IN PURSUIT OF *YOUR CURE.*™

Targeted Therapy in Sarcomas Beyond GIST

Gina D'Amato, MD

Associate Professor of Medicine

Sarcoma Medical Oncology

Assistant Director of Clinical Research

Sylvester Comprehensive Cancer Center

University of Miami Miller School of Medicine

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Objectives:

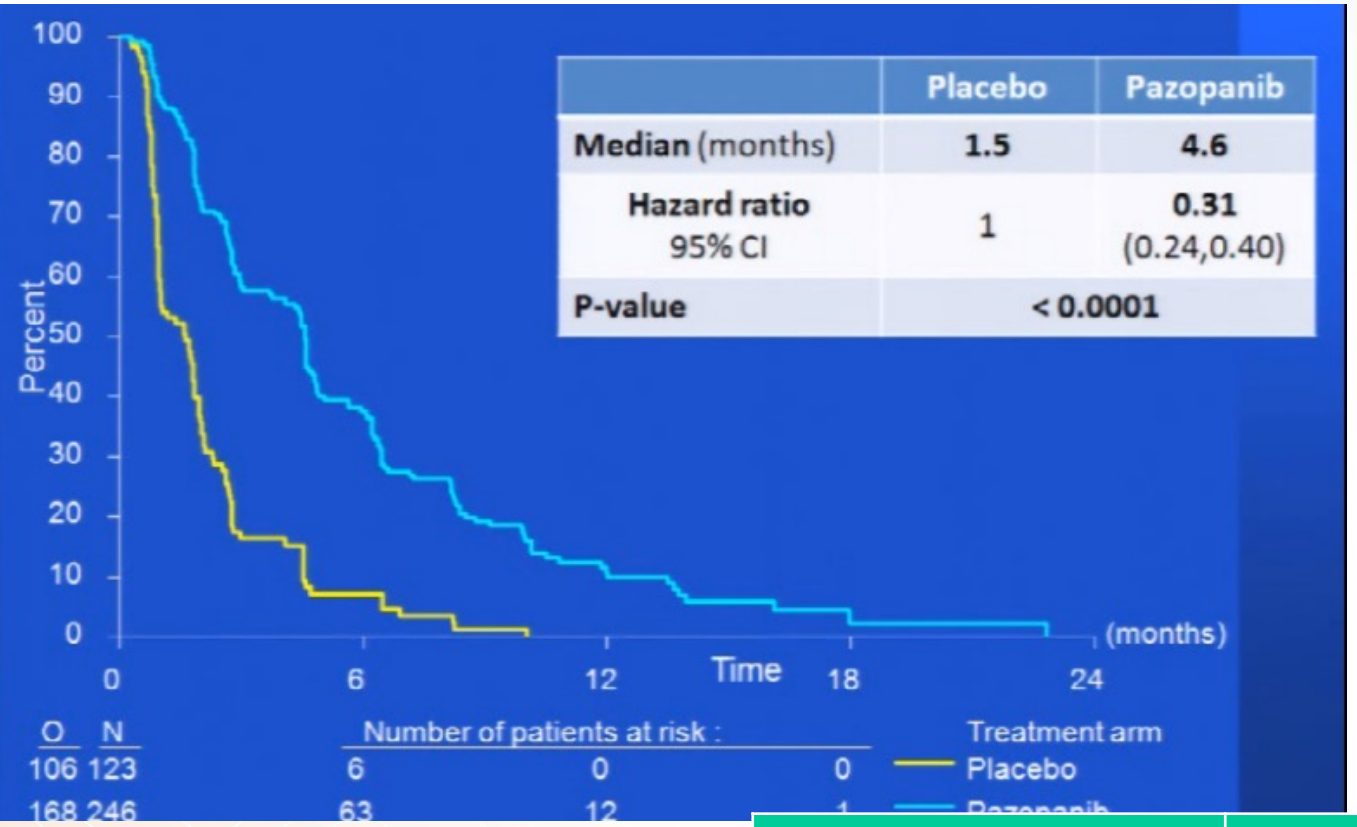
- Review Targeted therapies for sarcomas
  - FDA approved
  - Non-FDA approved
- Elaborate on the newest FDA Approvals in sarcomas
- Discuss the exciting new potential treatments in the horizon

FDA Approved Targeted Therapies for Soft Tissue Sarcoma

Medication	MOA	Molecular Target	Sarcoma Type	Date of Approval
Imatinib	Tyrosine Kinase Inhibitor	PDGFR-β	Dermatofibrosarcoma Protuberans	Nov 1, 2006
Pazopanib	Tyrosine Kinase Inhibitor	VEGFR-1,-2,-3; PDGFR-α,-β; c-kit; FGFR-1,-3; c-fms	Non-adipocytic STS	April 26, 2012
Larotrectinib	NTK inhibitor	NTK	TRK Fusion-Positive Tumors	November 26, 2018
Pexidartinib	Tyrosine Kinase Inhibitor	CSF1R; c-kit	TGCT	August 2, 2019
Entrectinib	NTK inhibitor	NTK	TRK Fusion-Positive Tumors	August 15, 2019
Tazemetostat	EZH2 Inhibitor	EZH2	Epithelioid Sarcoma	June 18, 2020

Vascular endothelial growth factor receptor (VEGFR); platelet derived growth factor receptor (PDGFR); stem cell growth factor receptor (c-kit); fibroblast growth factor receptor (FGFR); colony-stimulating factor-1 receptor (c-fms); tenosynovial giant cell tumor (TGCT); hepatocyte growth factor receptor (c-Met); anaplastic lymphoma kinase (ALK); inflammatory myofibroblastic tumor (IMT); mTOR (mammalian target of rapamycin); perivascular epithelioid tumor (PEComa)

Pazopanib PALETTE PFS Data



On April 26, 2012, the U. S. Food and Drug Administration approved pazopanib advanced soft tissue sarcoma who have received prior chemotherapy

Limitations of Use: The efficacy of pazopanib for the treatment of patients with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated

Recommended dose for STS 800 mg daily

Strata	N (%)	HR	mPFS (mo) P vs Pl		95% CI	P-value
Overall	369 (100%)	0.31	4.6	1.5	0.24-0.40	<0.0001
Leiomyosarcoma	158 (43%)	0.31	4.6	1.9	0.20-0.47	<0.0001
Synovial sarcomas	38 (10%)	0.19	4.1	0.9	0.23-0.60	0.0002
Other eligible tumor types	173 (47%)	0.36	4.6	1.0	0.25-0.52	<0.0001

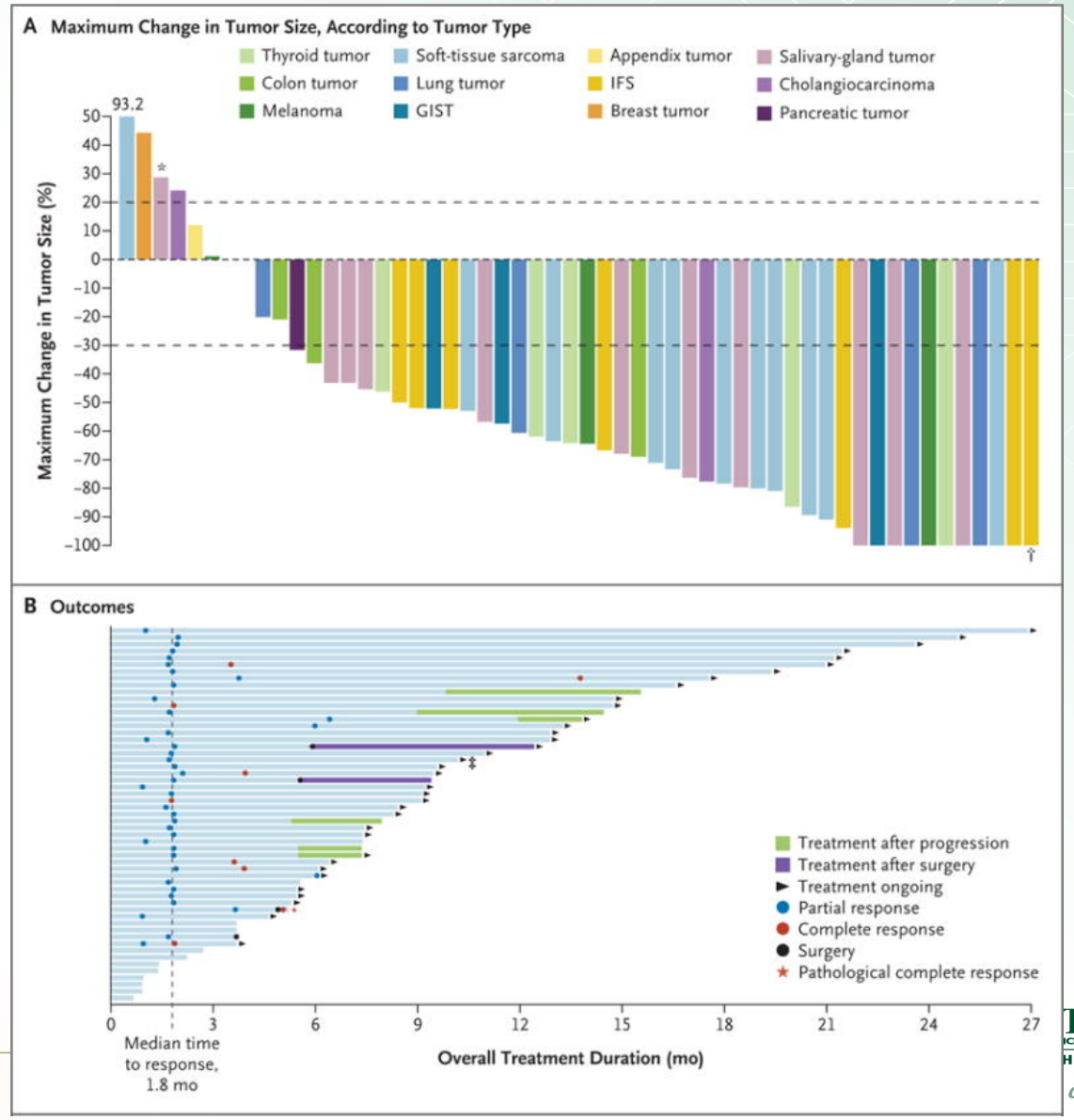
1. Van der Graaf WTA, et al. ASCO 2011 Annual Meeting. Abstract LBA10002

Tropomyosin Receptor Kinase Inhibitors: Larotrectinib

Published in final edited form as:
N Engl J Med. 2018 February 22; 378(8): 731–739. doi:10.1056/NEJMoa1714448.

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and **D.M. Hyman**

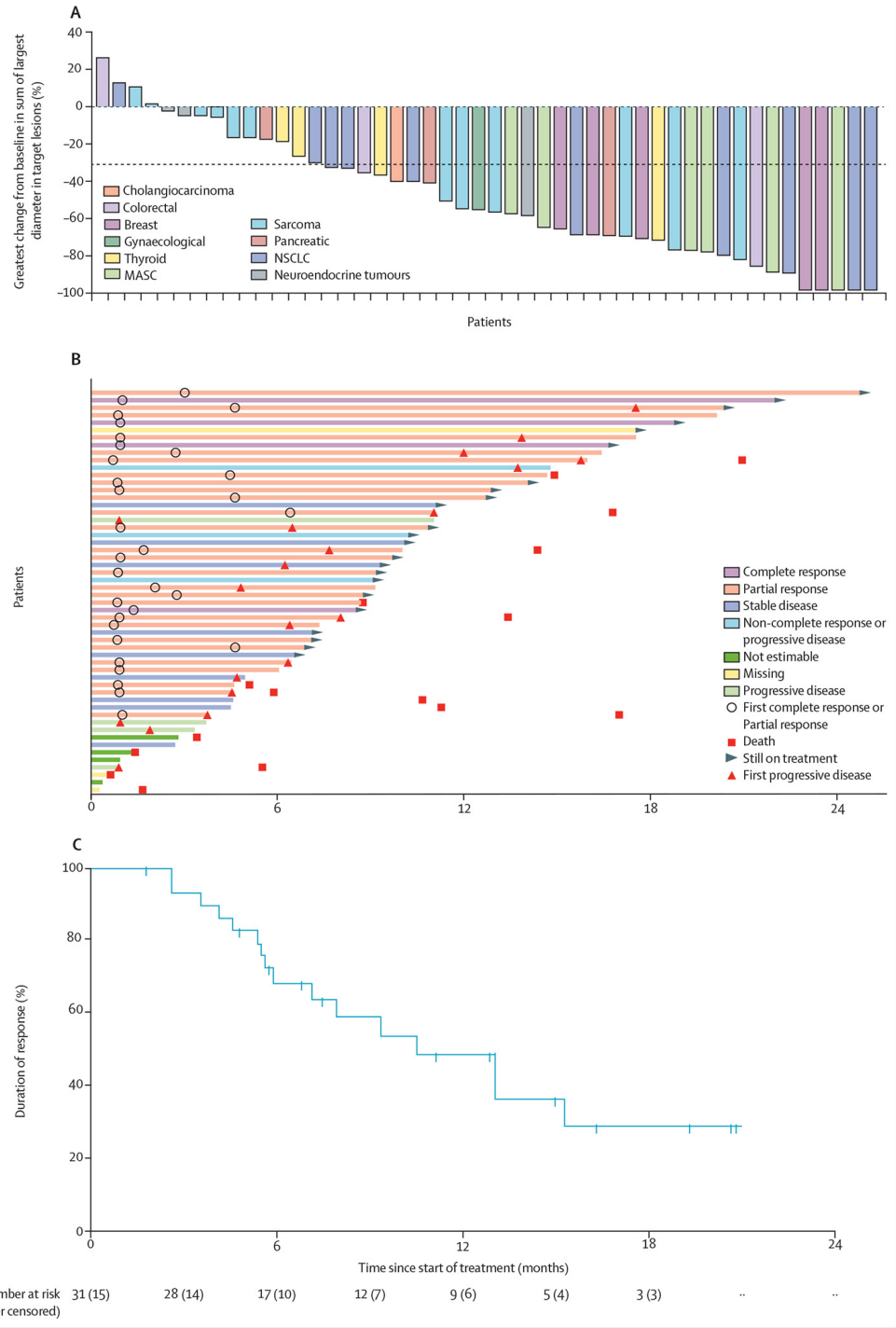


Tropomyosin Receptor Kinase Inhibitors: Entrectinib

Published in final edited form as:
Lancet Oncol. 2020 February ; 21(2): 271–282. doi:10.1016/S1470-2045(19)30691-6.

Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1–2 trials

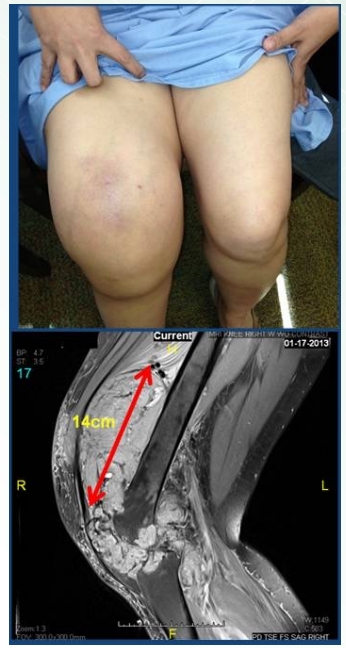
Robert C Doebele*, Alexander Drilon*, Luis Paz-Ares, Salvatore Siena, Alice T Shaw, Anna F Farago, Collin M Blakely, Takashi Seto, Byung Chul Cho, Diego Tosi, Benjamin Besse, Sant P Chawla, Lyudmila Bazhenova, John C Krauss, Young Kwang Chae, Minal Barve, Ignacio Garrido-Laguna, Stephen V Liu, Paul Conkling, Thomas John, Marwan Fakih, Darren Sigal, Herbert H Loong, Gary L Buchschacher Jr, Pilar Garrido, Jorge Nieva, Conor Steuer, Tobias R Overbeck, Daniel W Bowles, Elizabeth Fox, Todd Riehl, Edna Chow-Maneval, Brian Simmons, Na Cui, Ann Johnson, Susan Eng, Timothy R Wilson, George D Demetri on behalf of the trial investigators

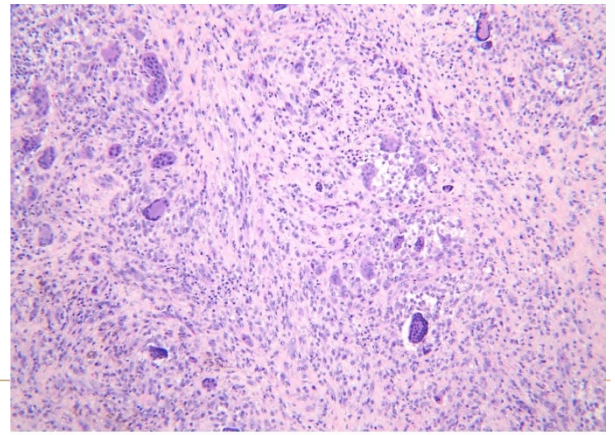


TGCT Overview

- TGCT formerly known as pigmented Villonodular synovitis (PVNS)
- Rare locally aggressive mesenchymal neoplasm arises in the synovium of joints, bursae or tendon sheaths
- A minority of cells within the TGCT are neoplastic
- Alterations in the colony-stimulating factor 1 (*CSF1)* gene locus on chromosome 1p13 lead to aberrantly expressing CSF1:COL6A3 [t(1;2)(p13;q37)]
- Dysregulated CSF1 attracts histiocytoid and inflammatory cells which compose the bulk of the tumor

- Clinical features include pain, swelling, limited range of motion and stiffness
- Affects individuals between 25-40 years ago (median 30)
- Slight female preponderance
- Annual TGCT incidence is estimated to be 43 cases per 1 million
- Localized, single nodule, in
- Diffuse type, infiltrative, locally aggressive tumor

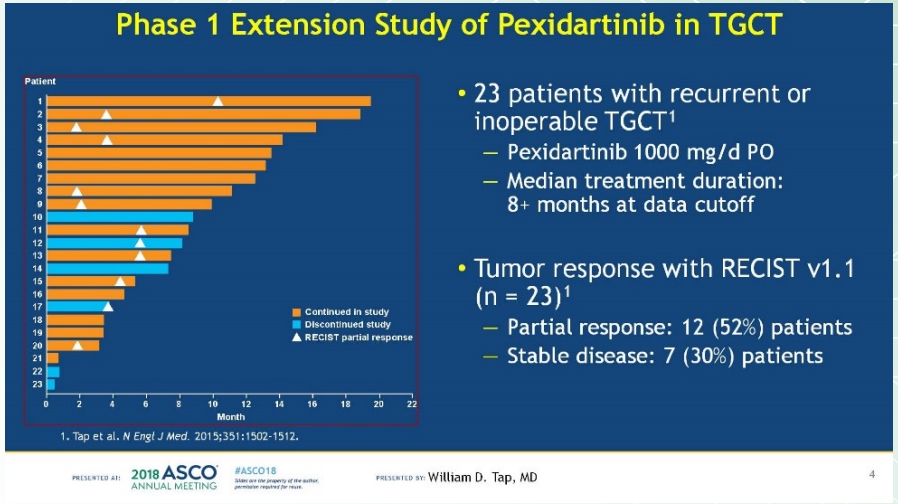




Staals, Ferrari, Donati, Palmerini *Eur J Cancer.* 2016; 63: 34-40
West RB Rubin BP Miller MA et al. *Proc Natl Acad Sci USA.* 2006; 103: 690-695
Cupp JS Miller MA Montgomery KD et al.*Am J Surg Pathol.* 2007; 31: 970-976
Tap et al. 2018 ASCO Annual Meeting

TCGT: Treatment

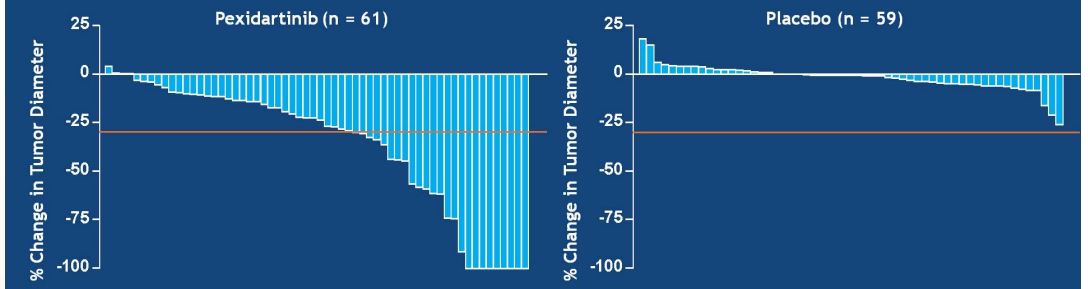
- Surgical Resection is standard primary treatment
- Imatinib: 19% ORR in advanced TGCT (n=27)
- Nilotinib 0% ORR at week 12 in advanced TGCT (n=51)
- Pexidartinib
  - TKI inhibits CSF1R, KIT, and FLT3-ITD
  - Phase 1 study (n=23) partial response 12 (52 %), stable disease 7 (30%) by RECIST
  - On August 2, 2019 the FDA approved pexidartinib for adult patients with symptomatic TGCT associated with severe morbidity or functional limitation and not amenable to improvement with surgery



Staals, Ferrari, Donati, Palmerini *Eur J Cancer.* 2016; 63: 34-40
Tap el al. *N Engl J Med*. 2015;1502-1512.
Cassier et al. *Cancer*. 2012:118:1649-1655.
Gelderblom et al. *Lancet Oncol.* 2018:1649-1655.
Cannarile et al. J Immunther. 2017;5(1):53.
Tap et al. 2018 ASCO Annual Meeting

Pexidartinib versus Placebo for Advanced Tenosynovial Giant Cell Tumour (ENLIVEN): A Randomised Phase 3 trial

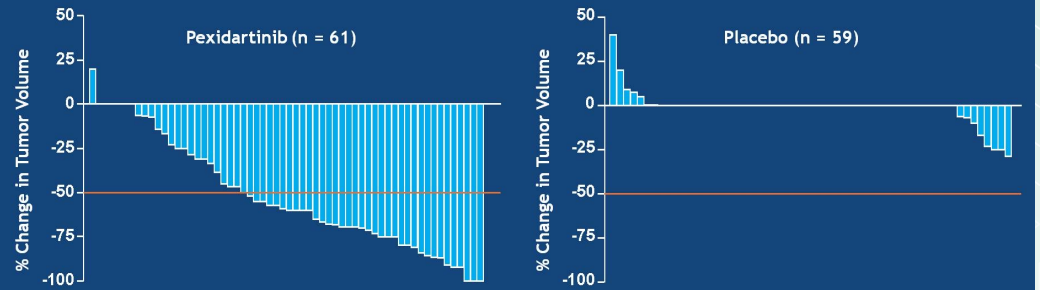
Primary Endpoint: Tumor Response by RECIST v1.1*
Week 25 Response (Blinded, Central MRI Review; ITT Population)



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.

Secondary Endpoint: Tumor Response by TVS*
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	3 (5)	31 (51)	14 (23)	1 (2)	12 (20)	34 (56) [43.3, 67.5] $P < 0.0001$
Placebo n = 59	0	0	45 (76)	2 (3)	12 (20)	0 [0, 6.1]

*Tumor volume is scored relative to the size of a normal synovial cavity, where 1 unit = 10% and 10 = 100%. Mean TVS at baseline was 15 and 12 for pexidartinib and placebo, respectively.

Hepatotoxicity

- 8 patients discontinued pexidartinib due to hepatic AEs
  - 4 cases were serious nonfatal AEs with increased bilirubin, 1 lasting ~7 months
  - All serious hepatic events emerged during the first 2 months of pexidartinib treatment

Liver Function, n (%)	Pexidartinib Part 1 n = 61	Placebo Part 1 n = 59	Pexidartinib Crossover 800 mg/d n = 30
AST or ALT ≥ 3 × ULN	20 (33)	0	4 (13)
TBili ≥ 2 × ULN	3 (5)	0	0
TBili ≥ 2 × ULN and AST or ALT ≥ 3 × ULN	3* (5)	0	0

*All were serious AEs with ALP ≥ 2.5 × ULN.

Conclusions

- Pexidartinib was generally well tolerated
  - Serious, nonfatal liver toxicity with increased bilirubin in 4% of patients
  - Majority of other AEs < grade 3
- Pexidartinib compared with placebo in advanced, symptomatic TGCT patients significantly improved ORR
  - RECIST: 39% vs 0%, $P < 0.0001$
  - TVS: 56% vs 0%, $P < 0.0001$
- Importantly, these responses correlated with improved patient symptoms and function

Pexidartinib, a novel CSF1 receptor inhibitor, may offer a relevant treatment option for patients with TGCT, which is associated with severe morbidity or functional limitations, and for which surgery is not recommended.

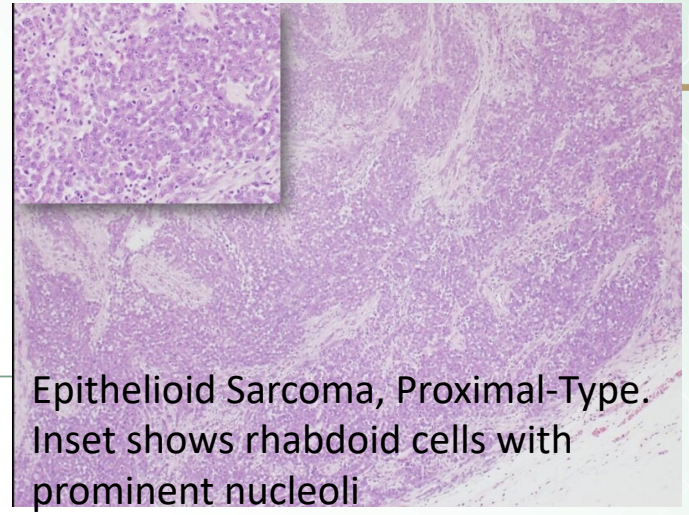
Tap et al *The Lancet* August 2019

New Dosing for Pexidartinib

- February 1, 2023 The new recommended dose of pexidartinib is 250 mg orally twice daily (taken as two 125 mg capsules) with a low-fat meal of approximately 11 to 14 grams of total fat until disease progression or unacceptable toxicity
- The previous dose was 400 mg orally twice daily on an empty stomach.
- As part of post-marketing requirements with the U.S. Food and Drug Administration (FDA), Daiichi Sankyo conducted pharmacokinetic studies to evaluate the effects of food
- a high-fat meal (approximately 55 to 65 grams of total fat) was found to increase the concentration of pexidartinib in the body and may increase the risk of adverse reactions, including hepatotoxicity
- These studies demonstrated that lowering the dose of pexidartinib and taking it with a low-fat meal helps to minimize the potential for drug overexposure in the event a patient did not carefully follow the dietary recommendations when taking the 200 mg capsule
- Similar efficacy with the lower dose + low-fat meal

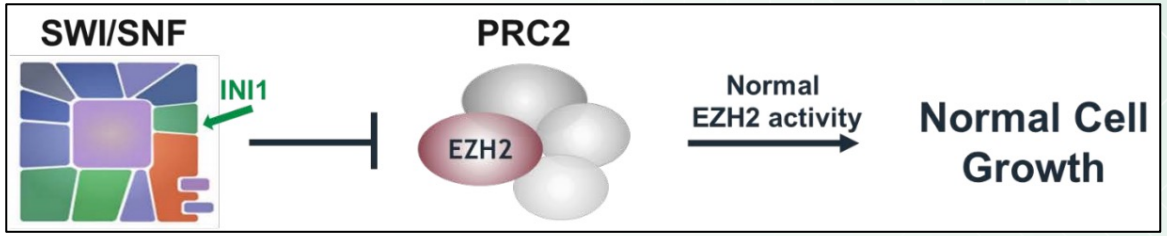
Tazemetostat in Epithelioid Sarcoma

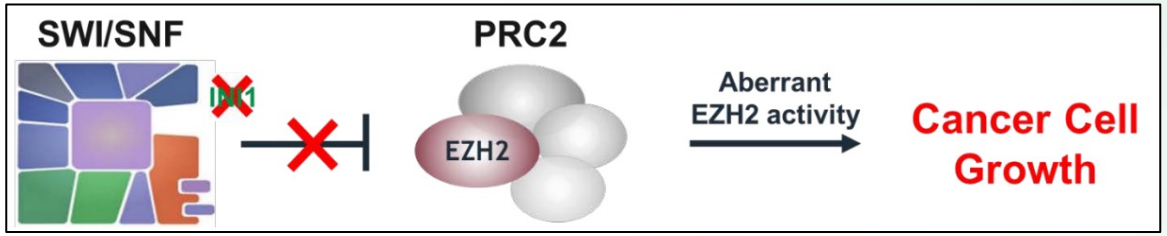
- Epithelioid sarcoma typically presents as a painless, slow-growing soft tissue swelling in the distal extremity of young adult males
- locally invasive and frequently metastasizes to **regional lymph nodes** and distant sites, most commonly to the lungs
- Epithelioid sarcoma is one of only a few tumors that characteristically lacks INI-1/SMARCB1 expression
- Loss of INI1 expression results in unopposed oncogenic activation of EZH2[2]
- Tazemetostat targets this oncogenic mechanism of ES through selective inhibition of EZH2[5]
- A phase 2 basket study was designed to evaluate the activity of Tazemetostat in patients with solid tumors with loss of INI1/*SMARCB1* or other SWI/SNF alterations[5]

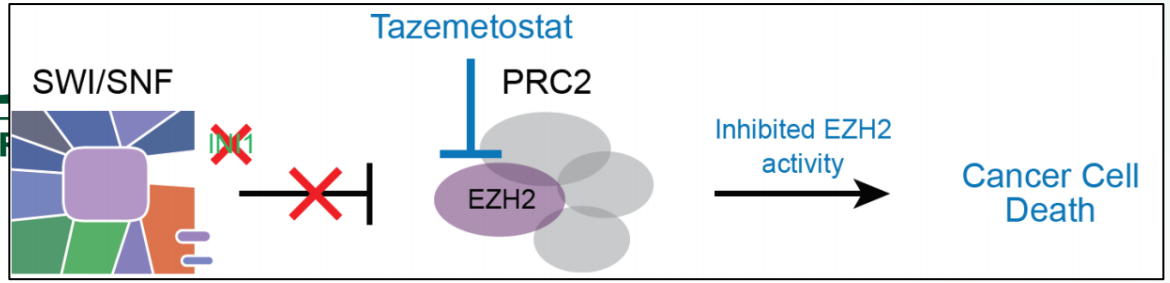


Epithelioid Sarcoma, Proximal-Type. Inset shows rhabdoid cells with prominent nucleoli

T OF *YOUR CURE.*™

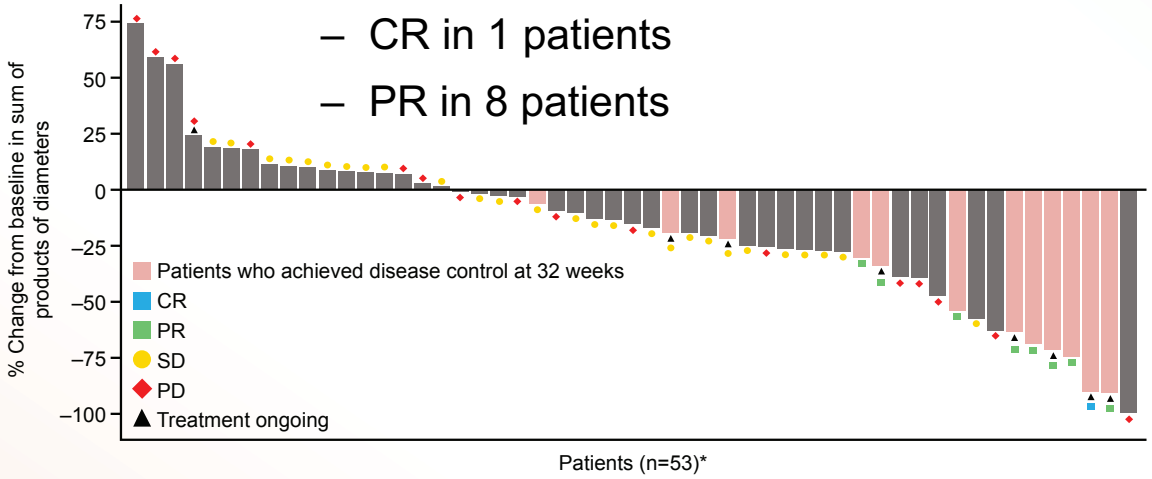




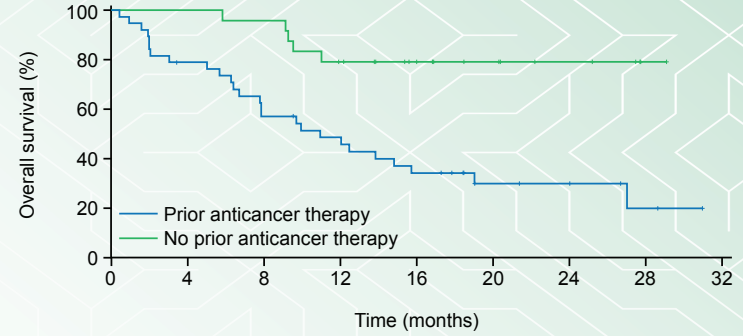


Tazemetostat Data in Epithelioid Sarcoma

- **ORR was 15% (95% CI, 7-26)**
  - CR in 1 patients
  - PR in 8 patients



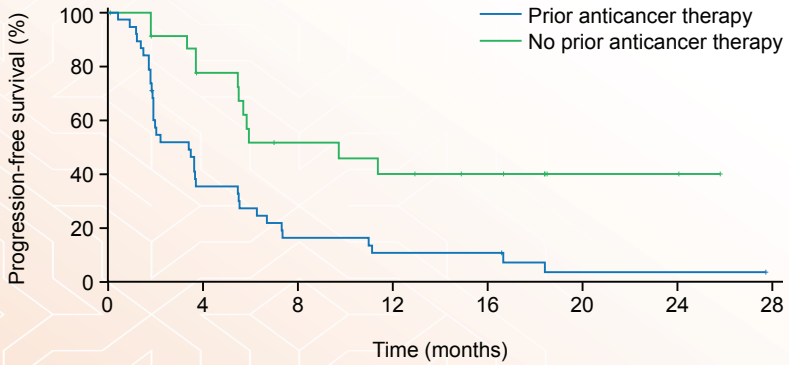
Exploratory Analysis: OS based on prior therapy



Number at risk (number censored)								
Prior anticancer therapy	38 (0)	29 (1)	21 (1)	17 (2)	12 (2)	6 (7)	4 (9)	2 (10)	0 (12)
No prior anticancer therapy	24 (0)	24 (0)	23 (0)	18 (1)	12 (7)	9 (10)	5 (14)	1 (18)	0 (12)

- **Median PFS was 9.7 months (95% CI, 5.5-NE) in treatment-naïve patients**
  - 12 of 24 patients (50%) had a progression event
- **Median OS was not reached (95% CI, NE-NE) in treatment-naïve patients**
  - 5 of 24 patients died (21%)

Exploratory Analysis: PFS based on prior therapy



Number at risk (number censored)								
Prior anticancer therapy	38 (0)	13 (1)	6 (1)	4 (1)	4 (1)	1 (2)	1 (2)	0 (3)
No prior anticancer therapy	24 (0)	15 (4)	9 (5)	7 (5)	5 (7)	2 (10)	1 (11)	0 (12)

- **Median PFS was 3.4 months (95% CI, 1.9-5.5) in previously treated patients**
  - 35 of 38 patients (92%) had a progression event
- **Median OS was 11.0 months (95% CI, 6.7-15.7) in previously treated patients**
  - 26 of 38 patients died (68%)

Supplement to: Gounder M, et al. *Lancet Oncol*. 2010;21(11):1423-1432.

Non-FDA Approved Targeted Therapies in Soft Tissue Sarcoma

Medication	Mechanism of Action	Target	Sarcoma Type	Efficacy Data
Regorafenib	Tyrosine Kinase Inhibitor	PDGFRα; VEGFR-1, -2, -3; c-kit	Non-adipocytic STS	mPFS (mo.) 3.5 LMS 5.6 SS, 2.9 O
			Angiosarcoma	ORR 17% mPFS 5.5
Sorafenib	Tyrosine Kinase Inhibitor	Raf Kinase; VEGFR-2, -3; PDGFR-β	Desmoid Tumor	ORR 33% 2year PFS rate 81%
Imatinib	Tyrosine Kinase Inhibitor	ABL; PDGFR; c-kit Possible CS1FR	TGCT	ORR 19% 74% SD
Sunitinib	Tyrosine Kinase Inhibitor	VEGFR-2, PDGFR-β	Solitary Fibrous Tumor	mPFS 6 mo.
			ASPS	mPFS 17 mo.
Lenvatinib	Tyrosine Kinase Inhibitor	VEGFR1-3; FGFR1-4; PDGFRα; c-kit; RET	Leiomyosarcoma LPS	mPFS 8.56 mo. 14mg/d levatinib 1.1mg/m2 Eribulin
Palbociclib Abemaciclib	CDK4/6 Inhibitor	CDK 4/6	WD/DD LPS STS with high CDK4 expression	P mPFS 17.9 wk A mPFS 30.4 wk P mPFS 5.9 m (high)

Recent FDA Approved Targeted Therapies for Soft Tissue Sarcoma

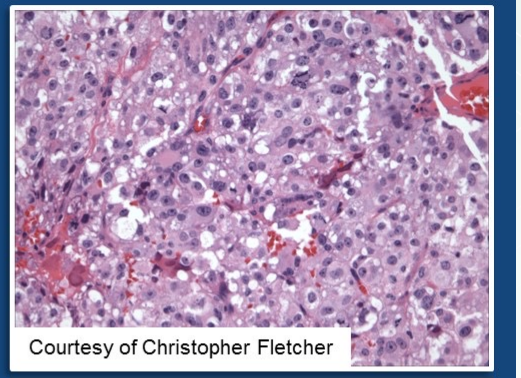
Medication	MOA	Molecular Target	Sarcoma Type	Date of Approval
nab-Sirolimus	mTOR inhibitor	mTOR Pathway	PEComa	November 22, 2021
Crizotinib	Tyrosine Kinase Inhibitor	c-Met; ALK; ROS1	Inflammatory myofibroblastic tumor (IMT)	July 14, 2022
Atezolizumab	Monoclonal Ab	PD-L1	Alveolar Soft Parts Sarcoma (ASPS)	December 9, 2022
Nirogacestat	Gamma Sectretase inhibitor		Desmoid Tumor/Aggressive Fibromatosis	November 27, 2023

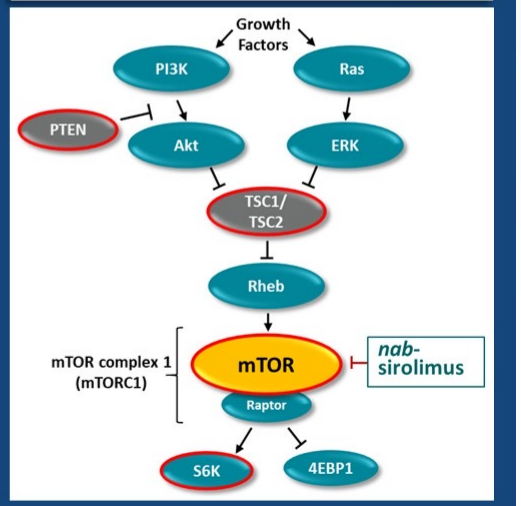
Vascular endothelial growth factor receptor (VEGFR); platelet derived growth factor receptor (PDGFR); stem cell growth factor receptor (c-kit); fibroblast growth factor receptor (FGFR); colony-stimulating factor-1 receptor (c-fms); tenosynovial giant cell tumor (TGCT); hepatocyte growth factor receptor (c-Met); anaplastic lymphoma kinase (ALK); inflammatory myofibroblastic tumor (IMT); mTOR (mammalian target of rapamycin); perivascular epithelioid tumor (PEComa)

ABI-009 (*nab*-sirolimus) in Advanced Malignant Perivascular Epithelioid Cell Tumors (PEComa): Preliminary Efficacy, Safety, and Mutational Status from AMPECT, an Open-label Phase 2 Registration Trial

Malignant Perivascular Epithelioid Cell tumor (PEComa)

- Rare sarcoma subtype with an undefined cell of origin
  - Distinctive cells that show a focal association with blood-vessel walls [1]
  - Usually express both melanocytic and smooth muscle markers [1]
  - High risk of metastases[1]
  - Historically, cytotoxic chemotherapy shows minimal benefit[2]
  - No drugs specifically approved for treatment of advanced PEComa
- mTOR pathway activation is common[2, 3]
  - Case reports of mTOR inhibitor treatment show substantial clinical benefit[3, 4]
  - PEComas can be associated with mutations (inactivation or deletions) of *TSC1* or *TSC2*, which encode negative regulators of the mTOR signaling pathway[5,6]

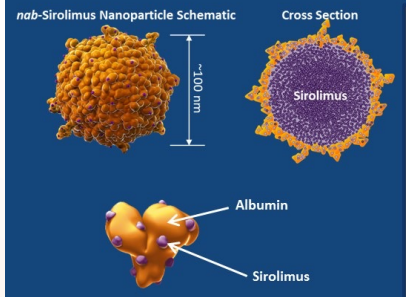

Courtesy of Christopher Fletcher



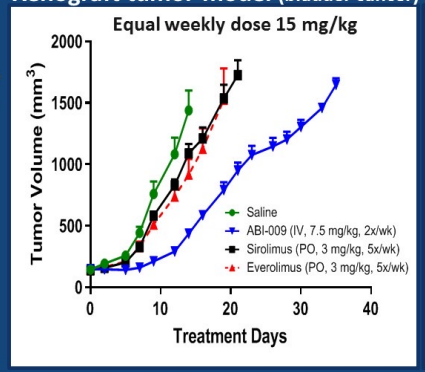
[1] Ben-Ami et al., Expert Opinion on Orphan Drugs 2018; [2] Bleeker et al., Sarcoma 2012; [3]Wagner et al., JCO 2010; [4]Dickson et al., Int J Cancer 2013; [5] Martignoni et al., Virchows Arch 2008; [6] Gao et al., Signal Transduction 2015

ABI-009 (*nab*-Sirolimus)

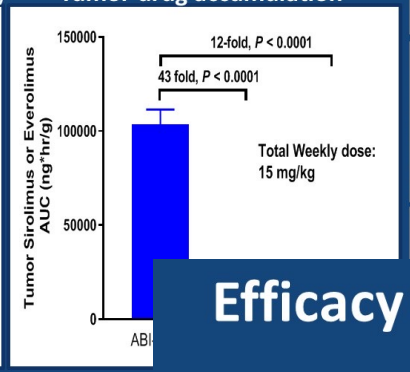
- Oral mTOR inhibitors have poor and variable absorption, often require therapeutic monitoring, and have incomplete target suppression
- *nab*-Sirolimus (nanoparticles of albumin-bound sirolimus; ABI-009) is a novel IV mTOR inhibitor with **significantly higher anti-tumor activity, intratumoral drug accumulation, and mTOR target (pS6) suppression at equal dose** vs oral mTOR inhibitors in preclinical models[1,2,3]



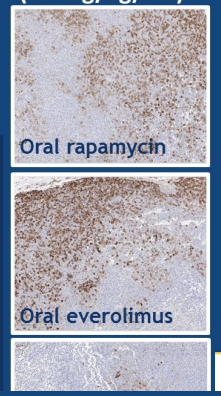
Xenograft tumor model (bladder cancer)



Tumor drug accumulation



Tumor IHC pS6 suppression: D7 post dose (15 mg/kg/wk)



[1] Hou et al., AACR 2019, #348
[2] Hou et al., AACR 2019, #3896
[3] Aadi Bioscience internal data

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 Slides are the property of the author, permission required for reuse. PRESENTED BY: Andrew Wagner, MD, PhD

AMPECT: *nab*-Sirolimus in Advanced Malignant PEComa

Phase 2 Registrational Open-label Multicenter Study Design

Key Eligibility
- ≥18 years old
- ECOG PS 0, 1
- Histologically confirmed malignant PEComa
- Locally advanced inoperable or metastatic disease
- No prior mTOR inhibitors

→ **Treatment Phase**: *nab*-Sirolimus 100 mg/m² IV D1,8 q 21d until progression or unacceptable toxicity → Quarterly Follow-up for survival

Sample Size: ORR of ~30% in 30 evaluable patients to exclude the lower bound of the 95% CI of 14.7%

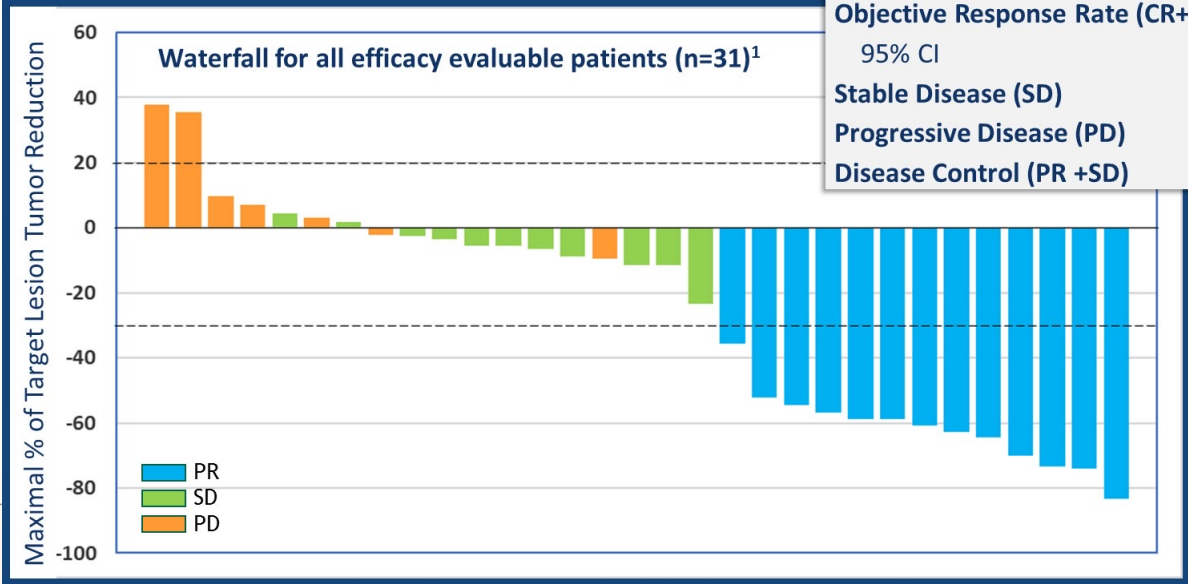
Efficacy Evaluable Patients: Must receive ≥1 dose of *nab*-sirolimus; must have centrally confirmed PEComa

- **Primary Endpoint –** ORR by independent assessment
  - CT/MRI (RECIST v1.1) every 6 weeks
- **Secondary Endpoints**
  - DOR, PFS at 6 months, median PFS, median OS
  - Safety
- **Key Exploratory Endpoints – *Data Presented***
  - Investigator response assessment
  - Biomarkers: mutational analysis (*TSC1/TSC2*), pS6 (IHC)

ClinicalTrials.gov: NCT02494570

Efficacy Summary, Investigator Assessed Responses

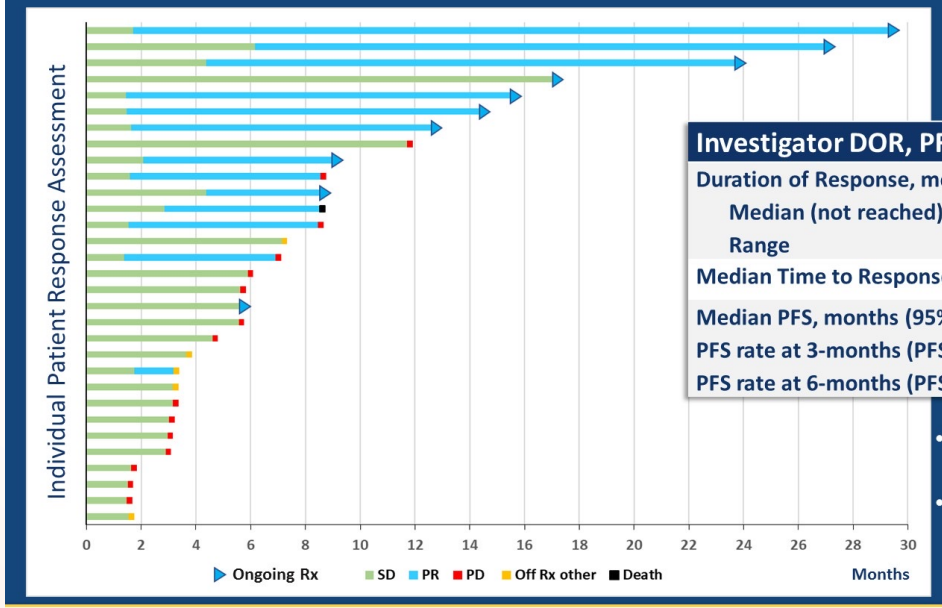
Response Assessment	All patients [1] (N = 31)
Objective Response Rate (CR+PR)[2]	13/31 (42%)
95% CI	(24.5%, 60.9%)
Stable Disease (SD)	11/31 (35%)
Progressive Disease (PD)	7/31 (23%)
Disease Control (PR +SD)	24/31 (77%)



Presented By Andrew Wagner at 2019 ASCO Annual Meeting

Nab-Sirolimus in PEComa

Duration of Response, Time to Response, Progression-free Survival

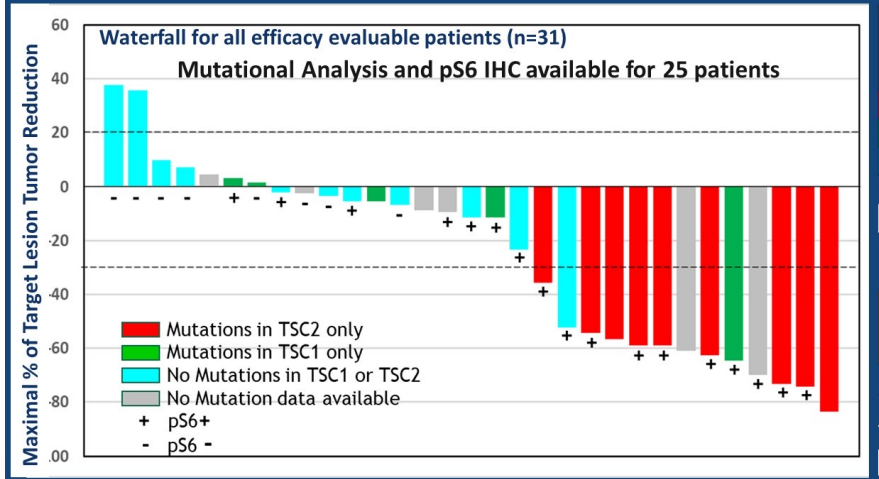


Investigator DOR, PFS, and TTR	N = 31
Duration of Response, months (95% CI)	
Median (not reached)	-- (6.2, --)
Range	1.5, 27.7+
Median Time to Response (TTR), months (95% CI)	1.4 (1.3, 2.7)
Median PFS, months (95% CI)	8.4 (5.5, --)
PFS rate at 3-months (PFS3), rate (95%CI)	80% (60.4%, 90.4%)
PFS rate at 6-months (PFS6), rate (95% CI)	61% (40.6%, 76.4%)

- 8/13 (62%) PR still ongoing
  - 3 pts ongoing tx >1yr and 3 pts >2 yrs
- 2/7 SD >11 months on therapy

Mutational Analysis and Biomarkers

Efficacy vs *TSC1/TSC2* mutations/deletions by NGS and pS6 by IHC



TSC1/TSC2 Mutational Analysis N = 25	Responders (PR) n = 11	Non-responders (SD+PD) n = 14
TSC2 (n=9)	9/9 (100%)	0
TSC1 (n=5)	1/5 (20%)	4/5 (80%)
No *TSC1* or *2* (n=11)	1/11 (9%)	10/11 (91%)
	P < 0.0001 (2x3 Fisher)	
Unknown status (n=6)	2/6 (33%)	4/6 (66%)

pS6 IHC N = 25	Responders (PR) n = 10	Non-responders (SD+PD) n = 15
pS6 + (n=17)	10/17 (59%)	7/17 (41%)
pS6 - (n=8)	0	8/8 (100%)
	P = 0.0077 (2x2 Fisher)	
Unknown status (n=6)	3/6 (50%)	3/6 (50%)

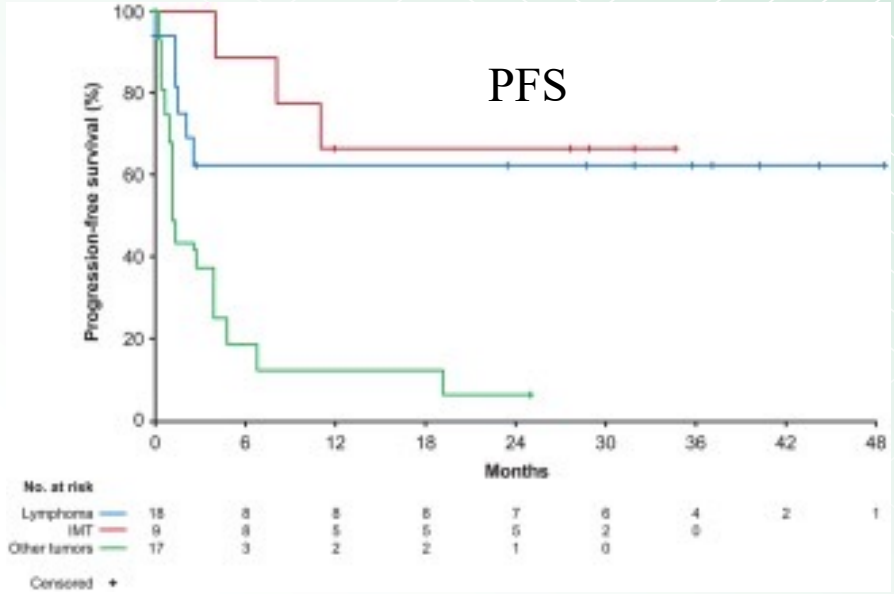
Biomarker lab: David Kwiatkowski, MD, PhD
Brigham and Women's Hospital/Harvard Medical School

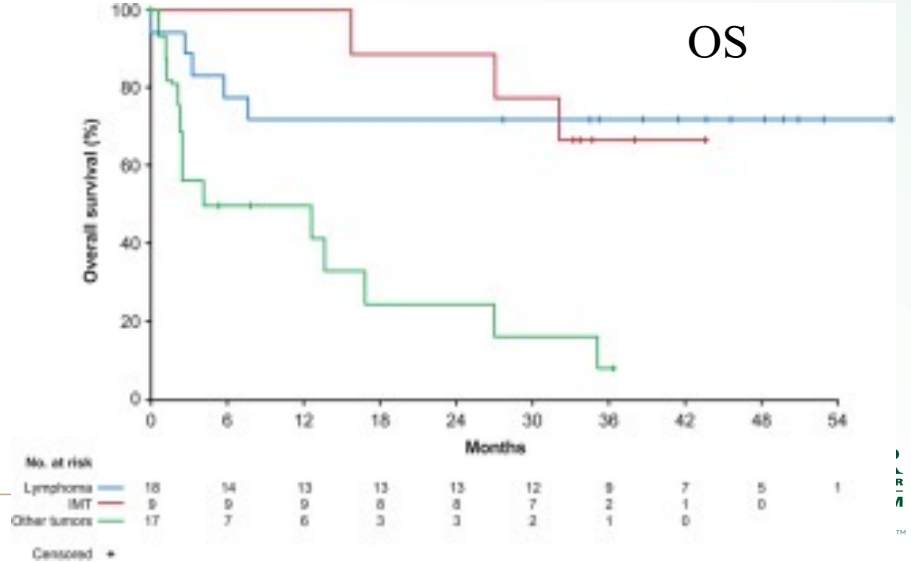
Data as of May 10, 2019

Presented By Andrew W

Crizotinib in Inflammatory Myofibroblastic Tumor

- Rare mesenchymal neoplasm with myofibroblastic-type cells intimately associated with lymphoplasmacytic inflammatory infiltrate
- Can occur anywhere but usually primary sites are lung, soft tissue of children and young adults
- Can present like lymphoma with B-symptoms and anemia
- ~50% harbor ALK translocation
- In phase 1b study of crizotinib the ORR 67% and 2-year PFS of 63% in the IMT arm





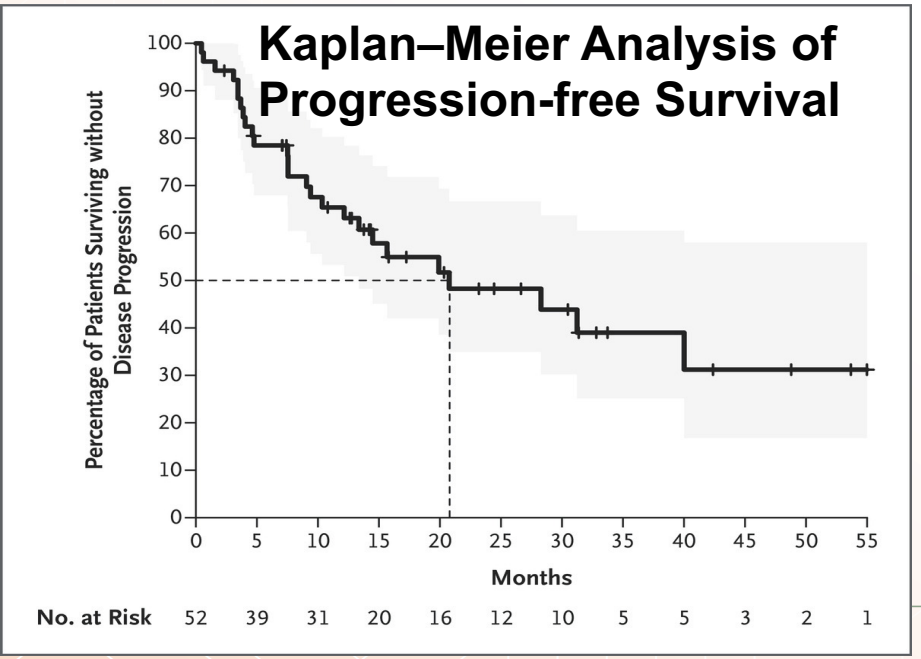
Atezolizumab in Alveolar Soft Parts Sarcoma (ASPS)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab for Advanced Alveolar Soft Part Sarcoma

Alice P. Chen, M.D., Elad Sharon, M.D., M.P.H., Geraldine O'Sullivan-Coyne, M.D., Ph.D., Nancy Moore, R.N., Jared C. Foster, Ph.D., James S. Hu, M.D., Brian A. Van Tine, M.D., Ph.D., Anthony P. Conley, M.D., William L. Read, M.D., Richard F. Riedel, M.D., Melissa A. Burgess, M.D., John Glod, M.D., Ph.D., Elizabeth J. Davis, M.D., Priscilla Merriam, M.D., Abdul R. Naqash, M.D., Kristin K. Fino, Ph.D., Brandon L. Miller, Ph.D., Deborah F. Wilsker, Ph.D., Asma Begum, Ph.D., Katherine V. Ferry-Galow, Ph.D., Hari A. Deshpande, M.D., Gary K. Schwartz, M.D., Brian H. Ladle, M.D., Ph.D., Scott H. Okuno, M.D., Jill C. Beck, M.D., James L. Chen, M.D., Naoko Takebe, M.D., Ph.D., Laura K. Fogli, Ph.D., Christina L. Rosenberger, Ph.D., Ralph E. Parchment, Ph.D., and James H. Doroshow, M.D.

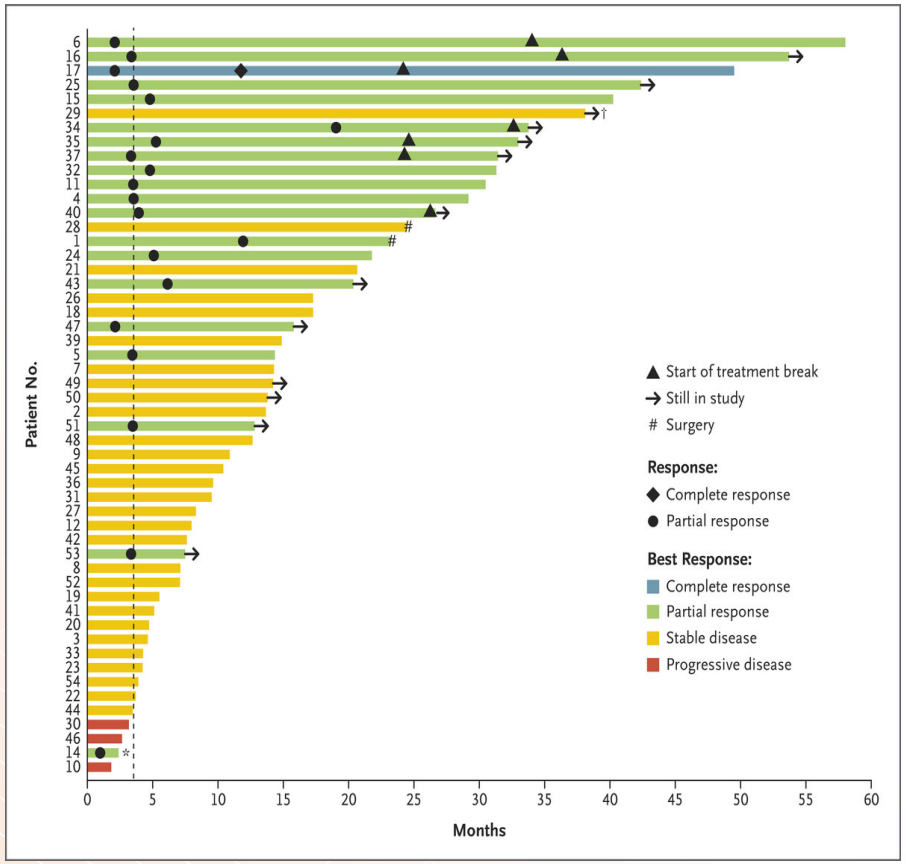


- ASPS ultrarare sarcoma, adolescents and young adults, usually indolent but poor prognosis because early mets 5yr OS 20-46%
- ASPL-TFE3 fusion proteins
- Axitinib + Pembrolizumab mPFS 12.4 mo OS NR

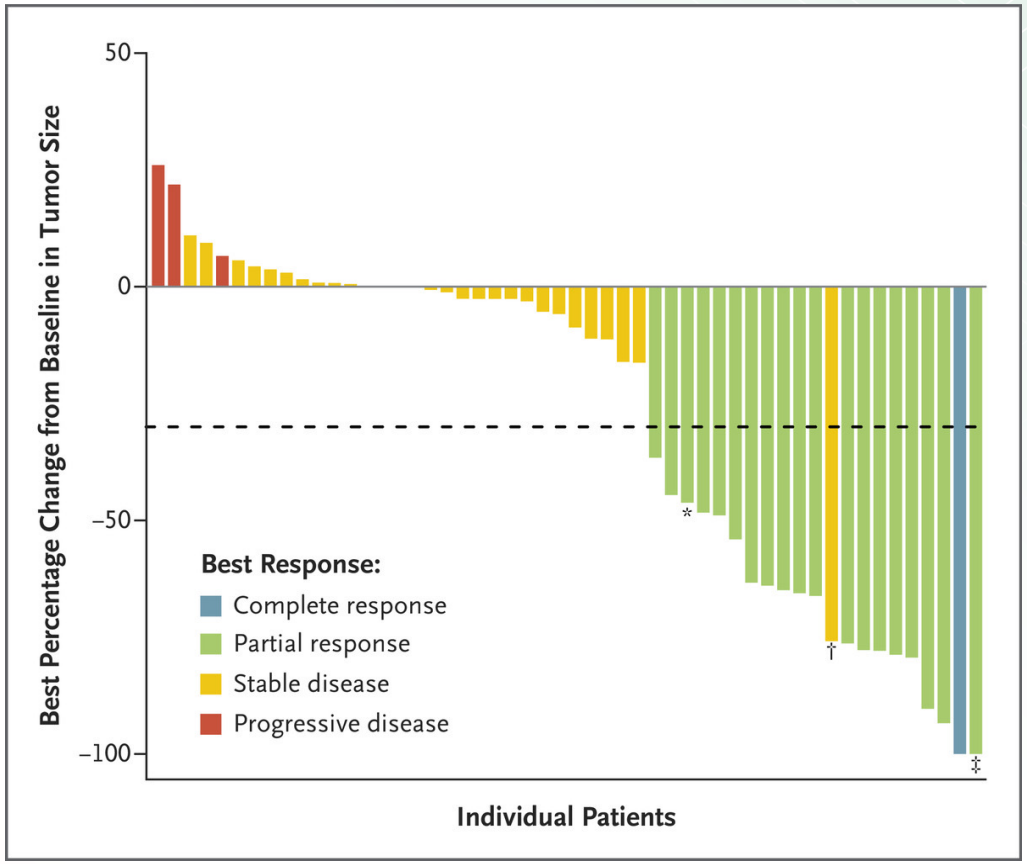
- Phase 2 study of PD-L1 atezolizumab in adult and pediatric patients with advanced Alveolar Soft Part Sarcoma (ASPS)
- Atlezolizumab 1200mg IV for age ≥ 18 or 15 mg/kg of body weight in patients <18 (cap 1200mg) q 21 days
- Median progression-free survival was 20.8 months

AP Chen et al. N Engl J Med 2023;389:911-921

Patient Responses to Atezolizumab



Best Target-Lesion Response



- 52 patients were evaluated
- Objective response in 19/52 (37%) with 1 complete response and 18 partial responses
- Median time to response was 24.7 (range 2.1 to 19.1)
- Median duration of response 24.7months (range, 4.1 to 55.8)

AP Chen et al. N Engl J Med 2023;389:911-921

Desmoid Tumors

- Desmoid tumors (DT) are rare, locally aggressive, and invasive soft-tissue tumors that are challenging to manage due to variable presentation, unpredictable disease course, and a lack of approved therapies
- Rare tumors: incidence of 900-1000 new cases annually in the United States
- ~20% of patients with desmoid tumors carry a mutation is APC gene=FAP
- Subset of sarcomas, but technically benign tumors but can be “locally malignant”
- Depending upon primary location and growth rate can be quality of life threatening and rarely even life threatening
- The theory that they can regress over time without treatment was finally confirmed in a trial of sorafenib vs placebo
- Treatment should be individualized to optimize tumor control and improve symptom burden, including pain, physical function, and overall quality of life

DeFi: A Phase 3 Trial of Nirogacestat for Progressing Desmoid Tumors (DT)

Bernd Kasper, Ravin Ratan, Thierry Alcindor, Patrick Schöffski, Winette T. van der Graaf, Breelyn A. Wilky, Richard F. Riedel, Allison Lim, L. Mary Smith, Stephanie Moody, Steven Attia, Sant Chawla, **Gina D'Amato**, Noah Federman, Priscilla Merriam, Brian A. Van Tine, Bruno Vincenzi, Shivaani Kummar, Mrinal Gounder, on behalf of the DeFi Study Investigators

- There is mechanistic rationale for the use of gamma secretase inhibitors (GSI) in DT as these tumors highly express Notch, which can be blocked by GSIs
- Nirogacestat is an investigational, oral, selective, small-molecule GSI that has shown evidence of antitumor activity in DT in Phase 1 and 2 trials with a manageable adverse event profile

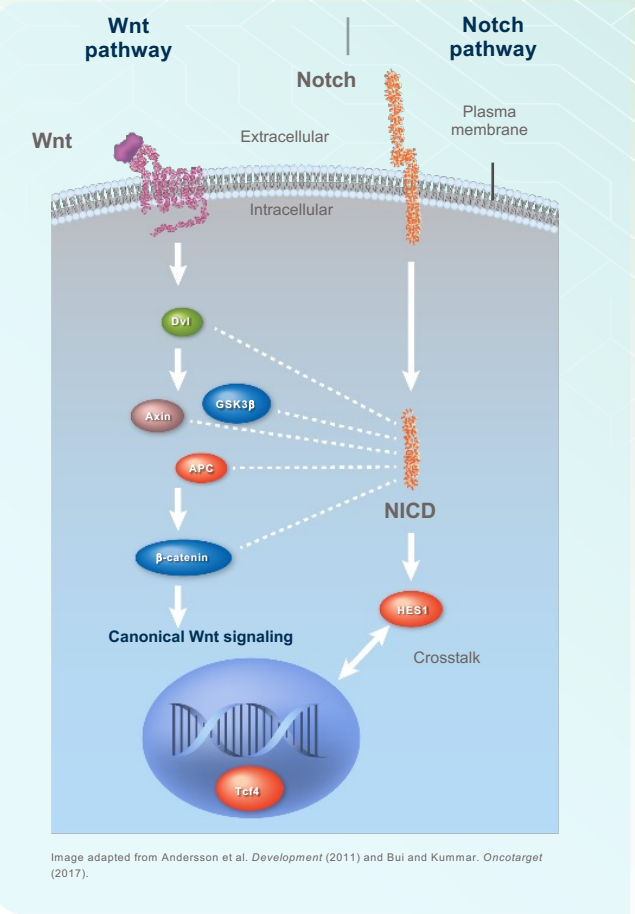


Image adapted from Andersson et al. *Development* (2011) and Bui and Kummar. *Oncotarget* (2017).

Trial Summary

- Global, randomized, double-blind, placebo-controlled, Phase 3 trial comparing the efficacy, safety, and tolerability of nirogacestat vs placebo in adult patients with progressing DT
- 142 patients randomized across 37 sites in North America and Europe

Key Endpoints

- **Primary:** Progression-free survival[b]
- **Secondary:** Objective response rate and patient-reported outcomes, including symptom burden, physical/role function, and overall quality of life[c]

Adult Eligible Patients

- Histologically confirmed DT with progressive disease per RECIST v1.1[a]
  - Treatment-naïve with DT not amenable to surgery, or
  - Refractory or recurrent disease (after ≥1 line of therapy)

Randomized 1:1 Stratified by tumor location (intra- vs extra-abdominal)

28-day cycles

- Nirogacestat 150 mg BID
- Placebo BID

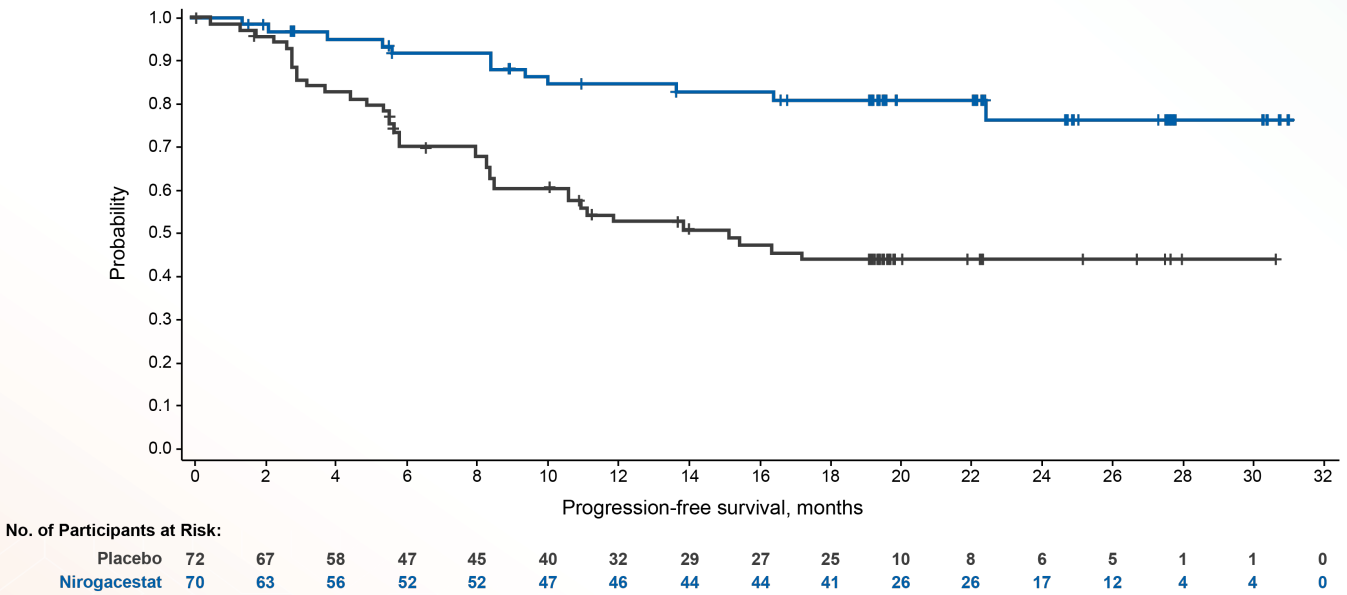
Radiographic progressive disease[d]

Open-label nirogacestat 150 mg BID

Primary Analysis Data Cutoff: April 7, 2022

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM
IN PURSUIT OF *YOUR CURE.*™

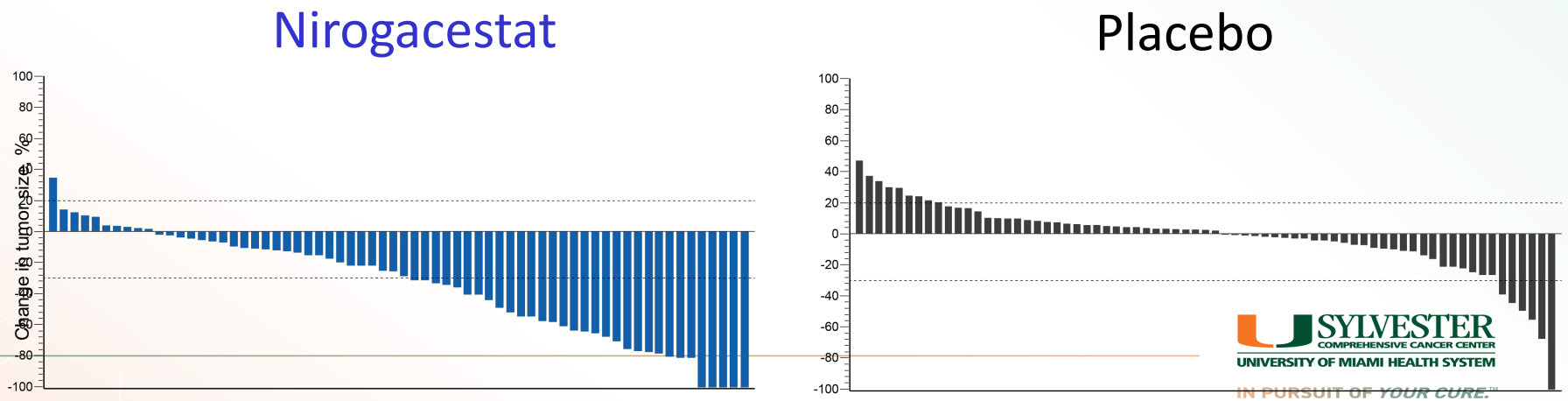
Nirogacestat Significantly Reduced the Risk of Disease Progression



	No. of Patients	No. of Events	Median (95% CI)	Hazard ratio (95% CI)
Nirogacestat	70	12	NE (NE, NE)	0.29 (0.15, 0.55) *P*<0.001
Placebo	72	37	15.1 (8.4, NE)	

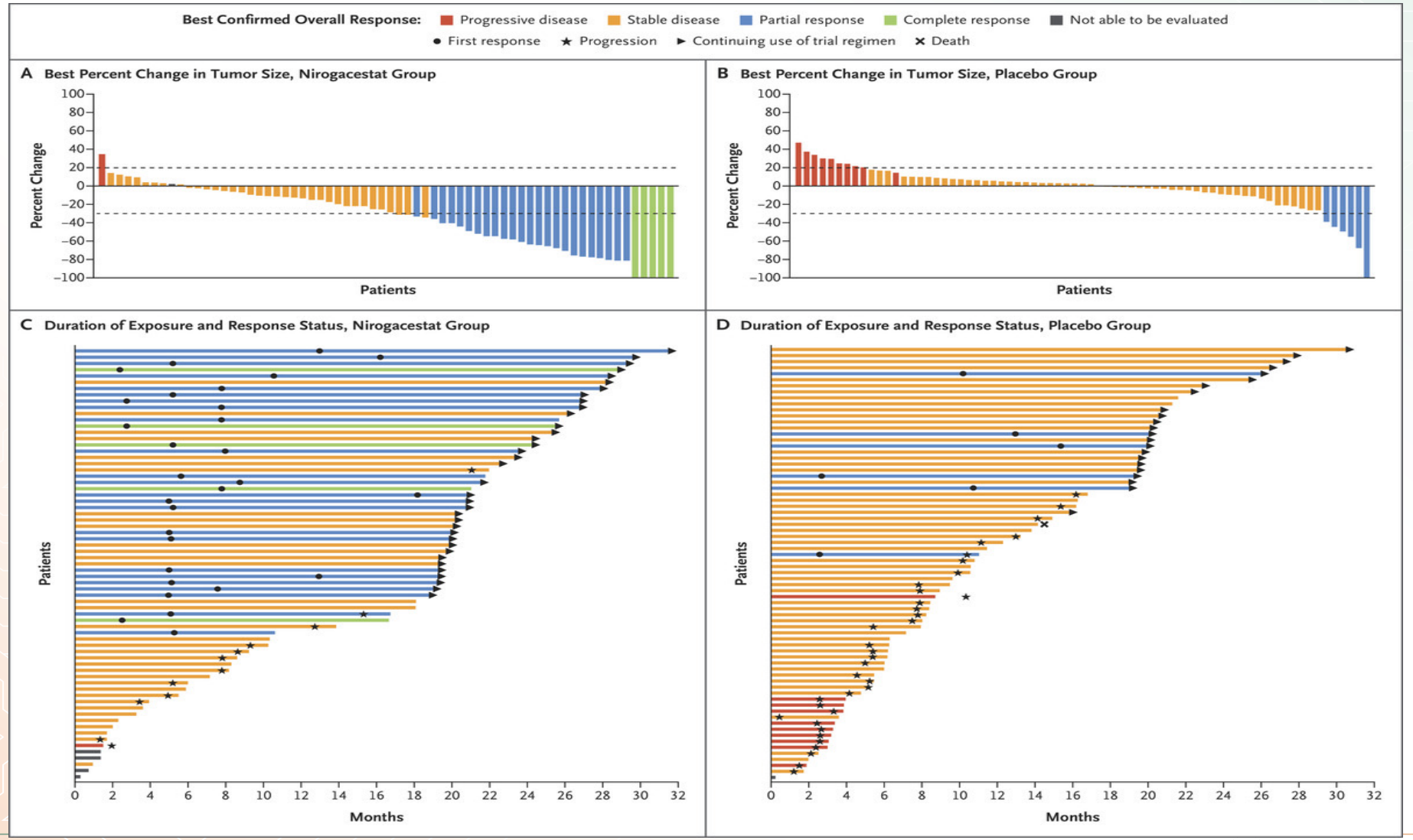
71% reduction in the risk of disease progression as compared with placebo

Nirogacestat Resulted in Substantial Reductions in Tumor Size



SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM
IN PURSUIT OF *YOUR CURE.*™

Change in Tumor Size and Best Overall Response



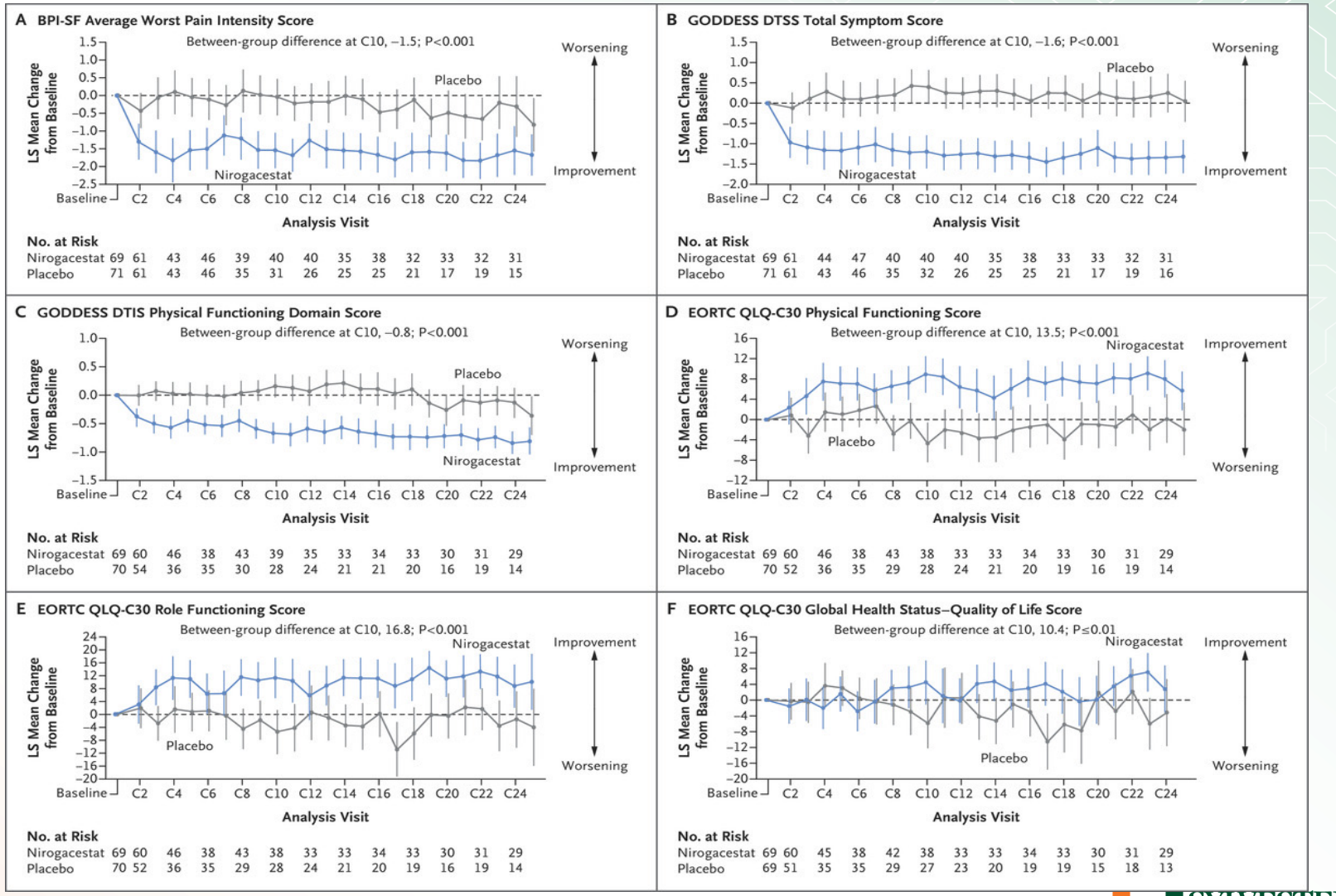
Objective response rate of 41%, including a 7% complete response rate

M Gounder et al. N Engl J Med 2023;388:898-912

Improved Patient-Reported Outcomes

Nirogacestat **significantly** lead to improvement in all patient reported outcomes

- Reduced Pain
- Reduced DT-Specific Symptom Severity
- Improved Physical/Role Functioning
- Improved Quality of Life (QoL)



M Gounder et al. N Engl J Med 2023;388:898-912

Nirogacestat Safety Profile

Safety population, n (%)	Nirogacestat (n=69)		Placebo (n=72)	
Duration of study drug exposure, median (range), mo	20.6 (0.3, 33.6)		11.4 (0.2, 32.5)	
Dose intensity, median (range), mg/d	288.3 (169, 300)		300.0 (239, 300)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any TEAE	69 (100)	39 (57)	69 (96)	12 (17)
TEAEs of any grade reported in ≥25% of patients in either arm				
Diarrhea	58 (84)	11 (16)	25 (35)	1 (1)
Nausea	37 (54)	1 (1)	28 (39)	0
Fatigue	35 (51)	2 (3)	26 (36)	0
Hypophosphatemia	29 (42)	2 (3)	5 (7)	0
Rash, maculopapular	22 (32)	4 (6)	4 (6)	0
Headache	20 (29)	0	11 (15)	0
Stomatitis	20 (29)	3 (4)	3 (4)	0
TEAEs leading to death	0		1 (1)[a]	
Dose reductions due to TEAEs	29 (42)		0	
Discontinuations due to TEAEs	14 (20)[b]		1 (1)[b]	

- **95% of TEAEs were Grade 1 or 2; the first onset of TEAEs in most patients occurred during Cycle 1**

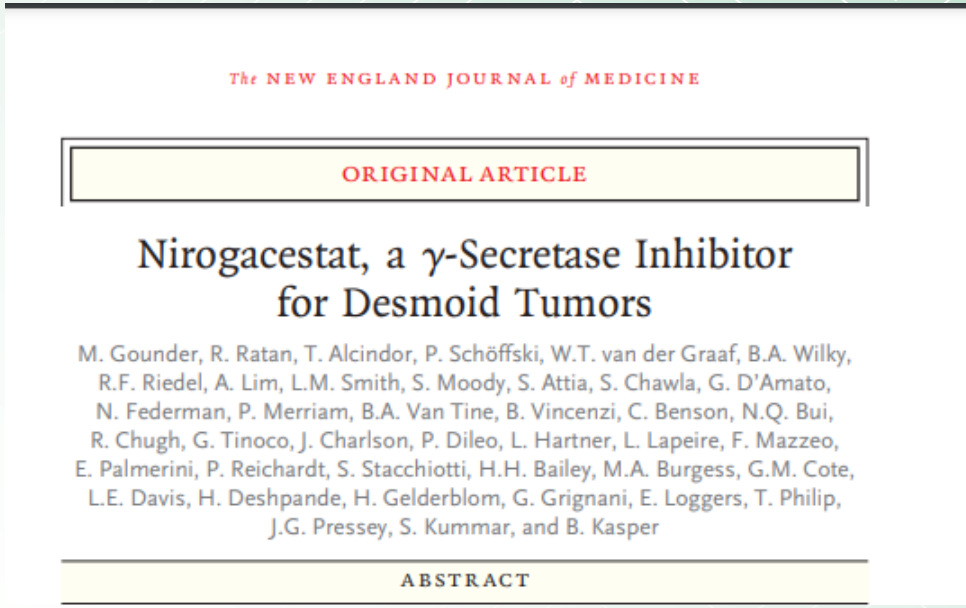
[a]Death due to sepsis. [b]TEAEs leading to discontinuations in ≥1 patient include gastrointestinal disorders (n=5 [4%]), **ovarian dysfunction (n=4 [3%]),** alanine aminotransferase increase (n=3 [2%]), aspartate aminotransferase increase (n=2 [1%]), and metabolism/nutritional disorders (n=2 [1%]). TEAE, treatment-emergent adverse event.

Kasper et al. Proffered Paper session presented at ESMO; September 9-13, 2022; Paris, France.

Ovarian dysfunction: Amenorrhea, premature menopause, menopause, ovarian failure
Occurred in 27/69 (39%)
27/36 (75%) women of childbearing potential

Summary

- DeFi represents the largest and most rigorous randomized controlled trial conducted to date in DT
- Nirogacestat demonstrated rapid, sustained, and statistically significant improvements in all primary and secondary efficacy endpoints
  - 71% reduction in the risk of disease progression as compared with placebo
  - Objective response rate of 41%, including a 7% complete response rate
  - Statistically significant and clinically meaningful improvements in pain, disease-specific symptom burden, physical/role functioning, and overall quality of life ($P \leq 0.007$)
- Nirogacestat exhibited a manageable safety profile, with 95% of all treatment-emergent adverse events being Grade 1 or 2
- Nirogacestat has the potential to become the standard of care for patients with DT requiring systemic treatment



On November 27, 2023, the FDA approved nirogacestat for adult patients with progressing desmoid tumors who require systemic treatment. This is the first approved treatment for desmoid tumors

Medications in Development for Various Soft Tissue Sarcoma Histologies

Medication	Mechanism of Action	Target	Sarcoma Type	Status/Efficacy Data
AL102	γ-Secretase Inhibitors	Notch and Wnt/β-catenin pathway	Desmoid Tumor	Phase 2/3 study ongoing
Anlotinib	Tyrosine Kinase Inhibitor	VEGFR-2,-3; FGFR-1,-4; PDGFR-α,-β; c-Kit; Ret	ASPS Synovial Sarcoma Leiomyosarcoma	Results pending
Milademetan	MDM2 Inhibitor	P53	WD/DD LPS	Phase 3 trial didn't meet primary endpoint
BI 907828	MDM2 Inhibitor			Awaiting phase 3 results
Vimseltinib	Tyrosine Kinase Inhibitor	CSF1R	TGCT	Awaiting phase 3 results
FHD-609	BRD9 Inhibitor	ncBAF Complex	Synovial Sarcoma	Study closed

Anlotinib

Anlotinib as a maintenance treatment for advanced soft tissue sarcoma after first-line chemotherapy (ALTER-S006): a multicentre, open-label, single-arm, phase 2 trial

Bushu Xu,[a,h] Qiuzhong Pan,[a,h] Hua Pan,[a,h] Haomiao Li,[b] Xianan Li,[c] Jing Chen,[d] Danmei Pang,[e] Baoqing Zhang,[f] Desheng Weng,[a] Ruiqing Peng,[a] Meiyu Fang,[g,**] and Xing Zhang[a,*]

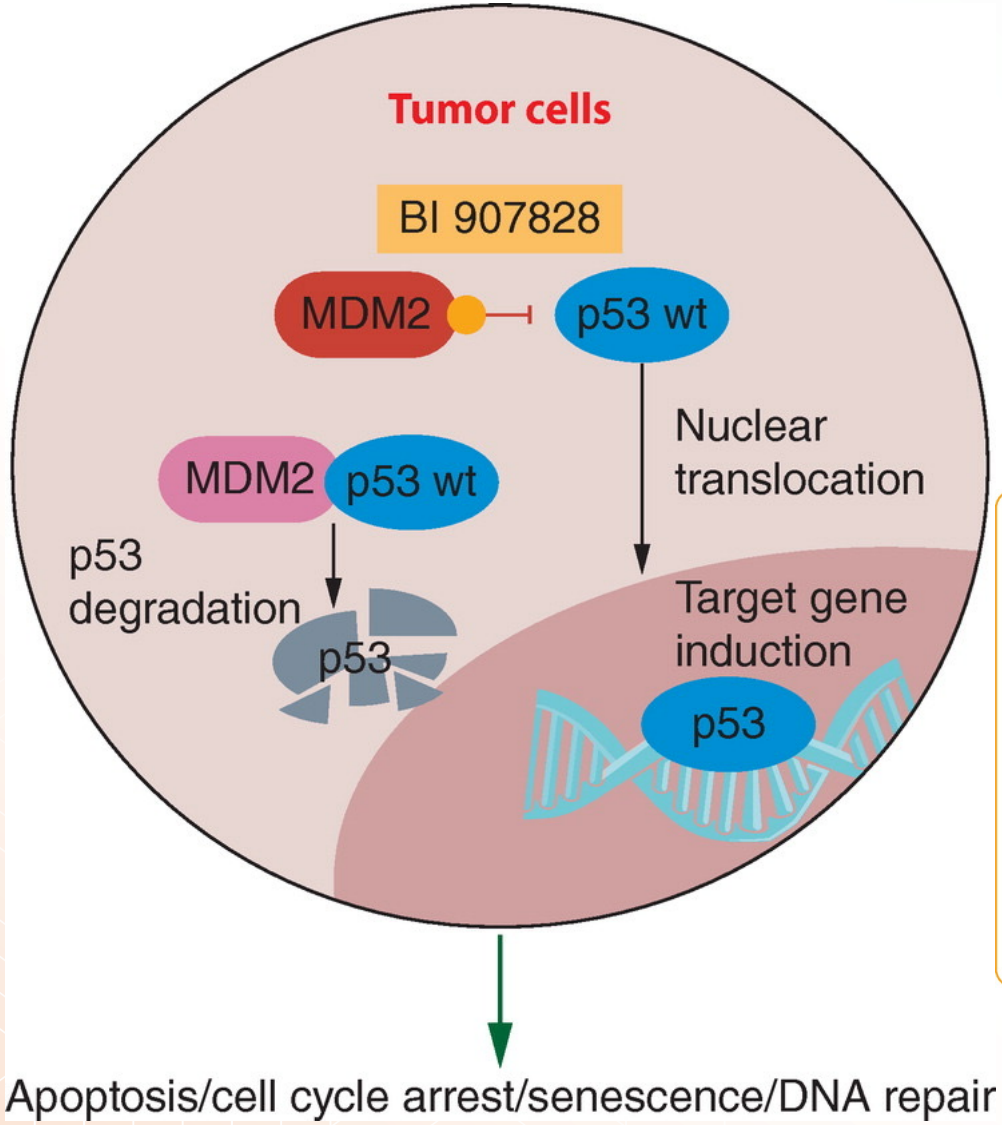
Histologic subtype	Patients	Best response							Median PFS[b] (95% CI)	1-year OS Rate (%)
		CR	PR	SD	PD	NA[a]	ORR (%)	DCR (%)		
Liposarcoma	17 (35)	0	2 (12)	15 (88)	0	0	12	100	12.5 (7.1–18.0)	100.0
WDLS	4 (8)	0	1 (25)	3 (75)	0	0	25	100	19.1 (3.0–35.2)	100.0
DDLS	11 (22)	0	1 (9)	10 (91)	0	0	9	100	9.0 (4.9–13.2)	100.0
Myxoid liposarcoma	2 (4)	0	0	2 (100)	0	0	0	100	NE (NE)	100.0
Leiomyosarcoma	15 (31)	0	2 (13)	12 (80)	1 (7)	0	13	93	7.7 (5.7–9.6)	100.0
Synovial sarcoma	4 (8)	1 (25)	0	1 (25)	1 (25)	1 (25)	25	50	19.1 (0–48.8)	100.0
Fibrosarcoma	3 (6)	0	1 (33)	2 (67)	0	0	33	100	3.6 (3.5–3.6)	100.0
Unclassified sarcoma	3 (6)	0	1 (33)	2 (67)	0	0	33	100	NE (NE)	100.0
Other subtypes[c]	7 (14)	0	1 (14)	6 (86)	0	0	14	100	7.8 (0–18.5)	85.7
Overall	49 (100)	1 (2)	7 (14)	38 (78)	2 (4)	1 (2)	16 (95% CI 7–30)	94 (95% CI 83–99)	9.1 (5.7–12.5)	98.0

Data are n (%), n/N (%) and median survival (95% CI). Responses were assessed in accordance with Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1). Only confirmed responses were included. CR = complete response. PR = partial response. SD = stable disease. PD = progressive disease. NA = not assessed. ORR = objective response rate. DCR = disease control rate. PFS = progression-free survival. CI = confidence interval. OS = overall survival. WDLS = well-differentiated liposarcoma. DDLS = dedifferentiated liposarcoma. NE = not evaluable. [a]The patient who lost to follow-up before the first scheduled post-baseline evaluation. [b]The median PFS for anlotinib maintenance treatment. [c]Other subtypes: angiosarcoma, undifferentiated pleomorphic sarcoma, low-grade myofibroblastic sarcoma, sclerosing epithelioid fibrosarcoma, epithelioid sarcoma, epithelioid haemangioendothelioma and extraskeletal myxoid chondrosarcoma.

Table 2: Responses and survival analysis according to different histological subtypes.

Milademetan in Dedifferentiated Liposarcoma

- Phase III MANTRA trial of milademetan did not meet the primary endpoint of progression free survival (PFS) by blinded independent central review compared to trabectedin, a standard of care treatment for dedifferentiated (DD) liposarcoma (LPS)
- Based on 115 events, the median PFS was **3.6** months for milademetan while it was **2.2** months for trabectedin– *UGH still better just not statistically significant!!*
- Nausea, thrombocytopenia, anemia, vomiting and neutropenia were the most common treatment emergent adverse events (TEAEs) observed in the milademetan treated group
- Further, Grade 3/4 TEAEs were also observed in the milademetan arm including neutropenia, anemia and thrombocytopenia
- Dose reductions in the milademetan arm and discontinuations in the milademetan arm due to AEs were observed as 44.2% and 11.6%, respectively, compared with trabectedin arm of 29.1% and 19.0%
- In the subgroup with dedifferentiated liposarcomas, the disease control rate and median progression-free survival were 58.5% (95% CI, 44.1 to 71.9) and 7.2 months overall (n = 53), and 62.0% (95% CI, 35.4 to 84.8) and 7.4 months with the recommended intermittent schedule (n = 16), respectively.



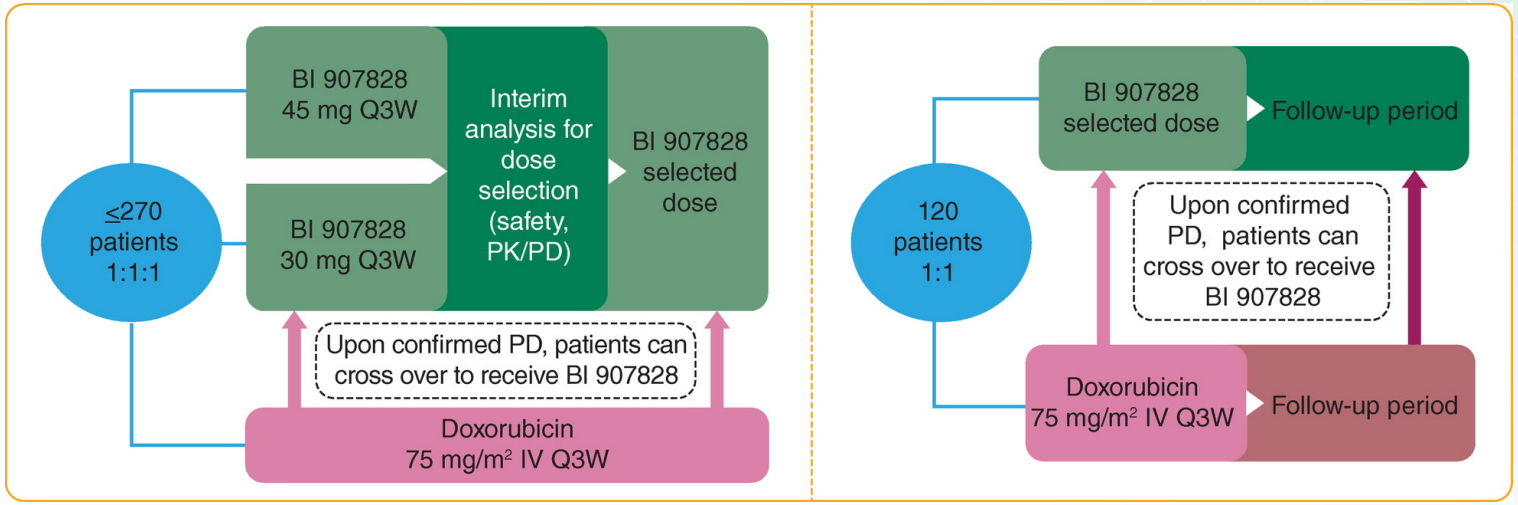
FUTURE ONCOLOGY, VOL. 19, NO. 9 | CLINICAL TRIAL PROTOCOL

Open Access

Brightline-1: phase II/III trial of the MDM2–p53 antagonist BI 907828 versus doxorubicin in patients with advanced DDLPS

Patrick Schöffski, Mehdi Lahmar, Anthony Lucarelli & Robert G Maki

Published Online: 29 Mar 2023 | https://doi.org/10.2217/fon-2022-1291



SAFETY AND EFFICACY UPDATES FROM A PHASE 1 STUDY OF VIMSELTINIB IN PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMOR

Hans Gelderblom, Albiruni Abdul Razak, Javier Martín-Broto, Breelyn A. Wilky, Piotr Rutkowski, Nicholas Bernthal, Supraja Narasimhan, Maitreyi G. Sharma, Rodrigo Ruiz-Soto, Matthew L. Sherman, William D. Tap

2023 ctos ANNUAL MEETING

Presented by:

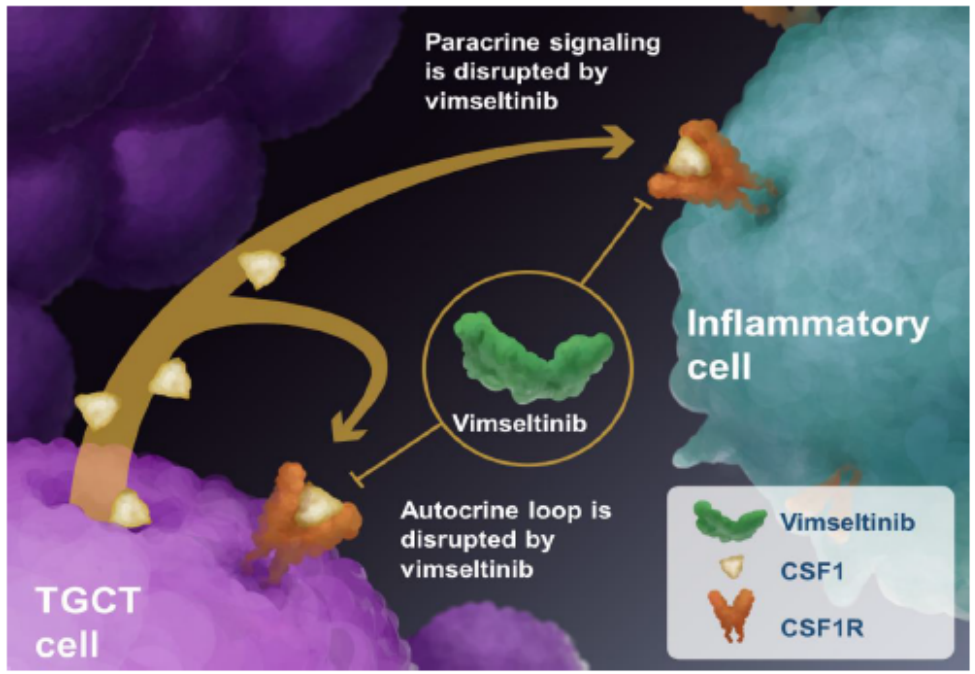
Hans Gelderblom, MD, PhD
Professor, Chair, Department of Medical Oncology,
Leiden University Medical Center, Leiden, Netherlands

ctos
Bringing together the world's sarcoma specialists

INTRODUCTION

- TGCT is a rare, locally aggressive neoplasm caused by aberrant expression of the *CSF1* gene[1]
- There is only 1 systemic agent approved by the US Food and Drug Administration for the treatment of patients with TGCT not amenable to surgery, and none by the European Commission or other regulatory agencies, leaving an unmet need for an effective, CSF1R-targeted therapy with a favorable safety profile[2]
- Vimseltinib is an investigational, oral switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit CSF1R[1]

Objective:
To report the long-term safety and efficacy of vimseltinib in patients with TGCT not amenable to surgery from the phase 1 dose-escalation part of a phase 1/2 study



1) Smith BD, et al. *Mol Cancer Ther*. 2021;20:2098-109. 2) Pexidartinib (TURALIO®). Prescribing information. Daiichi Sankyo, Inc.; 2022.
CSF1, colony-stimulating factor 1; CSF1R, CSF1 receptor; TGCT, tenosynovial giant cell tumor.

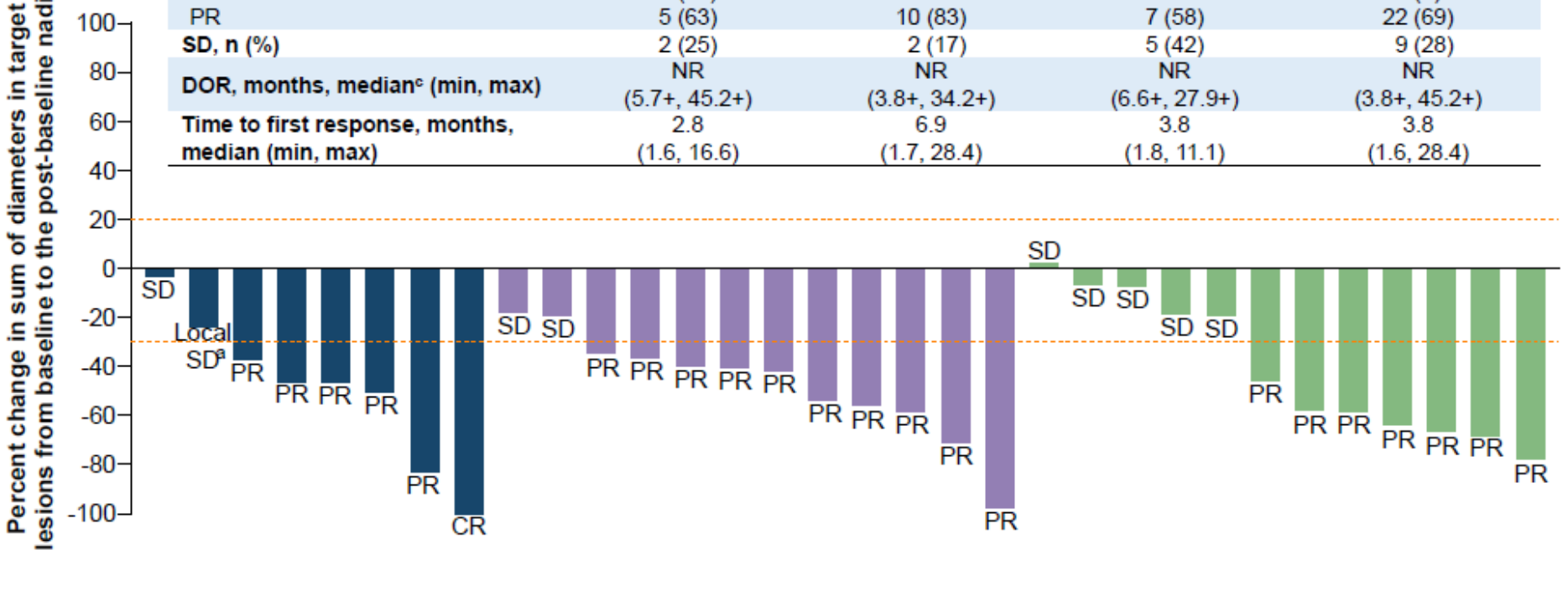
2023 ctos® ANNUAL MEETING

Presented by:
Hans Gelderblom, MD, PhD
Professor, Chair, Department of Medical Oncology,
Leiden University Medical Center, Leiden, Netherlands

ctos
Bringing together the world's sarcoma specialists

BEST OVERALL RESPONSE ASSESSED USING RECIST v1.1 BY IRR

	Cohort 5 (n = 8)[a]	Cohort 8 (n = 12)	Cohort 9 (n = 12)	Total (N = 32)
ORR[b], n (%)	6 (75)	10 (83)	7 (58)	23 (72)
CR	1 (13)	0	0	1 (3)
PR	5 (63)	10 (83)	7 (58)	22 (69)
SD, n (%)	2 (25)	2 (17)	5 (42)	9 (28)
DOR, months, median[c] (min, max)	NR (5.7+, 45.2+)	NR (3.8+, 34.2+)	NR (6.6+, 27.9+)	NR (3.8+, 45.2+)
Time to first response, months, median (min, max)	2.8 (1.6, 16.6)	6.9 (1.7, 28.4)	3.8 (1.8, 11.1)	3.8 (1.6, 28.4)



- Vimseltinib demonstrated robust antitumor activity with an ORR of 72% (23/32 patients) across all cohorts
  - The ORR at 6 months was 47% across all cohorts (15/32 patients)

Data cutoff: June 27, 2023.

+ denotes that response is ongoing at last assessment. The dotted line at 20% represents the threshold for progressive disease; the dotted line at −30% represents the threshold for PR.

[a]One patient had a local assessment for efficacy but will never have IRR data. This patient has been included in the SD assessment (cohort 5). [b]Best overall response of target lesions assessed using RECIST v1.1 by IRR; includes all available follow-ups. [c]Based on the Kaplan-Meier estimate. DOR is defined as the time from the first imaging results showing response to progressive disease.

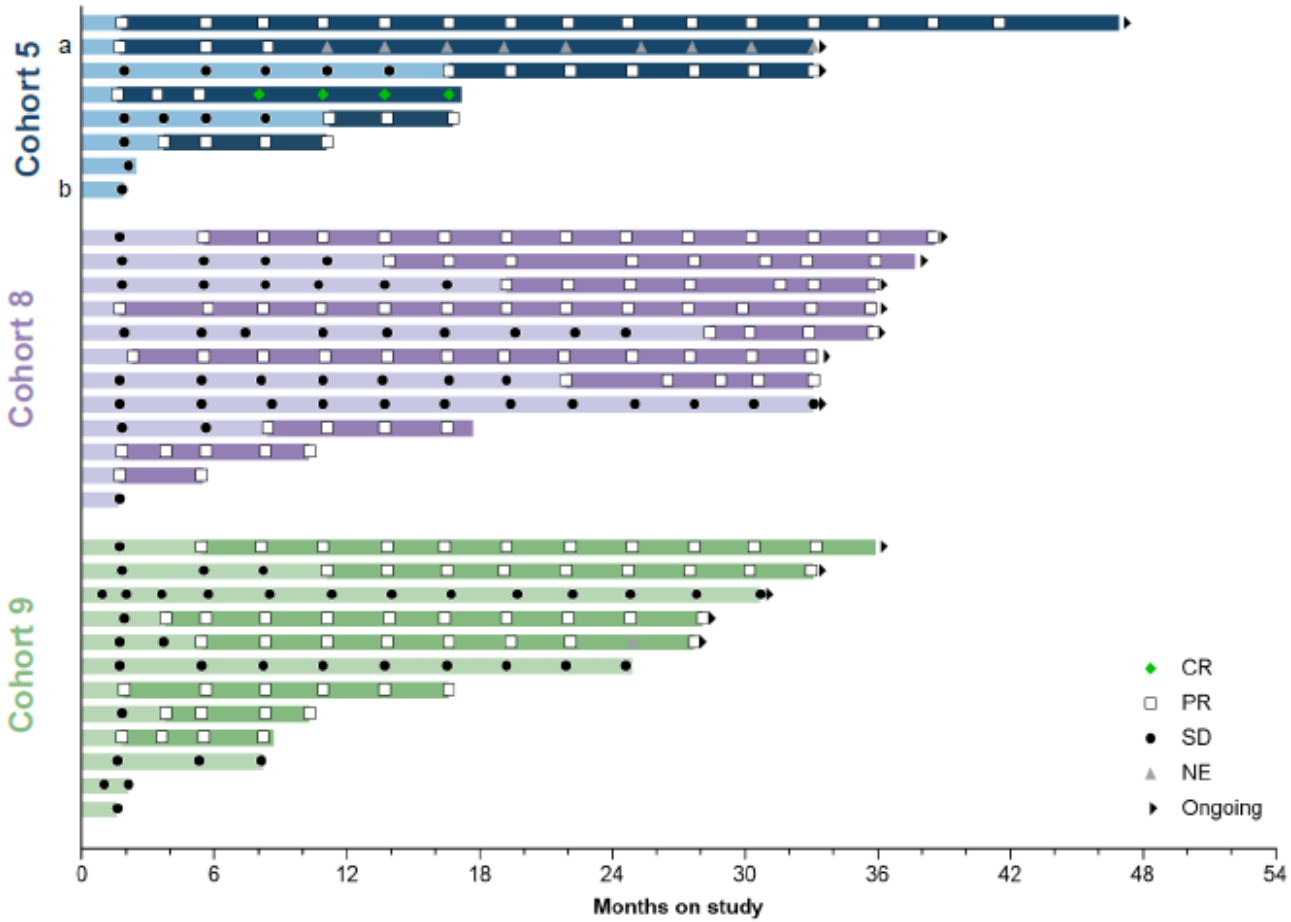
CR, complete response; DOR, duration of response; IRR, independent radiological review; max, maximum; min, minimum; NR, not reached; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

2023 ctos® ANNUAL MEETING

Presented by:

Hans Gelderblom, MD, PhD
Professor, Chair, Department of Medical Oncology,
Leiden University Medical Center, Leiden, Netherlands

DURATION OF TREATMENT AND RESPONSE



- The median treatment duration was 25.1 months (range, 0.7–46.9 months; mean, 21.8 months)
- Fifteen (47%) patients remain on treatment and have received vimseltinib for 2 or more years, with the longest time on treatment being approximately 4 years at the time of data cutoff
- Responses (n = 23) were durable and were observed before and after 6 months, demonstrating continued clinical benefit with prolonged treatment
  - By 6 months: 15/23
  - By 12 months: 18/23
  - By 24 months: 22/23
  - By 36 months: 23/23

Response was analyzed using RECIST v1.1 by IRR; includes all available follow-up visits. Dark shading represents the duration of response. Data cutoff: June 27, 2023.
[a]One patient had metallic artifacts at baseline; as the tumor reduced, metallic artifacts prevented accurate tumor measurements by IRR, resulting in NE assessments beyond 10 months in the study (cohort 5).
[b]One patient had a local assessment for efficacy but will never have IRR data. This patient has been included in the SD assessment (Cohort 5).
CR, complete response; IRR, independent radiological review; NE, not evaluable; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Presented by:

Hans Gelderblom, MD, PhD
Professor, Chair, Department of Medical Oncology,
Leiden University Medical Center, Leiden, Netherlands

CONCLUSIONS

- Vimseltinib demonstrated long-term tolerability and a manageable safety profile in patients with TGCT not amenable to surgery, which remained consistent with longer follow-up
  - Only 2 patients discontinued treatment due to AEs, and no new treatment-related SAEs were observed
- Nearly 50% of patients were on treatment for more than 2 years at the time of this analysis, with the longest time on treatment being approximately 4 years
- Vimseltinib demonstrated robust antitumor activity with an ORR of 72% across all cohorts
  - The ORR at 6 months was 47% and additional responses occurred after 6 months, demonstrating continued clinical benefit with prolonged treatment
  - No patients progressed on treatment, as assessed by IRR
- Vimseltinib could fulfill the unmet need for an effective systemic therapy with a favorable safety profile for patients with TGCT not amenable to surgery
- These results support continued evaluation of vimseltinib in the ongoing phase 2 part of this study (NCT03069469) and in the phase 3 MOTION trial (NCT05059262)

AE, adverse event; IRR, independent radiological review; ORR, objective response rate; SAE, serious AE; TGCT, tenosynovial giant cell tumor.

Presented by:

Hans Gelderblom, MD, PhD
Professor, Chair, Department of Medical Oncology,
Leiden University Medical Center, Leiden, Netherlands

In Summary

- Several new drugs FDA approved since 2020
  - Nirogacestat- Desmoid
  - Atezolizumab- ASPS
  - Nab-sirolimus-PEComa
  - Crizotinib - IMT
  - Tazemetostat - Epithelioid
  - Avapritinib- D842V mutated GIST
  - Ripretinib- 4th line GIST
- Promising multitargeted TKI, CSF-1 and MDM2 inhibitors in the horizon
- Molecular profiling is essential for sarcomas to optimize the limited treatment options

BEST Sarcoma Team EVER!!

Medical Oncology
Jon Trent
Gina D'Amato
Emily Jonczak
Aditi Dhir (Ped)
Steven Bialick

Pathology
Andrew Rosenberg
Elizabeth Montgomery
Daniel Cassidy
Jay-Lou Velez Torres

Radiology
Ty Subhawong
Francesco Alessandrino
Patricia Castillo

Nurse Practitioner
Morgan Mount
Solange Sierra
Alissette Naveda

Nursing
Arlen Pita
Rosie Jara
Jennifer Vila

Social Work
Arelys Rivero
Adriana Alverez(AYA)

Administrative
Amanda Martin
Hiram Correa
Napoleon Rios-Leiva
Lady Bello

Pharmacy
Sasha Watson

Nurse navigation
Jeanne Elfman

Orthopedic Oncology
Fran Hornicek
Tom Temple
Brooke Crawford
Mo Al Maaieh

Surgical Oncology
Nipun Merchant
Alan Livingstone
Neha Goel
Dido Franceschi
Julie Grossman

Radiation Therapy
Raphael Yechieli
Aaron Wolfson
Laura Freedman

Head & Neck Surgery
Donald Weed
Zoukaa Sargi
Frank Civantos

Thoracic Surgery
Dao Nguyen
Nestor Villamizar

Interventional Radiology
Shree Venkat
Felipe Ferreira de Souza
Prasoon Mohan

Gynecologic Oncology
Matt Schlumbrecht
Abdulrahman Sinno
Matt Pearson

Clinical Research
Irene Marino
Maria Casanova
Julie De Leon
Ravipal Luthra
Bianca Tercero
Adriana Martinez
Gianna Wendorff

Lab Research
Joanna DeSalvo
Luyuan Li, PhD
Karina Galoian
Josie Eid, PhD
Zenfeng Duan
Surinder Kumar
David Lombard
Gauthami Pulivendala
Robert Walker

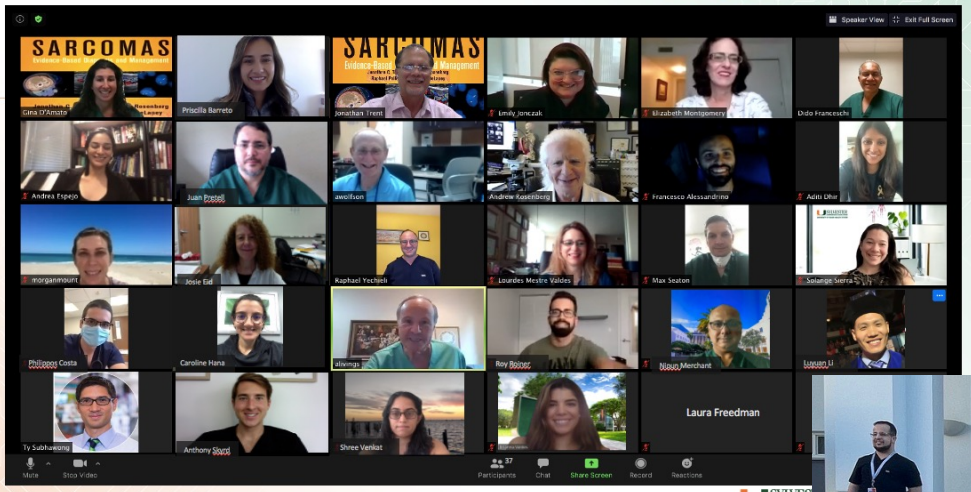
Fellows/Residents/Sarcoma Investigation Group
Shreya Saxena
Priscila Barreto Coelho
Brandon Rose
Leticia Campoverde
Seiya Lui
Kurt Statz-Geary

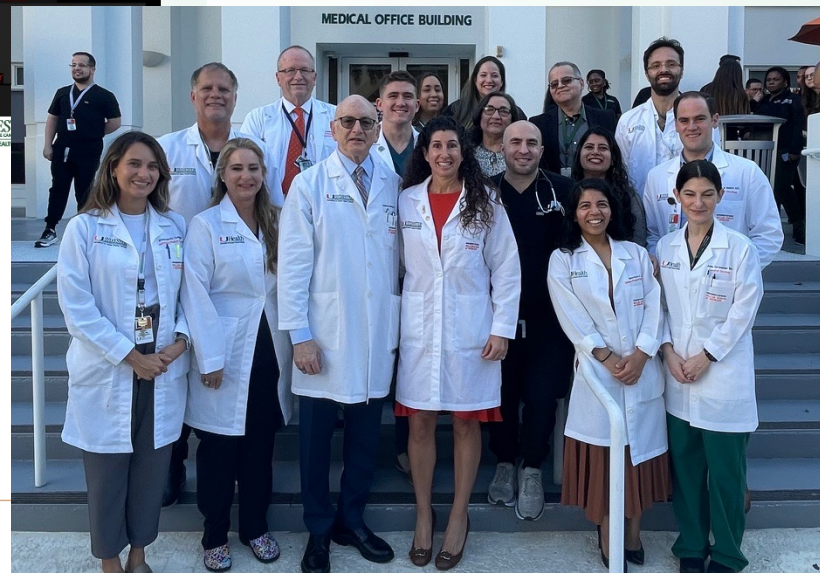
Inpatient NP
Maria Siero
Eda Augstin
Neylen Hernandez
Jessica Jorge
Michelle Von Der Hyde
Leonide Brunot

THANK YOU!!

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

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





Contact information:
Cell phone 404-219-0400
Administrative office: 305-243-2581
Fax: 305-243-0424
Sarcoma New Patient line: 305-243-4486
Email: gina.damato@med.miami.edu