LEIDS UNIVERSITAIR MEDISCH CENTRUM

Sarcoma Poster discussion session
#1479-1483
Hans Gelderblom

The selected posters:

1. 1479 Phase II sunitinib in aggressive fibromatosis
2. 1482 GIST phase II dasatinib first line
3. 1481 GIST phase II dovitinib after TKI failure
4. 1480 Denosumab in GCT of bone
5. 1483 INNO-206 in relapsed STS

A prospective multicenter phase II study of sunitinib in patients with advanced aggressive fibromatosis (desmoid)

Jae-Cheol Jo[1], Kyu-pyo Kim[1], Yong Sang Hong[1], Jae-Lyun Lee[1], Jeeyun Lee[2], Young Suk Park[2], Sun Young Kim[3], and Tae Won Kim[1]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [2]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul; [3]Center for Colorectal Cancer, National Cancer Center, Goyang,

서울아산병원 종양내과
Asan Medical Center Department of Oncology

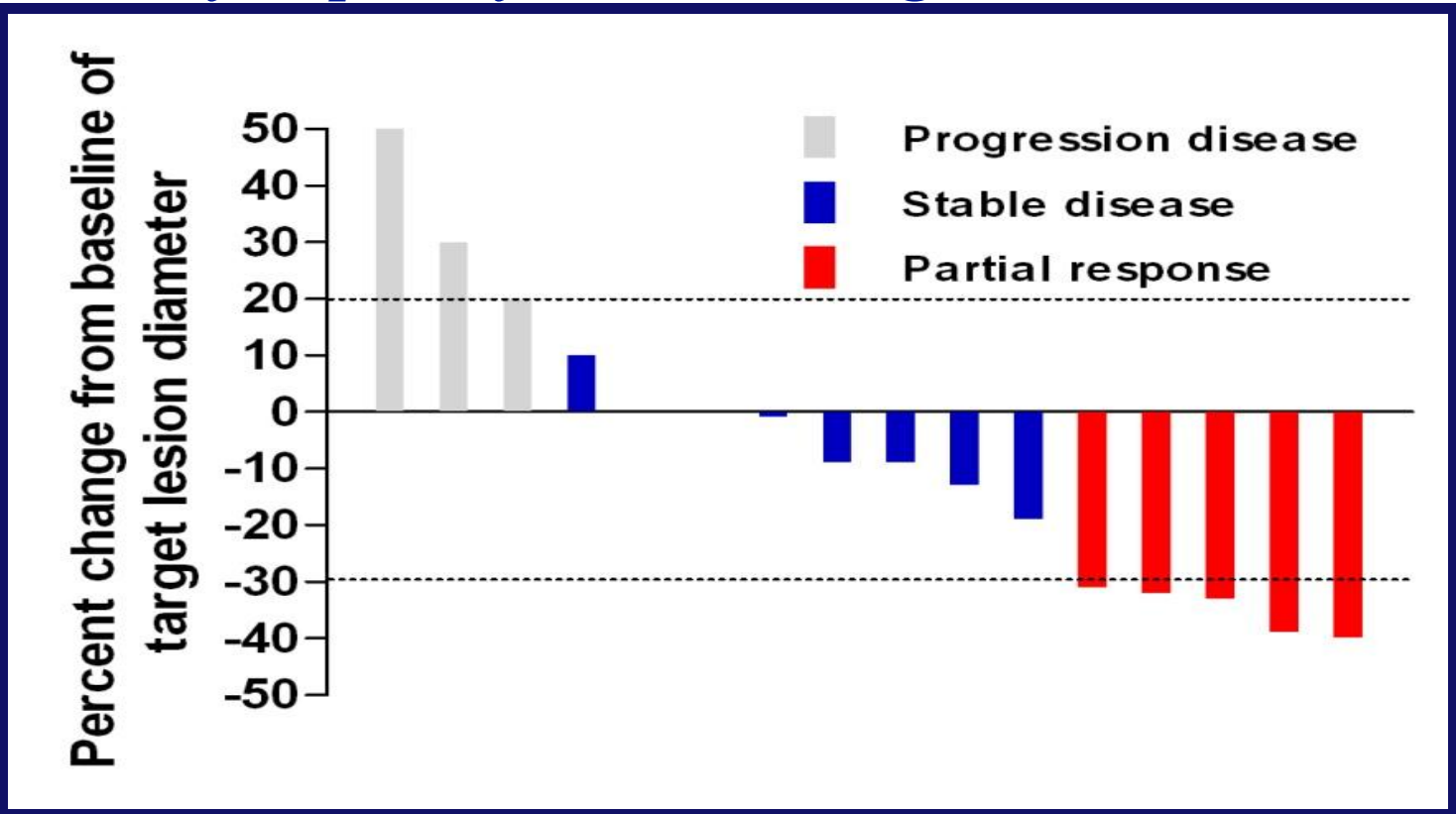
Study in desmoid type fibromatosis

- Background: desmoid is vascular tumour expressing PDGFR and suntinib blocks PDGFR and VEGFR
- Dose 37.5mg continously
- Primary endpoint response rate

Patient characteristics (n=19)

Characteristics	No. of patients (%)
Gender (male/female)	9/10
Median age, years	30 (22-67)
ECOG 1	19 (100%)
Known FAP	9 (47.4)
Sites of tumor	
Intra-abdominal	12 (63.2)
Trunk/Chest wall	5 (26.3)
Extremity	2 (10.5)
Tumor size	
< 5.0 cm	9 (47.4)
5-10 cm	7 (36.8)
> 10 cm	3 (15.8)
Multifocal AF	8 (42.1)
Prior radiation therapy	3 (15.8)
Prior surgery for AF	7 (36.8)
Prior systemic therapy	
NSAID	3 (15.8)
Anti-hormone	5 (26.3)
Cytotoxic chemotherapy	3 (15.8)

Waterfall plot of best radiologic outcome

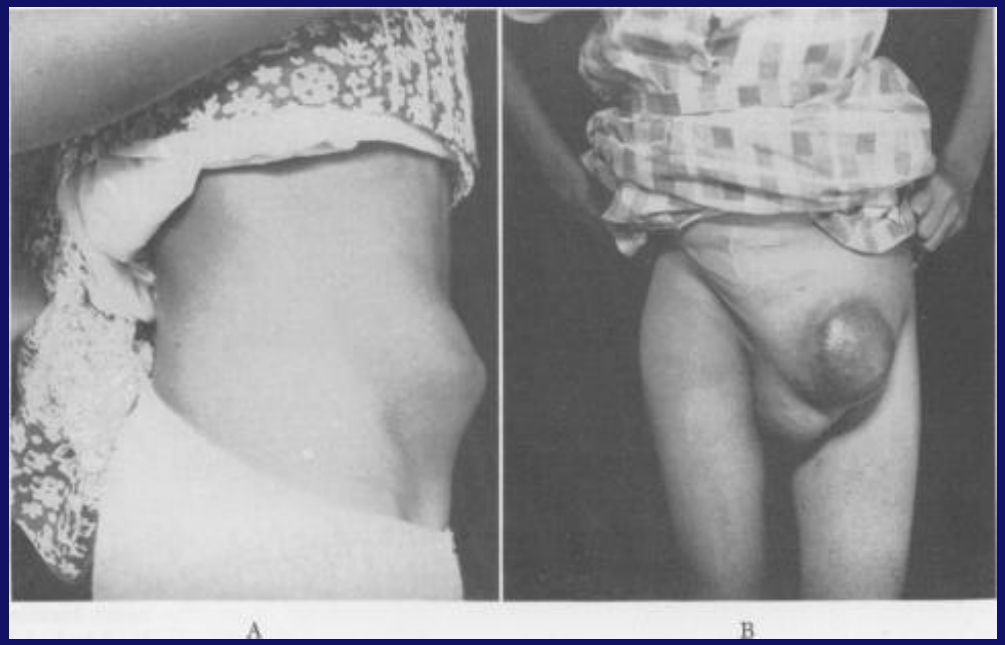


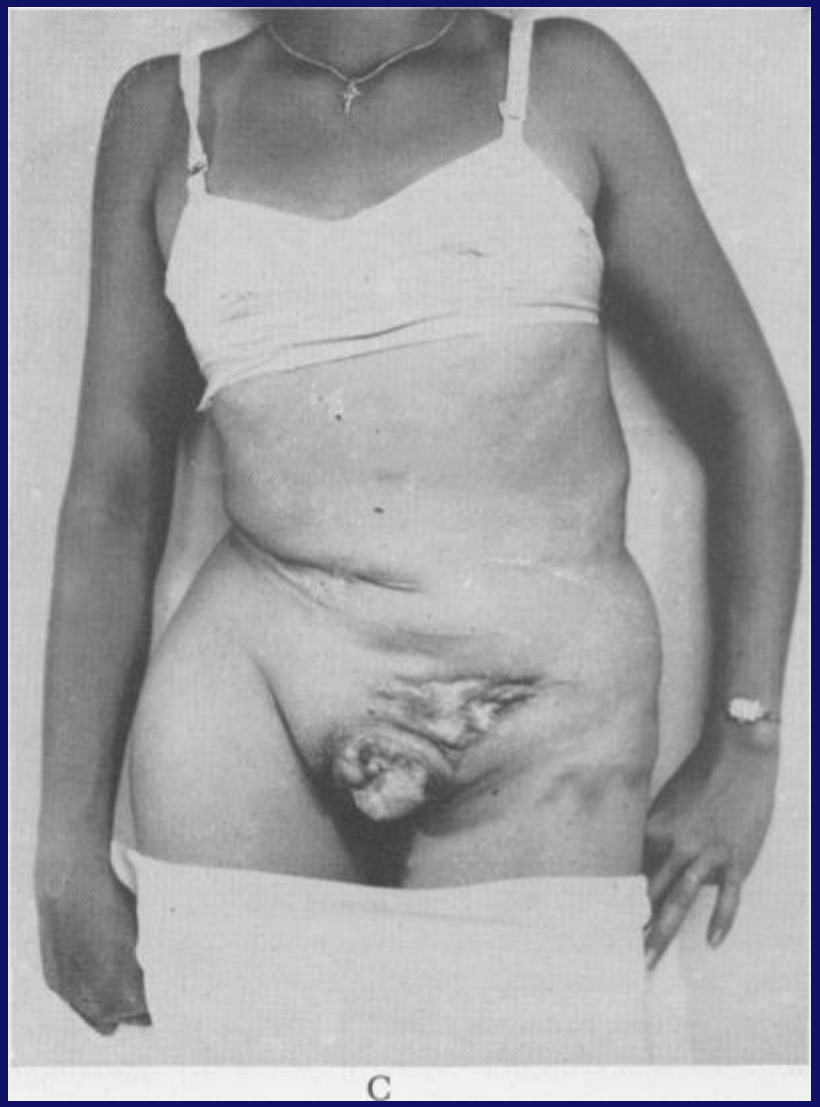
	RECIST response			
	PR	**SD**	**PD**	**NE**
N=19	**5 (26.3%)**	**8 (42.1%)**	**3 (15.8%)**	**3 (15.8%)**

Maximum grade toxicities (n=18)

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	6 (33.3%)	0	0	0
Leukocytopenia	2 (11.1%)	4 (22.2%)	1 (5.5%)	0
Neutropenia	1 (5.5%)	5 (27.7%)	5 (27.7%)	1 (5.5%)
Thrombocytopenia	9 (50%)	4 (22.2%)	0	0
Febrile neutropenia			1 (5.5%)	0
AST elevation	2 (11.1%)	0	1 (5.5%)	0
ALT elevation	3 (16.6%)	0	1 (5.5%)	0
Hyperbilirubinemia	1 (5.5%)	1 (5.5%)	0	0
Bleeding	1 (5.5%)	2 (11.1%)	1 (5.5%)	0
Fatigue	3 (16.6%)	2 (11.1%)	0	0
Anorexia	7 (38.8%)	1 (5.5%)	1 (5.5%)	0
Nausea	5 (27.7%)	0	0	0
Vomiting	3 (16.6%)	0	0	0
Stomatitis	2 (11.1%)	2 (11.1%)	0	0
Abdominal pain	4 (22.2%)	1 (5.5%)	0	0
Diarrhea	5 (27.7%)	3 (16.6%)	1 (5.5%)	0
Constipation	1 (5.5%)	1 (5.5%)	0	0
Alopecia	1 (5.5%)	0	0	0
Hand-foot syndrome	6 (33.3%)	1 (5.5%)	1 (5.5%)	0
Skin rash	4 (22.2%)	0	1 (5.5%)	0

Spontaneous regressions do occur *(Strode Ann Surg 1954)*





Treatment options in desmoid type fibromatosis

- Wait and see
- Surgery
  - Aim: neg.margins but not at all cost
  - ILP
- Radiotherapy
  - If: not candidate for surgery, but again consider toxicity
- Systemic
  - NSAID’s
  - Anti-estrogens
  - (Interferon)
  - Chemotherapy
  - TKIs

TKI's

	Study design	Treatment schedule	Patients (n)	Response
Imatinib				
Heinrich (CCR 2008)	Basket study	800mg daily	19-20	2-3 (10-16%)
Penel (Ann Oncol 2011)	Phase II	400mg daily	40	4/35 (12%)
Chugh (CCR 2010)	Phase II	600mg daily (BSA ≥1.5m^2), 400mg daily (BSA 1.0 - 1.5m^2), or 200mg daily (BSA <1.0m^2)	51	3 (6%)
Sorafenib				
Gounder (CCR 2011)	Retrospective	400mg daily	26	6/24 (25%)
Sunitinib				
Current study	Phase II	37.5mg daily	19	5 (26%)

Controversies around studies

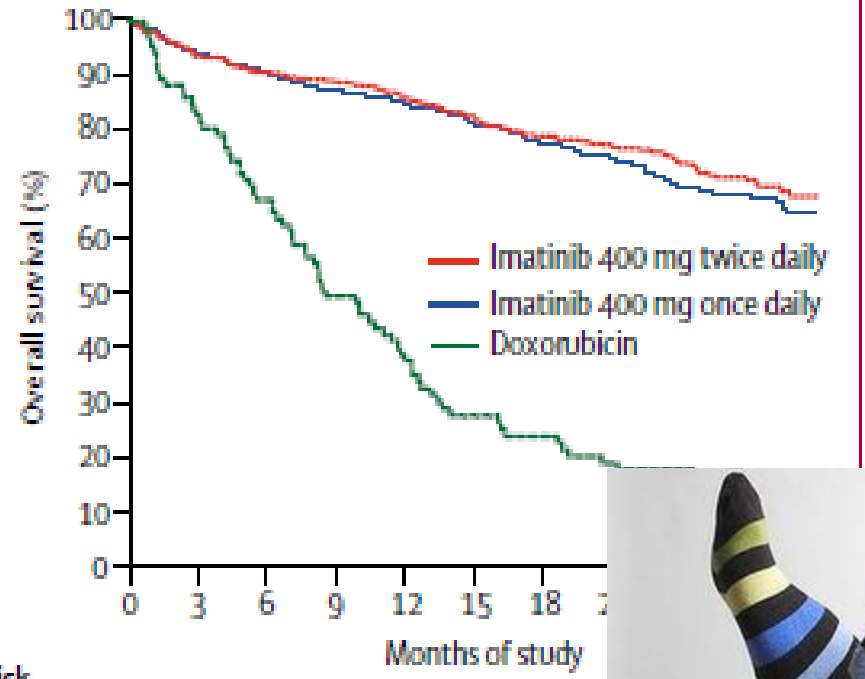
- Variable biological behaviour
  - Spontaneous regression
  - Location
- Very few prospective studies
  - Different classes of therapy
  - Different endpoints
- What is the aim of systemic therapy?
- At what costs?

- Only a randomised study or study considering growth modulation index wil give definite answers

Authors conclusions

- Sunitinib
  - Show promising antitumor activity in patients with AF
    - yes but no more than that
  - Well-tolerated toxicity
    - is it?
  - Further investigations on clinical and translational research of sunitinib in these patients are warranted
    - yes and randomised on patients with progressing tumours

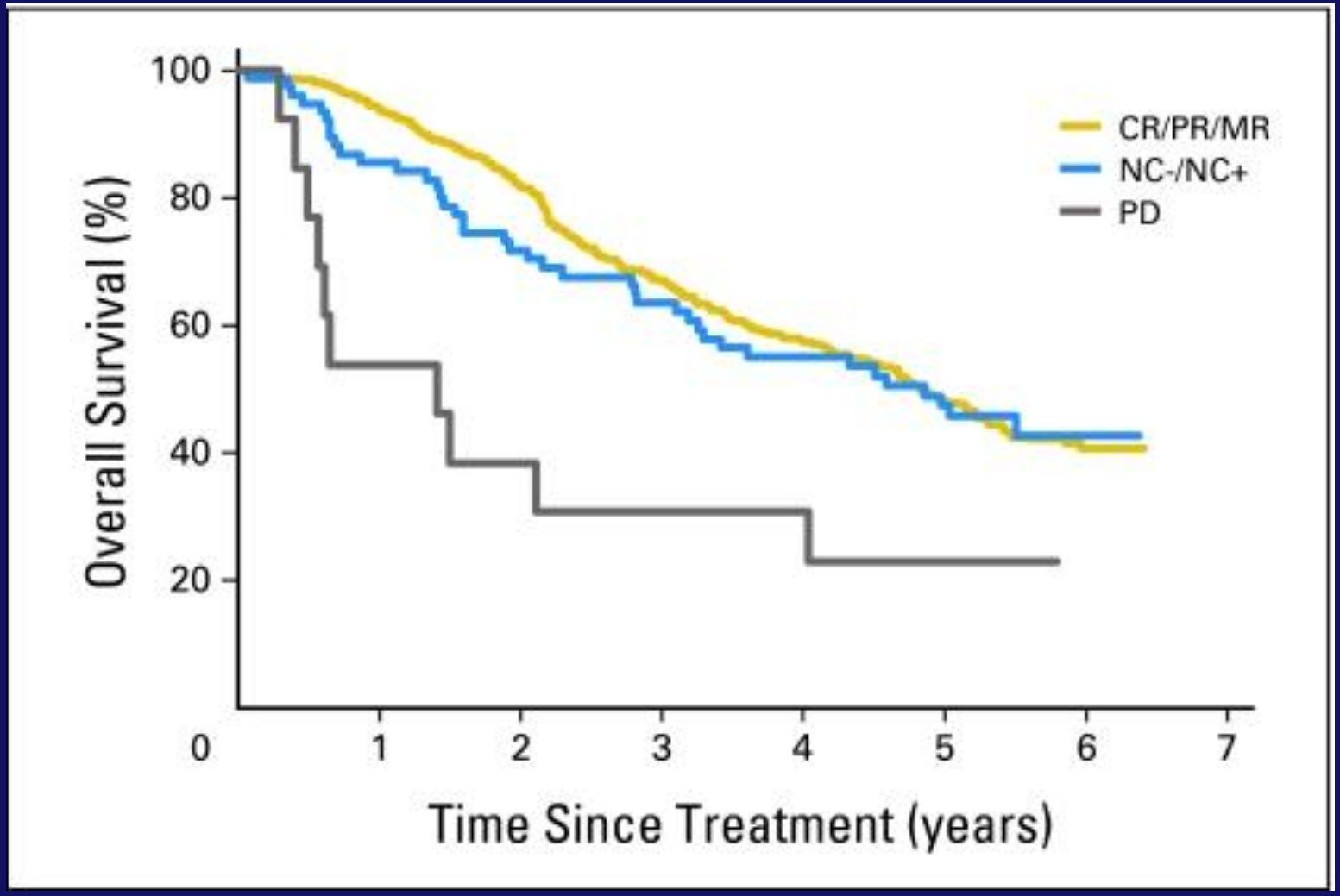
Metastatic GIST: can we sit back and relax?



Number at risk				
Imatinib 400 mg once daily	473	423	387	315
Imatinib 400 mg twice daily	473	427	399	323
Doxorubicin	86	57	31	19

Verweij et al Lancet 364, 1127-1134, 2004

What else do we know?



Le Cesne, JCO 27, 3969-74, 2009

And what do we know about dasatinib?

- Oral multi-target kinase inhibitor
- Inhibits BCR-ABL, SRC, PDGFR, KIT
- Inhibits imatinib-resistant PDGFRA D842V mutants[1]
- Dasatinib in GIST after imatinib failure (SARC 009 trial)[2]
  - N= 47 (80% also sunitinib failure)
  - PR= 22%
  - PFS= 2months
  - OS= 19months

1) Dewaele et al. Clin Cancer Res 2008
2) Trent et al ASCO 2011

Dasatinib first-line treatment in GIST

Multicenter phase II trial of the SAKK (SAKK 56/07)

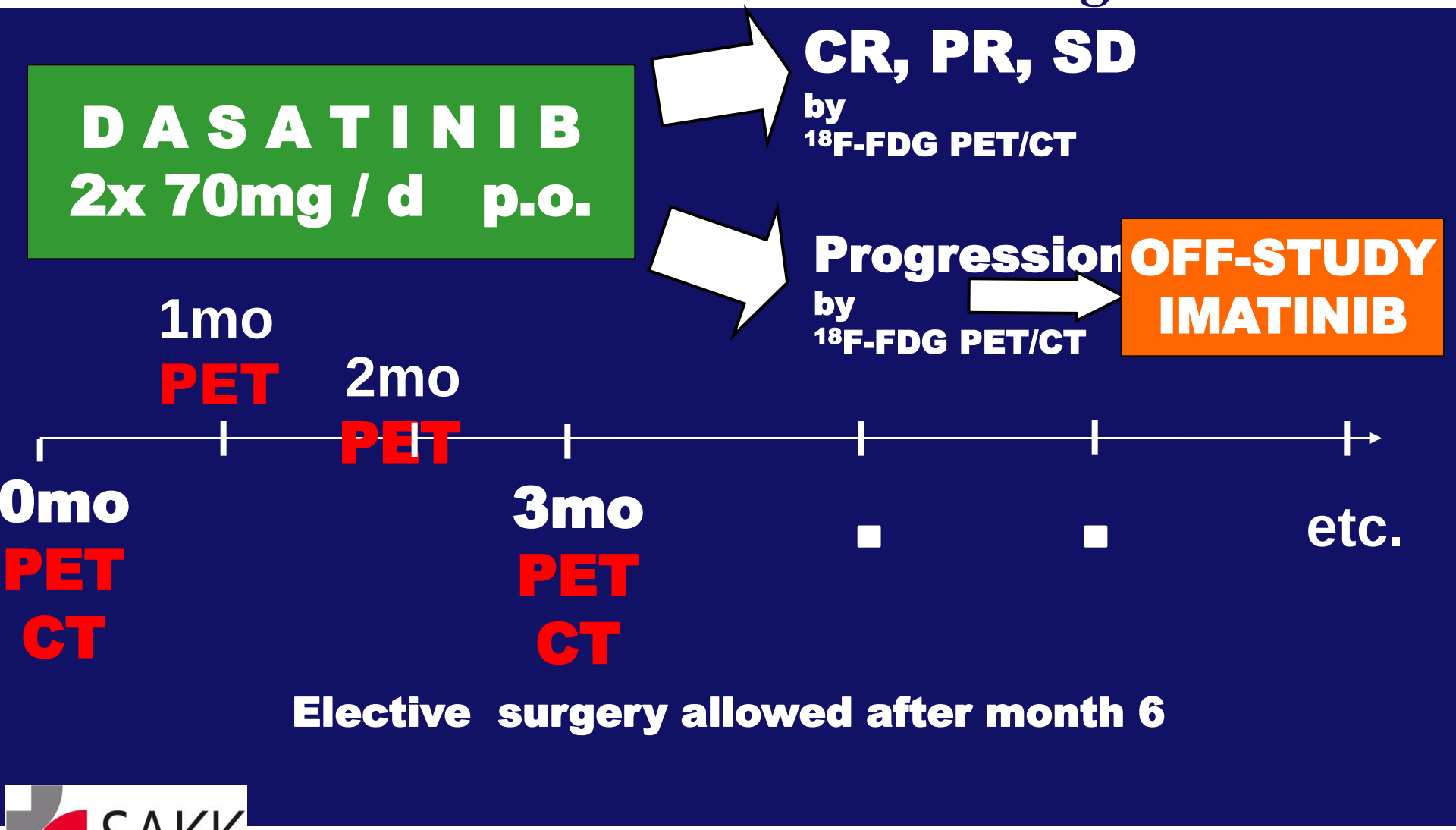
M. Montemurro[1], J. Domont[2], P. Rutkowski[3], A. Roth[4], R. von Moos[5], R. Inauen[6], D. Dietrich[7], C. Biaggi[7], J. Prior[1], S. Leyvraz[1]

on behalf of

Swiss Group for Clinical Cancer Research SAKK[7] (www.SAKK.ch)

1 Univ-Hospital Lausanne, Switzerland, 2 Institut Gustave Roussy, Villejuif, France, 3 Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, 4 Univ-Hospital Geneva, Switzerland, 5 Kantonsspital Graubünden, Chur, Switzerland, 6 Kantonsspital St Gallen, Switzerland, 7 SAKK, Bern, Switzerland

Dasatinib 1st-line in GIST – Trial design



SAKK

Safety / Toxicity

- Treatment was interrupted in 28 patients (65%)
- Dosage was reduced in 9 patients (21%)
- Treatment was stopped due to toxicity in 4 patients (9%)
- 38% of pts experienced a G3, 5% a G4 toxicity
- 3 deaths occurred
  - Clinical deterioration
  - GIST tumor bleeding
  - Cardiac arrest

SAKK

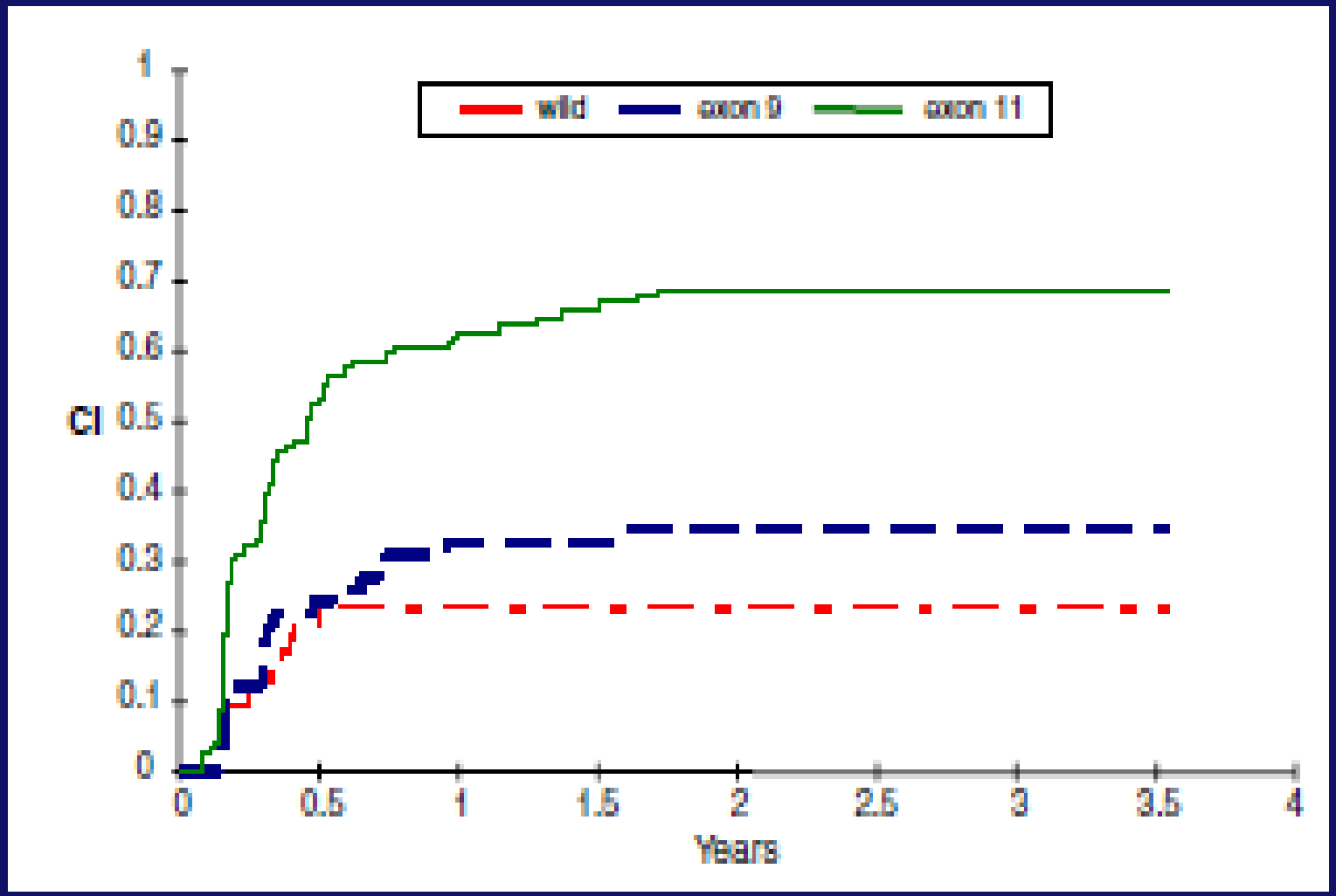
PET Response (Primary Endpoint)

- **CR+PR PET Response Rates**
  - **Overall** **77%** (n=42)
  - **KIT Exon 11** **80%** (n=25)
  - **Wild-Type** **71%** (n= 7)

	CR	PR	SD	PD	N.A.
All	15 (36%)	16 (41%)	7 (17%)	2 (5%)	2 (5%)
Kit Exon 11	9 (36%)	11 (44%)	3 (12%)	0	2 (8%)
Wild-Type	4 (57%)	1 (14%)	1 (14%)	1 (14%)	0
N.A.	2 (25%)	4 (50%)	2 (25%)	0	0

SAKK

CT responses on imatinib first line



Debiec-Rychter Eur J Cancer 42, 2006

Survival *(Secondary Endpoint)*

- Median Follow-Up 12.4 months
  - On trial 15 pts (36%)
  - Off-trial 27 pts (64%)

Progression	Elective Surgery	Toxicity	Death	Decision Local PI	2 years completed
12	6	4	3	1	1

- Median PFS 11.1 months
- Median OS not reached

Authors conclusion

- Dasatinib shows promising efficacy
- My conclusion
  - Maybe for response
  - But PFS is short
  - Considerable toxicity
  - Interesting endpoint for neoadjuvant studies, but PFS % is better endpoint for first line studies

Kang et al: dovitinib after failure of ≥ 2 TKI's

- **multi-kinase inhibitor KIT,PDGFR,VEGFR1-3,FGFR1-3,RET,TrkA,CSF1R,and FLT3with IC50s < 40nM**
- **Primary endpoint DCR at 24 wks**
- **Secondary: a.o. PET and CT response rate**

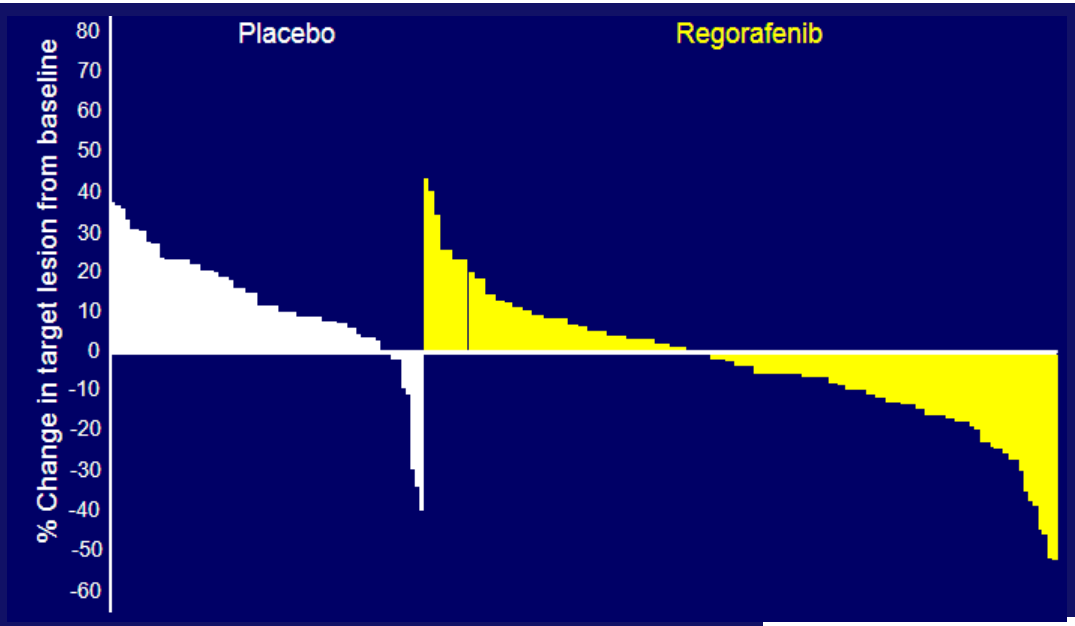
PD 1481 Kang et al: Dovitinib

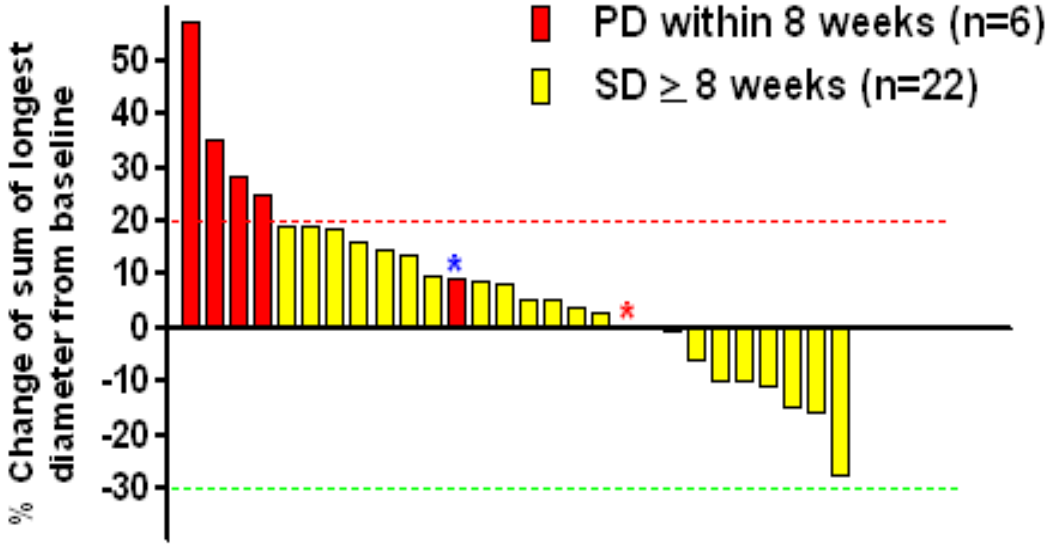
(N=30)	No	(%)
Age: median (range)	57.5 (35-76)	
ECOG PS 0-1	24	(80)
Failure by Progression		
Imatinib	30	(100)
Sunitinib	28	(93)
Exposure to other TKIs		
Nilotinib (N)	8	(27)
Regorafenib (R)	2	(7)
both N and R	3	(10)
Genotype (n=28)		
KIT exon 11	20	(71)
KIT exon 9	5	(18)
PDGFRα exon 18	1	(4)
Wild	2	(7)

G3/4 toxicities (%)

Asthenia	6	(20.0)
Neutropenia	4	(13.3)
Thrombocytopenia	3	(10.0)
Hypertriglyceridemia	3	(10.0)
Diarrhea	2	(6.6)
Hypertension	2	(6.6)
Anemia	1	(3.3)
Vomiting	1	(3.3)
Thrombosis	1	(3.3)
ALT elevation	1	(3.3)
Proteinuria	1	(3.3)

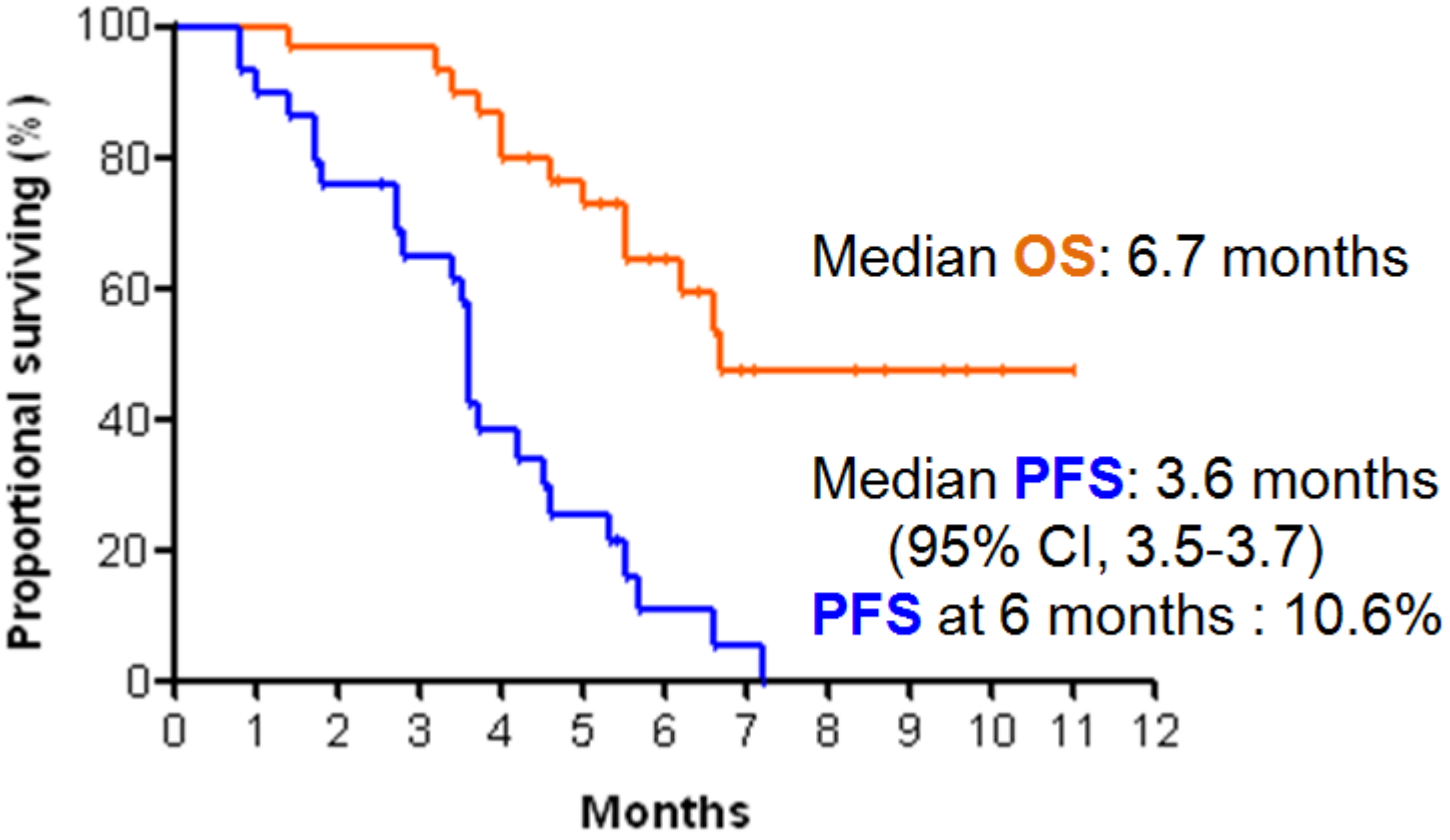
Response


Placebo
Regorafenib
% Change in target lesion from baseline
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60

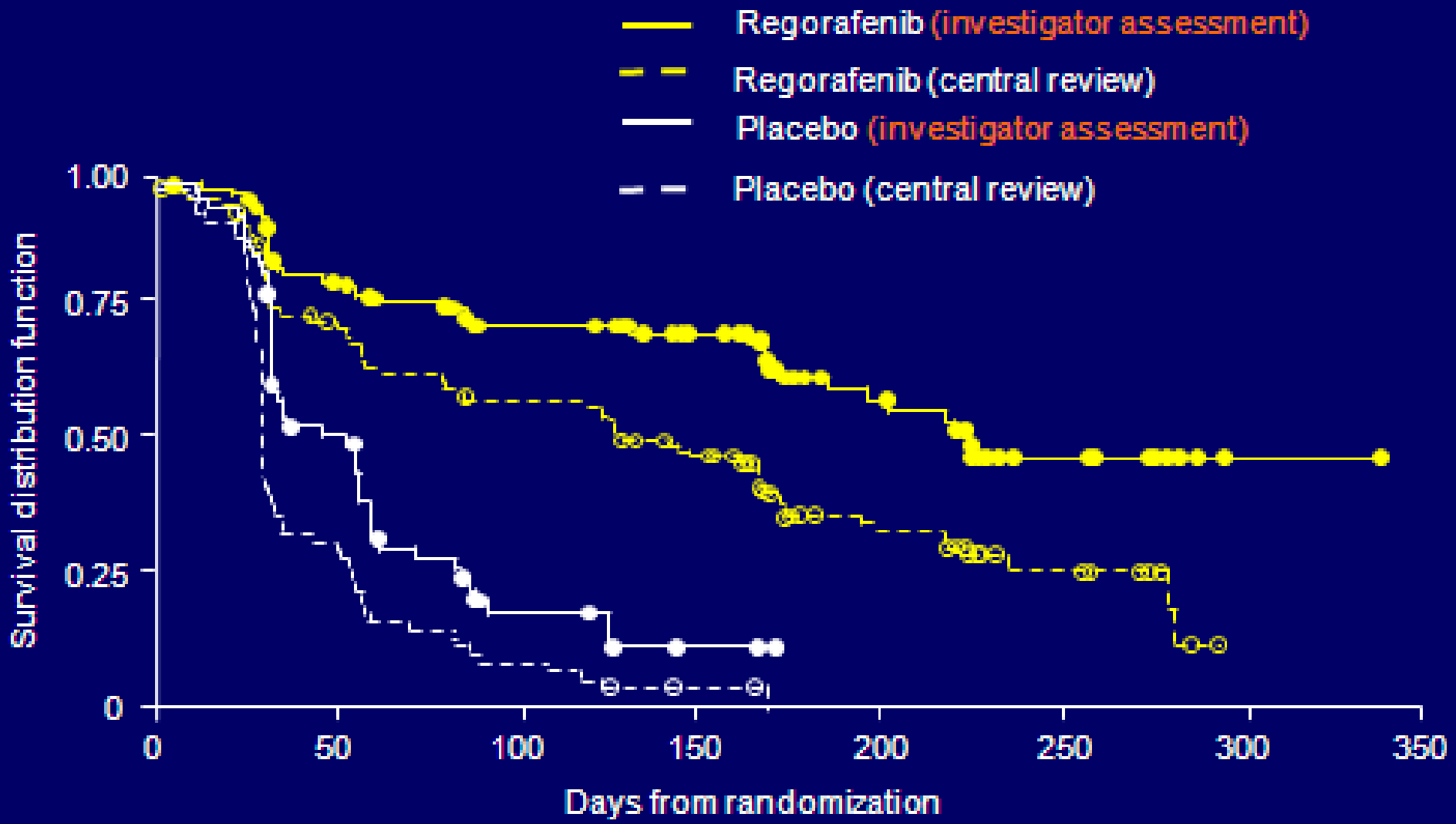

PD within 8 weeks (n=6)
SD ≥ 8 weeks (n=22)
% Change of sum of longest diameter from baseline
50
40
30
20
10
0
-10
-20
-30
*
*

PFS and OS

With a median follow-up of 6.4 months (range: 4.3-11.0) in surviving patients

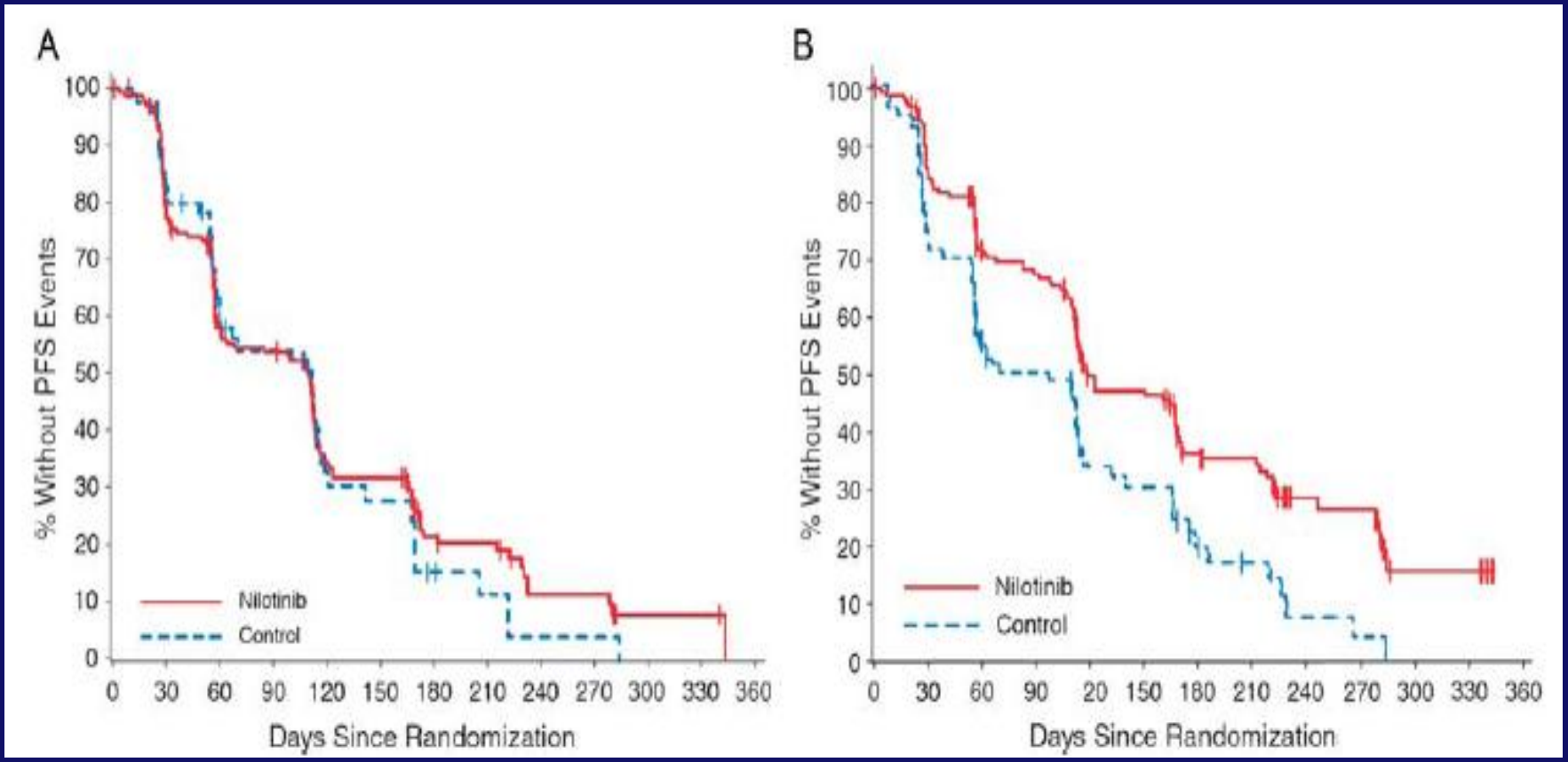


Progression-free survival: Comparison of Central Review *vs.* Investigator Assessments



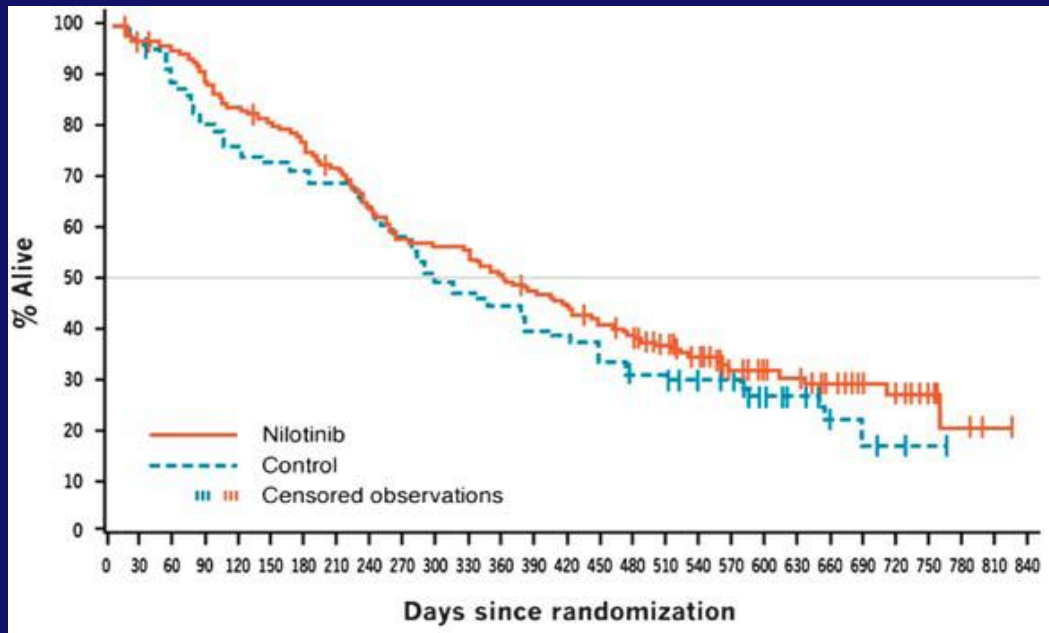
Reichardt, ESMO 2012

Also with nilotinib



Reichardt *et al* Ann Oncol 23, 1680-1687,2012

Survival difference in true third-line 3 months



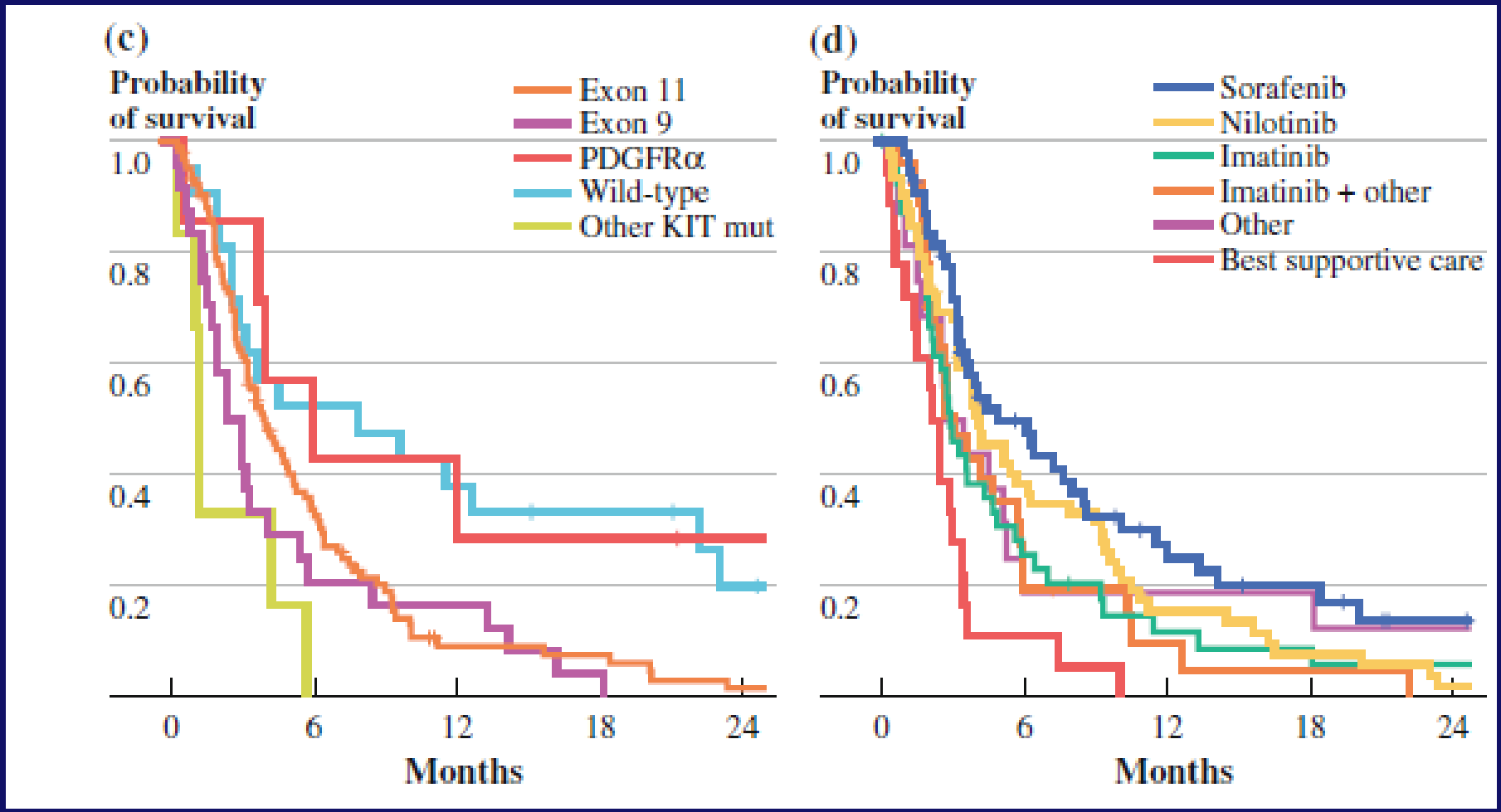
A

Overall survival, ITT population (N=248)	*P*=.28
Median (days) (nilotinib vs control)	361 vs 300
HR (95% CI)	0.84 (0.62, 1.15)

B

Overall survival, true-third-line–only (N=197)	*P*=0.02
Median (days) (nilotinib vs control)	405 vs 280
HR (95% CI)	0.67 (0.48, 0.95)

3rd line patterns in 223 pts



So where are we after imatinib and sunitinib?

- Reintroduction?
- Nilotinib failed
- Regorafenib succeeded
- Dovitinib showed activity and manageable toxicity

- Where to go?
  - Compete in first to third line?
  - Additional fourth line?
  - At least a randomised study similar to GRID may lead to rapid registration and access for the patients

Efficacy and Safety of Denosumab in Giant Cell Tumor of Bone: Updated Results with Independent Imaging Assessment of Response

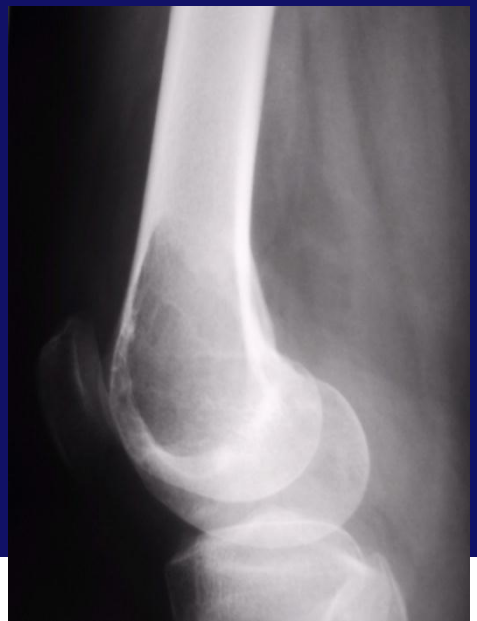
Jean-Yves Blay[1]; Sant Chawla[2]; Edwin Choy[3]; Robert Grimer[4]; Stefano Ferrari[5]; Peter Reichardt[6]; Piotr Rutkowski[7]; David Thomas[8]; Yi Qian[9]; Ira Jacobs[9]

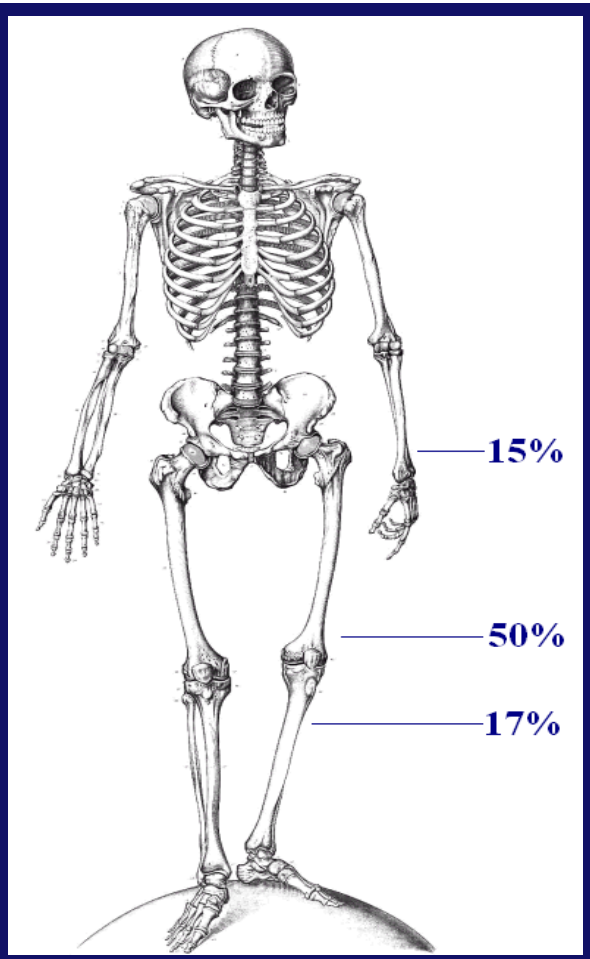
[1]University Claude Bernard Lyon I, Lyon, France; [2]Sarcoma Oncology Center, Santa Monica, CA, USA; [3]Dana Farber/Harvard Cancer Center, Massachusetts General Hospital, Boston, MA, USA; [4]Royal Orthopaedic Hospital, Birmingham, UK; [5]Istituti Ortopedici Rizzoli, Bologna, Italy; [6]HELIOS Klinik Berlin-Buch, Berlin, Germany; [7]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [8]Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; [9]Amgen Inc., Thousand Oaks, CA, USA

Acknowledgements: Funding for this study was provided by Amgen, Inc. who provided writing and graphic support for the preparation of this poster.

GCT of bone

- Common bone tumour
- Typically in young adults
- More in females
- Most amenable to surgery
- Recurrence in 10-75%



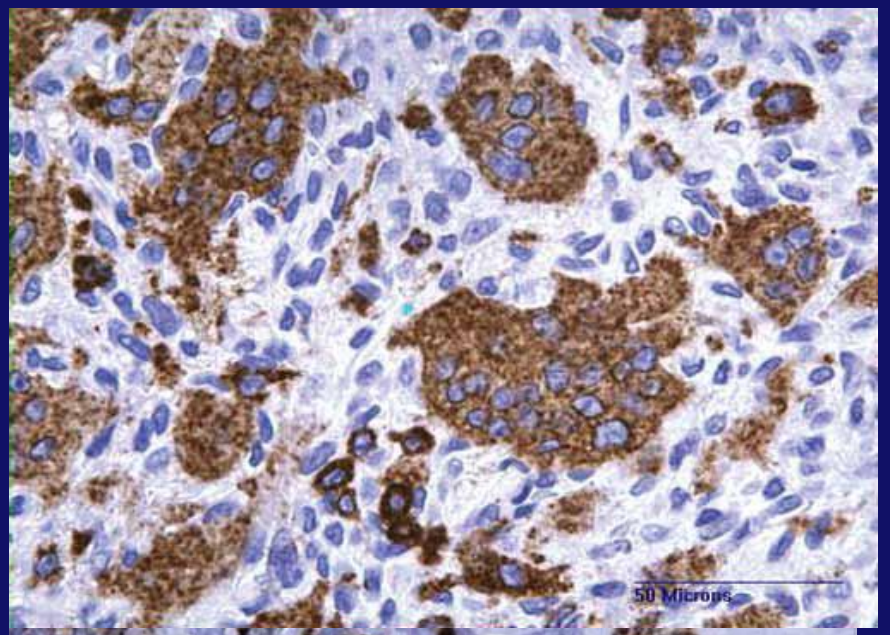


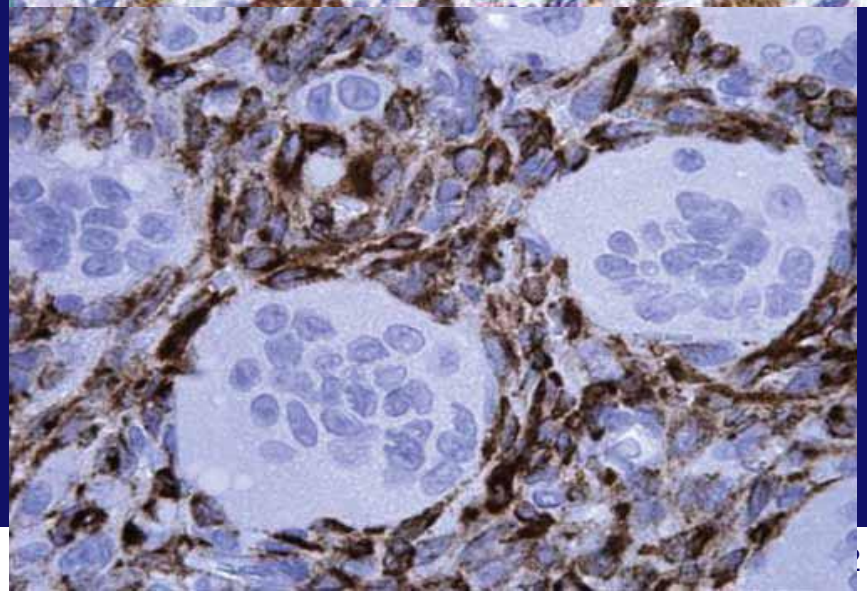
5% small bones
13% axial

Denosumab mechanism of action

- Osteoclast express RANK
- Stromal cells RANKL
- Denosumab inhibits RANKL

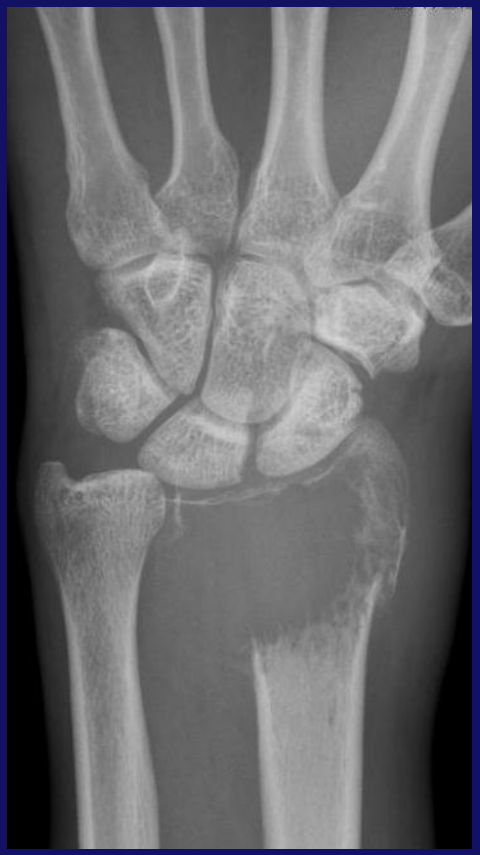
- Phase II, 37 pts
- 86% tumour response
- 84% clinical benefit
- No serious side effects





Thomas et al Lancet Oncol, 11, 2010

Response to denosumab



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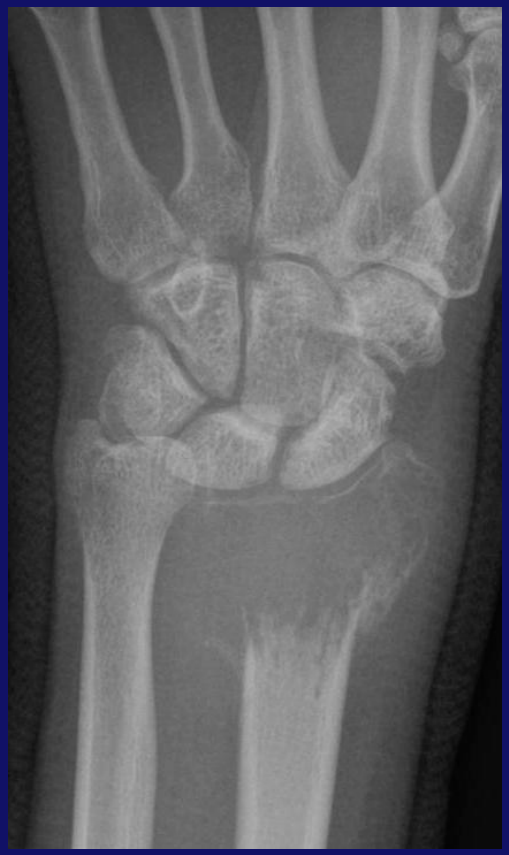

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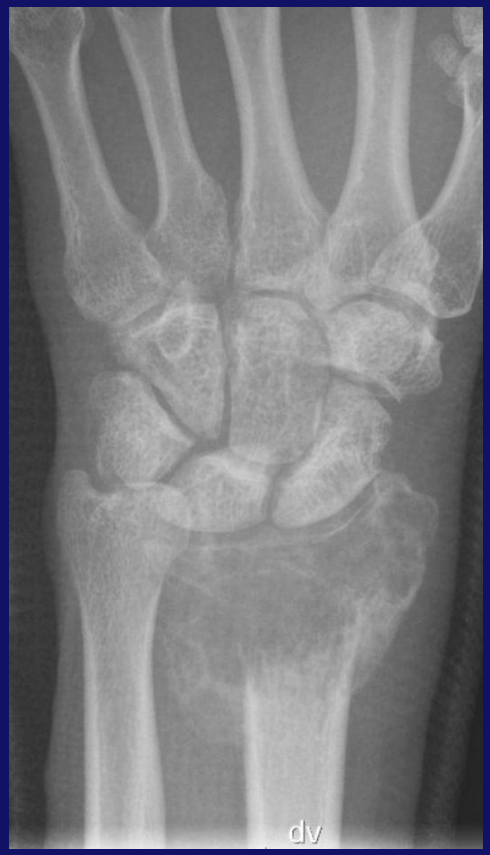

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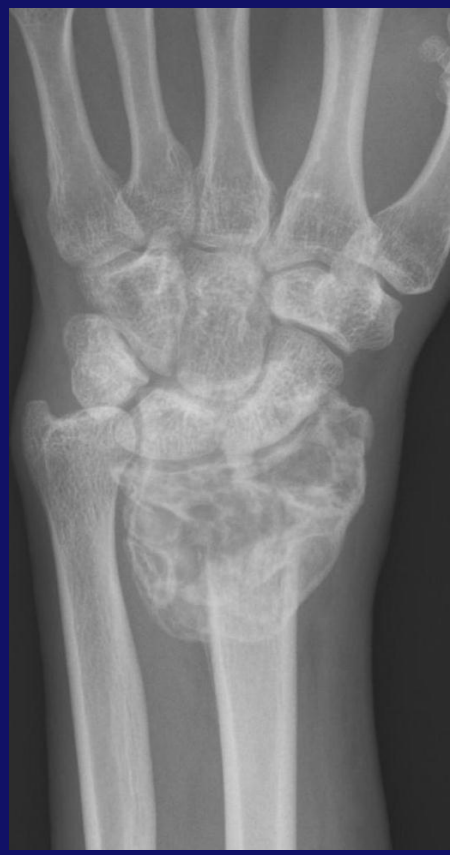


14-08-2012

Differential diagnosis important!

BENIGN	MALIGNANT
• Paget's disease	• (Giant cell) Carcinoma Metastases
• Brown tumour of Hyperparathyroidism	• Giant cell-rich MFH
• Non-Ossifying Fibroma	• Giant cell-rich Osteosarcoma
• Central Giant Cell Granuloma	• Malignant giant cell tumour?
• Cherubism	
• Aneurysmal Bone Cyst	
• Chondroblastoma	
• Chondromyxoid fibroma	
• Giant Cell Tumour	
• Osteoblastoma/Osteoid Osteoma	

Most giant cell containing tumours are benign

Courtesy Dr Bovee

Histological grading of GCT of bone (CvB)

Grade 1: no atypia, sporadic mitosis, many large giant cells

Grade 2: mild pleomorphism, regular mitoses (<1 / HPF),
less giant cells

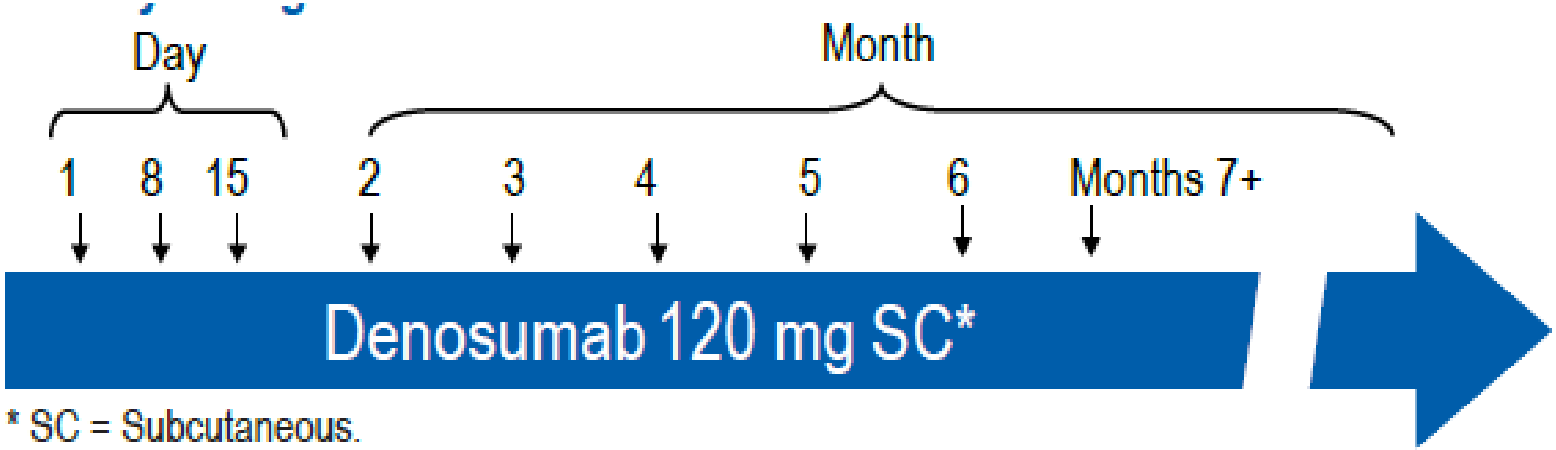
Grade 3: pleomorphism, >1 mitosis / HPF, less and smaller giant cells

Grade 4: progression to sarcoma

Recurrence rate:

	only curettage	curettage + adjuvant*	
• **Grade 1**	**13%**		**low**
• **Grade 2**	**55%**	**20%**	**low**
• **Grade 3**	**80% (and 3/13 mets)**		**high**
• **Grade 4**	**100%**		**high**

** Treated by curettage, application of adjuvant (phenol, alcohol) and cementation*



* SC = Subcutaneous.

All patients advised to take daily supplement of ≥ 500 mg calcium and ≥ 400 IU vitamin D

Adults or skeletally mature adolescents with GCTB

Cohort 1: Surgically unsalvageable GCTB

- Disease progression
- Disease status and clinical benefit
- Objective tumor response†
- Tumor control†
- Safety

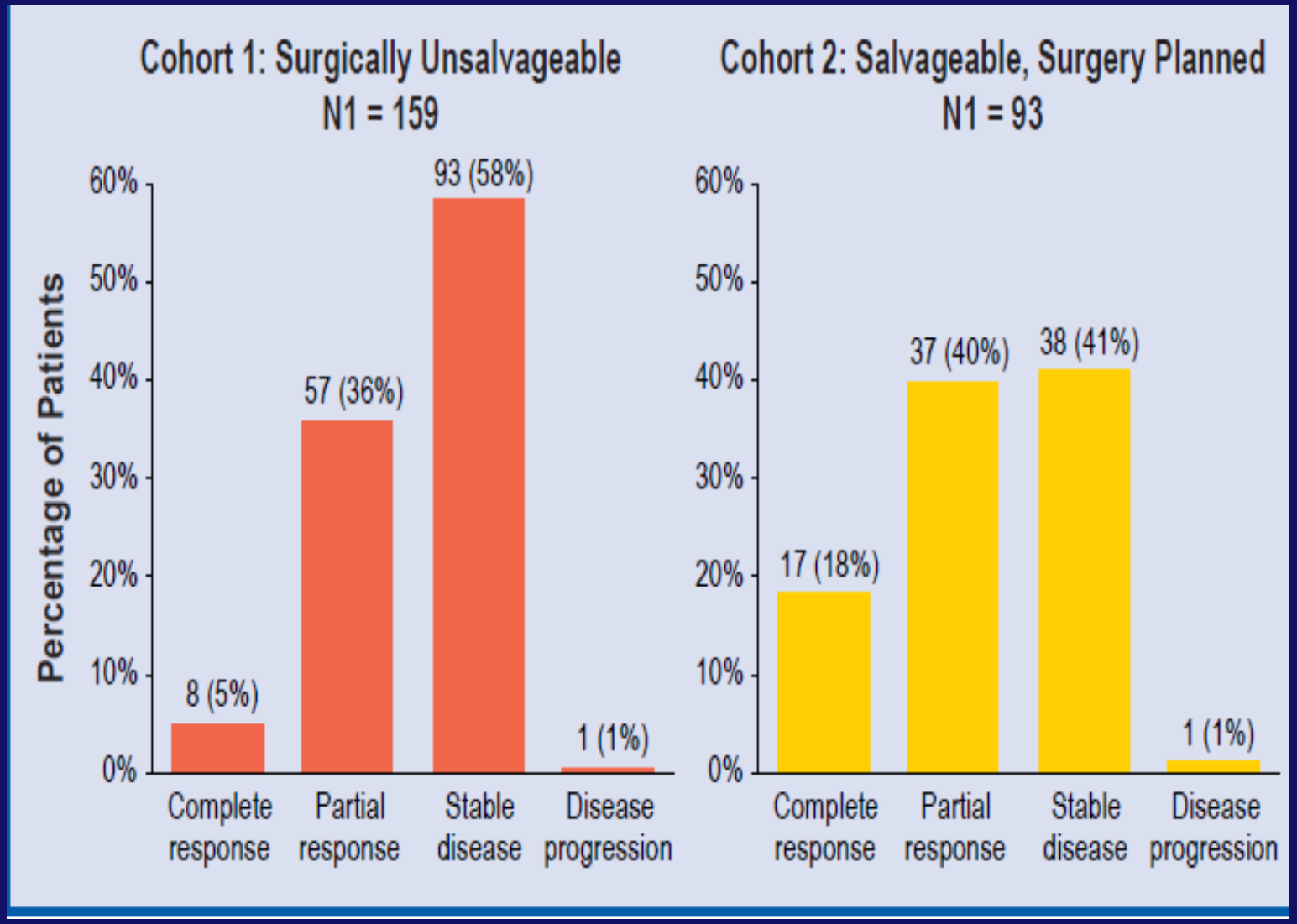
Cohort 2: Salvageable GCTB with planned surgery

- Surgery: delay, avoidance, or reduced morbidity
- Disease progression
- Disease status and clinical benefit
- Objective tumor response†
- Tumor control†
- Safety

Cohort 3*: Patients who transitioned from previous denosumab GCTB study[12]

- Disease progression
- Disease status and clinical benefit
- Safety

Investigator determined disease status



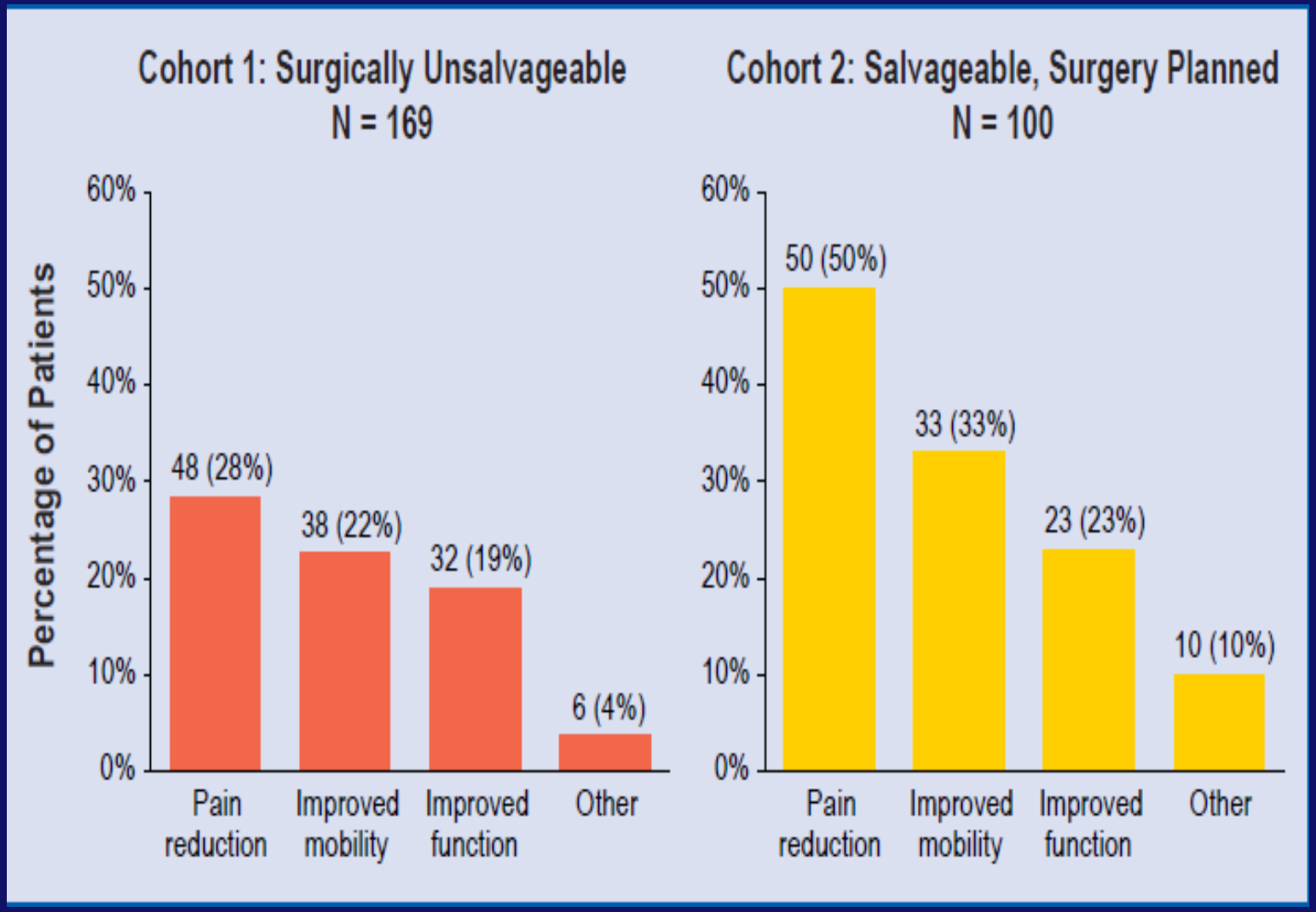
Independent Imaging Assessment: Objective Tumor Response and Tumor Control

	Patients with objective tumor response % (n/N1)	Median time to objective tumor response (months)	Patients with objective tumor response sustained ≥ 24 weeks % (n/N1*)	Patients with tumor control sustained ≥ 24 weeks % (n/N1*)
Overall	**72 (136/190)**	**3.1**	**68 (76/111)**	**98 (109/111)**
RECIST	25 (47/187)	not reached	24 (26/109)	99 (108/109)
EORTC	96 (25/26)	2.7	92 (11/12)	100 (12/12)
Modified Choi	76 (134/176)	3	75 (76/102)	99 (101/102)

N1 = Patients with ≥ 1 evaluable timepoint assessment
* Patients with timepoint assessments ≥ 24 weeks apart

- **An objective tumor response (defined as complete or partial response) was observed in 72% of patients based on the best response using any response criteria.**
- **Objective tumor responses were observed in a median 3.1 months, and were sustained for at least 24 weeks in 68% of patients.**
- **Nearly all patients (109 of 111, 98%) had sustained tumor control (defined as complete or partial response or stable disease) for at least 24 weeks.**

Investigator determined clinical benefit



Less frequent and less extensive surgery

Surgical Procedure, n*	Baseline Planned (N =100)	Actual Total (N = 26)
Total number of surgeries*	**100**	**26**
Major surgeries	**44**	**3**
Hemipelvectomy	4	0
Amputation	17	0
Joint/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	**N/A**	**74**

- **Of 71 patients who had an opportunity to be on study for at least 6 months, 64 (90%) did not have surgery by month 6.**
- **Overall, 90 patients (90%) had no surgery or underwent a less morbid procedure compared with the baseline planned surgical procedure by the analysis cut-off date (74 with no surgery; 16 with less morbid surgery).**
- **The estimated median time to surgery was 23.8 months.**

Adverse events

Patients with Adverse Events, n (%)	All Subjects N = 281*
Overall safety summary	236 (84)
Adverse events occurring in ≥ 10%	
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)
Serious adverse events	25 (9)
Adverse events leading to treatment discontinuation	14 (5)
Adverse event of interest	
Adjudicated positive ONJ	3 (1)
ONJ resolved	2 (1)
Hypocalcemia (none serious)	15 (5)
Serious infections	5 (2)
New primary malignancy	3 (1)

Denosumab in GCT

- Clearly one of the most effective drugs in “oncology”
  - Clinical improvement
  - Less and less morbid surgery

- Challenges remain:
  - First: FDA/EMA approval

  - Can we stop treatment?
  - What is the correct dose?
  - Adjuvant treatment?
  - Does it work in other giant cell rich lesions?

Doxorubicin in sarcoma

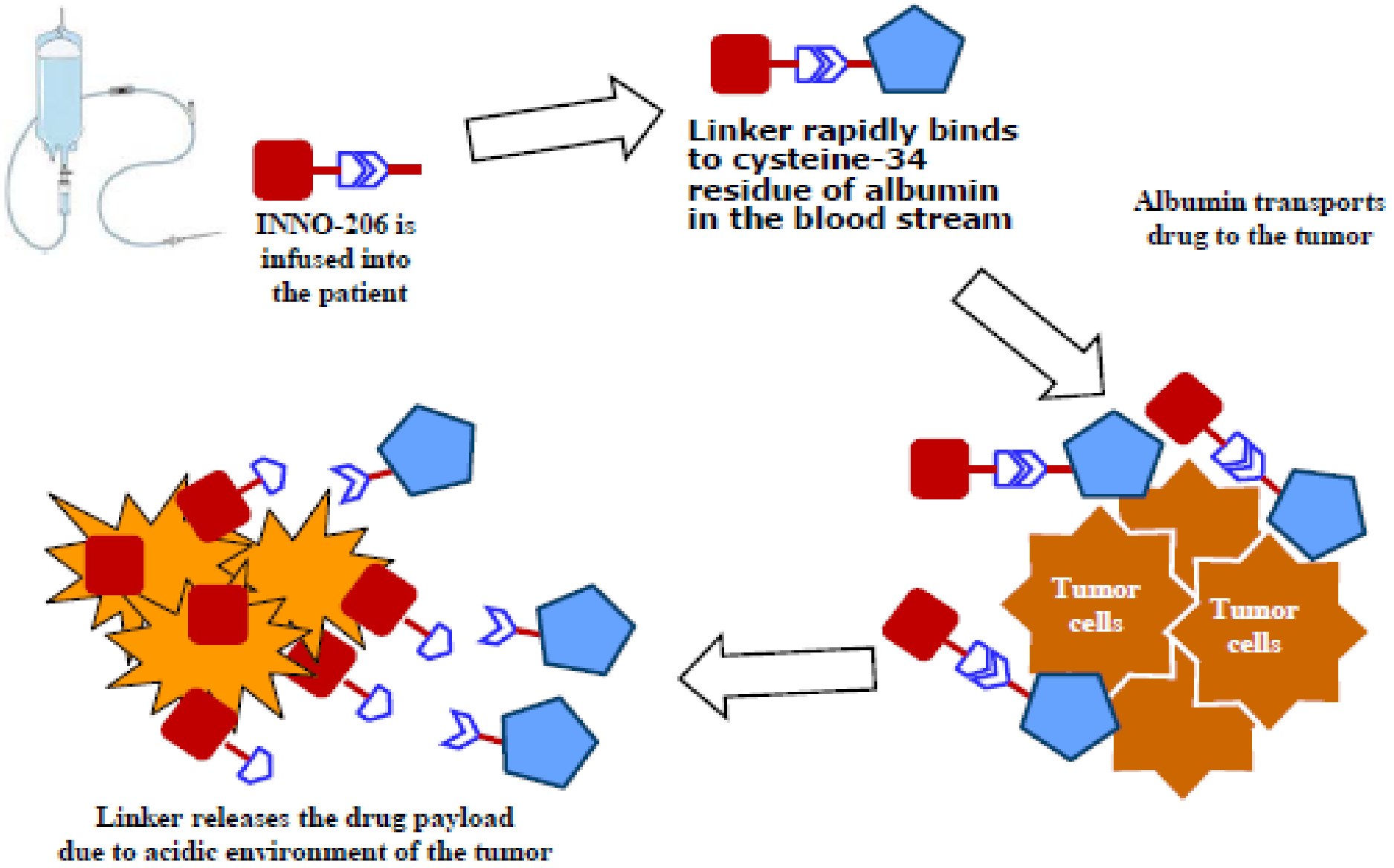
- Backbone of Ewing and osteosarcoma treatment
  - ISG 1.3-2%
- Standard first line in metastatic STS
  - Limited to 6 cycles

INNO-206 (Aldoxorubicin) is an active drug for relapsed advanced soft tissue sarcoma

S. Chawla[1], V.S. Chua[1], A. Hendifar[1], D. Quon[1], S. Nagre[1], K.N. Ganjoo[2], K. Sankhala[3], Y. Lavinski[4], S. Wieland[1], D. Levitt[1]

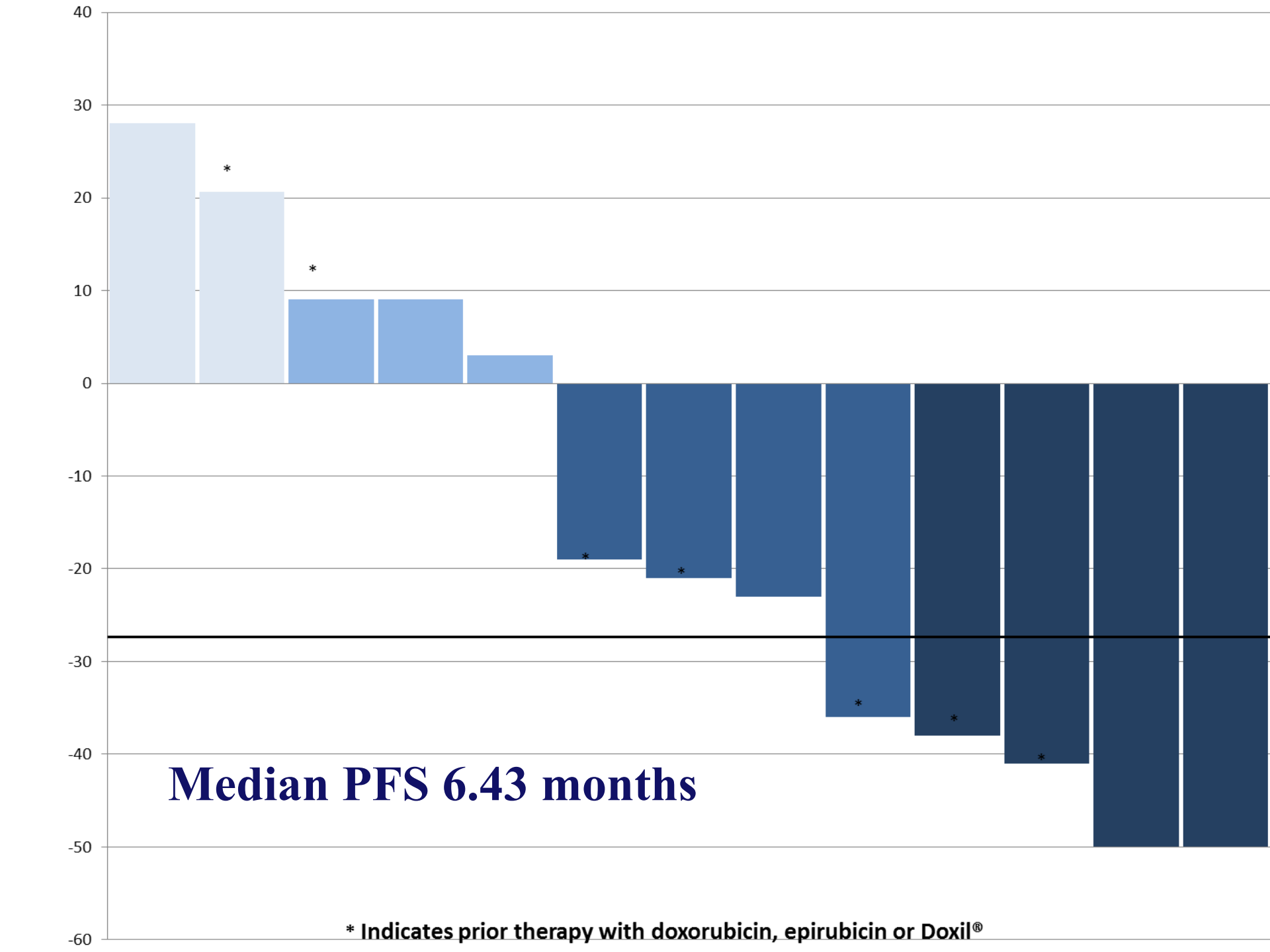
[1]Los Angeles, CA/US, [2]Palo Alto, CA/US, [3]San Antonio, TX/US, [4]Newport Beach, CA/US

Proposed Mechanism of Action



Study design

- 13 STS pts with a median of 2 prior regimens
- Dose 350*mg/m^2/d1 q 3wks x 8
- *260 mg/m^2 doxorubicin equivalent
- Scans every 2 months
- Toxicity
  - No sign. Cardiotoxity (1<55%)
  - Hematological tox (3FN, 2 sepsis)


40
30
20
10
0
-10
-20
-30
-40
-50
-60
Median PFS 6.43 months
* Indicates prior therapy with doxorubicin, epirubicin or Doxil®

In conclusion

- Doxorubicin is cornerstone of all sarcoma treatment
- Cardiotoxicity is concern and limiting factor
- Innovative analogues such as aldoxorubicin are needed
- Attention point is haematological toxicity

- Further points:
  - Improved activity?
  - Development in other tumour types

Thank you for your attention