Denosumab (AMG 162) for bone metastases from solid tumours and multiple myeloma

September 2008

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Denosumab (AMG 162) for bone metastases from solid tumours and multiple myeloma

Target group
For treatment of bone metastases to prevent skeletal-related events in patients with:
• Solid tumours including:
  o breast cancer
  o prostate cancer (progressed after treatment with at least one hormonal therapy)
• Multiple myeloma (MM)

Background
Solid tumours frequently metastasise to bone. While visceral metastases are more likely to be fatal, patients with only metastases of the bone can survive up to 10 years or more. Factors secreted by tumour cells in bone activate osteoclasts that are responsible for bone resorption. In turn, bone resorption by osteoclasts releases growth factors from the bone matrix that may stimulate tumour growth. This interaction results in bone destruction and increased tumour burden. Skeletal complications of malignancy include fracture, bone pain, hypocalcaemia and spinal cord compression.

Technology description
Denosumab (AMG 162) is a fully human monoclonal antibody that specifically targets the receptor activator of nuclear factor kappa B ligand (RANKL) and neutralises its activity, thereby inhibiting osteoclast differentiation, activation, and survival which suppresses bone resorption. Denosumab is administered monthly at a dose of 120mg by subcutaneous (SC) injection and is intended to be used in conjunction with standard antineoplastic therapies as a substitute for bisphosphonates (BP). Denosumab suppresses bone resorption regardless of previous BP exposure.

Denosumab is also in phase III development for the prevention of cancer treatment-induced bone loss, and in phase II trials in rheumatoid arthritis.

Innovation and/or advantages
Denosumab is first in class for this indication. Its SC route of administration distinguishes it from some existing products which are administered intravenously (IV). Denosumab may also have a better adverse effect profile compared to bisphosphonates.

Developer
Amgen Inc.

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

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

Relevant guidance
Metastatic disease
• NICE clinical guideline. Diagnosis and management of metastatic malignant disease of unknown primary origin. Expected May 2010.
Breast cancer
- NICE technology appraisals for advanced breast cancer: gemcitabine (2007\textsuperscript{2}), trastuzumab (2002\textsuperscript{3}), vinorelbine (2002\textsuperscript{4}), taxanes (docetaxel and paclitaxel, 2001\textsuperscript{1}). NICE has recommended capecitabine (2003\textsuperscript{6}) as an option for treatment in line with the licensed indication for locally advanced or metastatic breast cancer.
- NICE technology appraisal. Lapatinib for the treatment of advanced or metastatic breast cancer. Publication date to be announced.
- NICE cancer service guidance. Improving outcomes in breast cancer. 2002\textsuperscript{7}.
- SIGN clinical guideline. Management of breast cancer in women. 2005\textsuperscript{8}.

Prostate cancer
- NICE technology appraisal. Docetaxel for the treatment of hormone refractory metastatic prostate cancer. 2006\textsuperscript{9}.
- NICE clinical guideline. Prostate cancer: diagnosis and treatment. 2008\textsuperscript{10}.

Multiple myeloma
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma. October 2007\textsuperscript{12}.
- NICE technology appraisal. Lenolidamide for multiple myeloma in people who have received at least one prior therapy. Expected January 2009.
- NICE cancer service guideline. Haemato-oncology. 2003\textsuperscript{13}.
- British Committee for Standards in Haematology. Guidelines on the use of colony-stimulating factors in haematological malignancies. 2003\textsuperscript{15}.

Clinical need and burden of disease
Bone metastases from breast and prostate cancers account for more than 80% of all cases of metastatic bone disease\textsuperscript{16}. The incidence of bone involvement in advanced breast and prostate cancer is around 65-75%, and in advanced multiple myeloma is 95-100%\textsuperscript{17}. Survival rates for patients with bone metastases vary depending on the primary tumour type. The clinical course of bone metastases in multiple myeloma can be relatively short, with a median survival of 20 months after diagnosis of bone metastases, and a 10% probability of surviving 5 years. In breast cancer, median survival is 24 months with a 5 year survival rate of 20%. The best prognosis is in prostate cancer, with a 5-year survival rate of 25% and a median survival of 40 months\textsuperscript{17}.

Between 16-20% of women presenting with breast cancer have advanced disease with distant metastases\textsuperscript{3}, while up to 22% of newly diagnosed prostate cancers are advanced by time they are detected\textsuperscript{18}. On the basis that 65-75% of patients with advanced breast and prostate will have bone metastases, and all new cases of multiple myeloma, the potential patient group population for denosumab is estimated to be between 12,000 – 14,500 patients in England and Wales\textsuperscript{19,20,21}.

Existing comparators and treatments
- Bisphosphonates – clodronate (oral), pamidronate (IV), ibandronate (oral and IV) and zoledronic acid (IV) are used in the management of bone damage and relief of
pain from bone lesions in advanced malignancies. Apart from zoledronic acid, licenses are restricted to use in certain cancers.

- Palliative radiation therapy to reduce localised bone pain.
- Chemotherapy.
- Orthopaedic surgery to repair fractures.

### Efficacy and safety

<table>
<thead>
<tr>
<th>Trial code</th>
<th>Prostate, breast or MM – denosumab vs IV BP; phase II</th>
<th>Breast cancer – denosumab vs IV BP; phase II</th>
<th>MM relapsed or plateau – denosumab; phase II</th>
<th>MM or breast cancer – denosumab vs IV pamidronate; phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Amgen Inc</td>
<td>Amgen Inc.</td>
<td>Amgen Inc.</td>
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<tr>
<td>Status</td>
<td>Published abstract</td>
<td>Published abstract</td>
<td>Published abstract</td>
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<tr>
<td>Location</td>
<td>USA, Europe</td>
<td>USA, Europe</td>
<td>USA, Europe</td>
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</tr>
<tr>
<td>Design</td>
<td>Randomised, active comparator</td>
<td>Randomised, active comparator</td>
<td>Single arm cohort</td>
<td>Randomised double-blind, active comparator</td>
</tr>
<tr>
<td>Participants in trial</td>
<td>n=111; prior BP use (mainly zoledronic acid). Randomised to continue IV BP every 4 weeks; or denosumab 180mg SC every 12 weeks, or every 4 weeks.</td>
<td>n=254; IV BP naïve; confirmed metastasis. Randomised to 1 of 5 increasing doses of denosumab (30-180mg every 4 weeks or 60-180mg every 12 weeks) or IV BP.</td>
<td>n=85; relapsed or plateau disease. Received denosumab 120mg every 4 weeks (loading dose 120mg on days 1, 8, and 15 of 1st cycle) for 6 months.</td>
<td>n=54 (breast cancer n=29; MM n=25). Confirmed metastasis. Randomised to single dose denosumab (0.1-3.0 mg/kg SC); or pamidronate (90mg IV).</td>
</tr>
<tr>
<td>Follow-up</td>
<td>25 weeks.</td>
<td>25 weeks efficacy; 57 weeks safety.</td>
<td>1-12 months.</td>
<td>Single dose study.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Bone resorption marker - urinary NTx (uNTx) &lt;50nM at week 13.</td>
<td>Median reduction uNTx at week 25.</td>
<td>Complete (CR) or partial response (PR) - includes ≥50% reduction serum M protein.</td>
<td>Reduction in uNTx.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Skeletal related events (SREs); safety.</td>
<td>uNTx &gt;65% reduction; ≥1 SRE; safety.</td>
<td>25% reduction in serum M protein; safety.</td>
<td>Change in serum NTx.</td>
</tr>
<tr>
<td>Key results</td>
<td>uNTx &lt;50nM at week 13: denosumab 71% vs IV BP 29%. At week 25: 64% denosumab vs 37% IV BP. At 25 weeks denosumab associated with fewer SREs (8%) than IV BP (20%).</td>
<td>uNTx reduction: denosumab 75% vs 71% IV BP. On study SRE 12% denosumab vs 16% BP. No denosumab antibodies detected at week 57.</td>
<td>No CR or PR observed. 25% of relapsed cohort had stable disease for &gt;6 months vs 59% in plateau cohort. 6-13% in respective cohorts reached secondary endpoint.</td>
<td>Denosumab (1mg/kg) 73% reduction in uNTx (breast cancer), 77% reduction (MM) vs 30% and 24%, respectively for pamidronate. Reduction sustained for at least 84 days with denosumab.</td>
</tr>
<tr>
<td>Adverse events (AE)</td>
<td>Bone pain, nausea, anaemia. One serious AE (hypophosphatemia)</td>
<td>Grade 3 or 4 AEs similar between groups. 28% denosumab vs 47%</td>
<td>Serious AEs in 19 patients – included thrombocytopenia</td>
<td>Grade 3 or 4 AEs similar between both groups.</td>
</tr>
<tr>
<td>Trial code</td>
<td>Prostate cancer - denosumab vs zoledronic acid; phase III; NCT 00321620</td>
<td>Breast cancer (advanced) - Denosumab vs zoledronic acid; phase III; NCT 00321464</td>
<td>Advanced cancer (excluding breast and prostate), or MM - denosumab vs zoledronic acid; phase III; NCT00330759</td>
<td>MM relapsed or plateau; phase II; NCT00259740</td>
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<td>Location</td>
<td>Worldwide (inc UK)</td>
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<td>Worldwide (inc UK)</td>
<td>USA and Australia</td>
</tr>
<tr>
<td>Participants in trial</td>
<td>n=1,700; failure of at least one hormonal therapy; rising PSA; BP naïve; at least 1 bone metastasis. Randomised to denosumab 120mg with IV placebo, or zoledronic acid 4mg IV with SC placebo; every 4 weeks.</td>
<td>n=1,960; BP naïve; at least 1 bone metastasis. Randomised to denosumab 120mg with IV placebo or zoledronic acid 4mg IV with SC placebo; every 4 weeks.</td>
<td>n= 1,690; BP naïve; at least 1 bone metastasis. Randomised to denosumab 120mg with IV placebo or zoledronic acid 4mg IV with SC placebo; every 4 weeks.</td>
<td>n=96; BP deprived for at least 2 weeks. Denosumab 120mg on day 1 of a monthly cycle (loading dose 120mg on days 1, 8, and 15 of 1st cycle).</td>
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<tr>
<td>Follow-up</td>
<td>At least 33 months (event driven; 745 required).</td>
<td>Event driven; 745 required.</td>
<td>Event driven.</td>
<td>6 months.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Time to first on-study SRE (non-inferiority).</td>
<td>Time to first on-study SRE (non-inferiority).</td>
<td>Time to first on-study SRE (non-inferiority).</td>
<td>Complete response (CR) or partial response (PR).</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Time to first on-study SRE (superiority); laboratory values; anti-denosumab antibodies.</td>
<td>Time to first on-study SRE (superiority).</td>
<td>Time to first on-study SRE (superiority).</td>
<td>CR, PR or minor response (MR); CR-only; safety.</td>
</tr>
</tbody>
</table>

**Estimated cost and cost impact**

The cost of denosumab is currently unknown. As a subcutaneous therapy, the cost of administration will be reduced compared to IV therapies.
### Drug Dose Annual cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>Bone metastases in breast cancer or MM.</td>
<td>90mg IV (over 1-2h) every 4 weeks.</td>
<td>£2,145</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Advanced malignancies involving bone.</td>
<td>4mg IV (over 15 minutes) every 3-4 weeks.</td>
<td>£2,535 - £3,315</td>
</tr>
<tr>
<td>Ibandronic acid</td>
<td>Bone metastases in breast cancer.</td>
<td>6mg IV every 3-4 weeks or 50mg daily (oral).</td>
<td>£2,535</td>
</tr>
</tbody>
</table>

### Potential or intended impact – speculative

**Patients**
- ☑ Reduced morbidity
- ☑ Improved quality of life for patients and/or carers
- ☑ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ Reduced mortality or increased survival
- ☐ Other:
- ☐ None identified

**Services**
- ☑ Increased use
- ☐ Service reorganisation required
- ☐ Staff or training required
- ☑ Decreased use: SC rather than IV administration
- ☑ Other: patient training will be required if self-administration is planned
- ☐ None identified

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

### References

22 Fizazi K, Lipton A, Mariette X et al. Denosumab in patients with bone metastases from prostate, breast and other cancers and elevated urinary N-telopeptide (uNTx) during intravenous bisphosphonate (IV BP) therapy: Final results of a phase II study. ASCO Annual Meeting 2008 (abstract 3596).

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