
Children's Oncology Group: Bone Sarcoma Activites

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Osteosarcoma: Biology

Bone Sarcoma Committee

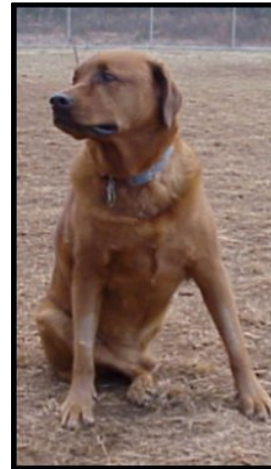
- **Correlative studies will enhance knowledge of osteosarcoma biology and lead to the identification of new therapeutic targets**

Osteosarcoma: Biology

Pre-clinical modeling



Comparative
Oncology
Program



COG Clinical
Trials



- Spontaneous osteosarcoma in pet dogs more common than in humans
- Dog model
 - Rapid evaluation of agents or strategies useful in humans
 - Advantage: rapid evaluation
- First compound: mTOR inhibitor

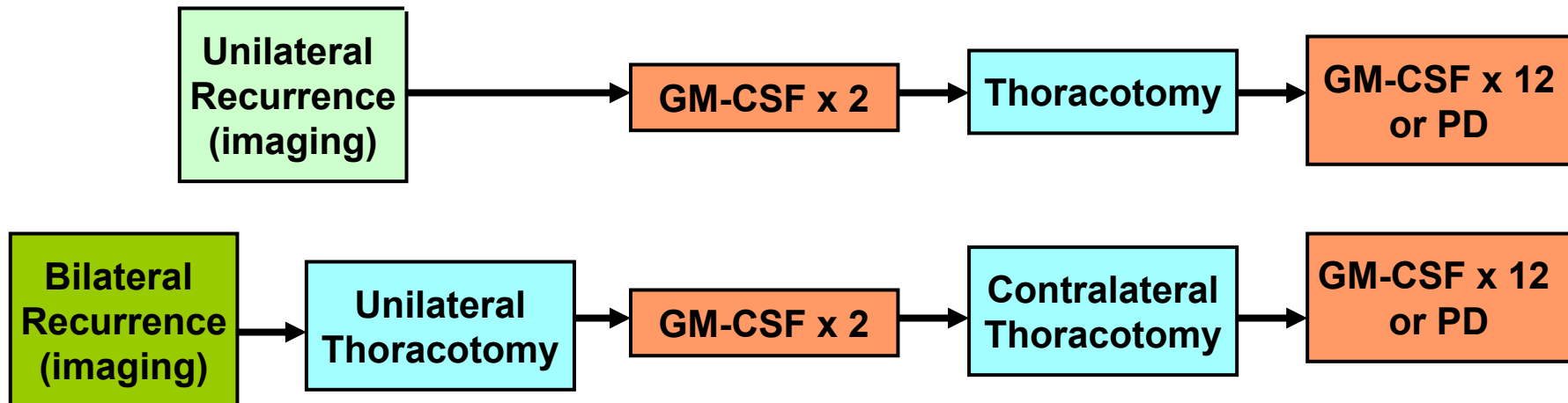
CureSearch

Children's Oncology Group

Osteosarcoma:

- GM-CSF: Stimulates proliferation & differentiation hematopoietic cells & affects immune function
- Local GM-CSF: enhance antitumor activity
- Lung metastases: major site of recurrence & immunomodulation attractive
- Study to evaluate Fas/FasL in tumor resected after 2 cycles inhaled GM-CSF (AOST-0221)

Experimental Design



Inhaled GM-CSF: Results

- **43 patients**
- **Median age 15 years (7-25 years)**
- **Recurrence:**
 - **16 bilateral**
 - **27 unilateral**
- **Number of lesions**
 - **Median 2 (1-15)**

AOST0221

FAS and FAS Ligand Results

Score (Pre)	FAS (Pre)	FAS Ligand (Pre)
0	5 N (5 P)	10 N (10 P)
1	7 N (6 P)	5 N (5 P)
2	4 N (4 P)	1 N (1 P)
3	3 N (2 P)	3 N (2 P)

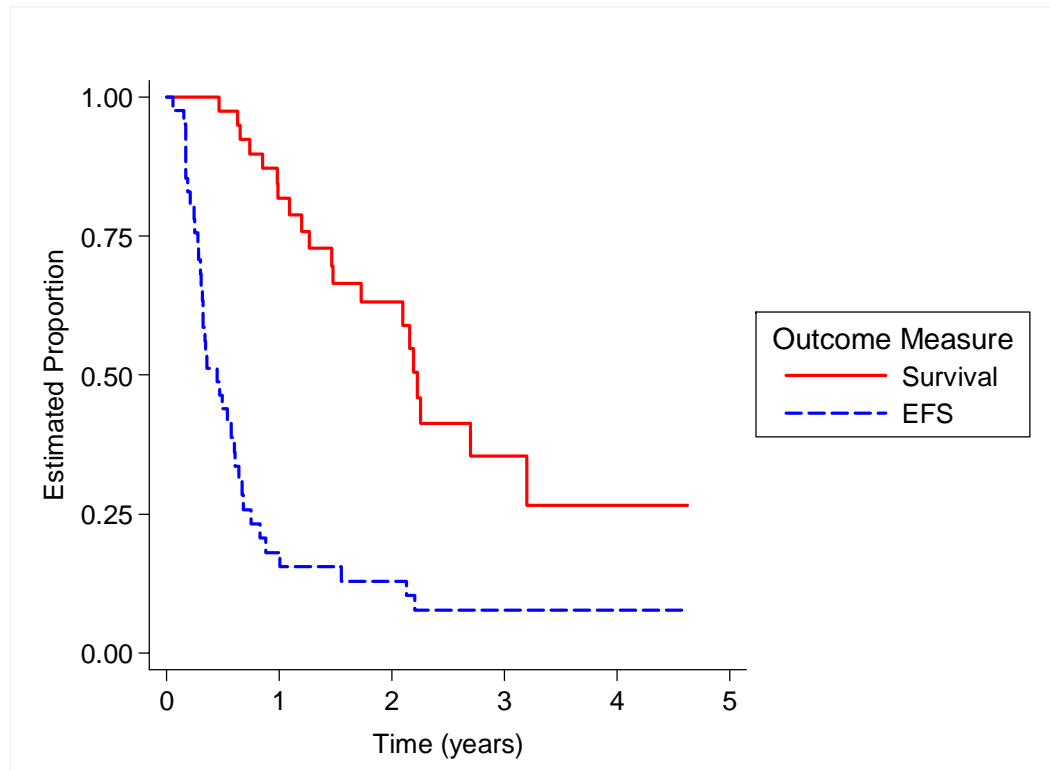
Score (Post)	FAS (Post)	FAS Ligand (Post)
0	28 N (20 P)	31 N (24 P)
1	9 N (9 P)	7 N (7 P)
2	2 N (2 P)	5 N (5 P)
3	8 N (8 P)	4 N (4 P)

AOST0221

Staining for Dendritic Cells

	CD1a Neg	CD1a Pos	S100 Neg	S100 Pos	Clusterin Neg	Clusterin Pos
Pre Treatment	5	2	4	3	6	1
Post Treatment	19	11	26	4	24	6

Outcome Inhaled GM-CSF



Osteosarcoma: New Agents

Bone Sarcoma Committee

- Correlative studies will enhance knowledge of bone tumor biology and lead to the discovery of new therapeutic targets
- **Incorporation of new agents or active drug combinations will improve outcome**

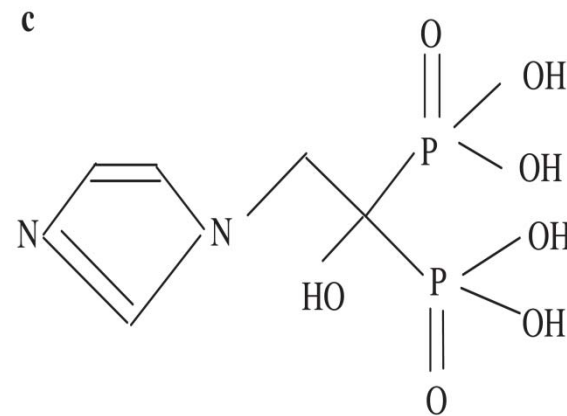
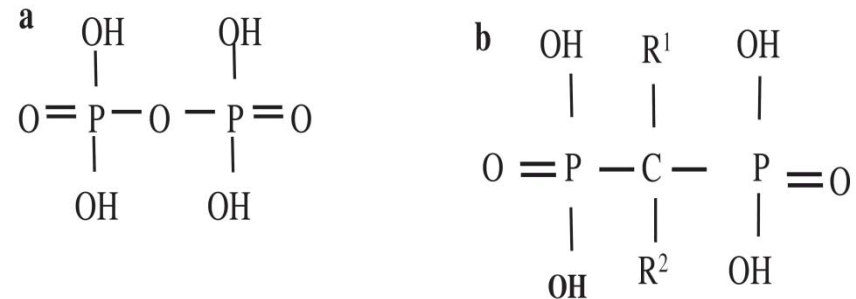
Osteosarcoma: Bisphosphonates

- **Decrease skeletal-related events**

- Easy administration
- Well established safety profile

- **Zoledronic acid**

- Most potent ↑
- Affects osteolytic & osteoblastic lesions



AOST06P1: Treatment Schema

Week	1	4	5	6	9	10	13	16	17	20	21	24	27	30	31	34	35	3
Biopsy	C/A-ZA	M	M	C/A-ZA	M	M	I/E-ZA	M	C/A-ZA	M	I/E-ZA	M	C/A-ZA	M	i/A-ZA	M	M	I/E-ZA

Primary site surgery
Secondary site surgery*

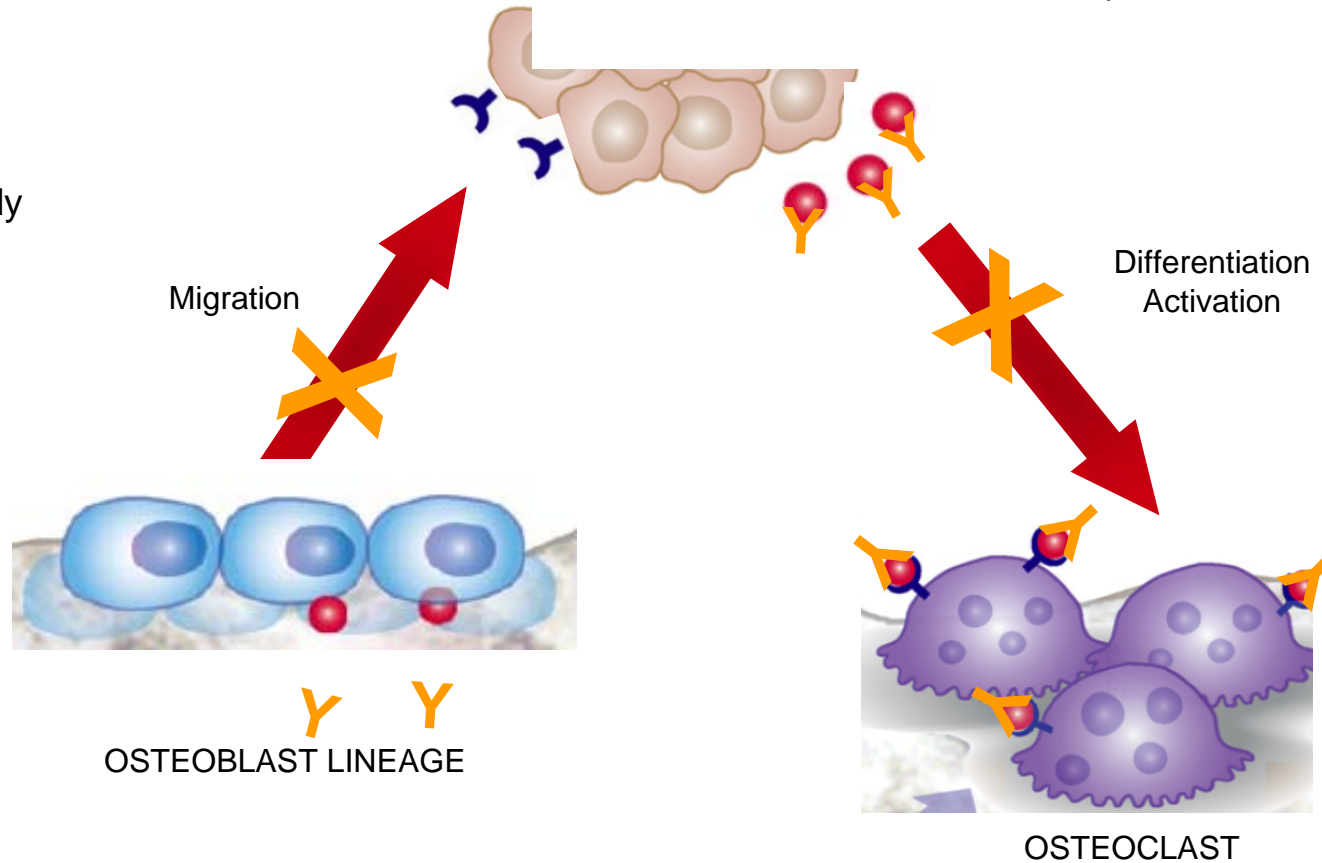
C = cisplatin 60 mg/m²/d x2 days
 A = Adriamycin 37.5 mg/m²/d X 2 days with dexrazoxane 375 mg/m² before each dose
 M = methotrexate 12 grams/m² with leukovorin rescue
 I = ifosfamide 2.8 grams/m²/day X 5 days with Mesna
 E = etoposide 100 mg/m²/day X 5 days
 i = ifosfamide 1.8 grams/m²/day X 5 days with Mesna
 * - if feasible

Background: Receptor activator of NFκB ligand (RANKL)

Osteosarcoma:
57% of human OS express RANK
100% of human OS express RANKL



Y RANKL antibody



Overview

- Randomized phase II preceded by a run-in to establish tolerability
- 2 cohorts: Ensure adequate safety evaluation in young / small subjects
- Stratification: “Low” risk group defined as in second CR OR solitary pulmonary metastasis no pleural invasion

Cycle	1			2			3			4			5			6		
Week	1	2	3	4	5	6	7*	8	9	10	11	12	13*	14	15	16	17	18
IE+D:	I E D			I E			I E			I E			I E D			I E D		
OR																		
IE:	I E			I E			I E			I E			I E			I E		

Summary

- **Our committee is using bone tumor biology to identify agents with new mechanisms of action**
- **Those agents are incorporated into feasibility trials in patients with recurrent or metastatic disease**
- **Promising agents are incorporated into randomized controlled trials**