Axitinib as an option for second line advanced renal cell carcinoma with progression after tyrosine kinase inhibitor (or other first-line therapy)

January 2013

Summary

Axitinib (Inlyta®, Pfizer) is an orally administered multi-targeted kinase receptor inhibitor that has been licensed in the EU for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine. There are currently no treatments approved by NICE for use in people with advanced RCC who have failed to respond to prior systemic therapy. However, sunitinib and everolimus are occasionally prescribed as second-line treatments through the Cancer Drugs Fund; and are also suggested as second line treatment options in guidelines from the European Association of Urology.

No trials have compared axitinib with best supportive care. The licensing of axitinib is based on data from a phase III trial (AXIS) comparing it with sorafenib in 723 patients who have failed to respond to either sunitinib or cytokine therapy (clinical data in the temsirolimus refractory and bevacizumab with interferon-alpha refractory populations in the trial were considered insufficient to draw any firm conclusions). Axitinib improved progression-free survival (PFS) compared to sorafenib regardless of prior systemic regimen and baseline performance status (median 6.7 months vs. 4.7 months with sorafenib; hazard ratio 0.67, 95% CI 0.54 to 0.81; p<0.0001). Axitinib also improved response rate and time to deterioration. The study was not powered to assess overall survival, although updated overall survival data has been presented at ESMO. The most common adverse effects of grade 3 or higher were hypertension, diarrhoea and fatigue. The manufacturer cautions use in people with hypertension and history of thrombotic events.

ESMO 2012 guidelines recommend axitinib as an option for second-line treatment of clear-cell mRCC following cytokine or TKI therapy and recommends everolimus as an option for third-line treatment following two tyrosine kinase inhibitors. Standard options for first-line treatment according to ESMO include sunitinib, bevacizumab with interferon, and pazopanib.

The request to CDF for axitinib funding is for patients who have received pazopanib or sunitinib as a first-line therapy. However, the AXIS study and subsequent license are both restricted to post sunitinib or cytokine therapy. Everolimus is currently recommended for funding via the CDF for advanced and/or metastatic Renal Cell Carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy, i.e. the line of therapy for everolimus funding is not currently stipulated.

Based on the estimate of 63.6% of first line patients going on to receive treatment with a second line agent (= 1964 or 3.56 patients per 100,000), and if the relative dose intensity from the AXIS trial is used, the cost per 100,000 population would be £96,150.
Background

Disease
Renal cell carcinoma (RCC) originates in the lining of the tubules of the kidney and accounts for 90% of kidney cancers and approximately 3% of all adult cancers. In England and Wales, kidney cancer is the 6th most common cancer in men and the 9th most common in women.¹

Treatment
Early stage and locally advanced cancers may be treated surgically with the aim of cure. Advanced or metastatic RCC are usually resistant to chemotherapy, radiotherapy and hormonal treatment, and are most commonly treated with biological therapies for the relief of physical symptoms and maintenance of function, rather than cure. First line treatments include sunitinib, pazopanib and cytokine-based immunotherapy.²

A 2010 Cochrane systematic review identified RCTs of targeted agents in the treatment of advanced RCC to assess the clinical benefit of these agents compared to the current standard of care. Two phase III studies in people who have failed to respond to prior systemic therapy were identified. One compared sorafenib with placebo in people who had received prior cytokine therapy, and found that sorafenib improved progression free survival (PFS; 5.5 vs. 2.8 months; hazard ratio, 0.44, 95% CI 0.35 to 0.55), but had no effect on overall survival. The other study compared everolimus with placebo in people who had received prior anti-vascular endothelial growth factor receptors [VEGFR] therapy, and found that everolimus improved PFS (4.0 vs. 1.9 months; HR 0.30, 95% CI 0.22 to 0.40), but had no effect on overall survival.²

There are currently no treatments approved by NICE for use in people with advanced RCC who have failed to respond to prior systemic therapy.² However, sunitinib and everolimus are occasionally prescribed as second-line treatments through the Cancer Drugs Fund.²

According to guidelines from the European Association of Urology (2010)³:

- Sorafenib is recommended as a second-line treatment for metastatic RCC after cytokine failure
- Everolimus can be recommended as second-line treatment after failure of tyrosine kinase inhibitors (TKI)

ESMO clinical practice guidelines, 2012, state the following algorithm for systemic treatment of metastatic renal cell carcinoma (mRCC):

<table>
<thead>
<tr>
<th>Histology and setting</th>
<th>Risk group</th>
<th>Standard treatment</th>
<th>Alternative options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear-cell first line</td>
<td>Good or intermediate risk</td>
<td>Sunitinib</td>
<td>Cytokines (including high dose IL2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab and interferon Pazopanib</td>
<td>Sorafenib</td>
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<tr>
<td></td>
<td>Poor prognosis</td>
<td>Temsirolimus</td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Clear-cell second line</td>
<td>Post-cytokines</td>
<td>Sorafenib</td>
<td>Sunitinib</td>
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<tr>
<td></td>
<td></td>
<td>Pazopanib</td>
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<td></td>
<td></td>
<td>Axitinib</td>
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<tr>
<td>Clear-cell third line</td>
<td>Post-TKIs</td>
<td>Everolimus</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axitinib</td>
<td></td>
</tr>
<tr>
<td>Non-clear-cell histology</td>
<td>Post-2 TKIs</td>
<td>Everolimus</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td></td>
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<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sorafenib</td>
</tr>
</tbody>
</table>

¹. London Cancer New Drugs Group

². National Institute for Health and Care Excellence (NICE)

³. European Association of Urology (EAU)
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London Cancer New Drugs Group

The ESMO guidelines, therefore, recommend axitinib as an option for second-line treatment of clear-cell mRCC following cytokine or TKI therapy.5

Axitinib (Inlyta®, Pfizer)

Axitinib is a protein kinase inhibitor of vascular endothelial growth factor (VEGF) receptors that inhibits VEGF-mediated endothelial cell proliferation and survival. It is licensed in the UK for the treatment of adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine.4 It is available in 1mg and 5mg tablets, and the recommended starting dose is 5mg twice daily, with dose adjustments made according to individual safety and tolerability, up to 10mg twice daily.4

Epidemiology

In the UK in 2009, there were 9286 new cases of kidney cancer, with an age standardised incidence rate of 11.6 per 100,000. There were 7607 new cases in England with a rate of 11.4 per 100,000. RCC is the most common (90%) type of kidney cancer in adults equating to 10.3 cases per 100,000. Using the British Association of Urological Surgeons (BAUS) figures, 26% of these would be stage 3, and 19% would be stage 4. Therefore 45% would be diagnosed with advanced or metastatic cancer, meaning that 4.6 per 100,000 may be estimated to be diagnosed with advanced or metastatic RCC.2

Published data

No phase III trials comparing axitinib with placebo or standard care have been conducted. One RCT has evaluated axitinib for people who have failed to respond to prior systemic therapy and formed the basis of the licensing approval. The AXIS trial* compared axitinib with sorafenib (which is not NICE approved as a second-line treatment) in 723 patients with RECIST-defined progressive disease after one prior systemic first-line regimen. Randomisation was stratified according to type of prior first-line regimen:5

- sunitinib-based (n=389; 54% of randomised population)
- cytokine-based (n=251; 35%)
- bevacizumab plus interferon-alpha-based (n=59; 8%)
- temsirolimus-based (n=24; 3%)

Patients on axitinib (n=361) received 5mg BD for two weeks then if this was tolerated and no hypertension was present, the dose was increased to 7mg BD and then to 10mg BD using the same criteria. Sorafenib (n=362) was given at a dose of 400mg BD which could be reduced to once daily or alternate day dosing if required. Treatment was continued until disease progression, withdrawal of consent, withdrawal due to adverse effects or patient death. The primary outcome was PFS.5

The following findings were reported:

The median duration of treatment in the trial was 6.4 months for axitinib and 5.0 months for sorafenib.

At the point of last data collection (August 2010), 61% of patients in the axitinib group (221/361) and 71% of patients in the sorafenib group (256/362) had discontinued treatment, of which 44% (160) and 50% (180), respectively had done so due to disease progression.

The PFS was improved with axitinib compared to sorafenib (median 6.7 months vs. 4.7 months with sorafenib; hazard ratio [HR] 0.67, 95% CI 0.54 to 0.81; p<0.0001).

Median duration of response was 11 months with axitinib and 10.6 months with sorafenib (p not given).

Axitinib improved the secondary outcome of response rate, which was 19% with axitinib vs. 9% with sorafenib (p=0.0001).

Axitinib improved PFS for people who had received first-line sunitinib (4.8 months axitinib vs. 3.4 months sorafenib; 0.74, 0.57 to 0.96; p=0.0107) and who had received first-line cytokine-based therapy (12.1 months axitinib vs. 6.5 months sorafenib; 0.46; 0.32 to 0.68; p<0.0001). It also appeared to improve PFS compared to sorafenib regardless of performance status.

Axitinib improved the composite endpoint of time to deterioration; this ranged from 3.1 to 3.7 months for axitinib vs 2.8 to 2.9 months for sorafenib, depending on the symptom scale used.

This study concluded that axitinib is linked to a statistically significant improvement in median PFS compared with sorafenib in patients with advanced RCC. The study was not powered to assess overall survival: 417 events were required to give the analysis 80% power and 223 occurred. The authors report that survival data will be reported later when mature. Updated survival data has been presented at ESMO conference 2012.6 The median overall survival was 20.1 months in the axitinib arm (95% CI 16.7–23.4 months) and 19.2 months in the sorafenib arm (95% CI 17.5–22.3 months) (hazard ratio 0.969; P=0.3744).
Safety

In the AXIS trial, the most frequent adverse effects associated with axitinib were diarrhoea, hypertension, fatigue, decreased appetite, nausea and dysphonia, with each affecting more than 30% of participants. The most common adverse effects of grade ≥3 were hypertension (16%), diarrhoea (11%) and fatigue (11%). In comparison, the most frequent adverse effects associated with sorafenib (affecting >30%) were diarrhoea, palmar-plantar erythrodysoxiaethesia, fatigue, rash and alopecia. The most common adverse effects of grade ≥3 with sorafenib were palmar-plantar erythrodysoxiaethesia (affecting 16%), hypertension (11%), hypophosphataemia (16%) and lipase elevation (15%). Serological abnormalities that were more common with axitinib were elevated haemoglobin (10% vs. 1% of sorafenib), elevated thyroid stimulating hormone (TSH ≥10mU/L: 32% vs. 11%) and elevated creatinine (55% vs. 41%). Serological abnormalities that were more common with sorafenib were anaemia (affecting 52% vs. 35% with axitinib), hypophosphataemia (50% vs.13% with axitinib), hypocalcaemia (59% vs. 39% with axitinib), and lipase elevation (46% vs. 27% with axitinib).²

Overall 4% of axitinib-treated patients (14/359) discontinued due to treatment-related adverse events, compared to 8% of sorafenib-treated patients (29/355). The most common reasons for withdrawal from axitinib were fatigue (4 events) and transient ischaemic attack (3 events). The most common reasons for withdrawal from sorafenib were palmar-plantar erythrodysoxiaethesia (4 events), diarrhoea (3 events) and asthenia (3 events).²

Prescribing information for axitinib cautions that hypertension, including hypertensive crisis, has been observed and blood pressure should be well controlled prior to starting treatment and monitored.² Prescribing information from Pfizer also cautions that arterial and venous thrombotic events have been observed and caution exercised in people who are at increased risk for these events.²

Cost

No economic evaluations were identified of axitinib for advanced or metastatic RCC that has failed to respond to prior systemic treatment.²

According to Pfizer, the estimated patient population for axitinib based on current UK epidemiology and its internal marketing projections is as follows:⁷

- Number of newly diagnosed kidney cancers in UK per year = 8163
- 90% of UK kidney cancers are RCC = 7347
- From total, 26% and 17% expected to have stage III and IV disease, respectively = 3159
- From total, number of former stage I and II patients with recurrence (33%) = 1382
- Total = 4541
- Proportion of total eligible for first line treatment = 68% = 3088

Therefore the proportion of first line patients going on to receive treatment with a second line agent (63.6%) = 1964 or 3.56 patients per 100,000.⁷

The cost of 56 tablets of 1mg axitinib is £844 (including VAT). The cost of 56 tablets of 5mg axitinib is £4220 (including VAT). The mean relative dose intensity for axitinib in the AXIS study was 10mg daily. The median treatment duration in the AXIS trial for axitinib was 6.4 months. The cost of treatment for 6.4 months would therefore have been £27,000 per patient (including VAT). Locally agreed discount schemes are available.

Assuming 3.56 patients per 100,000 would be eligible for axitinib, this would mean a cost of £96,150 per 100,000 population.

Service implication

Axitinib, like other tyrosine kinase inhibitors is an orally administered medication. Axitinib would be an option as second-line therapy and other second-line therapies are also oral medications. Therefore the service implication would be minimal.
### References


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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for this treatment)</th>
<th>Average duration of treatment (taken from trial data)</th>
<th>Cost per month/cycle</th>
<th>Cost per 100,000 population per month/cycle</th>
<th>Cost per 100,000 for average treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>Second-line advanced renal cell carcinoma with progression after tyrosine kinase inhibitor (or other first-line therapy)</td>
<td>3.56/100,000</td>
<td>6.4 months</td>
<td>Using relative dose intensity of 10mg daily, £4220 including VAT every 28 days</td>
<td>Using relative dose intensity of 10mg daily, £15,000 including VAT every 28 days</td>
<td>£96,150</td>
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Details of search strategy:

NeLM
EMA
NICE
CSAS
BioSpace

NHS Evidence: Search History:

1. EMBASE; exp AXITINIB/; 1211 results.
2. EMBASE; exp KIDNEY CARCINOMA/; 37268 results.
3. EMBASE; 1 AND 3; 514 results.
4. EMBASE; 4 [Limit to: Human and English Language and Publication Year 2012-Current]; 65 results.
5. MEDLINE; axitinib.ti,ab; 146 results.
6. MEDLINE; exp CARCINOMA, RENAL CELL/; 19997 results.
7. MEDLINE; 6 AND 7; 42 results.
8. MEDLINE; 6 AND 7; 42 results.
9. MEDLINE; 8 [Limit to: English Language and Humans and Publication Year 2012-Current]; 6 results.

The document reflects the views of LCNDG and may not reflect those of the reviewers

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