Pexidartinib in Tenosynovial Giant Cell Tumors

US Food & Drug Administration

Oncologic Drugs Advisory Committee

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Introduction

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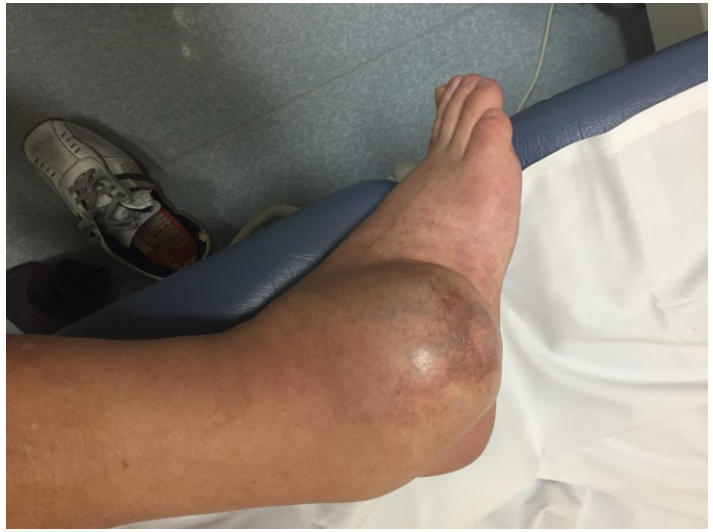
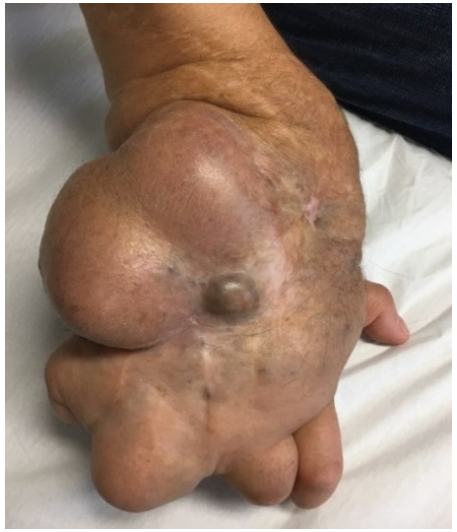
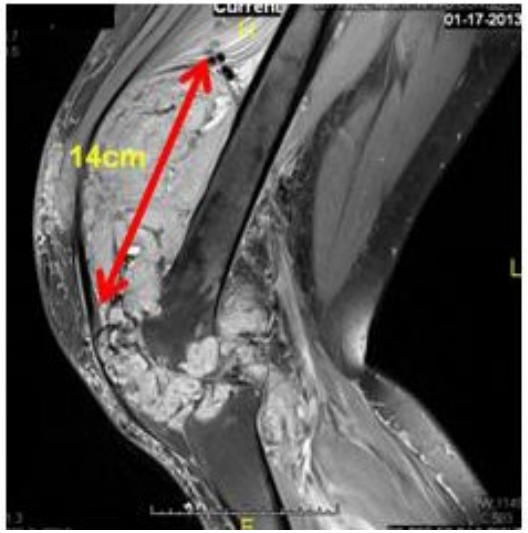
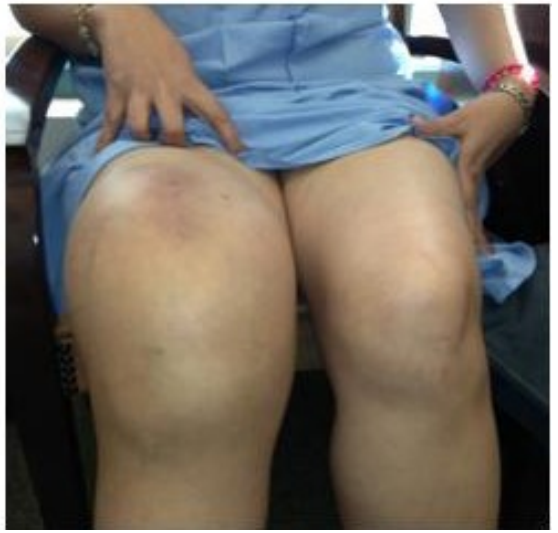
Daiichi Sankyo, Inc.

Tenosynovial Giant Cell Tumor (TGCT) Represents an Unmet Need

- Rare, non-malignant tumor of synovium affecting musculoskeletal joints
  - Symptoms: pain, stiffness, functional impairment
- Primary treatment: surgical resection
  - *Diffuse disease* not always amenable to surgery
  - No approved systemic therapies

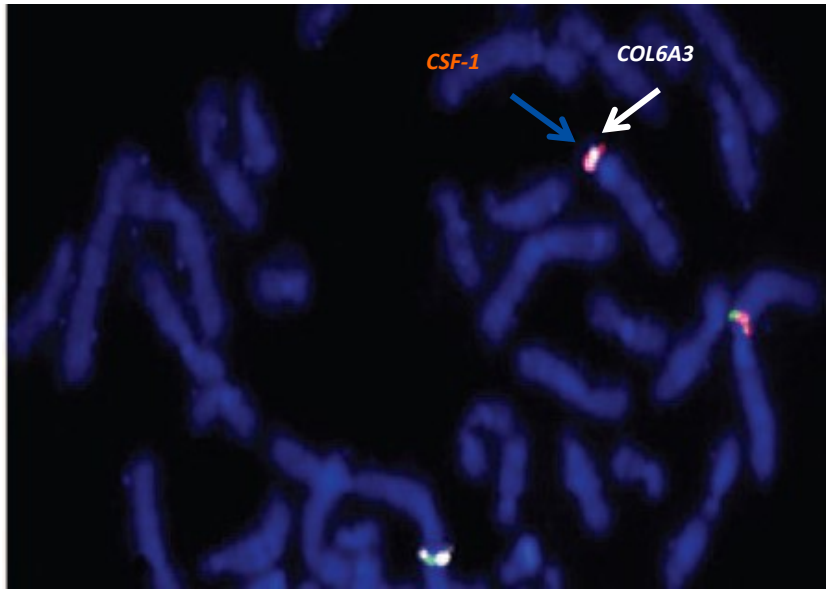






Ankle and knee MRI images courtesy of Tap WD, et al. ASCO 2018, abstract 11502. Hand image courtesy of Tap WD, et al. *Lancet*, in press. Knee image at far right reprinted from Tap WD, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med*. 2015;373:428-437. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

TGCT Is Driven by CSF-1 Overexpression

***CSF-1/COL6A3* translocations in TGCT specimen by FISH**



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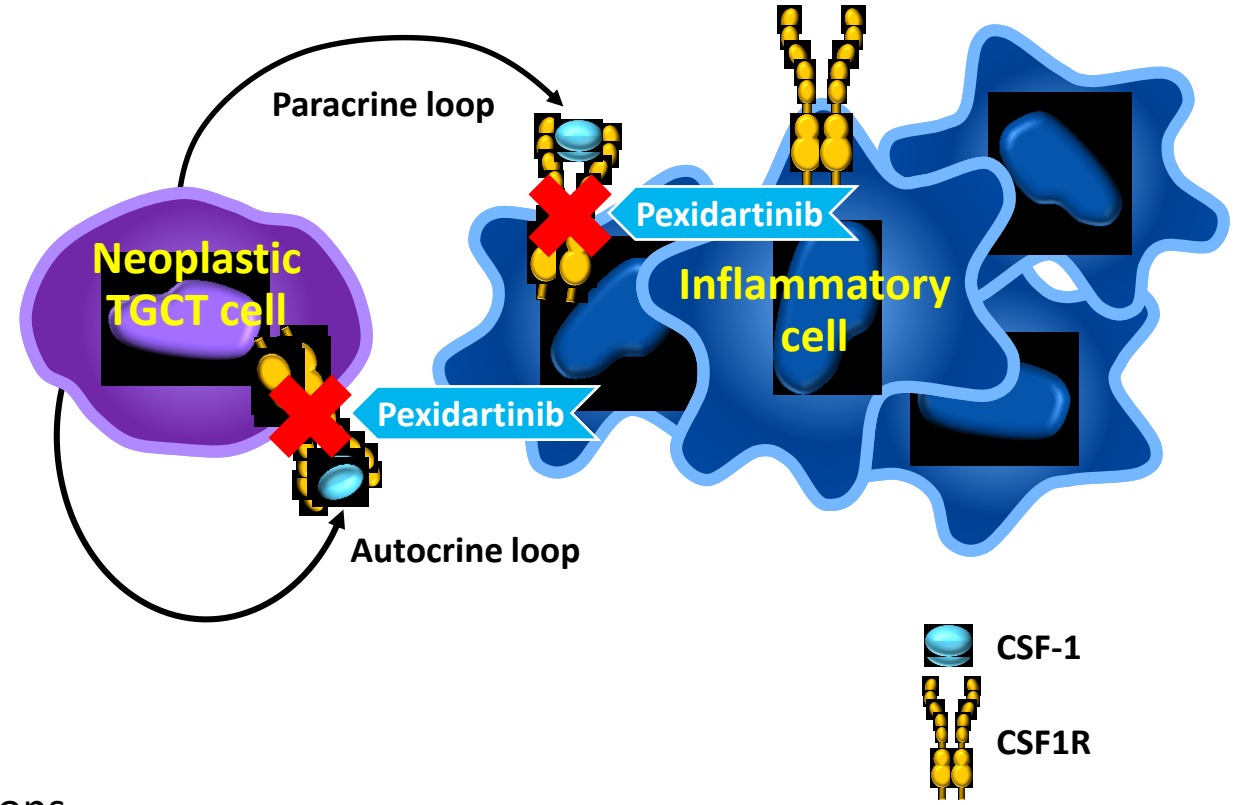
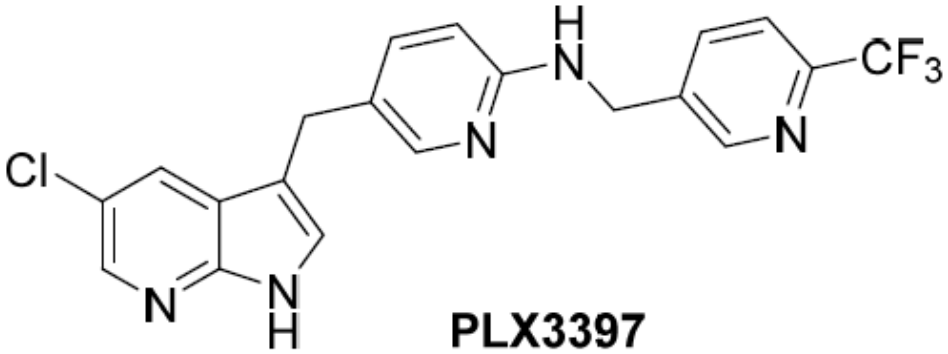


- Translocation results in CSF-1 overexpression
- Controls various monocyte/macrophage functions

CSF-1=colony stimulating factor-1; FISH=fluorescence in situ hybridization; R=receptor.

Staals EL, et al. *Eur J Cancer*. 2016;63:34-40; Mouchemore KA, et al. *Crit Rev Clin Lab Sci*. 2012;49(2):49-61; Pixley FJ, Stanley R. *Trends Cell Biol*. 2004;14(11):628-638; West RB, et al. *Proc Natl Acad Sci U S A*. 2006;103(3):690-695. Richman DM, et al. *J Clin Imaging Sci*. 2015;5:13.

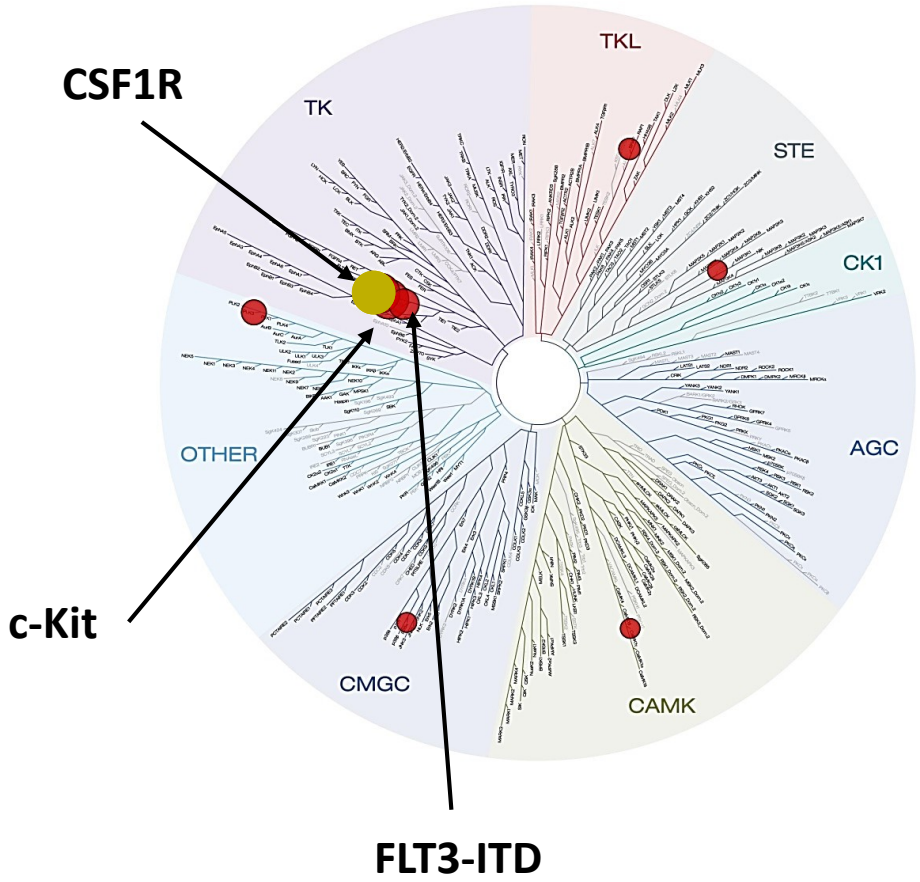
Pexidartinib: a Highly Selective, Small Molecule, CSF1R Inhibitor



PLX3397

Target	Pexidartinib IC_{50} in vitro
CSF1R	17 nM
c-Kit	12 nM

Target profile: CSF1R, c-Kit, FLT3-ITD



FLT3-ITD=FMS-like tyrosine kinase-internal tandem duplication; IC_{50}=50% inhibitory concentration.

Images reprinted from Tap WD, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med*. 2015;373:428-437.

Pexidartinib Clinical Pharmacology

- Orally bioavailable
- Terminal half-life = 27 hours
- Highly metabolized mainly by UGT1A4 and CYP3A4
  - Major metabolite has minimal pharmacologic activity
  - Dose reduction with strong UGT1A and CYP3A4 inhibitors
- Less than 40% change in exposure in subjects with renal impairment
- No effect of mild and moderate hepatic impairment on exposure
- Not associated with QTc prolongation

CYP3A4=cytochrome P450 3AH; QTc=corrected QT Interval; UGT1A4=UDP glucuronyltransferase 1A4

Comprehensive Clinical Development Program

Studies in TGCT

	PHASE 1 **Safety and Efficacy**	ENLIVEN Phase 3 **Efficacy and Safety**
DESIGN	First-in-human, open-label, 3+3 dose-escalation	Double-blinded, randomized
DOSE	200-1200 mg/day, 1000 mg/day	1000 mg/day x 2 wks 800 mg/day x 24 wks
TGCT	Extension Cohort n=39	Pexidartinib: n=61 Placebo: n=59 Crossover: n=30

TGCT exposure

- Median duration ~70 wk (0-5 yr)

Patients Treated with Pexidartinib

- TGCT: 130
- Monotherapy in cancer: 286
- Combination therapy in cancer: 352
- DDI study in TGCT or cancer: 30
- **Total: 798**

Proposed Indication and Dosing Regimen

Proposed Indication:

Pexidartinib is indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

- **Dosage Form**: 200 mg capsules
- **Dosing Regimen**: 400 mg (2 × 200 mg capsules) twice daily on empty stomach

What You Will Hear Today

Disease Background	• High unmet medical need in TGCT • No systemic anti-tumor agent approved • CSF-1 overexpression drives tumor biology
Efficacy	• Efficacy clearly established by robust tumor response rate and clinically meaningful improvement in function and disease symptoms, as measured by clinical and patient reported outcomes
Safety	• Safety is well-established and generally manageable • Serious cases of mixed or cholestatic hepatotoxicity have been observed • Risk mitigation measures, including a black box warning, medication guide, and REMS with patient registry, have been proposed
Benefit-Risk	• The benefit-risk profile is favorable in a TGCT population with severe morbidity or functional limitations, and which is not amenable to improvement with surgery

Agenda

Introduction	**Eric Richards, MS, MPH** Daiichi Sankyo, Inc.
Disease Background/Unmet Need	**Nicholas Bernthal, MD** David Geffen School of Medicine at UCLA
Clinical Development and Efficacy	**William D. Tap, MD** Memorial Sloan Kettering Cancer Center
General Safety	**Antoine Yver, MD, MSc** Daiichi Sankyo, Inc.
Hepatic Safety	**Laurie DeLeve, MD, PhD** University of Southern California Keck School of Medicine
Risk Evaluation and Mitigation Strategy	**Eric Richards, MS, MPH** Daiichi Sankyo, Inc.
Clinical Perspective/Benefit-Risk	**William D. Tap, MD**

List of Consultants

Ralph D'Agostino, Jr., PhD, FASA
Professor of Biostatistics and Data Science
Wake Forest University School of Medicine

James Lewis, MD, FACP, FACG, AGAF, FAASLD
Professor of Medicine
Director of Hepatology, Division of Gastroenterology
Georgetown University Hospital

TGCT Disease Background and Treatment Landscape

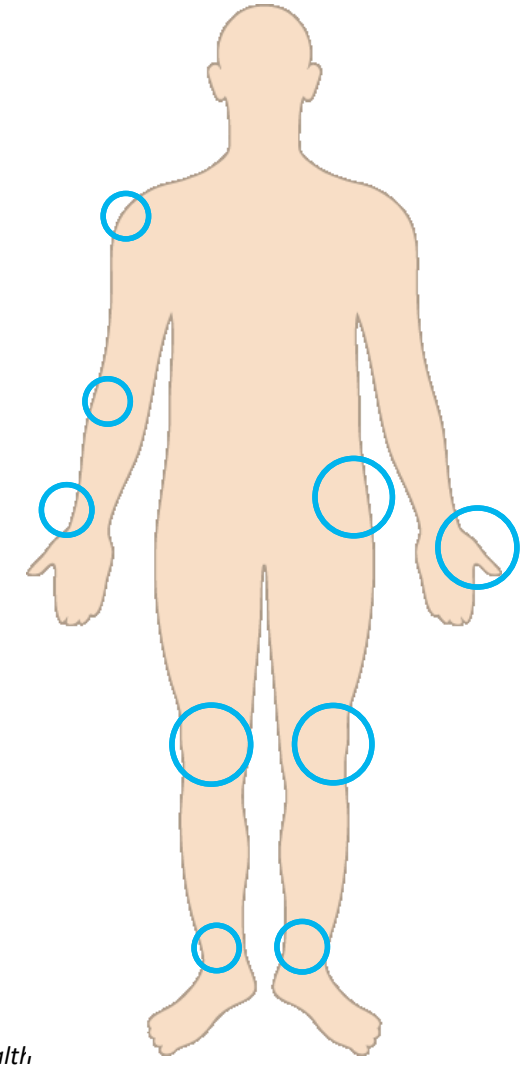
Nicholas Bernthal, MD

Chief, Division of Musculoskeletal Oncology
Department of Orthopaedic Surgery
David Geffen School of Medicine at UCLA

TGCT Affects Young, Otherwise Healthy People

TGCT symptoms include

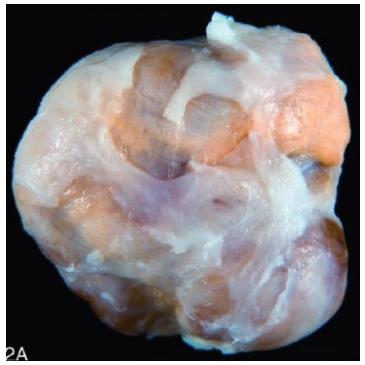
- Pain (analgesic/opioids use is common)
- Swelling
- Stiffness
- Joint instability
- Decreased range of motion (ROM)

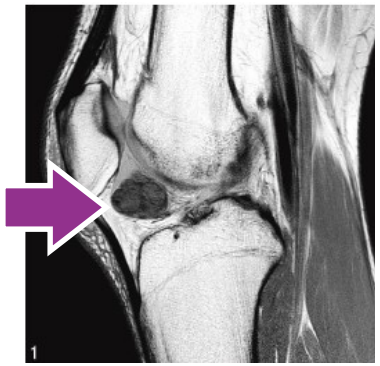


de Saint Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM, Bridge J, Hogendoorn P, Mertens F, eds. *World Health Organization Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon, France. IARC Press; 2013:102-103; Ottaviani S, et al. *Semin Arthritis Rheum*. 2011;40(6):539-546; Botez P, et al. *Int Orthop*. 2013;37(4):729-733; Gelhorn HL, et al. *Clin Ther*. 2016;38(4):778-793; Mastboom MJL, et al. *Interact J Med Res*. 2018;7(1):e4.

TGCT Represents Two Distinct Clinical Presentations[a-c]

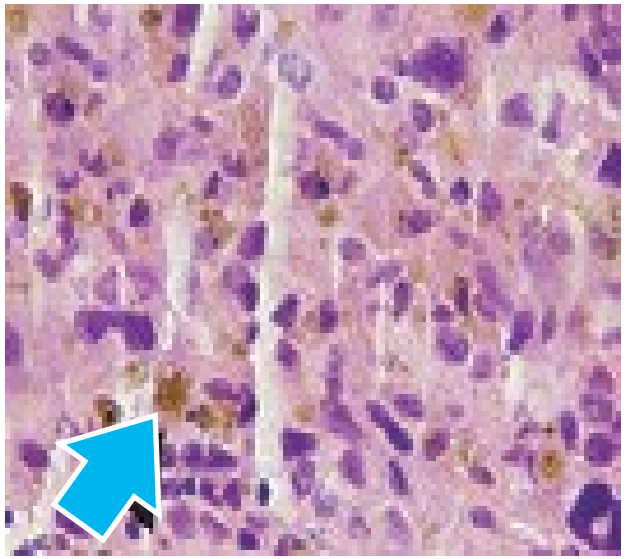
Localized-TGCT





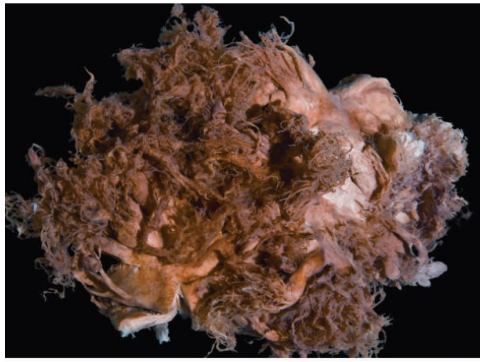
Reprinted from Lucas DR.[e]

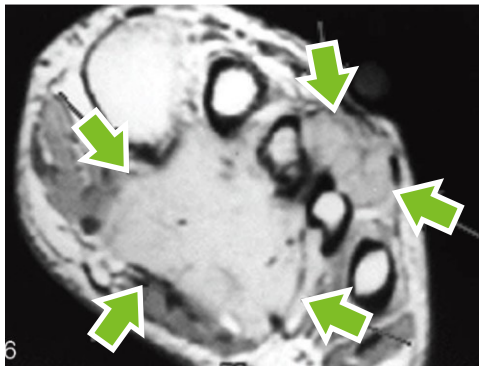
Hemosiderin deposition



Reprinted from Richman DL, et al.[d]

Diffuse-TGCT



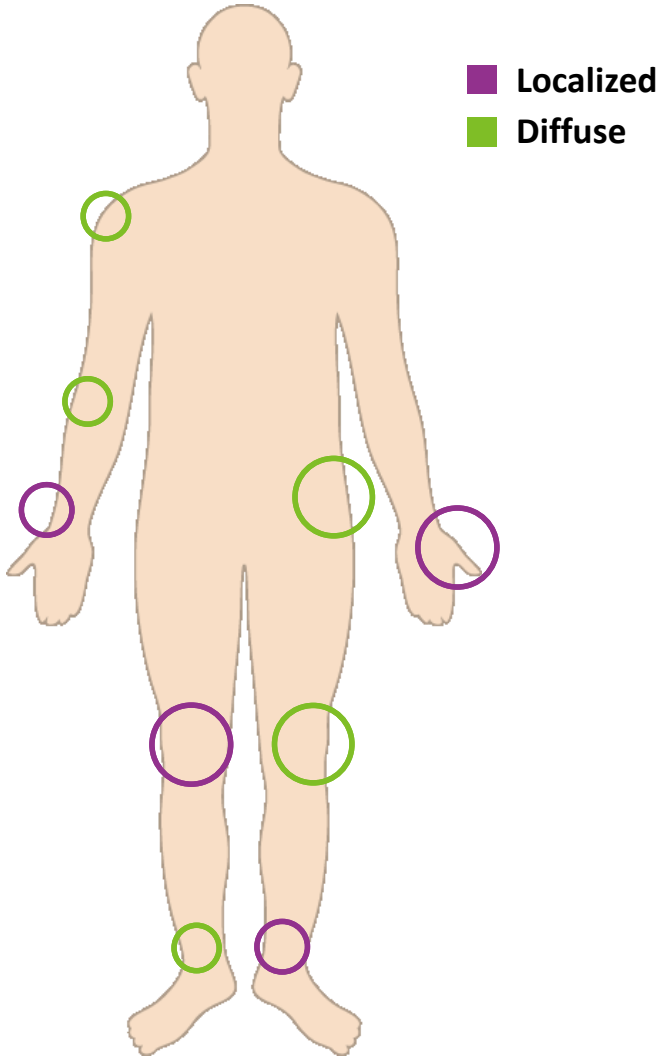


Reprinted from Lucas DR.[e]

[a] de Saint Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM, Bridge J, Hogendoorn P, Mertens F, eds. *World Health Organization Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon, France. IARC Press; 2013:102-103;
[b] Cheng XG, et al. *Clin Rheumatol*. 2004;23(1):31-34; [c] Brahmi M, et al. *Curr Treat Options Oncol*. 2016;17(2):10;
[d] Richman DM, et al. *J Clin Imaging Sci*. 2015;5:13; [e] Lucas DR. *Arch Pathol Lab Med*. 2012;136(8):901-906.

Most TGCT Patients Present with Localized Disease

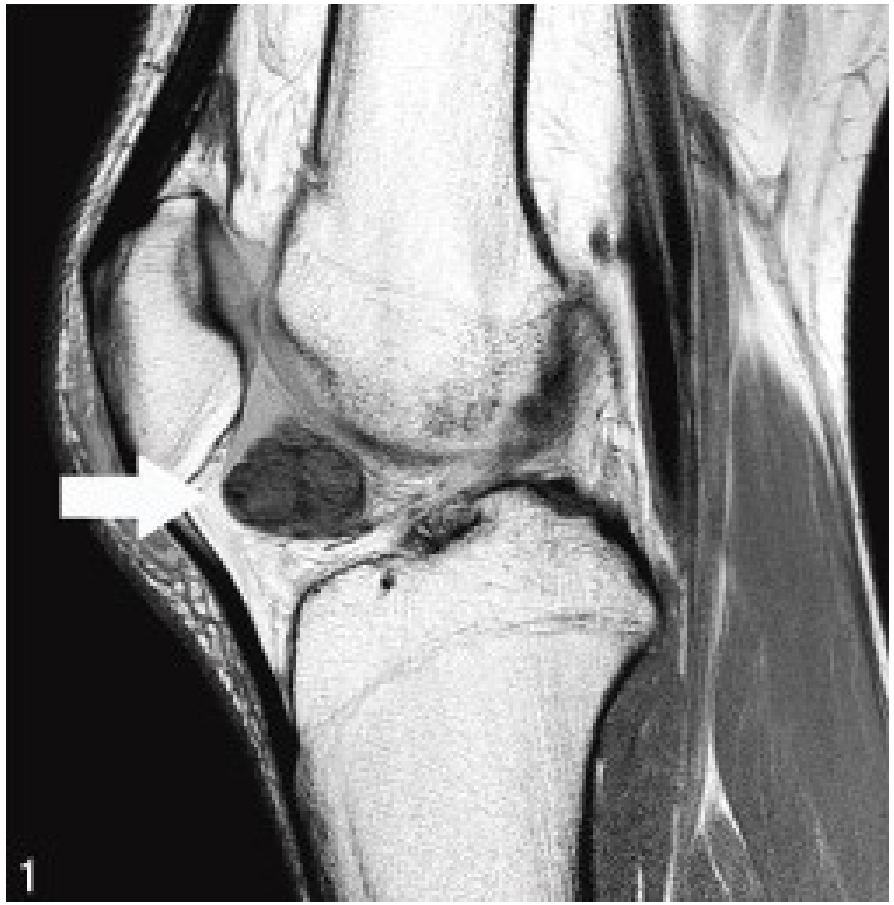
TGCT type	2019 US incidence
Localized ~90% of TGCT cases	~15,000 new cases
Diffuse ~10% of TGCT cases	~1500 new cases



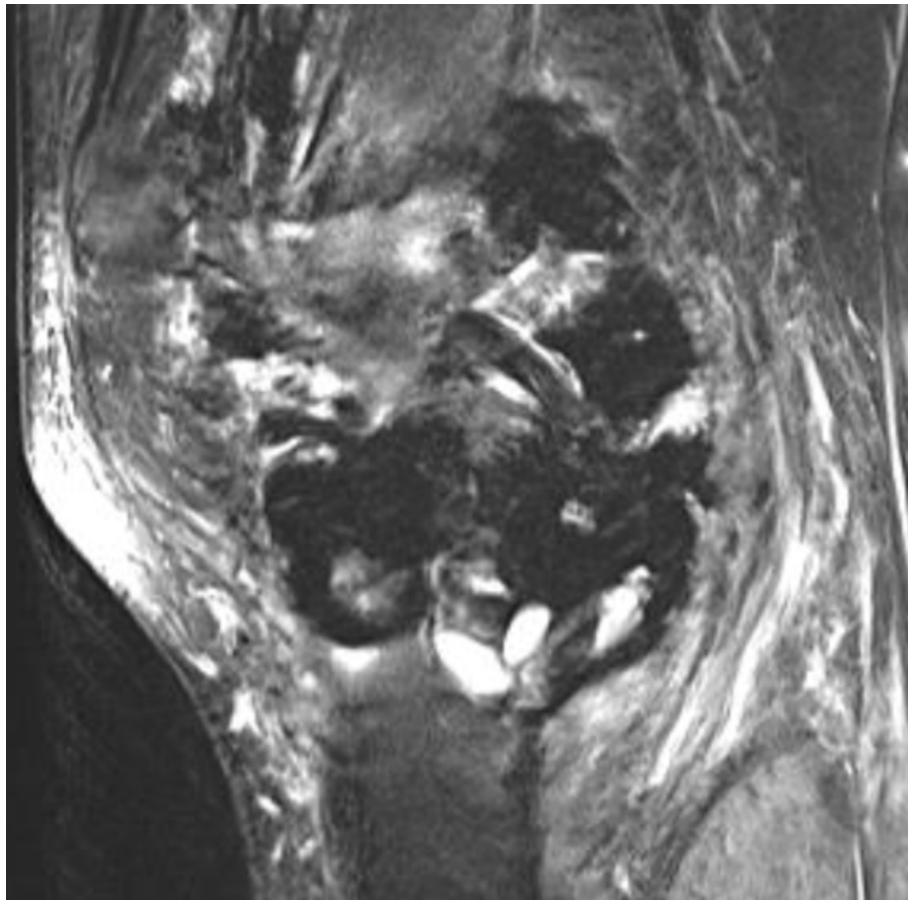
Census Bureau: Projected Population by Single Year of Age, Sex, Race, and Hispanic Origin for the United States: 2016 to 2060; Myers BW, Masi AT. *Medicine (Baltimore)*. 1980;59(3):223-238; Mastboom MJL, et al. *Acta Orthop*. 2017;88(6):688-694.

Localized and Diffuse Tumor Presentation

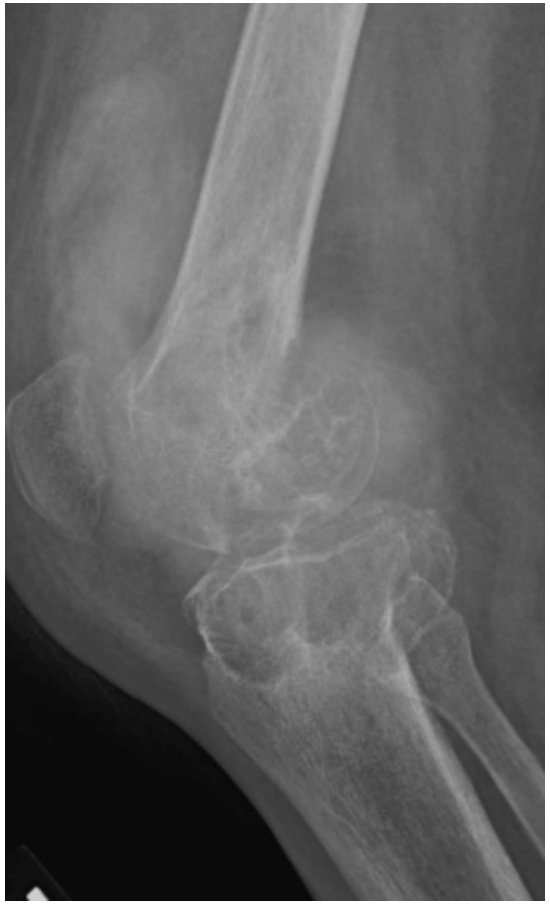
Localized



Diffuse

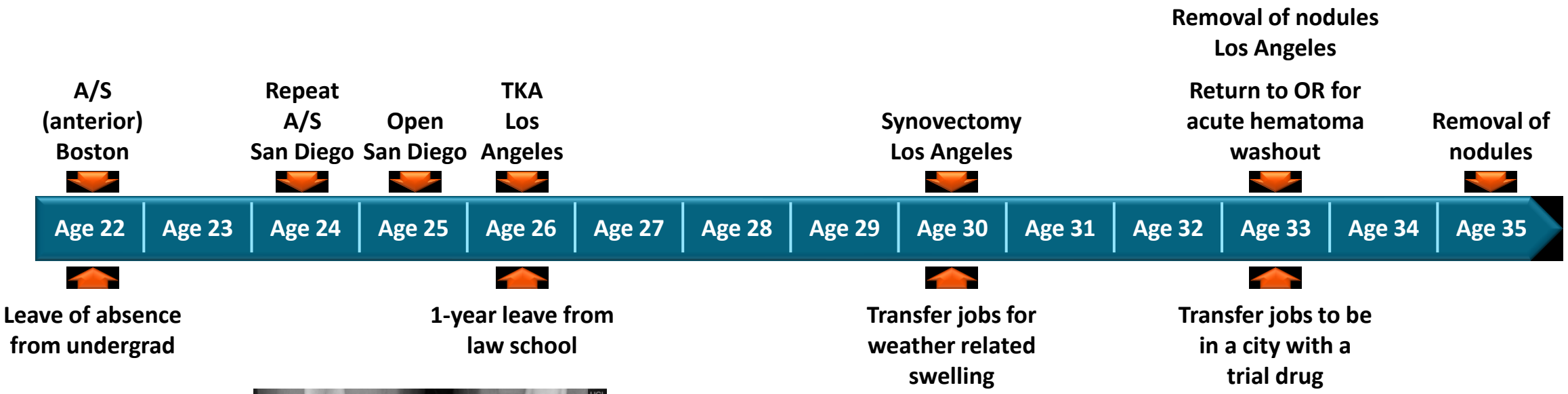


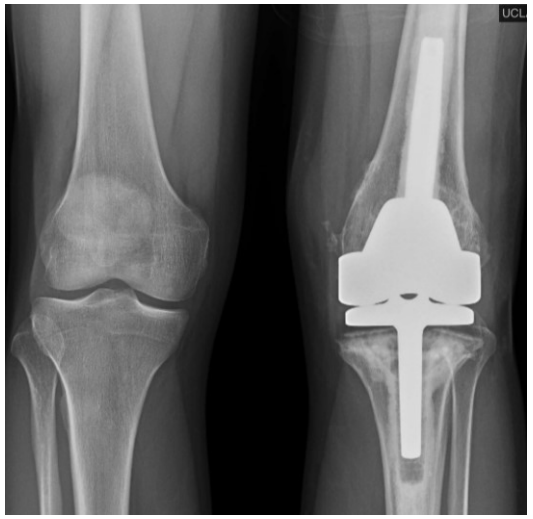
Diffuse



Left image Lucas DR. *Arch Pathol Lab Med*. 2012;136(8):901-906. Center and right images courtesy of Nicholas Bernthal, MD.

Diffuse TGCT: Typical Patient Journey



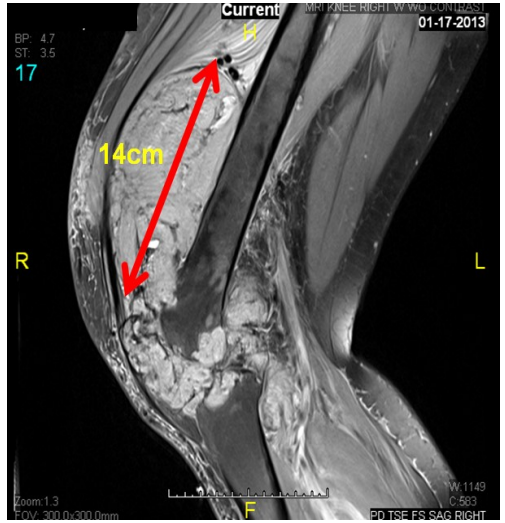


- Over 750 “days off”
- Intermittent physical therapy for 18 years
- Dozens of braces, compression socks, ice machines

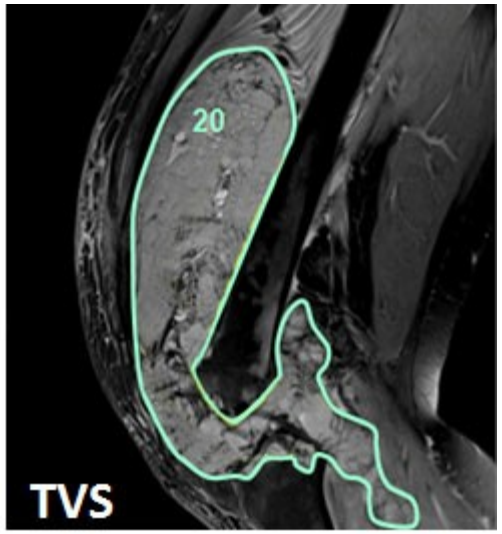
A/S=arthroscopic surgery; TKA=total knee arthroplasty; OR=operating room. Images courtesy of Nicholas Bernthal, MD.

Radiographic Assessment of Diffuse Disease

- Highly irregular tumor shape
- Does not grow circumferentially



- TVS calculates tumor volume as percentage of the entire synovium
  - Partial response: ≥50% ↓ TVS vs baseline
  - Progressive disease: ≥30% ↑ TVS vs nadir

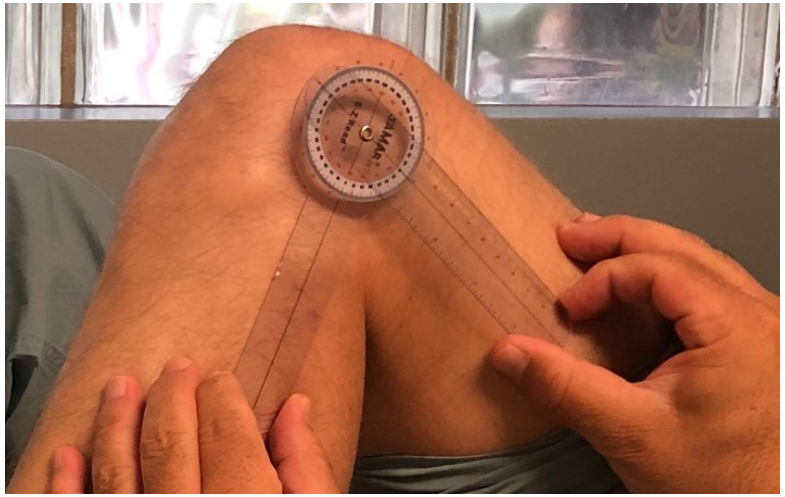


TVS = tumor volume score.

Bottom image from Tap WD, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med*. 2015;373:428-437.

Assessing Clinical Impact of Disease

- Range of Motion (ROM)
  - Objectively measured by goniometer
  - Clinical impact is joint specific
- Knee specific[a]
  - Level walking (~65°)
  - Up and down stairs (~80°)
  - In and out of chair (~90°)
  - Most activities of daily living (~110°)



Images courtesy of Nicholas Bernthal, MD.

[a] Rowe PJ, et al. *Gait Posture.* 2000; 12(2):143-155.

Assessing Impact of TGCT With PROMIS-Physical Function

- Patient-Reported Outcomes Measurement Information System (PROMIS®)-Physical Function
  - Normalized against the US population
  - 50 represents average physical function
  - ~2-point change has been reported as a minimally important difference in RA[a]

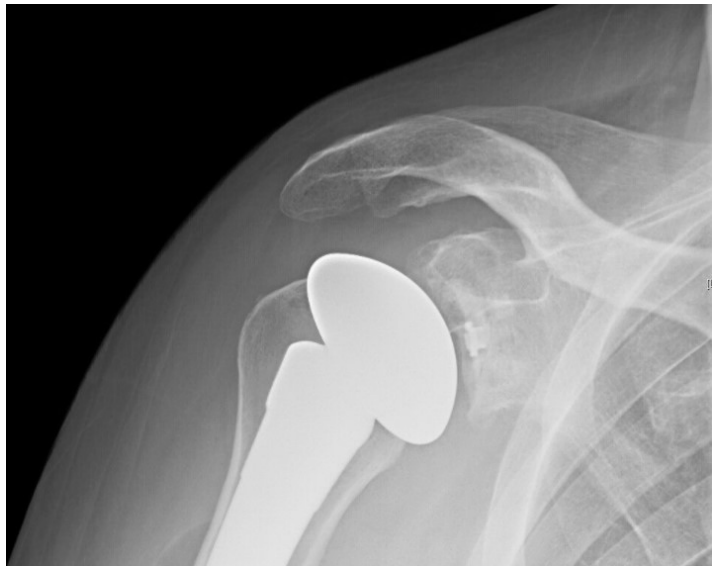
Examples of Lower Extremity Questions (n=13)

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

[a] Hays RD, et al. *Ann Rheum Dis*. 2015;74(1):104-107.
Gelhorn HL, et al. *J Patient Rep Outcomes*. 2019;3(1):6.

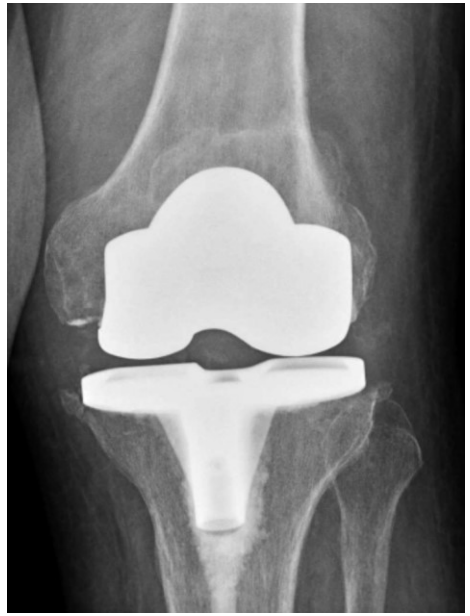
Contextualizing PROMIS-PF

Total Shoulder Replacement[a]



Procedure	Pre-op PROMIS-PF	Post-op PROMIS-PF	Change
Shoulder	40.4	44.1	+3.7

Total Knee Replacement[b]

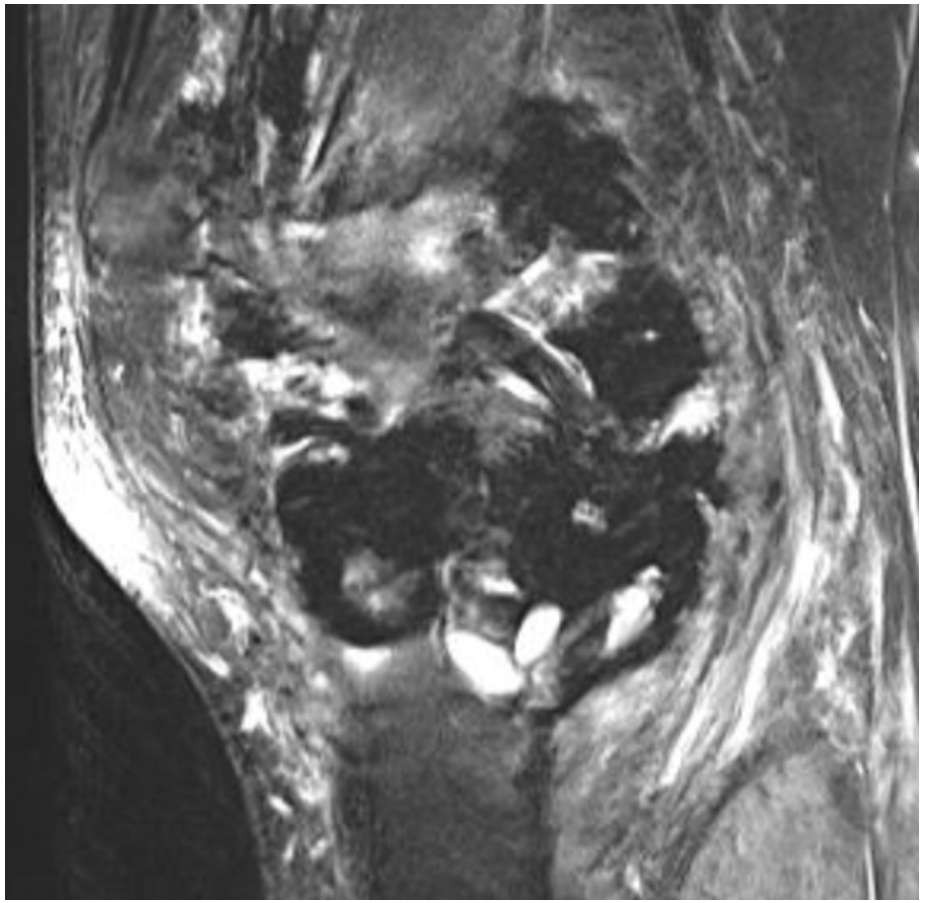


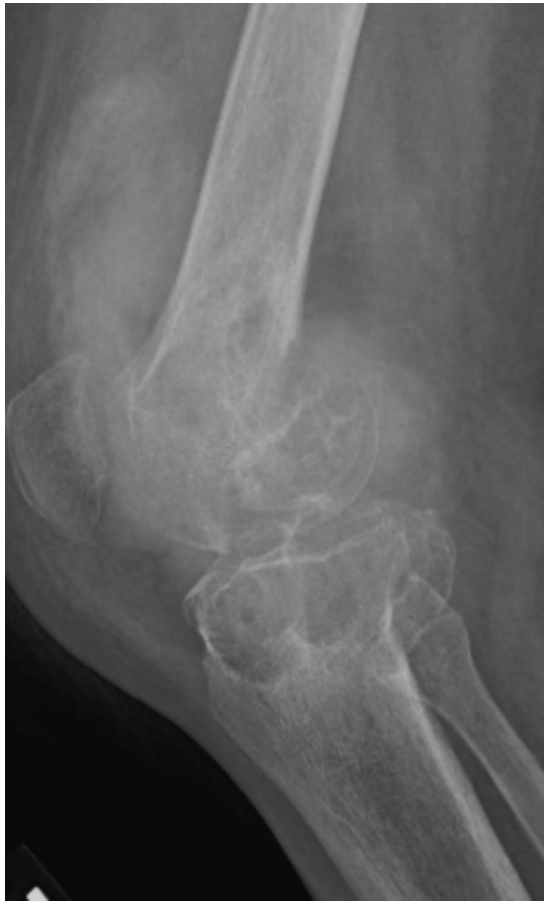
Procedure	Pre-op PROMIS-PF	Post-op PROMIS-PF	Change
Knee	38.7	47.3	+8.6

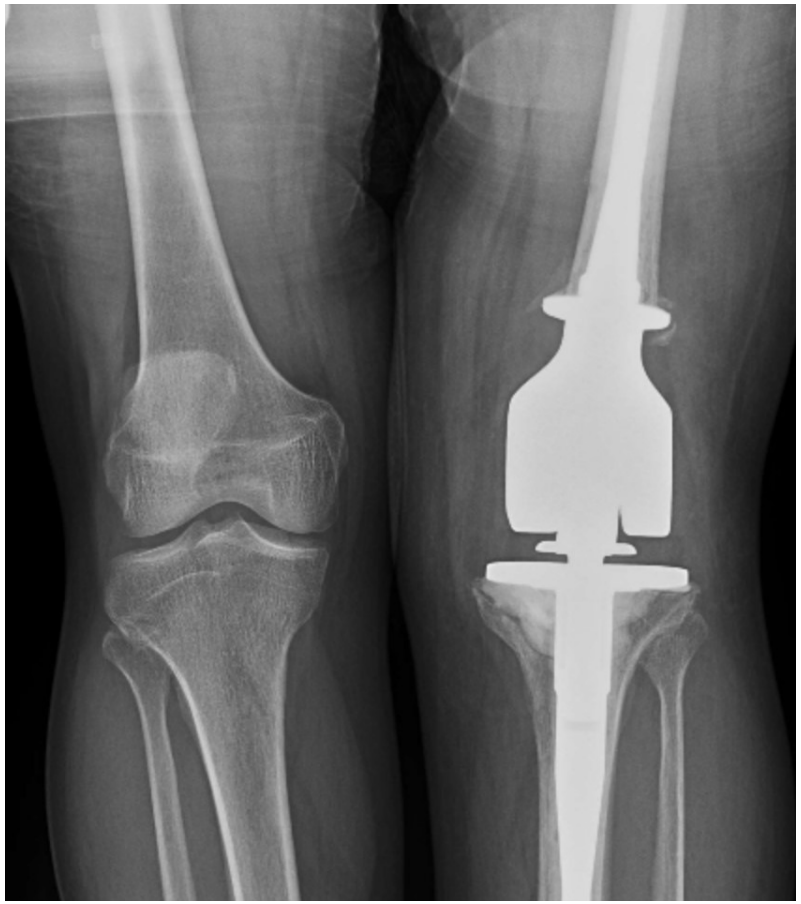
Images courtesy of Nicholas Bernthal, MD.

[a]Chen RE, et al. *J Shoulder Elbow Surg*. 2019;28(3):547-554.
[b]Kagan R, et al. *J Arthroplasty*. 2018;33(8):2471-2474.

Diffuse TGCT: Surgery Often Indicated, But Rarely Achieves Cure

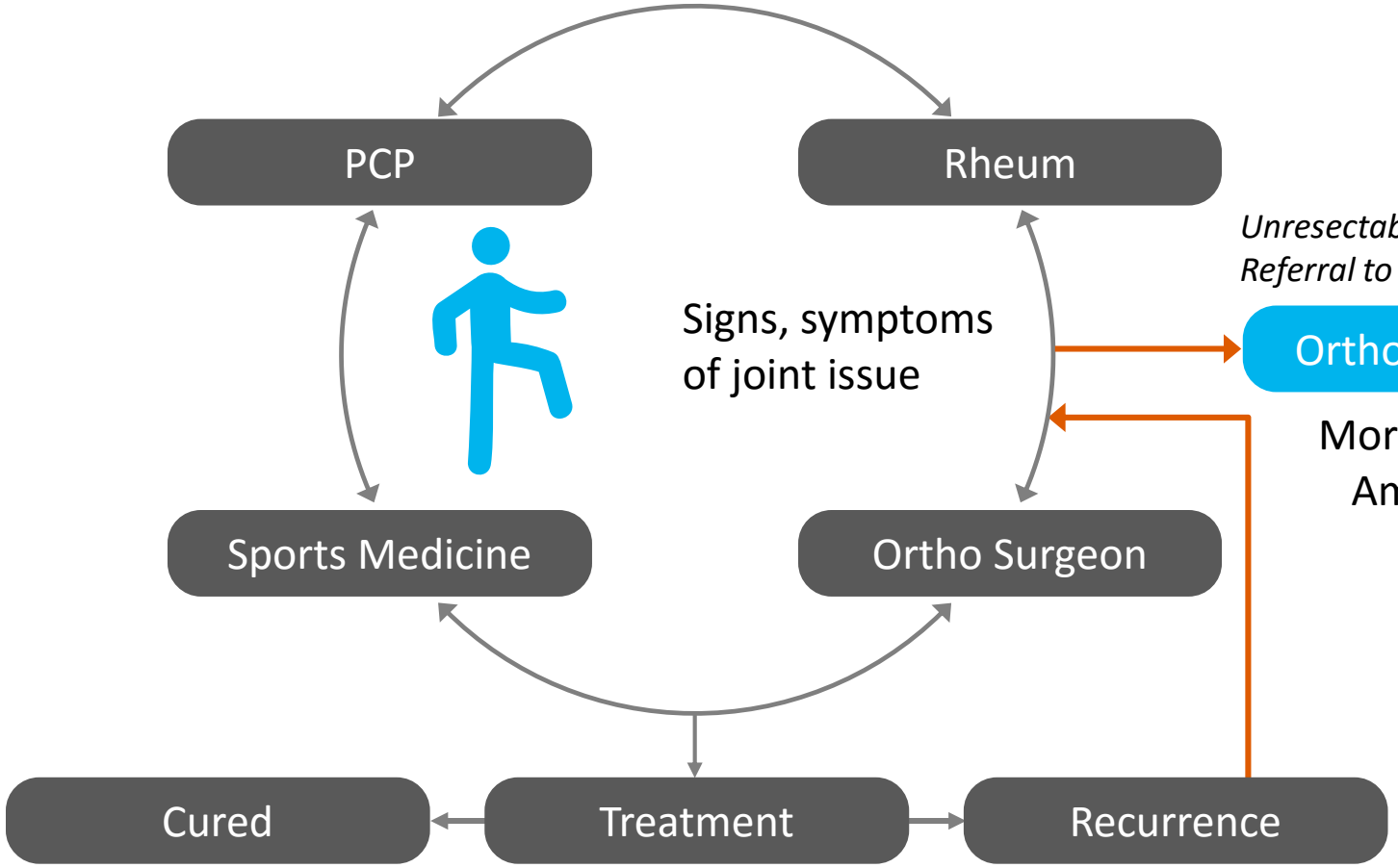






Images courtesy of Nicholas Bernthal, MD.

Patient Journey



Unresectable/Complicated cases
Referral to center of excellence

Ortho Oncologist

Morbid surgery
Amputation

Sarcoma Oncologist

Pexidartinib

TGCT Treatment

- Arthroscopic surgery
- Supportive care (pain management, physical therapy)

Development Program and Efficacy

William D. Tap, MD

Sarcoma Medical Oncology Service Chief
Memorial Sloan Kettering Cancer Center

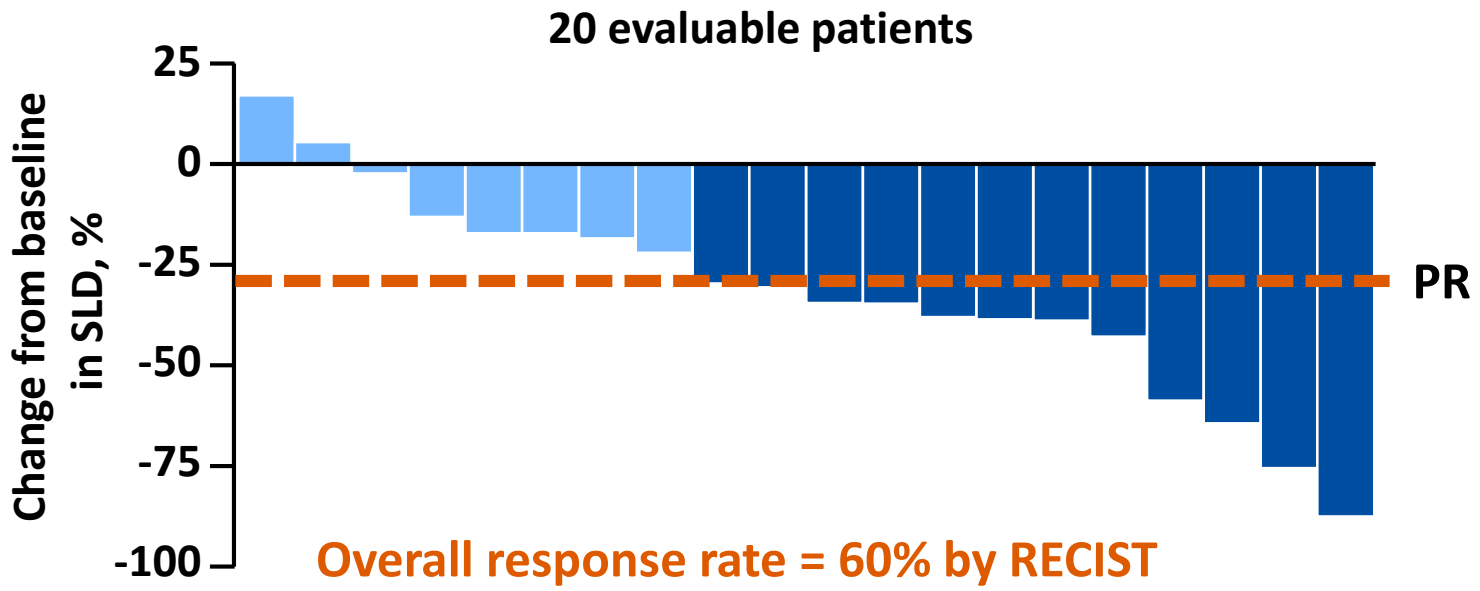
Pexidartinib Clinical Program in 159 TGCT Patients

Efficacy

Study	Enrolled	Pexidartinib treated
Phase 1 Extension TGCT cohort	39	39
Phase 3 ENLIVEN	120	61 Randomized 30 Crossed over
Total	**159**	**130**

Interim Results: Phase 1 Extension Study

- Dose escalation demonstrated MTD of 1000 mg/day
  - DLTs at 1200 mg/day (AST increased, anemia, neutropenia, and syncope)



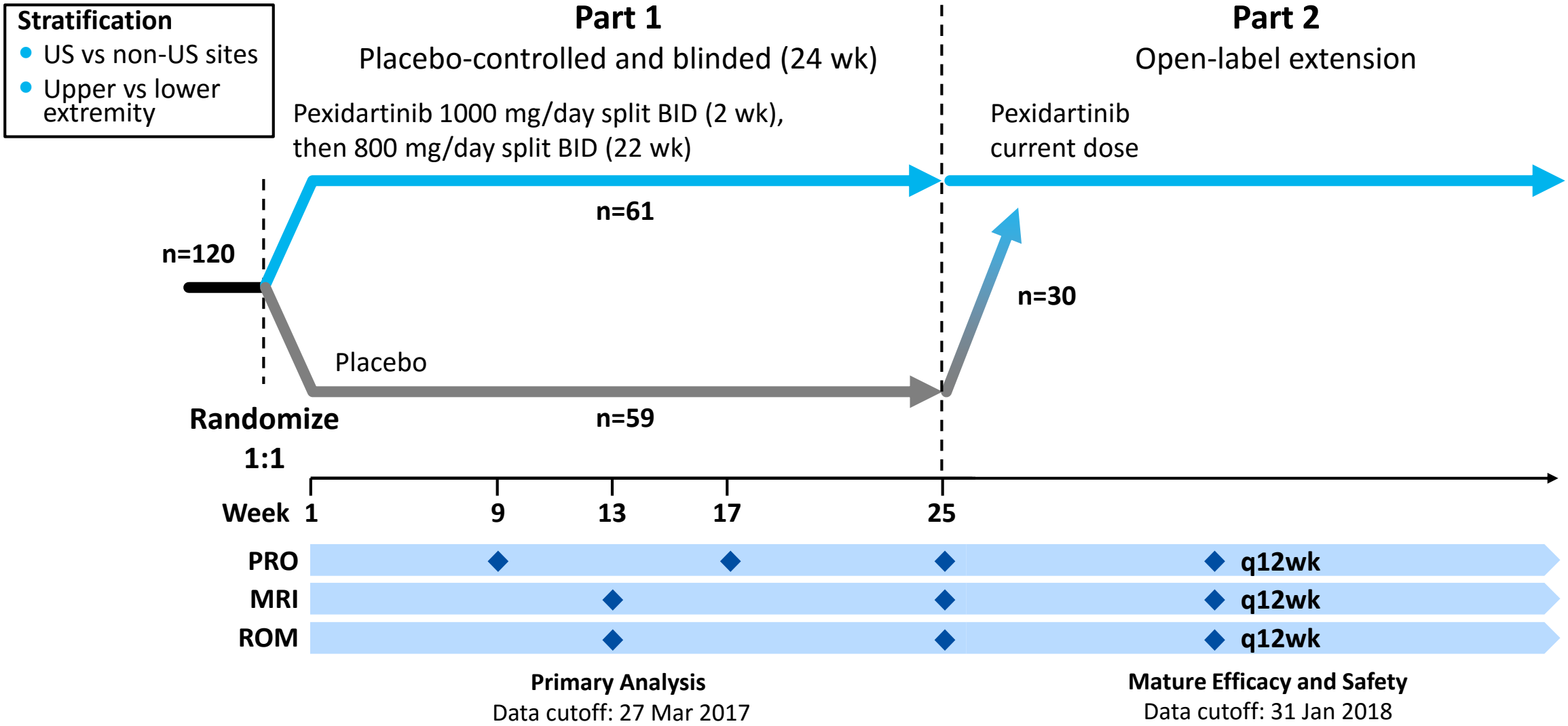
Key Inclusion Criteria

ENLIVEN

- Surgical resection would be associated with potentially worsening functional limitation or severe morbidity
- Histologically confirmed, advanced, symptomatic TGCT
- Measurable disease ≥2 cm by RECIST v1.1

Randomized, Double-Blind, Phase 3 Study Design

ENLIVEN



PRO=Patient-reported outcomes; q=every.

Study Endpoints
ENLIVEN

Primary endpoint: ORR at Week 25 based on blinded, central review of MRI (RECIST v1.1)

Secondary endpoint hierarchy	Definition
Range of motion (ROM)	Percentage of normal reference as measured by goniometer
Overall response rate by TVS	By blinded central review
PROMIS Physical Function scale	Patient-Reported Outcomes Measurement Information System-Physical Function (ability to perform activities of daily living)
Worst stiffness	Patient reported on scale 0 (none) to 10
Brief Pain Inventory worst pain response	≥30% improvement on scale 0 (none) to 10 (accounting for analgesic use)
Duration of response (RECIST/TVS)	

Statistical Design

ENLIVEN

- 90% power to detect a 25% difference in response rates assuming 35% active response and 10% placebo response
  - Sample size of 126 patients
  - 2-sided alpha = 0.05 significance level by Fisher's exact test

Study Conduct Changes (With FDA Consultation)
ENLIVEN

- DMC reviewed unblinded safety data following 2 cases of potential cholestatic hepatotoxicity in ENLIVEN
- Study changes implemented Sept 30, 2016
  - Accrual stopped (n=120 vs target of 126)
  - Patients on pexidartinib could continue under re-consent at investigator's discretion
  - Crossover from placebo to pexidartinib (at end of Part 1) was stopped
    - 30 patients had crossed over to 800 mg/day

DMC=Data Monitoring Committee

Patient Disposition

ENLIVEN Part 1 Randomized

	Patients, n (%)	
	Pexidartinib n=61	Placebo n=59
Received study drug	61 (100)	59 (100)
Early discontinuation and primary reason	9 (15)	11 (19)
Adverse event	8 (13)	0
Disease progression	0	1 (2)
Withdrawal of consent	1 (2)	6 (10)
Investigator decision	0	3 (5)
Patient noncompliance	0	1 (2)

Patient Demographics and Baseline Characteristics

ENLIVEN Part 1 Randomized

Parameter	Pexidartinib n=61	Placebo n=59
Median age, yr (range)	44 (22-75)	45 (18-79)
Sex, n (%)		
Male	26 (43)	23 (39)
Female	35 (57)	36 (61)
Disease location, n (%)		
Knee	34 (56)	39 (66)
Ankle	14 (23)	7 (12)
Hip	6 (10)	7 (12)
Other[a]	7 (11)	6 (10)

[a] Included wrist, foot, shoulder, spine, elbow, and finger.

Baseline Treatment History and Surgical Assessment

ENLIVEN Part 1 Randomized

Parameter		Patients, n (%) Pexidartinib n=61	Placebo n=59
Prior surgeries for TGCT	0	29 (48)	28 (47)
	1-2	20 (33)	24 (41)
	≥ 3	12 (20)	7 (12)
Prior systemic therapy	None	53 (86)	56 (95)
	Imatinib (off-label)	7 (12)	3 (5)
Prior analgesic use		53 (87)	46 (78)
		n=58	n=56
Predicted probability of complete resection	None	37 (66.1)	37 (63.8)
	Low	18 (31.0)	13 (23.2)
	Medium	2 (3.4)	3 (5.4)
	High	1 (1.7)	3 (5.4)
Predicted postoperative morbidity	Mild	2 (3.4)	1 (1.8)
	Moderate	24 (41.4)	25 (44.6)
	Severe	32 (55.2)	30 (53.6)

Baseline Functional and Disease Symptoms

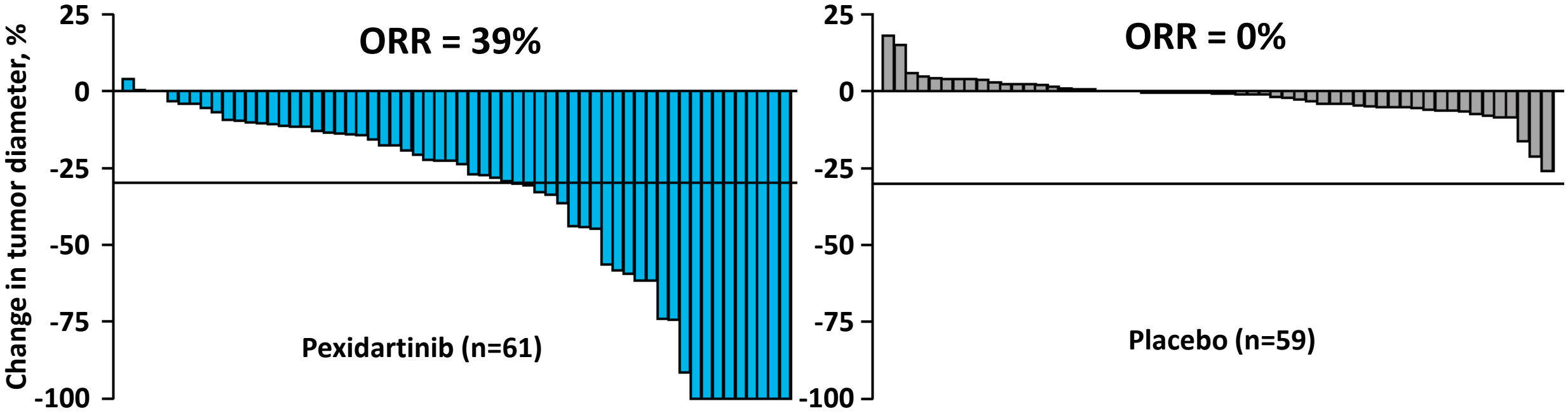
ENLIVEN Part 1 Randomized

Assessment	Mean (SD)	
	Pexidartinib n=61	Placebo n=59
Range of motion (% of reference)	62.5 (24.8)	62.9 (21.8)
PROMIS Physical Function score (0 to 100; 50 = normal)	37.5 (4.9)	38.9 (6.1)
Worst stiffness (0 to 10)	5.6 (1.7)	5.9 (1.9)
Worst pain (0 to 10)	5.6 (1.6)	5.7 (2.2)

Primary Endpoint Met: ORR at Week 25 (Blinded, Central Review)

ENLIVEN Part 1 Randomized

Treatment, n (%)	Complete Response	Partial Response	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]



Secondary Efficacy Endpoints at Week 25

ENLIVEN Part 1 Randomized

Endpoint in Sequential Hierarchy	Pre-Tx Mean	Pexidartinib	Placebo	P value (2-sided)
Range of motion % normal reference	62.7%	+15.1%	+6.2%	0.0043
Tumor volume score Response rate	13.5	55.7%	0	<0.0001
PROMIS Physical Function All population mean with normal average=50	38.2	+4.1	–0.9	0.0019
Worst stiffness Scale of 0 (normal) – 10	5.8	–2.5	–0.3	<0.0001
Worst pain response Response ≥30% improvement from baseline on scale of 0 (normal) – 10	5.7	31.1%	15.3%	0.052

Missing PRO Data at Week 25

ENLIVEN Part 1 Randomized

- Primary reasons
  - Discontinued early (17%)
  - Protocol adherence or technical issues (24%)
- Secondary endpoint hierarchy re-ordered to mitigate statistical impact
  - FDA consulted
  - By protocol amendment
  - Before database lock and unblinding
- Analyses specified before unblinding to assess impact of missing data

PRO Sensitivity Analyses[a]

ENLIVEN Randomized Part 1; Valid Baseline and ≥1 Post-BL Assessment

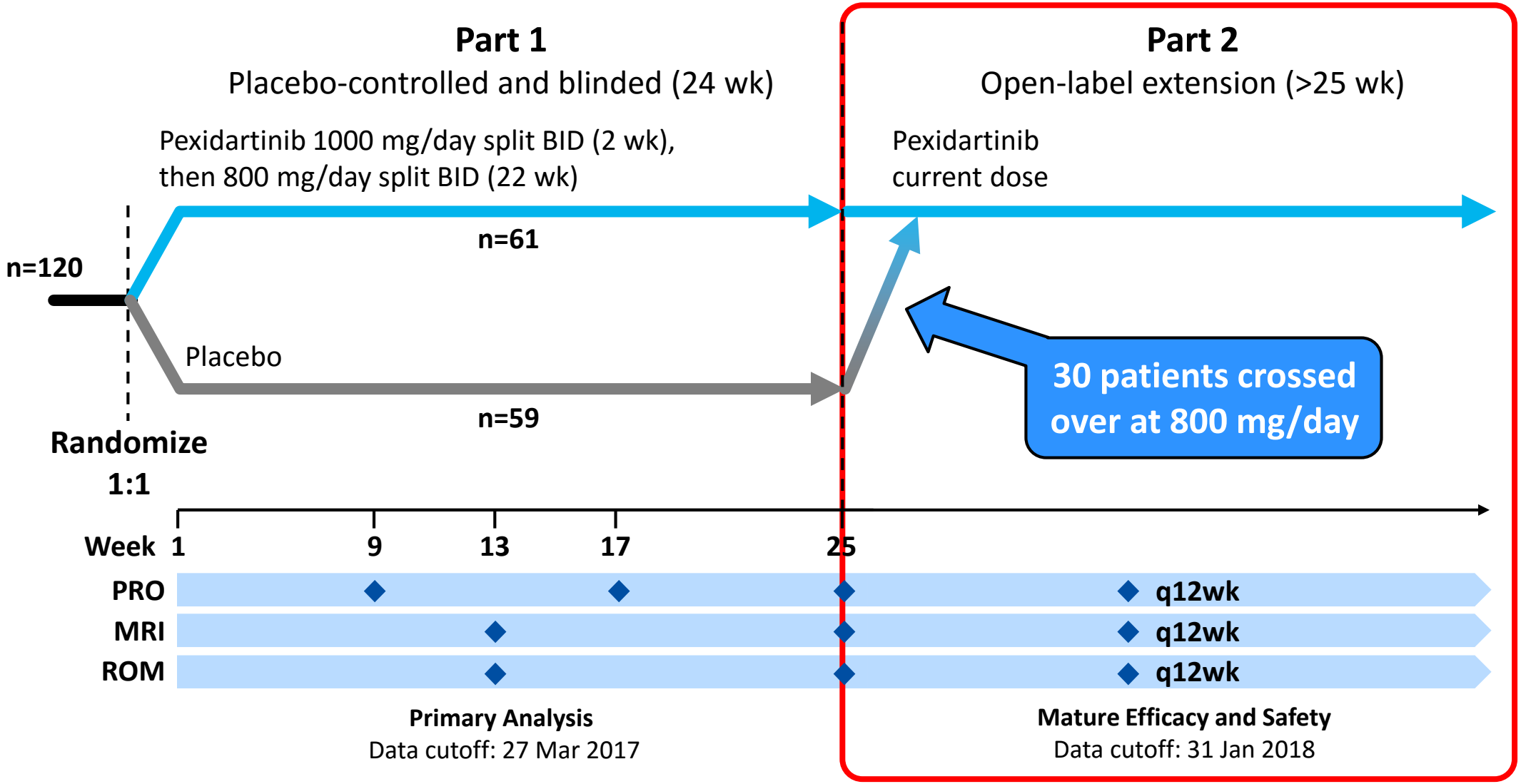
Endpoint	n	LS Mean Change		P value
		Pexidartinib	Placebo	
Range of motion	112	15.1%	6.2%	0.0043
PROMIS Physical Function	100	4.1	−0.9	0.0019
Worst stiffness	96	−2.5	−0.3	<0.0001
BPI worst pain	96	−2.5	−0.6	<0.0001

BPI=Brief Pain Inventory.

[a] Based on mixed model repeated measures (MMRM).

Part 2 Extension: Mature Results

ENLIVEN



Consistent Efficacy Across Pexidartinib-Treated Cohorts

Data Cutoff (Jan 31 2018)

Three TGCT cohorts

1. ENLIVEN: Pexidartinib arm Parts 1 and 2 (n=61)
2. ENLIVEN: Crossover to pexidartinib (800 mg/day) for Part 2 (n=30)
3. Phase 1: TGCT extension cohort (n=39)

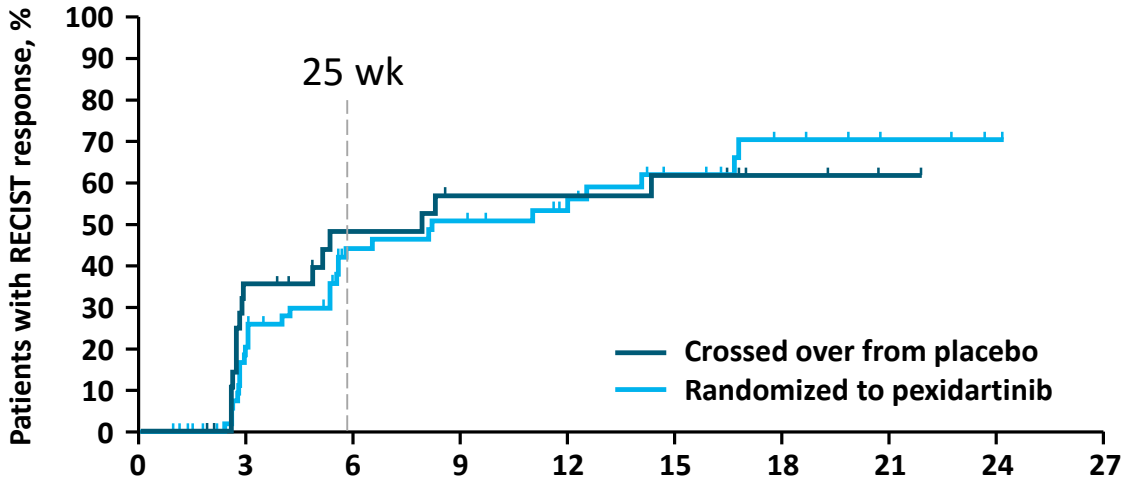
	ENLIVEN Randomized n=61	ENLIVEN Crossover n=30	Phase 1 TGCT cohort n=39	Overall n=130
Median time from first dose to data cutoff, mo (range)	22 (16-31)	19 (16-27)	49 (32-67)	**23** (16-67)
Median treatment duration, mo (range)	16	17	17	**17** (1-60+)
Best overall response rate (CR or PR) (95% CI)	53%	53%	56%	**54%** (45, 62)
Median duration of response, mo (95% CI)	N/R	N/R	34	**N/R** (34, N/R)
Range				2-53+

N/R=not reached.

Long-term Treatment Provides Increasing and Durable Response (RECIST): Kaplan-Meier Analysis

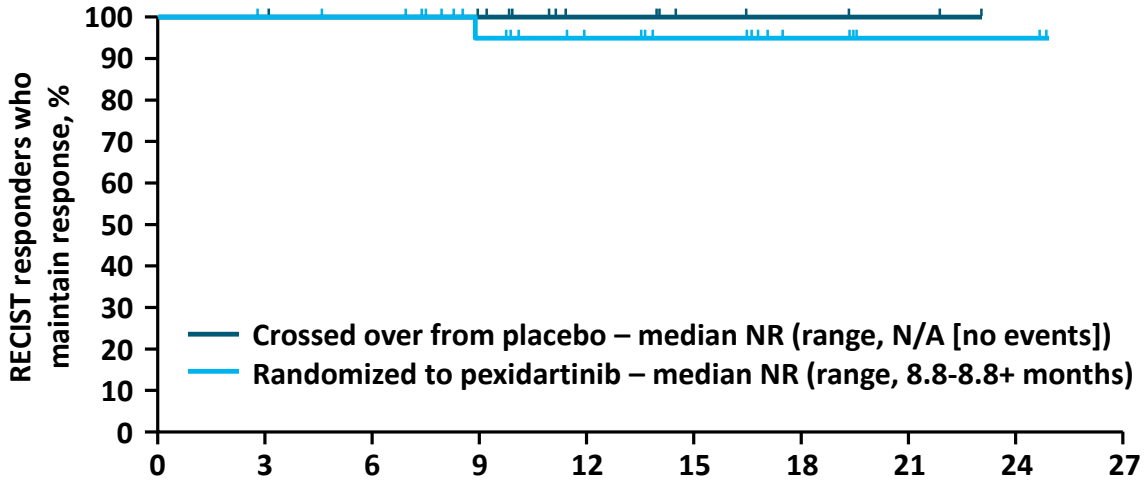
ENLIVEN (n=91)

Time to RECIST response



Responders										
Crossed over	0	10	13	15	15	16	16	16	16	
Pexidartinib	0	11	23	26	28	30	32	32	32	32

Duration of RECIST response

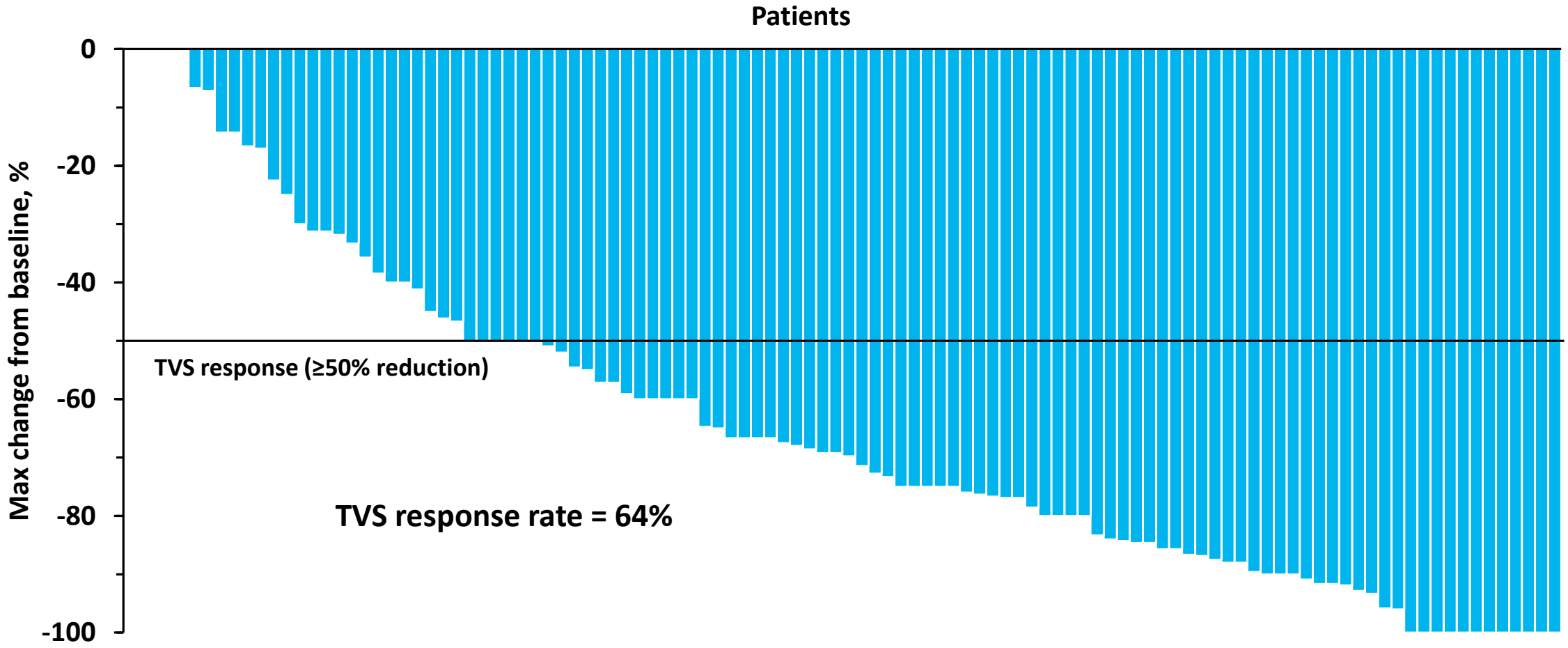


Remaining Responders (at risk)										
Crossed over	16	16	15	13	7	4	3	2	0	
Pexidartinib	32	31	30	18	13	10	5	2	2	0

N/A=not available; NR=not reached.

Proportion of Patient Experiencing Benefit via TVS

Phase 1 and ENLIVEN



Efficacy Summary

- Pexidartinib imparts meaningful clinical benefit in patients with advanced, symptomatic TGCT
  - Primary endpoint met, with significant increase in ORR
  - Clinically meaningful efficacy across secondary endpoints measuring functional and symptomatic improvement
  - Consistent efficacy across cohorts
  - Increasing and durable benefit with long-term treatment

General Safety Assessment of Pexidartinib

Antoine Yver, MD, MSc

Exec VP Global Head Oncology RD

Daiichi Sankyo, Inc.

Exposure & Safety Summary

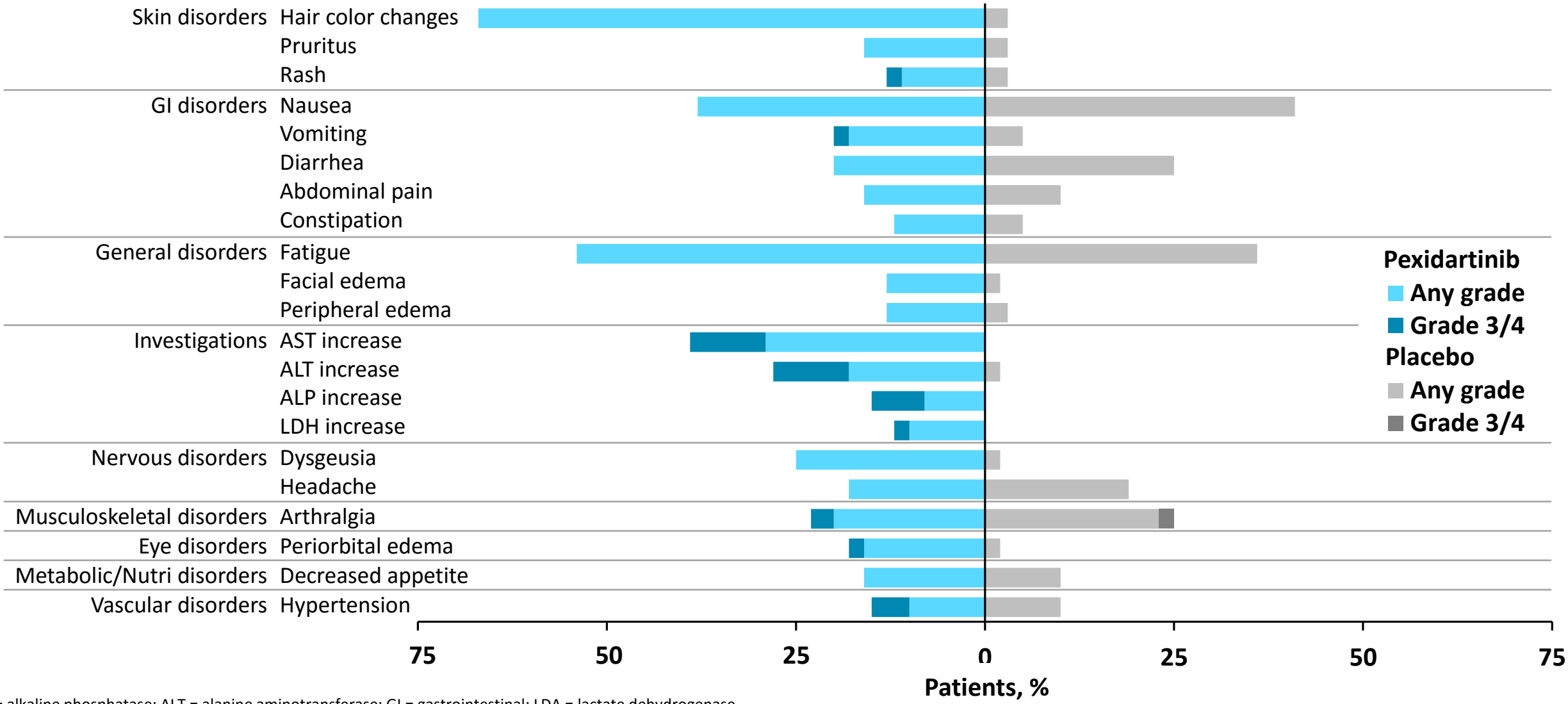
ENLIVEN Part 1 Randomized

	Patients, n (%)	
	Pexidartinib n=61	Placebo n=59
Exposure Mean weeks (SD)	22 (7)	22 (5)
Any AEs	**60 (98)**	**55 (93)**
Grade 3/4 AEs	27 (44)	7 (12)
Serious AEs	8 (13)	1 (2)
AEs associated with discontinuation	**8 (13)**	**0**
AEs associated with dose interruption/reduction	**23 (38)**	**6 (10)**

AE = adverse event; SD = standard deviation.

Most Frequently Reported TEAEs Occurring in ≥10% of Patients

ENLIVEN Part 1 Randomized



ALP = alkaline phosphatase; ALT = alanine aminotransferase; GI = gastrointestinal; LDA = lactate dehydrogenase.

TEAEs Associated With Discontinuation

ENLIVEN Part 1 Randomized

SOC/Preferred term	Pexidartinib (n=61), n (%)
Any TEAE	**8 (13.1)**
ALT increased	3 (4.9)
AST increased	3 (4.9)
Blood bilirubin increased	1 (1.6)
Blood LDH increased	1 (1.6)
Hepatic enzyme abnormal	1 (1.6)
Hepatotoxicity	1 (1.6)
Liver disorder	1 (1.6)
Hypertension	1 (1.6)

SOC = system organ class; TEAE = treatment-emergent adverse event.

TEAEs Associated With Dose Interruption/Reduction in >1 Patient

ENLIVEN Part 1 Randomized

SOC/Preferred term	Patients, n (%)	
	Pexidartinib n=61	Placebo n=59
Any TEAE	**23 (37.7)**	**6 (10.2)**
ALT increased	8 (13.1)	0
AST increased	8 (13.1)	0
Blood ALP increased	4 (6.6)	0
Blood bilirubin increased	2 (3.3)	0
GGT increased	2 (3.3)	0
Dizziness	2 (3.3)	0
Nausea	5 (8.2)	0
Vomiting	3 (4.9)	0
Abdominal pain	2 (3.3)	1 (1.7)
Hypertriglyceridemia	0	2 (3.4)

GGT = gamma-glutamyl transferase.

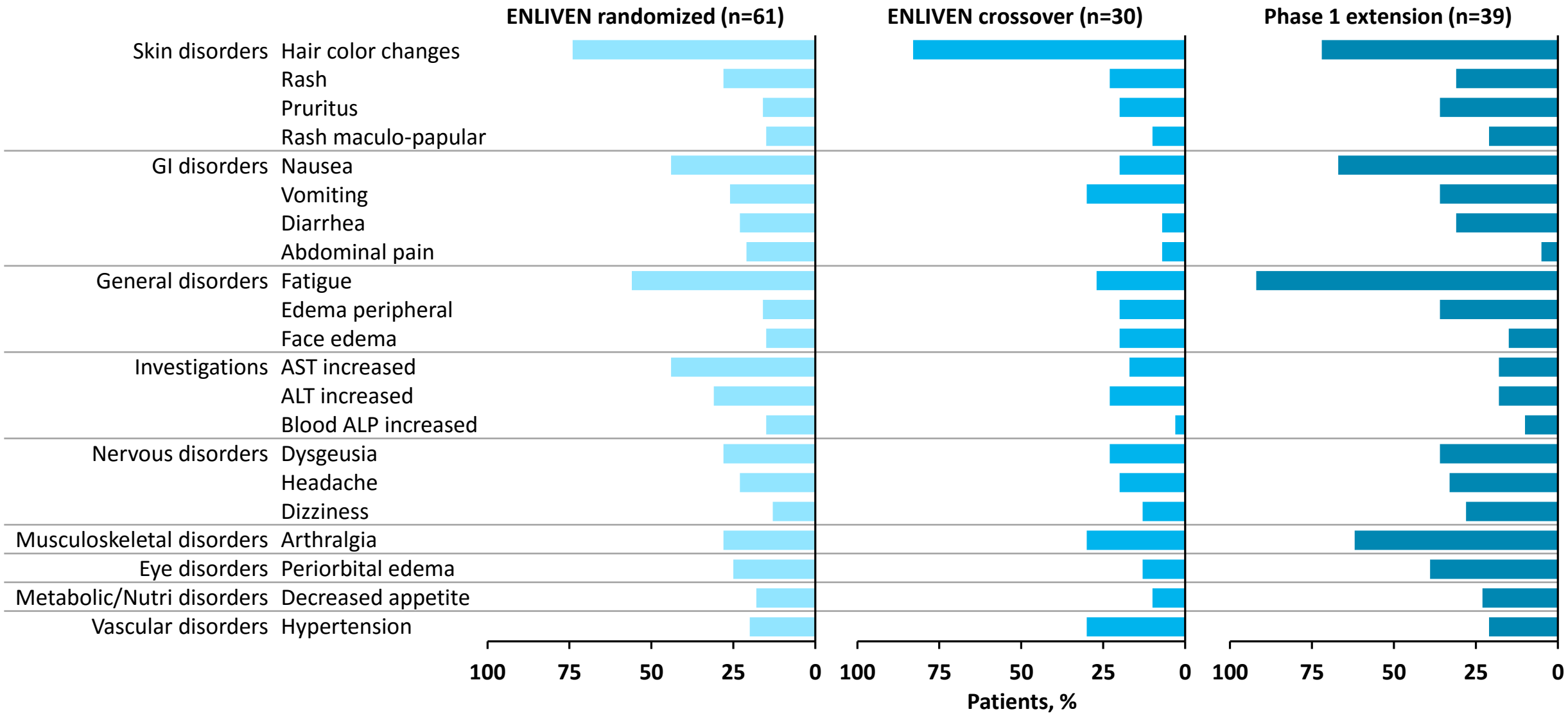
Long-Term Safety With Pexidartinib Across TGCT Cohorts

January 2018 Data Cut-Off

	Patients, n (%)		
	ENLIVEN		
	Pexidartinib Randomized n=61	Pexidartinib Crossover n=30	Phase 1 Extension n=39
Exposure Mean weeks (SD)	64 (34)	66 (29)	101 (80)
Any AEs	**61 (100)**	**30 (100)**	**39 (100)**
Grade 3/4 AEs	32 (52)	10 (33)	17 (44)
Serious AEs (SAEs)	8 (13)	3 (10)	5 (13)
AEs associated with discontinuation	**12 (20)**	**5 (17)**	**13 (33)**
AEs associated with dose interruption/reduction	**34 (56)**	**20 (67)**	**32 (82)**

Any Grade TEAEs Across TGCT Cohorts

January 2018 Cut-Off



General Safety Summary

- Most AEs were low grade and reversible
- Hair color changes, fatigue and edema were more frequent with pexidartinib
- Pexidartinib was generally well tolerated

Hepatic Safety

Laurie DeLeve, MD, PhD

Professor of Medicine
University of Southern California Keck School of Medicine
Division of Gastrointestinal and Liver Diseases

Two Clinically Distinct Types of Hepatic Adverse Reactions

1. **Aminotransferase elevations**
   - In absence of significant alkaline phosphatase or bilirubin elevation
   - Frequent, dose-dependent, generally low-grade
2. **Mixed or cholestatic hepatotoxicity**
   - Increase in alkaline phosphatase with or without aminotransferase elevations
   - Uncommon and idiosyncratic
     - Rarely serious, but can be life-threatening

Hepatic Adverse Reactions: Lab Data

ENLIVEN Part 1 Randomized

	Patients, n (%)	
	Pexidartinib n=61	Placebo n=59
Isolated aminotransferase elevations		
ALT or AST		
≥1 - <3 × ULN	35 (57)	18 (31)
≥3 - <5 × ULN	8 (13)	0
≥5 - <10 × ULN	5 (8)	0
≥10 - <20 × ULN	2 (3)	0
≥20 × ULN	2 (3)	0
Mixed or cholestatic hepatotoxicity		
ALT/AST ≥3, TBili ≥2, and ALP ≤2 × ULN (True Hy's law)	0	0
ALT/AST ≥3, TBili ≥2, and ALP >2 × ULN	3 (5)	0
TBili ≥2× ULN (in absence of ALT ≥3 or ALP >2 × ULN)	0	0

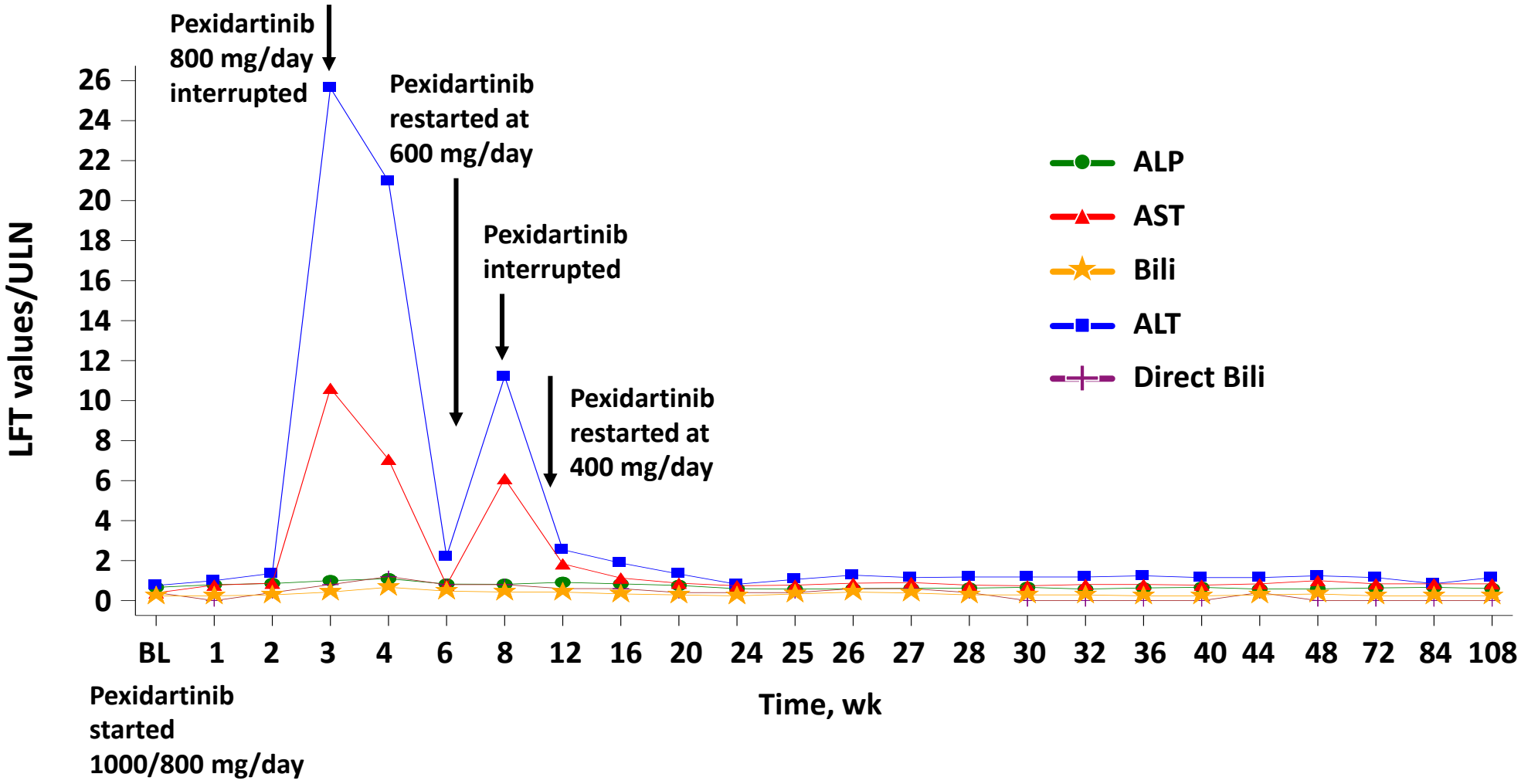
Tbili = total bilirubin; ULN = upper limit normal.

Aminotransferase Elevations Are Dose Dependent and Manageable

- Related to CSF-1R inhibition
- Dose dependent
- Manageable with dose modifications

Aminotransferase Elevations Are Dose Dependent and Manageable

ENLIVEN Subject #1001-0001



BL = baseline; LFT = liver function test.

Mixed or Cholestatic Hepatotoxicity in TGCT Patients (N=140)[a]
Adjudicated as "Probably" Related

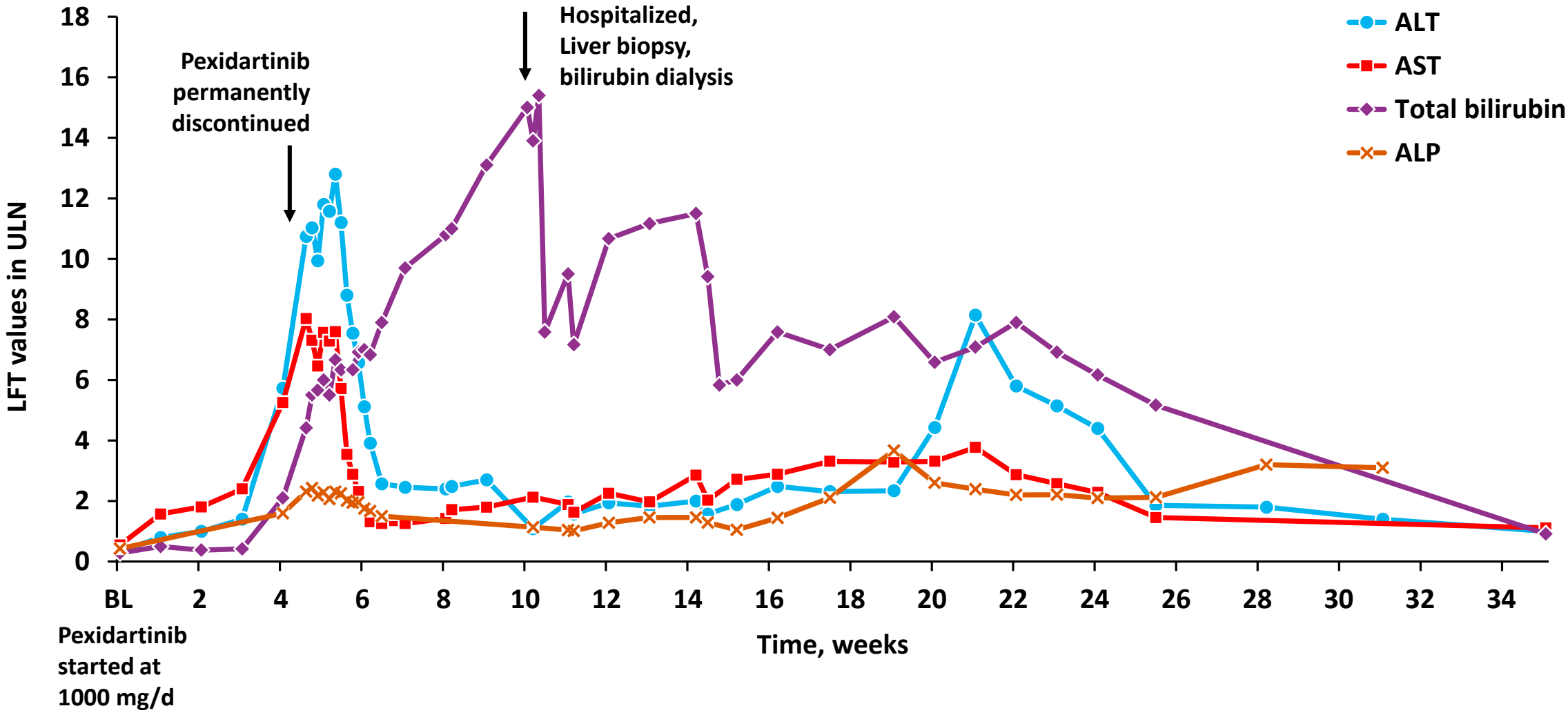
Case	Pexidartinib Starting Dose (Onset)	Type of Hepatic Injury	Outcome
ENLIVEN			
75 y/o female #6001-0003	1000 mg/day (Day 22)	Cholestatic hepatotoxicity (biopsy: ductopenia, severe cholestasis) Hyperbilirubinemia	Recovered 7 months
67 y/o female #1301-0004	1000 mg/day (Day 43)	Mixed hepatotoxicity Hyperbilirubinemia	Recovered 1 month
52 y/o male #1017-0003	1000 mg/day (Day 36)	Mixed hepatotoxicity Hyperbilirubinemia	Recovered 2 months
39 y/o female #1201-0004	1000 mg/d (Day 28)	Cholestatic hepatotoxicity Intermittent ALP increases due to 2 rechallenges	Recovered 1 month
DDI Study 126 (ongoing)			
43 y/o female #3001-0002	800 mg/day (Day 21)	Mixed hepatotoxicity Hyperbilirubinemia	Recovered 2 months

DDI = drug-drug interaction; y/o = year old.

[a] 140 patients from ENLIVEN, TGCT cohort PLX108-01 and post submission Phase 1 studies.

75 y/o Female With Ductopenia and 7 Months to Recovery

#6001-0003 (TGCT Patient From ENLIVEN)



Mixed and Cholestatic Hepatotoxicity in Non-TGCT Population (N=658)

Four Adjudicated as "Probably" Related

Patient ID # (Study #)	Non-TGCT Cases	Pexidartinib Starting Dose (Onset)	Type of hepatic injury (Biopsy Result)	Outcome
63573 (IST3397-006 [I-SPY2])	60 y/o female with early breast cancer	1200 mg/day Combined with paclitaxel (Day 18)	Cholestatic hepatotoxicity w/ vanishing bile duct syndrome (Cholestasis with duct damage and duct loss; severe steatosis)	Liver transplant at 20 months
01-104* (PLX108-13)	66 y/o female with vaginal melanoma	1000 mg/d (Day 21)	Cholestasis with hyperbilirubinemia	Death in context of progressing melanoma and cachexia 3 months after pexidartinib discontinued
01-205 (IST3397-001)	58 y/o female with advanced breast cancer	1000 mg/d with eribulin (Day 28)	Cholestasis and ductopenia (Only rare ducts seen without ductular reaction; lobular parenchyma showed cholestasis; rare necrotic hepatocytes)	Significant worsening of breast cancer on last PET-CT. Resolved at 5 months
09-118 (PLX108-07)	61 y/o female with ovarian cancer	600 mg/d with paclitaxel (Day 30)	Cholestatic hepatotoxicity (Bland cholestasis)	Prolonged case. Last ALP at 28 days after onset and still 8× ULN. Died due to underlying cancer progression.
04-21405 (PLX108-14)	75 y/o female	600 mg/d with pembrolizumab (Day 28)	Cholestatic hepatotoxicity (Cholestasis with moderate portal inflammation containing moderate numbers of eosinophils with focal granuloma formation and bile duct inflammation)	Progressive fallopian tube cancer. Resolved at 2 months

ID = identification; PET-CT = positron emission tomography-computed tomography.
*Adjudicated as insufficient data

Summary of Hepatic Adverse Reactions

- Aminotransferase elevations
  - Frequent, dose-dependent, and manageable
  - Mechanism related to CSF1R inhibition
- Mixed or cholestatic hepatotoxicity
  - Idiosyncratic and rarely severe
  - May be prolonged or irreversible
  - Onset observed in first 2 months of treatment
  - 10 out of 798 subjects (1.3%)
- Risk mitigation will identify hepatotoxicity early

Risk Evaluation and Mitigation Strategy (REMS)

Eric Richards, MS, MPH

Oncology Head Regulatory Affairs
Daiichi Sankyo, Inc.

Pexidartinib REMS: Overall Goal and Key Stakeholders

Designed to mitigate and further characterize the risk of serious and potentially fatal hepatotoxicity

- Pexidartinib will be available only to stakeholders who have been trained and certified
- Patient registry to further characterize hepatic safety profile

REMS Requirements for Prescribers

- **Process**
  1. Review Prescribing Information and REMS Training
  2. Pass Knowledge Assessment and submit Certification Form
  3. Complete Patient Enrollment, Status, and Adverse Event Forms
- **Key Risk Mitigation Measures**
  1. Counsel patient with the Patient Guide
  2. Perform liver blood tests at baseline and frequently during treatment
  3. Clear directions on when to withhold/ permanently discontinue pexidartinib based on liver function tests

REMS Requirements for Patients

- **Process**
  1. Review Patient Guide describing risks, liver blood testing requirements, and clinical signs or symptoms
  2. Enroll in REMS and Registry by completing the Patient Enrollment Form with the prescriber
- **Key Risk Mitigation Measures**
  1. Comply with liver blood tests
  2. Immediately **stop pexidartinib** and report signs or symptoms of potential hepatotoxicity to their doctor

REMS Requirements for Wholesalers & Specialty Pharmacies

- **Process**
  1. Complete certification
- **Key Risk Mitigation Measures**
  1. Verify prescriber is certified and obtain authorization prior to dispensing each prescription
  2. Ensure patient is enrolled in the registry and authorized to receive drug
  3. Only dispense a 30-day supply of pexidartinib for the first 3 months of therapy

Patient Registry: Required to Receive Pexidartinib

- **Further characterize risk of hepatotoxicity, especially long-term treatment, and inform risk mitigation strategies**

- **Data collected**
  - Demographic information
  - Baseline hepatic information
  - Current treatment status
  - Laboratory abnormalities
  - Related procedures

Pexidartinib REMS Supports the Positive Benefit:Risk Ratio of Pexidartinib

- **Mitigate risks through education on**
  - Risk of serious and potentially fatal liver injury
  - Liver monitoring requirements
  - Counsel patients about signs/symptoms of liver injury
- **Mitigate risk through controlled supply of pexidartinib**
- **Patient registry to further characterize risk of hepatotoxicity and inform risk mitigation strategies**

Clinical Perspective

William D. Tap, MD

Sarcoma Medical Oncology Service Chief
Memorial Sloan Kettering Cancer Center

Pexidartinib in TGCT: Benefit/Risk Assessment

Benefits

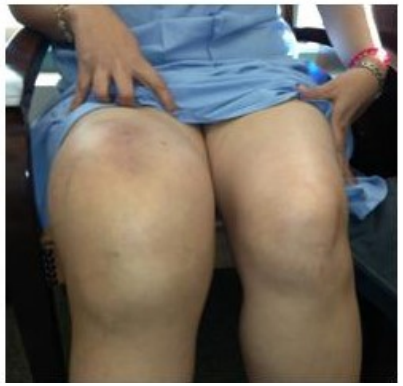
- Impressive tumor response
- Restores range of motion
- Reduces symptoms
- Durable functional improvement

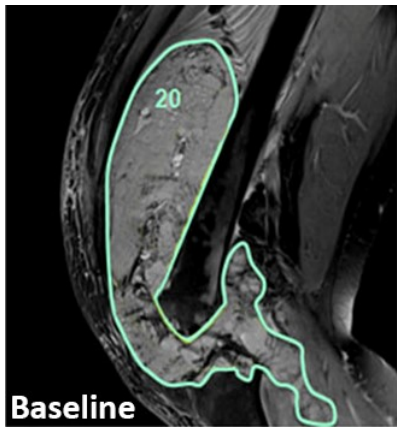
Risks

- Pigmentation changes and fatigue
- Aminotransferase elevations
- Cholestatic/mixed hepatotoxicity
  - Onset in first 8 weeks
  - Idiosyncratic, rarely serious, can be life-threatening

Treatment Options Limited and Patient Considering Amputation

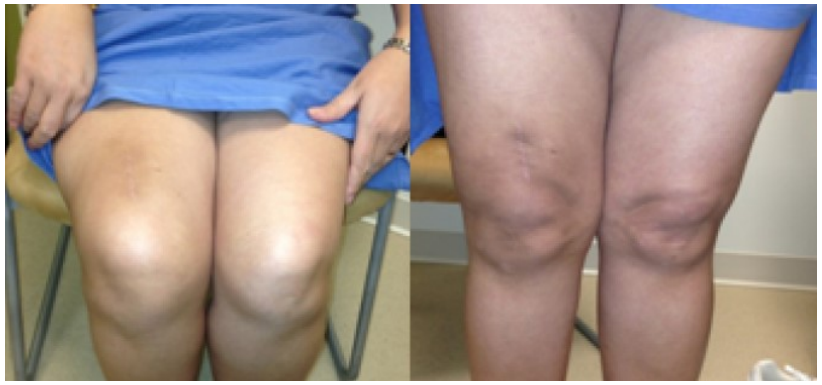
- Baseline
  - Unable to straighten knee
  - Taking narcotics
  - Unable to work

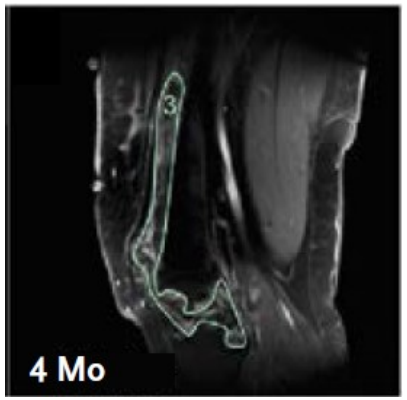




Pexidartinib

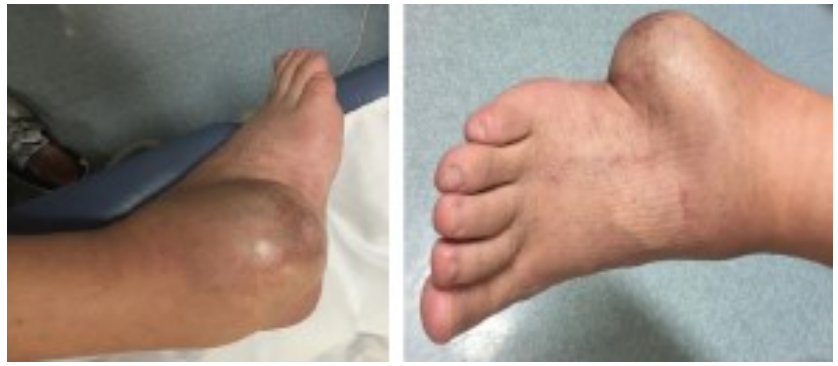
- 4 months (ongoing)
  - Swelling and range of motion improved
  - No longer needed narcotics
  - Returned to work

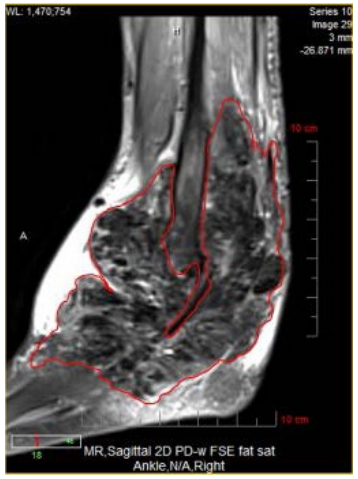




Functional Improvement Despite No Objective Response by RECIST

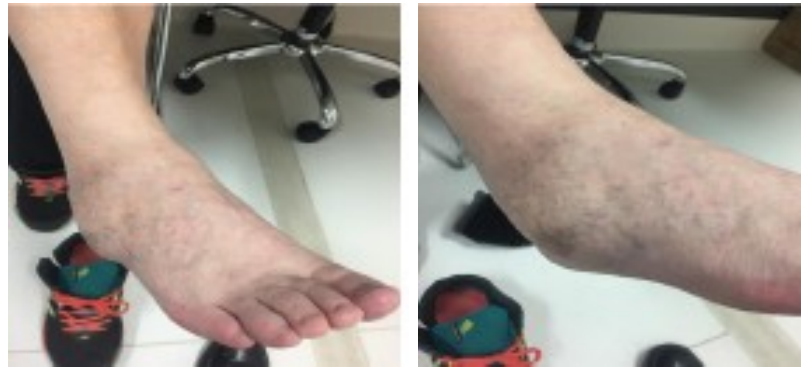
- Baseline
  - Mobility largely impacted
  - Planning to quit work

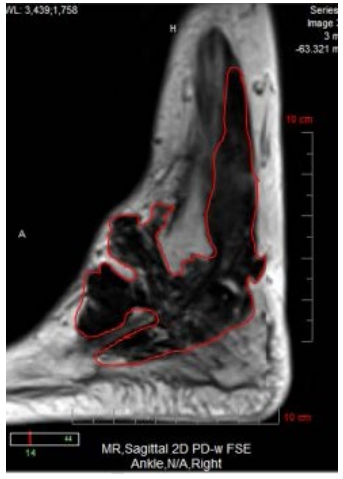




Pexidartinib

- 18 months (ongoing)
  - Ankle correctly aligned
  - Playing golf and tennis again

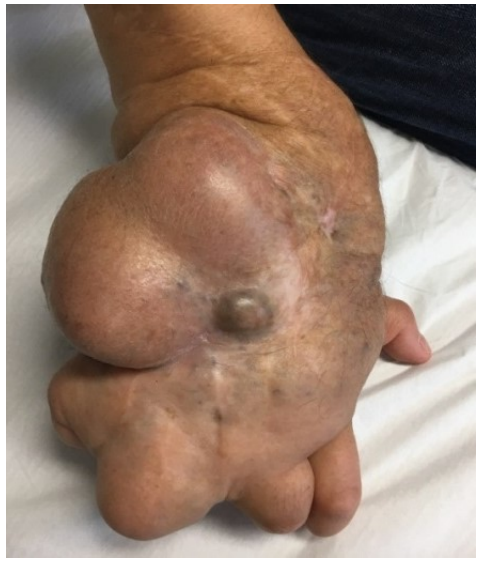




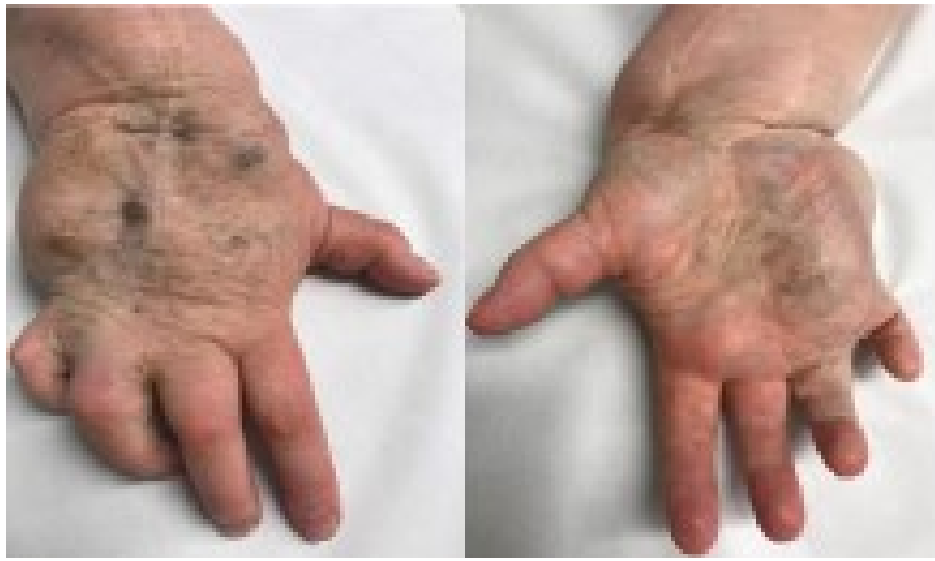
Dramatic Response After 25+ Years of Disfiguring Surgeries

- 56-year-old female diagnosed with TGCT in 1988
- Multiple prior surgeries, regular RBC transfusions

- 2.5 years (ongoing)
- Baseline pain: 5.6 → 0.6 at Week 25



Pexidartinib

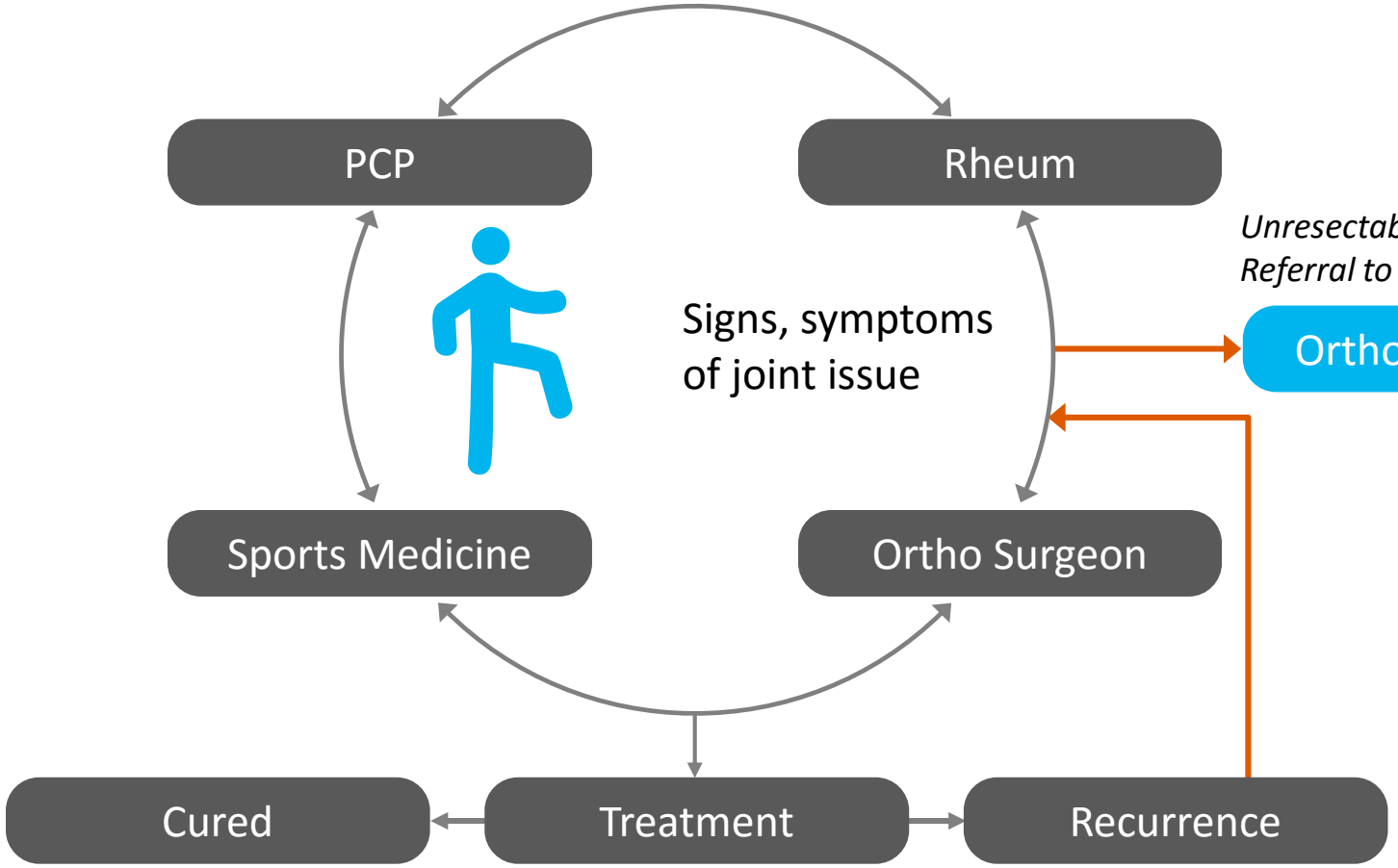


October 2016

May 2018

Image courtesy of Tap WD, et all. Lancet, in press.

Transforming the Patient Journey



Unresectable/Complicated cases
Referral to center of excellence

Ortho Oncologist ⇄ Sarcoma Oncologist

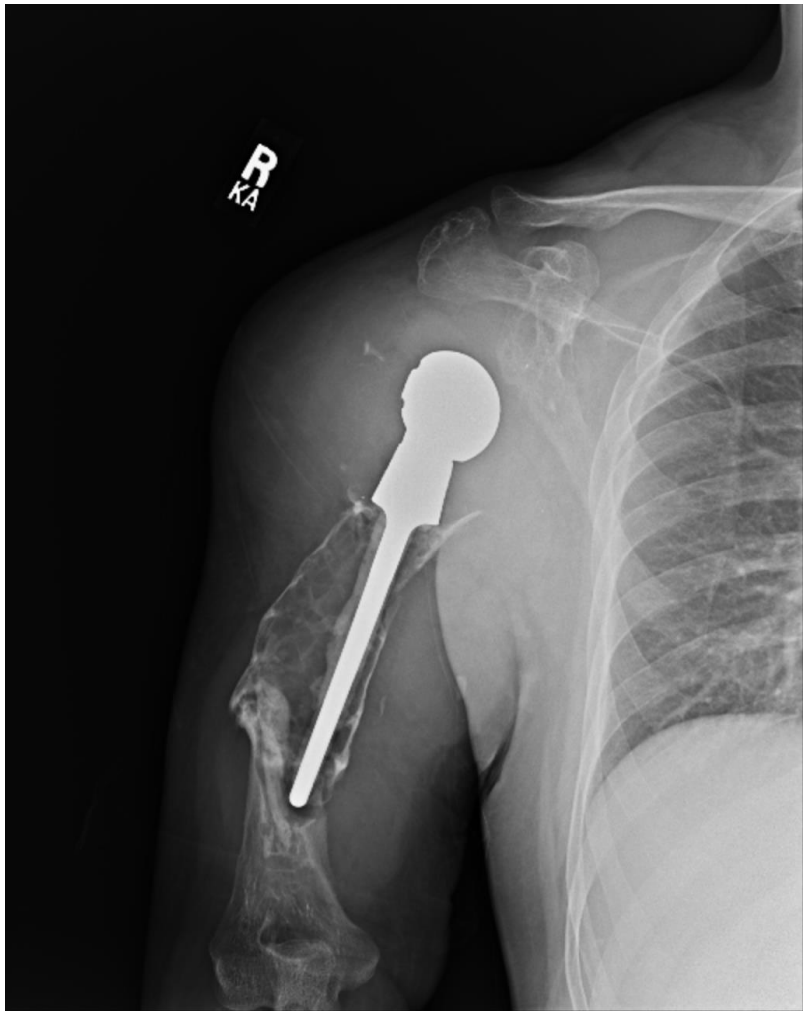
Pexidartinib

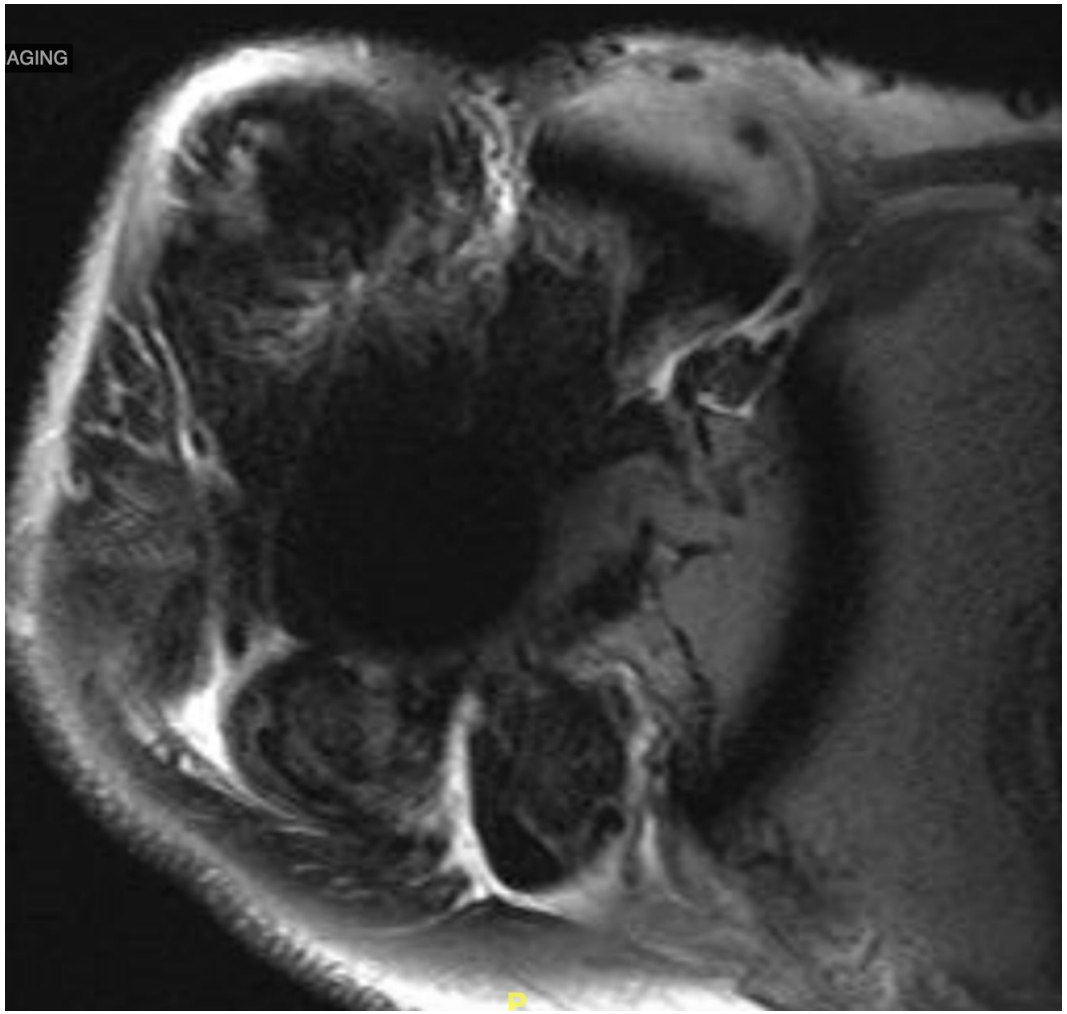
TGCT Treatment

- Arthroscopic surgery
- Supportive care (pain management, physical therapy)

Backup Slides

Advanced TGCT With No Surgical Options

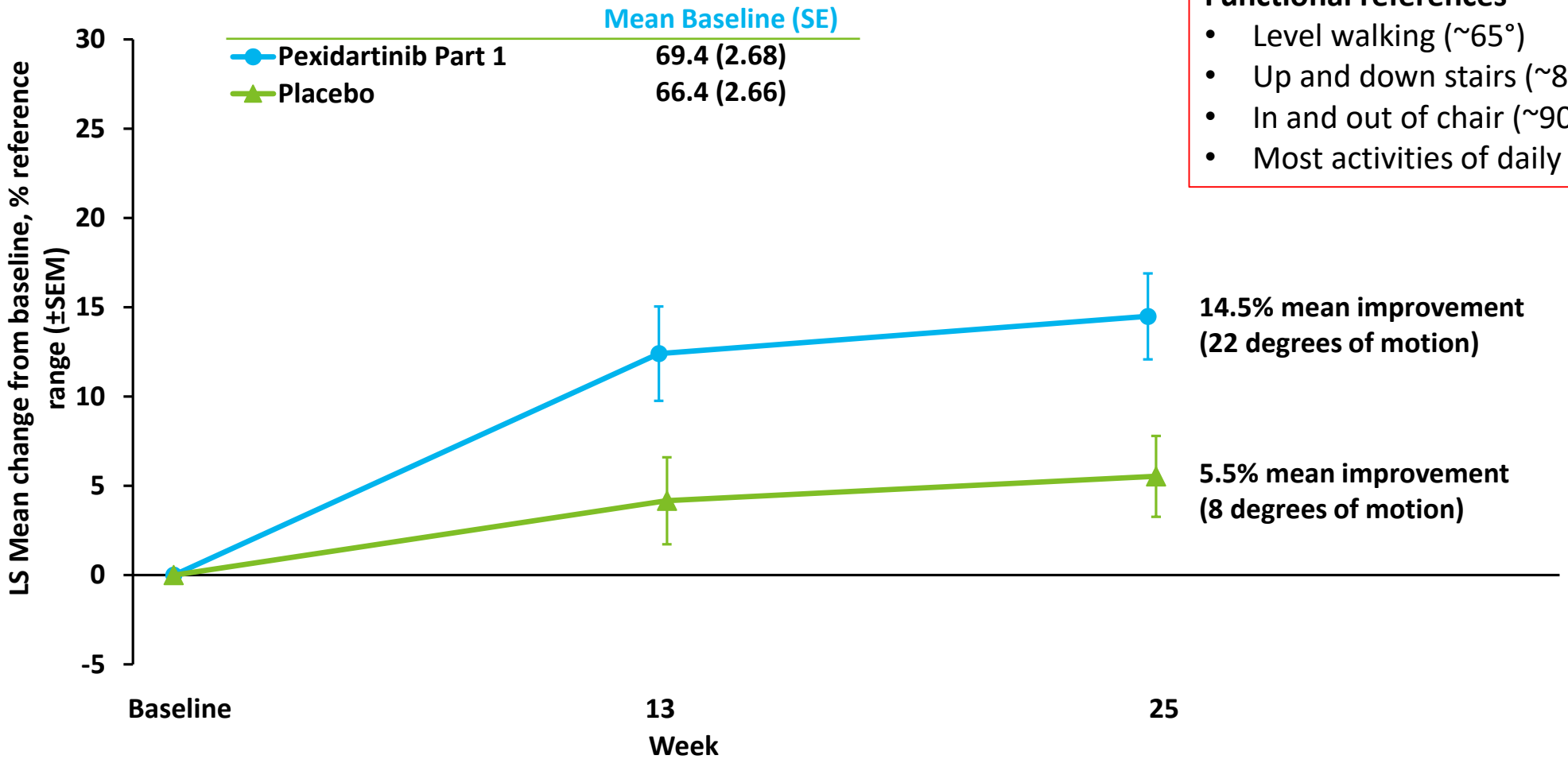




Images courtesy of Nicholas Bernthal, MD.

LS Mean Change from Baseline ROM-Knee

ENLIVEN



Functional references

- Level walking (~65°)
- Up and down stairs (~80°)
- In and out of chair (~90°)
- Most activities of daily living (~110°)

Patients, n			
Pexidartinib	34	28	25
Placebo	38	35	28

Worst Stiffness/Pain: Other Reasons for Missing Clinical Outcome Assessments

	Patients, n (%)							
		Other reasons						
Visit	All other reasons	Site scheduling of visit	Logpad issue	Patient non-compliance	Out of window	Programming rule	Missing baseline	Unknown
Worst Stiffness								
Pexidartinib (n=61)								
Baseline	2 (3.3)	2 (3.3)	0	0	0	0	0	0
Week 9	27 (44.3)	14 (23.0)	2 (3.3)	10 (16.4)	1 (1.6)	0	0	0
Week 17	15 (24.6)	10 (16.4)	0	4 (6.6)	0	1 (1.6)[a]	0	0
Week 25	18 (29.5)	7 (11.5)	3 (4.9)	8 (13.1)	0	0	0	0
Placebo (n=59)								
Baseline	1 (1.7)	1 (1.7)	0	0	0	0	0	0
Week 9	19 (32.2)	15 (25.4)	0	4 (6.8)	0	0	0	0
Week 17	18 (30.5)	9 (15.3)	0	9 (15.3)	0	0	0	0
Week 25	12 (20.3)	6 (10.2)	2 (3.4)	4 (6.8)	0	0	0	0

[a]Subject 10050001 (Randomized to Pexidartinib) did record BPI pain and worst stiffness in the week prior to the Week 17 visit, however due to an issue with visit dates, the Week 17 values were set to missing. This subject is therefore summarized in this table, in the Programming Rule column for Week 17.

Summary Mean Change From Baseline in ROM

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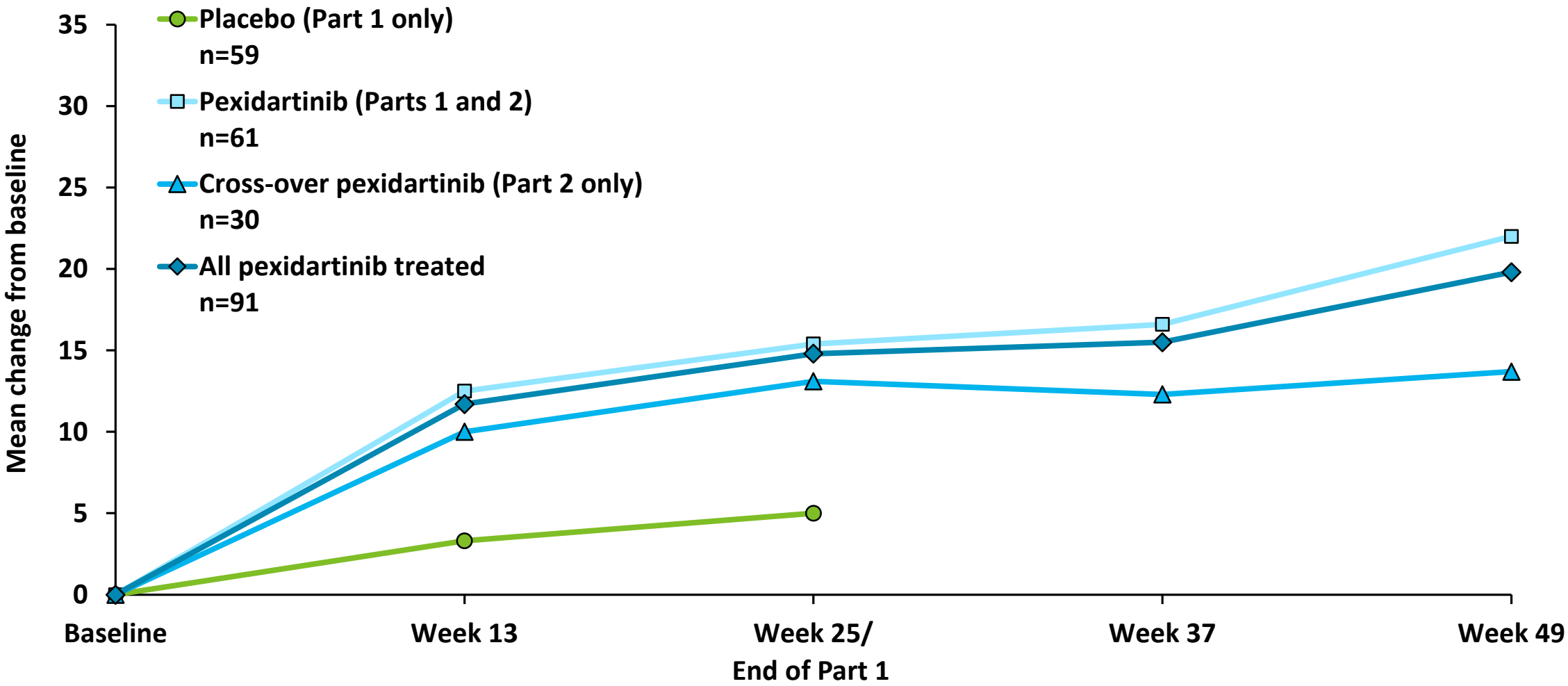

ROM Tipping Point Analysis[a]

Penalty Assigned When Missing Data on Pexidartinib are Imputed

Analysis		LS mean change from baseline to Week 25 (95% CI)		LS mean difference pexidartinib vs placebo at Week 25 (95% CI)	P value
		Pexidartinib	Placebo		
MMRM		**15.07 (10.93, 19.22)**	**6.20 (1.49, 10.91)**	**8.87 (2.85, 14.90)**	**0.0043**
Tipping point	Delta				
	-5	13.78 (9.58, 17.99)	5.23 (0.29, 10.16)	8.55 (2.37, 14.74)	0.0067
	-10	12.76 (8.42, 17.11)	5.22 (0.27, 10.17)	7.55 (1.28, 13.82)	0.0183
	-15	**11.74 (7.24, 16.25)**	**5.19 (0.07, 10.32)**	**6.55 (0.09, 13.01)**	**0.0470**
	-16	**11.56 (7.03, 16.09)**	**5.12 (-0.10, 10.34)**	**6.44 (-0.08, 12.96)**	**0.0531**

[a] By Pattern Mixture Model Multiple Imputation.

PROMIS-PF Tipping Point Analysis[a]

Penalty Assigned When Missing Data on Pexidartinib are Imputed

Analysis		LS mean change from baseline to Week 25 (95% CI)		LS mean difference pexidartinib vs placebo at Week 25 (95% CI)	P value
		Pexidartinib	Placebo		
MMRM		**4.06 (1.82, 6.30)**	**-0.89 (-2.95, 1.16)**	**4.95 (1.87, 8.03)**	**0.0019**
Tipping point	Delta				
	-0.5	3.83 (1.65, 6.02)	-0.86 (-2.93, 1.20)	4.7 (1.66, 7.73)	0.0024
	-1.0	3.57 (1.33, 5.80)	-0.84 (-2.94, 1.26)	4.41 (1.31, 7.50)	0.0052
	-3.5	**2.39 (0.09, 4.69)**	**-0.84 (-2.99, 1.31)**	**3.23 (0.04, 6.42)**	**0.0474**
	-3.6	**2.34 (0.04, 4.64)**	**-0.84 (-3.00, 1.32)**	**3.18 (-0.02, 6.38)**	**0.0513**

[a] By Pattern Mixture Model Multiple Imputation.