Mogamulizumab for adult T-cell leukaemia/lymphoma – second and subsequent line

SUMMARY

Mogamulizumab is intended to be used as second and subsequent line therapy for the treatment of adult T-cell leukaemia/lymphoma. If licensed, it would provide an additional treatment option for this patient group, who currently have limited treatment options and a poor prognosis in many cases. Mogamulizumab is a defucosylated, humanised monoclonal antibody targeting C-C chemokine receptor 4. It is not currently licensed in the EU for any indication.

Mature T-cell lymphomas account for around 6% of all non-Hodgkin lymphomas, the sixth most common cancer type in the UK. Adult T-cell lymphomas account for around 9.6% of all T-cell lymphomas, equating to around 58 new diagnoses per year in the UK. Survival rates vary, depending on subtype. Overall, the 5-year survival rate for adult T-cell lymphoma is estimated to be 14%, however for the acute and lymphomatous subtypes, median survival is less than one year.

Treatment is dependent on subtype, with active monitoring recommended for asymptomatic patients with smouldering or chronic type adult T-cell leukaemia/lymphoma. Where treatment is indicated, current options include chemotherapy regimens, supportive therapy, CNS prophylaxis anti-viral therapies with or without monoclonal antibodies, hematopoietic stem cell transplant, and novel agents (in the context of clinical trials). Mogamulizumab is currently in phase II clinical trials comparing its effect on overall response rate against treatment with the investigators choice of therapy. This trial is expected to complete in late 2015-early 2016.
TARGET GROUP

- Adult T-cell leukaemia/lymphoma (ATLL) – second and subsequent line.

TECHNOLOGY

DESCRIPTION

Mogamulizumab (AMG761; KW0761) is a defucosylated, humanised monoclonal antibody targeting C-C chemokine receptor 4 (CCR4). It selectively binds to and blocks the activity of CCR4, which may inhibit CCR4-mediated signal transduction pathways. Mogamulizumab acts through antibody directed cellular cytotoxicity and its activity is enhanced through antibody engineering. In clinical trials, mogamulizumab was administered via intravenous (IV) infusion at 1mg/kg once weekly for the first 28 days, followed by once every fortnight until disease progression.1

Mogamulizumab is not licensed in the EU for any indication.

Mogamulizumab is in phase II clinical trials for peripheral T-cell lymphoma and in phase III trials for cutaneous T-cell lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, mogamulizumab will provide an additional treatment option for this patient group, who currently have limited treatment options and a poor prognosis in many cases.

DEVELOPER

ProStrakan Limited.

AVAILABILITY, LAUNCH OR MARKETING

Mogamulizumab is a designated orphan drug in the EU and USA and is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

ATLL is a T-cell lymphoma, an aggressive malignancy of mature activated T-cells that can be found in peripheral circulating blood (leukaemia), lymph nodes (lymphoma), or in both.2 There are 4 subtypes: acute (occurring in around 57%); lymphomatous (19%); chronic (19%); and smouldering (5%)3. Symptoms vary, depending on subtype, but commonly include extranodal presentation and constitutional symptoms.4 In acute ATLL, symptoms develop rapidly and include fatigue, skin rash, generalised lymphadenopathy and hepatosplenomegaly. Hypercalcaemia may also occur, which can cause confusion, bone pain, severe constipation, and marked leucocytosis. Patients often have associated T-cell immunodeficiency which predisposes them to opportunistic infections such as

---

1 Expert personal opinion
Pneumocystitis jiroveci pneumonia and Strongyloidiasis. The lymphomatous variant of ATLL presents with enlarged lymph nodes without peripheral blood involvement. The chronic form is slow growing and symptoms include lymphadenopathy, skin rash and fatigue. Smouldering ATLL develops slowly and is characterised by a normal peripheral blood leucocyte count and infiltration of the skin. Chronic and smouldering forms of ATLL progress to the acute form in around 25% of cases. ATLL is associated with infection by the human T-cell lymphotropic virus type 1 (HTLV-1), however less than 5% of people with the virus will develop ATLL. It usually occurs in people from HTLV-1-endemic regions, such as Japan, the Caribbean, South America, Iran and parts of Central Europe. Aggressive forms of ATLL (acute and lymphomatous) carry a very poor prognosis due to intrinsic chemoresistance and severe immunosuppression, whilst the indolent forms (chronic and smouldering) have a better prognosis.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

Non-Hodgkin lymphomas (NHL) represent the sixth most common cancer type in the UK. Mature T-cell lymphomas are an uncommon form, accounting for around 6% of all NHLs, with an age-standardised incidence rate of around 0.9 per 100,000 population and approximately 600 new diagnoses each year. ATLL accounts for around 9.6% of all T-cell lymphomas, equating to approximately 58 new diagnoses per year in the UK. It is generally found in adults (cases in children are extremely rare) and in the UK it is more common in people of Caribbean descent. The median age at diagnosis is around 62 years, with a peak age incidence around a decade earlier in people from the Caribbean. Overall, the 5-year survival rate for ATLL is estimated at 14%. However, survival rates vary among the different subtypes, with 4-year survival rates being estimated at around 5.0% for acute, 5.7% for lymphomatous, 26.9% for chronic, and 62.8% for smouldering. Median survival is less than one year for the acute and lymphomatous subtypes. In 2012-13, there were 494 hospital admissions due to ATLL (ICD-10: C91.5) in England, accounting for 547 finished consultant episodes and 1,663 bed days. In England and Wales, 20 deaths were registered during 2012.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

None identified.
Other Guidance


CURRENT TREATMENT OPTIONS

Treatment is dependent on subtype and prognostic factors such as performance status, lactate dehydrogenase levels, number of involved sites and age. CCR4 expression and TP53 mutation are associated with a poor prognosis. Asymptomatic patients with smouldering or favourable chronic type ATLL should be actively monitored. In spite of increasing understanding of the pathogenesis of ATLL, treatment results remain disappointing. Where treatment is indicated, current options include:

- Chemotherapy – CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), VCAP (combination with vincristine, cyclophosphamide, doxorubicin, prednisolone), AMP (doxorubicin, ranimustine, prednisolone), VECP (vindesine, etoposide, carboplatin).
- Supportive and prophylactic therapy – G-CSF is usually required to support chemotherapy. CNS prophylaxis should be considered.
- Anti-viral therapy – zidovudine and interferon alpha (IFN-α), with or without monoclonal antibodies (anti-CD25, anti-CD4, anti-CD52, anti-CCR4, anti-transferrin receptor, in clinical trials).
- Hematopoietic stem cell transplant.
- Novel agents, in the context of clinical trials – arsenic trioxide, IFN-α; bortezomib.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00920790, 0761-002; mogamulizumab; phase II.</th>
<th>NCT01626664, 0761-009; mogamulizumab vs investigators choice of therapy; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Kyowa Hakko Kirin Company, Limited.</td>
<td>Kyowa Hakko Kirin Pharma, Inc.</td>
</tr>
<tr>
<td>Status</td>
<td>Published.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication, trial registry.</td>
<td>Trial registry.</td>
</tr>
<tr>
<td>Location</td>
<td>Japan.</td>
<td>EU (incl UK), USA, Brazil, and Peru.</td>
</tr>
<tr>
<td>Design</td>
<td>Uncontrolled, single arm.</td>
<td>Randomised, active-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=27; aged ≥20 years; ATLL; acute, lymphoma or unfavourable chronic; CCR4-positive; relapsed following at least one prior chemotherapy regimen.</td>
<td>n=70 (planned); aged ≥18 years; ATLL; acute, lymphoma or chronic; relapsed following at least one prior chemotherapy regimen.</td>
</tr>
<tr>
<td>Schedule</td>
<td>All participants received mogamulizumab, 1mg/kg IV, once weekly for 8 weeks.</td>
<td>Randomised to mogamulizumab, 1mg/kg IV, once weekly for 28 days, then once every other week until progression; or investigators choice of therapy, one of pralatrexate, 30mg/m² IV, weekly until progression, gemcitabine, 1,000mg/m² IV, with oxaliplatin, 100mg/m² IV, both every 2 weeks until progression, or DHAP (dexamethasone, 40mg on days 1-4 of each cycle, with, cisplatin, 100mg/m² IV.</td>
</tr>
</tbody>
</table>

b Expert personal opinion
and cytarabine, 2,000mg/m² IV, every 4 weeks until progression).

Follow-up
Active treatment 8 weeks; follow-up until death.
Active treatment until disease progression; follow-up until death.

Primary outcome/s
Overall response rate (ORR); pharmacokinetics.
ORR.

Secondary outcome/s
Progression-free survival (PFS); overall survival (OS). No quality of life measures included in trial outcomes.
PFS; duration of response; OS; quality of life; immunogenicity.

Key results
ORR, 50% (95% CI, 30%-70%); response according to subtype: acute, 43%; lymphoma, 33%, unfavourable chronic, 83%; median PFS, 5.2 months; median OS, 13.7 months.

Adverse effects (AEs)
AEs ≥10% (%): lymphopenia, 96; infusion reaction 89; fever, 82; leukocytopenia, 67; rash, 63; chills, 59; thrombocytopenia, 52; neutropenia, 52; elevated ALT, 41; elevated AST, 37; tachycardia, 33; hypertension, 30; albuminaemia, 30; reduced haemoglobin, 30; elevated alkaline phosphatase, 22; weight gain, 19; nausea, 19; hyponatraemia, 19; hypoaemia, 19; hypotension, 15; pruritus, 15; elevated y-glutamyl transpeptidase, 15; hypophosphataemia, 15; hyperuricemia, 15; hypercalcemia, 11; hypokalaemia, 11.

Expected reporting date
- Q4 2015-Q1 2016.

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
☐ 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: will require administration and monitoring by specialist centres c ☑ None identified

c Expert personal opinion
### Impact on Costs and Other Resource Use

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

### Other Issues

- Clinical uncertainty or other research question identified: Expert opinion raised several questions regarding this therapy:
  1. What are the immunosuppressive consequences of treatment given the severe immune compromise of these patients?
  2. Will there be any synergies or contraindications with combining with antiviral or chemotherapy regimens?
  3. Can this therapy be regarded an in vivo purging prior to transplantation?
- None identified

### REFERENCES