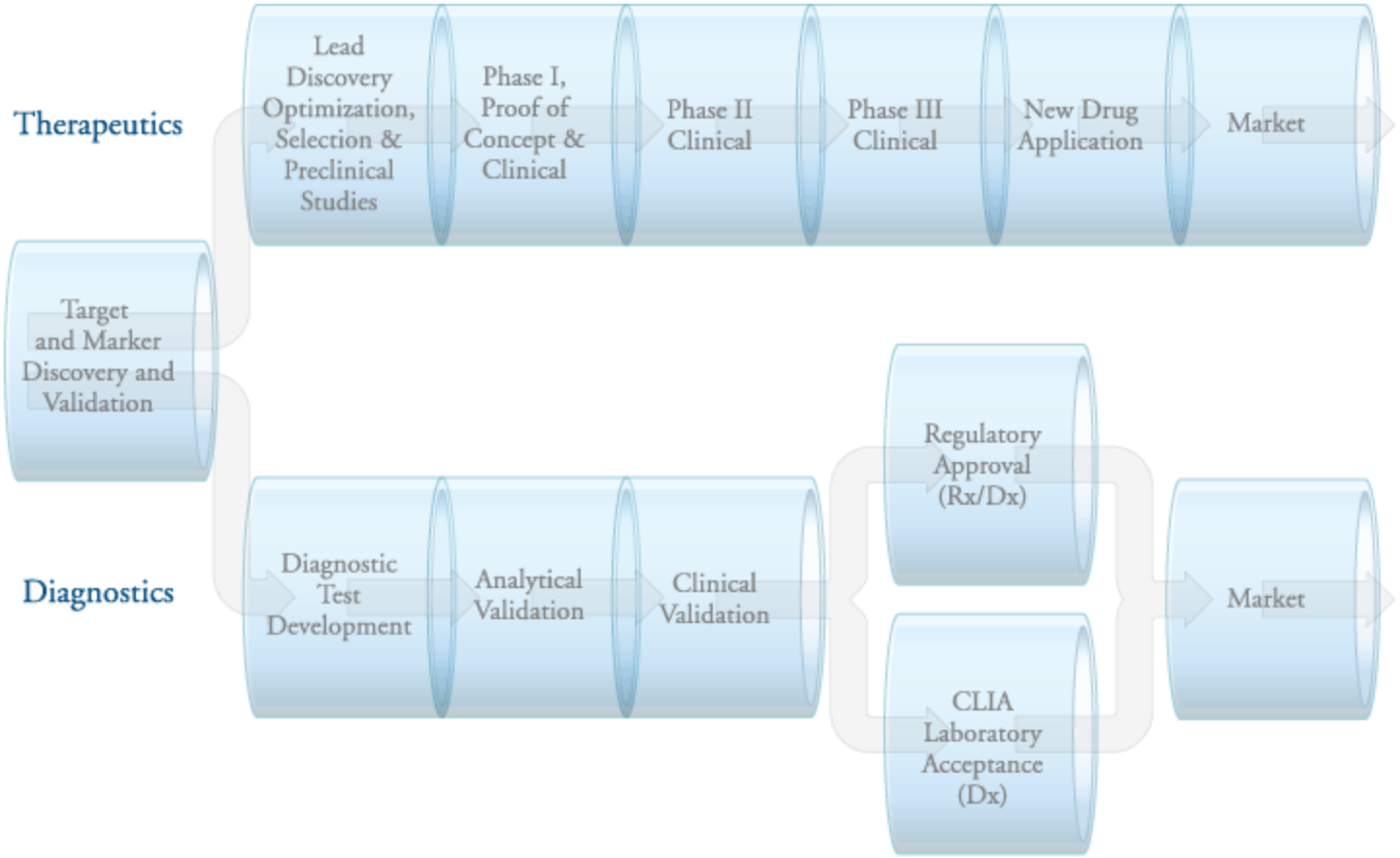
Clinical research in small patient populations: the investigator point of view

Jordi Rodon

VHIO VALL D'HEBRON Institute of Oncology

Clinical research in small patient populations: the investigator point of view

CoDevelopment of Diagnostics and Therapeutics



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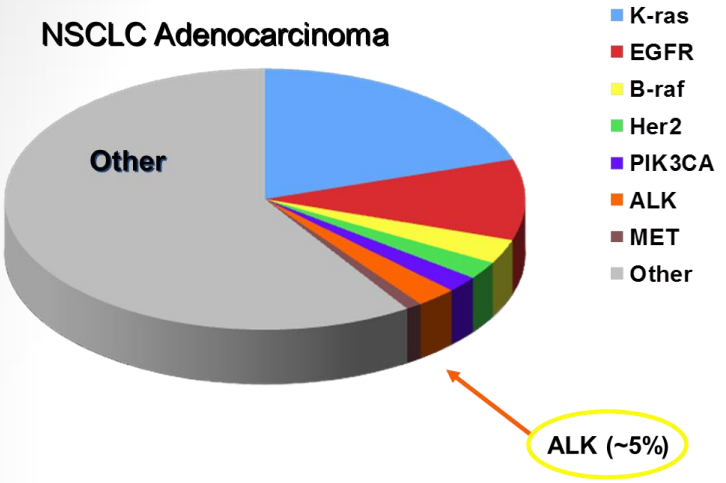
CoDevelopment of Diagnostics and Therapeutics

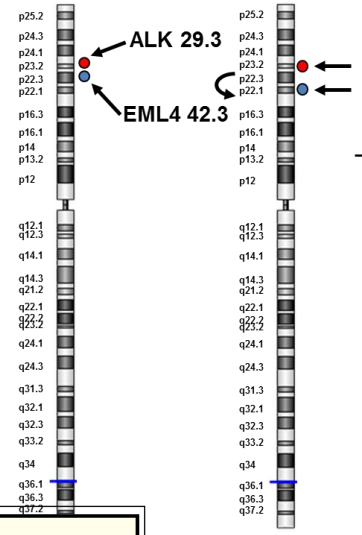
Table 1. Response rate of successful targeted therapies in molecularly-selected populations evaluated in early clinical trials

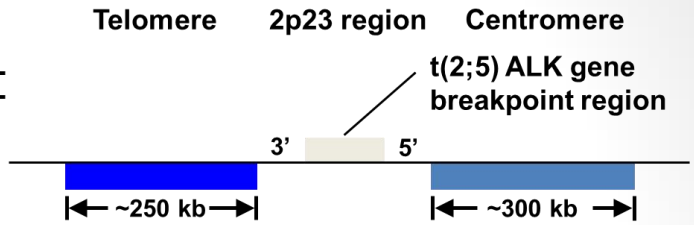
Marker/population	Agent	Mechanism of action	Response	Reference
HER2 overexpressed/amplified breast cancer	Trastuzumab	anti-HER2 antibody	12%	[6]
	Trastuzumab-DM1	anti-HER2 antibody + drug conjugate	44%	[12]
CD117 overexpressed GIST	Imatinib	c-KIT, PDGFR inhibitor	54%	[13]
BRCA1/2 mutant breast, ovarian and prostate cancer	Olaparib	PARP inhibitor	47%	[7]
BRAF V600E mutant melanoma	Vemurafenib	BRAF inhibitor	75%	[8]
	Dabrafenib	BRAF inhibitor	60%	[14]
Basal cell carcinomas (majority have inactivating mutations in PTCH1 or activation of SMO)	Vismodegib	SMO inhibitor (Hh pathway)	58%	[15]
ALK rearranged NSCLC	Crizotinib	ALK, MET inhibitor	57%	[9]
Medullary thyroid cancer (known to have *RET* mutations, MET expression and VEGF activation)	Cabozantinib	MET, VEGFR2, RET inhibitor	29%	[16]
PIK3CA mutant breast cancer	BYL719	selective PI3K alpha inhibitor	44%[a]	[10]
FGFR1 or *FGF* amplified breast cancer	E-3810	FGFR, VEGFR inhibitor	70%	[11]

CoDevelopment of Diagnostics and Therapeutics

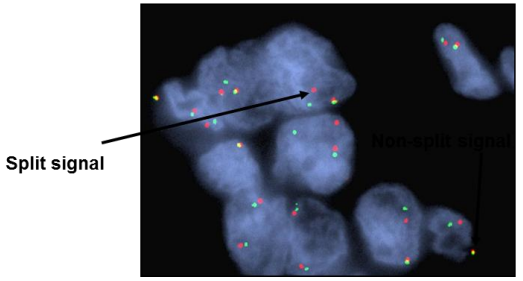
Crizotinib in ALK traslocated NSCLC

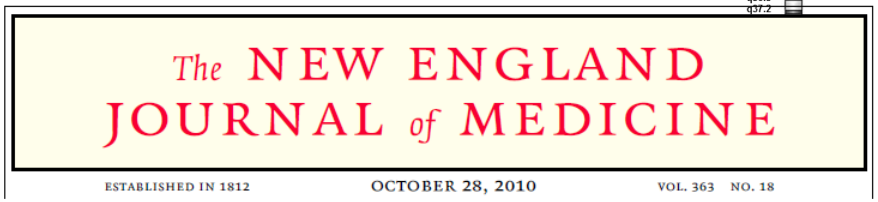






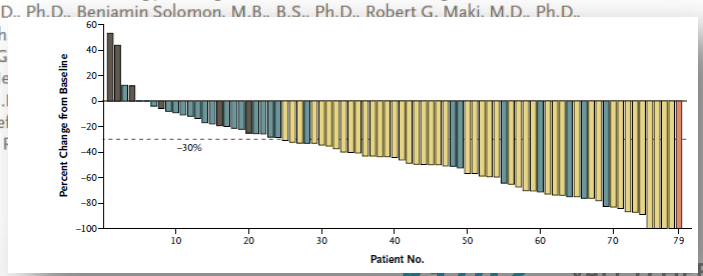
Break-apart FISH assay for *ALK*-fusion genes[1]




The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph... Marileila Varella-G... Hannah Stubbs, M.S., Je... Leena Gandhi, M.D., Ph.... Mark J. Ratain, M.D., Je... Keith Wilner, Ph.D., ...



<u>1500</u> patients screened by FISH (initially all; later, ADK).

ALK rearrangement occurred in about 5% (75 expected positive patients).

82 patients with ALK-rearranged NSCLC enrolled and evaluable.

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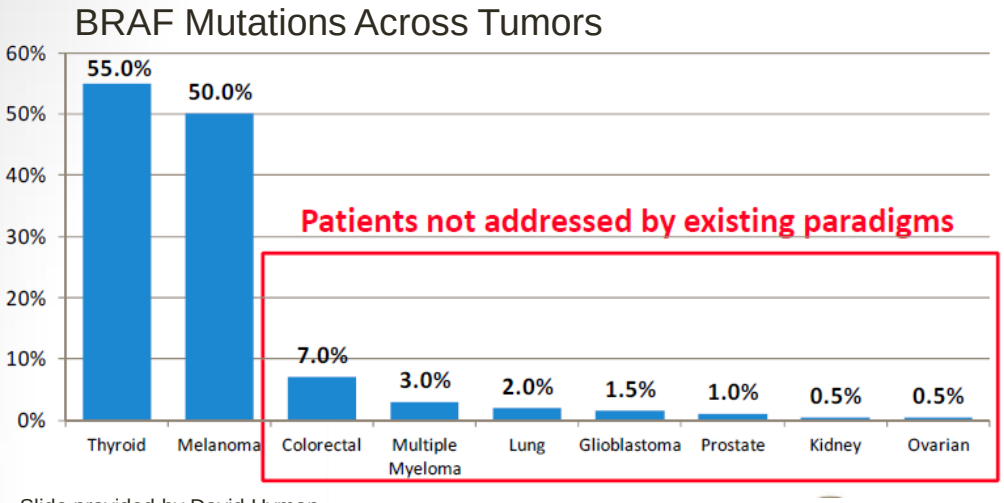
Kwak EL et al. N Engl J Med. 2010.

Importance of Basket Studies

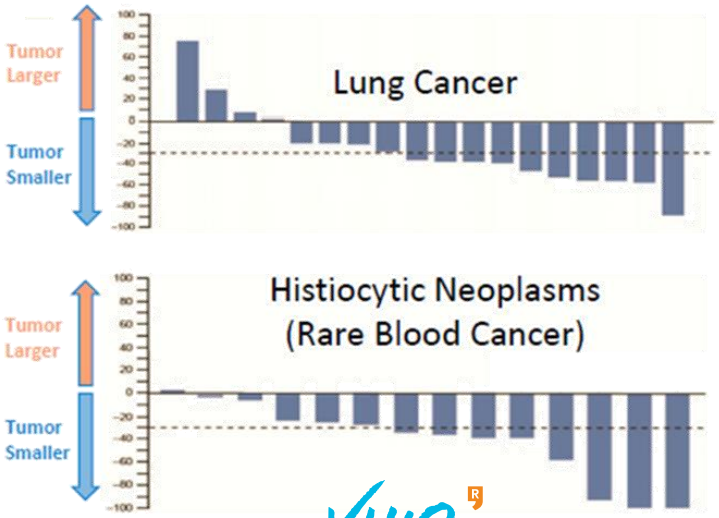


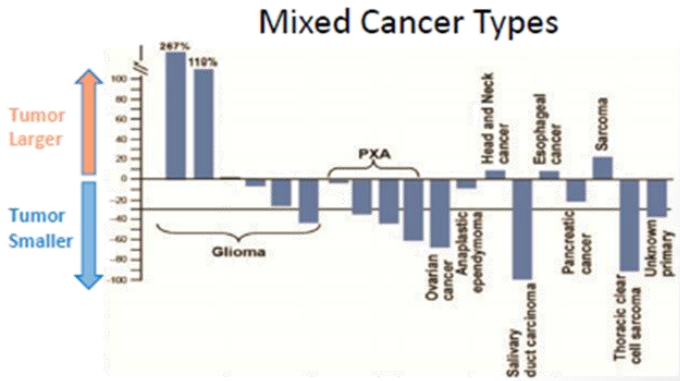
Slide provided by David Hyman

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

The NEW ENGLAND JOURNAL of MEDICINE





Each Bar Represents a Unique Patient

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Hyman Di, et al, N Engl J Med 2015; 373:726-736 August 20, 2015

Evolution of drug development

Paradigm changes in Drug Development

1. EDD trials include large early clinical trials with numerous arms in multiple indications.
2. Focusing in smaller and smaller patient populations (rare histologies or selected by the presence of a rare alteration).
3. Signal finding trials are been used as registration trials, under the claim that randomized trials are not feasible.
4. Drug/Companion diagnostic co-development: the “One drug, one biomarker, one test paradigm” is getting old.
5. Biotechnology allows multiplex analysis. Prescreening for trials vs companion diagnostics.

Key Players in Drug Development in Precision Medicine

Sample

Trials

Pharma

Physicians/Clinical Investigators

CDx

TRANSLATIONAL RESEARCH

Cost/ coverage

FINANTIALS

CLINICAL RESEARCH

Treatment

Multiplexing

Turnaround time

Robustness

REGULATORY

Research

Science

Cooperative groups

Translational scientists

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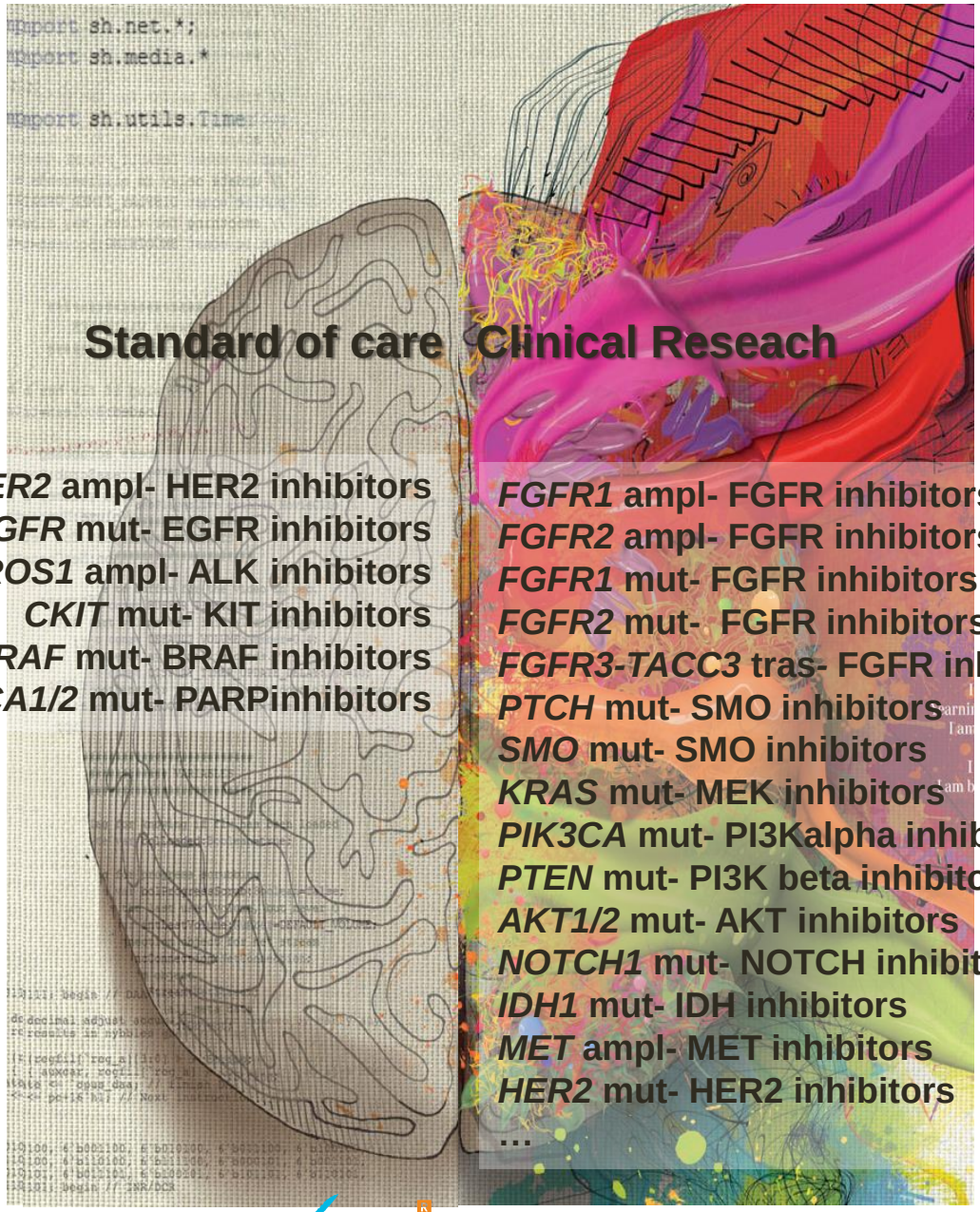
NEW TIMES, NEW CHALLENGES...

AND AFTER THE LOW HANGING FRUIT, WHAT?



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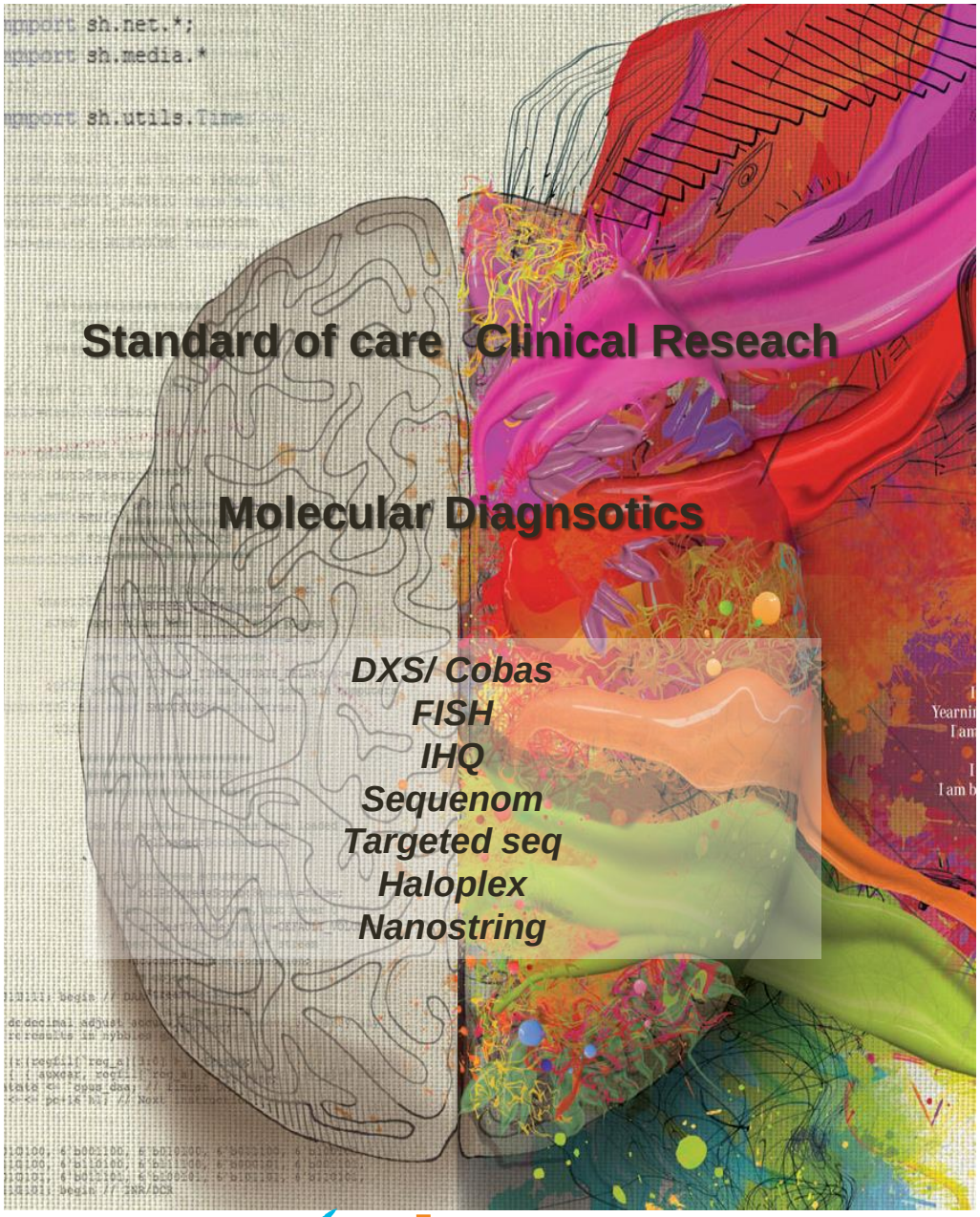

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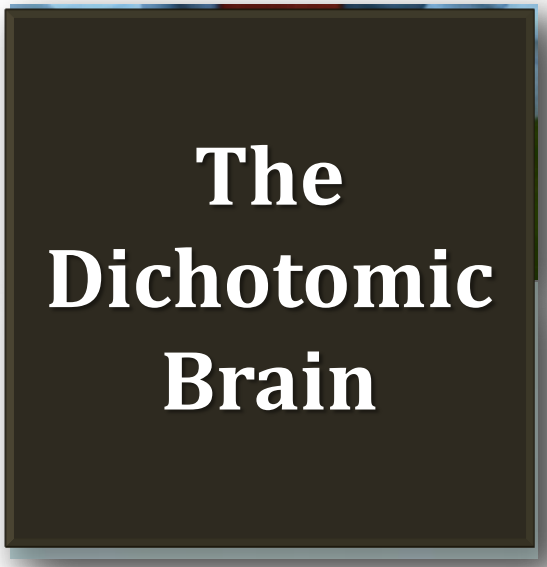
The conundrum:

The biology is complex…

Technology has improved…

…but the physician's brain is still dichotomic



MUTANT or **WILD TYPE**

INCLUDED or **EXCLUDED**

RESPONDER or **NOT RESPONDER**

DRUG A or **DRUG B**

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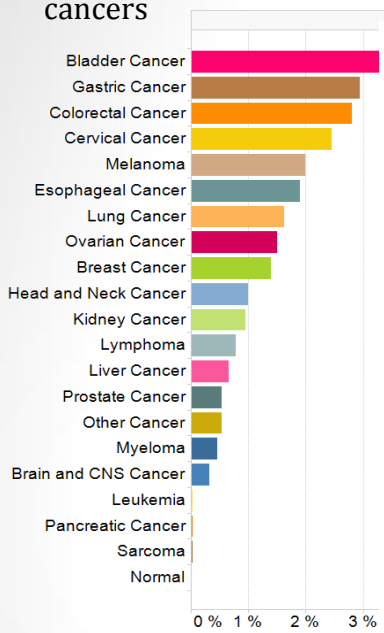
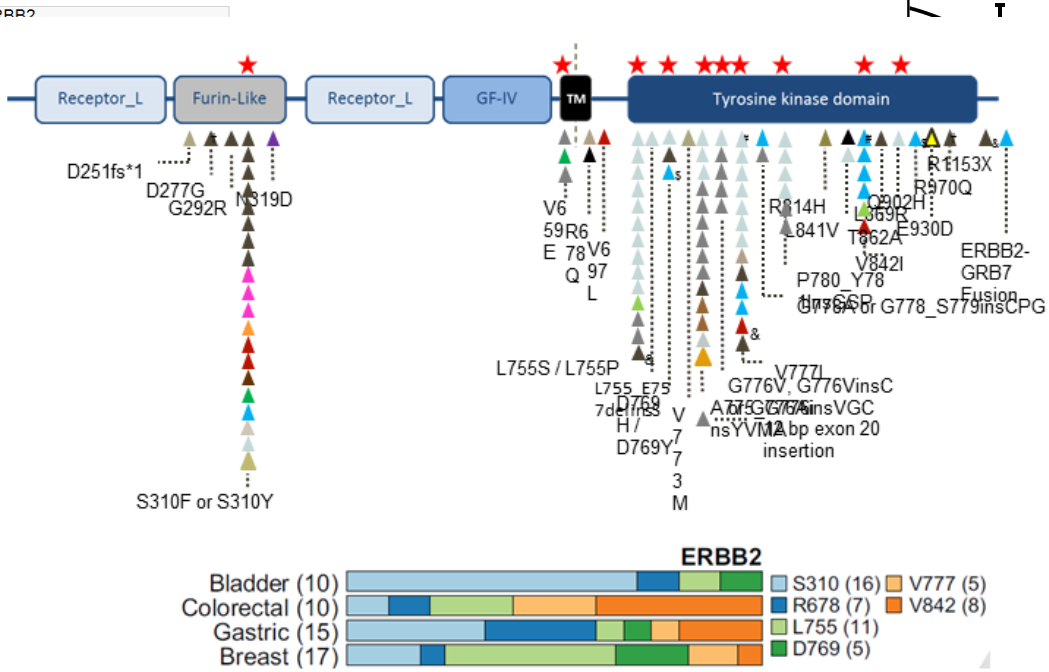
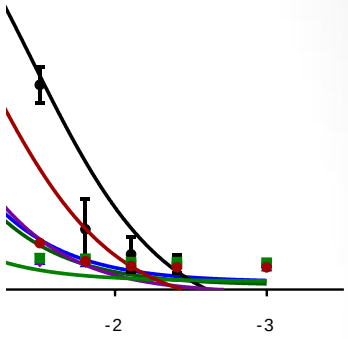
ERBB2 mutations & Neratinib

ERBB2 mutations may differing functional impact, sensitivity to antiHer2 therapies, and tumor specificity

Frequency of *ERBB2* mutations across cancers







72 concentration (Log μM)

TCGA; Ma et al, ASCO 2016; Wagle ASCO 2016; Desmedt et al, JCO 2016

ose et al. Cancer Discov 2013;3:224–37
ng et al. Nature Biotech 2016;34:155-63
armona et al. 2016 AACR, Abstract 298

Molecular test

Documented ERBB2 mutation from local testing in a CLIA- or regionally-certified lab.

- Sanger
- PCR-based
- AmpliconSeq
- Capture
- Exome seq

Patient eligibility

Eligible mutations are those that have are known or suspected to be pathogenic (activating) based on:

1) recurrence and frequency in clinical studies or public databases (COSMIC, cBioPortal, ClinVar, etc)
2) kinase domain location
3) bioinformatics
4) preclinical characterization
5) clinical responsiveness.

Novel variants of unknown significance are accepted for suspecting pathogenic mutations based on levels of evidence from criteria above.

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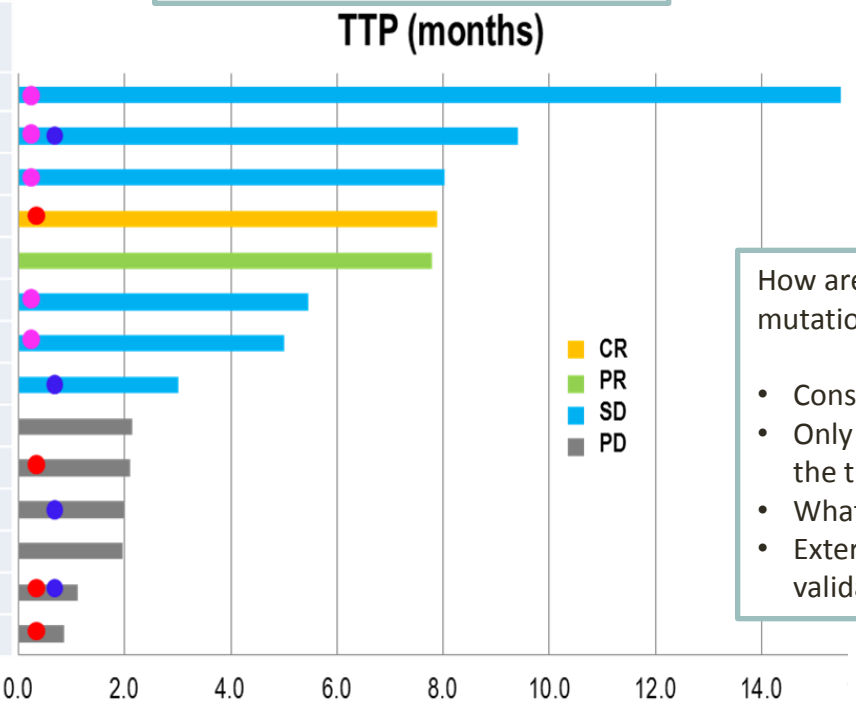
ERBB2 mutations & Neratinib

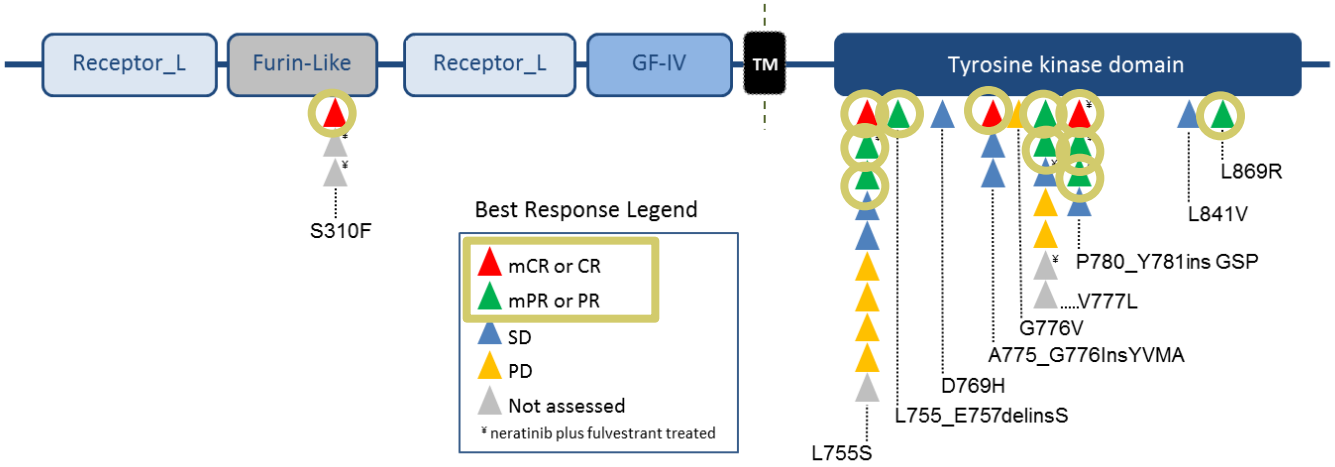
Prior # regimen for MBC	HER2 Mutation	Pt #
3	P780_Y781insGSP	13
3	L869R	16
2	S310F,V842I	14
3	V777_G778insGSP	15
4	L755S	9
8	L755S	8
4	A775_G776insYVMA	2
6	D769H	6
3	S310F	3
2	P780_Y781insGSP	1
2	L755S	12
2	L755S	11
2	L755S	7
10	L755S	10



How are we going to determine which mutations will get into the drug-label?

- Considering all equally important?
- Only those "significantly" explored in the trial?
- What role do we give to histology?
- External database with (preclinical) validation?

Distribution of *ERBB2* mutations in breast cancer cohort (best response to therapy)

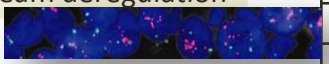


Cynthia Ma et al, ASCO 2016

FGFR alterations & FGFRi

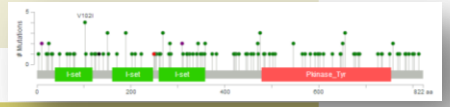
Amplification

- FGFR amplification is increasingly emerging as a potential therapeutic intervention strategy across numerous diseases
- Amplified transcript results in increased signal transduction and cellular events, which can lead to downstream deregulation



Point Mutations

- A recent screen of 210 different cancers found the FGF signaling pathway was the most commonly mutated system amongst the 1000 somatic mutations found
- Mutations can affect activation, dimerization, ligand binding, degradation, and loss of function

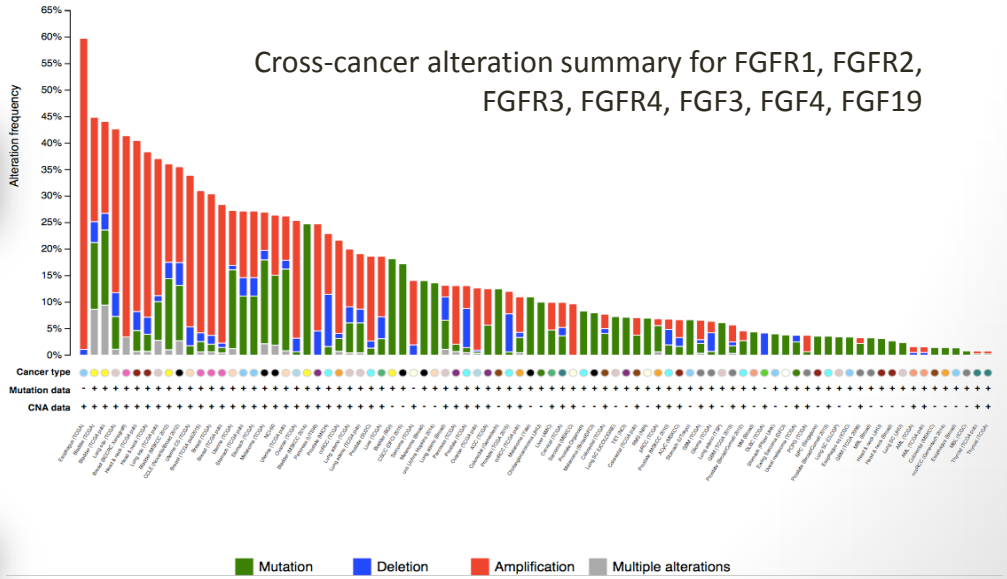


Chromosomal Translocation

- Can lead to an expression of fusion proteins with potent oncogenic function
- Many fusion proteins can result in constitutively or aberrantly activated signaling pathways

Possible indications (alphabetical order)	Genomic alterations (amplifications or activating mutations)
Bladder	15% *FGFR3* mut, 3% *FGFR3* fusions, 3% FGFR1 amp
Breast cancer (ER+, luminal)	10% *FGFR1* amp, 4% *FGFR2* amp, 2% *FGFR2* mut, 10% *FGFR4* amp
Colorectal cancer	5% *FGFR1* amp, 5% *FGFR3* mut
Endometrial	10% *FGFR2* mut
Esophagial SCC	10% *FGFR1* amp, 4% *FGFR2* amp
Gastric cancer	7% FGFR2 amp
NSCLC-SCC	17% *FGFR1* amp, 11% *FGFR2* amp
SCLC	6% *FGFR1* amp
Multiple Myeloma	20% *FGFR3* trans, <1% *FGFR3* mut
Prostate	12% *FGFR1* amp, 2% *FGFR2&3* mut

Cross-cancer alteration summary for FGFR1, FGFR2, FGFR3, FGFR4, FGF3, FGF4, FGF19



Ahmad Biochimica et Biophysica Acta 2012

Hierro C. et al_*Semin Oncol* 42:801-819 (2015); www.cbioportal.

FGFR alterations & FGFRi

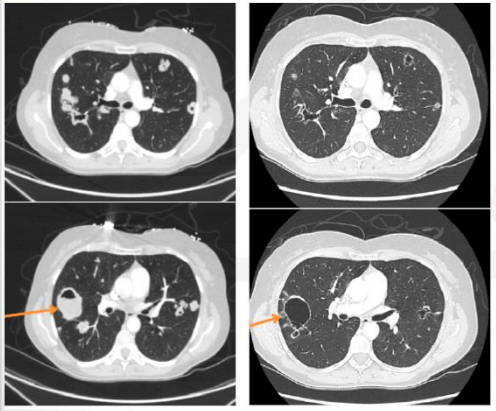
FGFR: Are the different alterations analogous between them?

- Mutations, amplifications, gene-fusions?
- *FGFR1* vs *FGFR2* vs *FGFR3*?

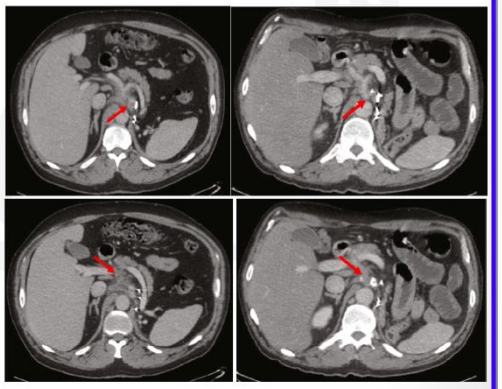
Is there a tissue-dependency based on specific FGFR aberrations?

Urothelial cancer (muscle-invasive)	FGFR1 amplification	11%
	FGFR3 mutation	15%
	FGFR3-TACC3 translocation	6%

Refractory metastatic bladder cancer with TACC3-FGFR3 translocation. PR at 9 mg with JNJ-42756493.

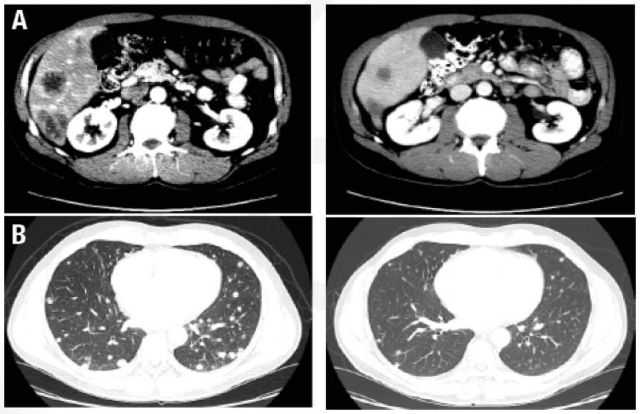


Refractory metastatic bladder cancer with FGFR3 germline mutation. Maintained PR at 80 mg BD with AZD4547.



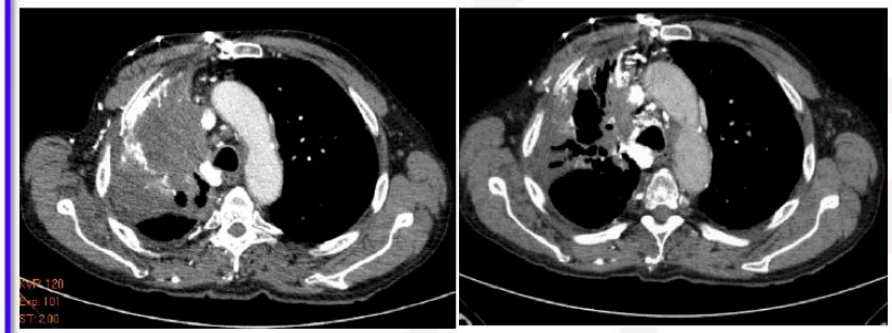
Biliary tract cancer	FGFR2 translocations	13%

Refractory cholangiocarcinoma with BICC-FGFR2 translocation. PR with BGJ398.



Squamous NSCLC	FGFR1 amplification	10-20%
	11q amplification	12%

Refractory squamous NSCLC with FGFR1 amplification. PR with AZD4547.



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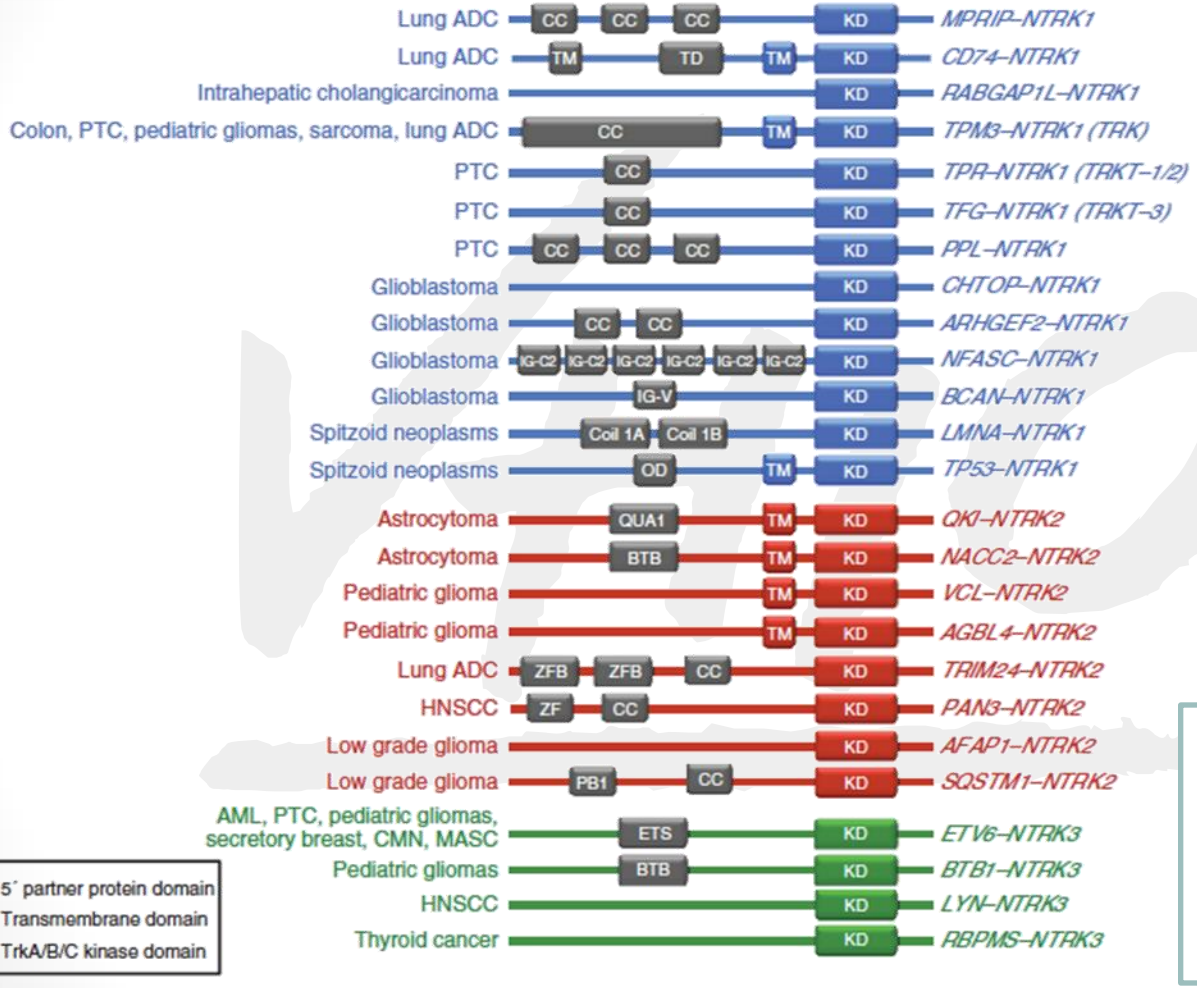
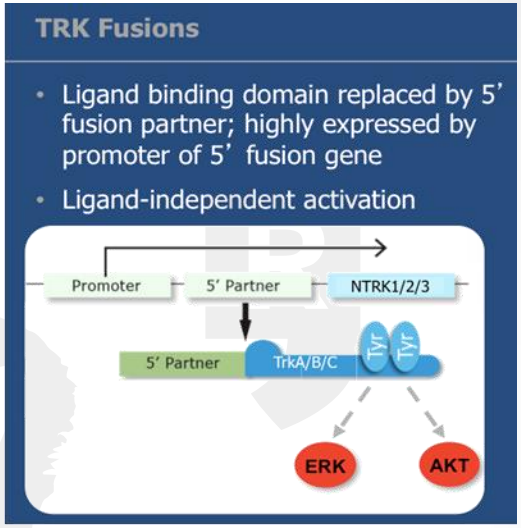
Bahleda R. et al_2014 *ASCO Meeting* abstract 2501; Tabernero J. et al_*J Clin Oncol* 20;33(30):3401-8 (2015); Rodriguez-Vida A.et al_*J Hematol Oncol*. 2015 Oct 24;8(1):119.

NTRK alterations & NTRK1-3i

NTRK translocations: seeking for the ambiguous fusion partner.





NTRK translocations represent a challenge in terms of assay complexity, due to high heterogeneity in fusion partners.

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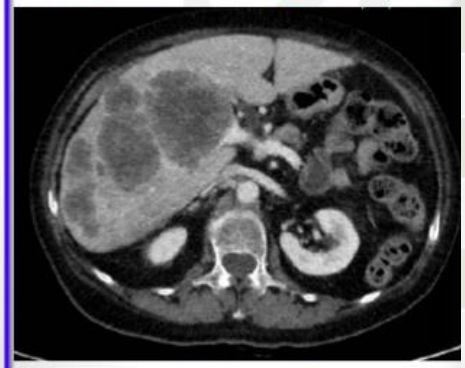
Vaishnavi A.et al_Cancer Discov 2015; 5:25-34.
Hong DS.et al_2016 AACR Annual Meeting.

NTRK alterations & NTRK1-3i

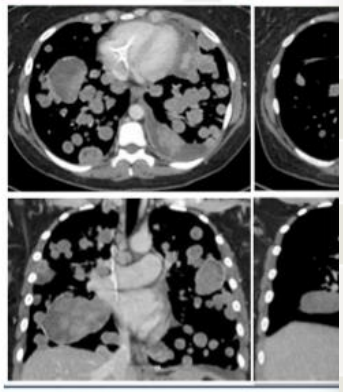
NTRK translocations: potent oncogenic drivers among solid tumors.

74-year old female patient in Italy with NTRK1 (including FOLFOX, FOLFIRI & cetuximab. PR wit



Baseline, March 2014

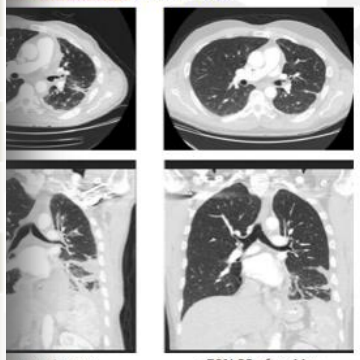
42-year old female patient with LMNA-NTRK1 rea prior lines of therapy, including epirubicin, ifosfar PR and quick clinical response at 100 mg BID with



Baseline PR

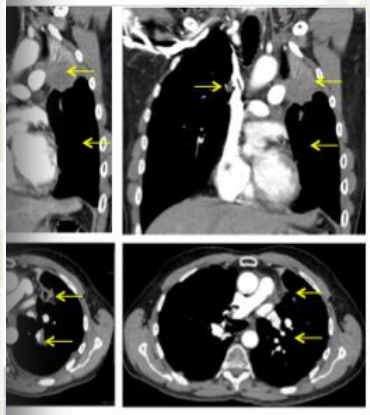
RXDX-101		
NRTK FUSION	TUMOR TYPE	BEST RESPONSE
LMNA-NTRK1	Colon cancer	PR
SQSTM1-NTRK1	NSCLC	PR
ETV6-NTRK3	MASC	PR
BCAN-NTRK1	Astrocytoma	PR
ETV6-NTRK3	Infantile fibrosarcoma	PR
LOXO-101		
LMNA-NTRK1	Undifferentiated sarcoma	PR
ETV6-NTRK3	GIST	PR
ETV6-NTRK3	MASC	PR
ETV6-NTRK3	MASC	PR
ETV6-NTRK3	Papillary Thyroid cancer	PR
TPR-NTRK1	NSCLC	SD

CLC refractory to 4 prior lines of therapy, including l, vinorelbine. ECOG 2, in hospice on supplemental ith entrectinib (RXDX-101).



7% PR day 26 - 79% PR after 11m

nged MASC refractory to 3 prior lines of therapy, T ABBV- 399. PR at 100 mg QD with LOXO-101.



3D1 PR C7D1

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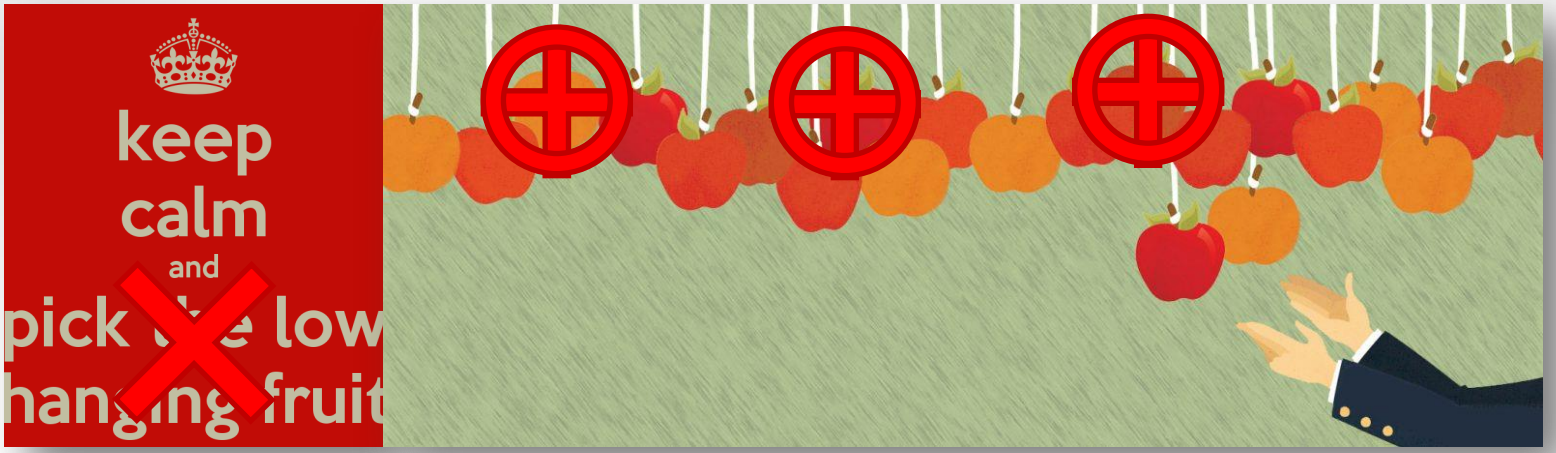
Drilon A.et al_2016 AACR Annual Meeting.
Hong DS.et al_2016 AACR Annual Meeting.



ARE ALL ALTERATIONS BORN EQUAL?

MOLECULAR HOMOLOGY... ?

HISTOLOGY AGNOSTIC...?

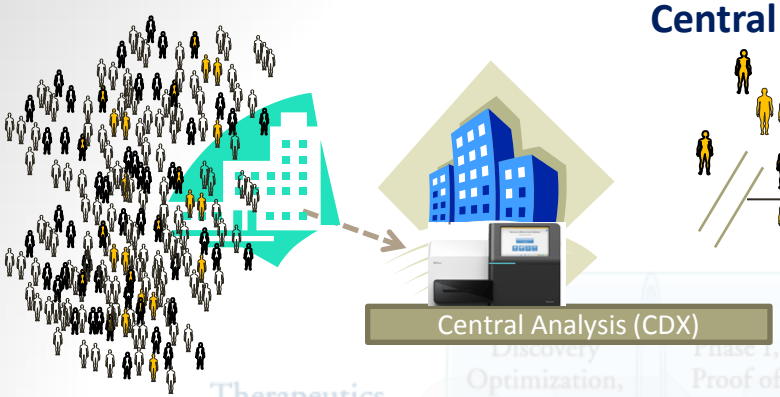
Dr. Livingstone, I presume?

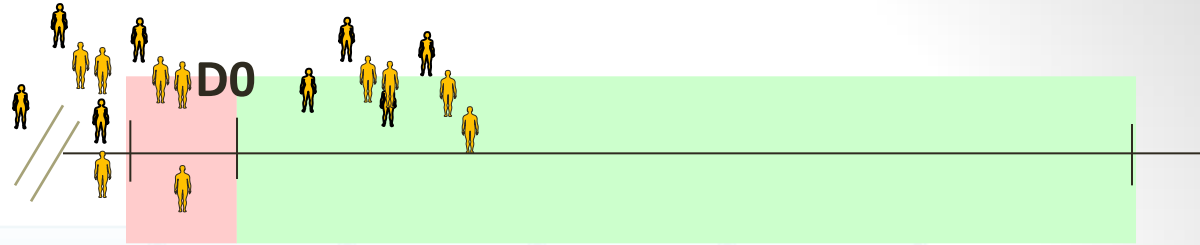
(Henry Morton Stanley)

FINDING PATIENTS THAT CAN BENEFIT...

...LIVINGSTON, I PRESUME

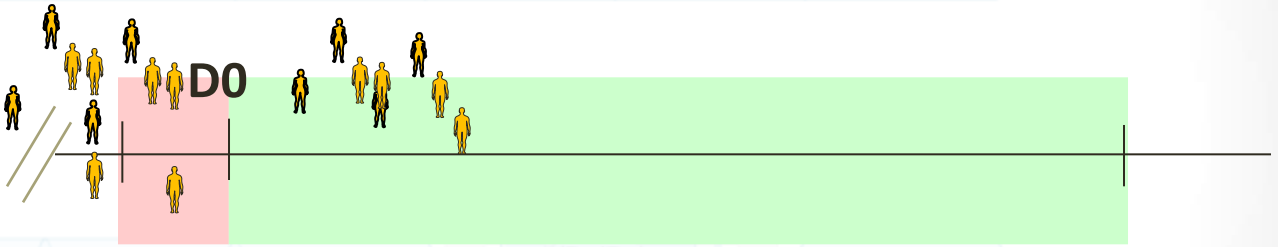
Central analysis of samples: CT eligibility and CDx development





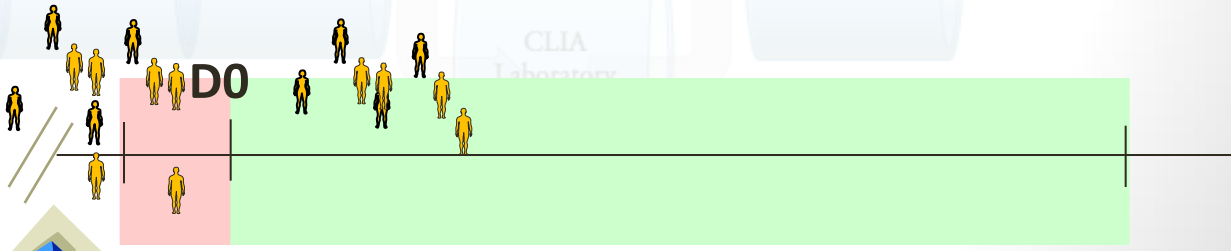
Trial A

Local analysis of samples: eligibility

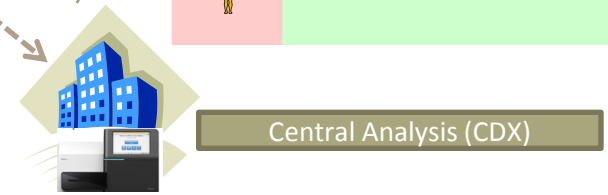


Trial A

Local analysis of samples (eligibility) and Central CDx development



Trial A



Challenges of central prescreening (forced by current CDx development paradigm)

FGFR & Patient selection:

Molecular screening in the BGJ398 trial

Breast	
Samples tested	229
FGFR1 amplification	26
FGFR2 amplification	3

Bladder	
Samples tested	95
FGFR3 mutation	7

Squamous lung	
Samples tested	147
FGFR1 amplification	14

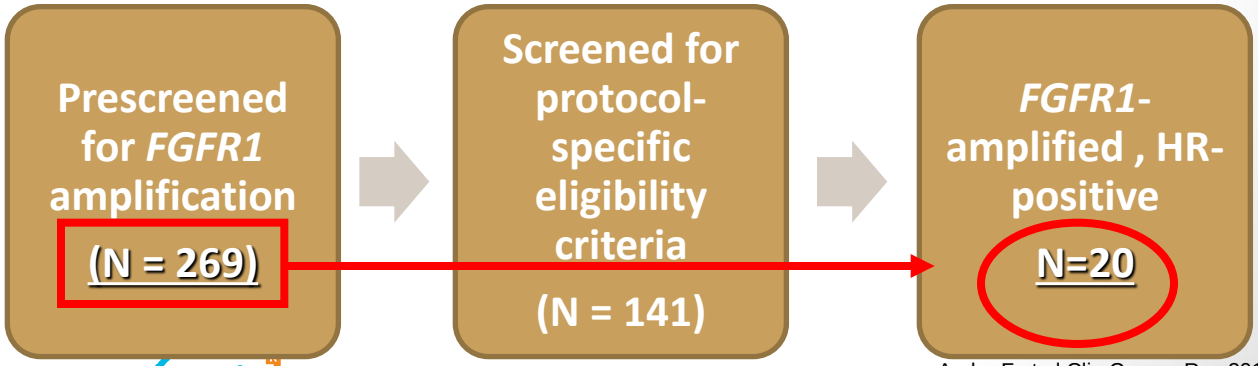
Gastric	
Samples tested	107
FGFR2 amplification	2

Other	
Samples tested	43
FGFR1 amplification	0
FGFR2 amplification	0

Lecia V. Sequist, American Association for Cancer Research 2014

Molecular screening in the TKI258 trial

56 centers, global trial
16 months recruitment



Andre F et al Clin Cancer Res 2013

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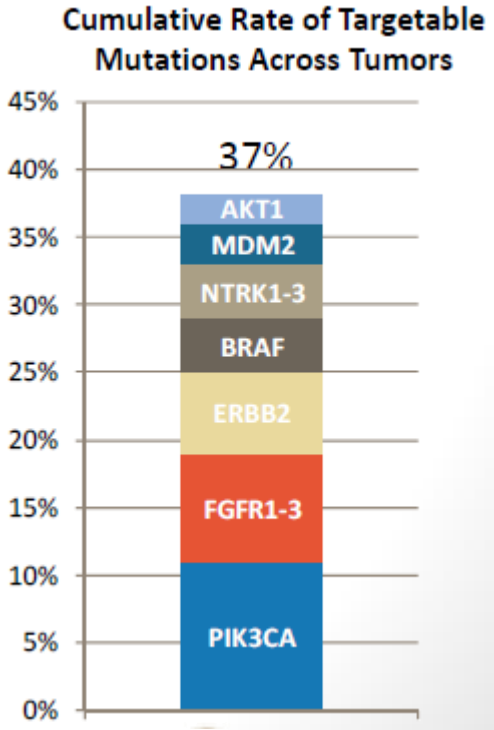
Small patient population trials

1. FGFRi: *FGFR1-4* mutations/ amplifications/ traslocations
2. *PIK3CA* mutations/amplifications
3. *BRAF* mutations
4. *EGFR* T790M
5. *NOTCH* mutations/amplifications, *FBXW7* mutations
6. *RSPO2/3* amplification/traslocation and *RNF43*, *ZNRF3* mutations
7. *MET* amplification/mutation
8. *ALK*, *ROS* mutation/traslocation
9. *HER2*, *HER3* mut
10. *TP53* wt
11. *IDH1* mutations
12. *NTRK1-3* mutations/ amplifications/ traslocations
13. *AKT1* mutations
14. *PTEN* or *PIK3CB* mutations



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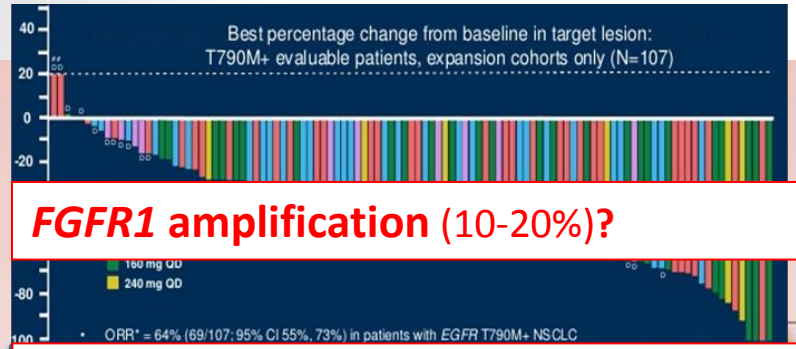
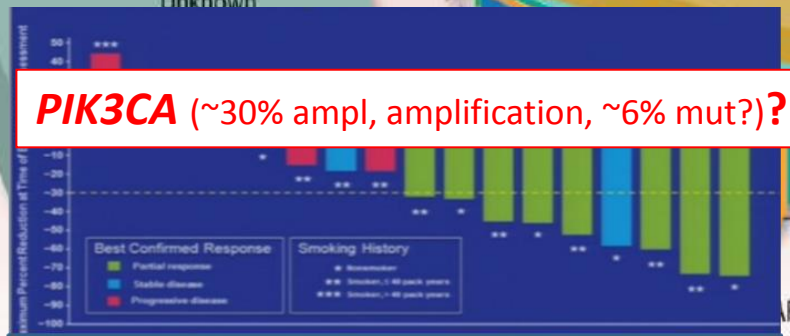
Enabling Stratified Medicine in NSCLC



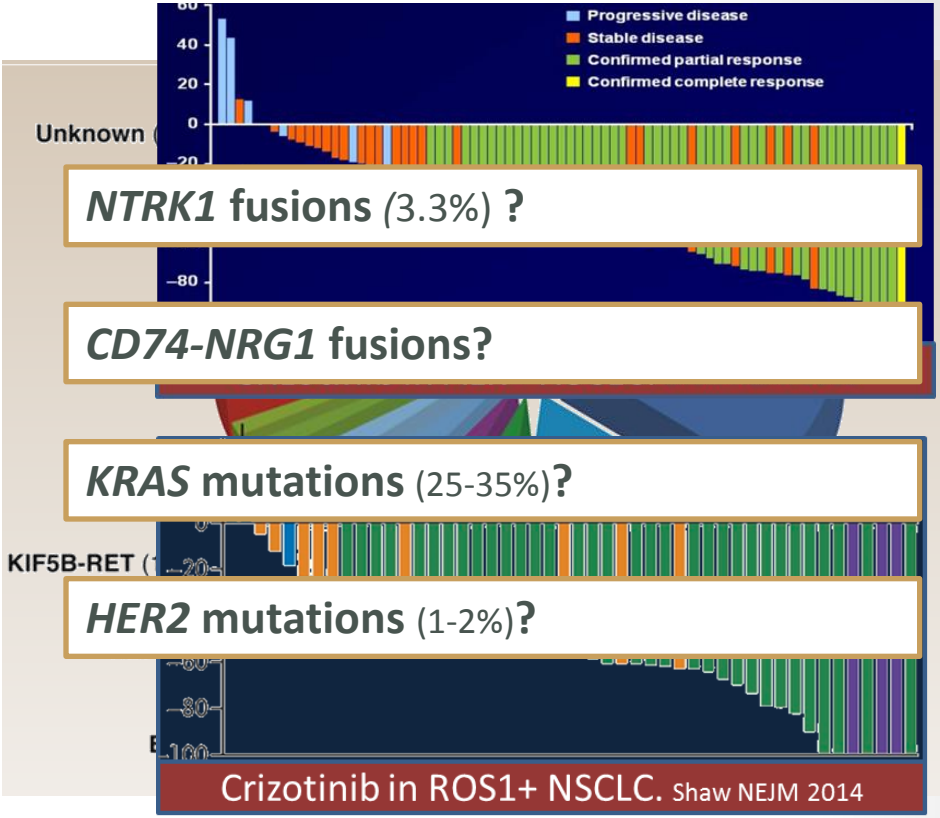
***FGFR1* amplification** (10-20%)?

Discoid Domain Receptor 2 mutation (2%) ?



PIK3CA (~30% ampl, amplification, ~6% mut?)?

Dabrafenib in BRAF+ NSCLC. Planchard ESMO 2014



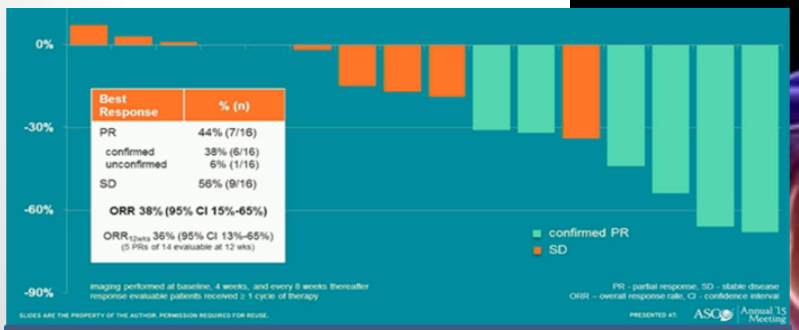
***NTRK1* fusions** (3.3%) ?

***CD74-NRG1* fusions?**

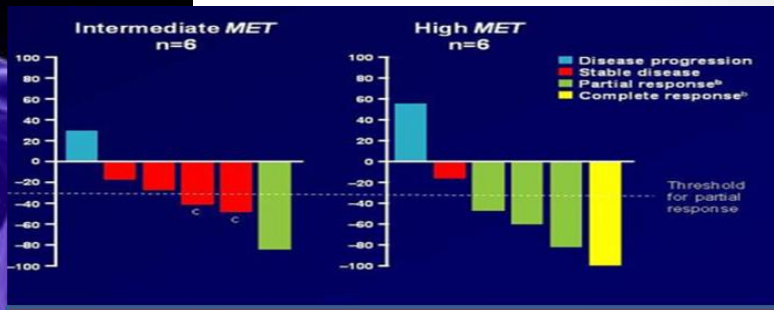
***KRAS* mutations** (25-35%)?

***HER2* mutations** (1-2%)?

Crizotinib in ROS1+ NSCLC. Shaw NEJM 2014



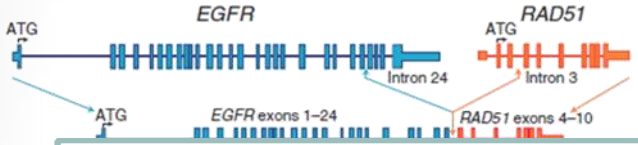
Cabozantinib in RET+ NSCLC. Drilon ASCO 2015



Crizotinib in MET+ NSCLC. Camidge ASCO 2014

EGFR Fusions as Novel Therapeutic Targets in Lung Cancer

Kartik Konduri[1,2], Jean-Nicolas Gallant[3], Young Kwang Chae[4,5,6], Francis J. Giles[4,5,6], Barbara J. Gitlitz[7,8], Kyle Gowen[9], Eiki Ichihara[10], Taofeek K. Owonikoko[11,12], Vijay Peddareddigari[13,14], Suresh S. Ramalingam[11,12], Satyanarayan K. Reddy[11,12], Beth Eaby-Sandy[13], Tiziana Vavalà[8,15], Andrew Whiteley[1], Heidi Chen[16], Yingjun Yan[10], Jonathan H. Sheehan[17,18], Jens Meiler[18,19], Deborah Morosini[9], Jeffrey S. Ross[9,20], Philip J. Stephens[9], Vincent A. Miller[9], Siraj M. Ali[9], and Christine M. Lovly[3,8,10,21]



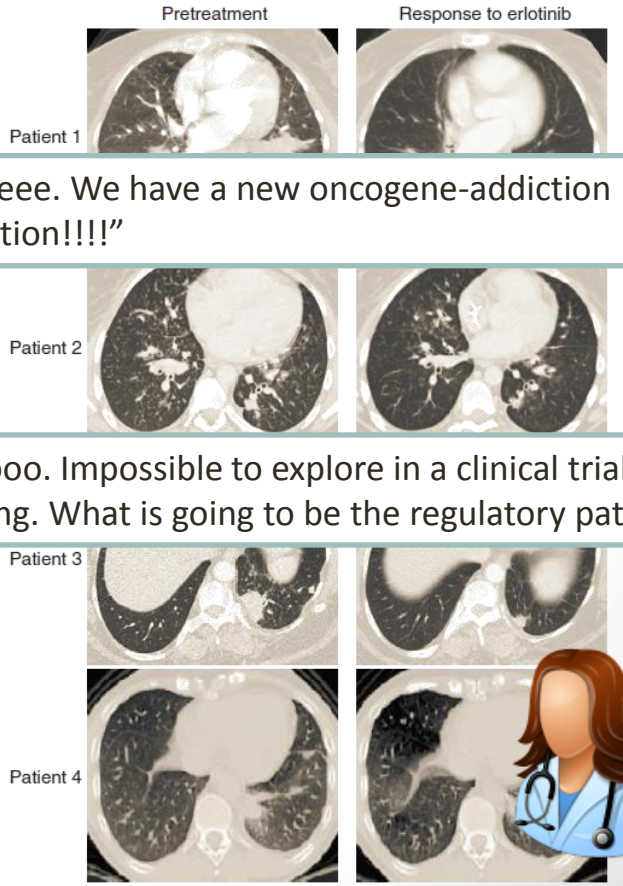
"We report for the first time the identification and therapeutic targeting of EGFR C-terminal fusions in patients with lung cancer and document responses to the EGFR inhibitor erlotinib"

"To determine the frequency of *EGFR* fusions in lung cancer, we analyzed data from ~ **10,000 clinical cases**. Fusion events, defined by a genomic breakpoint in *EGFR* exons 23 through intron 25, were detected **in 5 patients**".

Patient no.										
1					Breast Peritoneum Eye					
2										
3										
4	38	Male	Caucasian	Stage IV lung adenocarcinoma	Former light smoker (3 pack years)	Lung Lymph nodes Pleura Bone	- Cisplatin/ pemetrexed, 6 cycles - Maintenance pemetrexed, 11 cycles	*EGFR–RAD51*	Erlotinib	PR	6 months, ongoing
5	60				Never	Lung Lymph nodes Brain	- Craniotomy - RT to surgical bed - Carboplatin/ pemetrexed, 4 cycles - Maintenance pemetrexed, 6 cycles	*EGFR–RAD51*	N/A	N/A	N/A

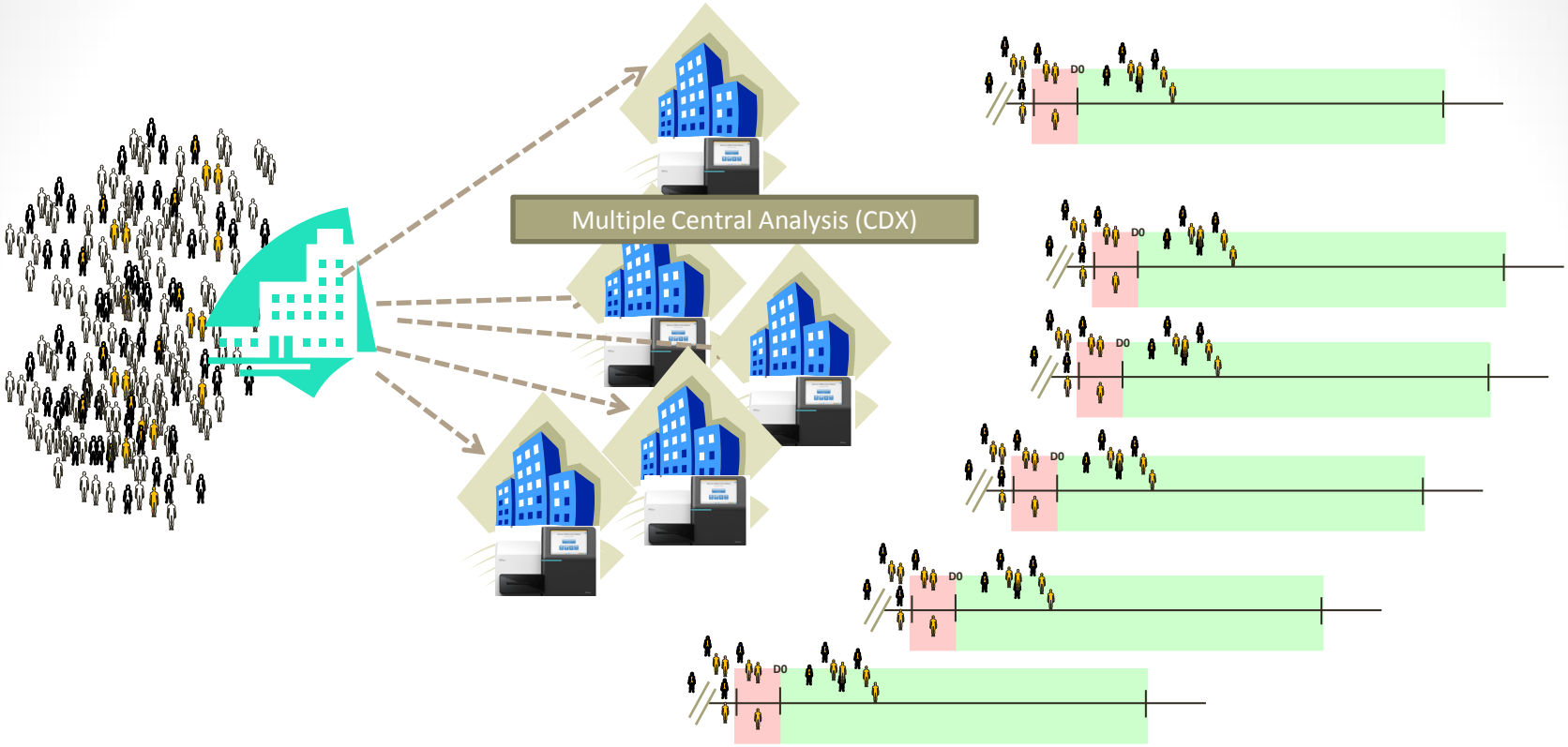
"Yeeeee. We have a new oncogene-addiction situation!!!!"

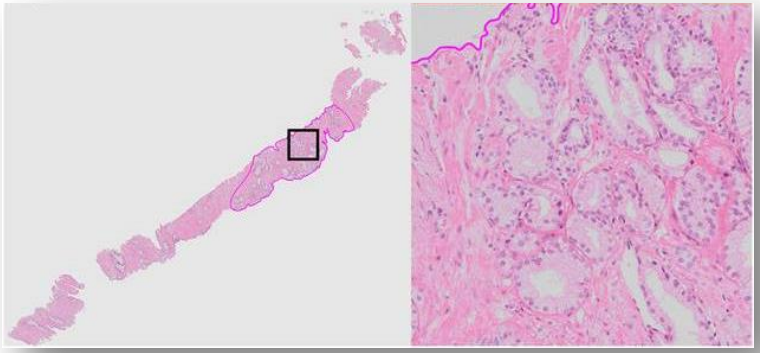
"Boooo. Impossible to explore in a clinical trial setting. What is going to be the regulatory path?"



Cancer Discovery April 21, 2016

Current situation: sample exhaustion



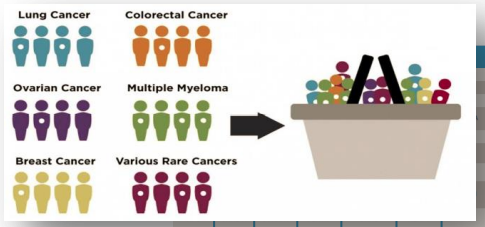


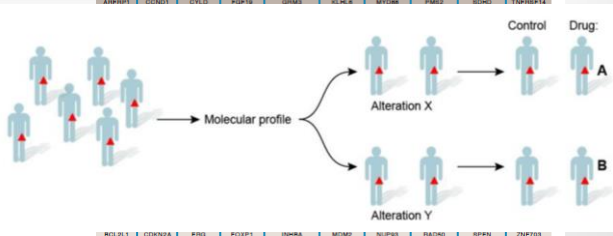
Life in a multiplexed era

Research in a multiplexed era

1. Basket trials include multiple histologies
2. Sites have multiple studies for molecular alterations
3. Trials may include multiple drugs (umbrella trials)
4. Tests analyze multiple alterations

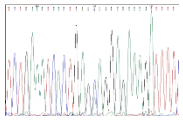
   (NGS= 300-400 genes)





Technology has really improved our clinics…

SANGER sequencing



RT-PCR

Sequenom/ SNAPshot

NGS

One test, one drug

Multicategorical model

Omnisciencist–reduccionist model

One Disease
One assay
One platform
One Drug

Multiplexed platform

Mutation A	Drug A
Mutation B	Drug B
Mutation C	Drug C
Mutation n	Drug n

One Assay (comprehensive)

Terabytes of data

Mutation A	Drug A
Mutation B	Drug B
Mutation C	Drug C
Mutation n	Drug n

Great amount of unused data (can explain resistance)

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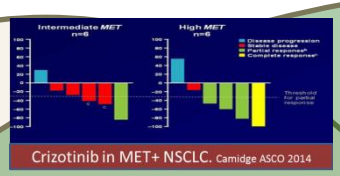
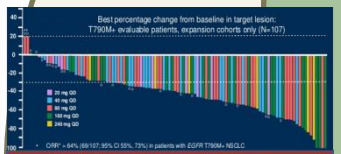
Dienstmann et al. J Clin Oncol 2013

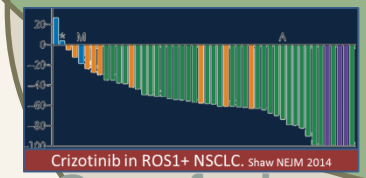
Technical complexity of detecting multiple alterations



Crizotinib in MET+ NSCLC. Camidge ASCO 2014



AZD9291 in T790M+ NSCLC. Jänne NEJM2015



Crizotinib in ROS1+ NSCLC. Shaw NEJM 2014

IHC derived techniques

Copy Number Alterations

Protein presence or loss

Protein phosphorilation levels

Hybridisation-based techniques

Point mutations & indels

Gene fusions

Gene expression

Sequencing-based techniques

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Trial or programme name	Platforms or techniques	Cancer types	Strategy		
Dana-Farber Cancer Institute, Boston, Massachusetts					
PROFILE	Sequenom	All solid tumours	Umbrella protocol	Single institution	Local lab
MD Anderson Cancer Center, Houston, Texas					
T9 Program	Sequenom	All solid tumours	Umbrella protocol	Single institution	Local lab
Clearing House protocol	PCR Illumina NS, Ion Torrent NS NS	All solid tumours	Umbrella protocol	Single institution	Local lab
Memorial Sloan-Kettering Cancer Center, New York					
IMPACT (NCT01775072)	Illumina HiSeq Sequenom or MiSeq	All solid tumours	Umbrella protocol	Single institution	Local lab
Vanderbilt-Ingram Cancer Center, Nashville, Tennessee					
PCMI	SNaPshot	Melanoma, NSCLC, CRC and breast cancer	Umbrella protocol	Single institution	Local lab
Massachusetts General Hospital, Boston					
NS	SNaPshot	NSCLC, CRC, melanoma and breast cancer	Umbrella protocol	Single institution	Local lab
Princess Margaret Cancer Centre, Toronto, Canada					
IMPACT (NCT01505400)	MiSeq Sequenom	Selected solid tumours	Umbrella protocol	Single institution	Local lab
Vall d'Hebron Institute of Oncology, Barcelona, Spain					
VHIO prescreening program	Sequenom Illumina GAIIx	Breast cancer, solid tumour phase I patients	Umbrella protocol	Single institution	Local lab
Cancer Research UK, London					
Stratified Medicine Programme	PCR FISH	Melanoma, NSCLC, CRC and breast, prostate and ovarian cancer	Umbrella protocol	Multiinstitutional	Several central labs
Gustave Roussy Institute, France					
MOSCATO 01 (NCT01566019)	aCGH PCR	Solid tumour phase I patients	Umbrella protocol	Single institution	Several Central labs
SAFIR01 (NCT01414933)	aCGH PCR	Breast cancer	Umbrella protocol	Multiinstitutional	Several Central labs
Netherlands					
Centre for Personalized Cancer Treatment	Ion Torrent PGM 5500xl SOLiD	Solid tumours	Umbrella protocol	Multiinstitutional	Several central labs
Norwegian Cancer Genomics Consortium					
Nationwide programme	NS	9 tumour types	Umbrella protocol	Multiinstitutional	Local lab
Curie Institute, Paris; French National Cancer Institute					
SHIVA (NCT01771458)	Ion Torrent PGM CytoScan HD	Solid tumors	Clinical trial	Multiinstitutional	Several central labs
WIN Consortium					
WINTHER (NCT01856296)	NGS CGH	Solid tumours	Clinical trial	Multiinstitutional and International	Central lab

Adapted from Bedard PL Nature 2013

IMPACT

Single institution
All solid tumors
Umbrella protocol

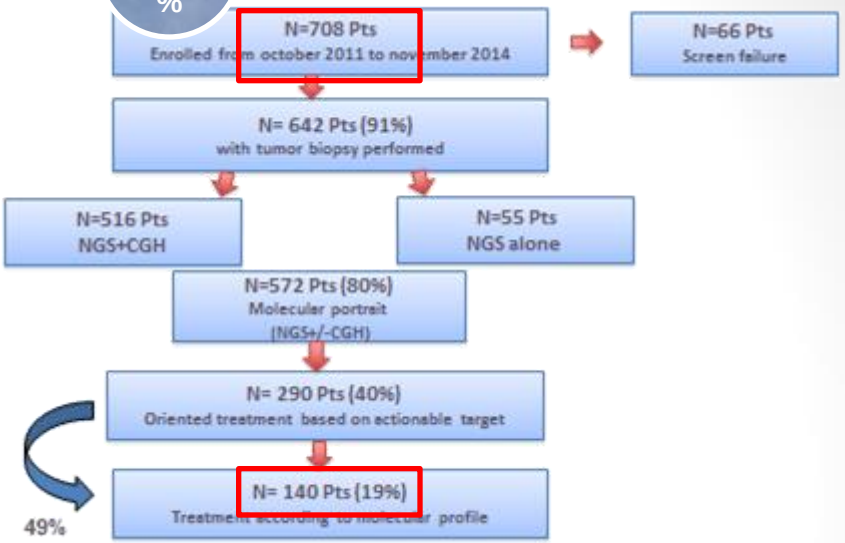
4 %

Patients Enrolled	N=678
Enrollment Period	March 1/12 – April 30/13
Median prior lines of treatment (range)	2 (1–11)
Screen Failure (%)	75 (11%)
Patients Genotyped with ≥1 Mutations	176 (42%)
Patients receiving treatment matched to genotype (% of patients with mutations)	43 (24%)
Patients enrolled in clinical trials matched to genotype (% of patients matched)	23 (53%)
Number of trial enrollments	25

MOSCATO 01

Single institution
All solid tumors
Umbrella protocol

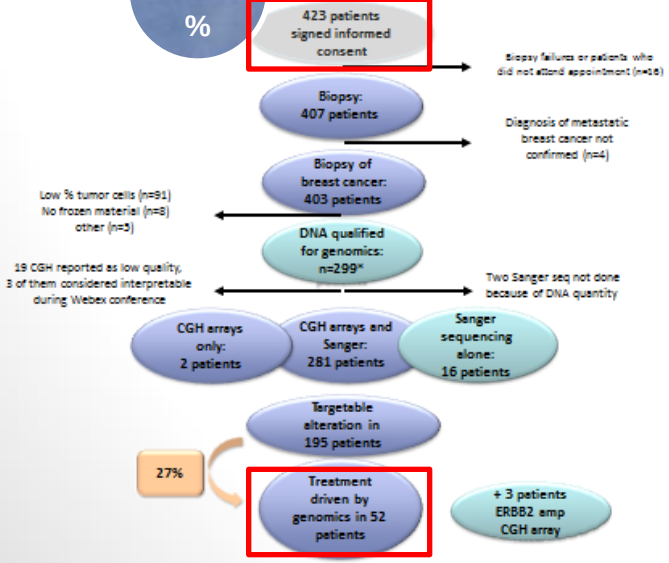
19 %



SAFIR

Multiple institutions
All solid tumors
Umbrella protocol

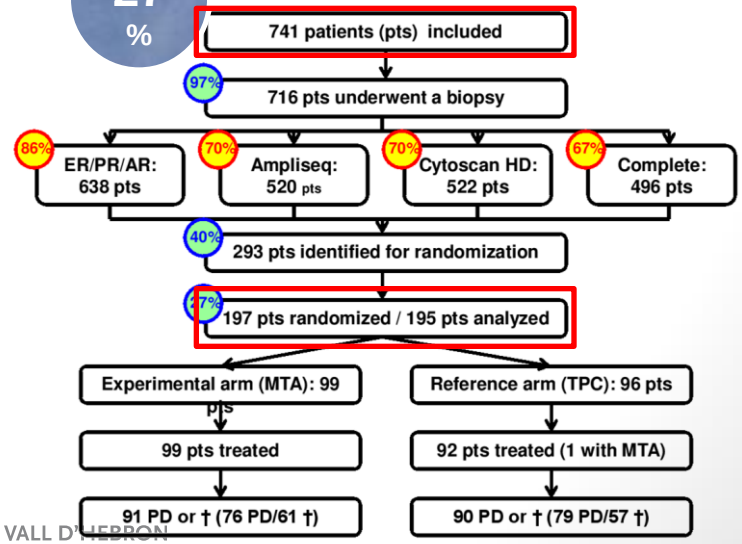
12 %



SHIVA

Multiple institutions
Breast cancer
Clinical trial

27 %



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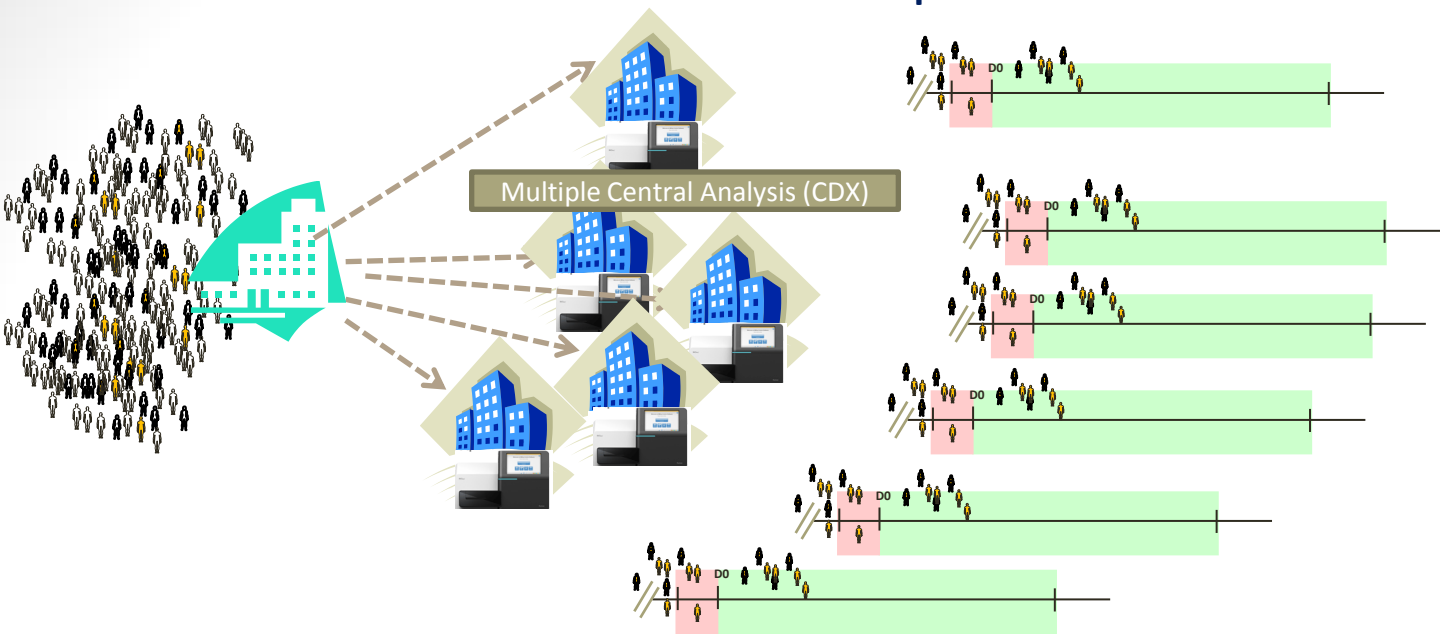
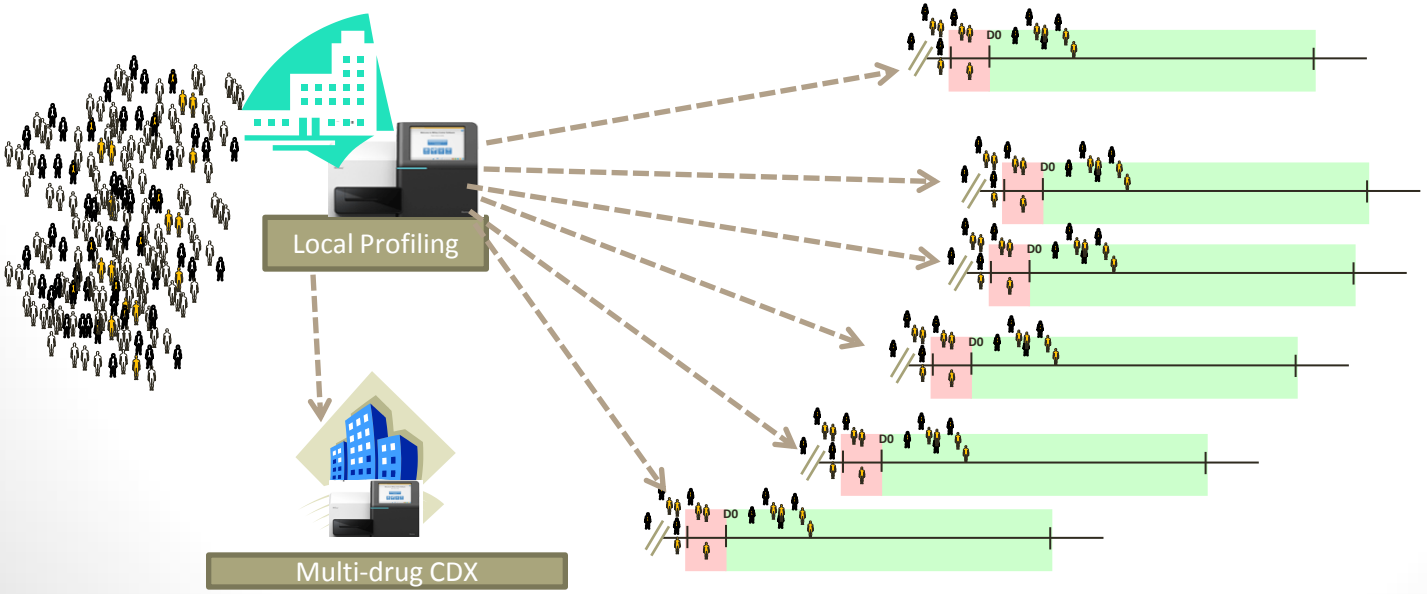
Current situation: sample exhaustion



Proposal: Facilitating collaboration, and development of MultiDrug CDx



Dr. Livingstone, I presume?

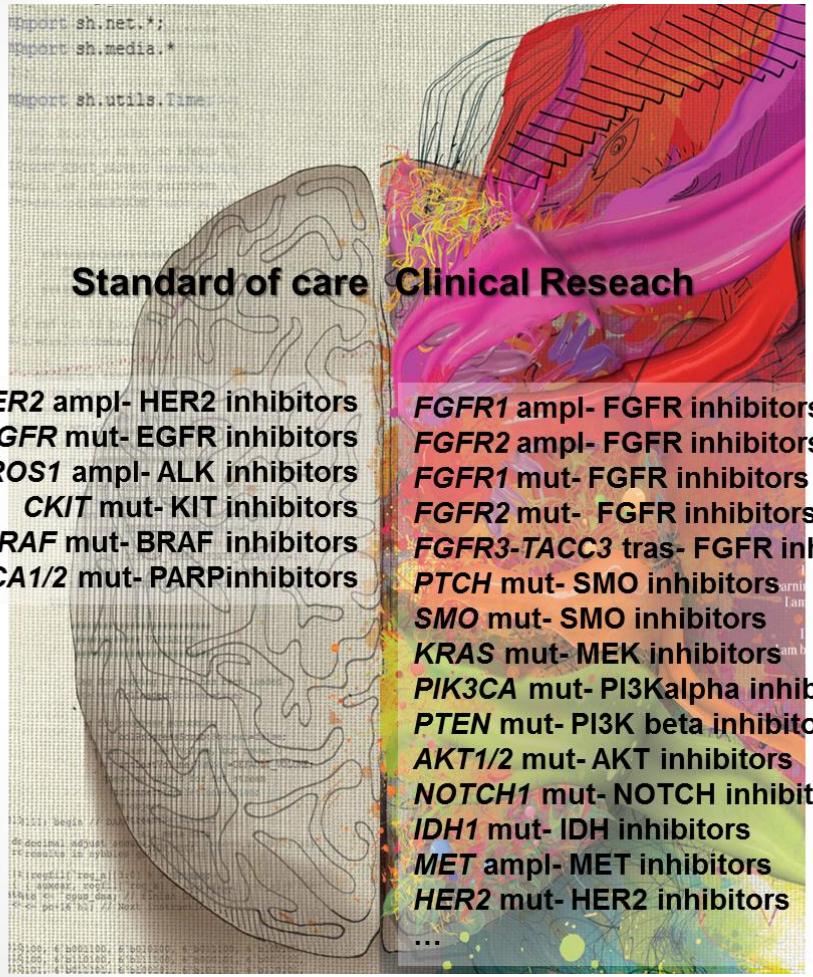
(Henry Morton Stanley)

FINDING PATIENTS THAT CAN BENEFIT...

...MULTI-DRUG COMPANION DIAGNOSTIC?

Proposed application of NGS in today's research and clinic

MultiDrug CDx and Research analytes coexistance

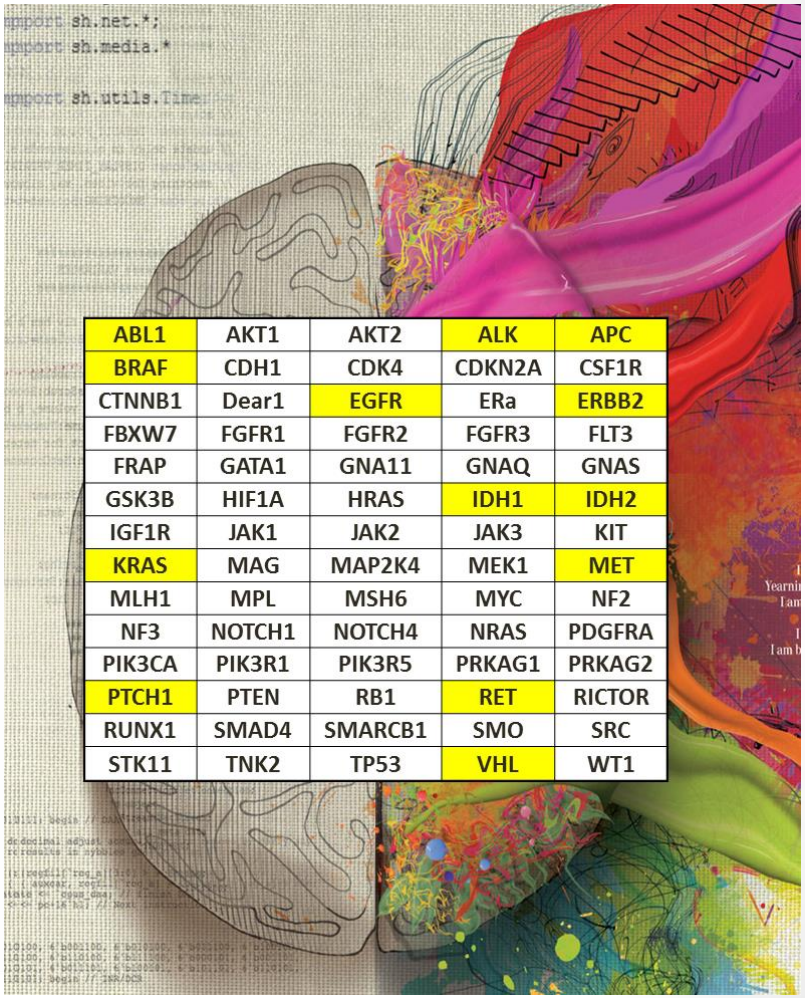


Standard of care

HER2 ampl- HER2 inhibitors
EGFR mut- EGFR inhibitors
ALK/ROS1 ampl- ALK inhibitors
CKIT mut- KIT inhibitors
BRAF mut- BRAF inhibitors
BRCA1/2 mut- PARPinhibitors

Clinical Reseach

FGFR1 ampl- FGFR inhibitors
FGFR2 ampl- FGFR inhibitors
FGFR1 mut- FGFR inhibitors
FGFR2 mut- FGFR inhibitors
FGFR3-TACC3 tras- FGFR inhibitors
PTCH mut- SMO inhibitors
SMO mut- SMO inhibitors
KRAS mut- MEK inhibitors
PIK3CA mut- PI3Kalpha inhibitors
PTEN mut- PI3K beta inhibitors
AKT1/2 mut- AKT inhibitors
NOTCH1 mut- NOTCH inhibitors
IDH1 mut- IDH inhibitors
MET ampl- MET inhibitors
HER2 mut- HER2 inhibitors
…



ABL1	AKT1	AKT2	ALK	APC
BRAF	CDH1	CDK4	CDKN2A	CSF1R
CTNNB1	Dear1	EGFR	ERa	ERBB2
FBXW7	FGFR1	FGFR2	FGFR3	FLT3
FRAP	GATA1	GNA11	GNAQ	GNAS
GSK3B	HIF1A	HRAS	IDH1	IDH2
IGF1R	JAK1	JAK2	JAK3	KIT
KRAS	MAG	MAP2K4	MEK1	MET
MLH1	MPL	MSH6	MYC	NF2
NF3	NOTCH1	NOTCH4	NRAS	PDGFRA
PIK3CA	PIK3R1	PIK3R5	PRKAG1	PRKAG2
PTCH1	PTEN	RB1	RET	RICTOR
RUNX1	SMAD4	SMARCB1	SMO	SRC
STK11	TNK2	TP53	VHL	WT1

ISO-certified

Clinical Reseach (masked)

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Conclusions

1. We now have more knowledge, better science, much better technology and better drugs, and social media, so clinical trials in small patient populations are feasible
2. Cancer has the opportunity to define multiple small subsets where specific drugs can achieve high efficacy
3. There are many opportunities to consider histology-agnostic approvals (*BRCA1/2* mut tumors, *FGFR* translocations, *NTRK1-4* translocations...).
4. Need to reconsider CDx development. Multi-drug companion diagnostic?