ESMO Sarcoma and GIST conference: Giant cell-rich mesenchymal tumors

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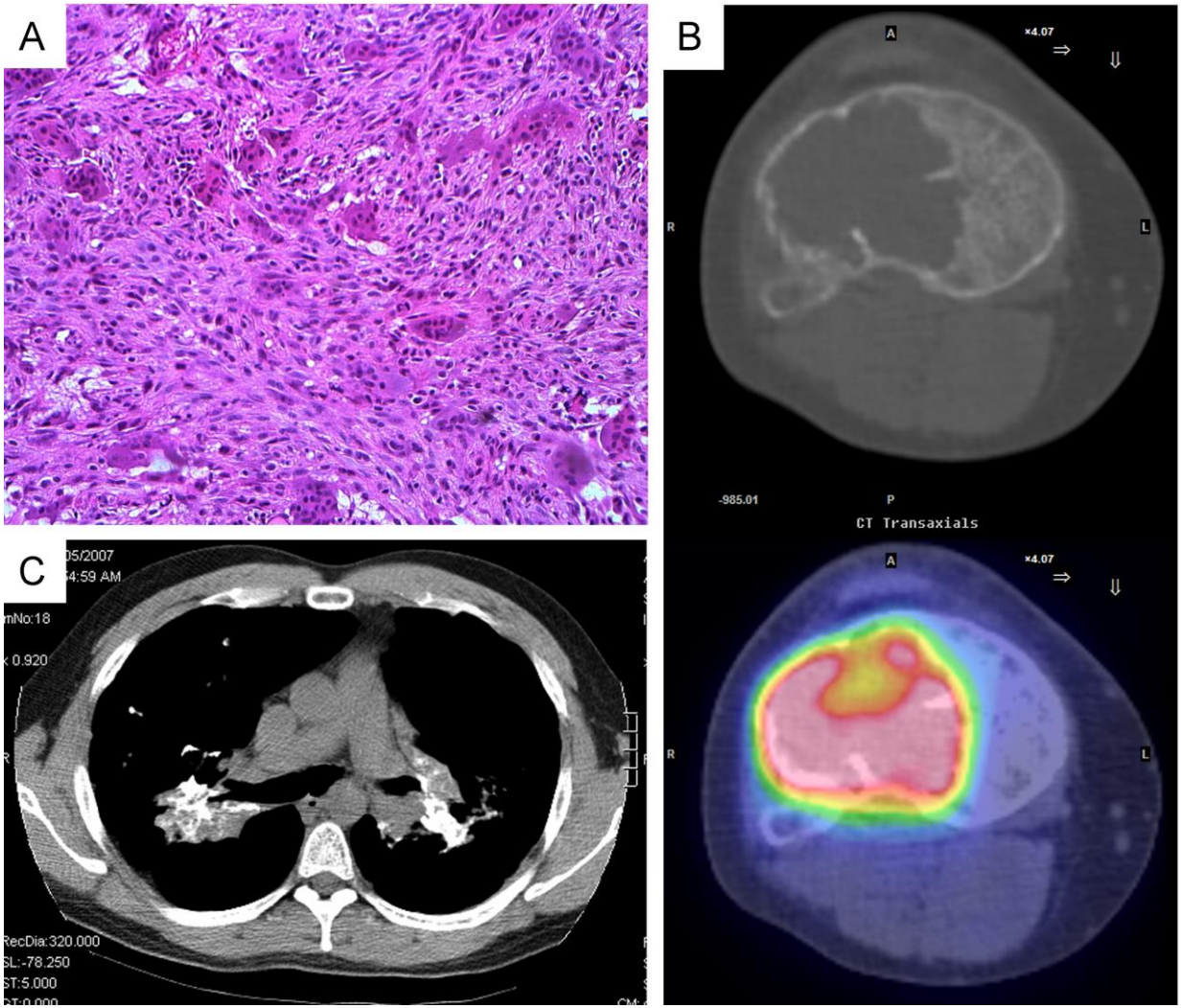
Acknowledgements and Disclosures

- I have received research support and consultant fees from Amgen Inc.

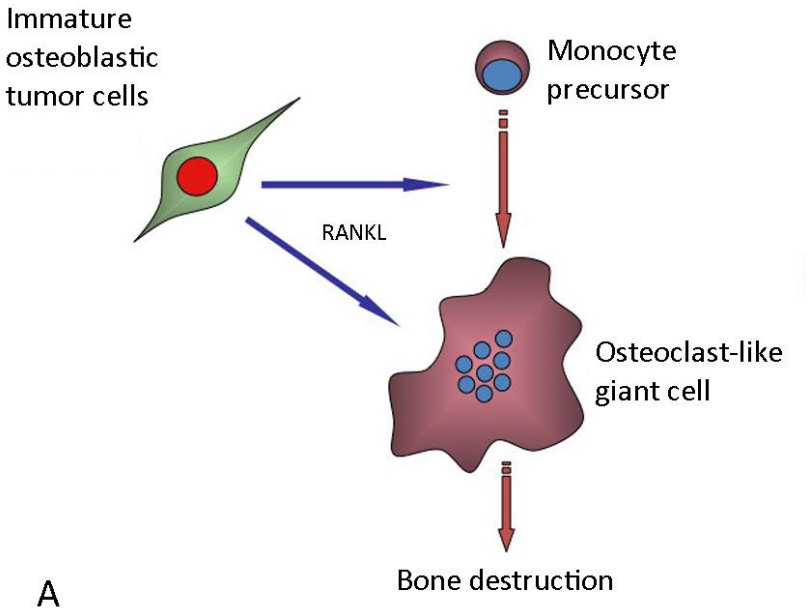
Giant cell tumor of bone



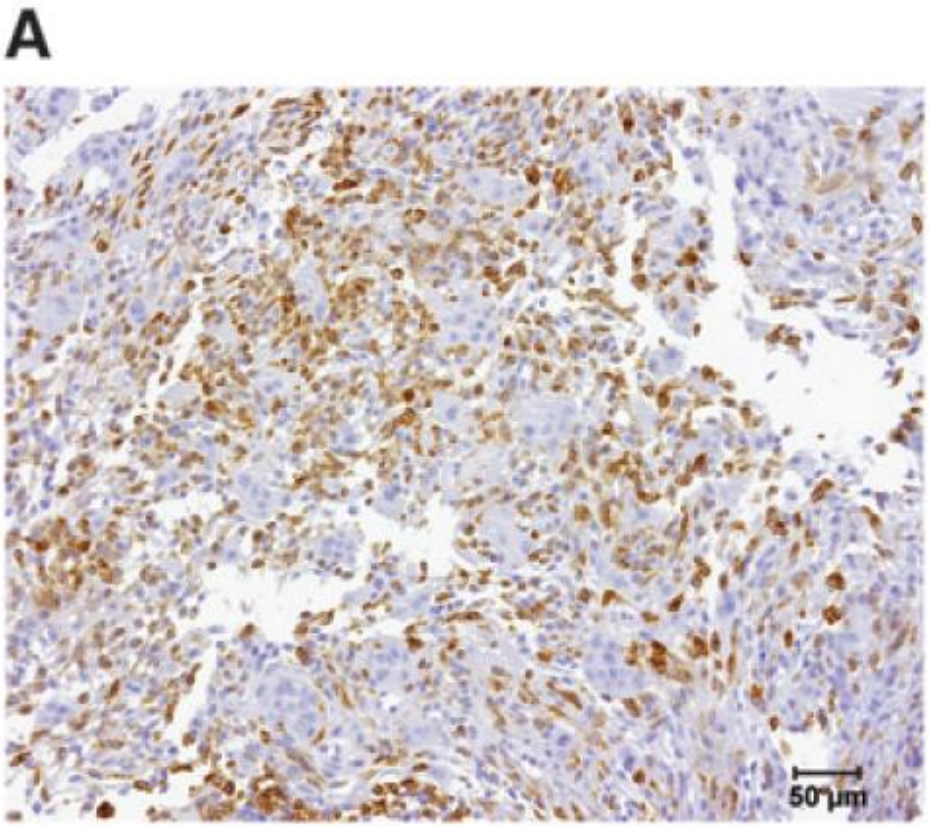
Background

- ‘Benign’ disease
- Young population
- High prevalence:incidence ratio
- Surgery is the only definitive therapy for patients with resectable tumours, but is often associated with significant morbidity
- Radiotherapy effective in 80% of cases, but concerns expressed regarding long-term sequelae

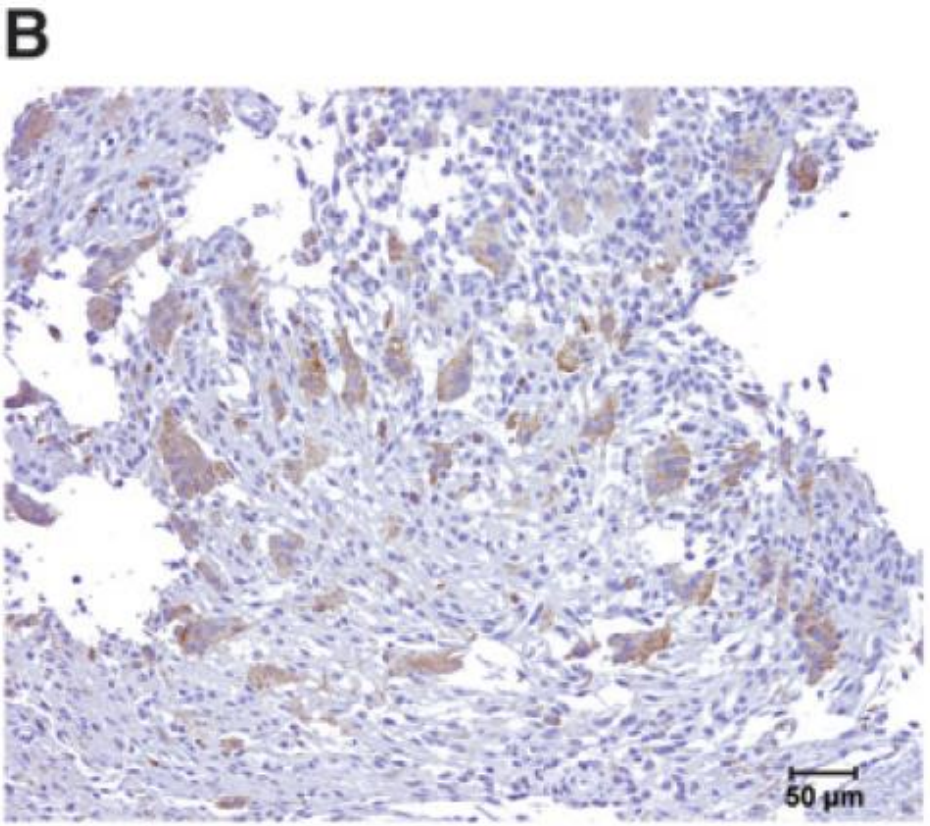
GCT biology


Immature
osteoblastic
tumor cells
Monocyte
precursor
RANKL
Osteoclast-like
giant cell
Bone destruction
A

Background



RANKL



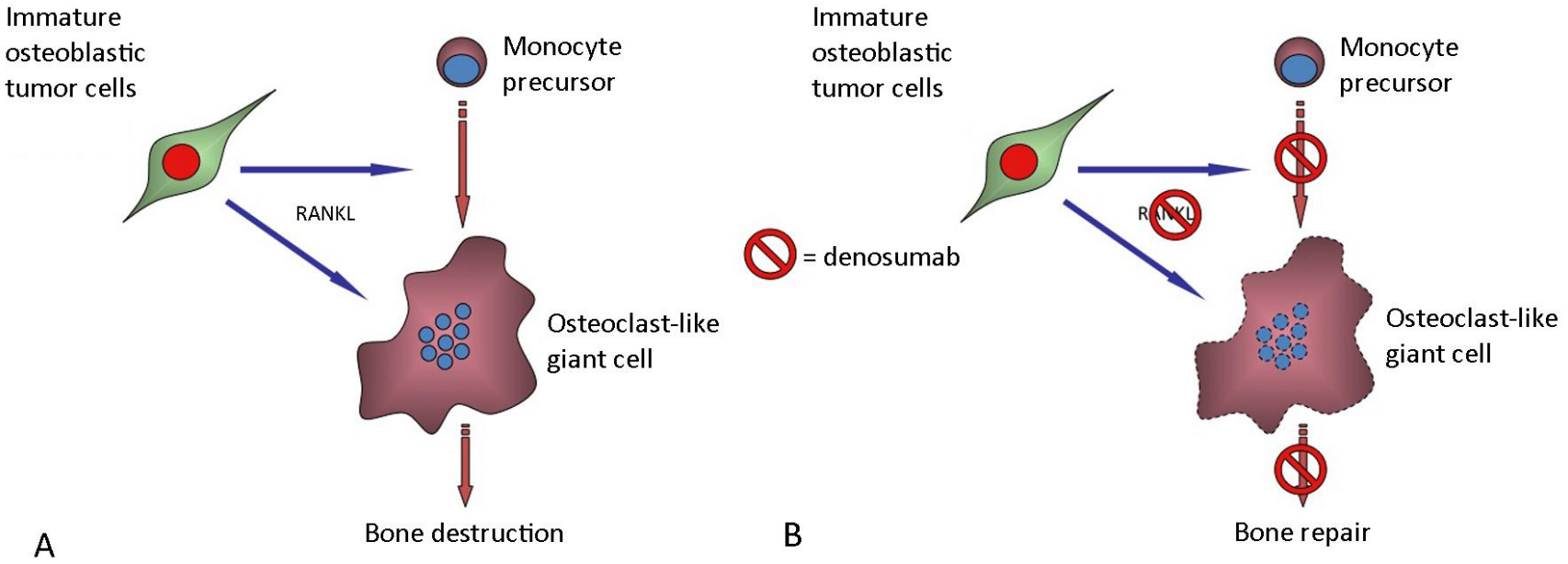
RANK

Clinical Cancer Research, 2012 Branstetter et al

Background

AMGEN developed Denosumab, a fully human monoclonal antibody that binds with high affinity and specificity to human RANKL

GCT biology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= denosumab
Osteoclast-like
giant cell
Bone repair
B

Initial phase 2 study

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

37 patients in initial study

30/35 evaluable patients had a response
- 20/20 by histology
- 10/15 by radiology

Well-tolerated

Lancet Oncology, 2009; 11:275

Second phase 2 study

Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study

Sant Chawla, Robert Henshaw, Leanne Seeger, Edwin Choy, Jean-Yves Blay, Stefano Ferrari, Judith Kroep, Robert Grimer, Peter Reichardt, Piotr Rutkowski, Scott Schuetze, Keith Skubitz, Arthur Staddon, David Thomas, Yi Qian, Ira Jacobs

Lancet Oncology, 2013; 14:901

	Cohort 1 (surgically unsalvageable; n=170)	Cohort 2 (salvageable, surgery planned; n=101)	Cohort 3 (patients from previous phase 2 study; n=11)
Female	102 (60%)	57 (56%)	5 (45%)
Median age, years (IQR)	33 (26–45)	34 (25–43)	30 (24–44)
Location of target lesion			
Femur, tibia, fibula, patella or knee, ankle	14 (8%)	60 (59%)	1 (9%)
Lung	43 (25%)	2 (2%)	4 (36%)
Sacrum	42 (25%)	4 (4%)	2 (18%)
Pelvic bone	23 (14%)	13 (13%)	0 (0%)
Humerus, radius, ulna, metacarpus, or phalanges	14 (8%)	18 (18%)	1 (9%)
Vertebrae (cervical, thoracic, or lumbar)	21 (12%)	3 (3%)	3 (27%)
Skull	8 (5%)	0 (0%)	0 (0%)
Pelvis (soft tissue only)	2 (1%)	0 (0%)	0 (0%)
Other*	3 (2%)	1 (1%)	0 (0%)
GCTB disease type			
Primary resectable	0 (0%)	63 (62%)	0 (0%)
Recurrent resectable	0 (0%)	38 (38%)	0 (0%)
Primary unresectable	48 (28%)	0 (0%)	2 (18%)
Recurrent unresectable	122 (72%)	0 (0%)	9 (82%)
Previous treatments for GCTB			
Surgery	130 (76%)	44 (44%)	0 (0%)
Radiation	42 (25%)	6 (6%)	0 (0%)
Chemotherapy or immunotherapy	24 (14%)	2 (2%)	0 (0%)
Intravenous bisphosphonates	32 (19%)	10 (10%)	0 (0%)
Oral bisphosphonates	7 (4%)	1 (1%)	0 (0%)

Data are n (%) unless otherwise specified. GCTB=giant cell tumour of bone. *Includes retrocrural soft tissue mass (one), retroperitoneum (one), cervical soft tissue (one), and hyoid bone (one).

Table 1: **Baseline demographics and disease characteristics**

	All patients (n=281)
Any adverse event	236 (84%)
Adverse events occurring in >10% of patients	
Arthralgia	55 (20%)
Headache	51 (18%)
Nausea	48 (17%)
Fatigue	45 (16%)
Back pain	42 (15%)
Pain in extremity	41 (15%)
Grade 3, 4, or 5 adverse events	50 (18%)
Hypophosphataemia	9 (3%)
Anaemia	3 (1%)
Back pain	3 (1%)
Pain in extremity	3 (1%)
Arthralgia	2 (1%)
Depression	2 (1%)
Headache	2 (1%)
Musculoskeletal pain	2 (1%)
Osteomyelitis	2 (1%)
Osteonecrosis of the jaw	2 (1%)
Weight gain	2 (1%)
Serious adverse events	25 (9%)
Adverse events leading to treatment discontinuation	14 (5%)
Adverse events leading to study discontinuation	13 (5%)
Adverse event of interest	
Adjudicated positive osteonecrosis of the jaw	3 (1%)
Resolved	2 (1%)
Hypocalcaemia (none serious)	15 (5%)
Serious infections	5 (2%)
New primary malignancy	3 (1%)

Data are n (%), in which n is the number of patients who received at least one dose of denosumab. Based on *Medical Dictionary for Regulatory Activities* (version 14.1) and Common Terminology Criteria for Adverse Events (version 3.0).

Table 2: **Adverse events**

Median follow-up of 13 months

	Planned (n=100)	Actual total (n=26)
Major surgeries	44	3
Hemipelvectomy	4	0
Amputation	17	0
Joint or prosthesis replacement	9	1
Joint resection	14	2
En-bloc resection	37	6
En-bloc excision	4	0
Marginal excision	1	0
Curettage	13	16
Other	1	1
No surgery	NA	74

Data are n in the efficacy analysis set. Procedures are in decreasing order of morbidity. NA=not applicable.

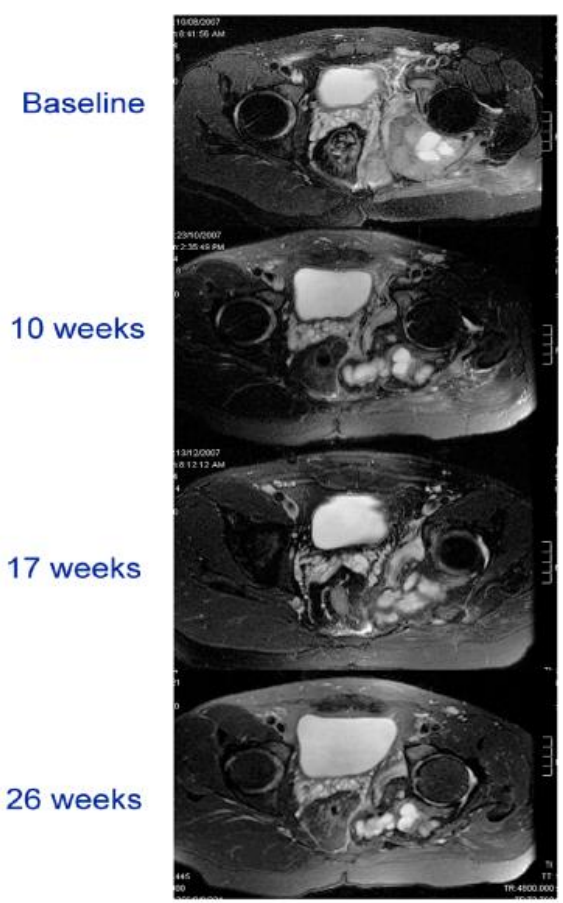
***Table 3*: Surgery in cohort 2**

	Cohort 1 (surgically unsalvageable)	Cohort 2 (salvageable, surgery planned)
Disease status		
Complete response	8/159 (5%)	17/93 (18%)
Partial response	57/159 (36%)	37/93 (40%)
Stable disease	93/159 (58%)	38/93 (41%)
Disease progression	1/159 (1%)	1/93 (1%)
Clinical benefit		
Pain reduction	48/169 (28%)	50/100 (50%)
Improved mobility	38/169 (22%)	33/100 (33%)
Improved function	32/169 (19%)	23/100 (23%)
Other	6/169 (4%)	10/100 (10%)

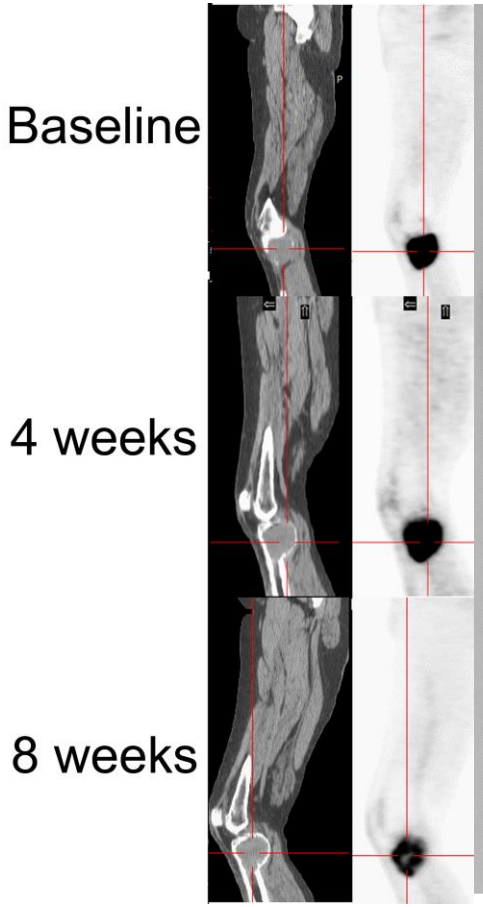
Data are n/N (%). For disease status, patients in the efficacy analysis set who had a disease status assessment were included. Results were based on the best response reported during the assessment period. For clinical benefit, enrolled patients who were eligible for the study and received at least one dose of denosumab were included. Results were based on the best response reported during the assessment period per the investigator's opinion and were independent of imaging, histology, and surgery.

***Table 4*: Investigator-determined disease status and clinical benefit in cohorts 1 and 2**

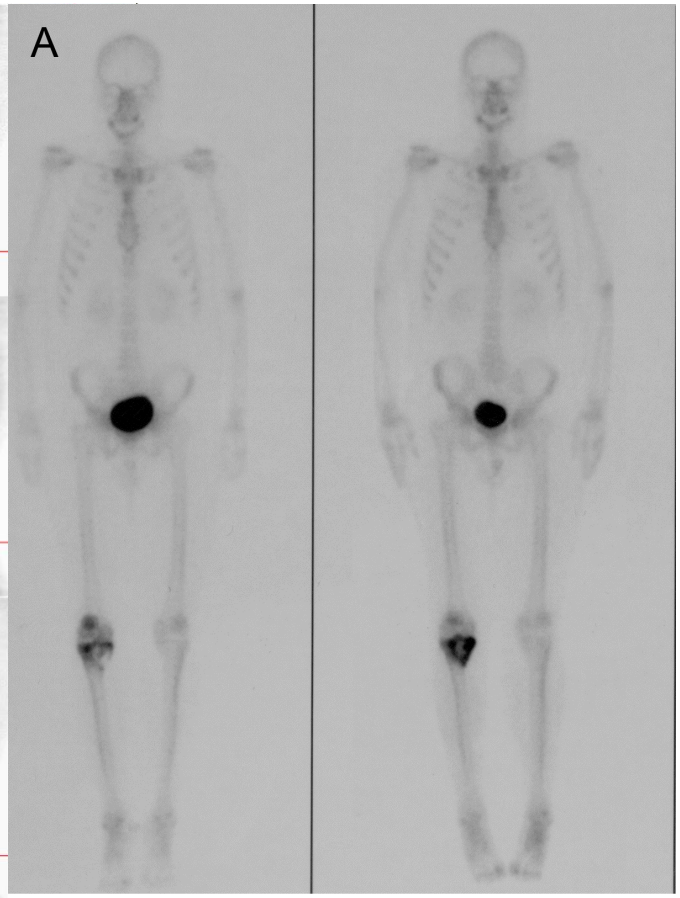
Radiologic responses



MRI

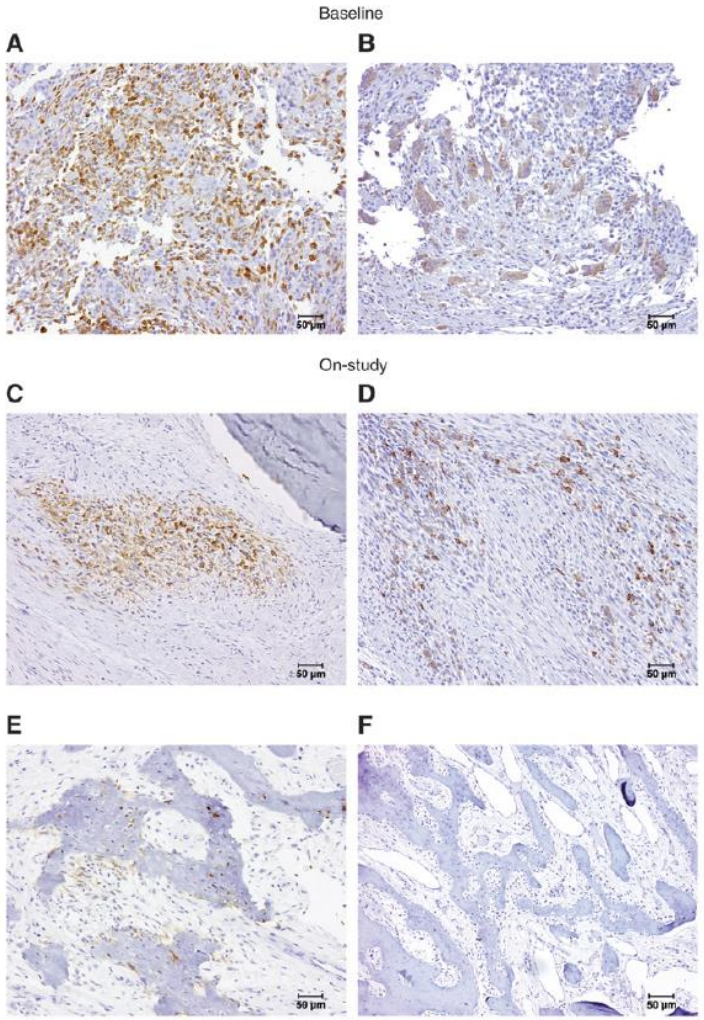


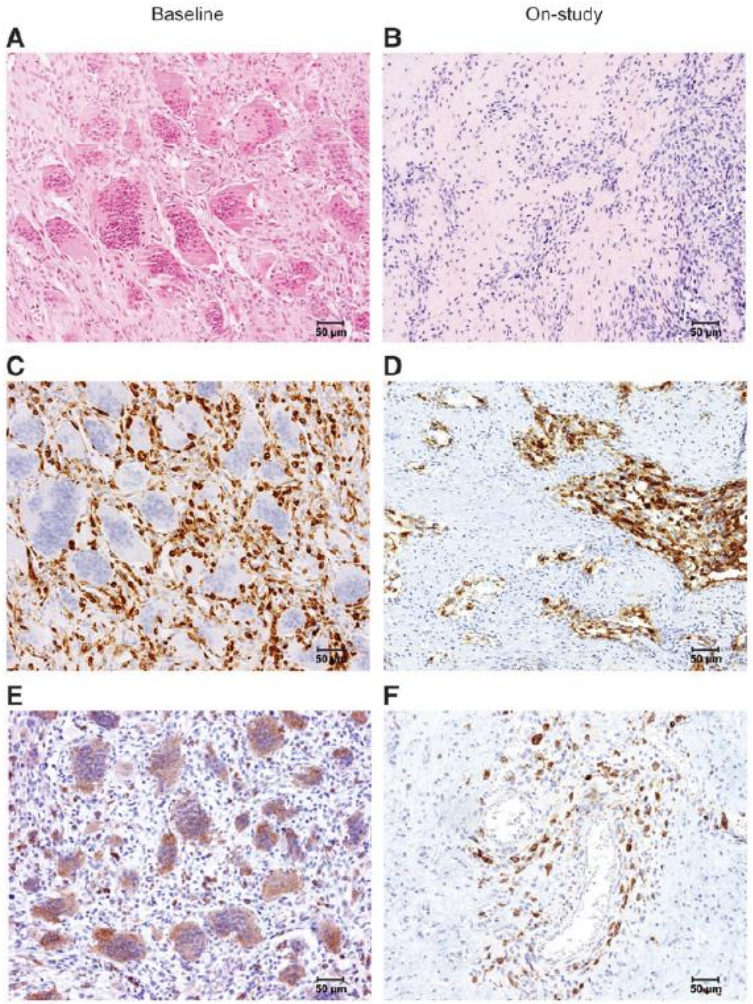
PET/CT



Bone scan

Histologic responses





Clinical Cancer Research, 2012, 18:4415

Major questions

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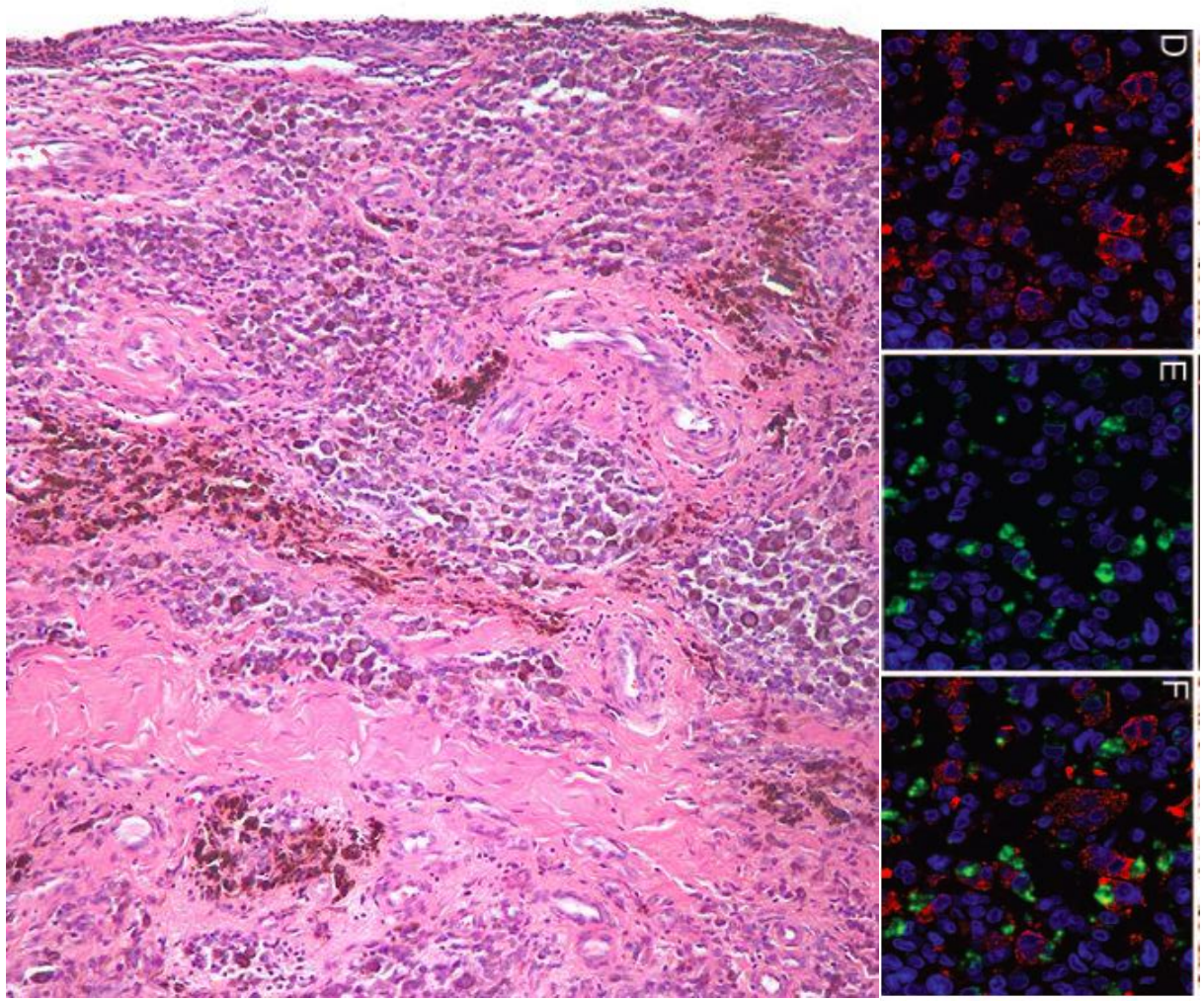
- If so, what is the optimal schedule?
- What are the long term sequelae (if any)?
- Adjuvant role: needs testing?
- Role for other giant cell-rich disorders?
  - Chondroblastoma, PVNS/TGCT, giant cell rich sarcomas, giant cell granuloma?

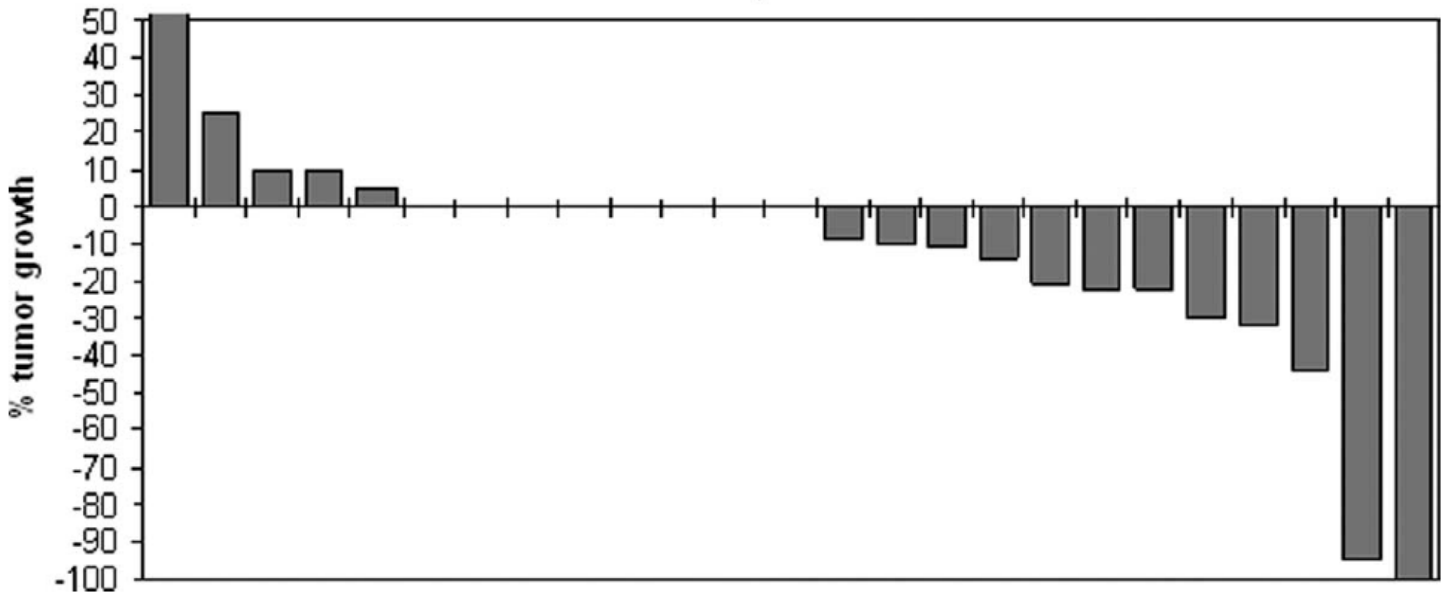
Localized and diffuse tenosynovial giant cell tumor



West et al PNAS 2006

Efficacy of Imatinib Mesylate for the Treatment of Locally Advanced and/or Metastatic Tenosynovial Giant Cell Tumor/ Pigmented Villonodular Synovitis

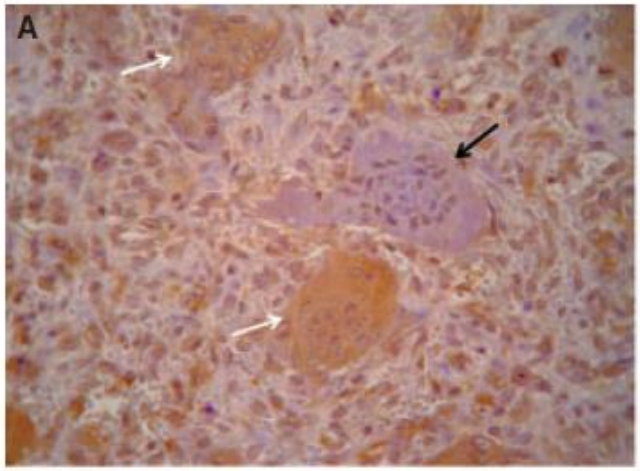
Philippe A. Cassier, MD[1]; Hans Gelderblom, MD[2]; Silvia Stacchiotti, MD[3]; David Thomas, MD[4]; Robert G. Maki, MD[5]; Judith R. Kroep, MD[2]; Winette T. van der Graaf, MD[6]; Antoine Italiano, MD[7]; Beatrice Seddon, MD[8]; Julien Dômont, MD[9]; Emanuelle Bompas, MD[10]; Andrew J. Wagner, MD[11]; and Jean-Yves Blay, MD[1,12]

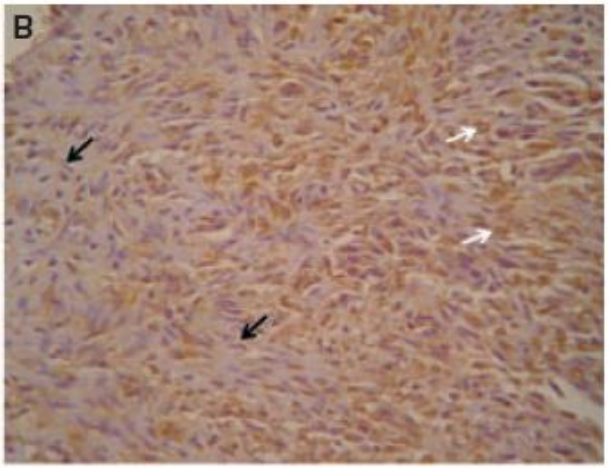


Cancer, 2012

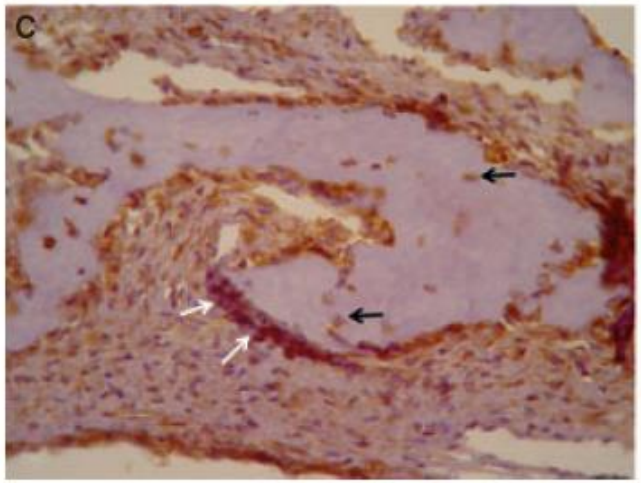
Giant cell granuloma of the mandible

RANKL
IHC

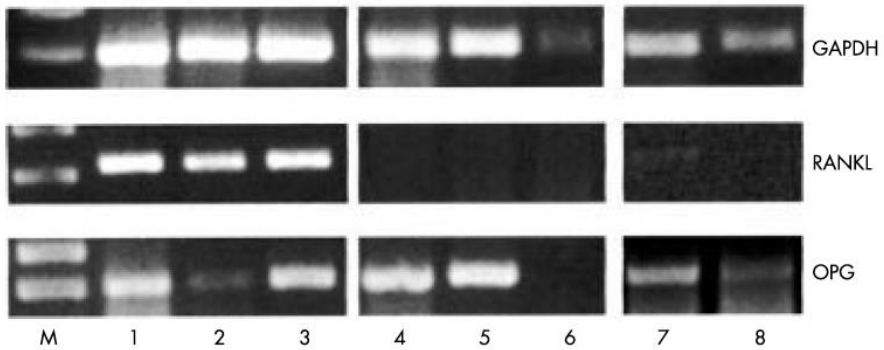




RANKL
ISH



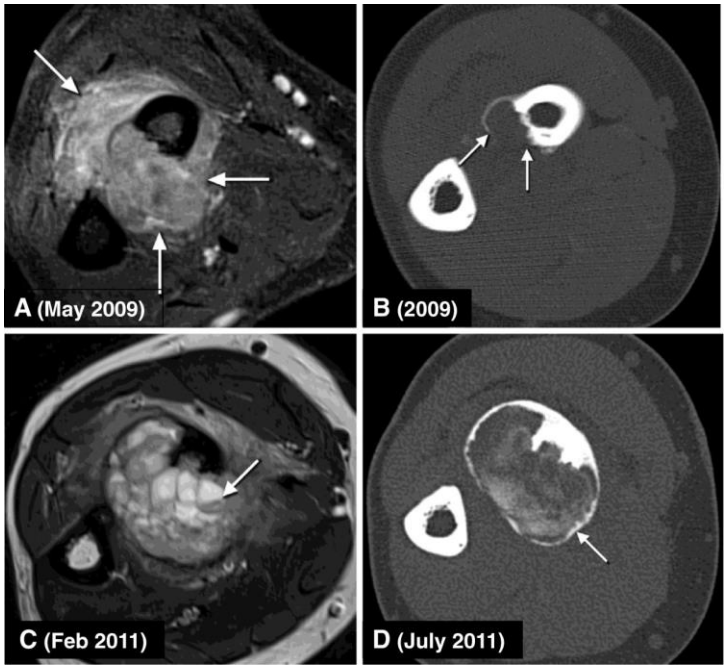
Others: chondroblastoma, aneurysmal bone cyst, giant cell-rich leiomyosarcoma



Chondroblastoma

Chondrosarcoma

Bone and cartilage



Denosumab effect in aggressive ABC

Huang et al J Clin Path 2003; Pauli et al., World J Surg Onc 2014