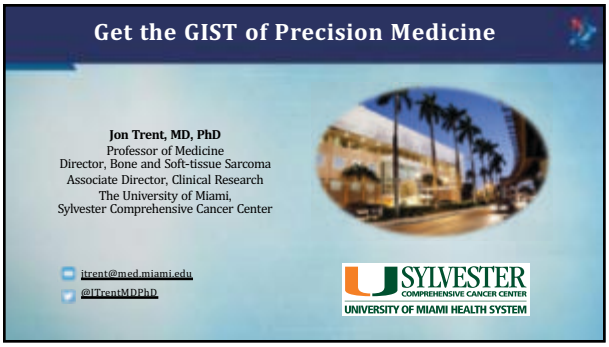

CHAMPIONING MEDICALLY INTEGRATED ONCOLOGY:
Celebrating
a Decade of Impact
2025 NCODA INTERNATIONAL
FALL SUMMIT

1


Get the GIST of Precision Medicine
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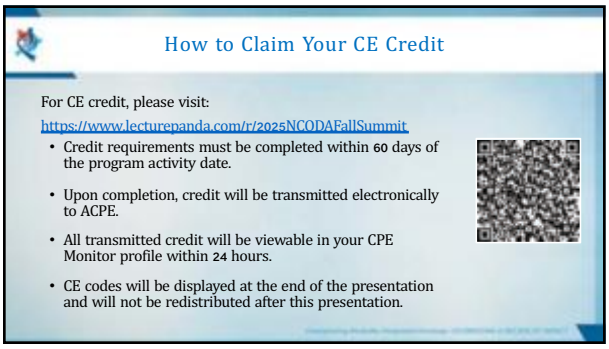
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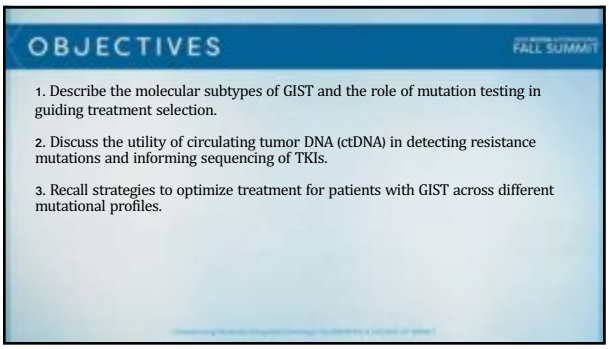
OBJECTIVES
FALL SUMMIT
1. Describe the molecular subtypes of GIST and the role of mutation testing in guiding treatment selection.
2. Discuss the utility of circulating tumor DNA (ctDNA) in detecting resistance mutations and informing sequencing of TKIs.
3. Recall strategies to optimize treatment for patients with GIST across different mutational profiles.

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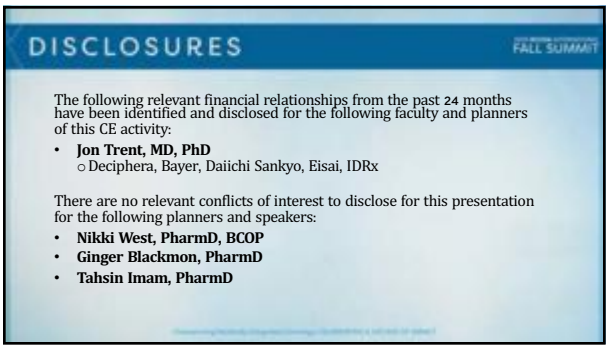
DISCLOSURES
FALL SUMMIT
The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty and planners of this CE activity:
• Jon Trent, MD, PhD
○ Deciphera, Bayer, Daiichi Sankyo, Eisai, IDRx
There are no relevant conflicts of interest to disclose for this presentation for the following planners and speakers:
• Nikki West, PharmD, BCOP
• Ginger Blackmon, PharmD
• Tahsin Imam, PharmD

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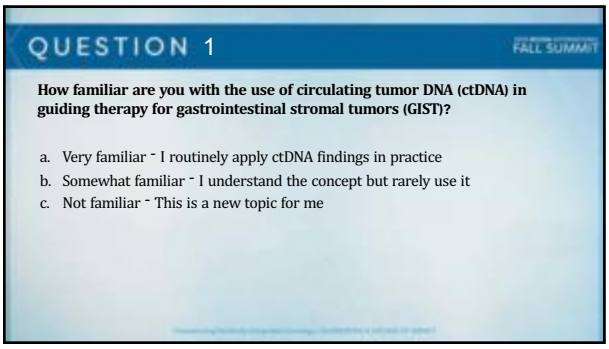
QUESTION 1
FALL SUMMIT
How familiar are you with the use of circulating tumor DNA (ctDNA) in guiding therapy for gastrointestinal stromal tumors (GIST)?
a. Very familiar - I routinely apply ctDNA findings in practice
b. Somewhat familiar - I understand the concept but rarely use it
c. Not familiar - This is a new topic for me

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GIST Overview

- Most common GI sarcoma
  - 0.2% of all GI tumors, but **80% of GI sarcomas**
- High frequency of **metastatic disease**
- **Gene mutations** drive phenotype and therapy
- Metastatic disease treated with tyrosine kinase inhibitors (TKIs)

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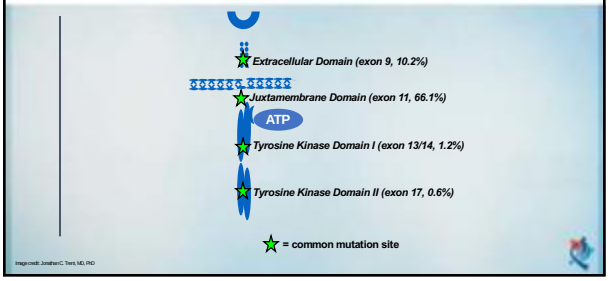
KIT Receptor Structure



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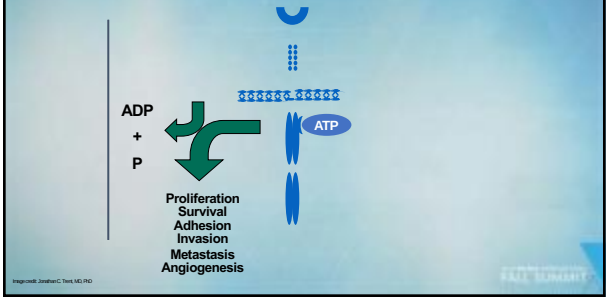
KIT Receptor Phenotype



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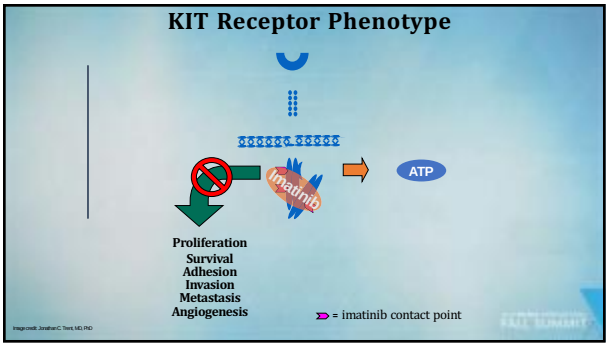
KIT Receptor Phenotype
ATP
Imatinib
Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis
= imatinib contact point

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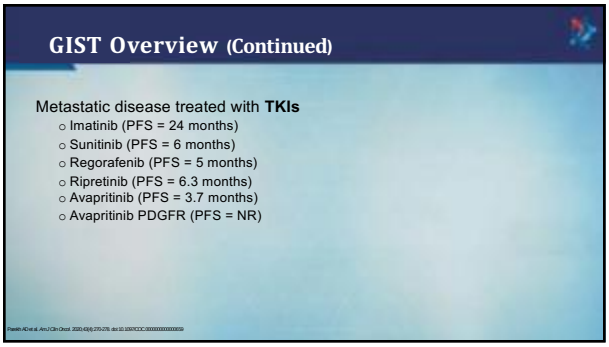
GIST Overview (Continued)
Metastatic disease treated with TKIs
Imatinib (PFS = 24 months)
Sunitinib (PFS = 6 months)
Regorafenib (PFS = 5 months)
Ripretinib (PFS = 6.3 months)
Avapritinib (PFS = 3.7 months)
Avapritinib PDGFR (PFS = NR)

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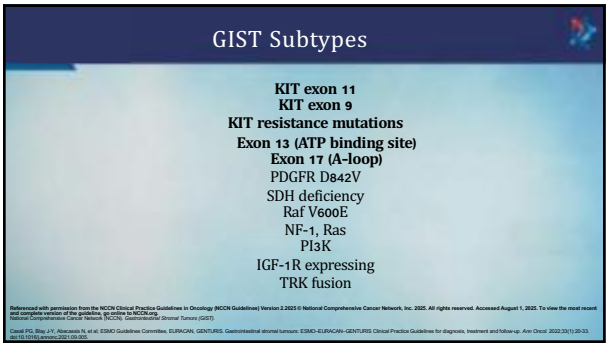
GIST Subtypes
KIT exon 11
KIT exon 9
KIT resistance mutations
Exon 13 (ATP binding site)
Exon 17 (A-loop)
PDGFR D842V
SDH deficiency
Raf V600E
NF-1, Ras
PI3K
IGF-1R expressing
TRK fusion

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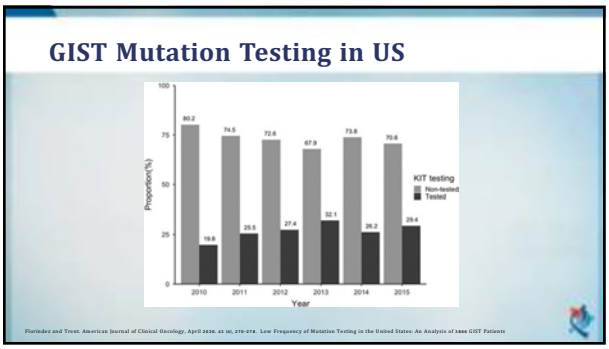
GIST Mutation Testing in US
Proportion(%)
Year
KIT testing
Non-tested
Tested
2010
2011
2012
2013
2014
2015

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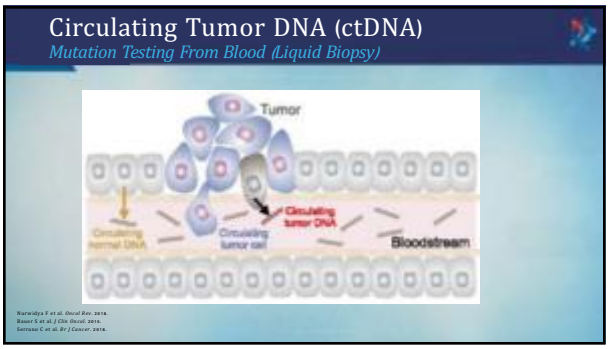
Circulating Tumor DNA (ctDNA)
Mutation Testing From Blood (Liquid Biopsy)
Tumor
Bloodstream

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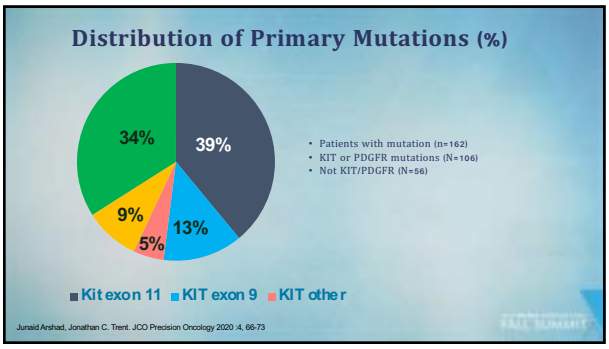
Distribution of Primary Mutations (%)
34%
39%
9%
13%
5%
Patients with mutation (n=162)
KIT or PDGFR mutations (N=106)
Not KIT/PDGFR (N=56)
Kit exon 11
KIT exon 9
KIT other
Junaid Arshad, Jonathan C. Trent. JCO Precision Oncology 2020 :4, 66-73

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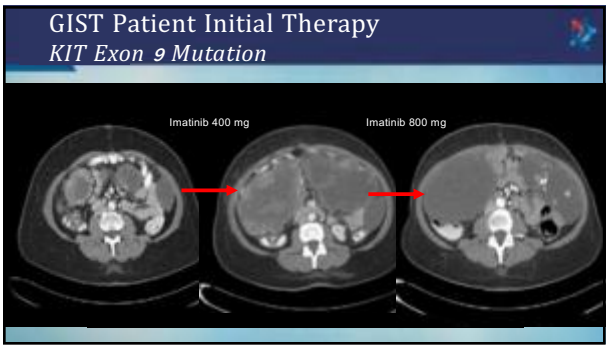
GIST Patient Initial Therapy
KIT Exon 9 Mutation
Imatinib 400 mg
Imatinib 800 mg

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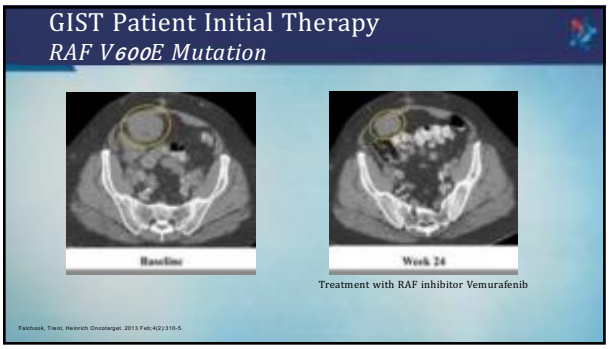
GIST Patient Initial Therapy
RAF V600E Mutation
Baseline
Week 24
Treatment with RAF inhibitor Vemurafenib
Falchook, Trent. Heinrich Oncotarget. 2013 Feb;4(2):310-5.

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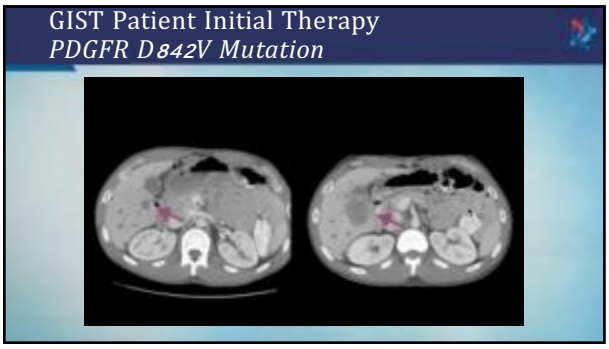
GIST Patient Initial Therapy
PDGFR D842V Mutation

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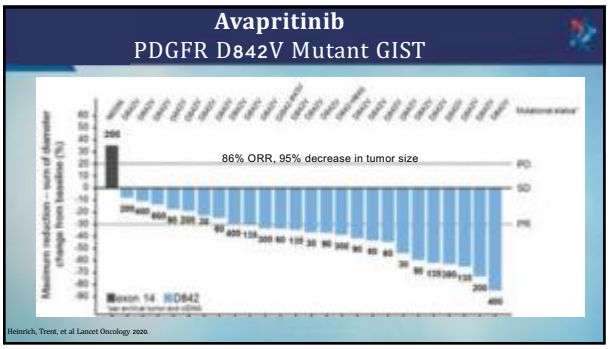
Avapritinib
PDGFR D842V Mutant GIST
86% ORR, 95% decrease in tumor size
PD
SD
PR
Heinrich, Trent, et al Lancet Oncology 2020.

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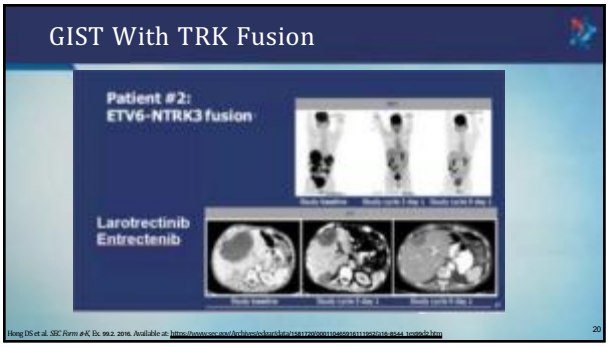
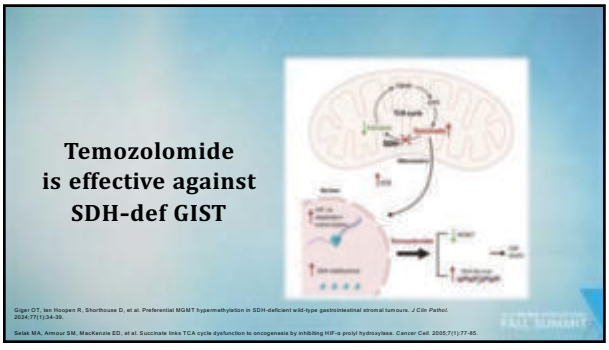

GIST With TRK Fusion
Patient #2:
ETV6-NTRK3 fusion
Larotrectinib
Entrectenib
20

20


Temozolomide
is effective against
SDH-def GIST

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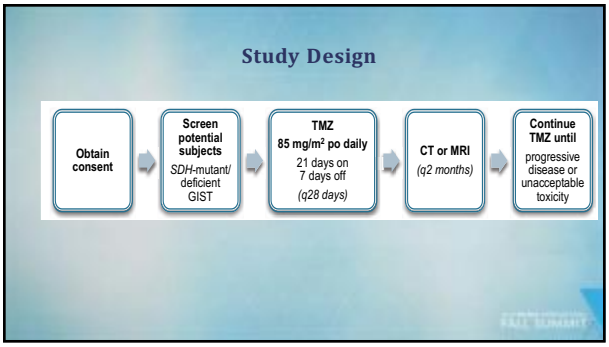
Study Design
Obtain consent
Screen potential subjects
SDH-mutant/ deficient GIST
TMZ
85 mg/m² po daily
21 days on
7 days off
(q28 days)
CT or MRI
(q2 months)
Continue TMZ until
progressive disease or unacceptable toxicity

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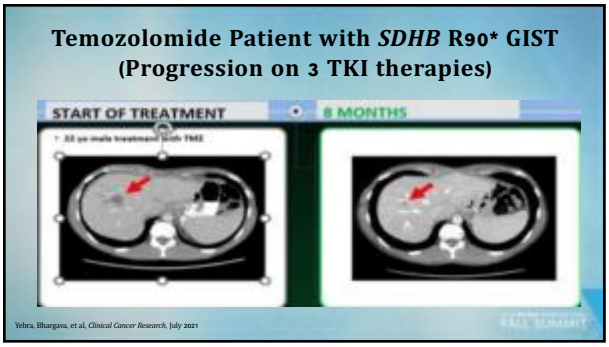
Temozolomide Patient with SDHB R90* GIST
(Progression on 3 TKI therapies)
START OF TREATMENT
8 MONTHS
Yebra, Bhargava, et al, Clinical Cancer Research, July 2021

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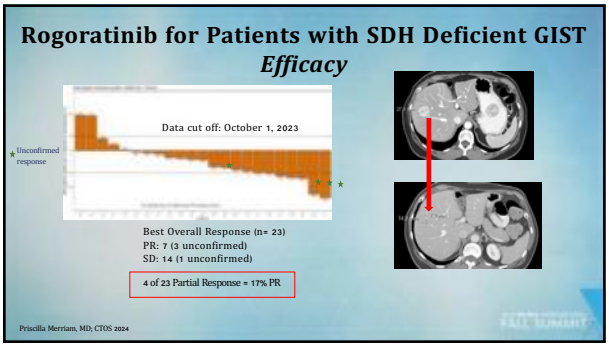
Rogoratinib for Patients with SDH Deficient GIST
Efficacy
Data cut off: October 1, 2023
Unconfirmed response
Best Overall Response (n= 23)
PR: 7 (3 unconfirmed)
SD: 14 (1 unconfirmed)
4 of 23 Partial Response = 17% PR
Priscilla Merriam, MD; CTOS 2024

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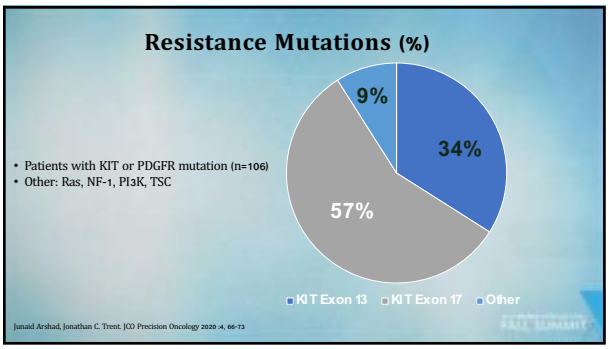
Resistance Mutations (%)
• Patients with KIT or PDGFR mutation (n=106)
• Other: Ras, NF-1, PI3K, TSC
9%
34%
57%
KIT Exon 13
KIT Exon 17
Other
Junaid Arshad, Jonathan C. Trent. JCO Precision Oncology 2020 :4, 66-73

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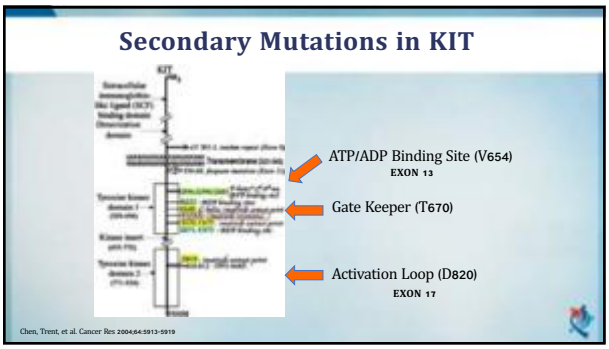
Secondary Mutations in KIT
ATP/ADP Binding Site (V654)
EXON 13
Gate Keeper (T670)
Activation Loop (D820)
EXON 17
Chen, Trent, et al. Cancer Res 2004;64:5913-5919

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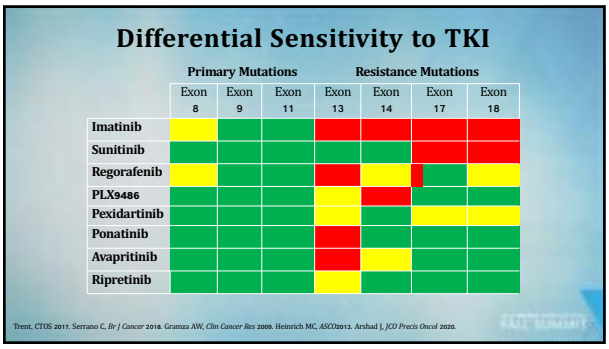
Differential Sensitivity to TKI
Primary Mutations
Resistance Mutations
Exon 8
Exon 9
Exon 11
Exon 13
Exon 14
Exon 17
Exon 18
Imatinib
Sunitinib
Regorafenib
PLX9486
Pexidartinib
Ponatinib
Avapritinib
Ripretinib
Trent, CTOS 2017. Serrano C, Br J Cancer 2018. Gramza AW, Clin Cancer Res 2009. Heinrich MC, ASCO2013. Arshad J, JCO Precis Oncol 2020.

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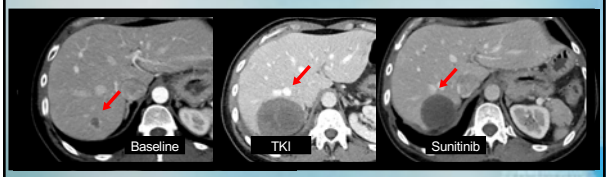
- 52 YO woman with small intestine, ***KIT* exon 11 (L576P)** mutant, GIST with liver metastases
- Initial response to imatinib durable for 2 years
- Progressive on imatinib placed on *KIT* inhibitor a**vapritinib**, rapid progression
- ctDNA revealed ***KIT* exon 13 V654A** resistance mutation
- Placed on s**unitinib** to target *KIT* exon 11 primary and *KIT* exon 13 resistance mutations



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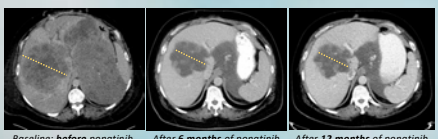
KIT exon 11 resistant GIST with Exon 17 resistance mutation



*Baseline; **before** ponatinib* *After **6 months** of ponatinib* *After **12 months** of ponatinib*

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UTILITY OF ctDNA IN GIST

	ctDNA Mutation+	Tumor FFPE Mutation+	Detection Rate
All Patients	22	36	61%
Primary Tumor	0	6	0%
Metastatic Low Volume	1	6	16%
Metastatic and Responding	0	3	0%
Metastatic and Progressive	21	21	100%

Junaid Arshad, Jon Trent, et al. *JCO Precision Oncology* no. 4 (2020) 66-73.
Arshad, Trent, et al. *JCO Precision Oncology* no. 4 (2020) 66-73.

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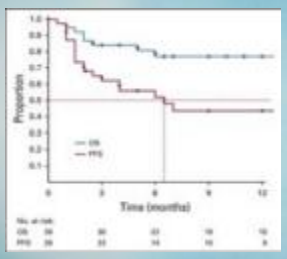
Outcome in the era of ctDNA IN GIST (N=39)



12 months from ctDNA testing (n = 39):

OS = 79.5%; CI 0.66-0.92
PFS = 46.2%; CI 0.32-0.65

Arshad, Trent, et al. *JCO Precision Oncology* no. 4 (2020) 66-73.

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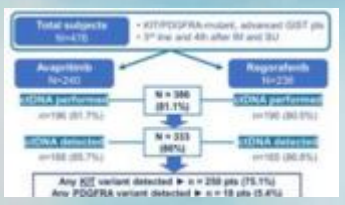
Voyager Trial ctDNA Analysis



ctDNA analyses in phase III VOYAGER trial: KIT mutational landscape and outcomes in pts with advanced GIST

Serrano, Trent, et al. ASCO 2022.

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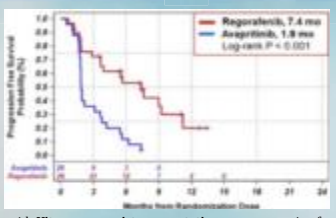
VOYAGER Trial



Patients with **Kit exon 13 resistance mutations** are progression free longer when treated with **regorafenib** over avapritinib

Serrano, Trent, et al. ASCO 2022.

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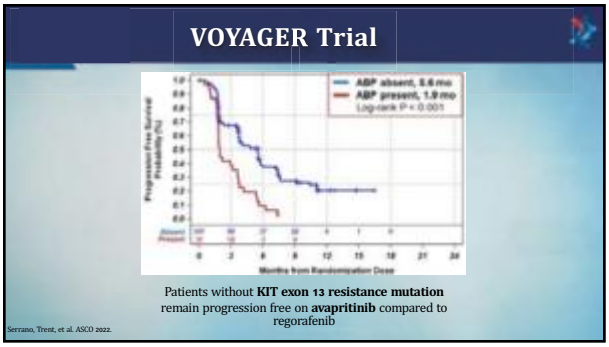
VOYAGER Trial
ABP absent, 5.6 mo
ABP present, 1.9 mo
Log-rank P < 0.001
Progression-Free Survival Probability (%)
Months from Randomization Dose
Patients without KIT exon 13 resistance mutation remain progression free on avapritinib compared to regorafenib
Serrano, Trent, et al. ASCO 2022.

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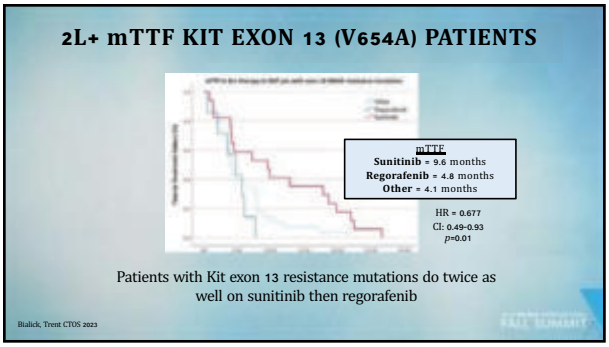
2L+ mTTF KIT EXON 13 (V654A) PATIENTS
mTTF
Sunitinib = 9.6 months
Regorafenib = 4.8 months
Other = 4.1 months
HR = 0.677
CI: 0.49–0.93
p=0.01
Patients with Kit exon 13 resistance mutations do twice as well on sunitinib then regorafenib
Bialick, Trent CTOS 2023

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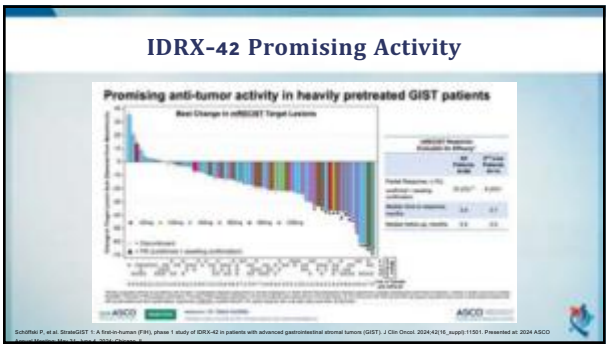
IDRX-42 Promising Activity
Promising anti-tumor activity in heavily pretreated GIST patients
Best Change in mRECIST Target Lesions
ASCO

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IDRX-42 Promising Activity

mRECIST Response Evaluable for Efficacy[1]	All Patients N=66	2nd Line Patients N=14
Partial Response, n (%) confirmed + awaiting confirmation	15 (23)[1,†]	6 (43)[‡]
Median time to response, months	2.6	3.7
Median follow-up, months	5.6	3.0

Schöffski P, et al. StrateGIST 1: A first-in-human (FIH), phase 1 study of IDRX-42 in patients with advanced gastrointestinal stromal tumors (GIST). J Clin Oncol. 2024;42(16_suppl):11501. Presented at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL.

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GIST Subtypes and Treatment

- Kit exon 11: **Imatinib 400 mg**
- Kit exon 9: **Imatinib 800mg (or tolerated dose)**
- PDGFR D842V: **Avapritinib**
- SDH deficiency: **Temozolomide or FGFR inhibitor**
- Raf V600E: **Raf inhibitor**
- NF-1, Ras: **Raf or Mek inhibitor**
- PI3K: **mTOR inhibitor**
- TRK fusion - **NTRK inhibitor (Laro, Entrectinib)**
- KIT resistance mutations
  - Exon 13 (ATP binding site): **Sunitinib 37.5 mg daily**
  - Exon 17 (A-loop): **Regorafenib or Ripretinib**

Jon Trent, MD, PhD

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Clinical Trials for GIST Patients

- Phase 1 Studies
  - Ripretinib + DCC-3116 (Autophagy inhibitor)
  - DCC-3009 (new KIT inhibitor)
  - NN-3201 KIT Antibody Drug Conjugate
  - Imatinib + Ziftomenib (Oral Menin Inhibitor)
  - IDRX-42 (new KIT inhibitor)
  - NB-003, THE-630
- Phase 2 ctDNA-guided therapy for GIST patients (IntelliGIST)
  - Any line prior therapy
  - Must have exon 13/14 or 17/18 resistance mutation
  - ctDNA testing provided
- Phase 3
  - Randomized Sunitinib +/- bezuclastinib (CGT-9486) in 2nd line for GIST patients
  - Randomized Ripretinib vs Sunitinib in KIT exon 17/18 resistant GIST patients (Insight)

Source: ClinicalTrials.gov and ASCO/ESMO 2024-2025 trial updates.

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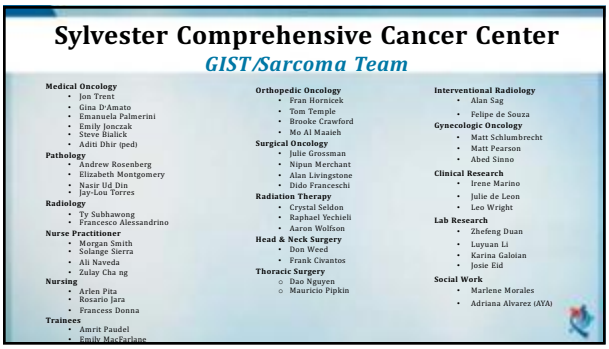
Sylvester Comprehensive Cancer Center
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Emanuela Palmerini
Emily Jonczak
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Aditi Dhir (ped)
Pathology
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Elizabeth Montgomery
Nasir Ud Din
Jay-Lou Torres
Radiology
Ty Subhawong
Francesco Alessandrino
Nurse Practitioner
Morgan Smith
Solange Sierra
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Raphael Yechieli
Aaron Wolfson
Head & Neck Surgery
Don Weed
Frank Civantos
Thoracic Surgery
Dao Nguyen
Mauricio Pipkin
Interventional Radiology
Alan Sag
Felipe de Souza
Gynecologic Oncology
Matt Schlumbrecht
Matt Pearson
Abed Sinno
Clinical Research
Irene Marino
Julie de Leon
Leo Wright
Lab Research
Zhefeng Duan
Luyuan Li
Karina Galoian
Josie Eid
Social Work
Marlene Morales
Adriana Alvarez (AYA)

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THANK YOU!

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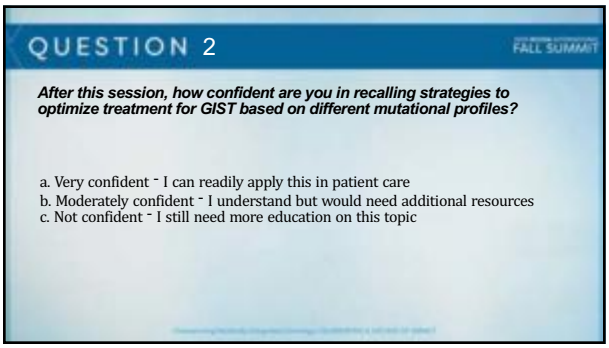
QUESTION 2
FALL SUMMIT
After this session, how confident are you in recalling strategies to optimize treatment for GIST based on different mutational profiles?
a. Very confident - I can readily apply this in patient care
b. Moderately confident - I understand but would need additional resources
c. Not confident - I still need more education on this topic

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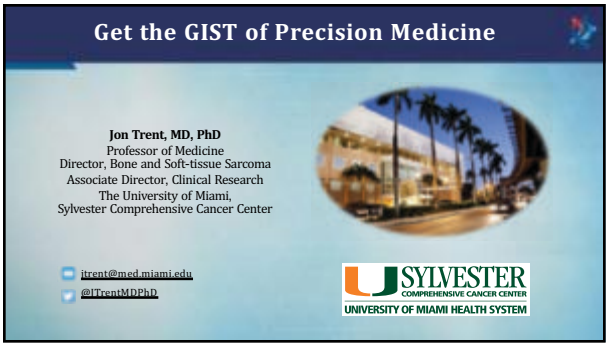
Get the GIST of Precision Medicine
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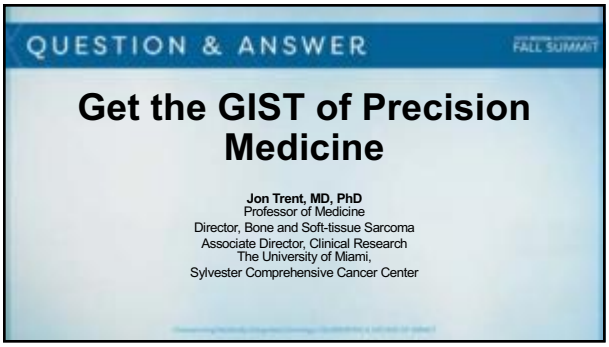
QUESTION & ANSWER
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