Osteosarcoma: New Treatments/Research

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Adjunct Clinical Professor of Pediatrics, Cancer and Blood Disease Institute, CHLA, Keck School of Medicine, USC
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
Multiple 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
for almost 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 might 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
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)
IGF1R amplification in OS


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

Behjati S1,2,3, Tarpey PS1, Haase K4, Ye H5, Young MD1, Alexandrov LB6, Farndon SJ1,7, Collord G1, Wedge DC6, Martincorenna I1, Cooke SL1, Davies H1, Mifsud W7, Lidgren M1, Martin S1, Latimer C1, Maddison M1, Butler AP1, Teague JW1, Pillay N5,9, Shlien A10, McDermott U1, Futreal PA1,11, Baumberger D12, Zaikova O13, Bjerkehagen B13, Myklebost O13,14, Amery MF5, Tirabosco R5, Van Loo P4,15, Stratton MR1, Fianangan AM5,9, Campbell PJ1,16.

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.
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

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

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

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
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
It's Not Just the Tumor Cells
Olaparib With Ceralasertib in Recurrent Osteosarcoma

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

**Sponsor:**
Dana-Farber Cancer Institute

**Collaborators:**
Osteosarcoma Institute
AstraZeneca

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

ClinicalTrials.gov Identifier: NCT04417062

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

See Contacts and Locations
Trastuzumab Deruxtecan for the Treatment of HER2+ Newly Diagnosed or Recurrent Osteosarcoma

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

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)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
M.D. Anderson Cancer Center

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ClinicalTrials.gov Identifier: NCT04668300

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

See Contacts and Locations
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: SARCO24 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.
Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study

Florence Duffaud, Olivier Mir, Pascaline Boudou-Rouquette, Sophie Piperno-Neumann, Nicolas Penel, Emanuelle Bompas, Corinne Delcambre, Elsa Kalbacher, Antoine Italiano, Olivier Collard, Christine Chevreaux, Esma Saada, Nicolas Isambert, Jessy Delaye, Camille Schiffler, Corinne Bouvier, Vincent Vidal, Sylvie Chabaud, Jean-Yves Blay, 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
ACTIONABLE BIOMARKER PANEL
- DNA CNA/MUTATION
- GENE EXPRESSION
- DNA METHYLATION
- TUMOR MUTATION BURDEN
- GERMLINE DNA SEQUENCING FOR CANCER RISK AND PHARMACOGENETIC MARKERS
- MULTIPLEX IMAGING

TUMOR MONITORING
- CIRCULATING cfDNA
- CLONALITY ANALYSIS

DRUG SENSITIVITY

THERAPEUTIC STRATIFICATION

PATIENT

GERMLINE DNA

TUMOR

METASTASIS

PDX
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