Trabectedin (Yondelis) for advanced and/or metastatic translocation-related sarcomas – first line

May 2011

This technology summary 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.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Trabectedin (Yondelis) for advanced and/or metastatic translocation-related sarcomas – first line

Target group
- Translocation-related sarcoma (TRS): advanced and/or metastatic – first line.

Background
Sarcomas are a rare and diverse group of cancers thought to have a common embryological origin that can be broadly divided into those arising in bone and those arising in soft tissue. Soft tissue sarcomas (STS) develop from cells in the supporting tissues of the body, including muscle, fat and blood vessels. They can arise anywhere in the body but most frequently occur in the limbs, with other common sites including the trunk, abdomen and pelvis. Researchers have further classified sarcomas into two main groups: (1) sarcomas with specific genetic alterations on a background of relatively few other chromosomal changes, and (2) sarcomas with no specific genetic alterations on a complex background of numerous chromosomal changes. One third of sarcomas fall into the first group and are characterised by specific recurrent chromosomal translocations. These translocations result in the formation of fusion genes, which in many cases encode deregulated transcription factors.

Technology description
Trabectedin (Yondelis; ecteinascidin 743; ecteinascidin-743; ET 743; ET-743; NSC 684766) is a tetrahydroisoquinoline alkaloid. Trabectedin is thought to act by binding to the DNA minor groove. Its antitumour effect results from interference with the binding of transcription factors and DNA-repair proteins to DNA. In myxoid liposarcoma tumours it is thought to prevent the interaction of the fusion protein (the FUS-CHOP transcription factor) produced by the t(12;16)(q13;p11) translocation with specific promoters, thus preventing its oncogenic action. There have been anecdotal observations suggesting a similar mechanism of action in several other translocation-related STS, including leiomyosarcomas, synovial sarcoma, Ewing’s sarcoma and endometrial stromal sarcoma.

Trabectedin is intended to be a substitute for the existing therapies doxorubicin and ifosfamide for the first line treatment of translocation-related STS. It is administered by continuous intravenous (IV) infusion at 1.5mg/m² over 24 hours every 3 weeks.

Trabectedin has been licensed in the EU for the second and third line treatment of patients with STS and in combination with pegylated liposomal doxorubicin for the treatment of relapsed platinum-sensitive ovarian cancer.

The most common adverse events (AEs) associated with trabectedin when used for the treatment of STS include elevated blood creatine phosphokinase, elevated blood creatinine, decreased blood albumin, neutropenia, thrombocytopenia, anaemia, headache, vomiting, nausea, constipation, anorexia, fatigue, asthenia, hyperbilirubinemia, elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated blood alkaline phosphatase and elevated gamma-glutamyltransferase.
**Innovation and/or advantages**

If licensed, trabectedin would offer the first ‘targeted’ therapy for translocation-related STS with a mechanism of action as a transcription interacting agent specifically for such tumours.\(^{15}\)

**Developer**

PharmaMar SA.

**Availability, launch or marketing dates, and licensing plans**

In phase III clinical trials. Trabectedin is a designated orphan drug in the EU.

**NHS or Government priority area**

This topic is relevant to the NHS Cancer Plan (2000) and Cancer Reform Strategy (2007).

**Relevant guidance**

- NICE technology appraisal. Trabectedin for the treatment of advanced soft tissue sarcoma. 2010\(^{16}\).
- NICE clinical guideline. Improving outcomes for people with sarcoma. 2006\(^{1}\).
- British Sarcoma Group. Guidelines for the management of soft tissue sarcomas. 2010\(^{17}\).
- European Society for Medical Oncology clinical recommendations. Soft tissue sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2010\(^{18}\).

**Clinical need and burden of disease**

STS is the 23\(^{rd}\) most common type of cancer in the UK, accounting for about 1% of all malignant tumours.\(^{1}\) The annual incidence of STS in England is estimated at 3.9 per 100,000 population, which is equivalent to around 2,000 cases per year.\(^{19}\) One third of STS carry specific recurrent chromosomal translocations.\(^{2,3}\) It was estimated in 2010 that each year there are 500-600 patients with advanced metastatic STS in England and Wales.\(^{18,20}\) In England there were 5,601 admissions for STS (ICD C49) resulting in 24,011 bed days and 5,999 finished consultant episodes in 2009-10.\(^{20}\)

Diagnosis of STS is often delayed as many sarcomas are painless while they grow.\(^{21}\) Other factors affecting survival include site, stage and grade of the tumour.\(^{1}\) Five-year survival can be up to 90% for non-metastatic STS but falls to 10-15% for metastatic STS where median survival is approximately 8-12 months.\(^{22}\) There were 607 deaths registered from STS (ICD C49) in England and Wales in 2008.\(^{23}\) It is reported that 79% of patients with advanced STS receive first line chemotherapy.\(^{19}\)

**Existing comparators and treatments**

Soft tissue sarcomas are a heterogeneous group of tumours that may arise at any site. Treatment is usually a combination of surgery, chemotherapy and radiotherapy. Guidelines recommend the following treatment options for chemotherapy.\(^{18}\):

- **First line treatment**
  - Doxorubicin (anthracycline) - DNA synthesis inhibitor; alone or in combination with ifosfamide.
Second line treatment

- Ifosfamide - DNA synthesis inhibitor.
- Trabectedin - DNA synthesis inhibitor; recommended if anthracyclines and ifosfamide have failed or are contraindicated.
- Imatinib - tyrosine kinase inhibitor; for dermatofibrosarcoma protuberance.
- Dacarbazine - alkylating agent; alone or in combination with gemcitabine.
- Taxanes, e.g. paclitaxel, docetaxel - mitosis inhibitors; for angiosarcoma (unlicensed).
- Gemcitabine - DNA synthesis inhibitor; alone or in combination with docetaxel (unlicensed).

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00796120; Eudra CT:2008-002326-11; trabectedin or doxorubicin with/without ifosfamide; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Pharma Mar SA.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^a), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc UK), USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=80 (planned); adults; translocation-related STS; unresectable, locally advanced or metastatic; measurable disease as defined by radiological RECIST(^a); ECOG(^b) PS score 0-2; adequate cardiac function. Randomised to trabectedin 1.5mg/m² given by continuous IV infusion over 24-hours; or doxorubicin 75mg/m² IV every 3 weeks; or doxorubicin 60mg/m² IV followed by ifosfamide in the range of 6 to 9g/m² every 3 weeks with appropriate hydration and ifosfamide chemoprotectant drugs.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment until disease progression, unacceptable toxicity or withdrawal of consent. Follow-up every 3 months during the first 2 years and every 6 months thereafter.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Progression free survival (PFS).</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>6 months PFS; response rate and duration of response by RECIST(^b). No quality of life outcome measure included in trial outcomes.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>The estimated reporting date is April/May 2012, however the company report that recruitment is currently behind schedule.</td>
</tr>
</tbody>
</table>

Estimated cost and cost impact

The cost of a 1mg vial for its current licensed indication is £1,366\(^{25}\), therefore the unit cost per 21 day cycle is £3,483\(^{26}\). The costs of other selected treatments for STS are as follows\(^{26}\):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost(^c) per 21 day cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>75mg/m² IV every 21 days</td>
<td>£247</td>
</tr>
<tr>
<td></td>
<td>60mg/m² IV every 21 days</td>
<td>£198</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>6 to 9 g/m² every 21 days</td>
<td>£452 - £678</td>
</tr>
</tbody>
</table>

\(^a\) Response Evaluation Criteria in Solid Tumours.
\(^b\) Eastern Cooperative Oncology Group Performance Status.
\(^c\) Based on an average surface area of 1.7m².


**Claimed or potential impact – speculative**

**Patients**

- Reduced mortality or increased length of survival
- Reduction in associated morbidity or improved quality of life for patients and/or carers
- Quicker, earlier or more accurate diagnosis or identification of disease
- None identified

**Services**

- Increased use: 24-hour continuous IV infusion required.
- Service organisation
- Staff requirements
- Other: there is a potential for portable pumps to be used for outpatient administration.
- None identified

**Costs**

- Increased unit cost compared to alternative
- Other: increased costs: more patients coming for treatment
- Other: increased costs: capital investment needed
- None identified

**Other issues**

- Clinical uncertainty or other research question identified:
- None identified

**References**

http://www.medicines.org.uk/EMC/medicine/20457/SPC/Yondelis+0.25+mg+powder+for+concentrate+for+s
olution+for+infusion/Yondelis+1+mg+powder+for+concentrate+for+solution+for+infusion/ Accessed 9
March 2011.

16 National Institute for Health and Clinical Excellence. Trabectedin for the treatment of advanced soft tissue
2010:566-182.
18 Casali PG and Blay JY. Soft tissue sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and
19 National Institute for Health and Clinical Excellence. Costing statement: trabectedin for the treatment of
October 2010.
22 National Institute for Health and Clinical Excellence. Final scope for trabectedin for the treatment of advanced
http://www.statistics.gov.uk
24 ClinicalTrials.gov. A Randomized, multicenter, phase III trial of trabectedin (yondelis) versus doxorubicin-
based chemotherapy as first-line therapy in patients with translocation-related sarcomas (TRS).

The National Institute for Health Research National Horizon Scanning Centre Research
Programme is funded by the Department of Health.
The views expressed in this publication are not necessarily those of the NHS, the NIHR or the
Department of Health

The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, 90 Vincent Drive, Edgbaston, Birmingham, B15 2SP, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.haps.bham.ac.uk/publichealth/horizon