Meet The Professor

Optimizing the Management of Soft Tissue Sarcoma and Related Connective Tissue Disorders

Tuesday, May 23, 2023
5:00 PM – 6:00 PM ET

Faculty

Brian Van Tine, MD, PhD

Moderator

Neil Love, MD

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Commercial Support

This activity is supported by educational grants from Genentech, a member of the Roche Group, and SpringWorks Therapeutics Inc.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

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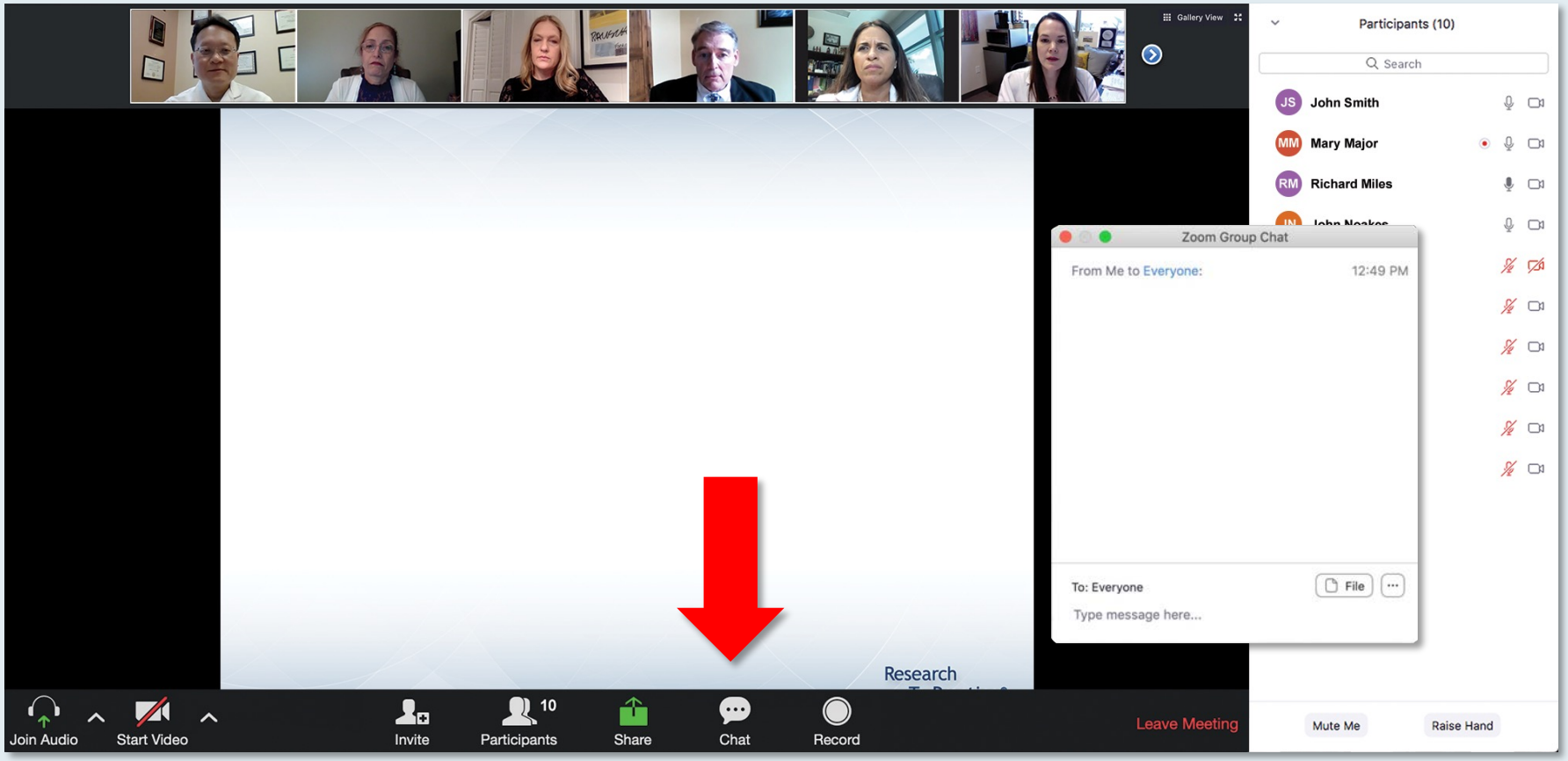
Nonrelevant Financial Relationship	Targeted Oncology, Total Health Conferencing

We Encourage Clinicians in Practice to Submit Questions



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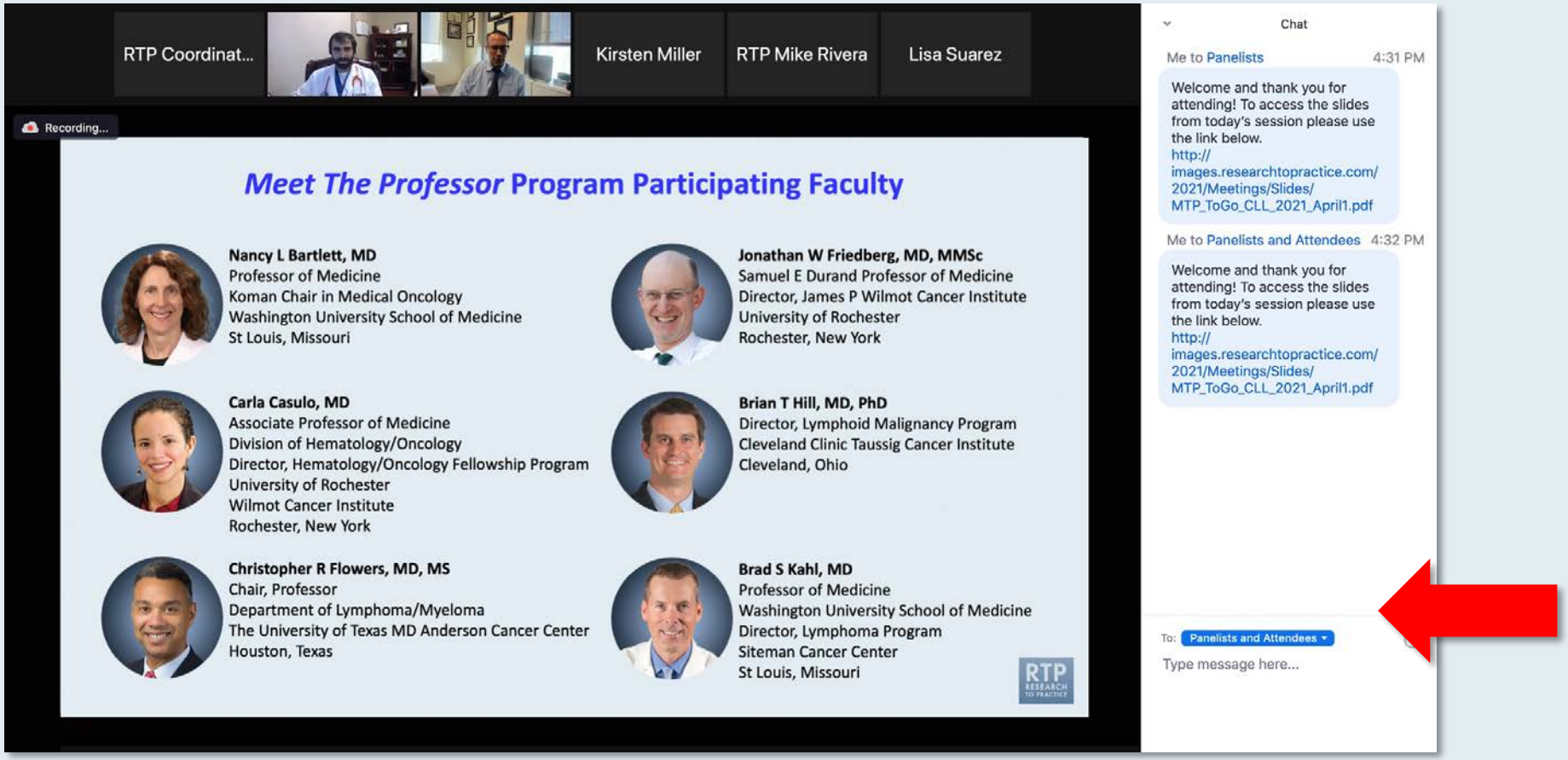
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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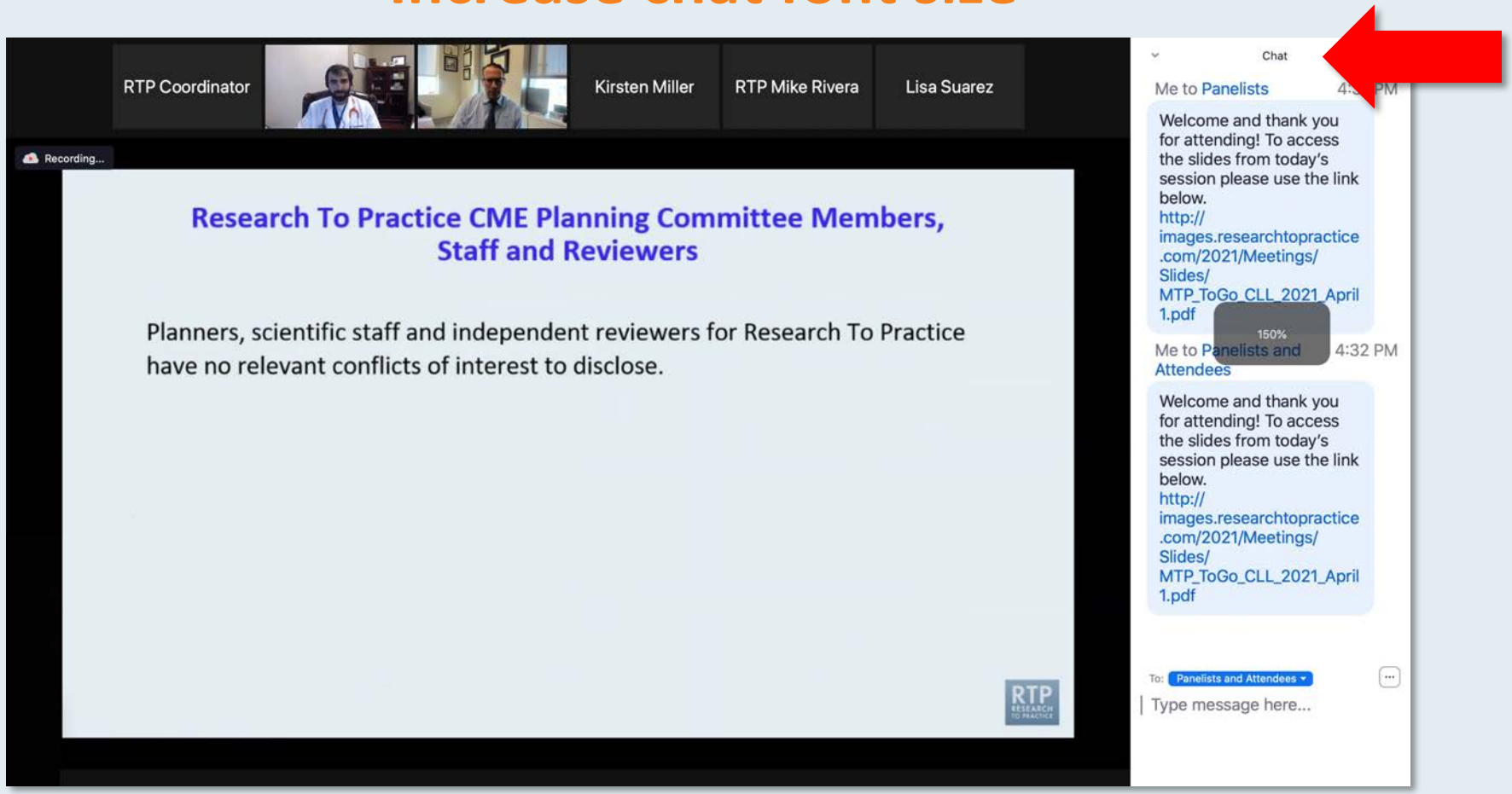
Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
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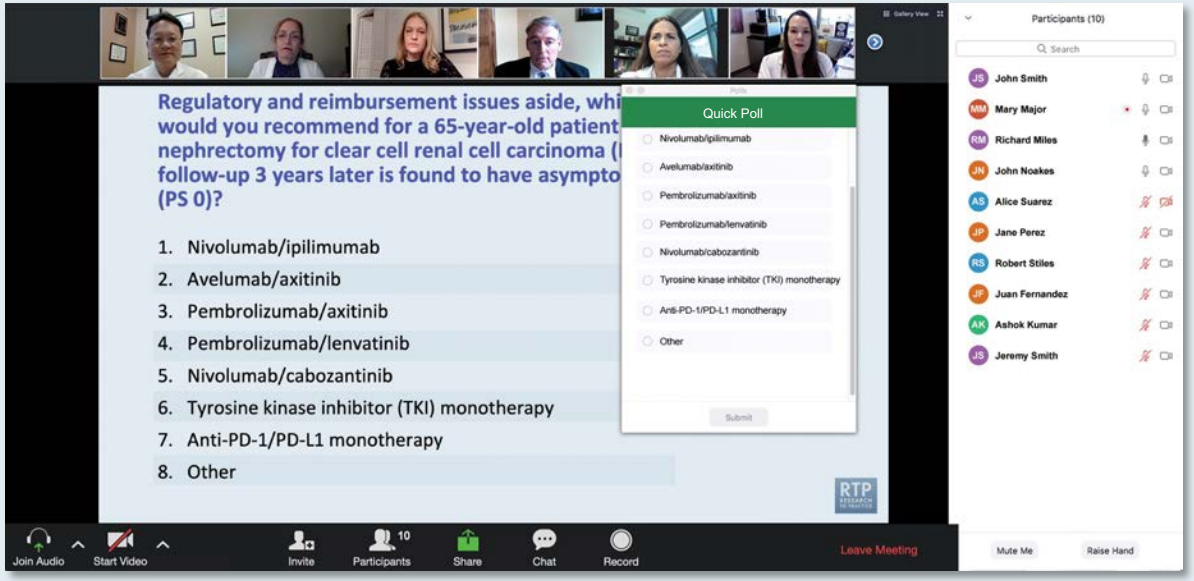

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of Desmoid Tumors

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Part 1 of a 3-Part Complimentary NCPD Webinar Series
in Partnership with the 2023 ONS Congress

Urothelial Bladder Cancer

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5:00 PM – 6:00 PM ET

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Jonathan E Rosenberg, MD

Moderator

Neil Love, MD

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Lunch with the Investigators: Gastroesophageal Cancers

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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Brian Van Tine, MD, PhD
Professor of Medicine and of Pediatrics
Director, Developmental Therapeutics (Phase 1) Program
Sarcoma Program Director
Barnes-Jewish Hospital
Washington University
St Louis, Missouri

Meet The Professor Program Participating Faculty

Richard F Riedel, MD
Associate Professor of Medicine with Tenure
Associate Director, Clinical and Translational Research
Duke Sarcoma Center
Duke Cancer Institute
Duke University
Durham, North Carolina

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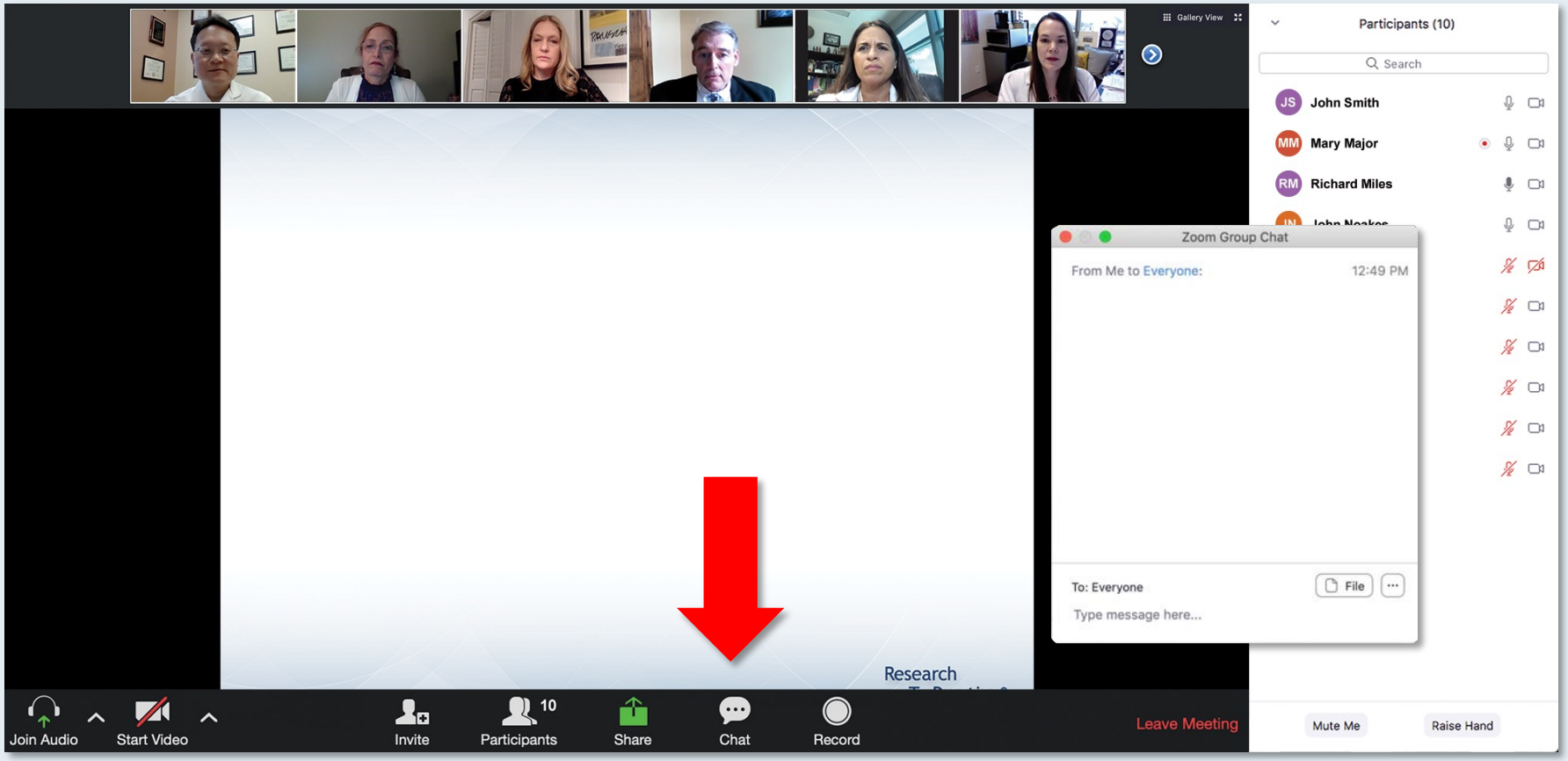

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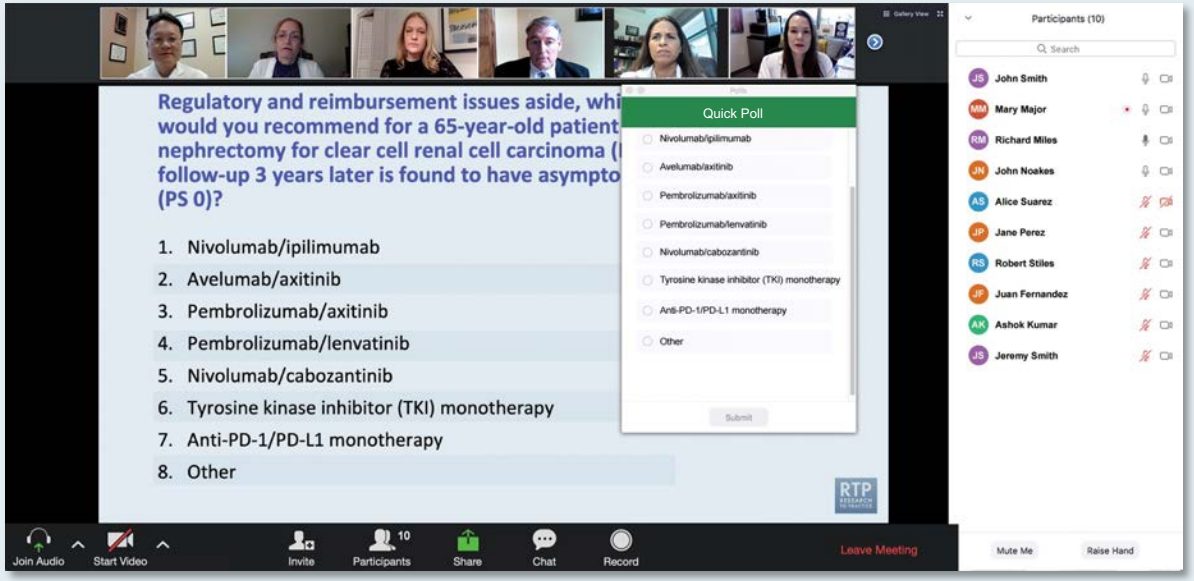

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Nam Q Bui, MD
Stanford Cancer Institute
Stanford, California

Atif Hussein, MD, MMM
Florida International University Herbert Wertheim College of Medicine
Hollywood, Florida

Melanie B Thomas, MD
Duke Cancer Institute
Durham, North Carolina

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Meet The Professor with Dr Van Tine

Introduction

MODULE 1: Immunotherapy in Soft Tissue Sarcomas — Alveolar Soft Part Sarcoma

MODULE 2: Desmoid Tumors

MODULE 3: Targeted Therapy

MODULE 4: Case Presentations

MODULE 5: Journal Club with Dr Van Tine

MODULE 6: Appendix

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“Back in the day, in 2019, our knowledge about germline testing was just beginning …”

Sandy Srinivas, MD
Prostate cancer satellite meeting
May 16, 2023

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2023;12(7):2561.

Journal of
Clinical Medicine

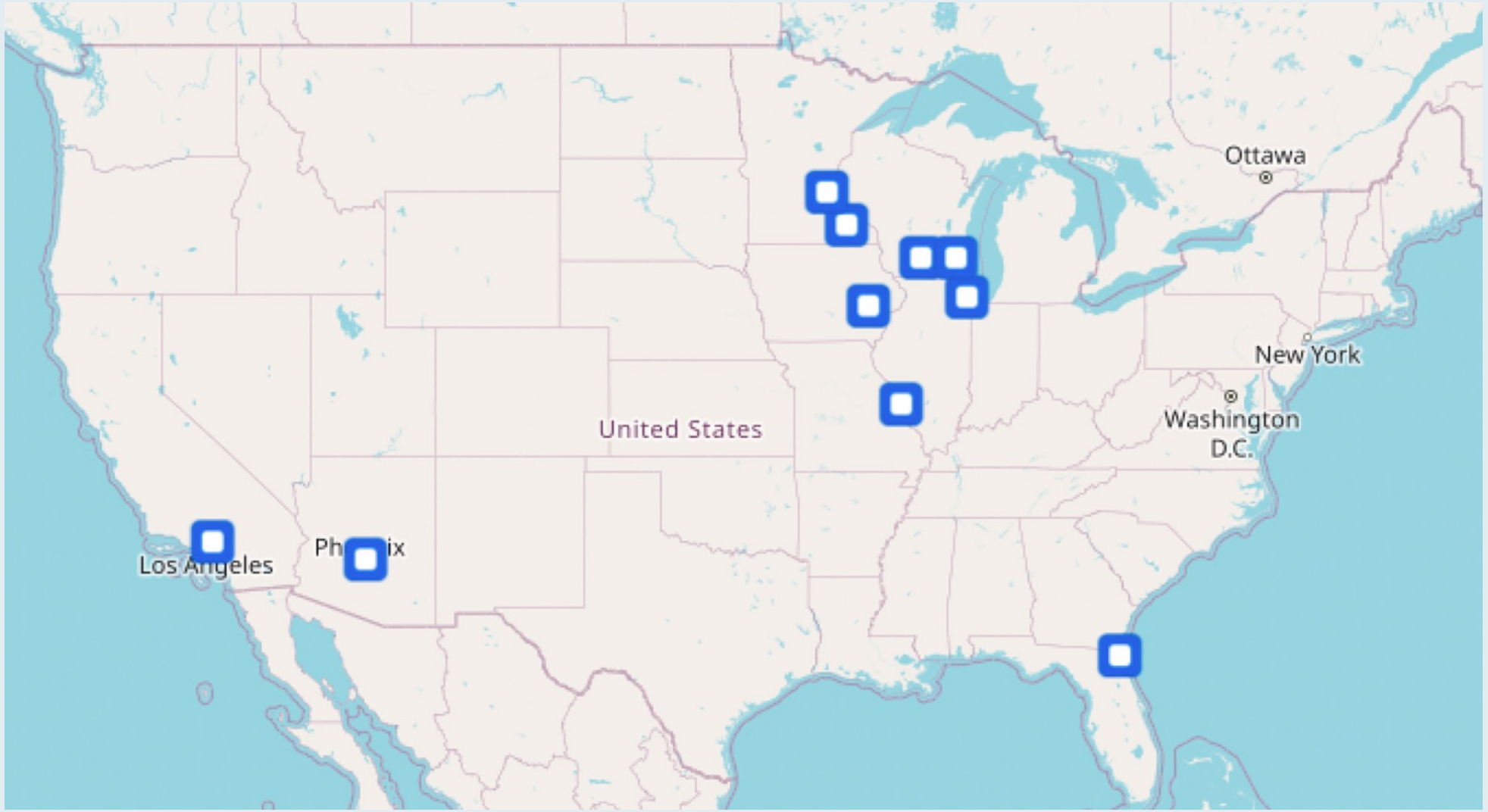
MDPI

Brief Report

The Midwest Sarcoma Trials Partnership: Bridging Academic and Community Networks in a Collaborative Approach to Sarcoma

Natalie K. Heater [1], Scott Okuno [2], Steven Robinson [2], Steven Attia [3], Mahesh Seetharam [4], Brittany L. Siontis [2], Janet Yoon [5], Sant Chawla [6], Mohammed M. Milhem [7], Varun Monga [7], Keith Skubitz [8], John Charlson [9], Angela C. Hirbe [10], Mia C. Weiss [10], Brian Van Tine [10] and Mark Agulnik [5,*]

Midwest Sarcoma Trials Partnership Anchor Site Locations



Heater NK et al. *J Clin Med* 2023;12(7):2561.

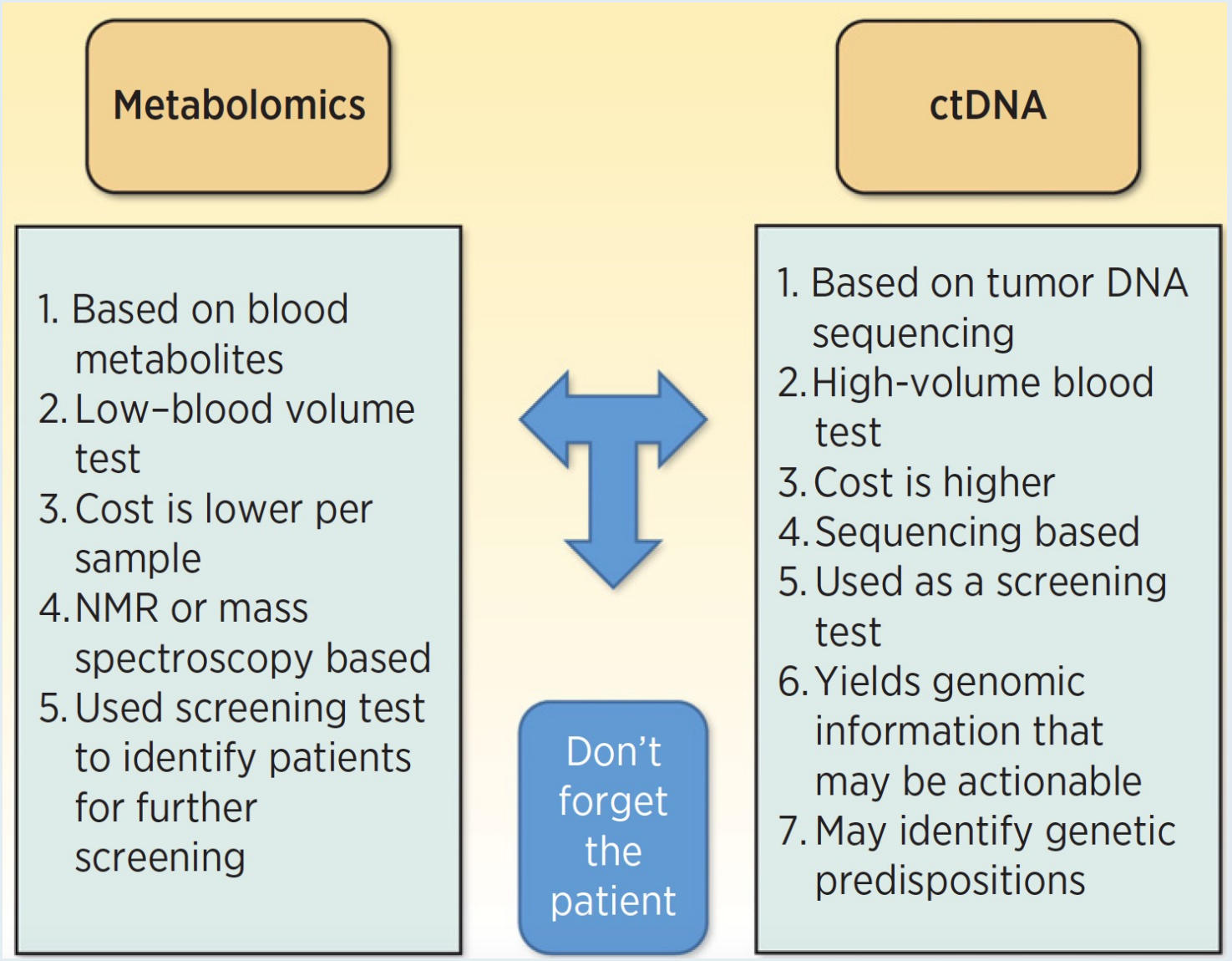
2022;28(8):1477-8.

CLINICAL CANCER RESEARCH | CCR TRANSLATIONS

In an Era of ctDNA, Is Metabolomics the New Kid on the Block?

Brian A. Van Tine[1,2,3] and Costas A. Lyssiotis[4,5,6]

Potentially Complementary Technologies of Metabolomics and ctDNA



Van Tine BA, Lyssiotis CA. *Clin Cancer Res* 2022;28(8):1477-8.

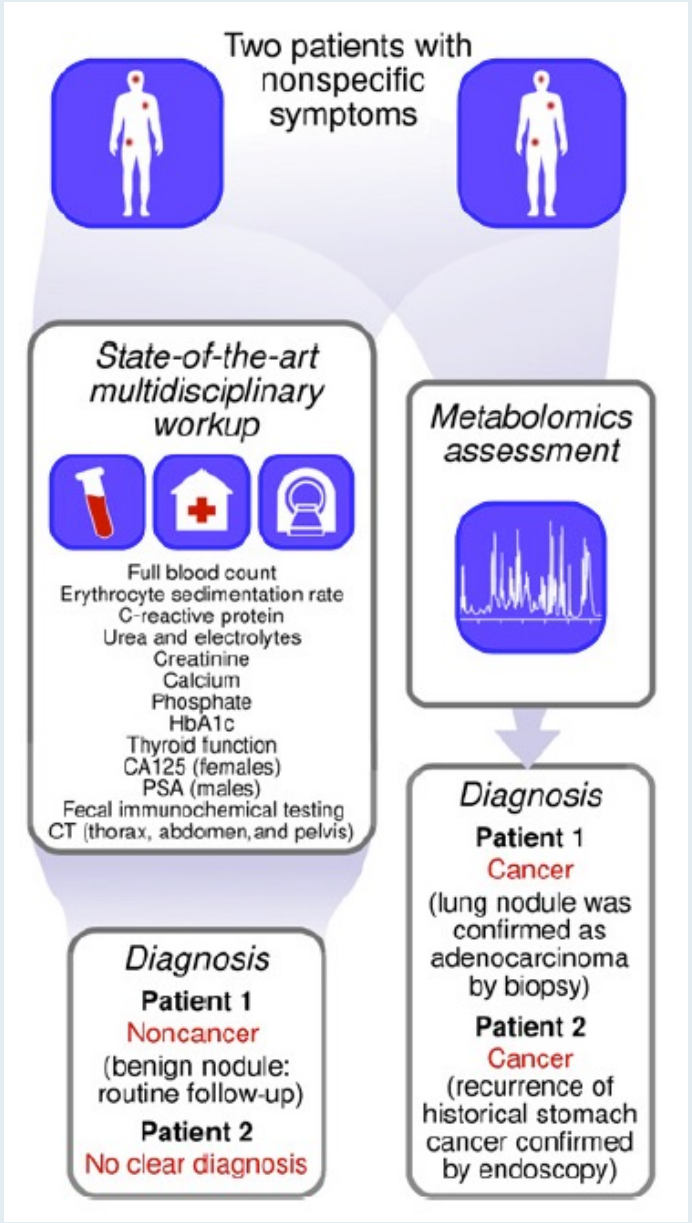
2022;28(8):1651-61.

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Metabolomic Biomarkers in Blood Samples Identify Cancers in a Mixed Population of Patients with Nonspecific Symptoms

James R. Larkin[1], Susan Anthony[2], Vanessa A. Johanssen[1], Tianrong Yeo[3,4,5], Megan Sealey[3], Abi G. Yates[3], Claire Friedemann Smith[6], Timothy D.W. Claridge[7], Brian D. Nicholson[6], Julie-Ann Moreland[2], Fergus Gleeson[1,2], Nicola R. Sibson[1], Daniel C. Anthony[3], and Fay Probert[3,7]

Example Patient Journeys: Diagnoses from Metabolomics and Multidisciplinary Diagnostic Center Workup



Larkin JR et al. *Clin Cancer Res* 2022;28(8):1651-61.

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Case Presentation: 34-year-old man with metastatic recurrence of alveolar soft part sarcoma of the shoulder who received ipilimumab/nivolumab – imaging scan suspect for pseudoprogression

Dr Nam Bui (Stanford, California)

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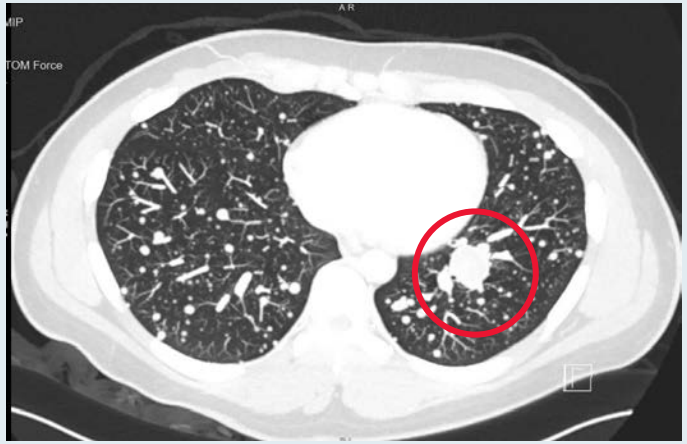
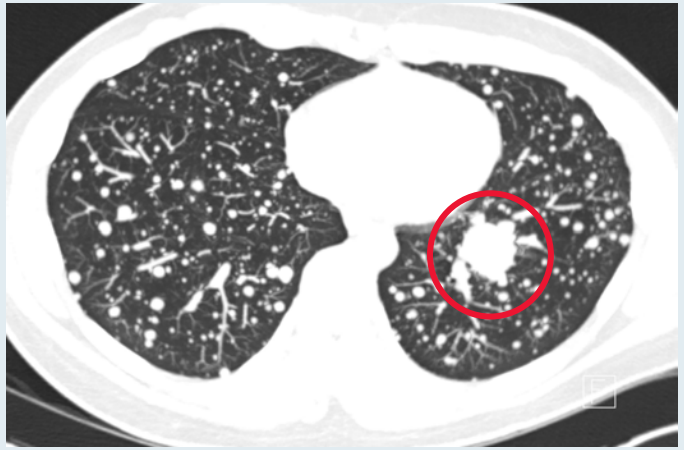
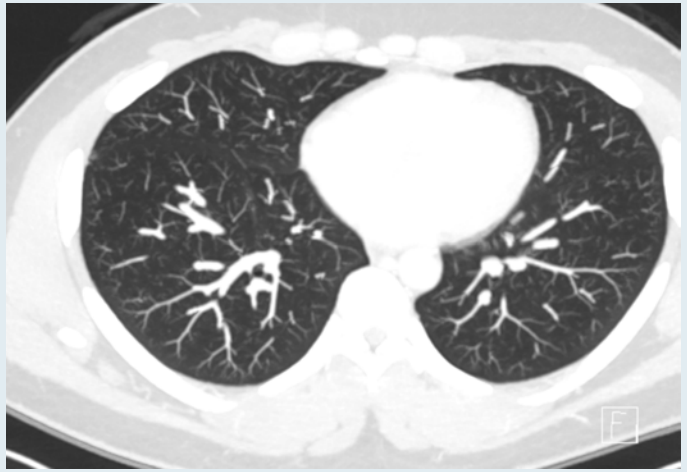
Baseline



Ipilimumab/nivolumab
1 cycle



Remission



NCCN Guideline-Recommended Agents and Regimens in the Metastatic Setting for Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS)

Preferred:

- Sunitinib
- Pazopanib
- Pembrolizumab
- Pembrolizumab with axitinib
- Atezolizumab

NCCN Guidelines version 2.2023 – Soft Tissue Sarcoma.

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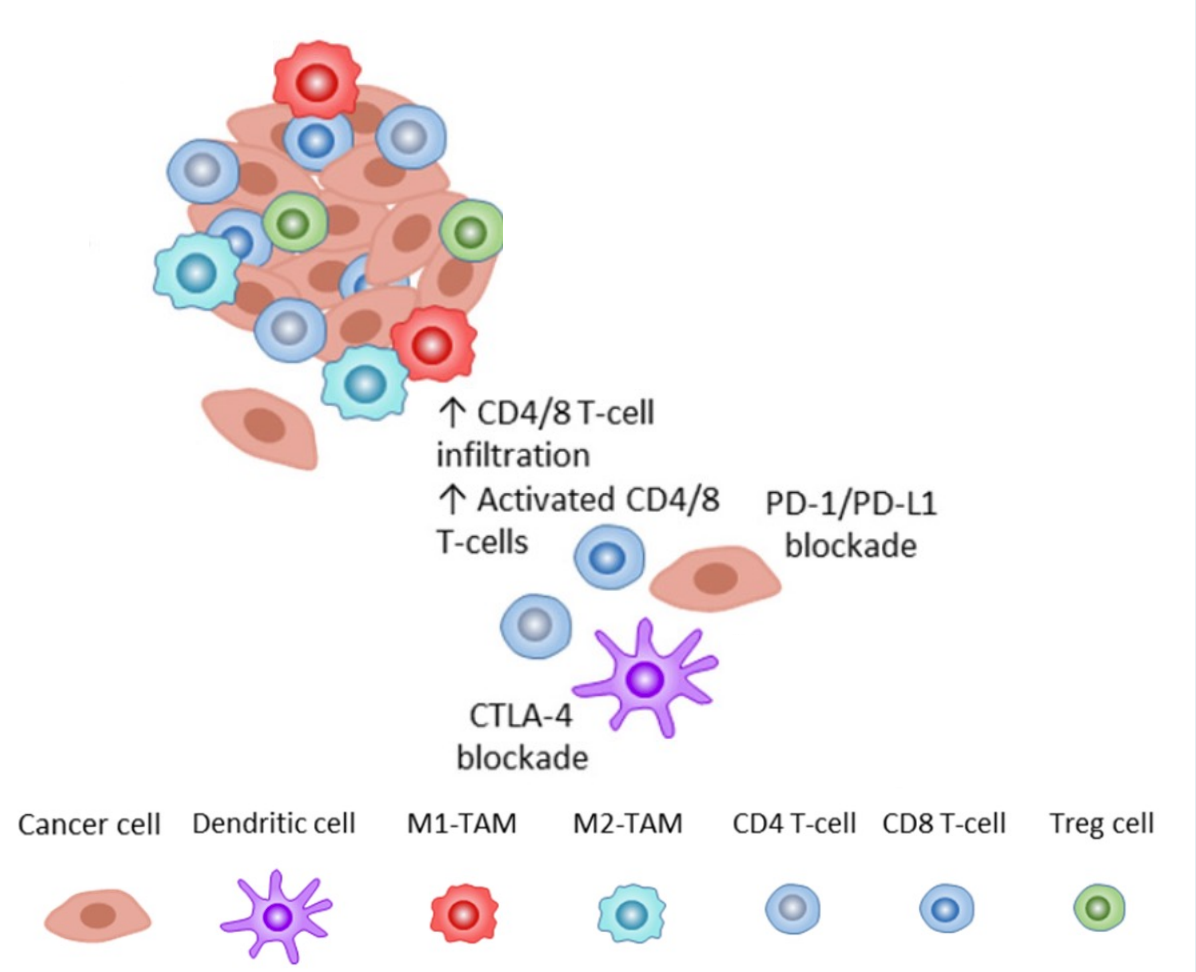
Immune Checkpoint Blockade in Sarcomas

- A variety of STS subtypes have been shown to contain dense infiltration by immune effector cells and gene expression profiles suggestive of an active intratumoral immune response.
- Interruption of inhibitory immune checkpoint signalling (such as the interaction of PD-1 with its ligand PD-L1) to tumour-infiltrating lymphocytes have been shown to successfully trigger an antitumour immune response.



Adapted from Kerrison WGJ et al. *Biomedicines* 2022;10:573.

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Pooled Analysis of Efficacy of PD-1/PD-L1 Antagonist in STS

- 384 patients from 9 multicenter clinical trials with previously presented/published results were included in the pooled analysis

Grade 3/4 TRAE (n = 260)	N	ORR
All patients (n = 384)	384	15.1%
Histological subtype		
Undifferentiated pleomorphic sarcoma	103	15.7%
Leiomyosarcoma	82	6.9%
Dedifferentiated liposarcoma	61	7.3%
Alveolar soft part sarcoma	41	48.8%
Efficacy by the therapeutic strategy		
PD-1/PD-L1 single agent	153	18.7%
Combination with other immunotherapy	114	11.4%
Combination with nonimmunological agent	117	14.0%

TRAE = treatment-related adverse event

Italiano A et al. *J Hematol Oncol* 2020;13(1):55.

FDA Grants Approval of Atezolizumab for Alveolar Soft Part Sarcoma

Press Release: December 9, 2022

"On December 9, 2022, the Food and Drug Administration (FDA) approved atezolizumab for adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS).

Efficacy was evaluated in Study ML39345 (NCT03141684), an open-label, single-arm study in 49 adult and pediatric patients with unresectable or metastatic ASPS. Eligible patients were required to have histologically or cytologically confirmed ASPS incurable by surgery and an ECOG performance status of ≤2. Patients were excluded for primary central nervous system (CNS) malignancy or symptomatic CNS metastases, clinically significant liver disease, or a history of idiopathic pulmonary fibrosis, pneumonitis, organizing pneumonia or active pneumonitis on imaging. Adult patients received 1,200 mg intravenously and pediatric patients received 15 mg/kg (up to a maximum of 1,200 mg) intravenously once every 21 days until disease progression or unacceptable toxicity.

The recommended atezolizumab dosage for adult patients is 840 mg every 2 weeks, 1,200 mg every 3 weeks or 1,680 mg every 4 weeks until disease progression or unacceptable toxicity. The recommended dosage for pediatric patients 2 years of age and older is 15 mg/kg (up to a maximum of 1,200 mg) every 3 weeks until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-approval-atezolizumab-alveolar-soft-part-sarcoma

RTP RESEARCH TO PRACTICE

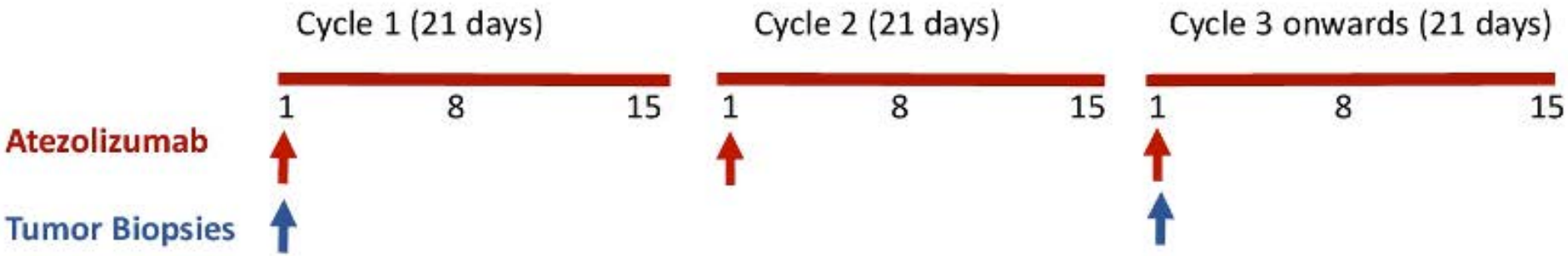
Phase II Study of Atezolizumab in Advanced Alveolar Soft Part Sarcoma (ASPS)

Naqash AR et al.

ASCO 2021;Abstract 11519.

Phase II Study of Atezolizumab in Advanced ASPS

- Histologically confirmed ASPS, age ≥ 2 years at the NCI Clinical Center (≥14 years at other participating sites) including patients with newly diagnosed, unresectable, metastatic, and measurable disease who show clinical evidence of disease progression.
- Exclusion criteria: prior anti-PD-1/PD-L1 therapy, history of grade 3/4 immune-related adverse events with anti-CTLA-4 therapy, RANK ligand use, history of autoimmune disease, and use of supraphysiologic steroid doses.

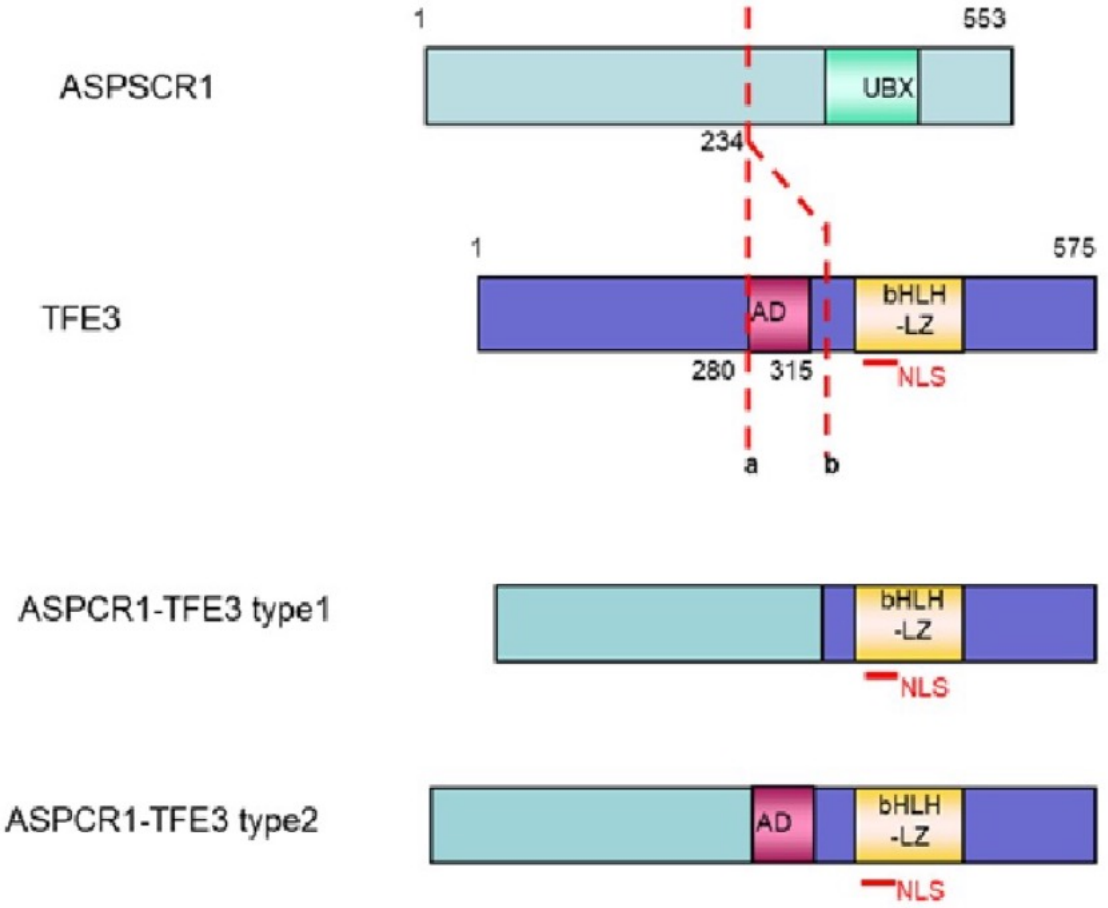


Multicenter, open-label, single-arm phase 2 study; atezolizumab is administered at a fixed dose of 1200 mg in adults or 15 mg/kg (1200 mg max) in pediatric patients aged ≥2 years once Q21 days. Tumor biopsies (mandatory) are collected from patients ≥18 years of age at baseline and prior to cycle 3 day 1 (±3 days). Data cutoff for analysis was set as April 20, 2021.

Naqash AR et al. ASCO 2021;Abstract 11519.

ASPS-TFE3 Fusion Variants

ASPS-TFE3 fusion variants: Breakpoints in the TFE-3 gene are marked as "a" and "b". The N-terminus of *ASPSCR-1* is fused in-frame with *TFE3* at exon 3 ("a") or exon 4 ("b"), resulting type-2 or type-1 fusions, respectively. At the molecular level, the first 234 amino-terminal amino acids from *ASPSCR-1* are fused to *TFE3* at amino acid positions 280 ("a") or 315 ("b"). Type 2 contains the activation domain of TFE3 while type 1 does not, but both form novel transcription factors and are functional.

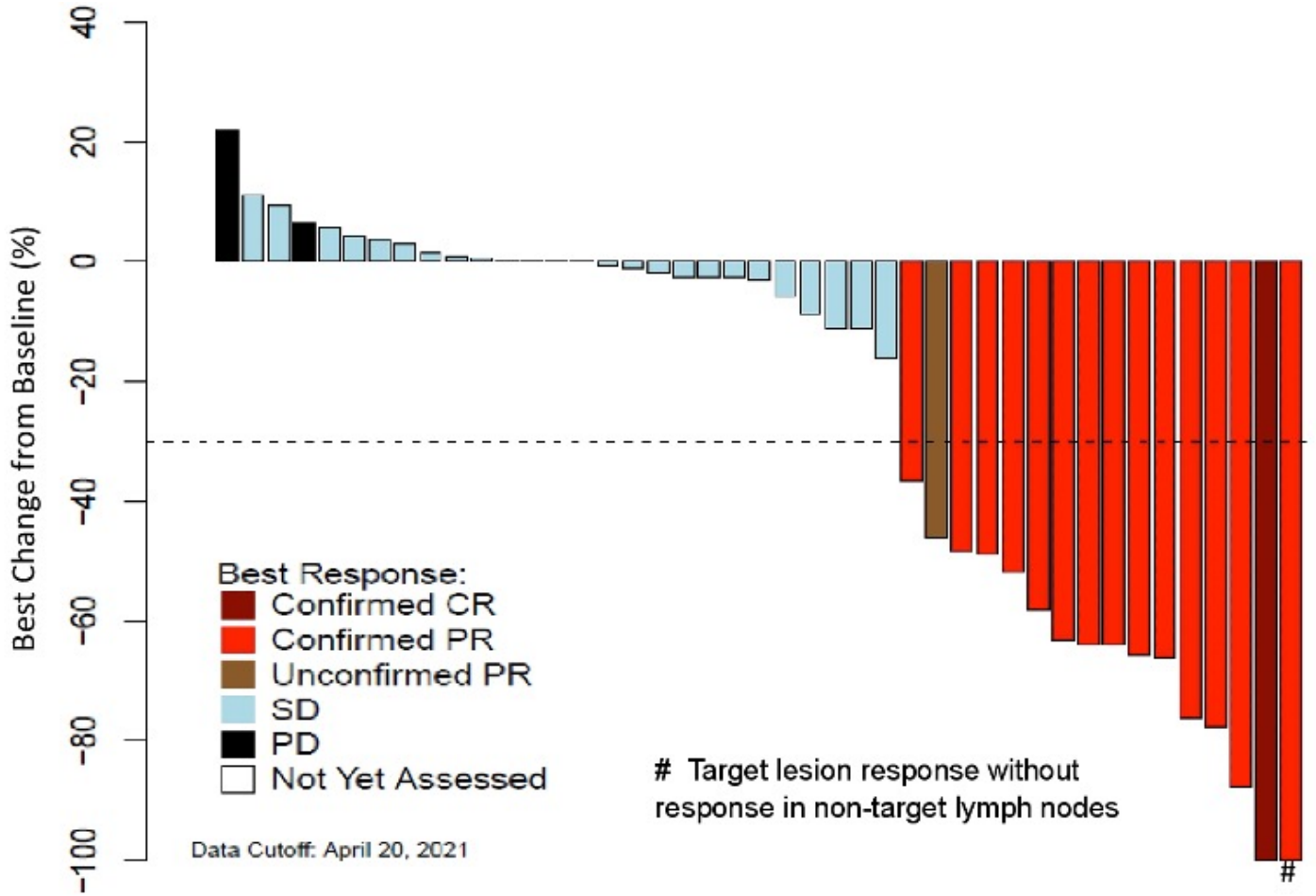


Naqash AR et al. ASCO 2021;Abstract 11519.

Outcomes with Atezolizumab in Advanced ASPS

Best Response	No. of Patients
CR	01
PR confirmed unconfirmed	 14* 01
SD	25
PD	02
Total evaluable	43

- Observed response rate: **37.2% (16/43)**
- Median time on study was **11.3 months** (range, 0.5–42.8)
- Median time to confirmed response: **3.5 months** (range, 2.1-14.9)
- Median duration of confirmed response: **16.6 months** (range, 7.4-40.6).
- **Three** patients have been on treatment holiday per protocol and have maintained PR after stopping therapy for a median of **8.6 months**



Naqash AR et al. ASCO 2021;Abstract 11519.

Safety Summary with Atezolizumab in Advanced ASPS

Adverse Events (AEs) Related to Atezolizumab	No. of Patients Evaluable for AEs (n=43)
	Grade 1-2 AEs; N (%) *(observed in ≥10% of patients)*
Anemia	9 (21.0)
Arthralgia	5 (11.6)
Alkaline Phosphatase Elevated	9 (21.0)
Fatigue	15 (34.8)
Fever	5 (11.6)
Thyroid Dysfunction Hypothyroidism Hyperthyroidism	 5 (11.6) 7 (16.3)
Hyponatremia	6 (14.0)
Lymphocyte count decreased	9 (21.0)
White blood count decreased	7 (16.3)
Nausea	7 (16.3)
Pruritis	6 (14.0)
Rash Maculopapular Acneiform	 6 (14.0) 8 (18.6)
Transaminitis	5 (11.6)

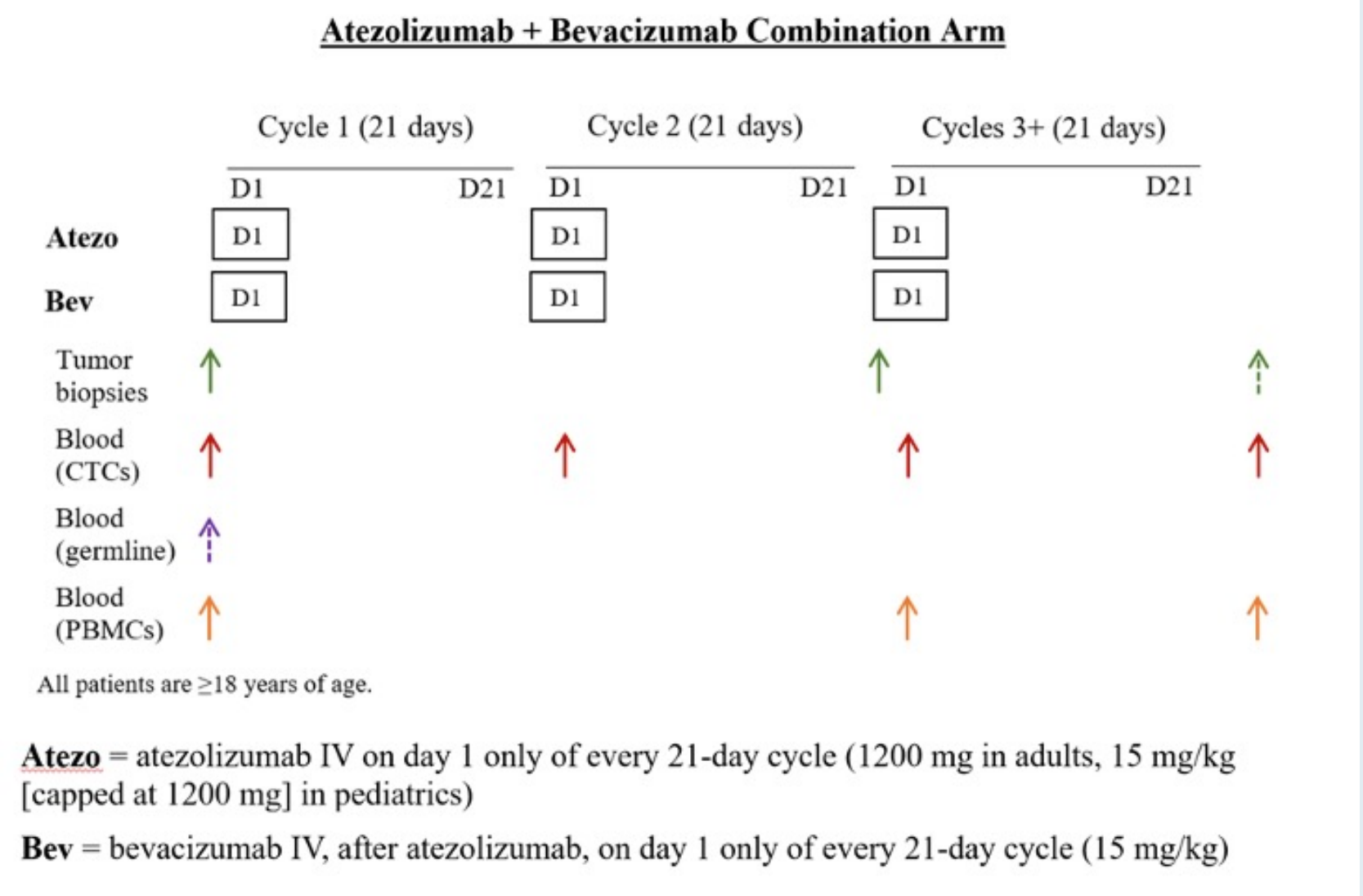
Naqash AR et al. ASCO 2021;Abstract 11519.

Atezolizumab and Bevacizumab in Patients Treated with Prior Atezolizumab in Alveolar Soft Tissue Sarcoma (ASPS)

Chen A et al.

ESMO Sarcomas and Rare Cancers Congress 2023;Abstract 49MO.

Atezolizumab and Bevacizumab for Previously Treated ASPS: Trial Administration



Chen A et al. ESMO Sarcomas and Rare Cancers Congress 2023;Abstract 49MO.

Results Summary for Atezolizumab and Bevacizumab in Patients with ASPS Previously Treated with Atezolizumab

- 8 patients crossed over
- All had SD as best response, no CR/PRs yet
- Median time on combination is 10.9 months (4.3-19.1 months) compared to 9.7 months (3.4-40.2) on single agent atezolizumab
- 6 patients are still on treatment
- Toxicities:
  - Grade 3: hypertension (1) lipase increase (1)
  - Grade 1 or 2: hypothyroidism, proteinuria, anemia, nausea, amylase increase, hyponatremia, hypokalemia, headache

Chen A et al. ESMO Sarcomas and Rare Cancers Congress 2023;Abstract 49MO.

Eulo *et al. Cancer Drug Resist* 2022;5:328-38
DOI: 10.20517/cdr.2021.127

Cancer
Drug Resistance

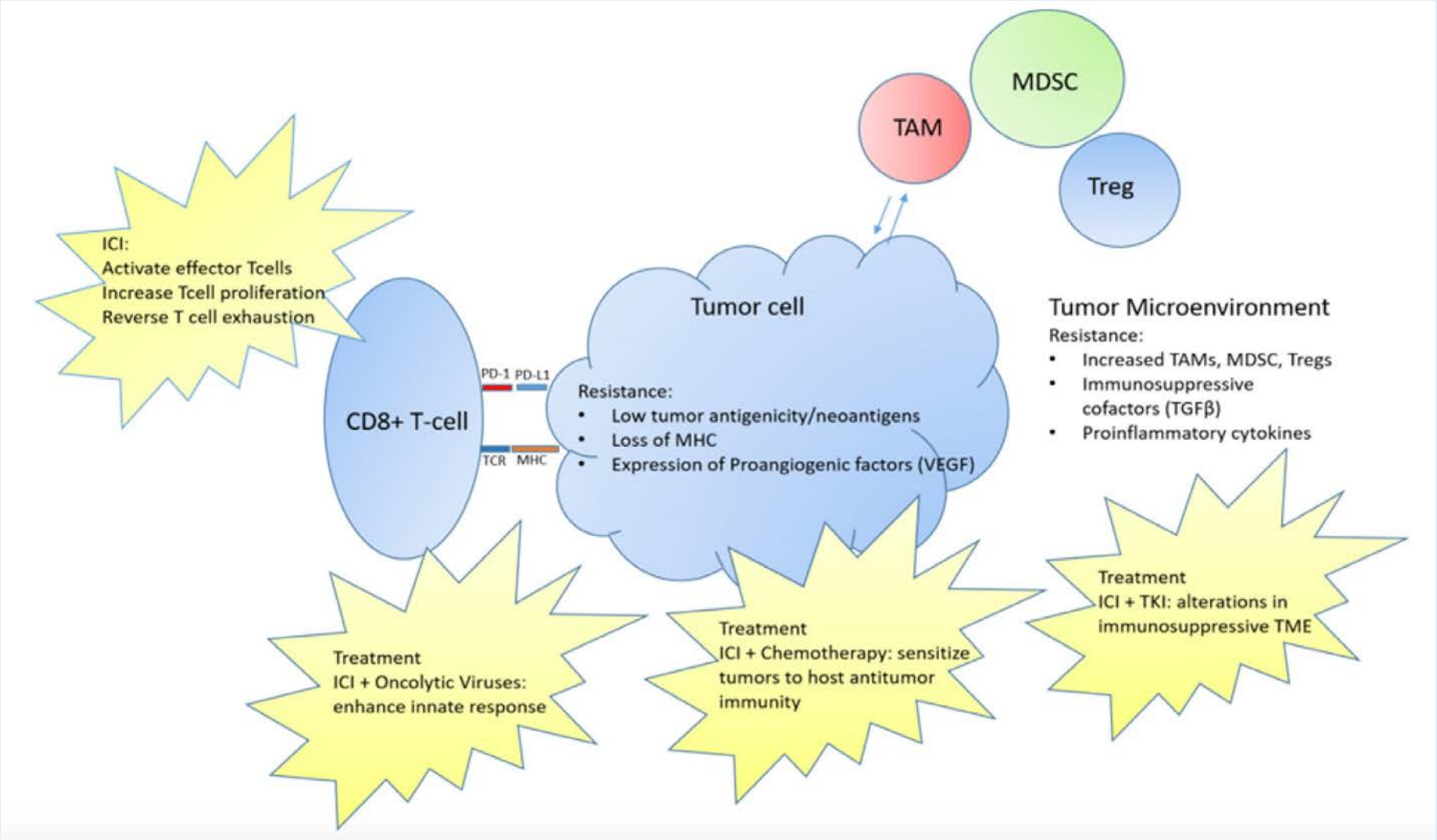
Review

Open Access

Immune checkpoint inhibitor resistance in soft tissue sarcoma

Vanessa Eulo[1], Brian A. Van Tine[2,3,4]

Resistance Mechanisms to Immunotherapy in Soft Tissue Sarcoma (STS) with Current Treatment Mechanisms Aimed at Overcoming Resistance



Eulo V, Van Tine BA. *Cancer Drug Resist* 2022;5(2):328-38.

original reports

Phase II Randomized Study of CMB305 and Atezolizumab Compared With Atezolizumab Alone in Soft-Tissue Sarcomas Expressing NY-ESO-1

Sant P. Chawla, MD[1]; Brian A. Van Tine, MD, PhD[2]; Seth M. Pollack, MD[3,4]; Kristen N. Ganjoo, MD[5]; Anthony D. Elias, MD[6]; Richard F. Riedel, MD[7]; Steven Attia, DO[8]; Edwin Choy, MD, PhD[9]; Scott H. Okuno, MD[10]; Mark Agulnik, MD[11,12]; Margaret von Mehren, MD[13]; Michael B. Livingston, MD[14]; Vicki L. Keedy, MD[15]; Claire F. Verschraegen, MD[16]; Tony Philip, MD[17]; G. Chet Bohac, MD[18,19]; Sergey Yurasov, MD, PhD[18,20]; Adam Yakovich, PhD[18,21]; Hailing Lu, MD, PhD[18,22]; Michael Chen, MSc[18,23]; and Robert G. Maki, MD, PhD[24]

J Clin Oncol 2022;40(12):1291-300.

ASCO 2023 Oral Abstracts – Immunotherapy in Sarcomas

Reichardt P et al. Efficacy and safety of nivolumab and trabectedin in pretreated patients with advanced soft tissue sarcomas (STS): Results of a phase II trial of the German Interdisciplinary Sarcoma Group (GISG-15, NitraSarc). Abstract 11500.

Wilky BA et al. A single-arm, open-label phase 2 trial of doxorubicin plus zalifrelimab, a CTLA-4 inhibitor, with balstilimab, a PD-1 inhibitor, in patients with advanced/metastatic soft tissue sarcomas. Abstract 11501.

Martin Broto J et al. ImmunoSarc2: A Spanish Sarcoma Group (GEIS) phase Ib trial of doxorubicin and dacarbazine plus nivolumab in first line treatment of advanced leiomyosarcoma. Abstract 11502.

Grilley-Olson JE et al. A multicenter phase II study of cabozantinib + nivolumab for patients (pts) with advanced angiosarcoma (AS) previously treated with a taxane (Alliance A091902). Abstract 11503.

Van Tine BA et al. Randomized phase II trial of cabozantinib combined with PD-1 and CTLA-4 inhibition versus cabozantinib in metastatic soft tissue sarcoma. Abstract LBA11504.

RTP
RESEARCH
TO PRACTICE

A Phase 2 Study of an Anti-PD-L1 Antibody (Atezolizumab) in Dedifferentiated Chondrosarcoma

Salkeni M et al.

ASCO 2023;Abstract 11533.

June 3, 2023

Poster Session Hall A

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Van Tine

Introduction

MODULE 1: Immunotherapy in Soft Tissue Sarcomas — Alveolar Soft Part Sarcoma

MODULE 2: Desmoid Tumors

MODULE 3: Targeted Therapy

MODULE 4: Case Presentations

MODULE 5: Journal Club with Dr Van Tine

MODULE 6: Appendix

Case Presentation: Woman in her mid 30s with a 3-cm desmoid tumor who refuses treatment and is followed for 4 years, now with spontaneous tumor regression

Dr Atif Hussein (Hollywood, Florida)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 19-year-old woman with an unresectable, massive 14-cm desmoid tumor who receives sorafenib but has poor tolerance to treatment

Dr Atif Hussein (Hollywood, Florida)

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RESEARCH
TO PRACTICE

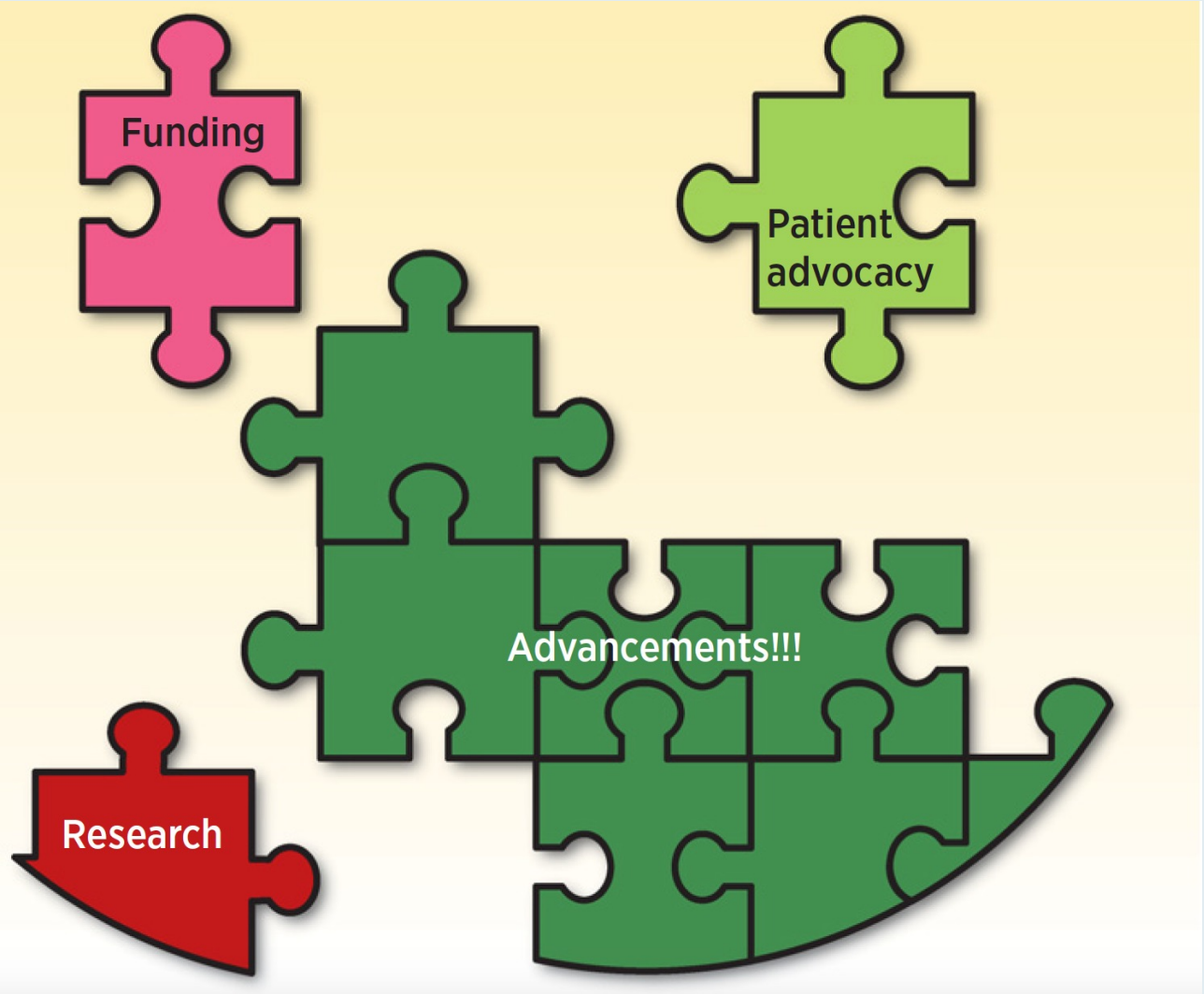
2022;28(18):3911-3.

CLINICAL CANCER RESEARCH | CCR TRANSLATIONS

Are the Pieces Starting to Come Together for Management of Desmoid Tumors?

Anna C. Greene[1] and Brian A. Van Tine[2,3,4]

Research Funding, Patient Advocacy and Dedicated Research Promote Advancements in the Understanding of Desmoid Tumors



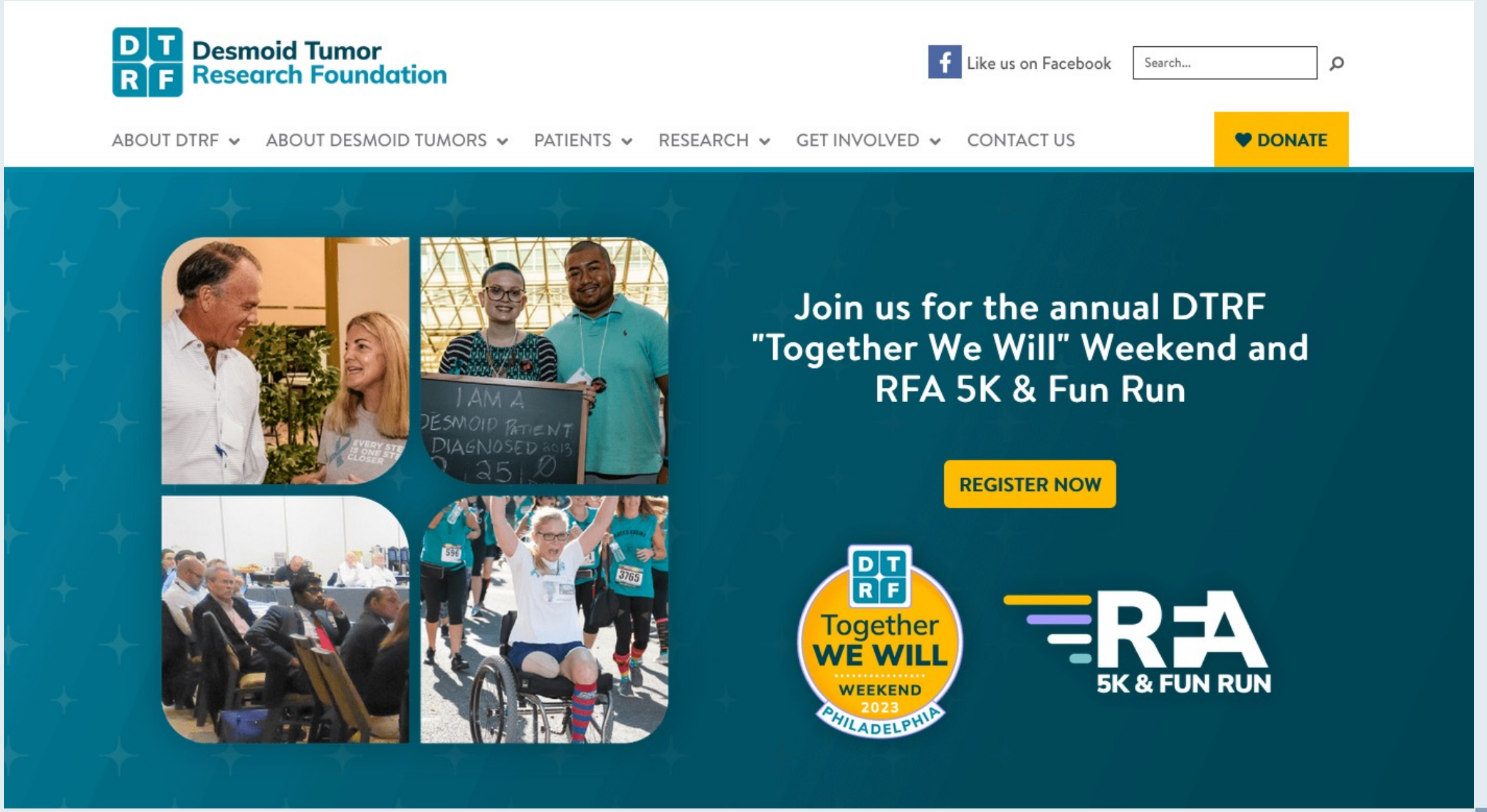
Greene AC, Van Tine BA. *Clin Cancer Res* 2022;28(18):3911-3.

2022;28(18):4027-32.

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

A Prospective Observational Study of Active Surveillance in Primary Desmoid Fibromatosis

Chiara Colombo[1], Marco Fiore[1], Giovanni Grignani[2], Francesco Tolomeo[2], Alessandra Merlini[2], Elena Palassini[3], Paola Collini[4], Silvia Stacchiotti[3], Paolo Giovanni Casali[3], Federica Perrone[4], Luigi Mariani[5], and Alessandro Gronchi[1]



dtrf.org. Accessed May 2023.

NCCN Guideline-Recommended Agents and Regimens in the Metastatic Setting for Desmoid Tumors

Desmoid tumors (aggressive fibromatosis)

Preferred:
- Sorafenib
- Methotrexate with vinorelbine or vinblastine
- Imatinib
- Liposomal doxorubicin
- Doxorubicin ± dacarbazine
- Pazopanib

Useful in certain circumstances:
- Sulindac or other NSAIDs, including celecoxib (for pain)

NCCN Guidelines version 2.2023 – Soft Tissue Sarcoma.

RTP RESEARCH TO PRACTICE

Rationale for Targeting the Gamma Secretase Complex and the NOTCH Pathway in 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[1,2]
- Treatment should be individualized to optimize tumor control and improve symptom burden, including pain, physical function, and overall quality of life[3]
  - A global consensus initiative has been launched by The Desmoid Tumor Working Group aiming to harmonize management strategies[4]
- 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[5,6]
- 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[1,7,8]

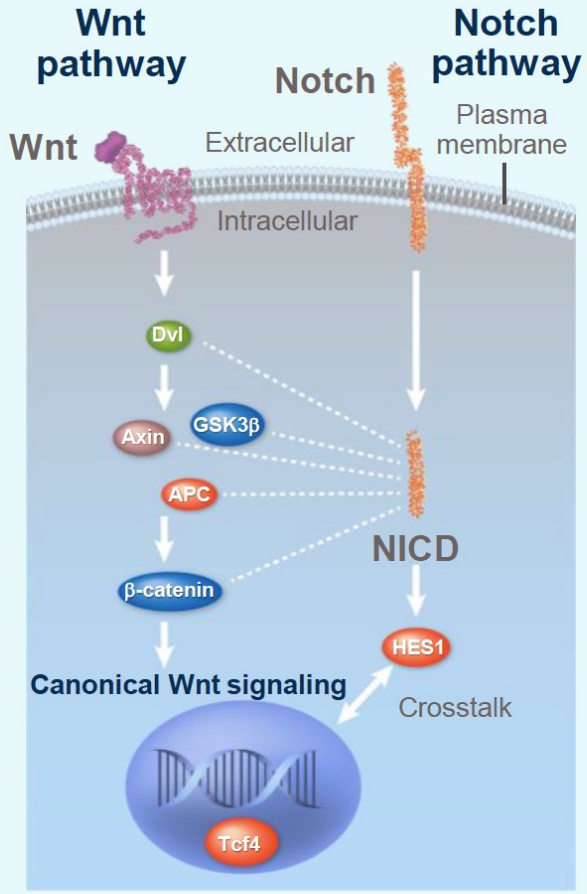


Image adapted from Andersson et al. *Development* (2011) and Bui and Kummar. *Oncotarget* (2017).

DT, desmoid tumor; GSI, gamma secretase inhibitor; NICD, Notch intracellular domain.

1. Villalobos et al. *Ann Surg Oncol.* 2018;25:768-775. **2.** Kasper et al. *Oncologist.* 2011;16:682-693. **3.** Gounder et al. *Cancer.* 2020;126:531-539. **4.** Desmoid Tumor Working Group. *Eur J Cancer.* 2020;127:96-107. **5.** Andersson et al. *Development.* 2011;138:3593-3612. **6.** Gounder et al. *Cancer.* 2015;121:3933-3937. **7.** Messersmith et al. *Clin Cancer Res.* 2015;21:60-67. **8.** Kummar et al. *J Clin Oncol.* 2017;35:1561-1569.

Kasper B et al. ESMO 2022;Abstract LBA2.

The NEW ENGLAND JOURNAL of MEDICINE

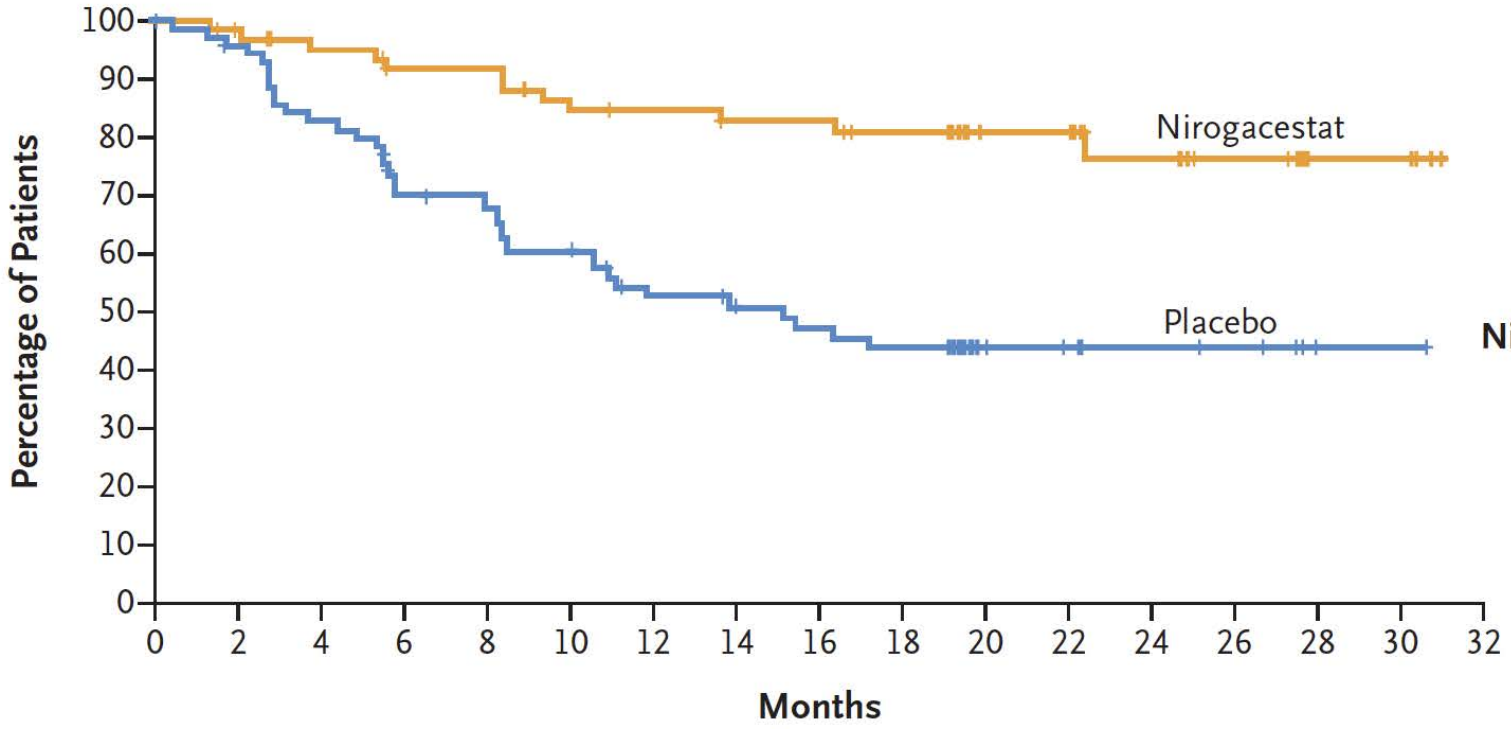
ORIGINAL ARTICLE

Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors

M. Gounder, R. Ratan, T. Alcindor, P. Schöffski, W.T. van der Graaf, B.A. Wilky, R.F. Riedel, A. Lim, L.M. Smith, S. Moody, S. Attia, S. Chawla, G. D'Amato, N. Federman, P. Merriam, B.A. Van Tine, B. Vincenzi, C. Benson, N.Q. Bui, R. Chugh, G. Tinoco, J. Charlson, P. Dileo, L. Hartner, L. Lapeire, F. Mazzeo, E. Palmerini, P. Reichardt, S. Stacchiotti, H.H. Bailey, M.A. Burgess, G.M. Cote, L.E. Davis, H. Deshpande, H. Gelderblom, G. Grignani, E. Loggers, T. Philip, J.G. Pressey, S. Kummar, and B. Kasper

2023;388:898-912.

DeFi Trial Primary Endpoint: Progression-Free Survival (PFS) with Nirogacestat for Patients with Progressive Desmoid Tumors



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Nirogacestat	70	12	NE (NE–NE)
Placebo	72	37	15.1 (8.4–NE)

Hazard ratio for disease progression or death, 0.29 (95% CI, 0.15–0.55)
P<0.001

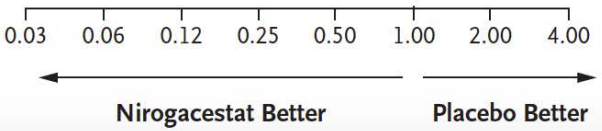
No. at Risk

Nirogacestat	70	63	56	52	52	47	46	44	44	41	26	26	17	12	4	4	0
Placebo	72	67	58	47	45	40	32	29	27	25	10	8	6	5	1	1	0

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

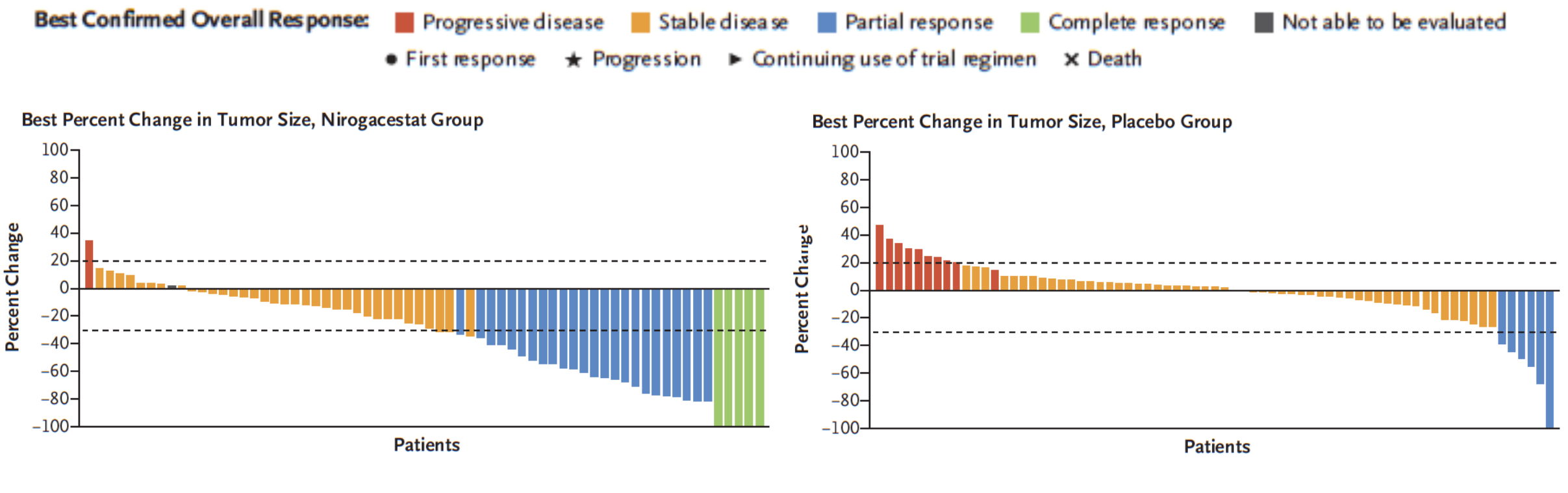
DeFi: PFS Subgroup Analysis

Subgroup	Nirogacestat (no. of events/no. of patients)	Placebo (no. of events/no. of patients)	Hazard Ratio for Disease Progression or Death (95% CI)
Sex			
Male	4/25	11/25	0.26 (0.08–0.82)
Female	8/45	26/47	0.30 (0.14–0.67)
Target-tumor location			
Intraabdominal	2/17	11/18	0.17 (0.04–0.76)
Extraabdominal	10/53	26/54	0.34 (0.16–0.70)
Family history of FAP			
Yes	2/11	8/13	0.24 (0.05–1.18)
No	10/59	29/59	0.30 (0.15–0.63)
APC mutation			
Yes	2/11	8/11	0.20 (0.04–1.00)
CTNNB1 mutation			
Yes	6/43	21/42	0.28 (0.11–0.70)
Focality			
Single	6/43	19/41	0.29 (0.11–0.72)
Multifocal	6/27	18/31	0.30 (0.12–0.77)
Previous surgery			
Yes	5/31	23/44	0.31 (0.11–0.81)
No	7/39	14/28	0.33 (0.13–0.83)
Previous chemotherapy			
Yes	5/24	17/27	0.24 (0.09–0.69)
No	7/46	20/45	0.32 (0.13–0.76)
Previous TKI treatment			
Yes	4/23	16/24	0.15 (0.05–0.45)
No	8/47	21/48	0.38 (0.17–0.87)
Treatment status			
No previous treatment	3/18	5/14	0.77 (0.18–3.23)
Refractory or recurrent disease after previous treatment	9/52	32/58	0.30 (0.14–0.63)



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

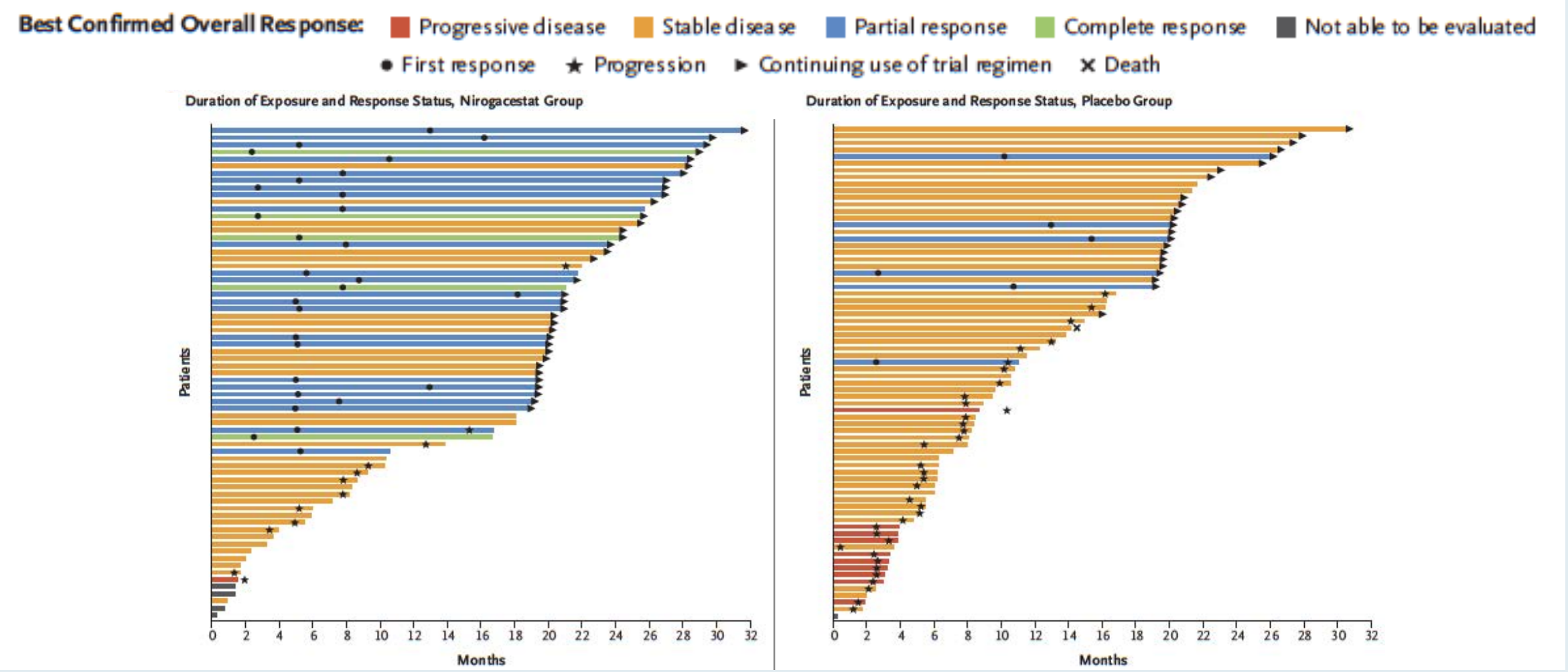
DeFi: Responses with Nirogacestat in Patients with Progressive Desmoid Tumors



Objective response rate (nirogacestat versus placebo): 41% versus 8% (p <0.001)

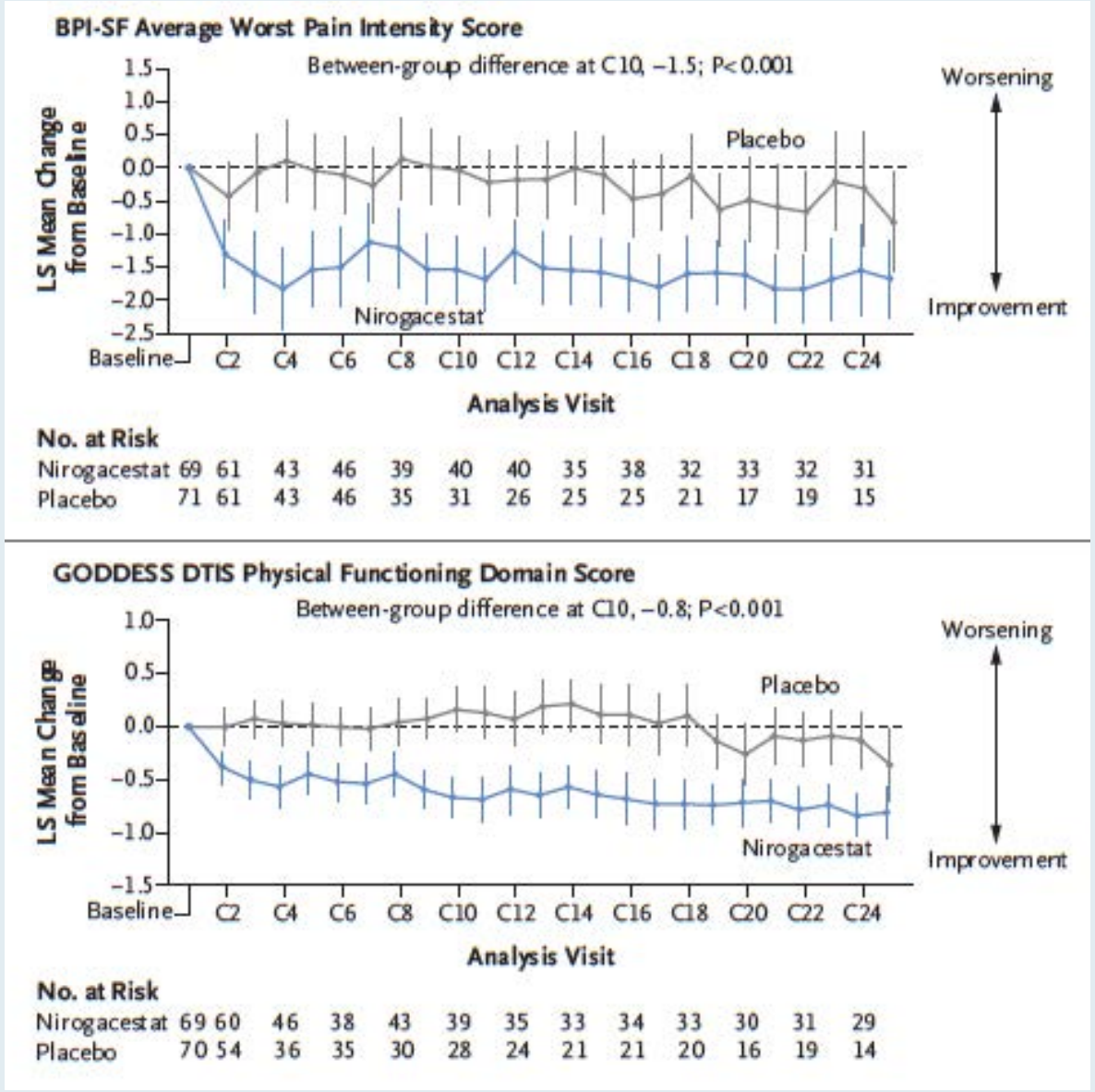
Gounder M et al. *N Engl J Med* 2023;388:898-912.

DeFi: Duration of Exposure and Response Status



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

DeFi: Patient-Reported Outcomes



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

DeFi: Select Adverse Events with Nirogacestat in the Safety Population

Select adverse events, n (%)	Nirogacestat (n = 69)	Placebo (N = 72)
Diarrhea	58 (84%)	25 (35%)
Nausea	37 (54%)	28 (39%)
Fatigue	35 (51%)	26 (36%)
Hypophosphatemia	**29 (42%)**	**5 (7%)**
Maculopapular rash	22 (32%)	4 (6%)
Ovarian dysfunction in women of childbearing potential in the safety population	**26/36 (75%)**	**0/37**

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

FDA Acceptance and Priority Review of New Drug Application for Nirogacestat for Adults with Desmoid Tumors

Press Release: February 27, 2023

"The US Food and Drug Administration (FDA) has accepted the Company's New Drug Application (NDA) for nirogacestat, an investigational gamma secretase inhibitor, for the treatment of adults with desmoid tumors. The NDA was granted Priority Review and has been given a Prescription Drug User Fee Act (PDUFA) action date of August 27, 2023.

The NDA is being reviewed under the FDA's Real-Time Oncology Review (RTOR) program and is based on the previously announced positive results from the Phase 3 DeFi trial, a global, randomized, double-blind, placebo-controlled trial evaluating nirogacestat in adult patients with desmoid tumors. The FDA granted Fast Track and Breakthrough Therapy designations to nirogacestat for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis. Nirogacestat has also received Orphan Drug designation from the FDA for the treatment of desmoid tumors."

https://ir.springworkstx.com/news-releases/news-release-details/springworks-therapeutics-announces-fda-acceptance-and-priority

PARIS 2022 ESMO congress

Initial Results of Phase 2/3 Trial of AL102 for Treatment of Desmoid Tumors (DT)

Mrinal Gounder, **Robin L Jones**, Rashmi Chugh, Mark Agulnik, Arun Singh, Brian A. Van Tine, Vladimir Andelkovic, Edwin Choy, Jeremy Lewin, Ravin Ratan, Atrayee Basu-Mallick, Bruce Brockstein, Nam Bui, Sant Chawla, Shadi Hadaddin, Hyo Song Kim, Alexander Lee, Javier Martin-Broto, Christopher Ryan, Gary Schwartz, Winette T. A. van der Graaf, Jason Kaplan, Jonathan Yovell, Gary Gordon, Bernd Kasper

Presentation #1488MO

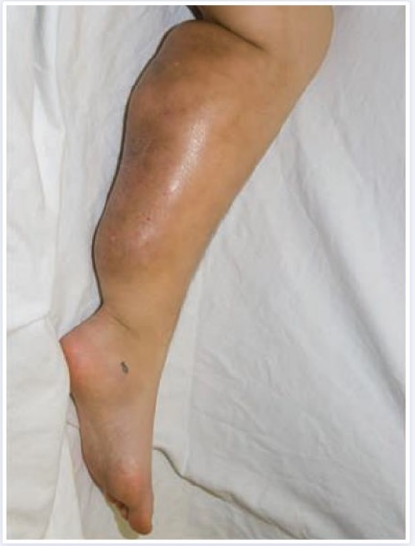
September 12, 2022
Paris, France

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Background

Desmoid tumor

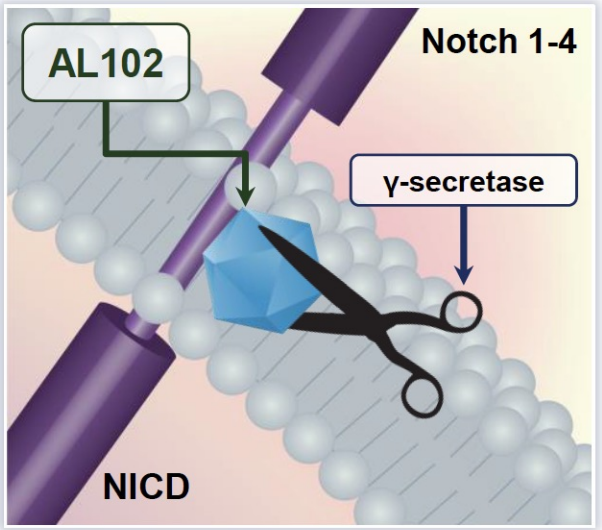
- Locally aggressive tumor
- Variable and unpredictable clinical course with pain, discomfort, and impact on quality of life (QOL)
- 5-6 cases per million people/year
- Peak incidence age 30 (range 15-60) years, female predominance
- 5-10% in the context of familial adenomatous polyposis (FAP)



McDonald, et al., RadioGraphics 2008

Gamma-secretase inhibitor (GSI)

- GSI have antineoplastic activity in DT
- Investigational new drug AL102 - a potent, oral inhibitor of gamma secretase



The Desmoid Tumor Working Group, European Journal of Cancer 127 (2020) 96-107; Quintini et al, Ann Surg. 2012; 255(3):511-6; Gounder et al, N Engl J Med 2018;379:2417-28; Trufero et al, Curr. Treat. Options in Oncol. (2017) 18:29

PARIS 2022 ESMO congress

Gounder M et al. ESMO 2022;Abstract 1488MO.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Safety Profile Consistent with GSIs

- AL102 was generally well tolerated with a manageable safety profile in all dose arms
- Most AEs were grade 1-2
- Grade 3 AEs were uncommon
- No grade 4 or 5 AEs
- 4 SAEs in 3 patients were assessed as unrelated to AL102 by the investigator
- AEs causing discontinuation included diarrhea, stomatitis, ALT elevation and rash
- AEs were consistent with mechanism of action of GSIs

Treatment-related AEs in ≥20% of Subjects

		1.2 mg QD (n=14)		4 mg BIW (n=14)		2 mg BIW (n=14)	
System Organ Class	Preferred Term	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Gastrointestinal disorders	Diarrhoea	11 (79)	1 (7)	8 (57)	1 (7)	7 (50)	-
	Nausea	5 (36)	-	5 (36)	-	3 (21)	-
	Dry mouth	5 (36)	-	5 (36)	-	-	-
	Stomatitis	6 (43)	1 (7)	2 (14)	-	-	-
General disorders	Fatigue	5 (36)	-	5 (36)	-	5 (36)	-
Investigations	AST Increased	2 (14)	-	3 (21)	-	1 (7)	-
Metabolism and nutrition	Hypophosphataemia	4 (29)	-	1 (7)	-	2 (14)	-
Reproductive system	Amenorrhoea	1 (7)	-	3 (21)	-	-	-
Skin and subcutaneous tissue	Alopecia	5 (36)	-	3 (21)	-	1 (7)	-
	Dry skin	6 (43)	-	3 (21)	-	-	-
	Pruritus	6 (43)	-	2 (14)	-	-	-
	Rash maculo-popular	4 (29)	-	1 (7)	-	1 (7)	-
	Rash	-	-	3 (21)	-	2 (14)	1 (7)
	Dermatitis acneiform	4 (29)	-	-	-	1 (7)	-
	Hair colour changes	3 (21)	-	1 (7)	-	-	-

Data cut: Jul 14, 2022. AE, adverse event, N, number of patients with data; BIW, twice weekly; QD, once daily
a. Data on in the table is showed as number of subjects (%)
b. Subjects are counted once at the highest grade per preferred term

PARIS 2022 ESMO congress

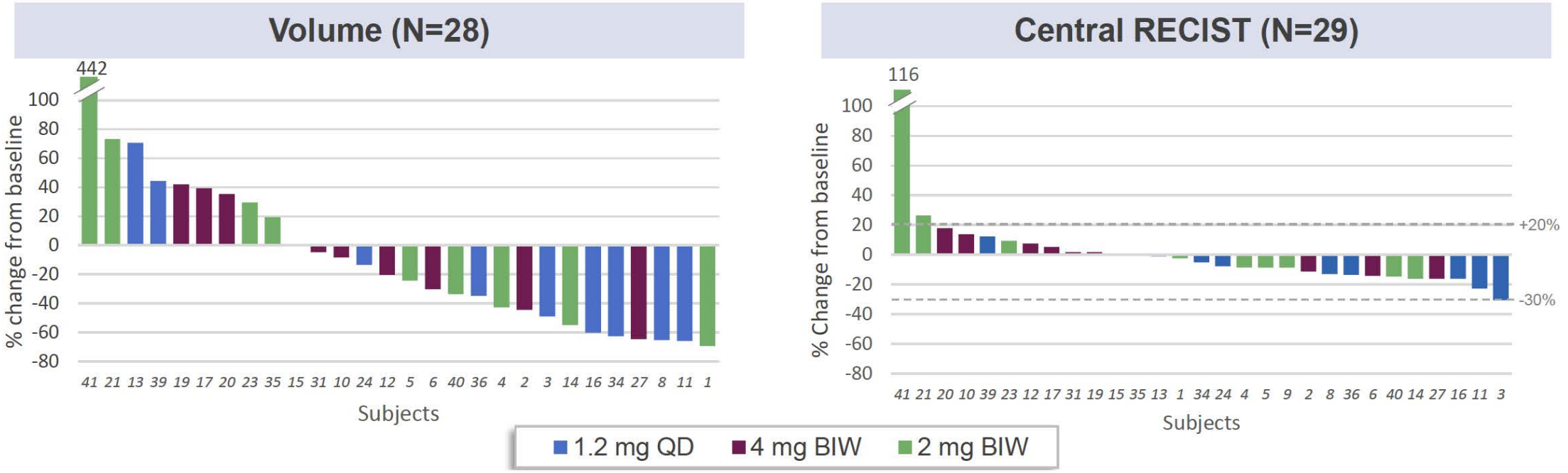
AEs = adverse events; SAEs = serious adverse events

Gounder M et al. ESMO 2022;Abstract 1488MO.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Early Volume and RECIST Response at Week 16

- Activity observed in all dose arms
- PR (central) observed at 16 weeks (confirmed 28 weeks)



PARIS 2022 ESMO congress

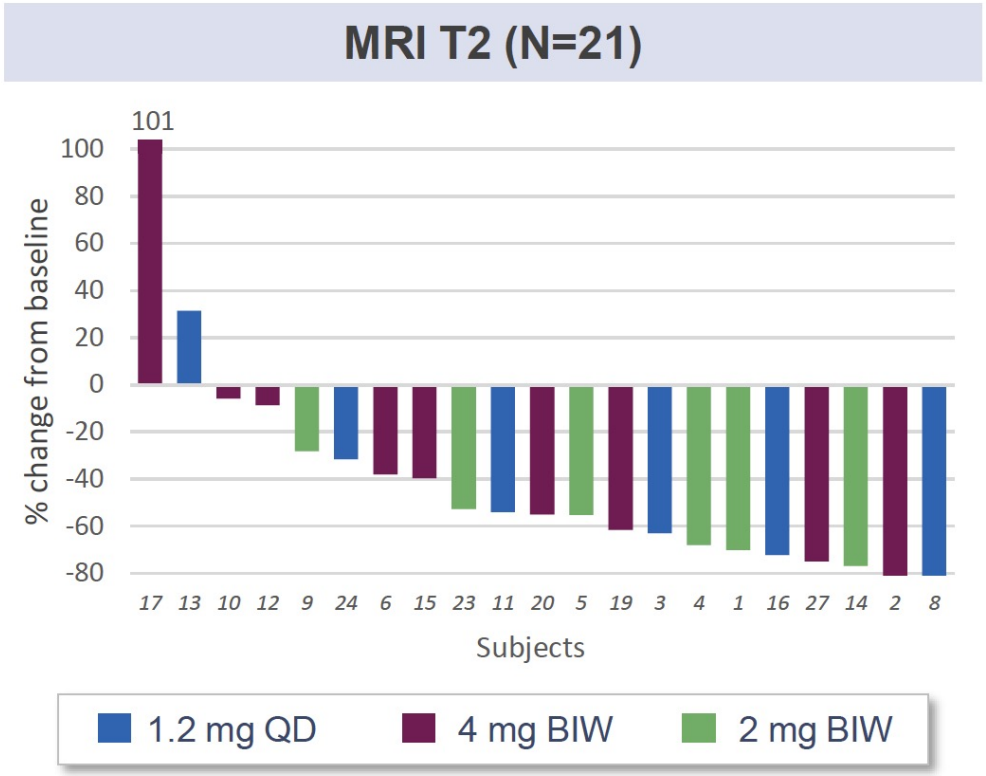
N, number of patients with data; BIW, twice weekly; QD, once daily; Data cut: Jul 14, 2022

PR = partial response

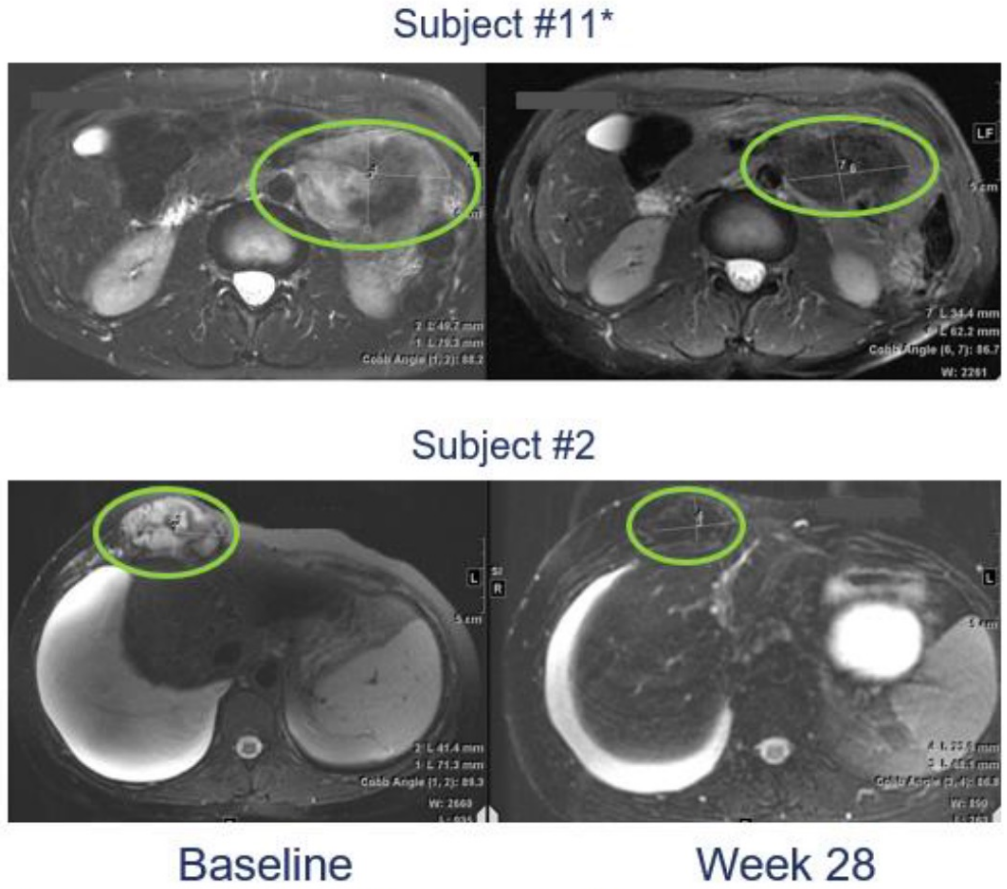
Gounder M et al. ESMO 2022;Abstract 1488MO.

T2 Changes Reflect Decrease in Cellularity

- Reduction of T2 intensity in 19 of 21 subjects at Week 16



- Reduction of T2 intensity and size in 2 subjects at Week 28



PARIS 2022 ESMO congress

N, number of patients with data; BIW, twice weekly; QD, once daily; Data cut: Jul 14, 2022; * Wk 28 for Subject #11 was obtained post-data cut

Gounder M et al. ESMO 2022;Abstract 1488MO.

RINGSIDE Phase 2/3 Trial of AL102 for Treatment of Desmoid Tumors (DT): Phase 2 Results

Gounder M et al.

ASCO 2023;Abstract 11515.

June 3, 2023

Poster Discussion Session S404

Meet The Professor with Dr Van Tine

Introduction

MODULE 1: Immunotherapy in Soft Tissue Sarcomas — Alveolar Soft Part Sarcoma

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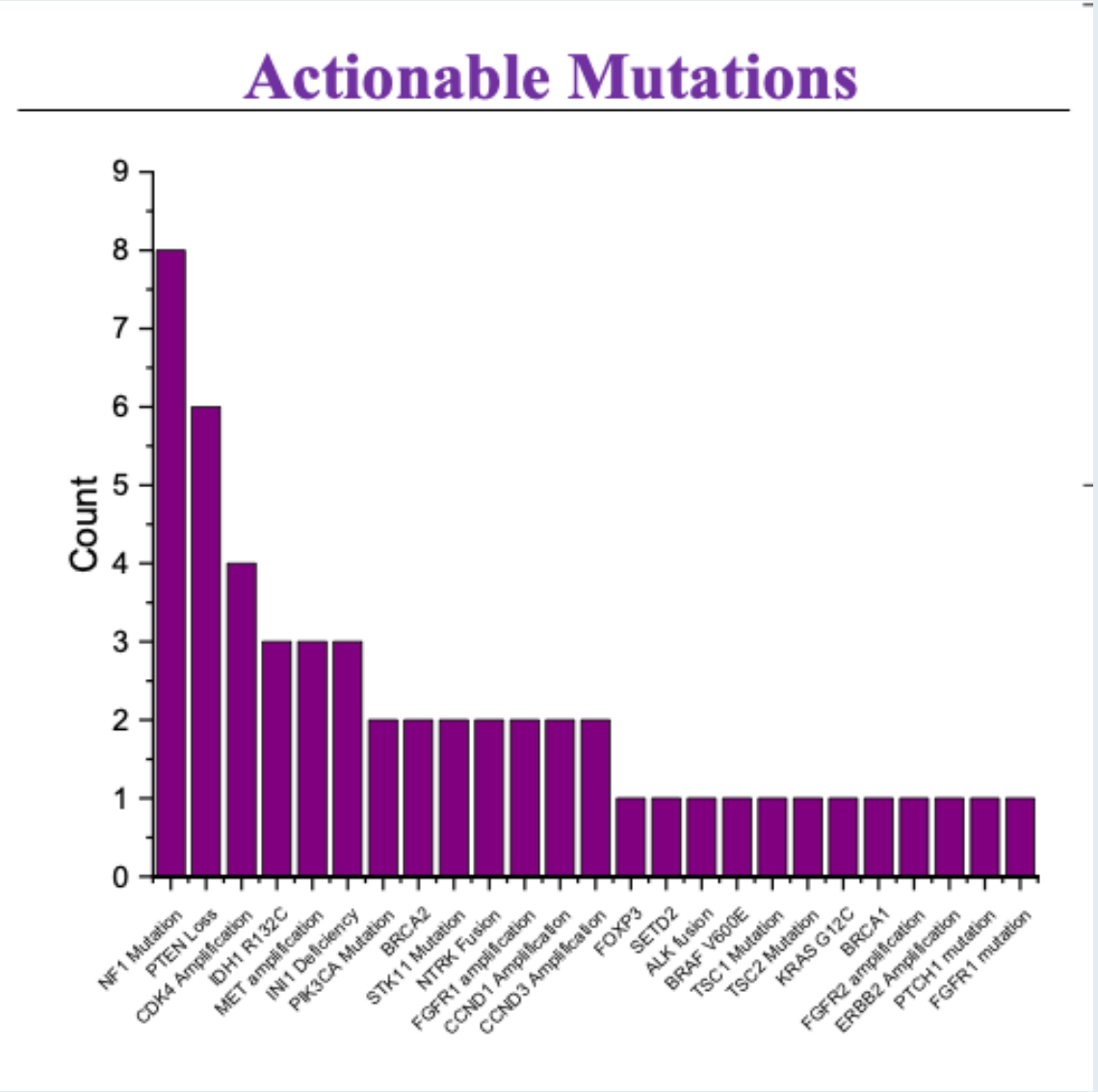
MODULE 6: Appendix

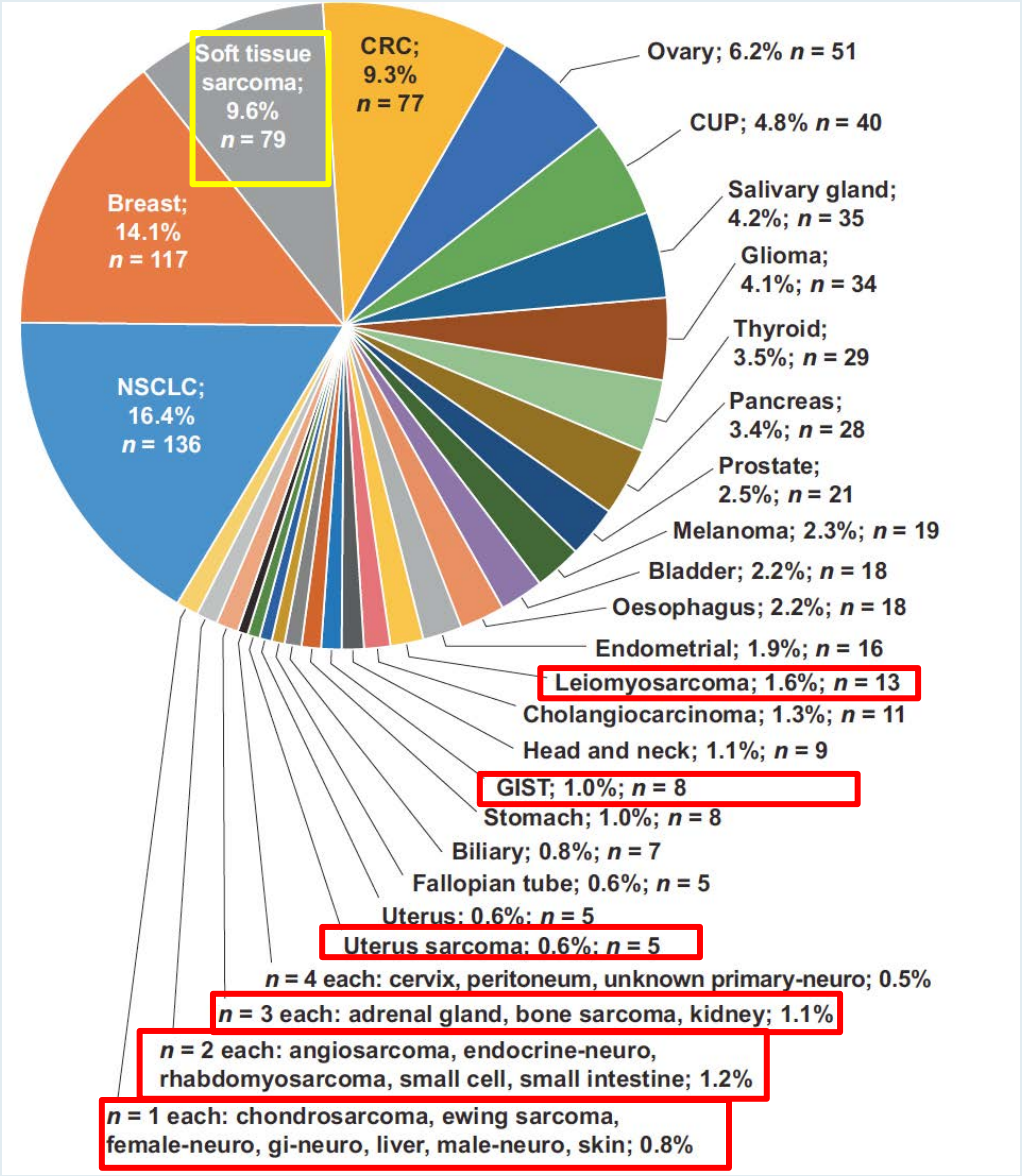
Next-Generation Sequencing (NGS) of Sarcomas

- An NGS analysis of 117 patients with sarcomas between 2014 and 2020 demonstrated that 34% of patients had potentially actionable mutations



Schulte B et al. Connective Tissue Oncology Society 2020;Abstract 106.

Prevalence of Cancer Types with NTRK Fusions



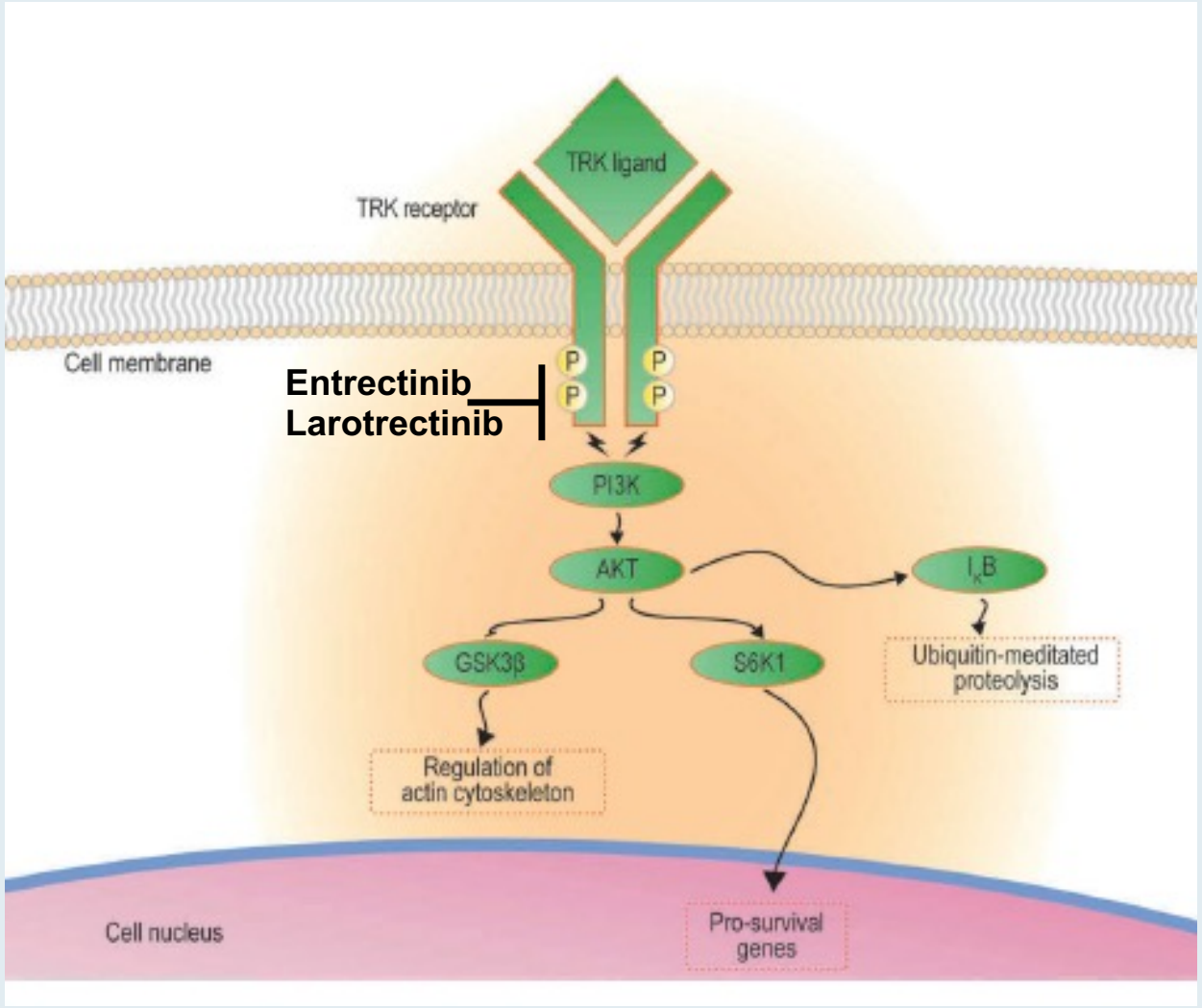
Westphalen CB et al. *NPJ Precis Oncol* 2021;5(1):69.

RTP RESEARCH TO PRACTICE

Targeted Inhibition of TRK Receptor Cell Signaling

- Entrectinib is an oral small-molecule inhibitor that is an ATP competitor and selective tyrosine kinase inhibitor of the TRK receptors, and of ROS1 and ALK.

- Larotrectinib is a highly selective, small-molecule TRK receptor inhibitor that blocks the ATP binding site on TRK receptors, thus preventing activation of downstream cell signaling.



Adapted from Federman N, Tuncbilek M. *Expert Rev Clin Pharmacol* 2019;2(10):931-9; Osman HM, Tuncbilek M. *Curr Med Chem* 2022;29(15):2602-16.

RTP RESEARCH TO PRACTICE

FDA Approvals of NTRK Inhibitors Entrectinib and Larotrectinib

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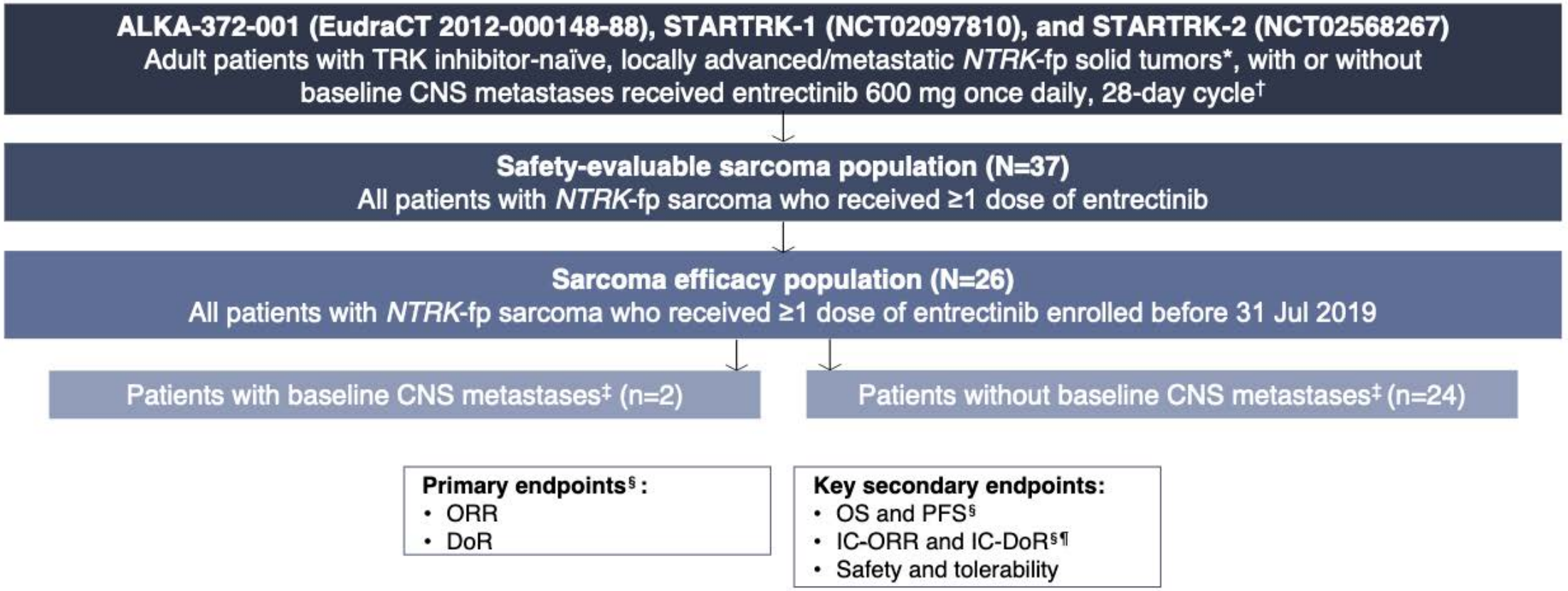
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc;
https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0

Updated Efficacy and Safety of Entrectinib in Patients with NTRK Fusion-Positive Sarcomas

Loong HHF et al.

Connective Tissue Oncology Society 2022;Abstract 23.

Integrated Analysis of ALKA-372-001, STARTRK-1 and STARTRK-2



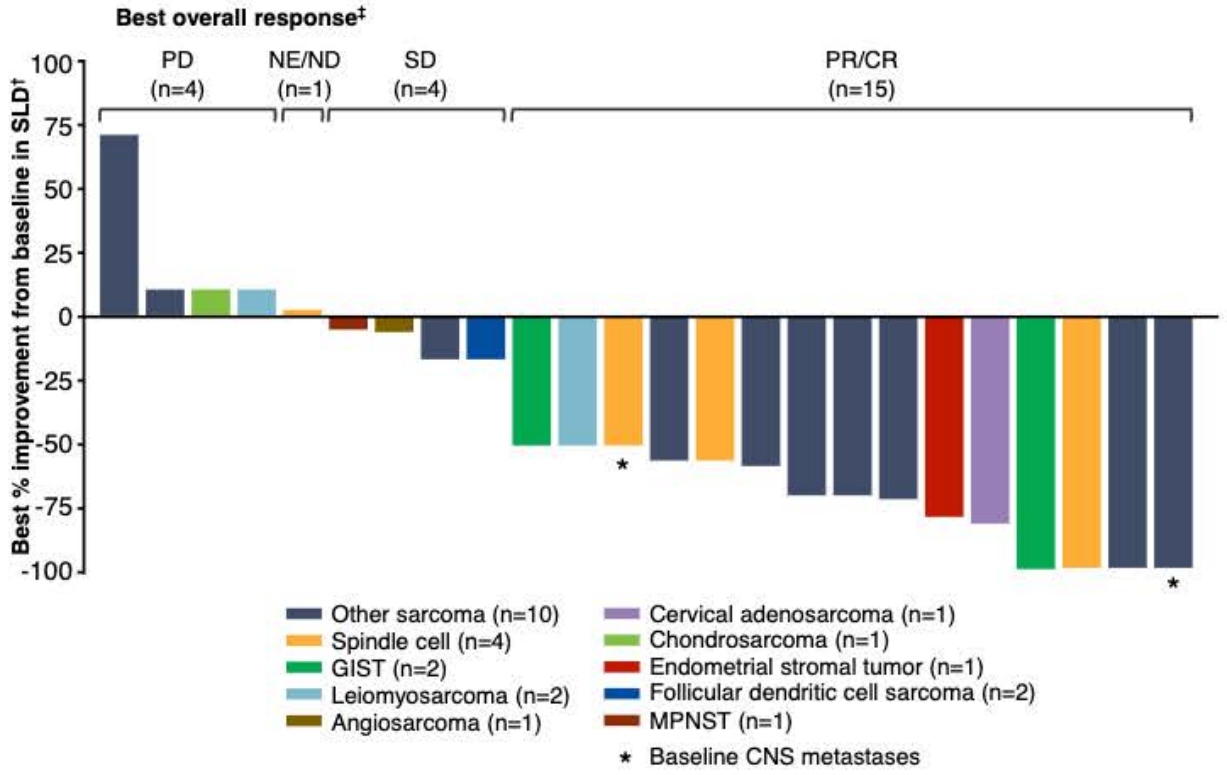
Data cut-off: 31 Aug 2020

**NTRK* fusion confirmed by nucleic acid-based methods (fluorescence in-situ hybridisation, quantitative PCR, DNA- or RNA-based next-generation sequencing); †Tumor response was assessed by BICR with RECIST v1.1 after 4 weeks and every 8 weeks thereafter; ‡CNS metastases assessed by investigator at baseline; §BICR-assessed endpoints; ¶Patients with measurable and non-measurable CNS lesions at baseline
BICR, blinded independent central review; DoR, duration of response; IC, intracranial; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

Loong HHF et al. Connective Tissue Oncology Society 2022;Abstract 23.

Updated Efficacy with Entrectinib in NTRK Fusion-Positive Sarcomas

Response	n/N (%)	Sarcoma tumor histology
BICR ORR	15/26 (57.7) (95% CI 36.9–76.7)	• Other sarcoma (7) • Spindle cell sarcoma (3) • GIST (2) • Cervical adenosarcoma (1) • Endometrial stromal sarcoma (1) • Leiomyosarcoma (1)
CR	3/26 (11.5)	• Other sarcoma (2) • GIST (1)
PR	12/26 (46.2)	• Other sarcoma (5) • Spindle cell sarcoma (3) • Cervical adenosarcoma (1) • Endometrial stromal sarcoma (1) • GIST (1) • Leiomyosarcoma (1)
SD	4/26 (15.4)	• Other sarcoma (1) • Angiosarcoma (1) • Follicular dendritic cell sarcoma (1) • MPNST (1)
PD	5/26 (19.2)	• Other sarcoma (2) • Chondrosarcoma (1) • Inflammatory myofibroblastic tumor (1) • Leiomyosarcoma (1)
Missing/unevaluable	2/26 (7.7)	• Spindle cell sarcoma (2)

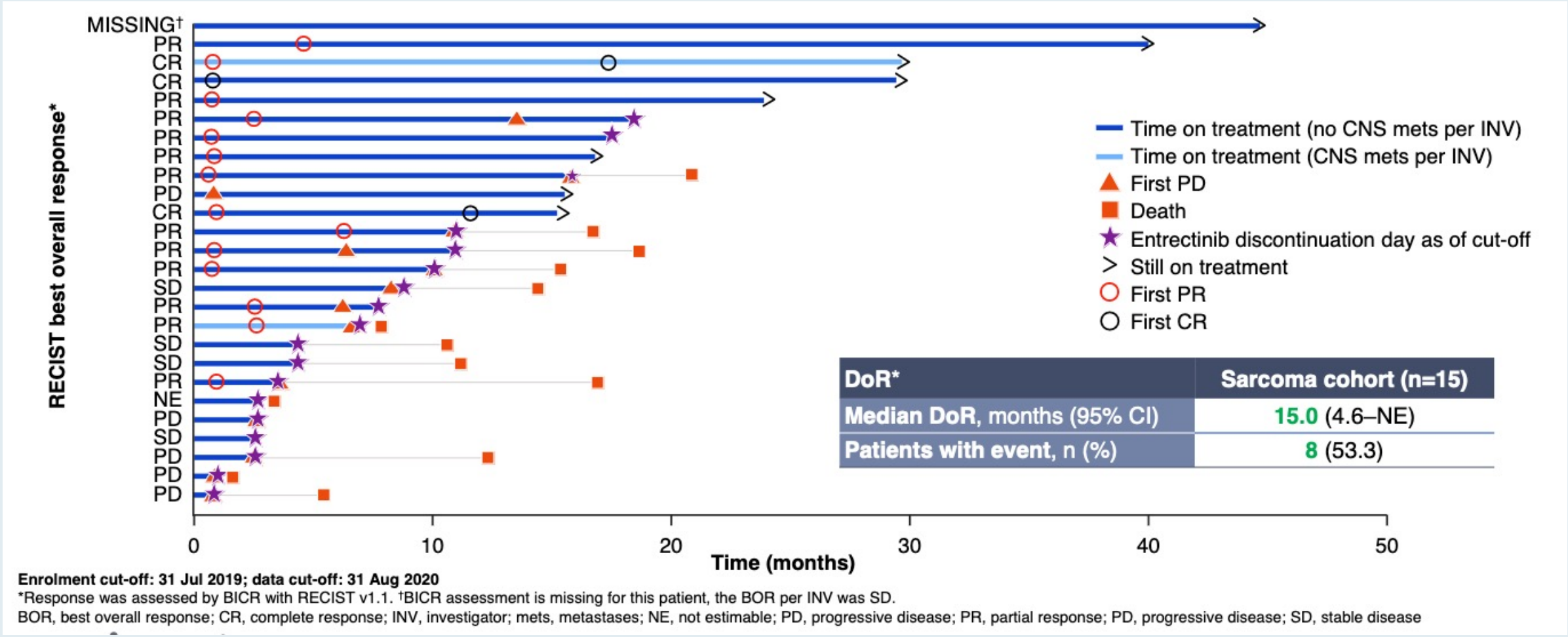


Enrolment cut-off: 31 Jul 2019; data cut-off: 31 Aug 2020

Patients without matched pre/post therapy scans were excluded and patient without measurable disease at baseline were excluded. *ORR was assessed by BICR as per RECIST v1.1; †Target lesions; ‡Response classification based on target and non-target lesions (RECIST v1.1) and assessed by BICR. CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Loong HHF et al. Connective Tissue Oncology Society 2022;Abstract 23.

Duration of Response with Entrectinib in NTRK Fusion-Positive Sarcomas



DoR*	Sarcoma cohort (n=15)
Median DoR, months (95% CI)	15.0 (4.6–NE)
Patients with event, n (%)	8 (53.3)

Enrolment cut-off: 31 Jul 2019; data cut-off: 31 Aug 2020

*Response was assessed by BICR with RECIST v1.1. †BICR assessment is missing for this patient, the BOR per INV was SD.

BOR, best overall response; CR, complete response; INV, investigator; mets, metastases; NE, not estimable; PD, progressive disease; PR, partial response; PD, progressive disease; SD, stable disease

Loong HHF et al. Connective Tissue Oncology Society 2022;Abstract 23.

RTP RESEARCH TO PRACTICE

Updated Safety Summary with Entrectinib in NTRK Fusion-Positive Sarcomas

- The median treatment duration was **7.0 months**
- **17** patients (45.9%) experienced a grade ≥3 TRAE
  - The most common grade 3 TRAE was weight increase in **10.8%** (n=4) of patients
  - One grade 4 TRAE was reported: hyperuricemia in **2.7%** (n=1) of patients
- TRAEs leading to dose reduction, interruption and discontinuation occurred in **18.9%** (n=7), **32.4%** (n=12) and **5.4%** (n=2) of patients, respectively
- No deaths due to TRAEs were reported

TRAEs reported in the *NTRK*-fp sarcoma cohort were comparable with those in the overall safety population

TRAEs reported in ≥5 patients from the *NTRK*-fp sarcoma safety population, n (%)	Sarcoma safety population* (n=37)	Overall safety population†,1,2 (n=193)
Blood creatinine increase	12 (32.4)	50 (25.9)
Diarrhea	12 (32.4)	60 (31.1)
Dizziness	12 (32.4)	48 (24.9)
Fatigue	12 (32.4)	53 (27.5)
Weight increase	12 (32.4)	53 (27.5)
Dysgeusia	11 (29.7)	68 (35.2)
Edema peripheral	11 (29.7)	35 (18.1)
AST increase	8 (21.6)	32 (16.6)
Constipation	8 (21.6)	50 (25.9)
Paresthesia	7 (18.9)	23 (11.9)
ALT increase	6 (16.2)	30 (15.5)
Anemia	6 (16.2)	33 (17.1)
Nausea	6 (16.2)	32 (16.6)
Neutrophil count decrease	5 (13.5)	15 (7.8)
Taste disorder	5 (13.5)	12 (6.2)
Myalgia	5 (13.5)	21 (10.9)

Data cut-off: 31 Aug 2020. 1. Demetri, et al. Clin Cancer Res 2022; 2. Roche data on file
*The sarcoma safety-evaluable population comprised all patients with *NTRK*-fp sarcoma who had received ≥1 dose of entrectinib.
Adverse events were encoded using MedDRA (version 23.0). †The overall safety population comprised all patients with *NTRK*-fp solid tumors (including sarcoma) who had received ≥1 dose of entrectinib.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event

Loong HHF et al. Connective Tissue Oncology Society 2022;Abstract 23.

Meet The Professor with Dr Van Tine

Introduction

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MODULE 6: Appendix

Case Presentation: 42-year-old woman with prior mastectomy for angiosarcoma of the right breast and recurrent disease who receives doxorubicin but develops a bleeding sigmoid mass and widespread metastases

Dr Melanie Thomas (Durham, North Carolina)

RTP
RESEARCH
TO PRACTICE

Comments: Importance of supportive care and pain management for patients with STS

Dr Melanie Thomas (Durham, North Carolina)

RTP
RESEARCH
TO PRACTICE

Comments: How I became interested in treating STS

Dr Atif Hussein (Hollywood, Florida)

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Case Presentation: 35-year-old man with a 5.5-cm leiomyosarcoma, 1 positive inguinal node and multiregimen-refractory disease

Dr Atif Hussein (Hollywood, Florida)

Case Presentation: 35-year-old man with a 5.5-cm leiomyosarcoma, 1 positive inguinal node and multiregimen-refractory disease (continued)

Dr Atif Hussein (Hollywood, Florida)

Case Presentation: 53-year-old woman with PMH of anemia, RCC and nephrectomy who is diagnosed with Grade I GIST, spindle cell type – c-KIT mutation

Dr Melanie Thomas (Durham, North Carolina)

RTP RESEARCH TO PRACTICE

Case Presentation: 56-year-old man with multiregimen-refractory metastatic mediastinal liposarcoma s/p resection, chemotherapy and eribulin – CDK4 amplification identified by NGS

Dr Melanie Thomas (Durham, North Carolina)

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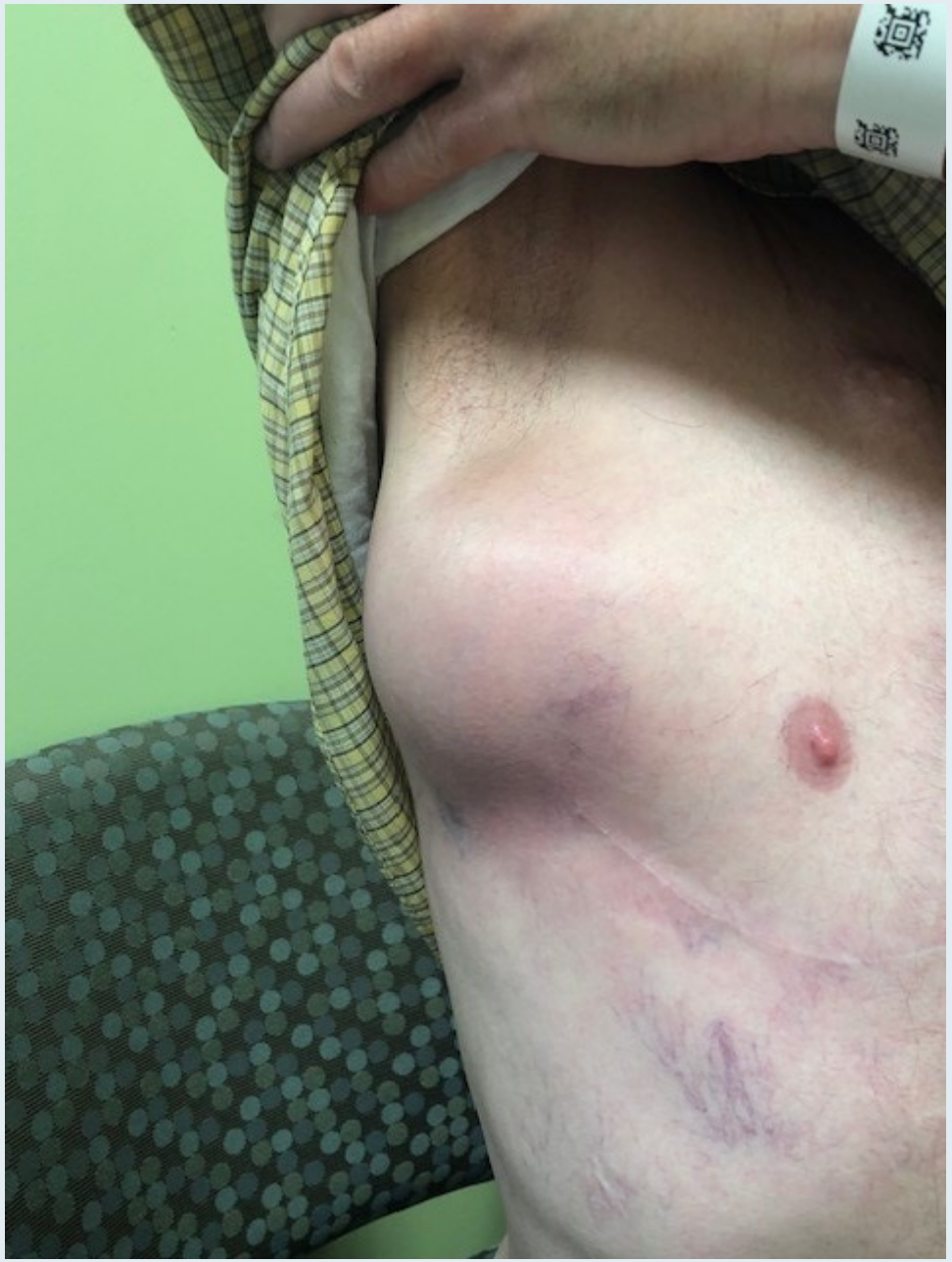
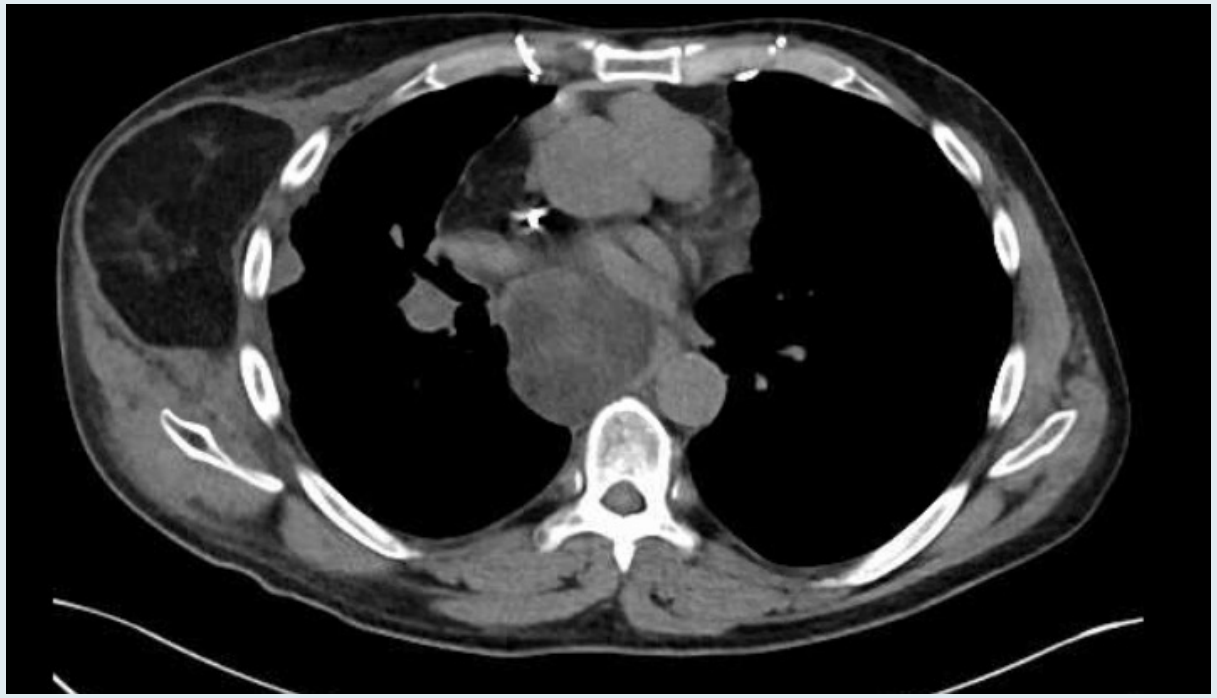
RESEARCH
TO PRACTICE





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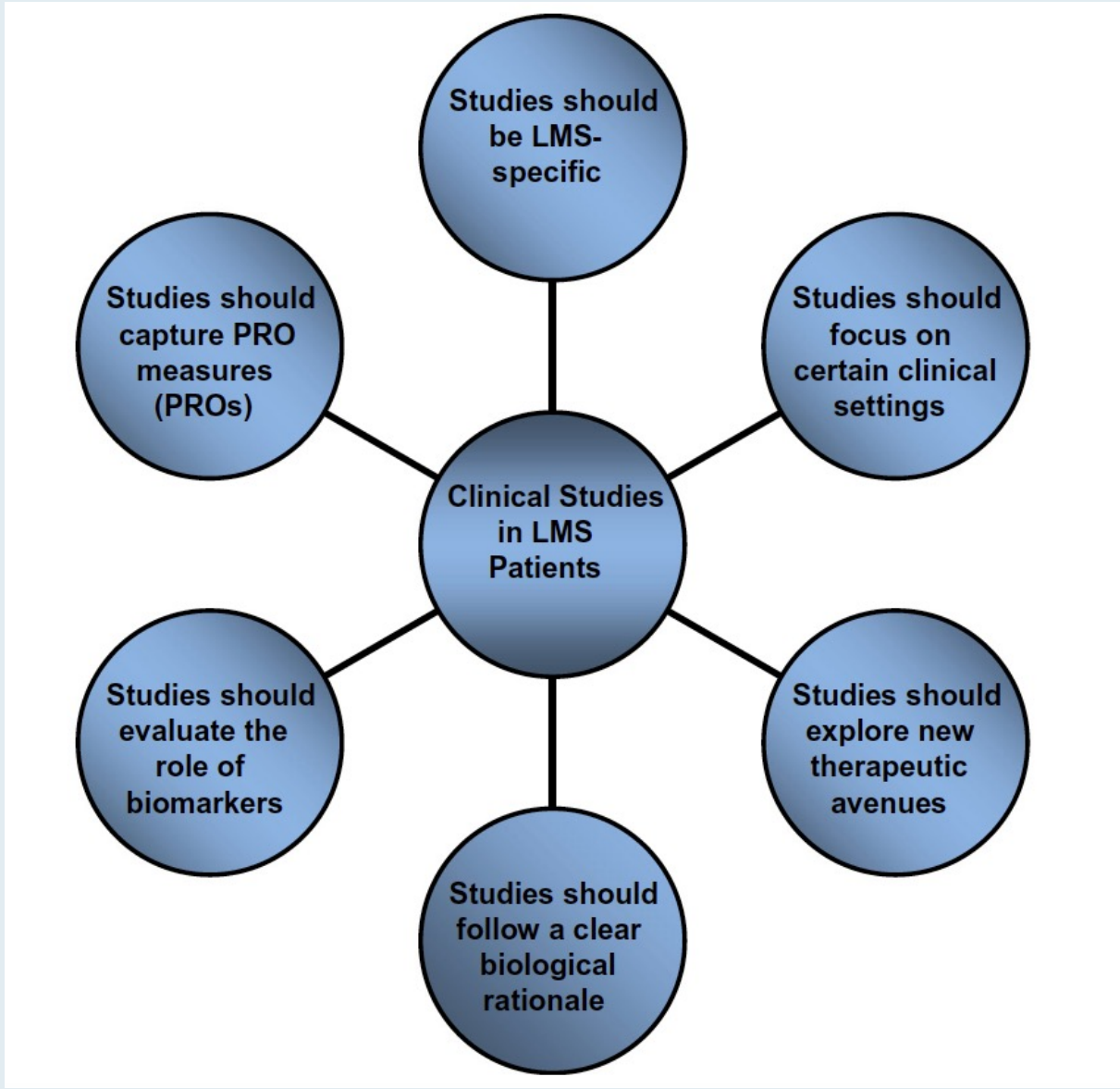
Curr. Treat. Options in Oncol. (2022) 23:439–449
DOI 10.1007/s11864-021-00928-y

Sarcoma (SH Okuno, Section Editor)

What Clinical Trials Are Needed for Treatment of Leiomyosarcoma?

Bernd Kasper, MD, PhD[1,*]
Lorenzo D'Ambrosio, MD[2]
Elizabeth J. Davis, MD[3]
Matthew Ingham, MD[4]
Javier Martin Broto, MD[5]
Jonathan C. Trent, MD, PhD[6]
Winan J. van Houdt, MD[7]
Brian A. Van Tine, MD, PhD[8]

Characteristics for Designing Clinical Studies in Leiomyosarcoma (LMS)



PRO = patient-reported outcome

Kasper B et al. *Curr Treat Options Oncol* 2022;23(3):439-49.

JACC: CARDIOONCOLOGY VOL. 5, NO. 1, 2023

EDITORIAL COMMENT

More Data to Support a Cardiac-Oncologic Partnership*

Ronald J. Krone, MD,[a] Brian A. Van Tine, MD, PhD[b,c,d]

Received: 8 December 2021 | Revised: 14 February 2022 | Accepted: 13 March 2022

2022;11(18):3471-8.

DOI: 10.1002/cam4.4707

Cancer Medicine Open Access WILEY

RESEARCH ARTICLE

Pregnancy outcomes related to the treatment of sarcomas with anthracyclines and/or ifosfamide during pregnancy

Devon Miller[1] | John A. Livingston[2] | Yeonhee Park[3] | Kristi Posey[2] | Sonia Godbole[4] | Keith Skubitz[5] | Steven I. Robinson[6] | Mark Agulnik[7] | Lara E. Davis[8] | Brian A. Van Tine[4] | Angela C. Hirbe[4] | Amanda Parkes[1]

J Clin Oncol 2022;40(22):2479-90.

original reports

Selinexor in Advanced, Metastatic Dedifferentiated Liposarcoma: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial

Mrinal M. Gounder, MD[1]; Albiruni Abdul Razak, MB[2]; Neeta Somaiah, MD[3]; Sant Chawla, MD[4]; Javier Martin-Broto, MD[5]; Giovanni Grignani, MD[6]; Scott M. Schuetze, MD[7]; Bruno Vincenzi, MD[8]; Andrew J. Wagner, MD[9]; Bartosz Chmielowski, MD[10]; Robin L. Jones, MD[11]; Richard F. Riedel, MD[12]; Silvia Stacchiotti, MD[13]; Elizabeth T. Loggers, MD[14]; Kristen N. Ganjoo, MD[15]; Axel Le Cesne, MD[16]; Antoine Italiano, MD[17]; Xavier Garcia del Muro, MD[18]; Melissa Burgess, MD[19]; Sophie Piperno-Neumann, MD[20]; Christopher Ryan, MD[21]; Mary F. Mulcahy, MD[22]; Charles Forscher, MD[23]; Nicolas Penel, MD[24]; Scott Okuno, MD[25]; Anthony Elias, MD[26]; Lee Hartner, MD[27]; Tony Philip, MD[28]; Thierry Alcindor, MD[29]; Bernd Kasper, MD[30]; Peter Reichardt, MD[31]; Lore Lapeire, MD[32]; Jean-Yves Blay, MD[33]; Christine Chevreau, MD[34]; Claudia Maria Valverde Morales, MD[35]; Gary K. Schwartz, MD[36]; James L. Chen, MD[37]; Hari Deshpande, MD[38]; Elizabeth J. Davis, MD[39]; Garth Nicholas, MD[40]; Stefan Gröschel, MD[41]; Helen Hatcher, PhD[42]; Florence Duffaud, MD[43]; Antonio Casado Herráez, MD[44]; Roberto Diaz Beveridge, MD[45]; Giuseppe Badalamenti, MD[46]; Mikael Eriksson, MD[47]; Christian Meyer, MD[48]; Margaret von Mehren, MD[49]; Brian A. Van Tine, MD[50]; Katharina Götze, MD[51]; Filomena Mazzeo, MD[52]; Alexander Yakobson, MD[53]; Aviad Zick, MD[54]; Alexander Lee, MD[55]; Anna Estival Gonzalez, MD[56]; Andrea Napolitano, MD[8]; Mark A. Dickson, MD[1]; Dayana Michel, MD[57]; Changting Meng, MD[57]; Lingling Li, PhD[57]; Jianjun Liu, MS[57]; Osnat Ben-Shahar, PhD[57]; Dane R. Van Domelen, PhD[57]; Christopher J. Walker, PhD[57]; Hua Chang, PhD[57]; Yosef Landesman, PhD[57]; Jatin J. Shah, MD[57]; Sharon Shacham, PhD[57]; Michael G. Kauffman, MD[57]; and Steven Attia, DO[58]

A Phase II Trial with Safety Lead-In to Evaluate the Addition of Sotigalimab, a CD40 Agonistic Monoclonal Antibody, to Standard-of-Care Doxorubicin for the Treatment of Advanced Sarcoma

Bose S et al.

ASCO 2023;Abstract 11565.

June 3, 2023

Poster Session Hall A

The SPEARHEAD-1 Trial of Afamitresgene Autoleucel (Afami-cel [Formerly ADP-A2M4]): Pooled Analysis of Cytokine Release Syndrome Across Cohorts in Patients with Advanced Synovial Sarcoma

D’Angelo S et al.

ASCO 2023;Abstract e14531.

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Systemic Treatment for Metastatic Soft Tissue Sarcoma (STS)

RTP
RESEARCH
TO PRACTICE

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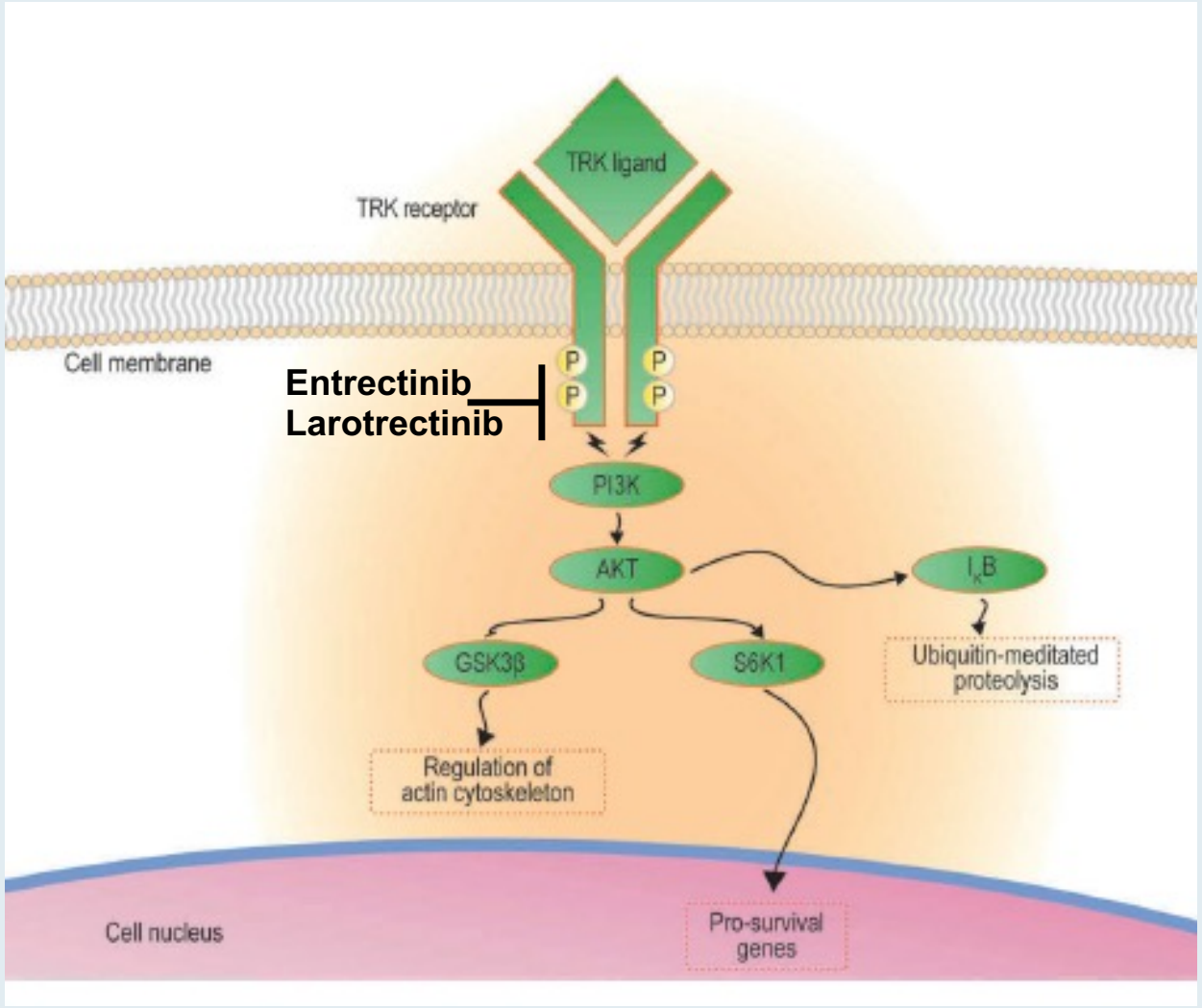

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RTP RESEARCH TO PRACTICE

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https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc;
https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0

Novel Approaches to the Management of Unique STS Subtypes

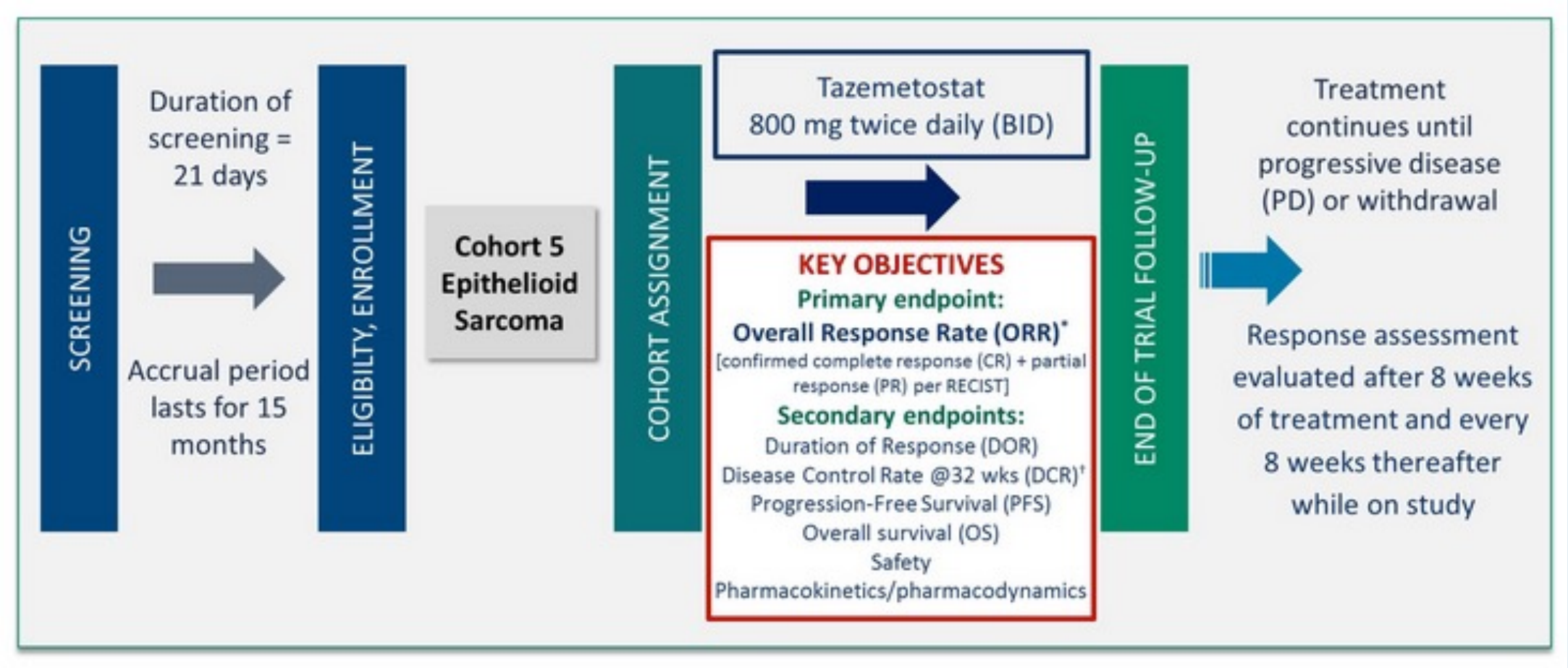
RTP
RESEARCH
TO PRACTICE

Tazemetostat in advanced epithelioid sarcoma with loss of INI1/*SMARCB1*: an international, open-label, phase 2 basket study

Mrinal Gounder, Patrick Schöffski, Robin L Jones, Mark Agulnik, Gregory M Cote, Victor M Villalobos, Steven Attia, Rashmi Chugh, Tom Wei-Wu Chen, Thierry Jahan, Elizabeth T Loggers, Abha Gupta, Antoine Italiano, George D Demetri, Ravin Ratan, Lara E Davis, Olivier Mir, Palma Dileo, Brian A Van Tine, Joseph G Pressey, Trupti Lingaraj, Anand Rajarethinam, Laura Sierra, Shefali Agarwal, Silvia Stacchiotti

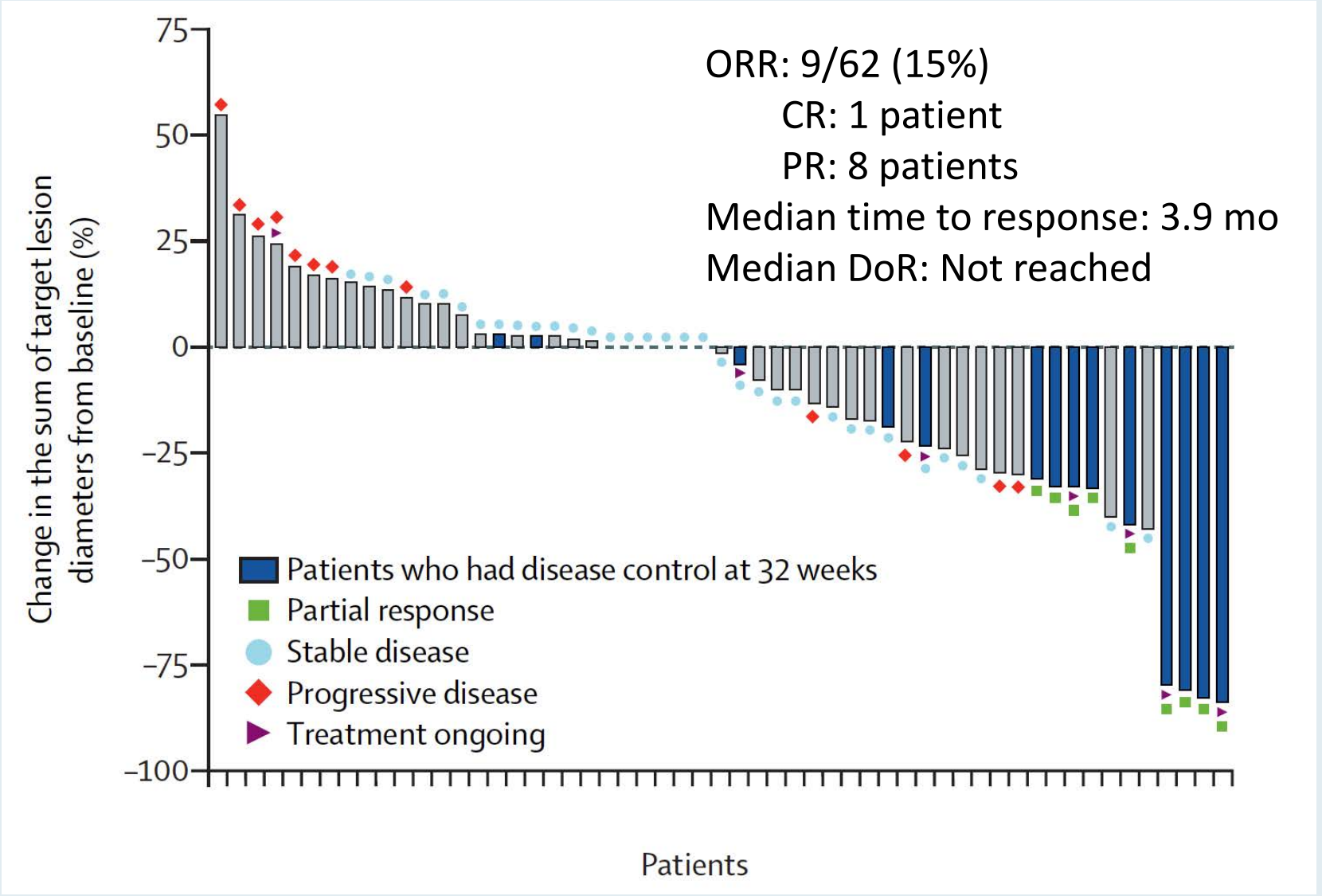
***Lancet Oncol* 2020;21(11):1423-32.**

Phase II Study Design of Tazemetostat in Epithelioid Sarcoma (Cohort 5)



Stacchiotti S et al. ASCO 2019;Abstract 11003.

Responses with Tazemetostat in Patients with Epithelioid Sarcoma



Gounder M et al. *Lancet Oncol* 2020;21(11):1423-32.

Select Treatment-Emergent Adverse Events (TEAEs) with Tazemetostat in Patients with Epithelioid Sarcoma

Grade 3/4 TEAE (n = 62)	Grade 3	Grade 4
Anemia	8 (13%)	0
Weight loss	4 (6%)	0
Pleural effusion	3 (5%)	0
Decreased appetite	3 (5%)	0
Cancer pain	3 (5%)	0

- Serious treatment-emergent adverse events occurred in 25 (40%) patients and included: pleural effusion (4 [6%]), hemoptysis (4 [6%]), death (4 [6%]), dyspnea (3 [5%]), cellulitis (2 [3%]) and cancer pain (2 [3%])

Gounder M et al. *Lancet Oncol* 2020;21(11):1423-32.

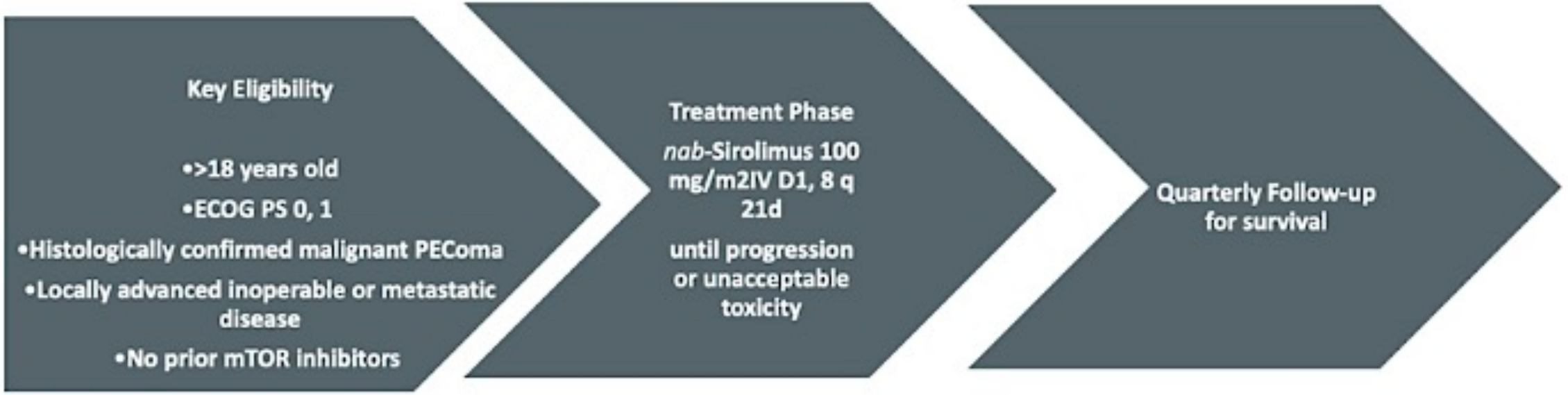
RTP RESEARCH TO PRACTICE

Final Analysis from AMPECT, an Open-Label Phase 2 Registration Trial of *Nab*-Sirolimus for Patients with Advanced Malignant Perivascular Epithelioid Cell Tumor (PEComa)

Wagner A et al.

Connective Tissue Oncology Society 2021;Abstract 108747.

AMPECT Phase II Registration Study Design



Primary Endpoint –ORR by Independent Radiology Review (RECIST v1.1)
–CT/MRI every 6 weeks for the 1styear, every 12 thereafter

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

Secondary Endpoints
–DOR, PFS at 6 months, median PFS, median OS
–Safety

Key Exploratory Endpoints–Investigator response assessment
–Biomarkers: mutational analysis (NGS, IHC, FISH)

Wagner A et al. Connective Tissue Oncology Society 2021;Abstract 108747.

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AMPECT Final Analysis: Best Responses by Independent Review with *Nab* Sirolimus

Clinical variable, n (%)	n = 31
Confirmed overall response rate	12 (39%)
Complete response	2 (7%)
Partial response	10 (32%)
Disease control rate	71%
Median DoR	Not reached

- 2 patients converted from a PR to a CR after 11 months and 34 months of treatment, respectively
- TSC2 mutations: 8/9 patients (89%) had confirmed ORR (1/9 patients had an unconfirmed response)
- Responses also occurred in some patients with TSC1 or no TSC1/TSC2 mutation or unknown mutational status

Wagner A et al. Connective Tissue Oncology Society 2021;Abstract 108747.

AMPECT Final Analysis: Select TRAEs

TRAEs (n = 34)	Any grade	Grade 3
Any TRAE	8 (13%)	Not reported
Thrombocytopenia	4 (6%)	0
Mucositis	3 (5%)	0
Fatigue	3 (5%)	0
Rash	3 (5%)	0

- No Grade 4 or 5 TRAEs
- Pneumonitis occurred in 7/34 patients (21%) and was Grade 1/2 only

Wagner A et al. Connective Tissue Oncology Society 2021;Abstract 108747.

Selection and Sequencing of Systemic Therapy for Patients with Advanced Gastrointestinal Stromal Tumors (GIST)

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FDA Approves Ripretinib for Advanced Gastrointestinal Stromal Tumor

Press Release: May 15, 2020

"On May 15, 2020, the Food and Drug Administration approved ripretinib for adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

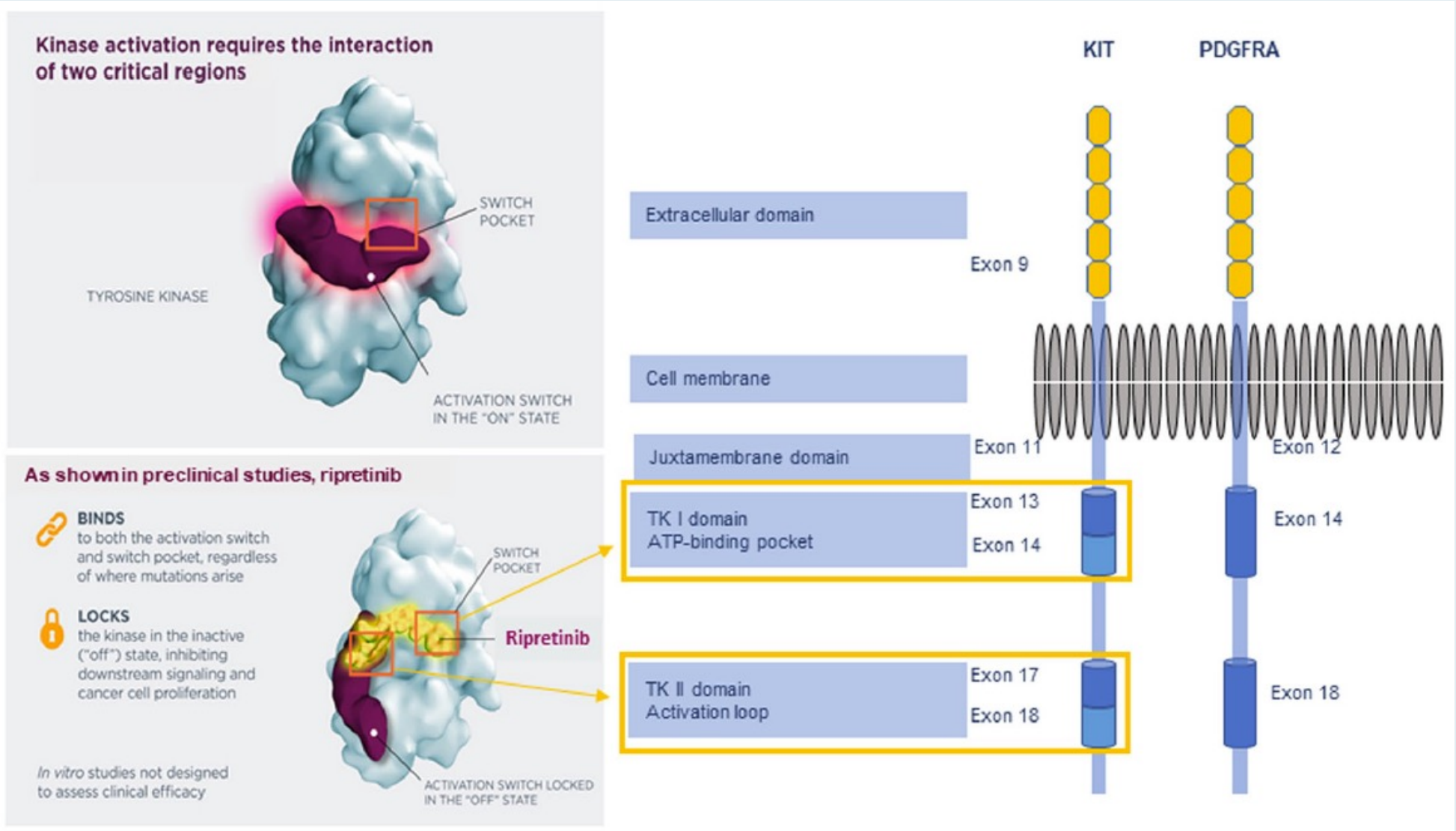
Efficacy was evaluated in INVICTUS (NCT03353753), an international, multicenter, randomized (2:1), double-blind, placebo-controlled trial in 129 patients with GIST who were previously treated with imatinib, sunitinib, and regorafenib. Patients received ripretinib 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. Crossover was permitted at disease progression for patients randomized to receive placebo.

The major efficacy outcome measure was progression-free survival (PFS) based on assessment by blinded independent central review (BICR) using modified RECIST 1.1 in which lymph nodes and bone lesions were not target lesions and a progressively growing new tumor nodule within a pre-existing tumor mass must meet specific criteria to be considered unequivocal evidence of progression.

The recommended ripretinib dose is 150 mg orally once daily with or without food."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ripretinib-advanced-gastrointestinal-stromal-tumor

Dual Mechanism of Action of the Switch Control Kinase Inhibitor Ripretinib



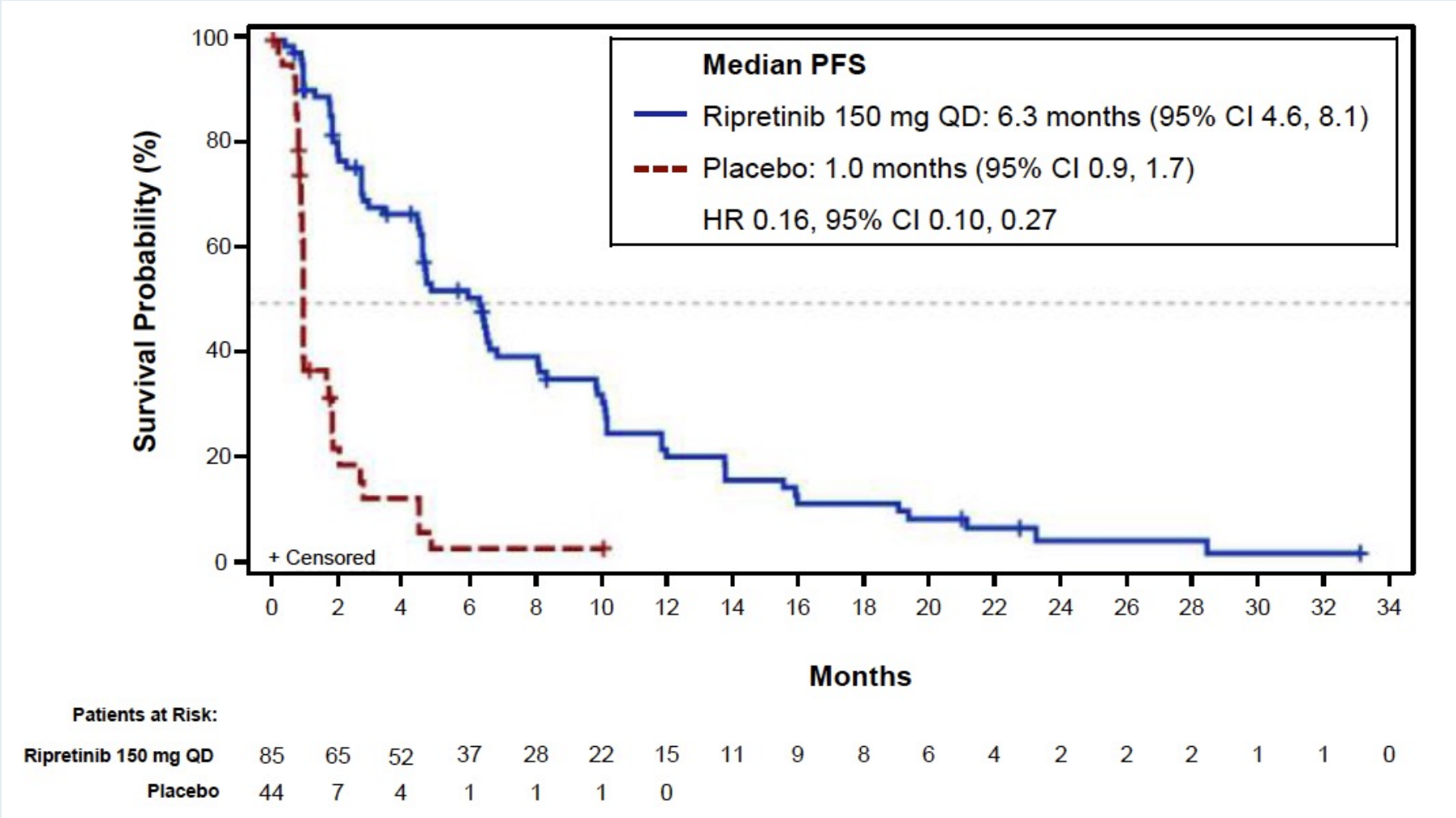
JR Zalcberg. *Ther Adv Gastroenterol* 2021;14:1-12.

Ripretinib as ≥4th-Line Treatment in Patients with Advanced Gastrointestinal Stromal Tumour (GIST): Long-Term Update from the Phase 3 INVICTUS Study

von Mehren M et al.

ESMO 2021;Abstract 1540P.

INVICTUS Long-Term Update: PFS with Ripretinib in Patients with Advanced GIST Who Were Resistant to Approved Therapies



von Mehren M et al. ESMO 2021;Abstract 1540P.

RTP RESEARCH TO PRACTICE

INVICTUS Long-Term Update: Estimated Overall Survival Estimates

	Ripretinib (n = 85)	Placebo (n = 44)
Events, n (%)	46 (54)	36 (82)
Censored, n (%)	39 (46)	8 (18)
OS 6 months, % (95% CI)	84.3 (74.5, 90.6)	55.9 (39.9, 69.2)
OS 12 months, % (95% CI)	65.1 (53.6, 74.5)	29.7 (16.8, 43.7)
OS 18 months, % (95% CI)	50.1 (38.5, 60.7)	29.7 (16.8, 43.7)
OS 24 months, % (95% CI)	42.8 (31.5, 53.7)	19.8 (9.4,33.0)

CI, confidence interval; ITT, intent-to-treat (all randomised patients); OS, overall survival.

- With 19 months of additional follow-up after the primary analysis:
  - mOS was 18.2 months with ripretinib vs 6.3 months with placebo (hazard ratio 0.41, 95% CI 0.26–0.65; **Figure 6**)
  - mOS was 10 months in the placebo patients who crossed over to ripretinib (**Figure 6**)
  - Estimated OS for patients randomised to ripretinib was 65.1% at 12 months and 42.8% at 24 months (**Table 3**)

von Mehren M et al. ESMO 2021;Abstract 1540P.

INVICTUS Long-Term Update: Select TEAEs with Ripretinib in Patients with Advanced GIST Who Were Resistant to Approved Therapies

TEAE, n (%)	Ripretinib (n = 85)		Placebo (n = 43)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Abdominal pain	34 (40%)	6 (7%)	13 (30%)	2 (5%)
Anemia	16 (9%)	9 (11%)	8 (19%)	6 (14%)
Hypertension	13 (15%)	6 (7%)	2 (5%)	0
Hypophosphatemia	9 (11%)	4 (5%)	0	0
Lipase increased	9 (11%)	4 (5%)	1 (2%)	0

von Mehren M et al. ESMO 2021;Abstract 1540P.

original reports

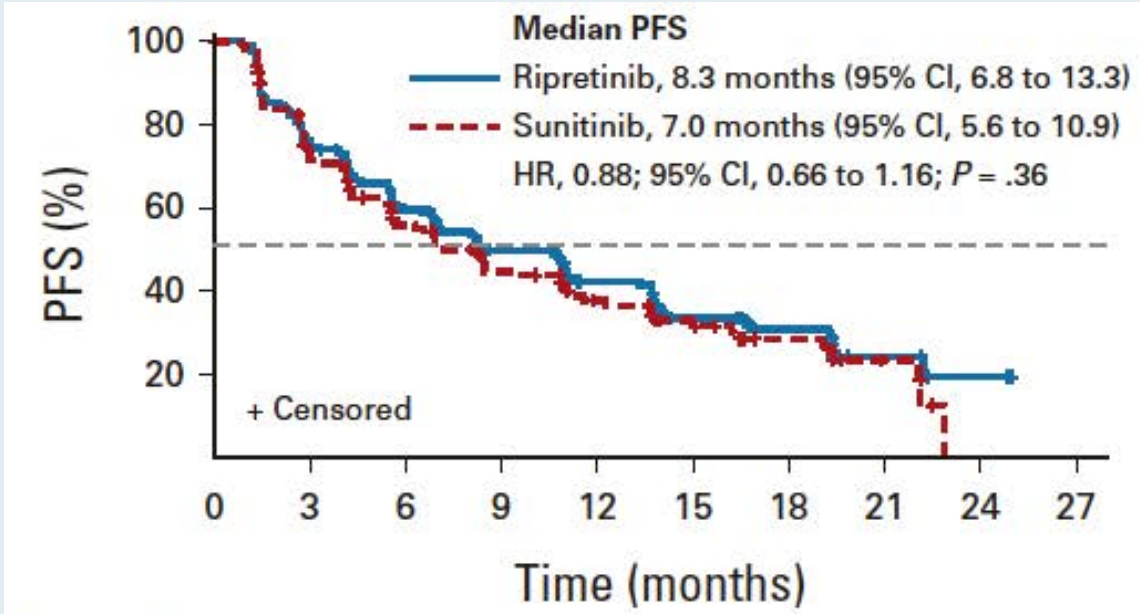
Ripretinib Versus Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumor After Treatment With Imatinib (INTRIGUE): A Randomized, Open-Label, Phase III Trial

Sebastian Bauer, MD[1,2]; Robin L. Jones, MD, MBBS[3]; Jean-Yves Blay, MD, PhD[4]; Hans Gelderblom, MD, PhD[5]; Suzanne George, MD[6]; Patrick Schöffski, MD[7]; Margaret von Mehren, MD[8]; John R. Zalcberg, MD, PhD[9]; Yoon-Koo Kang, MD, PhD[10]; Albiruni Abdul Razak, MRCP, MBBCh[11]; Jonathan Trent, MD, PhD[12]; Steven Attia, DO[13]; Axel Le Cesne, MD[14]; Ying Su, MD, PhD[15]; Julie Meade, MD[15]; Tao Wang, PhD[15]; Matthew L. Sherman, MD[15]; Rodrigo Ruiz-Soto, MD[15]; and Michael C. Heinrich, MD[16,17]

J Clin Oncol 2022;40(34):3918-28.

INTRIGUE: PFS with Ripretinib in Patients with Advanced GIST Previously Treated with Imatinib

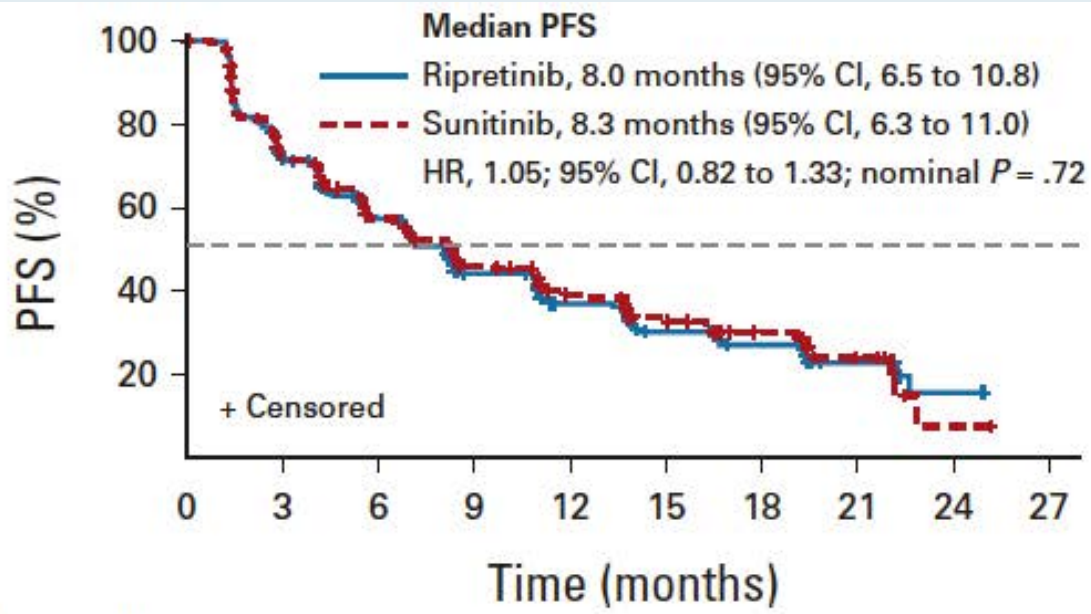
KIT Exon 11 ITT Population



No. at risk:

Ripretinib	163	115	88	61	46	31	18	6	3	0
Sunitinib	164	104	75	50	33	23	12	5	0	0

ITT Population



No. at risk:

Ripretinib	226	152	115	75	56	39	23	10	4	0
Sunitinib	227	143	108	68	45	29	16	8	1	0

Bauer S et al. *J Clin Oncol* 2022;40(34):3918-28.

RTP RESEARCH TO PRACTICE

INTRIGUE: Adverse Events with Ripretinib in Patients with Advanced GIST Previously Treated with Imatinib

	Ripretinib (n = 223)		Sunitinib (n = 221)	
Preferred Term	All Grades, No. (%)	Grade 3/4, No. (%)	All Grades, No. (%)	Grade 3/4, No. (%)
Alopecia	143 (64.1)	NA[b]	18 (8.1)	NA[b]
Fatigue	84 (37.7)	7 (3.1)	91 (41.2)	4 (1.8)
Myalgia	81 (36.3)	4 (1.8)	24 (10.9)	0
Constipation	78 (35.0)	1 (0.4)	48 (21.7)	0
Decreased appetite	60 (26.9)	2 (0.9)	54 (24.4)	2 (0.9)
Hypertension	59 (26.5)	19 (8.5)	104 (47.1)	59 (26.7)
Palmar-plantar erythrodysesthesia	59 (26.5)	3 (1.3)	113 (51.1)	22 (10.0)
Abdominal pain	58 (26.0)	6 (2.7)	38 (17.2)	6 (2.7)
Muscle spasms	55 (24.7)	1 (0.4)	12 (5.4)	0
Nausea	53 (23.8)	2 (0.9)	56 (25.3)	1 (0.5)
Pruritus	48 (21.5)	1 (0.4)	16 (7.2)	0
Diarrhea	42 (18.8)	2 (0.9)	106 (48.0)	6 (2.7)
Stomatitis	15 (6.7)	0	80 (36.2)	6 (2.7)

Bauer S et al. *J Clin Oncol* 2022;40(34):3918-28.

FDA Approves Avapritinib for Advanced Gastrointestinal Stromal Tumor with A Rare Mutation

Press Release: January 9, 2020

"On January 9, 2020, the Food and Drug Administration approved avapritinib for adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including D842V mutations.

Avapritinib is the first therapy approved for patients with GIST harboring a PDGFRA exon 18 mutation.

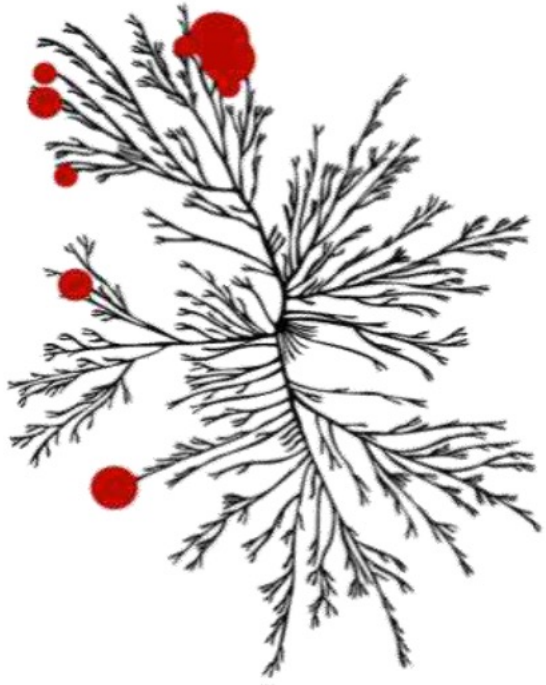
Efficacy was investigated in NAVIGATOR (NCT02508532), a multicenter, single-arm, open-label trial enrolling 43 patients with GIST harboring a PDGFRA exon 18 mutation, including 38 patients with PDGFRA D842V mutations. The trial initially enrolled patients at a starting dose of 400 mg orally once daily, which was later reduced to the recommended dose of 300 mg orally once daily due to toxicity. Patients received avapritinib until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) based on disease assessment by independent radiological review using modified RECIST 1.1 criteria. An additional efficacy outcome measure was response duration.

The recommended avapritinib dose is 300 mg orally once daily on an empty stomach, at least one hour before and two hours after a meal."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-avapritinib-gastrointestinal-stromal-tumor-rare-mutation

Avapritinib is a Highly Selective and Potent KIT/PDGFRA Inhibitor in GIST

GIST mutation(s)		Medical need by mutation	Avapritinib biochemical IC_{50}[1]
KIT Exon 11 deletion	JM domain	1L imatinib is effective 2L sunitinib/3L regorafenib have low ORR/short PFS	0.6 nM
KIT Exon 11 V560G			1 nM
KIT Exon 11/13	ATP binding site	Approved 2L/3L agents have low ORR/short PFS	11 nM
KIT Exon 11/14			28 nM
KIT Exon 11/17	Activation loop		0.1 nM
PDGFRα D842V		No highly effective therapy in any line	0.24 nM



Avapritinib kinome selectivity

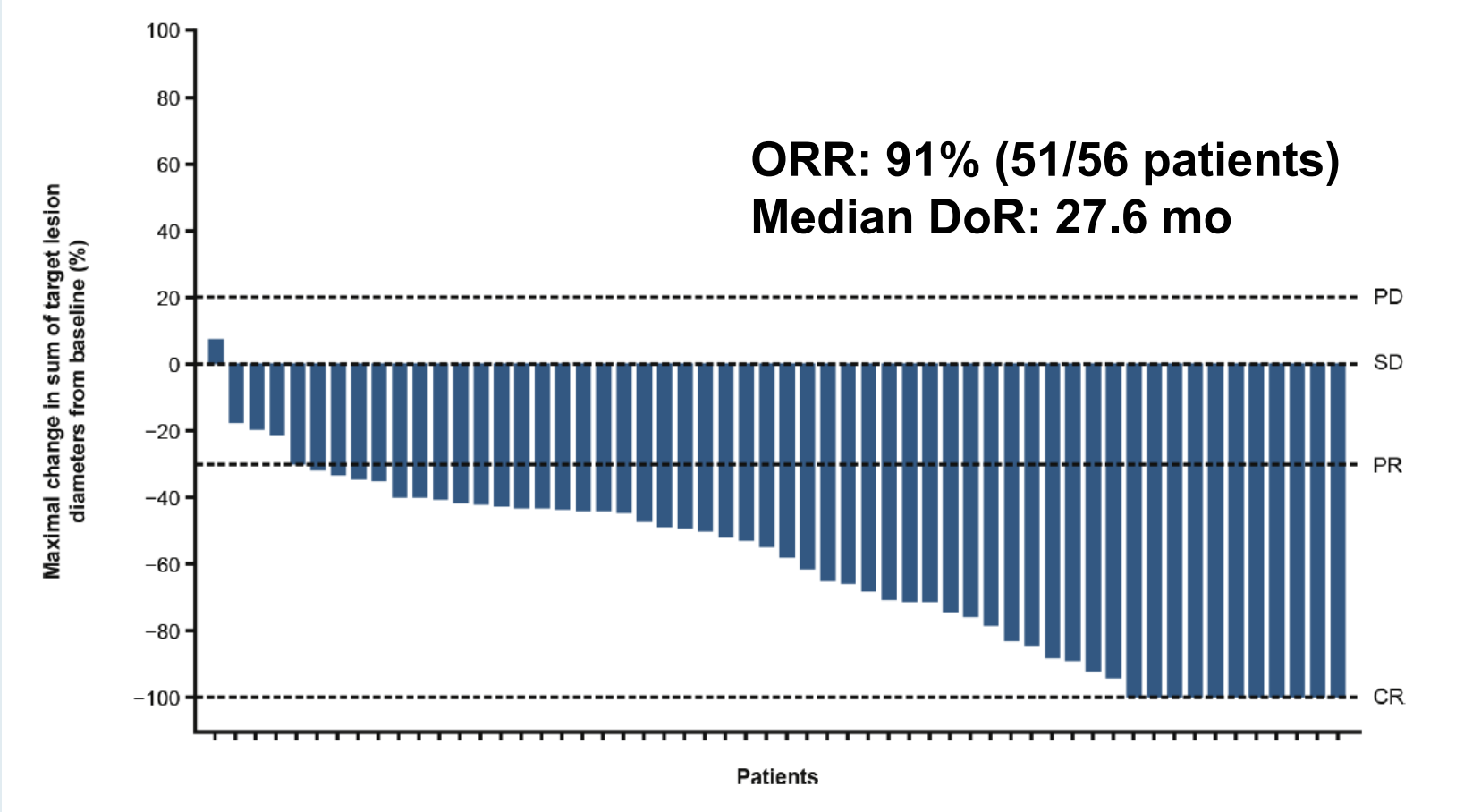
Heinrick M et al. Connective Tissue Oncology Society 2018;Abstract 3027631.

Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial

Robin L. Jones[a,*], César Serrano[b], Margaret von Mehren[c], Suzanne George[d], Michael C. Heinrich[e], Yoon-Koo Kang[f], Patrick Schöffski[g], Philippe A. Cassier[h], Olivier Mir[i], Sant P. Chawla[j], Ferry A.L.M. Eskens[k], Piotr Rutkowski[l], William D. Tap[m], Teresa Zhou[n], Maria Roche[n], Sebastian Bauer[o]

Eur J Cancer 2021;145:132-42.

NAVIGATOR: Long-Term Efficacy with Avapritinib in the PDGFRA D842V Population



- Median PFS was 34.0 mo and median OS was not reached

Jones RL et al. *Eur J Cancer* 2021;145:132-42.

NAVIGATOR: Long-Term Safety with Avapritinib in the PDGFRA D842V Population

Select adverse events, n (%)	PDGFRA D842V population (n = 56)	Safety population (N = 250)
Nausea	38 (68%)	161 (64%)
Anemia	37 (66%)	136 (54%)
Diarrhea	37 (66%)	112 (45%)
Memory impairment	23 (41%)	81 (32%)
Cognitive disorder	7 (13%)	28 (11%)
Intracranial bleeding	3 (5%)	7 (3%)

Jones RL et al. *Eur J Cancer* 2021;145:132-42.

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What I Tell My Patients: Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Part 1 of a 3-Part Complimentary NCPD Webinar Series
in Partnership with the 2023 ONS Congress

Urothelial Bladder Cancer

Thursday, May 25, 2023
5:00 PM – 6:00 PM ET

Faculty

Brenda Martone, MSN, NP-BC, AOCNP
Jonathan E Rosenberg, MD

Moderator

Neil Love, MD

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Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

CME and MOC credit information will be emailed to each participant within 5 business days.

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