The No-Name Cancer

Tumor-Agnostic→Rare→Ultra-Rare→N-of-1

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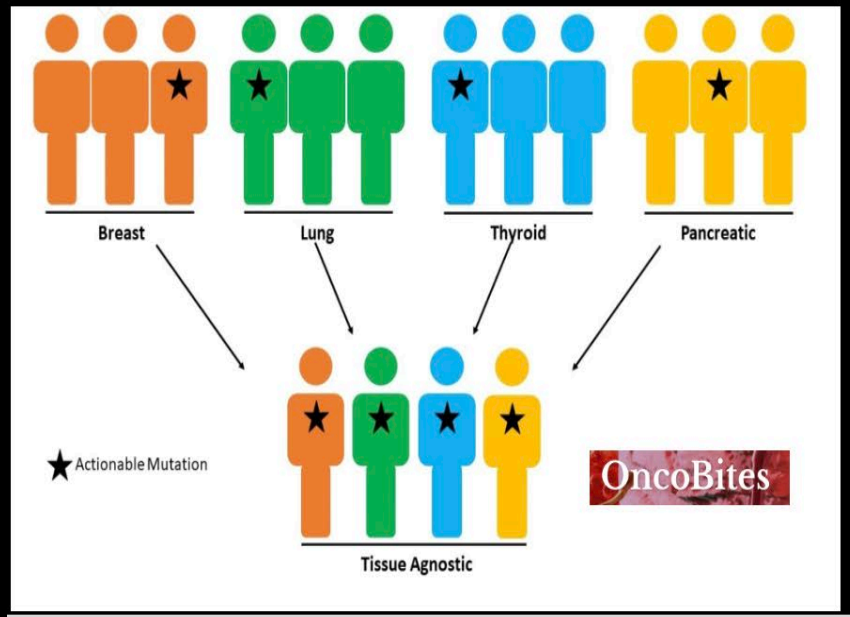
WIN Consortium for precision medicine (non-profit)



Disclosures

2019 to present

- Research funding from Boehringer Ingelheim, Debiopharm, Foundation Medicine, Genentech, Grifols, Guardant, Incyte, Konica Minolta, Medimmune, Merck Serono, Omniseq, Pfizer, Sequenom, Takeda, and TopAlliance;
- Consultant and/or speaker fees and/or advisory board for Actuate Therapeutics, AstraZeneca, Bicara Therapeutics, Inc., Biological Dynamics, Caris, Datar Cancer Genetics, LabCorp, Lanuaria, Merck, NeoGenomics, Neomed, Pfizer, Precirix, Prosperdtx, Regeneron, Roche, TD2/Volastra, Turning Point Therapeutics, X-Biotech
- Equity interest in CureMatch Inc. and IDbyDNA
- Serves on the Board of CureMatch and CureMetrix, and is a co-founder of CureMatch.

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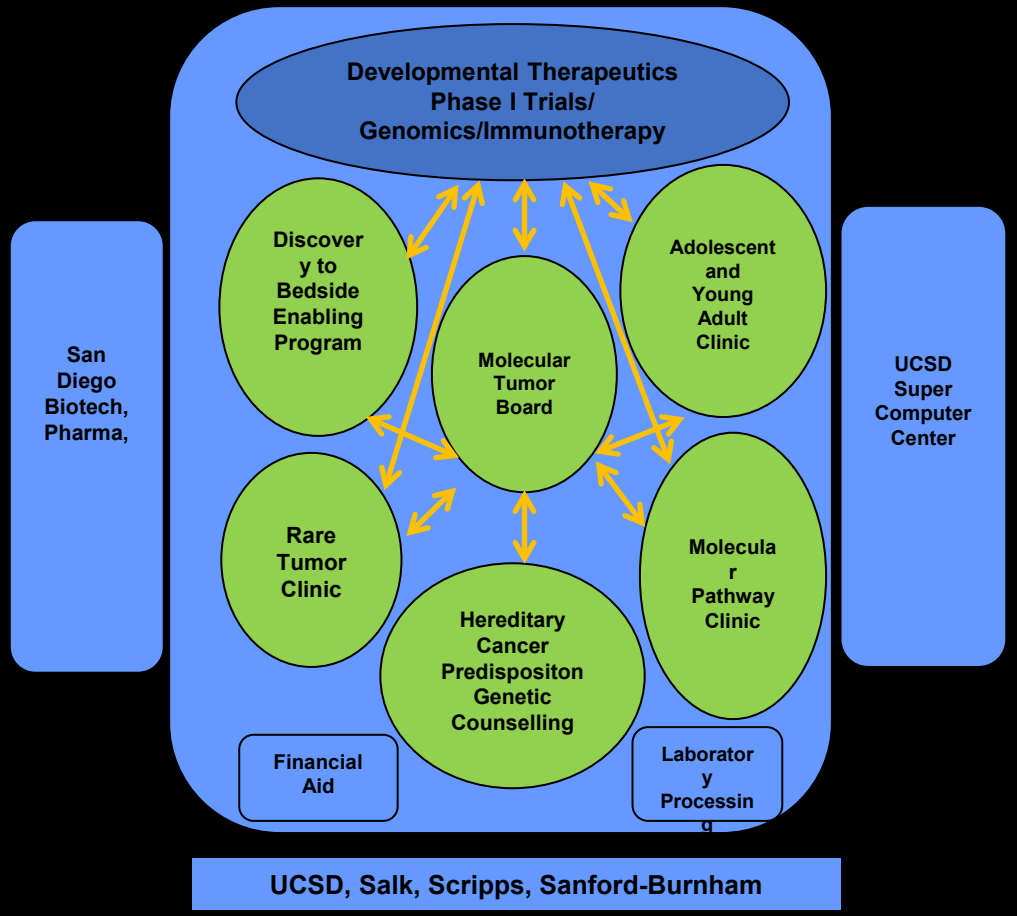
Precision Medicine in the Clinic: Experience

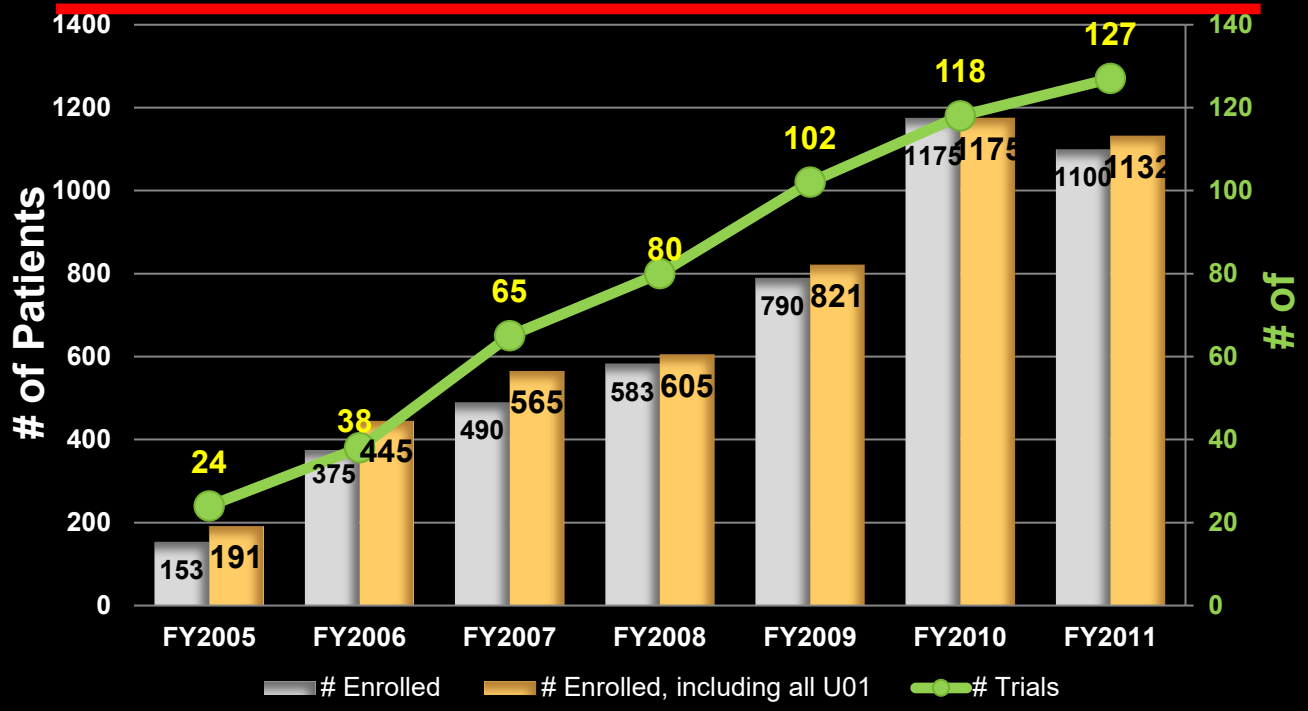
Founder and Director: Center for Personalized Cancer Therapy at UCSD Moores Cancer Center 2013-2021



Molecular profiling (N ~ 21,000 patients)

Founder and Chair, Dept of Investigational Cancer Therapeutics, MD Anderson Cancer Center 2004-2012

Phase I Trials / Patients Enrolled



- Over 950 peer-reviewed publications
- Oversight >500 early phase trials, including 8 drugs that have gone to FDA approval
- Clinical-grade genomic profiling >21,000 patients
- Leadership positions: SWOG, WIN, NCCN,

Take-home point

At the multi-omic level, every metastatic tumor is unique and complex

Tumor of origin→Rare→ ultra-rare→ N-of-1

The Light Microscope

Invented in 1590

Still used to diagnose cancer

Traditional method of deciding therapy based on clinical trials

Next Gen Sequencing
Actionable Cancer Gene Sequencing [CLIA]
The Molecular Microscope

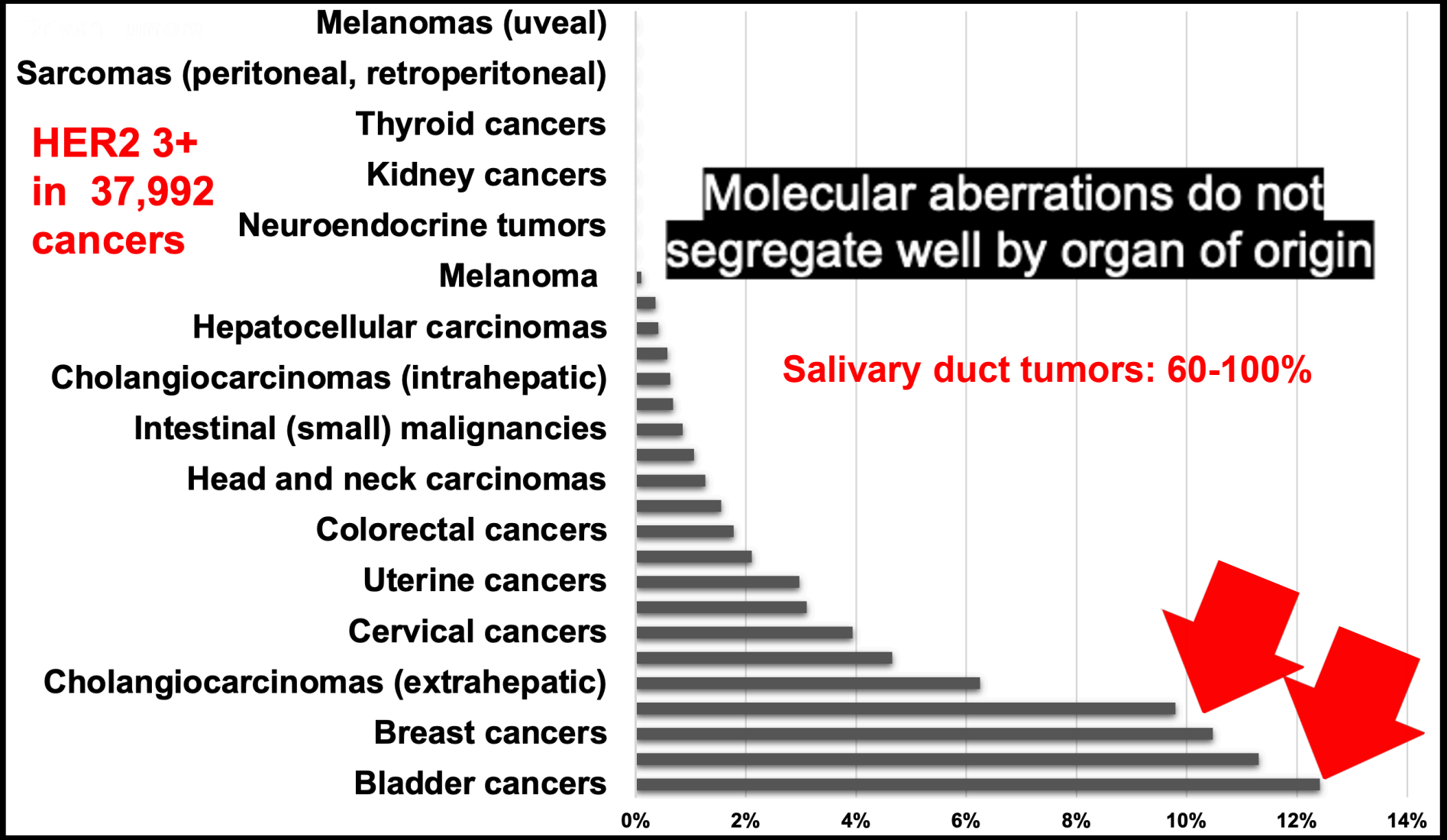
ABL1	BRCA2	CSMD2	EZH2	GNAS
ACVR1B	CARD11	CSMD3	FAM123B	HDAC9
ADAMTS12	CASP8	CTNNB1	FAM135B	HEATR7B2
AKAP3	CBL	CYLD	FAT3	HGF
AKT1	CD19	CYP2C19	FBXW7	HMCN1
ALK	CDH1	DAXX	FGFR1	HNF1A
APC	CDH10	DDR1	FGFR2	HNF1B
AR	CDH11	DDR2	FGFR3	HRAS
ARAF	CDK4	DNMT3A	FGFR4	HYDIN
ARID1A	CDK6	EGFR	FLG	IDH1
ASXL1	CDKN2A	ELN	FLT1	IDH2
ATM	CEBPA	EML4	FLT3	IGF1R
ATR	CHEK1	EP300	FLT4	IKZF1
ATRX	CHEK2	EPHA3	FOXL2	IL6R
AURKA	COL14A1	ERBB2	GABRA6	IRS1
AURKB	CPAMD8	ERBB3	GABRB3	ITGA4
BAI3	CREBBP	ERCC3	GATA1	JAK1
BAP1	CRIPAK	ERCC4	GATA3	JAK2
BRAF	CSF1R	ERCC5	GNA11	JAK3
BRCA1	CSMD1	ETV5	GNAQ	KCNB2

KDM6A	MLL3	PAX5	PTPN11	STK11
KDR	MPL	PBRM1	RAD51	SYK
KIT	MSH2	PCDH15	RAF1	SYNE1
KRAS	MSH6	PCLO	RB1	SYNE2
LAMA1	MTOR	PDGFRA	RELN	TBC1D4
LPHN3	MYD88	PDGFRB	RET	TET2
LRP1	NAV3	PIK3CA	RIMS2	TGFb1
LRP1B	NCOR1	PIK3CG	RNF213	TGFBR2
LRP2	NF1	PIK3R1	RUNX1	TNFAIP3
MAP2K1	NF2	PIKFYVE	RUNX1T1	TOP1
MAP2K4	NFKB2	PKHD1	RYR2	TOP2A
MAP3K1	NOTCH1	PKHD1L1	SETD2	TP53
MAP3K4	NOTCH2	PPP1R3A	SMAD4	TSC1
MDN1	NOTCH3	PPP2R1A	SMARCA4	TSC2
MECOM	NOTCH4	PPP2R4	SMARCB1	TSHR
MEN1	NPM1	PRDM1	SMO	USH2A
MET	NRAS	PRSS1	SOS1	VHL
MITF	NSD1	PTCH1	SPEN	WHSC1
MLH1	PALB2	PTEN	SPOP	WT1
MLL2	PAPPA2	PTK2	SPTA1	ZNF238
				ZNF536

Breathtaking Progress Unparalleled in Human History

Genome sequenced (publication year)	HGP (2003)	Venter (2007)	Watson (2008)	Current (2015)
Time taken (start to finish)	13 years	4 years	4.5 months	~1 days
Number of scientists listed as authors	> 2,800	31	27	
Cost of sequencing (start to finish)	$2.7 billion	$100 million	< $1.5 million	~$1000
Coverage	8-10 ×	7.5 ×	7.4 ×	30-50X
Number of institutes involved	16	5	2	
Number of countries involved	6	3	1	

The Reclassification of Cancer



HER2 aberrations in cancer: implications for therapy
Yan M.....Kurzrock R. Cancer Treatment Reviews 2014

Yan M,....Kurzrock R. HER2 expression status in diverse cancers: review of results from 37,992 patients. Cancer Metastasis Review. 2015

Trastuzumab deruxtecan (Enhertu)

April 5 2024
Solid tissue-agnostic
Approval
HER2 IHC3+

Antibody-drug Conjugate

NO NAME CANCER
Genomics IS the Diagnosis

› JAMA Oncol. 2016 Jun 1;2(6):719-20. doi: 10.1001/jamaoncol.2016.0078.

Universal Genomic Testing Needed to Win the War Against Cancer: Genomics IS the Diagnosis

Vivek Subbiah [1], Razelle Kurzrock [2]

Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: *Genomics Is the Diagnosis*

Vivek Subbiah, MD[1,2] and Razelle Kurzrock, MD[3,4]

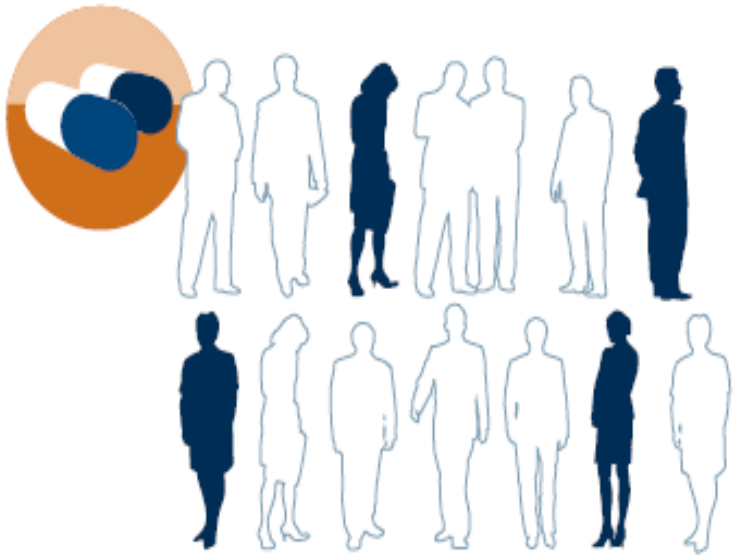
Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Evolution of Clinical Trial Design

Redesigning Cancer Trials: Stage 1

Smaller Trials, Bigger Chance for Success

OLD MODEL: Large numbers of patients, not selected by molecular characteristics; lower chance of demonstrating effectiveness, since many participants do not have the molecular defects being targeted



NEW MODEL: Small patient populations, all with the relevant mutations or genetic defects; greater chance of desired results, since all participants have the potential to respond

Tumor-agnostic basket trials

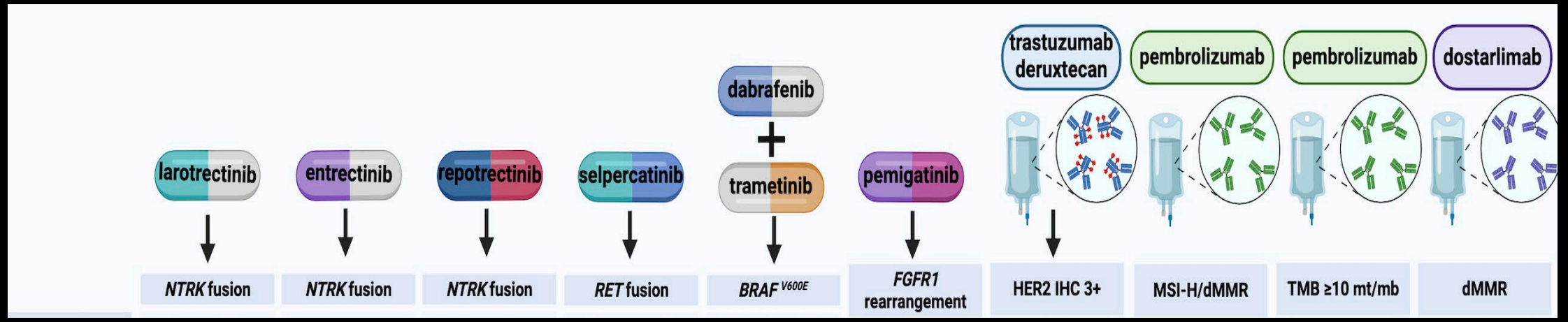
FDA approves pembrolizumab (anti-PD1) for solid tumors based on MSI-H (RR ~45%)

May 23, 2017

- Tissue agnostic approval
- Approval based on genomic marker
- **Approval based on retrospective/real-world data**

Ten Tumor-Agnostic Precision Medicine

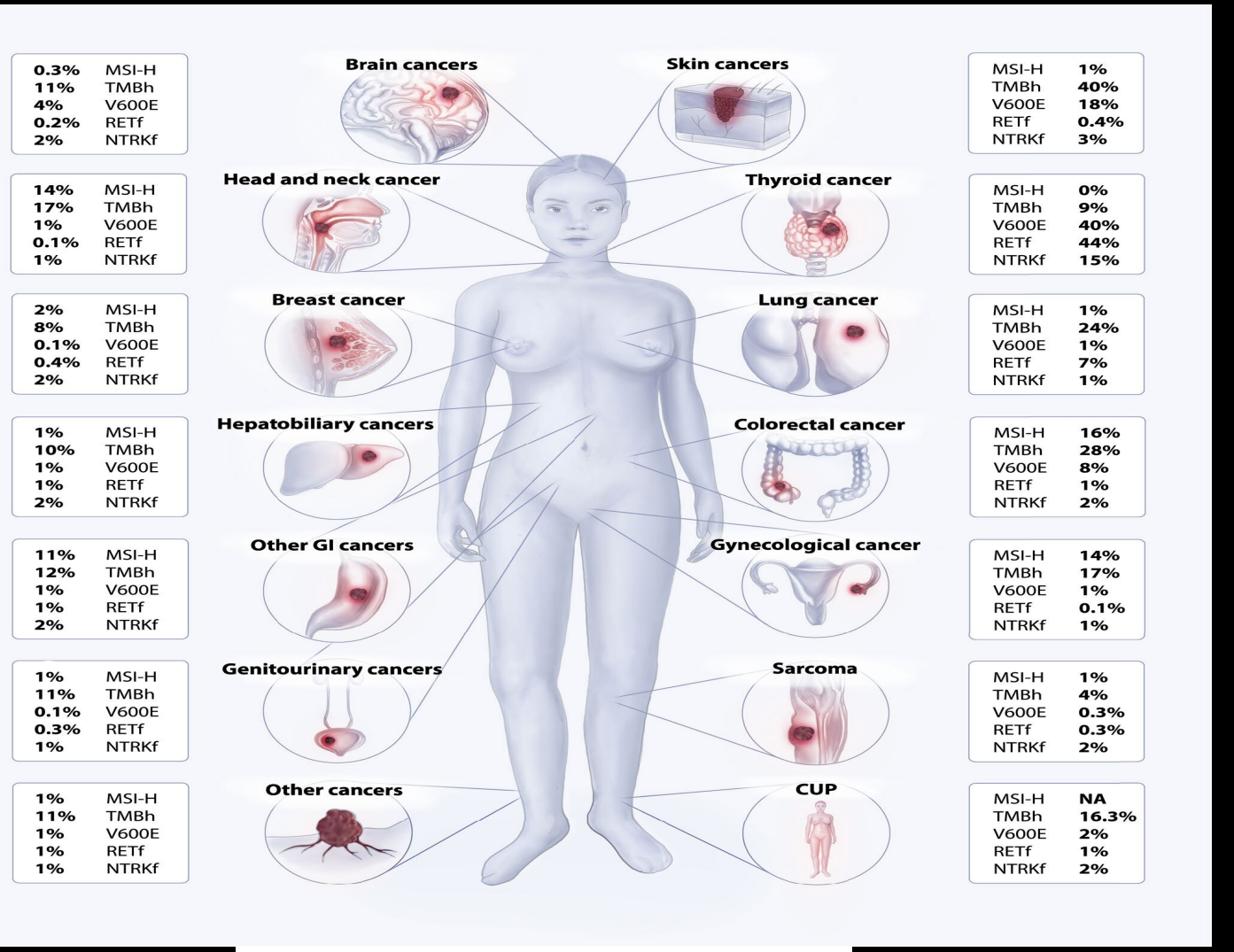
2 more expected this year (KRAS G12C, NRG1)



Pemigatinib for FGFR1 rearranged myeloid lymphoid neoplasms

Heme-agnostic

August 26, 2022



CA: A Cancer Journal for Clinicians
The flagship journal of the American Cancer Society

REVIEW ARTICLE | Open Access

The evolving landscape of tissue-agnostic therapies in precision oncology

Vivek Subbiah MD, Mohamed A. Gouda MD, Bettina Ryll MD, PhD, Howard A. Burris III MD, Razelle Kurzrock MD

First published: 30 May 2024 | https://doi.org/10.3322/caac.21844

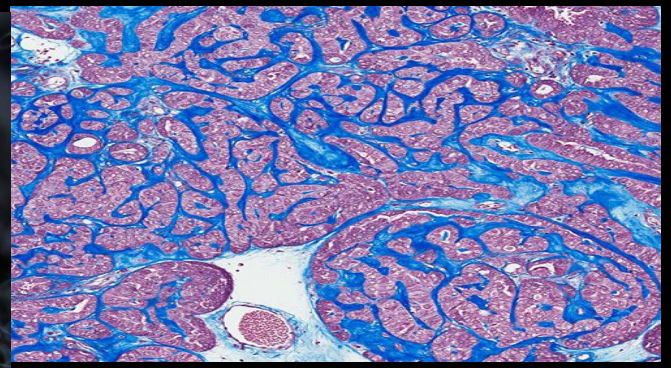
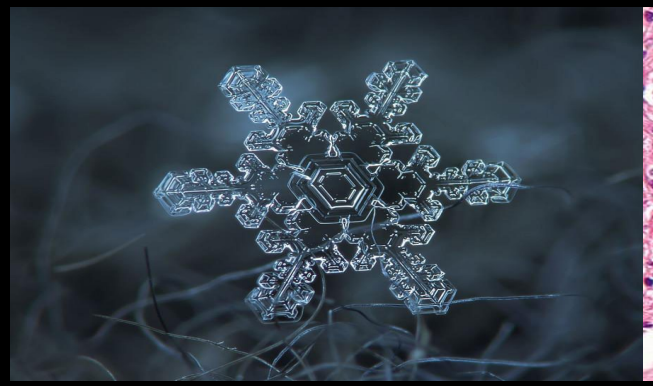
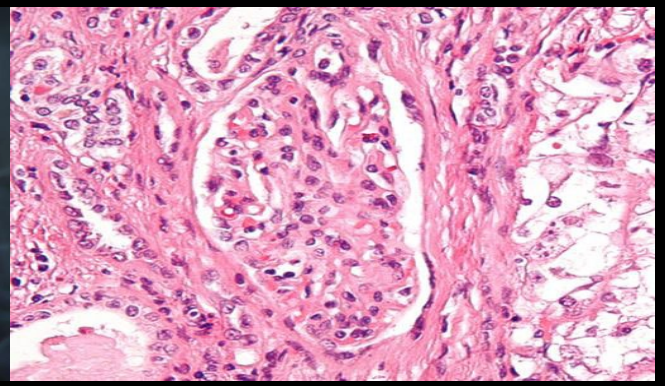
But wait!! There’s more!!

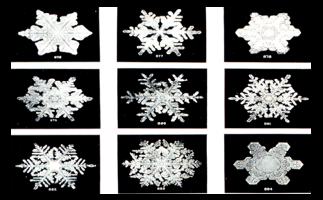
N-of 1 clinical trial design

→Multi-Omic interrogation
→Personalized combination therapies

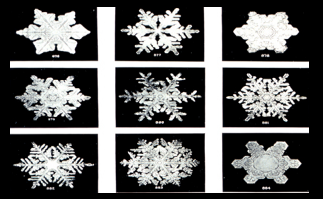
What if every metastatic cancer is different?

Malignant Snowflakes
Each is complex and distinct



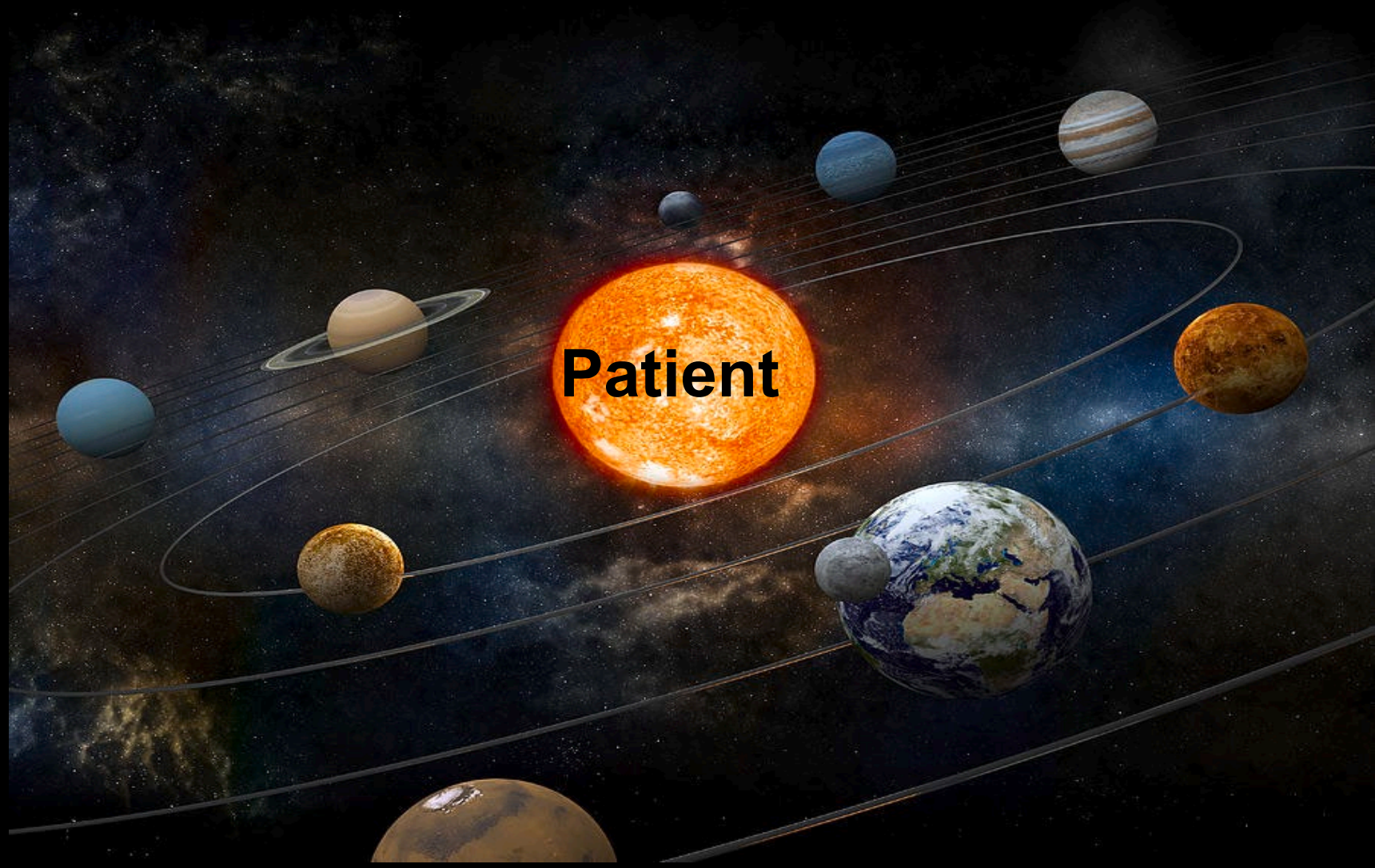
Malignant Snowflakes
Metastatic Breast Cancer



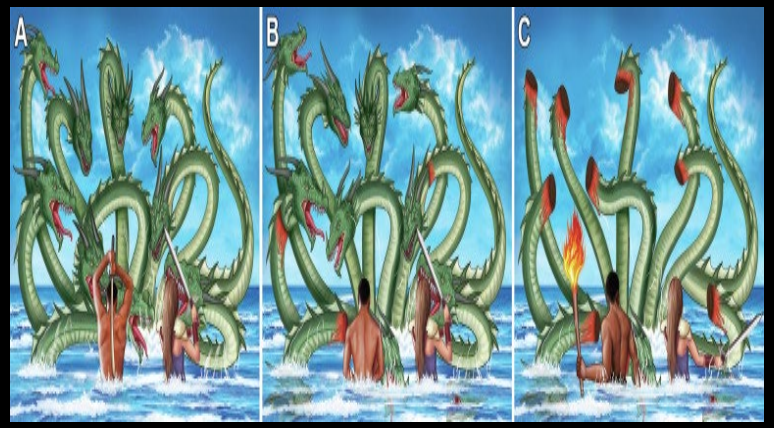
Pt number	Molecular Results (236 genes; NGS)—Breast Cancer
1	PIK3CA amplification, SOX2 amplification, TP53 G302fs*42, FLT3 L260*
2	AKT1 (E17K)
4	EGFR amplification, CCND1 amplification, CDKN2A/B loss, FGFR1 amplification, MYC amplification, TP53 P151A
42	ERBB2 amplification, PIK3CA H1047L, AURKA amplification, TP53 R342P, CREBBP P858S, ZNF217 amplification
25	ERBB2 amplification, MYC amplification, CDK6 amplification, TP53 R213*
7	ESR1 Y537S
13	GATA3 *445fs*2+
16	RET C634R, GATA3 P436fs*11+
18	AKT3 amplification, MYC amplification, MYCL1 amplification, TP53 R248Q
54	NF1 R1276Q

Wheler….Kurzrock. Oncotarget. 2014: Wheler….Kurzrock. Cancer Research, 2014; Kurzrock Giles. Cell Cycle. 2015


Drug(s)


Patient

Major treatment approaches



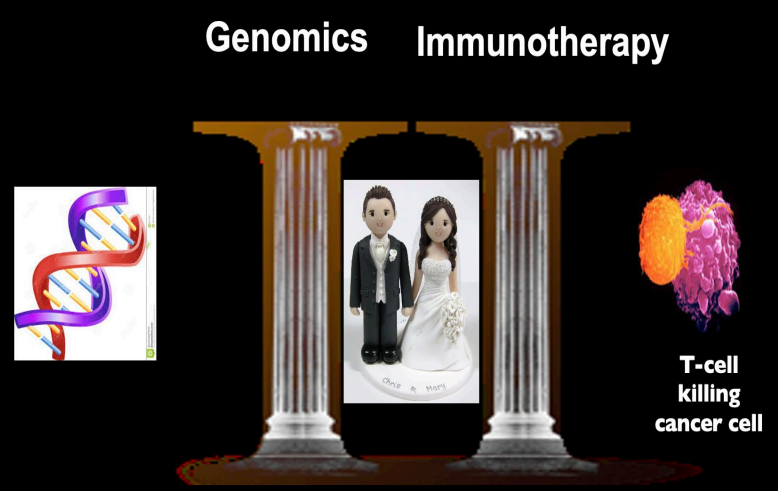
Genomic strategy:

- Treat earlier in the disease
- Attack the drivers such as fusions
- Hit all the drivers at once—cut all the Hydra's heads

Immunotherapy strategy

- Activate the immune system to kill the tumor
- Precision immunotherapy—know how the tumor has exploited the immune system

The Pillars of Precision/Personalized Medicine



I-PREDICT
N-of-1 approach

First N-of One Study

Prospective
Investigation of Profile-Related
Evidence Determining Individualized
Cancer Therapy

Study Novelty
- ***Customized combinations***
- ***Newly diagnosed patients with lethal advanced malignancies***

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

PI: Razelle Kurzrock, MD
Director, Center for Personalized Cancer Therapy

Activation Date: February 13, 2015
Consented: *N* = 506
Treated: *N* = 291

Treatment Decisions Guided by:
FoundationOne (Heme), Foundation ACT (ct DNA), PD-1/PDL-1 IHC, Tumor Mutational Burden,

Avera PI:
Brian Leyland-Jones

Master Protocol

Investigation of **P**rofile-**R**elated **E**vidence **D**etermining

Individualized **C**ancer **T**herapy

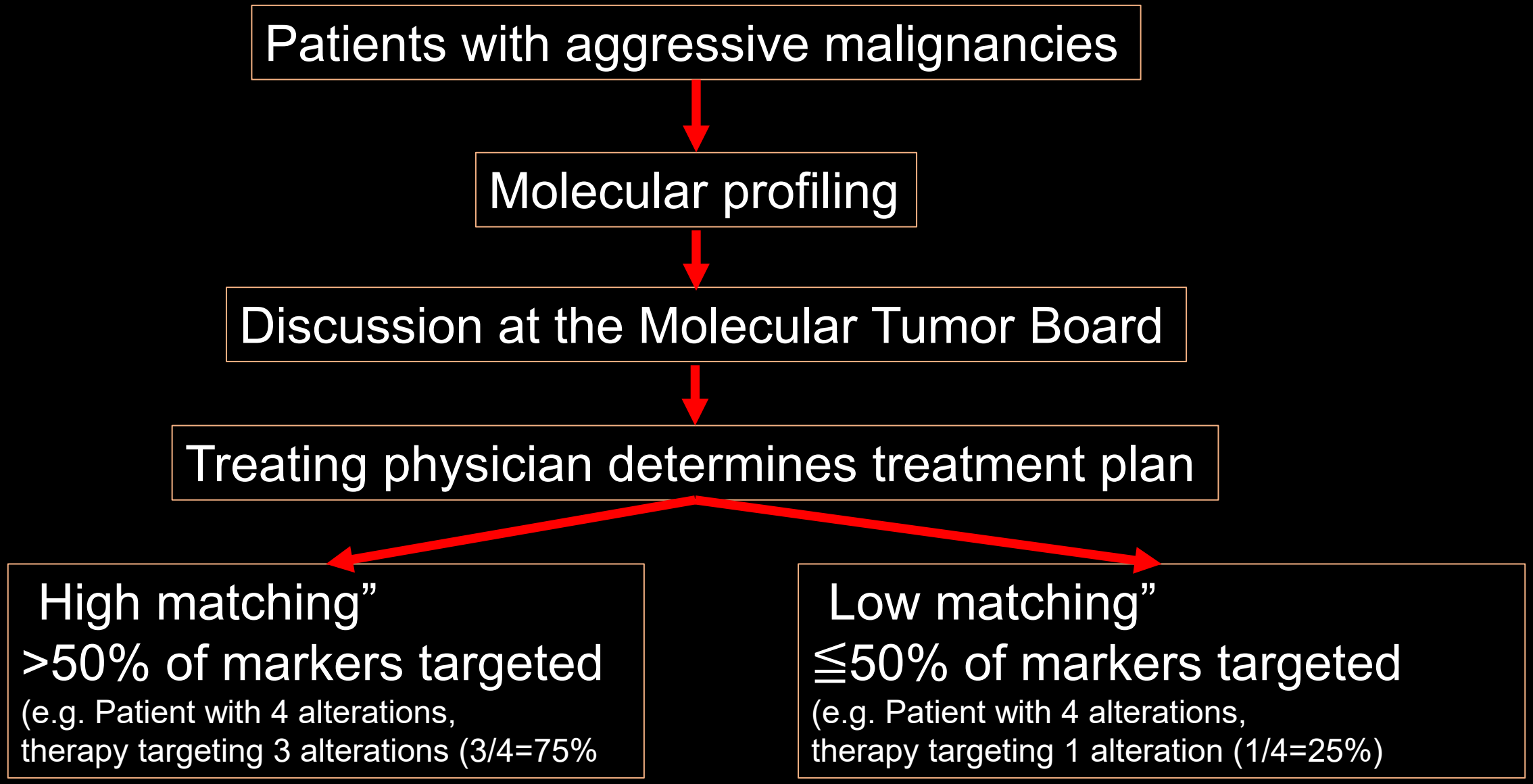
I-PREDICT

Basket

- **Histology-Independent targeted approach**
- **Multiple molecular aberrations assessed**
- **Patients matched with targeted agents**

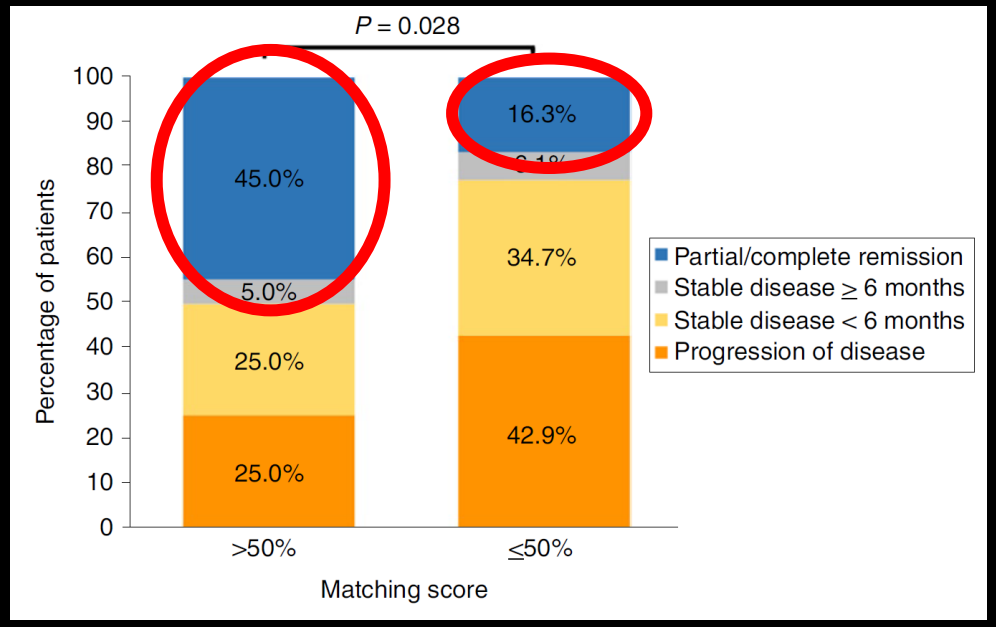
Umbrella

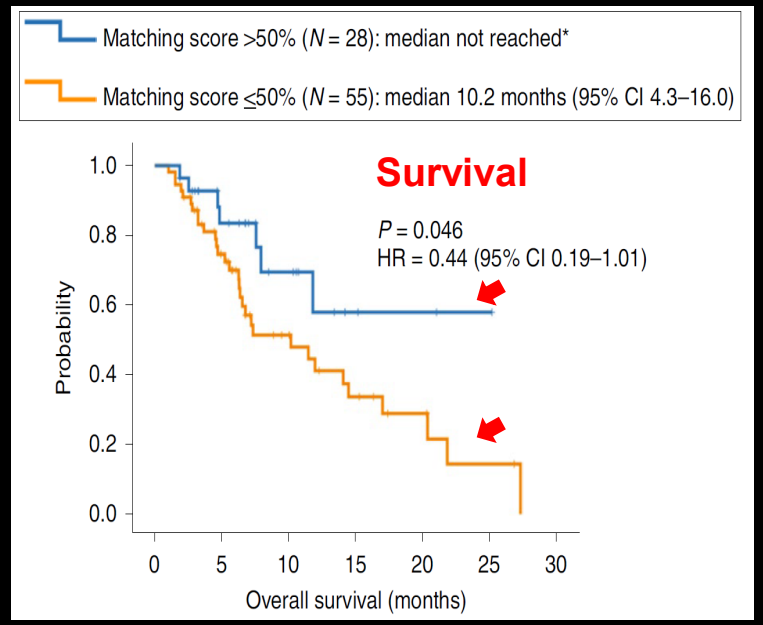
I-PREDICT Study



IPREDICT Study: Metastatic, treatment refractory

Sicklick…Kurzrock R. Nature Medicine 2019



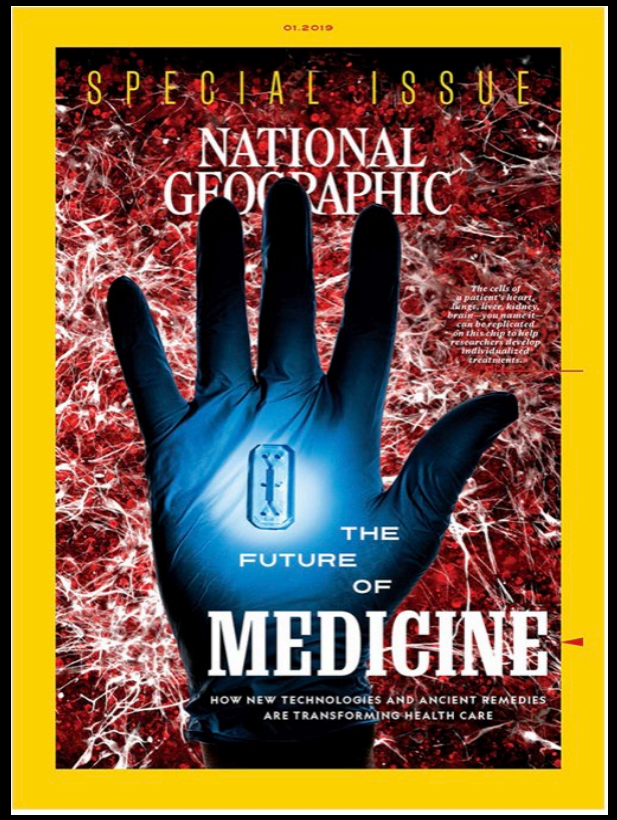


nature medicine

Higher matching score (>50%) translated into significantly better response rate, progression-free survival and overall survival

I-PREDICT featured in National Geographic and in NIH Director's Blog; Presented at Nobel Symposium September 2023

nature medicine

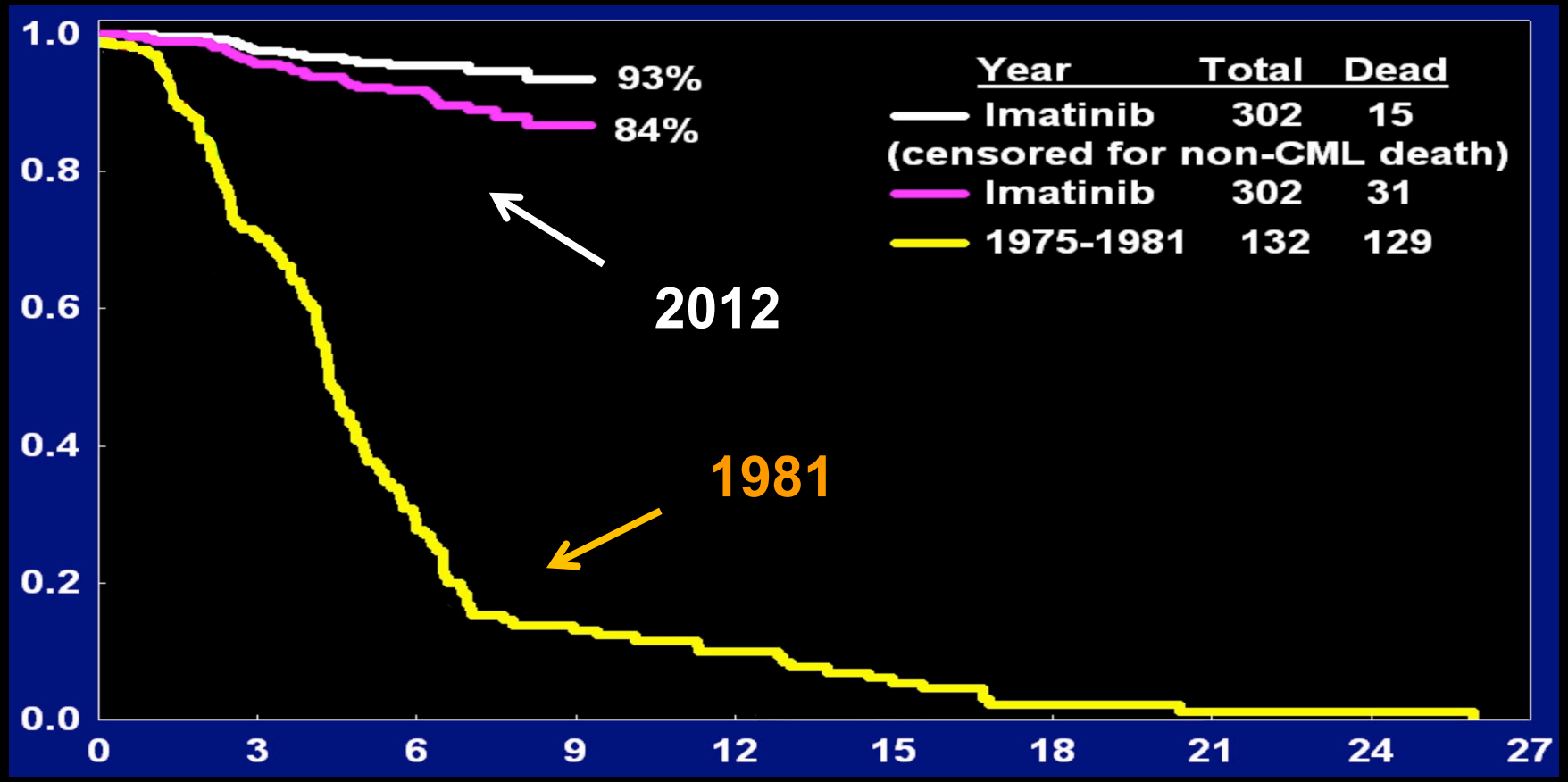


Lessons from the Chronic Myelogenous Leukemia (CML) Story
A Fatal Disease Transformed

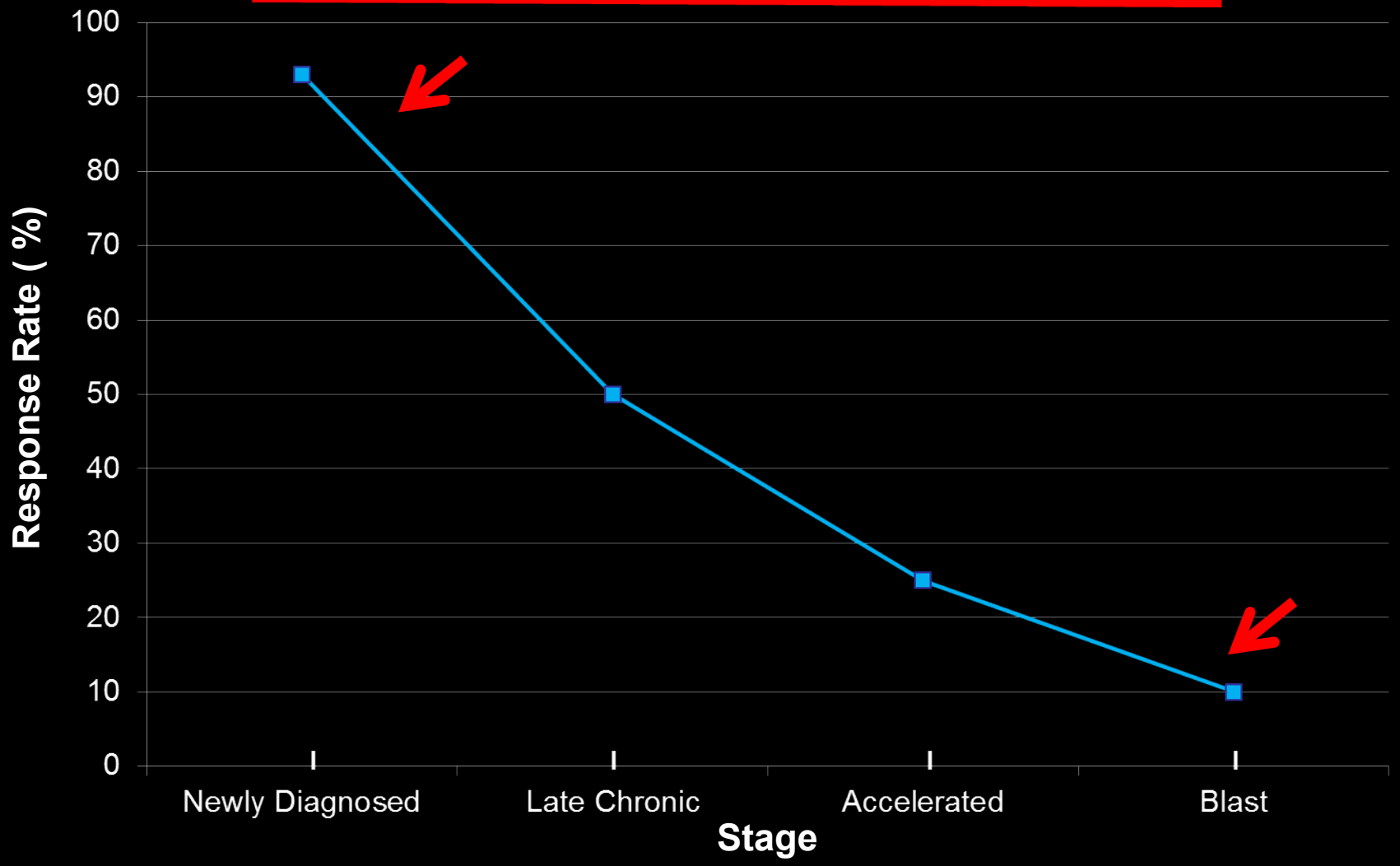
TREAT EARLY

Lessons from the Chronic Myelogenous Leukemia (CML) Story
A Fatal Disease Transformed

- Median survival in 1980s was about 4 years
- Median survival in 2012 is 20+ years



Response Rate of Chronic Myelogenous Leukemia Rises Rapidly in Newly Diagnosed Disease

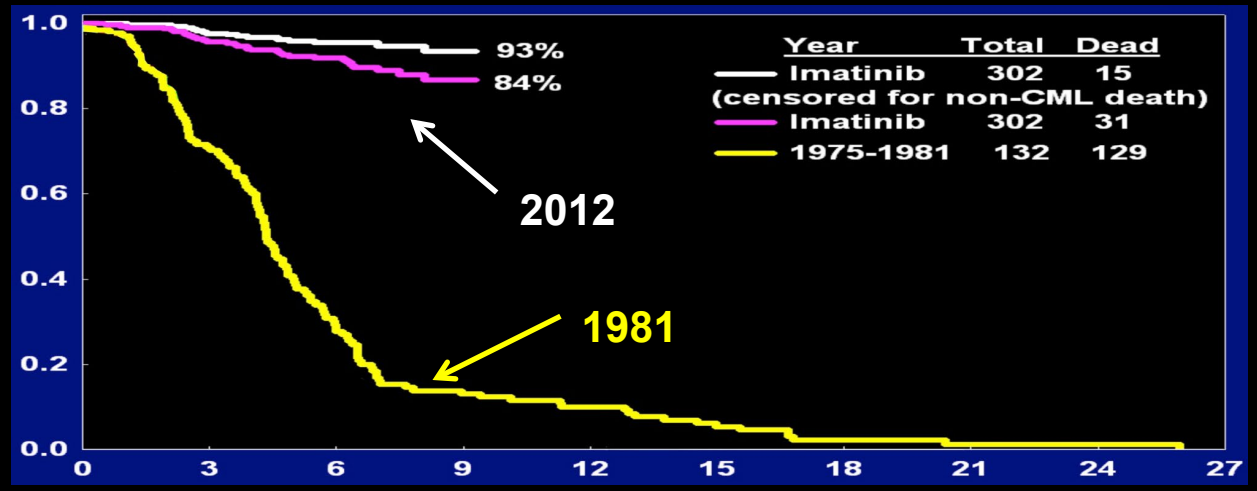


Key factors leading to the revolution in outcome of chronic myelogenous disease

Key factors:

- Known driver target (Bcr-Abl)
- Targeted agent (imatinib)

– Treat newly-diagnosed patients



Solid Tumor Metastases = Blast Crisis in Leukemia

The future of I-PREDICT is to **treat patients at diagnosis** before heterogeneity occurs

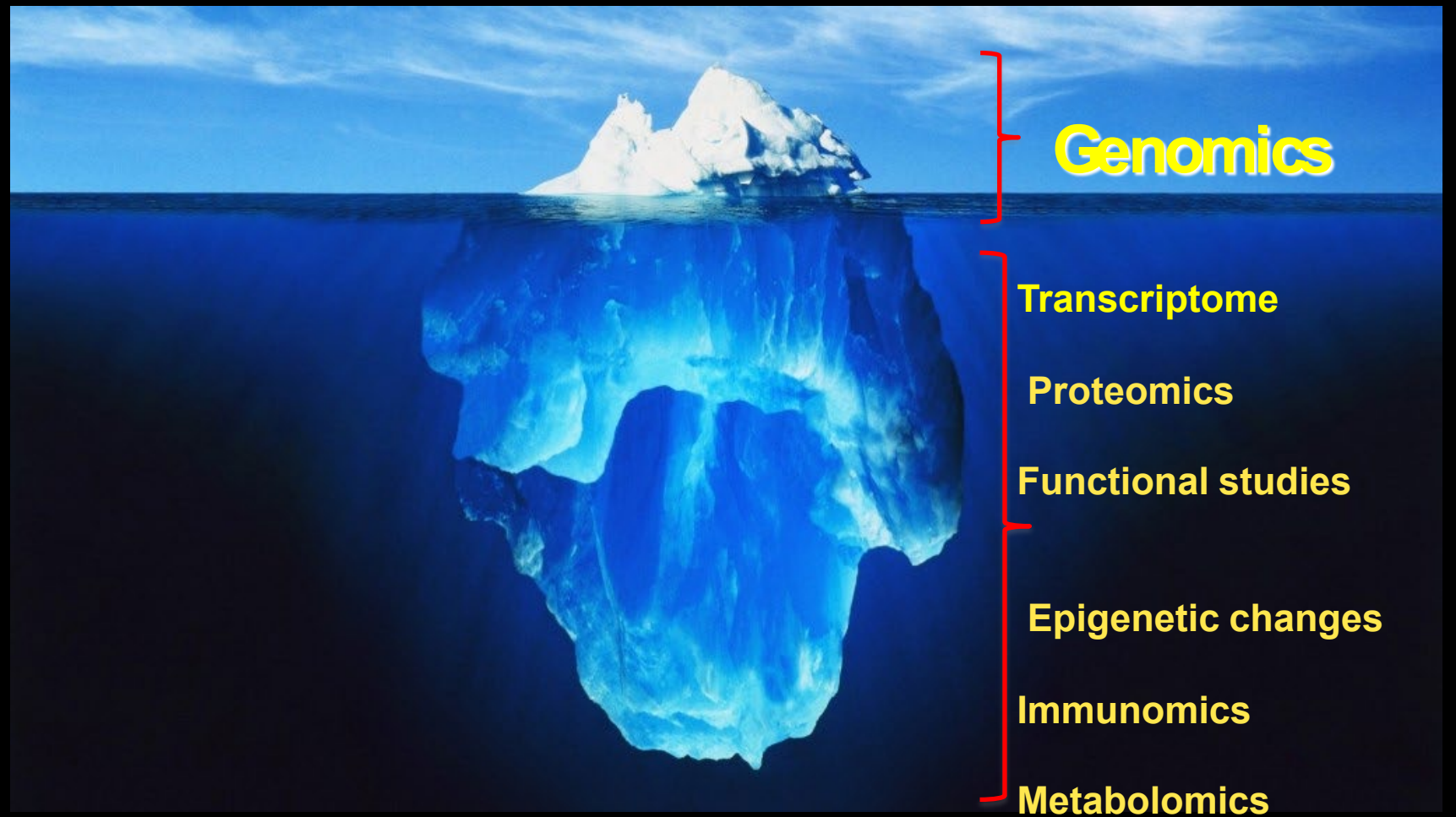
MCW I-PREDICT
N-of-1 in newly diagnosed cancer

Neoadjuvant

Approved

PIs: Ben George, MD and R Kurzrock MD

Tip of the Iceberg



Super-Responders

62-year-old man with poorly differentiated carcinoma of unknown primary

Treatment history:
No systemic or local therapy.

cfDNA:
***KRAS* T20A → Trametinib (MEK inhibitor**
***ARID1A* Splice site SNV → Olaparib (PARP inhibitor)**

Tissue NGS: Insufficient sample

Consented on I-PREDICT protocol (NCT02534675)

** Shen et al, Cancer Discovery 2015*

62-year-old man with poorly differentiated carcinoma of unknown primary

Trametinib/Olaparib

Pre-treatment

2 weeks post-treatment

16 weeks post-treatment

Mid-upper chest wall mass

PFS 26 months

Kato… Kurzrock , JCO PO 2021

DISCOVERY IN REAL TIME

Fibrolamellar Cancer

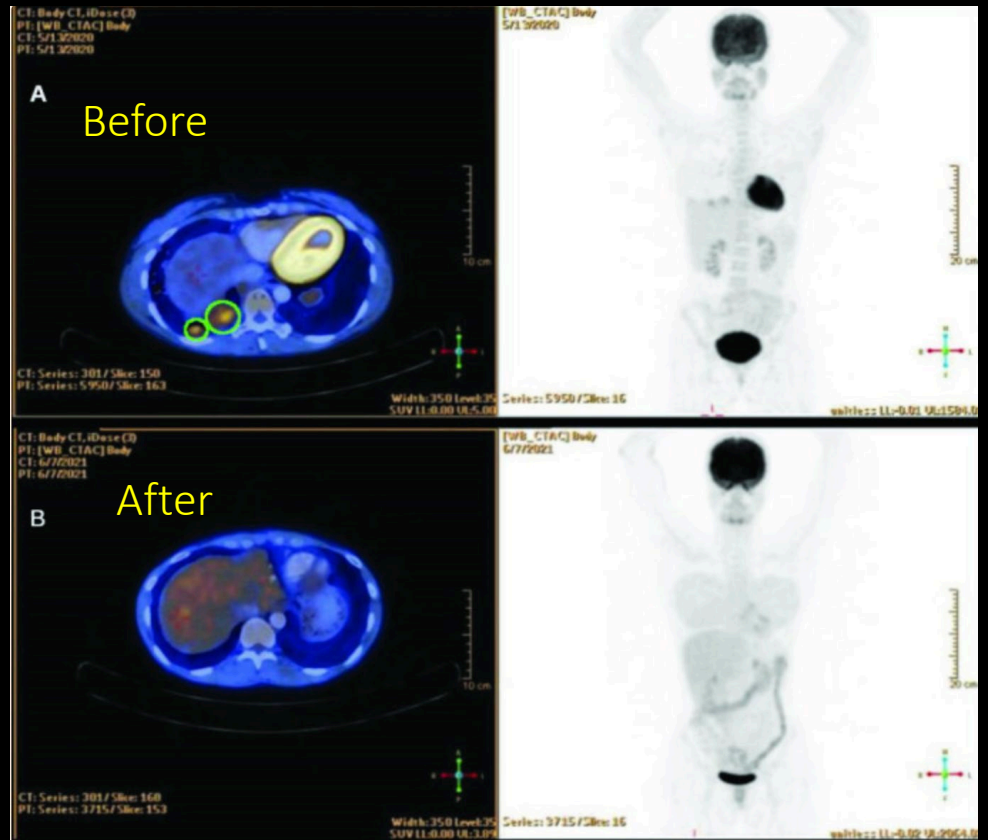
- DNAJB1-PRKACA→ a driver fusion, not yet druggable
- Exploiting multi-omics
- Transcriptomics/bioinformatics to explore synthetic lethality

Case Reports > J Immunother Cancer. 2022 Dec;10(12):e005620.
doi: 10.1136/jitc-2022-005620.

Fibrolamellar carcinoma transcriptomic-based treatment prediction: complete response after nivolumab and ipilimumab

Raanan Berger # [1], Gal Dinstag [2], Omer Tirosh [2], Eyal Schiff [2], David Kleiner [3], Kenneth D Aldape [3], Eytan Ruppin [4], Tuvik Beker # [5], Razelle Kurzrock # [6]

Affiliations



Non-Intuitive

- Low TMB
- PD-L1 negative
- Failed anti-PDL1
- Undruggable DNAJB1-PRKACA fusion

2+ years
complete remission

Undruggable fusions: Solution

- Look at RNA expression for targets
- Perform immunomic analysis for immunotherapy choice
- IHC panel: AR, ER, HER2, PD1, PDL1, FOLR1, Claudin18.2, Nectin4, Trop2, EGFR, LAG3, MGMT→ for antibody-drug conjugates
- Functional testing
- Bioinformatics: synthetic lethality, etc

What about the host?

Host and Toxicity/Response/Immunity/Microenvironments

Take-home points
Patient Rights

- **Right drug(s)**
- **Right patient**
- **Right time**
- **Right dose**
- **Right place**

NO NAME CANCER
Genomics IS the Diagnosis

› JAMA Oncol. 2016 Jun 1;2(6):719-20. doi: 10.1001/jamaoncol.2016.0078.

Universal Genomic Testing Needed to Win the War Against Cancer: Genomics IS the Diagnosis

Vivek Subbiah [1], Razelle Kurzrock [2]

Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: *Genomics Is the Diagnosis*

Vivek Subbiah, MD[1,2] and Razelle Kurzrock, MD[3,4]

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Looking into the Future

BEYOND CANCER
Changing the lives of patients

Bladder Cancer

FGFR3 Mutation

Dwarfism

Clinical trial with FGFR inhibitor infigratinib

There are ~7,000 rare diseases.

- Global numbers: ~350 million patients with a rare disease.
- US and Europe: ~60 million people with rare diseases.

PRECISION MEDICINE: 2033

ILLNESS

- SAME DAY MULTI-OMIC SEQUENCING
- *IN SILICO* MODELING DECIPHERS ABNORMALITY AND NEEDED COMPOUND
- COMPOUND INSTANTLY CREATED THROUGH CLICK CHEMISTRY AND 3-D PRINTING

Oncotarget. 2016 Jan 19; 7(3): 2155–2158.
Published online 2015 Dec 29. doi: 10.18632/oncotarget.6787

Click chemistry, 3D-printing, and omics: the future of drug development

Razelle Kurzrock[1] and David J. Stewart[2]

Thanks to Patients and Precision Medicine Team

Questions??

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