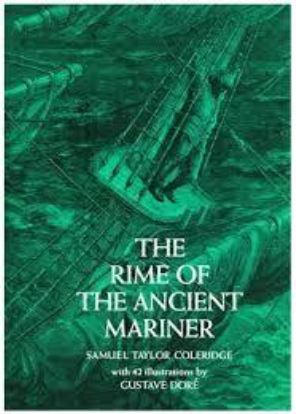
MADRID 2014 ESMO congress

ICR The Institute of Cancer Research

THE ROYAL MARSDEN

Targets, Targets everywhere but not a drug to give…..



Dr Udai Banerji FRCP, PhD

Reader in Molecular Cancer Pharmacology

The Institute of Cancer Research / The Royal Marsden Hospital

ESMO 2014

NHS National Institute for Health Research

ECMC

CANCER RESEARCH UK

Disclosure slide

- I will discuss the use of unlicensed anti-cancer agents

Outline of the talk

- Pre-clinical perceptions
- History of development of targeted treatment
- Challenges of personalized medicine today
- New realities in early clinical trials
- What next?

MADRID 2014 ESMO congress

Preclinical perspectives

Biological space

Chemical space

Drug like Chemistry Space = 10^{20}

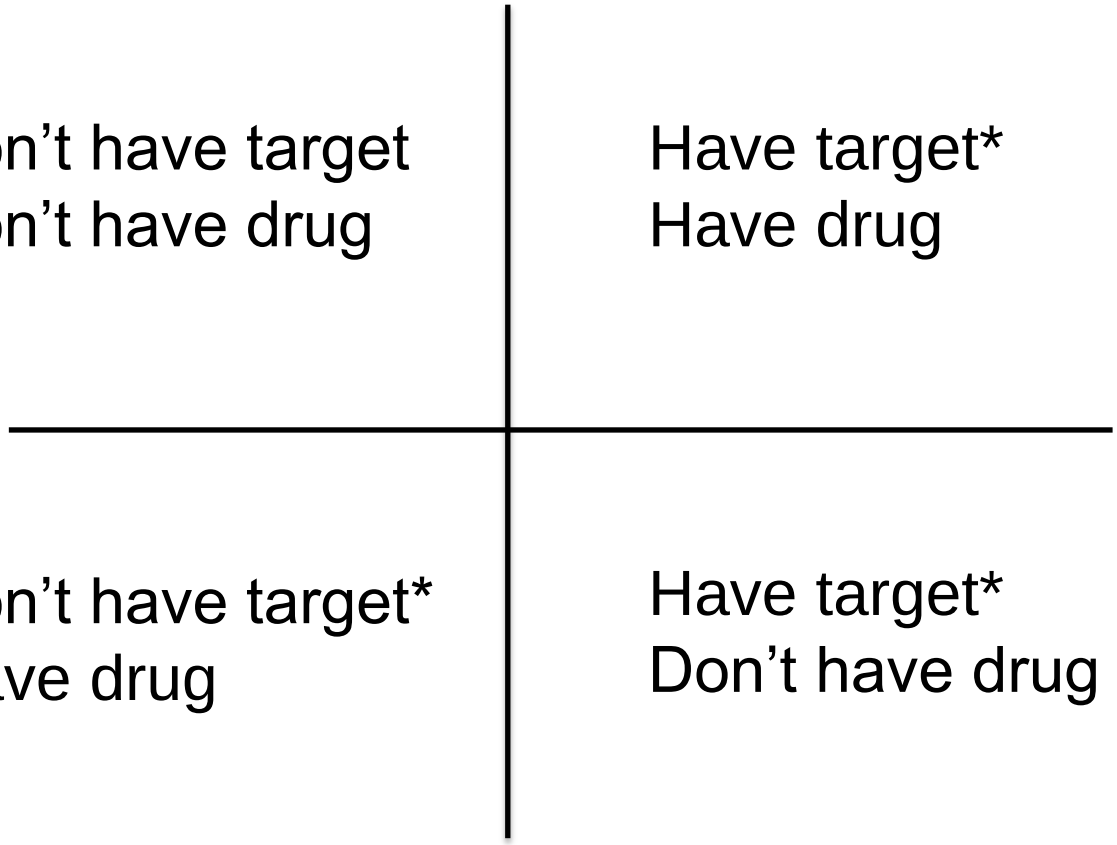
CAS Registry = 35,289,950

Patel MN, Nat Rev Drug Disc 2013:1:35-50

Outline of the talk

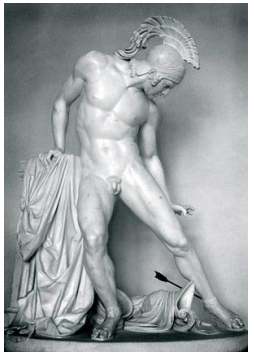
- Pre-clinical perceptions
- History of development of targeted treatment
- Challenges of personalized medicine today
- New realities in early clinical trials
- What next?

History of development of targeted treatment



* = target that drives the cancer

MADRID 2014 ESMO congress



Have drug and have target*

RTK

PI3K RAS

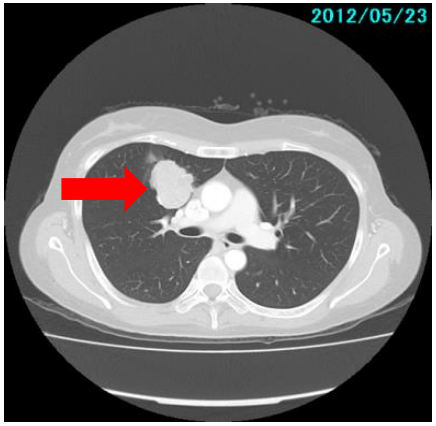
AZD5363 AKT RAF

m-TOR MEK

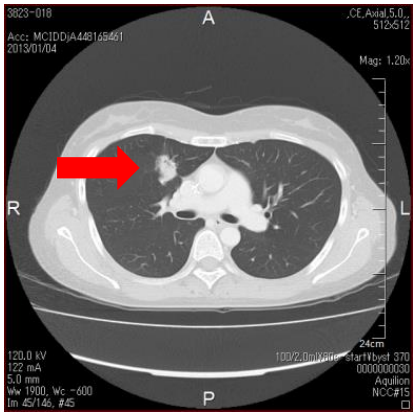
RO5126766

S6 ERK

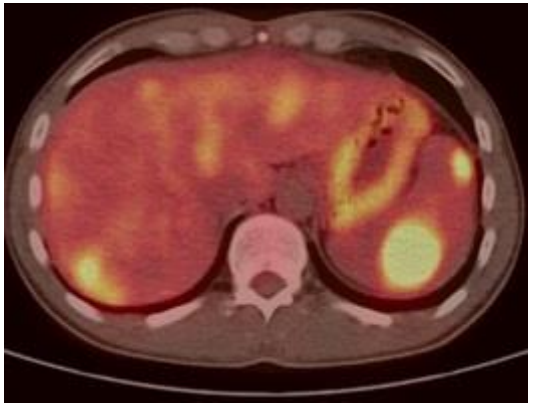
Pre-treatment



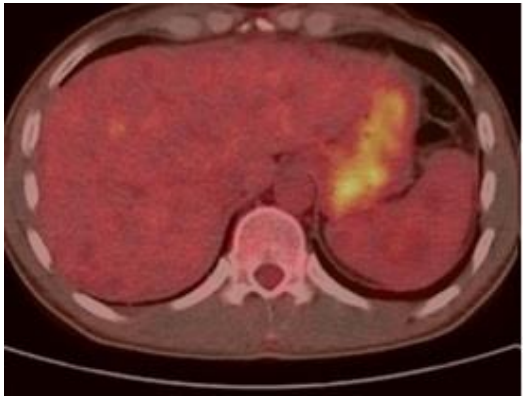
Post-treatment



Pre-treatment



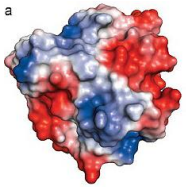
Post-treatment



Banerji U , AACR 2013 # LB66

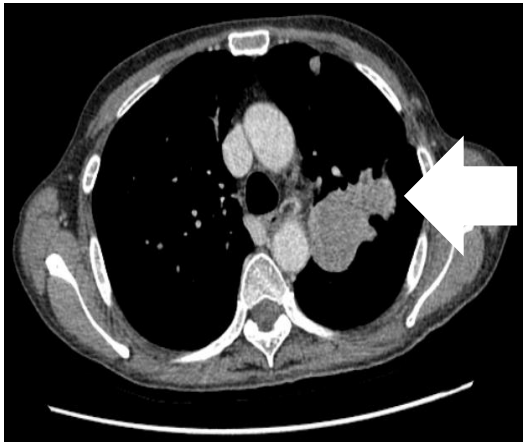
Banerji U , Soria JC Clin Cancer Res 2010, 16:1613-23

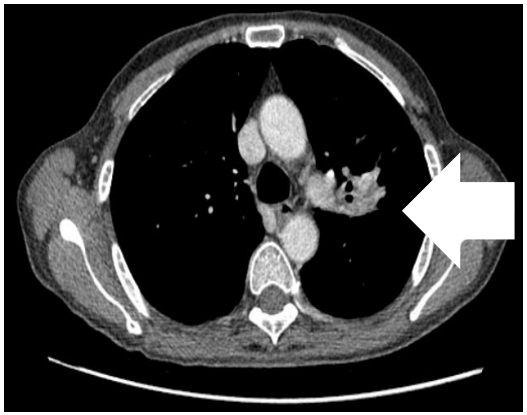
MADRID 2014 ESMO congress

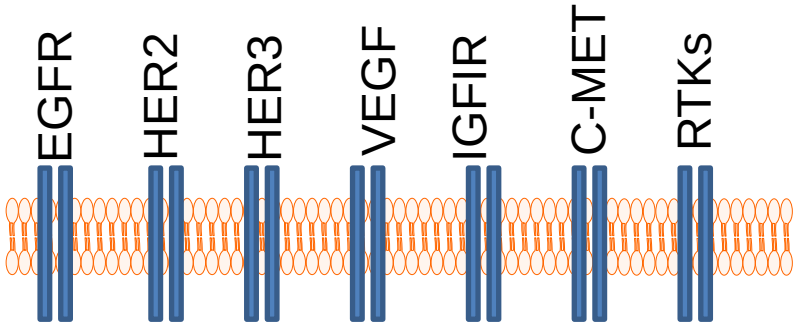


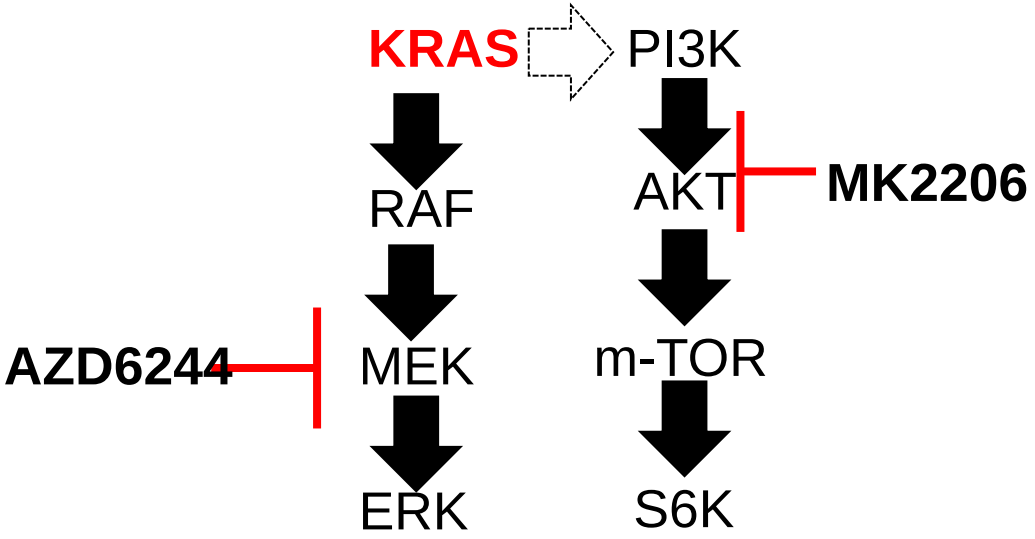
KRAS

Have a target*-don't have a drug…yet!





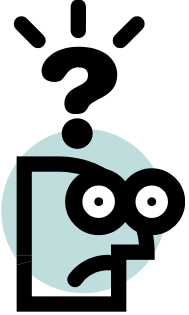


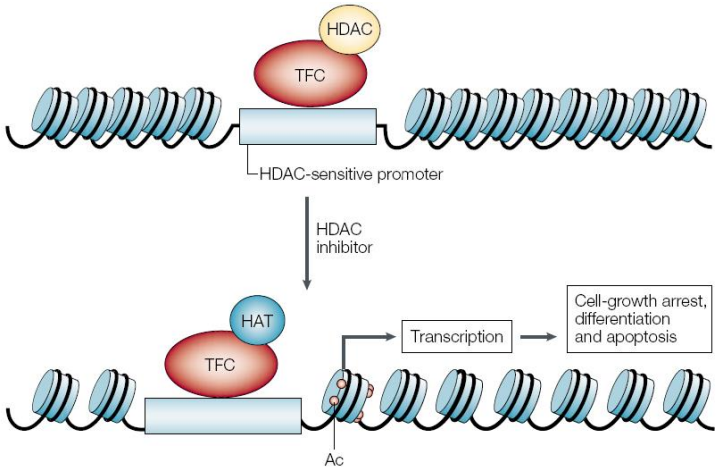


Tolcher A, De Bono J # 3004 ASCO 2011

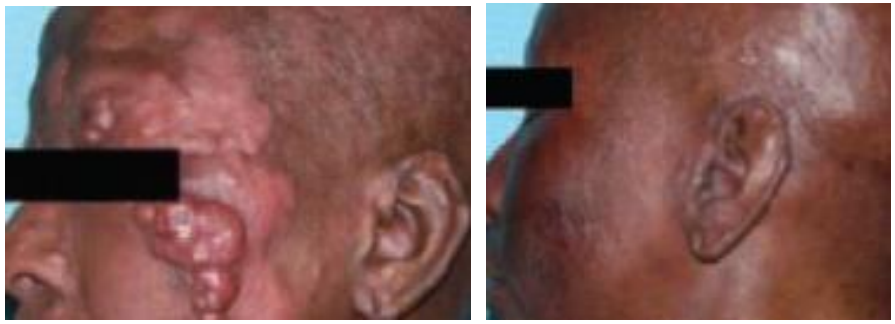
MADRID 2014 ESMO congress

Don’t have target*-Have drug

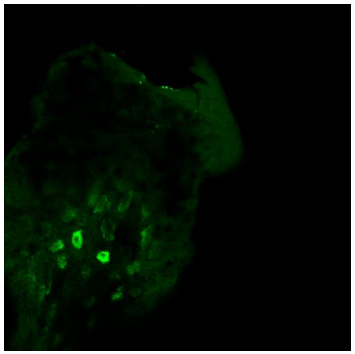




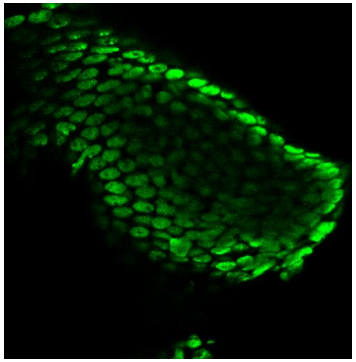
Histone acetylaton

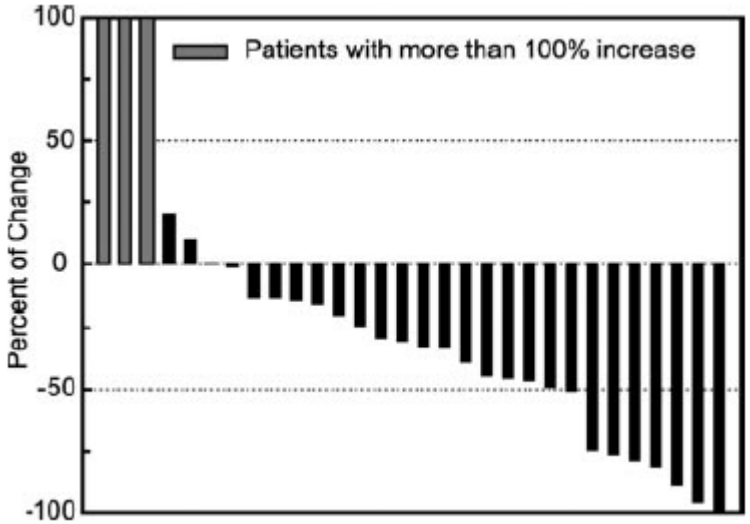


Pre Rx



Post Rx





Venugopal, Banerji Clin Cancer Res 2013, 19:4262-72

Duvic, M Blood 2007,109:31-9

Outline of the talk

- Pre-clinical perceptions
- History of development of targeted treatment
- Challenges of personalized medicine today
- New realities in early clinical trials
- What next?

When and where do we measure?

1996 – ER+V, HER2-VE breast cancer
Surgery→ FEC→tamoxifen
Nov 2004 – Zoladex+anastrozole
Jan 2007 – HER2+ve disease
Trastuzumab+docetaxel
Jan 2009 – Trastuzumab + letrozole
April 2009 – Lapatinib + capecitabine
April 2010 – AUY922
June 2010 – *PIK3CA* mutation

^{18}FDG PET

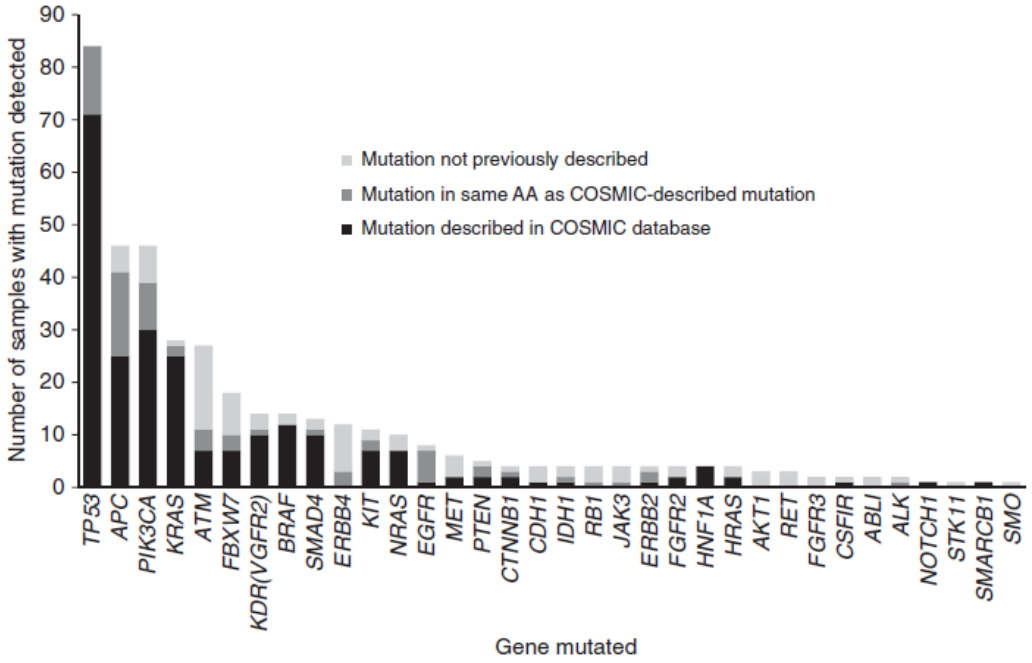
^{89}Zr-Trastuzumab PET

- **Intratumoral heterogeneity in time : Differences in genotype over time**
- **Intratumoral heterogeneity in space : Differences in genotype at one given time**

Gaykema SB, Schroder, Banerji Clin Cancer Res 2014,15:3945-54

MADRID 2014 ESMO congress

How do you interpret the data?



Sample ID	Mutations detected by Illumina MiSeq TSACP	Mutations detected by IT-PGM AmpliSeq Cancer Panel	Mutation concordance (%)
11/6	*MET* T992I (52%)	*MET* T992I (47%)	100
11/43	*NRAS* G12D (13%); *TP53* R213* (41%); *APC* K146fs*6 (25%)	*NRAS* G12D (22%); *TP53* R213* (53%); *APC* K146fs*6 (31%)	100
11/222	*PIK3CA* E545K (18%)	*PIK3CA* E545K (20%)	100
11/251	*KRAS* G12D (51%)	*KRAS* G12D (54%)	100
11/269	*MET* N375S (100%)	*MET* N375S (50%)	100
12/195	*EGFR* E746_A750 del (40%); *TP53* V274F (40%); *FGFR2* R255Q (5%)	*EGFR* E746_A750 del (34%), *TP53* V274F (36%)	66
12/374	*SMAD4* P356S (8%)	None	0
12/481	None	None	100
12/535	None	None	100
12/574	*APC* E1544* (64%); *BRAF* V600E (38%)	*APC* E1544* (66%); *BRAF* V600E (36%)	100
12/575	*KRAS* G12V (47%); *TP53* Y234H (68%)	*KRAS* G12V (34%); *TP53* Y234H (50%)	100
12/576	*APC* A1492fs*15 (46%); *KRAS* G12V (47%); *TP53* R248E (35%); *TP53* R158fs*11 (51%)	*APC* A1492fs*15 (40%); *KRAS* G12V (45%); *TP53* R248E (33%); *TP53* R158fs*11 (52%)	100

- ***Is it the driver?***
- ***Functional ?***
- ***Context specificity?***
- ***Depth of sequencing?***
- ***Allele frequency?***

Ong, M BJC, 2104,11:828-36

MADRID 2014 ESMO congress

How do you interpret the data?

FOUNDATION MEDICINE®

Partner Subject ID | Report Date | Diagnosis

Appendix:

About the Test:

Foundation Medicine Test was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). The Test has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. The Test may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

Diagnostic Significance/Lack of Significance of Reported Biomarkers: Foundation Medicine's Test identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test identifies biomarkers that lack detectable evidence of cancer- associated alterations. These alterations (and, in some cases, lack of alterations) are reported to a patient's treating physician in this report (Report).

Genes Assayed in T5a:

ABL1	GID4	CUL4B	FGF23	IRF4	MSH6	PDGFRA	RUNX1	WISP3
AKT1	CARD11	CYP17A1	FGF3	IRS2	MTOR	PDGFRB	RUNX1T1	WT1
AKT2	CASP8	DAXX	FGF4	JAK1	MUTYH	PDK1	SETD2	WTX
AKT3	CBFB	DDR2	FGF6	JAK2	MYC	PIK3C2G	SF3B1	XPO1
ALK	CBL	DIS3	FGF7	JAK3	MYCL1	PIK3C3	SH2B3	XRCC3
ALOX12B	CCND1	DNMT3A	FGFR1	JUN	MYCN	PIK3CA	SMAD2	ZNF217
APC	CCND2	DOT1L	FGFR2	KDM5A	MYD88	PIK3CG	SMAD4	ZNF703
APCDD1	CCND3	EGFR	FGFR3	KDM5C	MYST3	PIK3R1	SMARCA4	
AR	CCNE1	EMSY	FGFR4	KDM6A	NBN	PIK3R2	SMARCB1	
ARAF	CD79A	EP300	FLT1	KDR	NCOR1	PMS2	SMARCD1	
ARFRP1	CD79B	EPHA3	FLT3	KEAP1	NF1	PNRC1	SMO	
ARID1A	CDC73	EPHA5	FLT4	KIT	NF2	PPP2R1A	SOCS1	
ARID2	CDH1	EPHB1	FOXL2	KLHL6	NFE2L2	PRDM1	SOX10	
ASXL1	CDK12	ERBB2	GATA1	KRAS	NFKBIA	PRKAR1A	SOX2	
ATM	CDK4	ERBB3	GATA2	LMO1	NKX2-1	PRKDC	SPEN	
ATR	CDK6	ERBB4	GATA3	LRP1B	NOTCH1	PRSS8	SPOP	
ATRX	CDK8	ERG	GNA11	MAP2K1	NOTCH2	PTCH1	SRC	
AURKA	CDKN1B	ESR1	GNA13	MAP2K2	NOTCH3	PTEN	STAG2	
AURKB	CDKN2A	EZH2	GNAQ	MAP2K4	NOTCH4	PTPN11	STAT4	
AXL	CDKN2B	FAM46C	GNAS	MAP3K1	NPM1	RAD50	STK11	
BACH1	CDKN2C	FANCA	GPR124	MAP3K13	NRAS	RAD51	SUFU	
BAP1	CEBPA	FANCC	GRIN2A	MCL1	NSD1	RAD51B	SYK	
BARD1	CHEK1	FANCD2	GSK3B	MDM2	NTRK1	RAD51C	TBX3	
BCL2	CHEK2	FANCE	HGF	MDM4	NTRK2	RAD51D	TET2	
BCL2L2	CHUK	FANCF	HLA-A	MED12	NTRK3	RAD52	TGFBR2	
BCL6	CIC	FANCG	HRAS	MEF2B	NUP93	RAD54L	TIPARP	
BCOR	CRBN	FANCI	IDH1	MEN1	PAK3	RAF1	TNFAIP3	
BCORL1	CREBBP	FANCL	IDH2	MET	PAK7	RARA	TNFRSF14	
BLM	CRKL	FANCM	IGF1	MITF	PALB2	RB1	TOP1	
BRAF	CRLF2	FAT3	IGF1R	MLH1	PARP1	REL	TP53	
BRCA1	CSF1R	FBXW7	IGF2	MLL	PARP2	RET	TRRAP	
BRCA2	CTCF	FGF10	IKBKE	MLL2	PARP3	RICTOR	TSC1	
BRIP1	CTNNA1	FGF12	IKZF1	MPL	PARP4	RNF43	TSC2	
BTG1	CTNNB1	FGF14	IL7R	MRE11A	PAX5	RPA1	TSHR	
BTK	CUL4A	FGF19	INHBA	MSH2	PBRM1	RPTOR	VHL	

Select Rearrangements:

ALK	BRAF	ETV4	EWSR1	NTRK1	RARA	TMPRSS2
BCL2	EGFR	ETV5	MLL	PDGFRA	RET	
BCR	ETV1	ETV6	MYC	RAF1	ROS1	

FOUNDATION MEDICINE®

Partner Subject ID | Report Date | Diagnosis

FMI Partner:	**Partner Sample ID:**	**Date Received:**
Partner Study #:	**FMI Sample ID:**	**FMI Study #:**

About the Test:

The Foundation Medicine test is a next-generation sequencing (NGS) based assay which identifies genomic alterations within hundreds of cancer-related genes. Only known cancer related variants, not variants of unknown significance, are reported. T5a test was utilized (Please see attached.)

Specimen Description (Provided by the Partner):

Tumor Type:	**Specimen Type:**	**Date Collected:**
Gender:	**Date of Birth:**	**Initials:**

Note: This is a QUALIFIED report. This specimen failed to meet minimum performance standards following sequencing due to factors such as low tumor content or sub-standard sequence coverage. We can confirm the presence of the genomic alterations detailed in this report, but we cannot confirm the absence of other alterations.

Cancer Related Alterations Identified:

Gene	Alteration
KRAS	G12V
SMAD4	R445*
RB1	E837*

MADRID 2014 ESMO congress

How do you interpret the data?

MI PROFILE™
Molecular Intelligence Tumor Report

CARIS™ LIFE SCIENCES

Agents Associated with Potential BENEFIT

Agents	Test	Method	Result	Value†	Clinical Association: Potential Benefit	Clinical Association: Decreased Potential Benefit	Clinical Association: Lack of Potential Benefit	Data Level*	Reference
vemurafenib	BRAF	Next Gen SEQ	Pathogenic	V600E					1, 2
	BRAF	qPCR	V600E	Mutated	✓			●	1, 2
cisplatin, carboplatin	ERCC1	IHC	Negative	1+ 10%	✓			◐	5, 6, 7, 8
docetaxel, paclitaxel	PGP	IHC	Negative	0+ 100%	✓			○	14, 15
	TLE3	IHC	Negative	0+ 100%		✓		◐	13
	TUBB3	IHC	Negative	2+ 5%	✓			◐	9, 10, 11, 12
nab-paclitaxel	SPARC Monoclonal	IHC	Positive	2+ 30%	✓			◐	22, 23
	SPARC Polyclonal	IHC	Negative	2+ 10%		✓		◐	22, 23
everolimus, temsirolimus	PIK3CA	Next Gen SEQ	Wild Type						24, 25, 26
	PTEN	IHC	Negative	0+ 100%	✓			◐	24, 25, 26
fluorouracil, capecitabine, pemetrexed	TS	IHC	Negative	1+ 1%	✓			◐	34, 35, 36
gemcitabine	RRM1	IHC	Negative	2+ 2%	✓			◐	37
irinotecan	TOPO1	IHC	Positive	2+ 80%	✓			◐	44, 45, 46

*The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The data level of each biomarker-drug interaction is the average level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

● = Greater level of evidence
◐ = Intermediate level of evidence
○ = Lower level of evidence

† Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.

MI PROFILE™
Molecular Intelligence Tumor Report

CARIS™ LIFE SCIENCES

Agents Associated with Potential LACK OF BENEFIT

Agents	Test	Method	Result	Value†	Clinical Association: Potential Benefit	Clinical Association: Decreased Potential Benefit	Clinical Association: Lack of Potential Benefit	Data Level*	Reference
temozolomide, dacarbazine	MGMT	IHC	Positive	1+ 40%			✓	◐	3, 4
imatinib	c-KIT	Next Gen SEQ	Wild Type				✓	◐	16, 17, 18
	PDGFRA	Next Gen SEQ	Wild Type				✓	◐	19, 20, 21
sunitinib	c-KIT	Next Gen SEQ	Wild Type				✓	◐	16, 17, 18
trastuzumab	Her2/Neu	CISH	Not Amplified	1.19			✓	●	27, 28, 29, 30
	Her2/Neu	IHC	Negative	0+ 100%			✓	●	27, 28, 29
lapatinib	Her2/Neu	CISH	Not Amplified	1.19			✓	●	30, 31, 32, 33
	Her2/Neu	IHC	Negative	0+ 100%			✓	●	31, 32, 33
doxorubicin, liposomal-doxorubicin, epirubicin	Her2/Neu	CISH	Not Amplified	1.19			✓	●	38, 39
	PGP	IHC	Negative	0+ 100%		✓		◐	42, 43
	TOP2A	IHC	Negative	1+ 2%			✓	◐	40, 41

*The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The data level of each biomarker-drug interaction is the average level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

● = Greater level of evidence
◐ = Intermediate level of evidence
○ = Lower level of evidence

† Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.

Outline of the talk

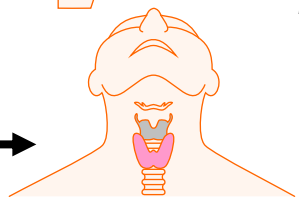
- Pre-clinical perceptions
- History of development of targeted treatment
- Challenges of personalized medicine today
- New realities in early clinical trials
- What next?

Clinical trial design- BASKET TRIALS-non single arm

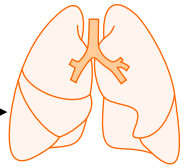
V600E *BRAF* mutation

BRAF inhibitor

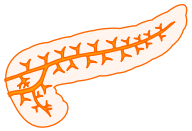
melanoma



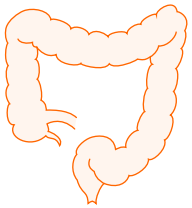
thyroid



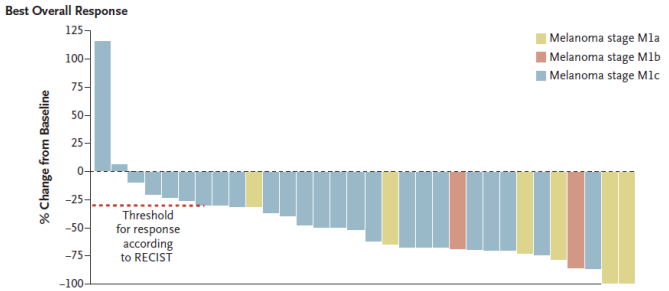
NSCLC

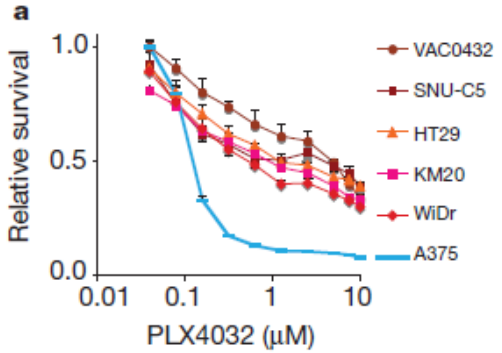


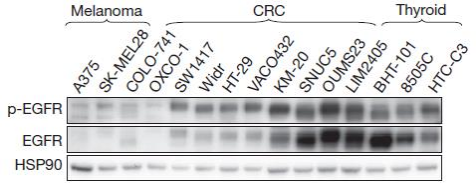
Biliary duct



Colon







Flaherty K. NEJM 2010 363: 809-19

Prahallad , Bernards Nature 2012, 483: 100-104

MADRID 2014 ESMO congress

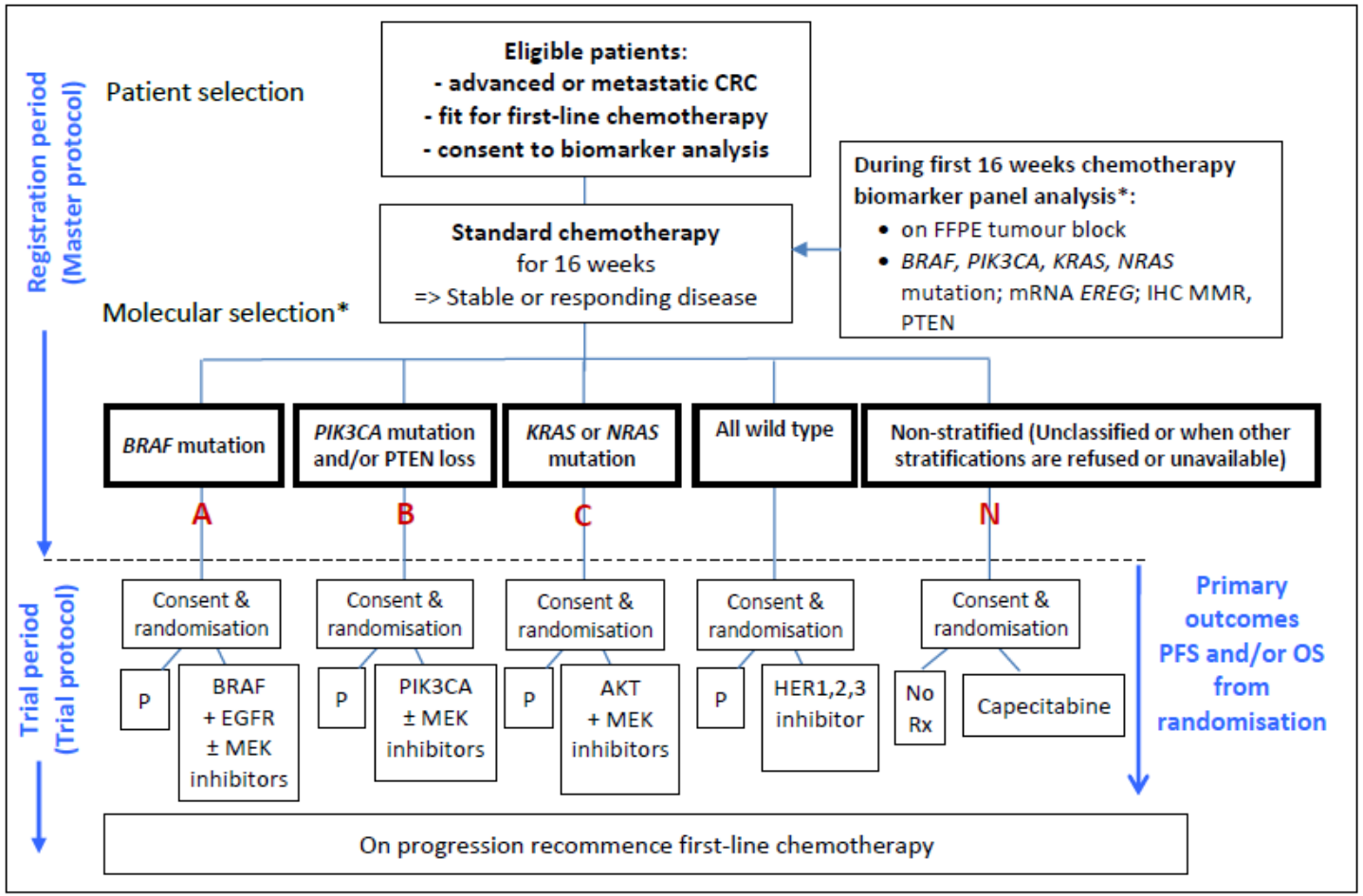
Clinical trial design- SHIVA- all tumour types- randomized

Table 1. Treatment algorithm in the experimental arm

Targets	Molecular abnormalities	Molecularly targeted agents
KIT, ABL1/2, RET	Activating mutation or amplification[a]	Imatinib 400 mg qd PO
PI3KCA, AKT1	Activating mutation or amplification	Everolimus 10 mg qd PO
AKT2,3, mTOR, RAPTOR, RICTOR	Amplification	Everolimus 10 mg qd PO
PTEN	Homozygous deletion or heterozygous deletion + inactivating mutation or heterozygous deletion + IHC confirmation	Everolimus 10 mg qd PO
STK11	Homozygous deletion or heterozygous deletion + inactivating mutation	Everolimus 10 mg qd PO
INPP4B	Homozygous deletion	Everolimus 10 mg qd PO
BRAF	Activating mutation or amplification	Vemurafenib 960 mg bid PO
PDGFRA/B, FLT3	Activating mutation or amplification	Sorafenib 400 mg bid PO
EGFR	Activating mutation or amplification	Erlotinib 150 mg qd PO
ERBB2/HER2	Activating mutation or amplification	Lapatinib 1000 mg qd PO + Trastuzumab 8 mg kg^{-1} IV followed by 6 mg kg^{-1} IV q3w
SRC	Activating mutation or amplification	Dasatinib 70 mg bid PO
EPHA2, LCK, YES1	Amplification	Dasatinib 70 mg bid PO
ER, PR	Protein expression >10%	Tamoxifen 20 mg qd PO (or letrozole 2.5 mg qd PO if contra-indication)
AR	Protein expression >10%	Abiraterone 1000 mg qd PO

Le Tourneau, C BJC 2014,111:17-243

Clinical trial design-FOCUS 4- tumour type specific (CRC)-randomized

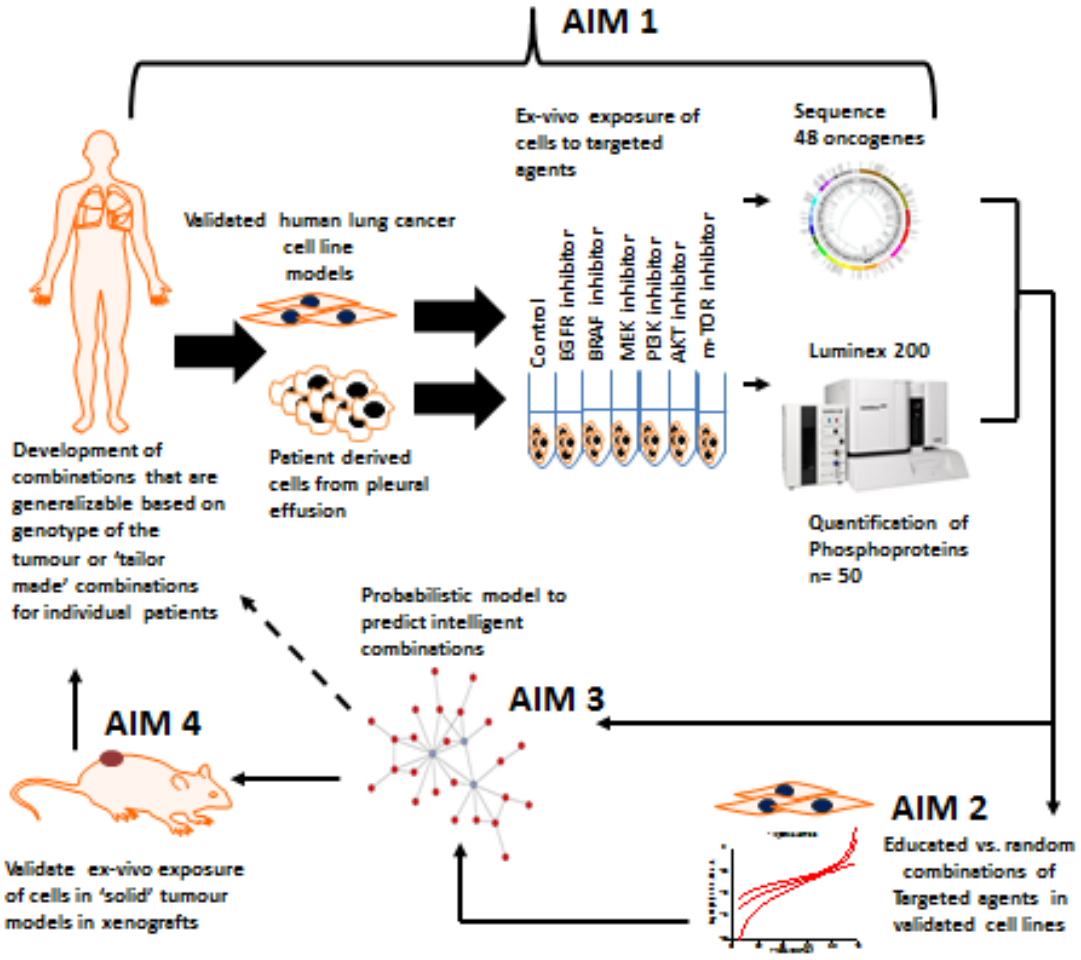


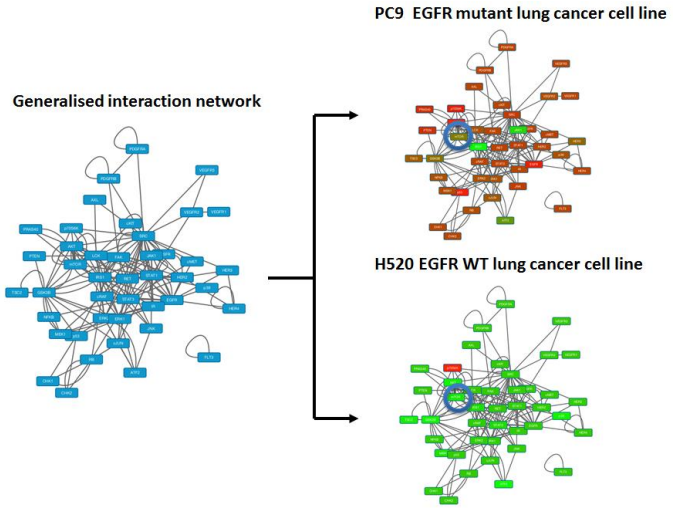
Outline of the talk

- Pre-clinical perceptions
- History of development of targeted treatment
- Challenges of personalized medicine today
- New realities in early clinical trials
- What next?

MADRID 2014 ESMO congress

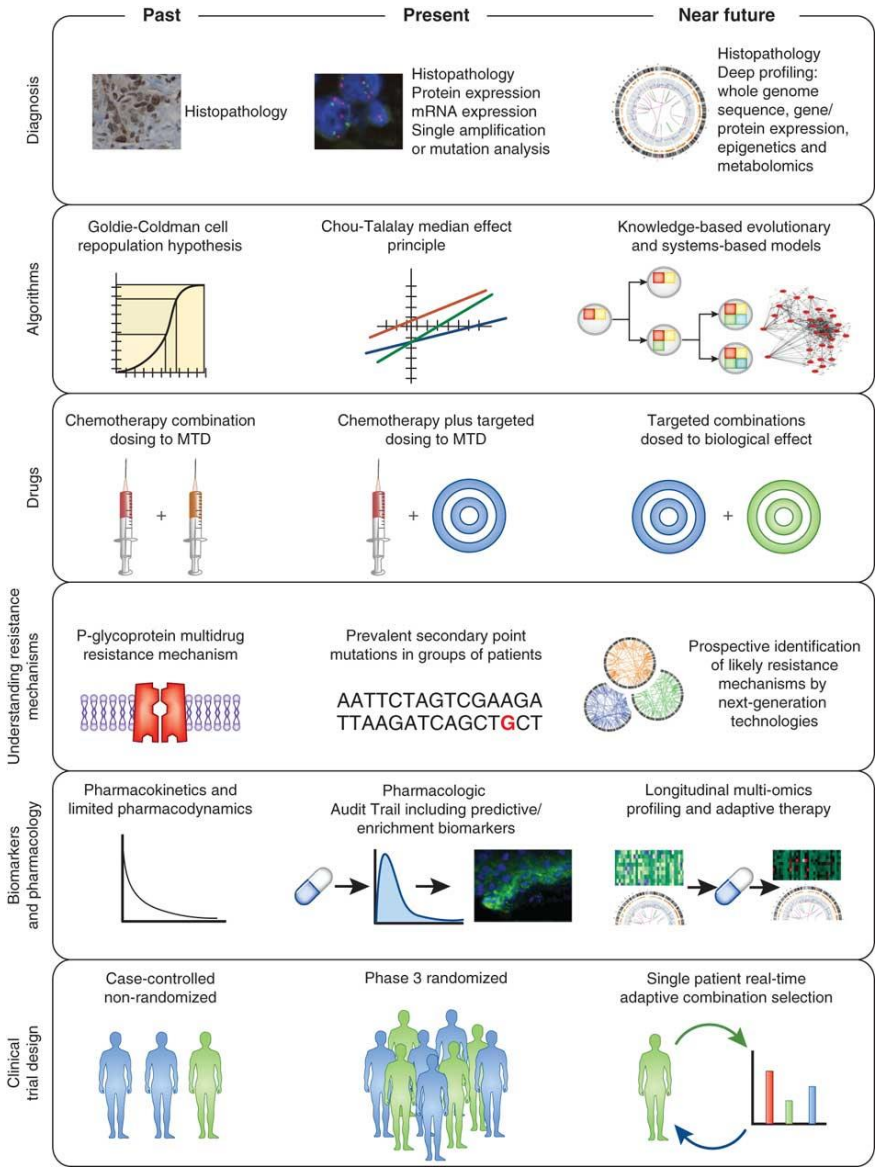
What next?





- **Attempt to integrate functional aspects of genomic data**
- **Understand dynamic biological changes to suggest intelligent combinations or sequences**
- **Be smart, cant solve this by brute force**

MADRID 2014 ESMO congress



Future of cancer treatment

- Interrogate more biological and chemical space to discover new anticancer drugs
- Biological basis of drivers of cancer and mechanisms of clinical resistance will be better understood
- Longitudinal assessment of biomarkers will change clinical trial design
- Drug combinations will be critically important

Al-Lazikani, Banerji, Workman
Nature Biotech 2012, 30:672-692

MADRID 2014 ESMO congress

Acknowledgements

ICR The Institute of Cancer Research

CANCER RESEARCH UK

THE ROYAL MARSDEN

ECMC

NHS National Institute for Health Research