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NHS National Institute for Health Research

NHSC National Horizon Scanning Centre

Pazopanib (Votrient) for advanced soft tissue sarcoma – second line

December 2010

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Pazopanib (Votrient) for advanced soft tissue sarcoma – second line

Target group

- Soft tissue sarcoma (STS): advanced – second line; where standard chemotherapy (including anthracycline based therapy) has failed or is not suitable.

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[1]. 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[1].

Technology description

Pazopanib hydrochloride (GW 786034; GW786034B; SB 786034; Votrient) is an oral multi-targeted tyrosine kinase receptor inhibitor with anti-tumour activity. Pazopanib inhibits vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3; platelet-derived growth factor receptor (PDGFR); and c-kit; which may result in inhibition of angiogenesis in tumours in which these receptors are upregulated. It is intended to treat patients with advanced STS when prior chemotherapy has failed, is contraindicated, or refused by patients. Pazopanib is administered at 800mg once daily as monotherapy until disease progression or unacceptable toxicity.

Pazopanib has a conditional Marketing Authorisation in the EU for first line treatment of patients with advanced renal cell carcinoma (RCC) and for those who have received prior cytokine therapy. It is in phase III clinical trials for non-small cell lung cancer and ovarian cancer. It is also in phase II development for a range of solid tumours including bladder cancer, advanced breast cancer, cervical cancer, thyroid cancer, nasopharyngeal cancer, neuroendocrine cancer and glioma.

The most common adverse events (AEs) associated with pazopanib when used to treat RCC, include decreased appetite, dysgeusia, hypertension, diarrhoea, nausea, vomiting, abdominal pain, hair colour change, fatigue, elevated serum alanine aminotransferase (ALT) and elevated serum aspartate aminotransferase (AST)[2].

Innovation and/or advantages

If licensed, pazopanib could provide a new treatment option for patients with advanced soft tissue sarcoma who have not responded adequately to first line chemotherapy agents.

Developer

GlaxoSmithKline (GSK).

Availability, launch or marketing dates, and licensing plans

In phase III clinical trial.

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[3].
- NICE clinical guideline. Improving outcomes for people with sarcoma. 2006[1].

- British Sarcoma Group. Guidelines for the management of soft tissue sarcomas. 2010[4].
- European Society for Medical Oncology (ESMO) clinical recommendations. Soft tissue sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2010[5].

Clinical need and burden of disease

STS is ranked as the 23rd 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[6]. It is estimated that each year there are 500-600 patients with advanced metastatic soft tissue sarcoma in England and Wales[6]. 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[7].

Diagnosis of STS is often delayed as many sarcomas are painless while they grow[8]. Other factors affecting survival include site, stage and grade of the tumour[1]. 5-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[9]. There were 607 deaths registered from STS (ICD C49) in England and Wales in 2008[10]. It is reported that 79% of patients with advanced STS receive first line chemotherapy, of whom 46% subsequently receive second line chemotherapy[6].

Existing comparators and treatments

STS arise in a variety of sites and are usually treated with a combination of surgery, chemotherapy and radiotherapy. Pharmacological treatment options for advanced STS include[3,5,11]:

- Alkylating agents, e.g. ifosfamide, trabectedin (recommended if anthracyclines and ifosfamide have failed or are contraindicated).
- Anthracyclines, e.g. doxorubicin alone or in combination with ifosfamide.
- Other neoplastic agents – dacarbazine (in combination therapy), taxanes, e.g. paclitaxel, docetaxel (unlicensed), gemcitabine alone or in combination with docetaxel (unlicensed), and imatinib (for dermatofibrosarcoma protuberance).

Efficacy and safety

Trial	PALETTE, NCT00753688; pazopanib or placebo; phase III.	NCT00297258; pazopanib; phase II.
Sponsor	GlaxoSmithKline, European Organisation for Research and Treatment of Cancer.	GlaxoSmithKline.
Status	Ongoing.	Published.
Source of information	Trial registry[12], manufacturer.	Trial registry[13], publication[14].
Location	EU (inc UK), USA, Australia, Brazil Japan and Korea.	EU (inc UK).
Design	Randomised, placebo-controlled.	Uncontrolled, single arm.
Participants and schedule	n=360 (planned); adults; STS; metastatic; high or intermediate grade (low grade tumours allowed if disease	n=142; adults; STS; advanced; high or intermediate grade; relapsed or refractory; incurable by surgery or

	progression); measurable disease by RECIST[a]; received ≤4 lines of prior systemic therapy; anthracycline based therapy and standard chemotherapy failed or contraindicated or refused by patient; not treated with angiogenesis inhibitors; WHO PS 0-1[b]. Randomised to pazopanib 800mg once daily or placebo.	radiotherapy; measurable disease by RECIST; disease progression within 6 months; ineligible for chemotherapy or received ≤2 prior cytotoxic agents; WHO PS 0-1. Four patient cohorts recruited based on diagnosis: adipocytic sarcomas (n=19), leiomyosarcomas (n=41), synovial sarcomas (n=37) and other eligible sarcomas (n=41). Received pazopanib 800mg once daily. Dose reductions to a minimum of 400mg once daily allowed on the basis of tolerability.
Follow-up	Active treatment period until disease progression, unacceptable toxicity or withdrawal of consent. Follow-up every 8 weeks until disease progression and every 3 months thereafter.	Active treatment period until disease progression, unacceptable toxicity or withdrawal of consent. Follow-up to 2 years and 2 months; median follow-up 677 days.
Primary outcome	Progression free survival (PFS).	Progression free rate (PFR) [complete response (CR) or partial response (PR) or stable disease (SD)] at week 12.
Secondary outcomes	Overall survival (OS); AEs	PFS; OS; duration of response (DR); response rate (RR); safety.
Key results	-	For adipocytic sarcomas, leiomyosarcomas, synovial sarcomas and other eligible sarcomas respectively: PFR at week 12 (%), 26, 44, 49, 39; no complete responses observed; PR (%), 0, 2, 14, 7. Median PFS (days), 80 (95% CI 62 to 113), 91 (95% CI 84 to 168), 161 (95% CI 80 to 193), 91 (95% CI 84 to 172); median OS (days), 197 (95% CI 128 to 610), 354 (95 % CI 318 to 544), 310 (95% CI 230 to 405), 299 (95% CI 245 to 671); 79% discontinued study due to disease progression at time of last documented follow-up.
Expected reporting date	Study expected to complete September 2012.	-

[a] Response Evaluation Criteria In Solid Tumors
[b] World Health Organisation Performance Status.

Adverse effects (AEs)	-	AEs occurred in at least 20% of participants. Most common AEs included leukopenia (42.2%), anaemia (74.6%), elevations in AST (46.4%) and ALT (50%), and proteinuria (51.4%). Most common drug related AEs included hypertension (40.1%), fatigue (36.6%), hypopigmentation (36.6%), and nausea (35.9%). Most frequent serious AEs (grade 3 to 4) included hyperbilirubemia (6.3%), hypertension (7.7%), and fatigue (7.7%). Treatment related toxicity resulted in study discontinuation in 6%.

Estimated cost and cost impact

The cost of pazopanib for the treatment of soft tissue sarcoma is not yet known. The cost of a comparable licensed drug for second line treatment of STS is as follows[3,11]:

Drug	Dose	Cost[c]:
Trabectedin (Yondelis; Pharma Mar)	1.5mg/m^2 IV every 21 days	£3,458 every 21 days

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
- ☐ Other:
- ☐ None identified

Services

- ☐ Increased use
- ☐ Service organisation
- ☐ Staff requirements
- ☐ Decreased use
- ☑ Other: potential for oral administration
- ☐ None identified

Costs

- ☐ Increased unit cost compared to alternative
- ☐ Increased costs: more patients coming for treatment
- ☐ Increased costs: capital investment needed
- ☐ New costs:
- ☐ Savings:
- ☑ Other: uncertain unit cost compared to alternative treatments

Other issues

- ☑ Clinical uncertainty or other research question identified:
  A lack of available data on the prevalence of metastatic sarcoma may make it difficult to determine the number of patients who could potentially benefit from pazopanib.
- ☐ None identified

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[c] Costing based on average surface area 1.7m^2

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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

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