THE BEST OF SARCOMA 2019

Anne Grand'Maison MD
Sarcoma Medical Oncology
Roswell Park Cancer Institute
October 5th 2019

THE BEST OF SARCOMA 2019

- No disclosure

- Slides from meeting
  - ASCO 2019
  - CTOS 2018

QUESTIONS

FNA is adequate biopsy to confirm the diagnosis of sarcoma in sarcoma?

1. True
2. False?

QUESTIONS

What is the response rate associated with Pembrolizumab in UPS (undifferentiated pleomorphic sarcoma)?

1. 40%
2. 10%
3. 23%
4. 75%

QUESTIONS

Which drug has recently been approved based on improvement in PFS compared to placebo in desmoid tumors?

1. Pazopanib
2. Trabectedin
3. Sorafenib
4. Pembrolizumab

QUESTIONS

Larotrectinib is a selective inhibitor of?

1. PDGFRA
2. NTRK gene fusion
3. C-KIT
4. VEGFR

SARCOMA

- Comprises < 1% of adult malignancies
- Heterogenous tumor of mesenchymal origin
  - 80 different soft tissue sarcomas
  - 30 bone sarcomas
- Each sarcoma subtype has its own biology, genetic and molecular alterations, different behavior and treatment response
- Sarcoma trials becoming more and more specific to sarcoma subtype and underlying genetic alterations

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Classification of Sarcomas

- Vascular STSs
  - Angiosarcoma
  - Hemangiosarcoma
  - Lymphangiosarcoma
  - Hemangioendothelioma
  - Hemangiopericytoma
  - Kaposi's Sarcoma
- Neural STSs
  - Malignant Peripheral Nerve Sheath Tumor
  - Malignant Paraganglioma
  - Neuroblastoma, Neuroepithelioma
  - Granular Cell Tumor
- Adipose STSs
  - ALT
  - Myxoid/Round cell Liposarcoma
  - Dedifferentiated Liposarcoma
- Smooth Muscle STSs
  - GI, GU, Cutaneous, Vascular
- Skeletal Muscle STSs
  - ARMS, ERMS
- Fibrous STSs
  - Fibrosarcoma
  - Fibromyxoid Sarcomas
  - Desmoid Tumor
  - Dermatofibrosarcoma
  - Inflammatory myofibroblastic tumor
- Unknown Tissue
  - Synovial Sarcoma
  - ASPS
  - Epithelioid Sarcoma
- Pleomorphic STSs
  - Lipo, MFH, Rhabdo
- Neuromuscular STS
  - GI Stromal Tumor
- Unclassified
- Bone Sarcomas
  - Osteosarcoma (+ variants)
  - Chondrosarcoma (+ variants)
  - Giant Cell Tumor of Bone
  - Ewing's Sarcoma Family of Tumors
- Extraskeletal Bone Sarcomas
  - Osteosarcoma
  - Ewing's Sarcoma Family
  - Chondrosarcoma

>200 Enzinger and Weiss

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Jonathan C. Trent, MD, PhD
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UNIVERSITY OF MIAMI HEALTH SYSTEM

SARCOMA - STATISTICS

- 12 390 new sarcoma cases per year with approximately 5000 deaths in US in 2017
- Median overall survival of 13-19 ms
- 5-year survival rates
  - Localized disease 81.4%
  - Metastatic disease 17.3%

SARCOMA - DIAGNOSIS

- Essential to obtain accurate histopathological diagnosis to decide on best treatment options
- Core needle biopsy, incisional or excisional biopsy preferred for diagnosis
- FNA is usually inadequate
- Inaccurate histopathological diagnosis can alter patient management and outcome

Localized, High-Grade, Soft-tissue Sarcomas

Objectives of Neoadjuvant Chemotherapy

- Decrease local recurrence rate
- Eradicate microscopic metastases
- Improve survival
- Alleviate tumor-related pain and suffering
- Down-stage unresectable tumor to enable resection (OSS)
- Determine individual tumor chemosensitivity

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SYLVESTER COMPREHENSIVE CANCER CENTER
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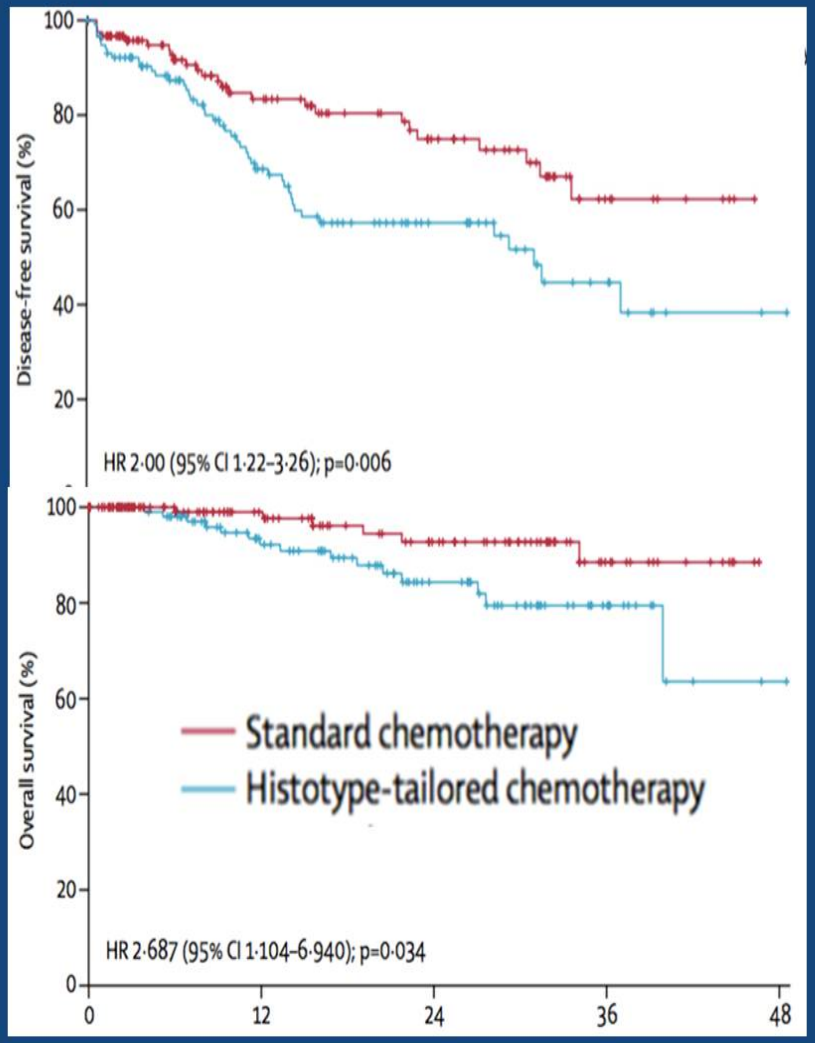
Histology-tailored Neoadjuvant STS

N=287



- STS, randomized
- Moderate Size
- Epirubicin (120) + Ifos (9) x 3 cycles
- Or, Histology-tailored therapy x 3 cycles
  - Synovial Sarcoma: HD Ifos 14 day CI
  - Myxoid LPS: trabectedin
  - Leiomyosarcoma: Gemcitabine+Dacarbazine
  - MPNST: Ifosfamide (9) + etoposide
  - Unclassified Pleomorphic: Gem + Docetaxel
- DFS 62% EI vs 38% histology-tailored

Gronchi et al, Lancet Oncol 2017

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Soft-tissue Sarcomas

Absolute Risk Reduction from Adjuvant Chemotherapy

Regimen	Local Recurrence	Distant Recurrence	Any Recurrence	Survival
Doxorubicin	3% (1-7%)	9% (4-14%)	9% (4-14%)	5% (6-21%)
Doxorubicin + Ifosfamide	**5% (1-12%)**	**10% (1-19%)**	**12% (3-21%)**	**11% (3-19%)**
Doxorubicin OR Doxorubicin + Ifosfamide	4% (0-7%)	9% (5-14%)	10% (5-15%)	6% (2-11%)

Absolute Risk Reduction (95% CI)

Pervaiz, Cancer 113:573-581

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Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial

Penella J Woll, Peter Reichardt, Axel Le Cesne, Sylvie Bonvalot, Alberto Azzarelli†, Harald J Hoekstra, Michael Leahy, Frits Van Coevorden, Jaap Verweij, Pancras C W Hogendoorn, Monia Ouali, Sandrine Marreaud, Vivien H C Bramwell, Peter Hohenberger, for the EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee

EORTC
The future of cancer therapy

	Control (n=176)	Chemotherapy (n=175)
Age (years)		
Median (range)	49·1 (17·5–71·4)	49·2 (17·3–68·5)
Sex		
Male	98 (56%)	96 (55%)
Performance status		
0	114 (65%)	124 (71%)
1	62 (35%)	51 (29%)
Tumour site		
Extremity	118 (67%)	116 (66%)
Limb girdle	24 (14%)	20 (11%)
Central*	34 (19%)	39 (22%)
Tumour size (cm)		
Median (range)	8·6 (0·3–35)	7·5 (1·2–38)

Data are number of patients (%) unless otherwise indicated. *Central includes head and neck and other.

Table 1: **Patient characteristics**

	Local diagnosis		Review diagnosis	
	Control (n=176)	Chemotherapy (n=175)	Control (n=136)	Chemotherapy (n=145)
Histological type				
MFH	51 (29%)	33 (19%)	25 (18%)	15 (10%)
Liposarcoma*	35 (20%)	24 (14%)	25 (18%)	20 (14%)
Leiomyosarcoma	22 (12%)	36 (21%)	23 (17%)	32 (22%)
Synovial sarcoma	22 (12%)	28 (16%)	18 (13%)	22 (15%)
Other	46 (26%)	54 (31%)	45 (33%)	56 (39%)
Trojani grade				
Grade I	0	0	7 (5%)	10 (7%)
Grade II	69 (39%)	72 (41%)	64 (47%)	70 (49%)
Grade III	107 (61%)	103 (59%)	66 (48%)	64 (44%)

Data are number of patients (%). 281 tumours were submitted for central pathological review. MFH=malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma). *Includes pleomorphic, myxoid, and dedifferentiated subtypes.

Table 2: **Tumour characteristics**

THE IMPACT OF CHEMOTHERAPY ON SURVIVAL OF PATIENTS WITH EXTREMITY AND TRUNK WALL SOFT TISSUE SARCOMA: REVISITING THE RESULTS OF THE EORTC-STBSG 62931 RANDOMISED TRIAL USING SARCULATOR, A VALIDATED NOMOGRAM-BASED RISK ASSESSMENT TOOL

Pasquali S*, Pizzamiglio S, Touati N, Litiere S, Marreaud S, Kasper B, Gelderblom H, Stacchiotti S, Verderio P, Casali PG, Woll PJ and Gronchi A, on behalf of the EORTC – Soft Tissue and Bone Sarcoma Group.

Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

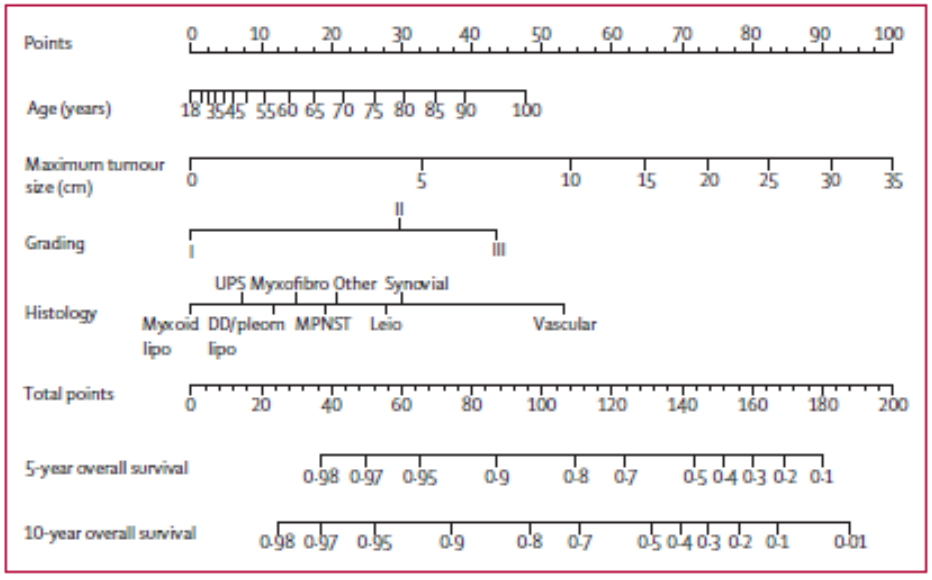
Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis

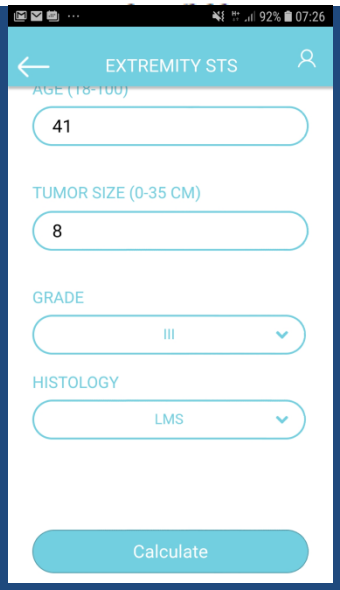
Dario Callegaro, Rosalba Miceli, Sylvie Bonvalot, Peter Ferguson, Dirk C Strauss, Antonin Levy, Anthony Griffin, Andrew J Hayes, Silvia Stacchiotti, Cecile Le Pechoux, Myles J Smith, Marco Fiore, Angelo P Dei Tos, Henry G Smith, Luigi Mariani, Jay S Wunder, Raphael E Pollock, Paolo G Casali, Alessandro Gronchi

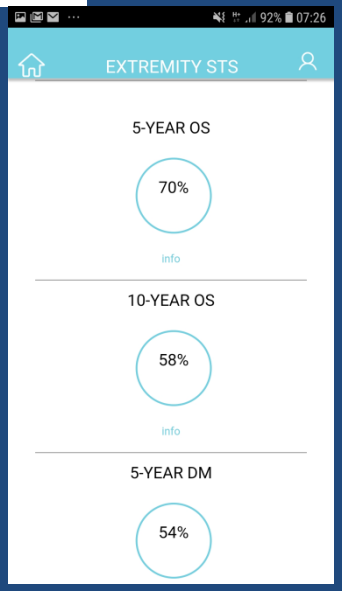
Summary

Background The current American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC)

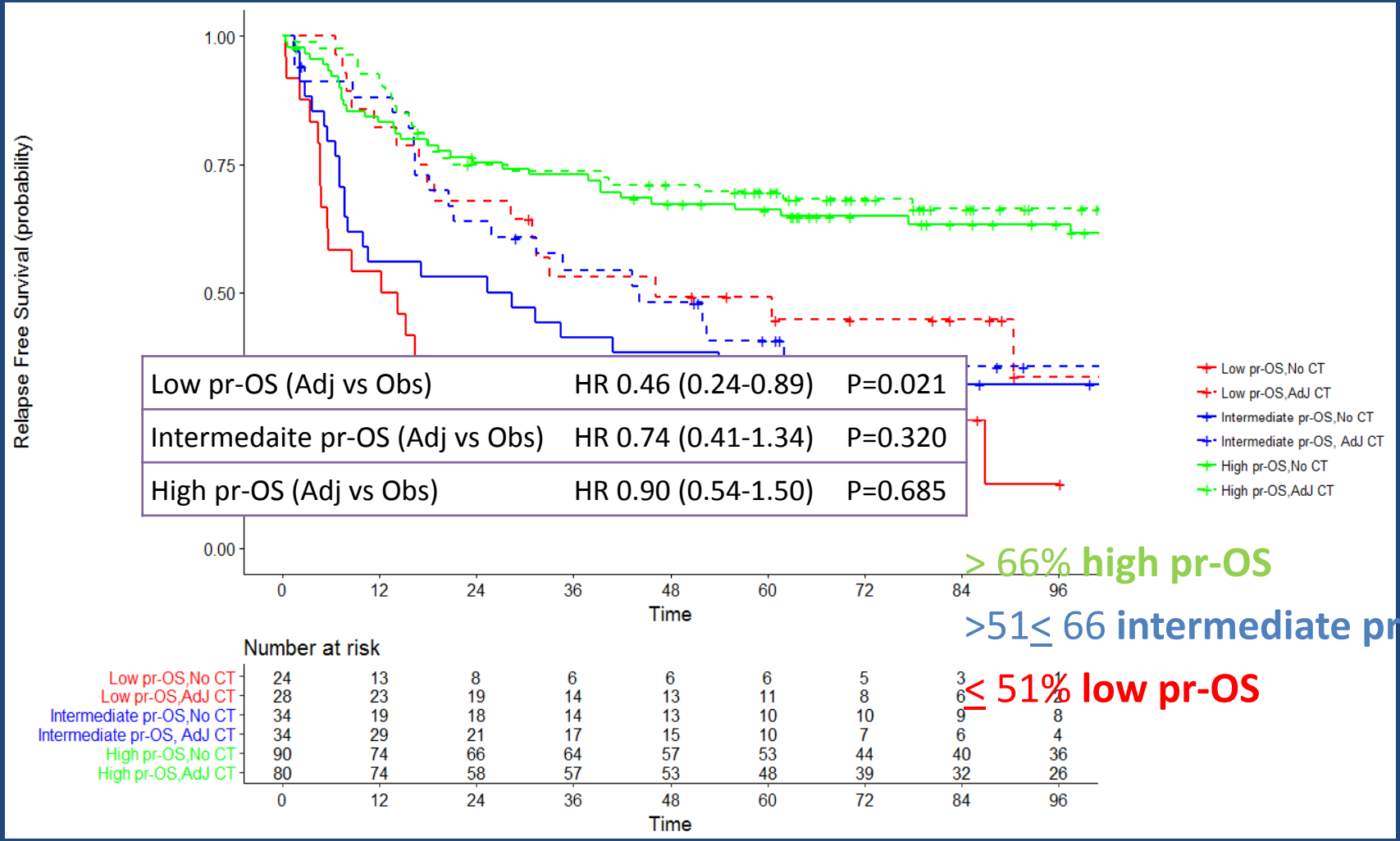
Lancet Oncol 2016; 17: 671–80



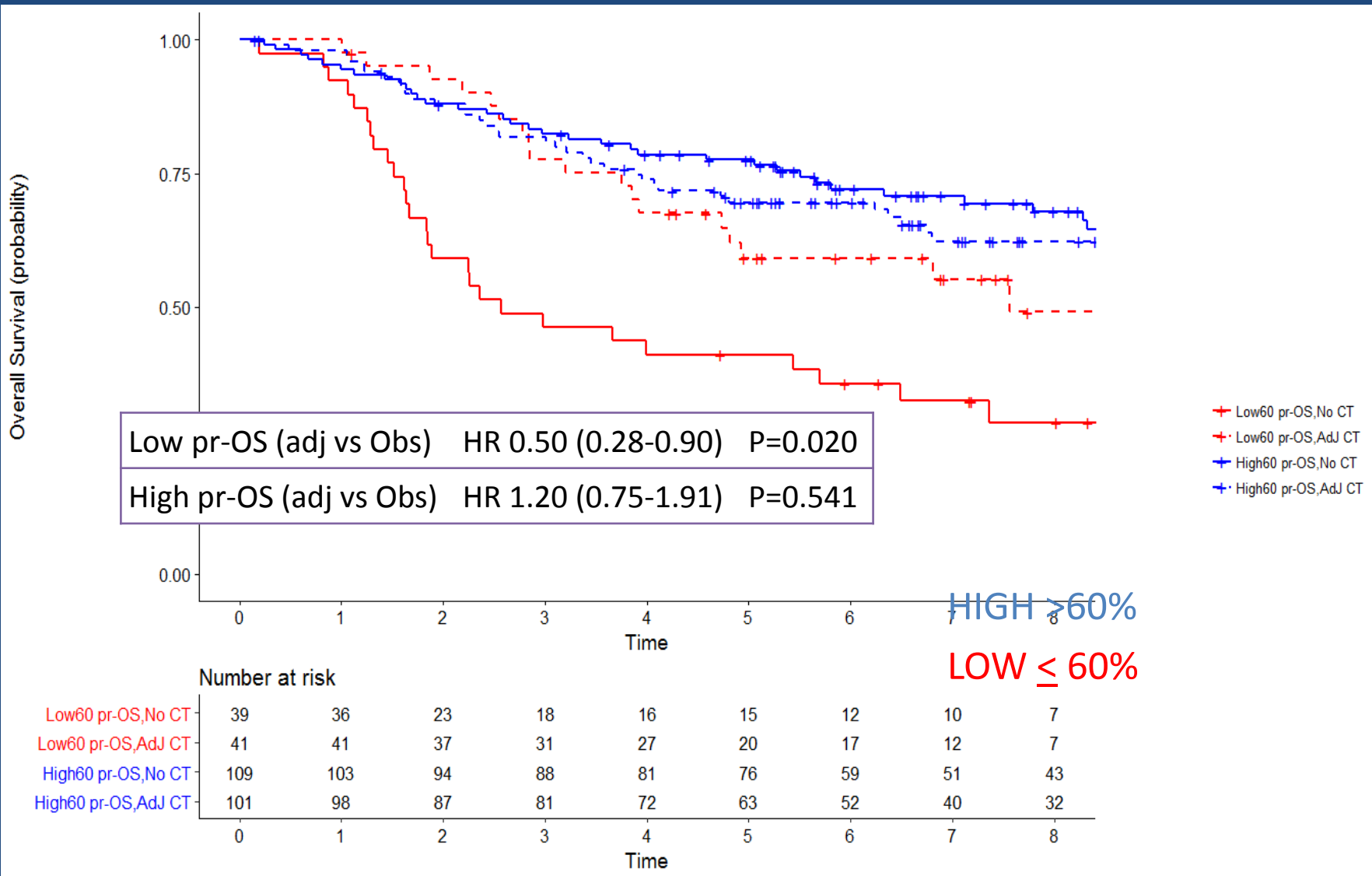




DISEASE-FREE SURVIVAL



OVERALL SURVIVAL



PERIOPERATIVE CHEMOTHERAPY IN SARCOMA

- There is a role for neoadjuvant and adjuvant chemotherapy in large high grade sarcomas with unfavorable histology
- Up to 50% reduction in risk of death (HR 0.5) in high risk patients (> 60% risk of distant disease) from reassessment of the EORTC study using predictive tool Sarculator
- In appropriate patient
- Tumor with sufficient risk of recurrence or metastases
- Using the most effective chemotherapy at the optimal doses

METASTATIC DISEASE

Metastatic, Unresectable STS: Reasons for Hope?

Although median OS after the development of distant metastases is 11-19 months[1,2] and the majority of patients with metastatic STS are incurable, systemic therapy can:

- Offer meaningful palliation
- Prevent rapid disease progression
- In some instances, prolong survival

1. Van Glabbeke M et al. *J Clin Oncol*. 1999;17:150-157. 2. Tap WD et al. *Lancet Oncol*. 2017;18:1089-1103.

METASTATIC DISEASE

Increasing Number of Newer Options Available or Being Tested in Advanced STS

Standard chemotherapy
Doxorubicin + ifosfamide, gemcitabine + docetaxel

Targeted therapy
Pazopanib, olaratumab (both approved)

Novel cytotoxics
Trabectedin, eribulin (both approved), aldoxorubicin (?)

The future?
Immune checkpoints (PD1), selective inhibitors of nuclear export (selinexor), EZH2 inhibitors, anti-endoglin antibodies, CDK4/MDM2 inhibitors, PARP inhibitors, TRK inhibitors

CHEMOTX AGENTS - OPTIONS

Decision based on PS, comorbidities, STS subtype

OLD AGENTS OR PROTOCOL	RR	NEWER AGENTS	RR
MAI (all STS)	40-88%	Pazopanib (all except LS)	< 10%
Gem-Tax (all STS)	16%	Trabectedin (LMS, MLS)	10%
Doxorubicin	14%	Eribulin (LMS, LS)	< 10%
Gemcitabine alone	8-18%	Doxo + Olaratumab (all)	< 10%
Paclitaxel (cutaneous angio)	15-20%	Aldoxorubicin (all but more in LS & LMS?)	8.2 %

Phase II Trial of Gemcitabine with Pazopanib or Gemcitabine with Docetaxel in Advanced Soft Tissue Sarcoma (STS)

Neeta Somaiah[1], Brian Andrew Van Tine[2], Elizabeth Goodwin Hill[3], Mohammed M. Milhem[4], Scott Schuetze[5], Christian Frederick Meyer[6], Daniel Y. Reuben[3], Anthony D. Elias[7], William L. Read[8], Sant P. Chawla[9], Amy E. Wahlquist[3], Elizabeth Garrett-Mayer[3], Andrew S. Kraft[10]

[1]Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Washington University in St. Louis, St. Louis, MO; [3]Medical University of South Carolina, Charleston, SC; [4]University of Iowa, Iowa City, IA; [5]University of Michigan, Ann Arbor, MI; [6]Johns Hopkins Hospital, Baltimore, MD; [7]University of Colorado Comprehensive Cancer Center, Aurora, CO; [8]Emory Clinic, Atlanta, GA; [9]Sarcoma Oncology Research Center, Santa Monica, CA; [10]Univ of Arizona Cancer Ctr, Tucson, AZ

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

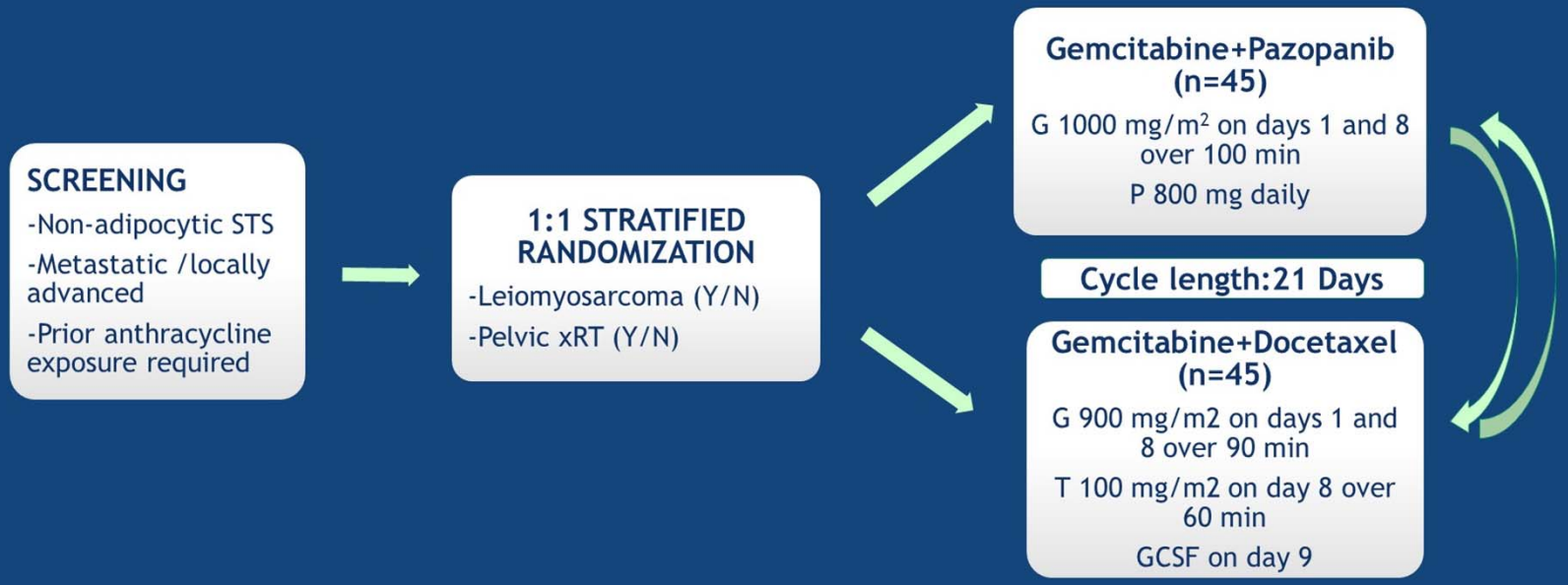
PRESENTED BY: Neeta Somaiah, M.D.

Phase II Trial of Gemcitabine with Pazopanib or Gemcitabine with Docetaxel in Advanced STS

- Trial designed to examine activity of Pazopanib when combined with Gemcitabine as an alternative to Gemcitabine combined with Docetaxel
- 90 pts (45 in each group)
- Cross over allowed
- Objectives
  - 1° PFS and AEs
  - 2° RR and OS
- Well balanced groups for age, gender, LMs, prior radiation, chemotherapy and surgery

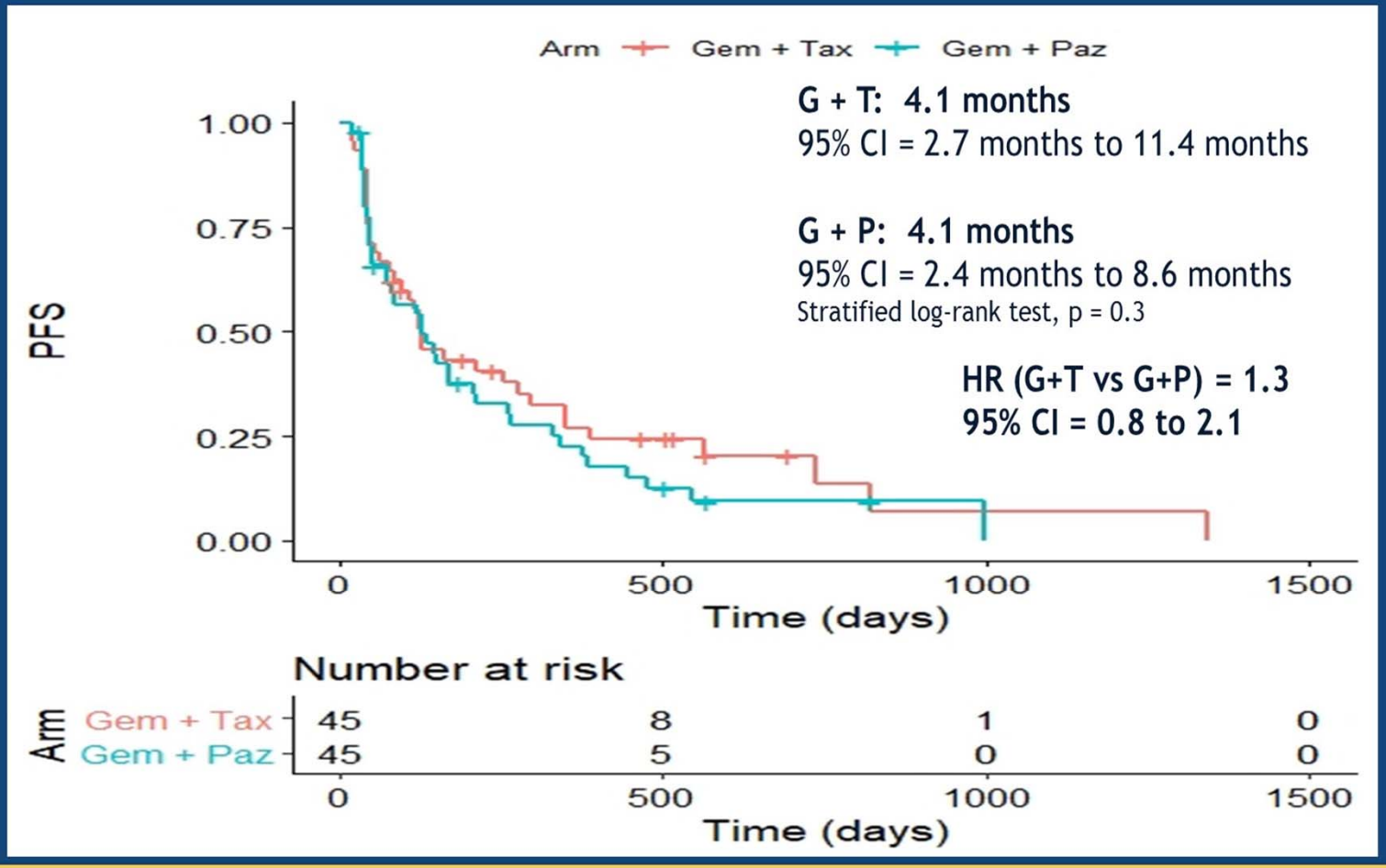
Phase II Trial of Gemcitabine with Pazopanib or Gemcitabine with Docetaxel in Advanced STS

Study Design



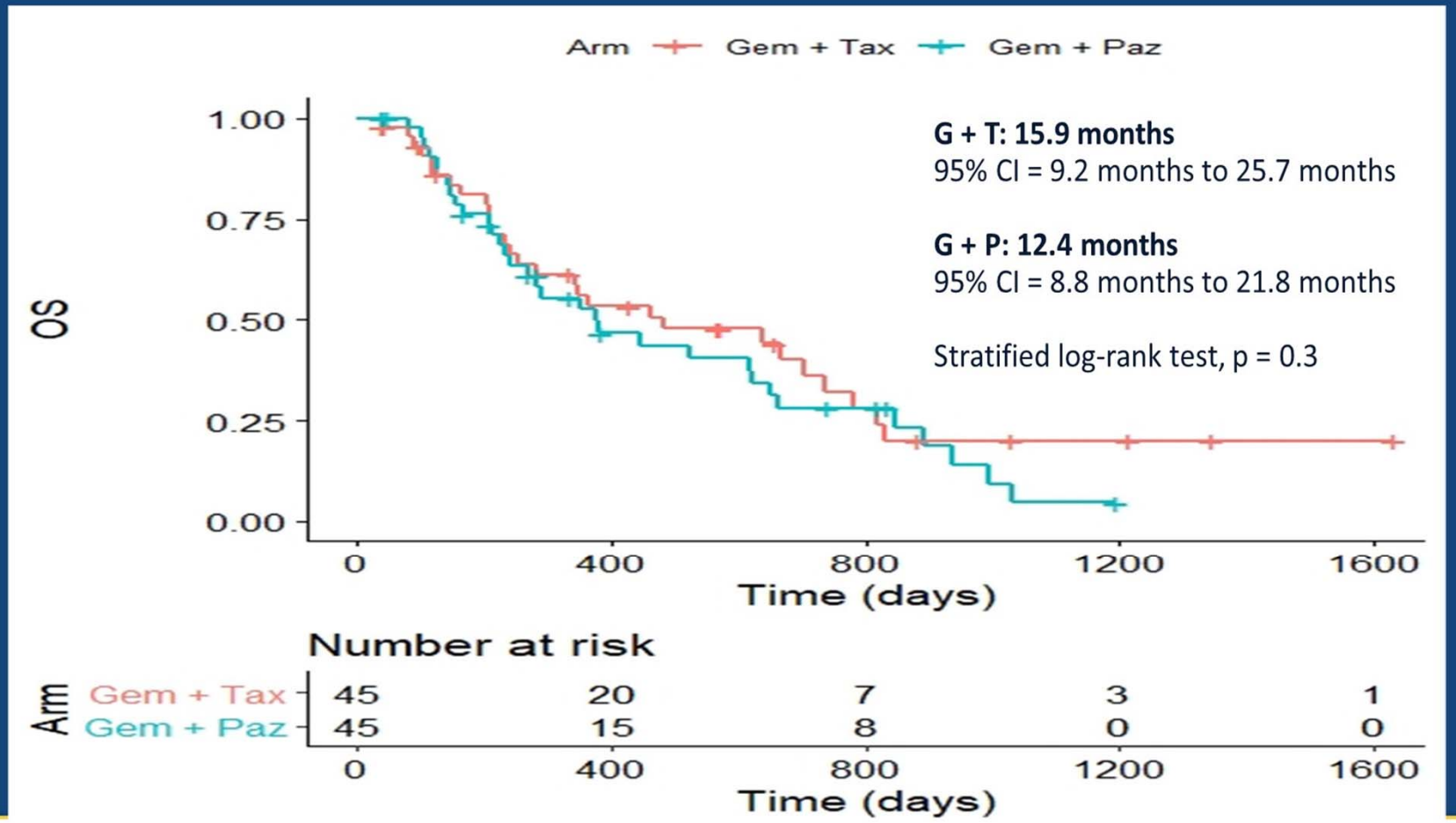
Phase II Trial of Gemcitabine with Pazopanib or Gemcitabine with Docetaxel in Advanced STS

Median PFS



Phase II Trial of Gemcitabine with Pazopanib or Gemcitabine with Docetaxel in Advanced STS

Median OS



Phase II Trial of Gemcitabine with Pazopanib or Gemcitabine with Docetaxel in Advanced STS

Overall Response Rate (RR) (RECIST 1.1)*

G+T (n=44)	G+P (n=43)
• PR (%): 8 (18)	• PR (%): 5 (12)
• SD (%): 21 (48)	• SD (%): 24 (56)
• PD (%): 15 (34)	• PD (%): 14 (33)

The clinical benefit rate (PR+SD) was 66% and 68% for G+T and G+P, respectively (p>0.99, based on Fisher's exact test).

*Locally assessed

Phase II Trial of Gemcitabine with Pazopanib or Gemcitabine with Docetaxel in Advanced STS

Conclusions

- Similar median PFS for Gemcitabine + Pazopanib and Gemcitabine + Docetaxel, in unselected advanced STS patients in the 2nd or 3rd line.
- Similar rate of toxicity with G+P and G+T. Majority needed dose reductions.
- G+P can be considered as an alternative in select patients who are not candidates for G+T / intolerant to T.

PEXIDARTINIB IN ADVANCED TENOSYNOVIAL GIANT CELL TUMOR

FDA APPROVED ON AUGUST 2ND 2019

Abstract 11502

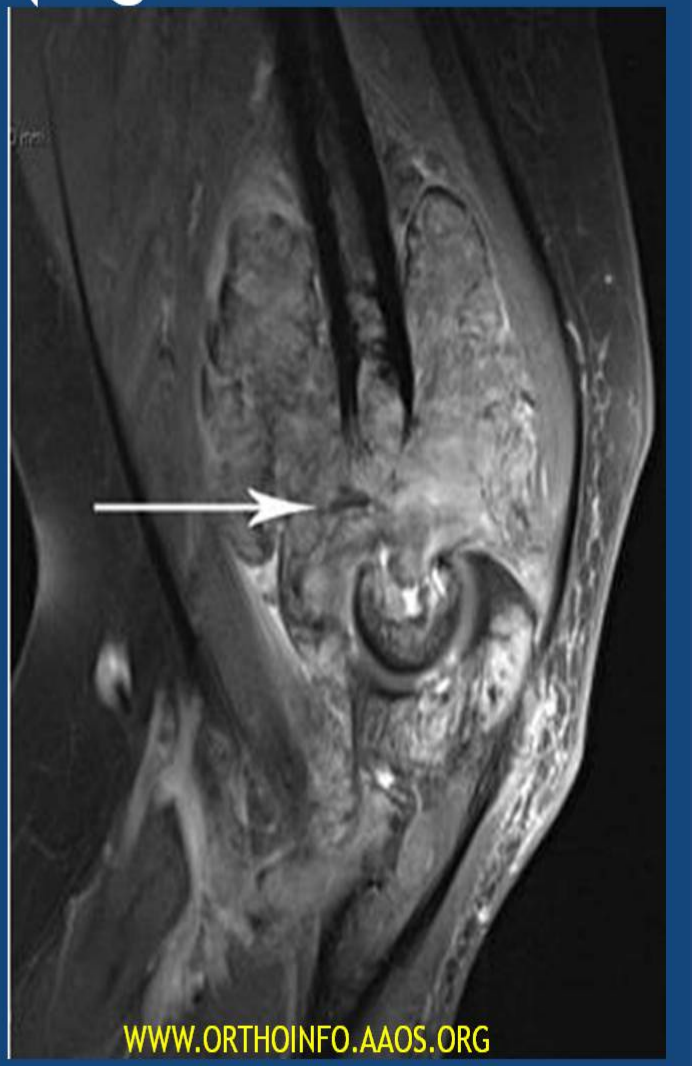
Final Results of ENLIVEN: A Global, Double-Blind, Randomized, Placebo-Controlled Phase 3 Study of Pexidartinib in Advanced Tenosynovial Giant Cell Tumor (TGCT)

William D. Tap,[1] Hans Gelderblom,[2] Silvia Stacchiotti,[3] Emanuela Palmerini,[4] Stefano Ferrari,[4] Jayesh Desai,[5] Sebastian Bauer,[6] Jean-Yves Blay,[7] Thierry Alcindor,[8] Kristen Ganjoo,[9] Javier Martin-Broto,[10] Christopher W. Ryan,[11] Dale E. Shuster,[12] Ling Zhang,[12] Qiang Wang,[12] Henry H. Hsu,[13] Paul S. Lin,[13] Sandra Tong-Starksen,[13] and Andrew J. Wagner[14]
on behalf of the ENLIVEN Investigators

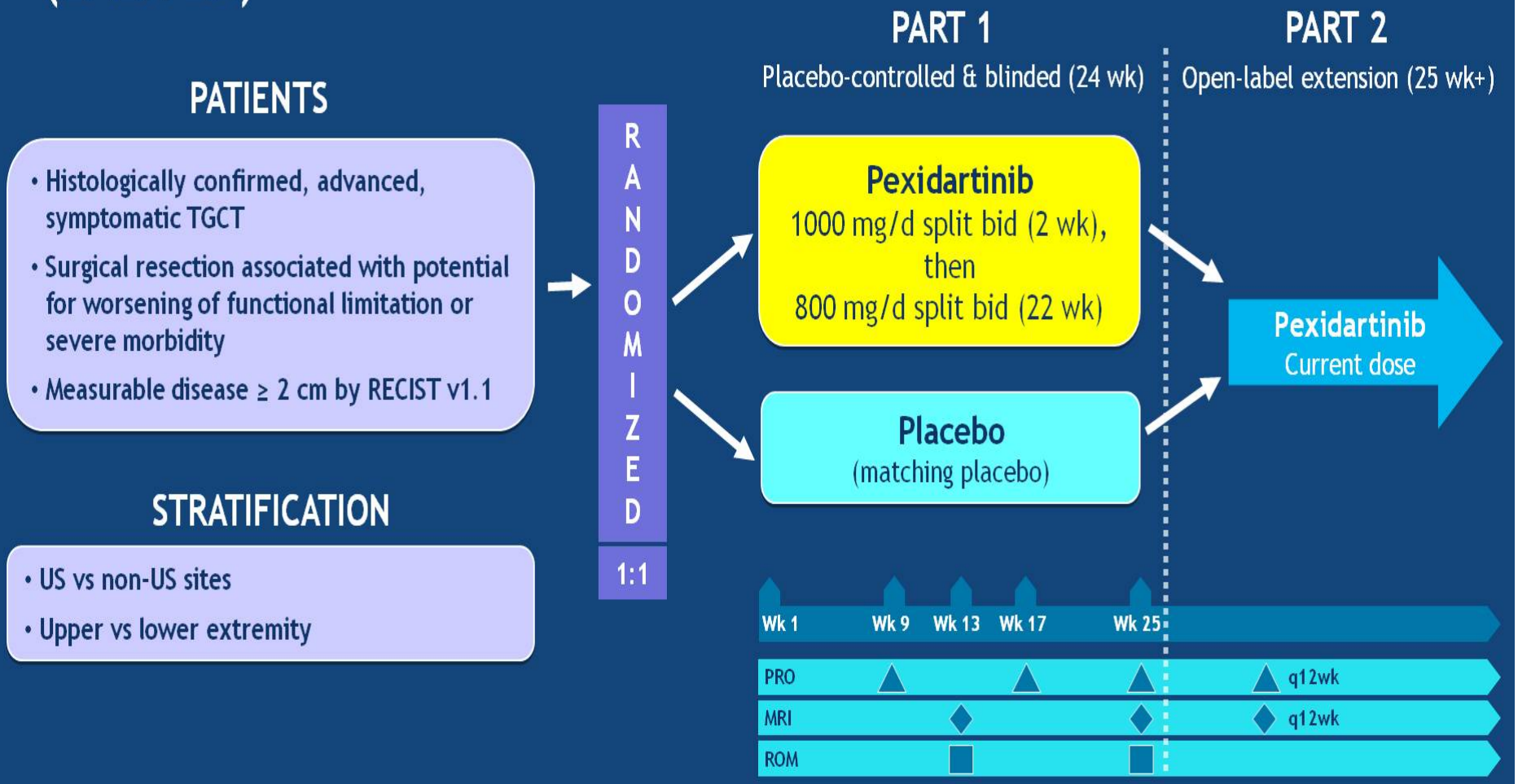
[1]Memorial Sloan Kettering Cancer Institute, New York, NY, USA; [2]Leiden University Medical Center, Rapenburg, Netherlands; [3]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [4]Istituto Ortopedico Rizzoli, Bologna, Italy; [5]Peter MacCallum Cancer Centre, Melbourne, Australia; [6]West German Cancer Center, University Hospital Essen, Essen, Germany; [7]Centre Léon Bérard, Lyon, France; [8]McGill University, Montreal, Quebec, Canada; [9]Stanford University, Palo Alto, CA, USA; [10]Hospital Universitario Virgen del Rocío, Seville, Spain; [11]Oregon Health & Science University, Portland, OR, USA; [12]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [13]Plexxikon Inc., Berkeley, CA, USA; [14]Dana-Farber Cancer Institute, Boston, MA, USA

Tenosynovial Giant Cell Tumor (Pigmented Villonodular Synovitis)

- Benign, though often highly morbid inflammatory neoplasm arising in joints.
- Driven primarily by a small proportion of cells harboring a *COL6A3-CSF1* translocation leading to excessive CSF1 expression (West et al. PNAS 2006)
- NO current approved therapies
- Current standard of care if surgery if not overly morbid

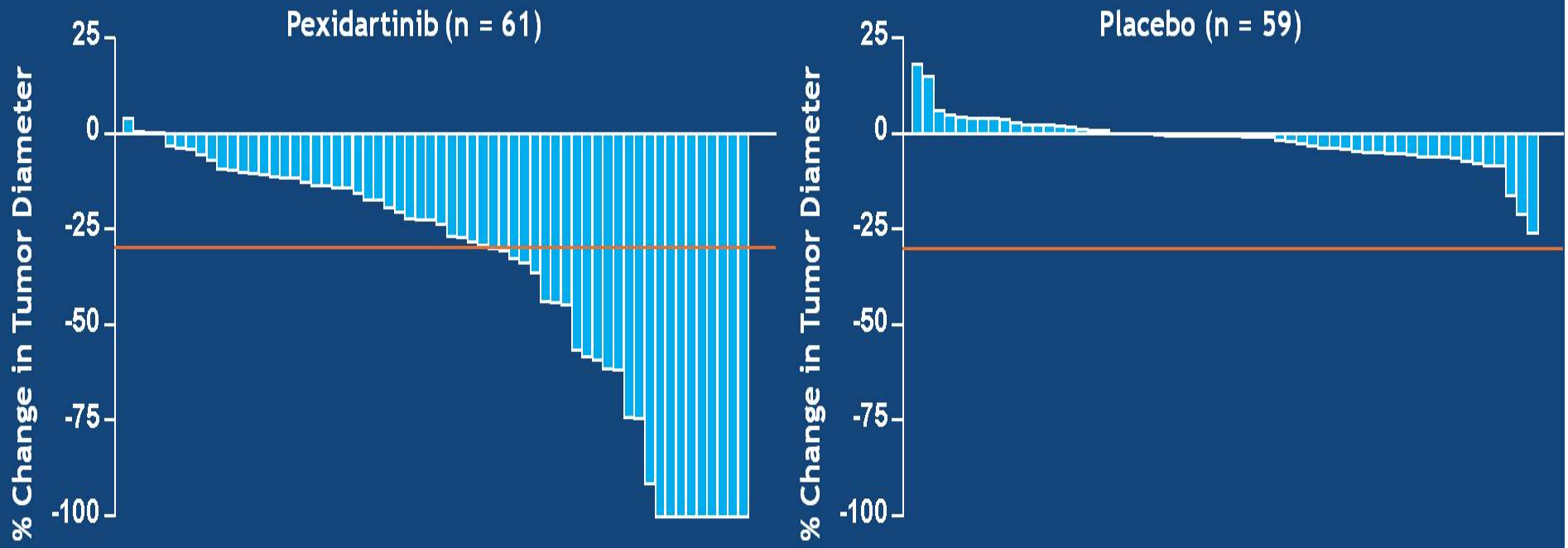


Randomized, Double-Blind, Phase 3 Study Design (ENLIVEN)



ClinicalTrials.gov Identifier: NCT02371369

Primary Endpoint: Tumor Response by RECIST v1.1*
Week 25 Response (Blinded, Central MRI Review; ITT Population)

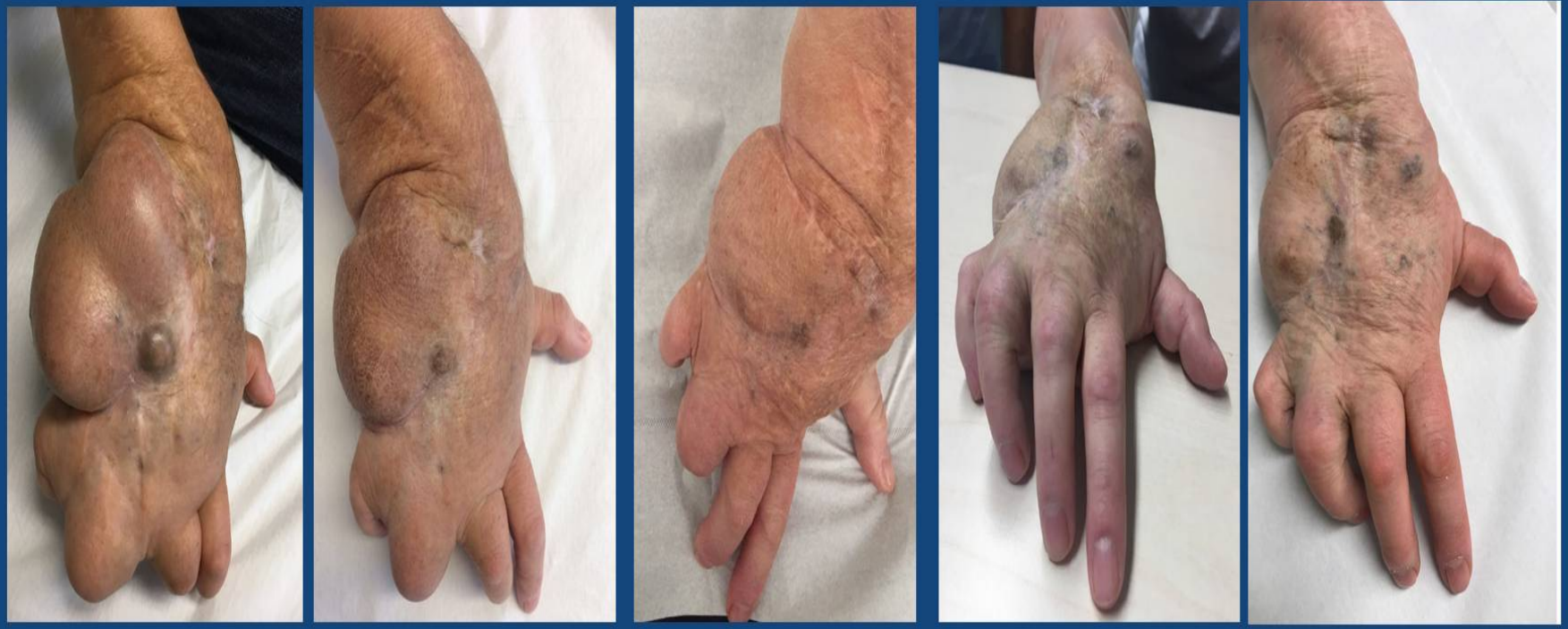


Treatment, n (%)	Complete	Partial	Stable Disease	Progressive Disease	Not Evaluable	Overall Response Rate [95% CI]
Pexidartinib n = 61	9 (15)	15 (25)	24 (39)	1 (2)	12 (20)	24 (39) [28.1, 51.9] *P* < 0.0001
Placebo n = 59	0	0	46 (78)	1 (2)	12 (20)	0 [0, 6.1]

*Baseline mean sum of the longest tumor diameters was 10.1 and 10.6 cm for pexidartinib and placebo, respectively.

ENLIVEN Patient

- 56-year-old female diagnosed w/TGCT Jun 10, 1988
- Multiple prior surgeries, regular RBC transfusions
- Started pexidartinib Sep 5, 2016, and still ongoing
- Baseline pain: 5.6, decreased to 0.6 at week 25



October 2016 | November 2016 | June 2017 | September 2017 | May 2018

Conclusions: Pexidartinib in Tenosynovial giant cell tumor

- Significantly improved ORR over placebo
  - RECIST: 39% vs 0%, $P < 0.0001$
  - TVS: 56% vs 0%, $P < 0.0001$
- Generally well tolerated
  - Serious, nonfatal liver toxicity with increased bilirubin in 4% of patients
  - Majority of other AEs < grade 3
- Improved patient symptoms and function on active study drug
- Will this study be sufficient for an approval?

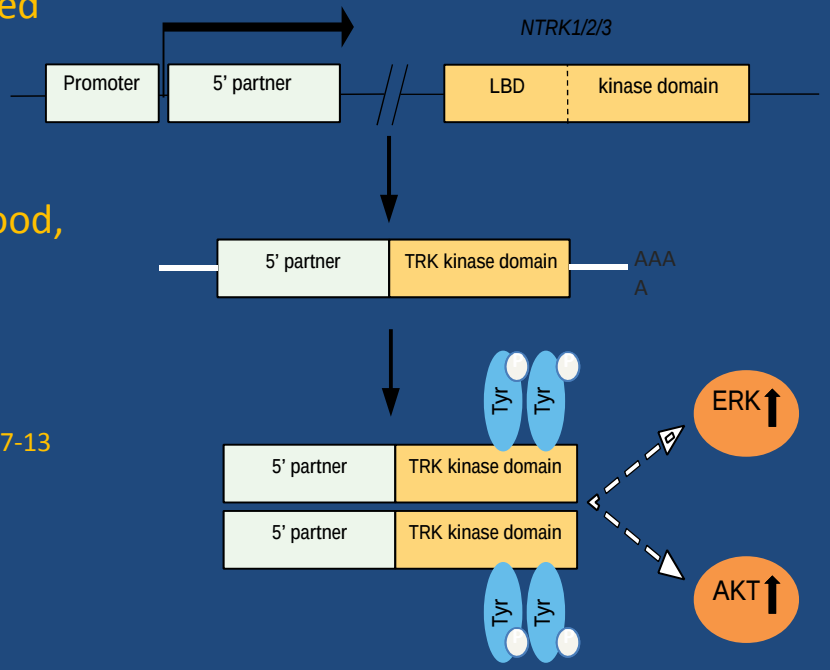
NTRK FUSION - LAROTRECTINIB

FDA APPROVED NOVEMBER 26TH 2019 FOR NTRK FUSION TUMORS

ROLE IN SARCOMA?

TRK fusions are oncogenic drivers

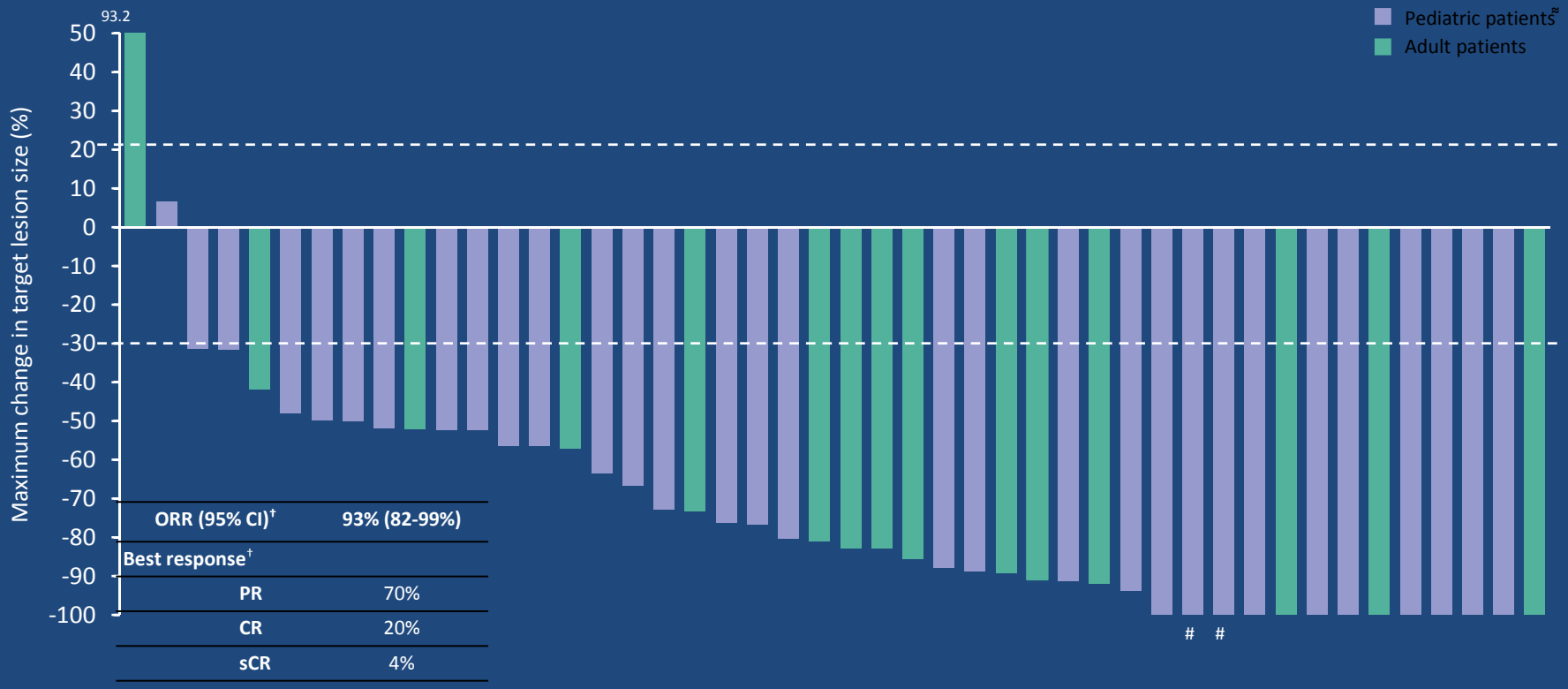
- After embryonal development, tropomyosin receptor kinases (TRK) expression is primarily limited to the nervous system[1]
- 3 structurally related neurotrophin receptors encoded by 3 distinct genes that regulate specific normal functions[2-6]
  - *NTRK1* → TRKA → Pain, thermoregulation
  - *NTRK2* → TRKB → Movement, memory, mood, appetite, body weight
  - *NTRK3* → TRKC → Proprioception
- Recurrent chromosomal fusion events have been identified across diverse pediatric and adult cancers[7-13]



NTRK FUSIONS IN SARCOMAS

- ✓Pediatric and young adult soft tissue sarcomas
- ✓Pan-negative gastrointestinal stromal tumors (GIST)
- ✓Adult sarcoma
- ✓Infantile fibrosarcoma

Efficacy of larotrectinib in patients with TRK fusion sarcoma

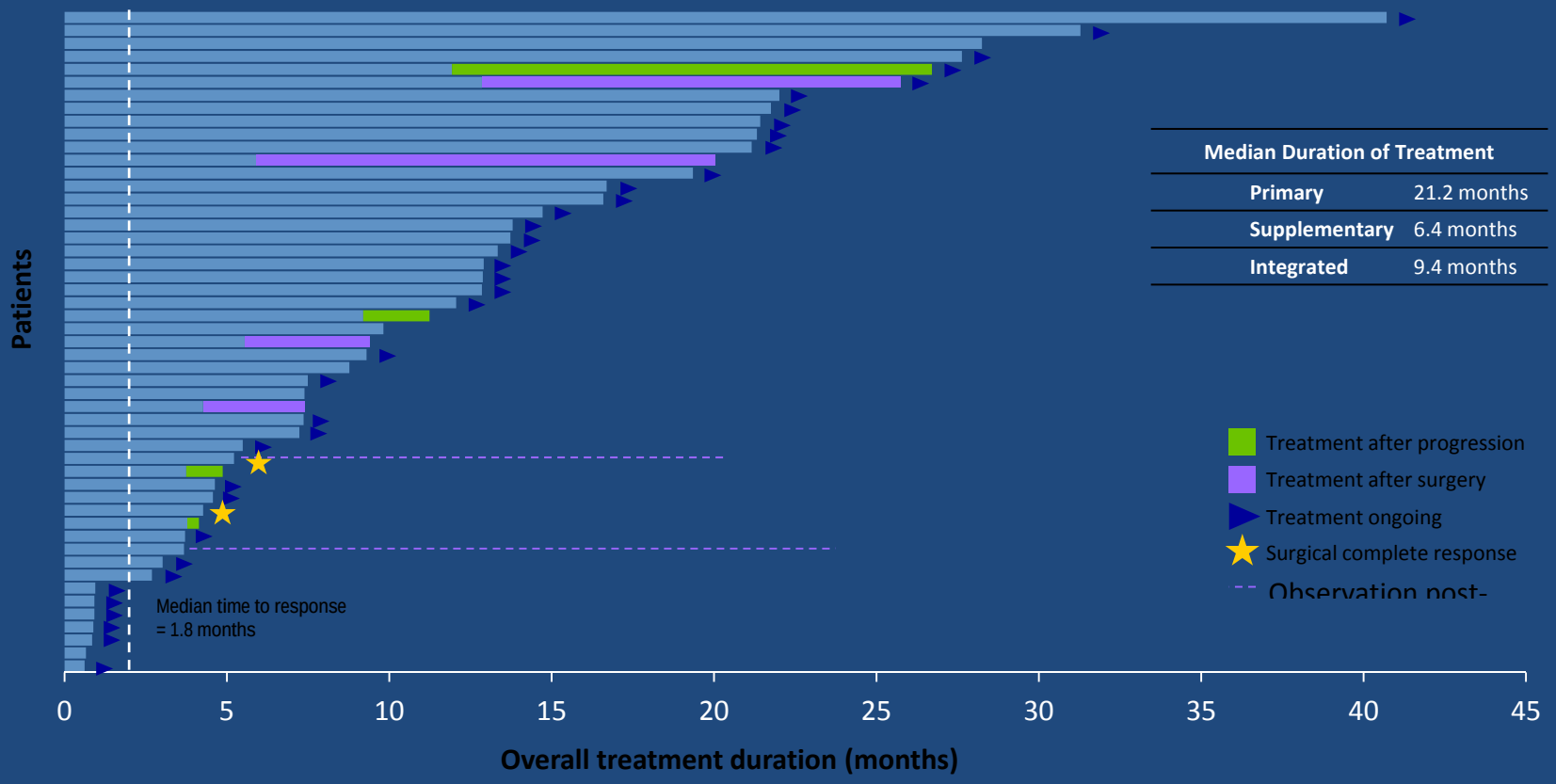


ORR (95% CI)†	**93% (82-99%)**
Best response†	
PR	70%
CR	20%
sCR	4%

†n=46 patients; includes 3 unconfirmed PRs pending confirmation; does not include 5 patients continuing on study and awaiting initial response assessment. Age <21 years. #sCR.
CR, complete response; ORR, objective response; PR, partial response; sCR, surgical complete response.

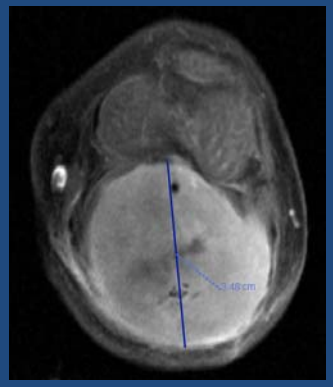
Investigator response assessments, as of 30 July 2018

Duration of treatment in patients with sarcoma

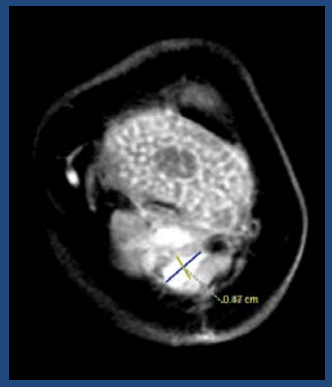


Investigator response assessments, as of 30 July 2018

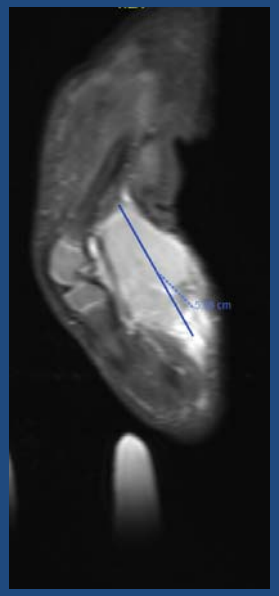
Patient with calf/popliteal *ETV6-NTRK3* infantile fibrosarcoma



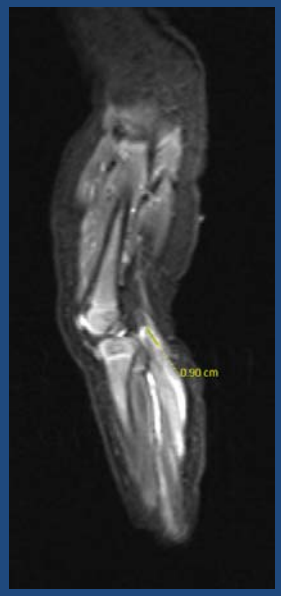
Baseline MRI



Cycle 3 Day 1 MRI



Baseline MRI



Cycle 3 Day 1 MRI

- 1 month-old infant boy with *ETV6-NTRK3* infantile fibrosarcoma
- Unresectable without potential major morbidity
- Started larotrectinib 100mg/m^2 PO BID
- Rapid response after 2 cycles
- R0 resection of residual 0.5cm mass after Cycle 6. No residual tumor in specimen
- Remains on therapy after 9 cycles

BID, twice-daily; MRI, magnetic resonance imaging; PO, orally.

Conclusions

- Oncogenic *NTRK* gene fusions can be detected in sarcomas
  - Frequency of *NTRK* gene fusions vary with type of sarcoma
- Larotrectinib demonstrates robust antitumor activity across the spectrum of TRK fusion sarcomas, including complete responses, in adult and pediatric patients
  - ORR of 93% (n=46) in the integrated dataset, per investigator assessment
- Responses to larotrectinib therapy were generally durable in TRK fusion sarcomas
  - The median duration of response has not yet been reached with a median follow-up of 17.5 months in the primary dataset
- Prolonged larotrectinib therapy was well tolerated
- Genomic profiling with assays capable of identifying *NTRK* gene fusions should be strongly considered in patients with sarcomas when determining systemic treatment options, especially in the setting of recurrence

ORR, objective response rate.

Alliance A091105: A phase III, double blind, randomized, placebo-controlled trial of sorafenib in desmoid tumors or aggressive fibromatosis (DT/DF)

Mrinal M. Gounder, Michelle R. Mahoney, Brian Andrew Van Tine, Vinod Ravi, Steven Attia, Hari Anant Deshpande, Alfred A. Gupta, Mohammed M. Milhem, Robert Martin Conry, Sujana Movva, Michael J. Arrowsmith, Richard E. Riedel, Derek Sabagh, William D. Tap, Melody De Sousa Horvat, Brian Bacchi, Lawrence Schwartz, Robert G. Maki, Hariolakshan P Agaram, Robert A Lefkowitz, Yousef Mazaheri, Pikkija Yamashiro, John Joseph Wright, Jongbae C. Dueck, Gary K. Schwartz

[illegible]

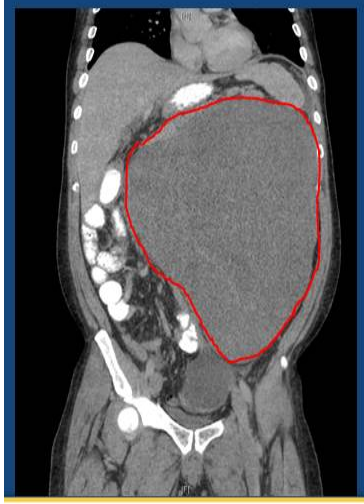
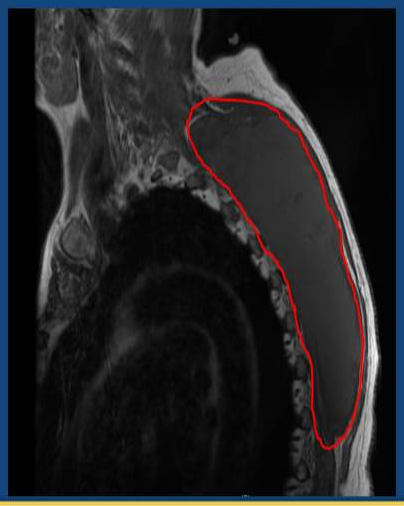
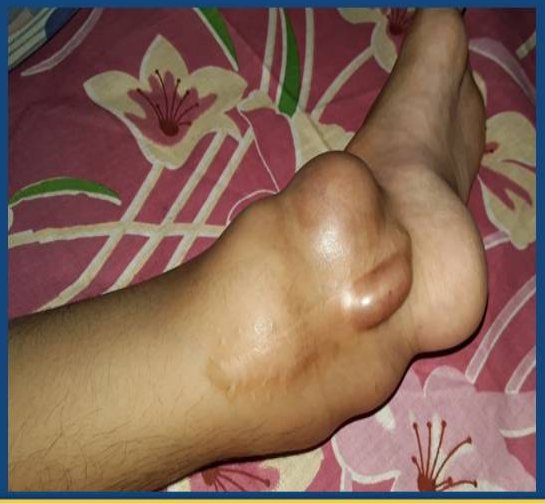
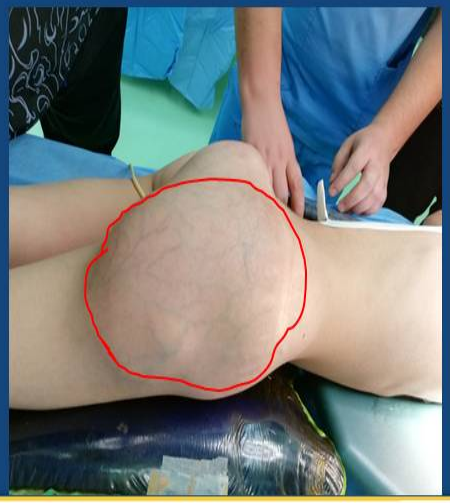
DESMOID TUMORS

Rare sarcoma: Incidence of 900 - 1000 new cases annually in the United States.

Surgery: primary therapy, but high recurrence and morbidity

Systemic therapy: No established first line. Tamoxifen +/- NSAIDs, doxorubicin, methotrexate, vinblastine and imatinib.

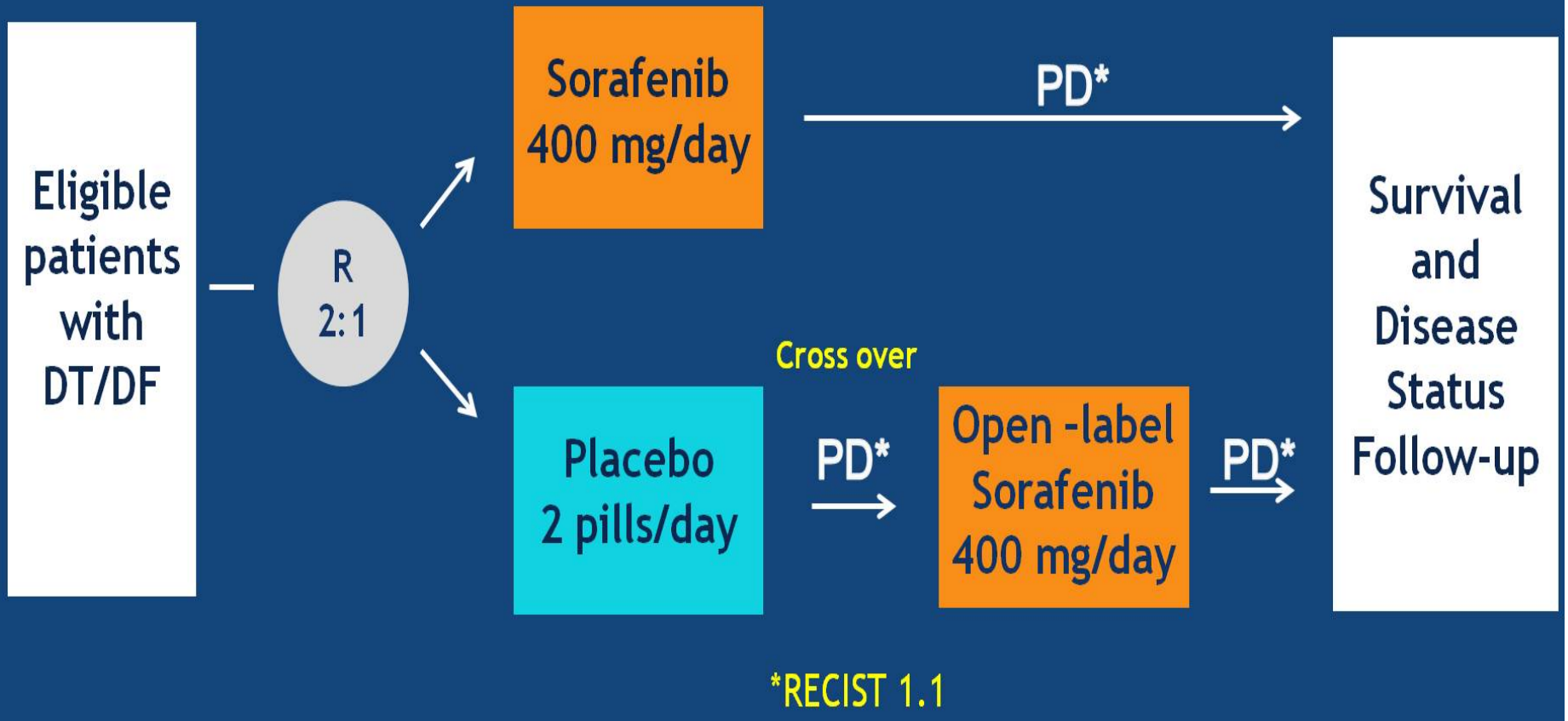
Observation - challenge of selecting the right patient

Von Mehren et. al. Soft Tissue Sarcoma, Version 2.2018 NCCN guidelines, JNCCN 2018

PRESENTED BY: Mrinal M. Gounder, MD
Memorial Sloan Kettering Cancer Center

Alliance A091105 Sorafenib vs Placebo (Gounder et al)
Phase III, double blind, randomized, placebo-controlled trial with crossover

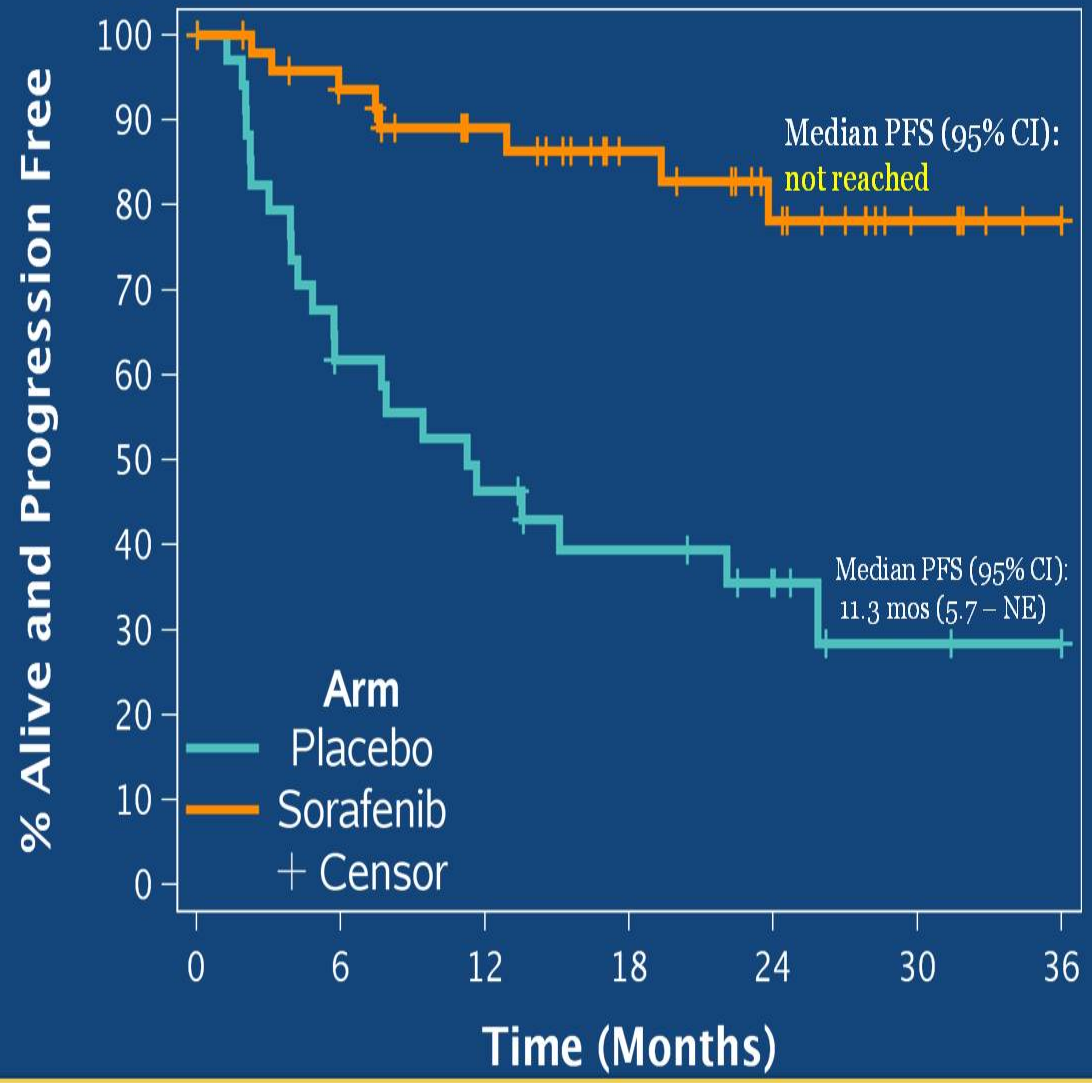


Key Eligibility

- Histological confirmation of desmoid tumor (local)
- Age > 18 years
- Measurable disease – RECIST 1.1
- ECOG 0 – 2

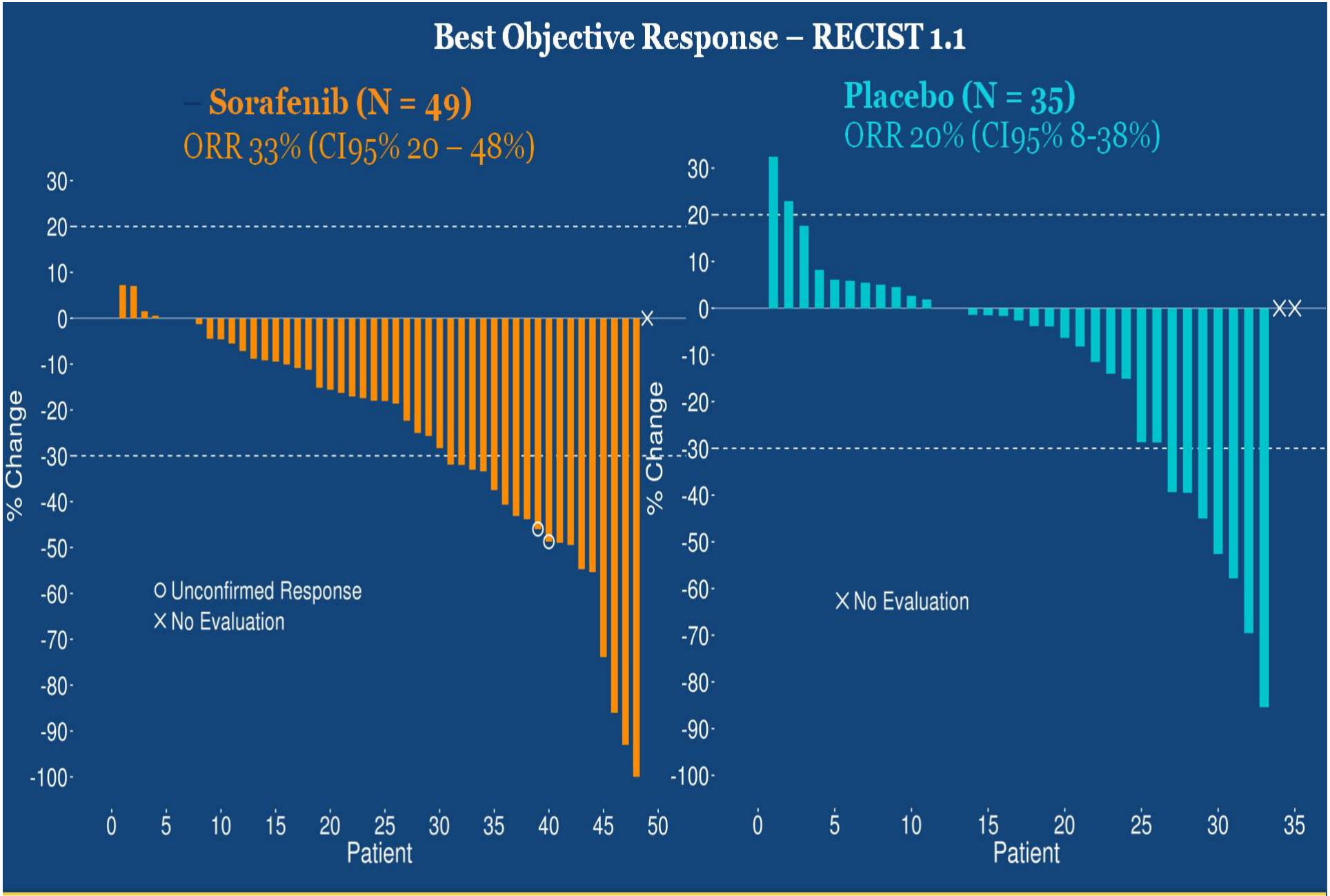
1) Unresectable or unacceptable surgical morbidity OR,
2) Progressive disease (10% by RECIST 1.1 within 6 months), OR
3) Symptomatic disease – Brief Pain Inventory score ≥ 3 and considering addition or increase in narcotics.

Sorafenib improved median progression free survival over placebo
Phase III study met its primary endpoint



HAZARD RATIO: 0.14
95% CI 0.06 – 0.33
p-value < 0.0001

Best Objective Response – RECIST 1.1



Complete Response with sorafenib (16 months, ongoing)

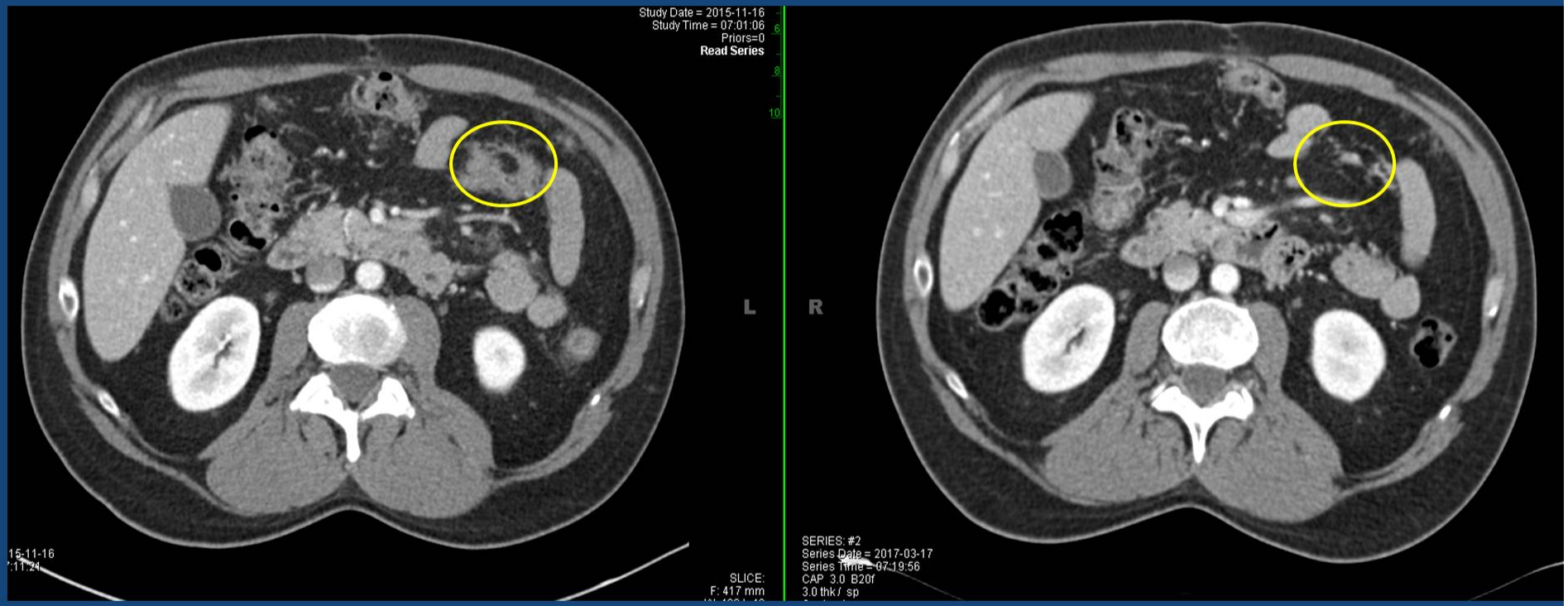


Image courtesy of Dr. Brian Van Tine

Conclusions

- This study met its primary endpoint - progression-free survival; a 7-fold reduction in risk for progression was observed with sorafenib, versus placebo (HR 0.14, p < 0.0001).
- Responses with sorafenib occurred late in treatment course.
- This randomized trial suggests that observation may be an appropriate treatment option in some select patients.
- In appropriate patients, these data support the use of sorafenib at 400 mg once daily in the first-line or subsequent line of therapy.

DOXORUBICIN- OLARATUMAB

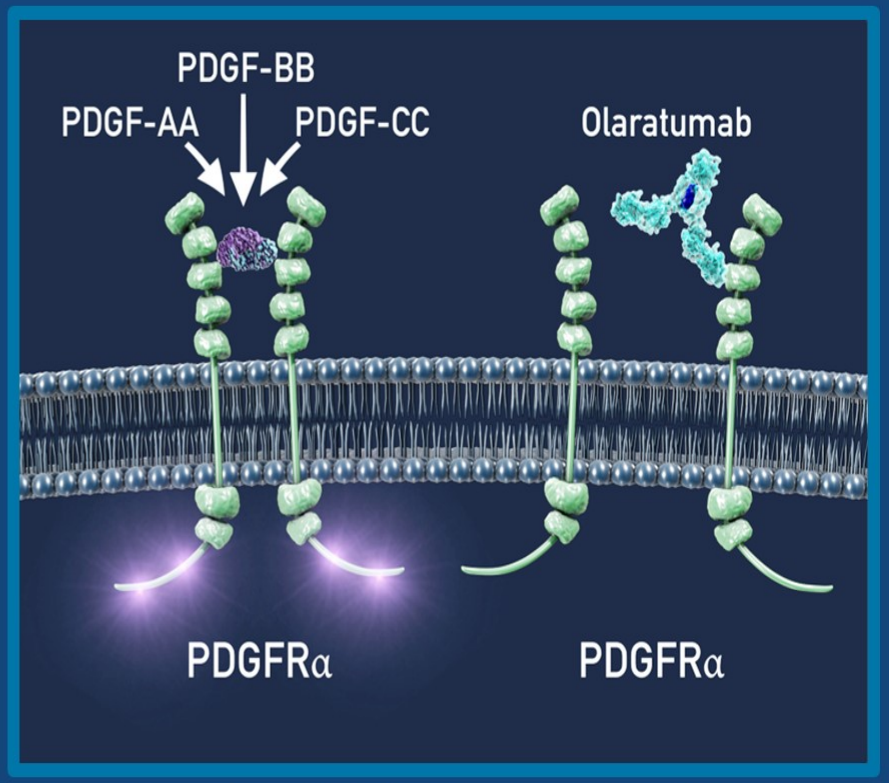
ANNOUNCE: A randomized, placebo-controlled, double-blind, phase 3 trial of doxorubicin + olaratumab vs doxorubicin + placebo in patients with advanced soft tissue sarcomas

William D. Tap, Andrew J. Wagner, Zsuzsanna Papai, Kristen Ganjoo, Chueh-Chan Yen, Patrick Schöffski, Albiruni Razak, Javier Martin Broto, Alexander Spira, Akira Kawai, Anders Krarup-Hansen, Axel Le Cesne, Brian A. Van Tine, Yoichi Naito, Se Hoon Park, Victoria Soldatenkova, Gary Mo, Ashwin Shahir, Jennifer Wright, Robin L. Jones

On behalf of the ANNOUNCE investigators

Olaratumab

- Fully human monoclonal antibody of immunoglobulin G class 1; selectively binds PDGFRα[1]
- Demonstrated antitumor activity alone[2] and synergy with doxorubicin in human sarcoma xenograft models[3]
- MOA in sarcoma or relationship to the mesenchymal tumor microenvironment is unknown

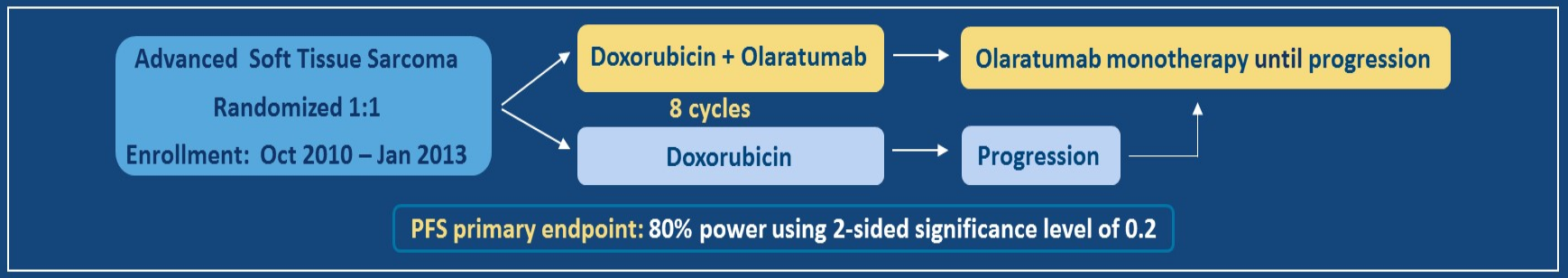


MOA, mechanism of action; PDGF, platelet derived growth factor; PDGFR, platelet derived growth factor receptor

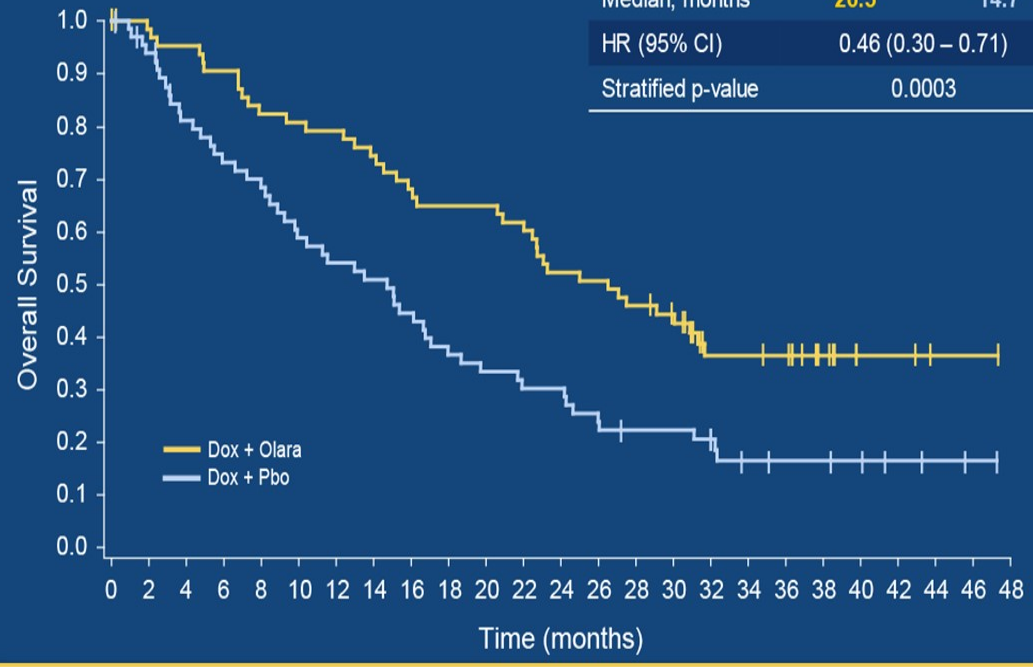
1. Olaratumab US prescribing information 2018; 2. Loizos N et al. *Mol Cancer Ther* 2005; 3. Heldin CH et al. *Biochim Biophys Acta* 1998;1378:F79-113

ANNOUNCE

Prior Phase 1b/2 Study: Design, PFS, and OS in Phase 2



	Dox + Olara	Dox + Pbo
Median, months	26.5	14.7
HR (95% CI)	0.46 (0.30 – 0.71)	
Stratified p-value	0.0003	



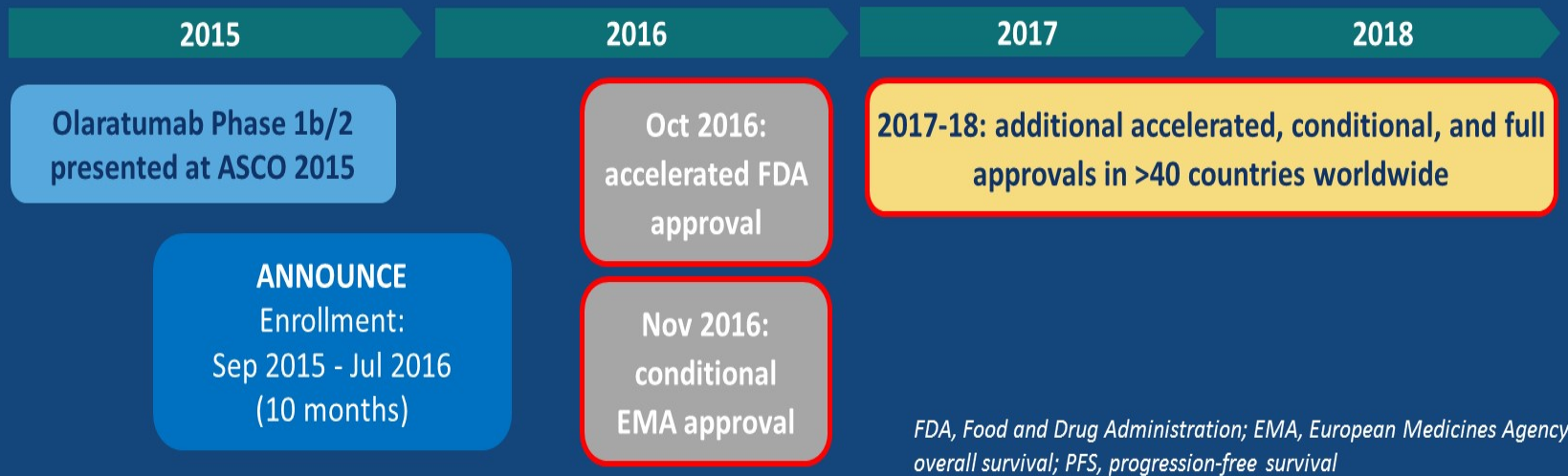
Dox, doxorubicin; Olara, olaratumab; OS, overall survival; PFS, progression-free survival; Pbo, placebo

Tap WD, et al. *Lancet* 2016;388:488-97 (updated 388:464)

ANNOUNCE

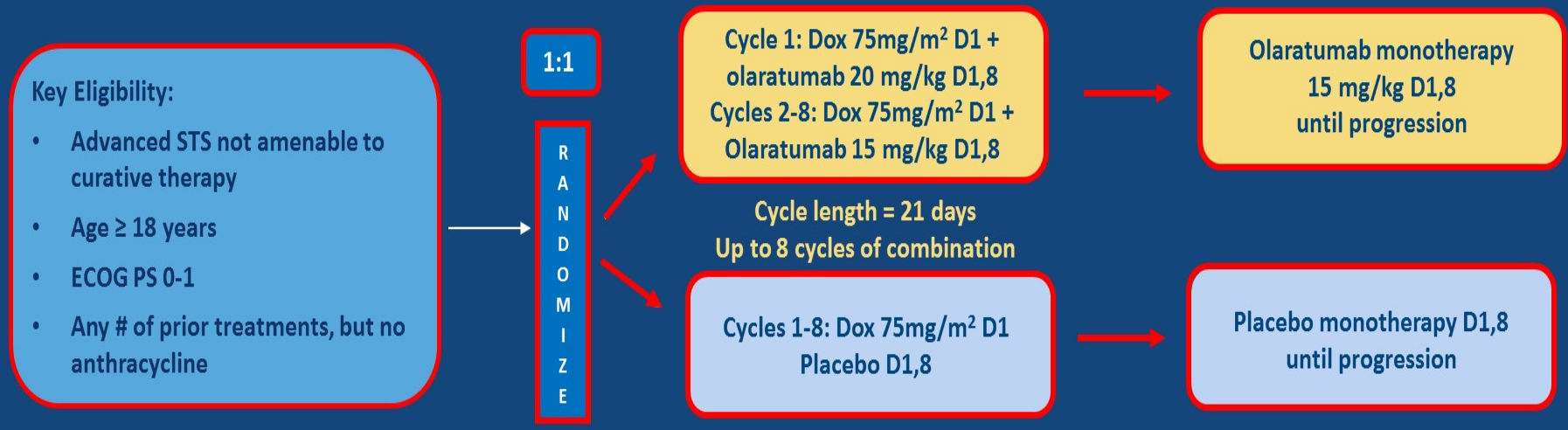
Olaratumab in Soft Tissue Sarcoma

- Smaller unblinded Phase 1b/2 trial with intent of signal finding
- PFS primary endpoint; large OS benefit
  - Large PFS/OS discrepancy
  - Unknown mechanism of action in sarcoma subtypes
- Multiple subgroup and sensitivity analyses of the Phase 2 did not show any meaningful imbalances or bias to explain results



FDA, Food and Drug Administration; EMA, European Medicines Agency ; OS, overall survival; PFS, progression-free survival

ANNOUNCE: Randomized, Double-blind, Placebo-controlled Phase 3 Study



Stratification factors: Number of prior therapies (0 vs ≥1), histology (LMS vs LPS vs UPS vs Other), ECOG PS (0 vs 1)

Primary endpoint: OS in the total STS & LMS populations

Key secondary endpoints: PFS, ORR, PROs, safety, PK, immunogenicity

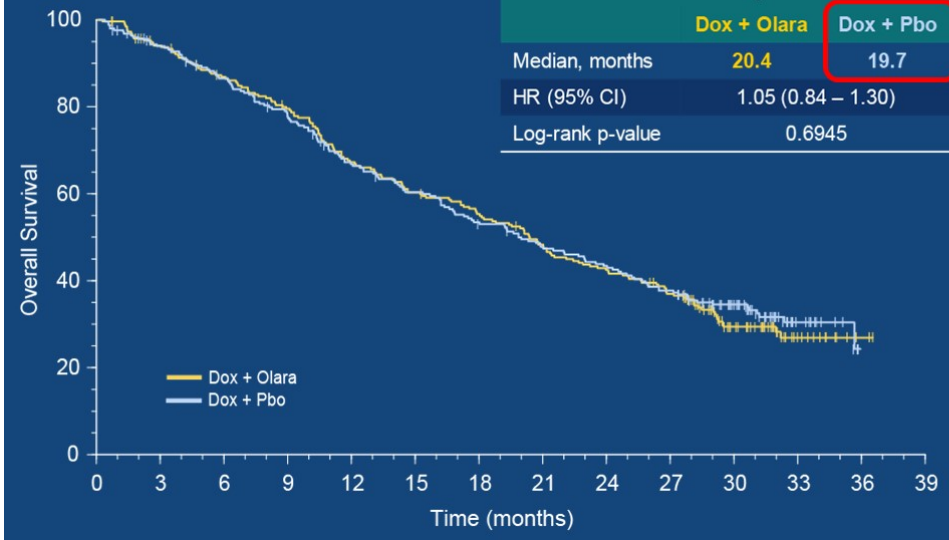
Exploratory: Biomarkers, subgroup analyses

Other features: Dexrazoxane use allowed at any cycle, cardiac monitoring of LVEF prior to cycles 5, 7, & 9 then q3 months

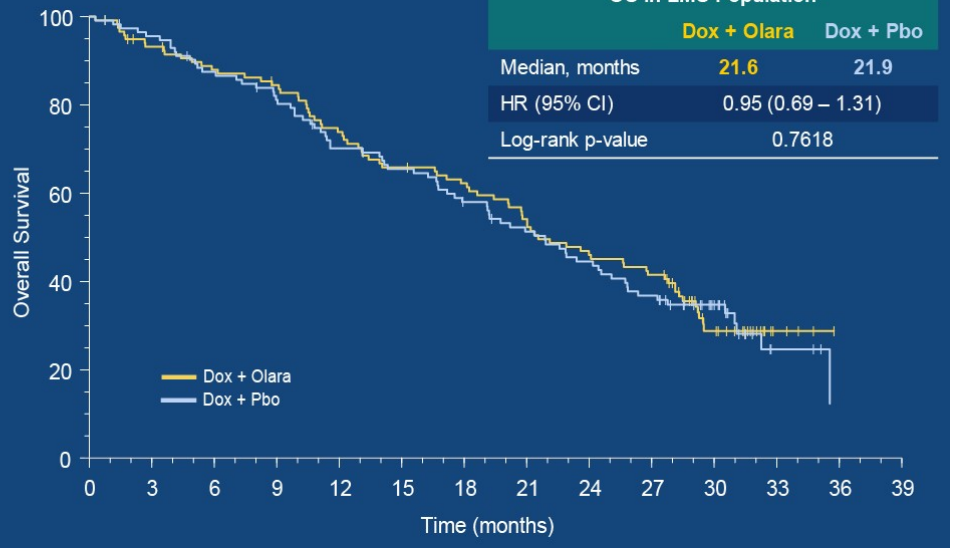
D, day; Dox, doxorubicin; ECOG PS, Eastern Cooperative Oncology Group performance status; LMS, leiomyosarcoma; LVEF, left ventricular ejection fraction; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcomes; q, every; STS, soft tissue sarcoma; UPS, undifferentiated pleomorphic sarcoma

ANNOUNCE

Overall Survival: tSTS and LMS Populations



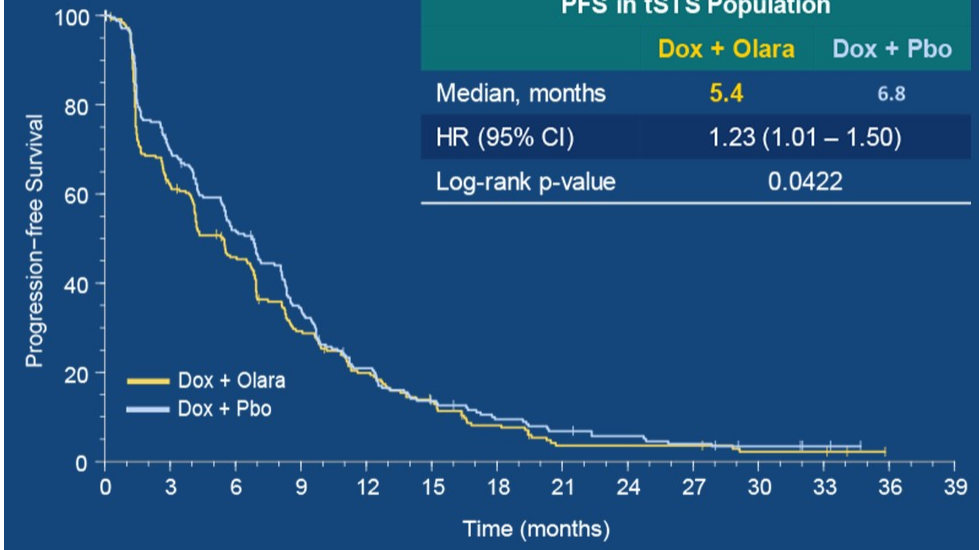
OS in tSTS Population	Dox + Olara	Dox + Pbo
Median, months	20.4	19.7
HR (95% CI)	1.05 (0.84 – 1.30)	
Log-rank p-value	0.6945	



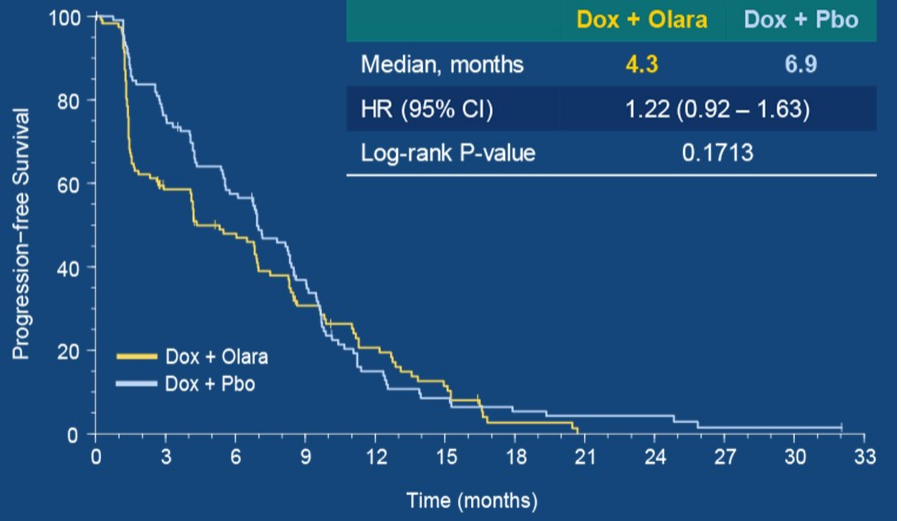
OS in LMS Population	Dox + Olara	Dox + Pbo
Median, months	21.6	21.9
HR (95% CI)	0.95 (0.69 – 1.31)	
Log-rank p-value	0.7618	

Dox, doxorubicin; LMS, leiomyosarcoma; Olara, olaratumab; OS, overall survival; Pbo, placebo; tSTS, total Soft Tissue Sarcoma

Progression-free Survival: tSTS and LMS Populations



PFS in tSTS Population	Dox + Olara	Dox + Pbo
Median, months	5.4	6.8
HR (95% CI)	1.23 (1.01 – 1.50)	
Log-rank p-value	0.0422	



PFS in LMS Population	Dox + Olara	Dox + Pbo
Median, months	4.3	6.9
HR (95% CI)	1.22 (0.92 – 1.63)	
Log-rank P-value	0.1713	

Dox, doxorubicin; Olara, olaratumab; Pbo, placebo; PFS, progression-free survival; tSTS, total Soft Tissue Sarcoma

Overall Response Rate: tSTS and LMS Populations

Response rate, %	tSTS		LMS	
	Doxorubicin + Olaratumab (N=258)	Doxorubicin + Placebo (N=251)	Doxorubicin + Olaratumab (N=119)	Doxorubicin + Placebo (N=115)
Best overall response				
Complete response (CR)	0.8	0.4	0.8	0
Partial response (PR)	13.2	17.9	12.6	22.6
Stable disease (SD)	53.5	57.4	49.6	60.0
Progressive disease	27.1	20.7	33.6	14.8
Objective response rate	14.0	18.3	13.4	22.6
	p=0.1837		p=0.0890	
Disease control rate (CR+PR+SD)	67.4	75.7	63.0	82.6
	p=0.0595		p=0.0011	

LMS, leiomyosarcoma; tSTS, total soft tissue sarcoma

Possible Reasons for ANNOUNCE Outcome

- Olaratumab is not effective with doxorubicin in STS
  - Small sample size, unrecognizable imbalances
    - Numerous represented histologies with disparate clinical behavior
  - Subsequent subtype specific treatments influenced OS

- Olaratumab has some activity in STS patients
  - Heterogeneity of study populations within and between studies
    - Diversity of sarcomas, Disease burden/behavior (albumin), PDGFR-status
  - Differences in study designs
  - ANNOUNCE control arm performed better than expected

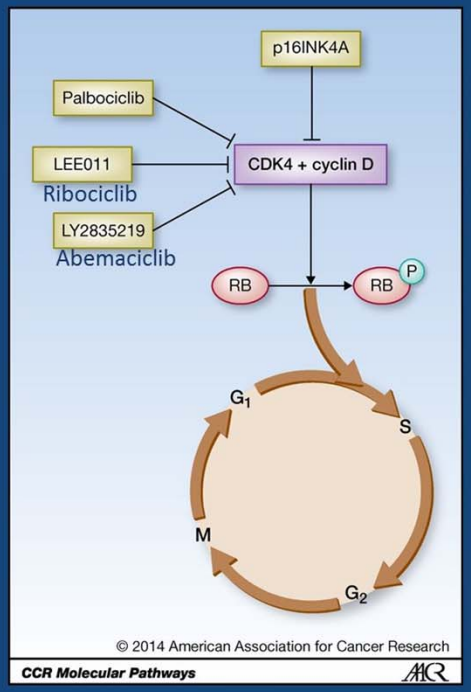
Phase 2 Study of the CDK4 Inhibitor Abemaciclib in Dedifferentiated Liposarcoma

Mark A. Dickson, Sandra P. D'Angelo, Mrinal M. Gounder, Mary L. Keohan, Ciara M. Kelly, Ping Chi, Cristina R. Antonescu, Jonathan Landa, Li-Xuan Qin, Andrew Koff, Aimee M. Crago, Samuel Singer, and William D. Tap

Memorial Sloan Kettering Cancer Center

Phase 2 study of the CDK4 inhibitor abemaciclib in dedifferentiated liposarcoma

CDK4 and cyclin D form a complex that phosphorylates Rb and drives progression through the cell cycle



Clin Cancer Res 2014;20:3379-3383

CDK4 Amplification in Liposarcoma

- Occurs in > 90% of well-differentiated / de-differentiated liposarcoma (WD/DDLS)[1]
- Highly amplified: > 10-fold increase vs. normal adipocytes[2]
- Specific to WD/DDLS vs. other liposarcoma subtypes and other soft-tissue sarcomas

[1]Binh MB et al., Am J Surg Pathol 2005

[2]Barretina J et al., Nature Genetics 2010

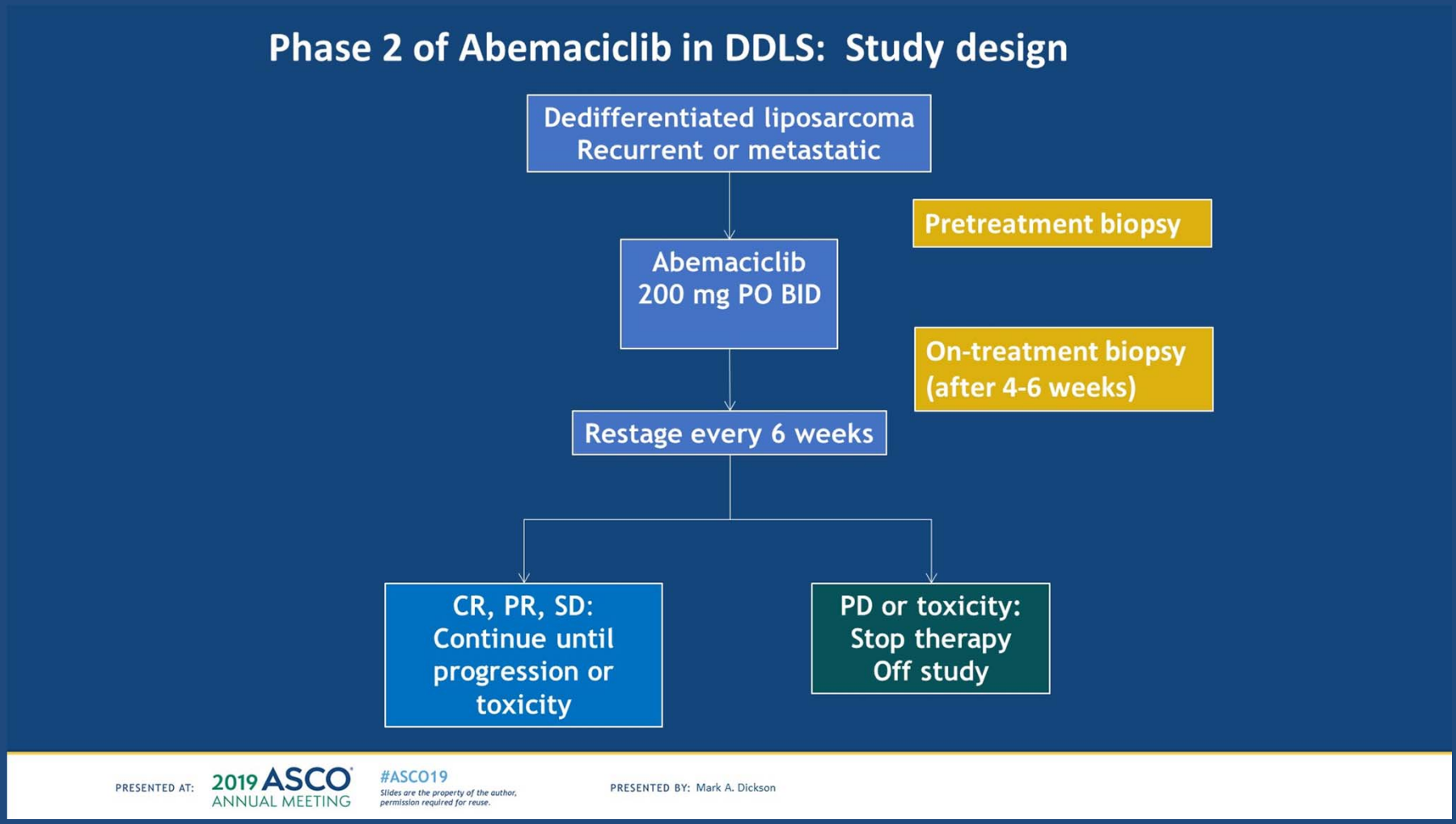
Phase 2 study of the CDK4 inhibitor abemaciclib in dedifferentiated liposarcoma

Prior Phase 2 Trials of Palbociclib in Liposarcoma

	2/1 schedule	3/1 schedule
Sample size	30	60
PFS at 12 weeks	66%	57%
Median PFS	18 weeks	18 weeks
Response Rate	3%	2%
Grade 3/4 Anemia	17%	22%
Grade 3/4 Neutropenia	50%	36%
Grade 3/4 Thrombocytopenia	30%	7%

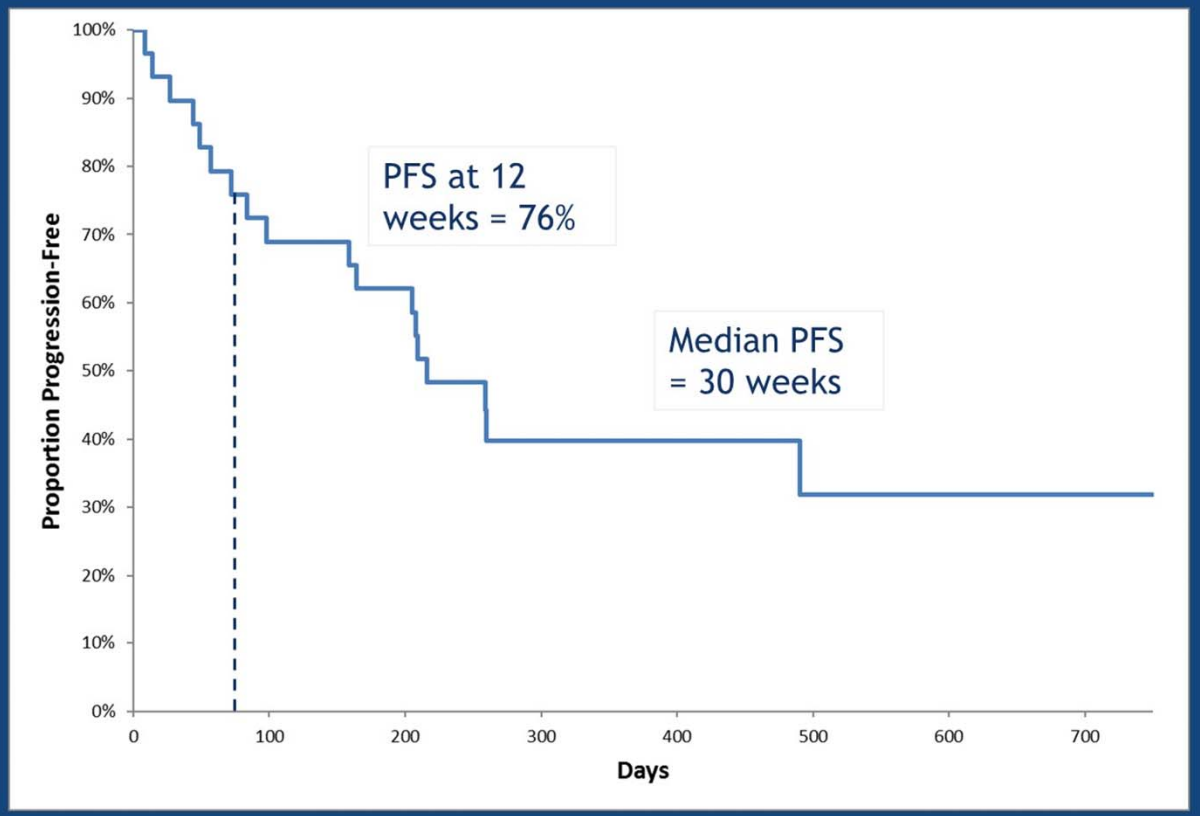
Dickson et al., J Clin Oncol 2013; JAMA Oncol 2016

Phase 2 study of the CDK4 inhibitor abemaciclib in dedifferentiated liposarcoma



Phase 2 study of the CDK4 inhibitor abemaciclib in dedifferentiated liposarcoma

Phase 2 of Abemaciclib in DDLS: Progression-Free Survival



Phase 2 study of the CDK4 inhibitor abemaciclib in dedifferentiated liposarcoma

- Study met primary endpoint
- In patients with advanced progressive DDLS, abemaciclib treatment result in favorable PFS of 76% at 12 weeks and median PFS of 30 weeks
- Encouraging results giving historical data with Palbociclib (mPFS of 18 weeks)
- Most myelotoxicity as AE with few grade 3
- A subset of patients have prolonged clinical benefit and some objective tumor response
- Evaluation of abemaciclib in DDLS in randomised Phase III is warranted

SARC028 expansion cohorts

- Clinical activity of pembrolizumab (P) in UPS and DDLS and PLS
- Additional 30 pts in each of 2 expansion cohorts for a total of 40 UPS and 40 LPS pts
- Primary endpoint was investigator-assessed response by RECIST v1.1.
- Secondary endpoints were safety, progression-free survival (PFS), 12-week PFS rate and overall survival (OS)
- Pts age ≥18 with advanced, refractory UPS or LPS received 200 mg of P IV every 3 weeks until progression or unacceptable toxicity

Final results of SARC028 expansion cohorts

- ORR

- In the UPS cohort was 23% (9/40), with an additional 5/30 PRs observed in the expansion cohort (total 2 CRs, 7 PRs)

- In the LPS cohort, the ORR was 10% (4/39 evaluable pts), with an additional 2/30 PRs observed (total 4 PRs).

- Median PFS

- In the UPS group, 3 months [95% CI: 2, 5]

- In the LPS group, 2 months [95% CI: 2, 4]

- 12-week PFS rate was 50% in UPS [95% CI: 35, 65] and 44% in LPS [95% CI: 28

- Median OS

- 12 months [95% CI: 7, 34] in UPS

- 13 months [95% CI: 8, NR] for the LPS group

- P was well tolerated with no unexpected toxicities

Tumor PDL1 Expression in responders

COHORT	PDL1 +	PDL1 -
UPS	6/8 (75%)	2/8 (25%)
LPS	0/3 (0%)	3/3 (100%)

CONCLUSION – SARC028

- The UPS cohort achieved its primary endpoint

- The activity of P in UPS deserves further evaluation in a randomized study

- The activity of P was not confirmed in the LPS cohort

- Most UPS tumor were PDL1 positive

- Ongoing biomarker analyses may direct better patient selection and guide future combination strategies

NEW PROMISING TARGETED THERAPIES GIST – PHASE III TRIALS

Avapritinib

- Highly selective inhibitor of KIT and PDGFRA mutant kinases (D842V)
- GIST with unresectable PDGFR D842V or other mutant GIST who progressed on Imatinib and ≥ 1 other TKI
- 237 pts included (172 KIT, 62 PDGFRA ex 18 -56 D842V)
- 111 in 4 line
- ORR 4th line 22% mDOR 10.2 ms
- Ex 18 ORR 86% MDOR not reached

NEW PROMISING TARGETED THERAPIES GIST – PHASE III TRIALS

Avapritinib

- Important activity in advanced GIST when no effective therapies
- ORR and DOR in 4 line exceeding approved 2nd and 3rd line
- Efficacy particularly in PDGFRA D842V and other Ex 18 PDGFRA GIST

- Phase III third line versus Regorafenib (VOYAGER)
- Phase III second line compared to Sunitinib (COMPASS)

NEW PROMISING TARGETED THERAPIES GIST – PHASE III TRIALS

DCC-2618

- Type II switch control kinase inhibitor of KIT and PDGFRα that has shown inhibition of a broad range of KIT primary and secondary mutations in GIST, preclinically and clinically
- Promising Phase I results
- Phase III second line compared to Sunitinib

Abstract ID: 3042511

SARC024: Regorafenib in Patients with Refractory 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], Steve Attia[14], Leo Mascarenhas[15], Robert G. Maki[16]

Oregon Health & Science University[1], Cancer Research and Biostatistics[2], Stanford Cancer Institute[3], Fred Hutchinson Cancer Research Center[4], Sarcoma Oncology Research Center[5], Northwestern University[6], Levine Cancer Institute[7], H. Lee Moffitt Cancer Center and Research Institute[8], Vanderbilt-Ingram Cancer Center[9], Indiana University[10], Mayo Clinic Rochester[11], SARC[12], Duke Cancer Institute[13], Mayo Clinic Jacksonville[14], Children's Hospital Los Angeles[15], Northwell Health & Cold Spring Harbor Laboratory[16]

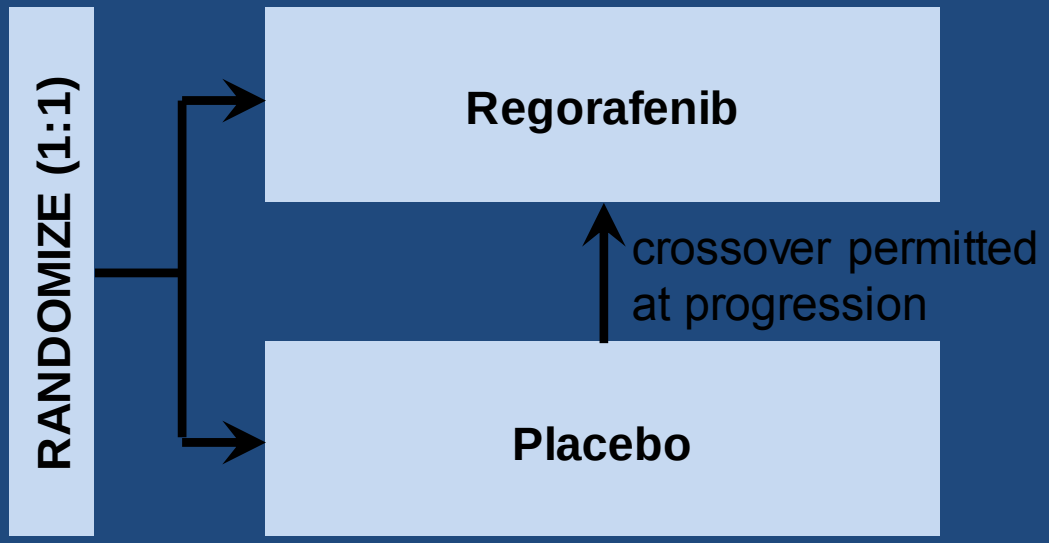
Background & Rationale

- Patients with metastatic osteosarcoma have an expected 4-month PFS of <20%.
- Despite substantial efforts, few new active agents have been identified over past 30 years, and outcomes have not changed.
- Recently, multi-kinase inhibitors such as sorafenib have shown promise.[1]
- Regorafenib is similar to but more potent than sorafenib.
  - 1 osteosarcoma patient on the regorafenib phase 1 trial had a durable partial response.[2]

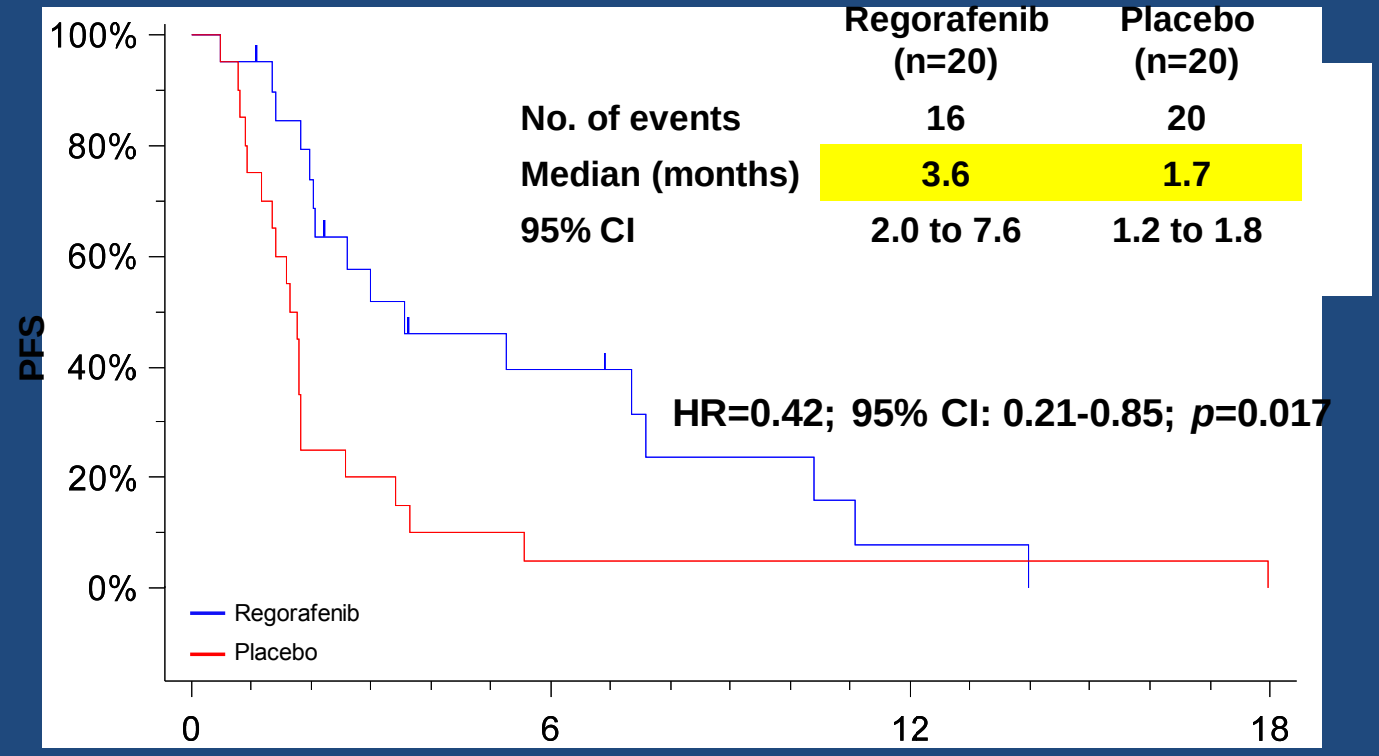
SARC024 Osteo: Study Design

Eligibility
Advanced osteosarcoma
Age ≥10
Measurable, progressive disease

Stratification
Performance status (0-1 or 2)
Prior lines of therapy (1 or ≥2)



SARC024 Osteo: Results – Progression Free Survival



No. at risk:						
Regorafenib	20	9	6	3	1	0
Placebo	20	4	1	1	1	1

SARC024 Osteo: Results

	Regorafenib	Placebo
Median PFS [primary endpoint]	3.6 mo	1.7 mo (p=0.017)
PFS @ 8 weeks	79.0%	25.0% (p=0.001*)
PFS @ 16 weeks	44.4%	10.0% (p=0.027*)
Objective response (PR)	3 (13.6%)	0

- At least one prior Rx
- Amenable to biopsy
- ECOG PS 0 or 1

SARC

*Fisher's exact test

SARC024 Osteo: Conclusions

Regorafenib is active in osteosarcoma:

Median PFS improved 1.7 → 3.6 months (*p*=0.017)
3 of 22 patients achieved partial response

Toxicity as expected

Confirms findings of French Sarcoma Group's REGOBONE trial[1]

TKI Efficacy in Osteosarcoma

	Sorafenib (n=35)[1]	Pazopanib (n=15)[2]	Apatinib (n=37)[3]	Lenvatinib (n=26)[4]	Cabozantinib (n=42)[5]	Regorafenib (n=26)[6]	Regorafenib (n=22)[7]
Objective response (PR)	3 (8%)	1 (7%)	16 (43%)	2 (8%)	5 (12%)	2 (8%)	3 (14%)
Median PFS (months)	4	6	4.5	3.4	6.2	3.8	3.6
4-month PFS	46%	NR	57%	33%	33% (6 mo)	35% (6 mo)	44%

- Amenable to biopsy
- ECOG PS 0 or 1

SARC

[1]Grignani et al, 2011; [2]Longhi et al, 2018; [3]Xie et al, 2018; [4]Gaspar et al, 2018; [5]Italiano et al, 2018; [6]Duffaud et al, 2018 ; [7]Davis et al, 2018

EMERGING FIELD OF SARCOMA RESEARCH

- > 100 different diseases
- Advancement in our understanding of disease biology promotes scientific discovery and drug development
- Genetic diversity offers research and treatment opportunities
- Subtype and disease-specific trials are key