The role of RANK ligand inhibitor in Giant cell tumors

JY Blay
Lyon, France
FSG, EORTC
Giant Cell Tumor of Bone (GCTB)

- Aggressive, primary osteolytic tumor
- Causes local pain and impairs mobility and function\(^1\)
- No approved or effective medical therapy
- Surgical intervention often associated with significant morbidity\(^2\)
- Tumors contain osteoclast-like giant cells expressing RANK and stromal cells expressing RANK ligand (RANKL), a key mediator of osteoclast formation, activation, function, and survival\(^3\)\(^-\)\(^6\)
- Excessive RANKL secretion causes an imbalance in bone remodeling in favor of bone breakdown\(^7\)\(^-\)\(^9\)

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RANKL is a Central Mediator of Bone Destruction in Giant Cell Tumor of Bone
Giant Cell Tumor of Bone (GCTB)

• Life threatening in specific sites
  − Vertebrae
  − Skull

• Metastasis (lung)
  − Often indolent
  − Sometimes life threatening

• Multifocal sites (rare)

• Transformation in sarcoma
Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study

David Thomas, Robert Henshaw, Keith Skubitz, Sant Chawla, Arthur Staddon, Jean-Yves Bley, Martine Roudier, Judy Smith, Zhishen Ye, Winnie Sohn, Roger Dansey, Susie Jun

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Objective

• To investigate whether denosumab, a fully human monoclonal antibody against RANKL, could inhibit bone destruction and eliminate giant cells

Pharmacologic Properties of Denosumab

• Fully human monoclonal antibody - IgG₂ isotype
• High affinity for human RANKL
• High specificity for RANKL
  – No detectable binding to TNF-α, TNF-β, TRAIL, or CD40L
• No neutralizing antibodies detected in clinical trials to date

TNF = tumor necrosis factor; TRAIL = TNF-α-related apoptosis-inducing ligand

Denosumab Treatment Suppressed sCTx Levels as Early as 28 Days
Results: Denosumab Treatment Resulted in an 86% Tumor Response

- 30 of 35 (86%; 95% CI 70%-95%) subjects responded to denosumab treatment
  - 20/20 by histology (if the subject met histology criteria, radiology criteria were not applied)
  - 10 by radiology
- Among 31 evaluable subjects 26 (84%; 95% CI 66%-95%) had substantial clinical benefit, including reduced pain, increased range of motion, and return to work
- 9 subjects (29%; 95% CI 14%-48%) experienced bone repair
Radiologic Response to Denosumab

Baseline

8 weeks
Patient COMM., Male, aged 23
GCT with lung mets, progressive following surgery and 2 lines of cytotoxic chemotherapy
Figure 1: Pretreatment (A) and week 13 post-treatment biopsy (B)
Cells stained with haematoxylin and eosin.
Denosumab in Giant Cell Tumor of Bone

• Fully human monoclonal antibody that binds to RANKL
• Inhibits osteoclast-mediated bone destruction
• In an initial open-label, proof-of-concept, phase 2 study of denosumab (N = 37):
  – Tumor response in 86% of patients with GCTB
  – Clinical benefit in 84% of patients (reduced pain or improvement in functional status per investigator report)
• Second phase 2 follow-on study in progress; safety and efficacy results from the prespecified second interim analysis are reported here.

Phase 2 Follow-on Study: Interim Analysis

Day
1 8 15

Month
2 3 4 5 6

Months 7–N

Denosumab 120 mg sc

Adults or skeletally mature adolescents with GCTB

Cohort 1: Surgically unsalvageable GCTB
- Safety
- Disease progression (investigators’ assessment)

Cohort 2: Salvageable GCTB, surgery planned
- Safety
- Surgery: delay, avoidance, or reduced morbidity

SC: subcutaneous
**Results (CTOS 2011)**

**Subject Demographics and Disease Characteristics**

<table>
<thead>
<tr>
<th>Characteristic (All enrolled subjects)</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgically Unsalvageable</td>
<td>Salvageable, Surgery Planned</td>
</tr>
<tr>
<td></td>
<td>N = 112</td>
<td>N = 50</td>
</tr>
<tr>
<td>Female, %</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>Age, median (min, max)</td>
<td>32 (13, 76)</td>
<td>34 (17, 56)</td>
</tr>
<tr>
<td>Location of target lesion, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur, tibia, patella/knee, or tarsus</td>
<td>6</td>
<td>64</td>
</tr>
<tr>
<td>Lung</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Sacrum</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Pelvic bone</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Humerus, radius, ulna, or metacarpus</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Vertebrae: cervical, thoracic, or lumbar</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Skull</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissue: cervical, thoracic pelvic, or abdominal</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

N = All enrolled subjects
# Results – Safety

## Denosumab Exposure and Adverse Events

<table>
<thead>
<tr>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 158</strong>*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (Q1,Q3) number of doses received</th>
<th>10 (6, 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Q1,Q3) months on study</td>
<td>7 (3, 12)</td>
</tr>
</tbody>
</table>

### Subjects with Adverse Events, %

<table>
<thead>
<tr>
<th>AEs of grade 3 or 4 considered related to denosumab</th>
<th>4.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatemia</td>
<td>2.5%</td>
</tr>
<tr>
<td>Dysmennorrhea</td>
<td>0.6%</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw (ONJ)</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

| Hypocalcemia (grade 1 or 2)                         | 4.4% |

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* N = number of subjects who received at least 1 dose of denosumab
Results – Efficacy

No Disease Progression in the Majority of Subjects

Cohort 1: Surgically Unsalvageable
N = 73*

Cohort 2: Salvageable, Surgery Planned
N = 23*

* N = the number of subjects who received denosumab, had the opportunity to be on study for ≥6 months, and had disease progression data at the time of analysis. The disease response data analysis was based on the best response reported during the assessment period.
Results: Cohort 2

At 12 Months, Most Subjects in Cohort 2 Had No Surgery or a Less Morbid Surgical Procedure Than Planned

<table>
<thead>
<tr>
<th>Surgical Procedure, n*</th>
<th>Planned (N = 23)</th>
<th>Actual (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of surgeries</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Major surgeries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemipelvectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Amputation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Joint/prosthesis replace</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Joint resection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Marginal excision, en bloc excision, or en bloc resection</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Curretage</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Other†</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>No surgery</td>
<td>N/A</td>
<td>15</td>
</tr>
</tbody>
</table>

* In order from most morbid to least morbid
† Other planned skeletal procedures included replacement of proximal tibia, sacral lesion/bone resection, and pelvic resection (1 each).
DF, female 31yo

*Tumor history*

2003: resection of a sphenoidal GCT
2005: local relapse, R2 resection, 6 courses of CT (doxo, ifo, VP16) +RT

Jan 2008: local relapse, interferon (slowly growing)

December 2008, local and sinusal relapse, incomplete resection on Jan 29.

February 2009: 2 cm residue, unresectable, decreasing vision on both eyes

July 2009: denosumab started

Slow regression since then, recovery of normal vision 2 months following initiation of treatment
Strategy for GCTB?

• Resectable GCTB
  - With limited functional impairment expected from surgical procedures:
    • Curettage
  - Functional impairment expected from surgical procedure
    • Neoadjuvant denosumab

• Relapsing GCTB
  - Curettage
  - Denosumab

• Metastatic /irresectable tumors
  - Denosumab

• Unsolved questions:
  - Optimal duration (neoadjuvant)
  - Adjuvant (whom?)
  - Long term follow-up : resistance ?
Conclusion: GCTB and denosumab

- Locally malignant disease
  - Occasionally life-threatening
  - Métastasis 5-10%
- Proof of concept for a targeted therapy
- No genomic alteration identified
- New standard approaches emerging