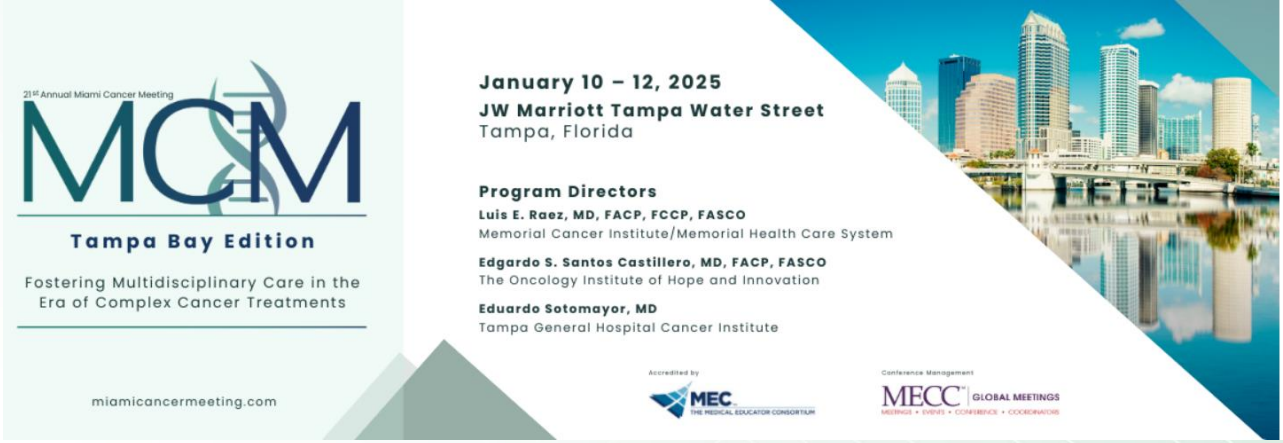

Novel Advances for Osteosarcomas in 2025

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January 10, 2025

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Agenda

- Osteosarcoma Overview
- Novel Advances in Curable Osteosarcoma
- Novel Advances in Metastatic Osteosarcoma
- Ongoing Clinical Trials

Osteosarcoma Epidemiology

- 800-900 cases of OS annually in US
- 2-3% of childhood cancers
- Most often between ages of 10-30yrs
- Bimodal age distribution
  - Peak with growth velocity: 13yrs for girls, 15-17years for boys
  - 10% occur after age 60
- Slight male predominance
- Higher incidence in some African countries

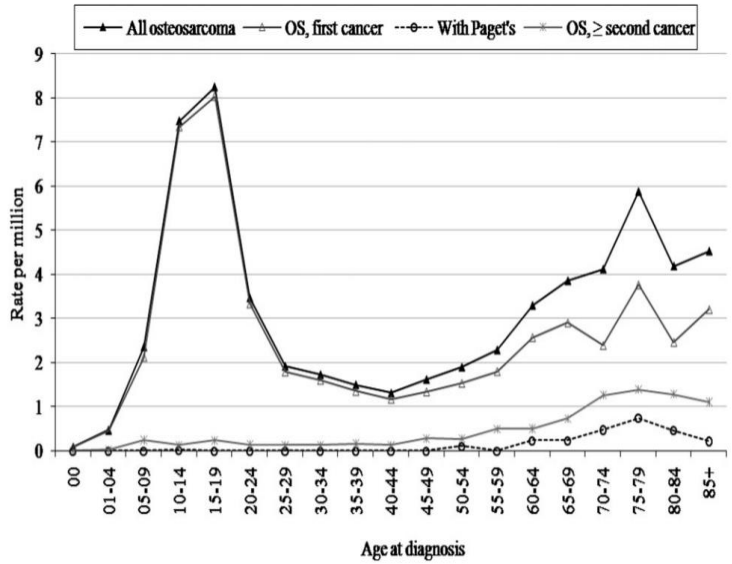

FIGURE 1. Osteosarcoma (OS) incidence by disease sequence based on the Surveillance, Epidemiology, and End Results 9 database, 1973 to 2004.

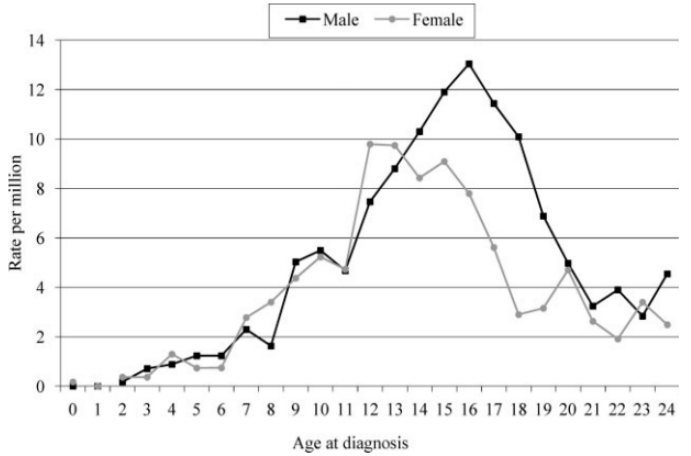

FIGURE 2. Age-specific incidence of osteosarcoma in children and adolescents by sex, Surveillance, Epidemiology, and End Results 9 date, 1973-2004.

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Predisposition to OS

Ionizing Radiation

- Median time of 9-11yrs after exposure
- Dose response (RT dose usually 45-60Gy)

Hereditary Rb

- Cumulative incidence of bone sarcoma ~8% at 20 yrs and 10% at 30yrs
- OS may develop within and outside of radiation fields
- Li Fraumeni
- Rothmund-Thomson Syndrome (RECQL4 gene)
- Werner syndrome
- Diamond-Blackfan anemia (DBA)
- Bloom Syndrome
- Paget's Disease

Estimates indicate that up to 10% of cases diagnosed before age 30 may be due to underlying TP53 or other germline mutations

Study 1004 patients with osteosarcoma 28.0% had a predisposition syndrome gene A higher than expected frequency of pathogenic or likely pathogenic variants was observed in genes not previously linked to osteosarcoma (eg, CDKN2A, MEN1, VHL, POT1, APC, MSH2, and ATRX)

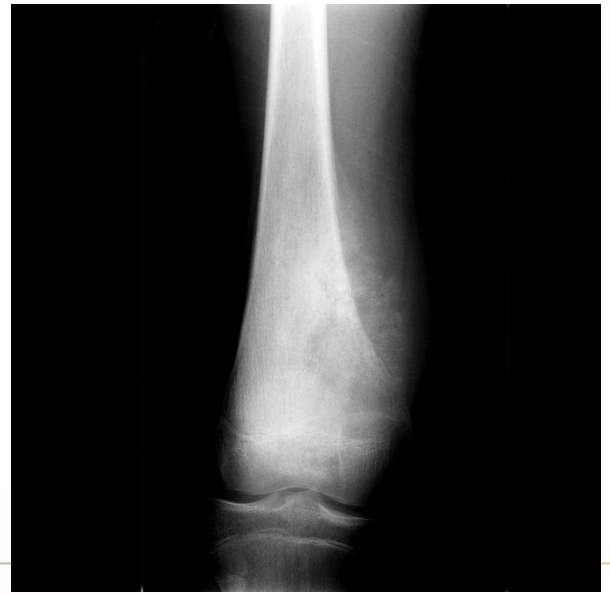
Clinical Presentation

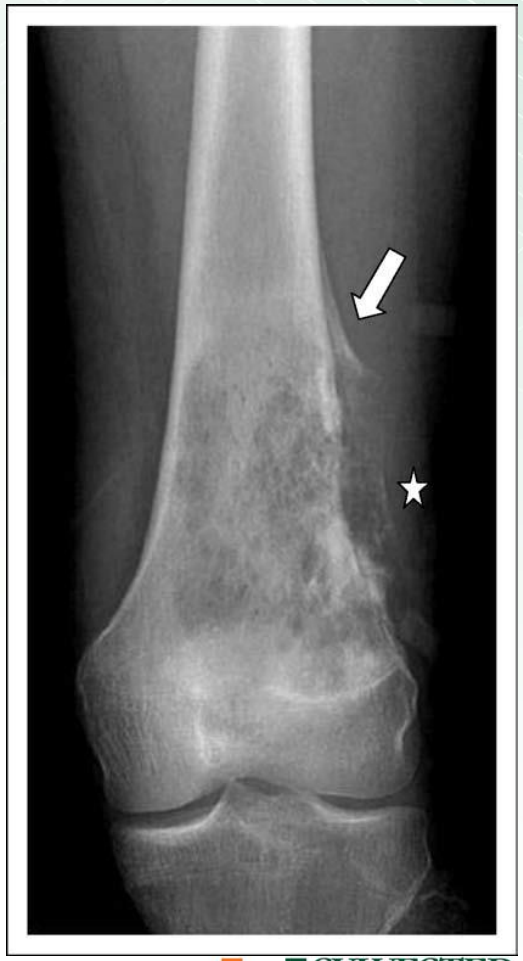
- Clinical presentation: pain; +/- mass at primary site, median symptom duration 2.5 months
- Most common primary sites :
  - Distal femur (55%)>proximal tibia (27%)->proximal humerus (11%)-> other
  - metaphyses of long bones involved
- Pattern of spread
  - Skip lesions- up to 20% of cases
  - Hematogenous- 15-20% metastatic at dx (lung > bone)

Overview of Diagnosis and Staging

- Staging Workup
  - Plain films of involved bone
    - Cortical destruction and expansion into soft tissue
    - Periosteal reaction:
      - Codman triangle- elevation of periosteum
      - Sunburst pattern- extension of tumor through periosteum
  - MRI of involved bone (remember to look for skip lesions)
  - CT of chest
  - PET or Bone scan

- Stage Assignment
  - Localized vs Metastatic
  - Resectable vs Unresectable





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Staging

American Joint Committee on Cancer (AJCC)
TNM Staging System for Bone *(Primary malignant lymphoma and multiple myeloma are not included)*

***Table 1.* Definitions for T, N, M**

Appendicular Skeleton, Trunk, Skull, and Facial Bones

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤8 cm in greatest dimension
T2	Tumor >8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

Spine

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one vertebral segment or two adjacent vertebral segments
T2	Tumor confined to three adjacent vertebral segments
T3	Tumor confined to four or more adjacent vertebral segments, or any nonadjacent vertebral segments
T4	Extension into the spinal canal or great vessels
T4a	Extension into the spinal canal
T4b	Evidence of gross vascular invasion or tumor thrombus in the great vessels

Pelvis

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one pelvic segment with no extraosseous extension
T1a	Tumor ≤8 cm in greatest dimension
T1b	Tumor >8 cm in greatest dimension
T2	Tumor confined to one pelvic segment with extraosseous extension or two segments without extraosseous extension
T2a	Tumor ≤8 cm in greatest dimension
T2b	Tumor >8 cm in greatest dimension
T3	Tumor spanning two pelvic segments with extraosseous extension
T3a	Tumor ≤8 cm in greatest dimension
T3b	Tumor >8 cm in greatest dimension
T4	Tumor spanning three pelvic segments or crossing the sacroiliac joint
T4a	Tumor involves sacroiliac joint and extends medial to the sacral neuroforamen
T4b	Tumor encasement of external iliac vessels or presence of gross tumor thrombus in major pelvic vessels

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed

Because of the rarity of lymph node involvement in bone sarcomas, the designation NX may not be appropriate and cases should be considered N0 unless clinical node involvement is clearly evident.

N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

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Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for Bone *(continued)*

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Bone or other distant sites

G	Histologic Grade
GX	Grade cannot be assessed
G1	Well differentiated — Low Grade
G2	Moderately differentiated — High Grade
G3	Poorly differentiated — High Grade

***Table 2.* AJCC Prognostic Groups**

There are no AJCC prognostic stage groupings for spine and pelvis.

	T	N	M	G
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
Stage IIA	T1	N0	M0	G2, G3
Stage IIB	T2	N0	M0	G2, G3
Stage III	T3	N0	M0	G2, G3
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Head and Neck Osteosarcoma

Table 1 Differences in key features of Non-HNOS and HNOS

From: Osteogenic Sarcoma of the Head and Neck: Is Chemotherapy Needed?

Characteristic	Non-HNOS	HNOS
Incidence	4–5 per million/year [14]	2–3 per million/year [15]
Median age at presentation	10–19 years [16]	30–39 years [17•]
Gender predominance	Male > female [14]	Male > female [14]
Common primary site(s)	Femur, tibia [14]	Mandible, maxilla [17•]
Most common histologic subtype	Osteoblastic [18]	Chondroblastic [19••]
Metastatic potential	Higher [20]	Lower [19••]
Local recurrence rate	Lower [3]	Higher [3]
5-year overall survival (localized disease)	65–70% [21]	43–86% [17•]
5-year overall survival (metastatic disease)	< 30% [20]	Not reported

Bialick et al Current Treatment Options in Oncology (2023) 24:528–541

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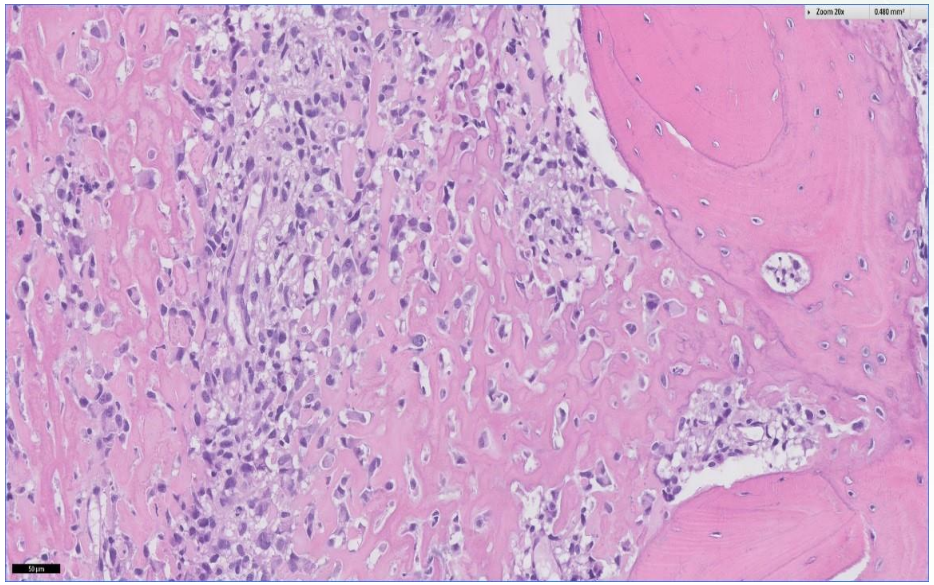
Pathology

WHO Classification 2020

- Central (medullary) tumors
  - Conventional OS (90%)
    - Osteoblastic OS
    - Chondroblastic OS
    - Fibroblastic OS
  - Secondary OS
  - Telangiectatic OS
  - Small round cell OS
  - Low grade central OS (intramedullary)



Osteoid formation pathognomonic for osteosarcoma

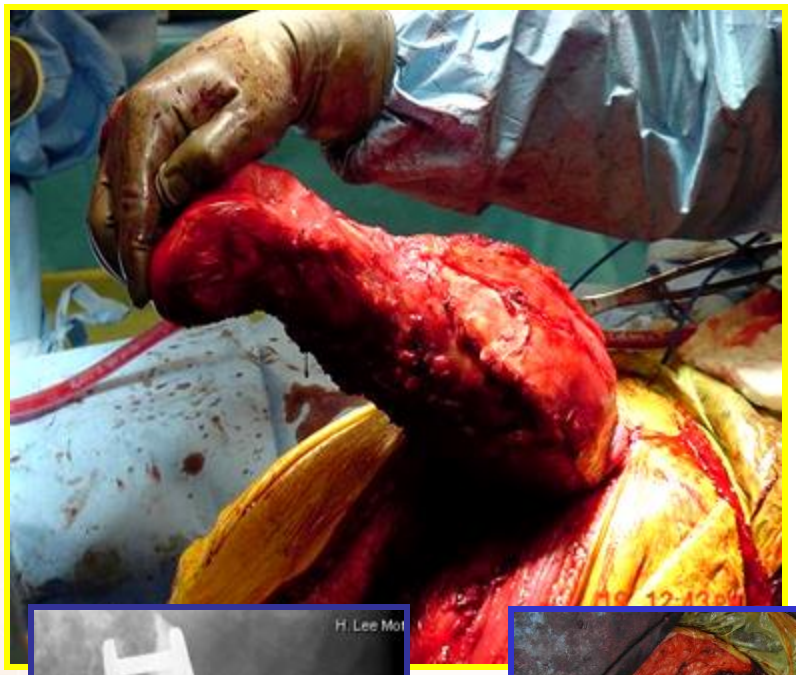
- Surface tumors
  - Parosteal OS (low grade)
  - Periosteal OS (intermediate grade)
  - High grade surface OS

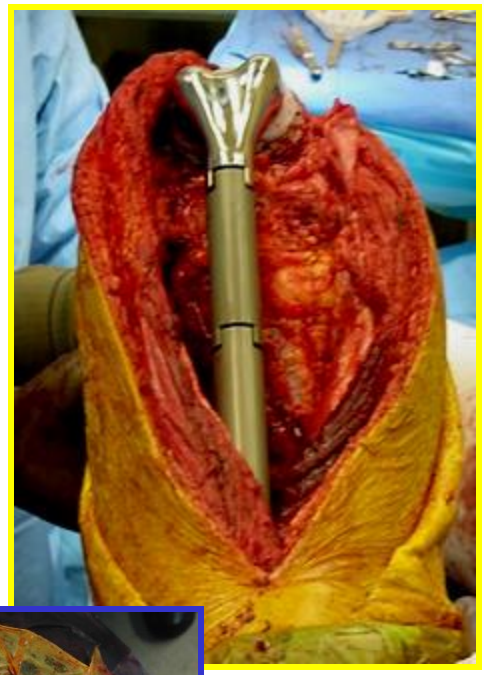
Standard Treatment: Curable Osteosarcoma

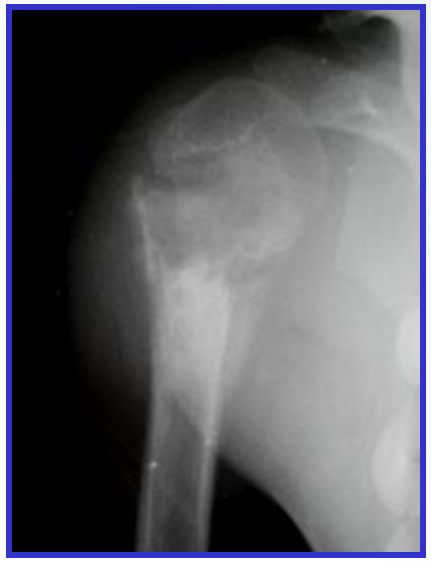
Treatment

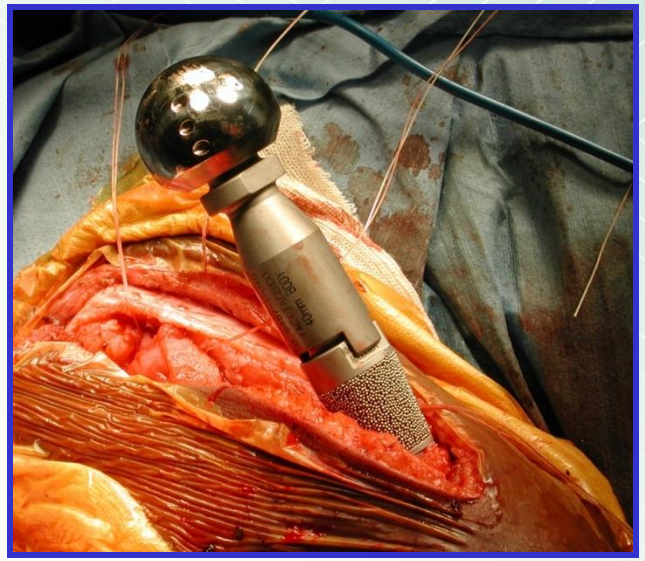
- Role of Surgery
  - Removal of all gross tumor with margins *en bloc* and biopsy site through normal tissue planes is required
  - Metastatic sites must be resected
- Surgical Options
  - Amputation vs limb salvage
  - NOW up to 97% of osteosarcoma surgeries are limb salvage!
  - Type of procedure depends on tumor location, size, extra-medullary extent, presence if metastases, age, skeletal development, and life style preferences
- Timing
  - Following neoadjuvant chemotherapy
  - Week 10

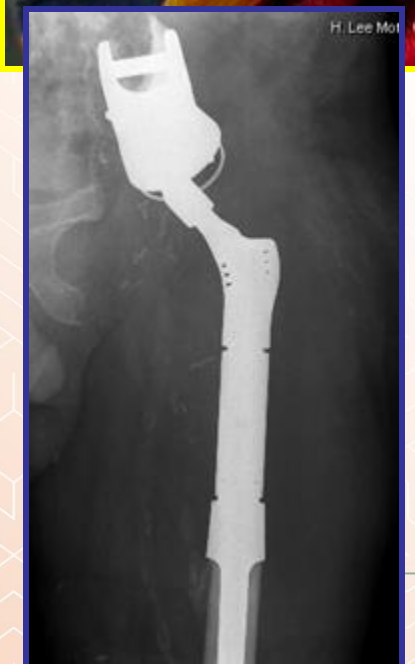
Limb Sparing Procedures: Endoprosthesis



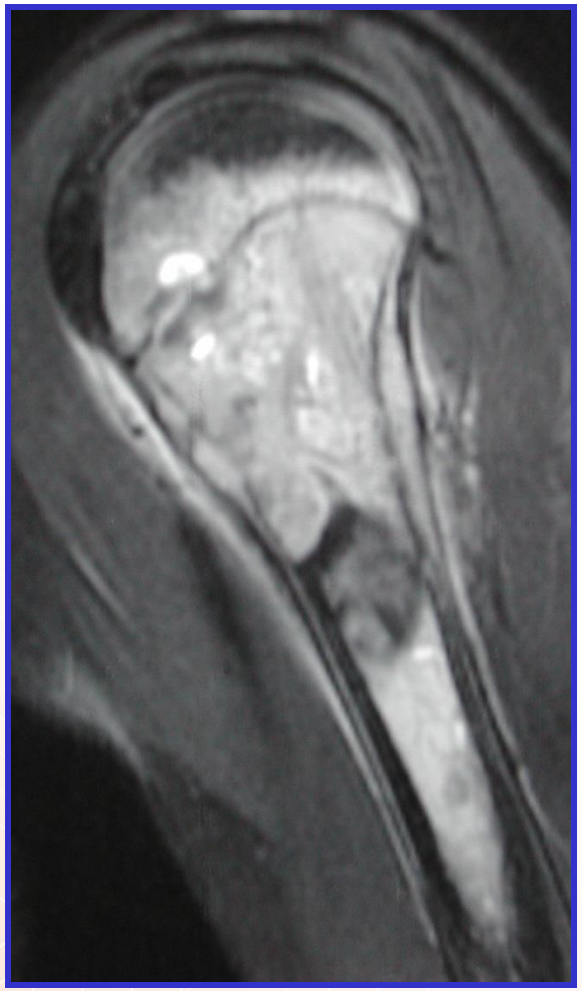


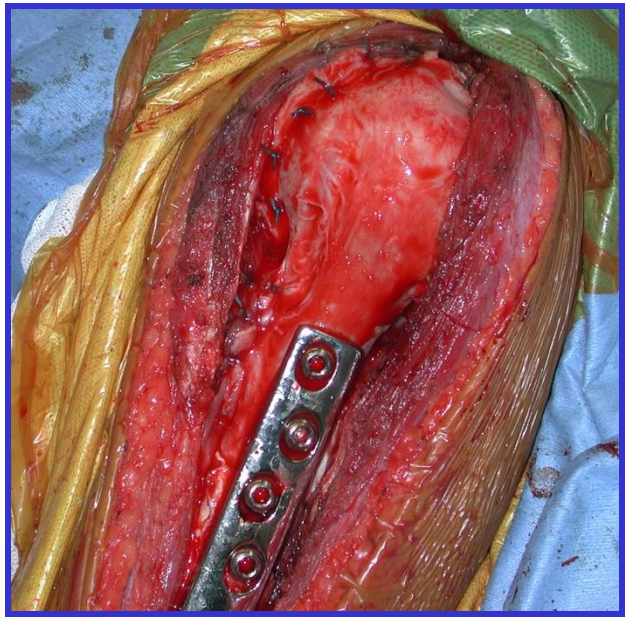


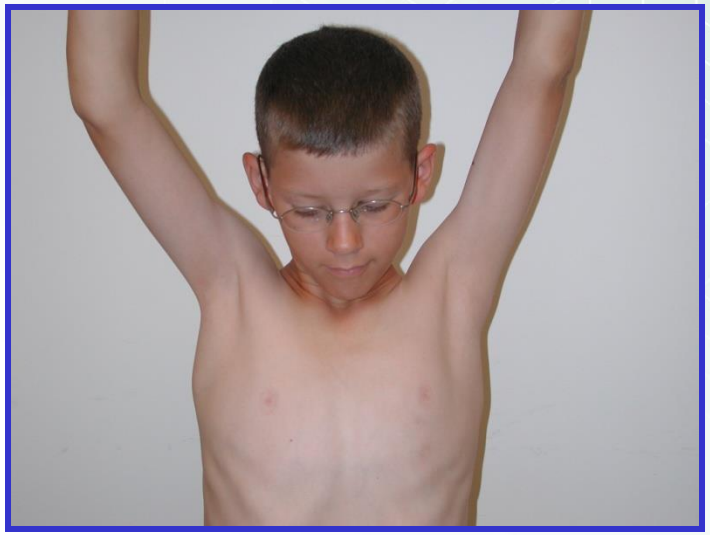




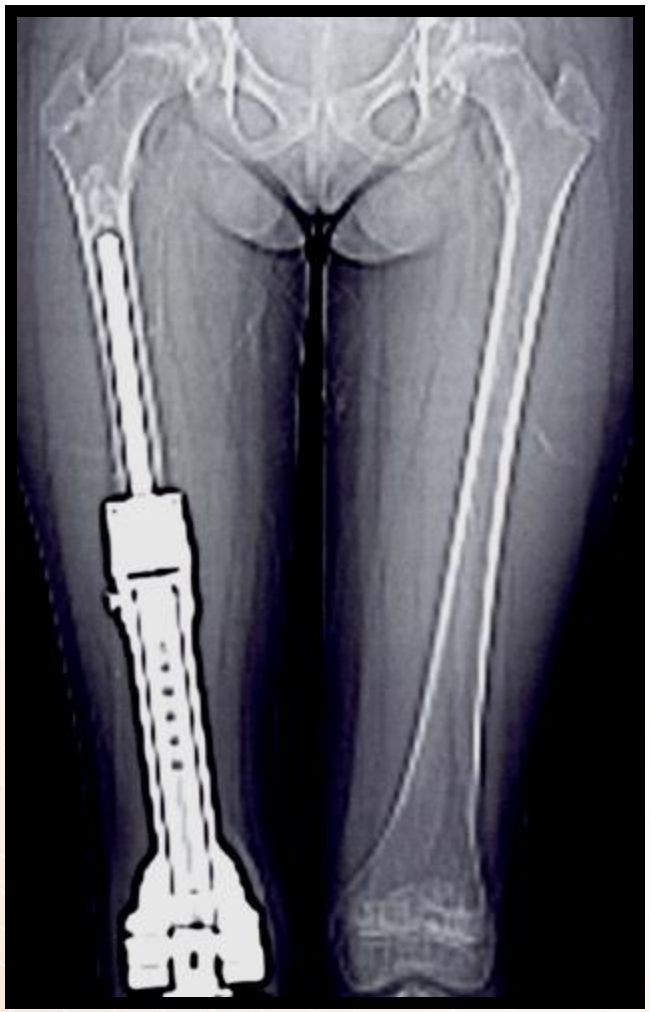
Limb Preservation Allograft

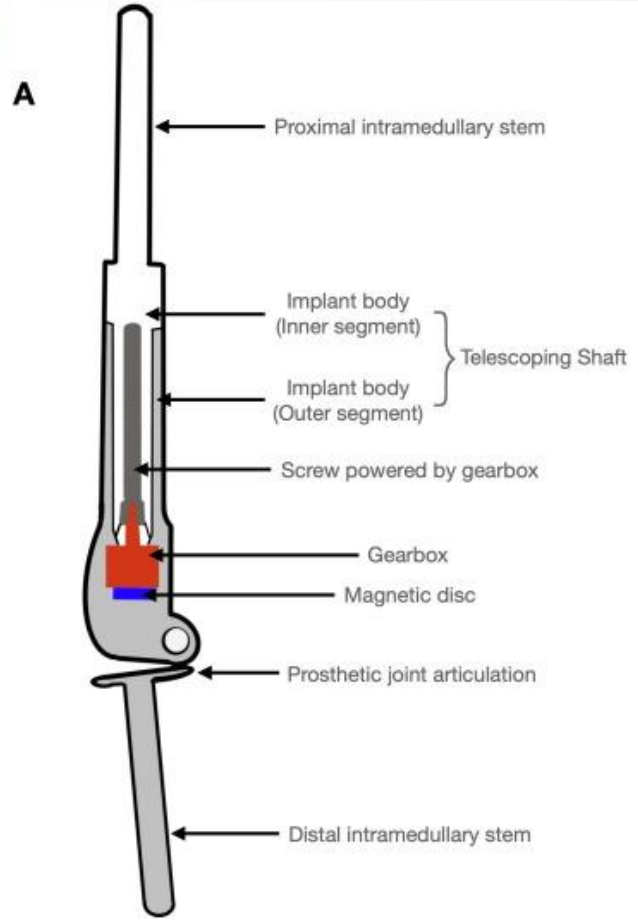


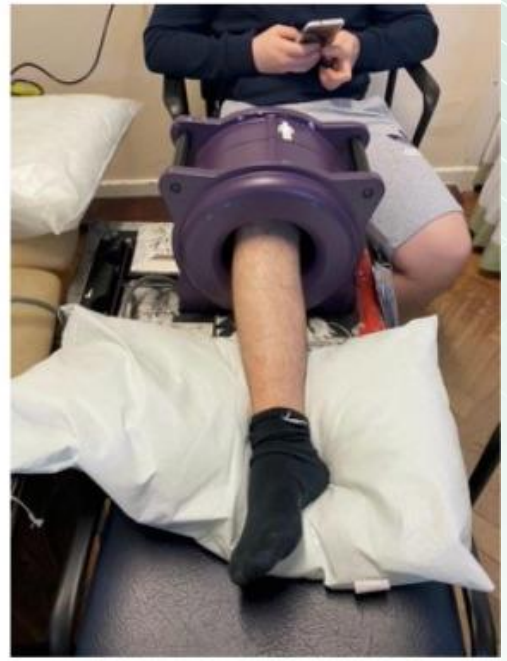




Expandable Prosthesis

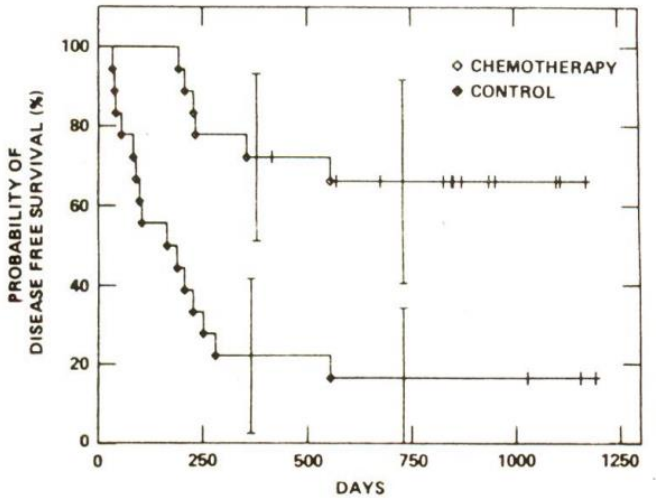






Treatment

- Multi-Institutional OS Study (MIOS)-
  - 1982-1984
  - 113 pts randomized to surgery alone vs surgery/chemo (MAP)
  - 6 yr OS surgery only 11% vs 61% combo
- MSKCC-
  - Neoadjuvant chemo introduced to T10 protocol to allow time for construction of prosthetic devices
  - May also allow for treatment of micrometastatic disease
  - 5 yr OS 65%



Surgery + Chemo (n=18)

Surgery (n=18)

Link et al. NEJM 1986;314:1600

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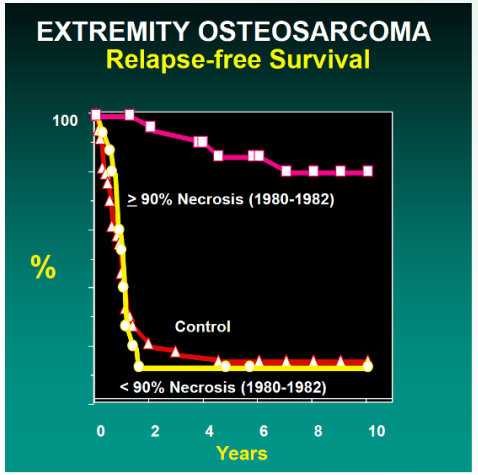
Treatment

- Standard now is neoadjuvant chemotherapy followed by surgery at week 10 and more chemotherapy post-op
- Neoadjuvant chemotherapy allows for :
  - Starting therapy more quickly
  - May facilitate limb salvage
  - Provides histologic response
- Agents
  - Localized/resectable disease: methotrexate doxorobucin/cisplatin (MAP)
  - Metastatic/unresectable disease: MAP (after studies showed no improvement in outcomes with addition of IE)

(6 cycles, AOST0331)

Prognosis

- Histology
  - Parosteal- favorable
  - Fibroblastic (>80% 8 yr DFS) or telangietatic (~75% 8 yr DFS) favorable
- Stage
  - Localized 3 yr EFS ~70%
  - Metastatic 5 yr EFS
    - Overall 30-40%
    - Unilateral pulm mets 20-40%
    - Bone or bilateral pulm mets <15%



- Grade, size of primary
- Site - appendicular vs. axial
- Extent of disease
- Morphology - conventional vs. variants
- Duration of symptoms
- Weight loss >4.5 kg
- Lytic appearance
- Response to preoperative chemotherapy

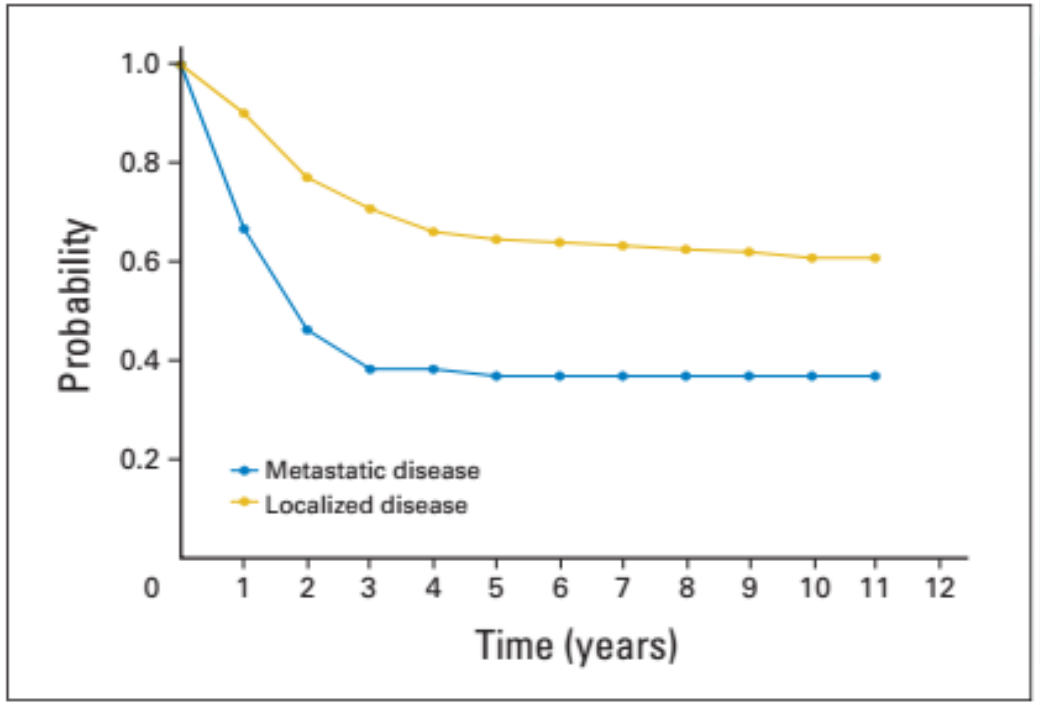


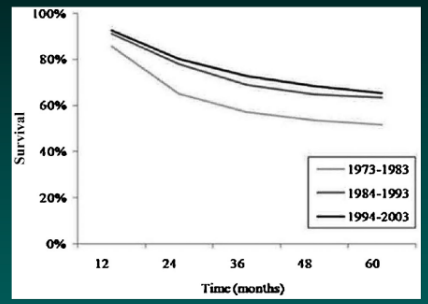
Fig 2. Event-free survival for patients with metastatic and localized disease enrolled onto the Children's Cancer Group/Pediatric Oncology Group Intergroup study INT0133 clinical trial.

Bacci et al. 2008; Meyers et al 1994; Ferrari et al 2001

Prognosis

Necrosis	EFS (localized disease)
>/= 90% good responder	3 yr EFS ~80% 5 yr EFS >90%
< 90% poor responder	3 yr EFS ~60% 5 yr EFS 50-60%

COG Study	#	Year	5 year EFS
P8651	100	86-93	65 %
INT0133	662	93-97	63%
P9754	242	99-02	64% (3 yr)



Five-year survival in patients age 0–24 years over 3 decades 1973–2003

Attempts to intensify therapy for those poor responders have not shown changes in OS

Attempts to intensify neo-adjuvant chemo increased #'s of good responders but did not change OS and decreased the prognostic value of tumor necrosis

Bielack et al. 2015; Marina et al 2016; Isakoff et al 2015

OS Complications/Late Effects

- Surgery
  - Functional outcomes
  - Body image
- Chemotherapy
  - Anthracycline-induced cardiomyopathy – 10% cumulative incidence in sarcoma pts after 300mg/m2
  - CDDP induced ototoxicity- 11% patients
  - Secondary malignancies 2-4%
  - infertility 1-2%

Novel Advances: Curable Osteosarcoma

Abstract #11529： Updated results from ALTER-S002: a single-arm multicenter trial of the combination of anlotinib with chemotherapy in patients with Stage IIB classic osteosarcoma of the extremity

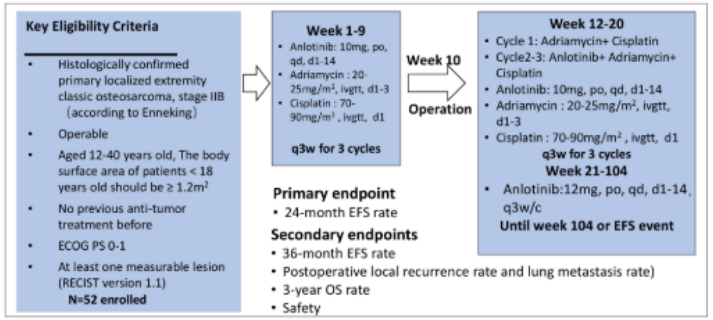
Fan Tang[1], Yong Zhou[1], Jie Ma[2], Dong Wang[3], Bing Zhang[4], Yi Luo[1], Longqing Li[1], Cuizhen Liu[2], Yuan Nie[3], Li Min[1]*, Chongqi Tu[1]**; [1]Orthopedics, West China School of Medicine/West China Hospital of Sichuan University (WCSM/WCH), Chengdu, China. [2]Oncology Department, The first affiliated hospital of guangxi medical university, Nanning, China. [3]Orthopedics, Guizhou Cancer Hospital/The Affiliated Cancer Hospital of Guizhou Medical University, Guiyang, China. [4]Bone and soft tissue oncology ,The Affiliated Hospital of Jiangxi University of TCM, Nanchang, China

Background:

- The overexpression of multiple tyrosine kinase receptors in osteosarcoma indicated a promising therapy targeting these receptors.
- Anlotinib is a multi-targeted tyrosine kinase inhibitor that potentially inhibits tanti-angiogenic drugs with chemotherapeutic agents is proposed to act synergistically to achieve favorable tumor control, especially as the neoadjuvant therapy.
- We had reported the neoadjuvant therapy data of anlotinib in combination with chemotherapy for treatment-naive stage IIB classical osteosarcoma of the extremity in the 2023 ESMO congress. Here we report an update on the effectiveness and safety of the follow-up.

Methods:

- This is a single-arm, open-label, multicenter phase II study (***Figure 1***)
- **Figure 1. Study design (ChiCTR2000033298)**



Assessments

- Tumor assessment was evaluated according to RECIST V1.1 by investigators.
- Adverse events(AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) V4.03.

- From May 2020 to April 2022, 52 patients(pts) were enrolled in 4 centers in China.
- Baseline characteristics were shown in Table 1.

Conclusion:

The updated results suggested that anlotinib combined with adriamycin and cisplatin in the perioperative period showed favorable efficiency and manageable adverse events in Stage IIB classic osteosarcoma of the extremity.

Results:

- From May 2020 to Apr 2022, 52 eligible pts were enrolled, while 51 pts underwent surgery after 3 cycles of neoadjuvant therapy.
- At the data cut-off date (Oct. 2023), the median EFS was not reached, 12 and 24-month EFS rates were 84.18% (95% CI :70.82, 91.77) and 73.43% (95% CI :57.40, 84.21), respectively (***Figure 2***) . The stratified analysis of EFS showed that the length and diameter of the target lesion are independent prognostic factors （***Figure 3***） . The median OS was not reached, the 24-month OS rate was 95.92% (95% CI :84.65, 98.96) (***Figure 4***) . Among the 51 pts who underwent surgical treatment, 12(23.53%, 95% CI: 12.79, 37.49) pts experienced recurrence or metastasis (***Figure 5***).
- The rate of treatment-related adverse events (TRAEs) were 100%, and grade 3/4 were 84.62%. Most TRAEs were grade 1-2. Grade 3/4 TRAEs (≥5%) included neutropenia (51.92%), leukopenia (38.46%), thrombocytopenia (36.54%) , anemia (32.69%), hypokalemia(17.31%), hypertension(15.38%), lymphopenia(13.46%)， Myelosuppression （7.69%）.

Table 1. Baseline characteristics

Characteristics		Pts (n=52)
Age, median (range)		18.0 (12.0-37.0)
Gender, n (%)	Male	29 (55.77)
	Female	23 (44.23)
ECOG PS, n (%)	0	21 (40.38)
	1	31 (59.62)
Primary lesion location, n(%)	upper limb	5 (9.62)
	lower limb	47 (90.38)
Sum of the longest diameters of target lesions at baseline(mm), n (%)	Median (range)	100.25 (40.00-212.00)
	≤100	25 (48.08)
	> 100	27 (51.92)

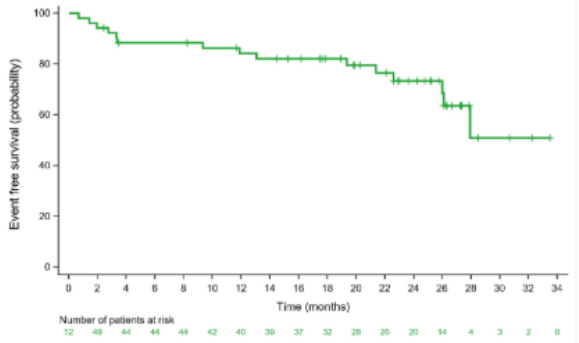


Figure 2. The event free survival(probability)

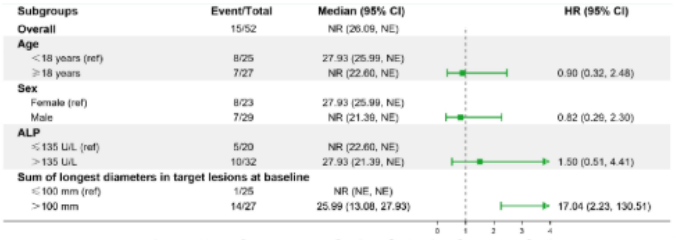


Figure 3. Subgroup analysis of EFS in the population.

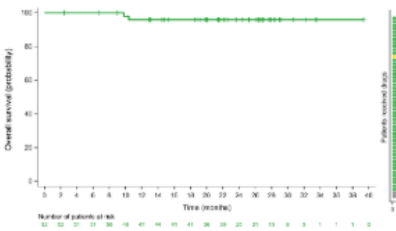


Figure 4. The overall survival(probability)

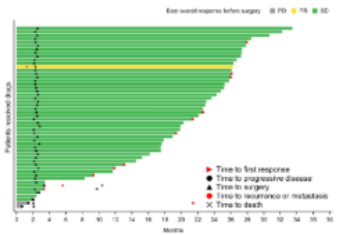


Figure 5. Swimmer plot represents the duration of responses.

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2024 ASCO ANNUAL MEETING

Prospective evaluation of pre-treatment ctDNA burden in localized osteosarcoma identifies patients with inferior outcomes: A report from the LEOPARD study

David S. Shulman, Kelly Klega, Nan Chen, Elliot Gohn, Donovan Henry, Edwin Choy, Thomas Cash, Kris Ann P. Schultz, Leo Mascarenhas, Rochelle Bagatell, Brian K. Turpin, Bhuvana A. Setty, Bradley D. DeNardo, Douglas S. Hawkins, Michael W. Bishop, Avanthi Shah, Luke Maese, Wendy B. London, Steven G. DuBois, Brian D. Crompton

David Shulman, MD

Dana-Farber Cancer Institute

LEOPARD
Liquid biopsy in Ewing sarcoma and osteosarcoma as a prognostic and response diagnostic

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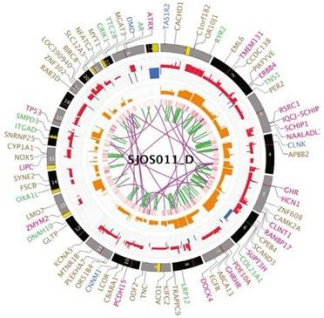
Background

- Osteosarcoma is an aggressive bone sarcoma for which outcomes have not improved substantively in decades
- Stage and pelvic primary site are the strongest prognostic factors at diagnosis
- Aneuploid genome with few recurrent SNVs
- No validated molecular biomarkers



Chen X, et al., *Cell Rep*, 2014

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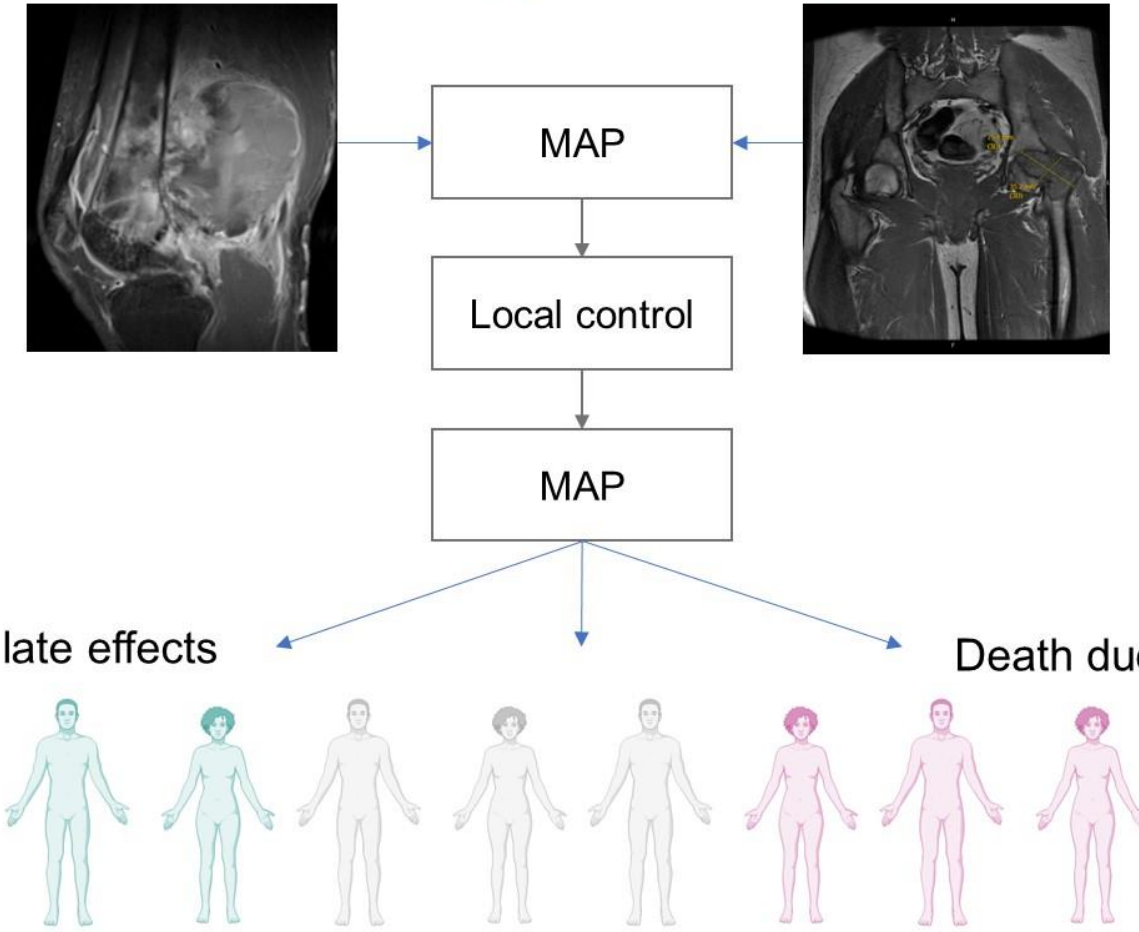
Lack of robust prognostic factors has precluded the prospective evaluation of risk-stratified therapy for most patients with osteosarcoma



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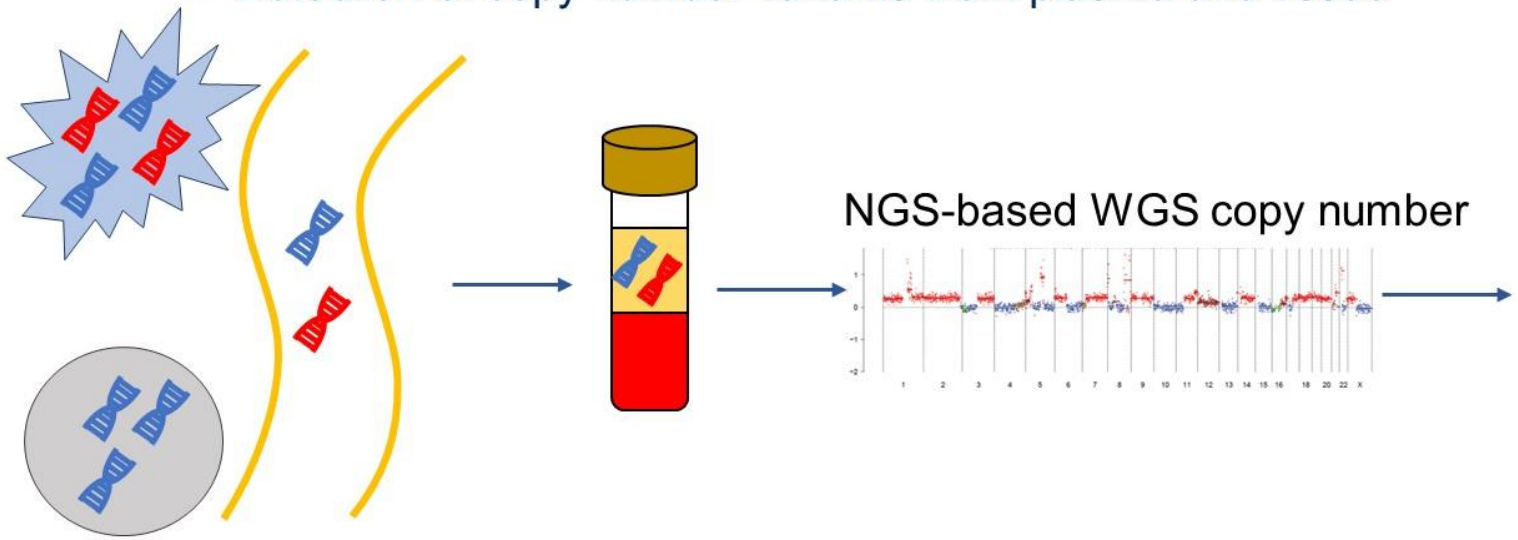
Methods: ctDNA analysis

Methods:

- *ctDNA analysis*:
  - ULP-WGS - Validated NGS-based assay for aneuploidy-based ctDNA quantification
  - Lower limit of detection: 3% ctDNA
  - Detection of copy number variants from plasma and tissue



Clinical ctDNA data

ctDNA Feature	Output
Aneuploidy %ctDNA	% ctDNA burden (i.e., 8%)
CNV	Y/N

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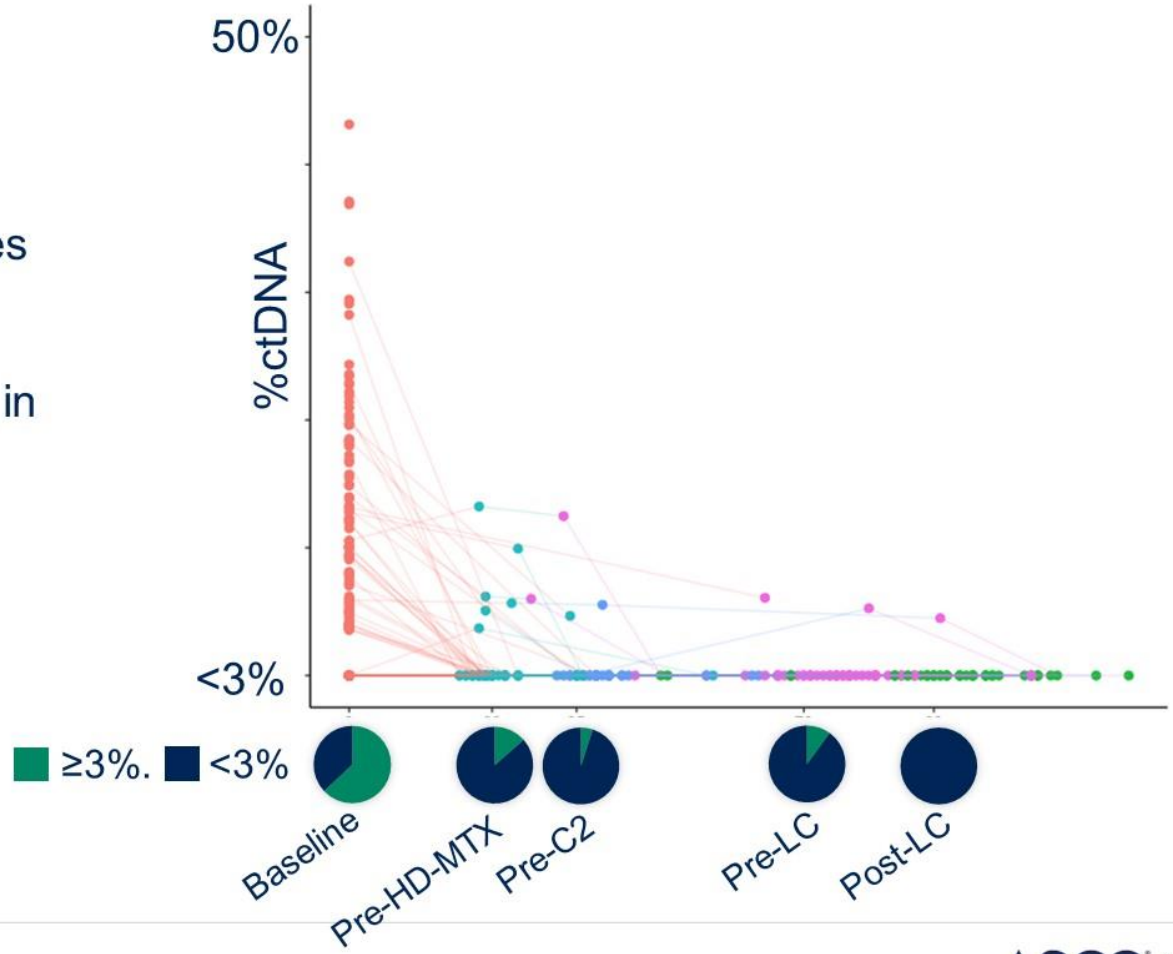
Results: Patients with localized osteosarcoma present with a wide range of ctDNA burden that fall with initiation of therapy

- ctDNA detectable in 63% of patients at baseline with a wide dynamic range
- 63 patients provided serial ctDNA samples
- ctDNA levels fall with initiation of therapy in most patients
- ctDNA levels undetectable in all patients following local control



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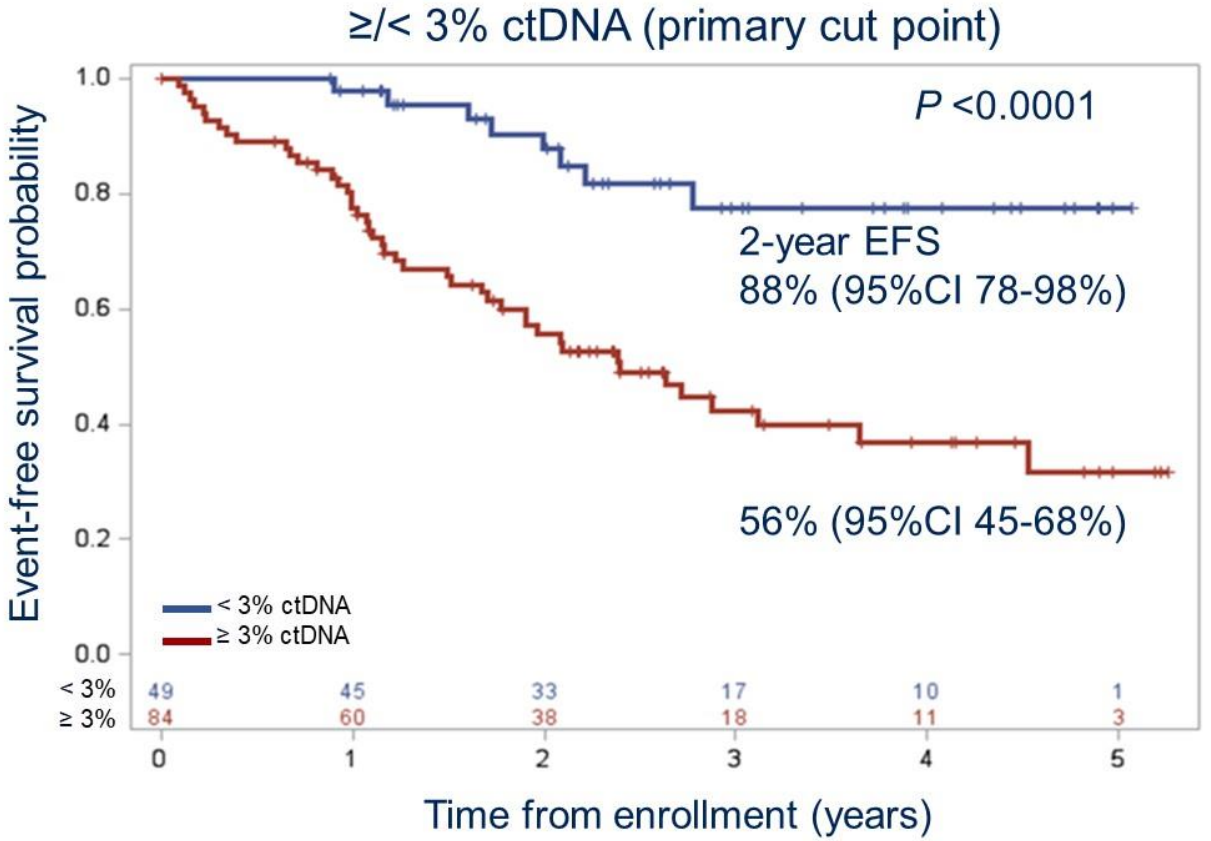
Results: Elevated baseline ctDNA burden is associated with inferior EFS in localized osteosarcoma

- In our primary analysis, patients with ≥3% ctDNA burden at baseline have inferior EFS
- ctDNA when evaluated as a continuous variable is also prognostic with a hazard of 1.04 for each 1% increase in ctDNA burden

Hazard Ratio for each 1% increase in ctDNA
1.04 (95% CI, 1.02–1.07; *P* < 0.001)



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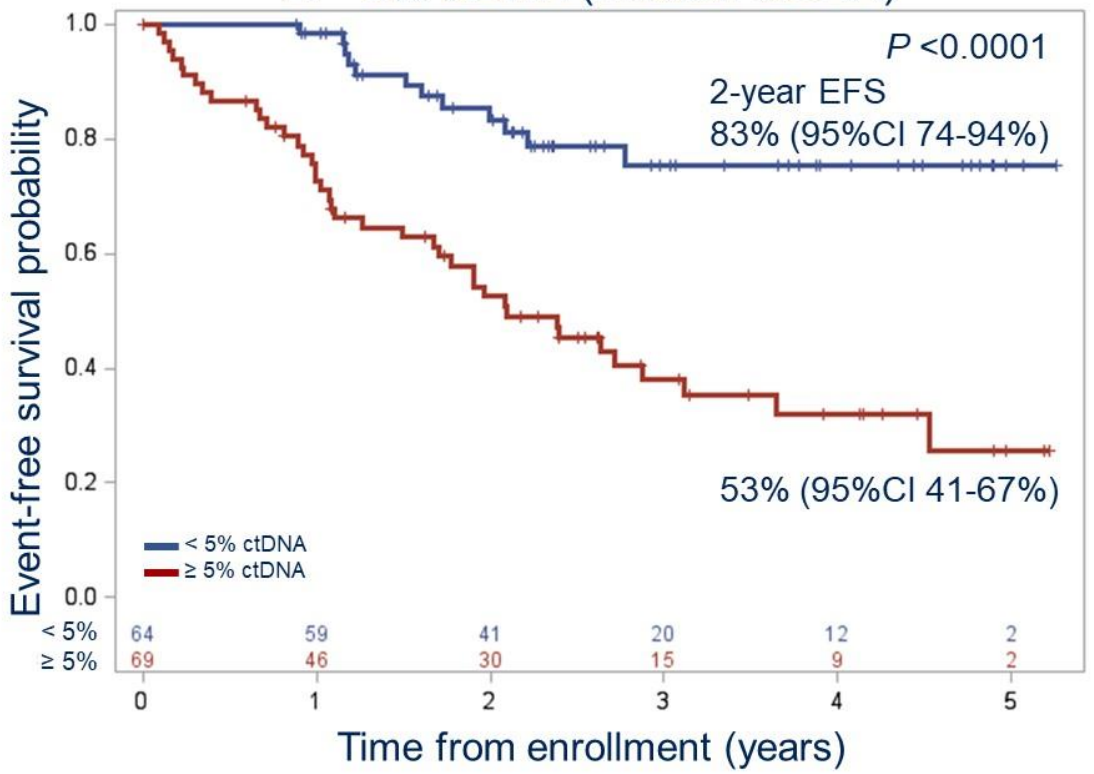
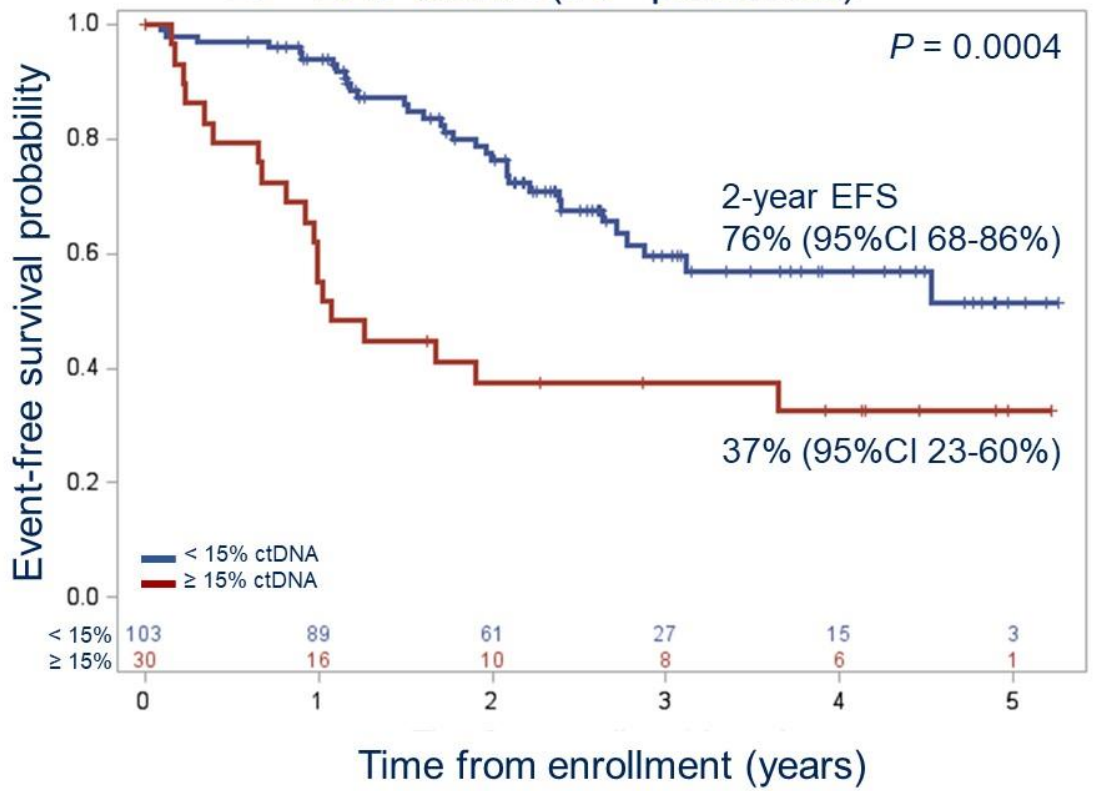
Results: Elevated baseline ctDNA burden is associated with inferior EFS in localized osteosarcoma

≥/< 5% ctDNA (median ctDNA)



≥/< 15% ctDNA (75th percentile)



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Results: ctDNA burden is not associated with clinical features

	Median Percent ctDNA	P-value
Indeterminate pulmonary nodules*		
Yes (n=17)	10.1	
No (n= 114)	5.2	0.29
Primary tumor size		
≥ 5 cm (n=116)	5.8	
< 5 cm (n=17)	4	0.53

*Pulmonary nodules that are visible on imaging, but do not meet the definition of definitive pulmonary disease per standard institutional practice.

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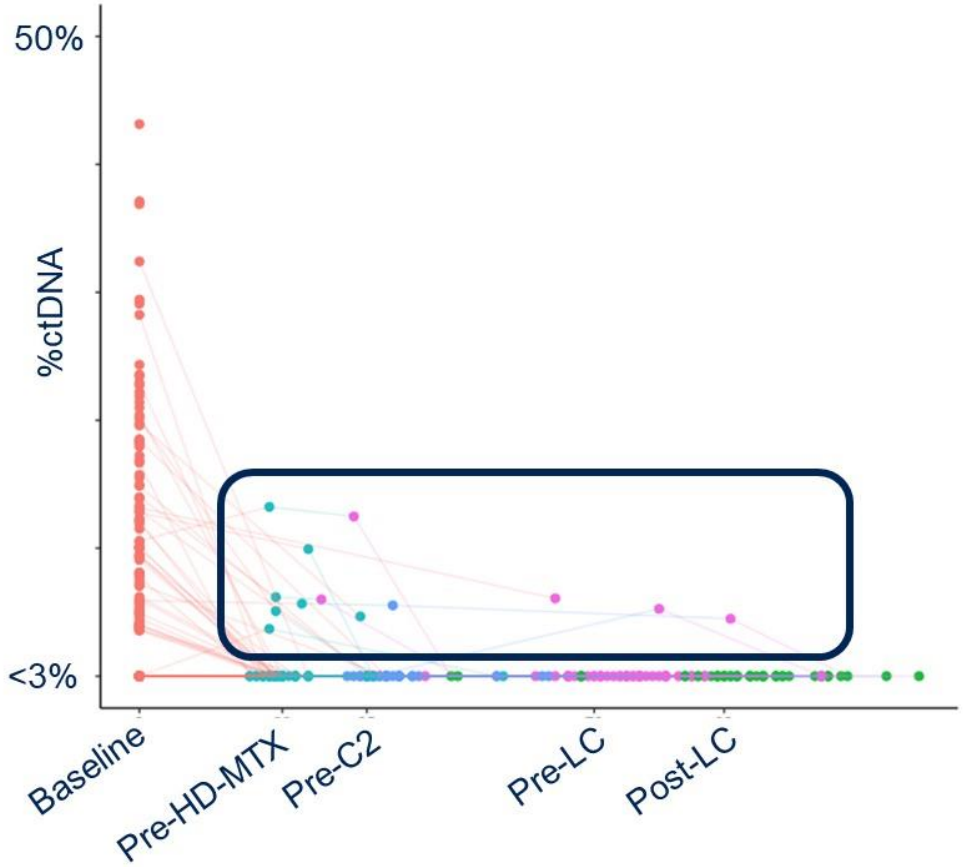
Implications and future directions

- Through an innovative prospective biomarker study we have identified patients with high-risk localized osteosarcoma at time of diagnosis
- Evaluation of on-therapy timepoints may provide further prognostic information
- We are evaluating surveillance samples to determine if we can identify relapse early



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Limitations

- Our study included patients with localized, non-pelvic osteosarcoma and may not be generalizable to all newly diagnosed patients.
- Our study utilized a validated research use-only assay that may not reflect methods utilized in commercial ctDNA assays.

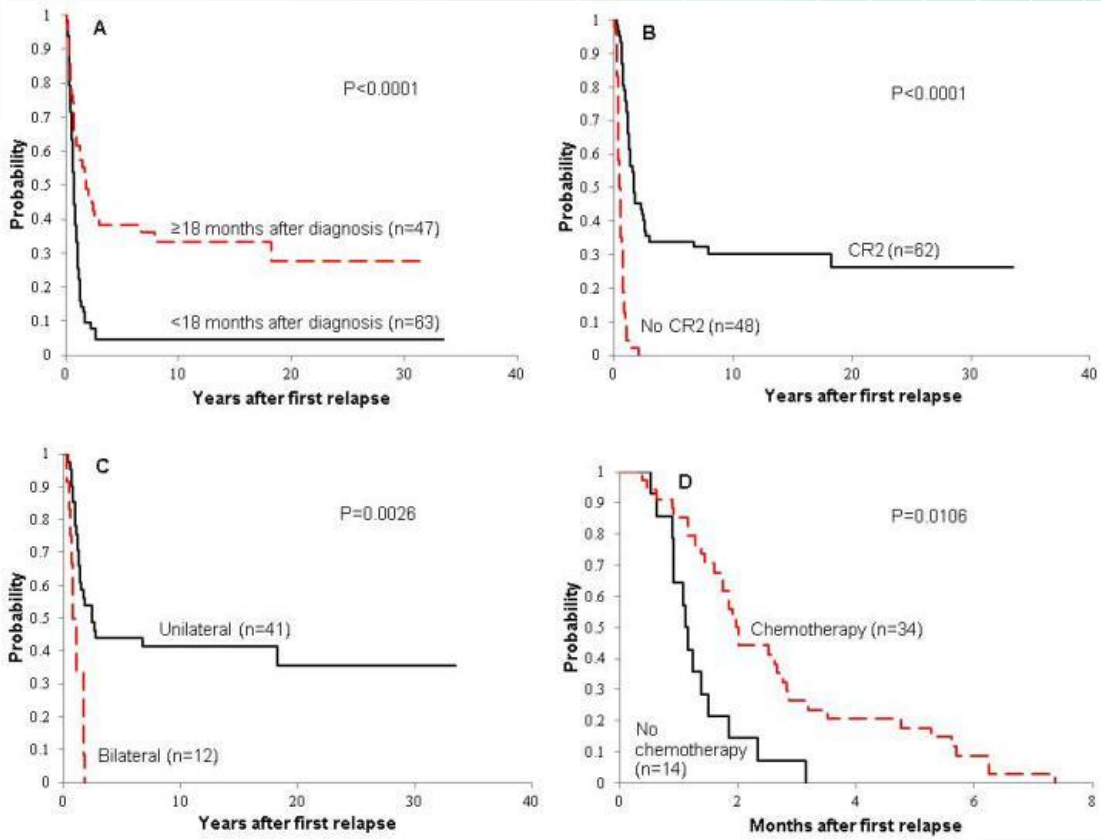
Conclusions

- These findings prospectively validate prior data associating elevated pre-treatment ctDNA burden with inferior EFS in patients with localized osteosarcoma.
- Pre-treatment ctDNA burden represents the first prospectively validated molecular biomarker in this disease.
- Baseline ctDNA burden is now positioned for implementation into future therapeutic trials as a prognostic biomarker.

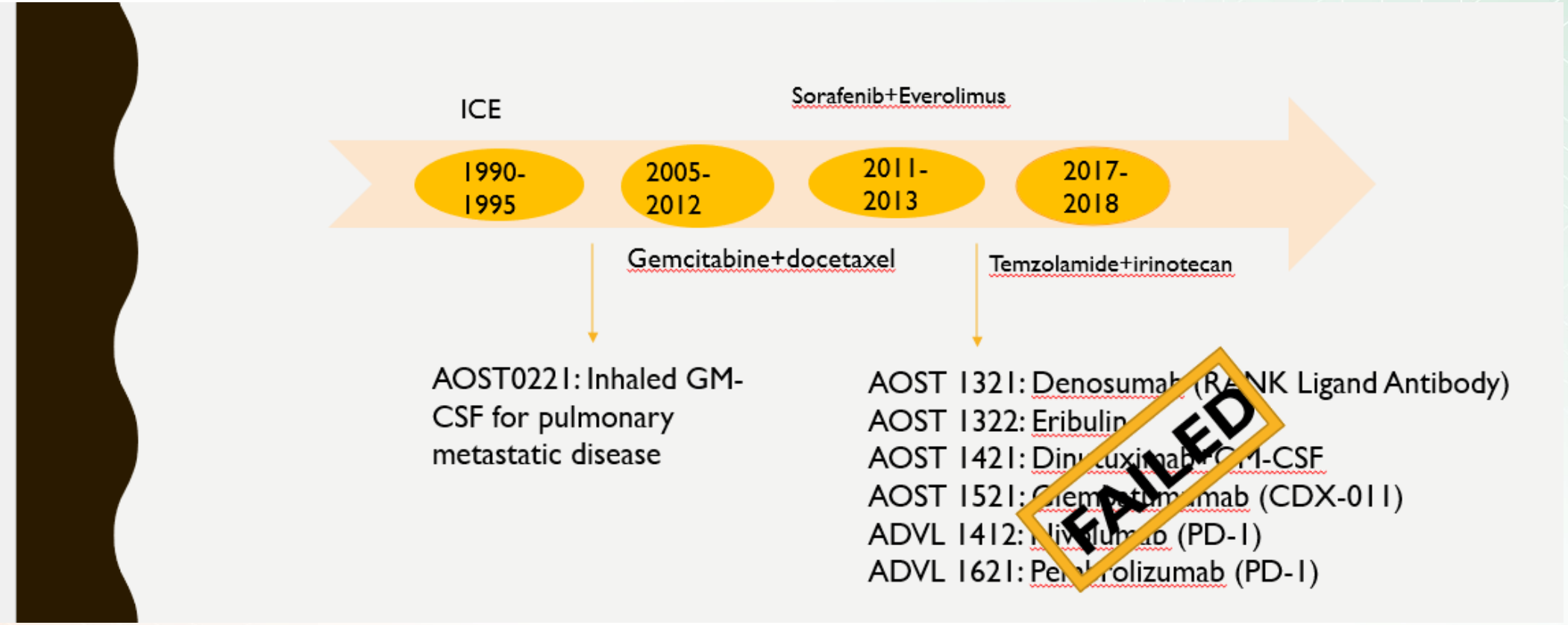
Current Treatments for metastatic Osteosarcoma

Relapsed or Refractory Disease

- Prognosis- overall poor
  - 10% OS and 20% EFS at 10 yrs
- Surgery is essential for survival
- Chemotherapy may slow disease progression
- Factors affecting Prognosis-
  - Late relapse (>/= 18 mos)
  - Surgical resection-> able to achieve a 2nd CR
  - Unilateral involvement (lungs)



RECURRENT/REFRACTORY OS



PEPN1924, a phase 2 study of trastuzumab deruxtecan (DS-8201a, T-DXd) in adolescents and young adults with recurrent HER2+ osteosarcoma:- reported 2023-FAILED

Relapsed or Refractory Disease

- No standard 2nd line option
- Surgery –lung metastatectomy
- Ifosfamide/etoposide
- Gemcitabine/docetaxel
- Sorafenib/everolimus
- Cyclophosphamide/Etopside
- 14 days of Ifosfamide
- Radiation for palliation

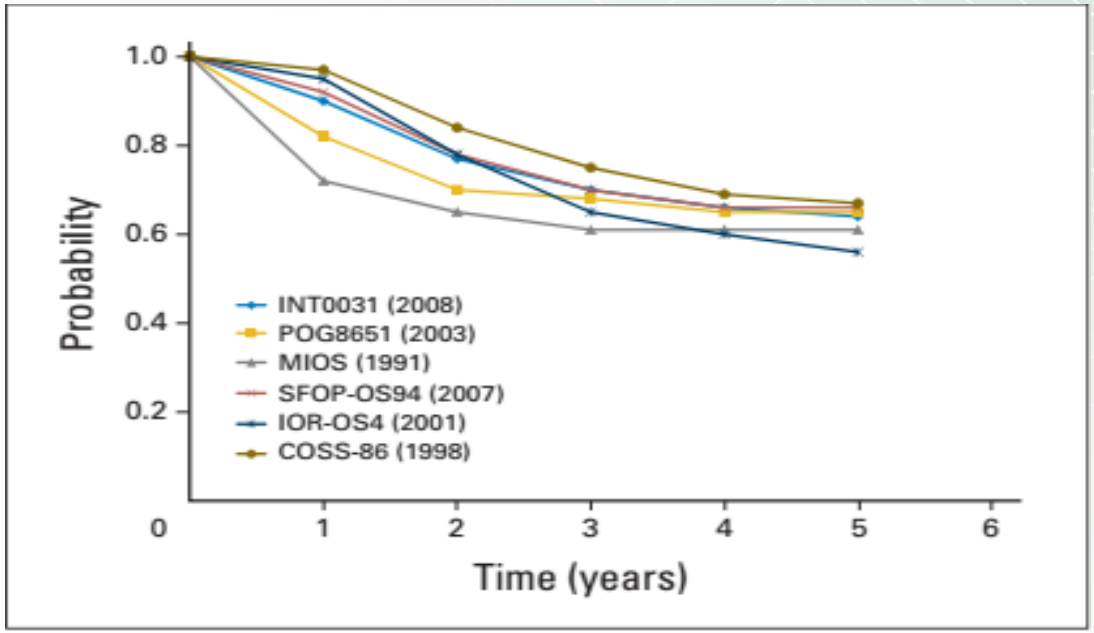


Fig 1. Event-free survival by clinical trial and year published for patients with nonmetastatic osteosarcoma.[5,10,25,28-30] COSS, Cooperative German-Austrian-Swiss Osteosarcoma Study Group; INT, Intergroup study; IOR, Istituto Ortopedico Rizzoli; MIOS, Multi-Institutional Osteosarcoma Study; POG, Periatric Oncology Group; SFOP, Société Française d'Oncologie Pédiatrique.

Drug(s)	Dosing	Efficacy			Reference
		ORR	PFS (RFS)	OAS	
First-line therapy					
Doxorubicin + cisplatin (AP)[α]	Doxorubicin 60–90 mg/m^2 IV + cisplatin 100–120 mg/m^2 IV or IA every 21 days	N/A	3-yr 47% 5-yr 44%	3-yr 65% 5-yr 55%	Souhami et al. [52]
High-dose methotrexate + doxorubicin + cisplatin (MAP)[α]	Methotrexate 8–12 g/m^2 (max. 20 g) IV + doxorubicin 60–75 mg/m^2 IV + cisplatin 120 mg/m^2 IV or IA[Δ]	N/A	(2-yr 78%) (5-yr 63%) (10-yr 59%)	2-yr 93% 5-yr 75% 10-yr 70%	Bacci et al. [53]
High-dose methotrexate + doxorubicin + cisplatin + high-dose ifosfamide (MAPI)[β]	Methotrexate 12 g/m^2 (max. 20 g) IV + doxorubicin 75 mg/m^2 IV + cisplatin 120 mg/m^2 IV + ifosfamide 15 g/m^2 IV[Δ]	N/A	(2-yr 21%)	2-yr 55%	Bacci et al. [54]
Second-line therapy					
High-dose ifosfamide ± etoposide[β]	Ifosfamide 10–17.5 g/m^2 IV ± etoposide 100 mg/m^2 IV (D1-5) every 21 days[Δ]	20%–59%	6-mo 51% 2-yr 43%	2-yr 30–55%	Goorin et al.; Magnan et al.; Palmerini et al.; Patel et al. [55, 56, 57••, 58]
High-dose methotrexate[α]	Methotrexate 12 g/m2 (max. 20 g) IV every 7–21 days	N/A	N/A	5-yr 55%	Comandone et al. [59]
High-dose methotrexate + etoposide + high-dose ifosfamide[α]	Methotrexate 12 g/m^2 (max. 20 g) IV + etoposide 75 mg/m^2 IV + ifosfamide 12 g/m^2 IV[Δ]	N/A	(3-yr 43%)	5-yr 76%	Le Deley et al. [60]
Regorafenib[β]	160 mg PO daily (D1-21) every 28 days	14%	8-wk 79%	2-yr 30%	Davis et al. [48]

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Drug(s)	Dosing	Efficacy			Reference
		ORR	PFS (RFS)	OAS	
Regorafenib[β]	160 mg PO daily (D1–21) every 28 days	14%	8-wk 79% 16-wk 44%	2-yr 30%	Davis et al. [48]
Sorafenib ± everolimus[β]	Sorafenib 400 mg PO BID ± everolimus 5 mg PO daily	14%	6-mo 29–45%	12-mo 17%	Grignani et al. [61, 62]
Cabozantinib[β]	Cabozantinib 60 mg PO daily	12%	6-mo 52% 12-mo 9% 24-mo 9%	6-mo 78% 1-yr 38% 2-yr 23%	Italiano et al. [63•]
Cyclophosphamide + topotecan[β]	Cyclophosphamide 250 mg/m^2 IV (D1–5) + topotecan 0.75 mg/m^2 IV (D1–5) every 21 days	11%	N/A	N/A	Saylors et al. [64]
Gemcitabine + docetaxel[β]	Gemcitabine 675–900 mg/m^2 (D1, D8) + docetaxel 75–100 mg/m^2 (D8) every 21 days	33%	4-mo 56%	N/A	Navid et al.; Palmerini et al. [65, 66]
Cyclophosphamide + etoposide[β]	Cyclophosphamide 4000 mg/m^2 IV (D1) + etoposide 200 mg/m^2 IV (D2–4) every 21–28 days	19%	4-mo 42%	1-yr 50%	Berger et al. [67]
Ifosfamide + carboplatin + etoposide (ICE)[β]	Ifosfamide 1800 mg/m^2 IV (D1–5) + carboplatin 400 mg/m^2 IV (D1–2) + etoposide 100 mg/m^2 IV (D1–5) every 21 days	36%	N/A	1-yr 41% 2-yr 26%	Van Winkle et al. [68]

ORR overall response rate; *PFS* progression free survival; *EFS* event free survival; *OAS* overall survival; *N/A* not available

[α]Efficacy data from study of osteosarcoma patients without metastatic disease

[β]Efficacy data from study of osteosarcoma patients with metastatic or progressive disease

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Recent Updates:
Recurrent/Metastatic Osteosarcoma

ARTEMIS-002: Phase 2 Study of HS-20093 in Patients with Relapsed or Refractory Osteosarcoma and Other Sarcomas

Lu Xie[1], Jie Xu[1], Xin Sun[1], Xin Liang[1], Kuisheng liu[1], Yi Yang[1], Zhaoming Ye[6], Jianning Zhao[7], Weitao Yao[8], Jin Wang[9], Xiana

[1]Musculoskeletal Tumor Center, Peking University People's Hospital, Beijing, China; [2]Tianjin Medical U Guangzhou, China;[4]Shanghai Sixth People's Hospital, Shanghai, China;[5]Shanghai General Hospital, Sl Hospital of Eastern Theater Command, Nanjing, China;[8]Henan Cancer Hospital, Zhengzhou, China;[9]Su Cancer Hospital, Hangzhou, China.

Presented b

Musculoskeletal Tumor Center, Peking

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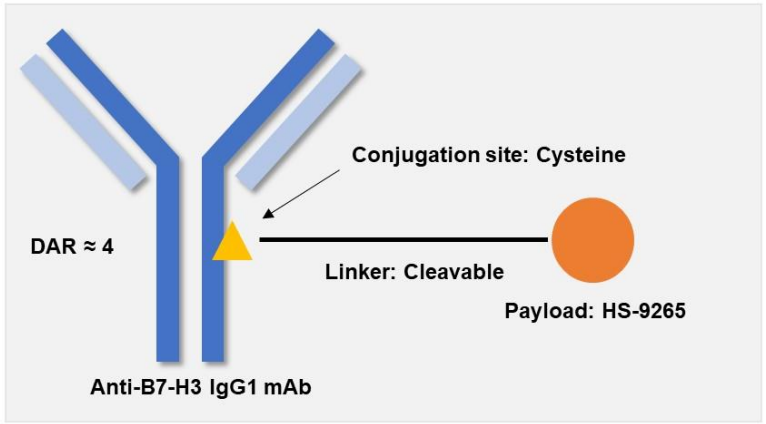
Unmet need in B7-H3 Expressing Sarcomas

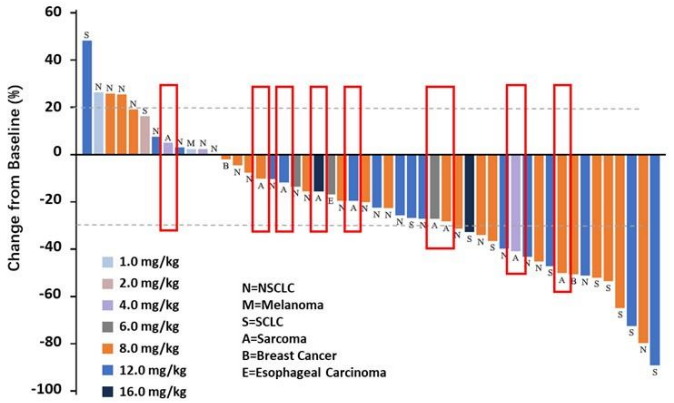
- Patients with relapsed and refractory (R/R) sarcoma have a poor prognosis with limited therapeutic options.
- HS-20093 is a novel B7-H3-targeted antibody-drug conjugate (ADC) composed of a fully-humanized anti-B7-H3 monoclonal antibody covalently linked to topoisomerase I inhibitor payload (an exatecan derivative) via a cleavable maleimide tetrapeptide linker.
- Preliminary anti-tumor response observed in sarcoma patients in the phase 1 ARTEMIS-001 study (NCT05276609).

Figure 3. Structure of HS-20093



DAR: drug-antibody ratio

Figure 4. ARTEMIS-001 Study- Sarcomas Subgroup[1]



1. Jie W, et al. ARTEMIS-001: Phase 1 Study of HS-20093, a B7-H3 Targeting Antibody-drug Conjugate, in Patients with Advanced Solid Tumor. 2023 ASCO. Abstract 3017

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Study Design

- The ARTEMIS-002 Study (NCT05830123): an open label, two-arm phase II trial in patients with R/R osteosarcoma or other sarcomas progressed upon standard systemic treatment.

Key eligibility criteria:

- ≥18 years
- Histologically confirmed osteosarcoma or other sarcomas
- Progressed upon ≥1 line systemic treatment
- At least one measurable lesion as per RECIST 1.1
- ECOG PS 0~1
- Agree to provide fresh or archival tumor tissue and peripheral blood samples

Cohort 1: R/R osteosarcoma patients (N=42)
- 8mg/kg Q3W, N=16
- 12mg/kg Q3W, N=26

Cohort 2: Other R/R sarcomas patients (N=20)
- 12mg/kg Q3W, N=20

- **Primary endpoint**
  - ORR per investigator
- **Secondary endpoints**
  - ORR per IRC
  - DCR, DoR and PFS per investigator
  - OS
  - Safety, pharmacokinetics and immunogenicity
- **Exploratory endpoints**
  - B7-H3 expression of archived sample was retrospectively evaluated by IHC in FFPE tissue
  - Soluble B7-H3 expression of PB

R/R: relapsed and refractory; ECOG: eastern cooperative oncology group; PS: physical fitness score; ORR: objective response rate; DCR: disease control rate; DoR: d
Q3W: once three weeks; IRC: independent review committee; IHC: immunohistochemistry; FFPE: formalin fixed paraffin embedded; PB: peripheral blood.

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Efficacy-Osteosarcoma

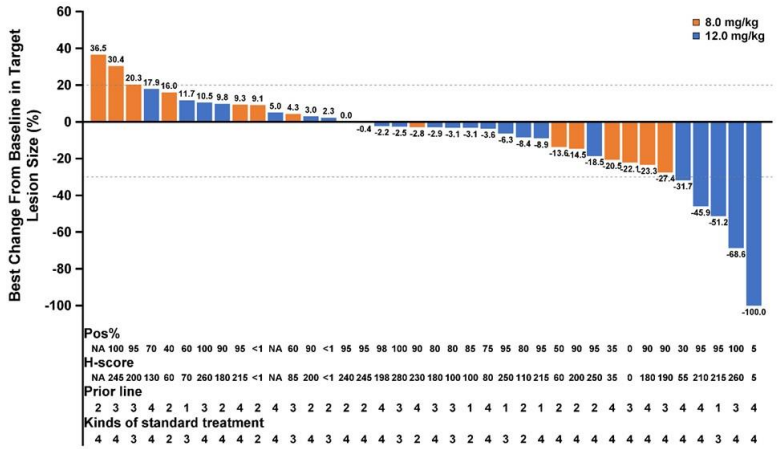
- Thirty-eight treated R/R osteosarcoma patients were evaluable for efficacy.
- HS-20093 showed promising anti-tumor responses especially at 12.0 mg/kg with 17.4% ORR.

	8.0 mg/kg (N=15)	12.0 mg/kg (N=23)	Total (N=38)
Median follow-up time (m)	8.2	2.8	3.3
ORR, n(%), (95% CI)	0 (0.0,21.8)	4(17.4) (5.0,38.8)	4(10.5) (2.9,21.1)
DCR, n(%), (95% CI)	10(66.7) (38.4,88.2)	20(87.0) (66.4,97.2)	30(78.9) (62.7,90.4)
Median DOR (m), (95% CI)	/	NA NA,NA	NA NA,NA

NA: not available.
Pos%: percentage of B7-H3 positive tumor cells.
H-score: histochemistry score of B7-H3 protein.

Data cut-off: March 20, 2024

Figure 5. Best change in tumor burden



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Efficacy-Osteosarcoma

- By the cutoff date (March 20, 2024), 52.6% (20/38) patients remained on treatment.
- At 8.0 mg/kg, the median PFS was 4.0 months with the median follow-up time of 8.2 months.
- At 12.0 mg/kg, the median PFS was not mature with the median follow-up time of 2.8 months.

Figure 6. Change of percentage in target lesion size from baseline over time

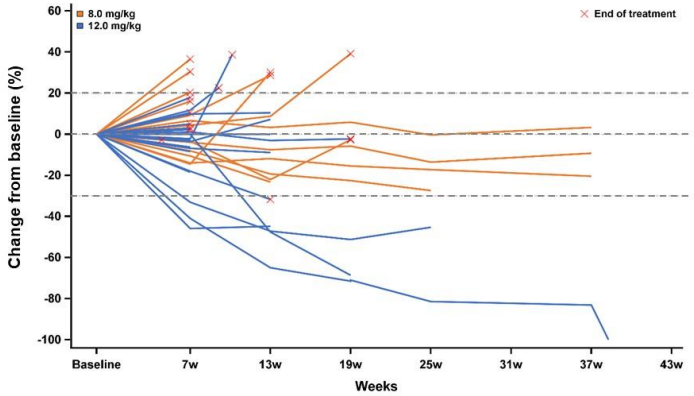
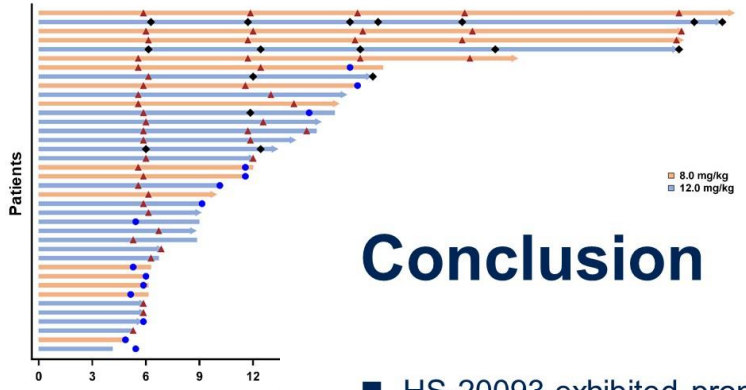


Figure 7. Response and duration of treatment



Data cut-off: March 20, 2024

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Conclusion

- HS-20093 exhibited prominent efficacy activity in patients with heavily-pretreated R/R osteosarcoma as well as in a broad range of sarcomas at 12.0 mg/kg.
  - Osteosarcoma patients：the ORR was 17.4%, and the median PFS was immature.
  - Other sarcomas patients: the ORR was 25.0%, and the median PFS was 7.1 months.
- No new safety signal was identified in this phase 2 trial.
- Further investigation, including exploratory biomarker study, is ongoing based on the observed antitumor activity of HS-20093 in patients with R/R osteosarcoma and other sarcomas.

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AOST2121: Phase 2 study of OST31-164 resection of recurrent osteosarcoma

- **Composite immunotherapeutic**
  - Live attenuated *Listeria monocytogenes* (*Lm*)-based immunotherapy developed for the treatment of HER2-overexpressing cancers
  - After uptake by APCs, OST31-164 escapes the phagosome and enter the cytosol, where it secretes listeriolysin O-cHER2 fusion proteins presented by MHC class I and II
- **Rationale**
  - Evidence suggests M2-TAMs are potential facilitators of metastasis in osteosarcoma
  - Significant reduction in the proportion of immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells
  - Stimulates the *de novo* generation of HER2-specific effector T cells

CHILDREN'S ONCOLOGY GROUP

Damon Reed, Kelly Bailey

AOST2121: Study Treatment and Design

- **Treatment**
  - OST31-164 $1x10^9$ CFU IV every 3 weeks x 48 weeks
  - 7-day course of antibiotic therapy will be administered to ensure clearance of *Lm*.
- **Study Design**
  - Single arm phase 2 trial
  - Endpoint: 12-month EFS based on benchmark COG historical data
  - Statistics
    - OST31-164 will be considered for further investigation if the probability of remaining analytic event-free in any particular individual is ≥ 50% (OR 2.3 vs. historical 30%)
    - With 39 patients, Type I error 10% and power 85%
  - Accrual: 2.3 patients per month, 2 ½ years + 1 year follow-up

Positive Results!

- 1-year Event Free Survival (EFS) of 32.5% vs. 20% 1-year EFS for comparator
- Interim 1-year and 18-month Overall Survival (OS) of 90.4%
- 0 Grade 3, 4 or 5 Treatment-related Adverse Events (AEs)
- 41 patient trial fully enrolled
- Primary endpoint 12-month EFS data and interim co-primary endpoint 12-month OS data to be released in the fourth quarter of 2024
- No novel therapeutic interventions for resected, recurrent osteosarcoma in 40+years

#11527: Apatinib combined with ifosfamide and etoposide versus ifosfamide and etoposide in relapsed or refractory osteosarcoma (OAIE/PKUPH-sarcoma 11): a multicenter, randomized controlled trial

Lu Xie[1], Jie Xu[1], Xin Sun[1], Xin Liang[1], Kuisheng Liu[1], Kunkun Sun[1], Yuan Li[1], Rong Liu[1], Du Wang[2], Shurong Shao[2], Zhongjiang Chen[2], Zheng Pang[2], Guangxin Zhou[3], Sujia Wu[3], Yingqi Hua[4], Haiyan Hu[5], Yi Yang[1], Tao Ji[1], Wei Guo[1], Xiaodong Tang[1]

[1]Peking University People's Hospital, China; [2]Jiangsu Hengrui Pharmaceuticals Co, Ltd., China; [3]Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, China; [4]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, China; [5]Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

BACKGROUND

- Retrospective studies have suggested the potential of apatinib, an anti-angiogenesis tyrosine kinase inhibitor, plus ifosfamide and etoposide (IE) over IE in advanced osteosarcoma.
- This trial aimed to further compared apatinib plus IE versus IE alone in patients with advanced osteosarcomas post first-line chemotherapy failure.

METHODS

- In this multicenter, randomized controlled trial, patients with osteosarcoma, progressing after at least one prior line of chemotherapy, were randomized (2:1) to receive either apatinib plus IE or IE.
- Apatinib was continued until disease progression or for a maximum of one year, and IE was administered for up to 10 cycles. **Local therapy was not permitted.**
- The primary endpoint was progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors 1.1.

Figure 1. First-line regimen for osteosarcoma in our center

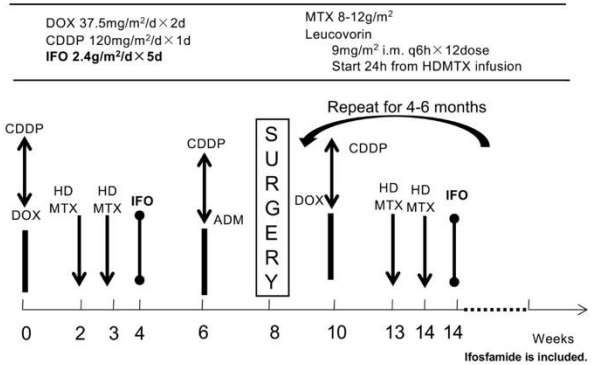
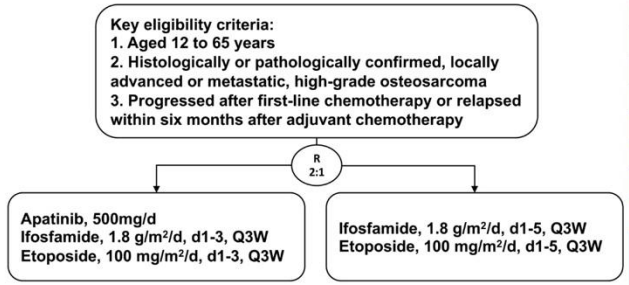


Figure 2. Study design



Apatinib plus IE demonstrated a significant improvement in PFS in patients with advanced osteosarcomas, with an acceptable safety.

RESULTS

Table 1. Baseline characteristics

Variables	Apa+IE group (n=53)	IE group (n=28)
Age, years, n (%)		
<18	29 (54.7)	15 (53.6)
≥18	24 (45.3)	13 (46.4)
Sex, n (%)		
Male	34 (64.2)	21 (75.0)
Female	19 (35.8)	7 (25.0)
Time since initial diagnosis, months, median (IQR)	12.1 (5.4, 18.8)	15.1 (8.6, 22.7)
ECOG PS*, n (%)		
0	14 (26.4)	10 (35.7)
1	32 (60.4)	16 (57.1)
2	3 (5.7)	0
3	4 (7.5)	2 (7.1)
Location of primary tumor, n (%)		
Limbs	37 (69.8)	14 (50.0)
Non-extremities	16 (30.2)	14 (50.0)
Sites of metastasis, n (%)		
Only lung	35 (66.0)	20 (71.4)
Others	18 (34.0)	8 (28.6)
Previous lines of therapy, n (%)		
1	40 (75.5)	22 (78.6)
≥2	13 (24.5)	6 (21.4)
Previous chemotherapy, n (%)		
Anthracyclines	53 (100.0)	28 (100.0)
Ifosfamide	47 (88.7)	26 (92.9)

*Only patients with an ECOG PS of 2-3 for amputation surgery were included.

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Table 2. Tumor response

Outcomes	Apa+IE group (n=53)	IE group (n=28)
Best overall response, n (%)		
Complete response	1 (1.9)	0
Partial response	16 (30.2)	7 (25.0)
Stable disease	31 (58.5)	10 (35.7)
Progressive disease	3 (5.7)	10 (35.7)
Not evaluable	2 (3.8)	1 (3.6)
ORR, n (%)	17 (32.1)	7 (25.0)
95% CI	(19.9, 46.3)	(10.7, 44.9)
DCR, n (%)	48 (90.6)	17 (60.7)
95% CI	(79.3, 96.9)	(40.6, 78.5)
TTR, months, median (95% CI)	1.4 (1.2, 3.1)	1.5 (1.3, 2.0)
DoR, months, median (95% CI)	3.9 (1.9, 7.8)	4.1 (1.7, NE)
TTP, months, median (95% CI)	5.1 (3.7, 5.7)	2.5 (1.4, 4.1)

Figure 3. Treatment exposure and duration of response

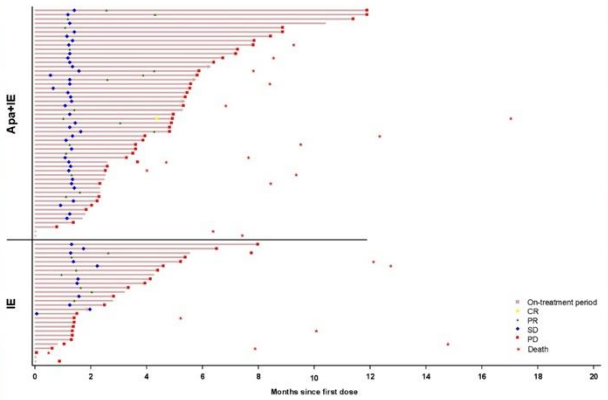
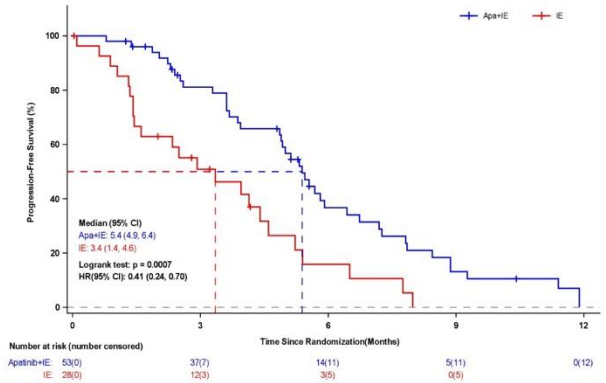


Figure 4. Kaplan-Meier curves of PFS



- The apatinib plus IE group showed a median PFS of 5.4 months (95% CI, 4.9 to 6.4), compared to 3.4 months (95% CI, 1.4 to 4.6) in the IE group, yielding a hazard ratio of 0.41 (95% CI, 0.24 to 0.70), P=0.0007.
- OS data have not matured.

Table 3. Treatment related adverse events

Events, n (%)	Apa+IE group (n=53)		IE group (n=28)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TRAE	52 (98.1)	37 (69.8)	25 (89.3)	18 (64.3)
Platelet count decreased	39 (73.6)	21 (39.6)	15 (53.6)	8 (28.6)
White blood cell decreased	37 (69.8)	27 (50.9)	19 (67.9)	17 (60.7)
Anemia	35 (66.0)	17 (32.1)	21 (75.0)	15 (53.6)
Neutrophil count decreased	32 (60.4)	26 (49.1)	19 (67.9)	15 (53.6)
Hypothyroidism	32 (60.4)	3 (5.7)	4 (14.3)	0
Proteinuria	18 (34.0)	2 (3.8)	2 (7.1)	0
Hypoproteinemia	10 (18.9)	0	3 (10.7)	1 (3.6)
Diarrhea	9 (17.0)	0	0	0
Hypertension	8 (15.1)	0	4 (14.3)	0
Hypocalcemia	8 (15.1)	0	2 (7.1)	0
Thyrotropin increased	7 (13.2)	3 (5.7)	0	0
Pneumothorax	6 (11.3)	3 (5.7)	0	0
Hypokalemia	5 (9.4)	0	3 (10.7)	0
Lymphocyte count decreased	3 (5.7)	0	3 (10.7)	2 (7.1)

Research design

Incorporation criteria
- Aged 12 to 65 years
- Histopathological confirmed osteosarcoma relapsed or refractory upon or within 6 months after first-line chemotherapy
- Measurable disease per RECIST v1.1
- ECOG performance status of 0~1

N=78

R 2:1

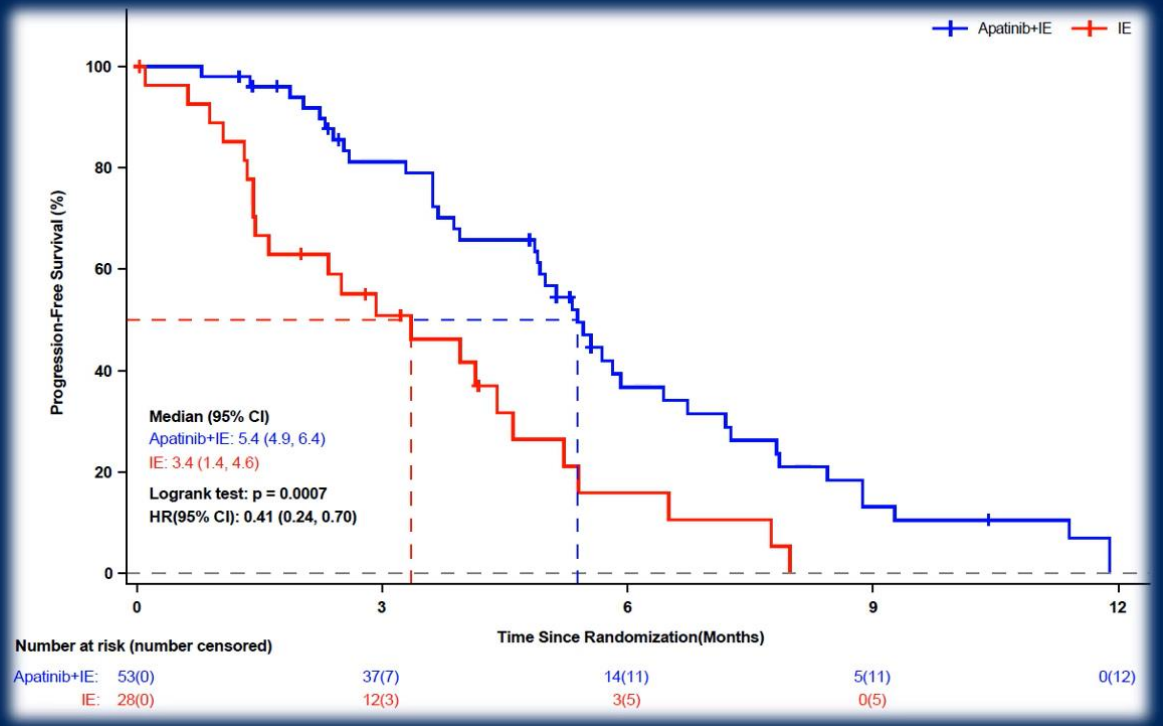
Apatinib + IE (N=52)
Apatinib 500 mg PO QD +
Ifosfamide 1.8 g/m^2/d d1-3 Q3W 10 cycles +
Etoposide 100 mg/m^2/d d1-3 Q3W 10 cycles

IE (N=26)
Ifosfamide 1.8 g/m^2/d d1-5 Q3W 10 cycles +
Etoposide 100 mg/m^2/d d1-5 Q3W 10 cycles

Apatinib maintenance
Apatinib 500 mg PO QD
Until progressive disease (PD) or up to one year

- Tumor assessment per RECIST v1.1
- Adverse events by NCI-CTCAE v5.0
- Quality of life by EORTC QLQ-C30

Primary Endpoint - PFS



2024 ASCO ANNUAL MEETING

Abstract 11530 - PHASE II STUDY IN PEDIATRIC AND AYA PATIENTS WITH NON-METASTATIC HIGH-GRADE EXTREMITY OSTEOSARCOMA WITH A RISK-ADAPTED STRATEGY BASED ON P-GLYCOPROTEIN (ISG/OS-2): A CORRELATIVE STUDY ON TUMOUR IMMUNE MICROENVIRONMENT

Emanuela Palmerini*, Maria Rosaria Sapienza*, Stefano A Pileri, Alberto Righi, Antonina Parafioriti, Alessandro Franchi, Claudio Agostinelli, Cristina Meazza, Virginia Ferraresi, Sebastian Dorin Asaftei, Luca Coccoli, Angela Tamburini, Marco Gambarotti, Massimo Serra, Davide Maria Donati, Franca Fagioli, Marilena Cesari, Katia Scotlandi, Maria Antonella Laginestra‡, Toni Ibrahim‡

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BACKGROUND:

- P-glycoprotein (Pgp) overexpression predicts for poor outcome in osteosarcoma.
- The ISG/OS-2 trial, evaluated the use of mifamurtide, an EMA-approved innate immunity-modulator, in Pgp-positive patients (pts)(NCT01459484).
- Here, we present a correlative study to develop a predictive classifier based on tumour immune microenvironment gene profiling.

METHODS:

- 62 pts with non-metastatic high-grade osteosarcoma were enrolled at diagnosis.
- RNA was extracted from pre-treatment FFPE and non-decalcified tissue.
- PanCancer Immune profiling panel (NanoString Technologies), including 730 immune genes, was used.
- Pgp-positive patients (33/62.53%) underwent chemotherapy (CT) and adjuvant mifamurtide.
- Pgp-negative patients (29/62 pts (53%) received CT alone.
- Preliminary findings were validated in Target-OS TCGA data set.

PRIMARY ENDPOINT:

- identification of prognostic signatures of osteosarcoma pts at diagnosis.
- Identification of prognostic signature in pts undergoing mifamurtide.

PATIENTS CHARACTERISTICS:

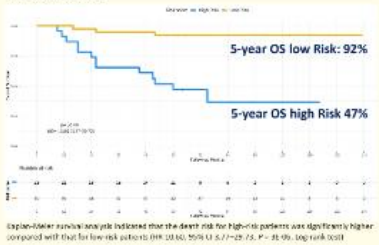
	n	%
	62	100
Age		
0-14 years	32	51.6
> 14 years	30	48.4
Gender		
Male	43	69.4
Female	19	30.6
Serum alkaline phosphatase (ALP)		
High	16	25.8
Normal	46	74.2
Lactate dehydrogenase (LDH)		
High	14	22.6
Normal	47	75.8
Unknown	1	1.6
Histologic Response		
Good response (GRs)	31	50
Poor response (PRs)	31	50
P-glycoprotein (Pgp)		
Pgp-	27	43.6
Pgp+ (mifamurtide)	34	54.8
Not evaluable	1	1.6

RESULTS:

Prognostic signature in non-metastatic osteosarcoma patients

Fig 1. 21- gene signature in 62 Primary Osteosarcoma - Discovery cohort

Overall Survival



Event Free Survival

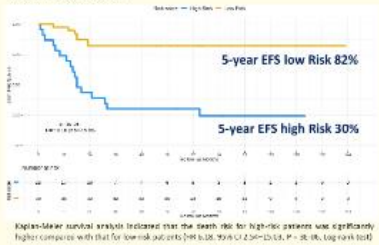
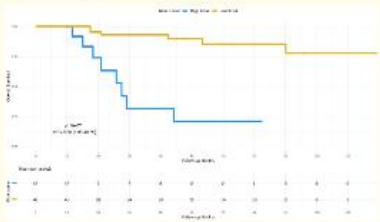
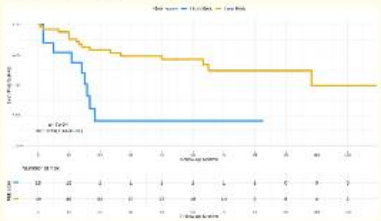


Fig 2. 21-gene signature in the Target-OS TCGA - Validation cohort

Overall Survival



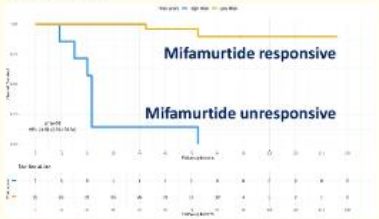
Event Free Survival



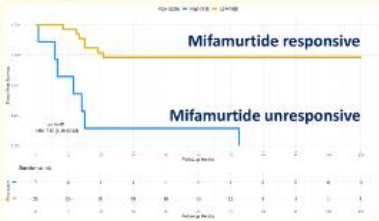
Mifamurtide sensitivity signature in Pgp positive patients

Fig 3. 31-gene signature in 33 PgP positive Primary Osteosarcoma

Overall Survival



Event Free Survival



MULTIVARIATE ANALYSIS:

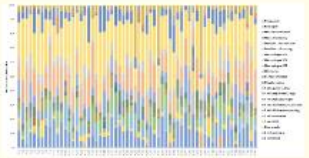
Prognostic performance of the 21-gene signature

Overall Survival Variable	Univariate Cox		Multivariate Cox	
	HR (95% CI)	P value	HR (95% CI)	P value
Discovery cohort (n = 62)				
Gene signature (high- vs low-risk)	10.80(3.77-29.73)	3.00E-06	9.83(2.74-35.2)	0.00044
Histologic Response (Prs vs Grs)	3.95(1.28-12.11)	0.016	4.21(1.24-14.21)	0.02
Age	0.99(0.93-1.04)	0.63	0.97(0.90-1.04)	0.51
Serum alkaline phosphatase (normal vs high)	0.46(0.17-1.22)	0.12	0.55 (0.17-1.74)	0.32

Mifamurtide sensitivity signature of the 31-gene

Overall Survival Variable	Univariate Cox		Multivariate Cox	
	HR (95% CI)	P value	HR (95% CI)	P value
PgP positive primary Osteosarcoma (n = 31)				
Gene signature (high- vs low-risk)	24.51(3.59-176.84)	1.00E-09	75.17(8.79-642.42)	0.000079
Histologic Response (Prs vs Grs)	3.06(0.76-12.36)	0.097	4.20(0.46-38.15)	0.25
Age	0.96(0.85-1.08)	0.47	0.93(0.80-1.08)	0.36
Serum alkaline phosphatase (normal vs high)	0.52(0.14-1.93)	0.31	2.16(0.29-16.30)	0.45

CIBERSORT:



OVERLAPPING GENES:

CONCLUSIONS:

- *Prognostic gene signatures* derived from the tumor immune microenvironment have been successfully identified for risk stratification of osteosarcoma patients, regardless of mifamurtide treatment.
- Importantly, for patients treated with *mifamurtide*, a distinct *gene signature* that predicts both OS and EFS was developed. This tool might be used to select patients who could benefit from adjuvant mifamurtide. A validation study is ongoing.

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Abstract #11539: Phase II study to evaluate surufatinib in patients with osteosarcoma and soft tissue sarcoma that has failed standard chemotherapy: Updated analysis

Authors: Xing Zhang[1*], Qiuzhong Pan[1], Bushu Xu[1], Qiyan Cai[1], Ruiqing Peng[1], Lihong Zhang[2], Hui Li[3], Shiying Yu[2]

1. Melanoma and Sarcoma Medical Oncology Unit, Sun Yat-sen University Cancer Center, Guangzhou, China; 2. Tongji Hospital Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China; 3. Fujian Cancer Hospital, Fuzhou, China.

Background/Methods:

- Therapeutic options are limited in China for osteosarcoma and soft tissue sarcoma (STS) patients progressed after first-line chemotherapy.
- Surufatinib is a multi-targeted, small-molecule inhibitor of VEGFR-1, 2, 3, FGFR-1 and CSF-1R.
- Surufatinib has shown single-agent activity in a single arm, phase II study presented at 2023 ASCO (Abs e23540).
- Herein, we reported the updated efficacy and safety data.

Methods:

- Single-arm, open-label, multi-center, phase II study (NCT05106777)

Key Eligibility Criteria

- Histologically or cytologically confirmed unresectable or metastatic osteosarcoma or STS
- 14-70 years (aged < 18 years, have a body surface area of ≥ 1.5 m^2)
- ECOG PS 0-1 (amputee 0-2)
- Patient failed prior standard systemic chemotherapy (defined as: disease progression during treatment or within 6 months after the last treatment; or intolerable toxic side effects during treatment)

→ **N=44**
Surufatinib 300mg, qd, po, q3w
Until progressive disease or unacceptable toxicity

→ **Primary endpoint**
- $PFR_{12weeks}$

Secondary endpoints
- DCR
- ORR
- OS
- PFS
- Safety

A Simon optimal 2-stage design was used. If more than 3 patients out of the first 13 patients had no disease progression at 12 weeks in stage 1, the study would proceed to stage 2. If more than 12 patients out of 43 patients achieved the primary endpoint, the study would be successful.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; qd: once daily; po: orally; PFR: Progression Free Rate; OS: Overall Survival; ORR: Objective Response Rate; DCR: Disease Control Rate; N: Number of patients; PFS: Progression Free Survival.

Results :

- At cutoff date (May 13 2024), 44 patients were enrolled and received treatment (demographics are shown in **Table 1**).
- All 44 patients were efficacy evaluable, ORR was 11.4%, DCR was 86.4% **(Fig. 1)**. Complete response was observed in 1 patients with angiosarcoma.
- 30 patients had no disease progression at 12weeks and $PFR_{12weeks}$ was 69.76% (**Fig. 2**).
- Median PFS was 4.27 months (95%CI: 2.84-5.70). In subgroup analysis, significantly longer median PFS was observed in patients who received surufatinib as 2nd line therapy than those as 3rd line or later (6.8m vs 2.7m, p=0.0029, **Fig. 3**). Median OS was not reached yet.
- All pts experienced 1 treatment emergent adverse events (TEAEs). No unexpected adverse events occurred.

Surufatinib showed encouraging survival benefits in advanced recurrent **osteosarcoma and soft tissue sarcoma** patients who failed in standard chemotherapy, especially as **2nd-line therapy**

No conflicts of interest to declare
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Acknowledgement: We are grateful to all the patients enrolled in this study. We also thank Jiancai Zhou, Xing Lv, and Xiaochong Tang from HUTCHMED Ltd. for their assistance in data analysis.

Table1. Baseline characteristics of 44 patients.

	Total (N=44)
Age, Median (range)	49 (22-68)
Gender, n (%)	
Male	22 (50.0)
Female	22 (50.0)
ECOG PS, n (%)	
0	13 (29.6)
1	31 (70.4)
Diagnosis, n (%)	
Leiomyosarcoma (LMS)	11 (25.0)
Liposarcoma (LPS)	8 (18.2)
Synovial sarcoma	4 (9.1)
Fibrosarcoma	4 (9.1)
Epithelioid hemangioendothelioma	3 (6.8)
Malignant tumors of mesenchymal origin	3 (6.8)
Epithelioid sarcoma	2 (4.6)
Undifferentiated sarcoma	2 (4.6)
Alveolar soft tissue sarcoma	2 (4.6)
Malignant peripheral nerve sheath tumor	1 (2.3)
Desmoplastic small round cell tumor	1 (2.3)
Osteosarcoma	1 (2.3)
Rhabdomyosarcoma	1 (2.3)
Angiosarcoma	1 (2.3)

	Total (N=44)
Distant metastasis, n (%)	
0	2 (4.6)
1	17 (38.6)
≥2	25 (56.8)
Location, n (%)	
Lung	29 (65.9)
Liver	12 (27.3)
Lymph node	9 (20.5)
Pelvic/abdominal	5 (11.4)
Kidney	4 (9.1)
Pleura/peritoneum/mesentery	4 (9.1)
Muscles	4 (9.1)
Iliac fossa/external iliac	3 (6.8)
Bone	3 (6.8)
Breast	2 (4.6)
Colon	2 (4.6)
Brain	2 (4.6)

	Total (N=44)
Therapeutic lines, n (%)	
2	24 (54.6)
3	11 (25.0)
≥4	9 (20.4)
Prior treatment, n (%)	
Surgery	37 (84.1)
Interventional therapy	5 (11.4)
Anti-VEGFR drugs	
Anlotinib	13 (29.6)
Bevacizumab	4 (9.1)
Apatinib	2 (4.6)
Sorafenib	1 (2.3)
Sunitinib	1 (2.3)
Lenvatinib	1 (2.3)
HDAC inhibitors	2 (4.6)
Immune checkpoint inhibitors	14 (31.8)

Fig.1 Best change in sum of target lesions from baseline.

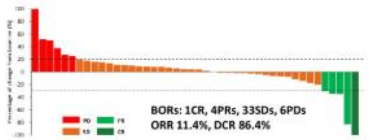

Fig.2 KM curve of PFS.

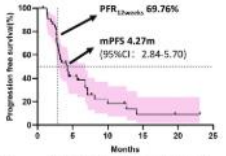

Fig.3 Subgroup analysis of PFS. 2 lines vs more than 3 lines (A), Prior anlotinib (B), LMS (C), and LPS (D).

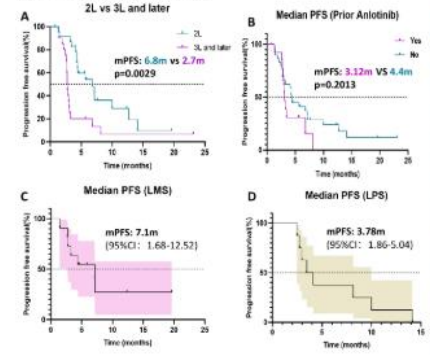

Table2. Treatment emergent adverse events.

Surufatinib (n=44)	Any grade n (%)	Grade ≥3 n (%)
Any TEAE	44 (100)	14 (31.8)
Proteinuria	30 (68.2)	3 (6.8)
Hypertension	26 (59.1)	4 (9.1)
Hypertriglyceridemia	24 (54.6)	2 (4.5)
Diarrhea	16 (36.4)	0
Urine occult blood	16 (36.4)	0
Hyperbilirubinemia	16 (36.4)	3 (6.8)
Creatinine increased	15 (34.1)	0
Hypoalbuminemia	15 (34.1)	0
Hyperuricemia	12 (27.3)	0
Hypercholesterolemia	11 (25.0)	0
Urine leukocytosis	10 (22.7)	0
Dropsy	7 (15.9)	0
Platelet count decreased	6 (13.6)	2 (4.5)
Neutrophil count decreased	6 (13.6)	1 (2.3)
Increased ALT	6 (13.6)	0
Hyponatremia	6 (13.6)	0
Abdominal distension	5 (11.4)	0
Lumbago	5 (11.4)	0
White blood cell count decreased	5 (11.4)	0
Increased AST	5 (11.4)	0
Fever	4 (9.1)	0
Haemorrhage	4 (9.1)	0
Anaemia	4 (9.1)	0
Lymphocyte count decreased	4 (9.1)	0
Hypokalemia	4 (9.1)	1 (2.3)

Future Directions for Research:

- We will continue to verify this results in a larger cohort, maybe in a randomized controlled trial.

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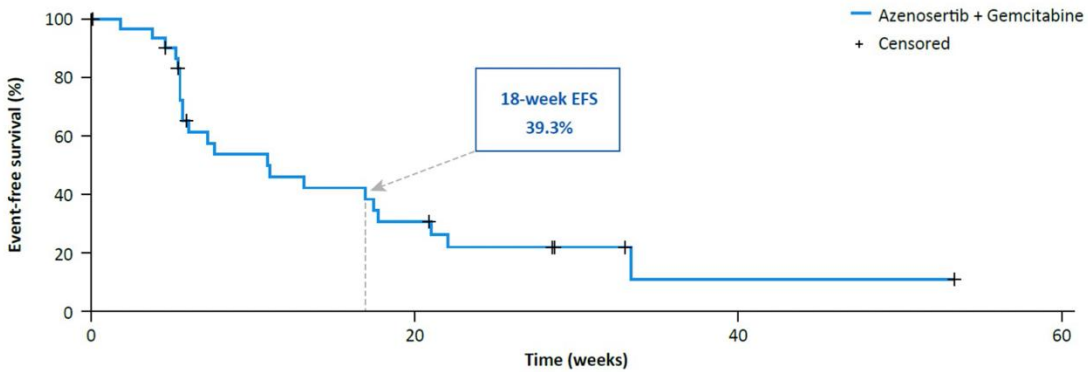
Phase 1 Results of the WEE1 Inhibitor, Azenosertib, in Combination With Gemcitabine in Adult and Pediatric Patients With Relapsed or Refractory Osteosarcoma

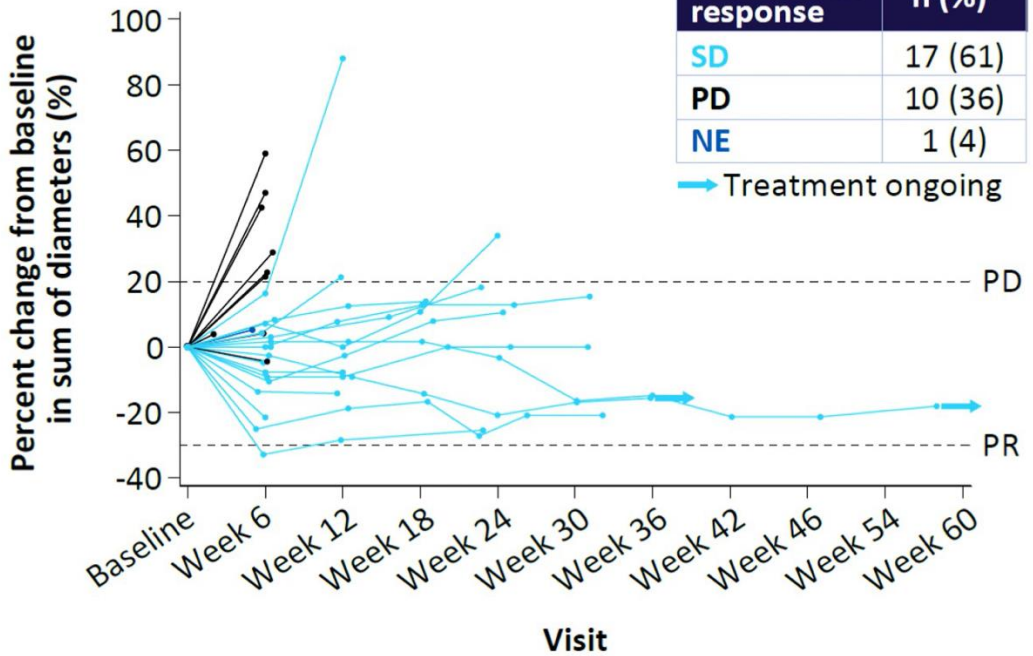
Viswatej Avutu[1], John Andrew Livingston[2], Noah Federman[3], Lee Cranmer[4], Nathalie Gaspar[5], Maud Toulmonde[6], Joseph Pressey[7], Mehdi Brahmi[8], Andrew Poklepovic[9]; Qing Shi[10], Nathan Jameson[10] Adrian M. Jubb[10], Chrystal U Louis[11], Sant P. Chawla[12]* and William Tap[1]*

Event-Free Survival Among Patients Receiving Azenosertib + Gemcitabine



Clinical data as of 9 Jan 2024.

Percent Change From Baseline in the Sum of Longest Diameters for Target l



Best overall response	n (%)[a]
SD	17 (61)
PD	10 (36)
NE	1 (4)

→ Treatment ongoing

Conclusions

- A safe and tolerable dose/schedule of azenosertib was identified in combination with gemcitabine:
  - The MTD was determined to be azenosertib 150 mg 5:2 + gemcitabine 800 mg/m^2 (D1, D8 on a 21-day cycle)
  - None of the patients treated at the MTD (n=6) required dose reductions of azenosertib due to adverse events and only 1 required a dose interruption
- The primary efficacy endpoint in this population (18-week landmark EFS) was 39%, three-fold higher than published 16-week EFS rates with salvage therapies (12%)[2]
  - Based on the historical benchmark for success set by the Children's Oncology Group (>30% of patients with EFS >4 months), the EFS outcomes with azenosertib + gemcitabine warrant further study[2]
- This promising efficacy and tolerability supports the continued evaluation of azenosertib with gemcitabine in patients with relapsed/refractory osteosarcoma in an upcoming investigator-initiated phase 2 trial

Open Clinical Trials

Preclinical/Data Collection

- An Organoid-based Functional Precision Medicine Trial in Osteosarcoma (PREMOST)- UCLA
- Biology of Osteosarcoma (BOOST) Registry and Biobank (BOOST)- University of Minnesota
- ICONIC: Improving Outcomes Through Collaboration in OsteosarComa (ICONIC)-UK
- Clinical Orthopaedic Data Bank (Acute and Chronic)- UF

Neo/Adjuvant

- Trilaciclib (highly effective, selective and temporarily reversible inhibitor of CDK4/6) Combing Chemotherapy in the Neoadjuvant Treatment of Osteosarcoma- China
- A Clinical Study of Surufatinib (CSF-1 inhibitor) Combined With Chemotherapy as Neoadjuvant Treatment in Osteosarcoma-China

Open Clinical Trials: Metastatic

- Olaparib (*PARPi*) With Ceralasertib (*ATR inhibitor*) in Recurrent Osteosarcoma
  - This is a single arm, phase 2, open-label clinical trial to evaluate the use of olaparib in combination with ceralasertib in 2 cohorts of patients aged 12-40 with recurrent osteosarcoma.
- Mistletoe Immunotherapy for Recurrent Osteogenic Sarcoma
  - Age ≥ 8 years of age and <30 years of age.
  - This will be a phase II, single arm study of osteosarcoma patients with fully resected pulmonary metastases
- Study to Assess Safety and Efficacy of Vactosertib (TGF-β) type 1 receptor inhibitor).in Adolescents and Adults With Recurrent, Refractory or Progressive Osteosarcoma
  - Age ≥14 years
- Thoracotomy vs thoracoscopy in oligometastatic osteosarcoma

Open Clinical Trials: Metastatic

- A Phase II, Randomized, Open-label Study to Assess the Efficacy, Safety, and Pharmacokinetics (PK) of Maintenance Cabozantinib (XL184) Plus Best Supportive Care (BSC) Versus BSC in Children, Adolescents and Young Adults (AYA) With Unresectable Residual Osteosarcoma Either at Diagnosis or at First Relapse After Standard Treatment
- Study of CAR T-Cells Targeting the GD2 With IL-15+iCaspase9 for Relapsed/Refractory Neuroblastoma or Relapsed/Refractory Osteosarcoma
- Cabozantinib With Ifosfamide in Ewing's Sarcoma and Osteosarcoma
- Natalizumab in Recurrent, Refractory or Progressive Pulmonary Metastatic Osteosarcoma
- Abemaciclib for Bone and Soft Tissue Sarcoma With Cyclin-Dependent Kinase (CDK) Pathway Alteration
- A Phase I/Ib Study of Losartan in Combination With Sunitinib in the Treatment of Pediatric and Adult Patients With Relapsed or Refractory Osteosarcoma
- Atezolizumab and Cabozantinib for the Treatment of Adolescents and Young Adults With Recurrent or Metastatic Osteosarcoma, TACOS Study

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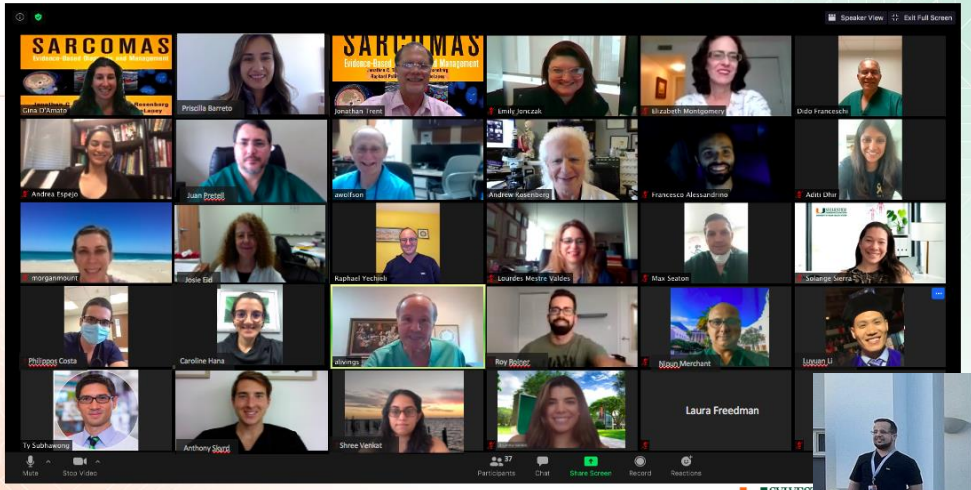
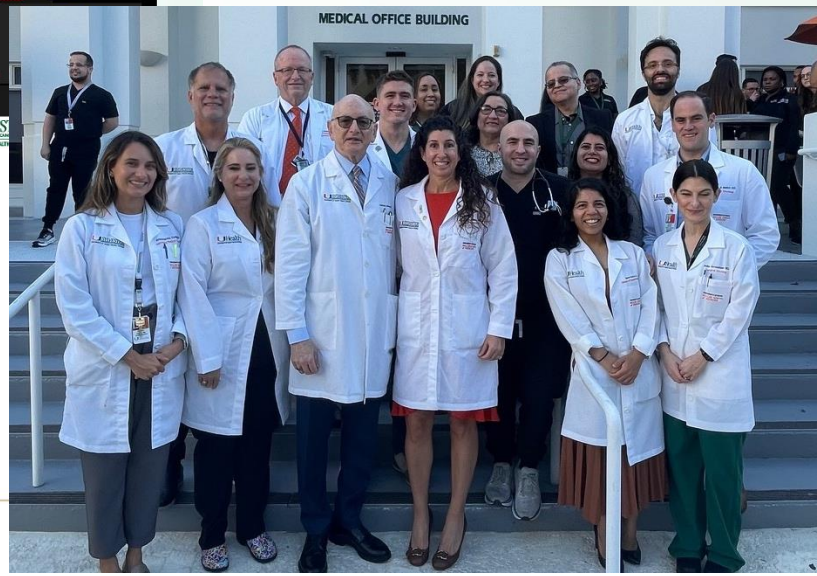
THANK YOU!!

Thank you so much for your attention and the patients for being so patient and my amazing sarcoma team !!

Team Sarcoma at Sylvester Comprehensive Cancer Center
IN PURSUIT OF *YOUR CURE.*™





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