GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

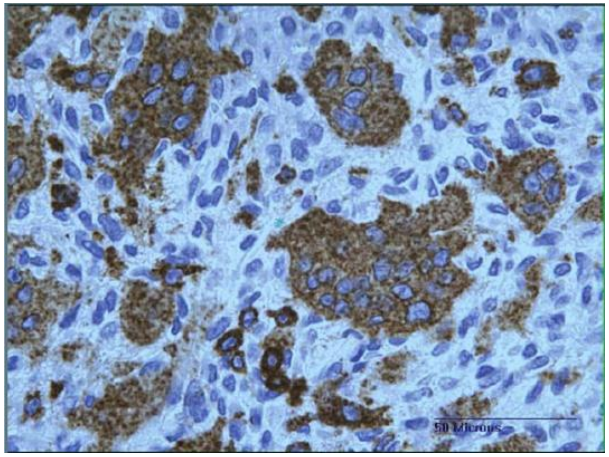
www.esmo.org

The role of RANK ligand inhibitor in Giant cell tumors

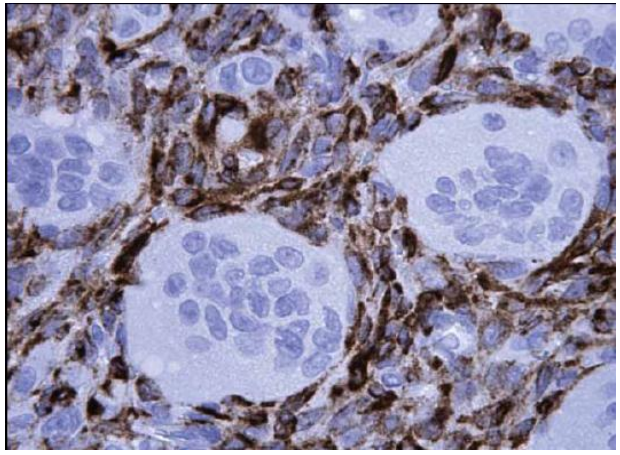
JY Blay
Lyon, France
FSG, EORTC

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]



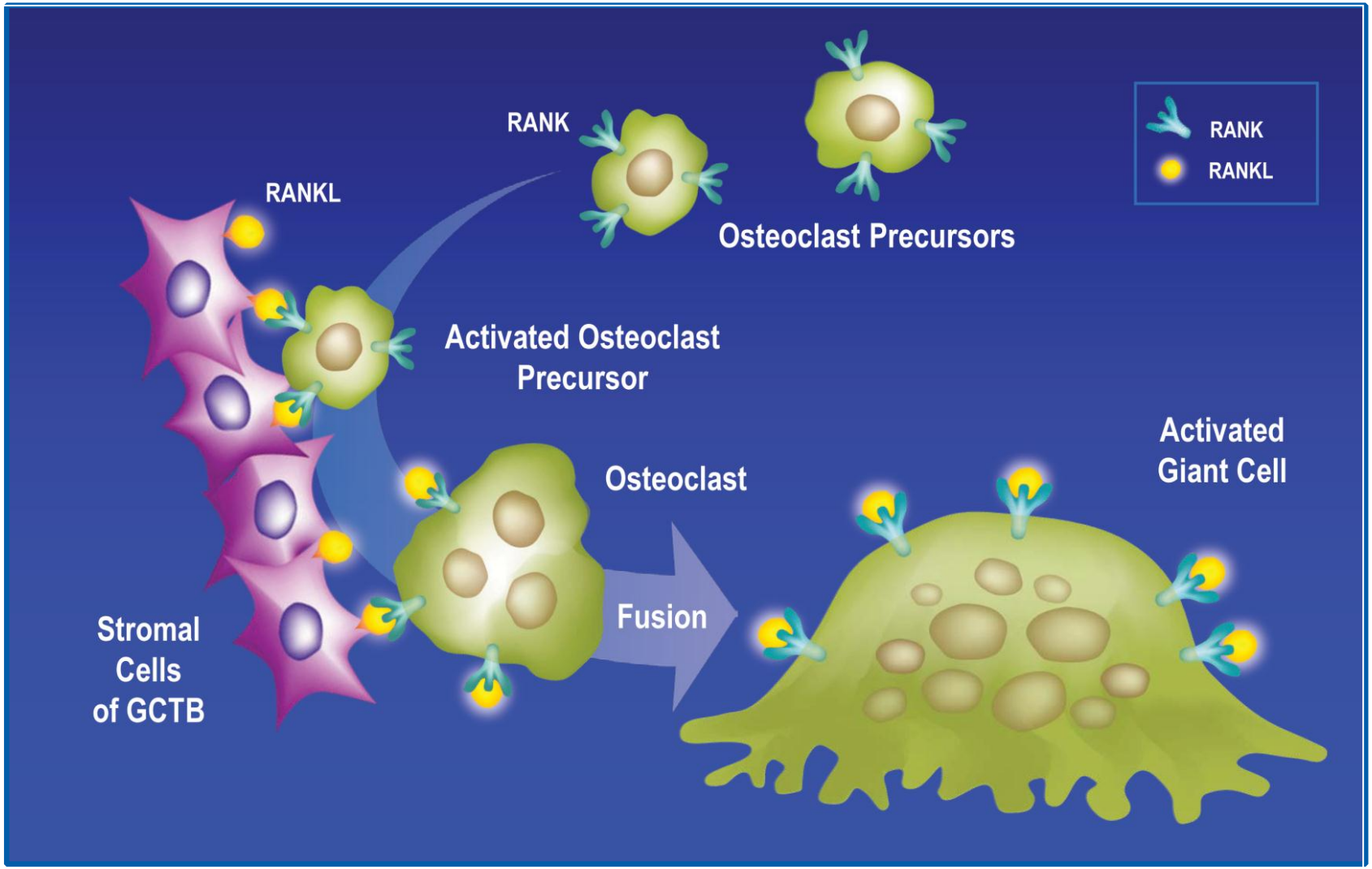
RANK expression in GCTB[10]



RANKL expression in GCTB[10]

1. Mendenhall WM et al. *Am J Clin Oncol*. 2006;29:96–9. 2. Balke M et al. *J Cancer Res Clin Oncol*. 2009;135:149–58. 3. Atkins GJ, et al. *J Bone Miner Res*. 2006; 21:1339–49. 4. Huang L, et al. *Am J Pathol*. 2000;156:761–7. 5. Kartsogiannis V, et al. *Bone*. 1999;25: 525–34. 6. Roux S, et al. *Am J Clin Pathol*. 2002; 117:210–6. 7. Burgess TL, et al. *J Cell Biol*. 1999;145:527–38. 8. Lacey DL, et al. *Cell*. 1998;93:165–76. 9. Yasuda H, et al. *Proc Natl Acad Sci USA*. 1998;95:3597–602. 10. Bekker PJ et al. *J Bone Miner Res*. 2004;19:1059–66.

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 Blay, Martine Roudier, Judy Smith, Zhishen Ye, Winnie Sohn, Roger Dansey, Susie Jun

www.thelancet.com/oncology Published online February 10, 2010 DOI:10.1016/S1470-2045(10)70010-3

Objective

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

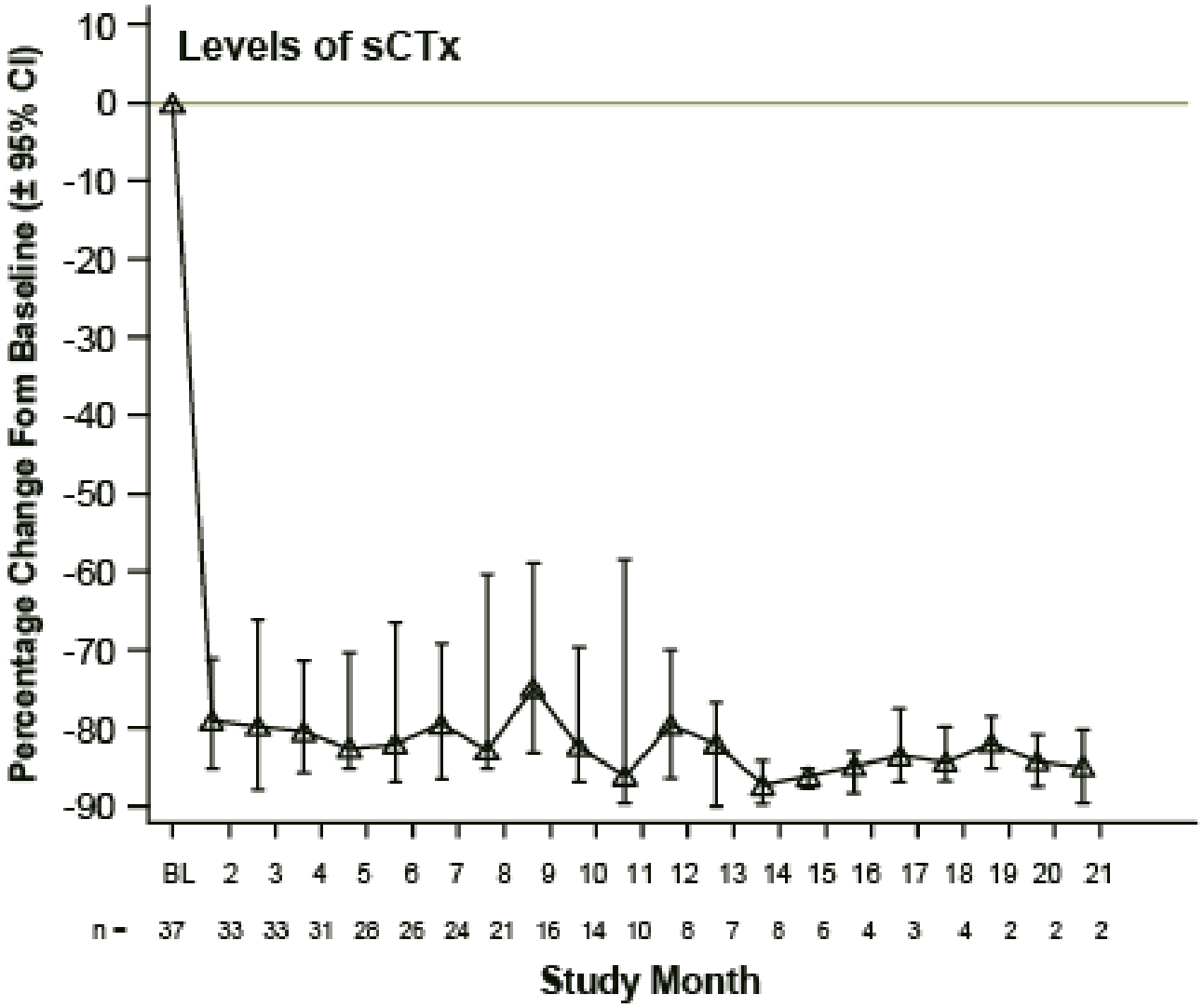
Pharmacologic Properties of Denosumab

- Fully human monoclonal antibody - IgG_2 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

Bekker PJ, et al. *J Bone Miner Res.* 2004;19:1059-1066; Elliott R, et al. *Osteoporos Int.* 2007;18:S54. Abstract P149; McClung MR, et al. *New Engl J Med*. 2006;354:821-31.

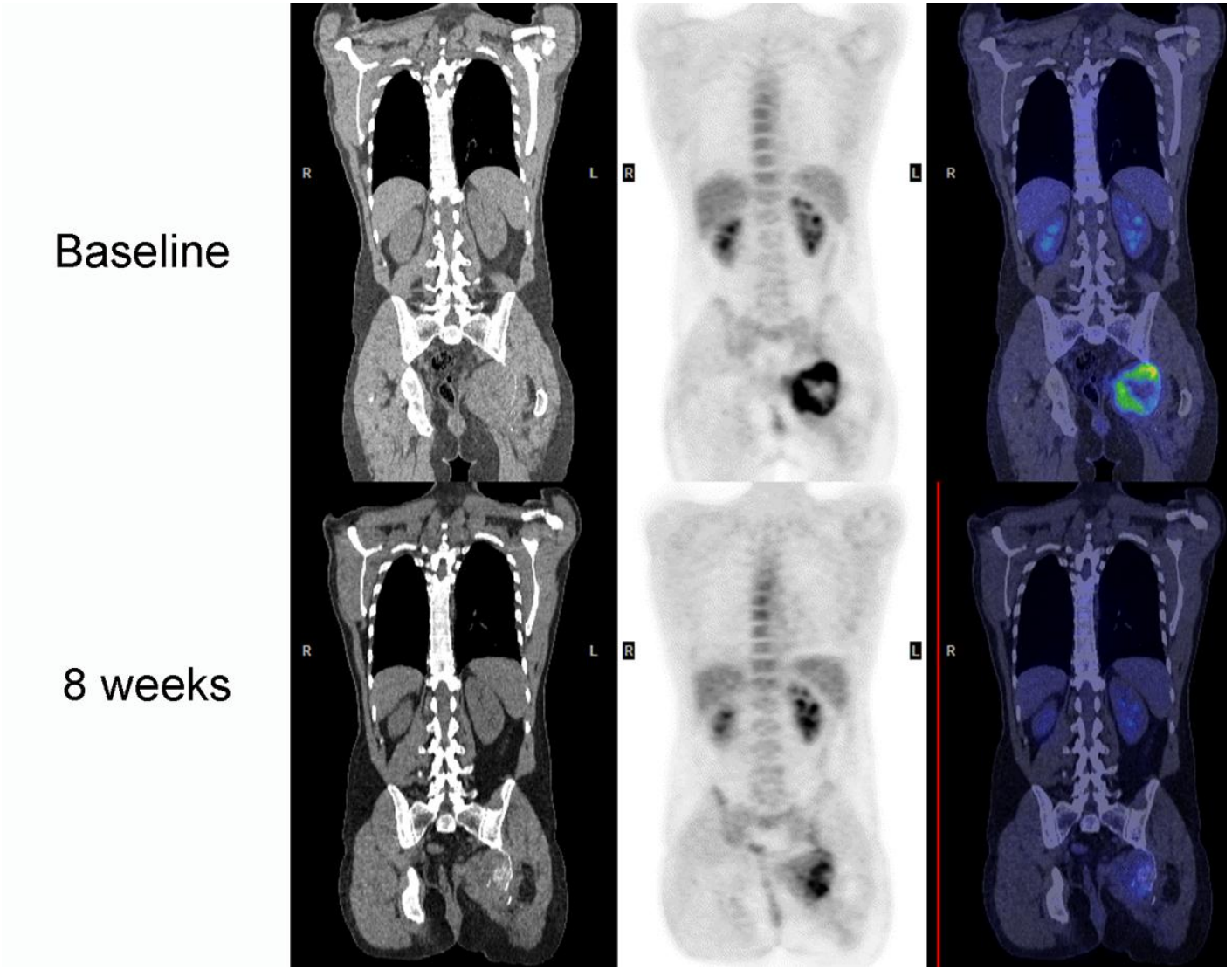
Denosumab Treatment Suppressed sCTx Levels as Early as 28 Days



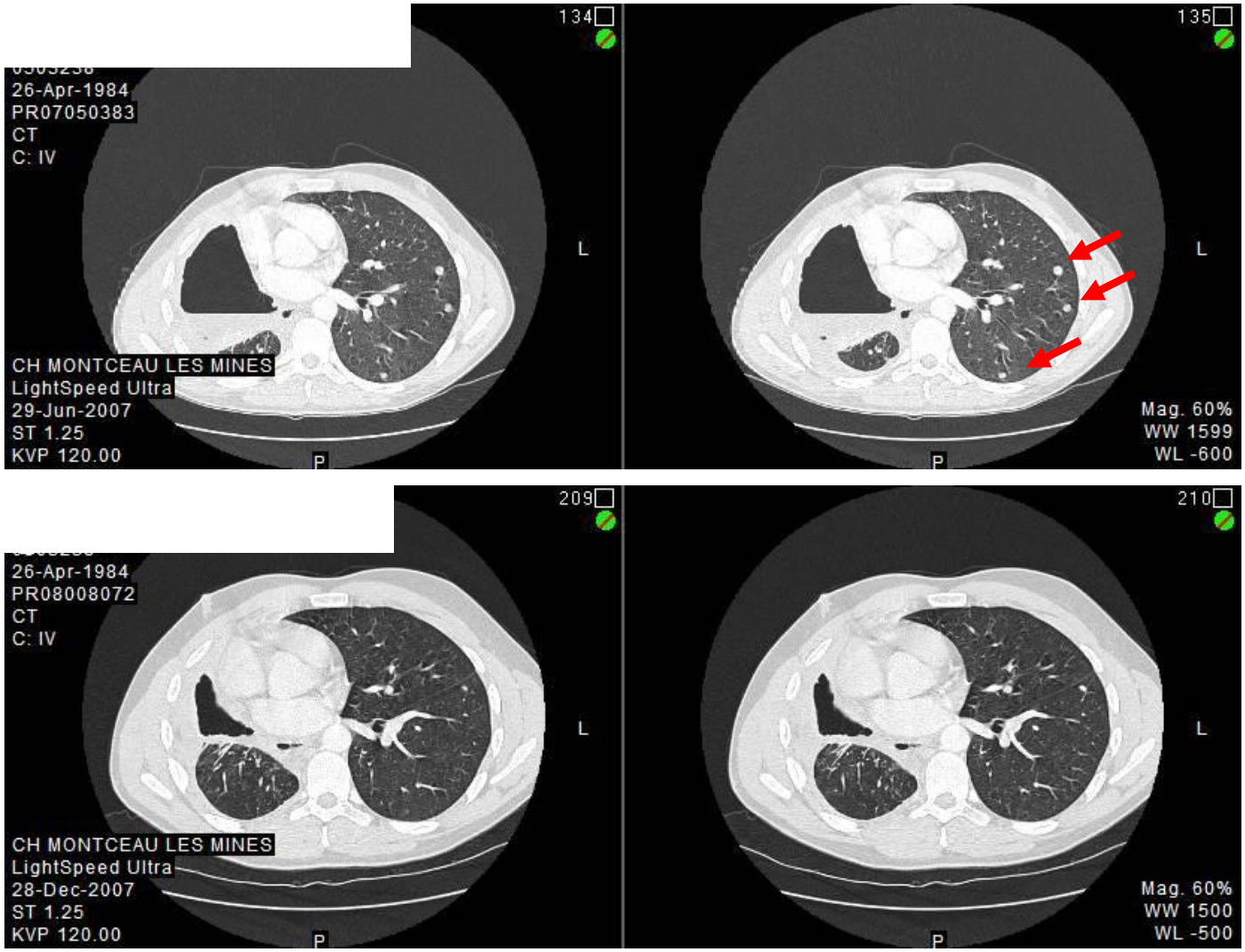
Results: Denosumab Treatment Resulted in an 86% Tumor Response

- 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



Patient COMM., Male, aged 23
GCT with lung mets, progressive following surgery and 2 lines of cytotoxic chemotherapy



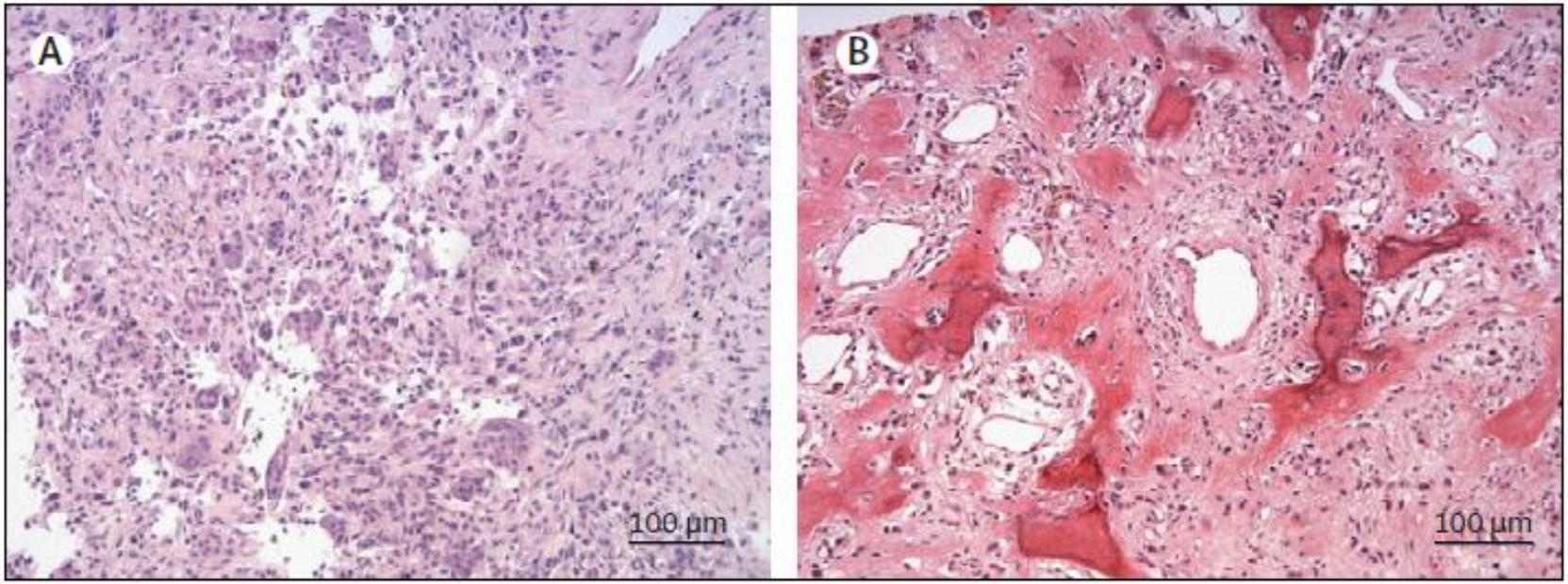


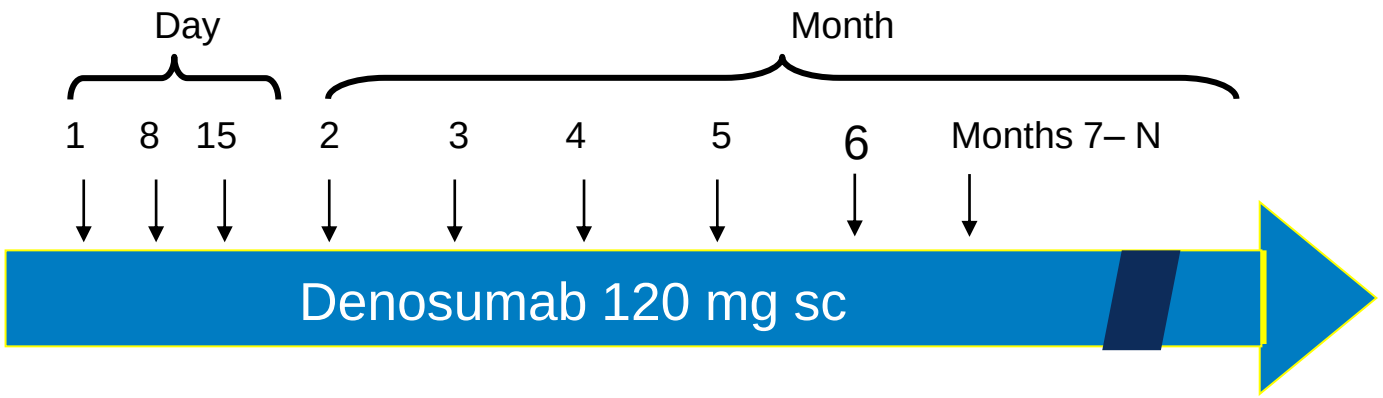
Figure 1: Pretreatment (A) and week 13 post-treatment biopsy (B)
Cells stained with haematoxylin and eosin.

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.

1. Bekker PJ et al. *J Bone Miner Res*. 2004;19:1059–66.
2. Thomas D et al. *Lancet Oncol*. 2010;11:275–80.

Phase 2 Follow-on Study: Interim Analysis



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

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

N = All enrolled subjects

Results – Safety
Denosumab Exposure and Adverse Events

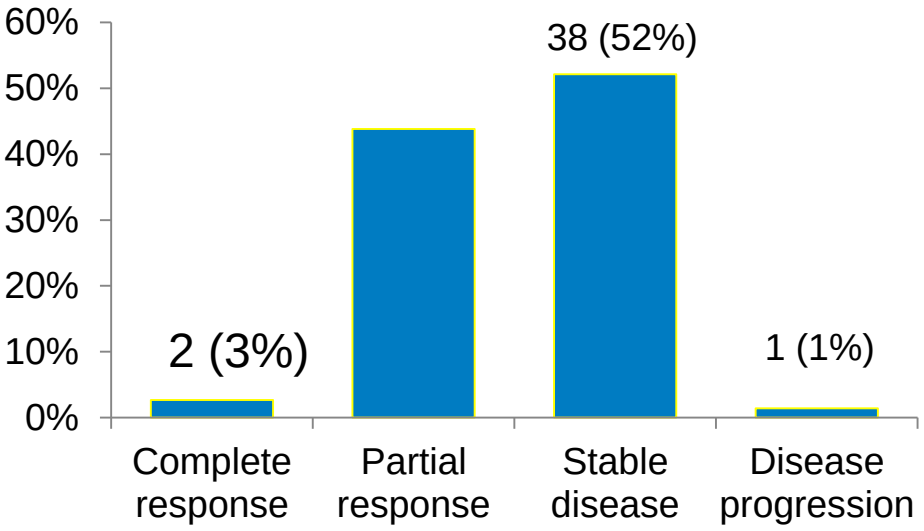
	All Subjects N = 158*
Median (Q1,Q3) number of doses received	10 (6, 15)
Median (Q1,Q3) months on study	7 (3, 12)
Subjects with Adverse Events, %	
AEs of grade 3 or 4 considered related to denosumab	4.4%
Hypophosphatemia	2.5%
Dysmennorrhea	0.6%
Osteonecrosis of the jaw (ONJ)	1.9%
Hypocalcemia (grade 1 or 2)	4.4%

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

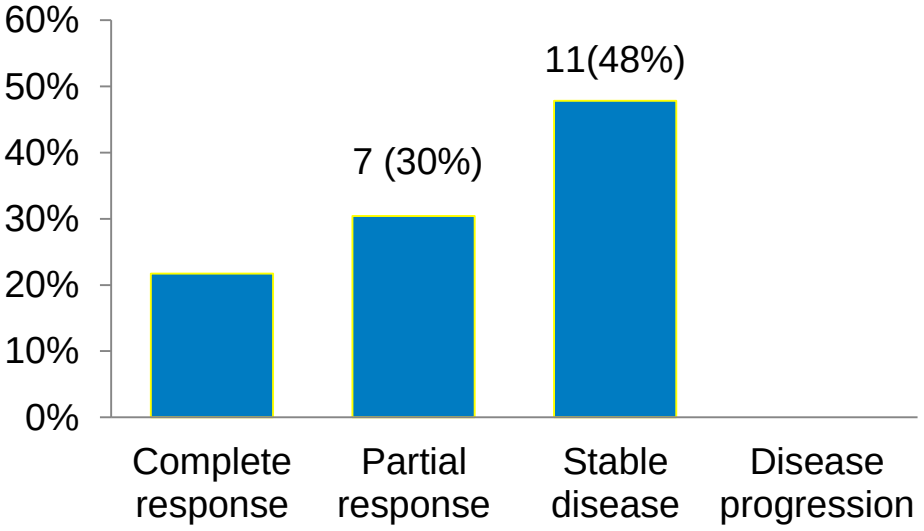
Results – Efficacy

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

Surgical Procedure, n*	Planned (N = 23)	Actual (N = 23)
Total number of surgeries	23	8
Major surgeries	10	3
Hemipelvectomy	1	0
Amputation	2	0
Joint/prosthesis replacement	5	1
Joint resection	2	2
Marginal excision, en bloc excision, or en bloc resection	7	0
Curretage	2	4
Other†	4	1
No surgery	N/A	15

* 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