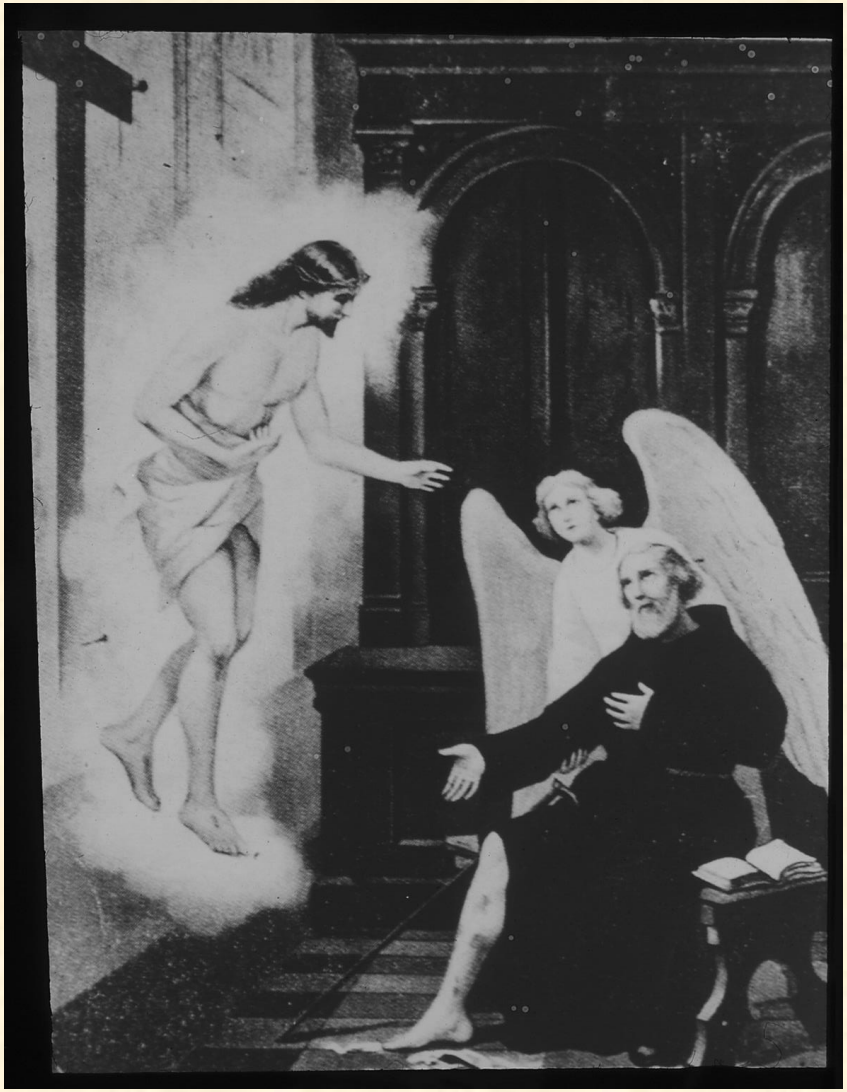
Selecting Therapy for Breast Cancer Patients in the Genomic Era

Marc Lippman, MD

The Sylvester Comprehensive Cancer Center at the University of Miami




BOTTLED AT THE SOURCE, S. PELLEGRINO ITALY
PELLEGRINO
SPARKLING NATURAL MINERAL WATER
NATURAL MINERAL WATER
WITH NATURAL CARBONATION (CO2) ADDED
NET 8.45 fl. oz - 250 ml

PERSONALIZED MEDICINE FOR BREAST CANCER PATIENTS

- A WORKING DEFINITION: SUFFICIENT KNOWLEDGE ABOUT THE MOLECULAR FEATURES OF THE TUMOR OR HOST TO MAKE SPECIFIC THERAPEUTIC CHOICES WHICH MAXIMIZE EFFECTIVENESS AND MINIMIZE TOXICITY.

PERSONALIZED MEDICINE FOR BREAST CANCER PATIENTS

- Perhaps not quite such new thing…

PERSONALIZED MEDICINE FOR BREAST CANCER PATIENTS

- Perhaps not quite such new thing…
- A BRIEF HISTORICAL PERSPECTIVE – **THE TUMOR**
  - THE ESTROGEN/PROGESTERONE RECEPTOR AXIS
  - HER2/neu/ERBB2
  - CLONOGENIC AND OTHER IN VITRO SENSITIVITY ASSAYS
  - PDX MODELS FOR CUSTOMIZED TESTING

PERSONALIZED MEDICINE FOR BREAST CANCER PATIENTS

- A BRIEF HISTORICAL PERSPECTIVE – **THE HOST**
  - CUSTOMIZED DRUG DOSING
    - MTX, PLATINUM,
  - CUSTOMIZED ANALYSES OF PHARMACOGENOMICS
    - TAMOXIFEN

The Evolution of Targeted Therapies for Cancer

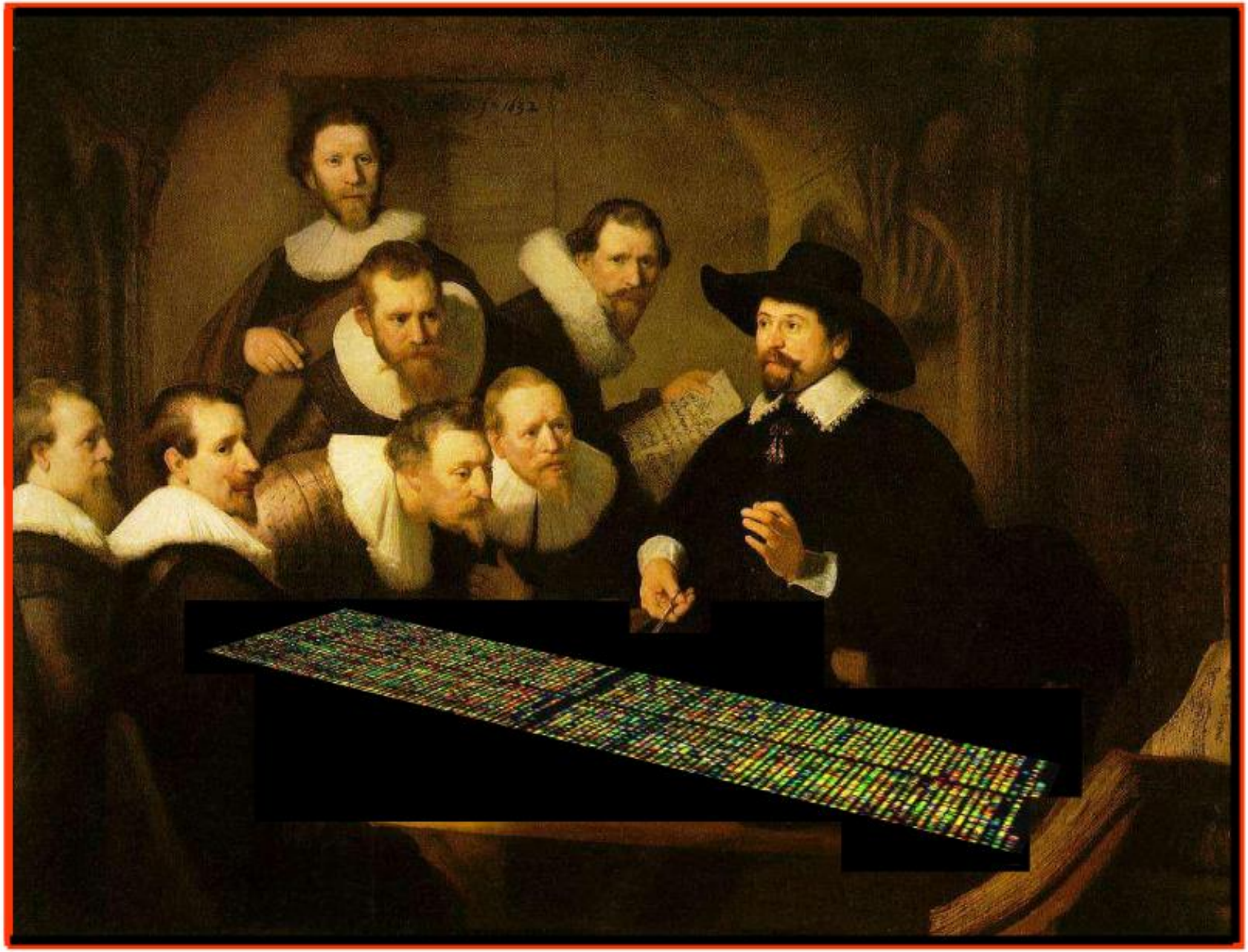
- 1970: ER Testing and Hormonal Therapy for Breast Cancer
- 1990: Cytogenetics/FISH Testing and Therapy for Heme Malignancies
- 1998: *HER2* Testing and Trastuzumab for Breast Cancer
- 2001: *BCR-ABL* Testing and Imatinib for CML
- 2003: *EGFR* Mutation Testing and Erlotinib for NSCLC
- 2007: *KRAS* Mutation Testing and Cetuximab/Panitumumab for CRC
- 2010: *EML4-ALK* Testing and Crizotinib in NSCLC
- 2011: *BRAF* Mutation Testing and Vemurafenib in Melanoma
- 2012: *ROS1* and *RET* Fusion Testing for Crizotinib and RET inhibitors in NSLC
- 2013: *HER2* mutation identification and anti-HER2 targeted therapy in NSCLC, breast cancer and micropapillary urothelial cancer
- 2013: *NTRK1* Fusion Testing and crizotinib in NSCLC
- 2014: PD1 and PDL1 and Immunotherapies

The era of companion diagnostics or drug-test combinations has begun in earnest for anti-cancer drugs and biologics. It is now an era of predictive pathology. It is the next generation of pathology.

Selected Examples of Cancer Genome Sequencing and Anti-Cancer Drug Selection

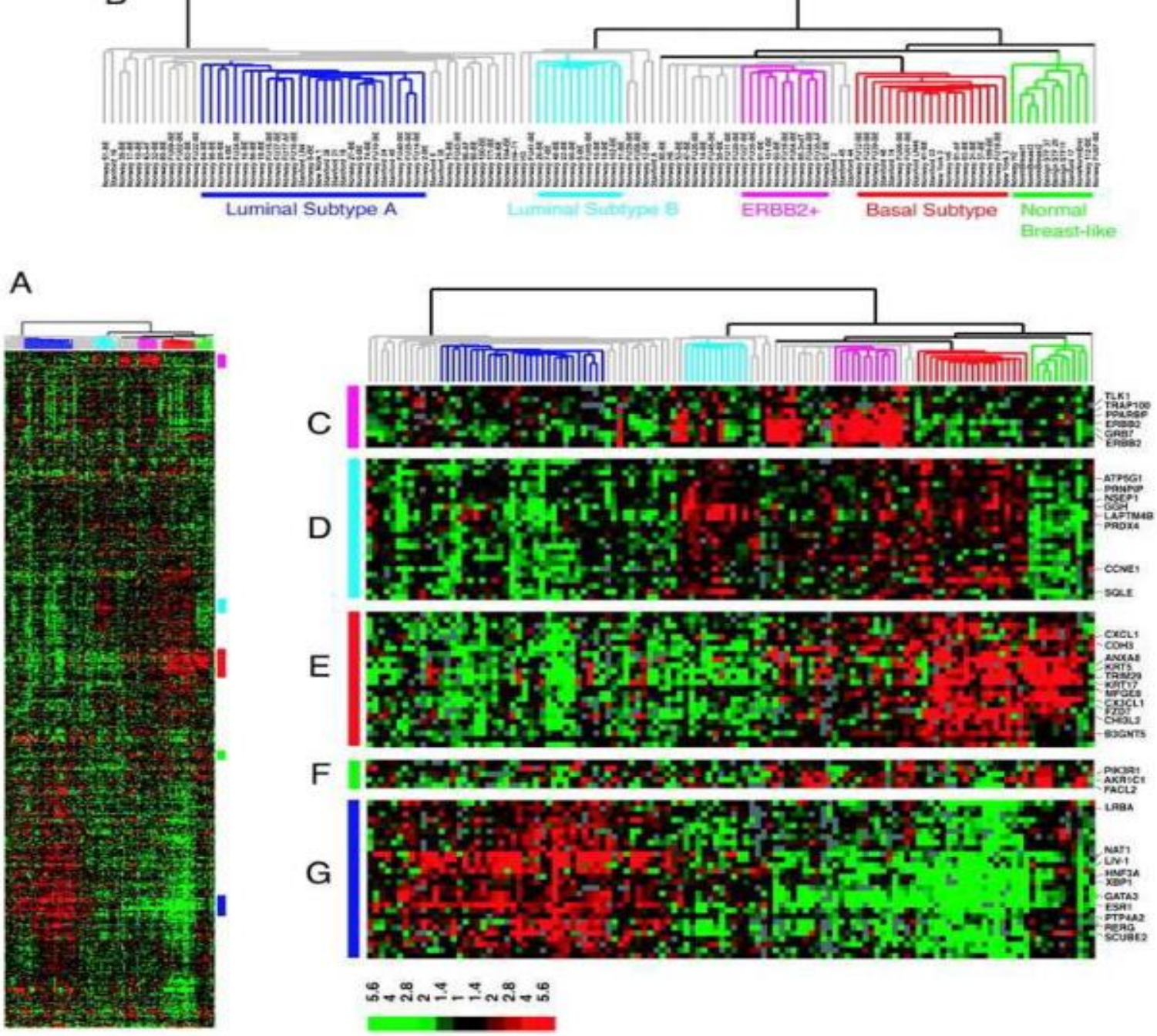
Genetic Event	Disease	Drug
***KRAS* Mutation**	CRC	Cetuximab/Panitumumab (contraindicated by KRAS mutation)
***BRAF* Mutation**	Melanoma	Vemurafenib/Dabrafenib
***EGFR* Mutation**	NSCLC	Gefitinib/Erlotinib/Afatinib
***EML4-ALK* Translocation**	NSCLC	Crizotinib
***KIT* Mutation**	GIST/melanoma	Imatinib/Sunitinib/Regorafenib/Pazopanib
***BCR-ABL* Translocation**	CML	Imatinib/Dasatinib/Nilotinib/Bosutinib
***PML-RARA* Translocation t(15;17)**	APL	ATRA
HER2* Gene Amplification	Breast and Upper GI Cancer	Trastuzumab/Lapatinib
***ROS1* Fusion**	NSCLC	Cabozantinib (investigational)
***RET* Fusion**	NSCLC	Cabozantinib (investigational)

Rembrandt's anatomy lesson of professor Nicolaes Tulp (1632)

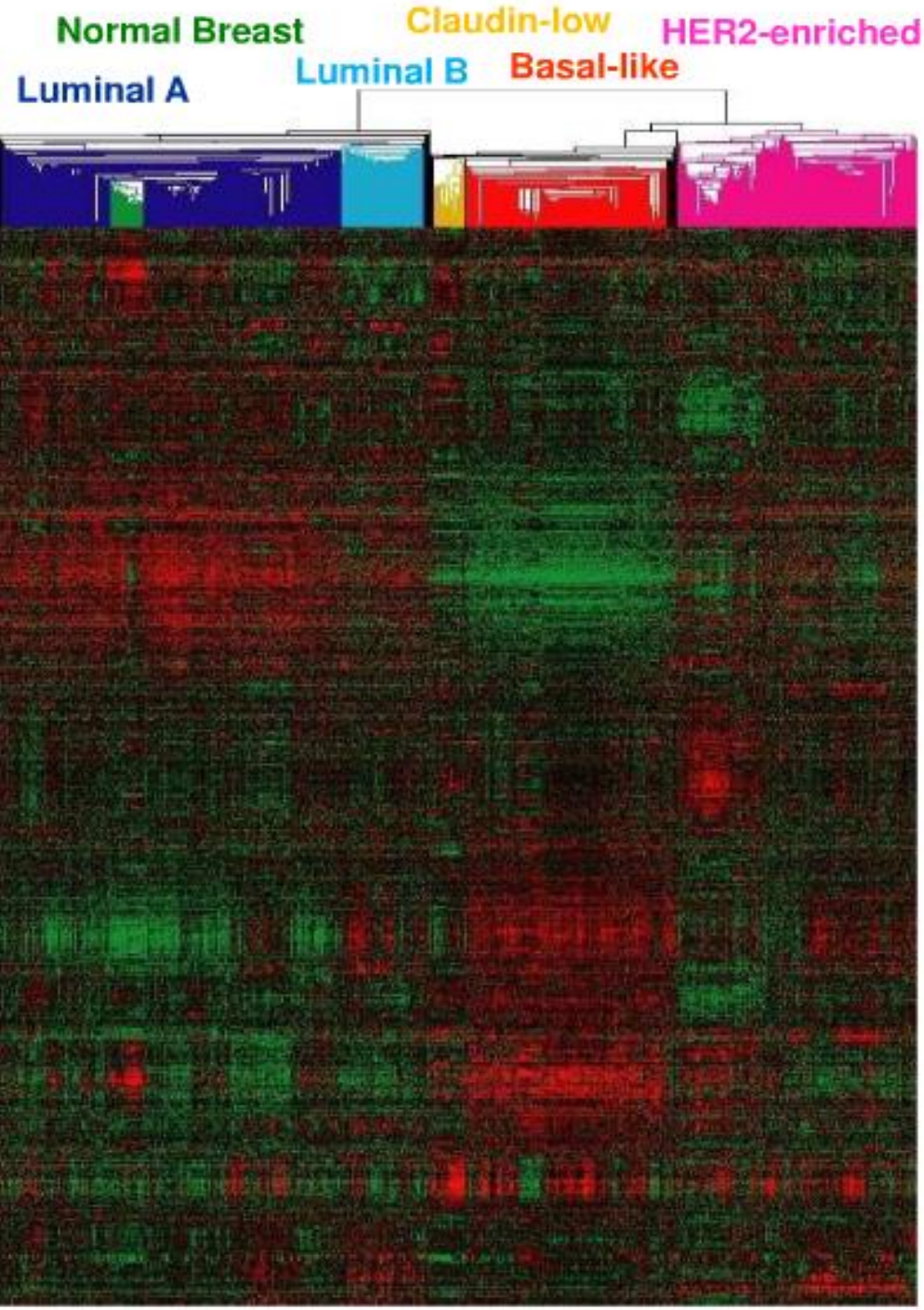


Courtesy of Carlos Cordon-Cardo, M.D., Ph.D. Columbia University

THE END OF COUNTRY OF ORIGIN AS THE CRITICAL FACT DETERMINING CANCER TREATMENT ??

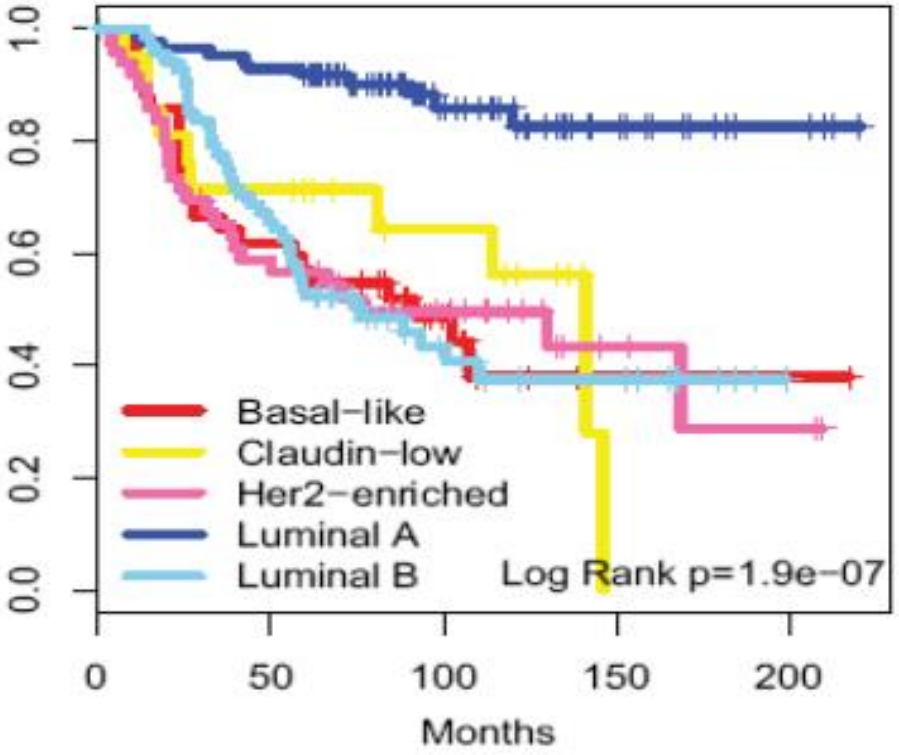


Sorlie, T et al. (2003) Proc. Natl. Acad. Sci. USA 100, 8418-8423

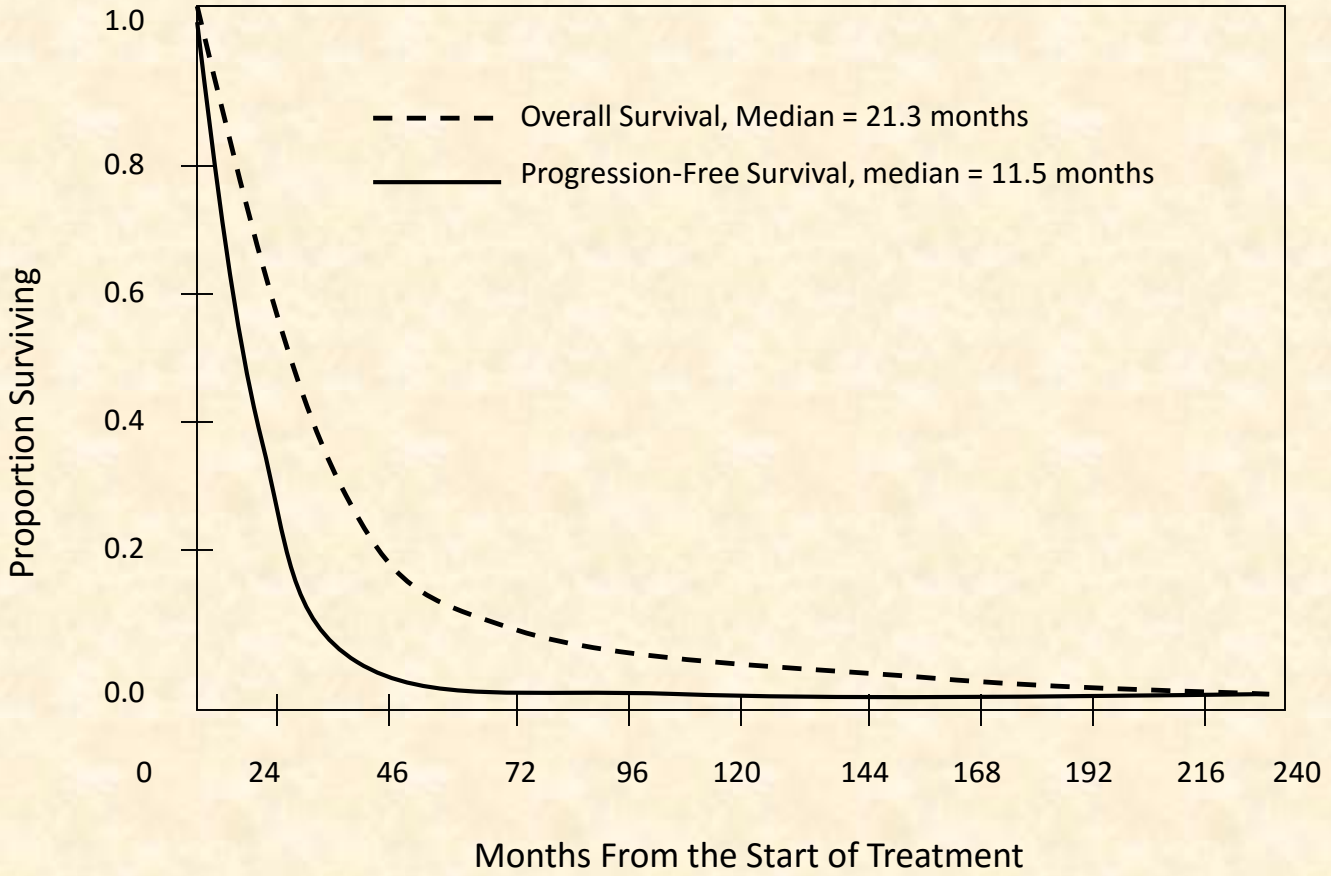


Intrinsic Subtypes

Perou et al., Nature, 2000
Sorlie et al., PNAS, 2001
Sorlie et al., PNAS, 2003
Hu et al., BMC Genomics, 2006
Perreard et al., BCR 2006
Herschkowitz et al., GB, 2007
Mullins et al., Clin Chem, 2007
Parker et al., JCO, Feb 2009
Prat et al., Submitted

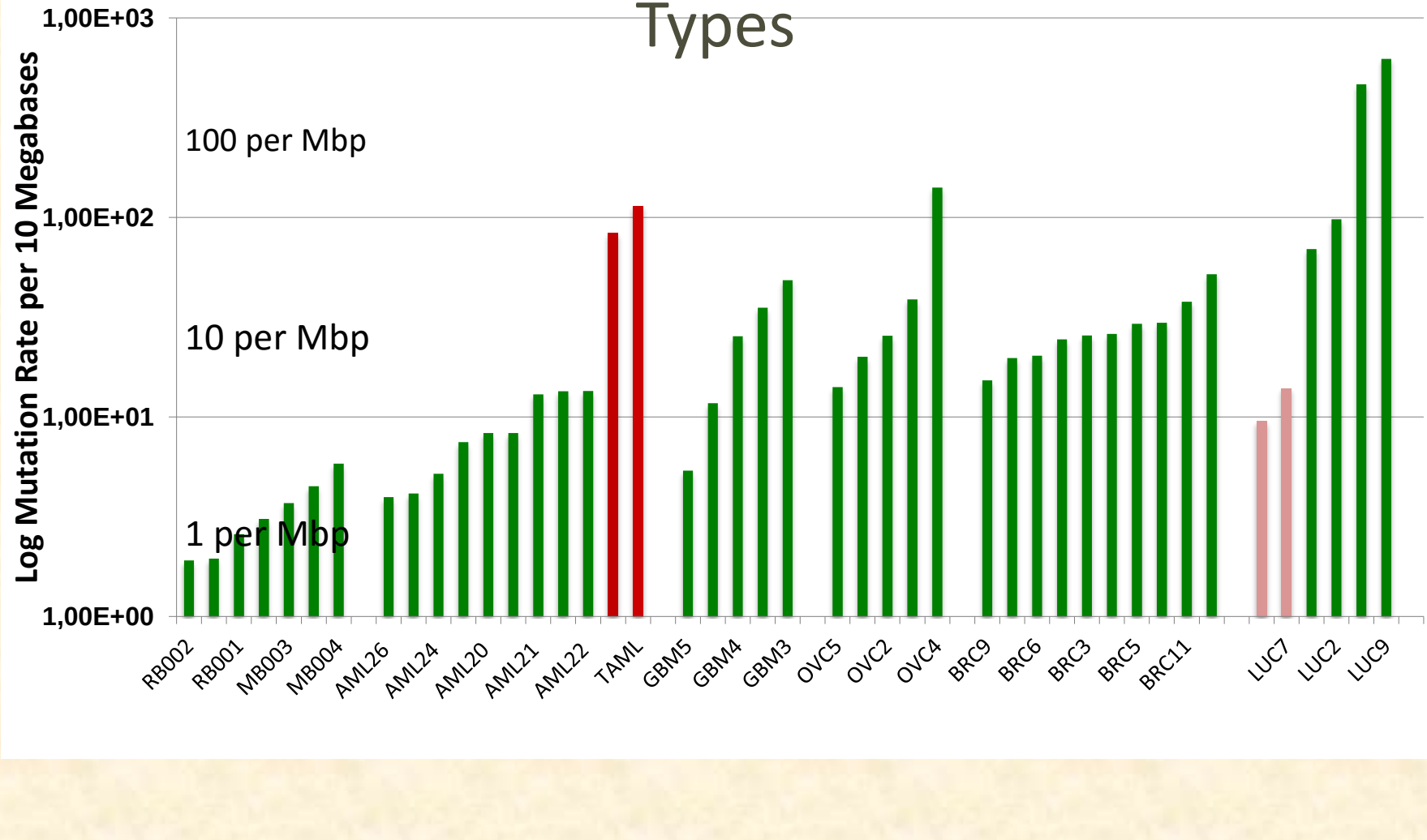


SURVIVAL FOLLOWING THE DIAGNOSIS OF METASTATIC BREAST CANCER

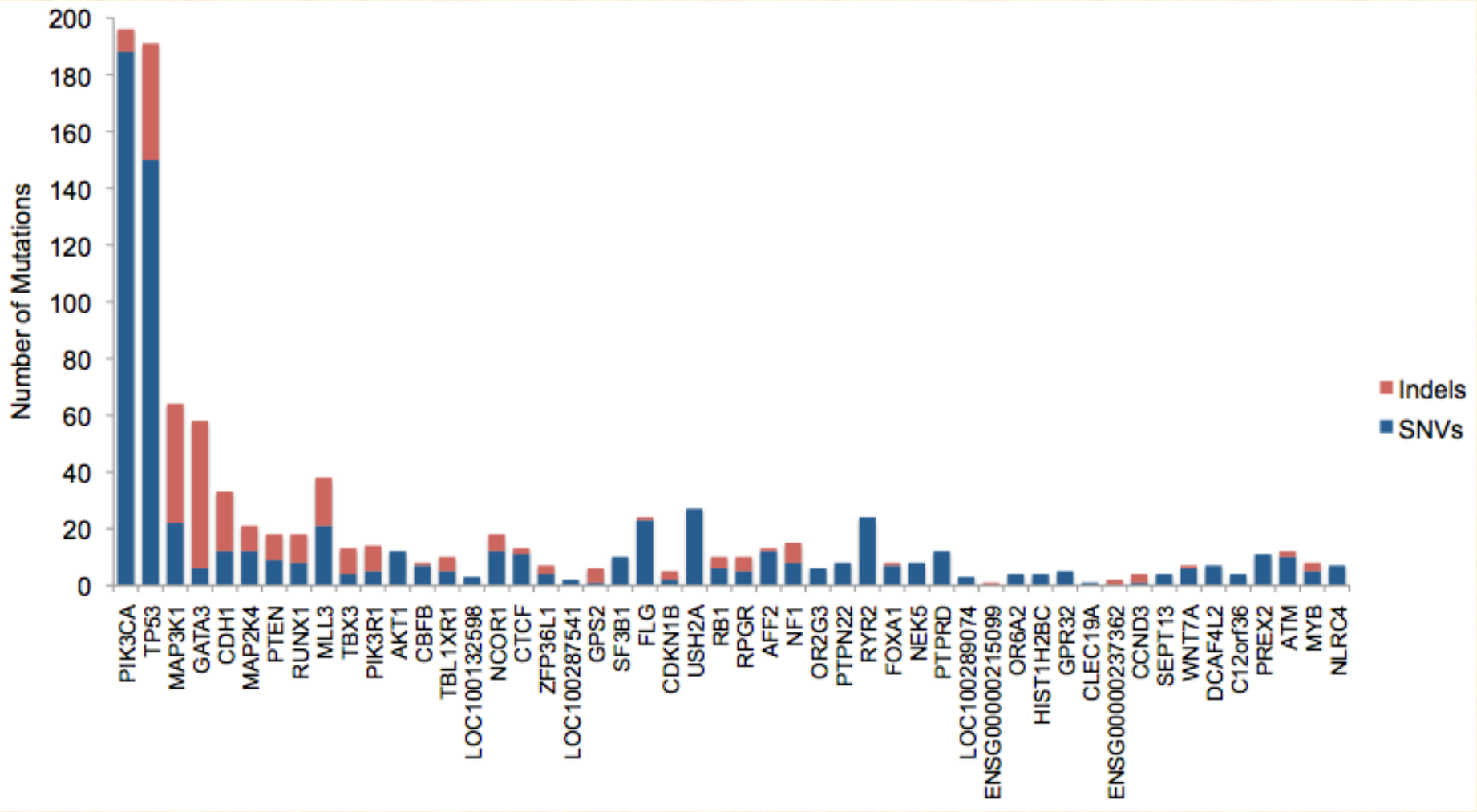


Overall and progression free survival of 1581 patients with metastatic breast carcinoma treated on 18 successive, doxorubicin-containing standard dose chemotherapy protocols from 1973 to 1982 at the M.D. Anderson Cancer Center.

Background Mutation Rates Across Different Cancer Types

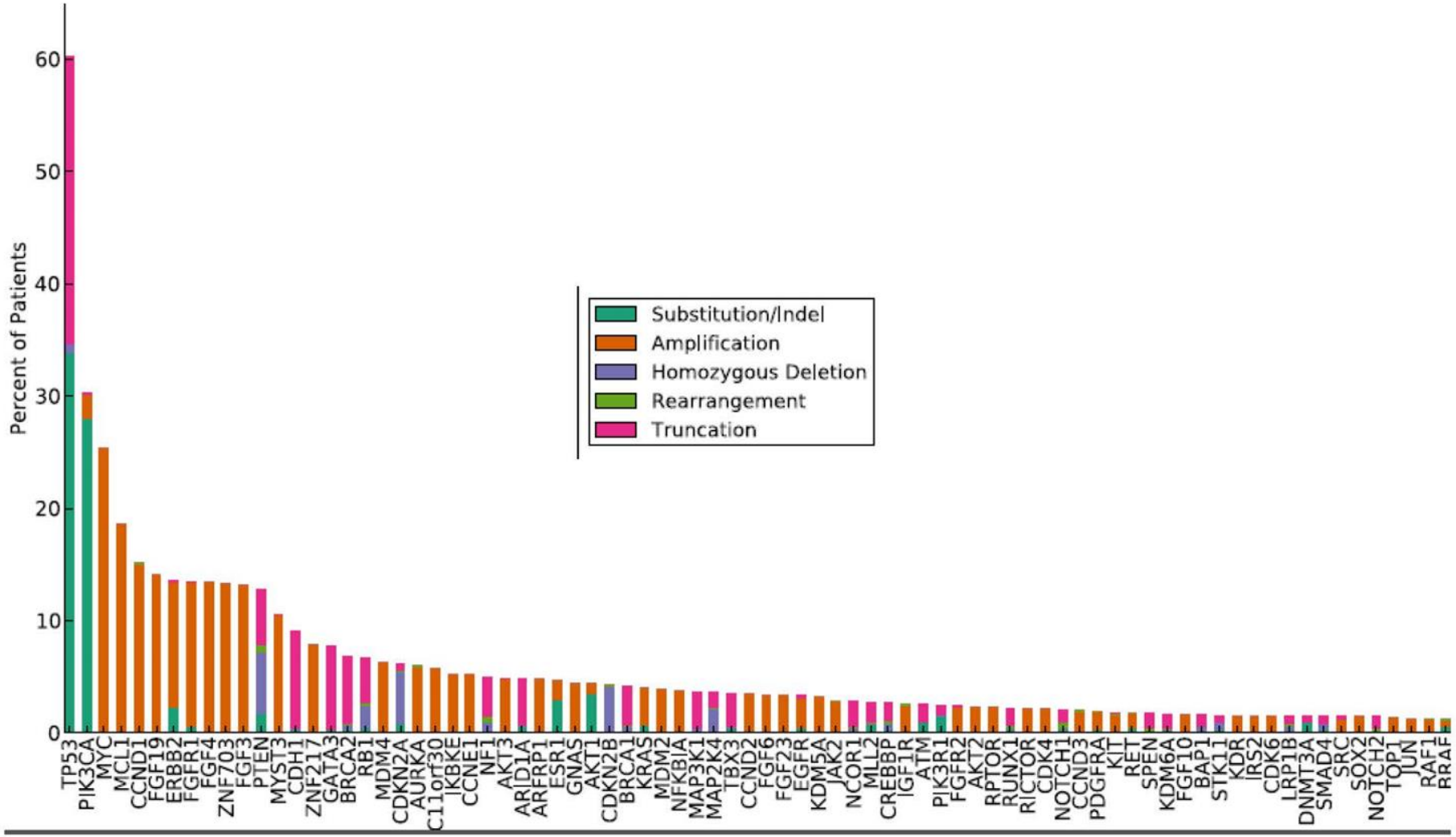


Significantly Mutated Genes (All 507 Cases) (FDR<0.15)



SMGs with FDR<0.15 by at least two tests (Fisher's, LR, or Convolution)

Genomic Alterations in 1,445 Relapsed/Refractory Invasive Breast Cancers

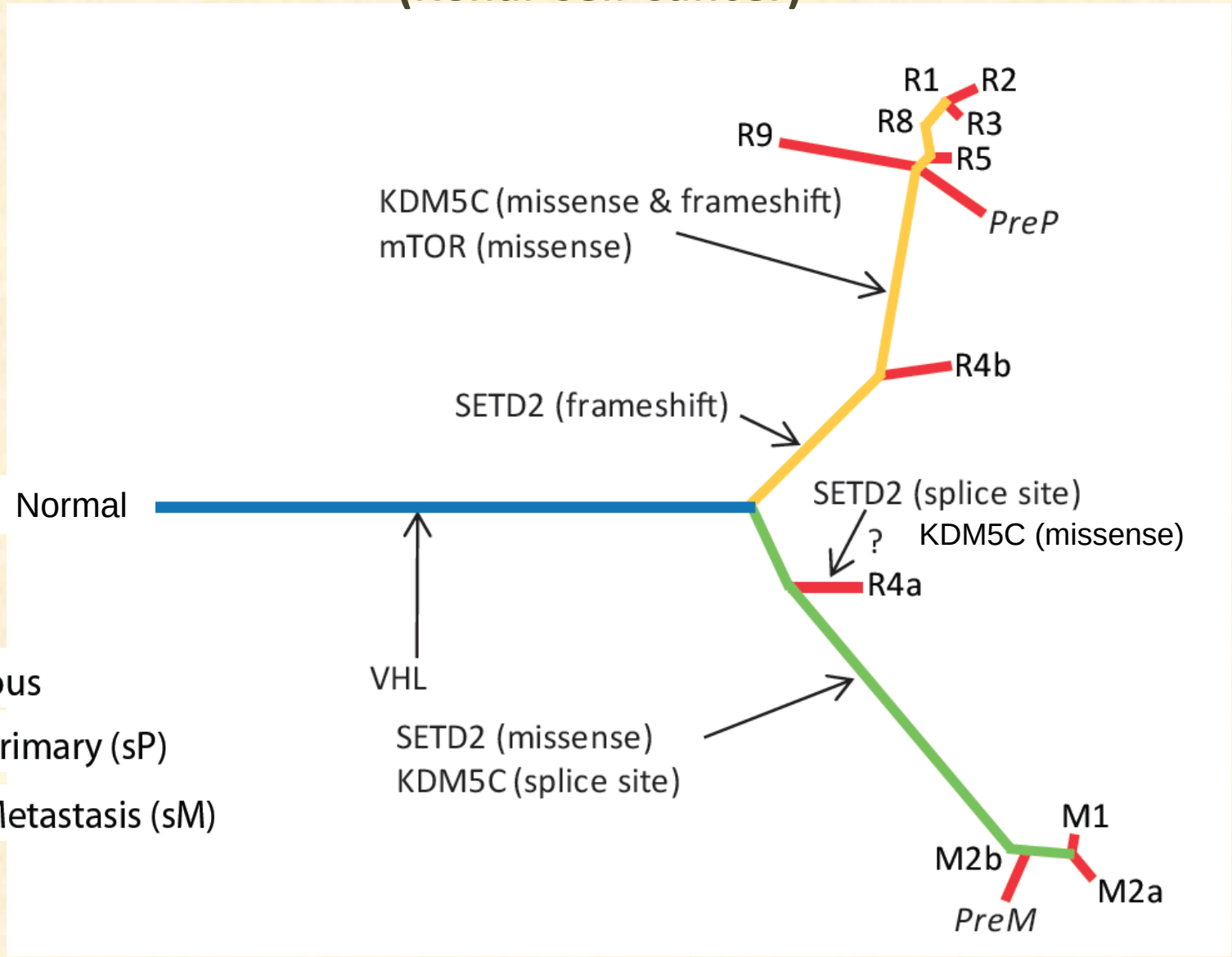


Genomic Alterations in 1,445 Invasive Breast Cancers

Gene	% of samples
TP53	60
PIK3CA	30
MYC	25
MCL1	19
CCND1	15
FGF19	14
ERBB2	14
FGFR1	13
FGF4	13
ZNF703	13

Gene	% of samples
FGF3	13
PTEN	13
MYST3	11
CDH1	9
ZNF217	8
GATA3	8
BRCA2	7
RB1	7
MDM4	6
CDKN2A	6

Tumour Phylogenetic Evolution (Renal Cell Cancer)



Gerlinger, M., et al.; N Engl J Med; 2012

The NEW ENGLAND JOURNAL of MEDICINE

368:1199-209, 2013

ORIGINAL ARTICLE

Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

Sarah-Jane Dawson, F.R.A.C.P., Ph.D., Dana W.Y. Tsui, Ph.D., Muhammed Murtaza, M.B., B.S., Heather Biggs, M.A., Oscar M. Rueda, Ph.D., Suet-Feung Chin, Ph.D., Mark J. Dunning, Ph.D., Davina Gale, B.Sc., Tim Forshew, Ph.D., Betania Mahler-Araujo, M.D., Sabrina Rajan, M.D., Sean Humphray, B.Sc., Jennifer Becq, Ph.D., David Halsall, M.R.C.Path., Ph.D., Matthew Wallis, M.B., Ch.B., David Bentley, D.Phil., Carlos Caldas, M.D., F.Med.Sci., and Nitzan Rosenfeld, Ph.D.

Circulating Plasma Cell Free Tumor DNA in Breast Cancer

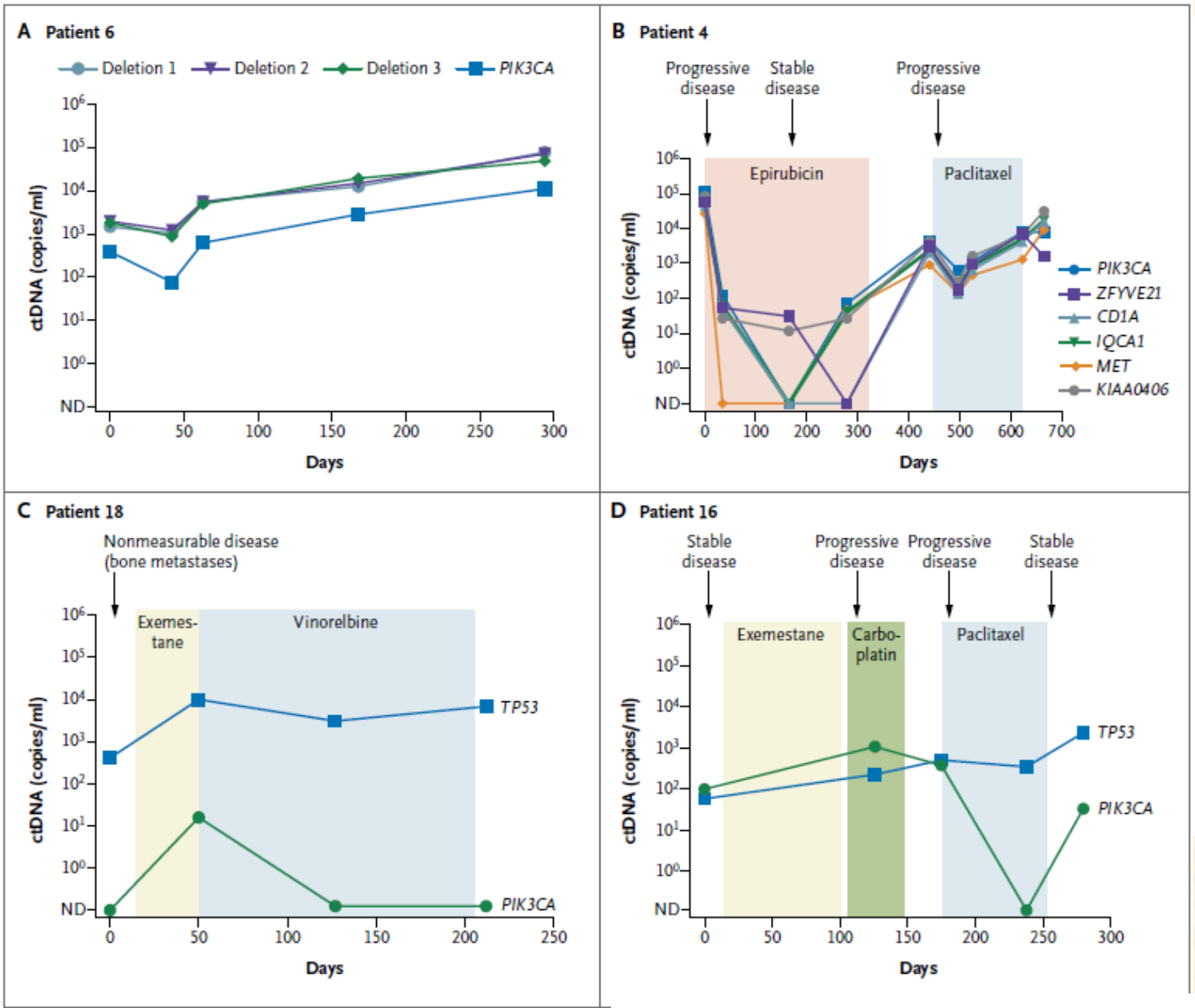


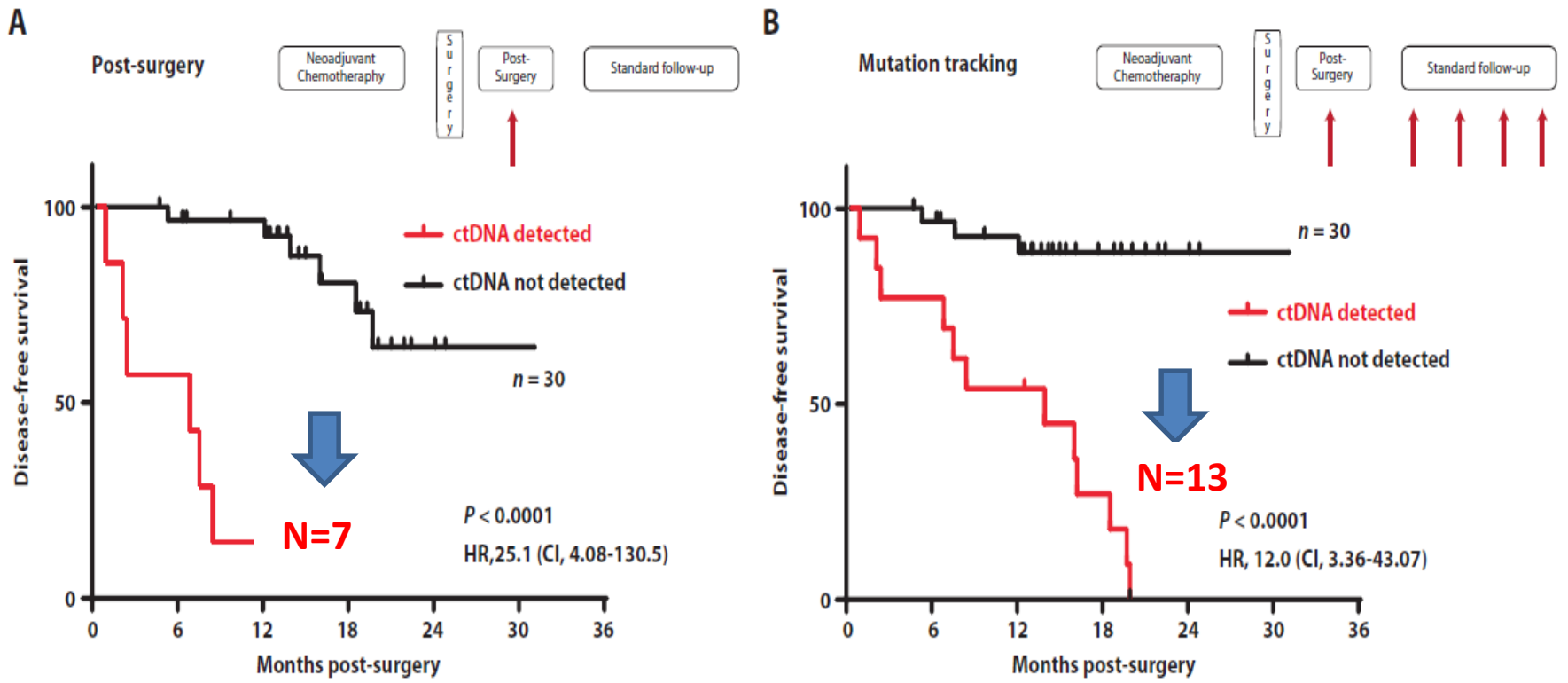
Figure 2. Monitoring Multiple Point Mutations and Structural Variants

Dawson et al. N Engl J Med 368:1199-209, 2013

Mutation Tracking of ptDNA May Be More Prognostic than a Single Point in Time

Single time- point post Surgery

Multiple time-points for Mutational Tracking



Garcia-Murllias et al Science Translational Med 2015

Personalized approach improves cancer treatment outcomes

Published Ahead of Print on August 24, 2015 as 10.1200/JCO.2015.61.5997
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.61.5997

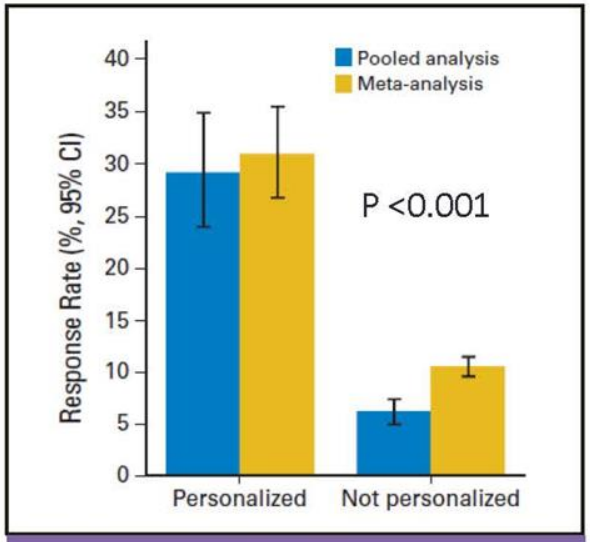
JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials

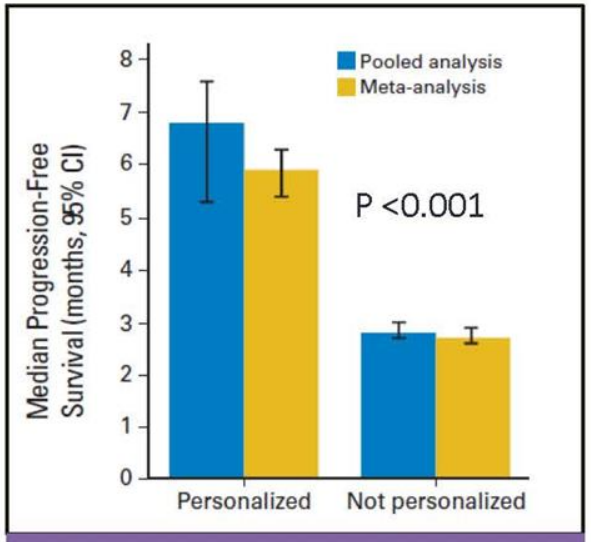
Maria Schwaederle, Melissa Zhao, J. Jack Lee, Alexander M. Eggermont, Richard L. Schilsky, John Mendelsohn, Vladimir Lazar, and Razelle Kurzrock

Genomics-matched targeted therapy = BEST OUTCOME

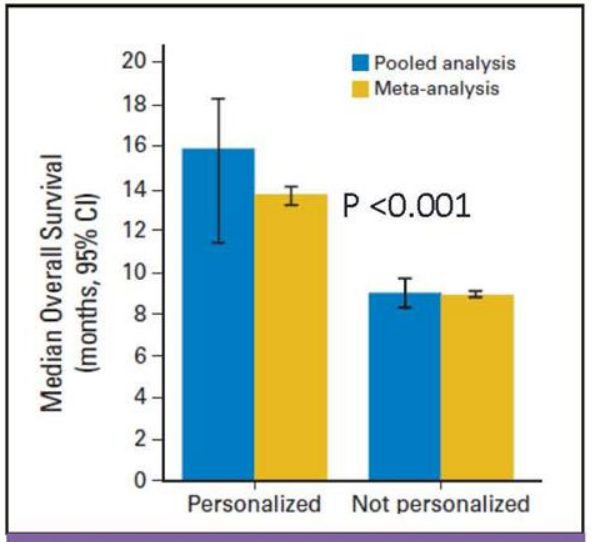
Targeted therapy w/o mutation matching = Worst outcome



Response Rate to Therapy



Progression Free Survival

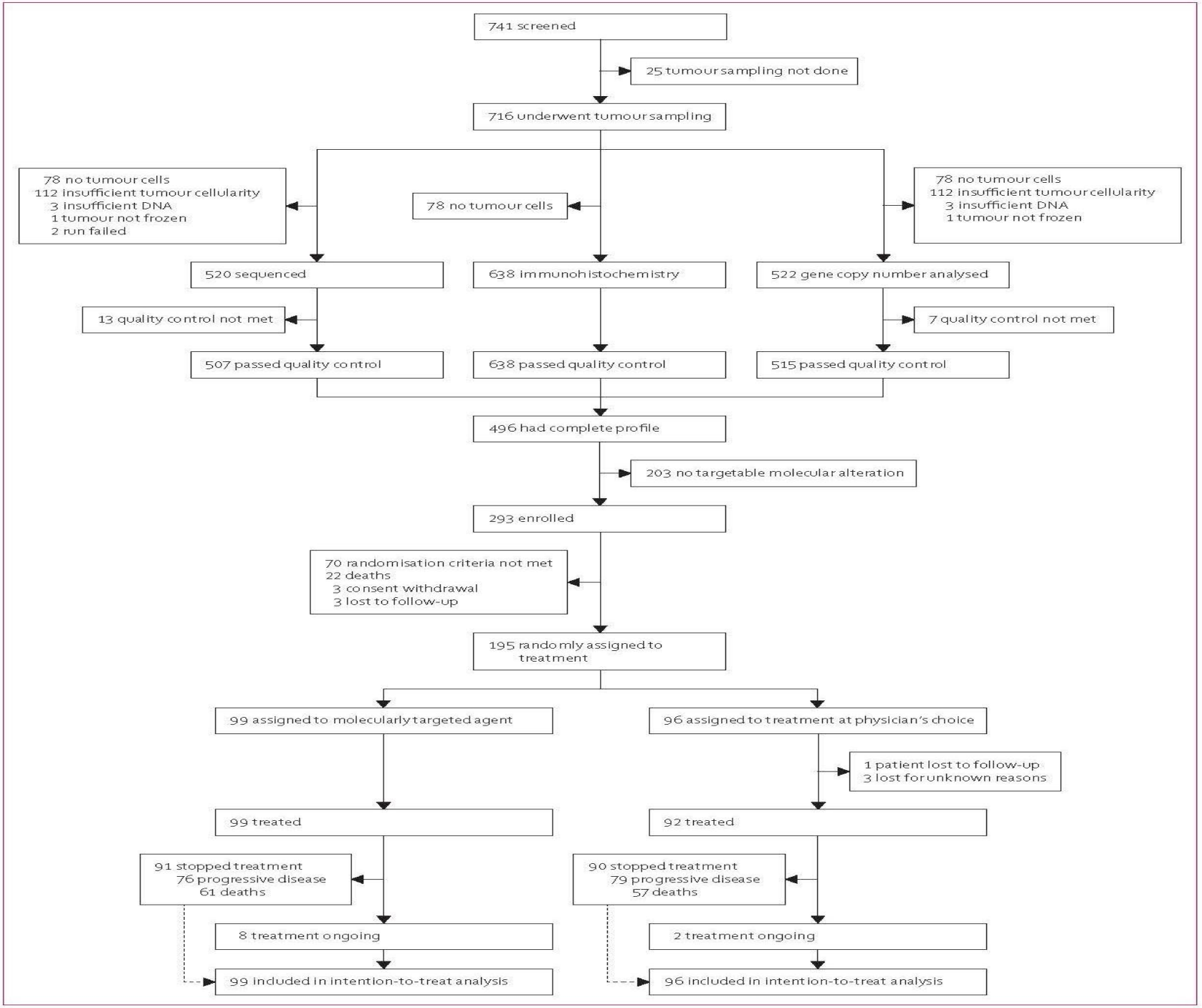


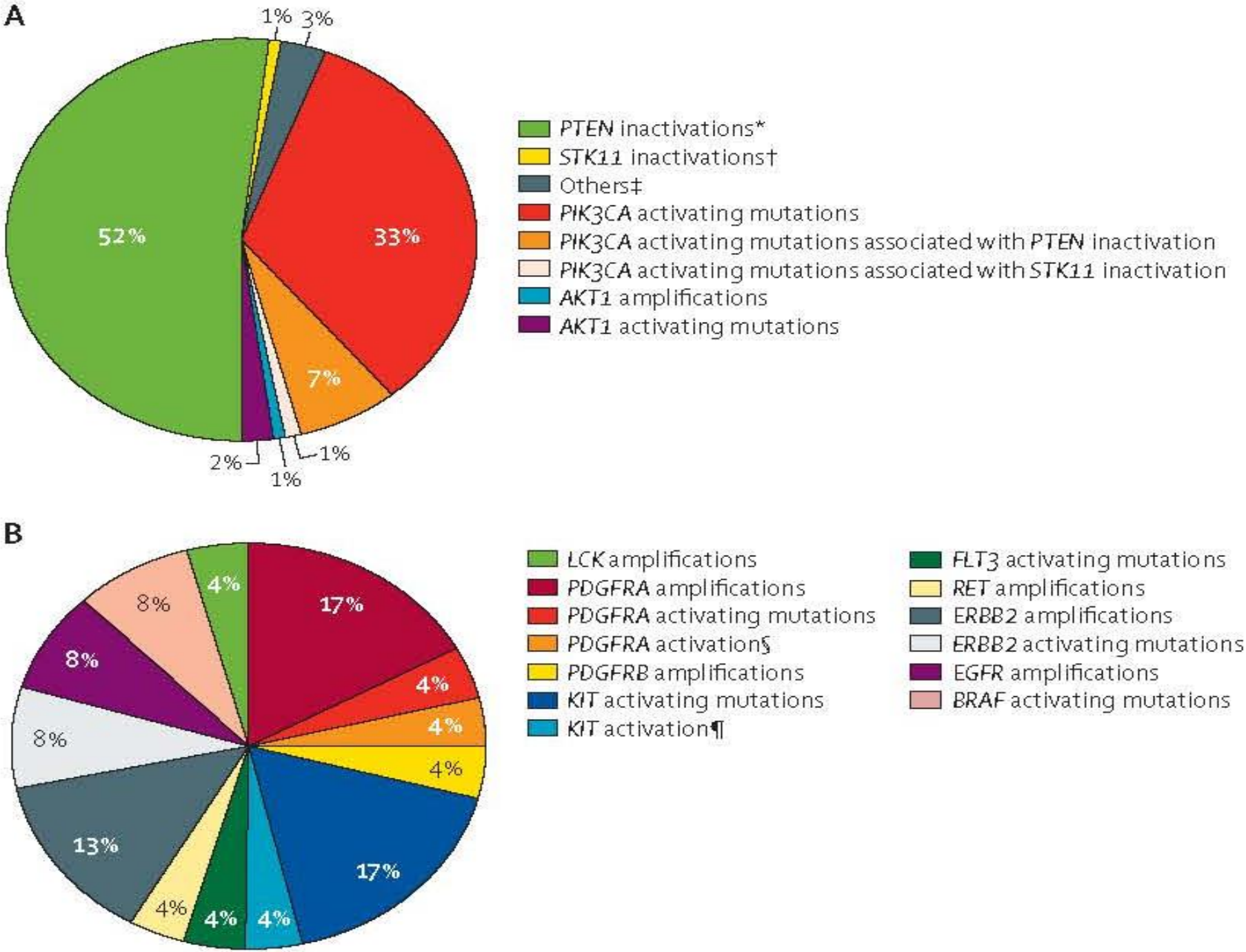
Overall Survival

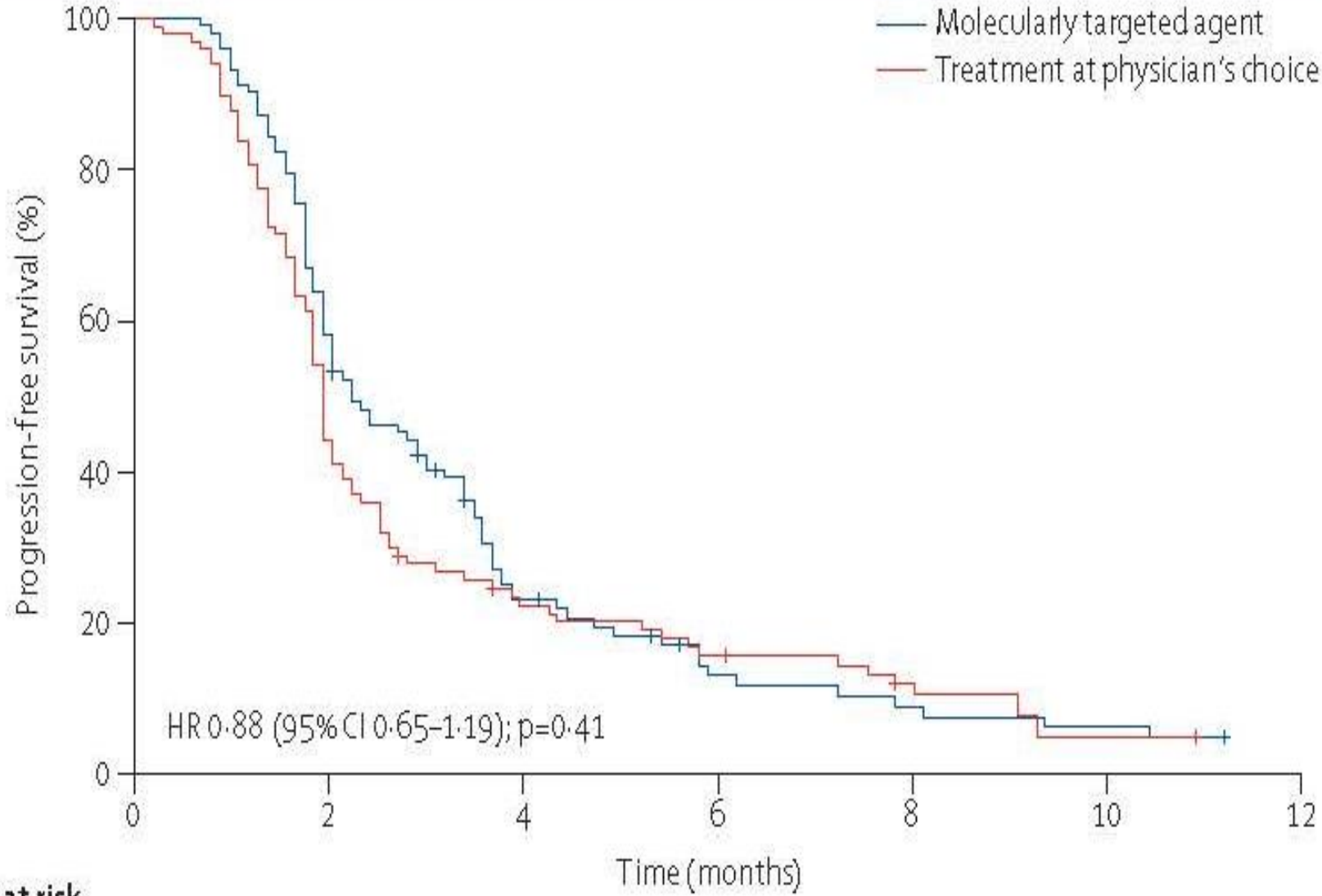
(Ref: Schwaederle et al., JCO 2015)

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators

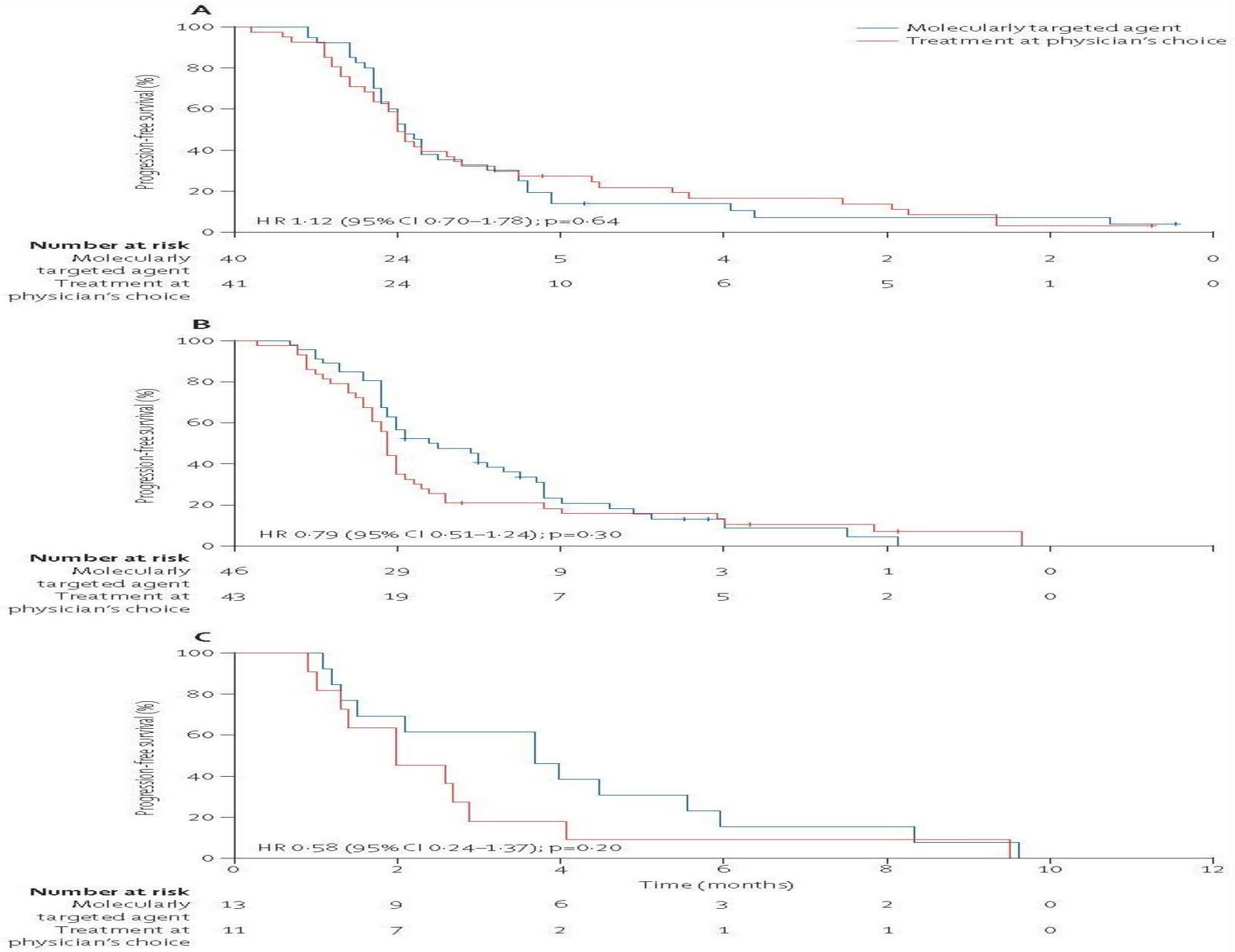

741 screened
25 tumour sampling not done
716 underwent tumour sampling
78 no tumour cells
112 insufficient tumour cellularity
3 insufficient DNA
1 tumour not frozen
2 run failed
78 no tumour cells
78 no tumour cells
112 insufficient tumour cellularity
3 insufficient DNA
1 tumour not frozen
520 sequenced
638 immunohistochemistry
522 gene copy number analysed
13 quality control not met
7 quality control not met
507 passed quality control
638 passed quality control
515 passed quality control
496 had complete profile
203 no targetable molecular alteration
293 enrolled
70 randomisation criteria not met
22 deaths
3 consent withdrawal
3 lost to follow-up
195 randomly assigned to treatment
99 assigned to molecularly targeted agent
96 assigned to treatment at physician's choice
1 patient lost to follow-up
3 lost for unknown reasons
99 treated
92 treated
91 stopped treatment
76 progressive disease
61 deaths
90 stopped treatment
79 progressive disease
57 deaths
8 treatment ongoing
2 treatment ongoing
99 included in intention-to-treat analysis
96 included in intention-to-treat analysis


A
1%
3%
52%
33%
7%
2%
1%
1%
PTEN inactivations*
STK11 inactivations†
Others‡
PIK3CA activating mutations
PIK3CA activating mutations associated with PTEN inactivation
PIK3CA activating mutations associated with STK11 inactivation
AKT1 amplifications
AKT1 activating mutations
B
4%
17%
8%
8%
4%
4%
8%
4%
13%
17%
4%
4%
4%
LCK amplifications
PDGFRA amplifications
PDGFRA activating mutations
PDGFRA activation§
PDGFRB amplifications
KIT activating mutations
KIT activation¶
FLT3 activating mutations
RET amplifications
ERBB2 amplifications
ERBB2 activating mutations
EGFR amplifications
BRAF activating mutations



Number at risk

Molecularly targeted agent	99	62	20	10	5	2	0
Treatment at physician's choice	95*	50	19	12	8	1	0


A
Molecularly targeted agent
Treatment at physician's choice
Progression-free survival (%)
100
80
60
40
20
0
HR 1·12 (95% CI 0·70–1·78); p=0·64
Number at risk
Molecularly targeted agent 40 24 5 4 2 2 0
Treatment at physician's choice 41 24 10 6 5 1 0
B
Progression-free survival (%)
HR 0·79 (95% CI 0·51–1·24); p=0·30
Number at risk
Molecularly targeted agent 46 29 9 3 1 0
Treatment at physician's choice 43 19 7 5 2 0
C
Progression-free survival (%)
HR 0·58 (95% CI 0·24–1·37); p=0·20
0 2 4 6 8 10 12
Time (months)
Number at risk
Molecularly targeted agent 13 9 6 3 2 0
Treatment at physician's choice 11 7 2 1 1 0

A PAIR OF INFORMATIVE EXAMPLES

FOUNDATIONONE

[redacted]

Report Date
30 July 2015

Tumor Type
Breast invasive ductal carcinoma (IDC)

APPENDIX

GENES ASSAYED IN FOUNDATIONONE

FoundationOne is designed to include all genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 315 genes as well as introns of 28 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

ABL1	BRAF	CHEK1	FANCC	GATA3	JAK2	MITF	PDCD1LG2	RBM10	STAT4
ABL2	BRCA1	CHEK2	FANCD2	GATA4	JAK3	MLH1	PDGFRA	RET	STK11
ACVR1B	BRCA2	CIC	FANCE	GATA6	JUN	MPL	PDGFRB	RICTOR	SUFU
AKT1	BRD4	CREBBP	FANCF	GID4 (C17orf39)	KAT6A (MYST3)	MRE11A	PDK1	RNF43	SYK
AKT2	BRIP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PIK3C2B	ROS1	TAF1
AKT3	BTG1	CRLF2	FANCL	GNA11	KDM5C	MSH6	PIK3CA	RPTOR	TBX3
ALK	BTK	CSF1R	FAS	GNA13	KDM6A	MTOR	PIK3CB	RUNX1	TERC
AMER1 (FAM123B)	C11orf30 (EMSY)	CTCF	FAT1	GNAQ	KDR	MUTYH	PIK3CG	RUNX1T1	TERT (promoter only)
APC	CARD11	CTNNA1	FBXW7	GNAS	KEAP1	MYC	PIK3R1	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL (MYCL1)	PIK3R2	SDHB	TGFBR2
ARAF	CBL	CUL3	FGF14	GRIN2A	KIT	MYCN	PLCG2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PMS2	SDHD	TNFRSF14
ARID1A	CCND2	DAXX	FGF23	GSK3B	KMT2A (MLL)	NF1	POLD1	SETD2	TOP1
ARID1B	CCND3	DDR2	FGF3	H3F3A	KMT2C (MLL3)	NF2	POLE	SF3B1	TOP2A
ARID2	CCNE1	DICER1	FGF4	HGF	KMT2D (MLL2)	NFE2L2	PPP2R1A	SLIT2	TP53
ASXL1	CD274	DNMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PREX2	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP1B	NOTCH1	PRKAR1A	SMAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKCI	SMARCA4	U2AF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SMARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SMO	VHL
AXIN1	CDK4	EPHA7	FLCN	IGF1R	MAP2K1	NRAS	PTCH1	SNCAIP	WISP3
AXL	CDK6	EPHB1	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	IKBKE	MAP2K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	MAP3K1	NTRK2	QKI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	INHBA	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRFI1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	IRF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EZH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	MET	PBRM1	RB1	STAT3	

Select Rearrangements

ALK	BRAF	BRD4	ETV4	FGFR1	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	

Specimen ID: US12-3778 B1 Pathologist: Not Provided

ABOUT THE TEST:
FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

7 genomic alterations

7 therapies associated with potential clinical benefit

0 therapies associated with lack of response

37 clinical trials

TUMOR TYPE: BREAST INVASIVE DUCTAL CARCINOMA (IDC)

Genomic Alterations Identified†

ERBB2 amplification
PIK3CA E545K
MYC amplification – equivocal‡
TP53 L194H
CREBBP S23*
LRP1B splice site 7514-1G>A
PIK3C2B amplification – equivocal‡

†For a complete list of the genes assayed and performance specifications, please refer to the Appendix
‡See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
ERBB2 amplification	Ado-trastuzumab emtansine Lapatinib Pertuzumab Trastuzumab	Afatinib	Yes, see clinical trials section
PIK3CA E545K	Everolimus	Temsirolimus	Yes, see clinical trials section
MYC amplification - equivocal	None	None	Yes, see clinical trials section
TP53 L194H	None	None	Yes, see clinical trials section
CREBBP S23*	None	None	None
LRP1B splice site 7514-1G>A	None	None	None

Genes on the Guardant360 Panel

Genes with Complete Exon and Partial Intron Coverage

Gene	LOD	Gene	LOD	Gene	LOD	Gene	LOD
APC	< 0.1%	***AR***	< 0.1%	*ARID1A*	< 0.1%	***BRAF***	< 0.1%
BRCA1	< 0.1%	*BRCA2*	< 0.1%	*CCND1*	< 0.1%	*CCND2*	< 0.1%
CCNE1	< 0.1%	***CDK4***	< 0.1%	***CDK6***	< 0.1%	*CDKN2A*	< 0.1%
CDKN2B	< 0.1%	***EGFR***[#]	< 0.1%	***ERBB2***	< 0.1%	***FGFR1***	< 0.1%
FGFR2	< 0.1%	*HRAS*	< 0.1%	***KIT***	< 0.1%	***KRAS***	< 0.1%
MET	< 0.1%	***MYC***	< 0.1%	*NF1*	< 0.1%	*NRAS*	< 0.1%
PDGFRA	< 0.1%	***PIK3CA***	< 0.1%	*PTEN*	< 0.1%	***RAF1***	< 0.1%
TP53	< 0.1%						

Genes in bold are those that are also analyzed for copy number variations (CNVs).
[#] *EGFR indels in exon 19 and 20*

Genes with Critical Exon Coverage

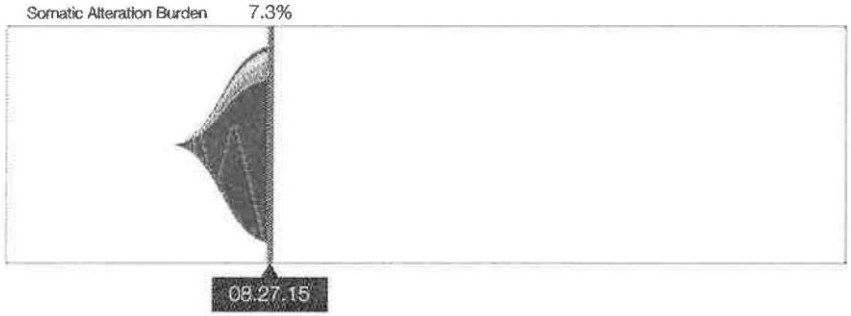
Gene	LOD	Gene	LOD	Gene	LOD	Gene	LOD
AKT1	< 0.1%	*ALK*	< 0.1%	*ARAF*	< 0.1%	*ATM*	< 0.1%
CDH1	< 0.1%	*CTNNB1*	< 0.1%	*ESR1*	< 0.1%	*EZH2*	< 0.1%
FBXW7	< 0.1%	*FGFR3*	< 0.1%	*GATA3*	< 0.1%	*GNA11*	< 0.1%
GNAQ	< 0.1%	*GNAS*	< 0.1%	*HNF1A*	< 0.1%	*IDH1*	< 0.1%
IDH2	< 0.1%	*JAK2*	< 0.1%	*JAK3*	< 0.1%	*MAP2K1*	< 0.1%
MAP2K2	< 0.1%	*MLH1*	< 0.1%	*MPL*	< 0.1%	*NFE2L2*	< 0.1%
NOTCH1	< 0.1%	*NPM1*	0.1%	*NTRK1*	< 0.1%	*PTPN11*	< 0.1%
RET	< 0.1%	*RHEB*	< 0.1%	*RHOA*	< 0.1%	*RIT1*	< 0.1%
ROS1	< 0.1%	*SMAD4*	< 0.1%	*SMO*	< 0.1%	*SRC*	< 0.1%
STK11	< 0.1%	*TERT*	< 0.1%	*VHL*	< 0.1%		

Rearrangements

Gene	LOD	Gene	LOD	Gene	LOD	Gene	LOD
ALK	< 0.1%	*NTRK1*	< 0.1%	*RET*	< 0.1%	*ROS1*	< 0.1%

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the relative changes of observed cfDNA at different sample submission time points. The "Somatic Alteration Burden" value below refers to the maximum % cfDNA detected at each time point. Amplifications are not plotted.



7 Total Alteration(s) Detected

5 with Associated Therapy
0 Associated with Lack of Response
Multiple Clinical Trials Available

Summary of Alterations & Associated Treatment Options

The percentage, or allele frequency, of altered cell-free DNA (% cfDNA) circulating in blood is related to the unique tumor biology of this patient. Factors that may affect the amount/percentages of detected genomic alterations in circulating cell-free DNA in blood include tumor growth, turn-over, size, heterogeneity, vascularization, disease progression, or treatment.

Alteration		% cfDNA	cfDNA Amplification	FDA Approved in Indication	Available for Use in Other Indications	Clinical Drug Trials
TP53	*R175H*	7.3		None	None	Trials Available
ESR1	*D538G*	0.2		None	None	Trials Available
	Y537S	0.2		None	None	Trials Available
FGFR1	*R56W*	0.2	The functional consequences and clinical significance of this gene variant are not established. The relevance of therapies targeting this alteration is uncertain. Similar to other alterations in circulating cfDNA, the monitoring of this variant may be reflective of disease progression or treatment; clinical correlation is advised.			
ARID1A	*L2106M*	0.1	The functional consequences and clinical significance of this gene variant are not established. The relevance of therapies targeting this alteration is uncertain. Similar to other alterations in circulating cfDNA, the monitoring of this variant may be reflective of disease progression or treatment; clinical correlation is advised.			
ERBB2	*AMP*		++	Ado-trastuzumab emtansine, Lapatinib, Pertuzumab, Trastuzumab	Afatinib	Trials Available
RAF1	*AMP*		+	None	Regorafenib, Sorafenib, Trametinib	Trials Available

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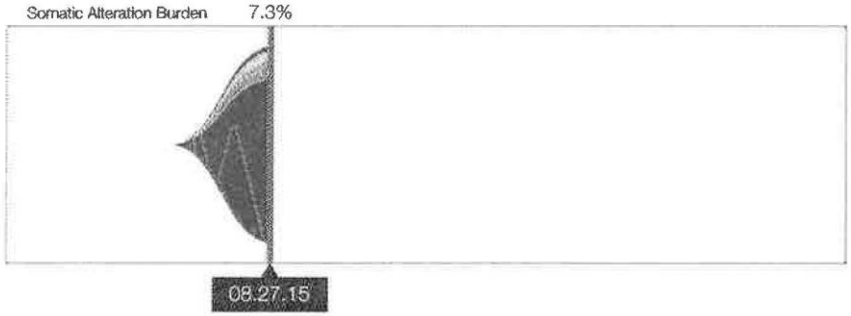

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RAF1	*AMP*		+	None	Regorafenib, Sorafenib, Trametinib	Trials Available

Non-Amplification *ERBB2* (*HER2*) Alterations in 7,300 Consecutive Solid Tumors

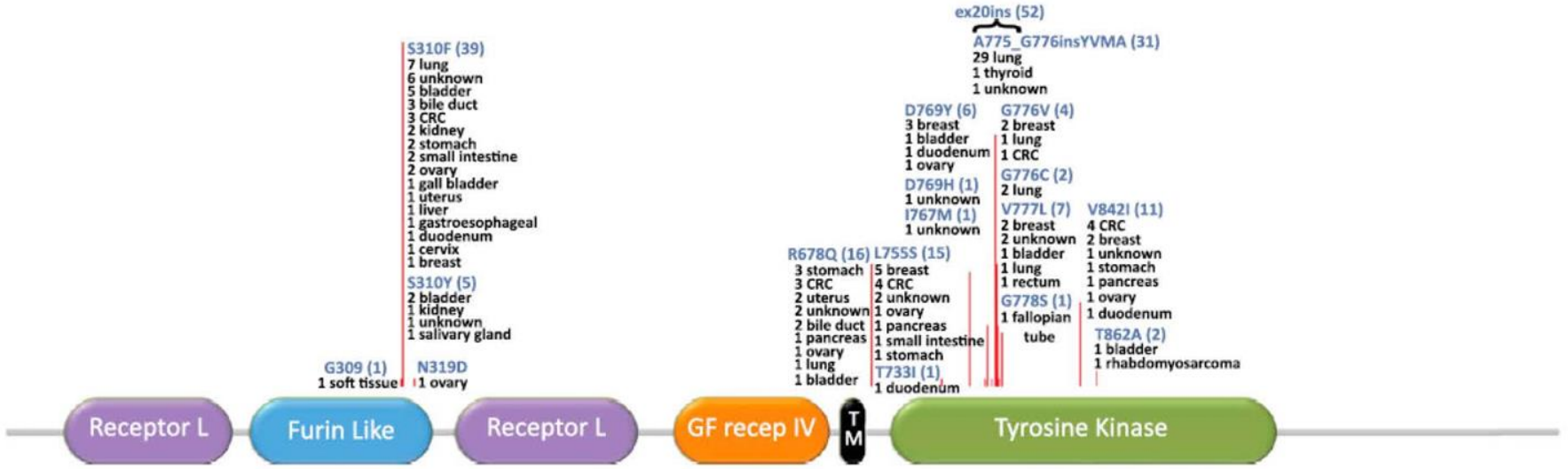


Figure 2. Schematic diagram of mutations observed in *ERBB2*. Mutation frequency at each residue is depicted by vertical red bars. All exon 20 insertions (ex20ins) are graphed in red; however, only the most frequent site is labeled (A775_G776insYVMA). For a complete list of exon 20 alterations and the diseases in which they occur, see supplemental online Table 3.

Abbreviation: CRC, colorectal cancer.

Chmielecki et al The Oncologist, Jan 2015

Distribution of ERBB2 Alterations Across Tumor Types

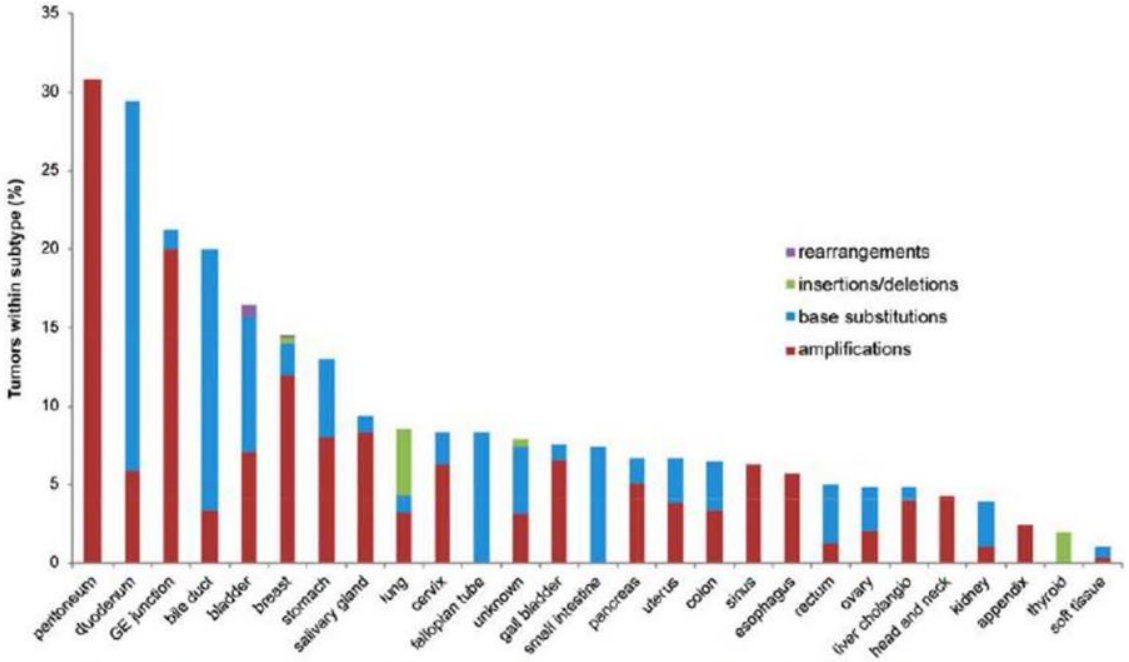


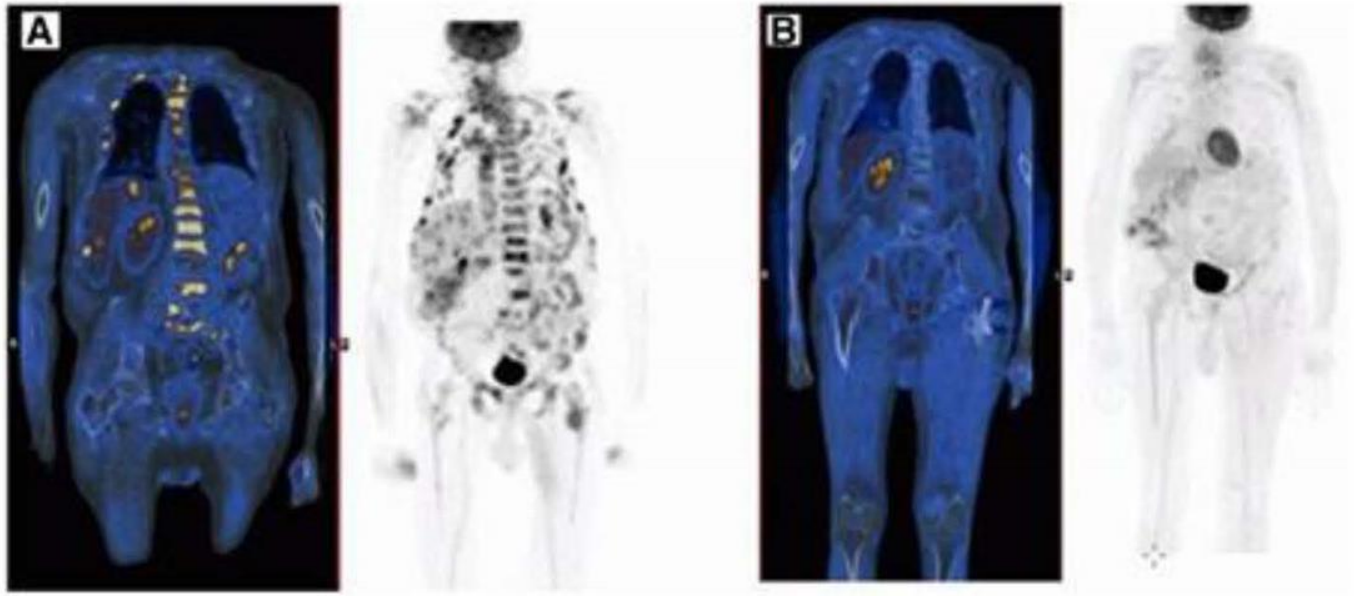
Figure 1. Distribution of *ERBB2* alterations across diseases. Mutations, amplifications, and rearrangements involving *ERBB2* were identified in 403 tumors across 27 disease types. Data are expressed as a percentage compared with the total number of tumors within that subtype in our data set.

Chmielecki et al The Oncologist, Jan 2015

ERBB2 Alterations in 5,605 BC SABCS 2015

- 698 (12.5%) of 5,605 mBC featured *ERBB2* alterations
- 596 (10.6%) featured *ERBB2* amplifications and 137 (2.4%) featured *ERBB2*mut
- 35 (0.6%) of total mBC had both *ERBB2*amp and *ERBB2*mut, which accounted for 5.0% of all *ERBB2* altered
- Of the 137 *ERBB2*mut cases, 8 featured more than 1 *ERBB2* mut
- There were 124 (85%) *ERBB2* kinase domain mutations and 15 (10%) extra-cellular domain *ERBB2*mut
- The most common genes co-altered in *ERBB2*mut mBC were *TP53* (49%), *PIK3CA* (42%), *CDH1* (37%), *MYC* (17%), and *CCND1* (16%)
- The enrichment of *ERBB2*mut in *CDH1* mut mBR was significant (p=0.0006) and associated with relapsed lobular mBC
- Multiple case examples of kinase domain and extra-cellular domain *ERBB2*mut mBC responding to a variety of anti-HER2 targeted therapies will be presented

Response of a HER2 FISH/IHC Negative Cutaneous Adnexal Carcinoma with an *ERBB2* S310f Mutation to anti-HER2 Targeted Therapy



Vornicova O et al. The Oncologist 2014;19:1006-1007

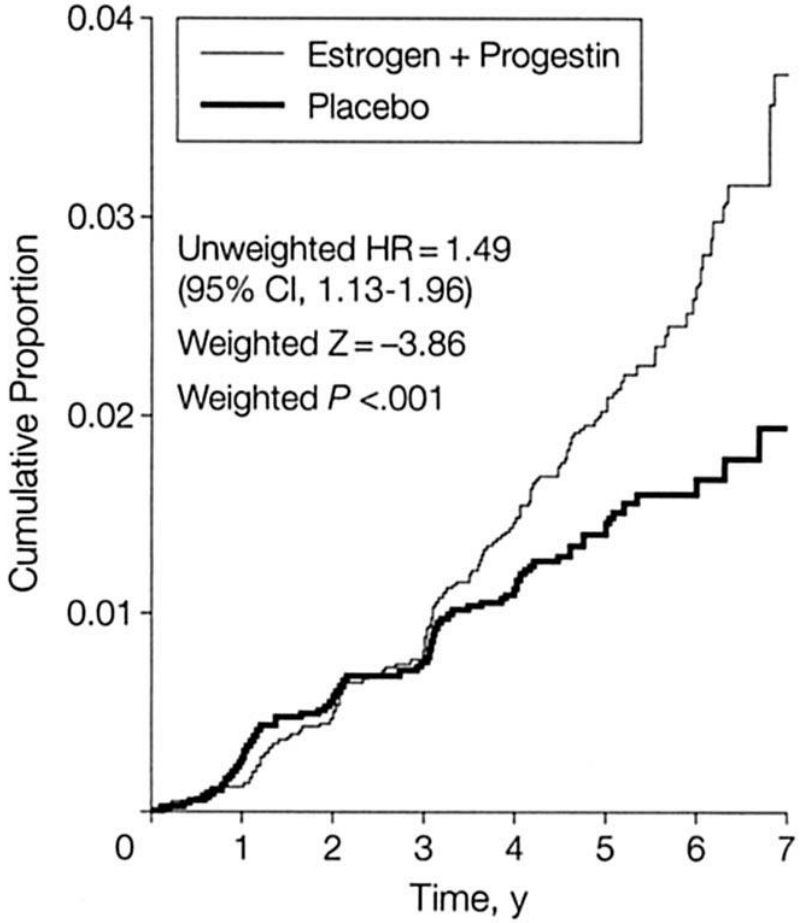
The Oncologist

IMPLICATIONS

- IT SEEMS TO ME WE ARE EITHER GOING TO HAVE TO FIGURE OUT FEASIBLE STRATEGIES TO VALIDATE THESE THERAPIES EARLIER IN THE CLINICAL COURSE, **OR,**
- WE MAY NEED TO RETHINK OUR PARADIGMS AND FOCUS MORE ON THE HOST.

ENDOCRINE THERAPY

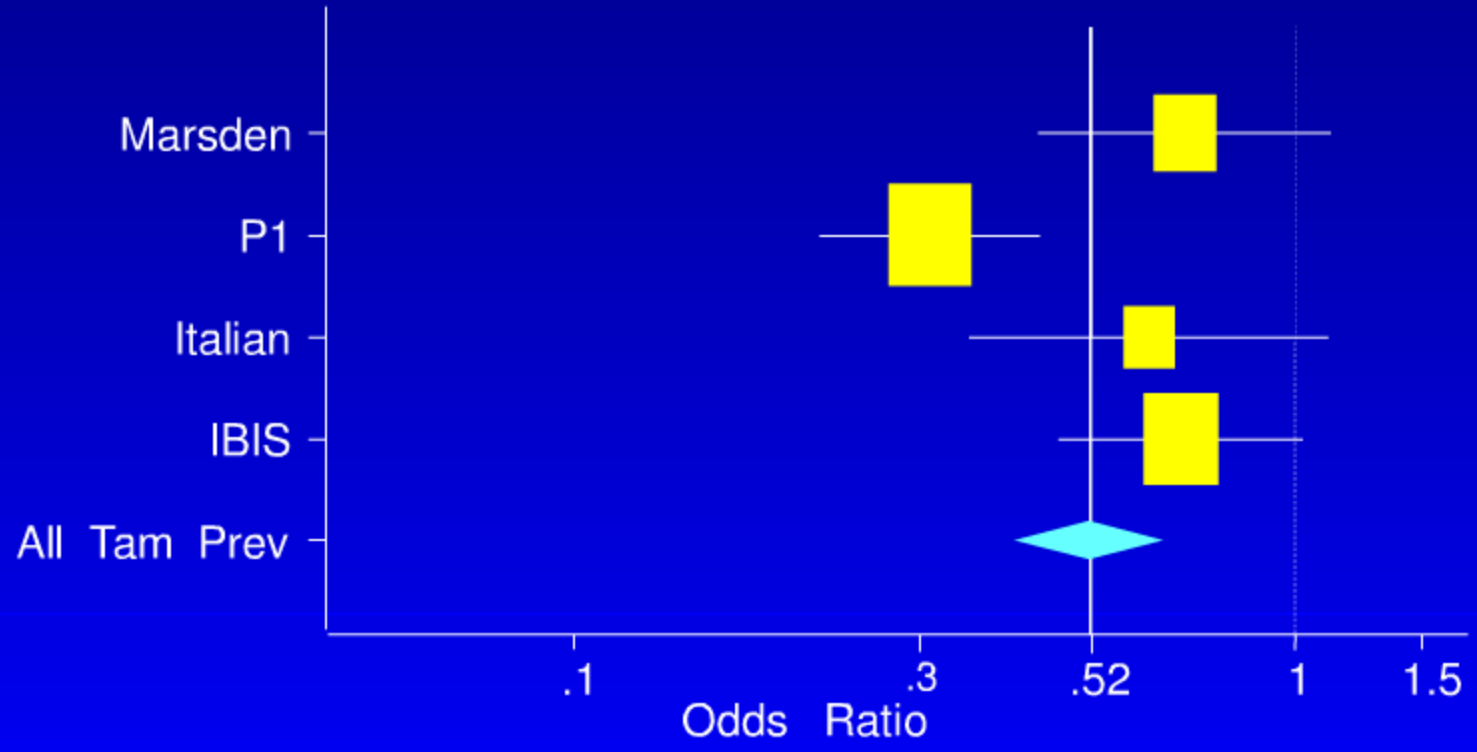
Figure 2. Sensitivity Analysis of Invasive Breast Cancers in Adherent Participants by Treatment Group



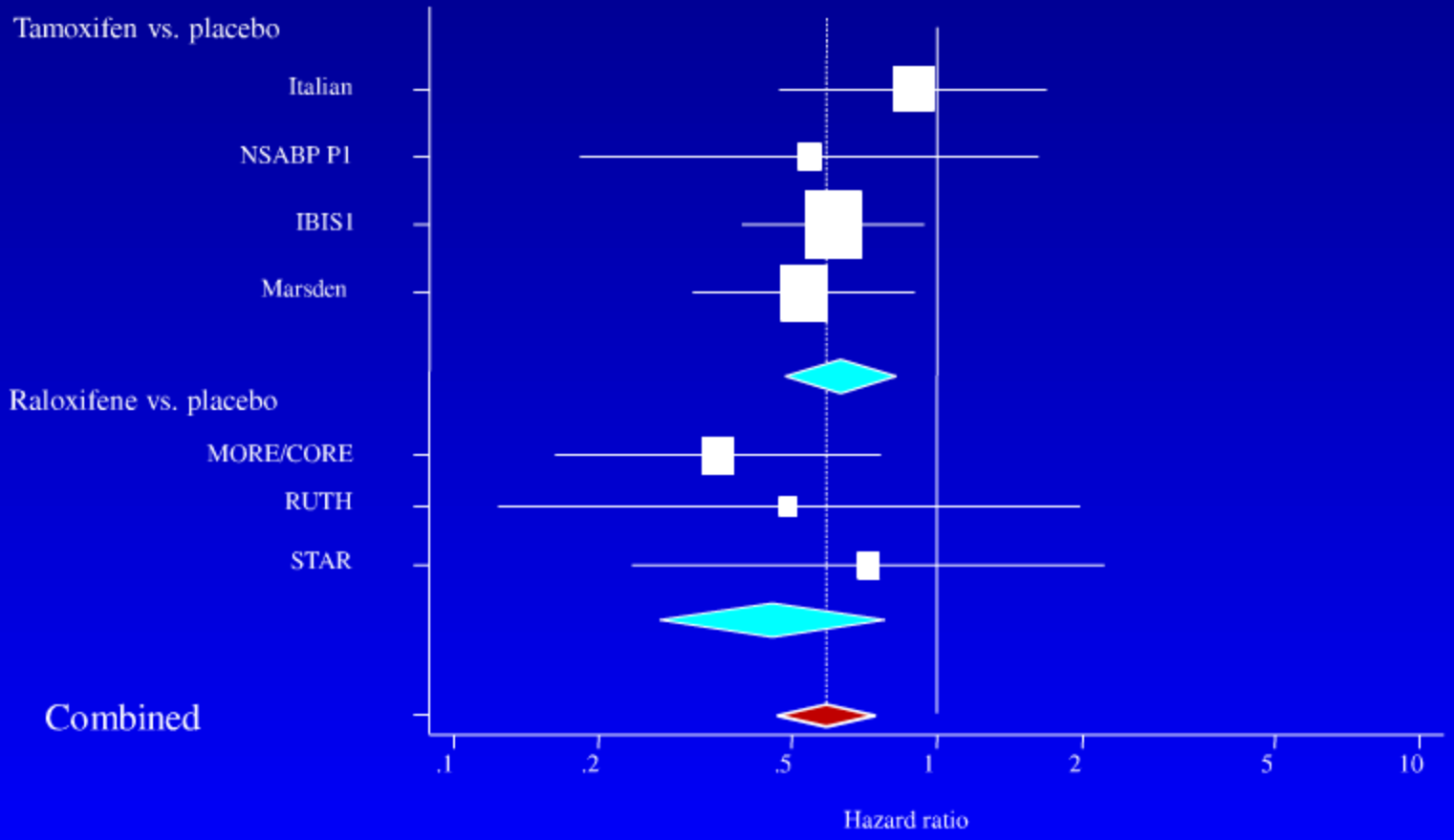
No. at Risk

Estrogen + Progestin	8506	6158	5195	4556	4013	2658	1305	565
Placebo	8102	6403	5562	4801	4230	2672	1199	415

Tamoxifen Overview : ER Positive
Invasive Breast Cancer



All ER+ Invasive breast cancers, 5-10y SERM vs. placebo

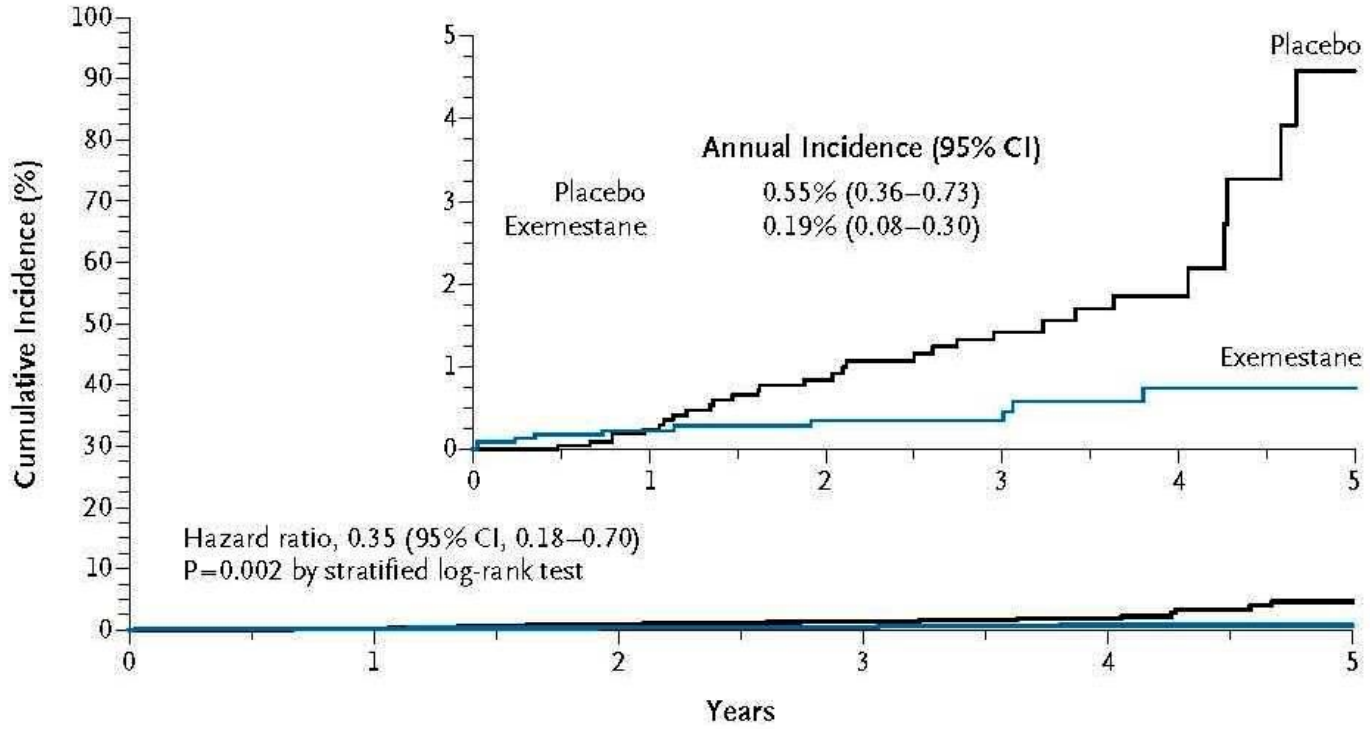


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2011 VOL. 364 NO. 25

Exemestane for Breast-Cancer Prevention in Postmenopausal Women

Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., José E. Alés-Martínez, M.D., Ph.D., Angela M. Cheung, M.D., Ph.D., Rowan T. Chlebowski, M.D., Ph.D., Jean Wactawski-Wende, Ph.D., Anne McTiernan, M.D., John Robbins, M.D., Karen C. Johnson, M.D., M.P.H., Lisa W. Martin, M.D., Eric Winquist, M.D., Gloria E. Sarto, M.D., Judy E. Garber, M.D., Carol J. Fabian, M.D., Pascal Pujol, M.D., Elizabeth Maunsell, Ph.D., Patricia Farmer, M.D., Karen A. Gelmon, M.D., Dongsheng Tu, Ph.D., and Harriet Richardson, Ph.D., for the NCIC CTG MAP.3 Study Investigators*



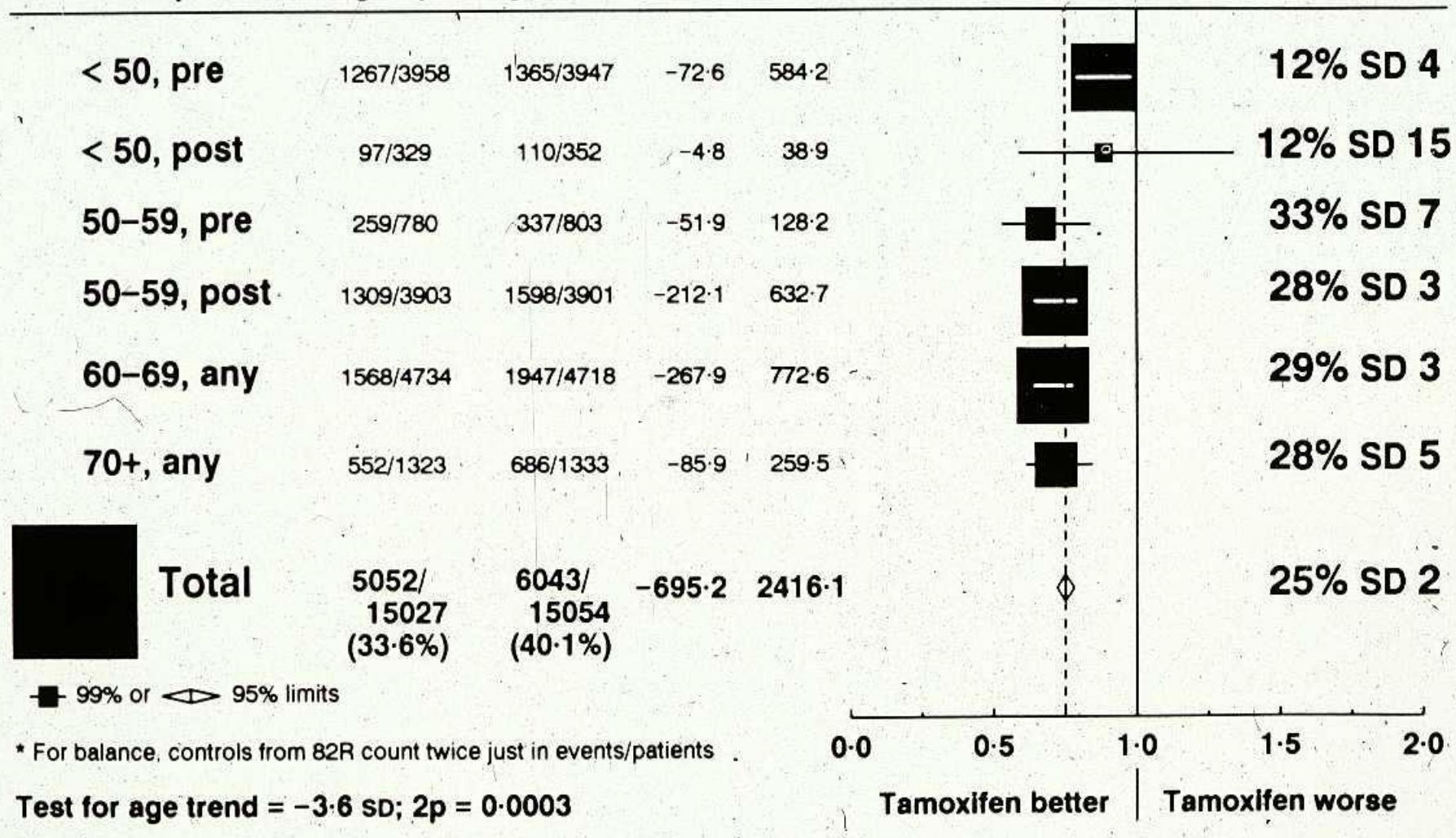
No. at Risk						
Placebo	2275	1905	1468	986	477	82
Exemestane	2285	1902	1468	980	464	77

Figure 1. Cumulative Incidence of Invasive Breast Cancer.

CI denotes confidence interval.

5R— Recurrence in tamoxifen trials

Age and menopause	Events / patients: Tam. group	Events / patients: Control group *	Tam. events: Obs. −Exp.	Tam. events: Var. of O−E	Annual odds of event: Ratio (& conf. limits), tamoxifen : control	Reduction (% & SD)
< 50, pre	1267/3958	1365/3947	−72·6	584·2		12% SD 4
< 50, post	97/329	110/352	−4·8	38·9		12% SD 15
50–59, pre	259/780	337/803	−51·9	128·2		33% SD 7
50–59, post	1309/3903	1598/3901	−212·1	632·7		28% SD 3
60–69, any	1568/4734	1947/4718	−267·9	772·6		29% SD 3
70+, any	552/1323	686/1333	−85·9	259·5		28% SD 5
Total	5052/15027 (33·6%)	6043/15054 (40·1%)	−695·2	2416·1		25% SD 2



* For balance, controls from 82R count twice just in events/patients

Test for age trend = −3·6 SD; 2p = 0·0003

Test for menop. trend = −2·8 SD; 2p = 0·006

Treatment effect 2p < 0·00001

Fig 5—Subtotals by age and menopausal status of tamoxifen trial results.

For explanation, see foot of fig 5M.

THE EXACT SAME THERAPY WHICH CAN PREVENT BREAST CANCER GIVEN BEFORE DIAGNOSIS AND CURE SOME PATIENTS IN THE ADJUVANT SETTING CURES NO ONE IN THE METASTATIC SETTING. WHY WILL ANY OTHER KIND OF THERAPY BE DIFFERENT ?

ESR1 Mutation in Breast Cancer

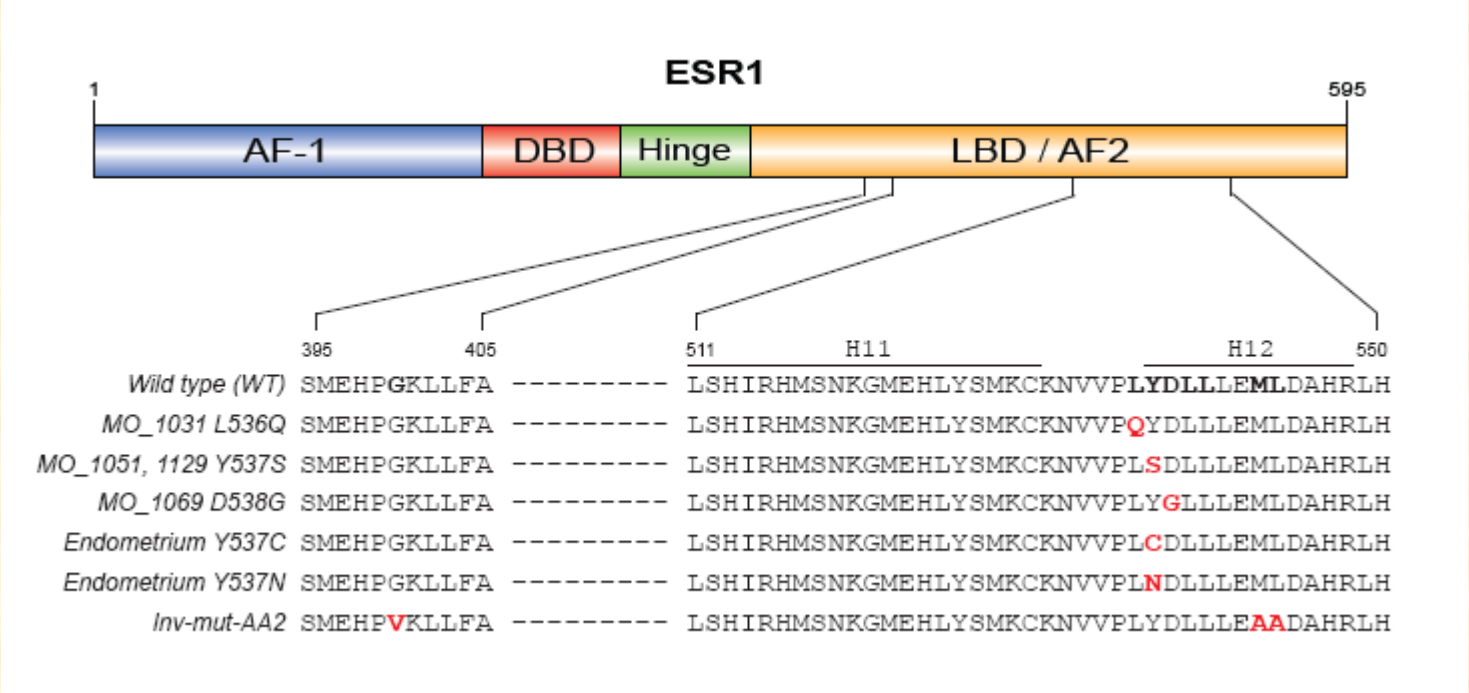
- NGS study of 249 breast cancers
- 12% frequency of ESR1 somatic mutations in relapsed ER+ breast cancer
- Primary tumors were ESR1 WT
- Pre-clinical models show ESR1 activation and resistance to endocrine therapy
- ESR1 mutation testing can explain hormonal therapy resistance and can personalize therapy selection in ER+ metastatic breast cancer

Jeselsohn R, Yelensky R, Buchwalter G et al. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor positive breast cancer. Clin Cancer Res. 2014 Jan 7.

ESR1 MUTATIONS

- Hypothesis
  - Prior Endocrine therapy selects for ESR1 variants
  - These variants:
    - Are still estrogen sensitive
    - But also estrogen independent
    - AIs no longer effective
  - Patients with ESR1 variants may respond to high doses of SERMs or SERDs.

Identification of Mutations in ESR1 in Patients with ER+ Metastatic Breast Cancer (and Endometrial Cancers)

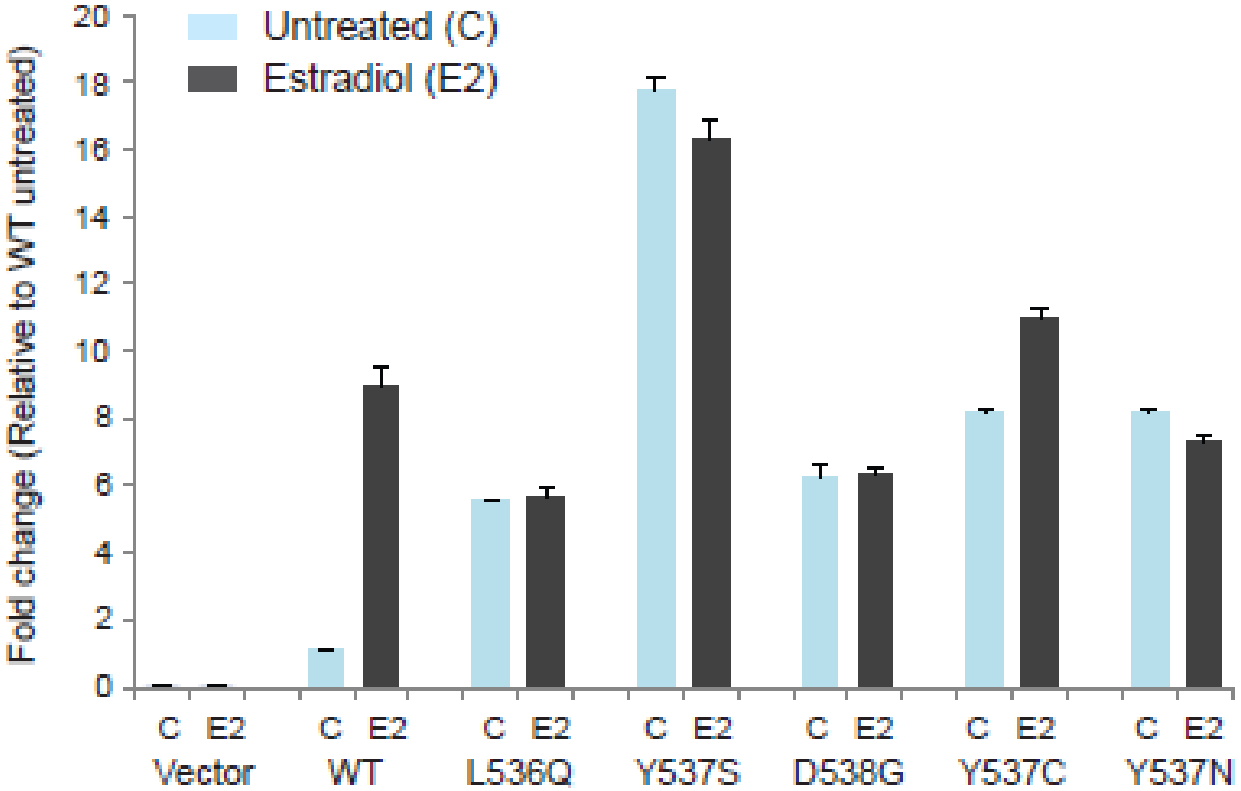


- First identified in 1997 Fuqua in a single patient with metastatic breast cancer treated with diethylstibesterol (but since then thought to be rare)
- 6 out of 11 ER+ metastatic breast cancer (all are post- aromatase Rx)
- Not in ER- breast cancers
- Not in ER+ tamoxifen only treated patients
- 4 of 373 endometrial cancers (from TCGA)

Robinson et al, *Nature Genetics* 2013

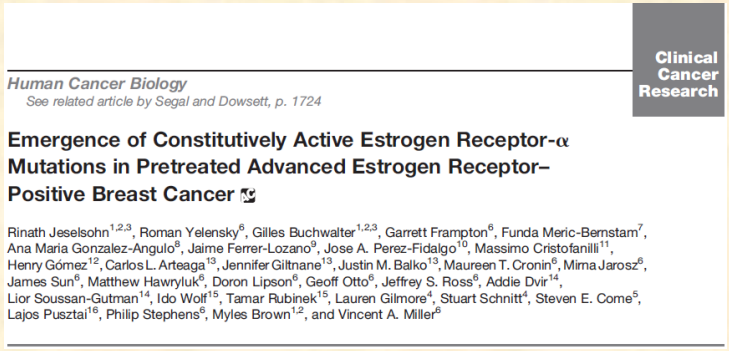
ESR1 Mutant Signaling Is Estrogen Independent

HEK-293T human embryonic kidney cells transfected with ESR (WT or Mutant)



Robinson, et al., Nat Genet 2013

ESR1 activating mutations are not present in primary tumors



Clinical Cancer Research

Human Cancer Biology

See related article by Segal and Dowsett, p. 1724

Emergence of Constitutively Active Estrogen Receptor-α Mutations in Pretreated Advanced Estrogen Receptor–Positive Breast Cancer

Rinath Jeselsohn[1,2,3], Roman Yelensky[6], Gilles Buchwalter[1,2,3], Garrett Frampton[6], Funda Meric-Bernstam[7], Ana Maria Gonzalez-Angulo[8], Jaime Ferrer-Lozano[9], Jose A. Perez-Fidalgo[10], Massimo Cristofanilli[11], Henry Gómez[12], Carlos L. Arteaga[13], Jennifer Giltnane[13], Justin M. Balko[13], Maureen T. Cronin[6], Mirna Jarosz[6], James Sun[6], Matthew Hawryluk[6], Doron Lipson[6], Geoff Otto[6], Jeffrey S. Ross[6], Addie Dvir[14], Lior Soussan-Gutman[14], Ido Wolf[15], Tamar Rubinek[15], Lauren Gilmore[4], Stuart Schnitt[4], Steven E. Come[5], Lajos Pusztai[16], Philip Stephens[6], Myles Brown[1,2], and Vincent A. Miller[6]

- 134 ER+ samples
  - 58 primary BCs
  - 76 metastatic samples
- 115 ER- samples
- 9/76 (12%) samples contained a somatic mutation in codon 537 or 538
- None of the primary tumors, treatment naïve ER+ cancers or ER- tumors harbored the mutation

Cancer Research

Priority Report

D538G Mutation in Estrogen Receptor-α: A Novel Mechanism for Acquired Endocrine Resistance in Breast Cancer

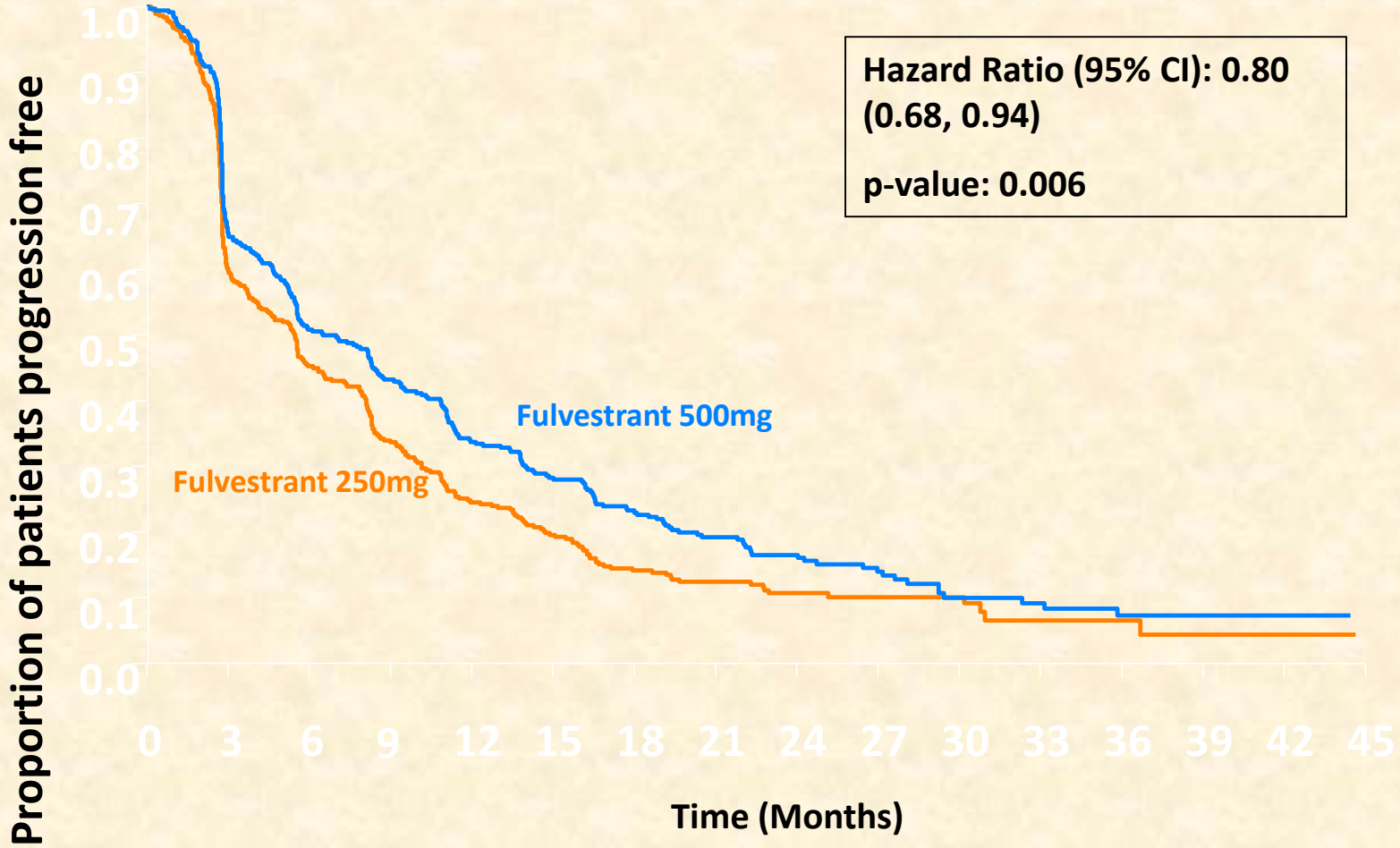
Keren Merenbakh-Lamin[1,2], Noa Ben-Baruch[5], Adva Yeheskel[3], Addie Dvir[6], Lior Soussan-Gutman[6], Rinath Jeselsohn[8], Roman Yelensky[9], Myles Brown[8], Vincent A. Miller[9], David Sarid[1], Shulamith Rizel[7], Baruch Klein[4], Tami Rubinek[1], and Ido Wolf[1,2]

- 13 ER+ samples
- 5/13 patients contained the D538G mutation in liver mets
- The mutation was not detected in the primary tumors prior to endocrine treatment

ESR1 MUTATIONS

- Conclusions
  - Uncommon in Primary Cancers
  - Appear to be selected by ET
  - Focused in Ligand Binding Domain
    - AA 536-538
  - Confer Ligand–independent Signaling
  - Remain dependent on ER signaling pathway
  - Resistance:
    - ?Absolute to E2 depletion (AI)
    - Relative to SERM/SERD

CONFIRM Study: PFS



Di Leo, et al., J Clin Oncol 28:4594-600, 2010

Conclusions

Somatic variants in ESR1 are common (~20%) in advanced metastatic BC.

Tumors with these mutation are signaling through the ER pathway

Tumors are resistant to endocrine therapies

A FEW CONCLUDING COMMENTS

- UNQUESTIONABLY THE NOTION THAT THERE IS ENORMOUS CANCER DIVERSITY IMPLIES THAT THERE MUST BE DIVERSE TREATMENTS.
- AND IT ALSO IMPLIES THAT IF WE COULD ONLY MIX AND MATCH THESE CORRECTLY TO OUR PATIENTS WE WOULD ACHIEVE GREAT THINGS.

A FEW CONCLUDING COMMENTS

- UNQUESTIONABLY THE NOTION THAT THERE IS ENORMOUS CANCER DIVERSITY IMPLIES THAT THERE MUST BE DIVERSE TREATMENTS.
- HOWEVER, GIVEN THE REMARKABLE NUMBER OF POTENTIALLY CONTRIBUTORY MUTATIONS AND THE [RELATIVELY] INFREQUENT NUMBER OF AGENTS TO TARGET THESE MUTATIONS AND GIVEN THE LACK OF DURABLE SUCCESS WHEN THOSE AVAILABLE AGENTS ARE USED [AT LEAST IN THE ADVANCED DISEASE SETTING] WE OBVIOUSLY HAVE A VERY LONG WAY TO GO BEFORE ‘’PERSONALIZED MEDICINE’’ IS THE REALITY WE WOULD ALL HOPE IT TO BE…..

A FEW CONCLUDING COMMENTS

- IT SEEMS TO ME WE ARE EITHER GOING TO HAVE TO FIGURE OUT FEASIBLE STRATEGIES TO VALIDATE THESE THERAPIES EARLIER IN THE CLINICAL COURSE, **OR,**
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