Pazopanib (Votrient) for renal cell carcinoma – adjuvant therapy

SUMMARY

Pazopanib (Votrient) is intended to be used as adjuvant therapy for the treatment of localised or locally advanced renal cell carcinoma (RCC) following nephrectomy. Pazopanib is an oral multi-targeted tyrosine kinase receptor inhibitor with anti-tumour activity. It inhibits vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3, platelet-derived growth factor receptor (PDGFR), and c-kit; this may result in inhibition of angiogenesis in tumours in which these receptors are upregulated. Pazopanib is currently licensed for the first-line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced RCC. It is also licensed for the treatment of selective types of advanced soft tissue sarcoma.

In 2009, there were 8,163 new cases of kidney cancer registered in England and Wales. In that year it was the sixth most common cancer among men in the UK and the ninth most common among women, accounting for 3% and 2% of all new cancer cases respectively. It is estimated that 57% of patients presenting each year have stage I or II RCC and 29% of these are expected to progress to stage III each year. Ten-year survival rates in England and Wales have almost doubled in the last 40 years. In 2011, 3,706 deaths from kidney cancer were registered in England and Wales.

Surgical intervention remains the standard of care for localised or locally advanced RCC. Pazopanib is currently in a phase III trial comparing its effects on disease-free survival against placebo. The trial is expected to complete in April 2019. The relative merits of adjuvant therapy with different tyrosine kinase inhibitors is not yet known.
### TARGET GROUP

- Renal cell carcinoma (RCC): localised or locally advanced – adjuvant, following nephrectomy.

### TECHNOLOGY

#### DESCRIPTION

Pazopanib (Votrient) is an oral multi-targeted tyrosine kinase 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; this may result in inhibition of angiogenesis in tumours in which these receptors are upregulated. Pazopanib is administered orally at an initial dose of 600mg daily for 8-12 weeks. This can be subsequently increased to 800mg daily.

Pazopanib is currently licensed for the first line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced RCC. It is also licensed for the treatment of selective types of advanced soft tissue sarcoma in patients who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. Common recognised adverse effects (>10%) include decreased appetite, dysgeusia, headache, hypertension, diarrhoea, nausea, vomiting, abdominal pain, hair colour change, palmar-plantar erythrodysaesthesia, alopecia, rash, fatigue and increased liver enzymes (alanine aminotransferase and aspartate aminotransferase). Pazopanib is also in phase III clinical trials for the maintenance treatment of women with stage II-IV ovarian, fallopian tube or primary peritoneal cancer who have not progressed after receiving first line chemotherapy.

### INNOVATION and/or ADVANTAGES

If licensed, pazopanib will present a new treatment option for this patient group who, following surgery, currently receive no treatment until disease recurrence.

### DEVELOPER

GlaxoSmithKline.

### AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

### PATIENT GROUP

#### BACKGROUND

RCC accounts for 90% of kidney cancers and around 3% of all adult cancers in the UK. It is characterised by a lack of early warning signs, diverse clinical manifestations, and resistance to radiation and chemotherapy. RCC may remain clinically occult for most of its course; only 10% of patients present with the classic symptoms of flank pain, haematuria, and flank
mass\textsuperscript{3}. Smoking is a major preventable risk factor for kidney cancer, with smokers having on average a 50% increase in risk. Other risk factors for kidney cancer include obesity, a history of hypertension and a family history of kidney cancer\textsuperscript{4}. Around half of people diagnosed in England survive for at least five years after diagnosis\textsuperscript{4}.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).

**CLINICAL NEED and BURDEN OF DISEASE**

In 2009, there were 8,163 new cases of kidney cancer registered in England and Wales\textsuperscript{5}. In that year, it was the sixth most common cancer among men in the UK and the ninth most common among women, accounting for 3% and 2% of all new cancer cases respectively\textsuperscript{5}. Kidney cancer incidence is strongly associated with age. In the UK (2007-2009) 62% of cases were diagnosed in people aged 65 years and over\textsuperscript{5}. It is estimated that 57% of patients presenting each year have stage I or II RCC and 29% of these are expected to progress to stage III each year\textsuperscript{6}. Ten-year survival rates in England and Wales have almost doubled in the last 40 years\textsuperscript{4}. In 2011 there were 6,263 nephrectomies (OPCS M02) and 1,150 partial nephrectomies (OPCS M03) carried out in England\textsuperscript{7}. In 2011, 3,706 deaths from kidney cancer (ICD C64-66, C68) were registered in England and Wales\textsuperscript{8}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Renal cell carcinoma (advanced) – axitinib. Expected May 2013\textsuperscript{9}.
- NICE technology appraisal. Everolimus for the second-line treatment of advanced renal cell carcinoma. April 2011\textsuperscript{10}.
- NICE technology appraisal. Pazopanib for the first-line treatment of advanced renal cell carcinoma. February 2011\textsuperscript{11}.
- NICE technology appraisal. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. August 2009\textsuperscript{12}.
- NICE technology appraisal. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. March 2009\textsuperscript{13}.
- NICE guidance on cancer sevices. Improving outcomes in urological cancers. September 2002\textsuperscript{14}.

**Other Guidance**

- European Society for Medical Oncology (ESMO). Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2012\textsuperscript{16}.
EXISTING COMPARATORS and TREATMENTS

Surgical intervention remains the standard of care for localised or locally advanced RCC. Partial nephrectomy is recommended as the preferred option in organ confined tumours (T1 tumours <7cm) whereas laparoscopic radical nephrectomy is recommended for T2 tumours (>7cm). For locally advanced RCC (T3 and T4), open radical nephrectomy can be considered along with the laparoscopic approach. There is currently no recommended adjuvant treatment, although a number of trials are ongoing. Alternative approaches to nephrectomy include ablative treatments and active surveillance.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>PROTECT, NCT01235962, 113387; pazopanib vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>GlaxoSmithKline.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=1,500 (planned); aged ≥18 years; RCC, non-metastatic; following nephrectomy.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to oral pazopanib 600mg daily for 8-12 weeks or placebo. Dose can be increased to 800mg daily based on safety evaluation.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment 12 months, follow-up 9 years.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Disease-free survival (DFS).</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Overall survival; DFS at yearly time points; safety; quality of life measured by Therapy-Kidney Symptom Index-19 and EuroQOL-5D.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Estimated study completion date April 2019.</td>
</tr>
</tbody>
</table>

ESTIMATED COST and IMPACT

COST

The cost of pazopanib for this indication is not yet known. However, pazopanib is already marketed in the UK; the price for a pack of 30 x 400mg tablets for its currently licensed indications is £1,121, and for a pack of 30 x 200mg tablets is £560.50. The 28 day cost of pazopanib at a dose of 600mg daily would be £1,681.50, whilst the cost at a dose of 800mg daily would be £2,242. Expert opinion suggests that in cases of advanced renal cancer 800mg daily is likely to be the standard dose.

IMPACT - SPECULATIVE

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

* Expert personal communication.
Impact on Services

- Increased use of existing services: *regular blood tests during therapy*.
- Re-organisation of existing services
- Other
- Decreased use of existing services
- Need for new services
- None identified

Impact on Costs

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

Other Issues

- Clinical uncertainty or other research question identified: *other studies of tyrosine kinase inhibitors (sorafenib and sunitinib) have been carried out in the same clinical setting. These may become the standard of care if proved to be beneficial. The relative merit of adjuvant therapy with different tyrosine kinase inhibitors is not yet known*.
- None identified

REFERENCES


---

\(^b\) Expert personal communication.


