Everolimus for advanced pancreatic neuroendocrine tumours (pNET)

Summary prepared September 2011

Disease background

Pancreatic neuroendocrine tumours (pNETs) are a group of rare tumours of the endocrine pancreas, with an approximate prevalence rate of 10 per million (1 per 100,000). The tumours may be functional, producing peptides which cause characteristic hormonal syndromes (insulinoma, gastrinoma, glucagonoma, vasoactive intestinal peptidoma), or non-functional but capable of causing general symptoms (1).

Although pNET is typically considered an indolent disease, patients with unresectable, locally advanced or metastatic disease and recent disease progression represent a subset with a poor prognosis and an expected survival of 1-3 years (2). In most patients surgery is not possible and treatment consists of symptom palliation. Treatment options include surgery for primary and metastatic lesions and/or liver-directed therapies such as hepatic artery chemoembolisation, radiofrequency ablation therapy or ethanol injection (1). For patients with extrahepatic disease or in whom liver directed therapies are not appropriate, systemic therapy may be considered.

Guidelines from the National Comprehensive Cancer Network (NCCN) for pancreatic endocrine tumours note that patients with unresectable disease who are asymptomatic with low tumour burden and stable disease should be observed; with marker assessment and imaging conducted every 3-12 months until significant disease progression occurs. For symptomatic patients or those with clinically significant disease progression, several options can be considered – these include biologically targeted agents (everolimus or sunitinib), cytotoxic chemotherapy, or somatostatin analogues (3).

Although somatostatin analogues may be useful for hormonal symptom control for patients with functional tumours, their role as anti-tumour agents for pNETs is unproven (1). Systemic chemotherapy with agents including streptozocin, doxorubicin, and fluorouracil is associated with response rates of 6-70%, but uncertain improvement in survival (4). Chemotherapy has a limited impact in the metastatic setting (2). The targeted agents everolimus and sunitinib have recently been confirmed to have anti-tumour efficacy and to improve progression-free survival (PFS) in patients with advanced pNETs.

Everolimus

Everolimus (Afinitor®) is licensed in the UK for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy (5). In September 2011, its license was extended to include the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease (6).

Everolimus is a selective inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase that stimulates cell growth, proliferation and angiogenesis. It is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours in vitro and in vivo (5).
Overview of evidence to support use of everolimus for pNET

The main evidence used to support the use of everolimus in the treatment of advanced pNETs consists of one fully published placebo-controlled Phase III study (RAD001 in Advanced Neuroendocrine Tumours, third trial [RADIANT-3]) (7).

**Study design:** International, multicentre, double-blind study evaluating whether everolimus would prolong progression-free survival (PFS), compared to placebo, in patients with advanced pNETs.

**Participants:** Adults with low-grade or intermediate-grade advanced (unresectable or metastatic) pNETs and radiological documentation of disease progression within the previous 12 months, and a World Health Organisation (WHO) performance status of ≤2. The previous use of antineoplastic therapy (aside from mTOR inhibitors) was permitted; however those who had undergone hepatic artery embolisation within the previous six months or cryoablation or radiofrequency ablation within the previous two months were excluded.

**Treatments:** 410 patients were randomised to double-blind treatment with everolimus (10mg once daily; n=207) or placebo (n=203), both in conjunction with best supportive care (BSC; this included use of somatostatin analogue therapy in around 40% of patients). Treatment was continued until disease progression or unacceptable toxicity. The treatment assignment could be disclosed to the investigator if the criteria for disease progression had been met, so those assigned to placebo could be crossed over to everolimus. The authors say that they recognise the potential impact of this on the analysis of overall survival.

**Endpoints:** The primary endpoint was PFS, according to RECIST criteria (intention-to-treat analysis). Those who had not progressed at the time of the final data analysis had their data censored at the time of the last adequate tumour assessment (those without any adequate post-baseline assessments were censored at day 1). Secondary endpoints included objective response rate (ORR), duration of response, overall survival (OS) and safety.

**Patient characteristics:** The median age of participants was around 58 years (range 20-87 years) and there were roughly equal numbers of men and women. More than 80% had well differentiated disease, over 90% had liver metastases, and approximately 60% had been diagnosed with pNET >2 years before entering the study. Similar proportions of the two treatment groups had received previous radiotherapy (23% in the everolimus group and 20% in the placebo group), chemotherapy (50% in both) and somatostatin analogue therapy (49% and 50%, respectively). The majority of patients (around 97%) had a WHO performance status (PS) of 0-1.

**Main efficacy results:** The median treatment durations were 8.8 months in the everolimus group and 3.7 months in the placebo group; mean dose intensities were 0.86 and 0.97, respectively. The main results, after a median follow-up of 17 months, were as follows:

- Median PFS, as assessed locally, was 11.0 months (95% CI 8.4-13.9 months) in the everolimus group and 4.6 months (3.1 to 5.4 months) in the placebo group (HR 0.35; 95% CI 0.27-0.45; p<0.001)
- Median PFS according to independent central assessment was similar: 11.4 months (10.8-14.8 months) for everolimus versus 5.4 months (4.3-5.6 months) for placebo (HR 0.34; 0.26-0.44; p<0.001)
- Estimated rates of PFS at 18 months were 34% (26-43%) and 9% (4-16%), respectively
Pre-specified subgroup analyses suggested that the benefit associated with everolimus was maintained across subgroups (e.g. previous use of chemotherapy or somatostatin analogues, tumour grade, and others). These results suggest that everolimus increases median PFS by around 6 months compared to placebo in this setting.

Confirmed tumour responses (all partial) were seen in 10 patients (5%) receiving everolimus and 4 (2%) receiving placebo – therefore the primary PFS benefit of everolimus appears to have been related to stabilisation of disease (which was the best response in 73% and 51%, respectively) or minor tumour shrinkage.

A total of 73% of patients who were initially randomised to placebo subsequently crossed over to everolimus, and this will confound the detection of any treatment-related benefit. Median overall survival had not been reached at the time of the reported analysis and no significant difference was detectable between the groups. The final overall survival analysis will be performed once approximately 250 deaths have occurred.

**Main toxicity results:**

The authors of the study note that the safety findings were consistent with the known safety profile of everolimus. The most common adverse events included stomatitis (64% in the everolimus group and 17% in the placebo group), rash (49% versus 10%), diarrhoea (34% vs. 10%), fatigue (31% vs. 14%) and infections (23% vs. 6%) (7). Most adverse events were grade 1 or 2. The most common grade 3/4 drug-related adverse events reported in association with everolimus in the main publication are listed in Table 1.

**Table 1: Most common drug-related grade 3/4 events in the Phase III study (6)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Everolimus</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Stomatitis</td>
<td>14 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>11 (5%)</td>
<td>4 (2%)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>8 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Infections</td>
<td>5 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>5 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
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Infections, as well and pneumonitis and interstitial lung disease (mainly grade 1 or 2), represented some of the most important clinical concerns. Glucocorticoids were administered to 6 of 7 patients with grade 3/4 non-infectious pneumonitis or interstitial lung disease (5 of these [2%] were considered drug-related). Three atypical infections were seen in patients receiving everolimus: pulmonary tuberculosis; bronchopulmonary aspergillosis; reactivation of hepatitis B (each in one patient) (7).

Overall, treatment with everolimus was discontinued due to toxicity in 13% of patients (most commonly due to pneumonitis, fatigue and interstitial lung disease). Eight deaths (7 in the everolimus group and one in the placebo group) were attributed to adverse events and one of these (everolimus) was related to the study drug (acute respiratory distress syndrome) (7).
Estimated cost

In 2008 there were 8,085 newly diagnosed cases of pancreatic cancer in the UK (crude incidence rate of 13.2 per 100,000 population) (7). pNETs represent around 1.3% of all cases of pancreatic cancer (7) and therefore it can be estimated that the incidence is approximately 0.17 cases per 100,000 in the UK. The cost of supplying everolimus for the treatment of pNET could therefore be estimated at approximately £4,500 per 100,000 per year.

<table>
<thead>
<tr>
<th>Drug cost estimates (Exc. VAT)</th>
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<tr>
<td>Cost per month (10mg daily x 30 days)</td>
<td>£2,970</td>
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<tr>
<td>Average duration of therapy</td>
<td>8.8 months*</td>
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<tr>
<td>Cost per patient</td>
<td>£26,136</td>
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</table>

*This was the median duration of treatment seen in the everolimus group in the Phase III study

Summary

There has been one fully published Phase III study evaluating everolimus in the treatment of advanced pNET – this showed that, compared with placebo, it increased the median PFS by around 6 months. The findings suggest that one out of every eight patients will discontinue everolimus treatment due to toxicity, rather than disease-progression. No head to head comparisons of everolimus with other agents in this setting are available. As 73% of patients randomised to placebo in the study crossed over to everolimus following disease progression, the final analysis of overall survival (to occur after approximately 250 events have occurred) will be compromised. Median overall survival had not been reached at the time of the reported analysis (median follow-up of 17 months), and it remains to be seen whether the improvement in PFS will translate into improved overall survival.

References

1. Scottish Medicines Consortium drug advice (April 2011): Sunitinib for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults
2. European Medicines Agency: Variation Assessment Report for Sutent® (sunitinib)