Osteosarcoma: New Treatments/Research

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Outline

- **History of therapy for OS**
- **Current Understanding of biology of OS**
- **Need for new clinical trial design**
- **New treatment approaches**
  - Immunotherapy
  - Targeted therapy

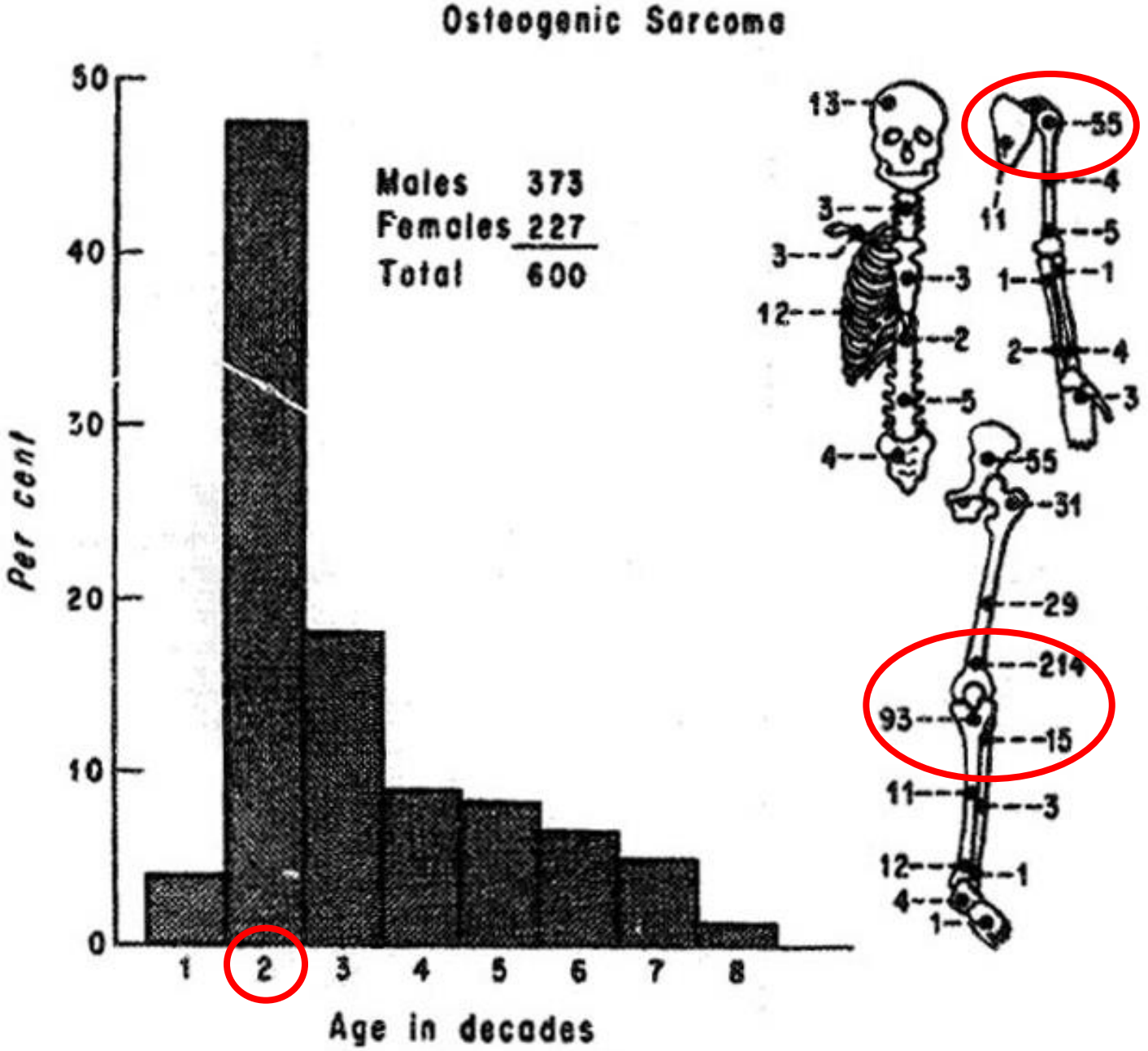


FIG. 1

Skeletal, age, and sex distribution of 600 cases of osteogenic sarcoma.

History of Treatment

A BRIEF HISTORY OF

OSTEOSARCOMA TREATMENT

PRIOR TO 1970

Prior to 1970's–treatment of OS was amputation of involved site if possible

1970

Mulitple investigators began testing chemotherapy agents for treating recurrent osteosarcoma–

1980

First randomized study performed comparing survival of patients with localized OS treated with complete surgical resection followed by adjuvant chemotherapy

1986

Results of this study published demonstrating unequivocal survival advantage of adding chemotherapy following surgery–this became standard practice

1990

The standard chemotherapy became MAP (Methotrexate, Adriamycin and Cisplatin) with Ifosfamide with or without Etoposide used for salvage chemotherapy

2000'S

Between 2005–2012 several studies conducted showed conflicting reports on activity of MTP–PE (mifamurtide),

2019

2 studies (in Europe and the US) demonstrated activity of regorafenib in recurrent OS

TODAY

No new drugs have been approved for use in osteosarcoma patients foralmost 40 years

Where are we in the treatment of Osteosarcoma: MAP has been standard Rx for more than 25 years

- **Tumors typically occur in rapidly growing bones at metaphysis (growth plate). Peak age several years earlier in girls than boys (growth spurt earlier by several years in girls)**
  - What is this telling us?
- **More than 95% of tumors have deficient p53**
  - Most common alterations of p53 are translocations involving exon 1
- **50% have RB mutations**
- **Currently no accepted prognostic factors other than presence or absence of metastases at Dx**
  - Hints that several genetic alterations my have prognostic implications
    - TP53
- **Most common genetic features are aneuploidy and sCNAs**
  - Many CNAs are recurrent (10-20%)
  - These include *MYC*, *CCND3, CDKN2A, CDK4*, *CCNE1, PTEN, VEGFA* and *IGF1R*.
- **Bloom syndrome, Werner's syndrome and Rothmund-Thomson have increased risk of OS (RecQ helicases)**
- **Most common site of metastases is lung**

Challenges to Progress

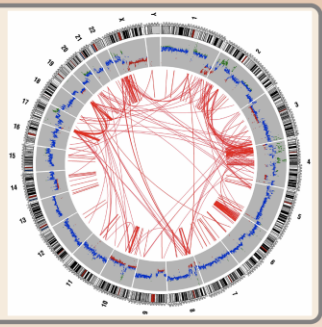
Despite the dramatic progress in Treatment of Osteosarcoma:

- **Failure rate is unacceptable**
  - Advanced/recurrent disease
- **Present treatment is toxic and complicated**
- **Restrictions in study design**
  - Relatively small patient numbers
  - Currently no way to stratify patients in groups based upon genetics

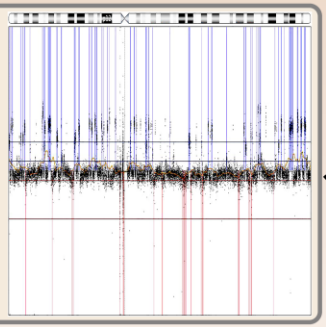
Current Understanding of the Biology

The Turbulent Genome of Osteosarcoma

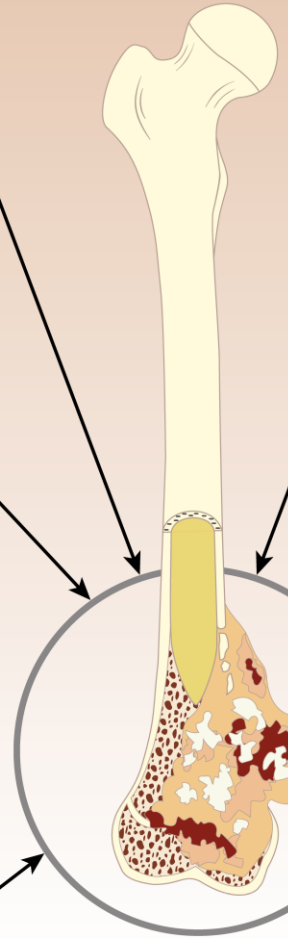
GENOME COMPLEXITY
(several mechanisms alter genome structure, copy number, and DNA sequence)

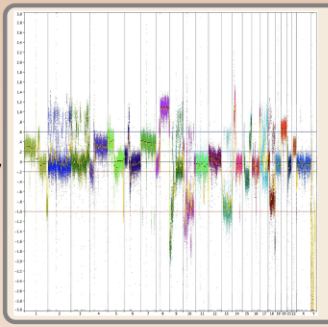


CHROMOTHRIPSIS
(shattered chromosomes with large regions of oscillating copy number)

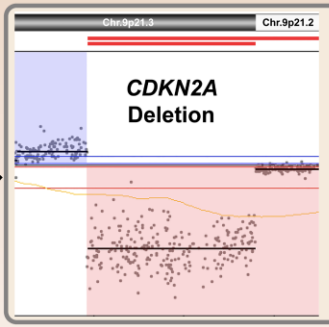


GENE DISRUPTIONS
(red arrowheads mark DNA breakpoints joined in an inactivating rearrangement of *TP53*)

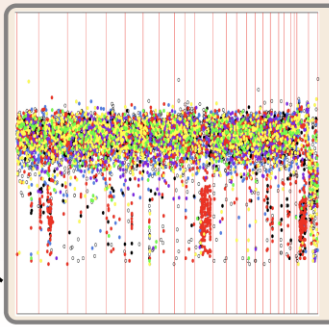




EXTENSIVE COPY NUMBER ABNORMALITIES



HOMOZYGOUS DELETIONS



KATAEGIS
(clustered single nucleotide variants)

IGFIR amplification in OS

Nat Commun. 2017 Jun 23;8:15936. doi: 10.1038/ncomms15936.

Recurrent mutation of IGF signalling genes and distinct patterns of genomic rearrangement in osteosarcoma.

Behjati S[1,2,3], Tarpey PS[1], Haase K[4], Ye H[5], Young MD[1], Alexandrov LB[6], Farndon SJ[1,7], Collord G[1], Wedge DC[8], Martincorena I[1], Cooke SL[1], Davies H[1], Mifsud W[7], Lidgren M[1], Martin S[1], Latimer C[1], Maddison M[1], Butler AP[1], Teague JW[1], Pillay N[5,9], Shlien A[10], McDermott U[1], Futreal PA[1,11], Baumhoer D[12], Zaikova O[13], Bjerkehagen B[13], Myklebost O[13,14], Amary MF[5], Tirabosco R[5], Van Loo P[4,15], Stratton MR[1], Flanagan AM[5,9], Campbell PJ[1,16].

Author information

Abstract

Osteosarcoma is a primary malignancy of bone that affects children and adults. Here, we present the largest sequencing study of osteosarcoma to date, comprising 112 childhood and adult tumours encompassing all major histological subtypes. A key finding of our study is the identification of mutations in insulin-like growth factor (IGF) signalling genes in 8/112 (7%) of cases. We validate this observation using fluorescence in situ hybridization (FISH) in an additional 87 osteosarcomas, with IGF1 receptor (IGF1R) amplification observed in 14% of tumours. These findings may inform patient selection in future trials of IGF1R inhibitors in osteosarcoma. Analysing patterns of mutation, we identify distinct rearrangement profiles including a process characterized by chromothripsis and amplification. This process operates recurrently at discrete genomic regions and generates driver mutations. It may represent an age-independent mutational mechanism that contributes to the development of osteosarcoma in children and adults alike.

Translational Oncology
www.transonc.com

Volume 10 Number 5 October 2017 pp. 846–853 846

Activation Status of Receptor Tyrosine Kinases as an Early Predictive Marker of Response to Chemotherapy in Osteosarcoma

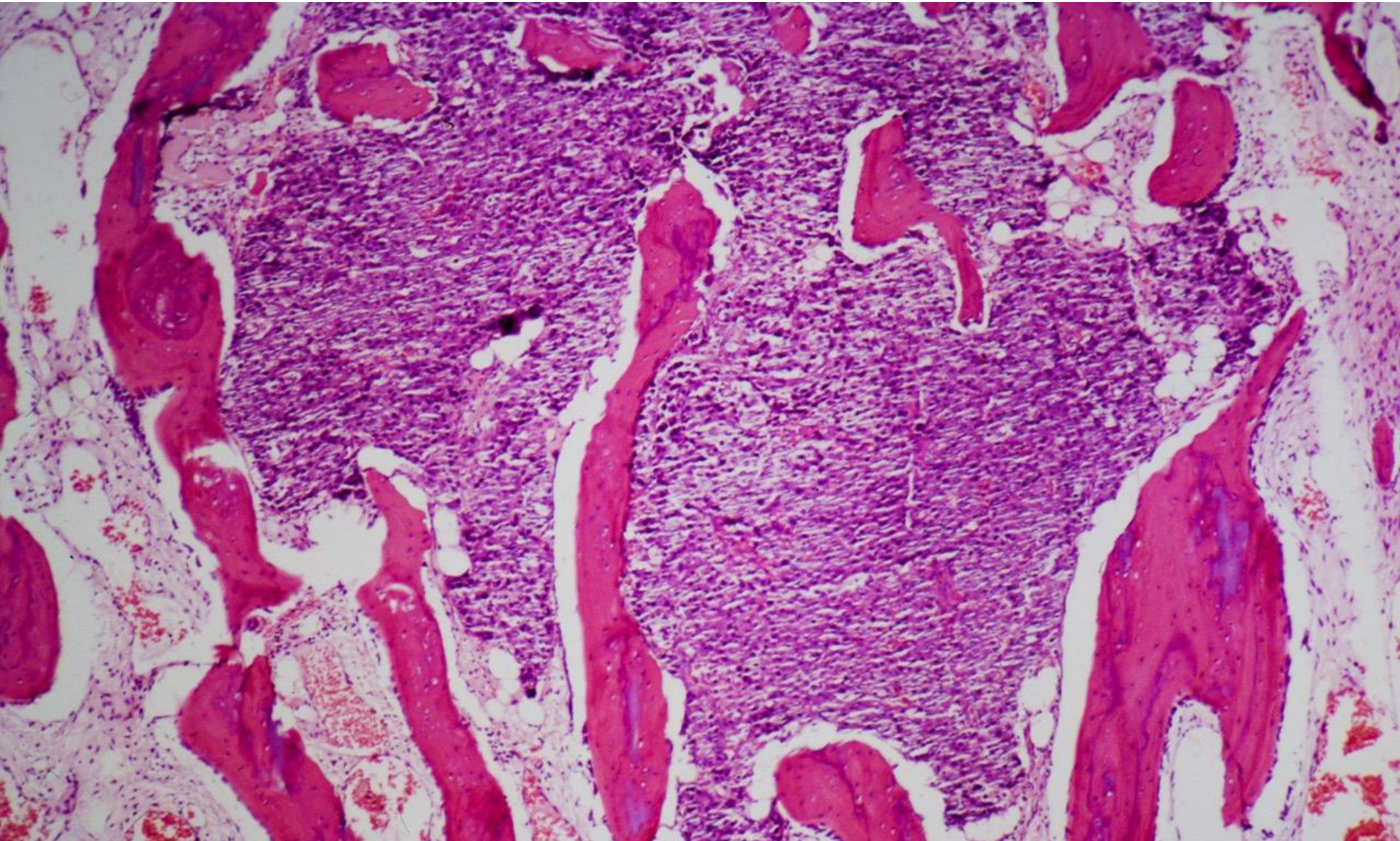
Parunya Chaiyawat*, Jeerawan Klangjorhor*, Jongkolnee Settakorn†, Voraratt Champattanachai‡,§, Areerak Phanphaisarn*, Pimpisa Teeyakasem*, Jisnuson Svasti‡,§ and Dumnoensun Pruksakorn*,¶

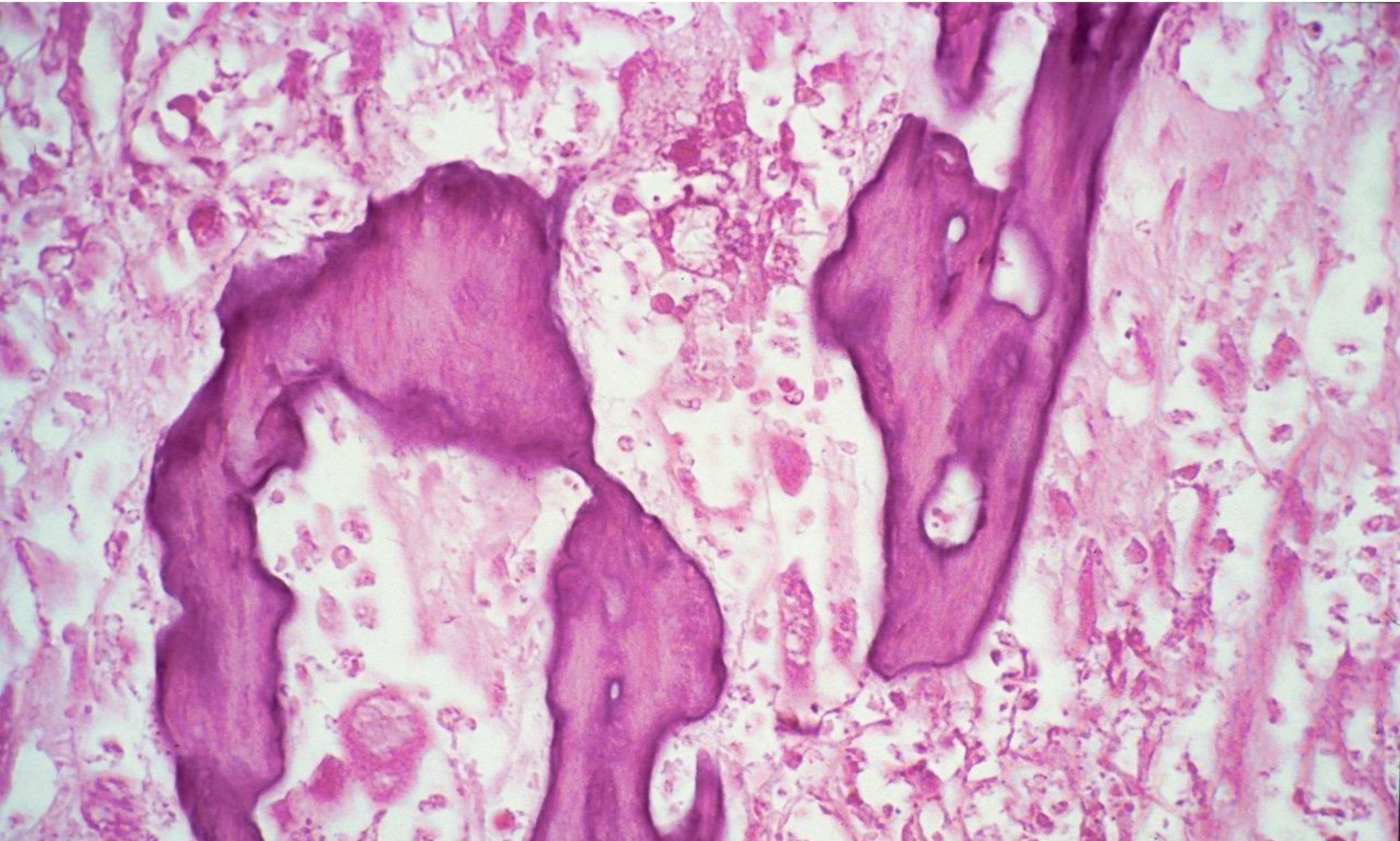
*Orthopedic Laboratory and Research Network (OLARN) Center, Department of Orthopedics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; †Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; ‡Applied Biological Sciences Program, Chulabhorn Graduate Institute, Bangkok, Thailand; §Laboratory of Biochemistry, Chulabhorn Research Institute, Bangkok, Thailand; ¶Excellence Center in Osteology Research and Training Center (ORTC), Chiang Mai University, Chiang Mai, Thailand

A

RTKs	pTyr-c-Kit	pTyr-VEGFR2	pTyr-c-Met	pTyr-HER2	pTyr-FGFR1	pTyr-PDGFRα
Patients	11/32	9/32	8/32	12/32	22/32	29/32
Percentage	34%	28%	25%	38%	69%	91%

Need for New Clinical Trial Design





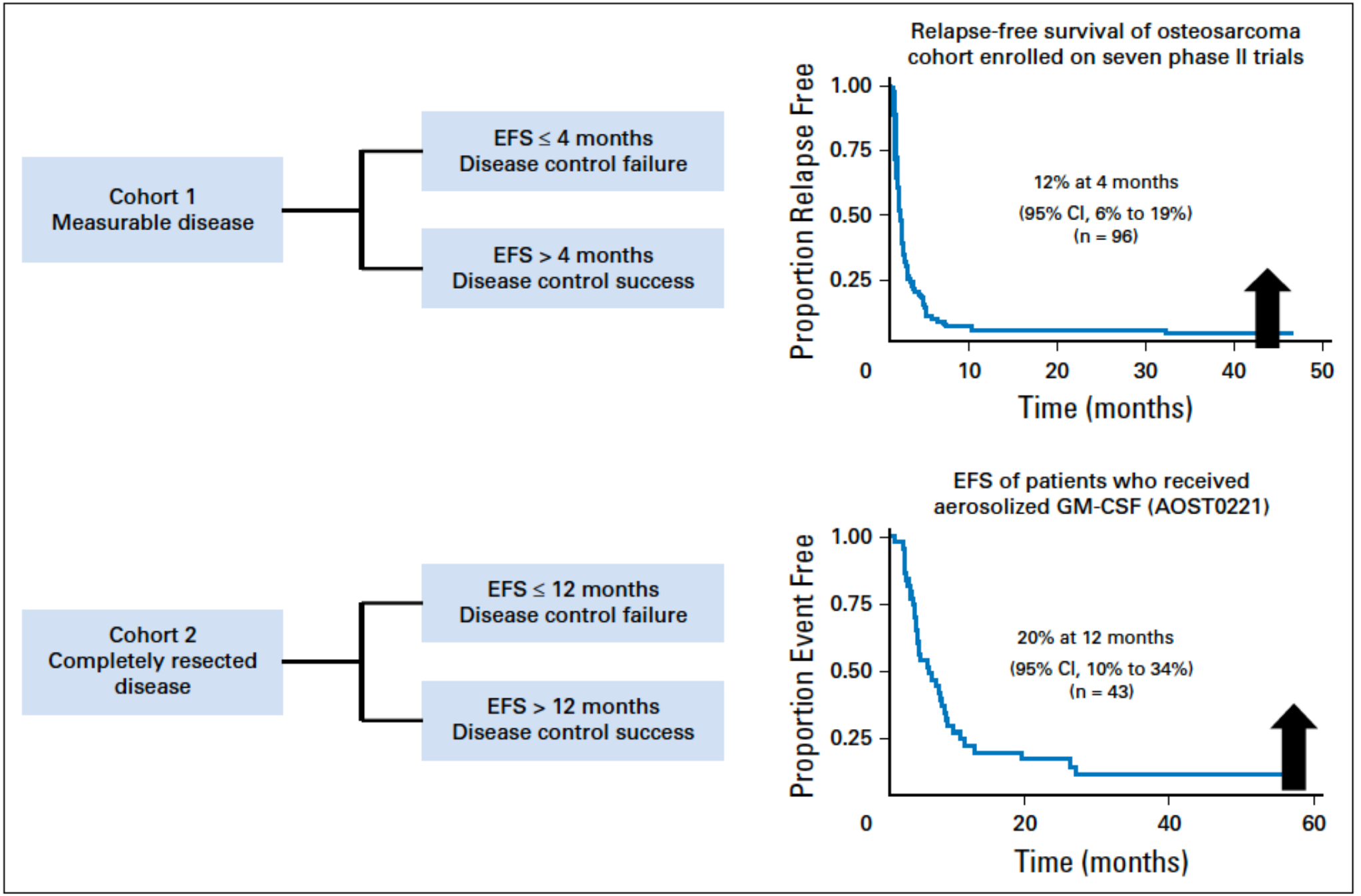


Fig 3. Future phase II osteosarcoma study design. EFS, event-free survival; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Lagmay JP et al. JCO 34:3031, 2016

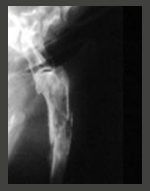
Comparative Approach

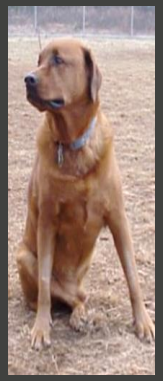
Toward improving our understanding of osteosarcoma biology

Rodent Models

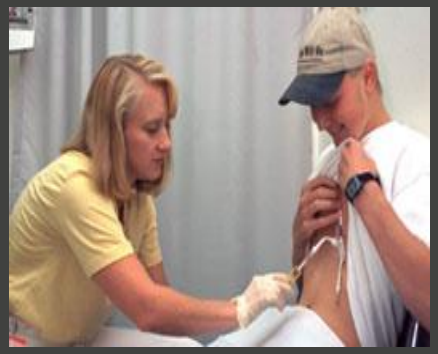
Genetically Engineered Models
Xenografts PDX models?

Canine Model
CCR – Comparative Oncology Program





How to use these models to inform/accelerate progress in human osteosarcoma



Improved Understanding of Biology and Improved Treatment Outcomes

New Treatment Approaches

- **Immunotherapy**
- **Targeted Therapy**

Publication of MTP in Canine OS-1989

J Natl Cancer Inst. 1989 Jun 21;81(12):935-8.

Therapy for osteosarcoma in dogs with intravenous injection of liposome-encapsulated muramyl tripeptide.

MacEwen EG[1], Kurzman ID, Rosenthal RC, Smith BW, Manley PA, Roush JK, Howard PE.

Author information

Abstract

Canine osteosarcoma is a spontaneous malignancy in dogs, characterized by micrometastasis to pulmonary and extrapulmonary tissues at the time of diagnosis. Standard treatment involves amputation of the affected leg, but median survival time is 3-4 months with death due to metastasis. A randomized double-blind trial was conducted to evaluate liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (liposome/MTP-PE) as a treatment for metastasis in dogs undergoing amputation for osteosarcoma. Fourteen dogs were treated with liposome/MTP-PE, and 13 were treated with empty liposomes. Median survival time was 222 days for dogs treated with liposome/MTP-PE, compared to 77 days for dogs treated with empty liposomes (P less than .002). In the liposome/MTP-PE-treated group there were still four dogs alive and free of metastasis at greater than 1 year post surgery. Treatment was well tolerated; no significant toxic effects were noted except for mild elevations in body temperature (1-2 degrees C) for 2-6 hours post injection.

Other Hints of Immune Responses to OS

- **Coley's Toxin**
  - Killed *Strep. Pyogenes and Serratia marcescens*
    - Studied for 70 years-cures reported in literature in many sarcoma patients, including OS, finally shut down by FDA in 1970s
    - Tumor regressions associated with fever induced by toxins

- **Dog limb-salvage studies**

Children's Hospital LOS ANGELES
CHILDREN'S CENTER FOR CANCER AND BLOOD DISEASES

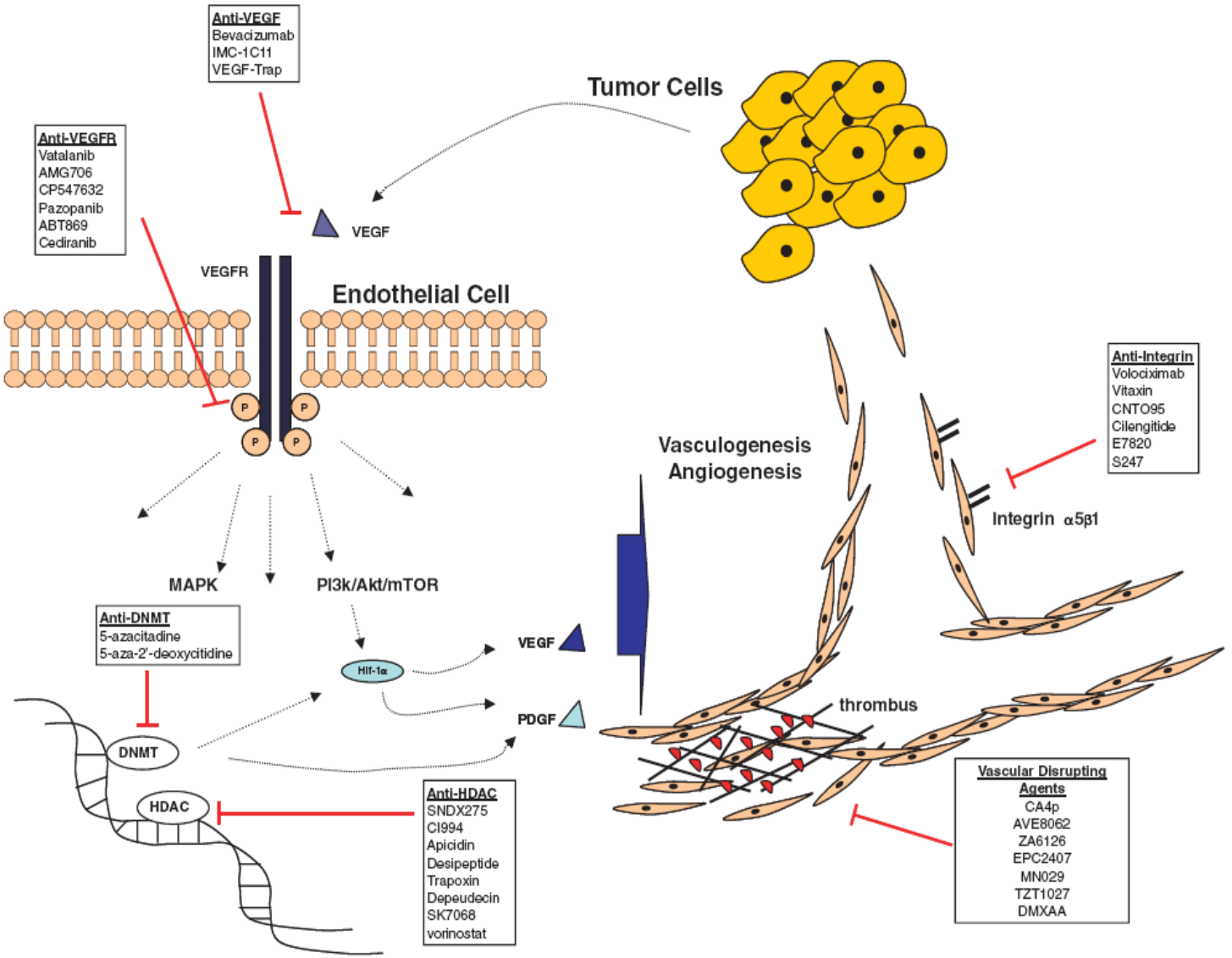
USC Norris Comprehensive Cancer Center
Keck Medicine of USC

osteosarcoma INSTITUTE

COG AOST 1822-Phase 2b Study

- **Advaxis developed vaccine, Osteosarcoma Therapeutics bought vaccine to conduct this study in collaboration with COG**
- **Using LM HER2 vaccine**
- **Primary objective: To determine whether ADX vaccine increases disease control at 12 months in patients with HER2-expressing, completely resected recurrent OS compared to historical controls**

Its Not Just the Tumor Cells



Olaparib With Ceralasertib in Recurrent Osteosarcoma

ClinicalTrials.gov Identifier: NCT04417062

Recruitment Status : Recruiting
First Posted : June 4, 2020
Last Update Posted : December 2, 2020

See **Contacts and Locations**

Sponsor:
Dana-Farber Cancer Institute

Collaborators:
Osteosarcoma Institute
AstraZeneca

Information provided by (Responsible Party):
Katherine Janeway, MD, Dana-Farber Cancer Institute

Trastuzumab Deruxtecan for the Treatment of HER2+ Newly Diagnosed or Recurrent Osteosarcoma

ClinicalTrials.gov Identifier: NCT04616560

Recruitment Status : Recruiting
First Posted : November 5, 2020
Last Update Posted : August 31, 2021

See **Contacts and Locations**

Oleclumab and Durvalumab for the Treatment of Recurrent, Refractory, or Metastatic Sarcoma (DOSa)

ClinicalTrials.gov Identifier: NCT04668300

Recruitment Status : Recruiting
First Posted : December 16, 2020
Last Update Posted : March 29, 2021

See Contacts and Locations

Sponsor:
M.D. Anderson Cancer Center

Condition or disease	Intervention/treatment	Phase
Metastatic Angiosarcoma Metastatic Dedifferentiated Liposarcoma Metastatic Osteosarcoma Recurrent Angiosarcoma Recurrent Dedifferentiated Liposarcoma Recurrent Osteosarcoma Refractory Dedifferentiated Liposarcoma Refractory Osteosarcoma	Biological: Durvalumab Biological: **Oleclumab**	Phase 2

Clinical Trial > J Clin Oncol. 2019 Jun 1;37(16):1424-1431. doi: 10.1200/JCO.18.02374.
Epub 2019 Apr 23.

Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma

Lara E Davis [1], Vanessa Bolejack [2], Christopher W Ryan [1], Kristen N Ganjoo [3], Elizabeth T Loggers [4], Sant Chawla [5], Mark Agulnik [6], Michael B Livingston [7], Damon Reed [8], Vicky Keedy [9], Daniel Rushing [10], Scott Okuno [11], Denise K Reinke [12], Richard F Riedel [13], Steven Attia [14], Leo Mascarenhas [15], Robert G Maki [16]

Affiliations + expand

PMID: 31013172 PMCID: PMC7799443 DOI: 10.1200/JCO.18.02374

Free PMC article

Abstract

Purpose: SARC024 is a phase II clinical trial of the multikinase inhibitor regorafenib in specific sarcoma subtypes, including advanced osteosarcoma. We hypothesized that regorafenib would improve progression-free survival (PFS) in patients with sarcoma and report the results of the osteosarcoma cohort.

Patients and methods: This trial enrolled patients with progressive metastatic osteosarcoma with measurable disease by RECIST who had received at least one prior line of therapy. Patients were randomly assigned at a ratio of one to one to regorafenib or placebo. Crossover was allowed at time of disease progression. PFS was the primary end point of the study, which was powered to detect a difference of at least 3 months in median PFS.

Conclusion: The study met its primary end point, demonstrating activity of regorafenib in patients with progressive metastatic osteosarcoma. No new safety signals were observed. Regorafenib should be considered a treatment option for patients with relapsed metastatic osteosarcoma.

Clinical Trial > Lancet Oncol. 2019 Jan;20(1):120-133. doi: 10.1016/S1470-2045(18)30742-3. Epub 2018 Nov 23.

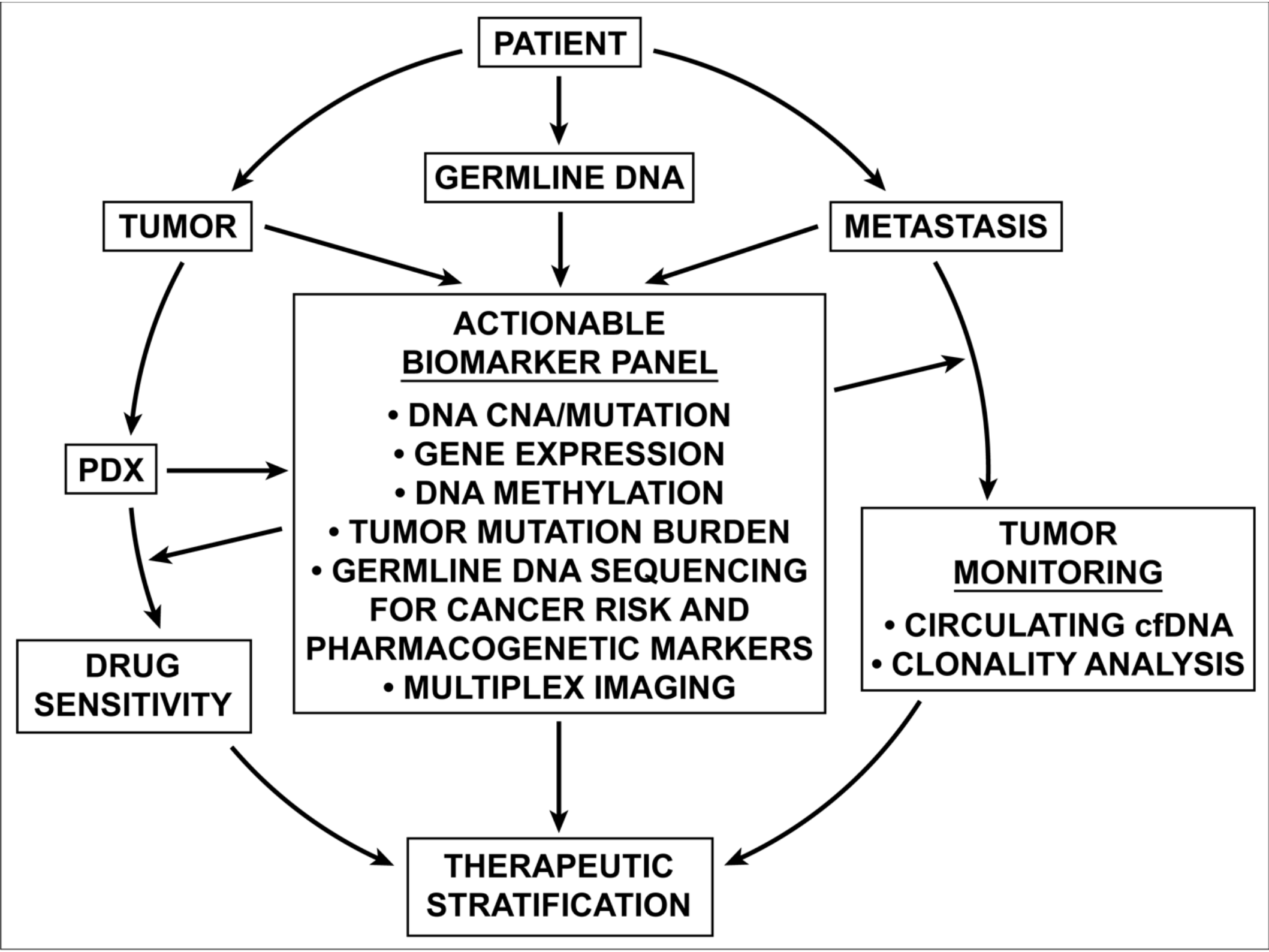
Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study

Florence Duffaud [1], Olivier Mir [2], Pascaline Boudou-Rouquette [3], Sophie Piperno-Neumann [4], Nicolas Penel [5], Emanuelle Bompas [6], Corinne Delcambre [7], Elsa Kalbacher [8], Antoine Italiano [9], Olivier Collard [10], Christine Chevreau [11], Esma Saada [12], Nicolas Isambert [13], Jessy Delaye [14], Camille Schiffler [15], Corinne Bouvier [16], Vincent Vidal [17], Sylvie Chabaud [15], Jean-Yves Blay [18], French Sarcoma Group

Interpretation: Regorafenib demonstrated clinically meaningful antitumour activity in adult patients with recurrent, progressive, metastatic osteosarcoma after failure of conventional chemotherapy, with a positive effect on delaying disease progression. Regorafenib should be further evaluated in the setting of advanced disease as well as potentially earlier in the disease course for patients at high risk of relapse. Regorafenib might have an important therapeutic role as an agent complementary to standard cytotoxic chemotherapy in the therapeutic armamentarium against osteosarcoma.

Conclusions

- **Identification of molecular alterations in specific sarcoma subtypes is leading to novel therapeutic options**
- **It is likely that as with chemotherapy, combinations of targeted agents will be necessary for long term benefit**
- **Opportunities for immunotherapy also exist, and should be considered in combinations**
- **Targeting rare subsets of rare tumors will require novel trial designs**


PATIENT
GERMLINE DNA
TUMOR
METASTASIS
ACTIONABLE
BIOMARKER PANEL
• DNA CNA/MUTATION
• GENE EXPRESSION
• DNA METHYLATION
• TUMOR MUTATION BURDEN
• GERMLINE DNA SEQUENCING
FOR CANCER RISK AND
PHARMACOGENETIC MARKERS
• MULTIPLEX IMAGING
PDX
DRUG
SENSITIVITY
TUMOR
MONITORING
• CIRCULATING cfDNA
• CLONALITY ANALYSIS
THERAPEUTIC
STRATIFICATION

Much Work Ahead

- **Accelerate pace of drug discovery and development**
- **Advance conduct of rationally based combination clinical trials**
- **Integrate and leverage use of advanced biomedical technologies**
- **Optimize use of information technology**
  - Make data accessible to all- to interrogate science-based tumor profiles and treatment options
- **Standardize biospecimen collection approaches**
- **Work with industry to facilitate IP issues**

osteosarcoma INSTITUTE concentrating on the cure