National Horizon Scanning Centre

Aflibercept (VEGF Trap) for advanced chemo-refractory epithelial ovarian cancer

December 2007

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Aflibercept (VEGF Trap) for advanced chemo-refractory epithelial ovarian cancer

Target group
- Ovarian cancer – advanced, third line monotherapy.

Technology description
Aflibercept (VEGF Trap) is a fusion protein that combines the constant region of a human IgG antibody with the ligand-binding portion of the vascular endothelial growth factor (VEGF). This new mode of action has a greater affinity for the VEGF ligand than anti-VEGF monoclonal antibodies (reportedly around a 1000 times greater than bevacizumab). Aflibercept inhibits VEGF-induced signalling and VEGF-driven angiogenesis, and blocks placental growth factor, which also appears to play a role in angiogenesis. This reduces vascularisation of tumours, thereby inhibiting tumour growth. Aflibercept is administered as an intravenous infusion. Based on clinical trials the dose may be 2 or 4 mg/kg every 2 weeks.

Aflibercept is also in clinical trials for:
- Second line treatment of non-small cell lung cancer (in combination with docetaxel) and colorectal cancer (in combination with folinic acid, 5-FU and irinotecan) – licensing applications expected in 2010.
- First line treatment of pancreatic cancer (in combination with a gemcitabine-based regimen), and hormone-refractory metastatic prostate cancer - licensing applications expected 2011.

Innovation and/or advantages
Aflibercept’s new mechanism of action may provide the potential for it to be a more powerful anti-angiogenesis agent than current options, prolonging stable disease in a group of patients with few therapeutic options.

Developer
Sanofi-Aventis

Place of use
- Home care e.g. home dialysis
- Community or residential care e.g. district nurses, physio
- Primary care e.g. used by GPs or practice nurses
- Secondary care e.g. general, non-specialist hospital
- Tertiary care e.g. highly specialist services or hospital
- Emergency care e.g. paramedic services, trauma care
- General public e.g. over the counter
- Other:

Availability, launch or marketing dates, and licensing plans:
A licensing application is anticipated during 2008 and may be based on the results of the completed phase II trial.

NHS or Government priority area:
This topic is relevant to the NHS Cancer Plan

Relevant guidance
- NICE clinical guideline in progress. Ovarian cancer - recognition and initial management (17th wave).
• NICE technology appraisal:

Clinical need and burden of disease
Ovarian cancer is the fourth most common cause of cancer mortality in women and resulted in 3,939 deaths in England and Wales in 2005. The total number of new cases in registered in 2004 in England and Wales was approximately 5,070. Around 85% of cases occur in women over 50 years. Epithelial ovarian cancer, which involves the formation of malignant cells in the tissue covering the ovary accounts for around 85-90% of all ovarian cancers. The 5-year survival rate in 2000-2001 is estimated at 40%. Ovarian cancer is often asymptomatic in the early stages and over 75% of cases are diagnosed with advanced stage III or stage IV disease, around 3,800 cases per year.

Between 55% and 75% of women whose tumours respond to first line therapy relapse within 2 years of completing treatment and studies suggest around 50% of patients will progress on second line treatment. On this basis, approximately 1,000 – 1,700 patients may be eligible for third line therapy.

Existing comparators and treatments
• Surgery with either neoadjuvant or adjuvant chemotherapy.
• First line chemotherapy with platinum-based therapy alone or in combination with paclitaxel (where the platinum agent is either carboplatin or cisplatin).
  First line options may be repeated for second (and subsequent) treatments. New options may include single-agent paclitaxel, PLDH (pegylated liposomal doxorubicin hydrochloride), gemcitabine, doxorubicin or topotecan.
• Second line chemotherapy is palliative and aims to reduce symptoms and prolong survival. Ovarian tumours eventually develop multi-drug resistance.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial name or code</th>
<th>Afiblercept monotherapy - recurrent epithelial multi-resistant ovarian cancer; phase II^8</th>
<th>Afiblercept monotherapy – advanced ovarian cancer with recurrent malignant ascites; phase II/III^9</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Sanofi-Aventis, Regeneron</td>
<td>Sanofi-Aventis, Regeneron</td>
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<tr>
<td>Status</td>
<td>Conference abstract and presentation</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Location</td>
<td>USA, Europe</td>
<td>USA</td>
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<tr>
<td>Design</td>
<td>Randomised, double-blind.</td>
<td>Randomised, double-blind, placebo-controlled.</td>
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<td>Participants</td>
<td>n=200; multi-resistant disease. Afiblercept administered i.v. (2 or 4 mg/kg) every 2 weeks. Average of 5 cycles received (range 1-15).</td>
<td>n=54; multi-resistant disease. Afiblercept administered i.v. every 2 weeks.</td>
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<tr>
<td>Follow-up</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Objective response rate at 2 different doses.</td>
<td>Time to repeat paracentesis.</td>
</tr>
<tr>
<td>Secondary</td>
<td>Time to progression; progression free</td>
<td>Ascites impact measure (patient)</td>
</tr>
<tr>
<td>outcomes</td>
<td>survival; overall survival; surrogate marker (CA-125) reduction; time to CA-125 progression; safety; quality of life (QoL)</td>
<td>questionnaires; 60-day frequency of paracentesis; safety, tolerability; tumour assessments; QoL</td>
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<td>Key results</td>
<td>Combined preliminary results in 162 patients (study remains blinded with regards to dose) showed partial response in 13 (8%); and stable disease in 77% at 4 weeks and 41% at 14 weeks. Of 23 with ascites, resolution occurred in 7, 13 remained stable. CA-125 protein levels were reduced by &gt;50% in 21 patients (13%).</td>
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<td>Expected reporting</td>
<td>Complete results expected mid 2008.</td>
<td>Not known</td>
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<td>Adverse effects</td>
<td>Most common grade 3/4 adverse events included hypertension (18%); proteinuria (7%) and headache (4%). 2 patients experienced bowel perforation (&lt;1%), but recovered.</td>
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</table>

**Estimated cost and cost impact**

The cost of aflibercept is currently unknown. Any costs will be additional to currently available chemotherapy regimens.

**Potential or intended impact – speculative**

**Patients**
- ✔ Reduced morbidity  
- ❑ Quicker, earlier or more accurate diagnosis or identification of disease  
- ✔ Reduced mortality or increased survival  
- ❑ Other:  
- ✔ Improved quality of life for patients and/or carers  
- ❑ Non identified

**Services**
- ✔ Increased use – additional intravenous therapy  
- ❑ Service reorganisation required  
- ❑ Staff or training required  
- ❑ Decreased use  
- ❑ Other:  
- ❑ Non identified

**Costs**
- ❑ Increased unit cost compared to alternative  
- ✔ New costs – additional therapy  
- ❑ Increased costs: more patients coming for treatment  
- ❑ Increased costs: capital investment needed  
- ❑ Savings:  
- ❑ Other:  

**References**

7Gordon AN, Fleagle JT, Guthrie D et al. Pegylated liposomal doxorubicin prolongs survival compared to topotecan as second-line treatment in women with platinum-sensitive ovarian cancer. Evidence-based oncology 2002; 3: 21-23.