

# GIST Update

## Circulating Tumor DNA and ImmunoOncology

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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**)
  - **Imatinib** (PFS = 24 months)
  - **Sunitinib** (PFS = 6 months)
  - **Regorafenib** (PFS = 5 months)
  - **Ripretinib** (PFS = 6 months)
  - **Placebo** (PFS = <1 month)



# 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

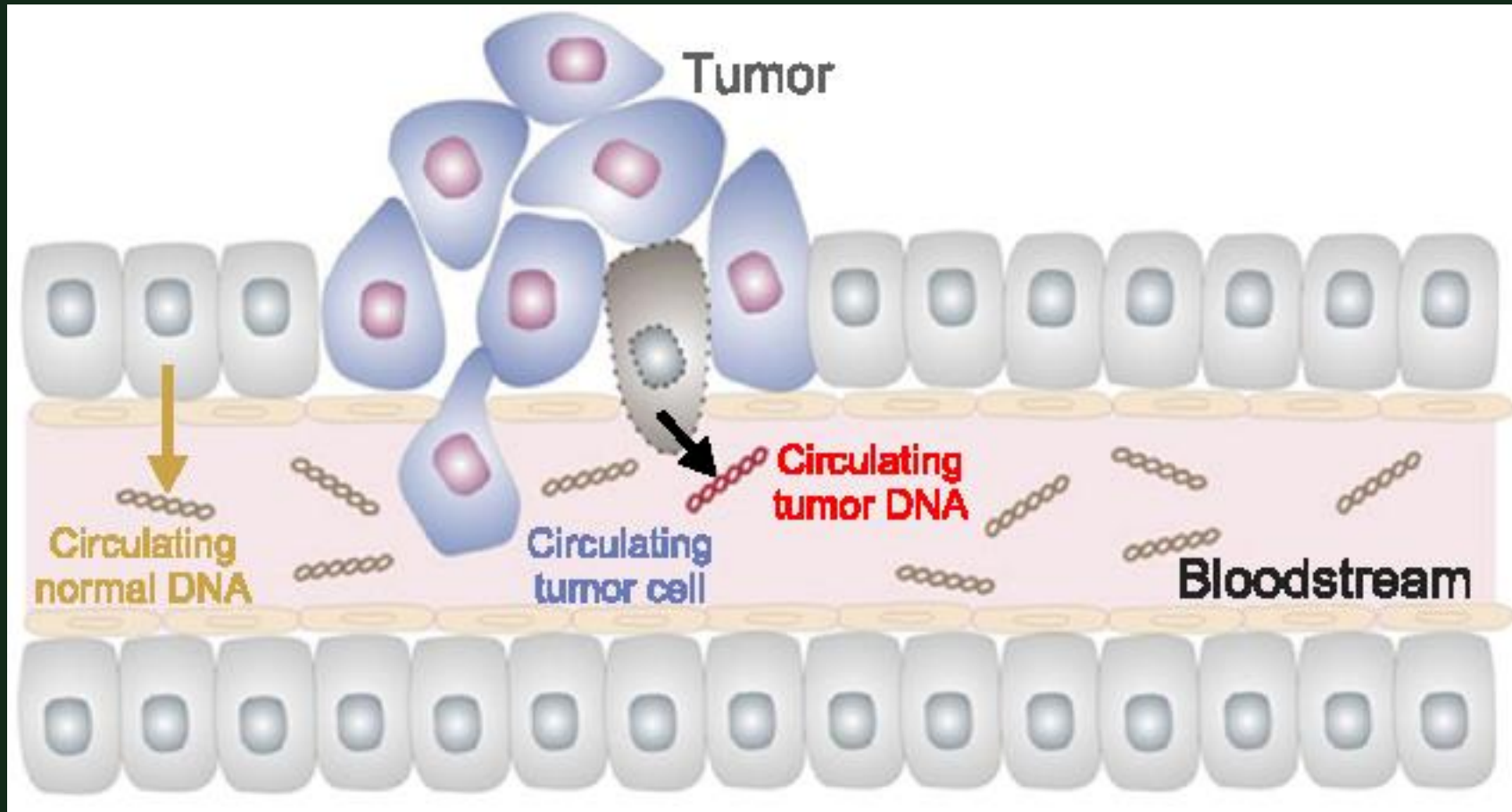
IGF-1R expressing

TRK fusion



# Circulating Tumor DNA

## *Mutation Testing From Blood (Liquid Biopsy)*



Nurwidya et al, 2018  
Bauer JCO 2015  
Serrano BJC 2018



*Utility of circulating tumor DNA in the  
management of patients with  
Gastrointestinal Stromal Tumor (GIST)*



# Study Design

- IRB-approved protocol
- Analysis of **243 GIST patients**
- Patient data extracted then stored in a HIPPA compliant database
- ctDNA extracted from blood samples
- **NGS sequencing** performed on blood (ctDNA) and tumor (FFPE)



# NGS Sequencing

- The ctDNA samples are tested using CAP accredited panel
  - 73 gene mutation
  - 18 genes amplifications
  - 6 gene fusions
  - 23 gene insertions or deletions
- FFPE sequencing by Sylvester GIST panel or external source



# Results

## *Patients and Samples*

<b>Patients</b>	<b>Samples</b>
243 tested	279 tested
45 single institution	62 single institution
198 other institution	217 other institution



# Results

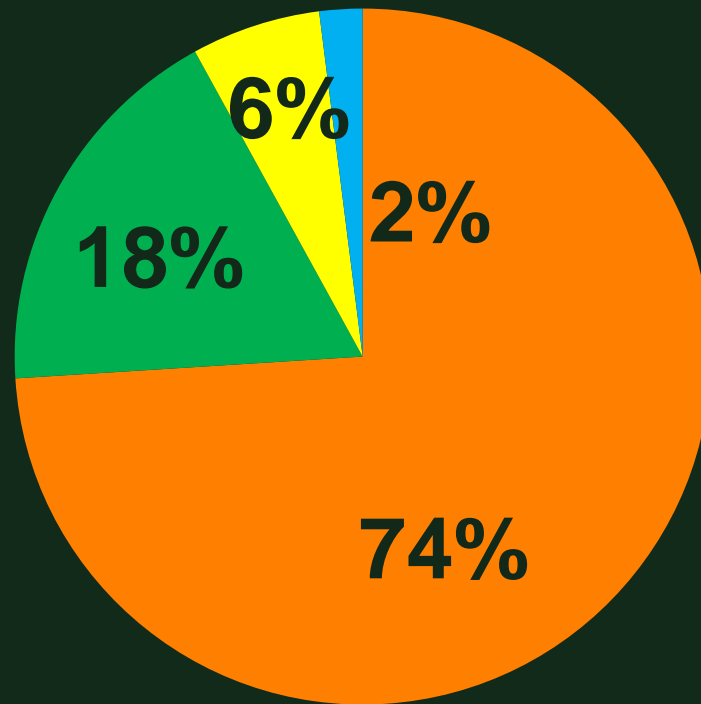
## *Tumor Characteristics*

<b>Tumor Variables</b>	<b>Characteristics (N=45)</b>
<b>Size (median, cm)</b>	10.7 (Range 1.7-35)
<b>Primary Location</b>	
<b>Stomach</b>	23 (51%)
<b>Small Intestine</b>	16 (35%)
<b>Colon</b>	2 (4%)
<b>Rectum</b>	1 (2%)
<b>Unknown</b>	3 (6%)
<b>Mitotic rate (median, /50hpf)</b>	6 (Range, 0-100)
<b>Localized/Metastatic</b>	
<b>Localized</b>	6 (13%)
<b>Metastatic</b>	39 (87%)



# Mutation Status

*Tumor FFPE (N=45)*



■ KIT Exon 11

■ Kit Exon 9

■ PDGFR

■ PDGFRD842V

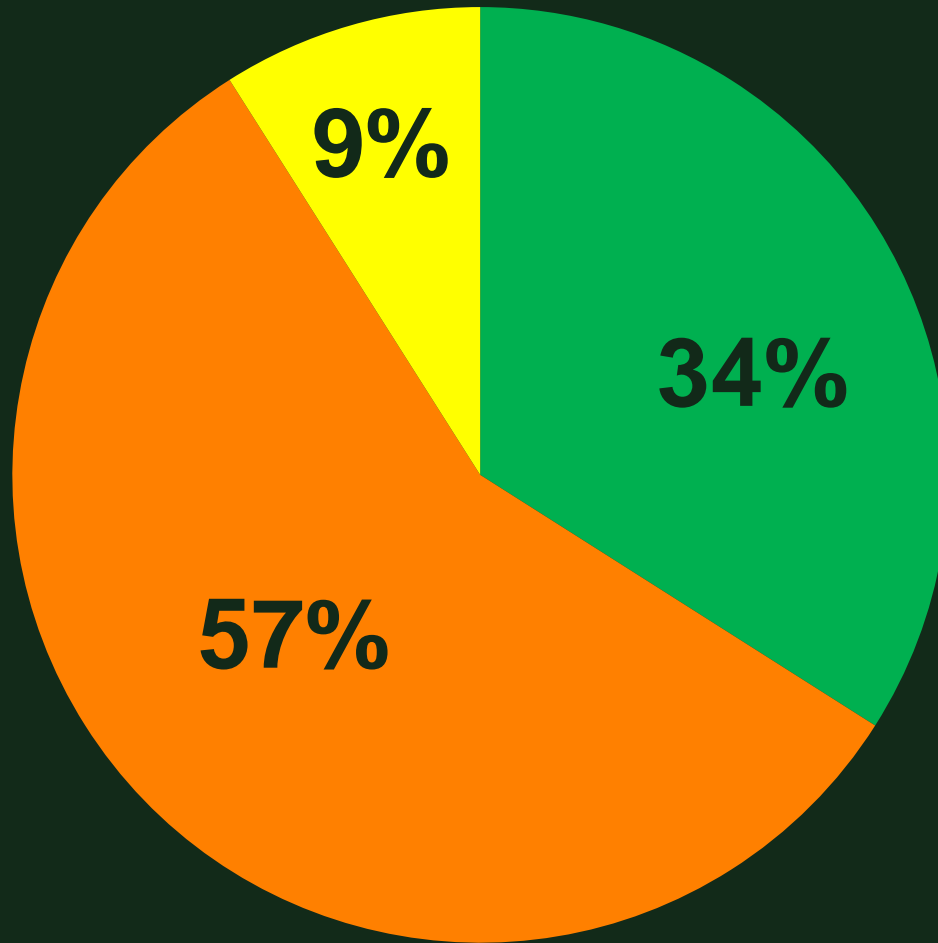


# ctDNA Subset Analysis (N=45)

	<b>ctDNA Mutation+</b>	<b>Tumor FFPE Mutation+</b>	<b>Detection Rate</b>
<b>All Patients</b>	30	45	67%
<b>Primary Tumor</b>	0	6	0%
<b>Metastatic Low Volume</b>	1	11	9%
<b>Metastatic and Responding</b>	0	4	0%
<b>Metastatic and Progressive</b>	29	35	83%



# Resistance Mutations (%)



- Patients with KIT or PDGFR mutation (n=106)
- Other: Ras, NF-1, PI3K, TSC

■ KIT Exon 13   ■ KIT Exon 17   ■ Other



# Differential Sensitivity to TKI

	Primary Mutations			Resistance Mutations			
	Exon 8	Exon 9	Exon 11	Exon 13	Exon 14	Exon 17	Exon 18
<b>Imatinib</b>	Yellow	Green	Green	Red	Red	Red	Red
<b>Sunitinib</b>	Green	Green	Green	Green	Green	Red	Red
<b>Regorafenib</b>	Yellow	Green	Green	Red	Yellow	Green	Yellow
<b>PLX9486</b>	Green	Green	Green	Yellow	Red	Green	Green
<b>Pexidartinib</b>	Green	Green	Green	Yellow	Green	Yellow	Yellow
<b>Ponatinib</b>	Green	Green	Green	Red	Green	Green	Green
<b>Avapritinib</b>	Green	Green	Green	Red	Yellow	Green	Green
<b>Ripretinib</b>	Green	Green	Green	Yellow	Green	Green	Green

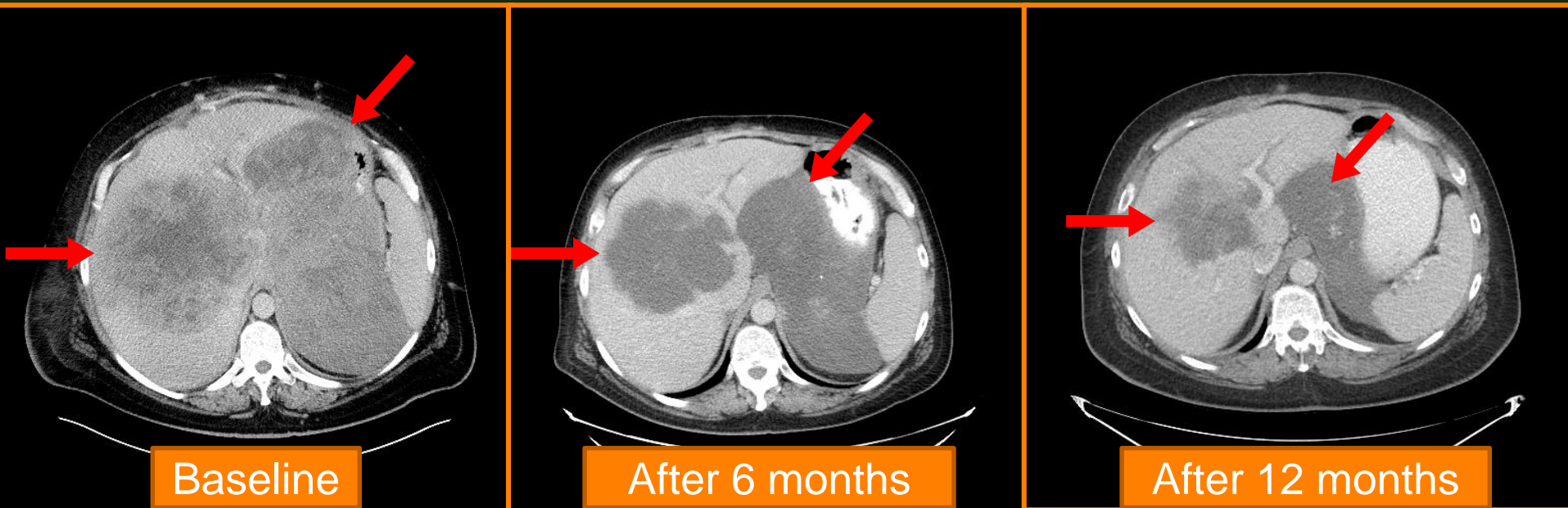
Trent, CTOS 2017; Serrano BJC 2018

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

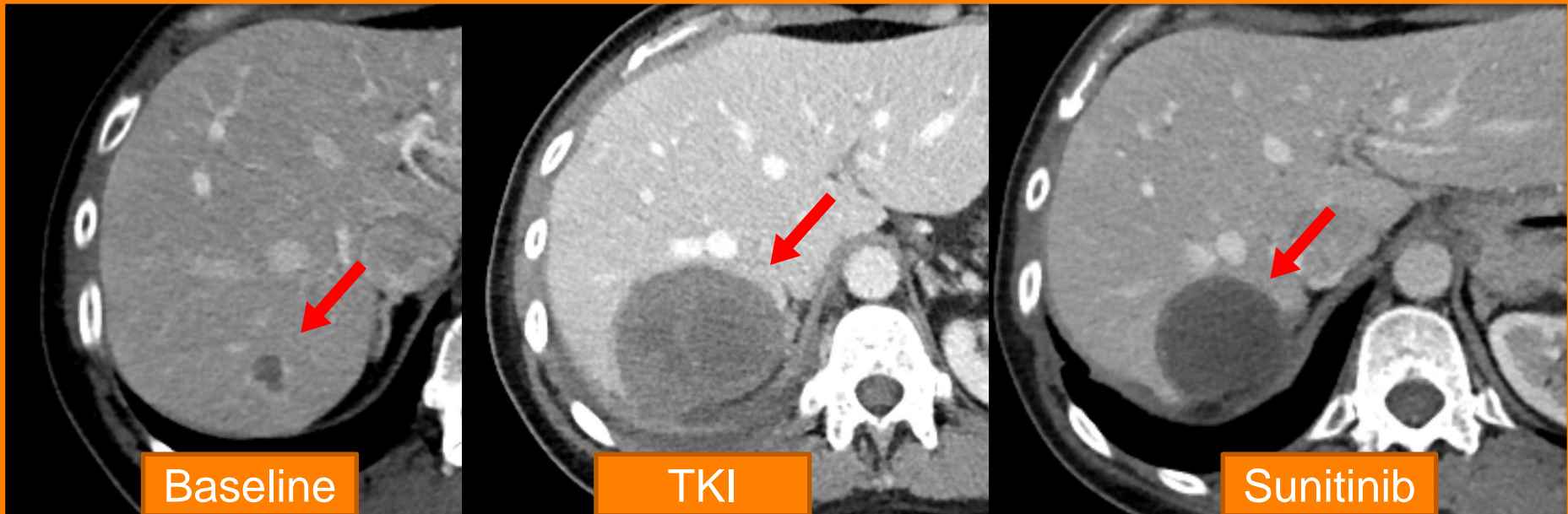
Heinrich et al, ASCO 2013 Poster/Abstract 10509



- 55 YO man with Gastric, **KIT exon 11 (W557-K558del)** mutant, GIST with liver metastases
- Progressive on imatinib, nilotinib, sunitinib, regorafenib.
- ctDNA revealed **KIT exon 17 Y823D** resistance mutation
- Placed on **Ponatinib** to target *KIT* exon 17



- 52 YO woman with small intestine, **KIT exon 11 (L576P)** mutant, GIST with liver metastases
- Progressive on imatinib placed on **TKI**, rapid progression
- ctDNA revealed **KIT exon 13 V654A** resistance mutation
- Placed on **Sunitinib** to target *KIT* exon 13



# Results

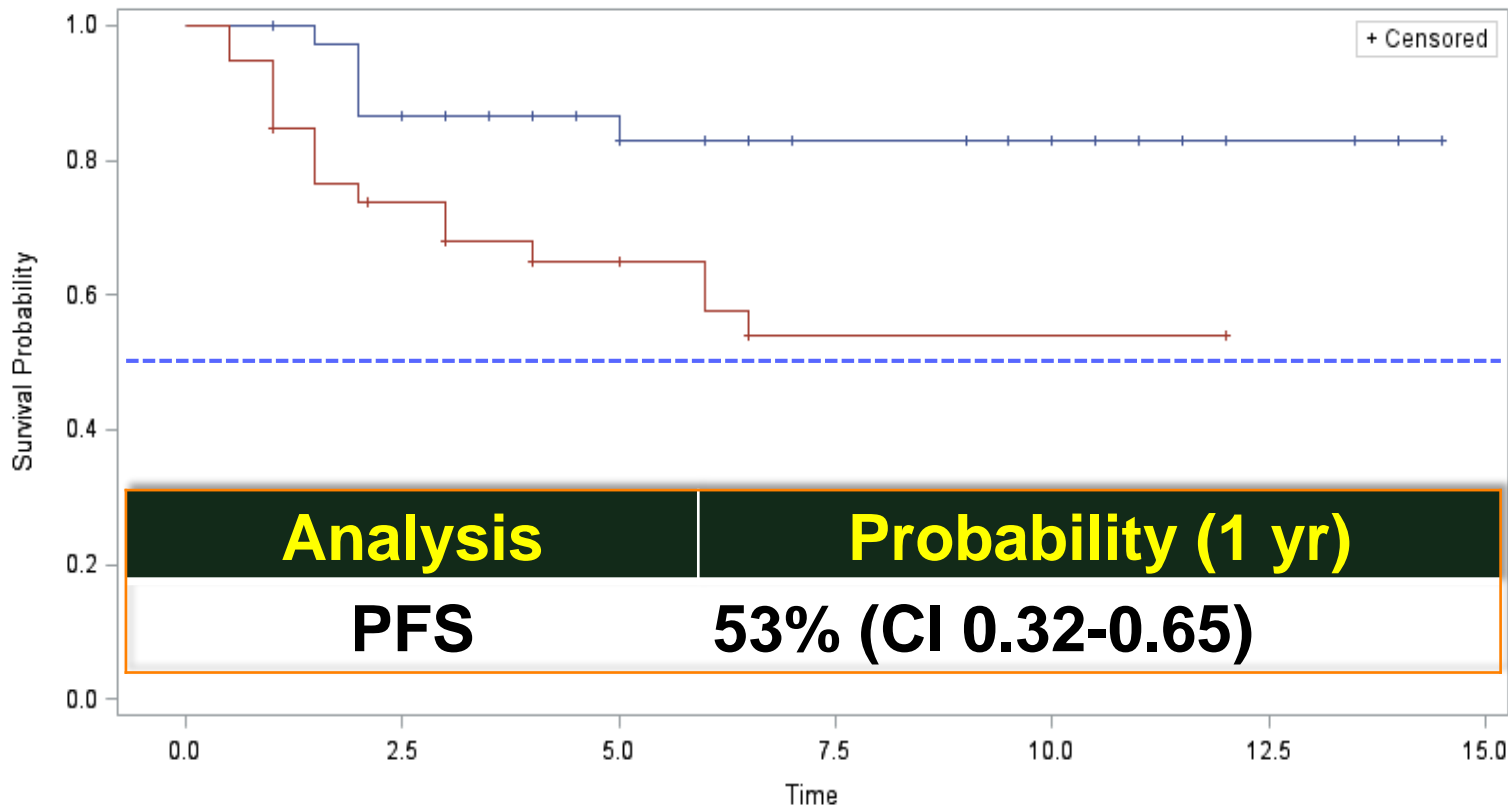
## *Treatment Characteristics (metastatic)*

<b>Variable</b>	<b>Treatment (N=39)</b>
<b>Lines of treatment (Median)</b>	3 (Range, 0-8)
<b>Imatinib (%)</b>	39 (100%)
<b>Sunitinib (%)</b>	23 (59%)
<b>Regorafenib (%)</b>	18 (46%)
<b>Ponatinib (%)</b>	5 (13%)
<b>Pazopanib (%)</b>	1 (3%)
<b>Clinical Trial (%)</b>	13 (33%)



# Outcome

## Patients Undergoing ctDNA Testing (metastatic patients, N= 39)



OS	39	32	24	14	11	3	0
PFS	39	26	19	14	14	0	



# Conclusion

- **NGS ctDNA** is a **useful, noninvasive** method for GIST patients
- Limitations include **low sensitivity** in patients with **primary** tumor, **low volume** disease, and those patients **responding** to TKI therapy
- The **OS and PFS were higher** than expected in heavily pretreated patients suggesting a benefit of ctDNA testing in select patients



# Future Directions

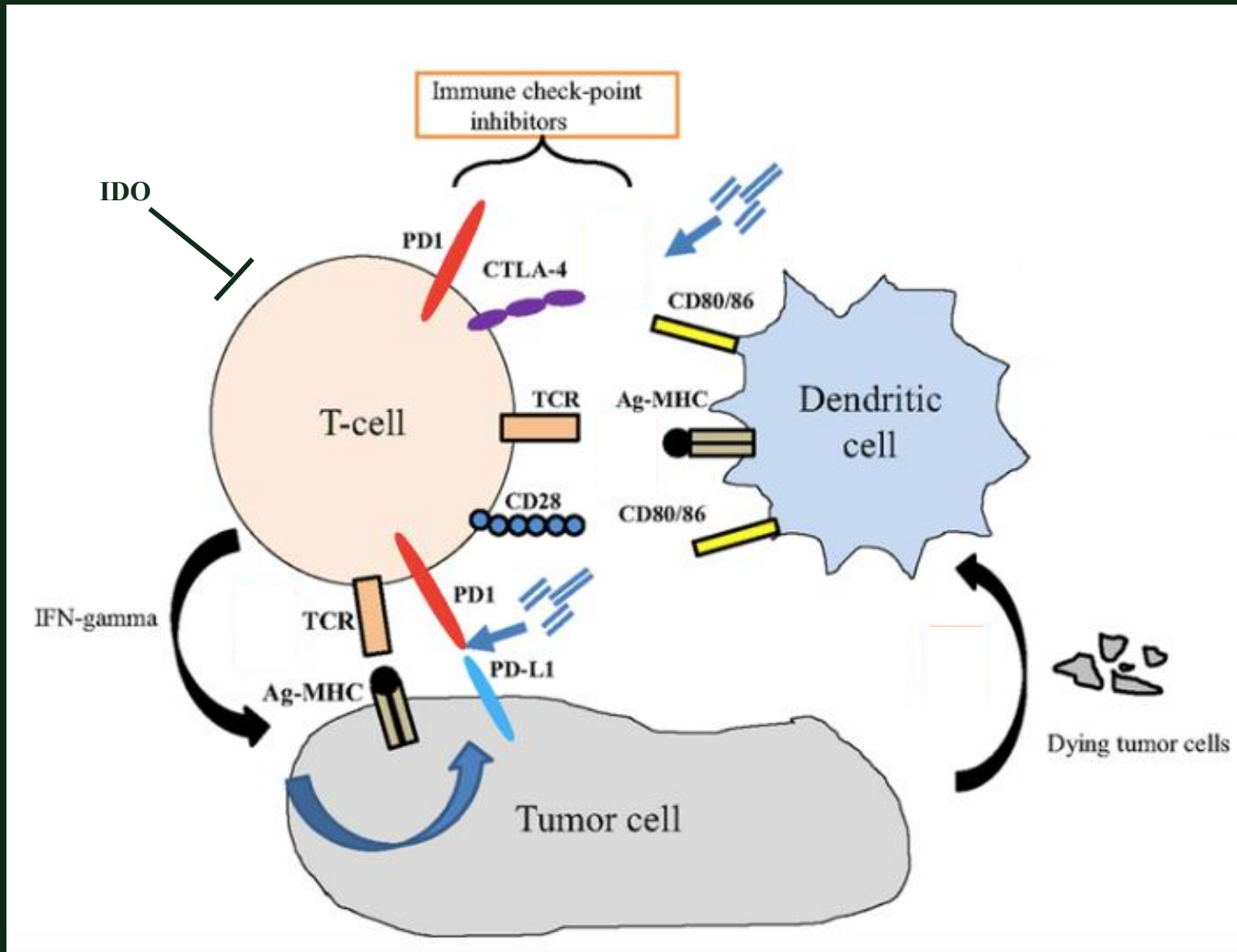
- Increasing the **sensitivity** of ctDNA assays
- Prospective **validation**



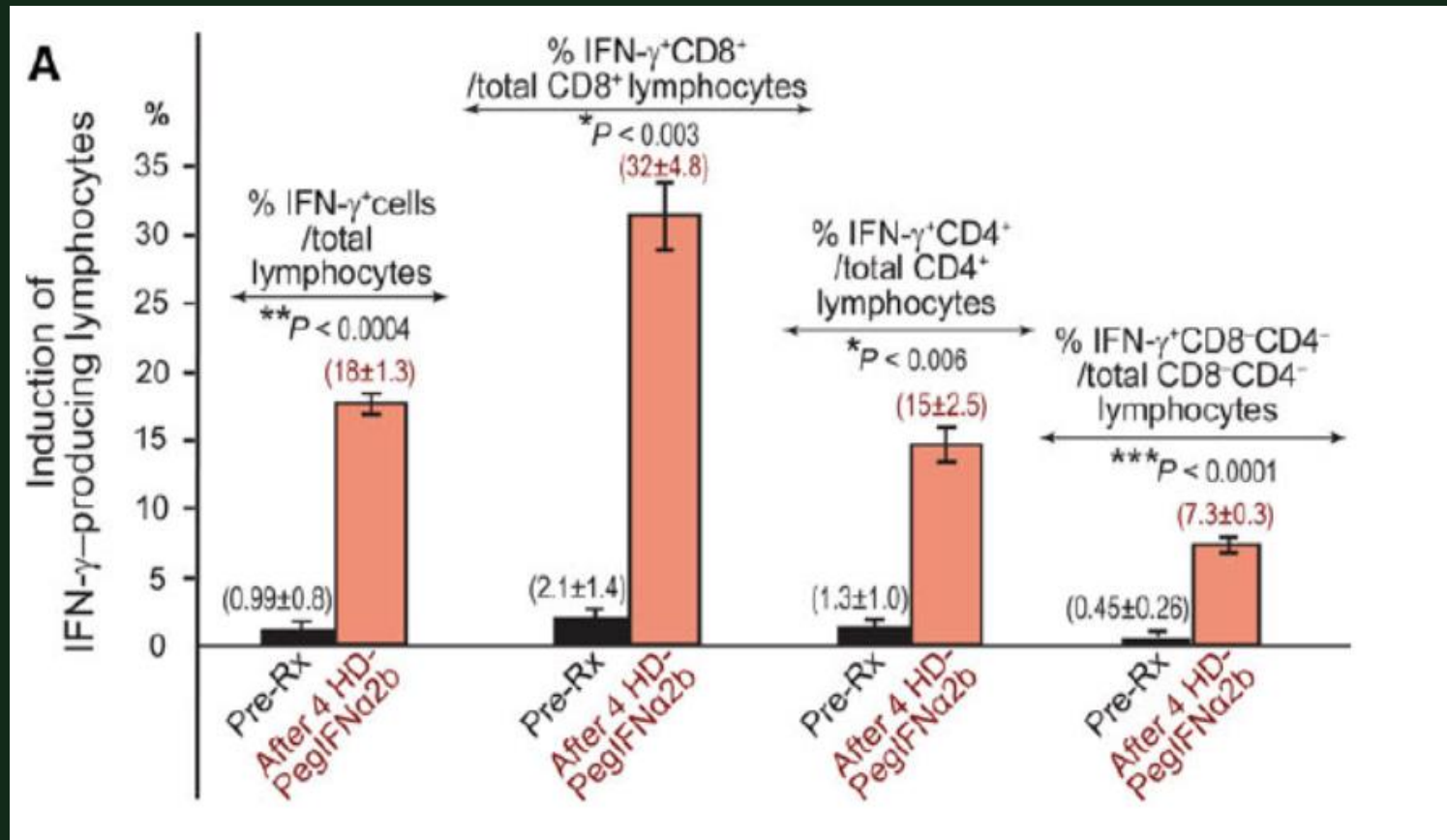
# Role of The Immune System To Treat GIST



# Principles of Immunotherapy



## Interferon Transforms T-Cells Into Cancer Killers

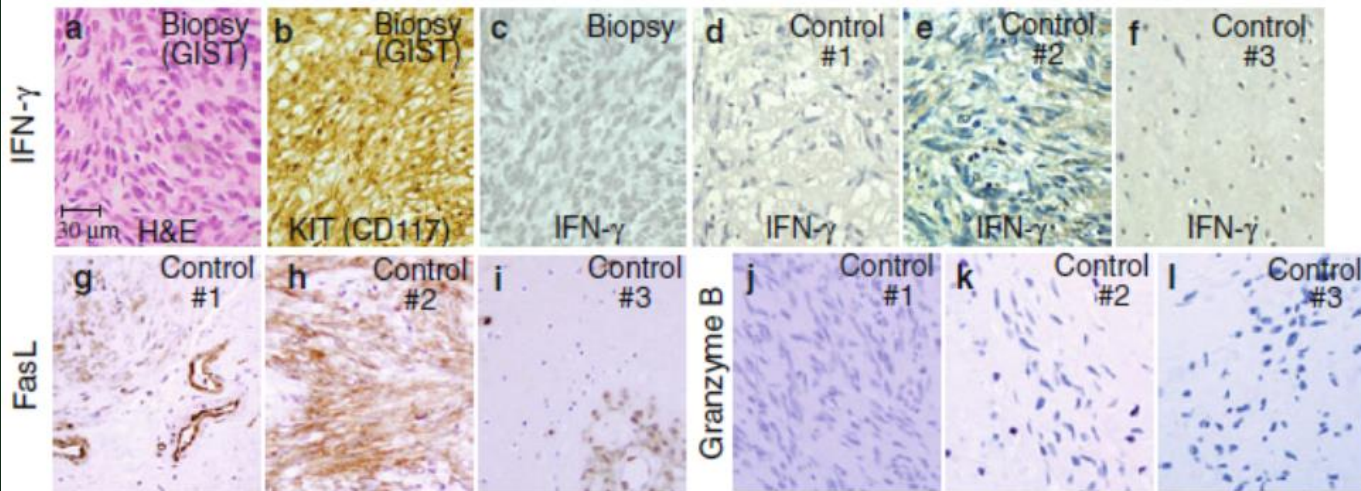


Chen, Trent, Patel, Lazar, et al Cancer Immunol Immunother, 2012.

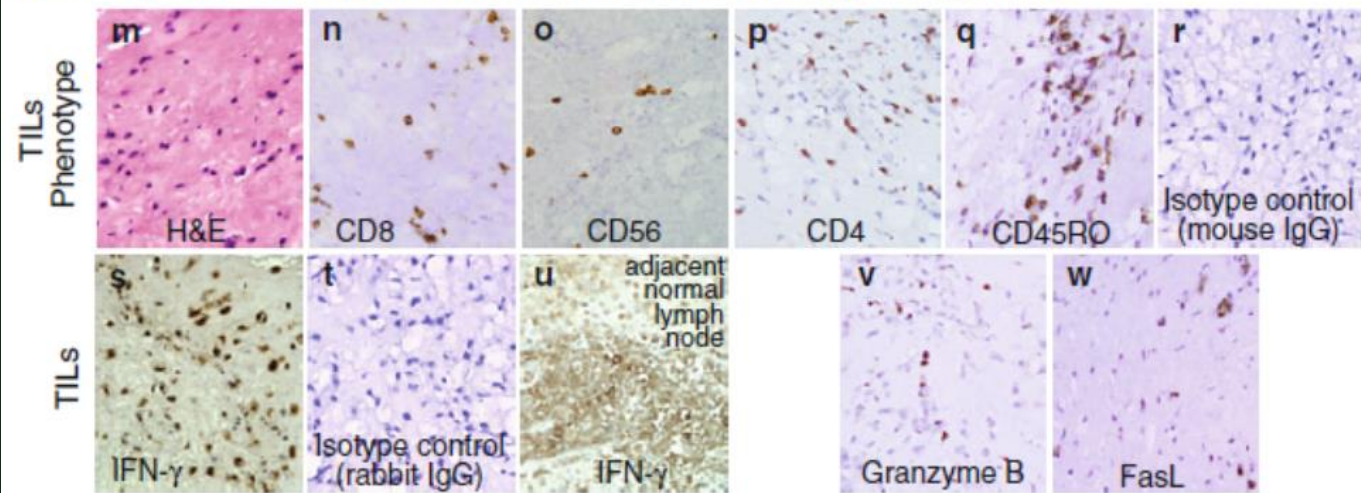


# Interferon Transforms T-Cells Into Cancer Killers

**A** Pt #4 biopsy before treatment and 3 control residual tumors post IM monotherapy



**B** Pt #4 residual mass post combination treatment with IM plus PegIFN $\alpha$ 2b

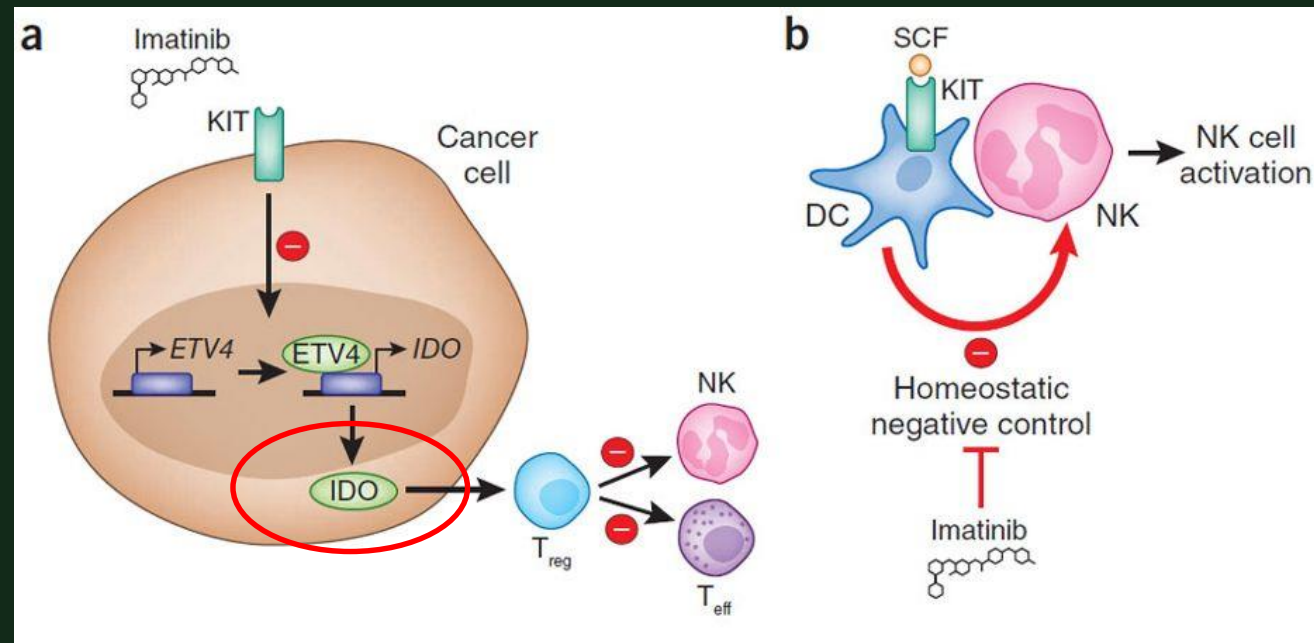


Cancer Immunol Immunother (2012) 61:1113–1124

# Imatinib Inhibits IDO which Suppresses the Immune System

## Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of IDO

Vinod P Balachandran<sup>1</sup>, Michael J Cavnar<sup>1</sup>, Shan Zeng<sup>1</sup>, Zubin M Bamboat<sup>1</sup>, Lee M Ocuin<sup>1</sup>, Hebroon Obaid<sup>1</sup>, Eric C Sorenson<sup>1</sup>, Rachel Popow<sup>1</sup>, Charlotte Ariyan<sup>1</sup>, Ferdinand Rossi<sup>2</sup>, Peter Besmer<sup>2</sup>, Tianhua Guo<sup>3</sup>, Cristina R Antonescu<sup>3</sup>, Takahiro Taguchi<sup>4</sup>, Jianda Yuan<sup>5</sup>, Jedd D Wolchok<sup>5,6</sup>, James P Allison<sup>5,7</sup> & Ronald P DeMatteo<sup>1</sup>

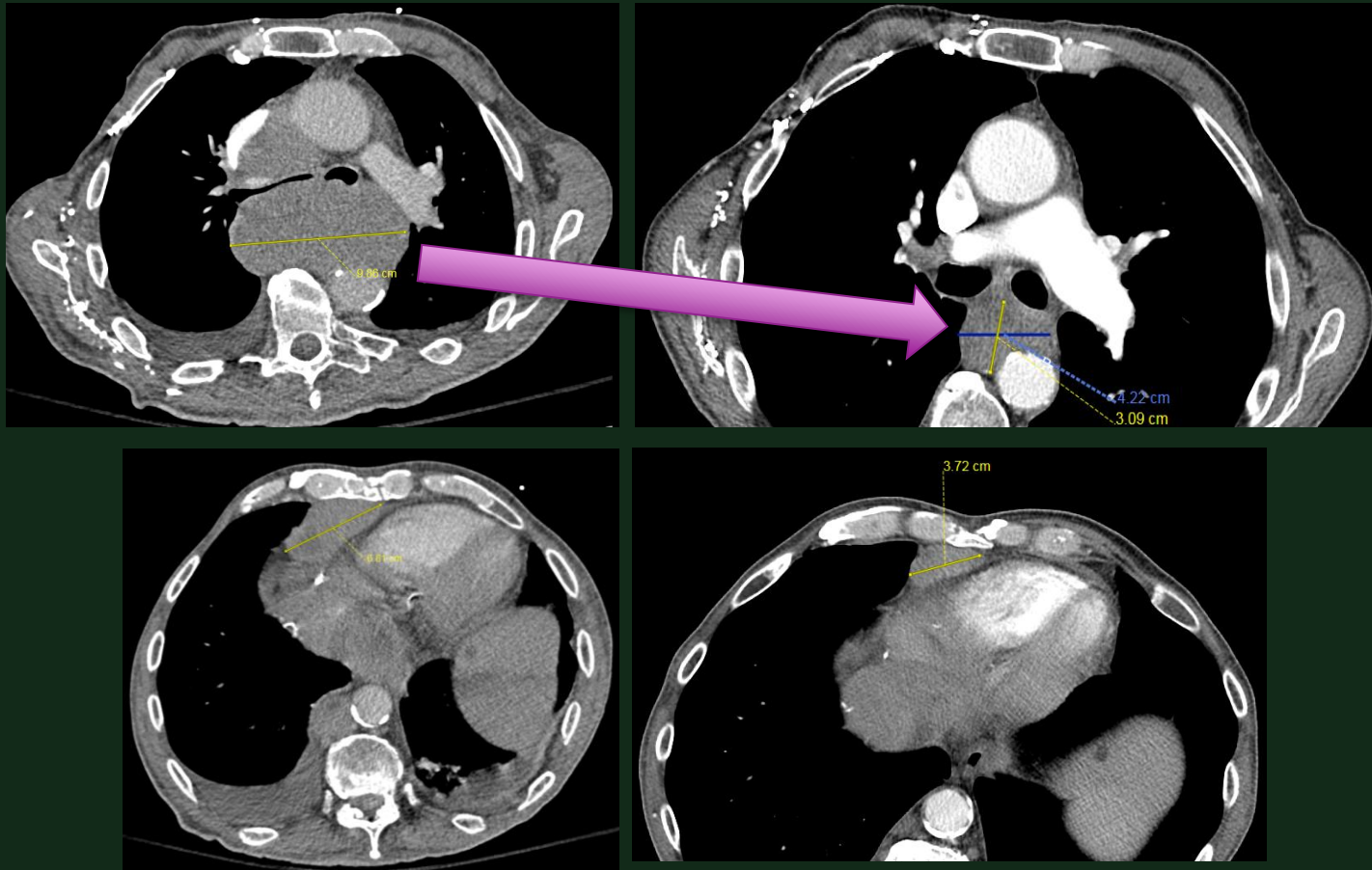


*Clin Cancer Res.* 2017 June 15; 23(12): 2972–2980.

VOLUME 17 | NUMBER 9 | SEPTEMBER 2011 NATURE MEDICINE



# EXCEPTIONAL RESPONDER TO NIVOLUMAB (NOT ON TRIAL)

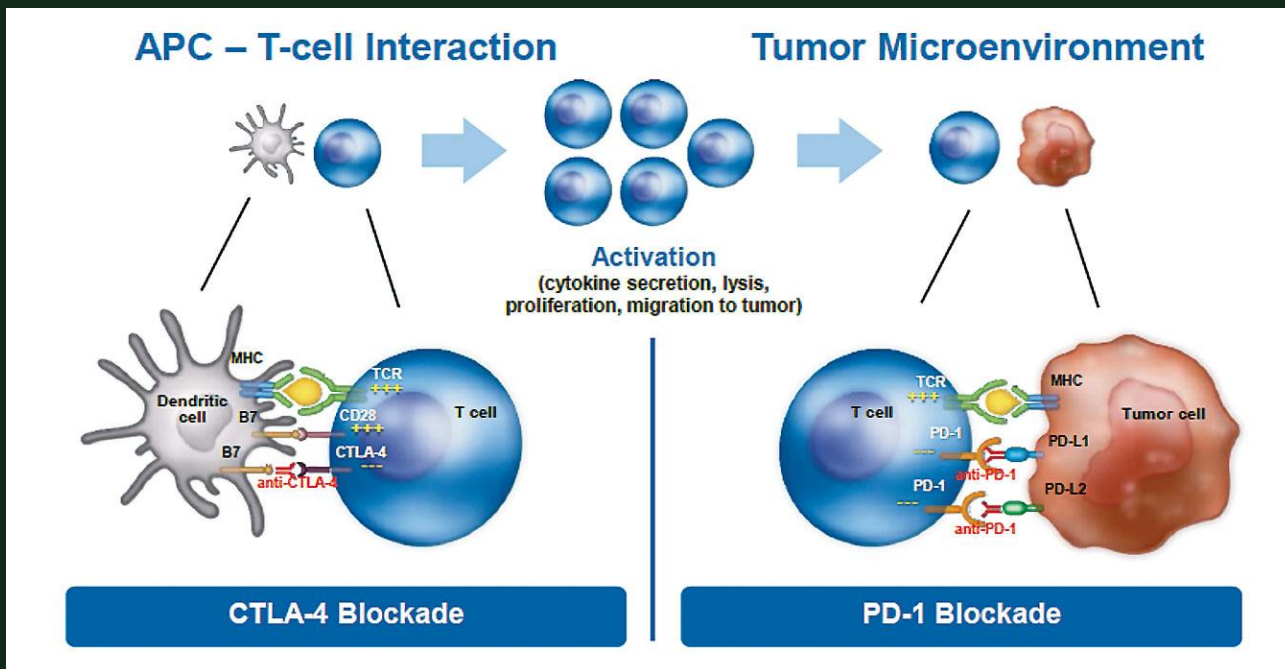


May 26, 2016

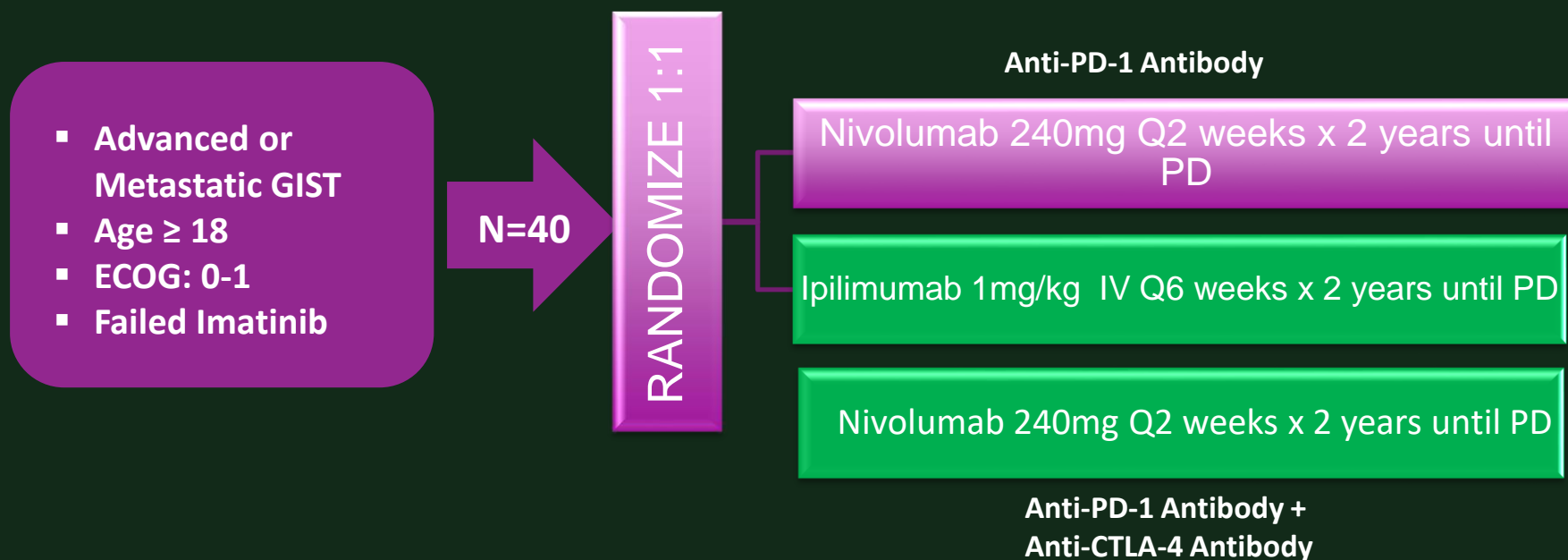


A Randomized Phase 2 Study of Nivolumab (PD-1 inhibitor) Monotherapy Versus Nivolumab Combined With Ipilimumab (CTLA-4 inhibitor) In Patients With Metastatic Or Unresectable Gastrointestinal Stromal Tumor (GIST)

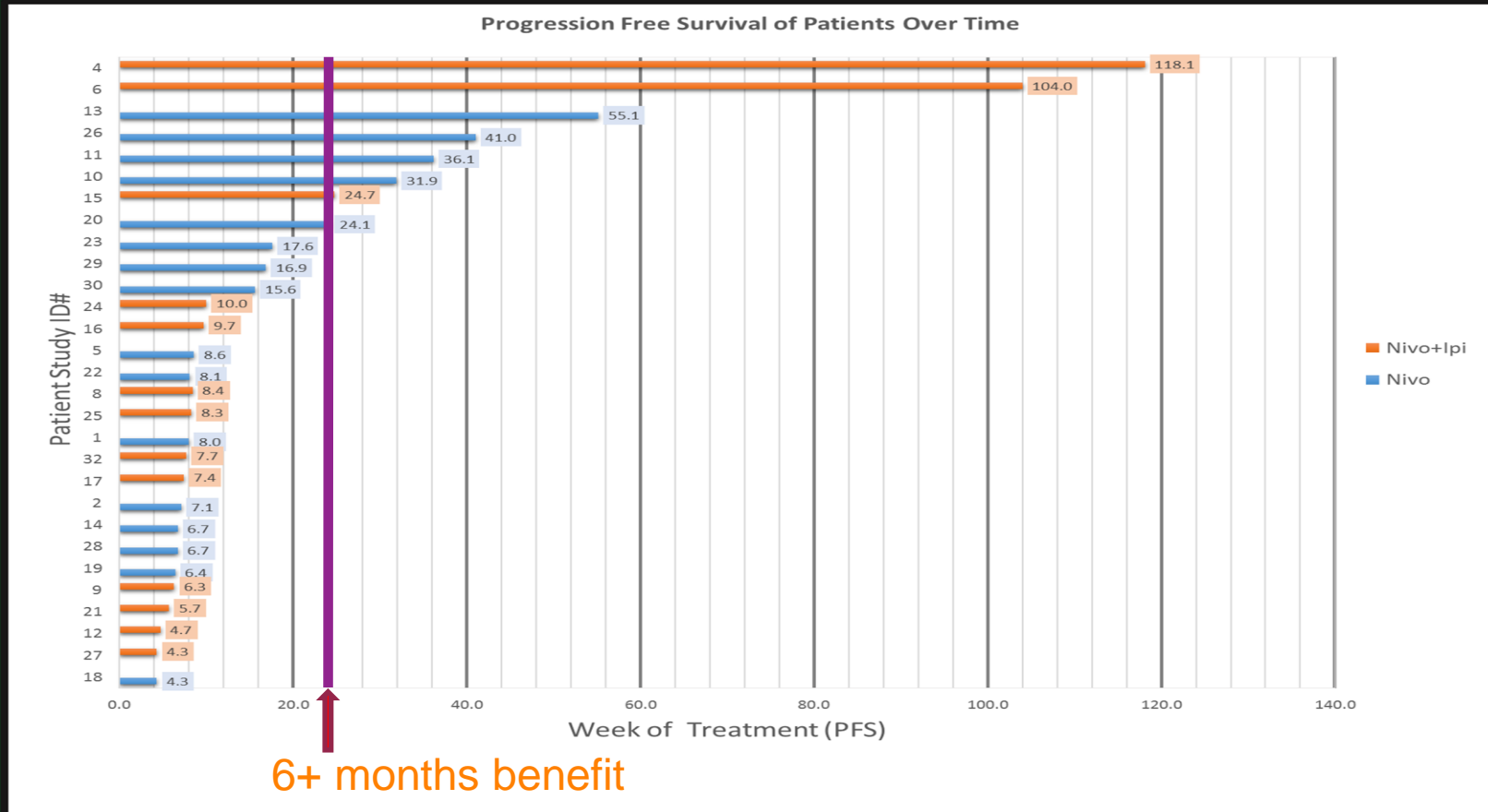
NCT#02880020



# A Randomized, Phase 2 Study of Nivolumab (PD-1 inhibitor) Monotherapy Versus Nivolumab Combined With Ipilimumab (CTLA-4 inhibitor) In Patients With Advanced GIST

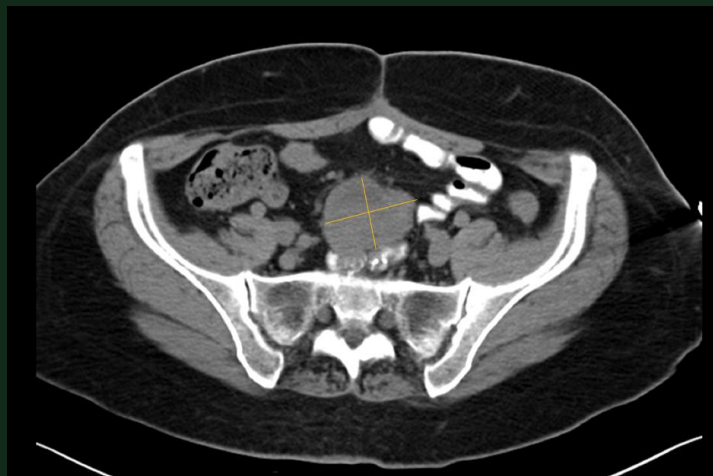


# Nivolumab (PD-1 inhibitor) Monotherapy Versus Nivolumab Combined With Ipilimumab (CTLA-4 inhibitor) In Patients With Advanced GIST



# Nivolumab (PD-1 inhibitor) Monotherapy Versus Nivolumab Combined With Ipilimumab (CTLA-4 inhibitor) In Patients With Advanced GIST

20 months on imatinib, intolerant to regorafenib, sorafenib and sunitinib



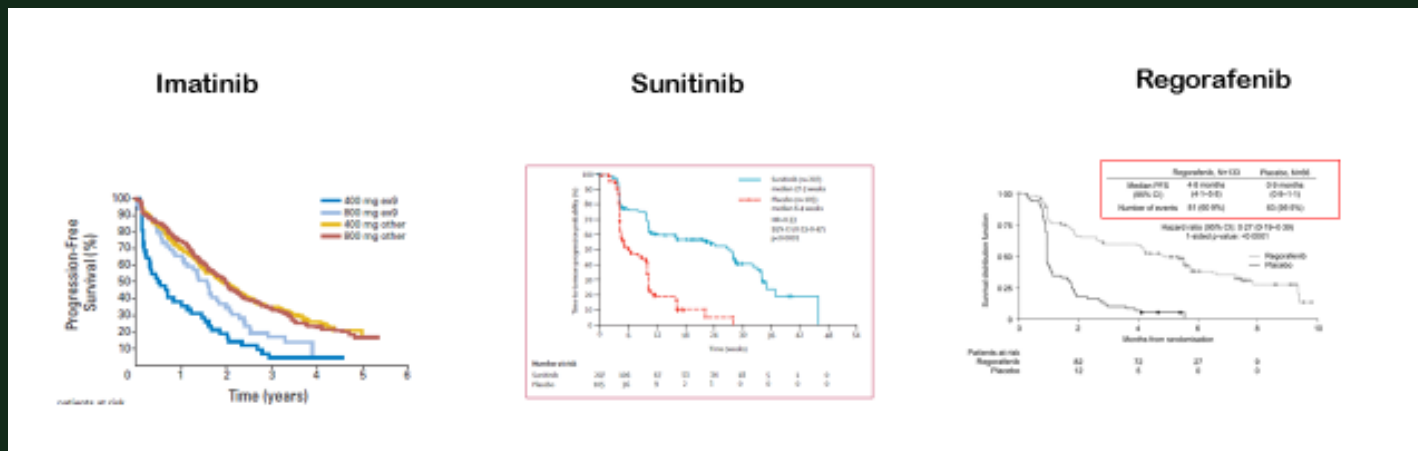
1/26/17 –  
Baseline  
52mm x 37mm



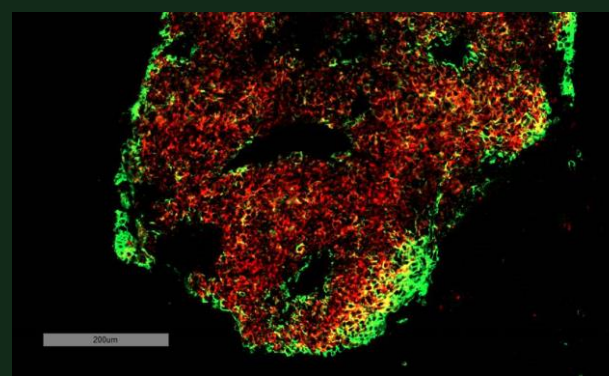
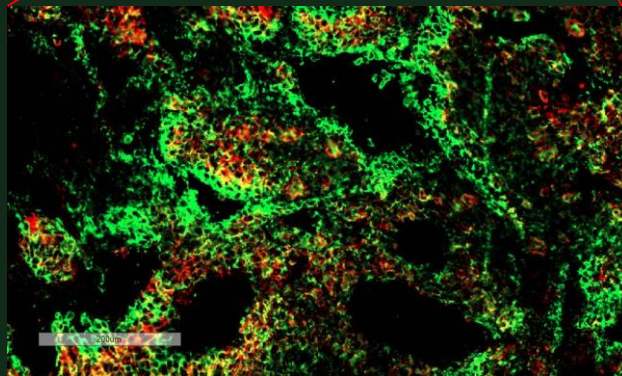
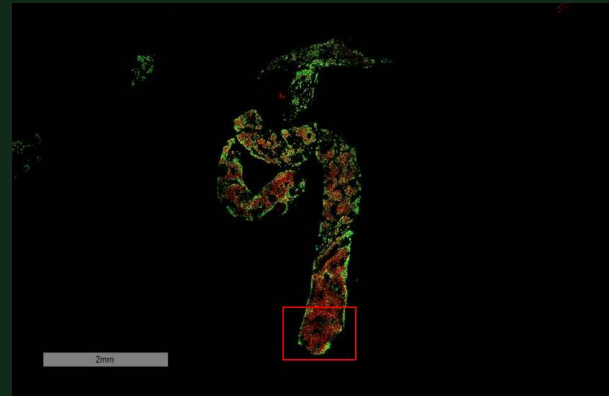
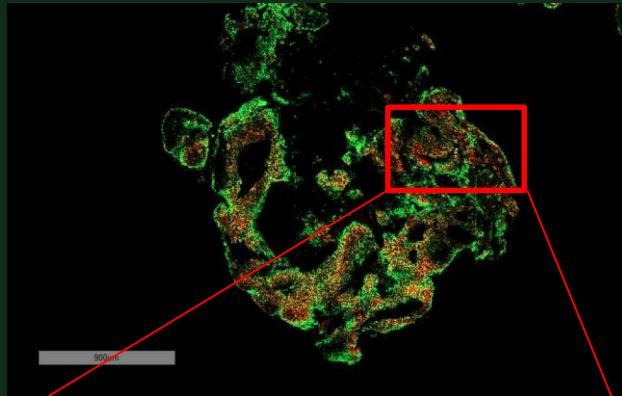
5/9/19  
12mm x 6mm

# Nivolumab (PD-1 inhibitor) Monotherapy Versus Nivolumab Combined With Ipilimumab (CTLA-4 inhibitor) In Patients With Advanced GIST

	NIVOLUMAB			NIVO + IPI		
	PR	SD	CBR(%)	PR	SD	CBR(%)
<b>BEST RESPONSE</b>	0/16	8/16	50%	1/13	2/13	23.1%
<b>PFS(MEDIAN, MEAN)</b>	12.1 wks, 18.4 wks			8.3wks, 24.6wks		
<b>PFS(6month)</b>	31.2% (Sunitinib: 16%) (Regorafenib: 38%)			23.1% (Sunitinib: 16%) (Regorafenib: 38%)		



# T Cell Infiltration Into Tumor Parenchyma Of A Responding Patient



Dog1

CD3

Pre-Treatment

On-Treatment



# Sylvester Comprehensive Cancer Center

## **Sarcoma Team.**

- **Medical Oncology**

- Jon Trent
- Gina D'Amato
- Emily Jonczak
- Matteo Trucco (Pedi)
- Warren Alperstein (Pedi)

- **Pathology**

- Andrew Rosenberg
- Jay Lou Torres

- **Radiology**

- Ty Subhawong
- Jean Jose

- **ARNP**

- Morgan Smith
- Yolanda Roper

- **Nursing**

- Eryka Lacayo
- Vilma Sanchez

- **Orthopedic Oncology**

- Sheila Conway
- Frank Eismont
- Juan Pretell
- Mo Al Maaieh

- **Surgical Oncology**

- Nipun Merchant
- Alan Livingstone
- Neha Goel

- **Radiation Therapy**

- Raphael Yechieli
- Aaron Wolfson

- **Head & Neck Surgery**

- Zoukaa Sargi
- Frank Civantos

- **Thoracic Surgery**

- Dao Nguyen
- Nestor Villamizar

- **Interventional Radiology**

- Shree Venkat
- Prasoon Mohan

- **Gyn Oncology**

- Marilyn Huang

- **Clinical Research**

- Tamara Leon
- Mirna Gonzalez
- Melissa Serna, RN

- **Lab Research**

- Josie Eid
- Joanna DeSalvo
- Luyuan Li
- Karina Galoian

- **Social Work**

- Marlene Morales
- Abby Thornton (AYA)



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## Circulating Tumor DNA and ImmunoOncology

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