FDA/OSI WORKSHOP:

Advancing Osteosarcoma Drug Development – Connecting Research and Regulatory Pathways for Improved Outcomes

Friday, October 10, 2025
9:30am – 5:00pm Eastern Time

Lincoln Square
555 Eleventh Street NW
Washington, DC 20004

And via Zoom Webinar

FDA

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Welcome

Opening Remarks & Introduction

9:30 – 9:45 AM

Lee Helman, MD (OSI)
Martha Donoghue, MD (FDA)
Nicole Drezner, MD (FDA)

Workshop Goals

1. To convene key stakeholders to share perspectives on the challenges to, and identify opportunities for, advancing clinical development of therapies for osteosarcoma through collaboration and communication.

2. To identify opportunities to increase efficiency within osteosarcoma drug development.

3. To develop strategies to address the most significant challenges in clinical trials design and implementation in osteosarcoma.

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Agenda

9:30 – 9:45 AM	Opening Remarks and Introduction to the Workshop
9:45 – 10:15 AM	SESSION 1: Patient and Advocate Insights
10:15 – 11:00 AM	SESSION 2: Clinical and Regulatory Landscape
11:00 – 11:20 AM	SESSION 3: Targeting Osteosarcoma
11:20 – 11:45 AM	Break
11:45 AM – 12:45 PM	SESSION 4: Trial Design and Endpoints in Osteosarcoma
12:45 – 1:30 PM	SESSION 5: Attendee and Panelist Question and Answer
1:30 – 2:15 PM	Lunch
2:15 – 3:00 PM	SESSION 6: A Fireside Chat – Changing the Landscape of Pediatric Cancer with Legislation
3:00 – 4:00 PM	SESSION 7: The Path Forward
4:00 – 4:45 PM	SESSION 8: Attendee and Panelist Question and Answer
4:45 – 5:00 PM	Closing Remarks and Adjourn

Housekeeping

- Workshop speakers will not be able to address individual patient questions regarding treatment.
- **OSI Connect** is a free, easy-to-use resource dedicated to supporting osteosarcoma patients and their families.

www.osinst.org/osi-connect

Housekeeping

- Questions during the workshop
  - Please state your name, organization, and the intended speaker (if specific)
  - Virtual attendees – Submit a question by using the “Q&A” tab at the bottom of your Zoom screen
  - Some questions may not be answered due to time and confidentiality constraints

- FDA Disclaimers
  - FDA staff have no financial relationships to disclose
  - No discussion of specific product development plans or off-label/investigational use
  - No formal advice will be provided
  - Views expressed are those of individual speakers, not official FDA positions

- Photography – Photos may be taken during the workshop. Please notify OSI staff if you prefer not to be photographed.

- **Slides and recording will be available after the event**

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Session 1

Patient & Advocate Insights

9:45 – 10:15 AM

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Session 1

Moderator: Mac Tichenor (OSI)	
Mikaela Naylon	MIB Agents 2025 Junior Advisory Board
MacKenzie Maddry	MIB Agents 2025 Junior Advisory Board
Ann Graham	MIB Agents
Justin Ingram, PhD	Alex's Lemonade Stand Foundation
Michael Egge, Esq.	Osteosarcoma Collaborative/OSI

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Session 2

Clinical & Regulatory Landscape

10:15 – 11:00 AM

Amanda Marinoff, MD (UCSF)
Jasmine Smith, MD (FDA)

UCSF Benioff Children's Hospitals

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Overview of current therapy and ongoing clinical trials for osteosarcoma

FDA/The Osteosarcoma Institute (OSI) Workshop: Advancing Osteosarcoma Drug Development – Connecting Research and Regulatory Pathways

October 10, 2025

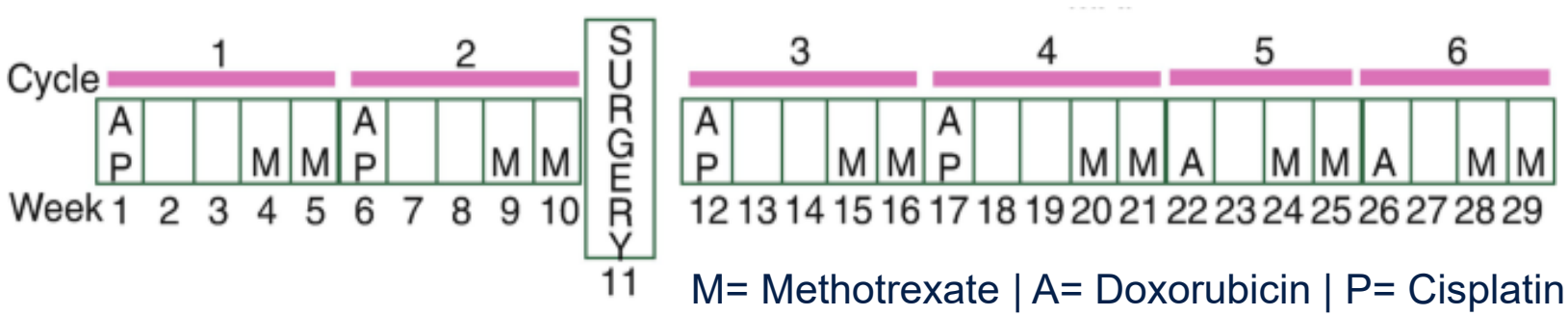
Amanda Marinoff, MD
Assistant Professor
University of California San Francisco

Disclosures

- I have no financial conflicts of interest.
- I have no relevant relationships to disclose.

Current treatment for osteosarcoma

- **Newly diagnosed:** Multi-agent intensive chemotherapy + surgery; no risk- or biology-adapted approach
- **Outcomes:** 5-yr overall survival (OS): 65-70% (localized); 5-30% (metastatic)[1-4]
- **Refractory/recurrent (R/R):** Salvage therapies are rarely curative; <20% long-term survivors[5]

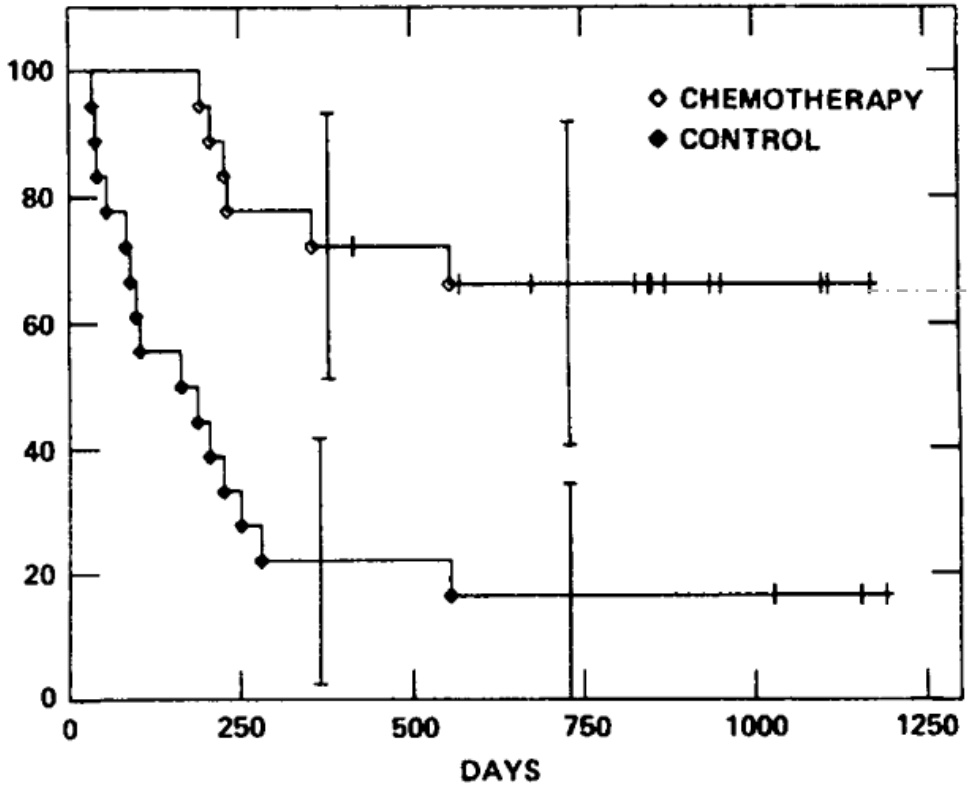


M= Methotrexate | A= Doxorubicin | P= Cisplatin

1 Smeland et. al, 2019
2 Kager et. al, 2003
3 Meyers et. al, 1993, 2016
4 Bielack et. al, 2002
5 Lagmay et. al, 2016

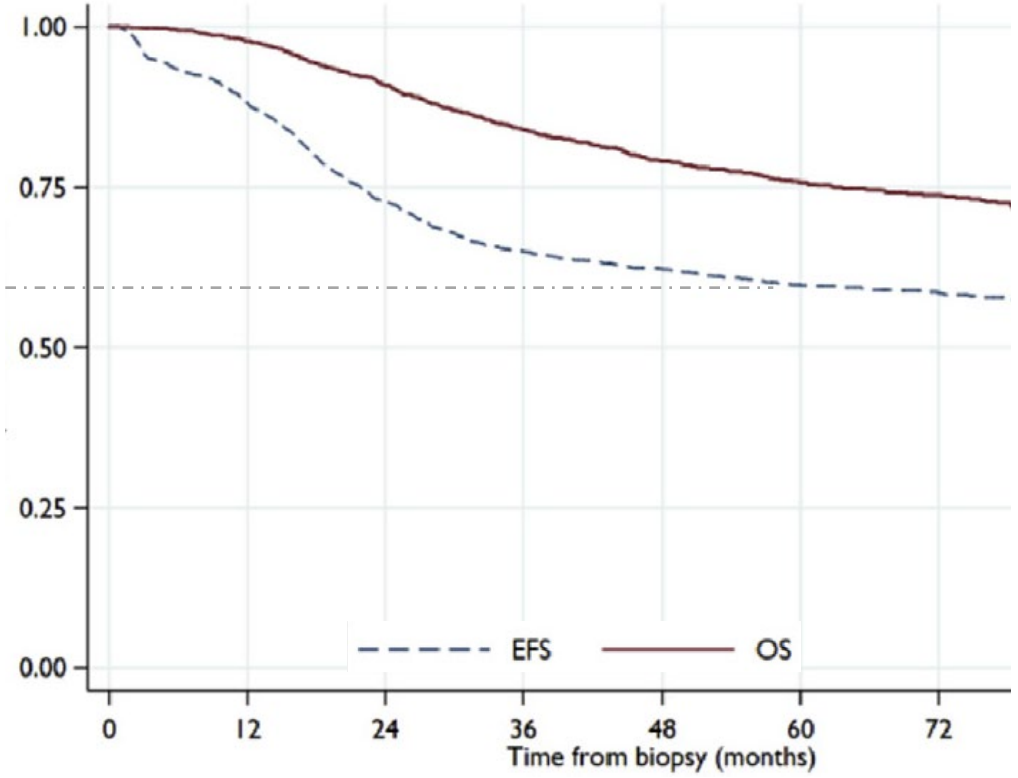
Survival has not improved in four decades

1986: 66% 3y EFS[1]



6 drug regimen x 45 weeks

2019: 65% 3y EFS[2]



3 drug regimen x 31 weeks

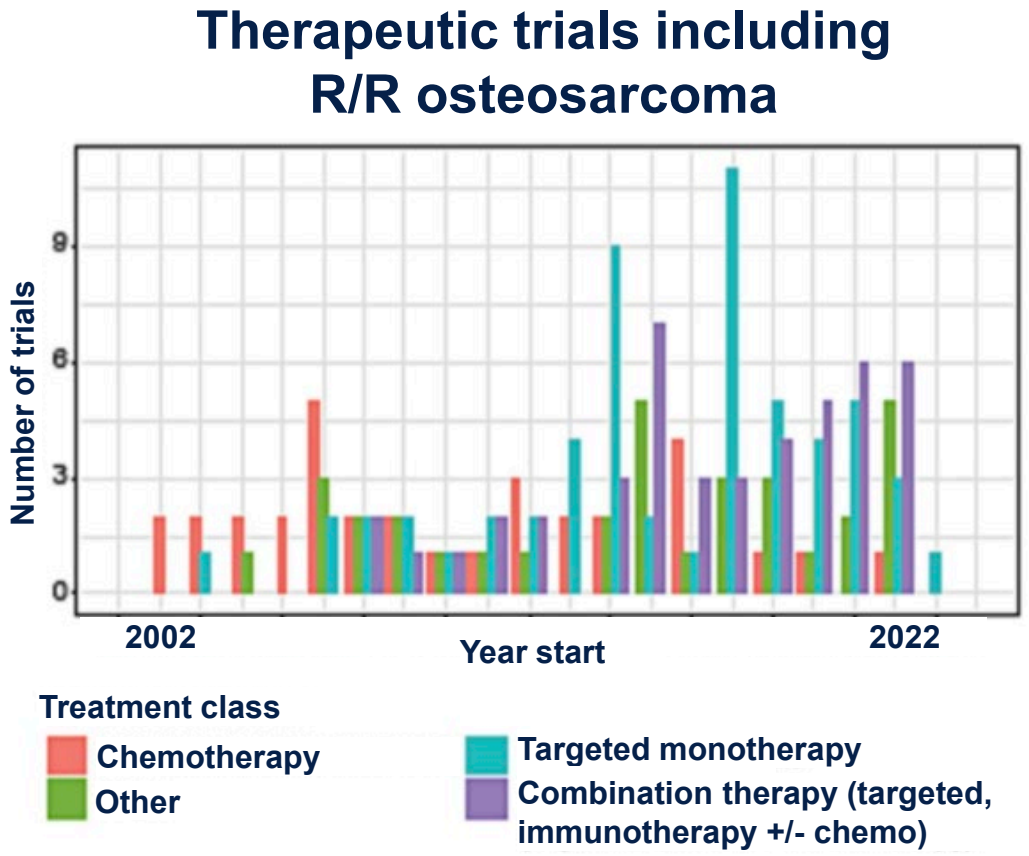
[1] Link et al. *N Engl J Med*, 1986
[2] Smeland et al, *European Journal of Cancer* 2019

Key barriers to progress

- Rare disease + young population challenge trial feasibility
- Clinical and biological heterogeneity
- Limited access to novel agents
- No validated prognostic or predictive biomarkers
- Scarce longitudinal biospecimens and poorly understood resistance mechanisms
- Endpoints are inconsistent across trials

What's changed in the phase II trial landscape over the last decade?

- Majority of trials included patients age <12y
- Osteosarcoma-specific endpoints more common
- Shift toward targeted therapies and immunotherapy



Adapted from R. van Ewijk et al, 2023

What hasn't changed?

- **Most trials fail to show benefit**
  - Only 20% met their primary efficacy endpoint
  - Median ORR: 5.3%
  - Median PFS: ~3 months; median OS: ~10 months
- **Trial design geared toward signal finding, not regulatory approval**
  - 90% single-arm, 62% monotherapy
  - Median enrollment: 18 patients/trial
  - Variation in design, endpoints, eligibility requirements

R. van Ewijk et al, 2023
Abbreviations: ORR: overall response rate; PFS: progression-free survival; OS: overall survival

Review of ongoing clinical trials

- Chemotherapy and surgery
- Multi-tyrosine kinase inhibitors (mTKIs)
- Immune checkpoint inhibition
- Immune modulatory agents
- Adoptive cellular therapy
- Antibody drug conjugates (ADC)
- DNA damage repair (DDR) inhibitors
- Targeted inhibitors

Review of ongoing clinical trials

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Completed phase II single-agent mTKI trials for R/R osteosarcoma

	Sorafenib[1]	Apatinib[2]	Regorafenib[3,4*]		Cabozantinib[5]
Key targets	VEGFR2/3 Raf	VEGFR1/2, SRC, c-KIT, RET	VEGFR1/2/3, PDGFRβ, c-KIT, RET		VEGFR1/2/3, MET, c-KIT, RET
N	35	37	26[3]	22[4]	42
ORR	8% (3 PR)	43% (16 PR)	8% (2 PR)	14% (3PR)	12% (5 PR)
Median PFS†	4.0	4.5	3.6	3.8	6.7
4-mo PFS	**46%**	**57%**	**35%**	**44%**	**71%**

*Randomized, placebo-controlled trials; all others single-arm studies in R/R, unresectable osteosarcoma; † in months

All studies met their primary efficacy endpoints.

[1]Grigani et al, 2012
[2] Xie et. al, 2019
[3]Duffaud et al, 2019 (REGOBONE)
[4]Davis et al, 2019 (SARC024)
[5]Italiano, et. al 2020 (CABONE)

Completed phase II combination trials with mTKIs (excluding IO)

Agents	Population	Outcomes in osteosarcoma
Sorafenib + Everolimus[1]	R/R osteosarcoma *(n=38)*; ≥18y	6-mo PFS 45%; ORR 13% (5 PR)
Pazopanib + Topotecan[2]	R/R STS, exploratory osteosarcoma cohort *(n=15)*; ≥18y	3-mo PFS 70%; ORR 13% (2PR)
Ifosfamide/Etoposide ± Lenvatinib[3*]	R/R osteosarcoma *(n=81)*; age 2-25	4-mo EFS 62% v. 61%; ORR 13% v. 8%

*Randomized controlled trial; all others single-arm

Combination mTKIs show modest activity in small single-arm studies.
In a randomized trial, adding lenvatinib to chemo did <u>not</u> improve EFS.

[1] Grigiani et al, 2014
[2] Schulte et. al, 2021
[3] Gaspar et. al, 2024

Active mTKI trials

Regimen	Phase	Population
MAP ± cabozantinib[1]	II/III	Newly diagnosed osteosarcoma; <40y
Ifosfamide + cabozantinib[2]	I	R/R Ewing sarcoma and osteosarcoma; 5-40y
Cabozantinib maintenance[3]	II	Unresectable osteosarcoma (at diagnosis/ first relapse); ≤30y
Cabozantinib maintenance[4]	II	High risk pediatric solid tumors with resected disease; 5-30y
Sunitinib + losartan[5]	I/Ib	R/R osteosarcoma; ≥10y
Atezolizumab + cabozantinib[6]	II	R/R osteosarcoma; ≥12y
Zanzalitinib[7]	II	R/R bone tumors ≥18y

[1]NCT05691478 [4]NCT05135975 [7]NCT07193550
[2]NCT06156410 [5]NCT03900793
[3]NCT06341712 [6]NCT05019703

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

AOST2032: A feasibility and randomized phase 2/3 study of cabozantinib + MAP for newly diagnosed osteosarcoma

Non-randomized:
high-risk only

Randomized:
standard-risk and high-risk

Primary endpoints: **feasibility and EFS**

Standard-risk: localized, resectable
High-risk: metastatic, pelvic and/or unresectable

NCT05691478

UCSF Benioff Children's Hospitals

Pediatric Strategy Forum on mTKIs
Key Conclusions

- Predictive biomarkers are poorly understood.
- Ideal characteristics of mTKIs are not defined.
- Trials should include children, adolescents, and adults when biology is shared.
- Feasibility *and* combination treatment should be evaluated within the same protocol as a randomized trial when feasible.
- Trials should be designed to support regulatory and payer requirements.

Pearson et. al, 2022
ACCELERATE in collaboration with the EMA with participation of the FDA

Review of ongoing clinical trials

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- **Immune checkpoint inhibition**
- Immune modulatory agents
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Completed trials of single-agent immune checkpoint inhibitors

Agent (target)	Phase	Population	Outcomes
Nivolumab (PD-1)[1]	I/II	Advanced solid tumors; ≤30y (n=85)	No responses
Pembrolizumab (PD-1)[2]	II	PD-L1+ advanced solid tumors/ lymphoma; ≤30y (n=154)	No responses*
Pembrolizumab (PD-1)[3]	II	R/R osteosarcoma; ≥18y (n=12)	No responses
Atezolizumab (PD-1)[4]	I/II	Advanced solid tumors; <30y (n=90)	Safe, minimal efficacy
Avelumab (PD-L1)[5]	II	R/R osteosarcoma, age 12-50 (n=18)	No responses

*except in lymphoma and 1PR in GBM with microsatellite instability

Single-agent checkpoint inhibitors are safe but have minimal efficacy.

[1]NCT02304458 (ADVL1412), Davis et al., 2020
[2]NCT02332668 (KEYNOTE-051), Pappo et al., ASCO, 2025
[3]NCT03013127 (PROMO), Boye et al., 2021
[4]NCT02541604 (iMATRIX), Geoerger et al., *Lancet*, 2020
[5]NCT03006848 (OSTPDL1), Bishop et al., ASCO, 2020

Completed immune checkpoint inhibitor combination trials

Agents (target)	Phase	Population	Outcomes in osteosarcoma
Nivolumab (PD1) ± Ipilimumab (CTLA4)[1]	I/II	Advanced solid tumors; ≤30y (n=13/85)	No responses
Nivolumab (PD1) + Sunitinib (mTKI)[2*]	II	Bone sarcomas; ≥18y (n=17/40)	2 PR (1 lasting > 1yr)
Camrelizumab (PD1) + Apatinib (mTKI)[3]	II	R/R osteosarcoma; ≥11y (n=43)	51% EFS at 6 mo
Nivolumab (PD1) + Regorafenib (mTKI)	II	R/R osteosarcoma (n=20); ≥5y	4mo PFS 40%; 2 PR, 5 SD

* Only study that met primary efficacy endpoint (EFS>15%) but 17/40 discontinued treatment due to toxicity

Modest activity with combination of PD1 blockade + mTKI; some patients may benefit

[1]NCT02304458 (ADVL1412), Davis et al., 2022
[2]NCT03277924 (IMMUNOSARC), Palmerini et. al, 2025
[3]NCT03359018 Xie et. al, 2020
[4]NCT04803877 (SARC 038), Navid F, Davis L, et. al, CTOS 2023

Active immune checkpoint inhibitor trials

Agents (target)	Phase	Population
Atezolizumab (PD-L1) + cabozantinib(mTKI)[1]	II	R/R osteosarcoma; ≥12y
Pembrolizumab (PD-1) + cabozantinib (mTKI)[2]	II	Advanced sarcomas, ≥18y
Oleclumab (CD73) + durvalumab (PD-L1)[3]	II	R/R or metastatic sarcomas; ≥12y
Nivolumab ± azacitidine[4]	II	Resectable R/R osteosarcoma; any age
Atezolizumab (PD-L1) + SBRT[5]	I	Pulmonary-only osteosarcoma relapse; ≤50y

SBRT= sterotactic body radiation therapy

[1] NCT05019703 (TACOS)
[2] NCT05182164 (PEMBROSARC)
[3] NCT04668300 (DOSa)
[4] NCT03628209
[5] NCT06492954

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Completed trials of immune modulatory agents

Agent	Trial (Phase)	Population	Outcome
IFN-α-2b +MAP	EURAMOS-1 (III)[1]	Newly diagnosed good responders	No EFS benefit compared to adjuvant MAP alone[1]
Aerosolized GM-CSF	AOST0221 (II)[2]	Recurrent pulmonary osteosarcoma	Feasible, no efficacy[2]
Mifamurtide (L-MTP-PE) + MAP (+ifosfamide in some cases)	INT0133 (III)[3] ISG/OS2 (II)[4] GEIS-33 (IV)[5] SARCOME-13 (II)[6]	Newly diagnosed localized osteosarcoma	▪ EFS not met, OS benefit[3*] ▪ Improved EFS[4,5†] ▪ SARCOME-13: results pending[6]

*led to EMA approval; †univariate analysis only

[1] Bielack et. al, JCO, 2015
[2] Arnt et. al, Cancer Res, 2011
[3] Meyers et. al, JCO, 2005 & 2008
[4] Palmerini et. al, JCO, 2025
[5] Braird et. al, BMC Open, 2019

Active trials of immune modulatory agents

Agent	Phase	Population
Aerosol aldesleukin (IL-2)[1]	I/II	Osteosarcoma cohort with lung metastases; age 12-50
OST31-164 (Listeria-HER2 vaccine)[2]	II	Resected R/R pulmonary osteosarcoma; age 12-39
Vactosertib (TGFβi)[3]	I/II	R/R osteosarcoma; ≥12y
RNA-lipid particle vaccine[4]	I/II	R/R osteosarcoma and pHGG; age 3-39
CRD3874-SI[5] (STING agonist)	Ia/b	Advanced sarcoma, Merckel cell carcinoma; ≥18y

[1]NCT01590069
[2]NCT04974008
[3]NCT05588648
[4]NCT05660408
[5]NCT06021626

Review of ongoing clinical trials

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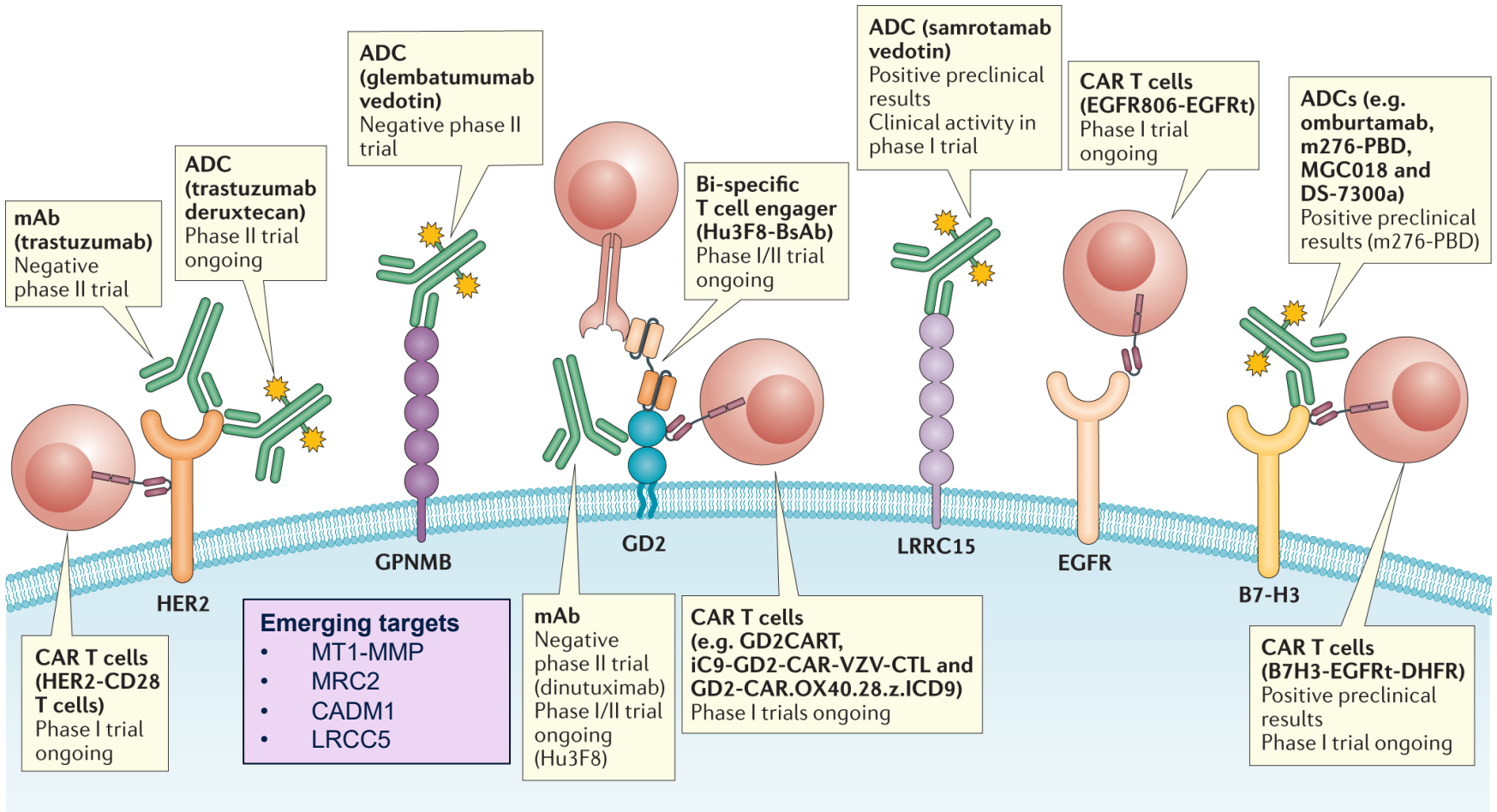
Strategies targeting the osteosarcoma surfaceome



adapted from Gorlick and Gill, *Nature Rev,* 2021

Recent ADC trials

Agent (Target)	Phase	Population	Key Outcomes
Glembatumumab vedotin (gpNMB)[1]	II	R/R osteosarcoma (n=22); 12-50y	1PR, 2 SD
Trastuzumab deruxtecan (HER2-DXd)[2]	II	R/R osteosarcoma (n=9); 12-39y	No responses (1 SD); halted for futility
ABBV-085 (LRRC15)[3]	I	Advanced solid tumors; ≥18y (n=10)†	Safe and tolerable; 4PRs‡
Mecbotamab vedotin (CAB-AXL-ADC)[4]	I/II	Advanced sarcomas; (n=11)†	3mo PFS 45.5%; mPFS 2.8mo; 2 PRs
HS-20093* (B7-H3)[5]	II	R/R sarcomas (n=34)†	2PRs#, 100% (10/10)#

*Ongoing trial. †Osteosarcoma cohort. ‡Osteosarcoma + UPS cohort; # 12mg/kg dose, median follow-up 4mos
Abbreviations: PR = partial response; SD = stable disease; mPFS = median PFS; DCR = disease control rate

Early-phase ADCs against select surfaceome targets show promise and warrant continued clinical evaluation.

[1] Kopp et. al, 2019
[2] Reed et. al, ASCO, 2023
[3] Demetri et. al, 2021
[4] Pollack et. al, ESMO, 2024; NCT03425279
[5] Xie et. al, ASCO, 2024; NCT05830123

Active chimeric antigen receptor (CAR) therapy trials

Agent (Target)	Phase	Population
GD2 CART[1]*	I	R/R osteosarcoma and neuroblastoma
B7-H3 CART[2]*	I/II	Advanced solid tumors; ≤26y
EGFR806[3]	I	Advanced EGFR+ solid tumors; 1-30y
FITC-E2-CART + folate-fluorescein (UB-TT170)[4]	I	R/R osteosarcoma; 15-30y
CAR.70 / IL-15 cord blood-derived NK cells[5]	I	Advanced CD70+ osteosarcoma, mesothelioma, RCC; 16-80y

*Feasible and safe, limited responses to date, ongoing correlative biology[1,2]

[1]NCT04539366 (GD2-CART PERSIST), Kaczanowska, et. al, 2024
[2]NCT04483778 (STRIvE02), Pinto et. al, 2024
[3]NCT04483778 (STRIvE01), Albert et. al, ASCO, 2022
[4]NCT05312411 (ENLIGHten-01), Albert et. al, ASCO, 2022
[5]NCT05703854

Other active cellular therapy trials

Agent	Phase	Population
Autologous tumor infiltrating lymphocytes[1]	I/II	Advanced solid tumors; ≤21y
AttIL12-T-cell therapy[2]	I	Advanced sarcomas; ≥12y
Donor NK cells + gemcitabine/docetaxel[3]	II	Advanced sarcomas; 2-40y
CRX100 (NKT-cell therapy) ± pembrolizumab[4]	I	Advanced solid tumors; ≥18y
Donor immune cells* + dinutuximab + chemo[5]	I	Advanced osteosarcoma and neuroblastoma:; ≥1y
Afamitresgene autoleucel (MAGE A4 TCR therapy)[6]	I/II	Advanced MAGE-A4 positive solid tumors; 2-21y

*Allogenic Ex Vivo Expanded Gamma Delta T Cells; Abbreviations: AttL12: T-cell membrane-anchored tumor targeted IL12; NK: natural killer; TCR: T-cell receptor therapy ; RNA-LP: ribonucleic acid lipid nanoparticle; pHGG: pediatric high-grade glioma

[1] NCT03449108
[2] NCT05621668
[3] NCT05634369 (TINKS)
[4] NCT04282044
[5] NCT05400603
[6] NCT05642455 (Spearhead-03)

Summary of immunotherapy approaches in ongoing trials

Checkpoint inhibitors	Immune modulators	Cellular therapy
• Atezolizumab (PD-1) + cabozantinib • Oleclumab (CD37) + durvalumab (PD-L1) • Nivolumab (PD-1) ± azacitidine[3] • Atezolizumab + SBRT	• Listeria-HER2 vaccine • Vactosertib (TGFβi) • RNA-LP vaccine • CRD3874-SI (STING agonist)	• GD2 CART • B7-H3 CART • EGFR806 CART • FITC-E2-CART • CAR.70/IL-15 CB NK cells • Afami-cel (MAGE-4) • Tumor infiltrating lymphocytes • AttIL12-T cell therapy • Donor NK cells + gemcitabine/docetaxel • CRX100 (NKT-cell therapy) +/- pembro • Donor Immune Cells, Dinutuximab, irino/tem, zolendronate

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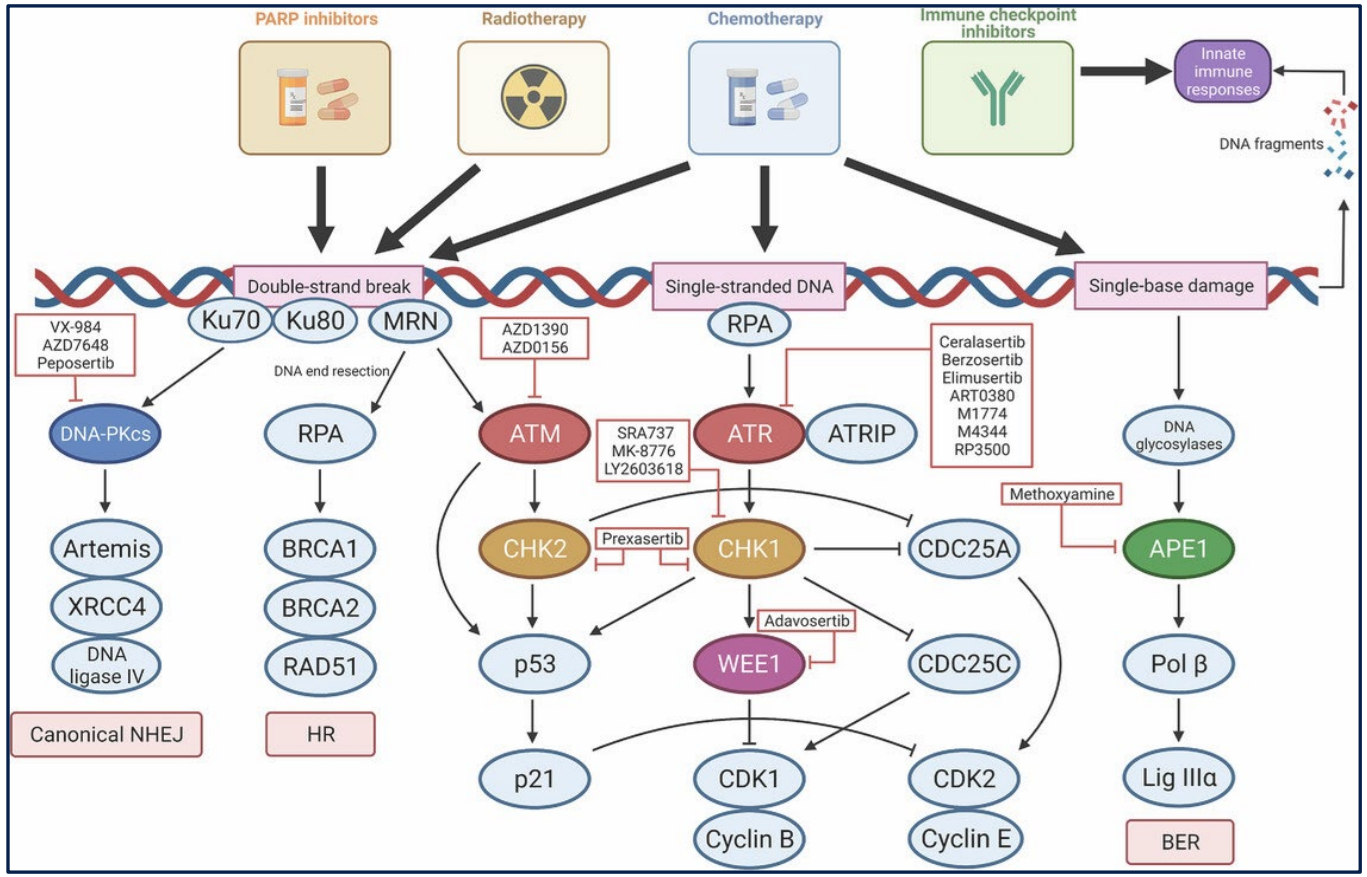
Targeting the DNA damage response (DDR)



"BRCA-like" biology in osteosarcoma suggest opportunities to drug DDR[1-3]

Chen et. al, 2022

[1] Kovac et. al, 2015
[2] Barenboim et. al, 2021
[3] Kinnaman et. al, 2022 (ASCO)

Recent trials targeting DDR in osteosarcoma

Agent(s)	Phase, N	Key Outcomes
Olaparib (PARPi) + Ceralasertib (ATRi)[1]	Phase II, 37 (measurable disease cohort)	4-mo EFS 13.5%; 1 PR
ZN-c3 (WEE1i) + Gemcitabine[2]	Phase I/II, 31	Well tolerated; 18-wk EFS 39%

- Ongoing efforts to develop new trials targeting DDR and explore predictive biomarkers
- Key determinant of agents selected for future trials = **access**

[1]NCT04417062; Forrest et, al, ASCO 2025
[2]NCT04833582; Avutu et. al, ASCO 2024

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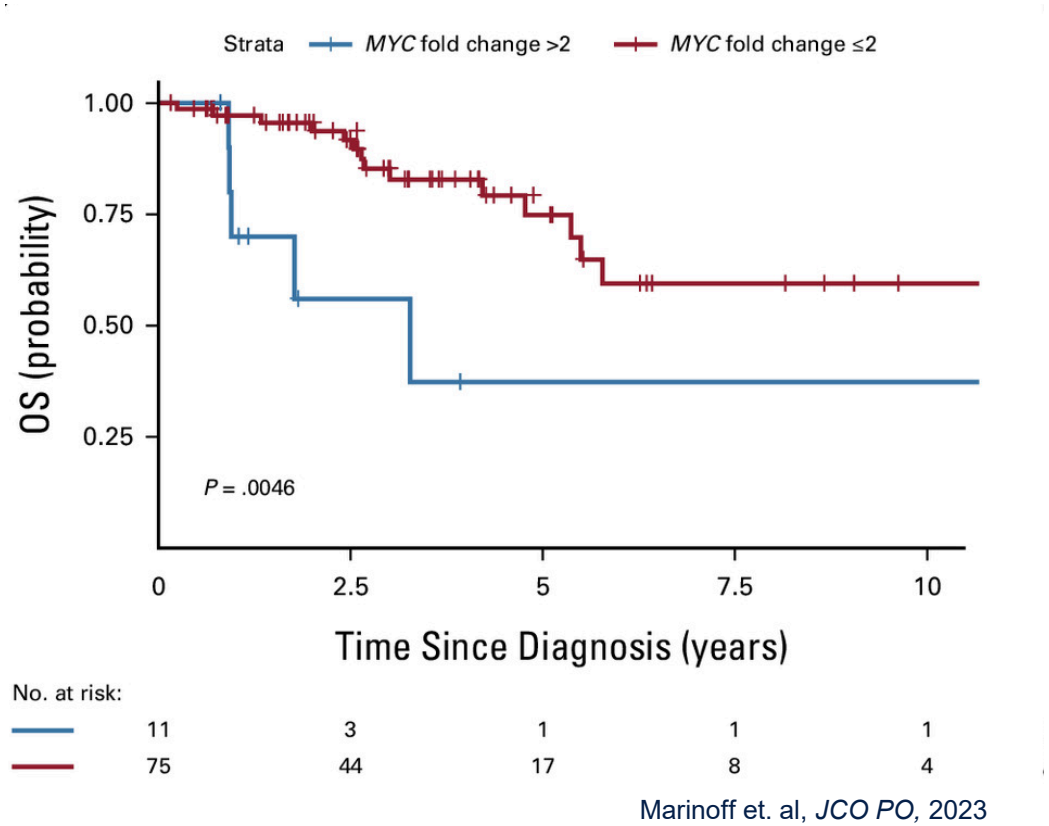
Active trials of targeted inhibitors

Agent (Target)	Phase	Population
Abemaciclib (CDK4/6)[1]	II	Sarcoma with CDK pathway alterations; ≥18y
Tegavivint (Wnt pathway)[2]	I/II	R/R solid tumors; 1–30y
Tegavivint (Wnt) + gemcitabine[3]	I	R/R osteosarcoma; 1–30y
OMO-103 (MYC)[4]	II	R/R osteosarcoma; ≥12y

[1] NCT03310879
[2] NCT07144254; Whittle et. al, ASCO, 2023
[3] NCT07144254
[4] NCT06650514

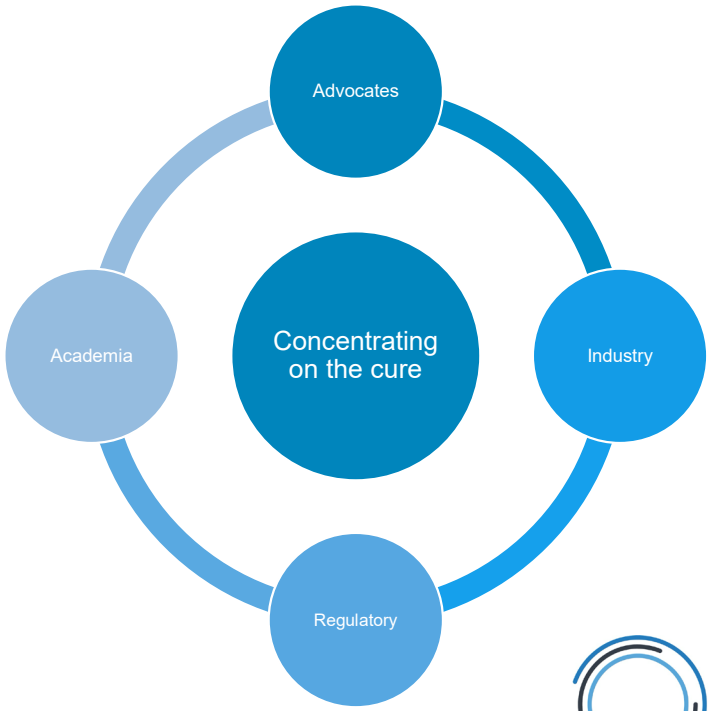
Multi-stakeholder partnerships enable the OSTEOMYC trial*

MYC-activated osteosarcoma is associated with poor prognosis[1-7]



Marinoff et. al, *JCO PO,* 2023

*Phase II pilot study of OMO-103 in advanced osteosarcoma



PEPTOMYC

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*NCT06650514

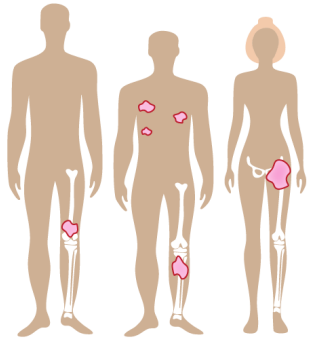
[1] Marinoff et. al, 2023.
[2] Smida et. al, 2010
[3] Meltzer et. al, 2020
[4] De Noon et. al, 2021
[5] Jiang et. al, 2022
[6] Van Ewjik et. al, 2025
[7] Nagy et. al 2025 (ASCO)

UCSF Benioff Children's Hospitals

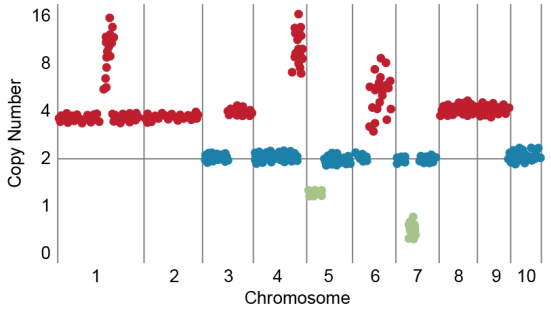
Ongoing efforts to define biomarkers in osteosarcoma

Prognostic and Biologic Risk Classifiers in Osteosarcoma

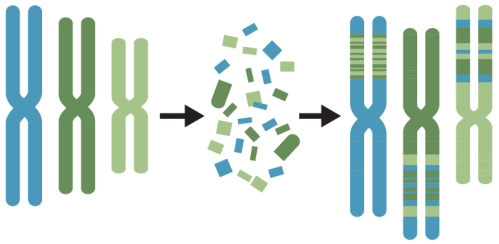
CLINICAL FEATURES



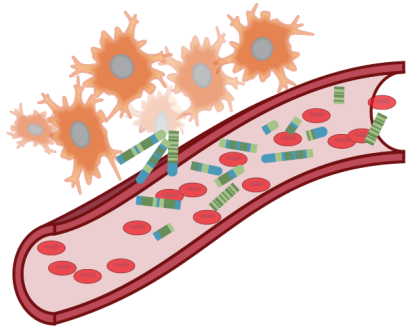
FOCAL COPY NUMBER ALTERATIONS



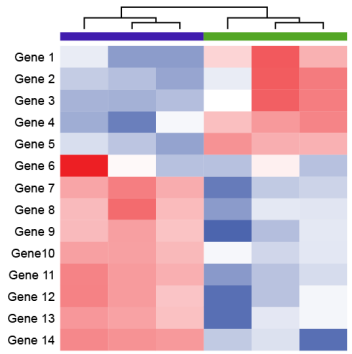
PATTERNS OF CHROMOSOMAL INSTABILITY



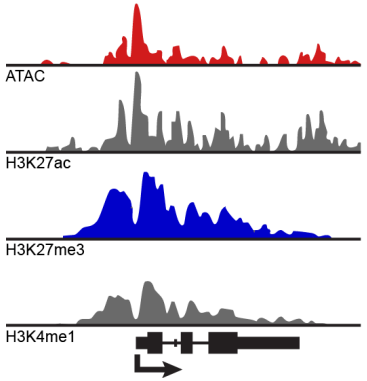
ctDNA LEVELS



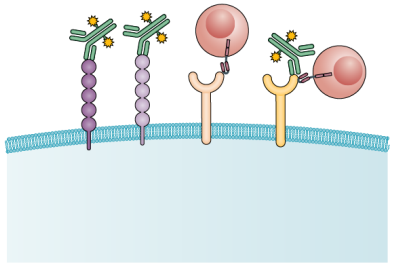
TRANSCRIPTOMIC SIGNATURES



EPIGENOMIC SIGNATURES



CELL SURFACE PROTEIN EXPRESSION



Clinical biomarkers for osteosarcoma stratification (cBOSS) international working group (manuscript in preparation)

Summary and conclusions

- No meaningful survival gains or new treatments approved in ~40 years
- Multiple strategies in the trial pipeline, but definitive breakthroughs remains elusive
- **Unmet needs require collaborative solutions**:
  - Access to novel drugs
  - Biology-driven approaches
  - Innovative trial designs
  - Multi-stakeholder partnerships

Thank you

Osteosarcoma Institute and FDA Oncology Center of Excellence

Leadership

Mac Tichenor
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Chand Khanna, DVM, PhD

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Alejandro Sweet-Cordero, MD
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Patients, families, and advocates who make progress possible

FDA U.S. FOOD & DRUG ADMINISTRATION
Oncology Center of Excellence

OSTEOSARCOMA INSTITUTE
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UCSF Benioff Children's Hospitals

FDA Regulatory Considerations for Rare Cancer Product Development

Jasmine Smith, MD
Medical Officer, Division of Oncology 3
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration

Disclosures

- I have no financial conflicts to disclose.

Presentation Outline

- **Role of FDA in Oncology Drug Development**
- Regulatory Framework
- Considerations for Rare Cancers
- Pediatric Regulations

FDA Mission

The Food and Drug Administration is responsible for protecting the public health by ensuring the **safety, efficacy, and security** of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

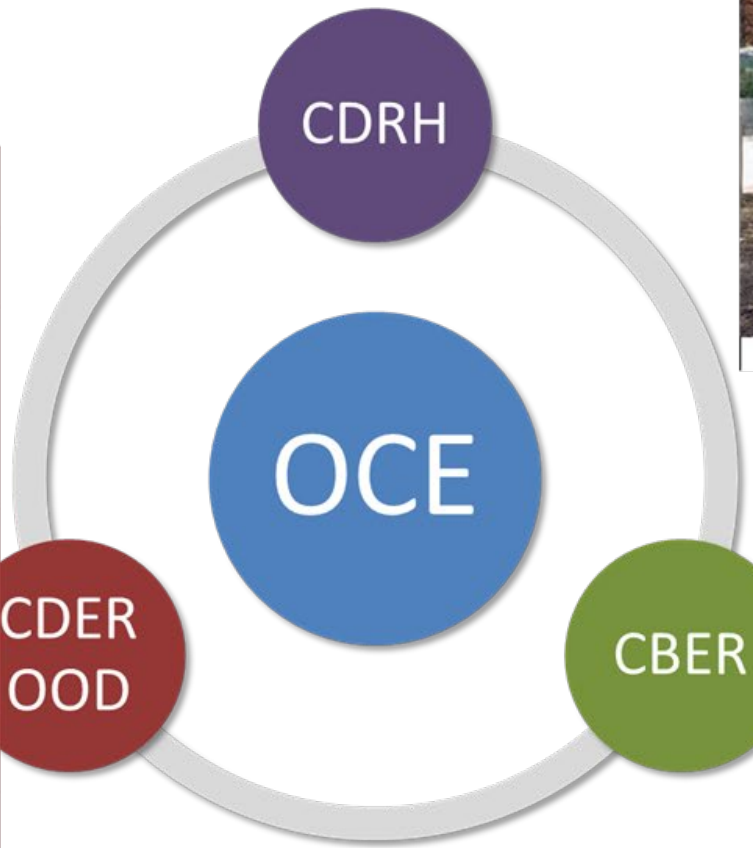
New drugs and biologics need to be proven **safe and effective** through adequate and well-controlled studies before they can be marketed.

<u>Important to note:</u>

- FDA **does not** consider cost or payment issues
- FDA **does not** regulate “practice of medicine”

Oncology Center of Excellence (OCE)

Division	Pediatric indications
DO1	N/A
DO2	Pediatric solid tumors, neuro-oncology, rare tumors
DO3	Sarcomas, skin cancers
DHM1	Acute leukemias
DHM2	Lymphomas
DHOT	Non-clinical pharmacology



Pediatric indications
Cell and gene therapies
Vaccines

Multidisciplinary Review Teams

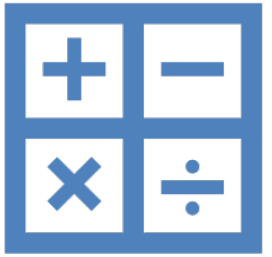
Project Management

Non-Clinical Pharmacology & Toxicology

Product Quality (CMC)

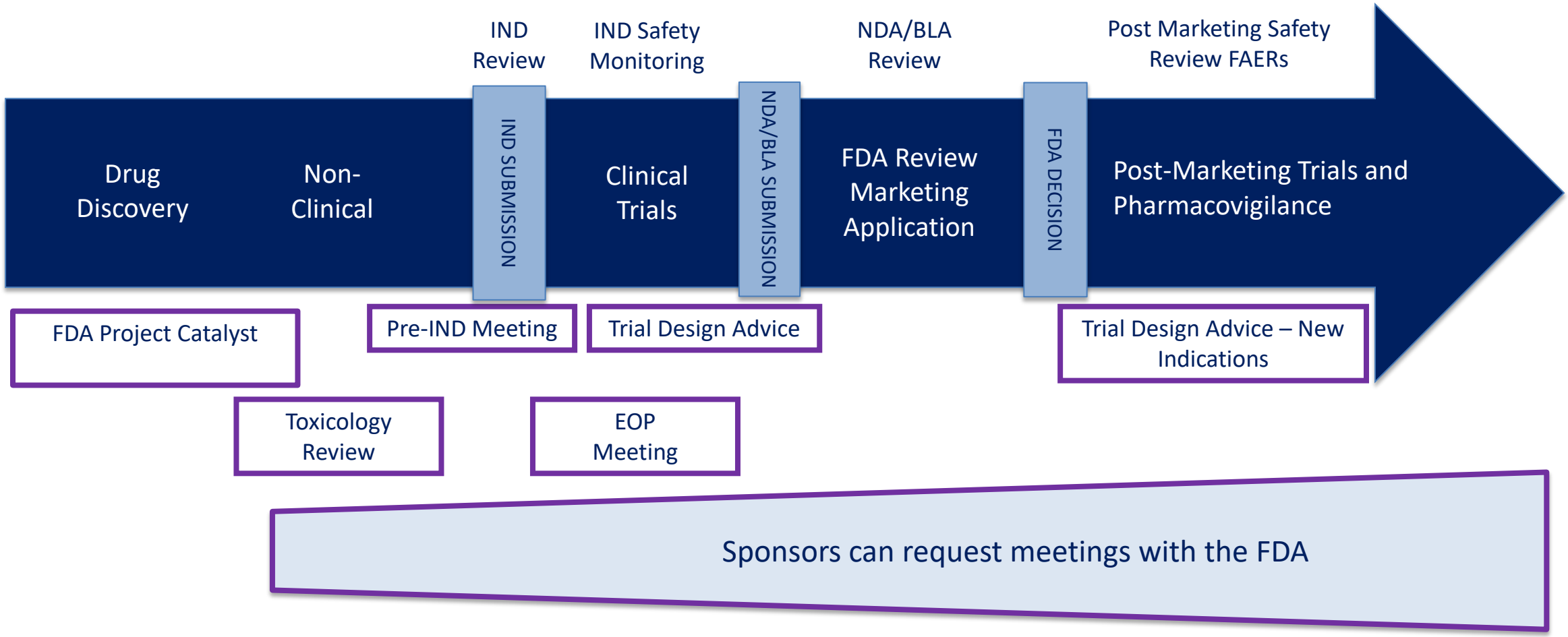
Clinical Pharmacology

Clinical Team (Specialty Expertise)



Statistics

Drug Development Process



Abbreviations: IND, Investigational New Drug Application; NDA, New Drug Application; BLA, Biologics License Application; FAERs, FDA Adverse Event Reporting System

Project Catalyst

- Fosters early-stage oncology product innovation and development
- Facilitates scientific discussion, education, guidance, and regulatory engagement
- OREEG: Oncology Regulatory Expertise and Early Guidance program

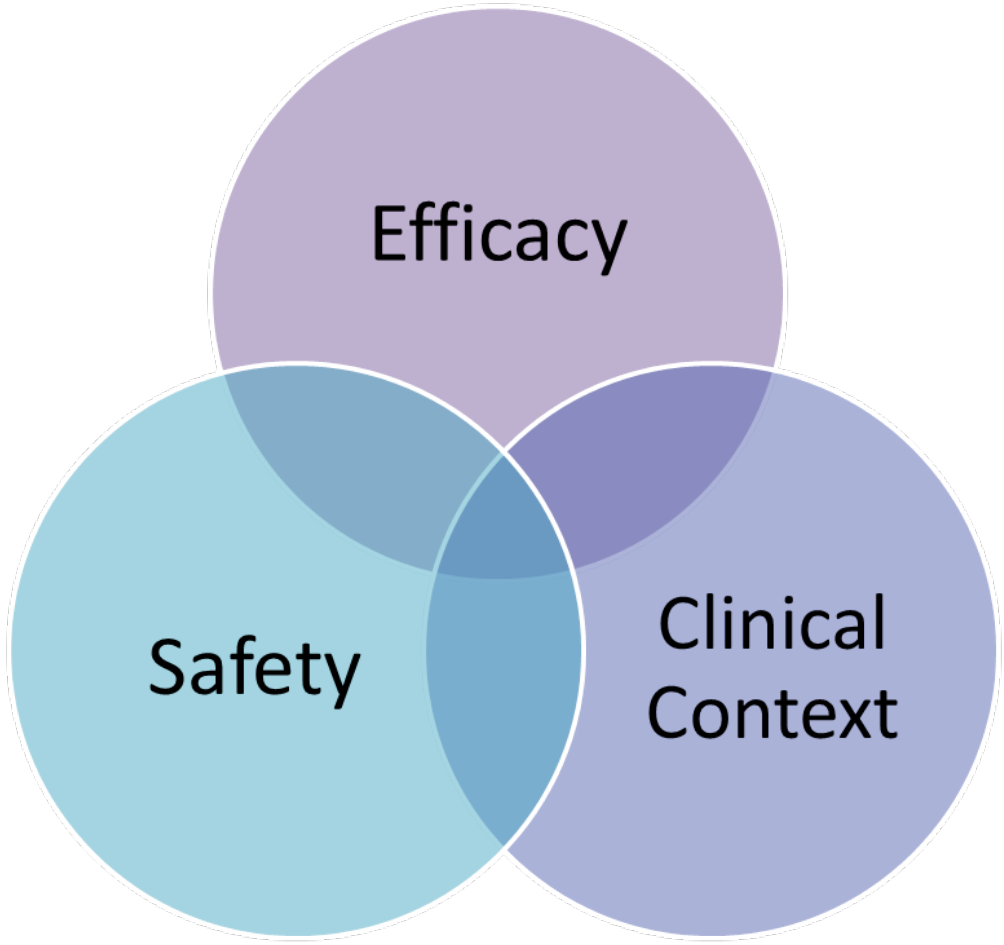
https://www.fda.gov/about-fda/oncology-center-excellence/project-catalyst

Presentation Outline

- Role of FDA in Oncology Drug Development
- **Regulatory Framework**
- Considerations for Rare Cancers
- Pediatric Regulations

Requirements for Drug Approval

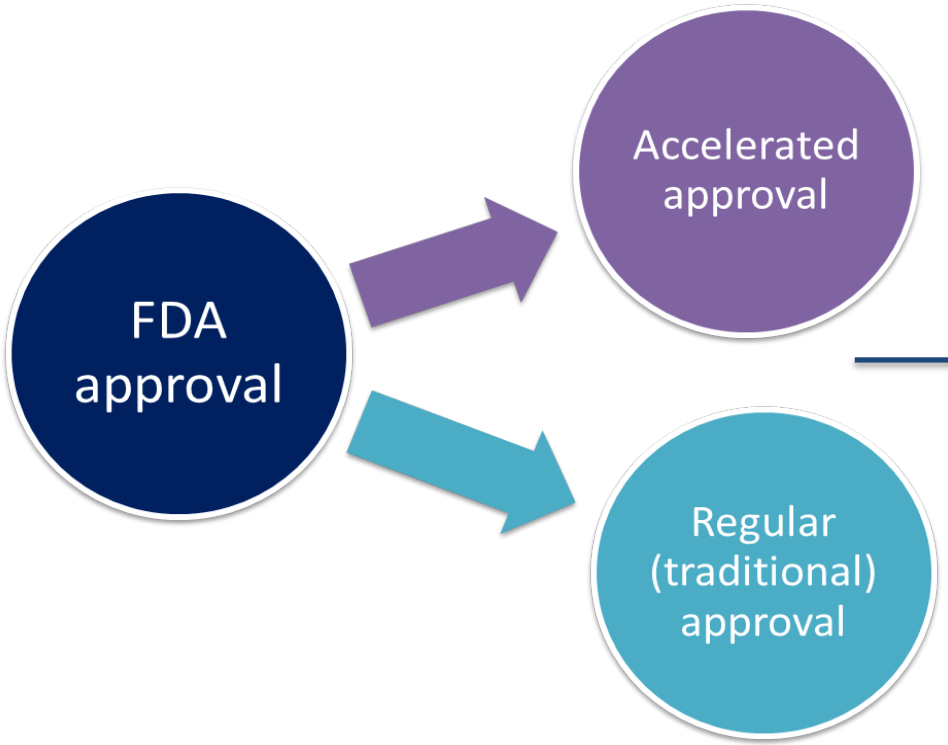
- Substantial evidence of effectiveness with acceptable safety in adequate and well-controlled studies
- FDA examines the evidence in the context of the disease, study design, endpoints selected, and strength of the evidence
- Ability to generate product labeling that:
  - Defines an appropriate patient population
  - Provides adequate information to enable safe and effective use



Federal Food, Drug, and Cosmetic Act, Section 505(d)

Approval Pathways

<u>Guiding principle:</u> The drug must demonstrate substantial evidence of effectiveness through adequate and well-controlled studies



- Intermediate clinical endpoint reasonably likely to predict clinical benefit
- Meaningful therapeutic benefit over available therapies
- May require confirmatory trial(s) to verify benefit

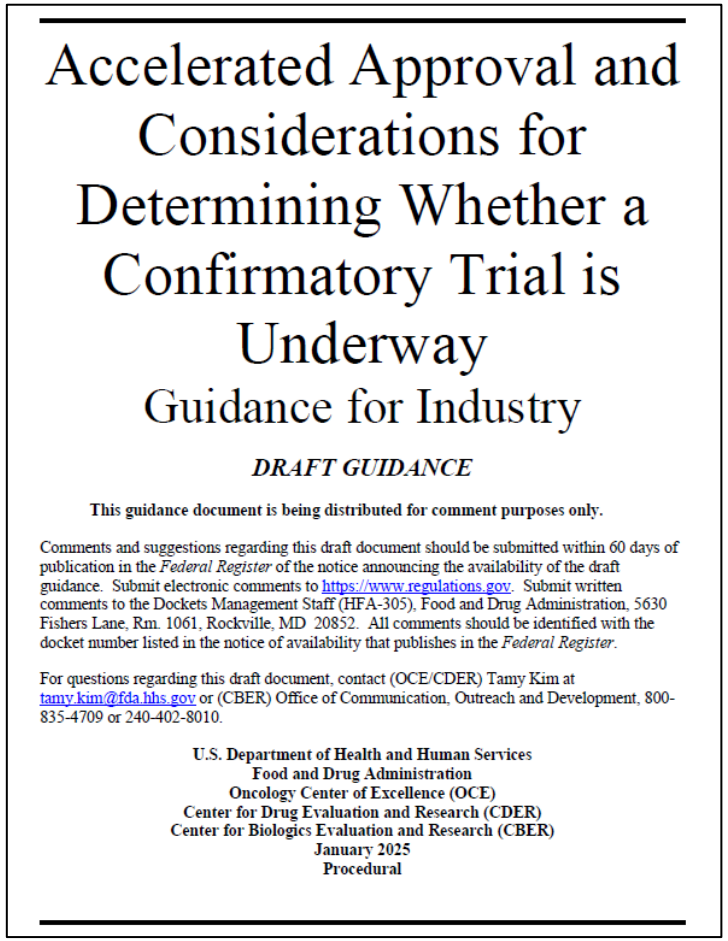
- No requirement to be better than available therapies
- Endpoint demonstrates direct clinical benefit

Accelerated Approval Additional Considerations

- Eligibility should be discussed during development (prior to submitting application)
  - Proposed endpoints for approval
  - Design and conduct of confirmatory trial(s)

- FDA generally intends to require that the confirmatory trial(s) be underway prior to the accelerated approval action.

- Can be withdrawn if confirmatory trial(s) not conducted or do not verify predicted clinical benefit



Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OCE/CDER) Tamy Kim at tamy.kim@fda.hhs.gov or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2025
Procedural

Presentation Outline

- Role of FDA in Oncology Drug Development
- Regulatory Framework
- **Considerations for Rare Cancers**
- Pediatric Regulations

Challenges for Rare Cancers

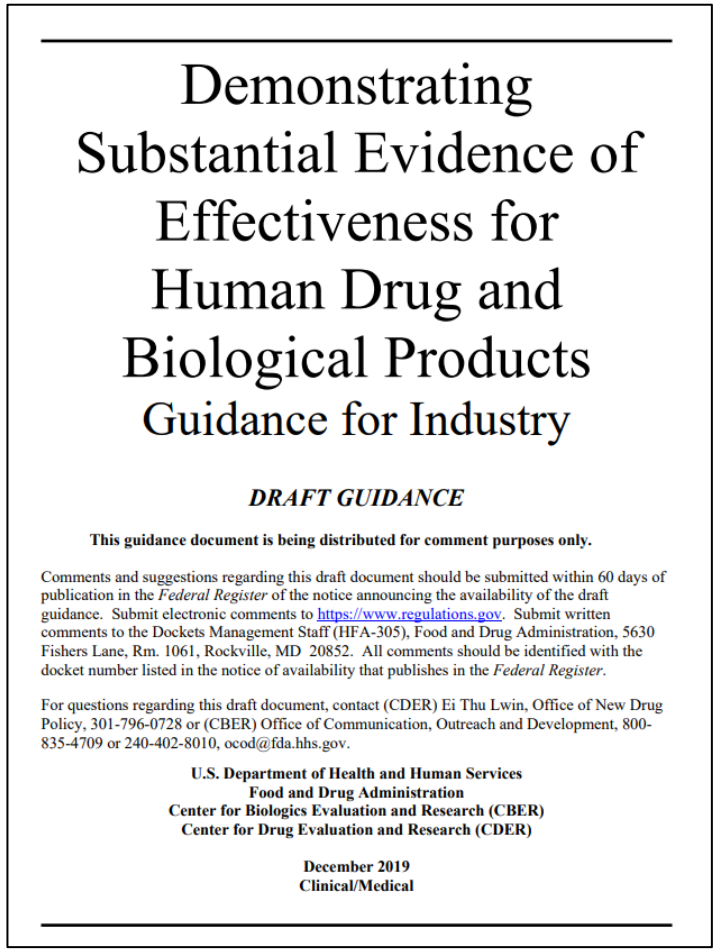
- Difficulty enrolling sufficient number of patients to clinical trials
- Decreased financial incentives for drug development
- Insufficient understanding of the cancer pathophysiology, molecular characteristics, and natural history
- Limited or lack of timely access to molecular testing to determine eligibility for treatment with targeted therapies
- Difficulty conducting randomized trials, due to small patient numbers or lack of appropriate therapy to use as a comparator
- Specific considerations are needed for pediatric populations (e.g., drug formulation for oral therapies)

Application Approval
FDA Regulations and Flexibility

- **21 CFR 314.105(c)**
  - FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards for safety and effectiveness

- **21 CFR 312, subpart E** – *Drugs intended to Treat Life-threatening and Severely-debilitating Illnesses*
  - FDA "has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness"

Potential Areas of Flexibility



Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Ei Thu Lwin, Office of New Drug Policy, 301-796-0728 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010, ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

December 2019
Clinical/Medical

- Number of Trials
- Trial Design
- Trial Endpoints
- Statistical Considerations

Expedited Programs

Intent: to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks

- For drugs and biologics:
  - Accelerated Approval
  - Fast Track Designation
  - Breakthrough Therapy Designation
  - Priority Review

Presentation Outline

- Role of FDA in Oncology Drug Development
- Regulatory Framework
- Considerations for Rare Cancers
- **Pediatric Regulations**

History of Pediatric Legislation

Early Legislation
1902 - Biologics Control Act
1906 - Pure Food and Drug Act
1938 - Food Drug and Cosmetic Act
1962 - Kefauver-Harris Amendment

PREA amended to require pediatric investigations of drugs directed at molecular targets considered relevant in pediatric cancer regardless of the adult indication

BPCA and PREA Programs

BPCA

- **Voluntary** studies
- Proposed Pediatric Study Request (PPSR)/Written Request (WR)
- No waiver
- Studies relate to entire moiety and **may expand indications**
- **6-month patent extension**

PREA

- **Mandatory** studies
- Adult submission /Initial Pediatric Study Plan (iPSP)
- Criteria for waiver
- **Studies only in indications under review**
- **Under FDARA, orphan indications no longer exempt**

FDA Reauthorization Act (FDARA)

Requires evaluation of certain new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer."

- Applies even if the adult cancer indication does not occur in the pediatric population
- Applies even if the drug is for an adult indication for which orphan drug designation has been granted
- Reports on the molecularly targeted pediatric cancer investigation required under section 505B(a)(3) of the FD&C Act must be submitted with the marketing application, unless FDA waives or defers the requirement

May 2021 Final Guidance - FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act

Presentation Outline

- Role of FDA in Oncology Drug Development
- Regulatory Framework
- Considerations for Rare Cancers
- Pediatric Regulations

Key Takeaways

- Development of drugs to treat rare cancers, like osteosarcoma, can be challenging but OCE has numerous resources that can be leveraged to help
- FDA approval requires substantial evidence of effectiveness irrespective of cancer prevalence
- FDA can exercise flexibility in applying statutory standards for safety and effectiveness when warranted, and under specific circumstances
- FDA encourages early and frequent meetings with sponsors/investigators during the drug development process
- FDA encourages interactions with stakeholders to discuss drug development programs for rare cancers

Relevant FDA Resources

- DRAFT Guidance for Industry
  - 2019: *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*
  - 2023: *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation*
  - 2023: *Pediatric Drug Development: Regulatory Considerations - Complying with PREA and Qualifying for Pediatric Exclusivity under BPCA*
  - 2022: *Tissue Agnostic Drug Development in Oncology*

- FINAL Guidance for Industry
  - 2023: *Rare Diseases: Considerations for the Development of Drugs and Biological Products*
  - 2021: *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*
  - 2020: *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*
  - 2019: *Consideration for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials*

OCE Rare Cancers Program

Promoting development of new drug and biological products to treat patients with rare cancers

Pediatric Oncology

Promoting the development of safe and effective new drugs and biologics to treat cancer in children

Acknowledgements

- Erica Horodniceanu
- Katie Barnett
- Kristin Wessel
- Nicole Drezner
- Martha Donoghue
- Leslie Doros
- Steven Lemery
- Angelo De Claro
- Richard Pazdur
- Oncology Center of Excellence
- The Osteosarcoma Institute

OSTEOSARCOMA INSTITUTE
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Session 3

Targeting Osteosarcoma

11:00 – 11:20 AM

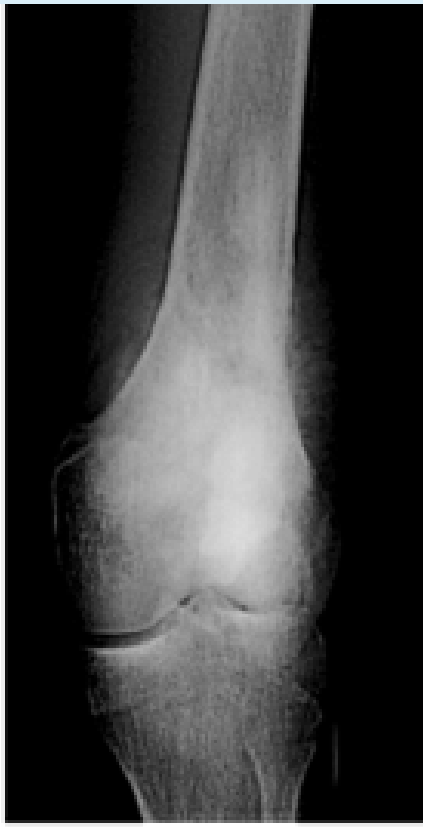
Alejandro Sweet-Cordero, MD (UCSF)

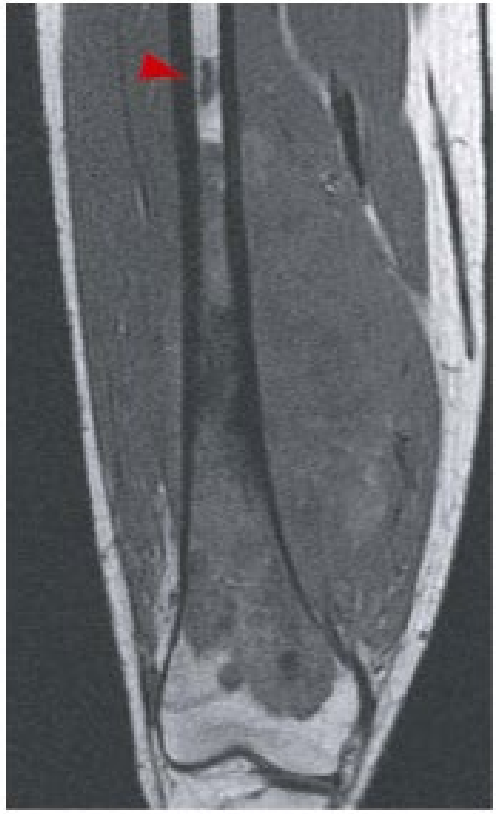
Emerging therapeutic opportunities in Osteosarcoma

E. Alejandro Sweet-Cordero, MD
Professor of Pediatrics
University of California San Francisco

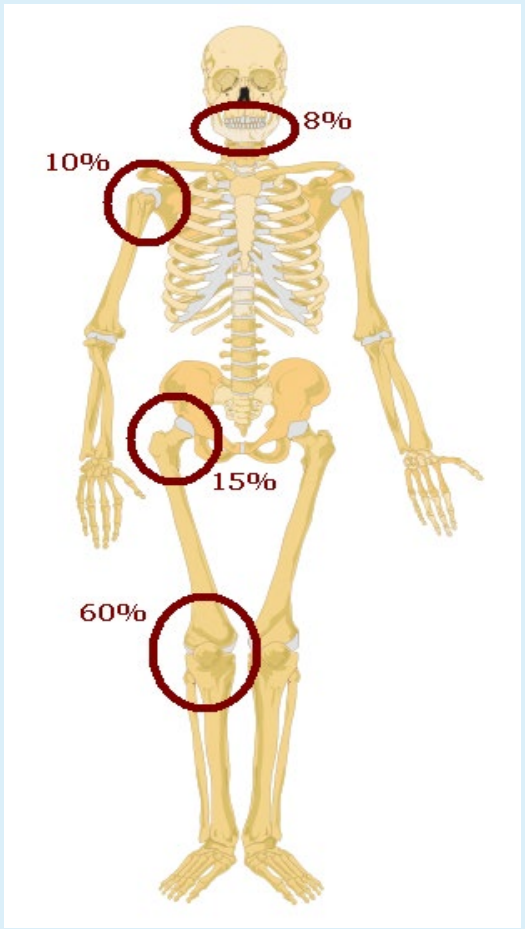
Osteosarcoma (OS): clinical perspectives

A rare disease:
800 patients/year in the US

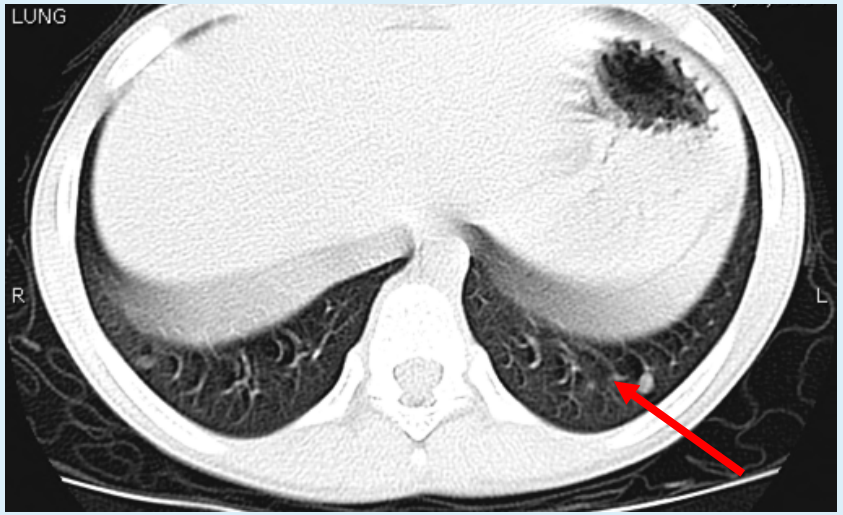




Peak incidence
at puberty

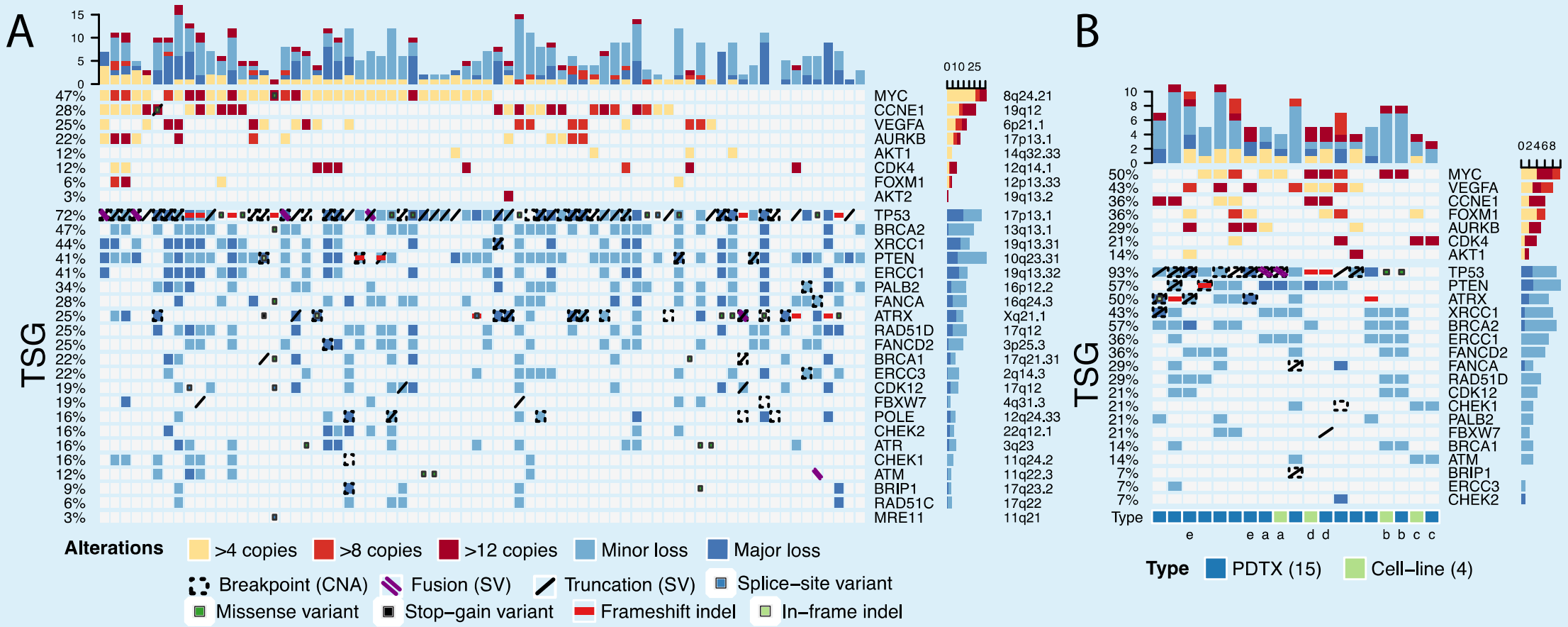


Metastasis is common

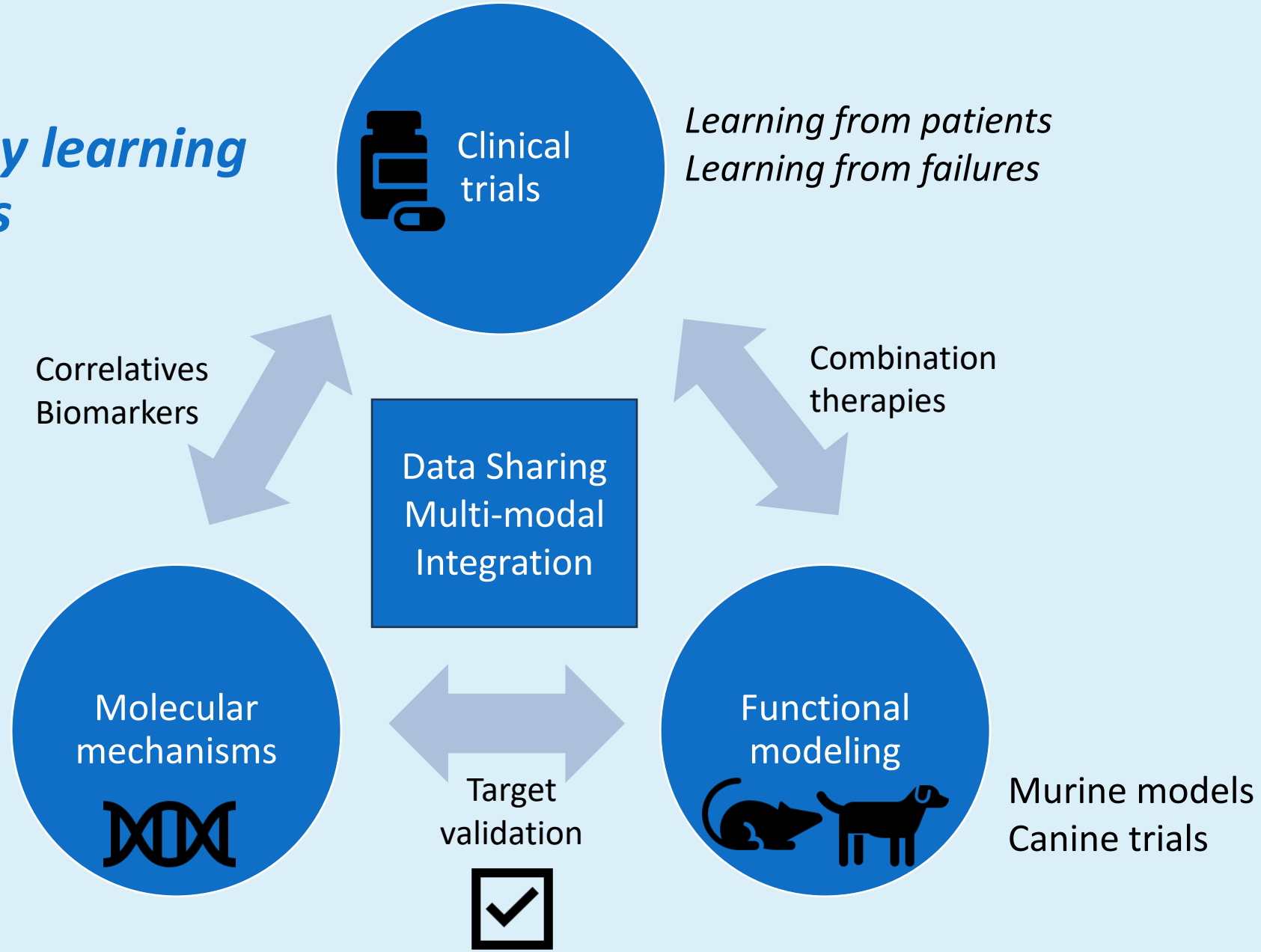


- Treatment (MAP+surgery)
  unchanged in 40 years

Genomic Alterations in DDR related pathways in osteosarcoma



Accelerating New therapies by learning from OS patients



Emerging tumor-cell directed therapies

- Kinase and other cell signaling inhibitors
  - TKIs (cabozantinib, reforafenib, etc.)
  - Trametinib
- MYC (omo-myc trial)
- DNA damaging agents
  - PARPi
  - ATRi
- Antibody-drug conjugates
  - B7H3, LRCC15, others.
  - Various payloads
- CDK inhibitors (CID-078, CDK12, etc.)
- Radiopharmaceuticals
- Her2

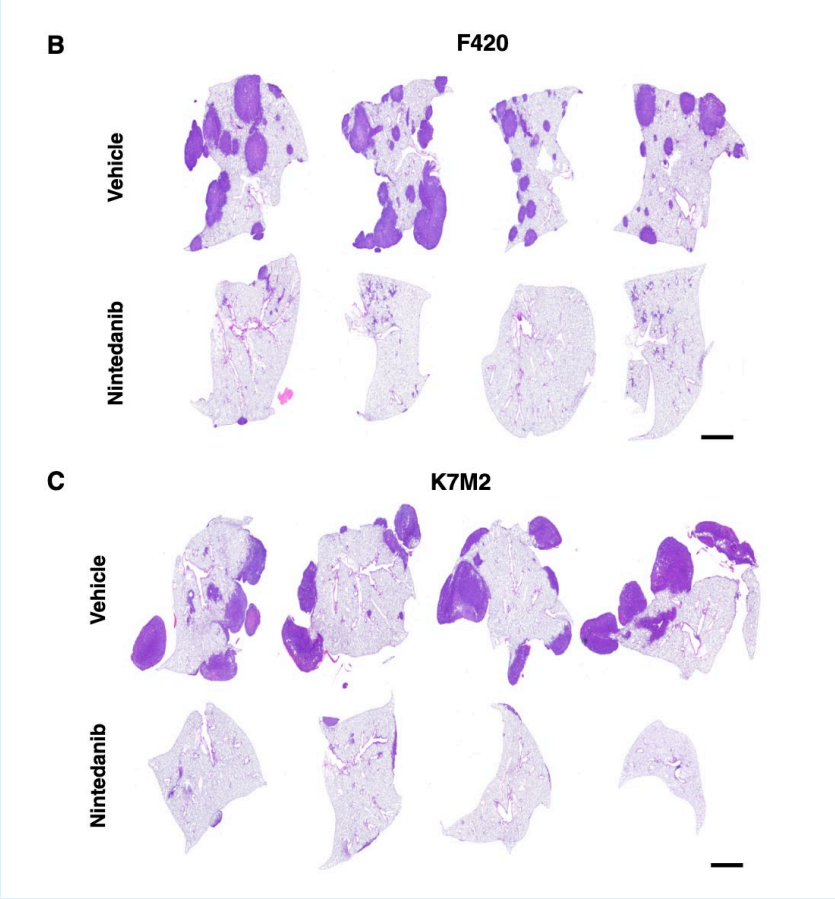
- *This is not an exhaustive list…*

Emerging immunomodulators

- STING agonists
- ENPP1 inhibitors
- TGFb inhibitors
- Checkpoint inhibitors

Targeting the metastatic microenvironment

- Nintedanib

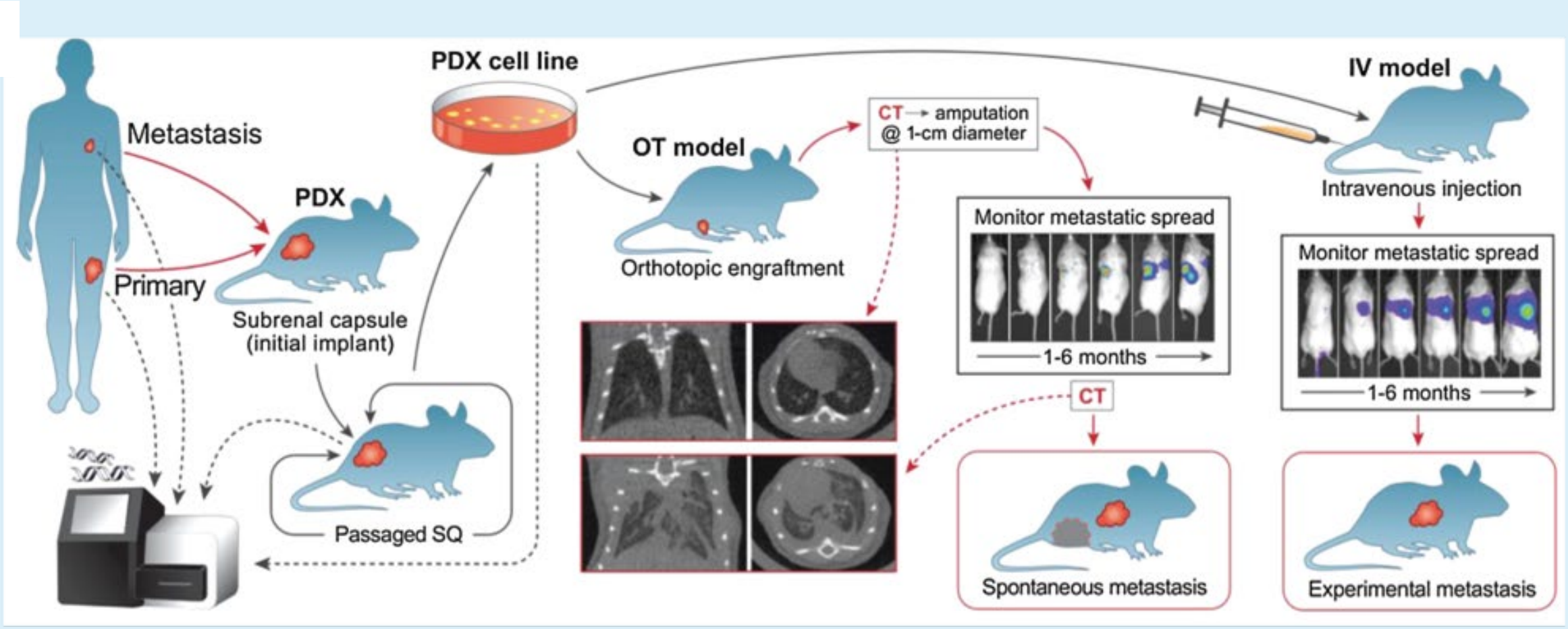


Reinecke et al Clinical Cancer Research, 2025

Preclinical models for drug testing

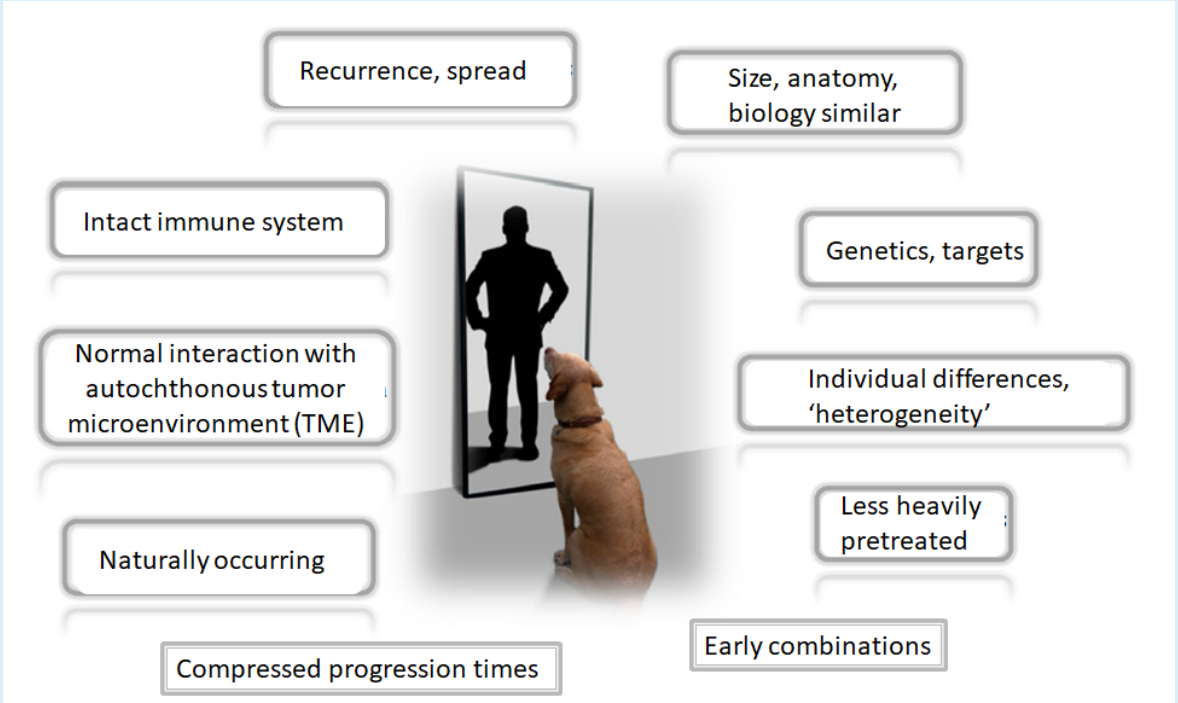
- Dogs
- Mice
- Ex vivo (PUMA assay, short-term tumor cultures)
- In vitro
  - Standard tissue culture (cell lines)
  - 3D models/organoids

Orthotopic human-in-mouse model to study primary and metastatic OS



Leveraging Canine Cancers for Preclinical Interrogation

- **Provide information regarding expected and unexpected adverse events, especially in the context of comorbidities; validated HRQoL**
- **Evaluate novel drug combinations/therapeutic modality integration**
- **Longitudinal assessments of individual patients with biomarker collection**
- **Similar imaging and intervention modalities with comparable outcome assessments**
- **Opportunity to treat naive macroscopic or microscopic disease**
- **Less regulatory oversight; rapid adaptation to clinical findings**
- **Intact immune system remodeled from past challenges**



Modified from Riccardo et al
Cancer Immunol Immunother (2015) 64:137–148
DOI 10.1007/s00262-014-1645-5

Important unanswered questions

- Are there subtypes of osteosarcoma with unique vulnerabilities?
  - Transcriptional/epigenetic subtypes
  - Genomic subtypes
  - Hot vs cold tumors
  - Alt driven vs non-alt driven
- Should clinical trials be powered to detect signal in subtypes that are still poorly defined?
- Should we design trial to treat metastatic disease vs. prevent emergence of metastasis?

Break

11:20 – 11:45 AM

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Session 4

Trial Design & Endpoints in Osteosarcoma

11:45 AM – 12:45 PM

Session 4

Speakers	
Kristin Wessel, MD	FDA
Katherine Janeway, MD, MMSc	Dana-Farber Cancer Institute (DFCI)
Melinda Merchant, MD, PhD	Normunity
Harpreet Singh, MD	Precision for Medicine

Regulatory Perspective on Endpoints and Trial Design in Osteosarcoma

Kristin Wessel, MD
Medical Officer, Division of Oncology 2
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration

Disclosures

- I have no financial conflicts to disclose.

FDA Role in Oncology Drug Development

Substantial Evidence of Effectiveness

- Approval requires "substantial evidence" of safety & effectiveness supported by "**adequate and well-controlled**" clinical data – 21 CFR 314.126
  - ***Regular Approval:*** Demonstration of direct clinical benefit
  - ***Accelerated Approval:*** Intermediate clinical endpoint reasonably likely to predict clinical benefit

- Evidentiary standards for marketing approval and change in clinical practice may differ

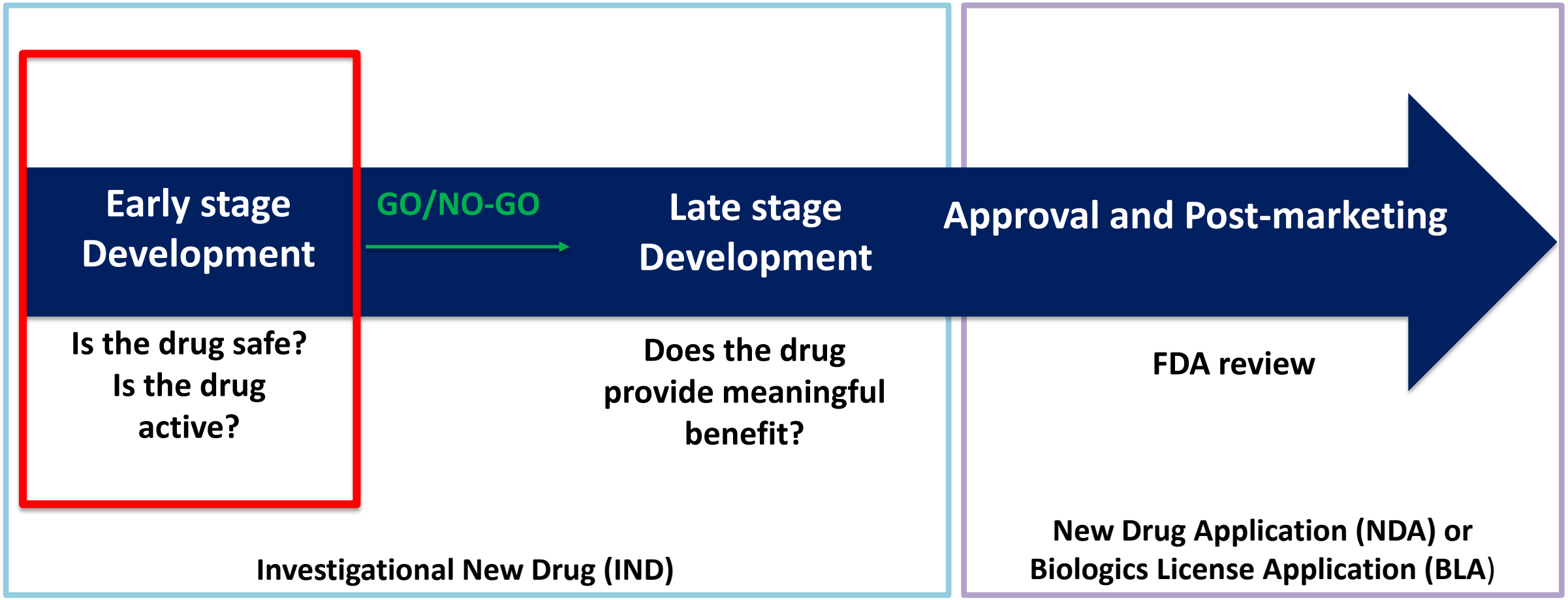
Endpoints in Oncology Clinical Trials

- **Objective Response Rate (ORR)**
  - Allows for single-arm design
  - Earlier measurement of effect
  - Imaging interpretation required → difficult in osteosarcoma disease context

- **Progression-Free Survival (PFS) or Event-Free Survival (EFS)**
  - Requires control arm
  - Earlier readout than overall survival
  - Event occurs prior to crossover

- **Overall Survival (OS)**
  - Generally requires control arm
  - Direct measure of clinical benefit, incorporates safety information
  - Easily measured
  - Longest to read out
  - May be confounded by cross-over and subsequent therapies

Appropriate Trial Design Depends on Stage of Development



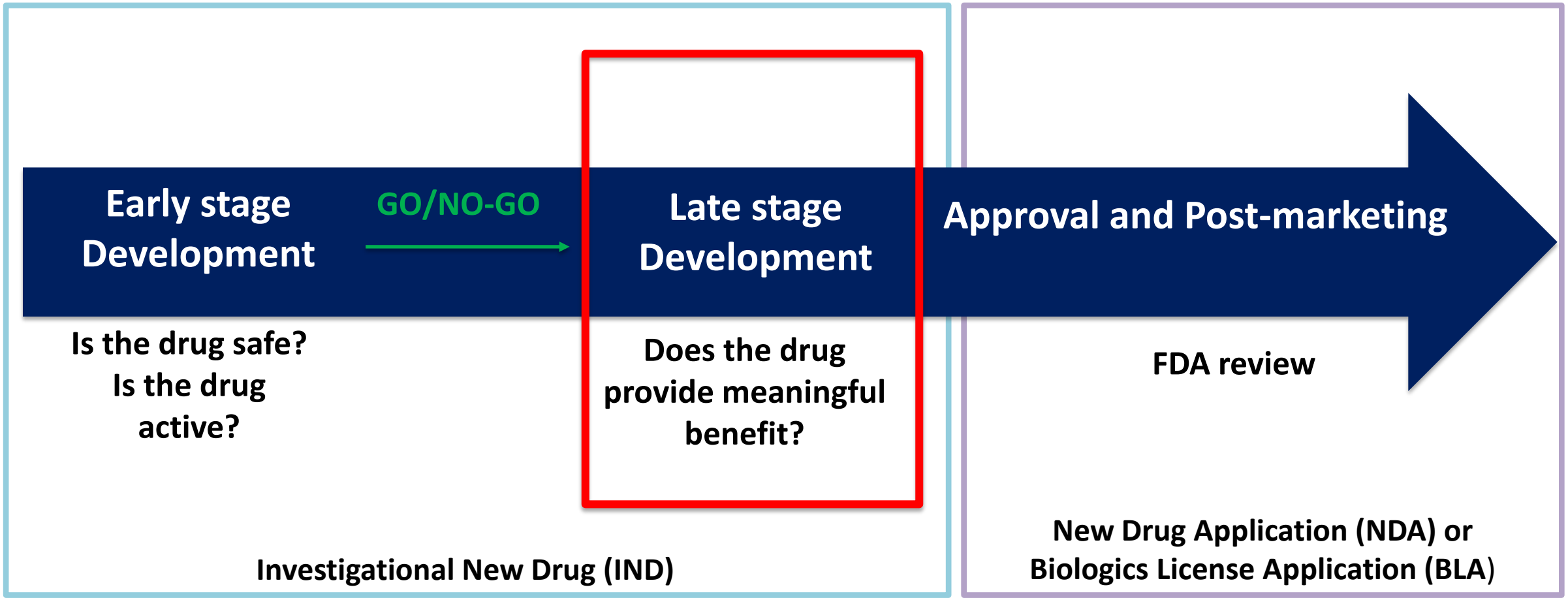
Signal-Finding Studies in Osteosarcoma

- Typically conducted in relapsed/refractory setting

- Goal is to **expeditiously** evaluate whether a drug has activity
  - Randomized trials often not feasible at this stage of development
  - ORR may underestimate drug activity

- **Historical benchmarks are reasonable to use in this setting**
  - Studies for patients with measurable disease: EFS>4 months
  - Studies for patients with resected disease: EFS>12 months

Appropriate Trial Design Depends on Stage of Development



Trial Design Considerations for Late-Stage Development in Osteosarcoma

- Dependent on multiple factors
  - Disease setting
    - Newly-diagnosed
    - Relapsed/refractory
    - Completed treatment with high risk of relapse ("maintenance")
  - Mechanism of action
  - Presence or absence of measurable disease
  - Observation of tumor shrinkage in signal-finding studies
  - Approval pathway
- Randomized controlled trials needed for interpretation of time-to-event primary endpoints (EFS, PFS, OS)
- Meet with FDA early to discuss trial design for a specific product

Potential Approaches for Randomized Controlled Trials

- Active comparator control arms
  - Investigator's choice
  - Add-on design
- Alternative randomization ratios (e.g., 2:1, 3:1)
- Platform trial with common control
- Crossover design
- Seamless design with adaptive elements

Incorporation of Novel Endpoints

- Common interest in development of novel endpoints (e.g., ctDNA) that enable earlier efficacy assessment

- Novel endpoints must be **prospectively validated** prior to use as a primary endpoint in a registrational trial

Project Endpoint

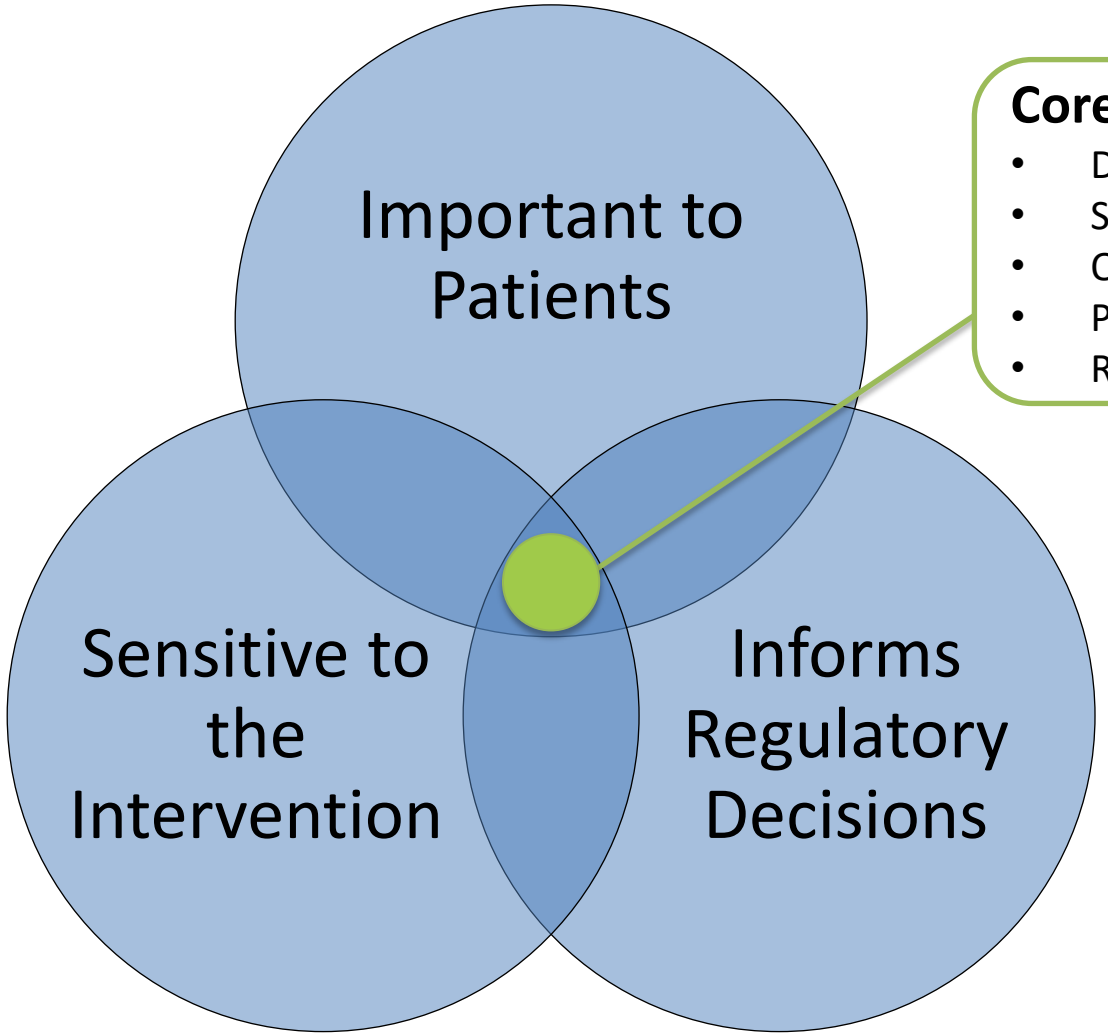
Advancing the use of endpoints in oncology drug development

GUIDANCE DOCUMENT

Use of Circulating Tumor Deoxyribonucleic Acid for Early-Stage Solid Tumor Drug Development; Guidance for Industry; Availability

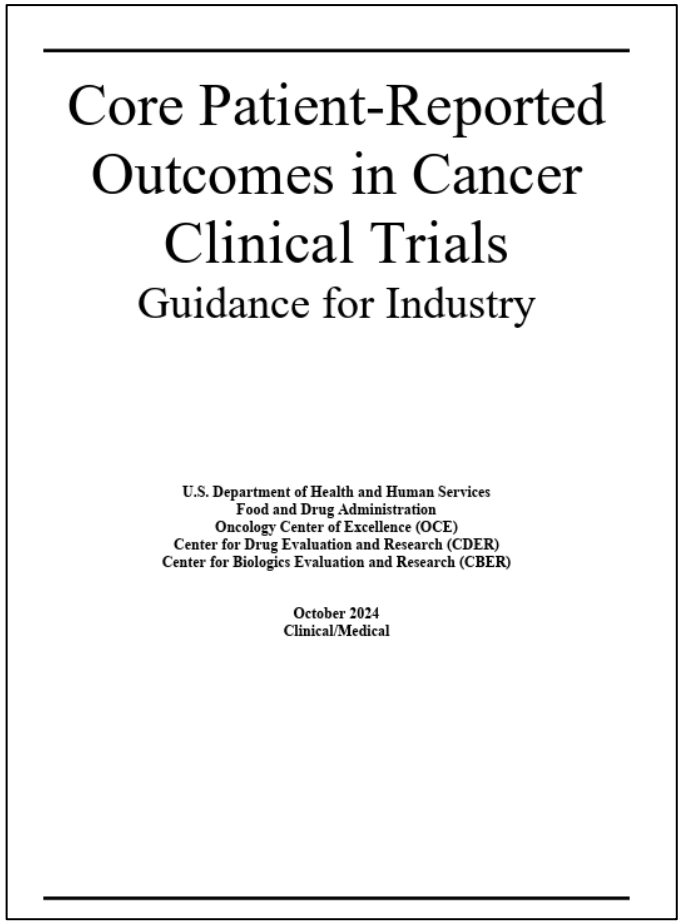
NOVEMBER 2024

Patient-Reported Outcomes (PROs)



Core Clinical Outcomes

- Disease-Related Symptoms
- Symptomatic Adverse Events
- Overall Side Effect Impact
- Physical Function
- Role Function



Core Patient-Reported Outcomes in Cancer Clinical Trials

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2024
Clinical/Medical

Kluetz, P.G., et al., *Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms.* Clin Cancer Res, 2016. **22**(7): p. 1553-8.

Enrollment of Pediatric Patients

- Patients 12 years of age and older should generally be included early in development
  - First-in-human trials: obtain initial safety data in adults

- Inclusion of patients <12 years of age as feasible (e.g., after initial safety data obtained)

- Extrapolation can generally be leveraged

Meetings with FDA

- Sponsors encouraged to meet with FDA early and often, throughout the drug development process
- Recommend inclusion of key academic investigators and patient advocacy representatives in Sponsor meetings
- Encourage involving FDA's Center for Devices and Radiological Health (CDRH) for advice on development of companion diagnostics
- Opportunities to engage FDA and international regulatory agencies together to reach alignment on key trial design issues

Acknowledgements

- Nicole Drezner
- Martha Donoghue
- Elizabeth Duke
- Oncology Center of Excellence
- The Osteosarcoma Institute
- The Osteosarcoma Patient and Advocacy Community

Clinical Trial Designs and Endpoints

Investigator and Clinician Perspective

October 10, 2025

Katherine A. Janeway, MD, MMSc

Associate Professor, Pediatrics, Harvard Medical School

Director, Clinical Genomics, Dana-Farber Cancer Institute

Chair, Bone Tumor Committee, Children's Oncology Group

HARVARD MEDICAL SCHOOL

Dana-Farber Cancer Institute

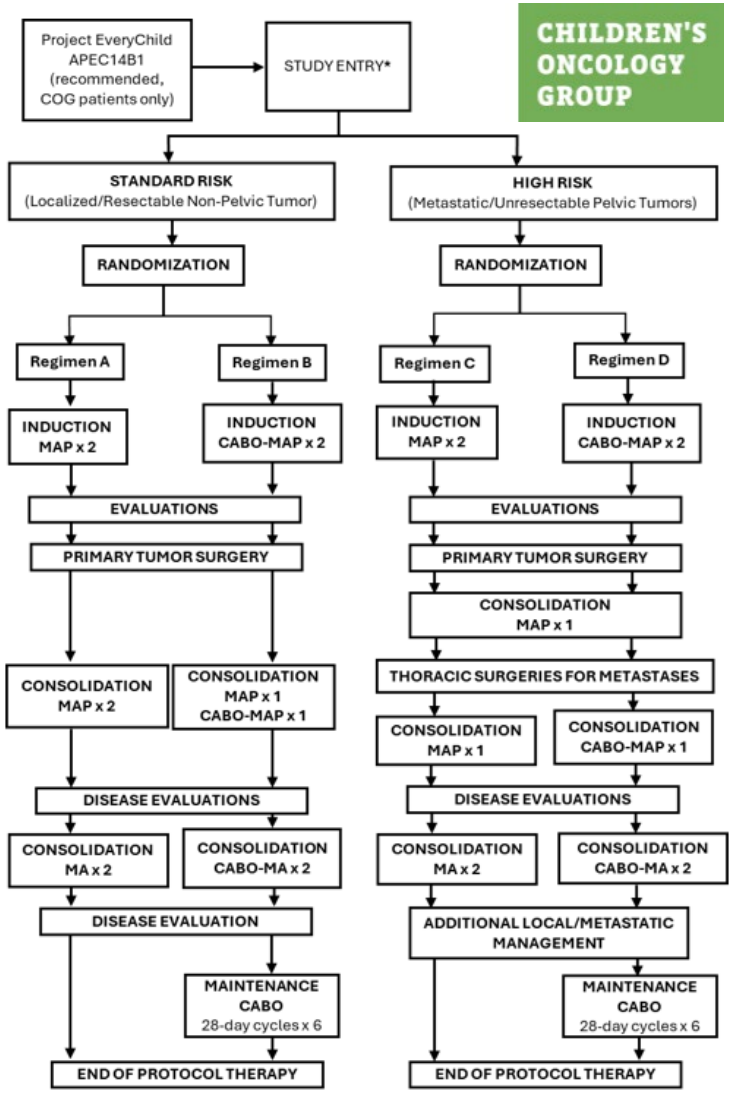
Boston Children's

Dana-Farber/Boston Children's Cancer and Blood Disorders Center

CHILDREN'S ONCOLOGY GROUP

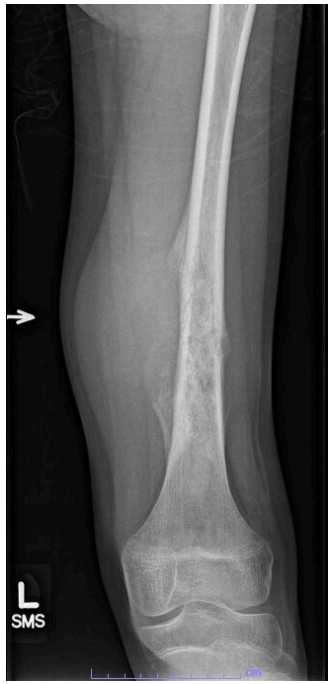
Trial to establish new SOC for Newly Diagnosed Patients

- Primary endpoint: Event-free survival
- Secondary endpoint: Overall survival
- Design: Randomized, SOC arm MAP chemotherapy
- Considerations: Patient populations, tumor resectability
  - Soon, biomarkers of outcome with MAP chemotherapy
- Accrual/duration
  - ∽ 700 localized, resectable patients
  - US cooperative group: 14 patients/month; ∽ 4 years accrual.
  - Results: ∽ 6-7 years
- One trial every decade
  - Signal finding trials in other patient populations essential (also for breakthrough therapy designation)
  - Typically performed in relapsed patients; relapse = metastatic in osteosarcoma

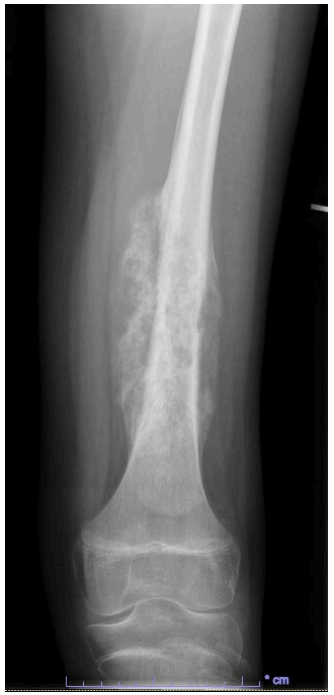


The Problem: Osteosarcoma has a calcified tumor stroma

X-rays in patients responding to MAP chemotherapy (proven to increase cure rates)
The tumor responds by becoming more calcified



PRE-chemo



POST-chemo

MRI WITHOUT RECIST RESPONSE

Guenther et al., *PBC 2017*

Osteosarcoma-specific endpoint

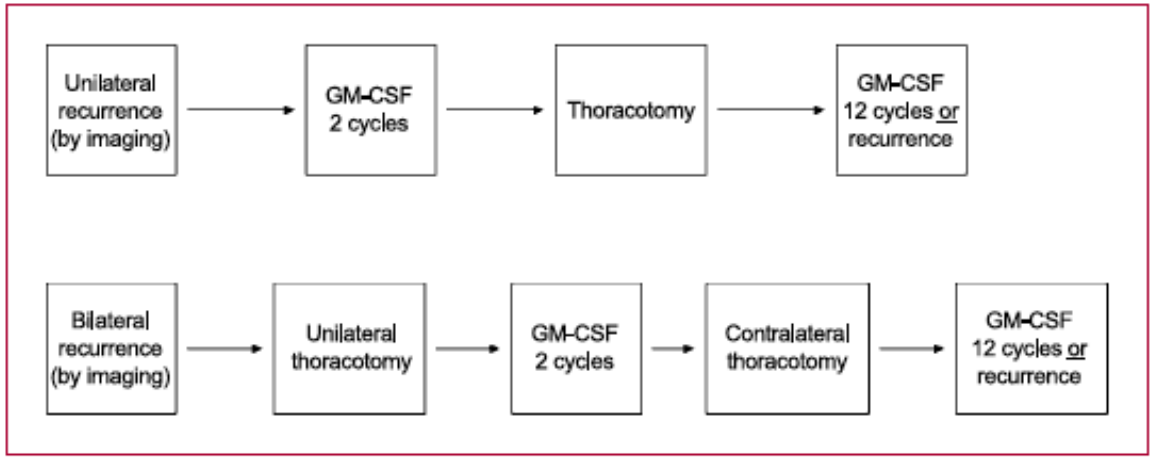
Additional background: Approximately 25% patients at recurrence rendered NED

Objective: Determine benchmark progression free survival in recurrent patients enrolling on phase 2 trials to enable signal finding trials in patients with recurrence (metastatic disease):

COHORT 1: Measurable disease = unresectable

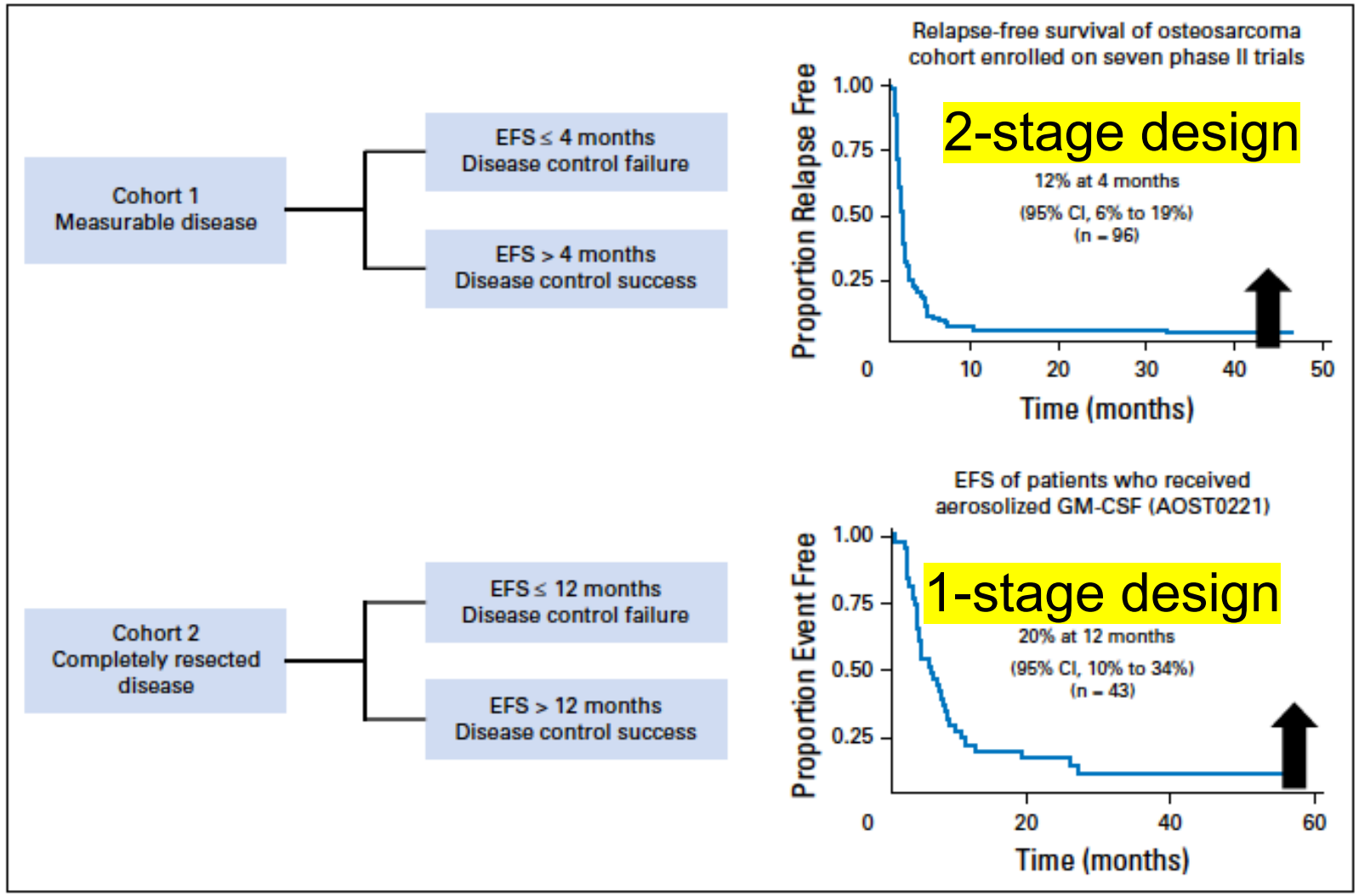
Characteristic	No. of Patients
All eligible patients	96
Study and drug	
A09713 (topotecan)	11
ADVL0122 (imatinib)	12
ADVL0421 (oxaliplatin)	13
ADVL0524 (ixabepilone)	11
CCG0962 (docetaxel)	22
P9963 (rebeccamycin)	17
P9761 (irinotecan)	10

COHORT 2: Resectable (resected) disease, N=42
Limited to pulmonary parenchyma



Osteosarcoma-specific trial design

- Cohort 1, measurable:
  - 4-mo PFS of 12% (95% C.I. 6-19%)
- Cohort 2, resected:
  - 12-mo PFS 20% (95% C.I. 34-43%)
- **No difference by number prior lines of therapy**



Lagmay, *JCO 2016*

CHILDREN'S ONCOLOGY GROUP

COG led phase 2 trials in recurrent osteosarcoma

Phase II Trial	Drug	Cohort Included	Target change in PF	Result	Accrued (N)	Duration (mos)
AOST 1322	Eribulin (microtubule inhibitor)*	Cohort 1	20%→40%	0/19 (0%) patients PF[1]	16	4
AOST 1521	Glembatumumab (ADC, GPNMB)*	Cohort 1	12%→40%	3/19 (16%) patients PF[2] Not correlated w/ GPNMB expression	21	6
AOST 1321	Denosumab* (RANKL Ab)	Cohort 1 Cohort 2	20%→40% 30%→50%	1/15 (7%) patients PF @ 4 mos 10/38 (26%) patients PF @ 12 mos No association with RANK / RANKL	16 / 38	6 / 22
AOST 1421	dinutuximab + GM-CSF (GD2Ab)	Cohort 2	20%→50%	11/39 (28%) patients PF @ 12 mos	38	24
AOST 2121	OST31-164 (Her2-directed Listeria)*	Cohort 2	30%→50%	13/40 (32.5%) patients PF @ 12 months	40	24

* First trial in pediatric age group

Isakoff PBC, 2018; Kopp EJC, 2019; Janeway, CCR in press; Hingorani, EJC 2022; Reed, MIB meeting, 2025

This data is unpublished and not yet sharable.

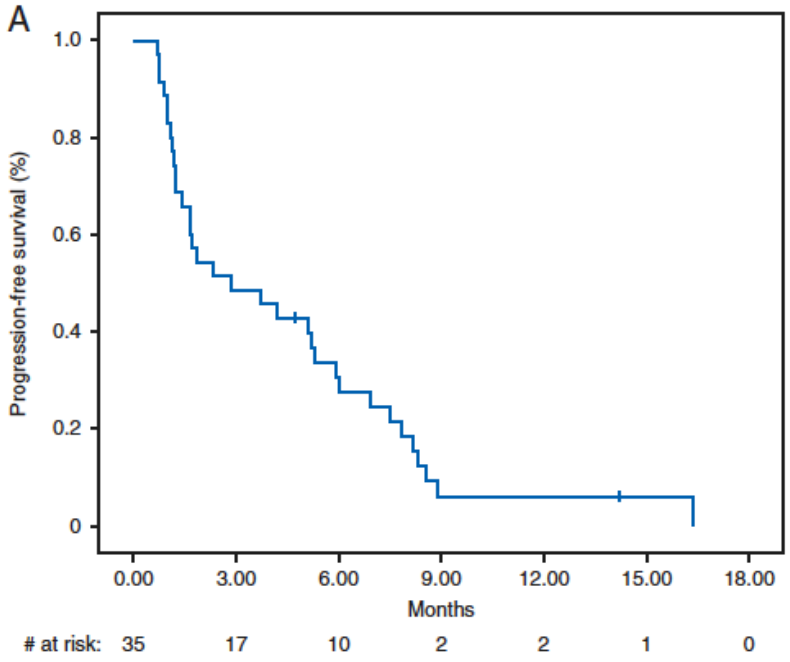
Limitations to single arm phase 2 signal finding trials in measurable disease population

- Combinations with agents active in recurrence (chemo, mTKIs)

Drug/Class	
Azenosertib (WEE1 inh)+ Gemcitabine	In Vitro + Biomarker (replication stress) 11/28 (38%) with 4.5 mo EFS

- These results need further investigation with a randomized trial
  - Single arm → randomized useful for:
    - combination dosing/tolerability data or biomarker assessment

Gemcitabine + Sirolimus (mTORinh)

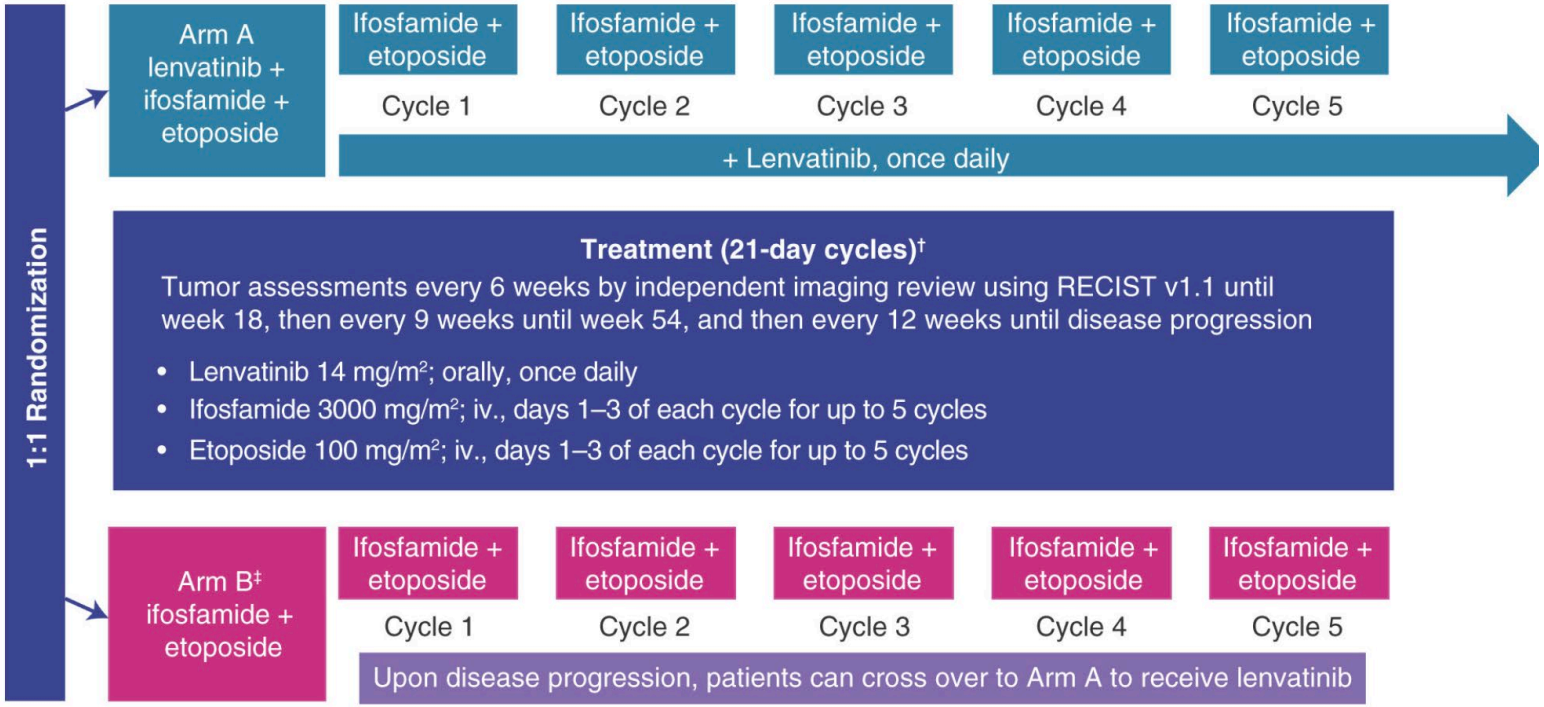


Matin-Broto, et al. Ann Oncol, 2017

This data is unpublished and not yet sharable.

Randomized trials in R/R Disease

Case Study Chemo vs. Chemo+: OLIE Trial



After cycle 5:
May continue therapy
May have surgery

Key Eligibility:

- 2-25 years
- Measurable or evaluable disease

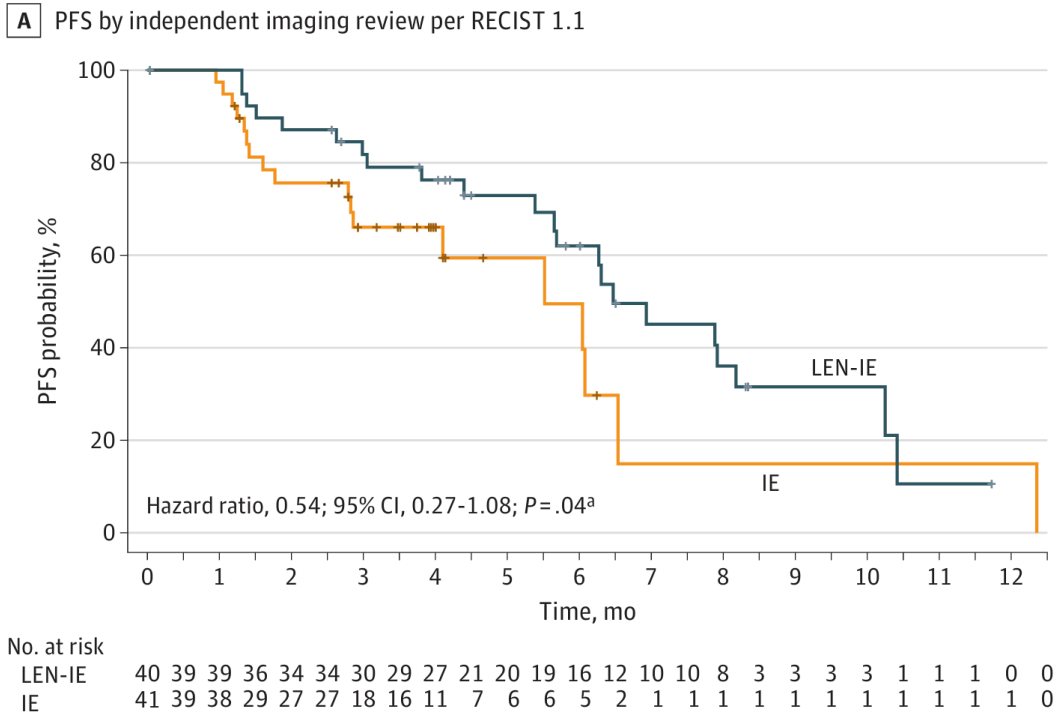
Table. Baseline Demographic and Disease Characteristics (continued)

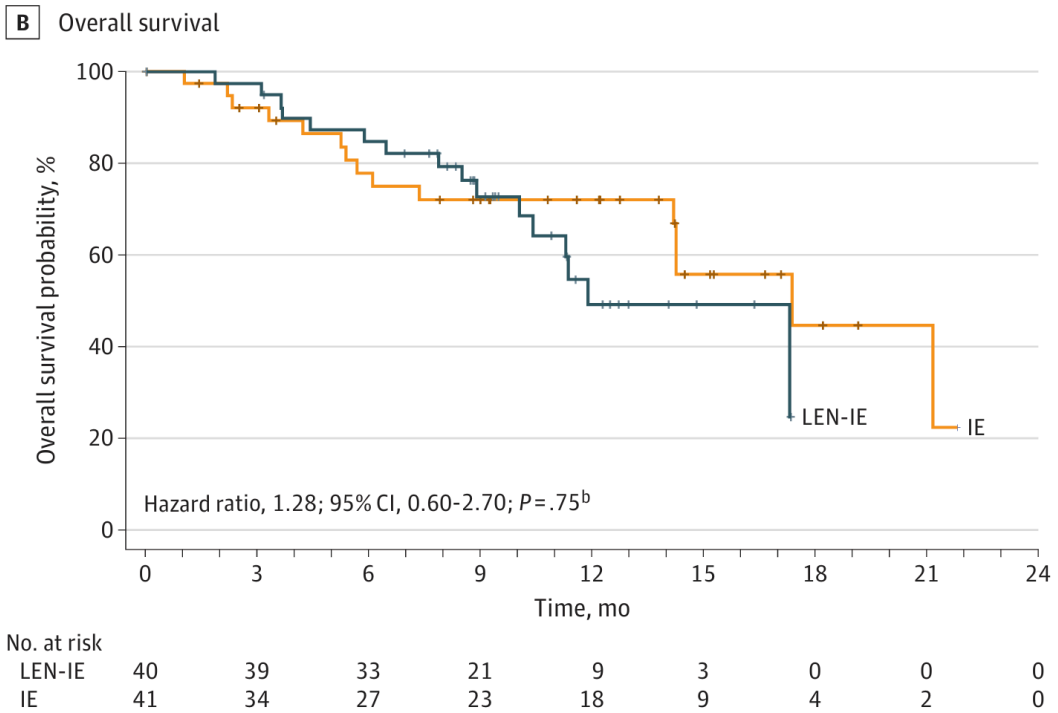
Characteristic	No. of patients (%) LEN-IE (n = 40)	IE (n = 41)
Measurable disease at baseline	34 (85.0)	32 (78.0)
Resectable disease at baseline	8 (20.0)	9 (22.0)
Sites of metastatic lesions[d,e]		
Lung	32 (80.0)	32 (78.0)
Bone	13 (32.5)	14 (34.1)
Brain	1 (2.5)	2 (4.9)
Other[f]	16 (40.0)	21 (51.2)
Age, median (range), y	15 (8-24)	14 (4-23)

21 countries
20 months accrual

Gaspar N, et al. JAMA Onc 2024

Randomized trials in R/R Disease

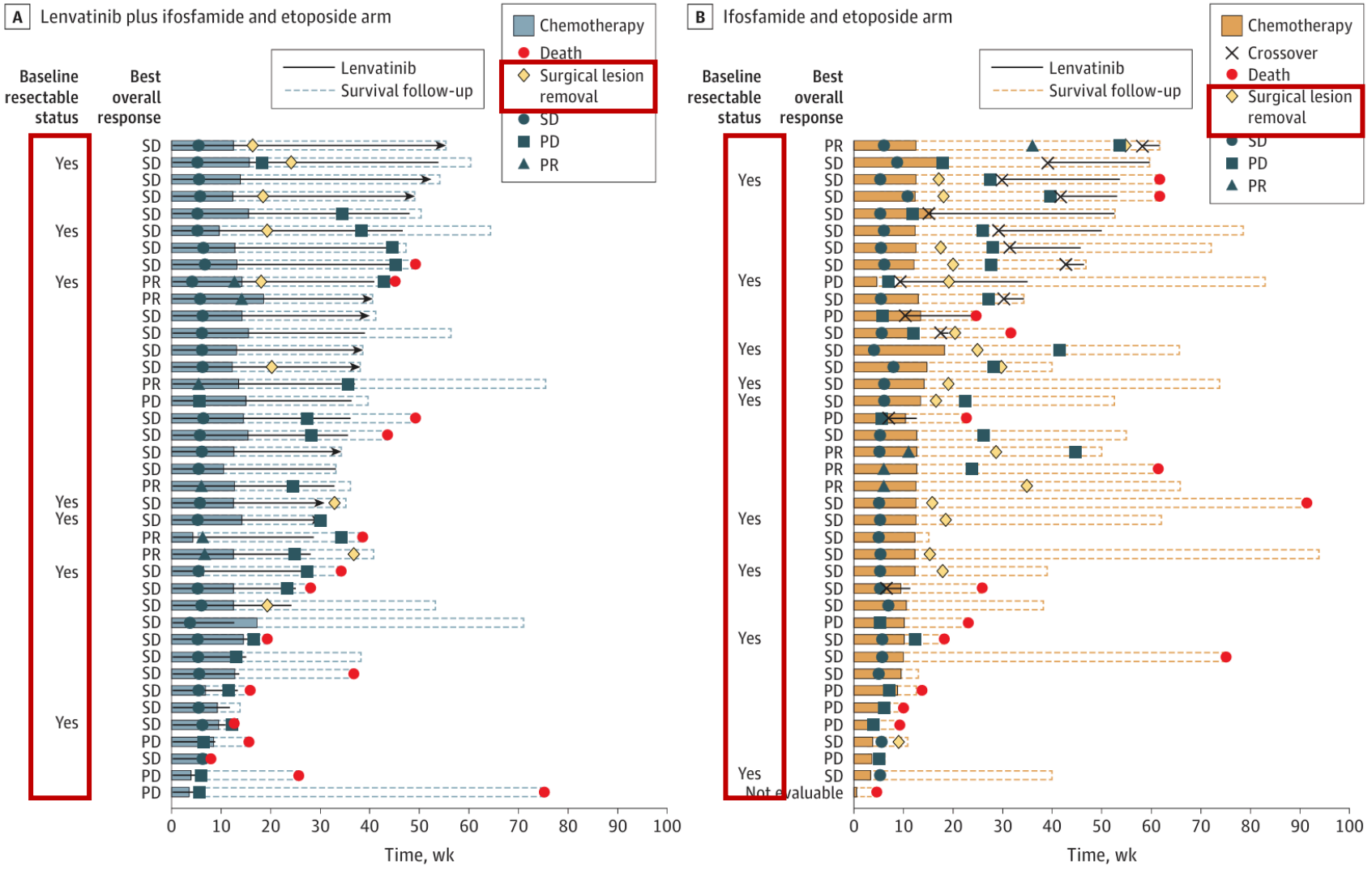




76.3%(95%CI,59.3%-86.9%) in LEN-IE
66.0%(95%CI, 47.7%-79.2%) in IE
Did not meet pre-defined evidence of activity

Crossover N=14

Randomized trials in R/R Disease: Lessons



Imbalance in surgery

- 19 in Arm B, IE
- 8 in Arm A, IE+Lenvatinib

Resection difficult to predict

- 5/18 resectable no surgery
- 15 not resectable surgery

Gaspar N, et al. JAMA Onc 2024

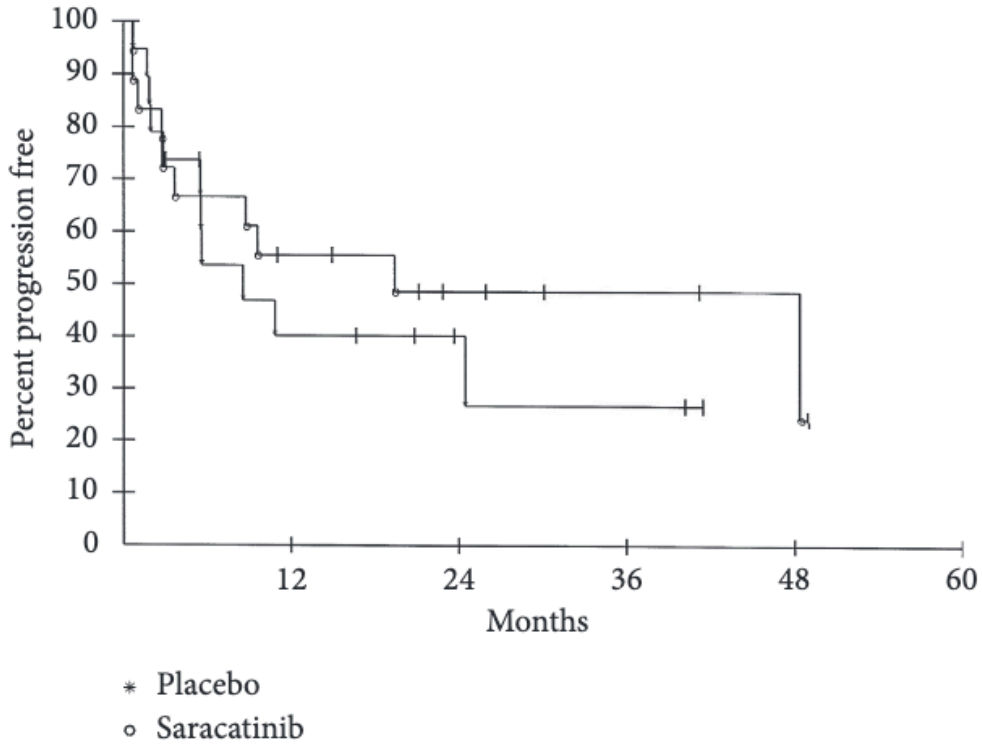
Randomization in R/R Disease: Adjuvant therapy following resection

DESIGN:

- Eligibility: resected pulmonary metastases, ≥15 years
- Accrual and duration: 88 patients in 4 years
- Randomization: Placebo vs. saracatinib, src inhibitor
- 60% relative improvement (from 33% to 53%) in 2-year PFS; 80% power, 1-sided p-value 0.1

RESULTS:

- 40 subjects enrolled in 5 years, median 22 years
- No statistically significant difference in EFS



In spite of this, randomization in this patient population should be feasible!
No placebo, ≥12 years, both arms with similar treatment (e.g., both PO), MANY centers, community engagement

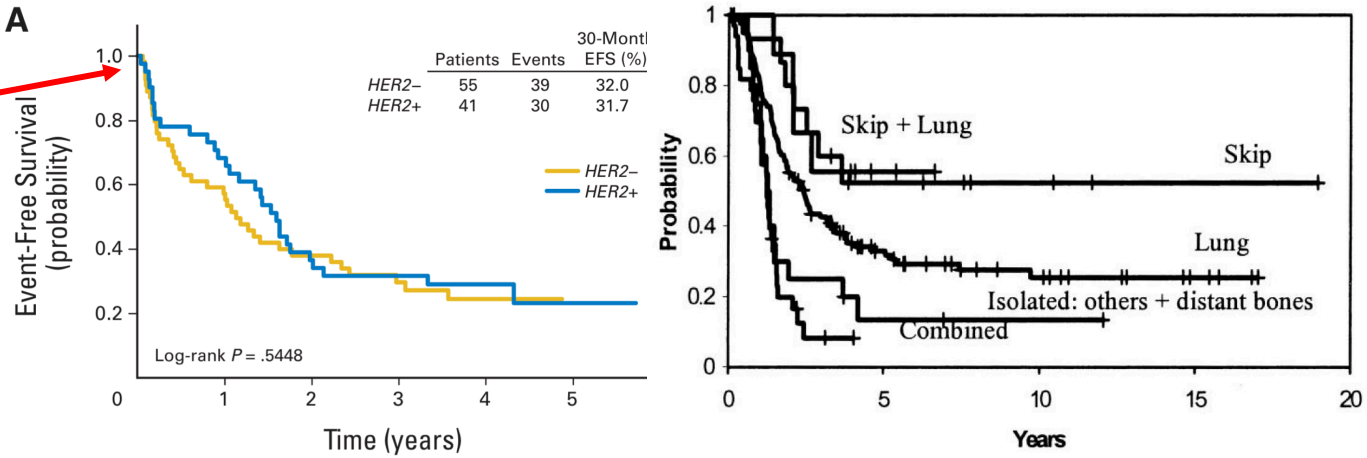
Baird K, et al., Sarcoma 2020

Other trials in Newly Diagnosed Patients?

- Novel approaches could be studied in patient populations with poor outcomes even with MAP
  - Metastatic disease
    - 60%: Lung only: outcome influenced by resectability
      - 1 patient per month in US cooperative group setting
    - 25%: Extra-pulmonary, usually bone
      - Very poor outcomes
      - 0.75 patient every month in US cooperative group setting
      - Favored population for radiopharmaceuticals
  - Eventually, biomarkers defined high-risk localized
- Additional data on biomarkers & outcomes needed
- Interventions
  - Maintenance BUT
  - MAP + novel agent
  - Other OS chemo + novel agent

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	HER2-Positive Patients (n = 41) No.	%	HER2-Negative Patients (n = 55) No.	%	Total Patients (N = 96) No.	%
Metastatic site						
Unilateral lung	1	2.4	0	0.0	1	1.0
Bilateral lung	26	63.4	33	60.0	59	61.5
Bone only	5	12.2	9	16.4	14	14.6
Bone and lung	9	22.0	13	23.6	22	22.9



Ebb D, et al. JCO, 2012; Kager L, et al., 2003

Key Takeaways

- AYA patient population
  - OS trials can precede pediatric phase 1 / development plans
- EFS is key endpoint in both relapsed/refractory and newly diagnosed disease
  - Because of tendency for calcification with response, measures of disease beyond cross-sectional imaging (e.g., PET, ctDNA) should be included
- For rapid assessment of novel agents, single arm signal finding trials in measurable/unresectable disease
  - Eligibility must match benchmark population; if combination with active agent, will need follow-on randomized trial
- Most randomized trials require a large number (100) of trial sites

Thank you!

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Session 5

Attendee and Panelist Q&A

12:45 – 1:30 PM

Moderators:
Lara E. Davis, MD (OHSU)
Nicole Drezner, MD (FDA)

Session 1-4 Panelists

Lunch Break

1:30 – 2:15 PM

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Session 6

Fireside Chat

Changing the Landscape of Pediatric Cancer with Legislation

2:15 – 3:00 PM

Nancy Goodman, Esq. (Kids v Cancer)
Mac Tichenor (OSI)

FDA

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Session 7

The Path Forward

3:00 – 4:00 PM

Session 7

Moderator: Melinda Merchant, MD, PhD (Normunity)	
Katie Barnett, MD	FDA
Nicole Drezner, MD	FDA
Alli Murdoff	Battle Osteosarcoma/OSI
Brigitte Widemann, MD	NCI
Davy Chiodin, PharmD	Day One Biopharmaceuticals
Tedi Soule, PharmD	GSK
Fernanda Arnaldez, MD	AstraZeneca
Dr. Jose Ricardo Pérez-Torrealba	Exelixis

Regulatory Overview: Expedited Programs and Efforts to Advance Product Development for Rare Cancers

Katherine Barnett, MD
Medical Officer, Division of Clinical Evaluation of Oncology
Office of Therapeutic Products
Center for Biologics Evaluation and Research (CBER)
U.S. Food & Drug Administration

Disclosures

- I have no financial conflicts to disclose.

Addressing Challenges in Drug and Biologic Development for Rare Cancers

- Expedited Programs
- Orphan Designation
- Other initiatives to facilitate development of products for rare cancers

FDA Expedited Development Programs

- **Fast Track (1988)**
- **Priority Review (1992)**
- Accelerated Approval (1992)
- **Breakthrough Therapy (2012)**
- **Regenerative Medicine Advanced Therapy (2016)**

These programs may be applicable to drugs or biologics intended to treat rare and serious conditions

Criteria for FT, BT, RMAT

Program	Fast Track (FT)	Breakthrough Therapy (BT)	Regenerative Medicine Advanced Therapy (RMAT)
Qualifying Criteria	• Treats serious condition(s) and • Fills an unmet medical need	• Intended to treat a serious condition and • Preliminary clinical evidence indicates the investigational product may demonstrate substantial improvement over available therapy on clinically significant endpoint(s).	• The product meets the definition of regenerative medicine therapy and • Intended to treat, modify, reverse, or cure a serious condition and • Preliminary clinical evidence indicates potential to address unmet medical needs for such condition

Expedited Programs for Serious Conditions | Drugs and Biologics | FDA
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Features of FT, BT, RMAT

Program	Fast Track (FT)	Breakthrough Therapy (BT)	Regenerative Medicine Advanced Therapy (RMAT)
Features	• **More frequent meetings w/ FDA** to discuss development plan & ensure collection of appropriate data needed to support approval • **More frequent written communication from FDA** about such things as design of proposed clinical trials and use of biomarkers • **Eligibility for Accelerated Approval and Priority Review**, if relevant criteria are met • **Rolling Review**	• **All Fast Track designation features** • Intensive guidance on an efficient drug development program, beginning as early as Phase 1 • Organizational commitment involving senior managers	• **All Breakthrough Therapy Designation features**, including early interactions to discuss any potential surrogate or intermediate endpoints • Statute addresses potential ways to support accelerated approval & satisfy post-approval requirements

Expedited Programs for Serious Conditions | Drugs and Biologics | FDA
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Priority Review

Criteria:

- Treats a serious condition, and,
- If approved, would provide a significant improvement in the safety or effectiveness of the treatment of the condition

Features:

- Shorter clock for review of marketing application (6 months versus 10-month standard review)
  - For applications under the Program the review clock begins at the conclusion of the 60-calendar day filing review period (total review time is 8 months versus 12-month standard review)

Expedited Programs for Serious Conditions | Drugs and Biologics | FDA

Orphan Drug Designation

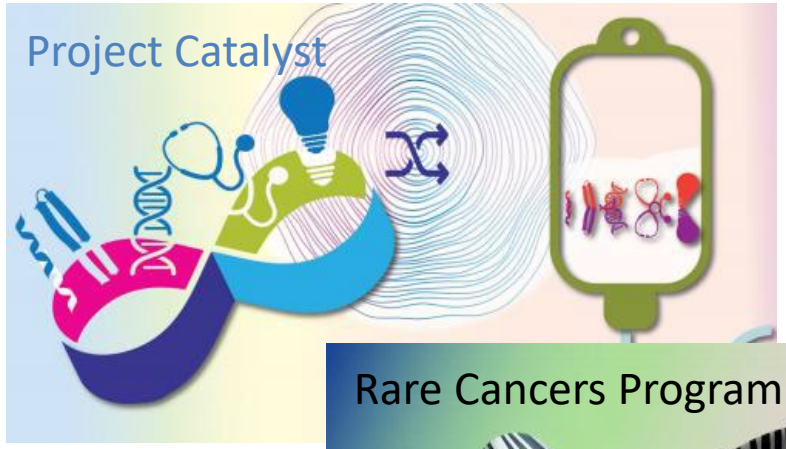
Orphan Drug Act (1983) for diseases with US prevalence < 200,000

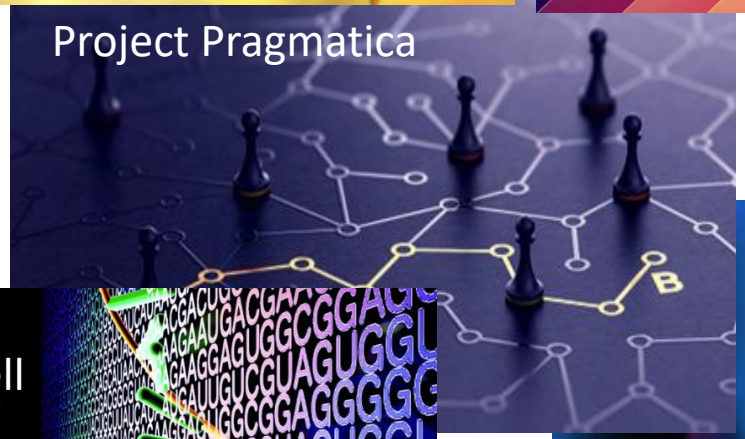
- Tax credits for qualified clinical trials
- Exemption from user fees
- Potential seven years of market exclusivity after approval

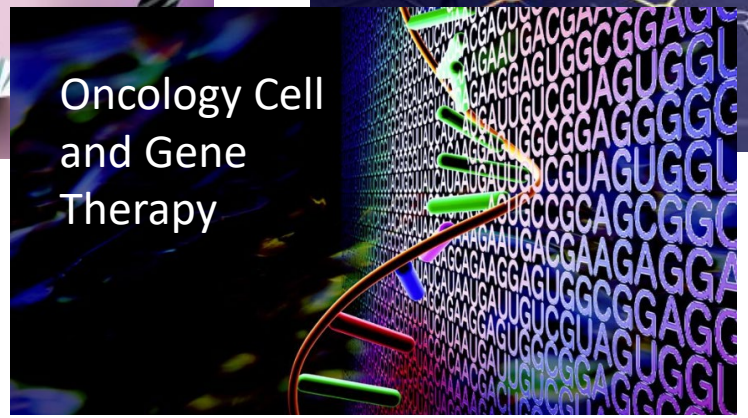
Orphan Products Grants Program

- Clinical Trials Grants Program
  - 2024 awards provide more than $17.2 million to clinical researchers over the next 4 years
  - Recent grants:
    - Palbociclib (CDK4/6i) combined with INCMGA0012 (PD-1 blockade) for well differentiated or dedifferentiated liposarcoma
    - Peptide vaccine targeting CMV antigen for pediatric malignant brain tumors
    - 177Lu-DOTATATE for children and young adults with recurrent/progressive high-grade CNS tumors and meningiomas that express somatostatin type 2A receptors
- Natural History Studies Grants Program

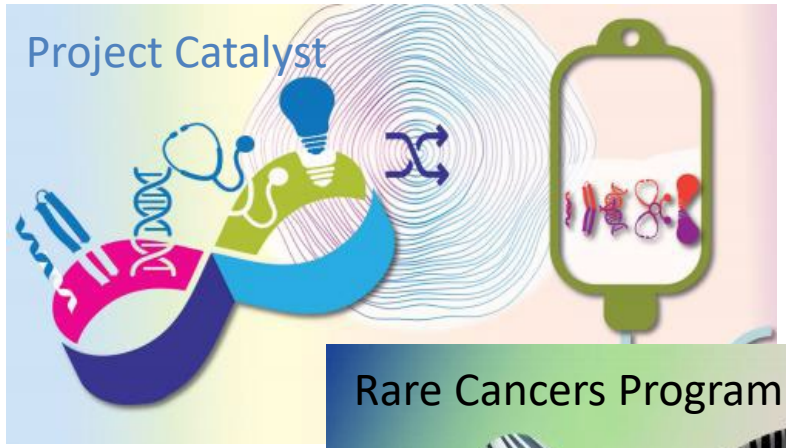
OCE Resources to Advance Product Development for Rare Cancers

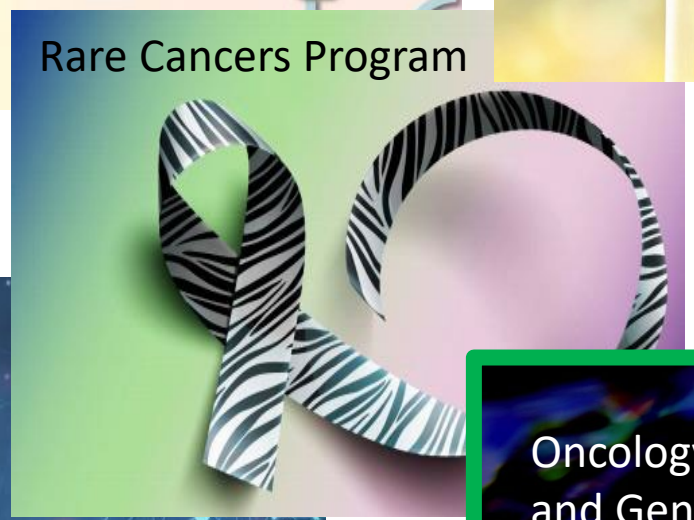






OCE Resources to Advance Product Development for Rare Cancers



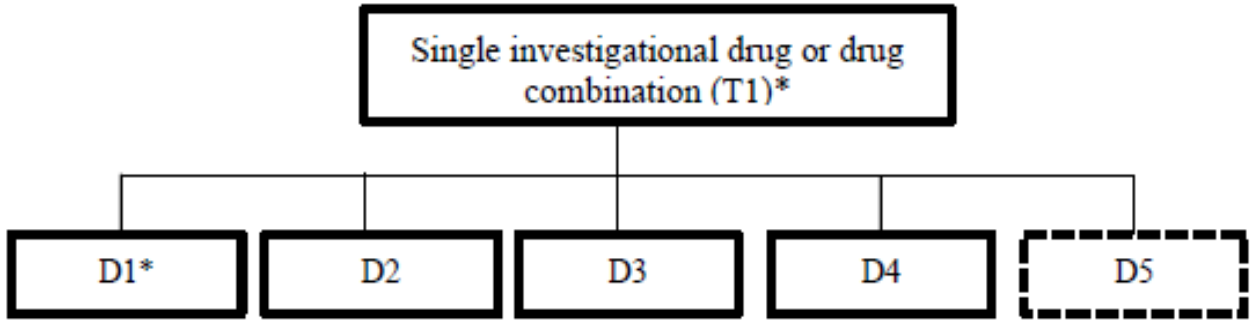


Unique Considerations for Cell and Gene Therapy Trials

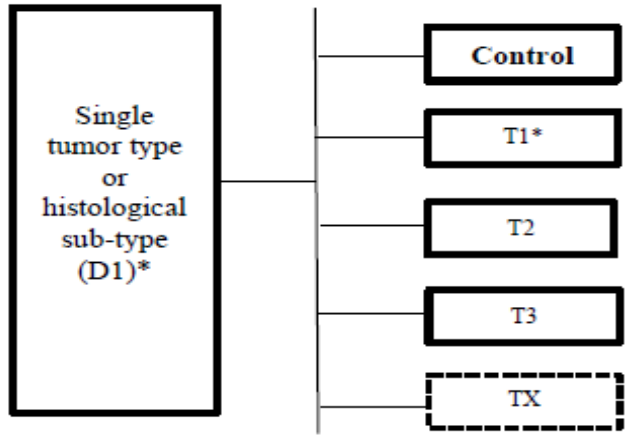
- Complex manufacturing
- Unique pharmacodynamics and/or pharmacokinetics
- Use of lymphodepletion and/or bridging chemotherapy
- Invasive procedures may be required
- Cells or gene may persist for extended period or produce sustained effect
  - Long-term follow up requirement
- Difficulty blinding for randomized trials

FDA supports the use of innovative trial designs

Master Protocol With *Basket Trial* Design



Protocol With *Umbrella Trial* Design



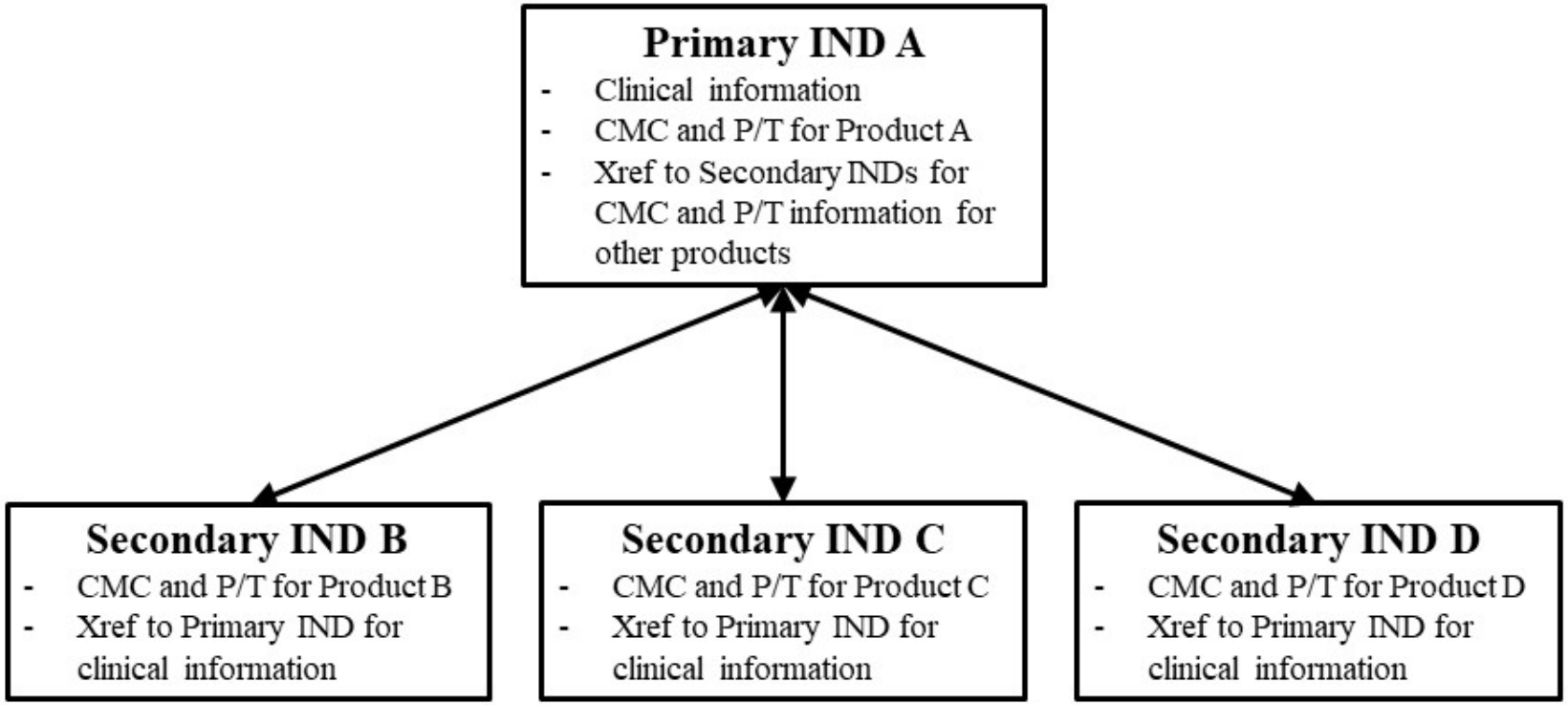
T = investigational drug or investigational drug combination; D = protocol defined subpopulation in single disease subtypes; TX = dashed lines indicate potential amendments to include future treatment arms.

Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry

FDA supports the use of innovative trial designs

Multiple Versions of a Cellular or Gene Therapy Product

Schematic Representation of the Primary and Secondary IND Framework



Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial Draft Guidance for Industry 2021

Conclusions

- Development of novel therapies for osteosarcoma poses unique challenges and requires more than a one-size-fits-all regulatory approach
- FDA offers multiple programs that can be leveraged to address challenges in developing new treatments for rare cancers
- Expedited programs facilitate early and continuous interactions with FDA during product development
- Collaboration among scientists, clinicians, sponsors, patients/patient advocates and regulators is key to advancing development and expediting access of promising therapies to patients with osteosarcoma

Relevant FDA Guidances

- Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations – September 2025 Draft Guidance
- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions - September 2025 Draft Guidance
- Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics – March 2023 Draft Guidance
- Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry – March 2022 Final Guidance
- Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry – March 2022 Final Guidance
- Rare Diseases: Considerations for the Development of Drugs and Biological Products – December 2023 Final Guidance
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial – November 2022 Final Guidance
- Rare Diseases: Natural History Studies for Drug Development – March 2019 Draft Guidance
- Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings – October 2018 Draft Guidance
- Expedited Programs for Serious Conditions | Drugs and Biologics - May 2014 Final Guidance

Acknowledgements

- Kristin Wessel
- Jasmine Smith
- Nicole Drezner
- Martha Donoghue
- Jessica Lee
- Sundeep Agrawal
- Asha Das
- Oncology Center of Excellence
- The Osteosarcoma Institute

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Session 8

Attendee and Panelist Q&A

4:00 – 4:45 PM

Moderators:
Lara E. Davis, MD (OHSU)
Nicole Drezner, MD (FDA)

Session 6-7 Panelists

FDA

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Closing Remarks

4:45 – 5:00 PM

Katherine Janeway, MD, MMSc (DFCI)
Kristin Wessel, MD (FDA)

Final Housekeeping

- Unanswered Questions – We will follow up on submitted questions not addressed during the workshop, if possible

- Post-Workshop Survey – Attendees will receive an email with a brief survey when the meeting concludes. Your feedback is greatly appreciated.

- Workshop recording and slides – Available on:
  - OSI YouTube (by Oct. 31): https://www.youtube.com/@osteosarcomainstitute
  - FDA event webpage (TBD): https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fdathe-osteosarcoma-institute-osi-workshop-advancing-osteosarcoma-drug-development-connecting

Thank You!

- FDA and OSI teams for the commitment to making this workshop a success
- Workshop speakers and panelists
- **The children, adolescents, and young adults with osteosarcoma and their families and advocates**
- **Thank you to all attendees for participating in this workshop!**

- Angelo De Claro, MD
- Richard Pazdur, MD
- Katherine Janeway, MD, MMSc
- Melinda Merchant, MD, PhD
- Lara E. Davis, MD
- Lee Helman, MD
- Michael Egge, Esq.
- Erica Horodniceanu, MPH
- Amy Lobner, MPH, CCRC
- Rachel Mau
- Mac Tichenor

FDA/OSI WORKSHOP:

Advancing Osteosarcoma Drug Development – Connecting Research and Regulatory Pathways for Improved Outcomes

Friday, October 10, 2025
9:30am – 5:00pm Eastern Time

Lincoln Square
555 Eleventh Street NW
Washington, DC 20004

And via Zoom Webinar

FDA

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