Masitinib for relapsed or refractory peripheral T-cell lymphoma

LAY SUMMARY

Peripheral T-cell lymphoma is a rare form of lymphoma, a cancer affecting a type of white blood cell called a lymphocyte. At the beginning, the symptoms of lymphoma can be very varied and difficult to diagnose, but as the lymph nodes get bigger, a painless swelling in the neck, armpit or groin is sometimes noticed. The condition generally affects people aged over 60 years of age and it is slightly more common in men than in women. By the time they are diagnosed, the lymphoma has often spread widely around the body. The main treatment is chemotherapy, but not all patients are well enough to manage this and the disease often returns after treatment.

Masitinib is a new drug for the treatment of peripheral T-cell lymphoma that is taken as a tablet twice a day. 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: 9696
TARGET GROUP

- Peripheral T-cell lymphoma: relapsed or refractory — second or subsequent line; in combination with dexamethasone or dexamethasone plus gemcitabine.

TECHNOLOGY

DESCRIPTION

Masitinib (AB1010; masitinib mesilate; masitinib mesylate) is a highly selective tyrosine kinase inhibitor that targets the c-kit, Lyn and Fyn signaling pathways. By combined targeting of these different pathways, masitinib is particularly efficient in controlling mast cell survival, differentiation and degranulation\(^1\). Masitinib has two potential mechanisms of action that may be effective in the treatment of peripheral T-cell lymphoma. Firstly, masitinib is a potent inhibitor of platelet-derived growth factor receptor, an important target in this condition. Secondly, pre-clinical data and clinical experience suggest that masitinib also acts as an immunotherapy through targeting the innate immune system comprising mast cells and macrophages; this may extend survival by controlling the aggressiveness, transformation, and dissemination of tumours\(^2\).

In a phase III clinical trial, masitinib is administered orally at 6.0mg/kg per day, as two divided doses until disease progression or toxicity, in combination with up to 6 cycles for dexamethasone and gemcitabine.

Masitinib is not currently licensed for any other indication and is currently being developed in 13 phase III indications; seven in oncology, three in inflammatory diseases, and three in neurodegenerative diseases. A range of phase II clinical trials are also ongoing, mainly in oncology.

INNOVATION and/or ADVANTAGES

If licensed, masitinib will offer an additional oral treatment option for patients with relapsed or refractory peripheral T-cell lymphoma, a group who currently have few effective therapeutic options available.

DEVELOPER

AB Science.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Peripheral T-cell lymphomas (PTCLs) are a group of rare and aggressive forms of non-Hodgkin lymphoma that develop from T-cells in different stages of maturity\(^3\). Subtypes are dependent on the characteristics of the T-cell, and include anaplastic large cell lymphoma,
angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma and other very rare types of PTCL. Initial symptoms vary, but a painless swelling in the neck, armpit, and groin is often a first sign, caused by enlarged lymph nodes. Other symptoms may include loss of appetite, tiredness, night sweats, unexplained high temperatures and weight loss. Most patients are refractory to first line therapy and there are few effective options for salvage therapy.

**NHS or GOVERNMENT PRIORITY AREA**


**CLINICAL NEED and BURDEN OF DISEASE**

PTCL is the largest group of T-cell lymphomas, accounting for around half of the cases seen and 3.7% of all lymphomas. In 2013, approximately 13,413 people were diagnosed with non-Hodgkin lymphoma in the UK, of whom around 10% (1,341) were diagnosed with PTCL. The condition generally affects people over 60 years of age and incidence is slightly higher in men than in women. Most people have widespread disease at diagnosis, requiring aggressive treatment. The 5-year failure-free and overall survival is about 20%. Experts state that the poor prognosis of these lymphomas is not only related to the lack of therapeutic options but also due to the fact that biologically they are an aggressive disorder. Most patients with PTCL who are fit and under the age of 65 years will receive conventional chemotherapy followed by an autologous transplant. This means that at relapse, therapeutic options are extremely limited. Thus the majority of patients are treated palliatively.

In 2014-15, there were 2,662 hospital admissions due to PTCL (ICD10 C84.4 and C84.5) in England, accounting for 2,904 finished consultant episodes and 7,951 bed days. In 2014, 258 deaths were registered in England and Wales.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

**Other Guidance**

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*Expert personal opinion.*
CURRENT TREATMENT OPTIONS

Relapsing PTCL often follows an aggressive course and patients may develop life-threatening complications. The choice of treatment is dependent on age and fitness, and for elderly and/or unfit patients, treatment will generally be palliative. It is recommended that refractory/relapsed patients are enrolled in clinical trials wherever possible. Current treatment options for relapsed or refractory PTCL include:

- Platinum-based chemotherapy regimens such as DHAP (dexamethasone, cisplatin, cytarabine), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), ICE (ifosfamide, carboplatin, etoposide), and MINE (mesna, ifosfamide, mitoxantrone, etoposide).
- GND — gemcitabine in combination with vinorelbine and doxorubicin.
- Newer agents as monotherapy, such as pralatrexate, romidepsin, bendamustine, brentuximab may have moderate efficacy, but none of them are available in the UK outside the context of a trial.
- Alemtuzumab as a single agent or in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone).
- Radiotherapy.
- Autologous or allogeneic stem cell transplant.

Experts state that there is no standard of care for relapsed PTCL. Treatment options are limited due to the age of the patient and the aggressive nature of the disorder and the prognosis at relapse is extremely poor. Salvage therapies with platinum and ifosfamide may occasionally be considered for elderly patients and single agent gemcitabine, occasionally with steroids, is also an option for older patients.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>AB10004; EudraCT2010-021091-28; masitinib with dexamethasone, gemcitabine with dexamethasone and the combination of masitinib, gemcitabine and dexamethasone, phase II/III trial.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>AB Science.</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; manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=267(planned); age ≥18 years; histologically/cytologically confirmed PCTL using the World Health Organization disease classification 2008; progression of disease after at least 1 previous chemotherapy cycle; minimum 1 bidimensionally measurable disease (more than 1.5cm) according to the Cheson criteria; Ann Arbor stage II–IV; no T-cell prolymphocytic leukaemia; no T-cell large granular lymphocytic leukaemia;</td>
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\(^b\) Expert personal opinion.
no mycosis fungoides; no Sezary syndrome; no primary cutaneous CD30+ T-cell lymphoproliferative disorders; no central nervous involvement of lymphoma; no previous allogeneic stem cell transplantation; no relapse less than three months after an autologous stem cell transplantation; no recent cardiac history (within 6 months).

Schedule
Randomised to: masitinib orally at 6mg/kg/day as two divided doses with dexamethasone 20mg once weekly for 3 out of 4 weeks; dexamethasone 20mg in combination with gemcitabine 1,000mg/m² administered intravenously (IV) once weekly for 3 out of 4 weeks; or masitinib orally at 6mg/kg/day as two divided doses in combination with dexamethasone 20mg and gemcitabine 750mg/m² IV once weekly for 3 out of 4 weeks.

Follow-up
Active treatment until disease progression or toxicity, and up to 6 cycles for dexamethasone and gemcitabine. A follow-up of patients who withdraw from the study will be maintained every 12 weeks until death.

Primary outcome/s
Overall survival.

Secondary outcome/s
Efficacy endpoints: survival at wks 12, 24 and then every 24 wks; median progression free survival (PFS); PFS at wks 12, 24 and then every 24 wks; median time to progression (TTP); TTP at wks 12, 24 and then every 24 wks; response rate at wks 12, 24 and then every 24 wks; best response rate during study treatment. Safety assessment: safety profile in each group using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 classification.

ESTIMATED COST and IMPACT

COST
The cost of masitinib is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers
✓ Reduced mortality/increased length of survival
✓ Reduced symptoms or disability
✓ Other: masitinib either in combination with steroids or in combination with steroids and gemcitabine would be a valuable addition to the treatment options in peripheral T-cell lymphoma. This would specifically be the case for the more elderly patients and those who have already had autologous transplant or are not fit for an intensive regime. Its novel mechanism of action targeting the platelet-derived growth factor receptor makes it unique and promising. It is unlikely that this will be curative but the hope will be that patient outcomes will be improved with minimal toxicity.".

* Expert personal opinion.
**Impact on Health and Social Care Services**

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

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs: None identified
- Other reduction in costs: None identified

**Other Issues**

- Clinical uncertainty or other research question identified: None identified

**REFERENCES**


