia/lymphoma and in phase I clinical trials for locally advanced or metastatic solid tumours.

INNOVATION and/or ADVANTAGES

If licensed, mogamulizumab will offer an additional treatment option for CTCL that is relapsed or refractory to skin directed therapy and one first line systemic therapy\(^b\). Expert opinion stresses the urgent need for further therapies for CTCL as there are currently no curative therapies and no new therapies have been approved since 1999\(^b\). Expert opinion also notes that there is a current significant unmet medical need due to the high degree of chemo-resistance in intermediate and advanced stages of disease\(^b\).

DEVELOPER

Kyowa Kirin International (part of Kyowa Hakko Kirin Co Ltd).

AVAILABILITY, LAUNCH OR MARKETING

Mogamulizumab is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

CTCL is a rare type of non-Hodgkin lymphoma (NHL) that affects the skin. It is caused by the uncontrolled growth of T-lymphocytes\(^4\). Many types of CTCL start as flat red patches (tumours) on the skin, which may be itchy and sometimes painful\(^2\). Some people with CTCL

\(^a\) Company provided information.

\(^b\) Expert personal opinion.
experience swelling of the lymph nodes\textsuperscript{4,5}. Early stage CTCL is typically indolent; some patients with early-stage CTCL do not progress to later stages at all, while others progress rapidly, with the cancer spreading to lymph nodes and/or internal organs\textsuperscript{6}.

The most common subtype of CTCL is mycosis fungoides (MF), which affects around half of those diagnosed with CTCL\textsuperscript{4,6}. Starting as an irregular shaped area of dry or scaly skin, MF is a very slow growing (low grade) form of CTCL\textsuperscript{4}. Patches may appear anywhere on the body but are commonly found on the chest, abdomen, back and buttocks\textsuperscript{4}. These abnormal areas of skin may form scaly raised patches, called plaques\textsuperscript{4}. In a small number of people, raised lumps (tumours) can also appear. In rare advanced cases of the disease the skin appears red, swollen and sore all over, and is termed erythrodermic mycosis fungoides\textsuperscript{4}.

Sézary syndrome (SS) is a less frequent erythrodermic variant of CTCL with leukaemic involvement\textsuperscript{7}. SS occurs in about 3\% of patients with CTCL and is diagnosed by the presence of Sézary cells (malignant T cells with cerebriform nuclei) in the blood in addition to erythroderma\textsuperscript{8}. Patients present with bright red skin that is usually pruritic. Patients often have fine scaling with thickened, scaly, and fissured palms and soles\textsuperscript{9}.

\textbf{NHS or GOVERNMENT PRIORITY AREA}

This topic is relevant to:


\textbf{CLINICAL NEED and BURDEN OF DISEASE}

The annual UK incidence of cutaneous lymphoma is around 0.4 per 100,000 population, and approximately 66\% of cutaneous lymphomas are of T-cell origin (CTCL) (approximately 0.27 per 100,000 population)\textsuperscript{4,11}. In England in 2014-15, there were 301 hospital admissions due to MF and 178 due to SS, equating to 333 and 207 finished consultant episodes and 1,134 and 448 bed days (ICD-10, C84.0 and C84.1), respectively\textsuperscript{10}. The majority of people with CTCL are aged between 40 and 60 years old, and it is twice as common in men than women\textsuperscript{4}.

Prognosis in MF and SS is related to age at presentation (worse if aged >60 years), advanced skin and overall clinical stage of the disease, increased serum lactate dehydrogenase levels, and large-cell transformation. Some clinical variants of MF have a better prognosis (such as hypopigmented MF, MF with lymphomatoid papulosis and poikilodermatous MF), whereas the folliculotropic variant of MF has a worse prognosis\textsuperscript{11,c}. MF is incurable in most patients, with the exception of those with stage 1A disease\textsuperscript{12}.

Approximately 30\% of patients present with advanced disease and of the 70\% presenting with early stage around 25\% progress to advanced disease\textsuperscript{13,d}. In England and Wales during 2014, 21 deaths from CTCL (MF) and 5 deaths from SS were registered\textsuperscript{14}.

\textsuperscript{c} Company provided information.
\textsuperscript{d} Expert personal opinion.
Expert opinion estimates that a maximum 50% of CTCL patients will be eligible for treatment with mogamulizumab.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**Other Guidance**


**CURRENT TREATMENT OPTIONS**

There is currently no curative treatment for CTCL. Response durations are frequently short lived and patients are treated with multiple consecutive therapies until loss of response. Patients with early stage disease are frequently treated with skin directed therapy. Patients with refractory disease may require systemic therapy. A number of treatment options can be used for CTCL, either alone or in combination:

- **Skin directed therapy**: appropriate for early stages; includes options such as topical steroids, psoralen ultraviolet light A (PUVA), narrow-band ultraviolet light B (UVB), superficial radiotherapy (for small areas of affected skin), total skin electron beam therapy (TSEB), topical retinoids (bexarotene gel) and topical cytostatic agents (e.g. mechlorethamine, nitrogen mustard, carmustine).
- **Extracorporeal photopheresis** is a safe and effective treatment for erythrodermic MF and SS.

Quality of life may be reduced from the debilitating skin lesions, severe pruritus, pain and lethargy. Symptomatic treatments of such symptoms may be required.

Systemic therapies for advanced or refractory disease include:

- **Chemotherapy**: methotrexate, gemcitabine, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), chlorambucil, liposomal doxorubicin, and purine analogues (deoxycoformycin, 2-chlorodeoxyadenosine, fludarabine).
- **Biological response modifiers**: interferon alpha, retinoids (bexarotene), and denileukin diftitox. Bexarotene and interferon alpha are the most common first line systemic agents.
- **Immunotherapy**: alemtuzumab (a CD52 antigen inhibitor).
- **Extracorporeal photopheresis** (ECP).

* Expert personal opinion.
Radiotherapy may also be used at more advanced stages for plaques and tumours.

- Histone deacetylase (HDAC) inhibitors (vorinostat\(^1\) and romidepsin).
- Allogeneic stem cell transplant (for patients achieving a near complete remission).

## EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01728805, 0761-010; mogamulizumab vs vorinostat(^1); phase III.</th>
<th>NCT00888927, 0761-001; mogamulizumab; phase I/II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Completed.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^1).</td>
<td>Publication &quot;&quot;, trial registry &quot;&quot;, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Australia and Japan.</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Non-randomised, uncontrolled.</td>
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<tr>
<td>Participants</td>
<td>n=373 (planned); aged 18 yrs and older; MF or SS; stage IB, IIA, IIB, III or IV; at least one prior course of systemic therapy.</td>
<td>n=42; aged 18 yrs and older; mycosis fungoides (MF) or Sézary syndrome (SS); failed ≥1 prior systemic therapy.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to mogamulizumab 1mg/kg IV once a wk for 4 wks, then every other wk; or vorinostat 400mg orally once daily.</td>
<td>Phase I: mogamulizumab IV once a wk for 4 wks; starting dose 0.1mg/kg, succeeding doses 0.3 and 1.0mg/kg based on “3 plus 3” dose-escalation scheme. Phase II: mogamulizumab IV at maximum tolerated dose from phase I for up to 4 additional infusions given fortnightly. Then duration of response is determined and the pt may continue therapy after consultation with an investigator.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment 36 mths or until disease progression, follow-up 36 mths.</td>
<td>Phase I: 2-wks observation. Phase II: until disease progression or withdrawal.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Progression free survival (PFS).</td>
<td>Maximum tolerated dose.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Pruritus evaluation (Likert scale &amp; Itchy QoL), overall response rate and quality of life assessments (Skindex-29, FACT-G and EQ-5D-3L).</td>
<td>Best response, time to progression, PFS and duration of response.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>42 patients received at least 1 dose and were included in the safety analysis. The maximum tolerated dose was 1.0 mg/kg. 38 patients were evaluable for efficacy. Best global response was 36.8%, with a higher rate in SS (47.1%) compared with MF (28.6%). Median time to response was 31.5 days, median PFS was 11.4 months, and median duration of response was 10.4 months. Overall response rate was 36.8%.</td>
</tr>
</tbody>
</table>

\(^1\) Vorinostat is not licensed in the EU, only in the USA.
No dose-limiting toxicities were observed. Most frequent AEs included nausea (31.0%), chills (23.8%), infusion-related reaction (21.4%), headache (21.4%), pyrexia (19.0%), fatigue (16.7%), and cutaneous drug eruption (16.7%). Twenty-four serious AEs were reported by 10 patients (23.8%) including hypotension, abdominal pain, and secondary T-cell malignancy.

**ESTIMATED COST and IMPACT**

**COST**

The cost of mogamulizumab is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Reduced symptoms or disability: symptomatic relief of itch. Improvement in PFS.¹
- 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
  - None identified: treatment could be delivered in any specialised CTCL centres without a requirement for additional services.²
- Other

**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

¹ Expert personal communication.
² Expert personal communication.
Other Issues

☑ Clinical uncertainty or other research question identified: It is unclear whether the drug will work as well for high tumour burden patients with bulky transformed disease compared to those with low grade but extensive disease (stage III/IVA1). Research is also needed into whether this drug will be more effective as a combination therapy and which combination is most effective.

☐ None identified

REFERENCES


h Expert personal communication.