Personalized Medicine in Oncology
Dawn of the Genomics and Immunotherapy Era

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SAN DIEGO
MEDICAL CENTER

MOORES CANCER CENTER

The Pillars of Targeted Therapeutics
Precision Medicine

Genomics Immunotherapy

Question: Is it precision medicine or personalized medicine?

Answer: Both

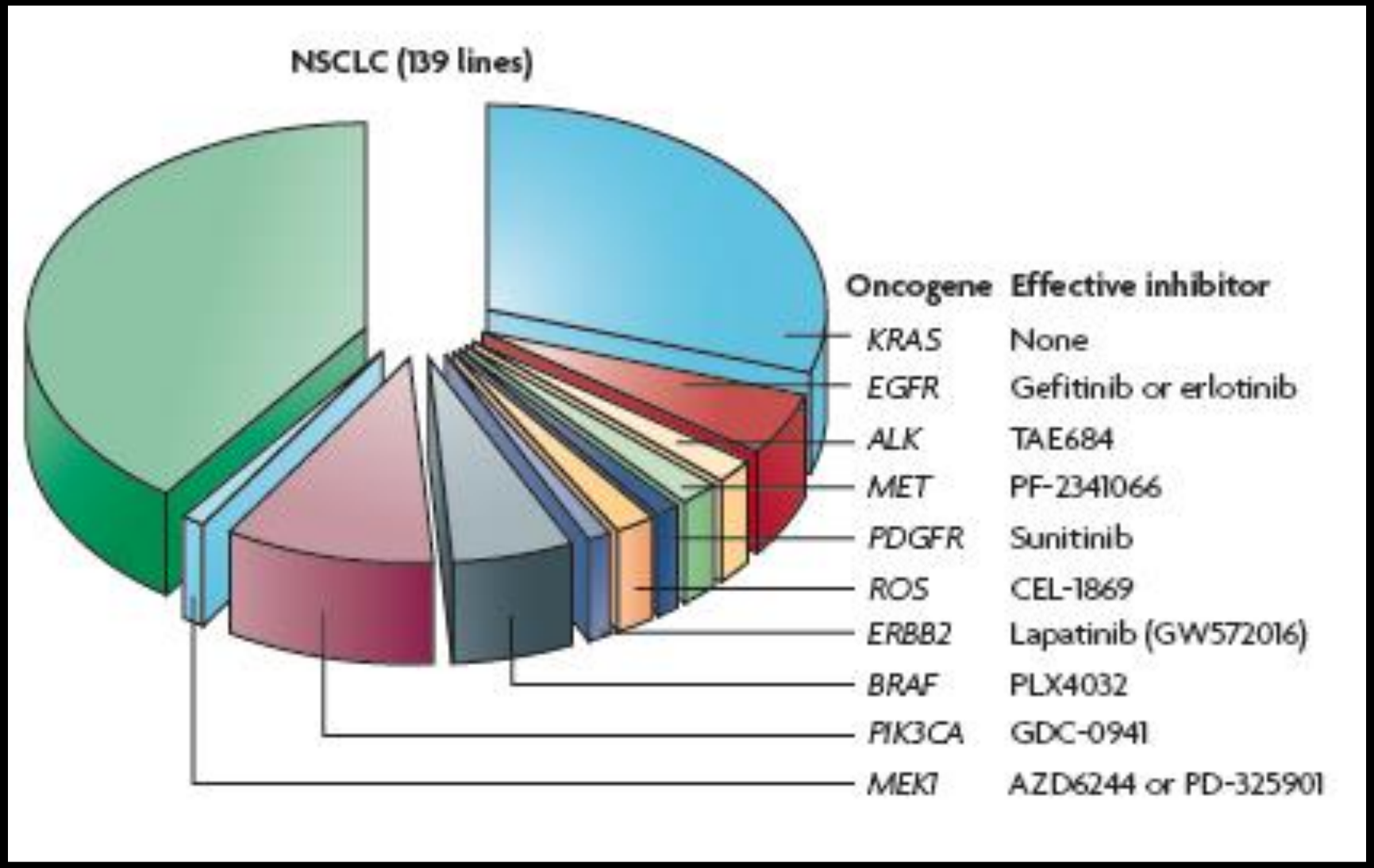
“Precisionalized Medicine”

What can patients expect from traditional drugs/clinical trial paradigms?

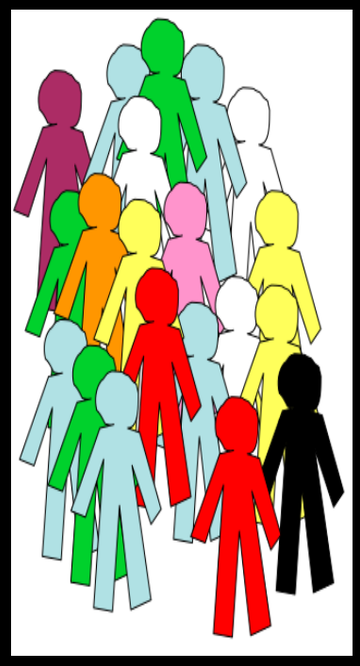
Drug	Tumor	Survival Gain	CR (single agent)
gemcitabine	pancreas	1.5 months	≈ 0%
bevacizumab	colon	2.2 months	≈ 0%
erlotinib	pancreas	11 days	≈ 0%
bevacizumab	Lung	2 months	≈ 0%
sorafenib	renal	2 months	≈ 0%
temozolamide	glioblastoma	2.5 months	≈ 0%
docetaxel	prostate	2.4 months	≈ 0%
cetuximab	colon	1.5 months	≈ 1-2 %

Why are cancers difficult to treat?

Divide and Conquer



Agents work only in those with a sensitizing aberration



Braiteh….Kurzrock, MCT 2007

Munoz J, Swanton C, Kurzrock R, Molecular Profiling and the Reclassification of Cancer; Am Soc Clin Oncol Educ Book. 2013:

Sharma, Nat Rev Cancer 2010

- **Targeted therapy in of itself is not effective**

- **Insulin is a great drug but not if given to patients with pneumonia**

- **Penumonia would be viewed as a difficult disease to treat if insulin and heart medications were given to the patients.**

- **It is about matching patients with the right therapy**

Meta Analysis of 32,149 Patients in Phase II Clinical Trials

- **Non-personalized targeted arms led to poorer outcomes than cytotoxics arms**

(**All P<0.0001, except P=0.048 for OS meta-analysis).**

Worst outcome

Best outcome

	POOLED Analysis			Meta-analysis		
ARMS type	RR (%)	PFS (Mos)	OS (Mos)	RR (%)	PFS (Mos)	OS (Mos)
Non-personalized targeted	4	2.6	8.7	7.5	2.5	8.3
Cytotoxic	12	3.3	9.4	16.1	3.3	9.3
Personalized targeted	30	6.9	15.9	31.3	6.1	13.7

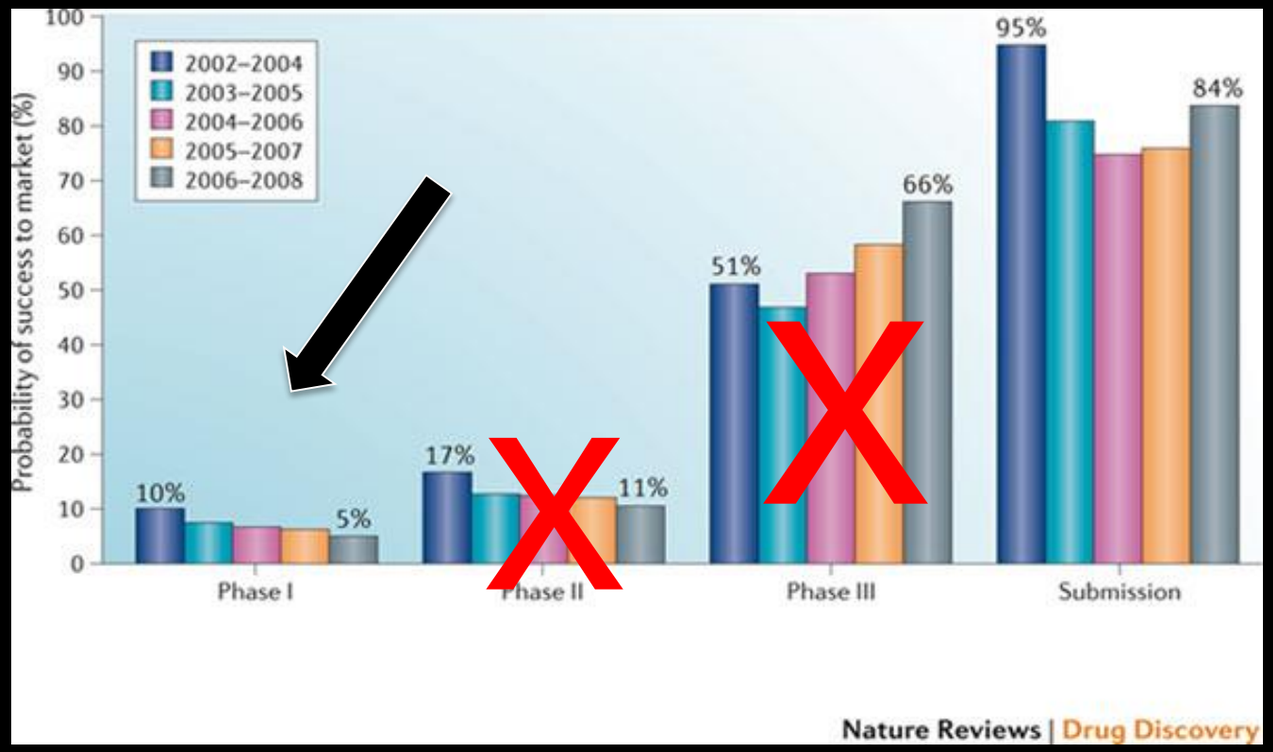
Schwaederle……Kurzrock, JCO, 2015

Precision Medicine

Lessons Learned

- Each patient has a unique and complex molecular portfolio
- Use combinations of matched drugs for metastatic or complex tumors
- Harness the immune system
- Omics is a disruptive technology; retrofitting the reality unveiled into traditional paradigms is suboptimal
- Transformative changes will require new models for clinical research and practice

Accelerated New Drug Development



Approval After Phase I:

Ceritinib Runs the Three-Minute Mile

THE GENOMICS & IMMUNOTHERAPY ERA

First generation studies

First generation technology

Master Protocol

Profile-**R**elated **E**vidence **D**etermining

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

PREDICT

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

The Reclassification of Cancer

PIK3CA mutations were found in 10% of 1,000 patients with advanced cancers

- Endometrial cancers (29%)
- Breast cancers (24%)
- Colon cancers (17%)
- Ovarian cancers (14%)
- Lung cancer (13%)
- Head and neck squamous cell cancers (13%)
- Pancreatic cancers (13%)

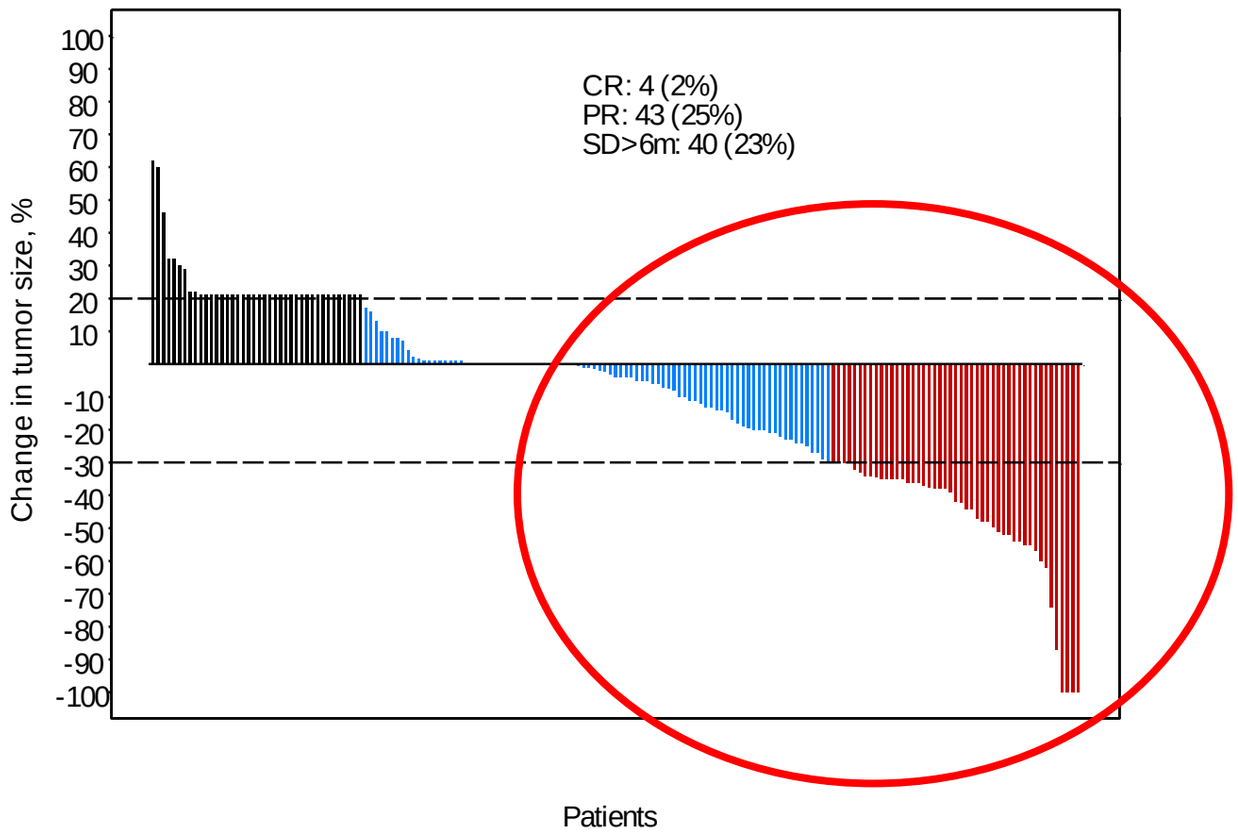
Molecular aberrations do not segregate well by organ of origin

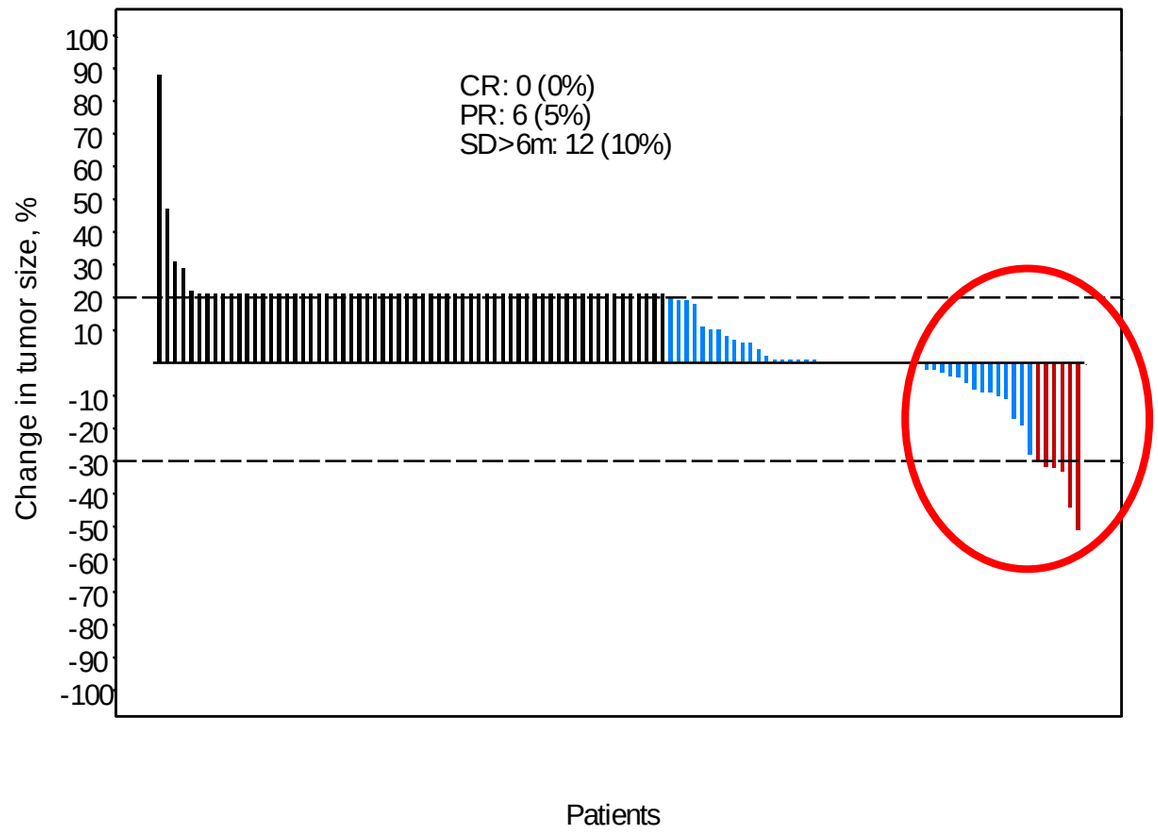
Matching patients with targeted drugs increases response rates

Matched therapy
N=175
Complete/Partial Response = 27%

Therapy without matching
N=116
Complete/Partial Response = 5%

p<.0001





Janku….Kurzrock, MCT, 2011; Tsimberidou….. Kurzrock, CCR, 2012;
Janku…..Kurzrock, JCO, 2012; Janku…..Kurzrock, Cell Reports, 2014

The Light Microscope

Invented in 1590

Still used to diagnose cancer

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

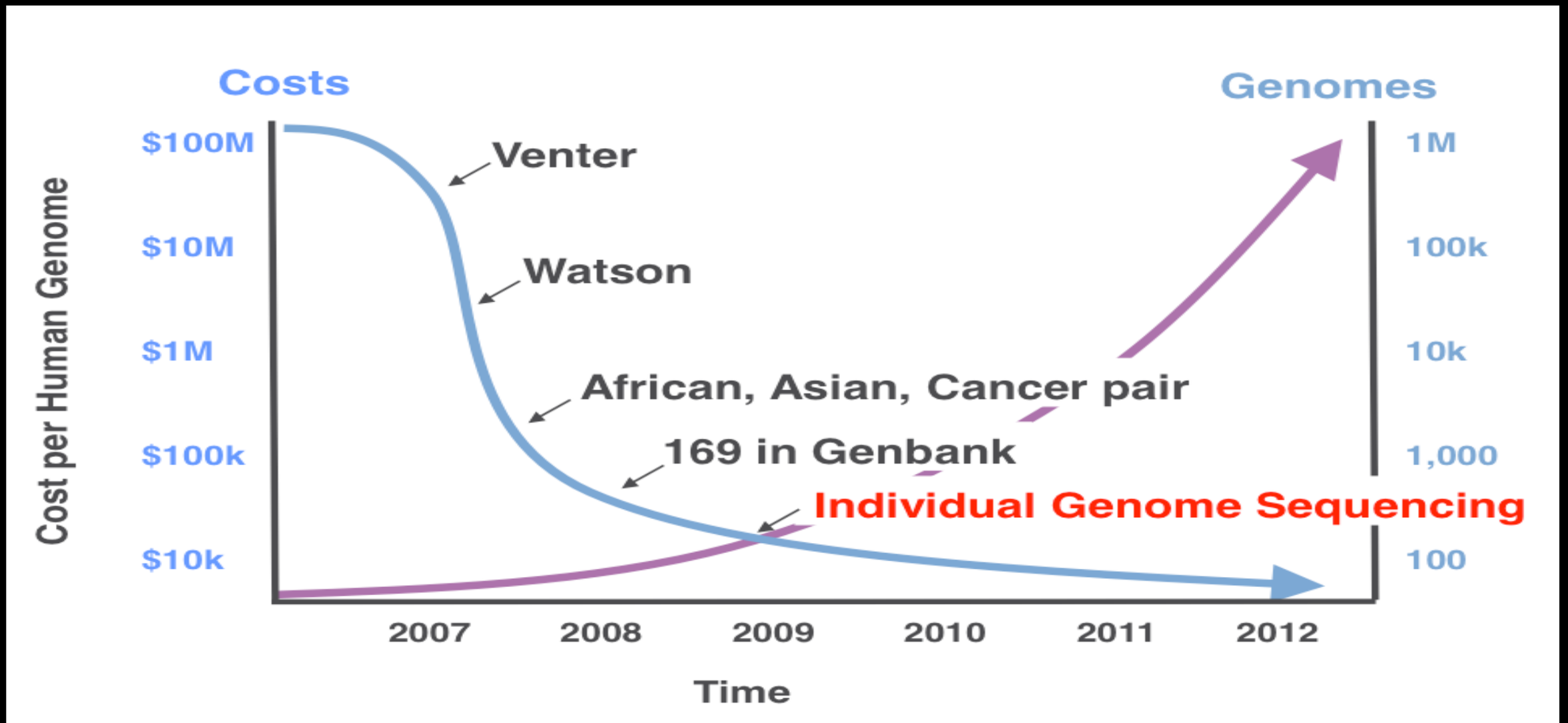
ABL1	BRCA2	CSMD2	EZH2	GNAS
ACVR1B	CARD11	CSMD3	FAM123B	HDAC9
ADAMTS12	CASP8	CTNNB1	FAM135B	HEATR7B2
AKAP3	CBL	CYLD	FAT3	HGF
AKT1	CD19	CYP2C19	FBXW7	HMCN1
ALK	CDH1	DAXX	FGFR1	HNF1A
APC	CDH10	DDR1	FGFR2	HNF1B
AR	CDH11	DDR2	FGFR3	HRAS
ARAF	CDK4	DNMT3A	FGFR4	HYDIN
ARID1A	CDK6	EGFR	FLG	IDH1
ASXL1	CDKN2A	ELN	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

Genomic Technology: Breathtaking Progress

QUICKER, SMALLER, CHEAPER

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	

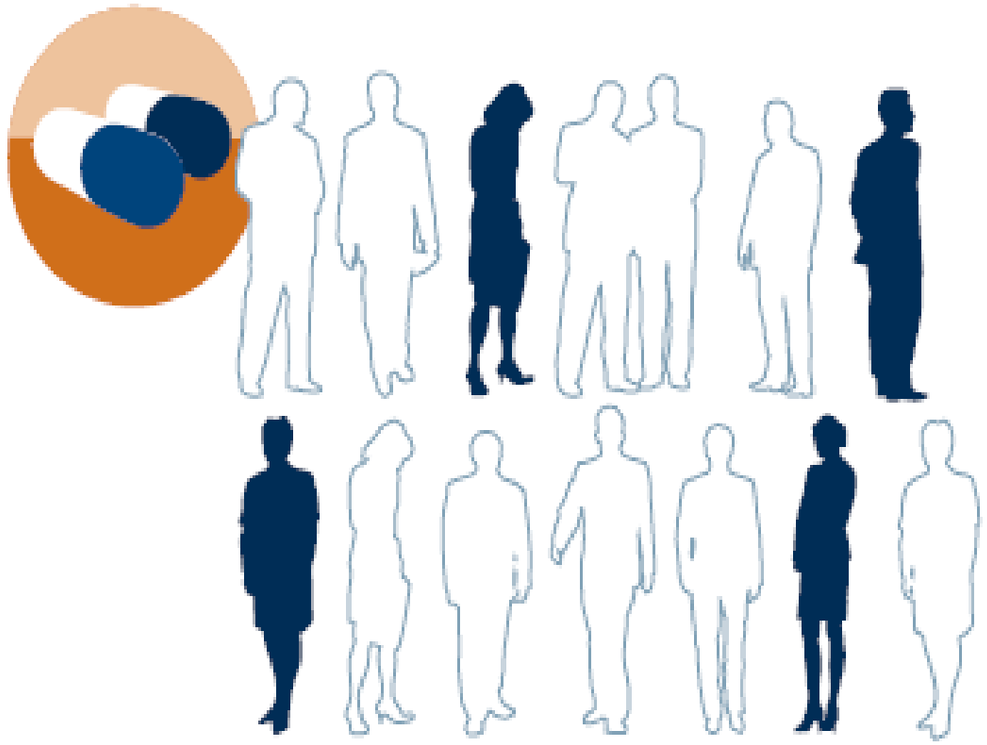


Evolution of Clinical Trial Design

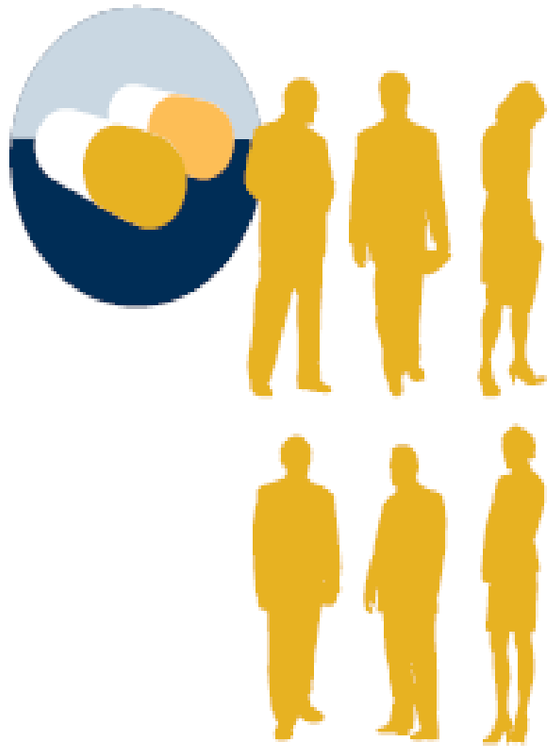
Redesigning Cancer Trials: Stage 1

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

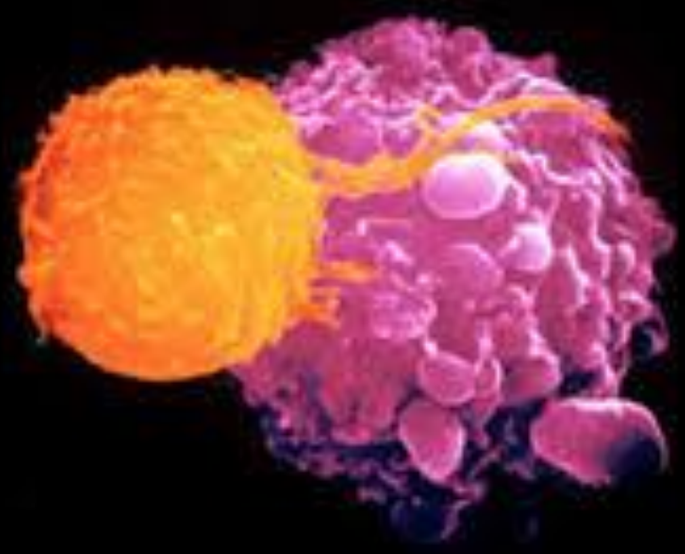


NEW MODEL: Small patient populations, all with the relevant mutations or genetic defects; greater chance of desired results, since all participants have the potential to respond



Harnessing the Immune System

The immune system is the epitome of machinery that is precise and personalized

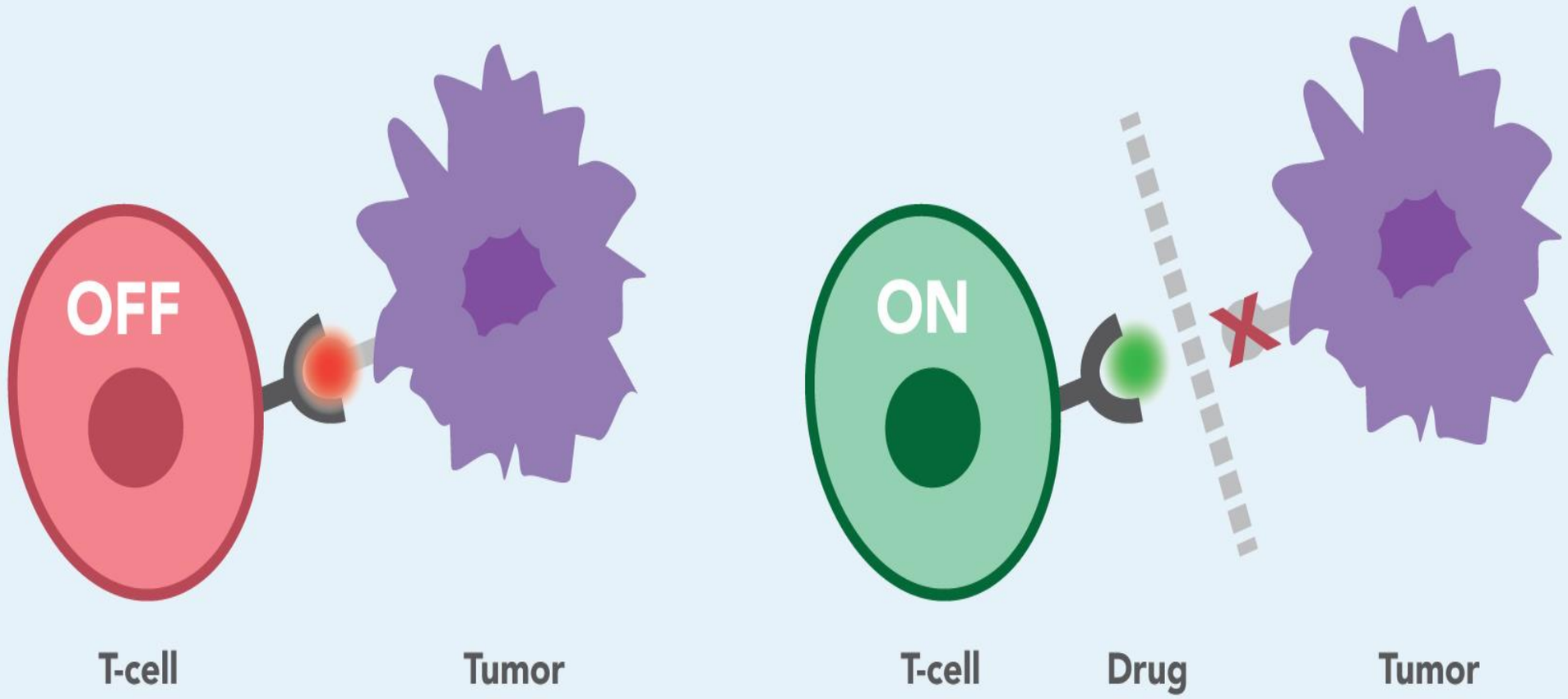


T-cell killing cancer cell

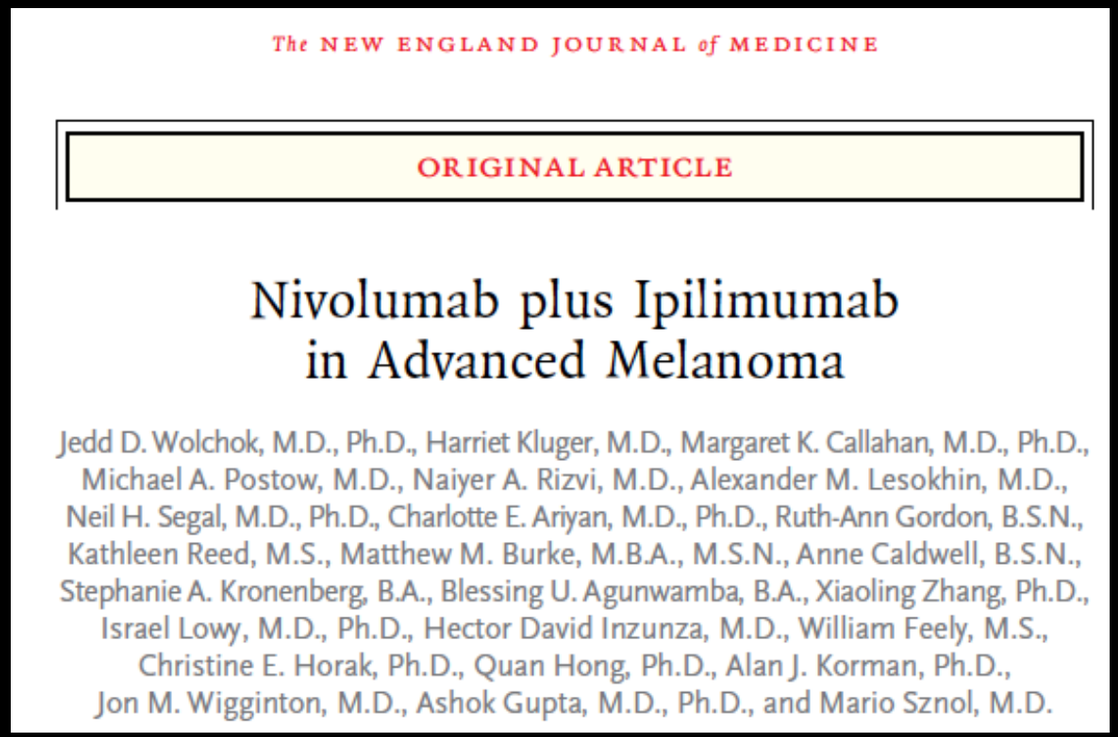
How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

Immunotherapy drugs can block tumor cells from deactivating T-cells



Combinatorial immune blockade is likely the rule, not the exception



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

- ASCO 2014 update
  - 2 year survival rate- 79%
    - Comparison: dacarbazine monotherapy 2-year survival rate- 18%
    - Prior therapies (1-3+) in 38%

Wolchok JD et al. N Engl J Med 2013;369:122-133

Predicting super-responders to immunotherapy

Biomarker

- PDL-1 negative: 0-17%
- PDL-1 positive: 36-100%

Patel and Kurzrock, MCT 2015

Unique characteristics

- Delayed responses with initial progression
- Subset of patients with advanced disease that have long-term complete remission (?cure)

Bridging
Genomics and Immunotherapy

Immune system responds to mutanome

High mutational burden and specific alterations
- PDL1 amplification
- MSI-H
- DNA repair gene alterations

Combination therapies (genomically and immunotherapeutically targeted)

Center for Personalized Cancer Therapy at Moores Cancer Center

San Diego Biotech, Pharma, Genomics

Developmental Therapeutics Phase I Trials/Immunotherapy

Discovery to Bedside Enabling Program

Molecular Tumor Board

Adolescent and Young Adult Clinic

Rare Tumor Clinic

Hereditory Cancer Predispositon Genetic Counselling

Molecular Pathway Clinic

Financial Aid

Laboratory Processing

UCSD Super Computer Center

UCSD, Salk, Scripps, Sanford-Burnham

Molecular Tumor Board

- Initiated December 12, 2012
- Three weeks per month
- Multidisciplinary discussion of patients
- Molecular profiling (N ~ 3500 patients)
- Targeted, tailored treatment recommendations

Schwaederle…..Kurzrock, Oncologist, 2014; Parker…..Kurzrock, JOP, 2015

Potential Actionability

- N = 439 patients
- NGS = 236 genes
- 20% actionable by on-label approved drug
- 70% actionable by on- or off-label approved drug
- 90% actionable by approved or experimental drug

Schwaederle M……Kurzrock R. On the Road to Precision Cancer Medicine: Genomic Actiaonability in 439 Patients. MCT, 2015

What about the host?

Host and Toxicity/Response/Immunity/Microenvironments

Cutting-Edge Technology

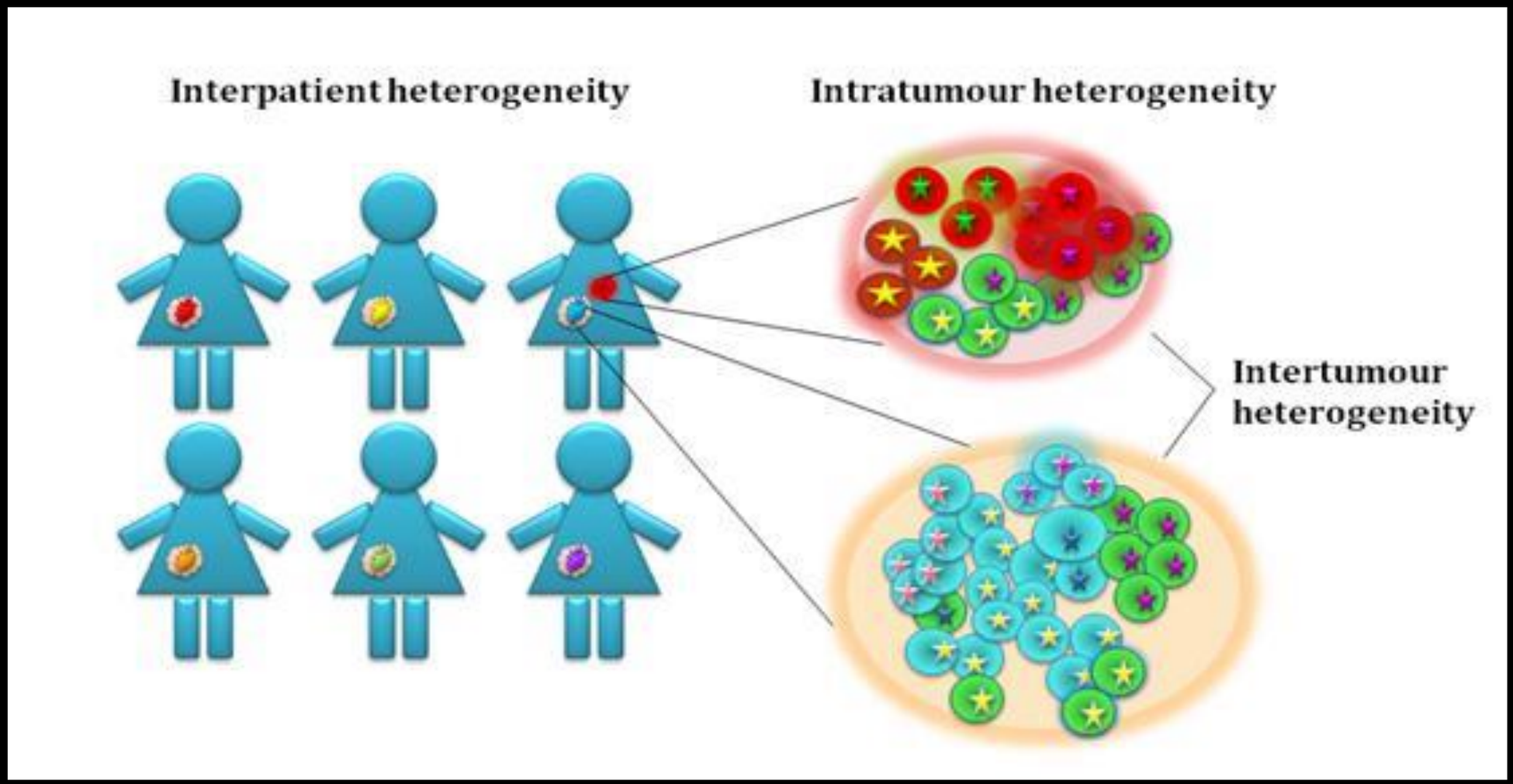
Liquid Biopsy Program

Doing genomics on DNA from a small tube of blood or from urine

No tissue biopsy

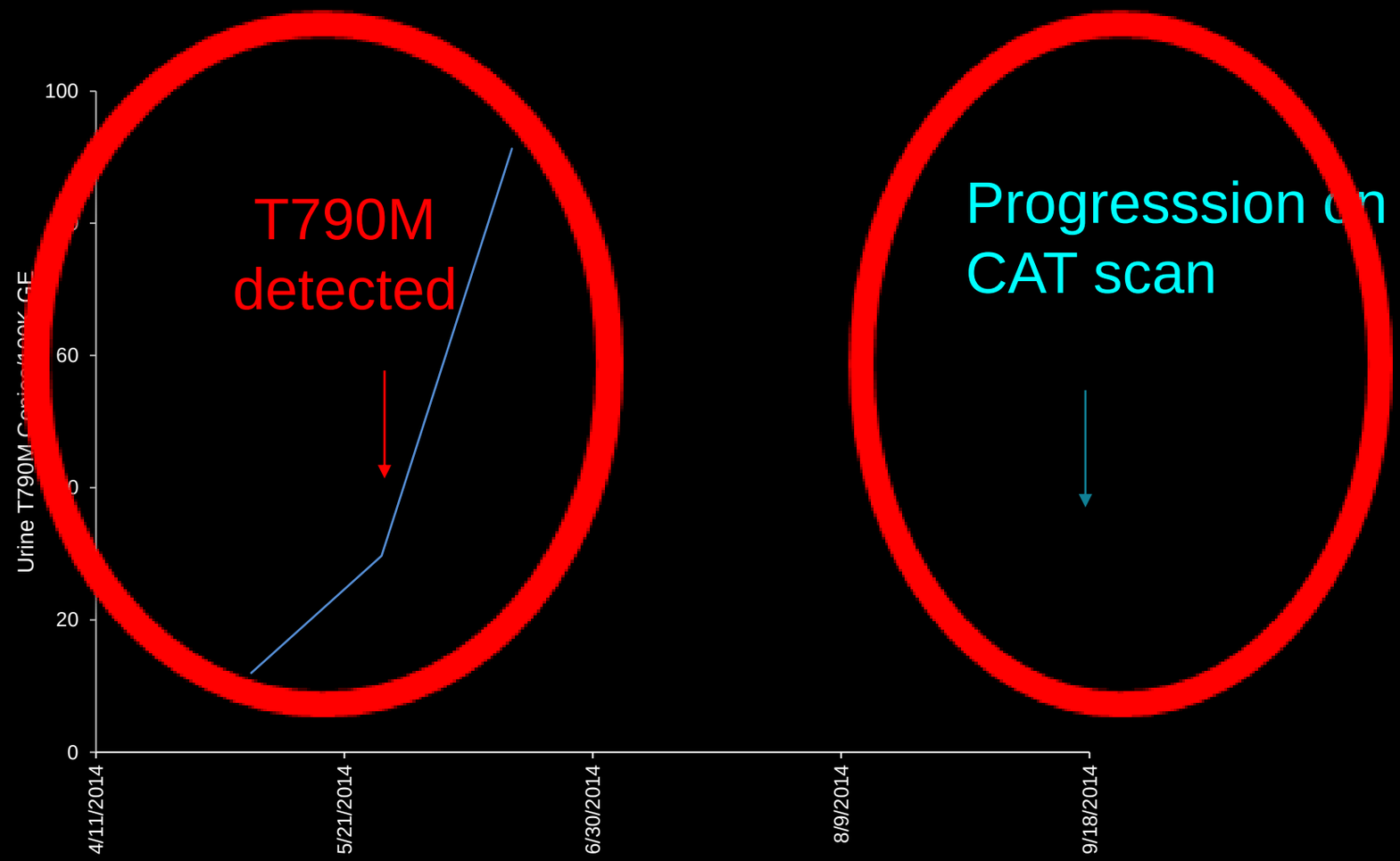
~1000 patients

Molecular Heterogeneity

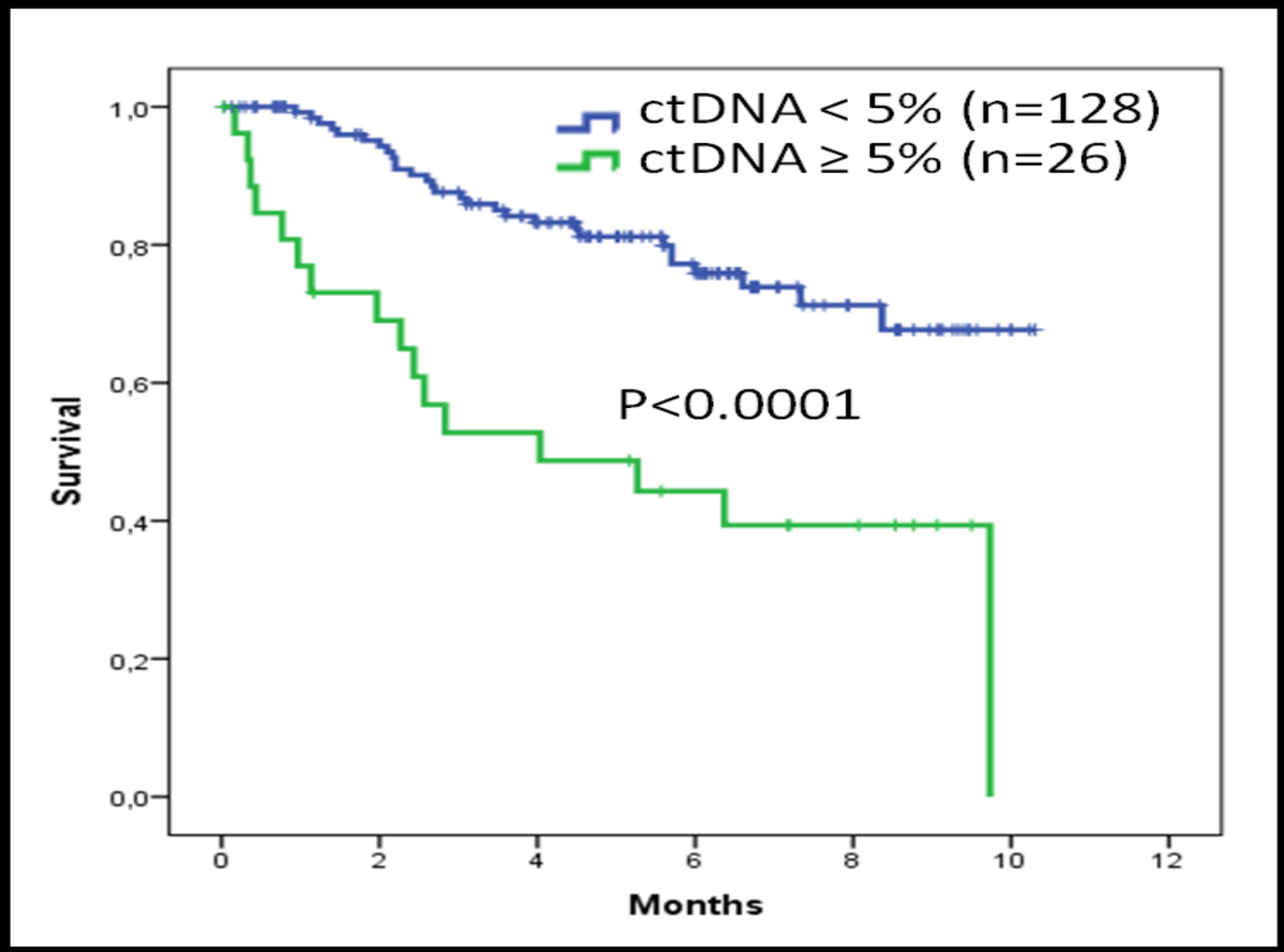


Lung Cancer
Early Detection of Progression

Urine



High Levels of Circulating Tumor DNA are Associated with Poor Survival

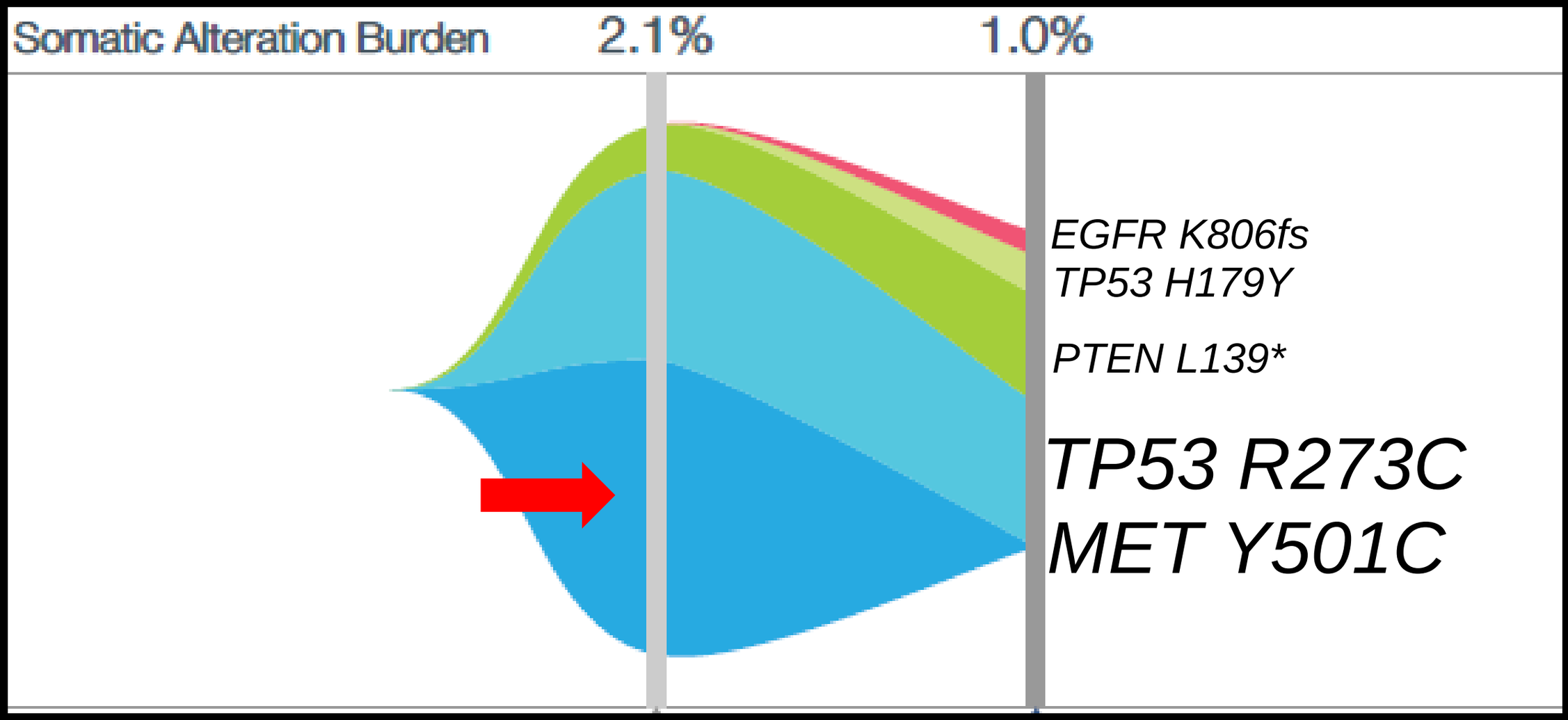


Circulating Tumor DNA Applications

- Serial levels for response
- Early detection of resistance alterations
- Assess shed DNA from multiple metastatic sites
- Assess difficult-to-biopsy patients
- More information on potentially actionable alterations

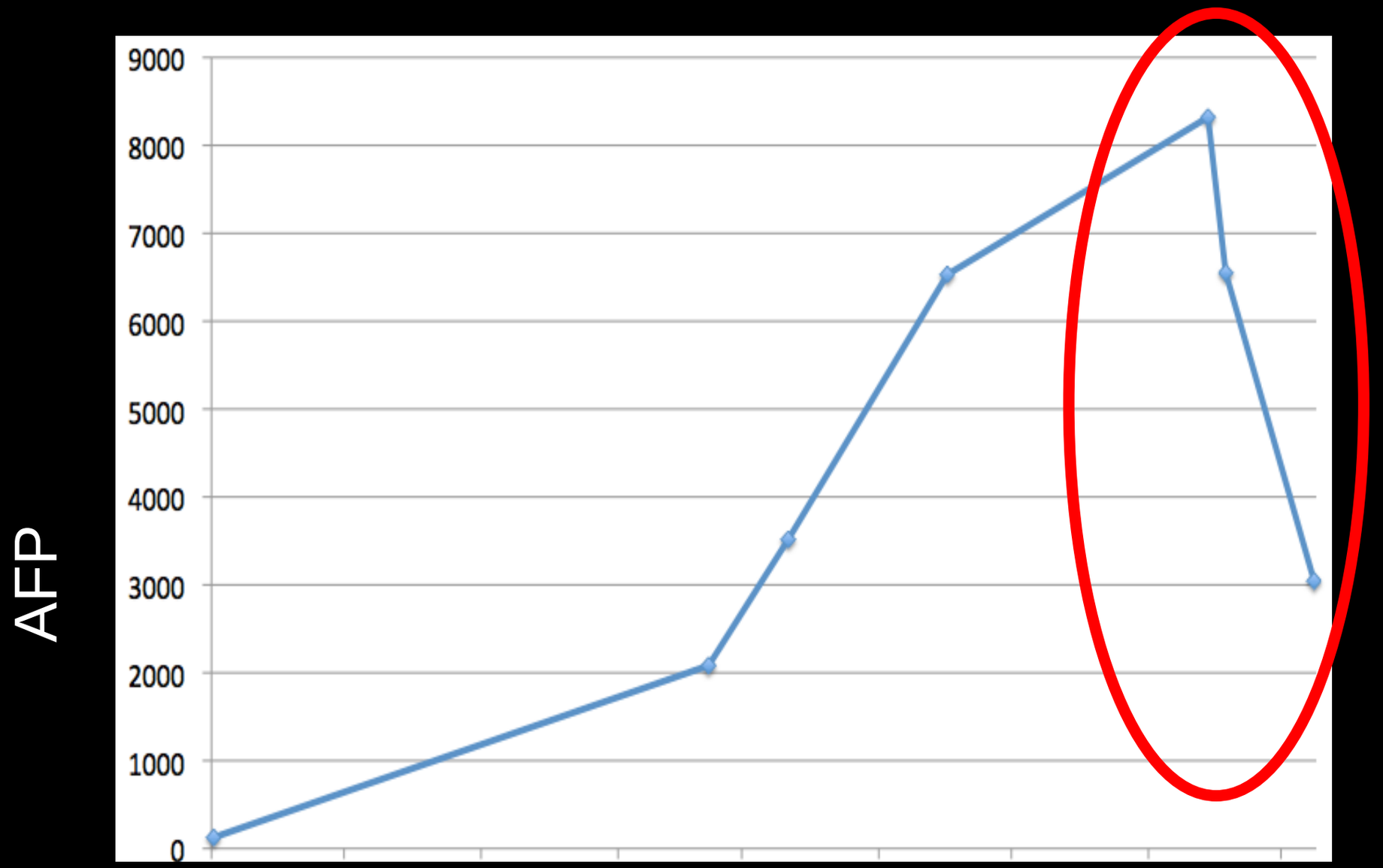
Case 1: Serial ctDNA (liquid biopsies)

MET mutation disappears on MET inhibitor



Hepatocellular Cancer

Tumor board discussion: Cabozantinib plus Sirolimus



Cabozantinib (METi)

Sirolimus

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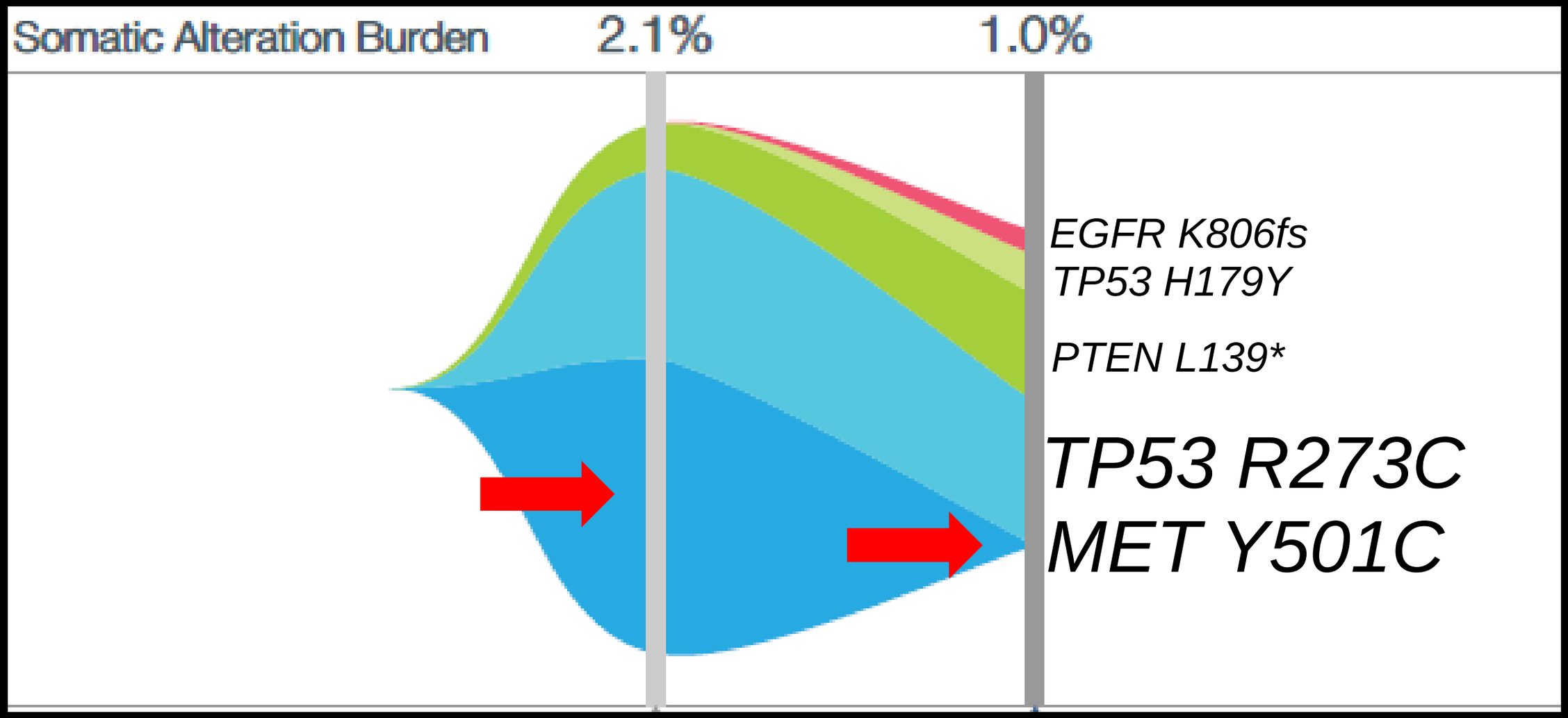
MET mutation disappears on MET inhibitor



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Genomics and Immunotherapy

Using genomics to find the
best immunotherapy match

PERFECTMATCH

Metastatic Basal Cell Carcinoma

Ultra-rare tumor

55 year old man, having failed multiple treatments

<u>Treatment history</u>

- Vismodegib (5/2014-10/2014), PD
- SBRT to right frontal lobe (11/2014)
- Paclitaxel/Cisplatin (11/2014-3/2015), PD
- Buparlisib/Sonidegib (4/28/2015-7/1/2015), PD
- Vismodegib + weekly taxol (7/2015-9/2015), intolerant
- Vandetanib (9/2015-9/2015), intolerant

Molecular profiling (liver biopsy tissue)

Next Generation sequencing, 315 genes:

***PDL1* amplification,**

***PDL2* amplification,**

***JAK2* amplification,**

***PTCH1* Q1366* W197*,**

***FLT1* E487K,**

***PDGFRA* E459K**

***PIK3R2* Q412*,**

***CDKN2A p16INK4a* P81L,**

***TP53* P278S,**

***CDKN1A* R140Q,**

***CTNNA1* R383H,**

***LRP1B* splice site 9121-1G>A, W2334*,**

***MLL2* splice site 4132-1G>A,**

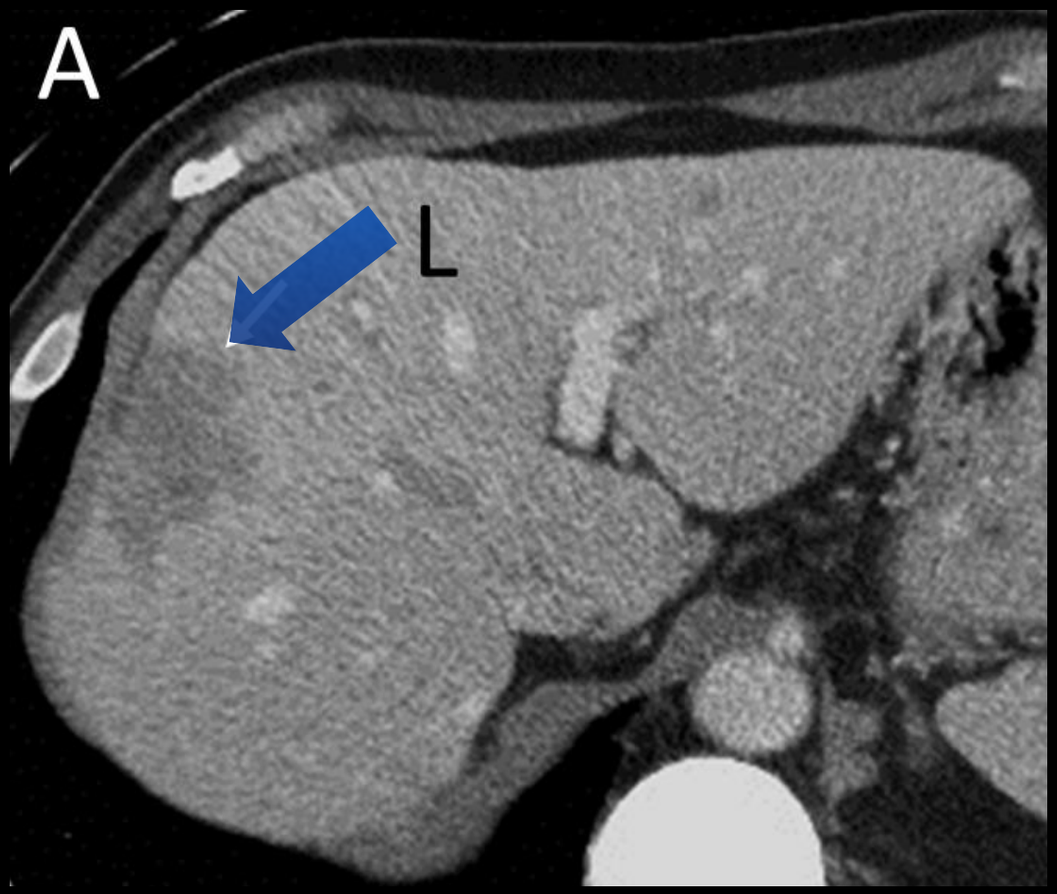
NOTCH1* W287

***SLIT2* K325*,**

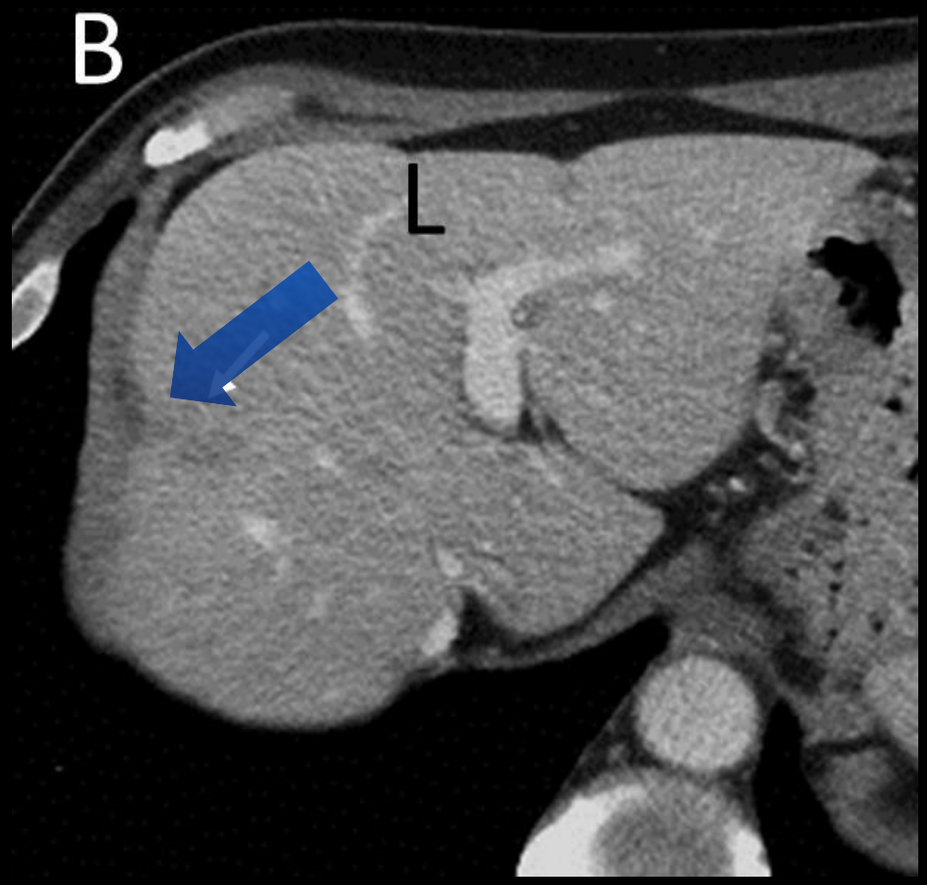
***SMARCA4* Q1166*,**

***TERT* promoter -139_-138CC>TT**

Response to Genomically Matched Immunotherapy



Pre-Nivolumab
(anti-PD1)



Post: 2 months

Summary

- Tumors and patients have unique AND complex molecular alterations
- Find the perfect match for each patient---customize
- Marry genomics and immunotherapy in combinations

The genomic/immunotherapy era will revolutionize

not just cancer medicine

BEYOND CANCER
Changing the lives of patients

Bladder Cancer

FGFR3 Mutation

Dwarfism

THANK YOU
for your time and interest

Questions??

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35 minutes and 10 minutes for questions