Axitinib (Inlyta) for advanced and/or metastatic renal cell carcinoma – first line

SUMMARY

Axitinib (Inlyta) is intended to be used as first-line therapy for the treatment of advanced and/or metastatic renal cell carcinoma (RCC). If licensed, it would offer an additional first line treatment option for advanced RCC. Axitinib is a potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2 and 3. The inhibition of VEGF receptors may reduce tumour size and delay tumour progression. Axitinib is not currently licensed for any other indication.

RCC accounts for 90% of kidney cancers and around 3% of all adult cancers in the UK. In England there were 16,005 admissions for kidney cancer, resulting in 77,899 bed days and 19,000 finished consultant episodes in 2010-11. Approximately 25% and 14% of patients with RCC present with advanced and/or metastatic disease (stage III or stage IV) respectively. The estimated five-year survival rate for RCC is 44%, which is reduced to 10% for metastatic disease. In 2010, there were 3,327 deaths registered from kidney cancer in England and Wales. Treatment of early-stage RCC is primarily surgical. Advanced and/or metastatic RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. Current therapeutic options for the treatment of advanced or metastatic RCC include pazopanib and sunitinib. Axitinib is currently in one phase III clinical trials comparing its effect on progression free survival against treatment with sorafenib. This trial is expected to complete in June 2014.
TARGET GROUP

- Renal cell carcinoma (RCC): advanced and/or metastatic – first line.

TECHNOLOGY

DESCRIPTION

Axitinib (Inlyta, AG-013736) is a potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2 and 3. Activation of VEGF receptors promotes tumour angiogenesis, supporting tumour growth. The inhibition of VEGF receptors may reduce tumour size and delay tumour progression. Axitinib is intended for the treatment of patients with advanced and/or metastatic RCC who have received no prior systemic first line therapy. It is administered orally at 5-10mg twice daily until disease progression.

Axitinib is in phase III clinical trials for the second-line treatment of advanced and/or metastatic RCC and in phase II clinical trials for the treatment of melanoma, sarcoma, hepatocellular carcinoma, adenoid cystic carcinoma, nasopharyngeal carcinoma, colorectal, thyroid, brain, breast, pancreatic, prostate, head and neck, and lung cancers.

INNOVATION and/or ADVANTAGES

If licensed, axitinib will offer an additional first line treatment option for advanced RCC.

DEVELOPER

Pfizer Limited.

PATIENT GROUP

BACKGROUND

RCC is a type of kidney cancer that usually originates in the lining of the tubules of the kidney. RCC accounts for 90% of kidney cancers and around 3% of all adult cancers in the UK\(^1,2,3\). RCC is nearly twice as common in men as in women, and most commonly affects adults aged 50-80 years\(^4\).

NHS or GOVERNMENT PRIORITY AREA

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

CLINICAL NEED and BURDEN OF DISEASE

There are approximately 8,163 incident kidney cancers in England and Wales diagnosed every year\(^5\). In England, there were 16,005 hospital admissions for kidney cancer (ICD C64-66, C68) resulting in 77,899 bed days and 19,000 finished consultant episodes in 2010-11\(^6\).
Approximately 25% and 14% of patients present with advanced and/or metastatic disease (stage III or stage IV) respectively. In addition, an estimated 33% of patients who have curative resection for earlier stages will develop recurrent and/or metastatic disease, representing around 4,456 patients diagnosed with advanced/metastatic RCC per year. The estimated 5-year survival rate for RCC is 44%, which is reduced to 10% for metastatic disease. In 2010, 3,327 deaths were registered from kidney cancer (ICD C64-66, C68) in England and Wales.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- 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. 2009.
- NICE technology appraisal. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. 2009.

Other Guidance


EXISTING COMPARATORS and TREATMENTS

It is estimated that 68% of patients with advanced/metastatic RCC are eligible for first line therapy, equating to approximately 3,030 patients eligible for fistline therapy per year. The main objectives of medical intervention are to relieve physical symptoms and extend survival. Treatment of early-stage RCC is primarily surgical. Advanced and/or metastatic
RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. Until recently, the standard treatment was immunotherapy with interferon alpha (IFN-alpha), or less commonly interleukin-2 (IL-2). Not all patients are suitable for immunotherapy, which achieves overall response rates of 4-31%. More recently, sunitinib has become the standard first-line therapy for advanced and/or metastatic RCC. Expert opinion also suggests IFN-alpha use is declining as clinical trials show improved efficacy with sunitinib compared to IFN-alpha.

Current therapeutic options for the treatment of advanced and/or metastatic RCC include:
- Pazopanib: tyrosine kinase inhibitor; first line therapy for patients with advanced RCC.
- Sunitinib: tyrosine kinase inhibitor; first line therapy for patients with advanced and/or metastatic RCC.
- Sorafenib: multiple kinase inhibitor; first line therapy for patients unsuitable for cytokine therapy or second line therapy following cytokine failure.
- Temsirolimus: tyrosine kinase inhibitor; first line therapy in patients with 3 or more poor prognostic indicators.
- Bevacizumab: monoclonal antibody; first line therapy in combination with IFN-alpha for patients with advanced and/or metastatic RCC.
- Everolimus: tyrosine kinase inhibitor advanced RCC after progression on or after treatment with VEGF targeted therapy.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
<th>Follow-up</th>
<th>Primary outcome/s</th>
<th>Secondary outcome/s</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00920816, A4061051; axitinib vs sorafenib; phase III.</td>
<td>Pfizer Ltd.</td>
<td>Ongoing</td>
<td>Trial registry</td>
<td>EU, USA and other countries.</td>
<td>Randomised, active-controlled.</td>
<td>n=447 (planned); adults; RCC; advanced; no prior systemic first line therapy, or progressed after 1 systemic first line regimen for metastatic disease.</td>
<td>Randomised to axitinib, oral, starting dose of 5mg twice daily, or sorafenib, oral, 400mg twice daily.</td>
<td>Active treatment period until disease progression; follow-up 3 years.</td>
<td>Progression free survival (PFS).</td>
<td>Overall survival (OS), response rate, safety.</td>
<td>For axitinib vs placebo respectively (n=112), (n=91): response rate 40.2% (95% CI, 31.0-49.9) vs 56.0% (95% CI, 40.2-60.0).</td>
</tr>
<tr>
<td>NCT00835978, A4061046; axitinib (continuous dose or dose titration) vs placebo; phase II.</td>
<td>Pfizer Ltd.</td>
<td>Ongoing and published in abstract.</td>
<td>Trial registry and abstract</td>
<td>EU, USA and other countries.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=200 (planned); adults; RCC; advanced; no prior systemic first line therapy received</td>
<td>Randomised to axitinib, oral, 5mg twice daily and axitinib dose titration (A), or axitinib, oral, 5mg twice daily and placebo dose titration (B), or axitinib, oral, 5mg twice daily (C).</td>
<td>Active treatment period until disease progression; follow-up 3 years.</td>
<td>Response rate.</td>
<td>PFS, OS, safety.</td>
<td></td>
</tr>
</tbody>
</table>

### Notes

- [a] Expert opinion.
- [b] Using the Response Evaluation in Solid Tumours (RECIST) criteria.
Adverse effects (AEs) -

45.2-66.4); PFS, 13.7 mths (95% CI 9.2–not estimable) vs 12.2 mths (95% CI 8.6-16.7).

AEs include hypertension, 61 (29%); diarrhoea, 15 (7%); fatigue, 13 (6%).

Expected reporting date -

Estimated study completion date June 2014. Estimated study completion date Aug 2013.

**ESTIMATED COST and IMPACT**

**COST**

The cost of axitinib (Inlyta) is not yet known. The costs of comparable drugs for the treatment of patients with advanced RCC are:21:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Period: 28 days</th>
</tr>
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<tbody>
<tr>
<td>Sunitinib (Sutent)</td>
<td>50mg for 4 weeks in a 6 week cycle</td>
<td>£2,092</td>
</tr>
<tr>
<td>Pazopanib (Votrient)</td>
<td>800mg once daily</td>
<td>£2,092</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>400mg twice daily</td>
<td>£2,980</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>10mg/kg once every 14 days*</td>
<td>£1,849</td>
</tr>
</tbody>
</table>

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

☑ Reduced mortality/increased length of survival ☑ Reduced symptoms or disability
☐ Other ☐ No impact identified

**Impact on Services**

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

**Impact on Costs**

☐ Increased drug treatment costs ☑ Reduced drug treatment costs
☐ Other increase in costs ☐ Other reduction in costs:
☑ Other: uncertain unit cost compared to alternative treatments ☐ None identified

**Other Issues**

☑ Clinical uncertainty or other research question identified: expert opinion suggests that comparison with sorafenib in the phase III trial may make implications difficult to determine as sorafenib is not current standard therapy in the first line setting
☐ None identified

*Costing based on average adult bodyweight, 76.9kg.
REFERENCES


