Olaratumab with doxorubicin for advanced soft tissue sarcoma

LAY SUMMARY

Soft tissue sarcoma is a group of rare cancers that can occur in any part of the body. Sarcoma is usually treated with surgery, but the cancer often returns or spreads to other parts of the body.

Olaratumab is a new drug for the treatment of soft tissue sarcoma that can no longer be treated with surgery. It is delivered directly into the bloodstream through a drip. Some studies have suggested olaratumab may work best in combination with a chemotherapy drug already used for the treatment of this disease called doxorubicin.

If olaratumab is licensed for use in the UK, it could be a new treatment option for patients with advanced soft tissue sarcoma that may improve survival.

NIHR HSRIC ID: 10912
TARGET GROUP

- Soft tissue sarcoma: advanced; not amenable to curative treatment with radiotherapy or surgery – in combination with doxorubicin.

TECHNOLOGY

DESCRIPTION

Olaratumab (Anti-PDGFRα mAb 3G3; IMC 3G3; LY 3012207) is a fully human IgG1 monoclonal antibody that targets platelet-derived growth factor receptor alpha (PDGFRα). PDGFRα is expressed on a number of tumour types and on accessory cells in tumours that are important for maintaining tumour growth. Studies have shown that PDGFRα plays a key role in regulating vascular endothelial growth factor (VEGF)-driven tumour angiogenesis. Olaratumab binds to PDGFRα, leading to blockade of ligand-dependent signalling in PDGFRα-expressing tumour cells and stromal cells in the tumour microenvironment. This provides a strategy for inhibiting tumour growth and angiogenesis in cancer. In the phase II clinical trial, olaratumab is administered at 15mg/kg via intravenous (IV) infusion on days 1 and 8 of a 21-day cycle, in combination with doxorubicin on day 1 of a 21-day cycle¹.

Olaratumab does not currently have Marketing Authorisation in the EU for any indication.

Olaratumab is currently in phase II clinical development for the following indications:
- Gastrointestinal stromal tumours; unresectable and/or metastatic.
- Glioblastoma; recurrent.
- Non-small cell lung cancer; locally advanced or metastatic (in combination with paclitaxel and carboplatin).
- Prostate cancer; metastatic and hormone relapsed (in combination with mitoxantrone and prednisolone).
- Ovarian cancer; advanced and platinum-refractory or platinum-resistant (in combination with liposomal doxorubicin).

INNOVATION and/or ADVANTAGES

If licensed, olaratumab will offer an additional treatment option for patients with advanced soft tissue sarcoma who are not amenable to treatment with surgery or radiotherapy.

DEVELOPER

Eli Lilly and Company Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Olaratumab is a designated orphan drug in the EU.

In phase II clinical trials.
Sarcomas constitute a heterogeneous group of rare solid tumours of mesenchymal cell origin and are usually divided into two broad categories: sarcomas of soft tissues (including fat, muscle, nerve and nerve sheath, blood vessels, and other connective tissues) and sarcomas of bone 10. Soft tissue sarcomas are the most frequent sarcomas 10; the most common primary sites of development are the arms and legs (60%), trunk (19%), retroperitoneum (15%), and head and neck (9%) 2,10. The causes of most sarcomas are unknown, however in a very small number of patients hereditary conditions lead to an increased susceptibility to sarcoma. These conditions include neurofibromatosis, Gardner's syndrome, Li-Fraumeni syndrome and retinoblastoma 2. Previous radiotherapy treatment and exposure to certain chemicals, such as vinyl chloride, are also considered risk factors 2.

Frequently, soft tissue sarcomas recur after initial treatment (in around 50% of patients); in some, these will be localised to the site of origin, however many will have metastasised, often to the lungs, although the liver and sometimes bones or lymphatic system can also be affected 3. Expert opinion suggests that the main clinical problem for patients with soft tissue sarcoma is the development of metastases, which is almost always fatal 8. It is possible to predict the risk of this occurring according to pre-treatment factors such as tumour grade, tumour size, site, depth, and adequacy of initial surgery a.

This topic is relevant to:

Soft tissue sarcomas are rare cancers, accounting for approximately 1% of all cancers diagnosed in the UK 4. Accurate data for sarcomas is difficult to establish due to the way the condition is reported and coded. The ICD-10 coding system is inadequate for coding soft tissue sarcomas as it classifies tumours by site of origin rather than the more appropriate morphology – and soft tissue sarcomas are defined by their morphology as well as by their location in the body 5. As a result only around 50% of sarcomas can reliably be captured with ICD-10 coding using the codes for Kaposi sarcoma (C46) and malignant neoplasms of connective and soft tissue (C47 and C49) 5. ICD-O 5 morphology codes are more appropriate, however these are often unrecorded or coded poorly; 20% of sarcomas diagnosed in the UK are coded as ‘not otherwise specified’ (NOS) 5.

The latest available data, using both ICD-10 and ICD-O coding, indicates that approximately 3,300 people were diagnosed with soft tissue sarcoma in the UK in 2010 (1,700 male, 1,600

---

a Expert personal communication.

b International Classification of Diseases for Oncology.
female)\(^6\). Approximately 43% of soft tissue sarcomas are diagnosed in people over the age of 65 years old; however the age profile varies between subtypes, with rhabdomyosarcoma in particular affecting young children\(^6\). Adult soft tissue and visceral sarcomas have an estimated incidence averaging 4-5 new cases per 100,000 people per year in Europe\(^11\). It is estimated that the incidence of advanced disease is approximately 550 cases per year in England with approximately 79% of these patients eligible to receive first line chemotherapy\(^7\).

In 2013-14, there were 7,068 hospital admissions recorded as malignant neoplasm of other connective and soft tissue (ICD-10 C46, C47 and C49), equating to 23,824 bed days and 7,557 finished consultant episodes in England\(^8\). Five-year survival from all types of soft tissue sarcoma in England was 56% in 2000-2004, however this varies between morphological type\(^5\). In 2013, there were 803 deaths from soft tissue sarcoma (ICD-10 C46, C47 and C49) registered in England and Wales\(^9\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Ridaforolimus for the maintenance treatment of metastatic soft tissue or bone sarcoma [ID415]. Expected date of issue to be confirmed.

**Other Guidance**

- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Soft tissue sarcoma. 2014\(^10\).
- European Society for Medical Oncology. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2012\(^11\).
- British Sarcoma Group. Guidelines for the management of soft tissue sarcomas. 2010\(^12\).
- South West Public Health Observatory. Standards and guidelines for the management of soft tissue sarcomas. 2004\(^13\).

**CURRENT TREATMENT OPTIONS**

Soft tissue sarcomas arise in a variety of sites and are usually treated with a combination of surgery, chemotherapy and radiotherapy. Treatment options for advanced and/or metastatic soft tissue sarcoma include\(^11,14,15\):

- **Surgery**
  - Excision of tumour.
- **Radiotherapy.**
- **Chemotherapy**
  - Doxorubicin +/- ifosfamide or dacarbazine.
  - Epirubicin +/- ifosfamide.
  - Gemcitabine +/- docetaxel.
Expert opinion suggests that the majority of patients with soft tissue sarcoma are initially treated by surgery with or without radiotherapy. Chemotherapy is given with curative intent for only a small proportion of patients with soft tissue sarcoma in the UK. Chemotherapy is predominantly used in the palliative setting (locally advanced or metastatic sarcoma).

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01185964, 14055, I5B-IE-JGDG, CP15-0806; olaratumab and doxorubicin vs doxorubicin alone; phase Ib/II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Eli Lilly and Company Ltd.</td>
</tr>
<tr>
<td>Status</td>
<td>Complete and published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=130; aged ≥18 years; malignant soft tissue sarcoma; advanced disease not amenable to treatment with surgery or radiotherapy; no prior treatment with doxorubicin, daunorubicin, idarubicin and/or other anthracyclines and anthracenediones; no prior radiation therapy to the mediastinal or pericardial area; patients with Kaposi sarcoma and gastrointestinal stromal tumour were excluded.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to olaratumab 15mg/kg IV on days 1 and 8 of a 21-day cycle, in combination with doxorubicin 75mg/m² IV on day 1 of a 21-day cycle; or doxorubicin 75mg/m² IV on day 1 of a 21-day cycle; both for a maximum of 8 cycles. For patients without disease progression following treatment of olaratumab with doxorubicin this is followed by olaratumab 15mg/kg IV on days 1 and 8 of each 21-day cycle until disease progression, unacceptable toxicity or any other reason for discontinuation of treatment.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 8 cycles.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Progression-free survival (PFS).</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Overall survival (OS), objective response rate (ORR).</td>
</tr>
<tr>
<td>Key results</td>
<td>For olaratumab and doxorubicin vs doxorubicin alone groups, respectively: median PFS, 6.6 months vs 4.1 months; median OS, 25.0 months vs 14.7 months; ORR, 18.8% vs 12.3%.</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>The following grade ≥3 AEs occurred in ≥5% of the population of olaratumab and doxorubicin vs doxorubicin alone groups, respectively: neutropenia (51.5% vs 33.8%), anaemia (12.5% vs 7.7%), fatigue (9.4% vs 3.1%), thrombocytopenia (9.4% vs 7.7%), febrile convulsion (12.5% vs 13.8%), infection (6.3% vs 10.8%).</td>
</tr>
</tbody>
</table>

**ESTIMATED COST and IMPACT**

The cost of olaratumab is not yet known. The cost of selected treatments for soft tissue sarcoma are as follows:

> Expert personal communication.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose$^d$</th>
<th>Cost per dose range$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>114.60 to 143.25mg once per 21-day cycle.</td>
<td>£237.69 to £300.36 per cycle.</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>9.55 to 11.46g once per 21 day cycle.</td>
<td>£650.20 to £780.24 per cycle.</td>
</tr>
<tr>
<td>Trabectedin (Yondelis)</td>
<td>2.87mg once per 21 day cycle.</td>
<td>£4,098.00 per cycle.</td>
</tr>
<tr>
<td>Pazopanib (Votrient)</td>
<td>Recommended maximum dose of 800mg once daily, to be adjusted in steps of 200mg according to tolerability.</td>
<td>£392.35 to £1,569.40 per cycle.</td>
</tr>
</tbody>
</table>

### IMPACT - SPECULATIVE

**Impact on Patients and Carers**
- ☑ Reduced mortality/increased length of survival
- ☐ No impact identified
- ☐ Other.
- ☑ Reduced symptoms or disability
- ☐ Other.

**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: Expert opinion suggests that no information is available regarding olaratumab infusion times; this could potentially have an impact on the chemotherapy service workload$^e$.
- ☐ None identified

**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
- ☑ Other reduction in costs.
- ☐ None identified

**Other Issues**
- ☑ Clinical uncertainty or other research question identified: expert opinion suggests that if olaratumab demonstrates a survival benefit in the palliative setting it is inevitable that there will be moves to explore its value as an adjuvant to primary treatment of high-risk patients. This is a much larger number of patients than those who currently receive palliative chemotherapy$^f$.
- ☐ None identified

$^d$ Assuming an average body surface area of 1.91m$^2$ (Health Survey for England 2013).
$^e$ Expert personal communication.
$^f$ Expert personal communication.
REFERENCES


