

UC San Diego Health

# Next-Gen Genomic Precision Medicine in Solid Tumors

## EHA-SfPM Precision Medicine Meeting Copenhagen, Denmark

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Leader, Sarcoma Disease Team | Moores Cancer Center

Co-Leader, Structural & Functional Genomics Program | Moores Cancer Center

Program Director, SOAS T32 Training Program | Department of Surgery & Moores Cancer Center

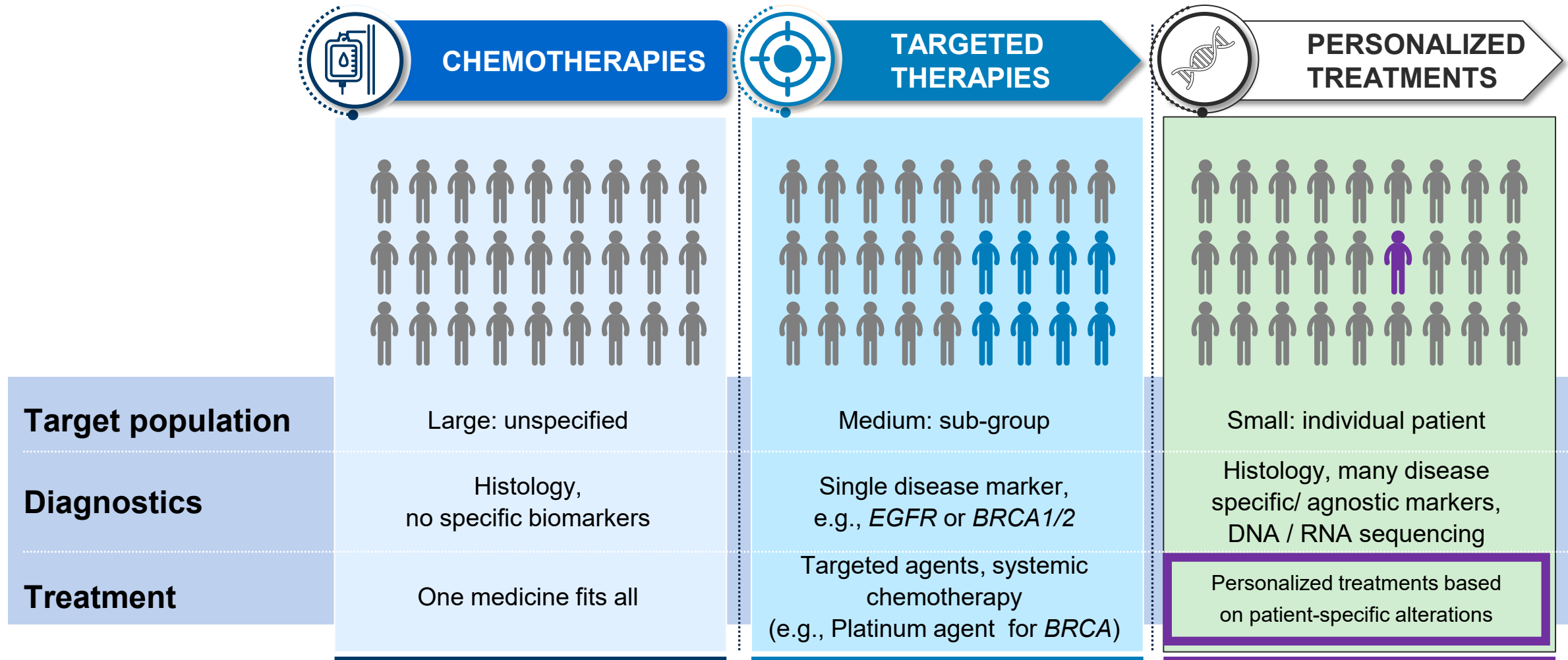


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[@JasonSicklick](https://twitter.com/JasonSicklick)

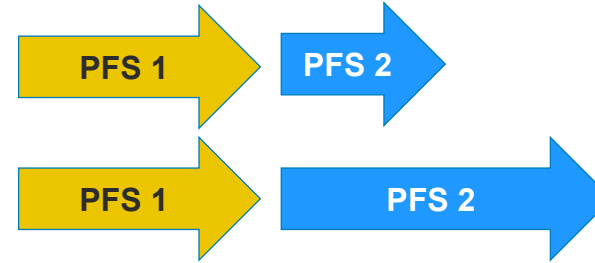
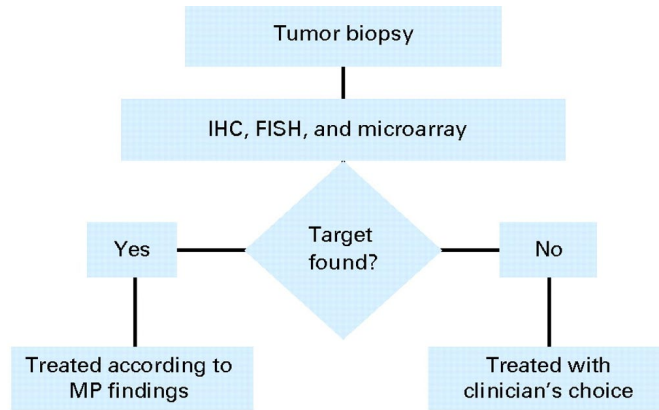
# The Promise of Precision Medicine: Sequence, Stratify, Match



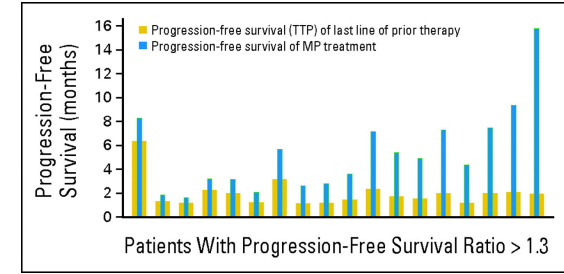
# Origins of current day precision oncology

**Von Hoff 1**  
 Combines RNA and DNA sequencing to guide therapy

2012



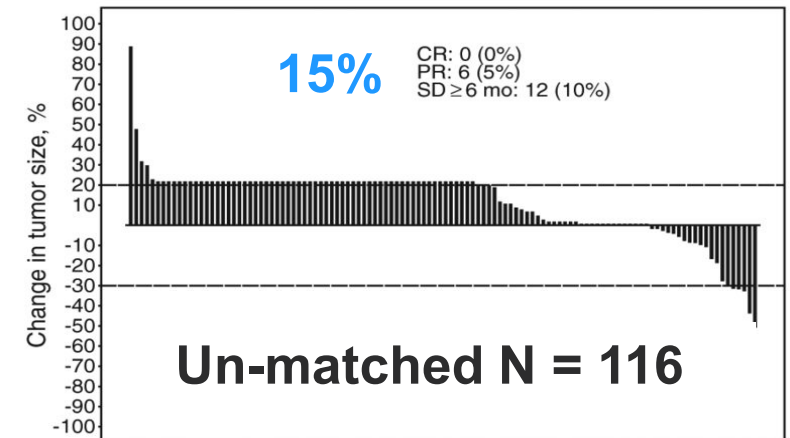
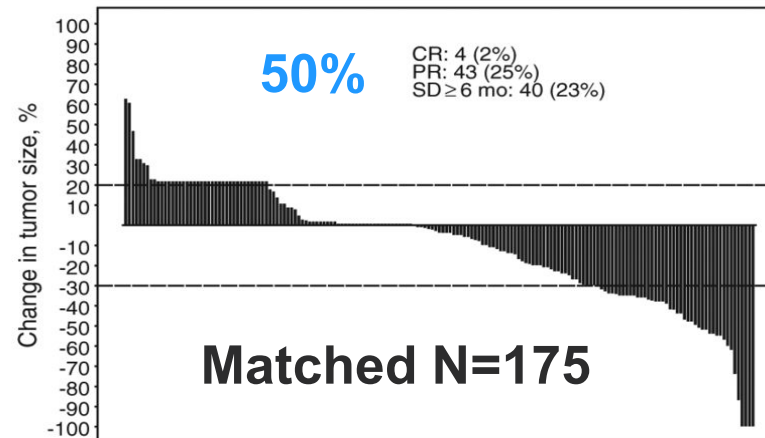
$PFS^2/PFS^1 > 130\%$   
 18 of 66 (27%) pts



2010

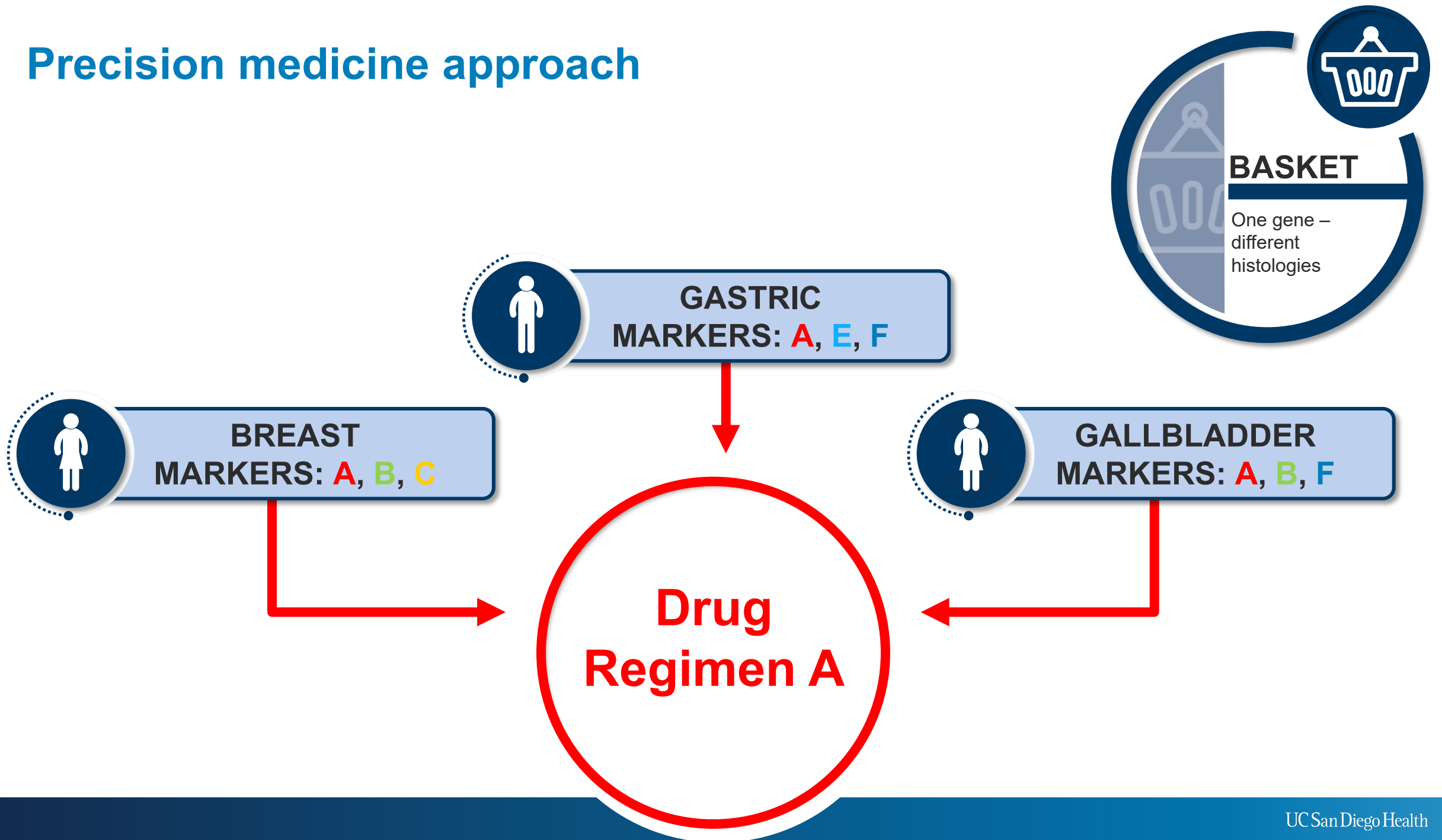
**PREDICT<sup>2</sup>**  
 Assessment of matched therapies guided by molecular profiling

**Disease Control Rate (DCR) = CR + PR + SD**

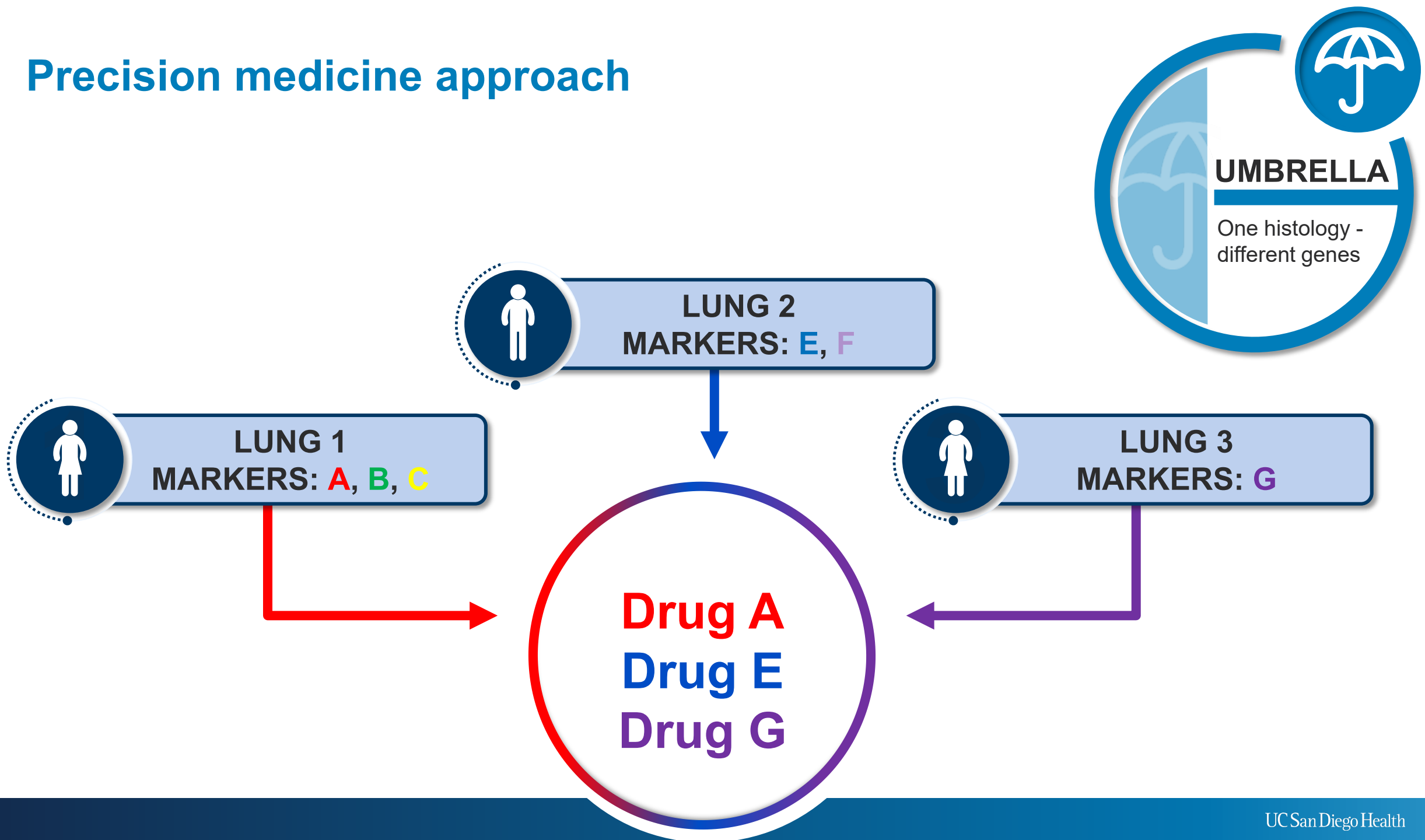


1. Von Hoff DD, et al., *J Clin Oncol.* 2010 Nov 20;28(33):4877-83;  
 2. Tsimberidou A et al., *Clin Cancer Res* 2012;18:6373-6383.

# Precision medicine approach

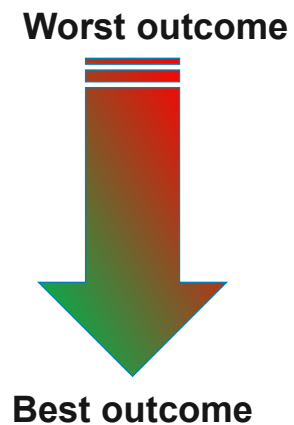


# Precision medicine approach



# Precision targeted therapies are effective in 30% of patients

Analysis of 85,000 patients in Phase 1/2 clinical trials



	Pooled Analysis			Meta-analysis		
ARMS type	RR (%)	mPFS (mos)	mOS (mos)	RR (%)	mPFS (mos)	mOS (mos)
Non-precision targeted	4	2.6	8.7	8	2.5	8.3
Cytotoxic	12	3.3	9.4	16	3.3	9.3
Precision targeted	30	6.9	15.9	31	6.1	13.7

Schwaederle et al., *JCO*, 2015; Jardim et al., *JNCI*, 2015; Schwaederle et al., *JAMA Oncology*, 2016.

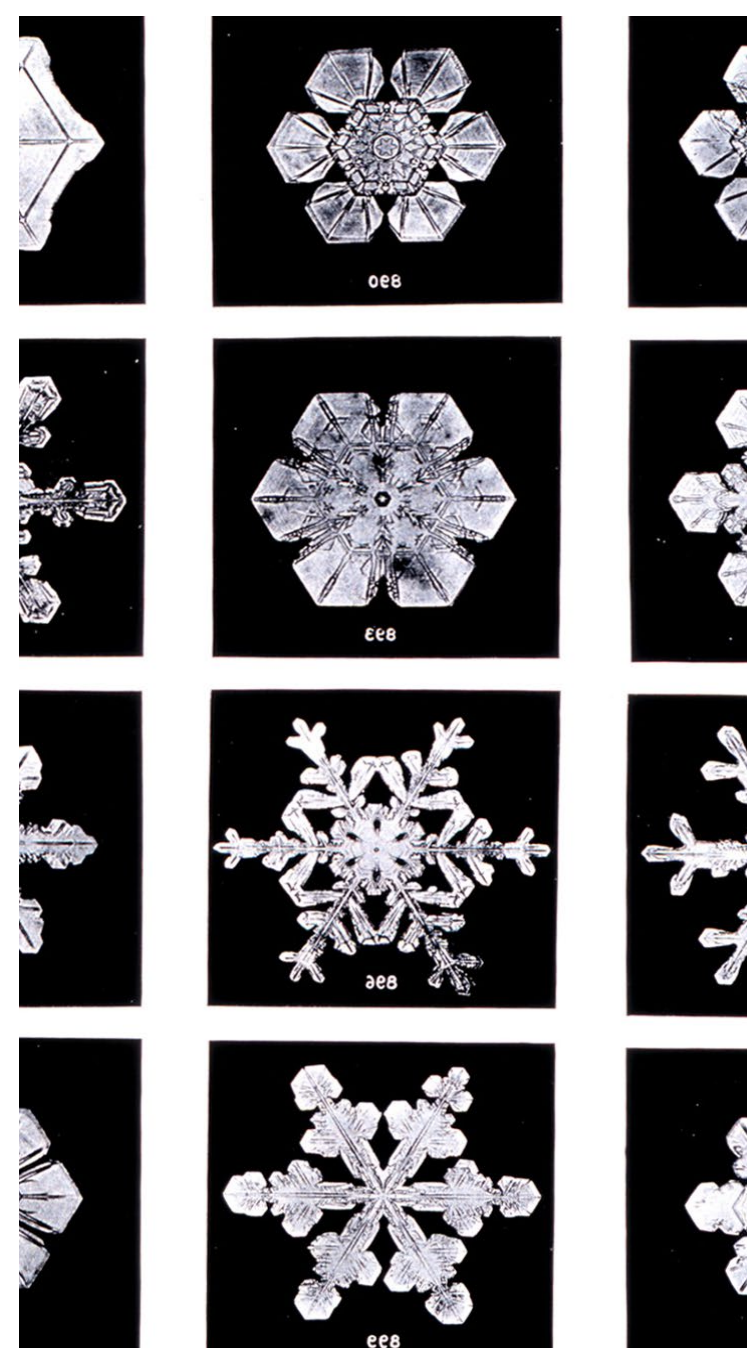
# Challenges to Current Targeted Therapy Approach

1

**Tumor Heterogeneity  
(Malignant Snowflakes)**

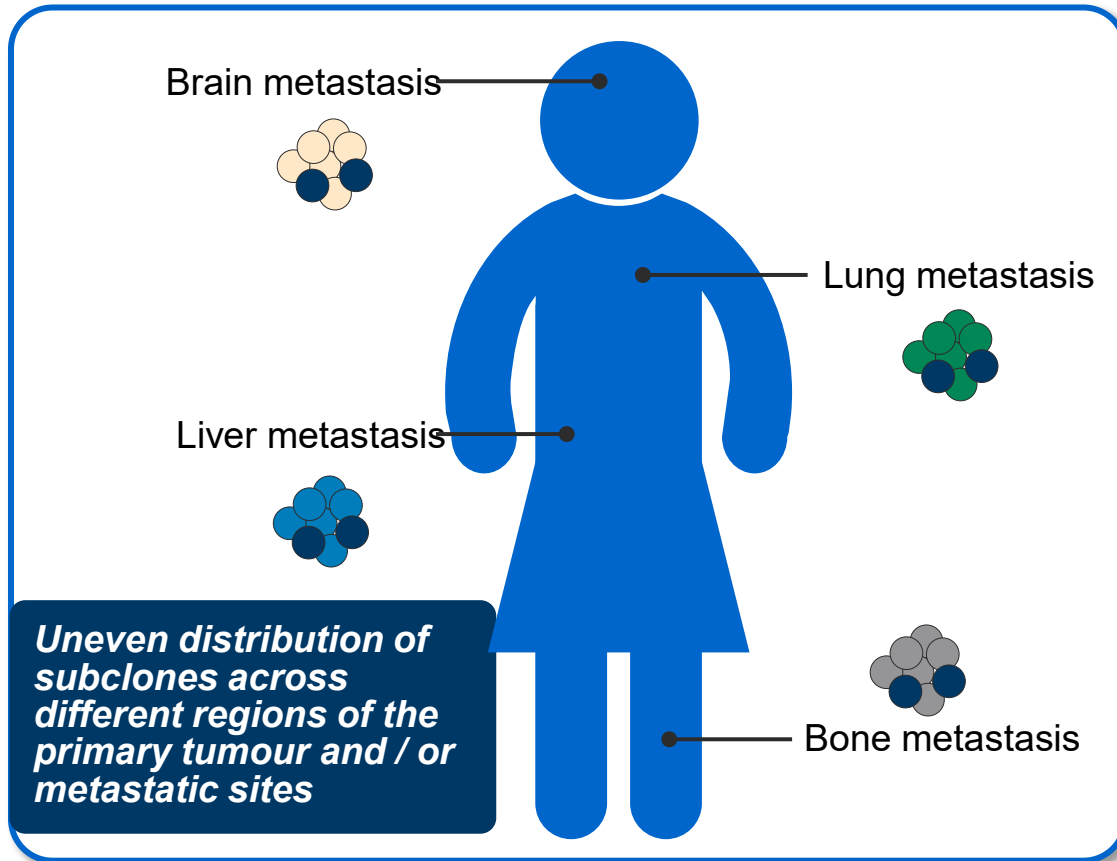
2

**Co-genomic Alterations**

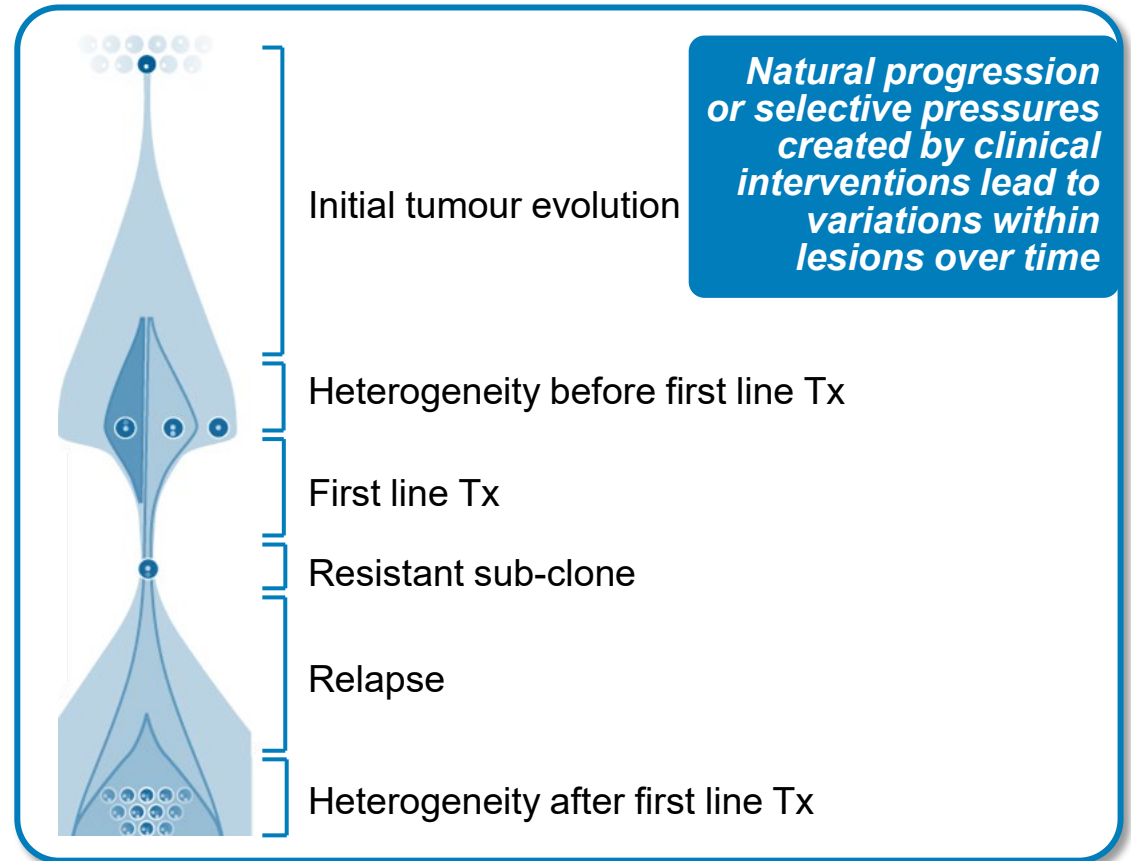


# Most tumors are highly heterogenous

## SPATIAL HETEROGENEITY

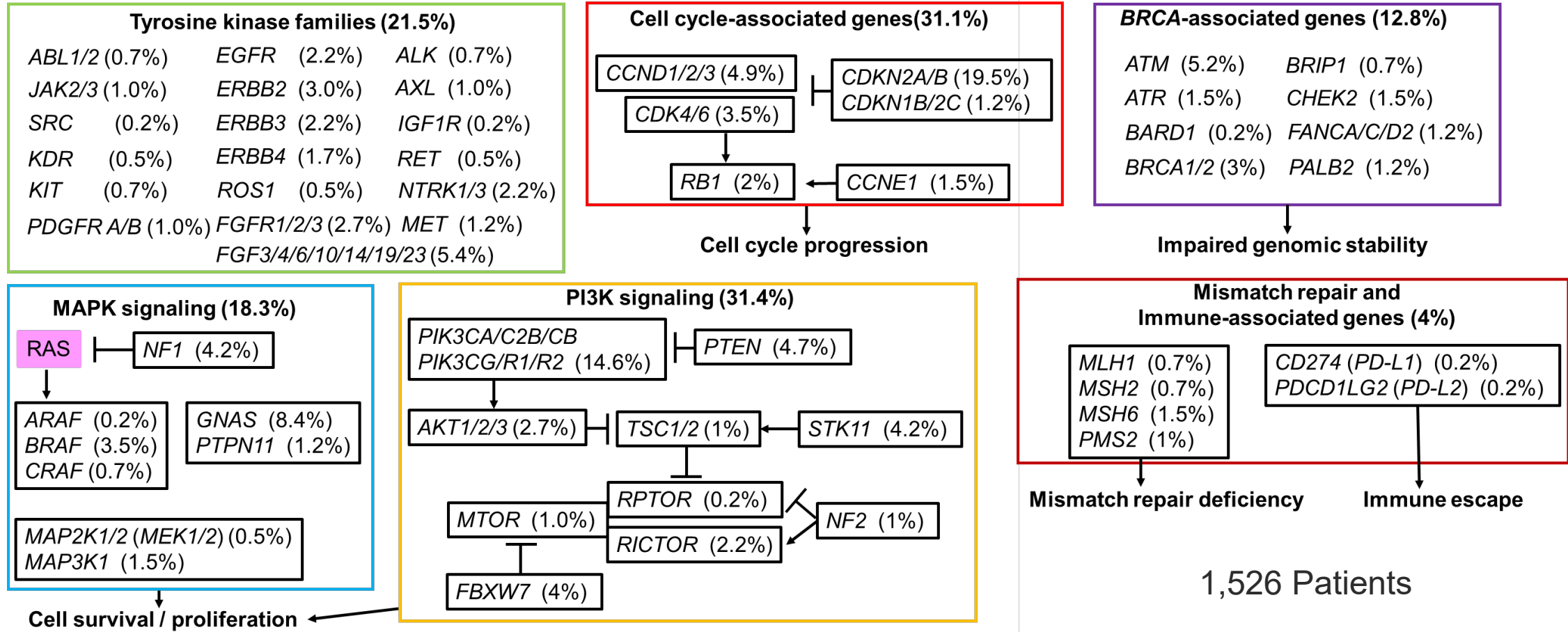


## TEMPORAL HETEROGENEITY





# Co-altered oncogenic pathways associated with RAS alterations



# Number and position of table legs predicts ability to collapse

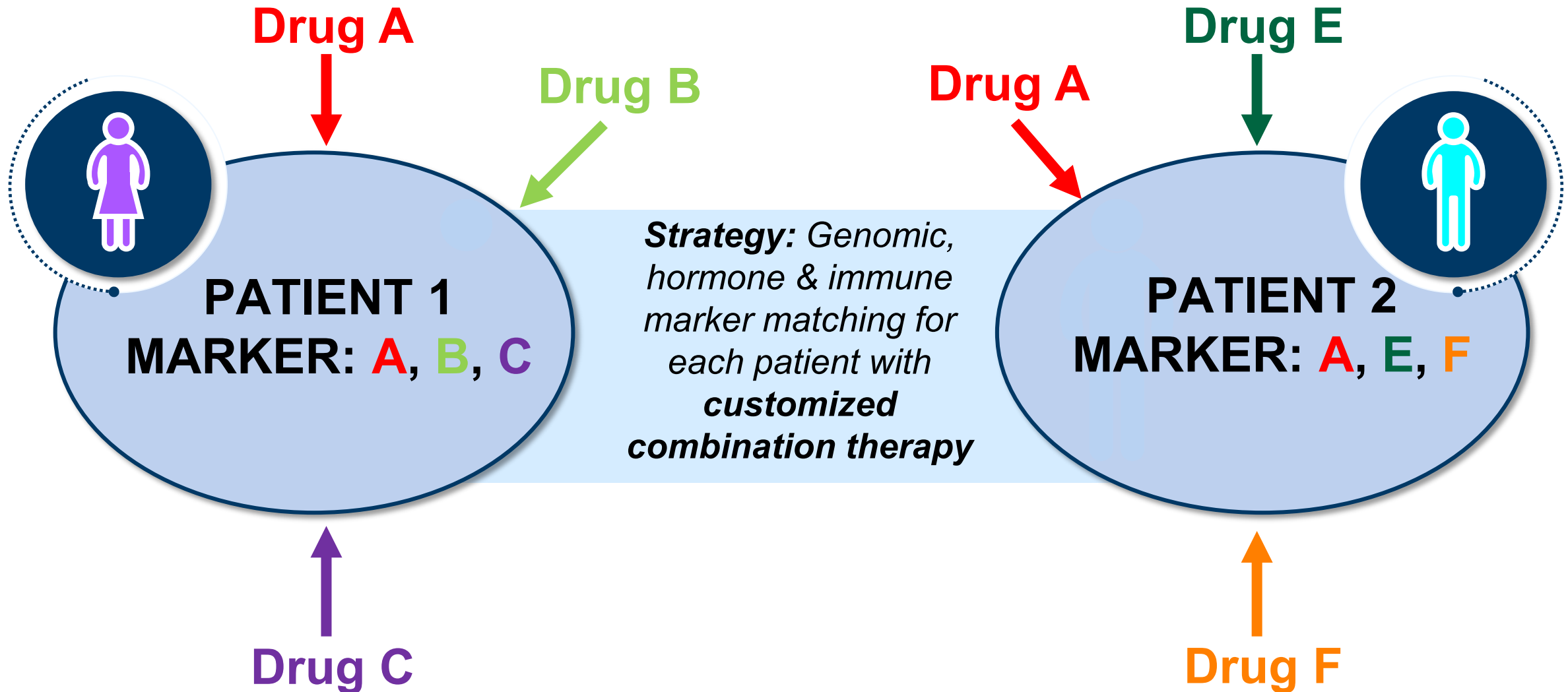
Table = Tumor

Leg = Genomic alteration

Position = Relative function



# Theory of a patient-centric trial (N-of-1)



# I-PREDICT: Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy

## Study novelty

- Patients with lethal malignancies (>50% 2-year mortality)
- Customized combinations

**Activation date: February 13, 2015**

**Consented:** N = 149

**Treated:** n = 83 (55.7%)

**Matched therapy:** N = 73 (49% of total; 88% of treated)

## Treatment decisions guided by:

FoundationOne<sup>®\*</sup>, including TMB and MSI,  
FoundationOne<sup>®</sup> Heme, FoundationACT<sup>®†</sup> (ctDNA) and IHC  
for PD-1 / PD-L1



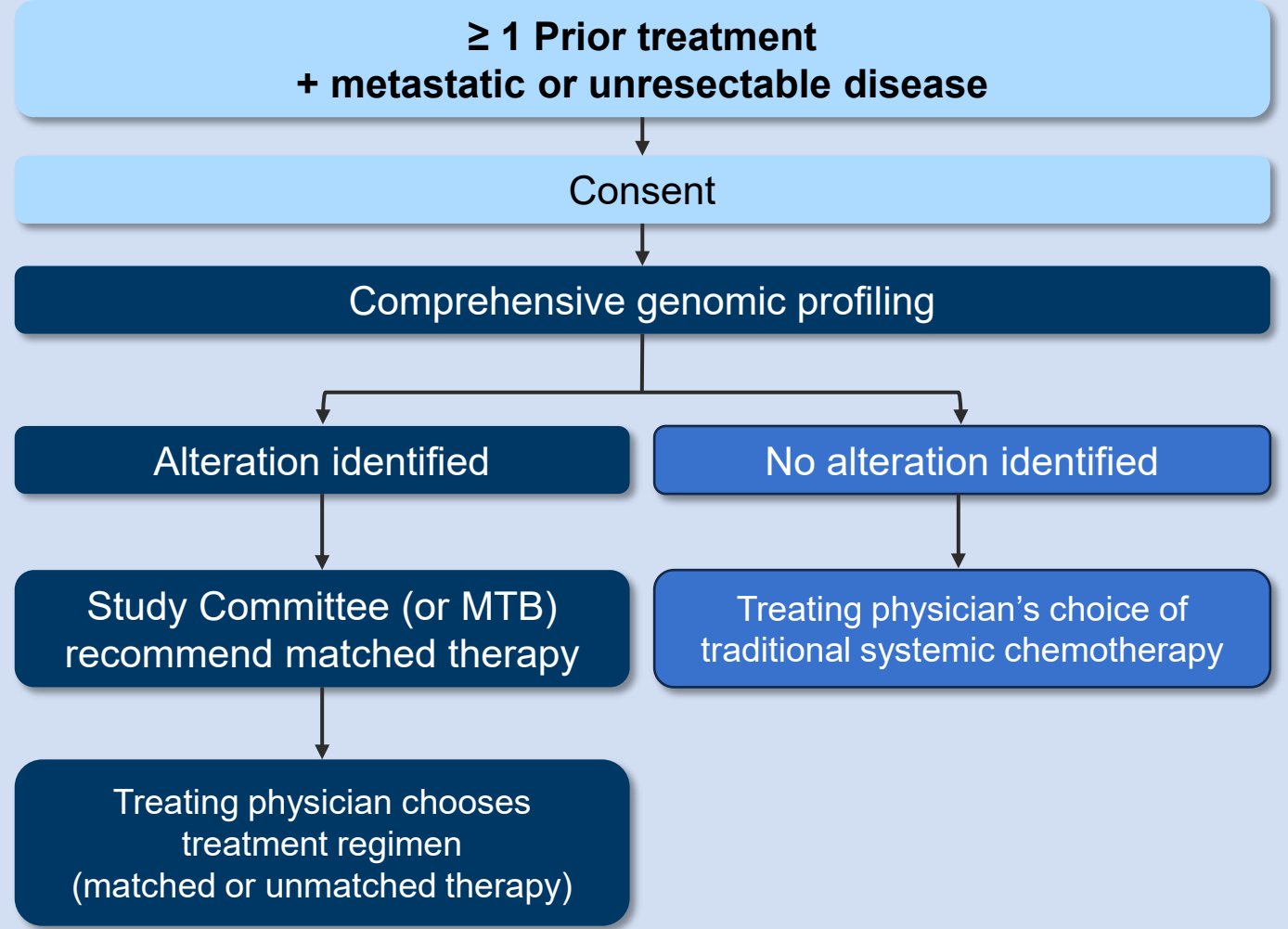
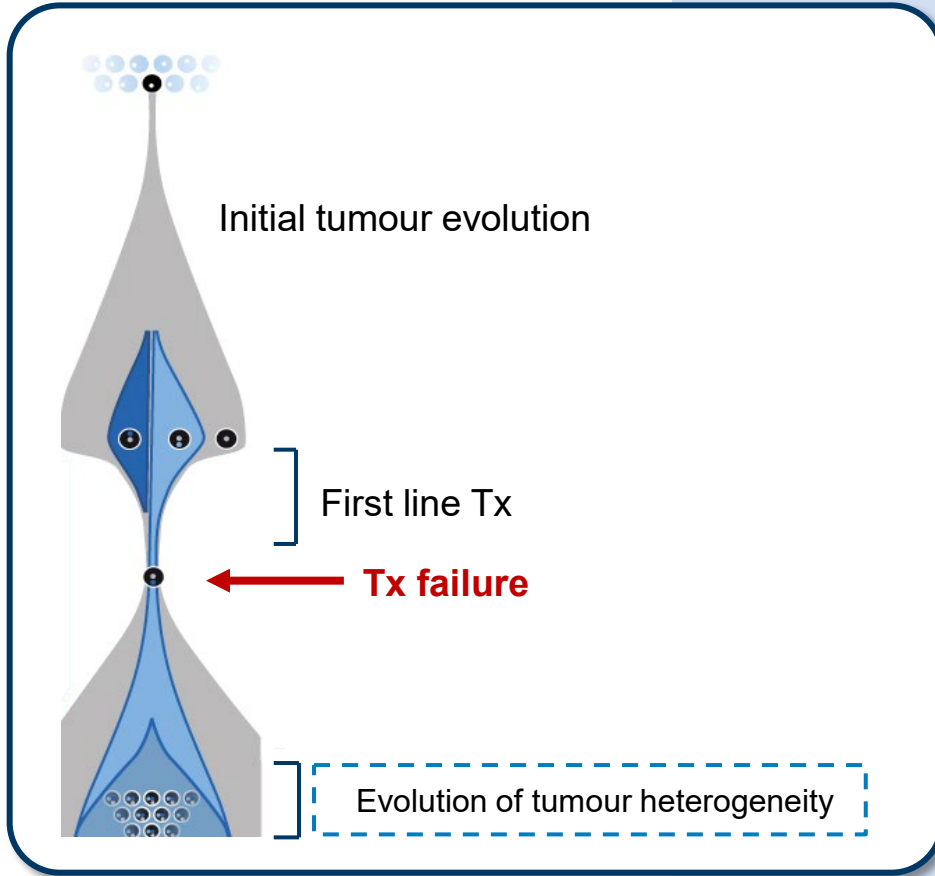
**PI: Jason Sicklick, MD, FACS**  
Professor of Surgery  
Division of Surgical Oncology



**Co-PI: Razelle Kurzrock, MD**  
Professor, Med Coll Wisconsin  
CMO of WIN Consortium

# I-PREDICT study protocol

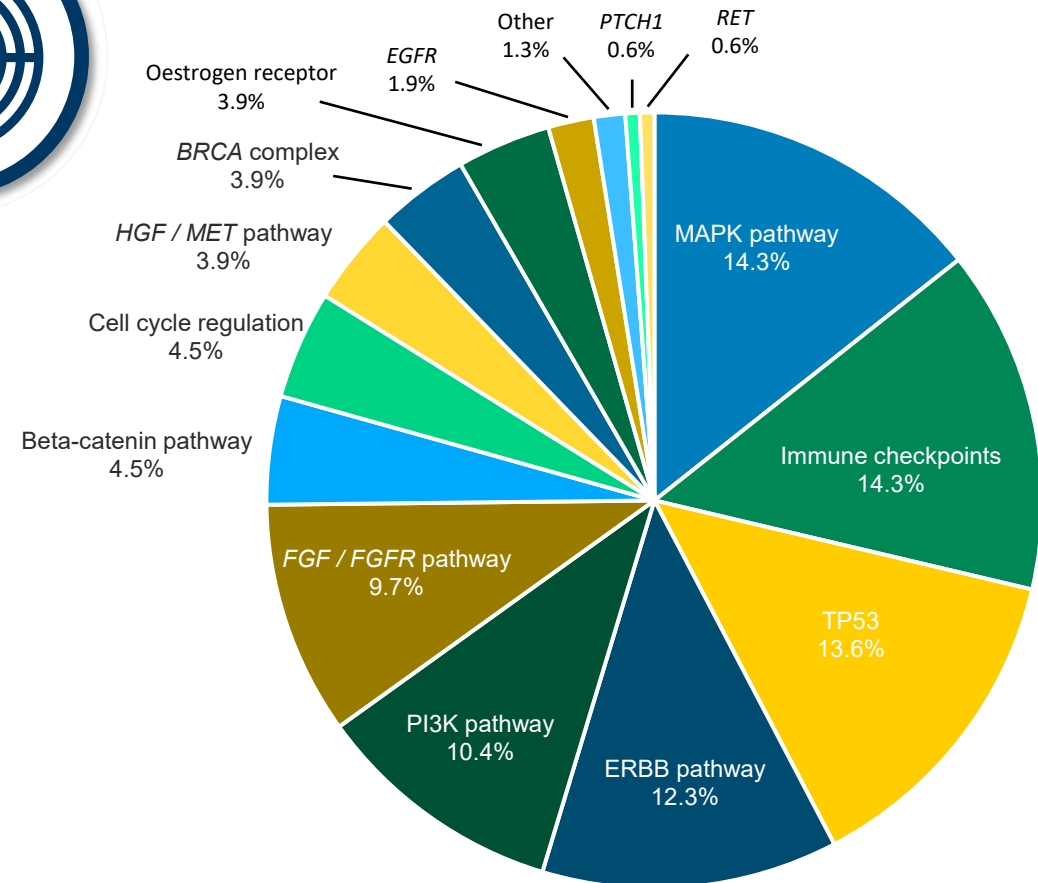
## Temporal heterogeneity



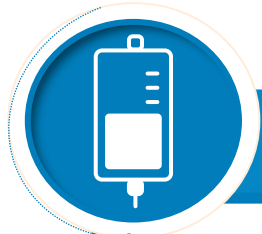
# Previously treated cohort & molecular pathways targeted



Consented patients (N)	149
Treated patients (N (% of consented patients))	83 (55.7)
<b>Patients with ≥1 matched treatment</b>	<b>73 (49.0)</b>
<b>Age (median (95% CI, range))</b>	
	62 (59-65, 21-86)
<b>Sex (N (%))</b>	
Women	55 (66.3)
Men	28 (33.7)
<b>Tumour type (N (%))</b>	
<b>Gastrointestinal and hepatopancreatobiliary</b>	<b>35 (42.2)</b>
Gynaecologic	14 (16.9)
Breast	12 (14.5)
Central nervous system	6 (7.2)
Genitourinary	3 (3.6)
Head and neck	3 (3.6)
Lung	3 (3.6)
Other	7 (8.4)
<b>Median number of prior therapies in the metastatic setting (median, IQR)</b>	<b>2 (1-3)</b>
<b>Number of total genomic alterations (median, range; VUS-excluded)</b>	<b>5 (1-19)</b>
<b>Number of administered drugs (median, range)</b>	<b>2 (1-5)</b>



# Matching score\*



For example:

Standard of care

BRCA2 N319fs\*8 → Cisplatin (Gemcitabine)

PIK3R1 splice site 1300-11\_1308del20 and PTEN V45fs\*7

**1/3 = 33% Matching Score**

BRCA2 N319fs\*8 → Carboplatin

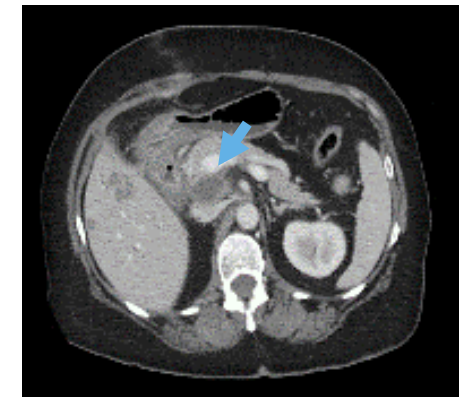
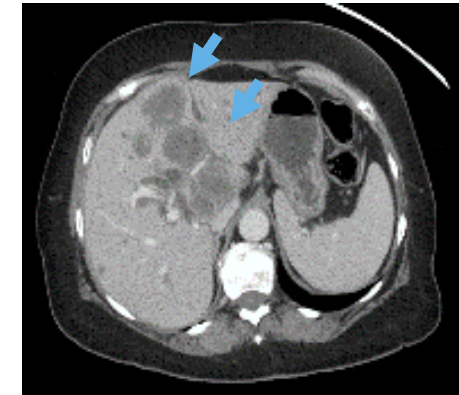
PIK3R1 splice site 1300-11\_1308del20 and PTEN V45fs\*7 → Everolimus

**3/3 = 100% Matching Score**



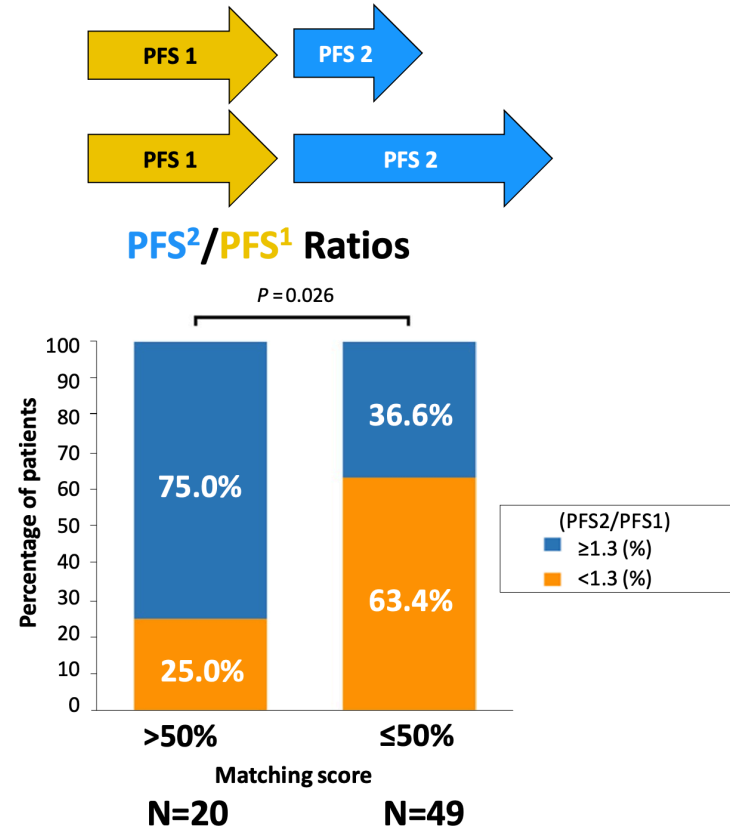
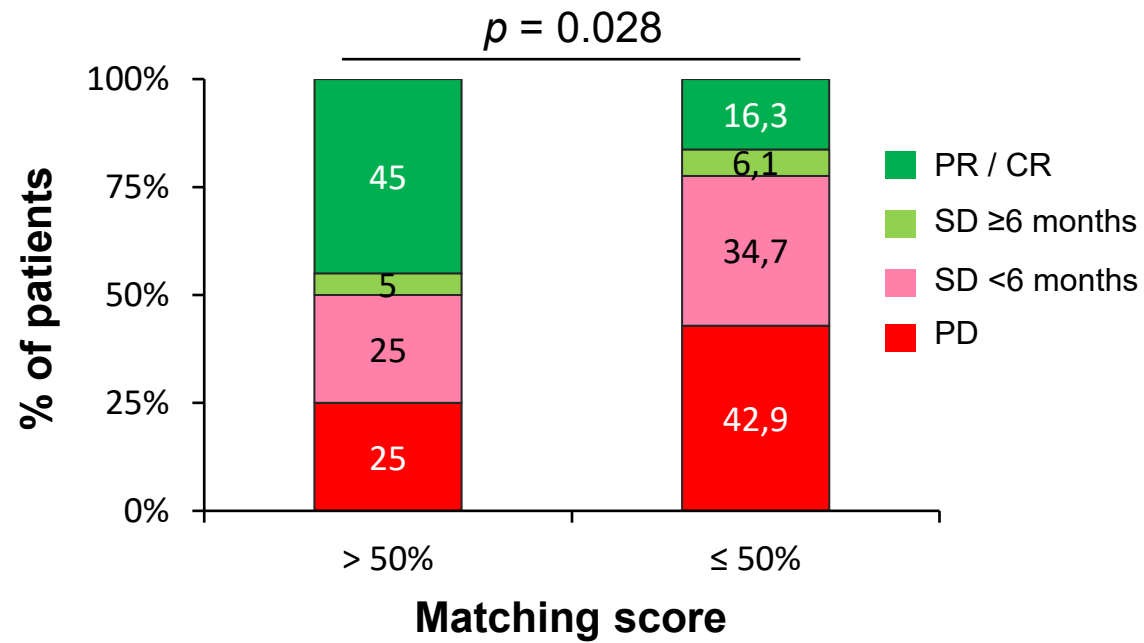
$$\frac{\text{\# Alterations Targeted}}{\text{\# Total Alterations}} = \text{Matching Score (\%)}$$

## Gallbladder cancer



\* Adopted from Wheler JJ, et al. *Cancer Research* 2016; **76**:3690-701.

# I-PREDICT: Higher matching scores resulted in better outcomes

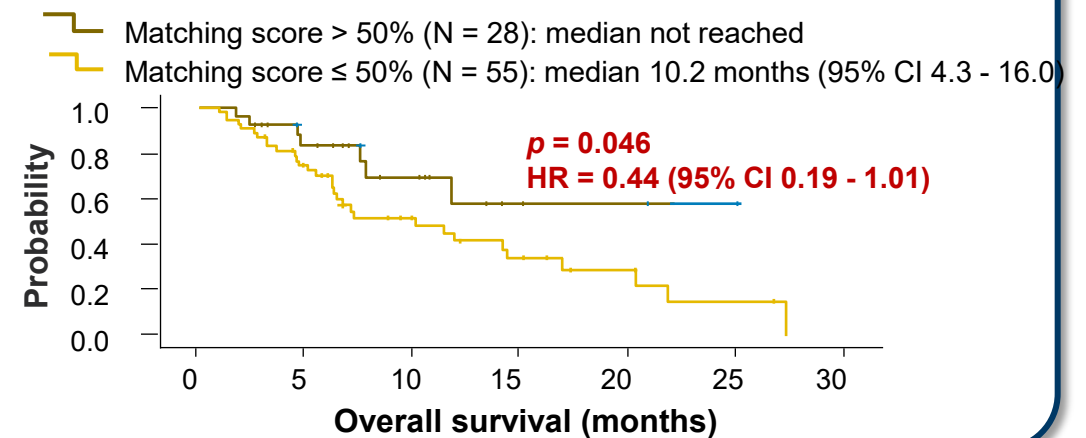
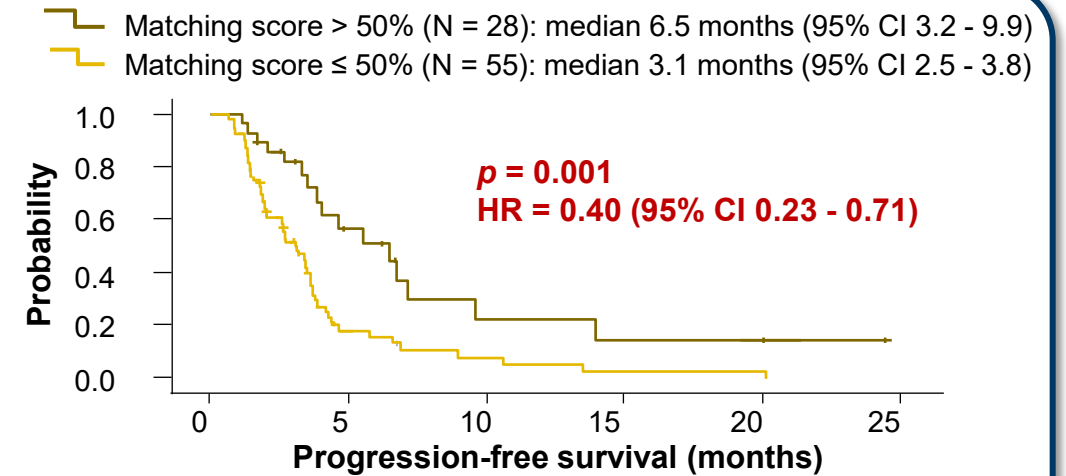
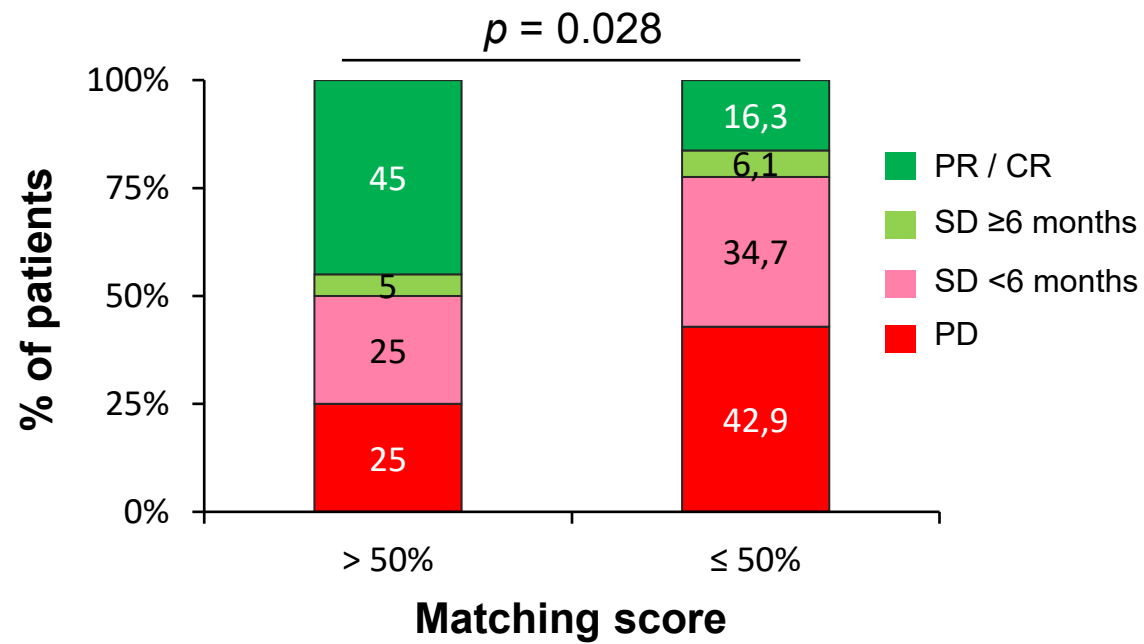


**Higher matching score (> 50%) translated into significantly better ORR (45%), PFS2/1 Ratio**

Sicklick JK, et al. *Nat Med* 2019; 25:744–750; Clinicaltrials.gov NCT02534675.



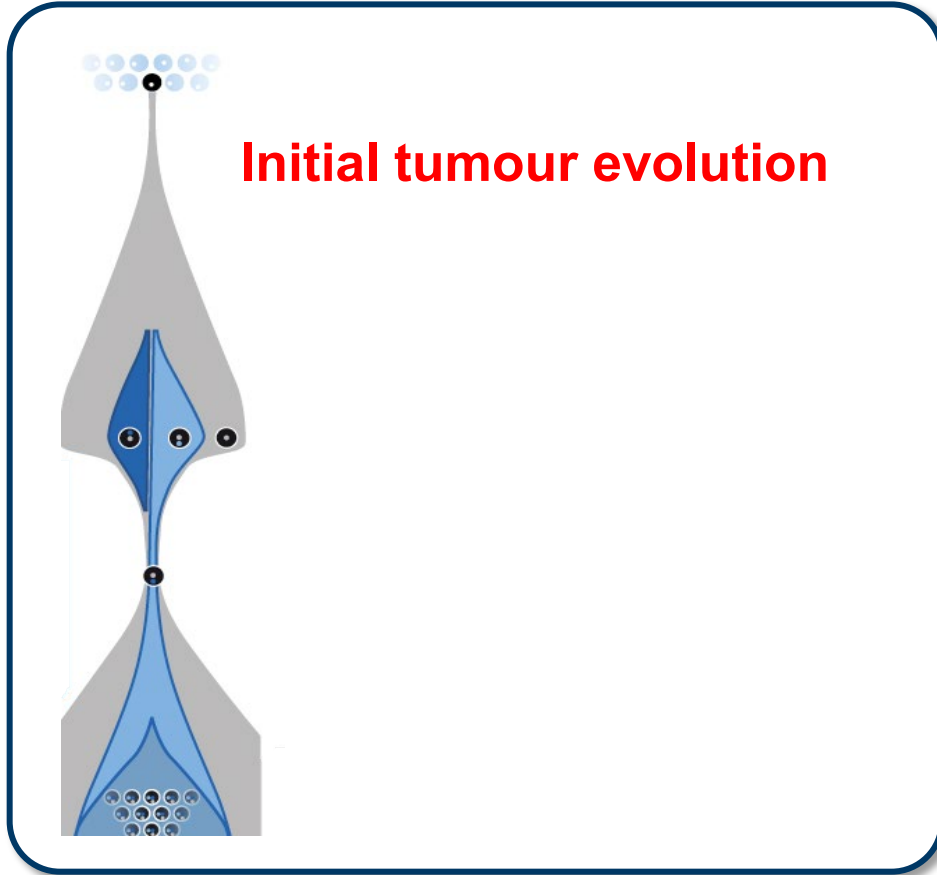
# I-PREDICT: Higher matching scores resulted in better outcomes



**Higher matching score (> 50%) translated into significantly better PFS and OS**

# Can we improve upon I-PREDICT disease control rates?

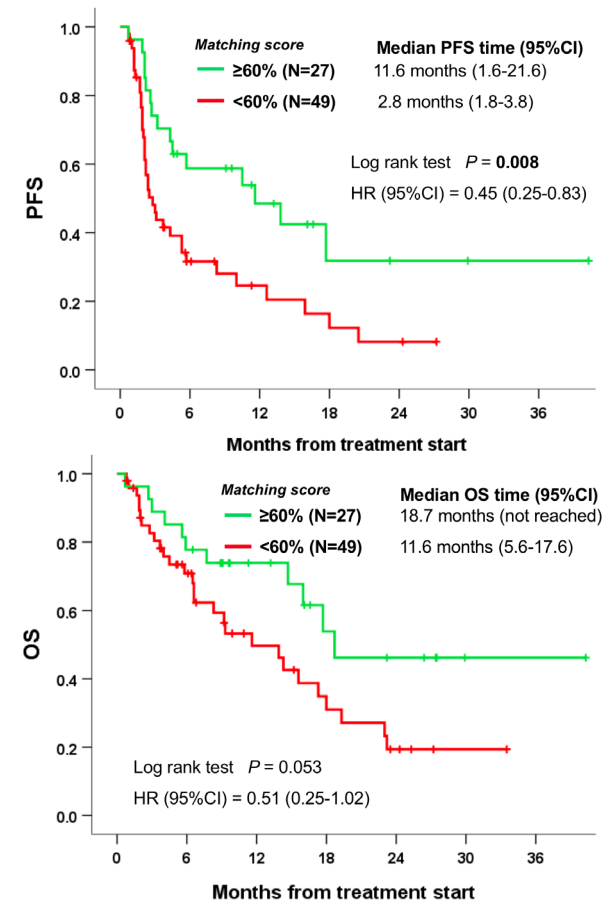
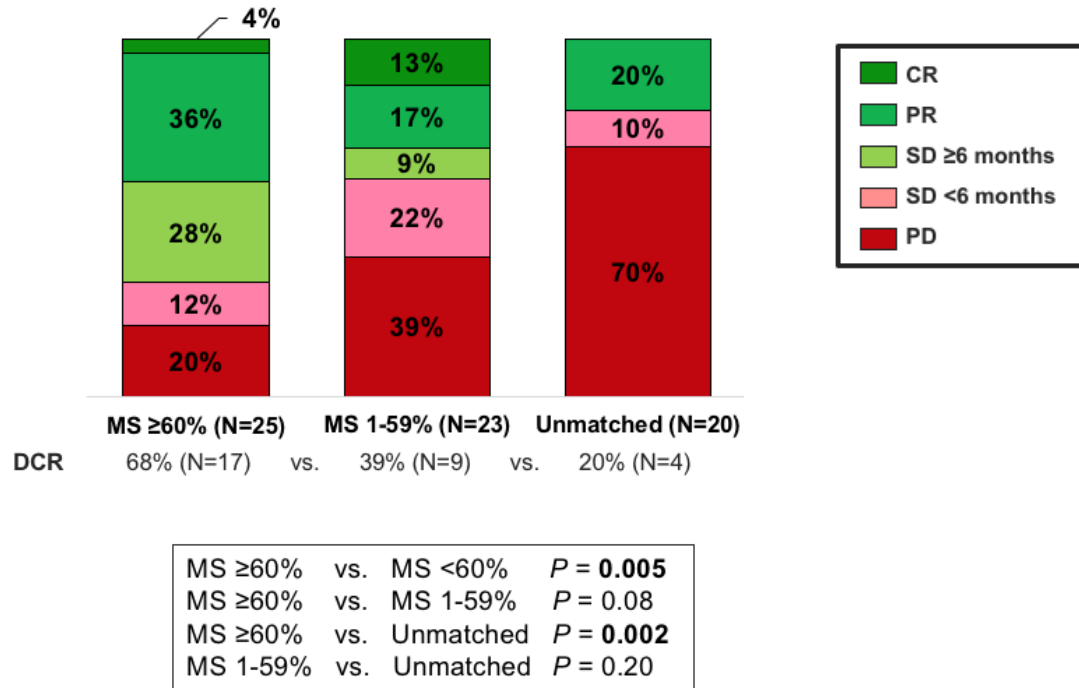
## Temporal heterogeneity



**Treat patients first-line**  
before heterogeneity occurs



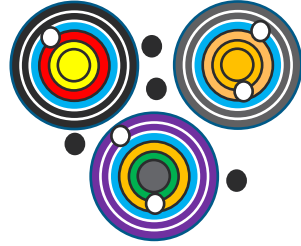
# I-PREDICT: Higher matching scores resulted in better outcomes



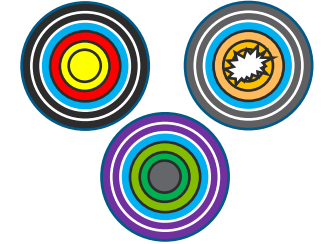
**Higher matching score (≥60%) translated into significantly better response, PFS and OS in treatment naïve patients**

# Better Outcomes with Better Matching Scores

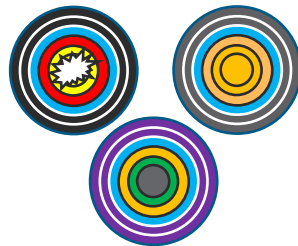
Unmatched chemotherapy (0%)



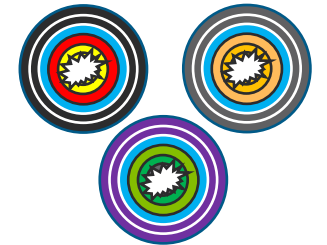
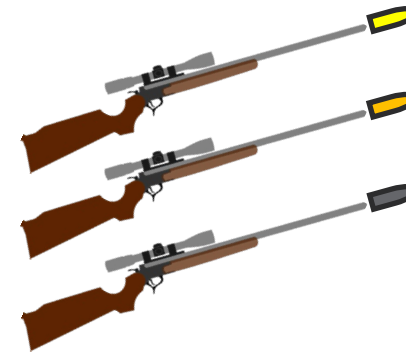
Poorly matched combination therapy (33%)  
(more and bigger ≠ better)



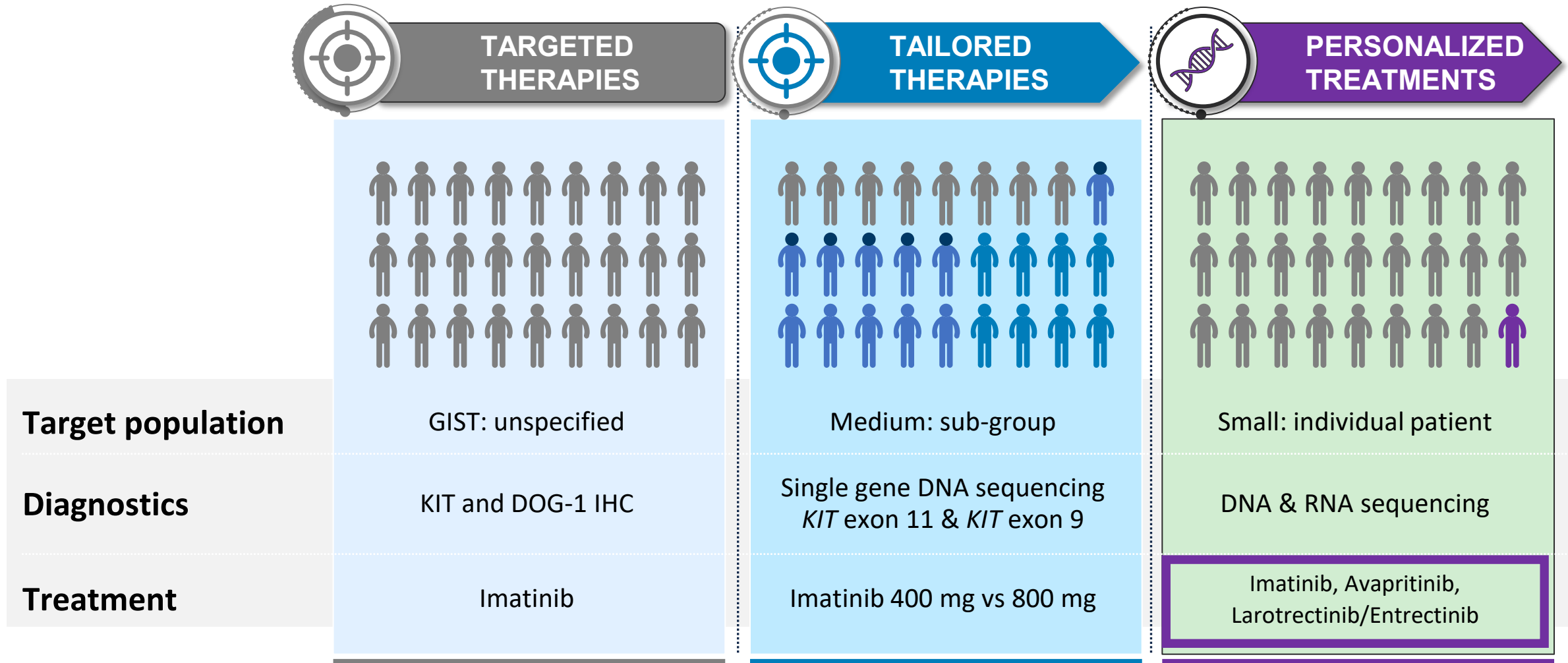
Targeted monotherapy (33%)



Targeted combination therapy (100%)

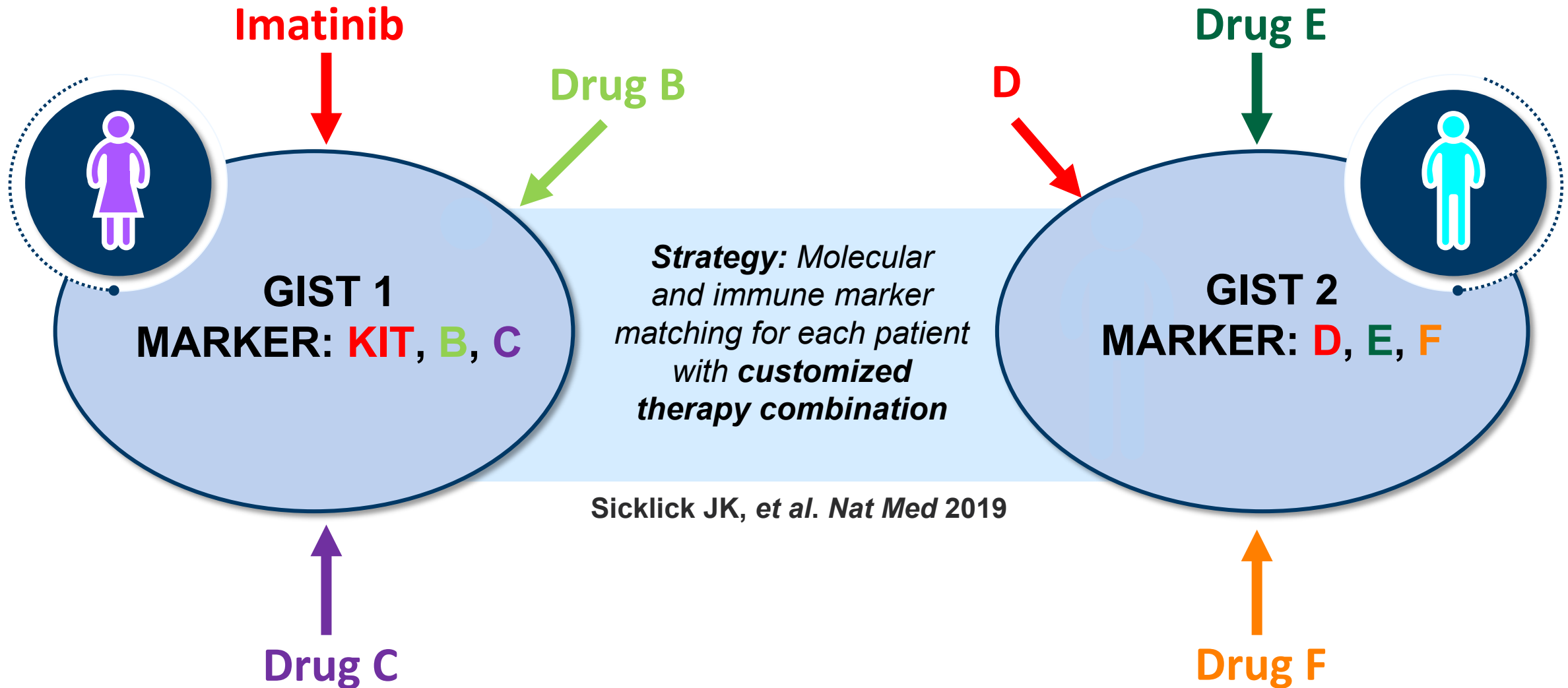


# Promise of Precision Medicine in GIST



GIST NCCN Guidelines. 2022.

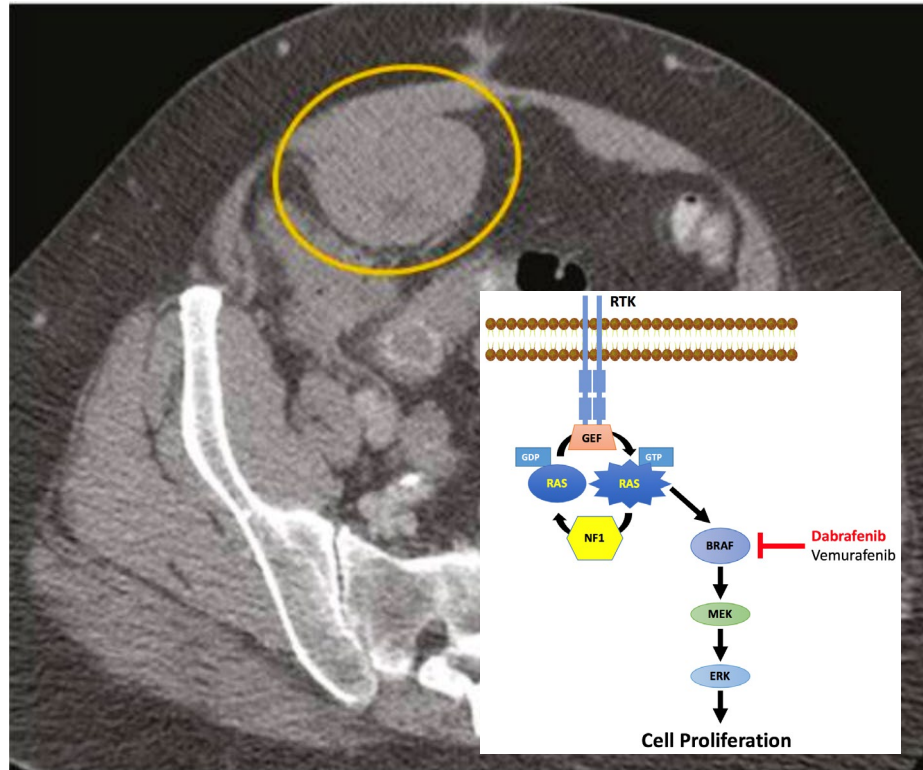
# Patient-Centric (N-of-1) Treatment for GIST



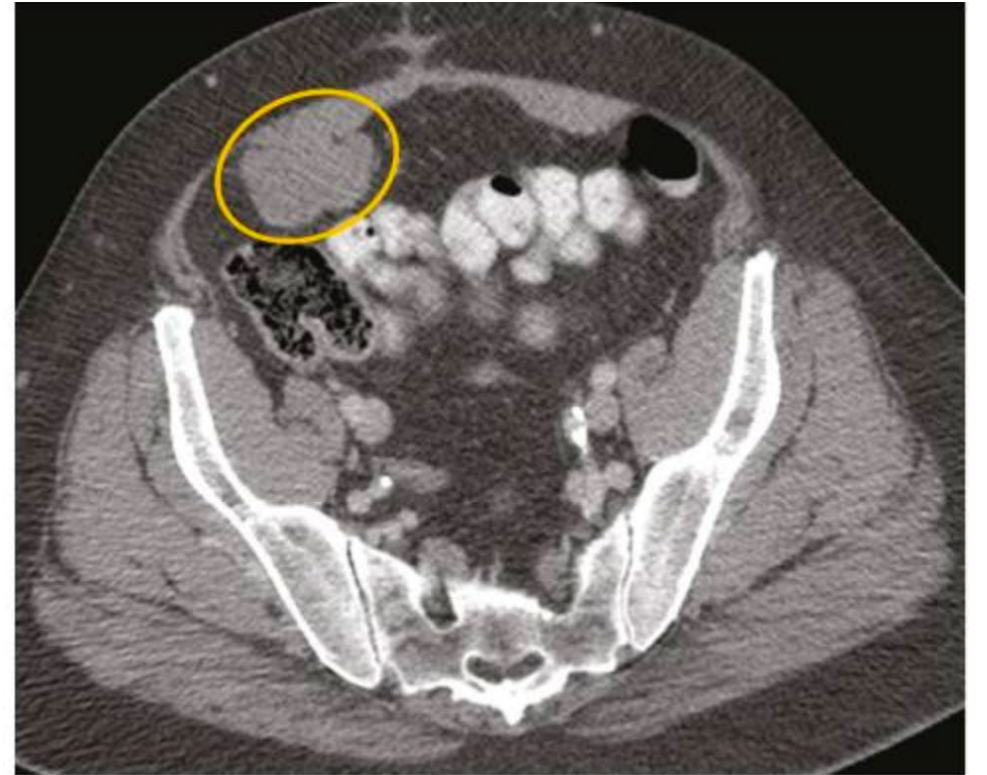
# Patient case: *BRAF*<sup>V600E</sup> mutant GIST

FEBRUARY 2007 (WEEK 0)

- Treatment with dabrafenib



MARCH 2008 (WEEK 24)

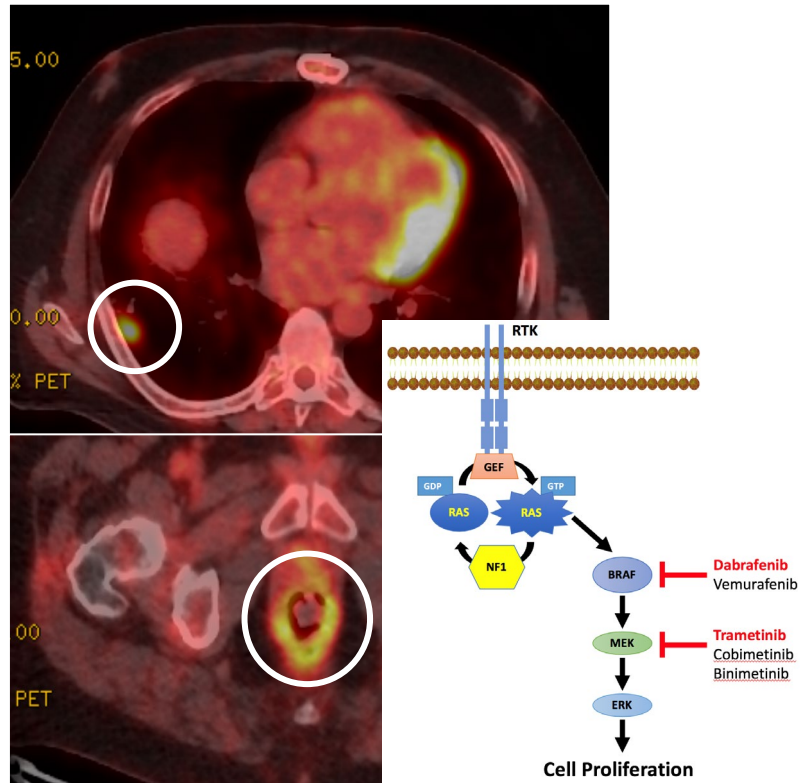


Falchook *et al.*, *Oncotarget* 2013

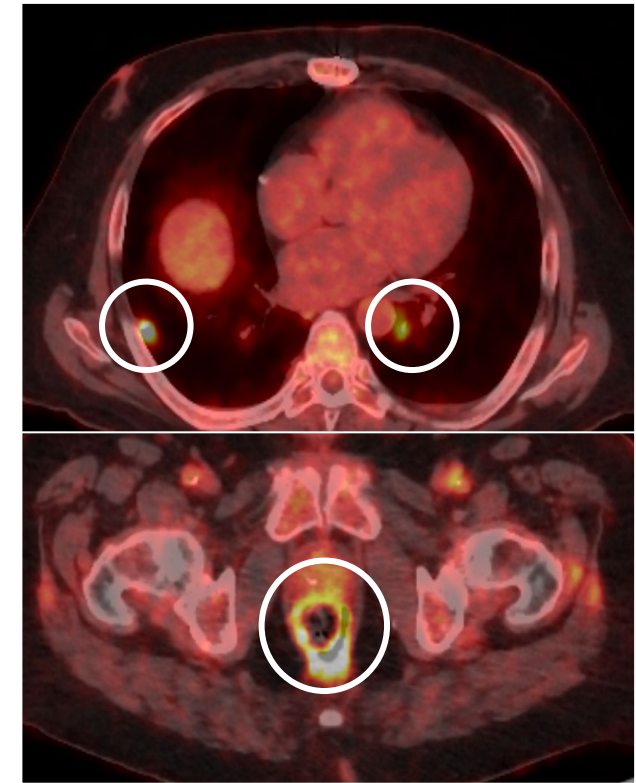
# Patient case: *BRAF*<sup>V600E</sup> mutant GIST

FEBRUARY 2018 (WEEK 0)

- FDA-approved treatment: dabrafenib + trametinib



APRIL 2018 (WEEK 8)



Kato et al., Clin Cancer Res 2021

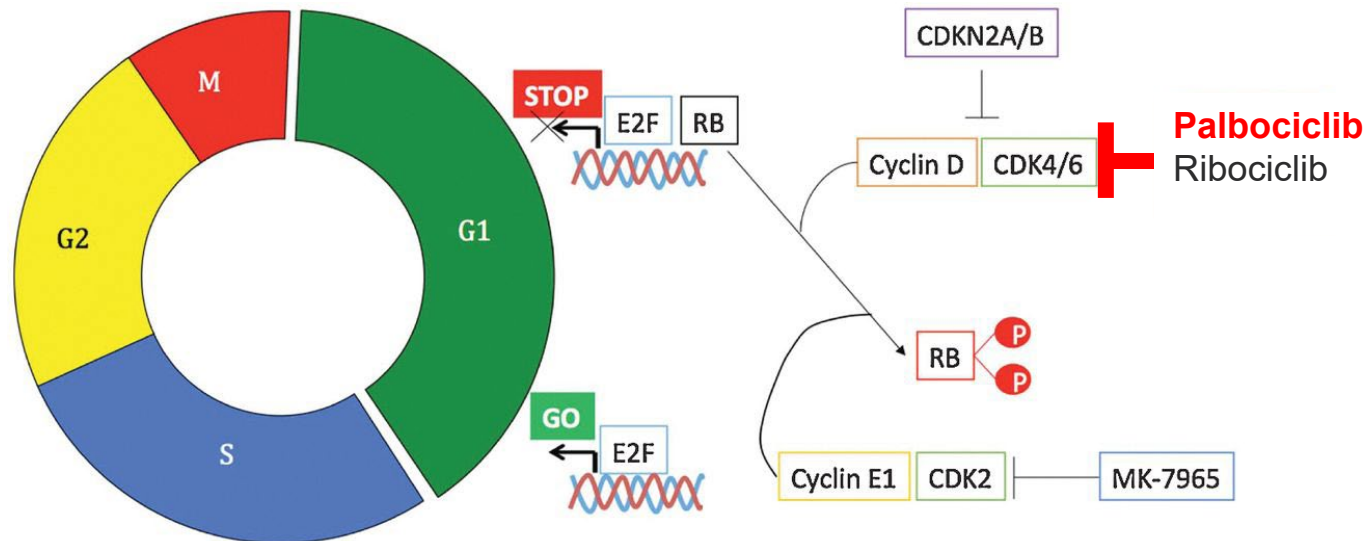


# Patient case: *BRAF*<sup>V600E</sup> mutant GIST

## NEXT GENERATION SEQUENCING

*BRAF* V600E

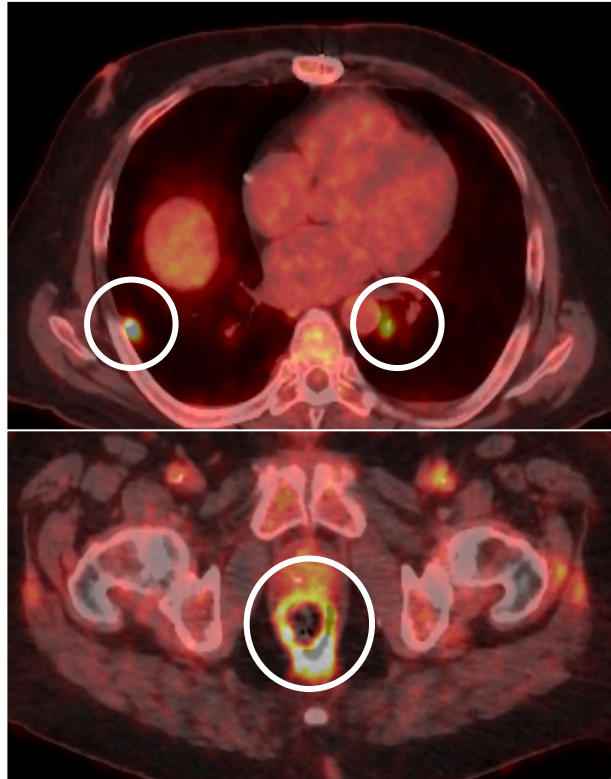
*CDKN2A* p16INK4a splice site 150+1G>A



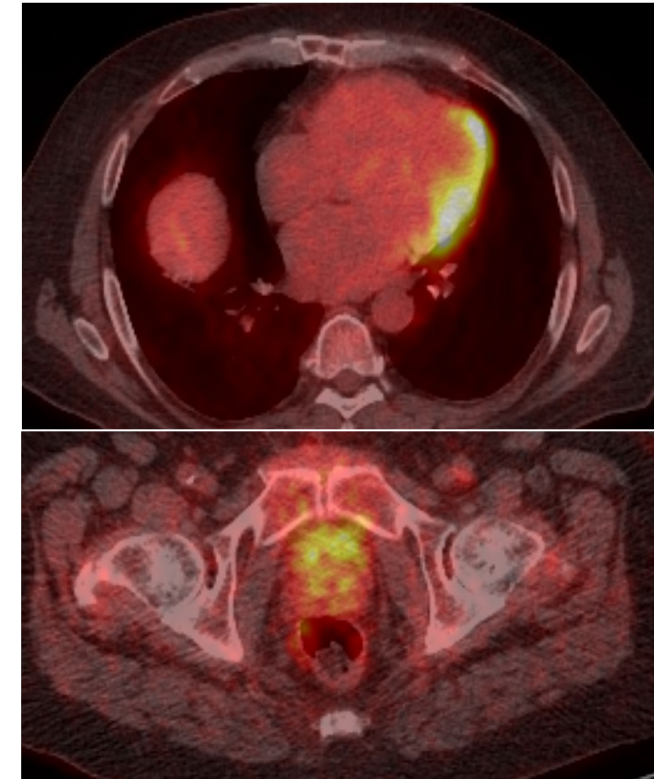
# Patient case: *BRAF*<sup>V600E</sup> mutant GIST

APRIL 2018 (WEEK 8/0)

- Dabrafenib + trametinib + palbociclib



JUNE 2018 (WEEK 16/8)



Kato et al., *Clin Cancer Res* 2021

# Lessons Learned

DNA, RNA, & IHC analyses provide the basis for clinical application of precision oncology

Single agent matched therapy is *often* inadequate to treat many lethal cancers

Multidisciplinary MTBs are crucial for implementing an effective precision oncology program

Combine genomically targeted therapies, immunotherapies, traditional chemotherapies, and hormone therapies

We can safely treat each unique tumor and its co-genomic alterations with customized, molecularly matched combination therapies

Moving towards an N-of-1 personalized-precision approach

# I-PREDICT

## Acknowledgements



FOUNDATION  
MEDICINE



**Razelle Kurzrock**



**Scott Lippman**



**Daisuke Nishizaki**



**Shumei Kato**



**Paul Fanta**



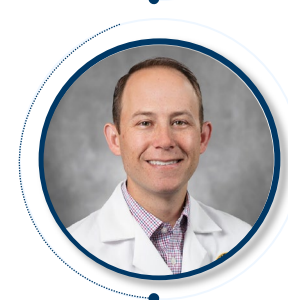
**Hirotaka Miyashita**



**Ryosuke Okamura**



**Treating Physicians  
& CTO Staff**



**Michael Hahn**

UC San Diego Health

THANK YOU

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Tuesday, October 1, 2024