

Gastrointestinal Stromal Tumor *LifeFest 2018*

Jon Trent, MD, PhD
Professor of Medicine
Director, GIST and Sarcoma Program
The University of Miami, Sylvester Cancer Center

jtrent@med.miami.edu
305-243-6199



@JTrentMDPhD

GIST Subtypes and Treatment

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

Metastatic Sites

Liver

Peritoneum

Bone

Lung

Lymph node

Spleen

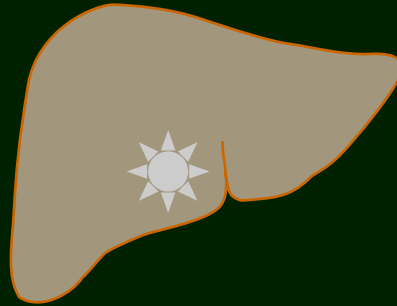
Brain

Heart

Skin

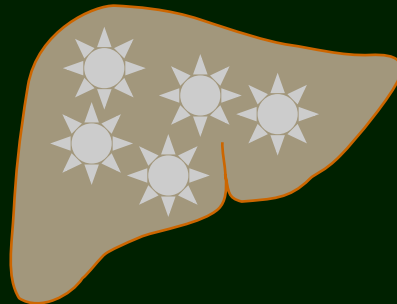
Patterns of Metastasis

Oligometastasis



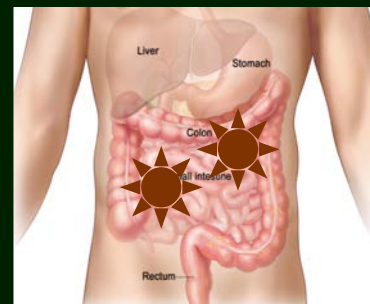
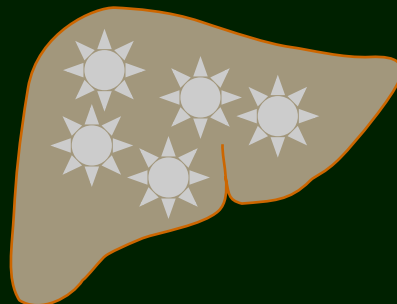
Systemic Therapy
Local Therapy

Single Organ Metastases



Systemic Therapy
Local Therapy

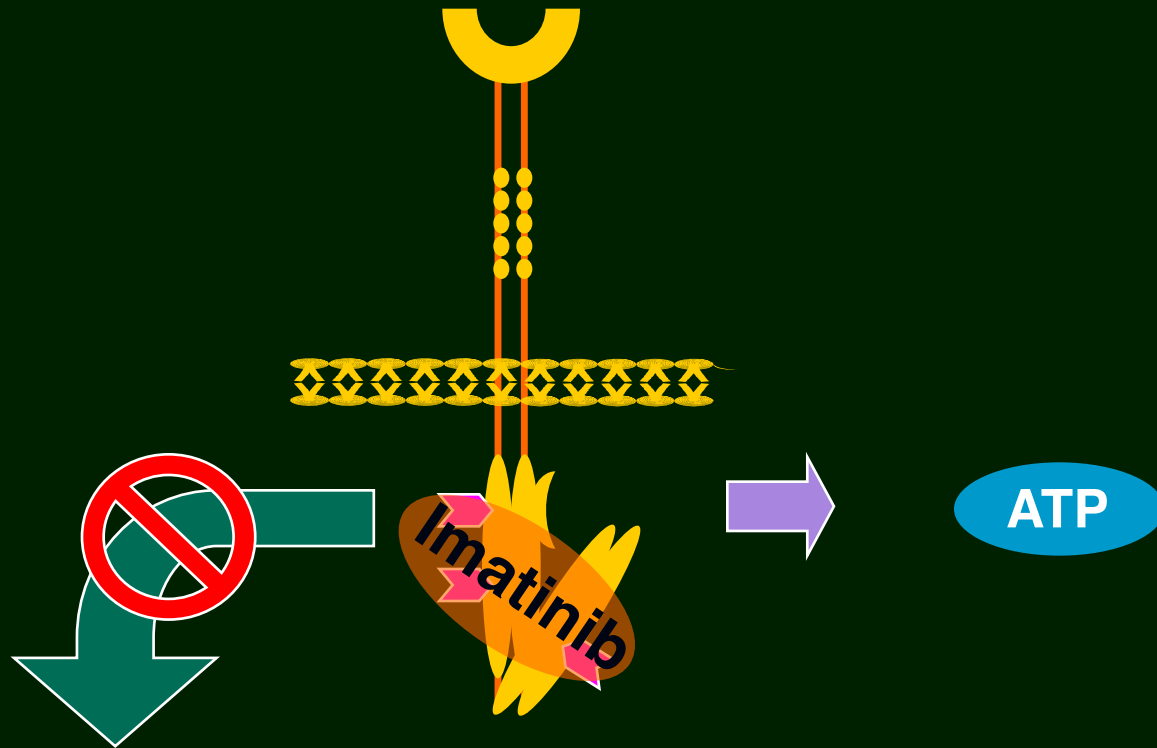
Multi-Organ Metastases



Systemic Therapy



Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

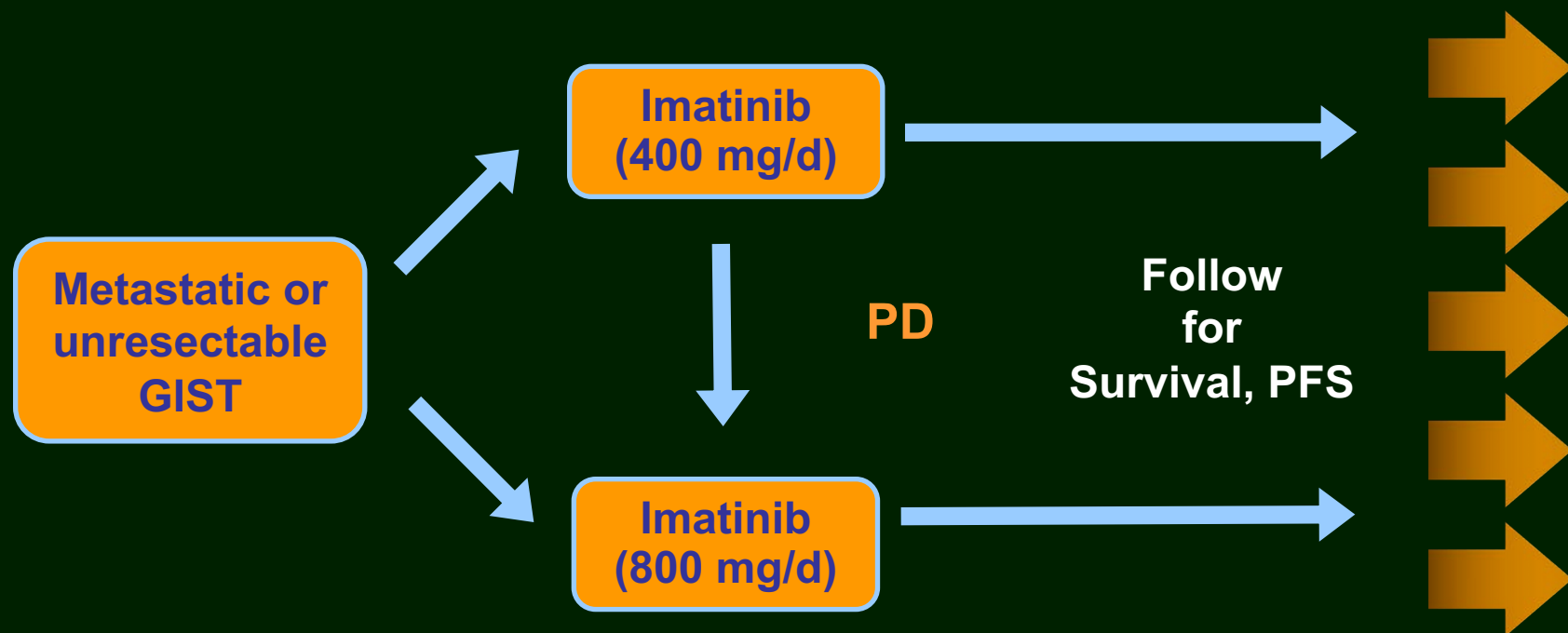
➤ = imatinib contact point

FDA-Approved Therapy

- Imatinib (Gleevec)
- Sunitinib (Sutent)
- Regorafenib (Stivarga)

Ph III Trials: 400 mg/d vs 800 mg/d Imatinib in Advanced GIST

- US Intergroup SWOG S0033 Study
- EORTC 62005 Study



Benjamin RS et al. *Proc Am Soc Clin Oncol*. 2003;22:814. Abst. 3271.

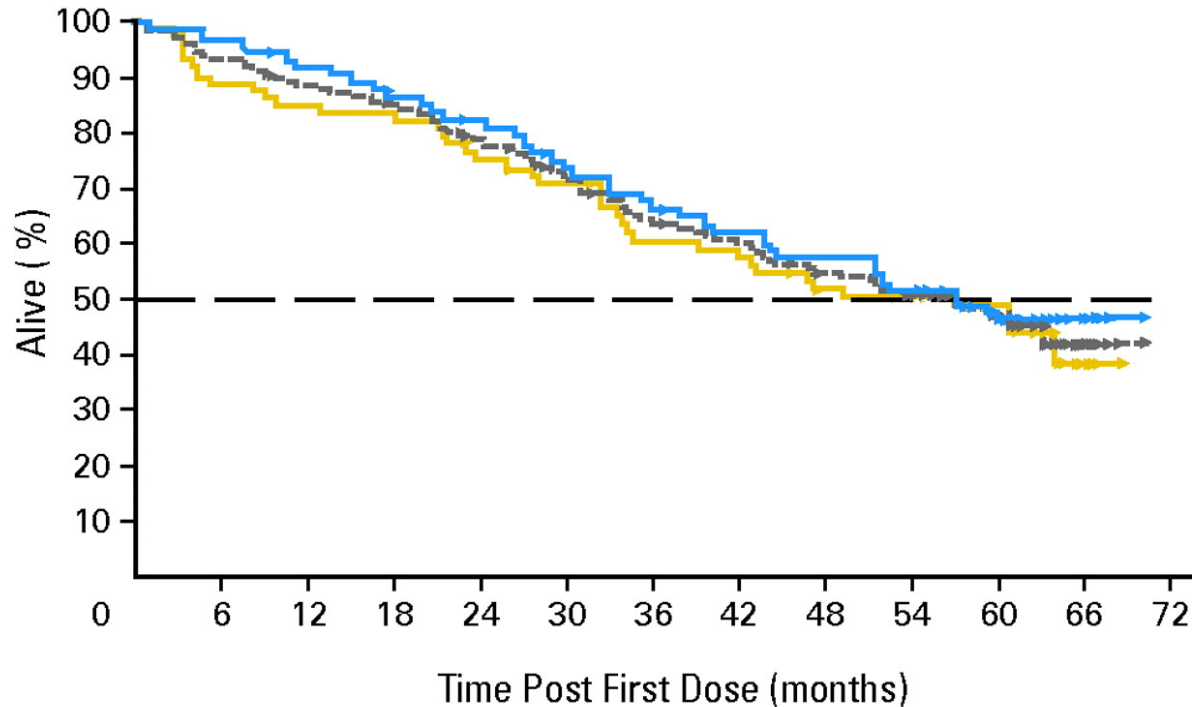
Rankin C et al. *Proc Am Soc Clin Oncol*. 2004;23:815. Abst. 9005.

Verweij J et al. *Proc Am Soc Clin Oncol*. 2003;22:814. Abst. 3272.

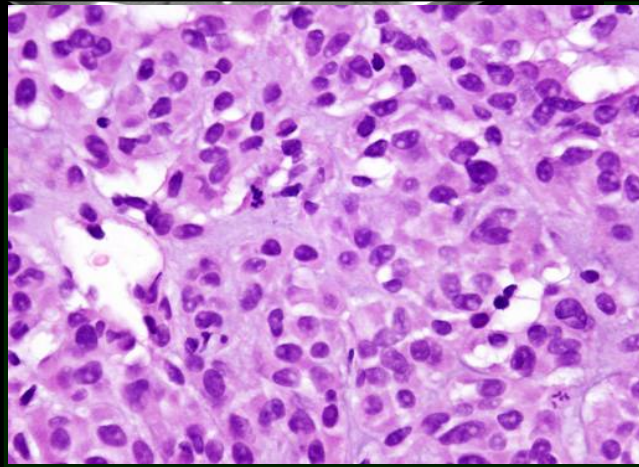
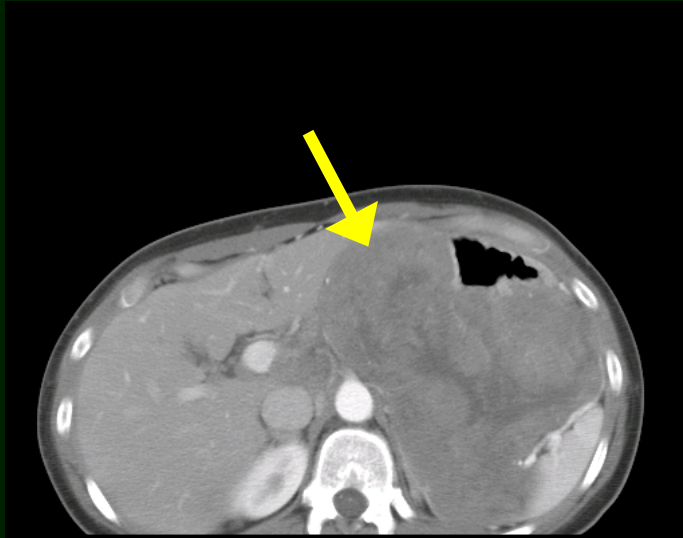
Blanke C et al. *J Clin Oncol*; 2008;26:620

Overall Survival

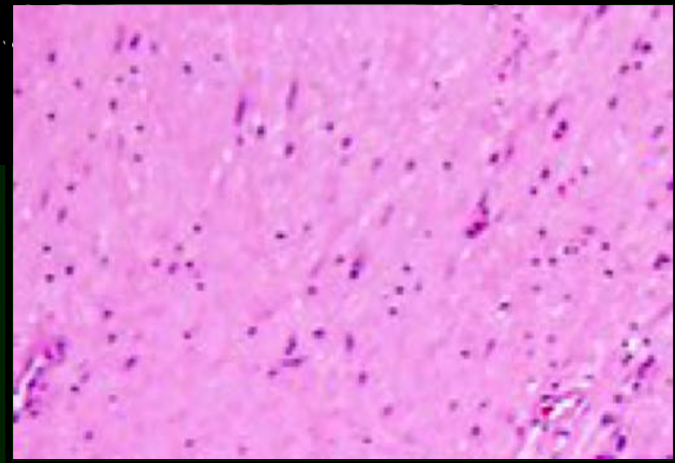
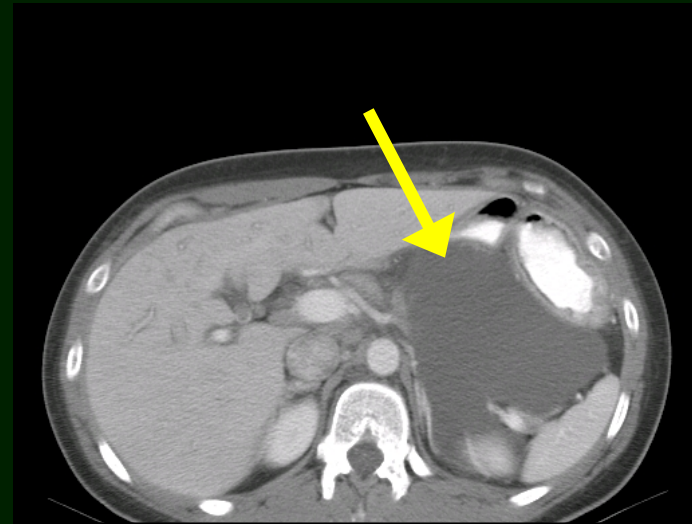
Treatment	No. at risk						Median duration (months)	95% CI	
	Months: 0	12	24	36	48	60		LL	UL
400mg	73	62	54	42	34	26	57	35	N/A
600mg	74	67	58	46	39	28	57	44	N/A
Pooled	147	129	112	88	73	54	57	44	N/A



GIST Response



Pre-Imatinib



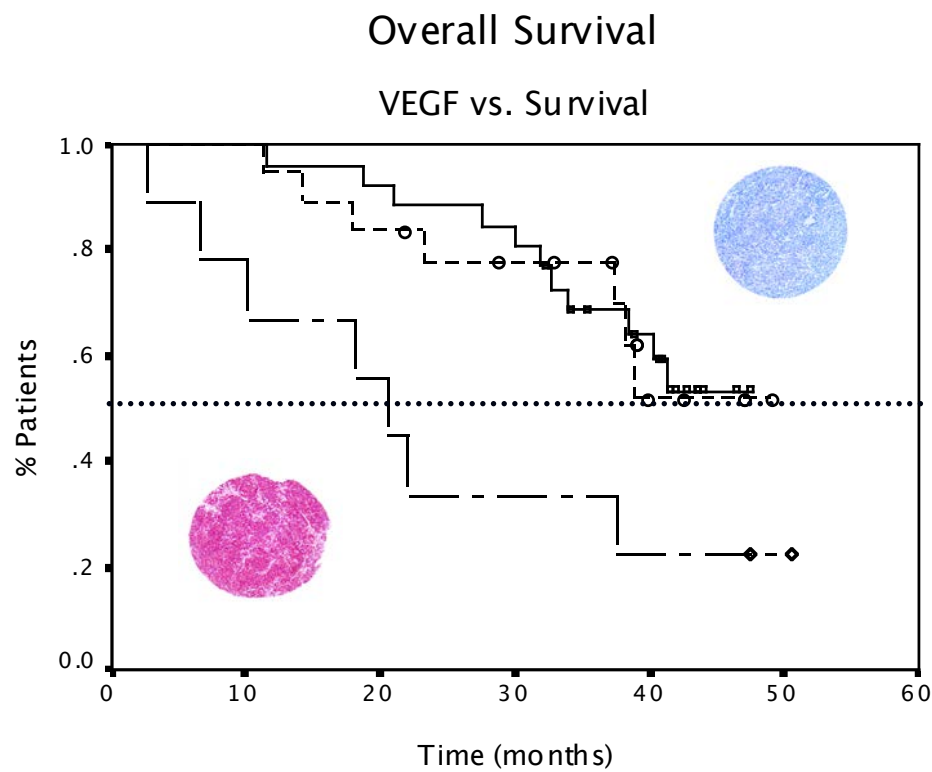
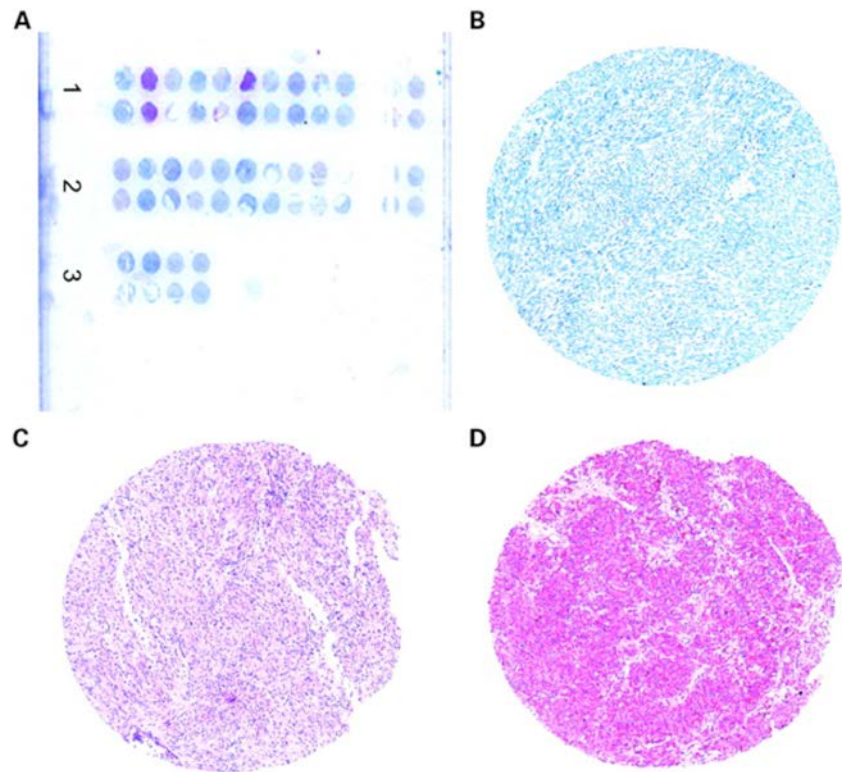
Post-Imatinib (8 weeks therapy)

Side effects: 400 vs. 800 mg

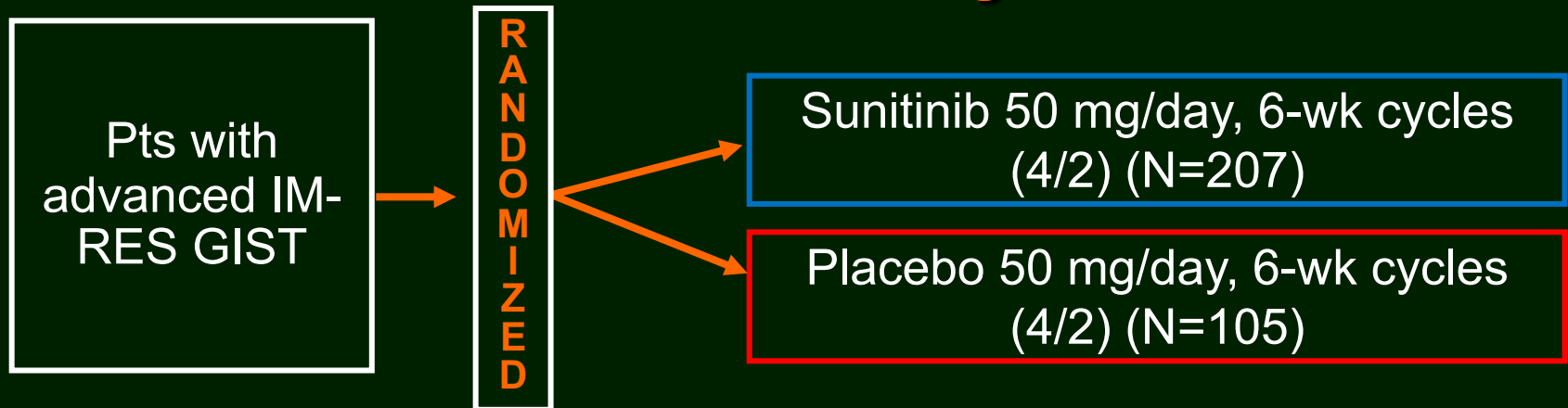
Toxic Event	Adjusted <i>p</i> -Value
Edema	<0.001
Anemia	<0.001
Rash	<0.001
Fatigue	<0.001
Nausea	<0.001
Hemorrhage	<0.001
Diarrhea	0.0026
Dyspnea	0.036
Pleuritic Pain	0.053

Association of Intratumoral Vascular Endothelial Growth Factor Expression and Clinical Outcome for Patients with Gastrointestinal Stromal Tumors Treated with Imatinib Mesylate

John C. McAuliffe¹, Alexander J.F. Lazar², Dan Yang¹, Dejka M. Steinert¹, Wei Qiao³, Peter F. Thall³, A. Kevin Raymond², Robert S. Benjamin¹ and Jonathan C. Trent¹



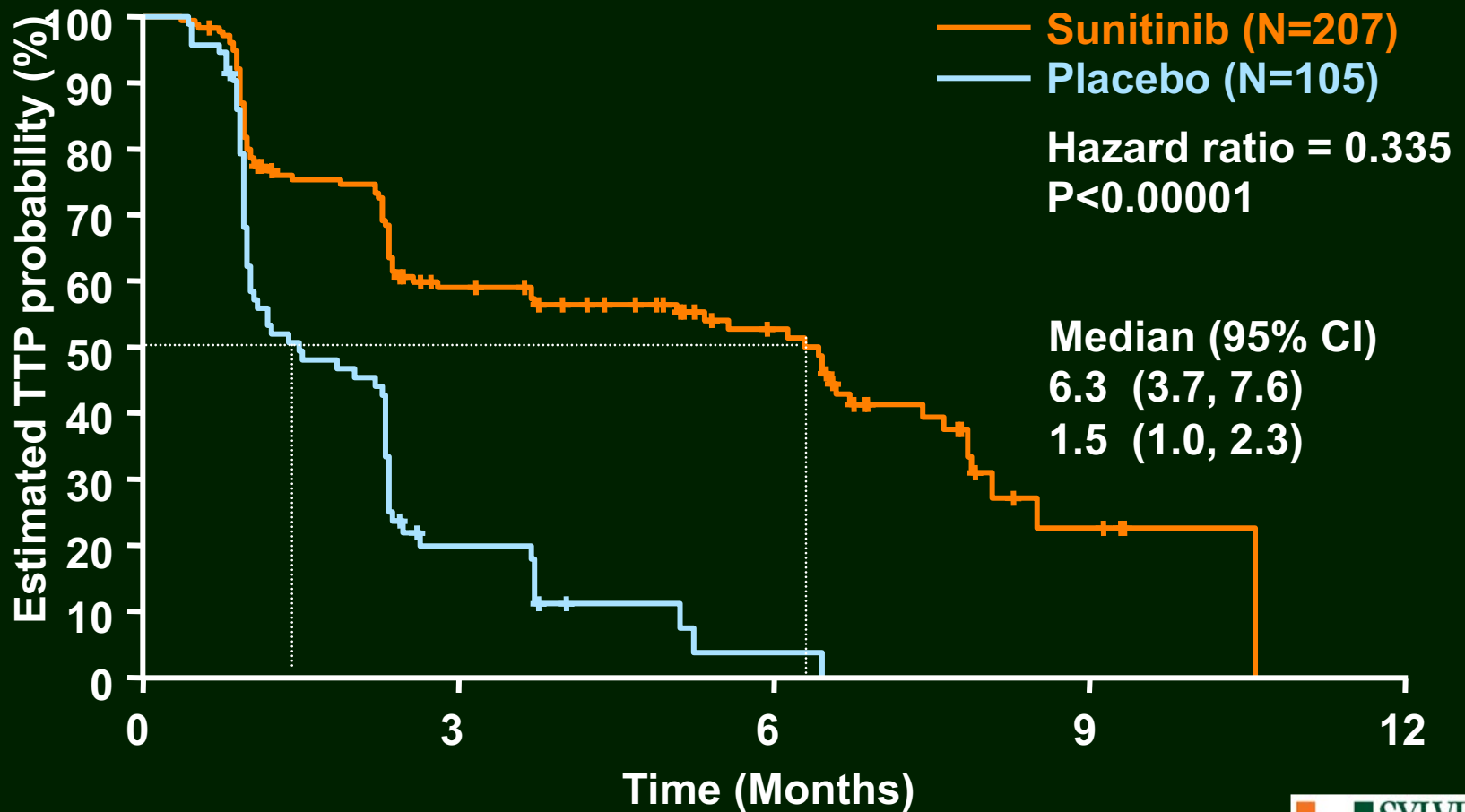
Sunitinib Efficacy in Patients With Imatinib-Refractory GIST



- Primary endpoint **2:1**
 - TTP, as defined using RECIST
- Secondary endpoints
 - PFS, OS, ORR, TTR, DOR, and duration of PS maintenance
- At RECIST-defined disease progression, pts receiving placebo were eligible for crossover

IM=imatinib; ORR=overall response rate; RES=resistant; TTP=time to progression; TTR=time to tumor response.

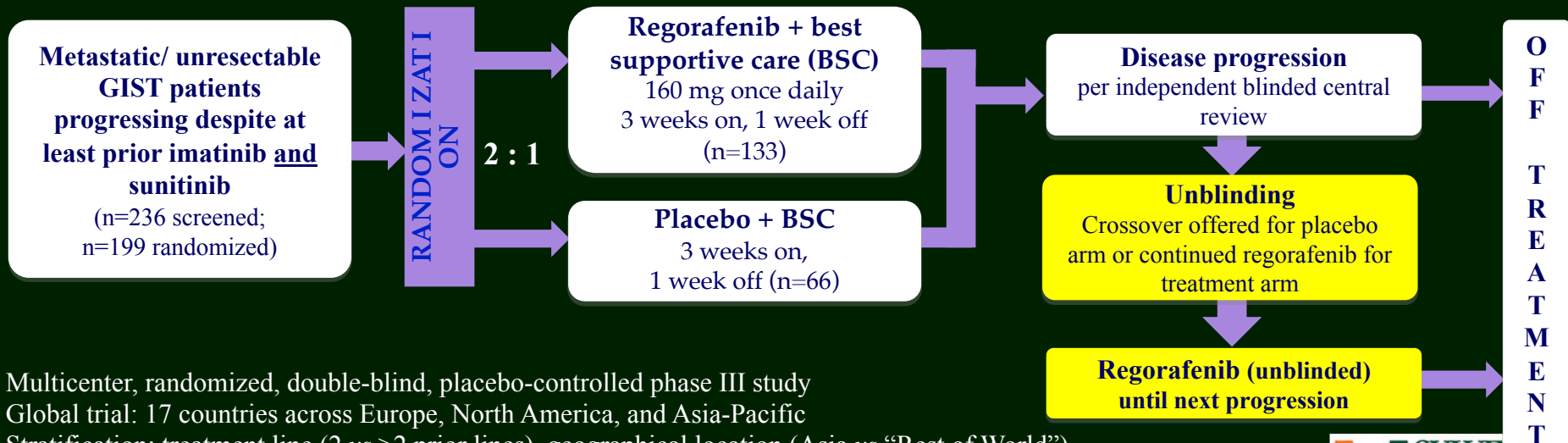
Time to Tumor Progression



Regorafenib For Imatinib-Resistant GIST

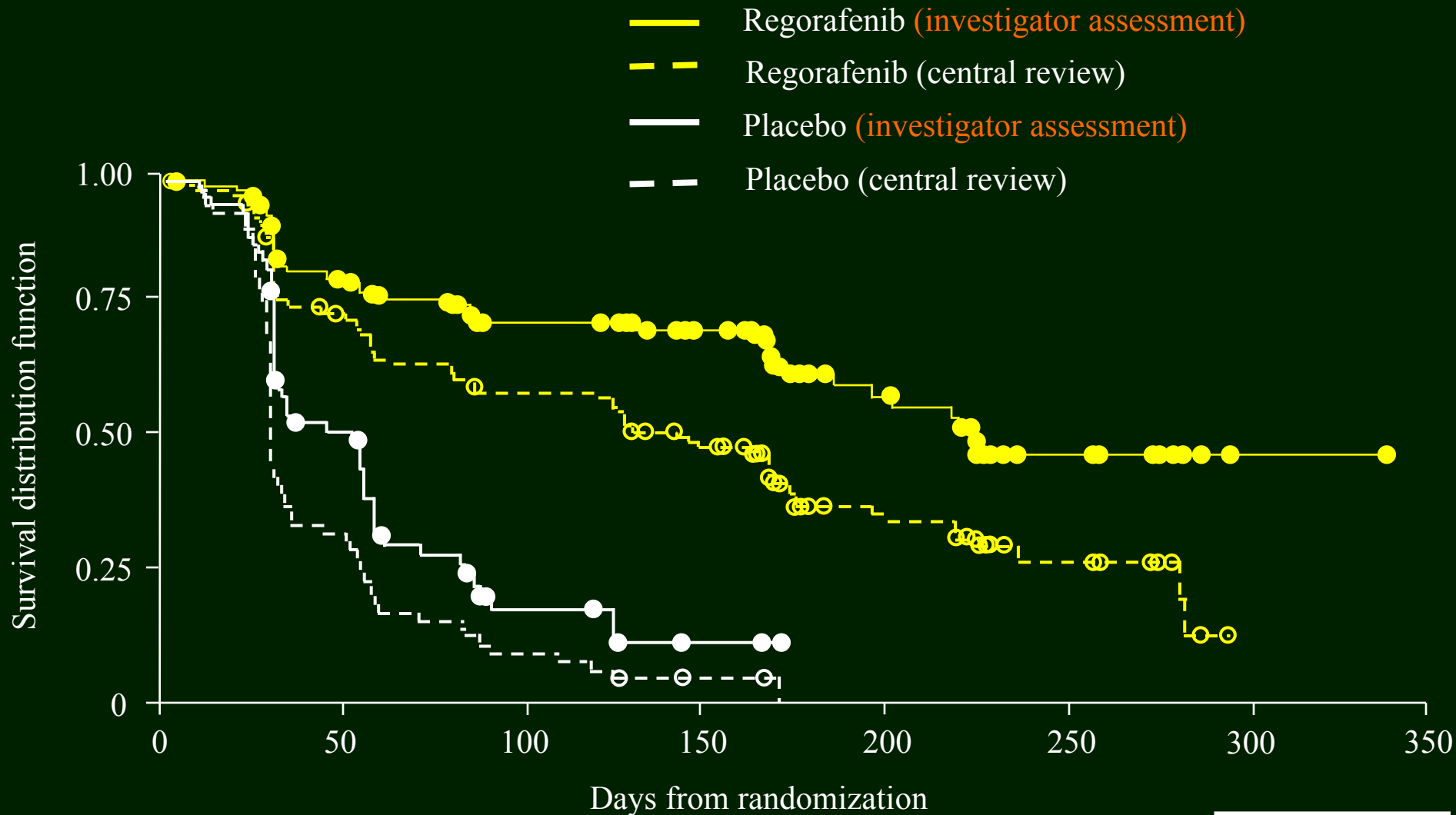
- >85% of patients progress after imatinib and sunitinib
- Regorafenib inhibits kinases including KIT, PDGFRA, FGFR, VEGFR 2,3, TIE-2, and B-RAF.

GIST – Regorafenib In Progressive Disease (GRID): Study design

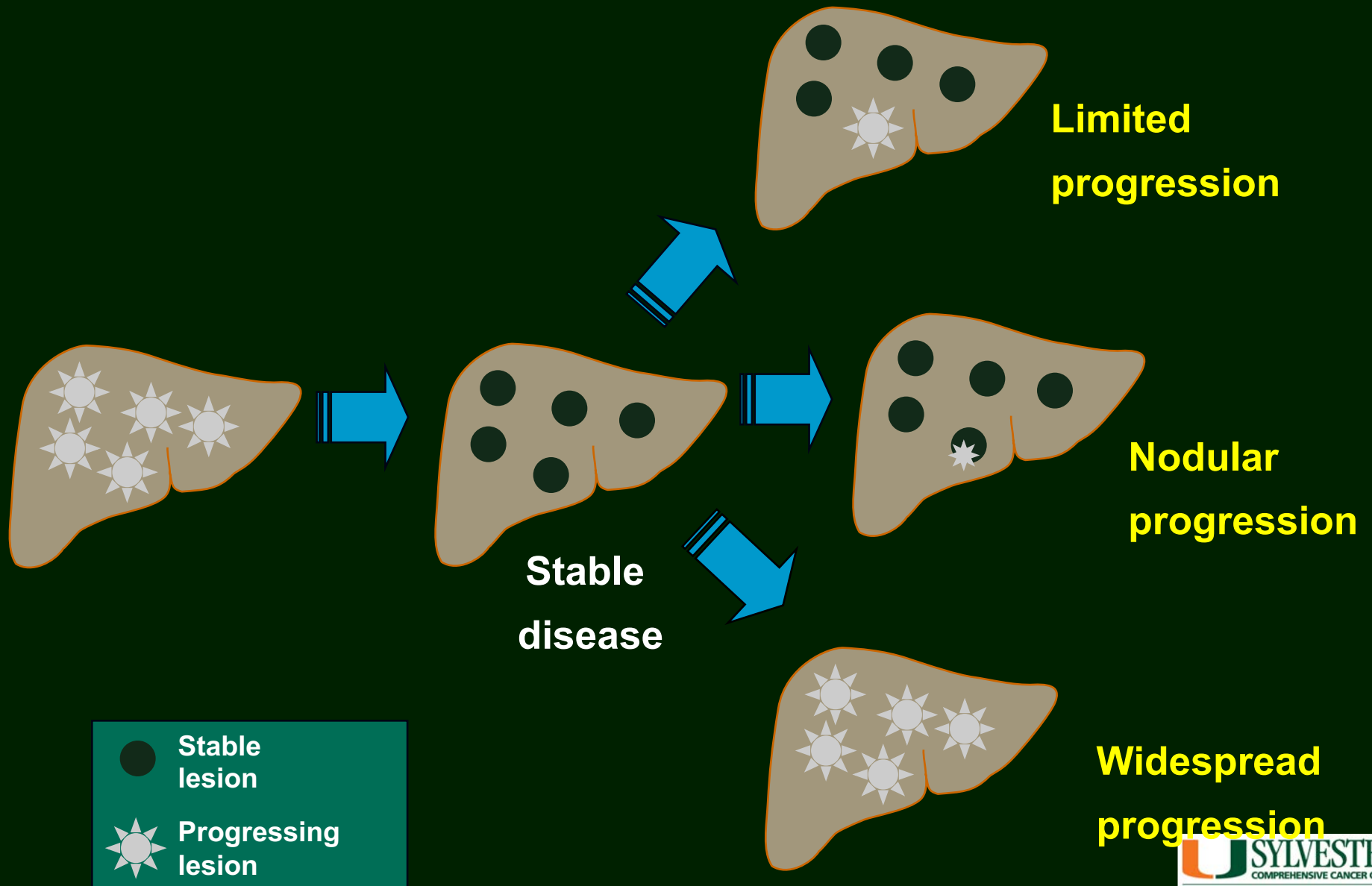


Multicenter, randomized, double-blind, placebo-controlled phase III study
Global trial: 17 countries across Europe, North America, and Asia-Pacific
Stratification: treatment line (2 vs >2 prior lines), geographical location (Asia vs “Rest of World”)

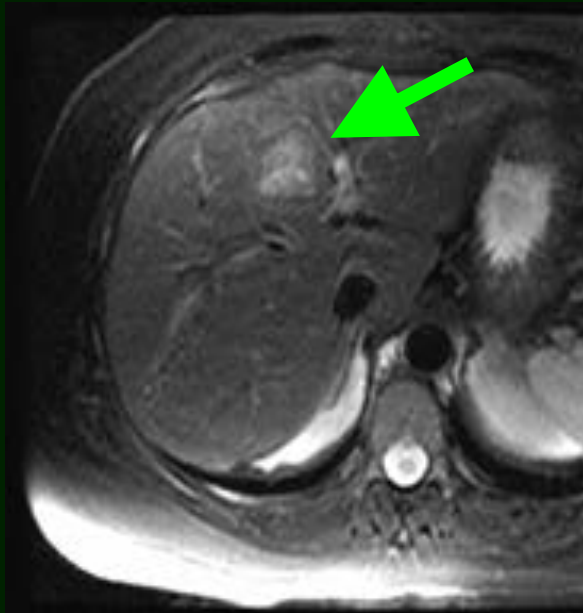
Progression-free survival: Comparison of Central Review vs. Investigator Assessments



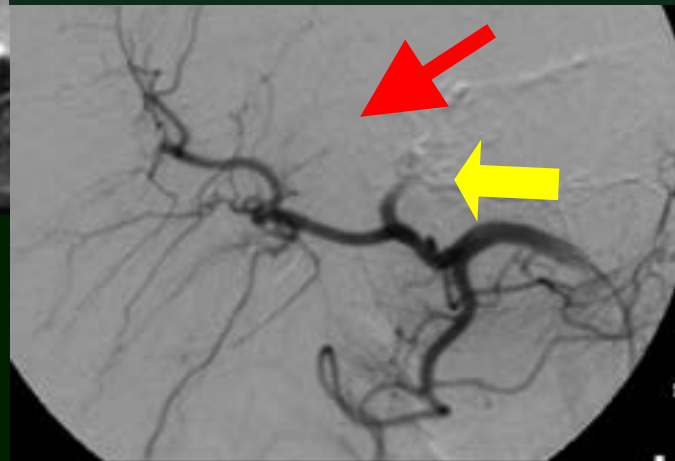
Type of Progression



Hepatic Artery Embolization



Pre-
embolization



Post-
embolization

Off-label with Rationale

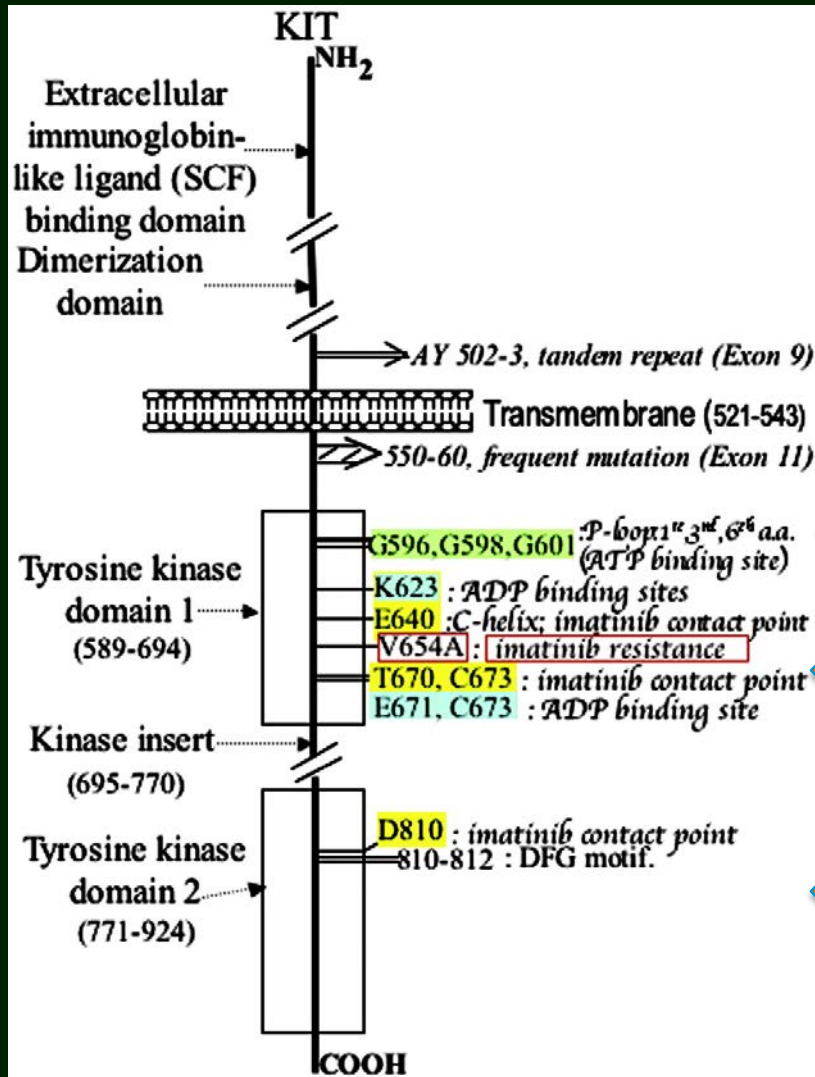
- KIT / PDGFR inhibitors
- RAF inhibitors
- mTOR inhibitors

Off-Label

FDA-approved but not for GIST

Class	Agent	Trial Phase	Results
KIT Inhibitors	Sorafenib	II	PR=13%, SD=58% PFS=5 months
	Dasatinib	II	PR=22%, SD=24% PFS= 2 months
	Nilotinib	I/II/III	PR=10%, SD=37% PFS=3 months
	Pazopanib	II	PazoGIST, PFS-1.9 months
	Ponatinib	II	Exon 11 CBR 37%, PFS 4.3 months
	Axitinib	ND	ND
RAF Inhibitors	Vemurafenib	ND	ND
	Dabrafenib	ND	ND
mTOR Inhibitors	Everolimus	II	PR=2%, SD=43% PFS=3.5 months
	Temsirolimus	ND	ND

Resistance Mutations in KIT



ATP/ADP Binding Site (V654)

Gate Keeper (T670)

Activation Loop (D820)

Primary Mutations

Protein Domain

Secondary Mutations

Drug Sensitivity

KIT Receptor

Exon 9 : 12%
Exon 11: 70%

Exon 13: 1%
K642E

Exon 17: 1%
N822H/K, D820Y

Ligand binding

JM

ATP binding

Activation Loop

Exon 13

Exon 14

Exon 17

Exon 18

V654A

T670I

D816A/G/H/V

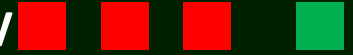
D820A/E/G/Y

N822H/K

Y823D

A829P

IM SU REG PON



Resistant
Intermediate
Sensitive

NR

Not reported

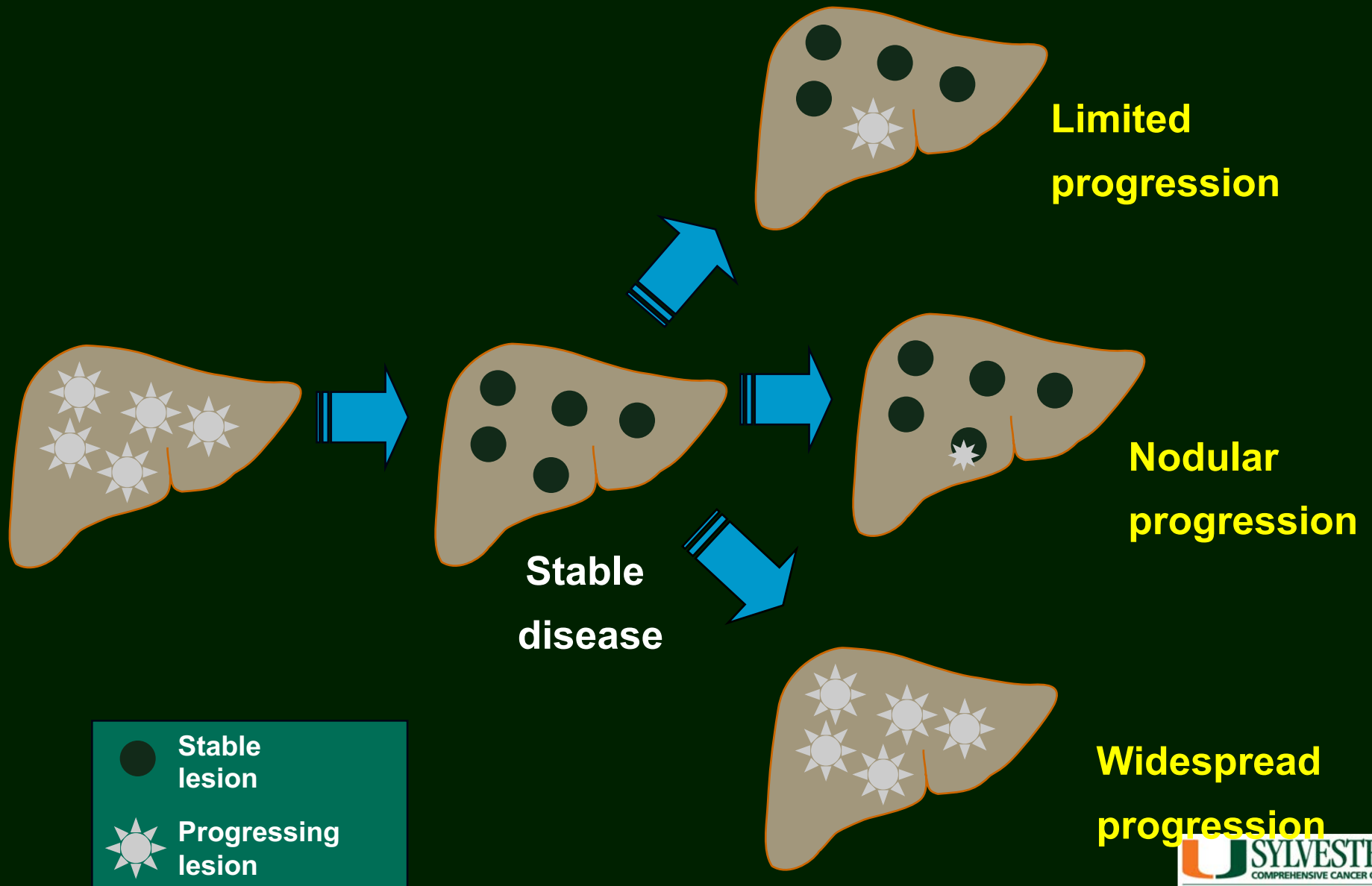


Trent, ASCO 2017

Gramza et al, Clinical Cancer Research 15:7510, 2009

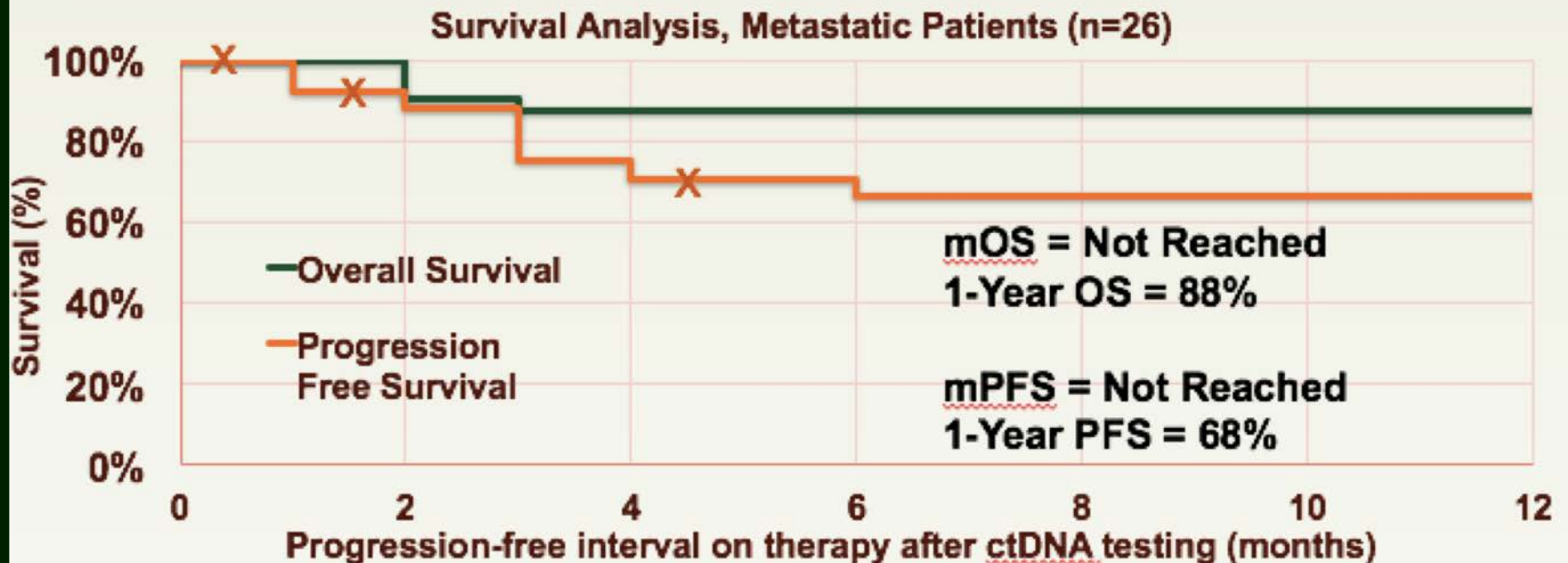
Heinrich et al, ASCO 2013 Poster/Abstract 10509

Type of Progression



Circulating Tumor DNA

Overall and Progressions-Free Survival



Ponatinib

Case: *KIT Exon 11(W557-K558del)*, *KIT Exon 17 (Y823D)* ctDNA

Baseline



6 months



12 months



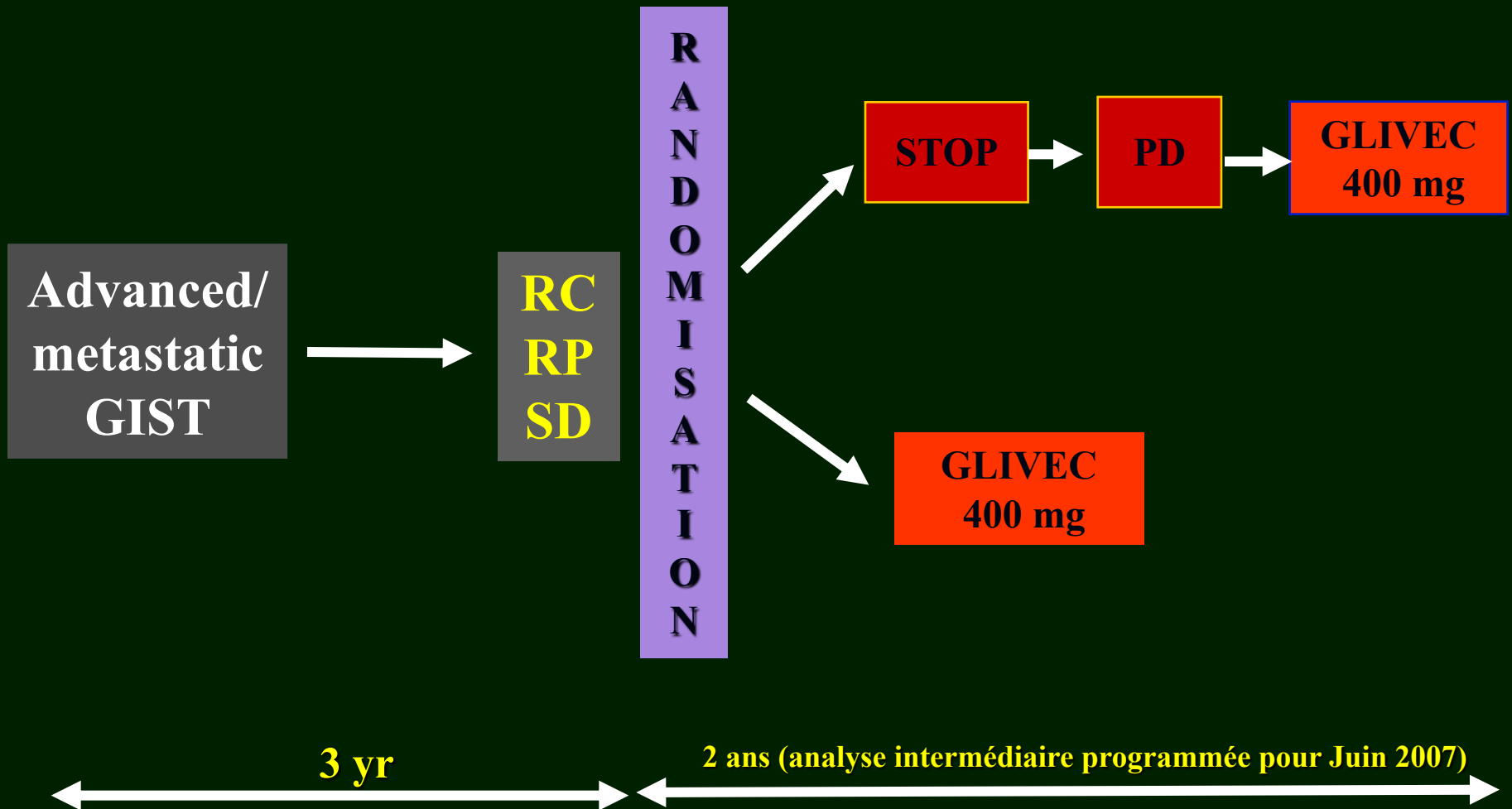
Clinical Trials

- KIT / PDGFR inhibitors
- KIT / PDGFR inhibitors plus Other
- Other
 - Downstream inhibitors
 - Immunotherapy including cellular therapy



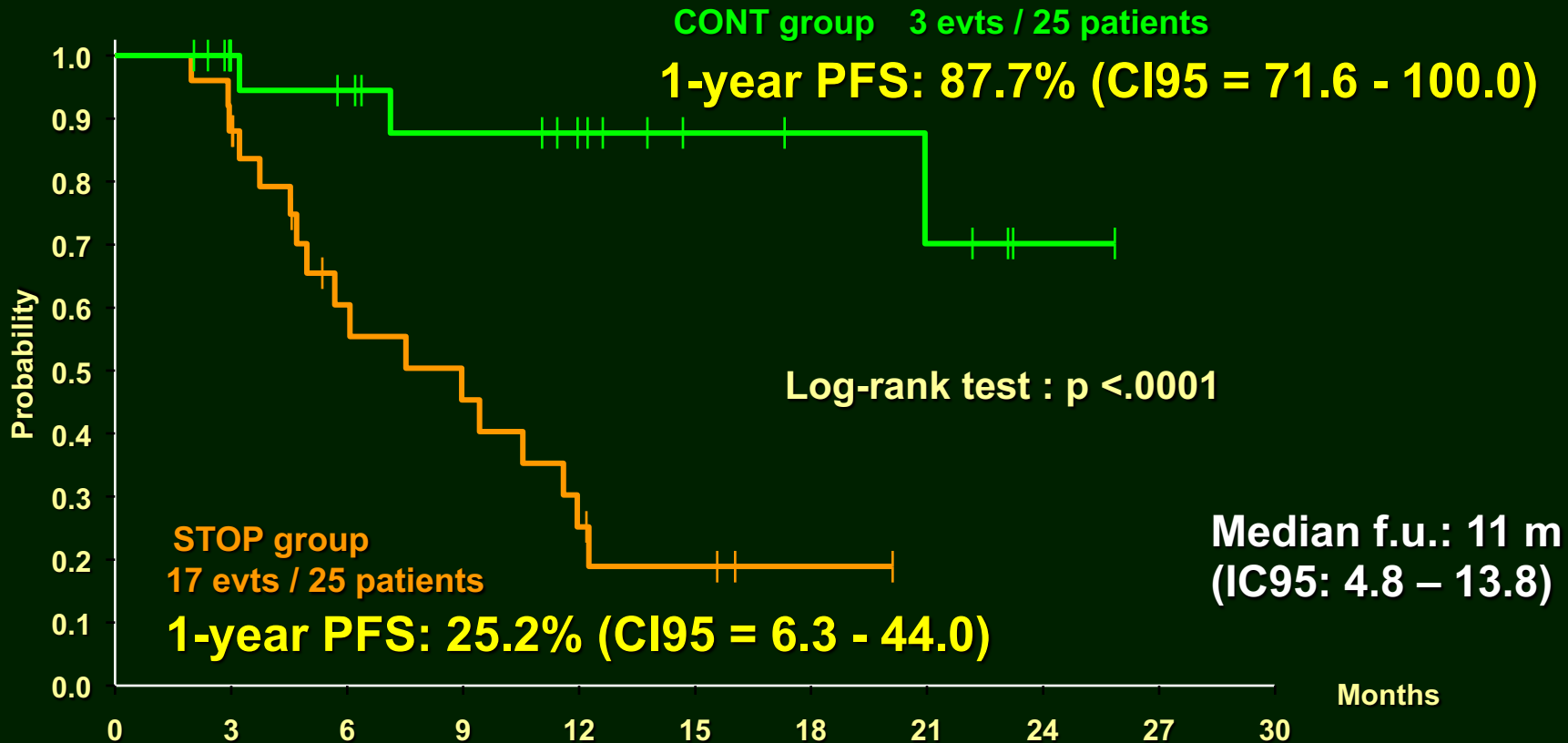
Why Continue KIT Inhibitors?

BFR14 3-yr randomization



BFR14 3-yr randomization

Progression Free Survival



**Rate of PD
in STOP group**

at 6 months: 40%
at 9 months: 55%
at 1 year: 75%

Molecular Decision-Making in GIST

Optimal therapy for GIST patients requires molecular decision-making

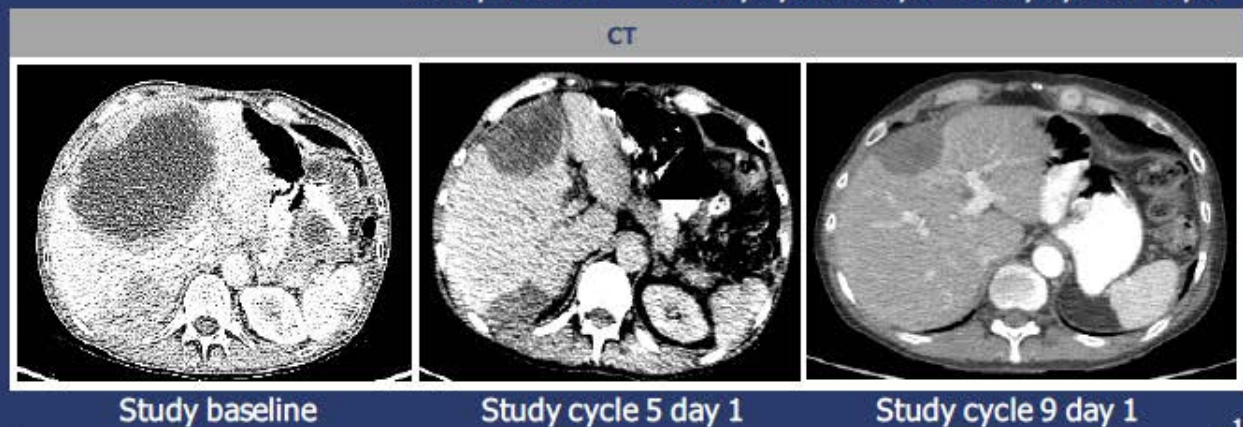
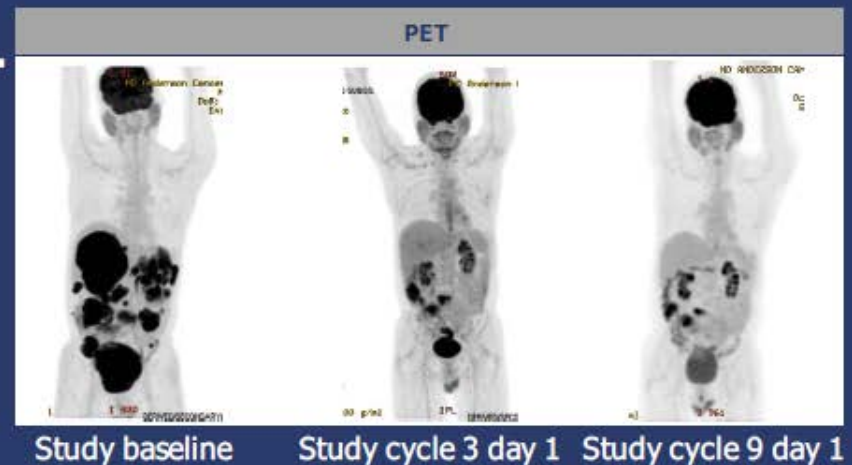
- Kit exon 9: **Imatinib 800mg (or tolerated dose)**
- PDGFR D842V: **anti-PDGFR trial**
- SDH-B deficiency: **Sunibitnib or Regorafenib**
- Raf V600E: **Raf inhibitor**
- NF-1, Ras: **Raf inhibitor?**
- PI3K: **mTOR inhibitor**
- KIT secondary mutations
 - Exon 13 (ATP binding site): **Sunitinib 37.5 mg daily**
 - Exon 17 (A-loop): **Regorafenib 120 mg daily**
- IGF-1R expressing – IGF-1R inhibitors
- TRK fusion – **LOXO-101**

Applying precision medicine to GIST

LOXO-101 AACR 2016

Patient #2: ETV6-NTRK3 fusion GIST

- 55 yo male with GIST progressed through imatinib, sunitinib, sorafenib, nilotinib, and regorafenib
- 150mg BID
- Confirmed partial response
- Currently on study in cycle 10



GIST Subtypes and Treatment

- Kit exon 11: Imatinib 400 mg
- Kit exon 9: Imatinib 800mg (or tolerated dose)
- PDGFR D842V: anti-PDGFR trial
- SDH deficiency: Sunitinib or Regorafenib
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf inhibitor?
- PI3K: mTOR inhibitor
- KIT resistance mutations
 - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
 - Exon 17 (A-loop): Regorafenib 120 mg daily
- IGF-1R expressing – IGF-1R inhibitors
- TRK fusion – LOXO-101 NTRK inhibitor

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 - Pat Benedetto
 - Matteo Truco
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 - Andrew Rosenberg
 - Darcy Kerr
- **Radiology**
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 - John Stewart Jarboe
- **Social Work**
 - Lisa Merheb

GIST Team

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