Nimotuzumab (Theraloc) for locally advanced head and neck cancer – first line

December 2010

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Nimotuzumab (Theraloc) for locally advanced head and neck cancer – first line

**Target group**
- Head and neck cancer: locally advanced, squamous cell – first line; in combination with cisplatin and radiotherapy.

**Technology description**
Nimotuzumab (Theraloc, OSAG 101, BIOMAb-EGFR, anti-EGFR, h-R3) is an epidermal growth factor antagonist and humanised monoclonal antibody. It is designed to target the epidermal growth factor receptor (EGFR) and inhibit the activation of protein tyrosine kinase. Nimotuzumab is administered by a 30-minute once weekly intravenous (IV) infusion at a dose of 200-400mg/m² in adults.

Nimotuzumab is in the following phases of clinical trials for the stated indications:

**Phase III**
- Glioblastoma.
- Glioma.
- Pancreatic cancer (phase II/III).

**Phase II**
- Brain cancer.
- Cervical cancer.
- Colorectal cancer.
- Non-small cell lung cancer.
- Oesophageal cancer.
- Prostate cancer.

**Innovation and/or advantages**
If licensed, nimotuzumab may provide a further treatment option for locally advanced head and neck cancer.

**Developer**
YM Bioscience and Oncoscience AG (EU marketing partner).

**Availability, launch or marketing dates, and licensing plans**
In phase III clinical trials.

**NHS or Government priority area**
This topic is relevant to the NHS Cancer Plan (2000) and Cancer Reform Strategy (2007).

**Relevant guidance**
- SIGN. Diagnosis and management of head and neck cancer. 2006.
Clinical need and burden of disease

Over 90% of head and neck cancers are squamous cell (epidermoid) carcinomas and are most commonly diagnosed in people over 59 years. There is significant male preponderance. The majority of head and neck cancers arise from the surface layers of the upper aerodigestive tract incorporating the lips, mouth (oral cavity), tonsils and throat (nasopharynx, oropharynx, larynx and pharynx). Other less common sites include the salivary glands, jaw, eye, paranasal sinuses and middle ear.

There were approximately 8,000 new registrations for head and neck cancer in England and Wales in 2007, and approximately 2,700 registered deaths in 2008. There is an increasing incidence globally, primarily in oropharyngeal and oral cavity tumours, with a trend towards younger age of diagnosis. The overall survival is around 50% at five years. This is variable depending on the stage of cancer or extent of disease, smoking status and geographical location.

It is estimated that 15-20% of head and neck cancer cases present with metastatic disease.

Existing comparators and treatments

Management options include:
- Surgery.
- Radiotherapy.
- Chemotherapy (e.g. docetaxel, cisplatin or carboplatin and 5-fluorouracil) to enhance the effect of radiotherapy, or neoadjuvant chemotherapy; can increase survival and local control.
- Biological therapies, such as cetuximab may be used in combination with radiotherapy for patients with locally advanced squamous cell carcinoma of the head and neck whose Karnofsky performance is 90% or greater and for whom all forms of platinum-based chemoradiotherapy are contraindicated.
- Photodynamic therapy (PDT) with tempoporfin may be used.

The acute and chronic toxicities from surgical and non-surgical treatments are often severe. The treatment of locally advanced disease would typically involve surgery with radiotherapy and chemotherapy, neoadjuvant chemotherapy followed by chemoradiotherapy, concomitant radiotherapy, or radiotherapy plus biological agents.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00957086, IHN01; Nimotuzumab vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>National Cancer Centre, Singapore.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
</tr>
<tr>
<td>Location</td>
<td>Singapore and 11 other countries (UK and Australia considering participation).</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=710 (planned); adults; squamous cell cancer of the head and neck; resectable stage III or IV; complete macroscopic resection. Randomised to nimotuzumab 200mg IV over 30 minutes once a week for 8 weeks, commencing first week of radiotherapy; or placebo; both in combination with cisplatin and radiotherapy.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 8 weeks; 5 year follow up.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Disease-free survival.</td>
</tr>
</tbody>
</table>
December 2010

<table>
<thead>
<tr>
<th>Secondary outcome</th>
<th>Overall survival; toxicity profile.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected reporting date</td>
<td>June 2014.</td>
</tr>
</tbody>
</table>

**Trial**

<table>
<thead>
<tr>
<th>Radiotherapy alone, or with nimotuzumab and/or chemotherapy; phase II.</th>
<th>Nimotuzumab in combination with radiotherapy vs placebo and radiotherapy; phase II.</th>
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</thead>
</table>

**Sponsor**

<table>
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<tr>
<th>Biocon Limited, Bangalore.</th>
<th>National Institute of Oncology and Radiobiology, Cuba.</th>
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**Status**

<table>
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<tr>
<th>Published.</th>
<th>Published.</th>
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**Source of information**

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<tr>
<th>Publication</th>
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</table>

**Location**

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<tr>
<th>India.</th>
<th>Cuba.</th>
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**Design**

<table>
<thead>
<tr>
<th>Randomised, active-controlled, open-label.</th>
<th>Randomised, placebo-controlled.</th>
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</table>

**Participants and schedule**

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<tr>
<th>n=92; adults; squamous cell carcinoma of the head and neck; advanced unresectable. Randomised to 4 arms. All patients received radiotherapy approximately 60 Gy over 6 weeks. Arm 2 also received nimotuzumab 200mg IV over 60 minutes once weekly. Arm 3 also received cisplatin 50mg IV over 2 hours once weekly. Arm 4 also received cisplatin and nimotuzumab as described.</th>
<th>n=106; adults; squamous cell carcinoma of the head and neck; advanced; unsuitable for chemotherapy. Randomised to nimotuzumab 200mg IV once weekly or IV placebo, both with radiotherapy delivered in doses of 2Gy once daily, 5 days per week to a total dose of 60–66Gy).</th>
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</table>

**Follow-up**

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<tr>
<th>Active treatment period 6-7 weeks; 30 month follow up.</th>
<th>Active treatment period 6-7 weeks; 4 and 12 month follow up.</th>
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**Primary outcome**

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<th>Overall response rate.</th>
<th>Complete response rate.</th>
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**Secondary outcome**

<table>
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<tr>
<th>Safety and efficacy; survival rate (progression free, disease free and overall); EGFR expression levels.</th>
<th>Safety; immunogenicity; survival benefit; quality of life.</th>
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**Key results**

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<th>Overall response rates at 24 weeks, 40%, 76%, 70% and 100% in arms 1, 2, 3 and 4 respectively (all ( p \leq 0.02 ) arm 1 vs arm 2, arm 3 vs arm 4). Progression free survival at 3 months was 13%, 35%, 22% and 57% in arms 1, 2, 3 and 4 respectively (all ( p \leq 0.08 ) arm 1 vs arm 2, arm 3 vs arm 4).</th>
<th>Antitumoural response documented in 75 patients; 59% of nimotuzumab and 34% of placebo achieved complete response (( p=0.038 )). Mean and median survival (months) 22.7 and 12.5, and 17.7 and 9.5, for nimotuzumab and placebo groups respectively.</th>
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</table>

**Adverse effects (AEs)**

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<th>AEs associated with nimotuzumab included asthenia, dizziness, microscopic hematuria, vomiting, loose stools, fever, chills, pruritus, rash, headache, hypertension and fluctuations in blood pressure. Only one serious nimotuzumab related AE reported (infusion reaction).</th>
<th>70.4% of nimotuzumab group and 57.7% of placebo group presented with AEs. 17 of 54 nimotuzumab patients reported AEs graded I or II, including asthenia 14.6%, fever 9.8%, headache 9.8%, chills 7.8%, anorexia 7.8%.</th>
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</thead>
</table>

**Trial**

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<tr>
<th>NCT00702481, IB/NCCS-01; Nimotuzumab, cisplatin and radiotherapy; phase II.</th>
<th>NCT00910117, HNTG-09-01; Nimotuzumab, cisplatin and radiotherapy; phase II.</th>
</tr>
</thead>
</table>
### Sponsor
National Cancer Centre, Singapore.  
Fudan University.

### Status
Ongoing.  
Ongoing.

### Source of information
Trial registry\(^{14}\).  
Trial registry\(^{15}\).

### Location
Singapore.  
China.

### Design
Uncontrolled, open-label.  
Uncontrolled, open-label.

### Participants and schedule
- **n=37 (planned); adults; squamous cell carcinoma of the head and neck; locally advanced.**  
  Patients receive nimotuzumab 200mg IV weekly for 8 weeks; with cisplatin 100mg/m\(^2\) IV on weeks 1, 4 and 7; and radiotherapy to primary tumour and upper neck at 2Gy per fraction once a day, 5 days a week, for 7 weeks.

- **n=40 (planned); adults; squamous cell carcinoma of the head and neck; locally advanced.**  
  Patients receive nimotuzumab 400mg IV day 1; cisplatin 75mg/m\(^2\) IV on day 1; and fluorouracil 750mg/m\(^2\) on days 1-5 of a 7 day cycle.

### Follow-up
- **Active treatment period 8 weeks; 16 week follow up.**
- **Active treatment period 6 weeks; 8 week follow up.**

### Primary outcome
- **Response rate.**
- **Response rate.**

### Secondary outcomes
- **Safety and tolerability.**
- **Pathological complete response.**

### Expected reporting date
- Apr 2011.
- Dec 2010.

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**Estimated cost and cost impact**

The cost of nimotuzumab is not yet known.

**Claimed or potential impact – speculative**

**Patients**
- ☑ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or improved quality of life for patients and/or carers
- ☑ Quicker, earlier or more accurate diagnosis or identification of disease
- ☑ None identified

**Services**
- ☑ Increased use: additional IV treatment
- ☑ Service organisation
- ☑ Staff requirements
- ☑ None identified

**Costs**
- ☑ Increased unit cost compared to alternative
- ☑ Increased costs: more patients coming for treatment
- ☑ Increased costs: capital investment needed
- ☑ Other: uncertain unit cost compared to alternative

**Other issues**
- ☑ Clinical uncertainty or other research question identified:
  Less common sites for head and neck cancer tend to be excluded from trials with systemic agents. Subgroups of patients with oral cancers associated with human papillomavirus (HPV) should be identified in trials as survival rates may be higher in these groups.
- ☑ None identified

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**References**


The National Institute for Health Research National Horizon Scanning Centre Research Programme is funded by the Department of Health. The views expressed in this publication are not necessarily those of the NHS, the NIHR or the Department of Health

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