Gastric Cancer
Drug Discoveries
what the future holds

March 2011
MARKET ANALYSIS

There is room for considerable change in the gastric cancer market as improved therapies seek to improve patient outcomes for advanced disease. Over the next seven years, Espicom expects to see the market grow by 133 per cent from US$846 million in 2010, to almost US$2 billion in 2017, with the targeted therapies accounting for most of this growth. While competition amongst these targeted therapies will intensify from 2013/4, Roche will continue to dominate this market with its HER2 inhibitor, Herceptin (trastuzumab).

CURRENT MARKET

Standard drug treatment for gastric cancer has traditionally been centred around combinations of chemotherapy agents such as 5-fluorouracil (5-FU), doxorubicin, methotrexate, epirubicin, etoposide and cisplatin, with a number of next-generation chemotherapies providing further options in recent years. With one exception, all existing branded chemotherapeutics are now also available generically. Nevertheless, chemotherapy dominates the market by sales value. Espicom estimates that the gastric cancer market for branded pharmaceuticals was worth US$796 million in 2010, with just 7 per cent, or US$50 million, of this attributable to targeted therapy. The market is set to expand considerably by 2017, with targeted therapies responsible for the majority of sales growth.

Gastric Cancer Sales by Therapy (2010)

Source: Espicom, company reports.

Next-Generation Chemotherapy

sanofi-aventis has had significant success with its taxane, Taxotere (docetaxel), which is approved for a wide range of cancers, by showing that in combination with cisplatin and 5-FU its survival advantage was significantly better than cisplatin and 5-FU alone. These results led to approvals for gastric cancer in Japan (April 2000), the US (March 2006) and the EU (April 2006). However, with the expiry of patents in both the US and EU in 2010, Taxotere is now subject to generic competition and has lost market share, although it still commands a substantial 14 per cent.

One notable success of recent years is Roche’s Xeloda (capecitabine), which is replacing 5-FU in the US and EU, where it has been approved as a first-line treatment in gastric cancer since March 2007. Xeloda is a tumour-selective prodrug of 5-FU that has been shown in clinical trials to be as effective as 5-FU, while requiring only two daily oral doses compared to other more complex intravenous chemotherapy regimens. With US patents in force until December 2013, Xeloda is the only branded chemotherapeutic for gastric cancer not facing generic competition at present. Espicom estimates that Xeloda sales in this indication amounted to US$109 million in 2010, or 13 per cent of total branded sales for gastric cancer. The product is currently filed in Japan.
Proof of Concept/Clinical Data

A Phase I trial conducted by scientists at the Institute of Cancer Research (ICR) and the Royal Marsden Hospital, working with AstraZeneca, included patients with inherited forms of advanced breast, ovarian and prostate cancers, caused by mutations in the BRCA1 and BRCA2 gene, who were treated with olaparib. The results, published in the NEJM (2009;361:123-134), showed that despite having previously received many standard therapies, in more than half of the patients, tumours shrank or stabilised. One of the first patients to be given the treatment was still in remission after two years. Of the 19 BRCA-carrier patients, 12 (63 per cent) derived clinical benefit from the drug by their tumour shrinking or stabilising for at least four months.

Breast Cancer

As reported at the 2009 ASCO meeting and in The Lancet (2010;376:235-244), in an AstraZeneca-funded, Phase II study of olaparib alone in women with BRCA1 or BRCA2 mutations and advanced BC who had received a median of three previous chemotherapy regimens, objective response rate was 11 out of 27 patients (41 per cent; 95% CI, 25 to 59) in the 400mg twice daily cohort, and six out of 27 (22 per cent; 95% CI, 11 to 41) in the 100mg twice daily cohort. Progression-free survival was 5.7 months.

Ovarian Cancer

An AstraZeneca-funded, Phase II study, results from which were presented at the 2009 ASCO meeting and published in The Lancet (2010;376:245-251), showed that olaparib can reduce the size of tumours in women with advanced hereditary OC with BRCA gene mutations. Of the 57 women enrolled, 33 per cent showed a significant shrinkage in the size of their tumours, and in some cases, complete disappearance of their tumours. The clinical benefit rate was 67 per cent and progression-free survival was 5.8 months.

Scientists at the ICR and the Royal Marsden Hospital, working with KuDOS Pharmaceuticals (now AstraZeneca), found that olaparib shrank or stabilised tumours in approximately half of OC patients bearing BRCA1 or BRCA2 mutations. As published in the Journal of Clinical Oncology (2010;28:2512-2519), after treatment with olaparib, 20 patients responded with their tumours shrinking or with significant falls in their OC marker, CA-125, or both. The disease also stabilised in a further three patients. Olaparib was effective for an average of seven months, while at the time of reporting, several patients were still taking the drug and had been for nearly two years.

The team found that the clinical benefit rate with olaparib was higher (70 per cent) among patients with platinum-sensitive disease (disease recurrence more than six months after previous platinum therapy). Crucially, however, the clinical benefit rate was still 46 per cent in platinum-resistant patients.

Development Risks

In clinical trials, to date, olaparib appears to be well tolerated. It targets cancer cells, but leaves healthy cells relatively unscathed. Toxicities from the drug have been mostly limited to Grade 1 or 2, including nausea, fatigue and anaemia.

The cost of screening for BRCA mutations and the relatively narrow market size has the potential to shift funding to other more promising areas. AstraZeneca has discontinued olaparib’s development for genetic BC and is currently focusing development on serous OC.

The failure of sanofi-aventis’ PARP inhibitor, iniparib, to meet significance for the co-primary endpoints of overall and progression-free survival in a Phase III TNBC trial raises concerns for the efficacy of this class of drugs in this indication.

Company Expertise

Olaparib was in development by KuDOS Pharmaceuticals (development name, KU 59436), which was acquired by AstraZeneca in January 2006. AstraZeneca is one of the leading companies in oncology, marketing a range of products including: the anti-oestrogens, Nolvadex (tamoxifen) and Faslodex (fulvestrant), the aromatase inhibitor, Arimidex (anastrozole), and the luteinising hormone-releasing hormone analogue, Zoladex (goserelin), for the treatment of BC; the anti-androgen, Casodex (bicalutamide), for the treatment of prostate cancer; and the epidermal growth factor receptor-tyrosine kinase inhibitor, Iressa (geftinib), for the treatment of lung cancer.
AstraZeneca adopted an aggressive acquisition strategy during 2006 and 2007, which saw the company purchase several leading biotech companies, with combined costs of nearly US$17 billion. The most important acquisitions have been of Cambridge Antibody Technology and MedImmune, which have bolstered the pipeline with an additional 14 candidate compounds. The purchase of MedImmune, in particular, has been significant to AstraZeneca, adding three new products to the company’s portfolio, including one blockbuster in Synagis (palivizumab). According to AstraZeneca, MedImmune had a further 100 biologics in development. AstraZeneca has supplemented this acquisition activity with a number of research and licensing agreements.

AstraZeneca’s key products remain the cholesterol-lowering drug, Crestor (rosuvastatin), and the antipsychotic, Seroquel (quetiapine). Despite its oncology segment currently containing two blockbuster products with sales in excess of US$1 billion (Arimidex and Zoladex), patent expires for these products are expected to lead to significant declines in oncology revenue for AstraZeneca within our forecast period. Perhaps because of this, AstraZeneca’s oncology pipeline is the largest of all its therapeutic areas and the company is involved in cancer research collaborations with Array Biopharma, Astex Therapeutics, Caprion Pharmaceuticals and Cell Signalling Technology. With such continued investment, AstraZeneca is likely to remain a key player within the oncology field for the foreseeable future.

Myriad Genetics is providing molecular diagnostic testing for ongoing clinical studies and has exclusive worldwide rights to diagnostic applications of findings from the trials. The company’s BRACAnalysis test searches for mutations in BRCA1 and BRCA2.

**Competition within the Market-place**

As a PARP inhibitor, olaparib is being specifically positioned to treat the subset of patients who carry mutations of the BRCA1 and BRCA2 genes, although other patient groups may benefit from this drug, particularly those who have mutations in other DNA repair genes. Whilst AstraZeneca reports that activity in single arm trials in gBRCA BC has been encouraging and supports further investigation, it is now focusing development on patients with BRCA positive serous OC due to substantial data that includes randomised Phase II trials. This decision puts olaparib ahead of the other PARP inhibitors under development for OC, that is sanofi-aventis’ iniparib, Abbott’s veliparib and Pfizer’s PF-1367338, although iniparib may launch for lung cancer in 2015.

Targeted therapies are being investigated in an effort to improve clinical outcome for patients with advanced gastric cancer, which is generally incurable. Survival times are currently disappointing; median survival is three to four months in patients not receiving chemotherapy, and little progress has been made with new triplet and doublet chemotherapeutic combinations in extending survival beyond one year. Roche’s Herceptin (trastuzumab) was launched in 2010, as the first targeted therapy for HER2-positive advanced gastric cancer and there are many candidates for advanced disease progressing through Phase III trials. Olaparib is the only PARP inhibitor under investigation for this disease, although with AstraZeneca focusing development efforts on OC, there is uncertainty surrounding the timing of a potential launch for gastric cancer before 2017.

**Competitor Ratio Analysis**

<table>
<thead>
<tr>
<th>Mode of Action</th>
<th>Novel PARP inhibitor.</th>
<th>6</th>
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<tbody>
<tr>
<td>Proof of Concept</td>
<td>Tumour shrinkage observed in Phase II OC trials.</td>
<td>5</td>
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<tr>
<td>Development Risks</td>
<td>Well tolerated in trials, to date. BC development no longer a focus.</td>
<td>6</td>
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<tr>
<td>Company Expertise</td>
<td>AstraZeneca promotes two oncology blockbusters that are now facing generic competition. Portfolio enhanced with the acquisition of KuDOS.</td>
<td>8</td>
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<tr>
<td>Competition</td>
<td>A number of PARP inhibitors under development, with olaparib ahead in OC. Uncertainty surrounding potential launch for gastric cancer.</td>
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**Total Score** 32
Teysuno

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<th>Generic Name</th>
<th>S-1</th>
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<td>Company</td>
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**Mode of Action**

S-1 is an oral fluoropyrimidine developed by Taiho Pharmaceutical (Otsuka) for the treatment of solid tumours, especially gastric cancer. S-1 combines tegafur (a prodrug of 5-FU), gimeracil (5-chloro-2, 4-dihydroxypyridine; CDHP) and oteracil (potassium oxonate). CDHP inhibits 5-FU degradation and oxonic acid reduces gastrointestinal tract toxicity.

**Current Status**

**Approvals/Filings**

S-1 has a wide variety of indications and has been available in Japan since 1999. It is used for the treatment of gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer (NSCLC), inoperable or recurrent breast cancer, and pancreas and biliary tract cancers. For gastric cancer, S-1 has become the standard chemotherapy in Japan. It is available in 20 and 25mg (as tegafur quantity) capsules. Teysuno is also authorised for the treatment of gastric cancer patients in South Korea, China, Singapore and Taiwan.

In March 2011, the EC granted marketing authorisation for S-1 for the treatment of adults with advanced gastric cancer when given in combination with cisplatin. The authorisation applies to the 27 member states and the three European Economic Area countries of the EU. The decision was based, in part, on the results of FLAGS (First-Line Advanced Gastric Cancer Study), the largest, international, Phase III trial conducted, to date, in patients with advanced gastric cancer. S-1 will be launched in Europe during the second half of 2011.

In December 2007, orphan designation was granted by the EC to sanofi-aventis, for S-1 for the treatment of gastric cancer. The sponsorship was transferred to Quintiles Ireland in February 2009, and subsequently to Taiho Pharma Europe, in May 2009. S-1 has also been granted orphan drug designation for gastric cancer in the US.

**Development**

In Japan, the drug is in Phase III trials for hepatocellular carcinoma and uterocervical cancer (the latter also in Asia), and Phase II studies for prostate cancer and renal cell carcinoma.

In the US, a Phase III for advanced gastric cancer (first-line treatment in combination with cisplatin) is active, although not recruiting patients, and was due for completion in February 2010. In addition, Phase I/II trials for both NSCLC and pancreatic cancer are ongoing.

Taiho is conducting a Phase II/III trial investigating S-1 and irinotecan in the treatment of advanced refractory gastric cancer, due to be completed in March 2012.

**Proof of Concept/Clinical Data**

**Advanced Gastric Cancer**

Results from the Japanese, open-label, Phase III SPIRITS trial in 298 advanced gastric cancer patients, presented at ASCO 2007, showed that overall survival with a two-year follow-up was significantly higher in the S-1+cisplatin arm over S-1 alone (13 vs 11 months, respectively; p=0.036). Likewise, progression-free survival was significantly longer, at six compared to four months, respectively.