

Case study 1

Afinitor and Renal Cell Carcinoma*

.....

Summary

Need

- Afinitor can prolong the time to disease progression and survival for patients with renal cell carcinoma (RCC).
- RCC occurs in 4.2 per 10,000 people. In England, some 4,000 are diagnosed each year, and only some of these patients will be prescribed Afinitor.

R&D

- Afinitor was developed by Novartis but it was first discovered from natural sources.
- Use in RCC reflects the discovery that its active ingredient was able to slow cancer cell growth, when used as an immune suppressant to prevent the rejection of organ transplants.
- The active ingredient in Afinitor treats other conditions too, some already established (such as anti-rejection of transplant organs), others still awaiting decisions (such as use in breast cancer). This illustrates the potential for a product that starts from an orphan indication to expand its use over time.

Regulatory Approval

Afinitor's approval by the EMA in 2009 was for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Afinitor is approved in many other countries too: earlier in Australia (in 2008) the same year in the US (in 2009), and later in Japan (2010).

Afinitor was originally given orphan drug designation, but subsequently was removed at the request of

Novartis. This suggests that the company saw some benefit to moving out of this categorisation.

Novartis will need to re-coup R&D costs, but the effective patent life may be relatively short with the first patent for Afinitor due to expire in 2016.

Payer Approval

Afinitor costs £2,970 for a 30 dose pack (2010 cost in UK).

The budget impact estimates we found ranged from £972,000 in year one rising to £1.12million by year five in Scotland.

The costs per QALY have a considerable range, for example from £51,375 to £92,074 in Scotland.

The opinions of agencies who consider clinical and cost effectiveness have been the same: not to recommend use. SMC came to this view in 2010, with NICE coming to the same view in 2011. This reflects concerns about the uncertainties in the evidence base (such as lack of mature survival data and cross over in the trial) and the overall value for money given a high cost of Afinitor. This was the view of NICE even with scope to apply flexibility in the cost per QALY threshold and the offer of a discount through a Patient Access Scheme.

Other countries have come to a different view however: France, and the Provinces of Ontario, British Columbia, Alberta and Saskatchewan in Canada have decided to fund Afinitor. Some are using special funding mechanisms though (in Ontario, Alberta and British Columbia).

Prescription

Afinitor is part of a broader pathway of treatment and prescription requires significant expertise.

.....

* 2020health is grateful for all of the insights from experts; the content however of this report is independent and may not reflect the views of experts and sponsors but represents only the views of the 2020health project team. The research was funded by an unrestricted educational grant from Pfizer, Genzyme and Shire.

Case study 1

Afinitor and Renal Cell Carcinoma

Introduction

Afinitor (everolimus) is an anti-cancer medicine, manufactured by Novartis. Afinitor has been shown in clinical trials to reduce cancer cells in patients with renal cell carcinoma (RCC), and can lengthen life (EMA, 2011c). RCC is a disease where cancer cells are found in particular tissues of the kidney (EMA, 2011c). It is also known as cancer of the kidney or renal adenocarcinoma.

Afinitor was awarded orphan drug designation for its use in RCC, and approved for use by the European Medicines Agency (EMA) in 2009 (EMA, 2011e). It has subsequently been removed from the Community Register of orphan medicinal products at the request of Novartis (EMA, 2012h).

The active ingredient also used to “*treat a type of brain tumour called ‘subependymal giant cell astrocytoma’ (SEGA) in patients with tuberous sclerosis using the branded name Votubia (authorised by EMA in 2011 and with an orphan drug designation)*” (EMA, 2012i).

A decision is pending relating to the approval for use in hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor (EMA, 2011d).

Need

RCC affects less than 4.2 in 10,000 people (Pubmed Health, 2012). The number of people diagnosed with advanced RCC each year is less than 4,000 in England, and those eligible for Afinitor (that is, those who received first-line sunitinib and still fit enough to receive a second-line treatment) would be lower (NICE, 2011b). In Scotland, Novartis estimated that 57 patients in year 1 and 66 in year 5 could possibly be prescribed Afinitor (SMC, 2010e).

Whilst the exact cause of RCC is unknown (Pubmed Health, 2012), the cancer is known to start in the lining of the tubules in the kidney. These tubules filter and clean the blood, helping to remove waste products and make urine. It occurs most often in men ages 50 -70

(Pubmed Health, 2012) and accounts for approximately 85% of all kidney cancers (EMA, 2011c).

Early signs of this cancer are often very difficult to detect which results in approximately half of patients being diagnosed when the disease has spread around the kidney or to distant parts of the body (EMA, 2011c).

Symptoms often include abdominal pain and swelling, back pain, blood in urine, swelling of the veins around a testicle (varicocele), flank pain and weight loss (Pubmed Health, 2012). Other symptoms that are known to occur with this disease include excessive hair growth in females, pale skin and vision problems (Pubmed Health, 2012).

As time progresses the impact upon the patient is considerable. The size of the tumor may develop to such an extent that it induces severe internal bleeding, requires emergency surgical interventions, such as embolization and nephrectomy, or may lead to kidney failure.

In terms of treatment, surgery is the most common approach, although this does not prevent the cancer appearing again (EMA, 2011c). Other options include chemotherapy, radiation therapy, hormone therapy and biological therapy (EMA, 2011c). Alongside Afinitor, sorafenib and sunitinib, are also authorised by EMA for treatment of RCC (EMA, 2011c). In instances of advanced RCC, Afinitor is prescribed when the disease has progressed on or after treatment with VEGF-targeted therapy (Orphanet, 2012c).

There were 3,848 deaths from kidney cancer in 2008 in the UK (over 2% of all cancer deaths for that year) (NICE, 2011b). Approximately 90% of people with metastatic RCC die within 5 years of diagnosis and, if untreated, the median survival is estimated to be less than 12 months (NICE, 2011b).

Research and development

Afinitor was developed by Novartis Pharmaceuticals but it was first discovered from natural sources. Afinitor is a derivation of rapamycin, originally produced from *Streptomyces hygroscopicus* (Chin et al, 2006).

Afinitor was originally developed as an immune system suppressant to prevent the rejection of organ transplants (21st Century Cancer Drugs, undated). Its

Case study 1

Afinitor and Renal Cell Carcinoma

use in RCC emerged after it was found that immune suppressant drugs can help prevent the production of ‘mammalian target of rapamycin’ (M-TOR), a protein which has been found to be a critical factor in the generation of cancer cells (21st Century Cancer Drugs, undated; Drugdevelopment-technology.com, 2012).

There are numerous patents related to Afinitor. The first patent is due to expire in July 2016 (eMed tv, 2012).

Regulatory approval

EMA approved Afinitor for use in advanced RCC for those whose disease has progressed on or after treatment with VEGF-targeted therapy in 2009 (EMA, 2011c; 2011d). Approval was granted on the basis of evidence that Afinitor could slow down disease progression.

Regulatory approval was supported by evidence from an international, multi-centre, randomized, double-blind trial which took place comparing Afinitor and a placebo. It was conducted in patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially (Novartis, 2012a).

In total, 416 patients were randomized with the demographics well balanced between the two arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially) (Novartis, 2012a). Afinitor was superior to the placebo for Progression Free Survival, with patients who took Afinitor living for an average of 4.9 months without the disease getting worse, compared with 1.9 months for the patients who took placebo (EMA, 2011d). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib.

Afinitor is also approved for use in RCC in Australia (in 2008) (Australian Government, Department of Health and Ageing, 2010a), Japan (in 2010) (Drugdevelopment-technology.com, 2012), the US (in 2009) (Pazdur, undated b) and in Canada (in 2009) (Health Canada, 2010).

Payer approval

Afinitor costs £2,970 for a 30 dose pack (2010 cost in UK) (East Midlands Specialised Commissioning Group, 2011)

Afinitor has been subject to consideration for both cost and clinical effectiveness by two key UK agencies: NICE and SMC. Based on our research on the latest guidance from these agencies:

- NICE does not recommend the use of Afinitor in RCC
- SMC does not recommend the use of Afinitor in advanced RCC

AWMSG indirectly does not recommend the use of Afinitor because it has decided not to appraise, given that NICE guidance was expected less than 12 months from projected receipt of submission to AWMSG (as at September 2009) (NHS Wales, 2012). NICE guidance supercedes AWMSG guidance in any case.

We look at each of these in more detail below.

NICE

NICE considered Afinitor sometime after its launch, producing final guidance in 2011 (TA219). NICE did not recommend Afinitor as a second treatment for people with advanced renal cell carcinoma. This was based on the concern that Afinitor did not provide enough benefits to patients to justify its high cost (NICE 2011b).

The Appraisal Committee considered the evidence supplied by Novartis and the review of Novartis’ submission by the Evidence Review Group (ERG). They noted that the key factor in determining the cost effectiveness of the drug was the estimate of overall survival (NICE, 2011b). They also noted that the difference in overall survival between patients receiving Afinitor was in the range of 5.2 months to 8.2 months, and that the lower estimate was more likely. The evidence on cost effectiveness suggested a cost per QALY of between £49,300 (derived by the manufacturer) to £51,700 per QALY gained (derived by the ERG) (NICE, 2011b).

Case study 1

Afinitor and Renal Cell Carcinoma

The Appraisal Committee were also able to draw on guidance on End of Life, which can place a higher weight on the benefits from treatment when:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- No alternative treatment with comparable benefits is available through the NHS.
- The treatment is licensed or otherwise indicated for small patient populations.
- And that estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

The Committee felt that these conditions were met (NICE, 2011b). In effect, this allows the Committee to recommend a product at higher cost effectiveness ratios than are normally accepted.

The Committee were also able to consider a patient access scheme agreed between Novartis and the Department of Health. The scheme offered the first treatment pack of Afinitor free to the NHS and following treatment packs cost £2,822 (constituting a 5% discount on the acquisition cost of Afinitor). Subsequently a revised patient access scheme was agreed, the details of which are confidential (NICE, 2011b).

However, taken together, the AC remained concerned about the high cost of Afinitor versus its benefits, and did not recommend use.

SMC

The SMC considered the use of Afinitor for the treatment of patients with advanced renal cell carcinoma (aRCC), whose disease has progressed on or after treatment with VEGF-targeted therapy. In

guidance published in 2010, they did not recommend use (SMC, 2010f).

SMC considered the manufacturers submission that suggested a cost per QALY of a cost per QALY of £61,330 (range: £51,375 to £92,074) versus best supportive care (BSC) in patients with advanced renal cell carcinoma whose disease has progressed on or after treatment with VEGF-targeted therapy. SMC noted some issues with the analysis, including confounding by cross over in the trial and some doubt over whether some treatments post-progression would be used in Scotland (SMC, 2010f).

Novartis estimated a budget impact of £972,000 in year one rising to £1.12million by year five based on 57 patients in year 1 and 66 in year 5 (SMC, 2010f).

Regional approaches

Afinitor has also been subject to local scrutiny. For example, The Yorkshire Cancer Network (YCN) Gateway Group and the Humber and Yorkshire Coast Cancer Network (YCCN) Cancer Drugs Policy Group and the Tri-Network Cancer Drugs Group have not routinely funded Afinitor for the second-line treatment of patients with metastatic renal cell cancer (mRCC) who are intolerant of, or whose disease has progressed, despite any prior VEGF receptor tyrosine kinase inhibitor therapy.

This is because, in their view, Afinitor provides a modest benefit at an additional cost that would be very unlikely to fall within a cost-effectiveness threshold of £30,000 per QALY. In addition, given uncertainty over the estimated survival benefit in the health economic model, the groups did not feel sufficiently assured that the additional cost would fall within an 'end of life' cost-effectiveness threshold (Yorkshire and the Humber Specialised Commissioning Group, 2010).

The East Midlands Specialised Commissioning Group (2011) are funding Afinitor via the Cancer Drugs Fund. They estimate that the cost of treating patients with everolimus is estimated at £1.4 million per year. This will cover Afinitor treatment for patients who have previously been treated with sunitinib or pazopanib,

Case study 1

Afinitor and Renal Cell Carcinoma

have not received prior therapy with an mTOR inhibitor, and have a performance status of 0 or 1 (East Midlands Specialised Commissioning Group, 2011).

International funding

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) who determine reimbursement by the Pharmaceutical Benefits Scheme (PBS), have rejected listing for the treatment of a patient with Stage IV RCC resulted in the PBAC. The decision reflected concerns about uncertain clinical benefit and a high and uncertain cost-effectiveness ratio. A further three submissions have been made with the latest taking place in November 2011 where the submission was rejected once more on the same grounds (Australian Government, Department of Health and Ageing, 2010a).

In the Canadian Province of Ontario, the Ministry of Health and Long Term Care has announced that Afinitor can be funded through the Exceptional Access Program (EAP). Reimbursement will apply to the treatment of metastatic renal cell carcinoma (MRCC) as second or third-line therapy in patients previously treated with sunitinib (Sutent), sorafenib (Nexavar). Renewal of this will be considered for those who have demonstrated benefit from therapy and is expected to continue to benefit from Afinitor therapy (Ontario Ministry of Health and Long Term Care, 2012b).

In the Canadian Province of British Columbia, from 1st February 2011, the Genitourinary Tumour Group and the Systemic Therapy Program in BC will fund Afinitor as a new therapy option for patients with advanced renal cell carcinoma (clear cell and non-clear cell) after failure of multi-target kinase inhibitors (sunitinib, sorafenib) (BC Cancer Agency, 2011).

In the Canadian Province of Alberta, Alberta Health Services announced that it would fund Afinitor for

Sales figures for Afinitor in treatment for RCC do not appear to be readily available and yet it is recognised to be a market with considerable unmet medical need (Atkins et al, 2009). In Europe, where Afinitor is also approved for treatment in the prevention of organ rejection following heart or kidney transplantation, the drug generated sales of €55 million in 2008 (Atkins et

second-line treatment for metastatic renal cell (mRCC) carcinoma effective from 1st February 2011. Alberta Health Services Ministerial Order amended its Schedule of Cancer Drugs to include Afinitor for mRCC on the basis that it must be prescribed only through named and authorized physicians as determined by Alberta's Genitourinary Tumour Program (Kidney Cancer Canada, 2012).

Similarly, the Canadian Province of Saskatchewan government also confirmed that it would fund Afinitor for second-line treatment for metastatic renal cell carcinoma effective from 1st February 2011 (Kidney Cancer Canada, 2012).

The Transparency Committee of the French National Authority for Health recommended inclusion of Afinitor in 2010, on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services (Haute Autorité de Santé, 2010).

Prescription

As with many anticancer treatments, use of Afinitor should be started and supervised by a doctor who has experience in this field (EMA, 2012h).

The recommended dose of Afinitor is 10 mg once a day, swallowed whole at the same time every day and should not be chewed or crushed. They should be taken consistently with or without food (EMA, 2012h).

Treatment should continue for as long as the patient benefits from it or until the patient develops unacceptable side effects. The doctor may reduce the dose or stop treatment for a short period if the patient has severe or intolerable side effects (EMA, 2012h).

al, 2009). Analysts suggest that Afinitor could have peak sales of US\$364 million in 2015 for other cancer indications such as gastric and breast cancers, tuberous sclerosis complex and neuroendocrine tumours (Atkins et al, 2009).