Memorial Sloan Kettering Cancer Center™

Drug registration strategies: How will these change with precision medicine?

2014. ESMO. Precision Medicine: Panacea or false dawn

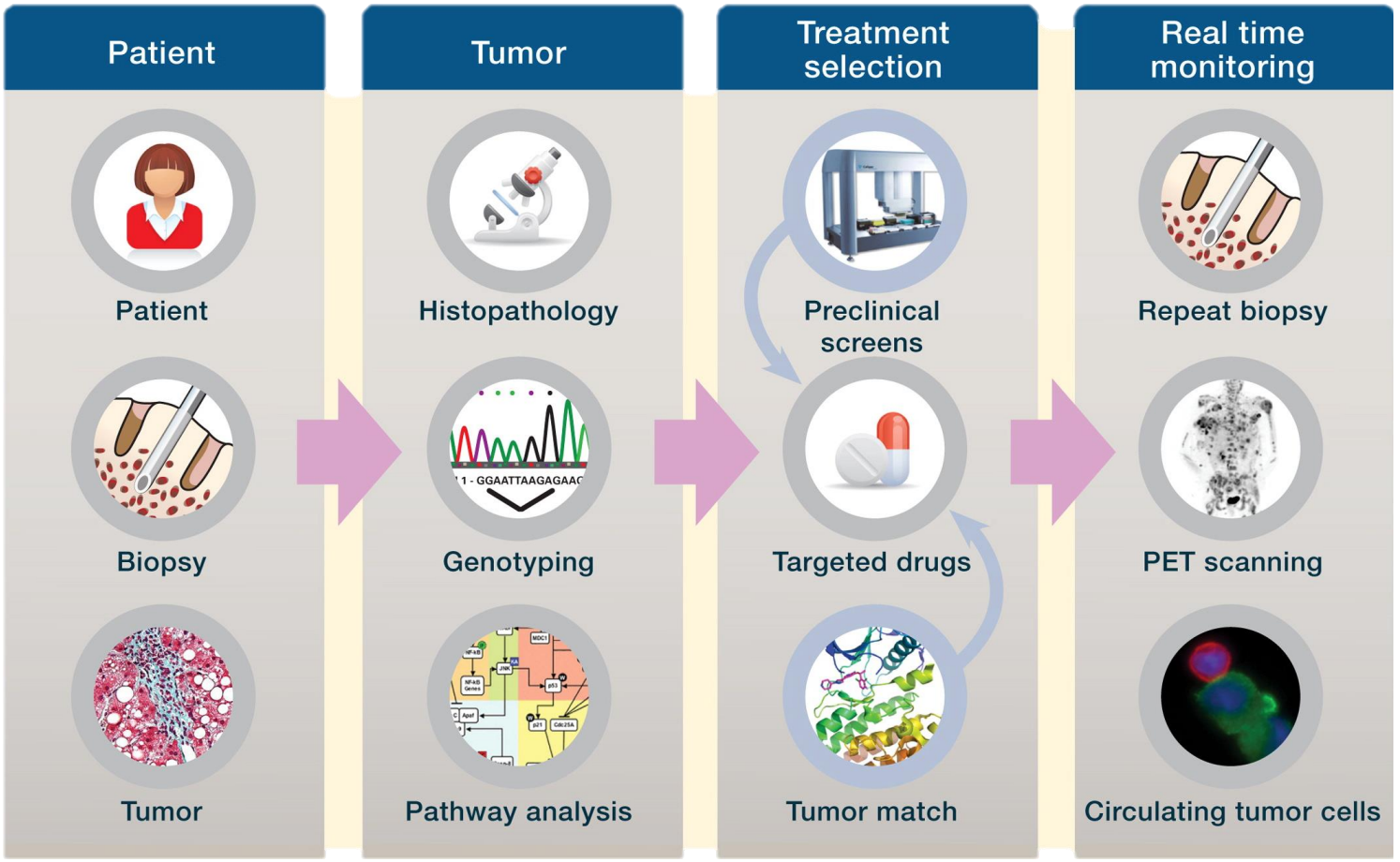
Jose Baselga
www. MSKCC.org

Disclosures

- Advisory/Scientific Committees
  - Novartis, Verastem, Eli-Lilly, Juno Therapeutics
- Board of Directors
  - Aura, Infinity

The Vision for "Precision Medicine" in Cancer

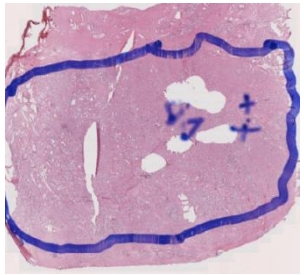
Genotype first, select target, monitor early response



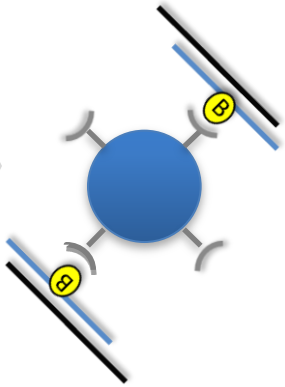
Haber, Gray, Baselga, *Cell*, 2011

MSK-IMPACT™:
Integrated Mutation Profiling of Actionable Cancer Targets

Prepare DNA from **Tumor** and **Normal** cells



Capture DNA for **341 cancer genes**



"Next gen" Sequencing (HiSeq 2500)

Align to genome and analyze

Won *et al.*, *Journal of Visualized Experiments*, Oct 2013

Somatic Alterations (specific to tumor):
Sequence Mutations
Copy Number Gains and Losses
Select Rearrangements

Selection of 341 Key Cancer Genes

Gene Selection Committee: Representatives from Pathology, Medical Oncology, Radiation Oncology, HOPP, and Computational Biology

Additional Input from solid tumor teams, phase I and immunotherapy clinics, CMBT, and clinical genetics service

ABL1	BARD1	CD79B	DDR2	ESR1	FOXP1	IKBKE	MAP2K1	MUTYH	PALB2	POLE	RET	SMARCB1	TNFRSF14
AKT1	BBC3	CDC73	DICER1	ETV1	FUBP1	IKZF1	MAP2K2	MYC	PARK2	PPP2R1A	RFWD2	SMARCD1	TOP1
AKT2	BCL2	CDH1	DIS3	ETV6	GATA1	IL10	MAP2K4	MYCL1	PARP1	PRDM1	RHOA	SMO	TP53
AKT3	BCL2L1	CDK12	DNMT1	EZH2	GATA2	IL7R	MAP3K1	MYCN	PAX5	PRKAR1A	RICTOR	SOCS1	TP63
ALK	BCL2L11	CDK4	DNMT3A	FAM123B	GATA3	INPP4A	MAP3K13	MYD88	PBRM1	PTCH1	RIT1	SOX17	TRAF7
ALOX12B	BCL6	CDK6	DNMT3B	FAM175A	GNA11	INPP4B	MAPK1	MYOD1	PDCD1	PTEN	RNF43	SOX2	TSC1
APC	BCOR	CDK8	DOT1L	FAM46C	GNAQ	INSR	MAX	NBN	PDGFRA	PTPN11	ROS1	SOX9	TSC2
AR	BLM	CDKN1A	E2F3	FANCA	GNAS	IRF4	MCL1	NCOR1	PDGFRB	PTPRD	RPS6KA4	SPEN	TSHR
ARAF	BMPR1A	CDKN1B	EED	FANCC	GREM1	IRS1	MDC1	NF1	PDPK1	PTPRS	RPS6KB2	SPOP	U2AF1
ARID1A	BRAF	CDKN2A	EGFL7	FAT1	GRIN2A	IRS2	MDM2	NF2	PHOX2B	PTPRT	RPTOR	SRC	VHL
ARID1B	BRCA1	CDKN2B	EGFR	FBXW7	GSK3B	JAK1	MDM4	NFE2L2	PIK3C2G	RAC1	RUNX1	STAG2	VTCN1
ARID2	BRCA2	CDKN2C	EIF1AX	FGF19	H3F3C	JAK2	MED12	NKX2-1	PIK3C3	RAD50	RYBP	STK11	WT1
ARID5B	BRD4	CHEK1	EP300	FGF3	HGF	JAK3	MEF2B	NKX3-1	PIK3CA	RAD51	SDHA	STK40	XIAP
ASXL1	BRIP1	CHEK2	EPCAM	FGF4	HIST1H1C	JUN	MEN1	NOTCH1	PIK3CB	RAD51B	SDHAF2	SUFU	XPO1
ASXL2	BTK	CIC	EPHA3	FGFR1	HIST1H2BD	KDM5A	MET	NOTCH2	PIK3CD	RAD51C	SDHB	SUZ12	YAP1
ATM	CARD11	CREBBP	EPHA5	FGFR2	HIST1H3B	KDM5C	MITF	NOTCH3	PIK3CG	RAD51D	SDHC	SYK	YES1
ATR	CASP8	CRKL	EPHB1	FGFR3	HNF1A	KDM6A	MLH1	NOTCH4	PIK3R1	RAD52	SDHD	TBX3	
ATRX	CBFB	CRLF2	ERBB2	FGFR4	HRAS	KDR	MLL	NPM1	PIK3R2	RAD54L	SETD2	TERT	
AURKA	CBL	CSF1R	ERBB3	FH	ICOSLG	KEAP1	MLL2	NRAS	PIK3R3	RAF1	SF3B1	TET1	
AURKB	CCND1	CTCF	ERBB4	FLCN	IDH1	KIT	MLL3	NSD1	PIM1	RARA	SH2D1A	TET2	
AXIN1	CCND2	CTLA4	ERCC2	FLT1	IDH2	KLF4	MPL	NTRK1	PLK2	RASA1	SHQ1	TGFBR1	
AXIN2	CCND3	CTNNB1	ERCC3	FLT3	IFNGR1	KRAS	MRE11A	NTRK2	PMAIP1	RB1	SMAD2	TGFBR2	
AXL	CCNE1	CUL3	ERCC4	FLT4	IGF1	LATS1	MSH2	NTRK3	PMS1	RBM10	SMAD3	TMEM127	
B2M	CD274	DAXX	ERCC5	FOXA1	IGF1R	LATS2	MSH6	PAK1	PMS2	RECQL4	SMAD4	TMPRSS2	
BAP1	CD276	DCUN1D1	ERG	FOXL2	IGF2	LMO1	MTOR	PAK7	PNRC1	REL	SMARCA4	TNFAIP3	

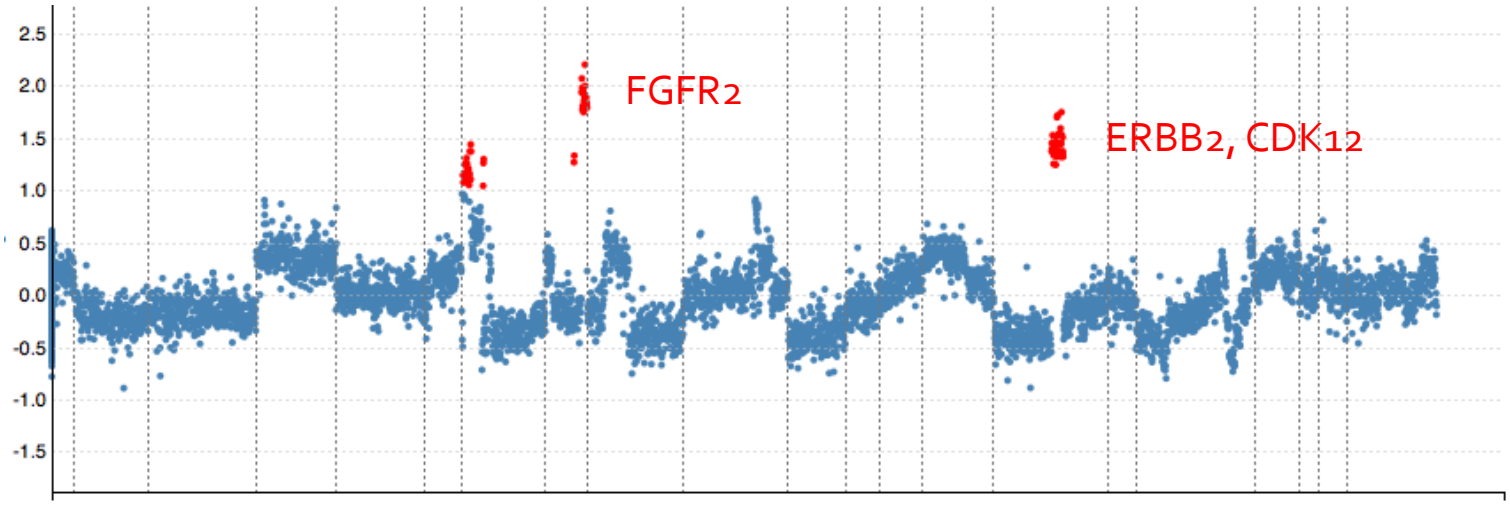
Case Example: Breast Cancer Patient

Several Important Alterations Found Using MSK-IMPACT

Mutations

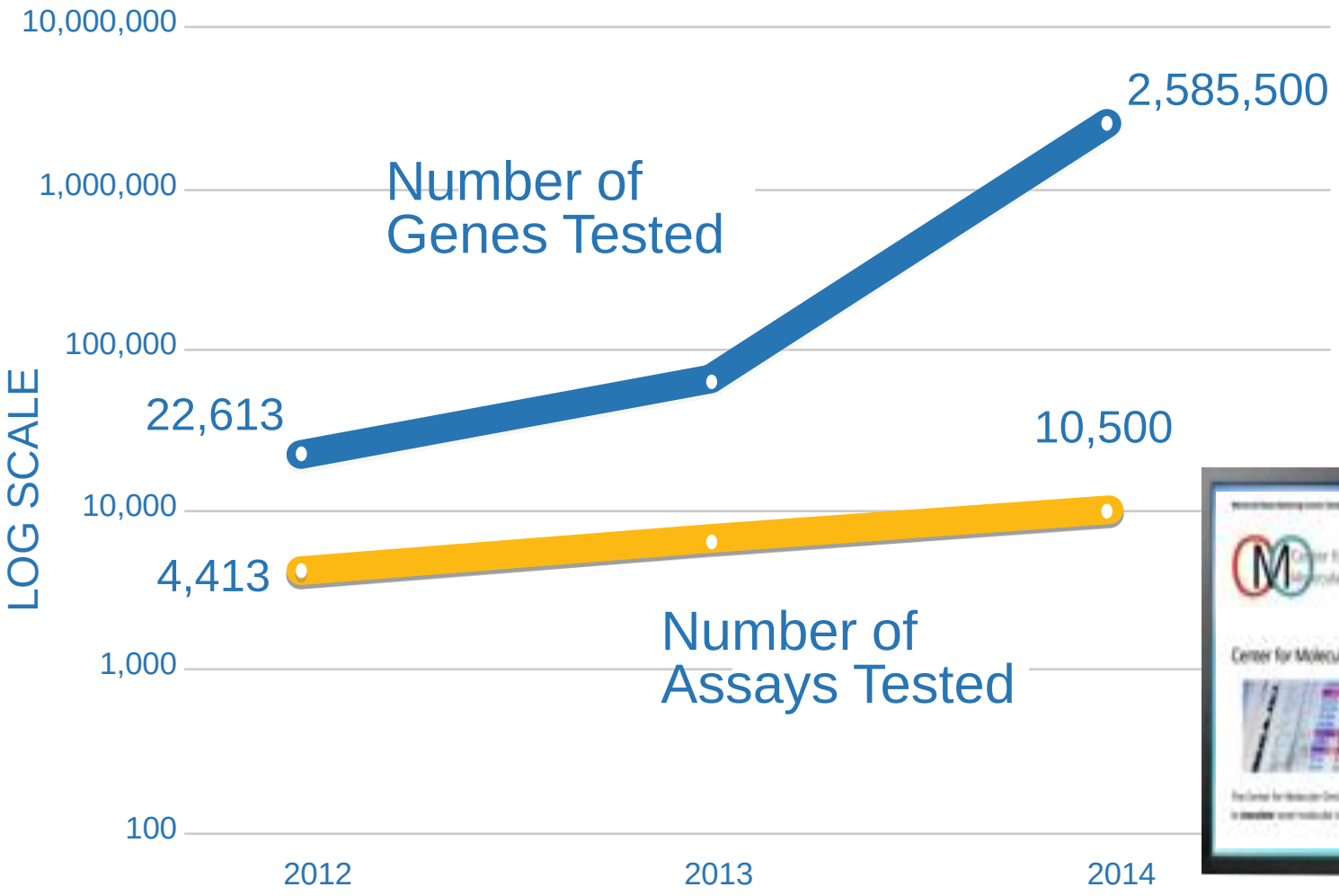
10	89720804	ACTTT	A	PTEN	exon8	NM_000314	c.956_959delCTTT	p.T319fs
17	7578397	TG	T	TP53	exon5	NM_000546	c.532delC	p.H178fs

Copy Number Alterations



Tumor DNA Sequencing

DIAGNOSTIC MOLECULAR PATHOLOGY LAB



cBioPortal: Cohort-Level Display (current)

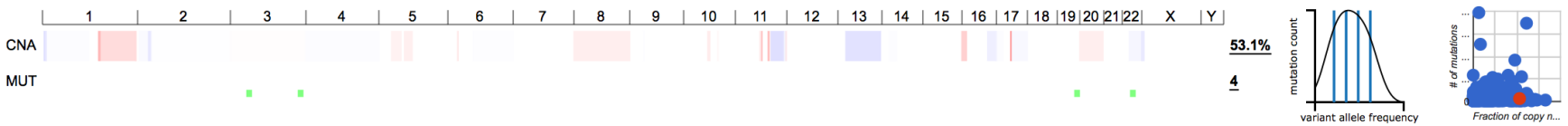
cBioPortal: Patient-Level Display (current)

DMP0197 More about this tumor

DMP MSK-IMPACT Clinical Runs (MSKCC 2014), NA

Summary | Mutations | Copy Number Alterations | Drugs | Clinical Trials

Genomic Overview



Mutations of interest (4 of 4)

Search:

Gene	Protein Change	Type	Allele Freq	Copy #	Cohort	cBioPortal	COSMIC	Mutation Assessor	Drugs
PIK3CA	*H1047R*	Missense	0.41	diploid	17.1%	516	1878	Neutral	
BAP1	*E642D*	Missense	0.11	diploid	2.8%	1		Low	
ERCC2	*A144V*	Missense	0.26	diploid	0.9%	3		Medium	
CHEK2	*V198L*	Missense	0.58	diploid	0.2%	1		Low	

Show all 4 mutations — Show 25 per page

CNA of interest (4 of 4)

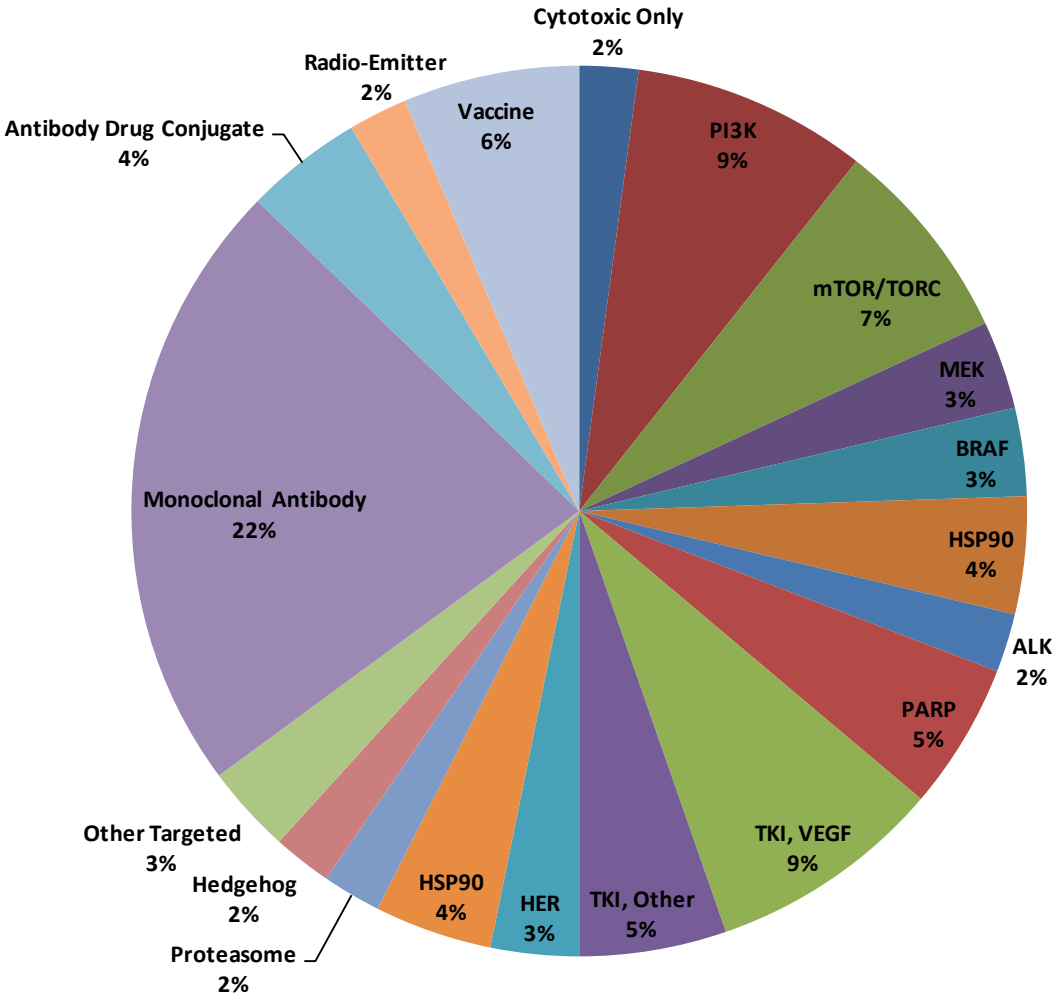
Search:

Gene	Cytoband	CNA	Cohort	Drugs
ERBB2	17q12	AMP	7.6%	
CDK12	17q12	AMP	4.1%	
RARA	17q21	AMP	2.1%	
EED	11q14.2-q22.3	AMP	0.4%	

Show all 4 CNAs — Show 25 per page

Clinical Trials are "Targeted": Need for Genomic Data

Drug Class/Target for Open Phase I-I/II Studies, MSKCC 2013*



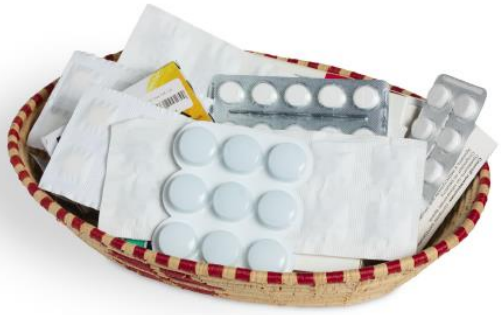
*Division of Solid Tumor, 85 Unique Protocols

- Only 2% standard "cytotoxics"
- Many genomic targets are low prevalence (< 5%) disease of interest
- Genomic data needed for
  - Eligibility
  - Biomarker development
- Genomic data associated with response to immunotherapy

Basket Studies

- First generation studies are underway:
  - PI3K, AKT, FGFR, ERBB2, BRAF, etc
- Second generation will add complexity:
  - i.e. BRAF + EGFR MAbs

'Basket studies' will hold intricate data for cancer drug approvals



Basket case: Researchers weave a new trial design on the basis of genetics, rather than cancer type.

The notion of targeting specific cellular mutations to make malignancies disappear got a boost in April when the director of the US National Cancer Institute (NCI), Harold Varmus, unveiled plans for the so-called MATCH trial. Announced at the annual meeting of the American Association for Cancer Research in Washington, DC, the trial aims to match at least 1,000 individuals with a variety of cancer types with therapies that target the specific mutations found in their tumors. In a separate study described by Varmus, the NCI will also genotype 100 'exceptional responders': trial participants who show noticeable improvements after treatment with cancer drugs that didn't provide much benefit to others, in the hope of finding mutations that explain why the medicines worked.

Such studies are meant to be exploratory, but they may offer a glimpse of the future. "What we'd like to do is try a therapy based on the specific genetics or molecular features of your tumor and see if that will work better than flying blind," says Levi Garraway, a cancer geneticist at the Dana-Farber Cancer Institute in Boston.

However, as excitement grows about studies organized around cancer mutations rather than cancer type, it remains unclear how they will fit into the regulatory approval pathway. "This is *terra incognita*," says José Baselga, physician-in-chief of the Memorial Sloan-Kettering Cancer Center in New York.

Baselga is pioneering this new type of genotype-focused clinical trial design. Last year, he and his colleagues launched a study to examine the effect of Zelboraf (vemurafenib), a drug from California's Genentech, in 101 patients with cancer with a mutation called *BRAF* V600E. *BRAF* V600E is relatively common in individuals with melanoma, for which the drug was approved in 2011, but also occurs less frequently in other types of cancer. The drug showed little efficacy in a phase 1 trial involving patients with *BRAF*-mutant colorectal cancer (*J. Clin. Oncol.* 28, 15s, 2010), but promising clinical activity in a recently published study involving three people with metastatic papillary thyroid cancer (PTC) harboring the mutation (*Thyroid*, http://doi.org/mh9, 2013). Baselga and his colleagues hope to find out who else the drug could help. The trial is open to individuals with multiple myeloma and almost any type of solid tumor that contains a *BRAF* V600E mutation, save melanoma and PTC.

This kind of trial is known as a 'basket study', and the approach is particularly useful when the cancer type or the mutation is rare. According to Memorial Sloan-Kettering cancer researcher David Solit, the goal generally is to enroll about 10–15 subjects per tumor type, but such studies also typically include an 'other' category for patients with rare types of cancer in which the mutation of interest was not previously known to occur. In such cases, a randomized clinical trial—the gold standard for drug approvals—may not be feasible because only a small number of people fit the profile for any given disease.

Regulatory agencies such as the US Food and Drug Administration (FDA) are not likely to approve a drug on the basis of data from only a couple of people. But if the drug worked for these participants, "then what you do is you enrich that cohort," Baselga says. In some cases, simply expanding the study to include more participants with a particular type of cancer might be sufficient for approval, especially when the results are striking and the need is great.

A numbers game

The FDA recognizes that recruiting study participants can be difficult in some cases. "We have approved drugs in small numbers of patients on single-arm trials cognizant of the fact that it would be difficult to enroll a large number of patients," says Richard Pazdur, head of the FDA's Office of Hematology and Oncology Products. In January 2012, for example, the FDA approved Genentech's Erivedge (vismodegib), the first drug for advanced basal cell carcinoma, off the back of positive efficacy results from a single-arm, phase 2 trial that had enrolled only 104 patients.

In other cases, the mutation or cancer type might be common enough to do a follow-up study. In 2010, Baselga launched a phase 1 basket study to examine the safety and efficacy of an experimental compound from Switzerland's Novartis called BYL719 in solid tumors that have mutations in the gene that encodes a subunit of the phosphatidylinositol 3-kinase protein. The drug seemed to work well in women with estrogen receptor–positive breast cancer, so Baselga and his colleagues now plan to test the efficacy of BYL719 combined with the hormone therapy fulvestrant in this subgroup.

It's not unfathomable that the FDA could approve a drug for a specific molecular target rather than a disease. "If we can show that what we do is safe and effective, I would suspect the FDA would welcome that," says Tomasz Beer, deputy director of the Oregon Health and Science University's Knight Cancer Institute in Portland. "It just has to be convincing."

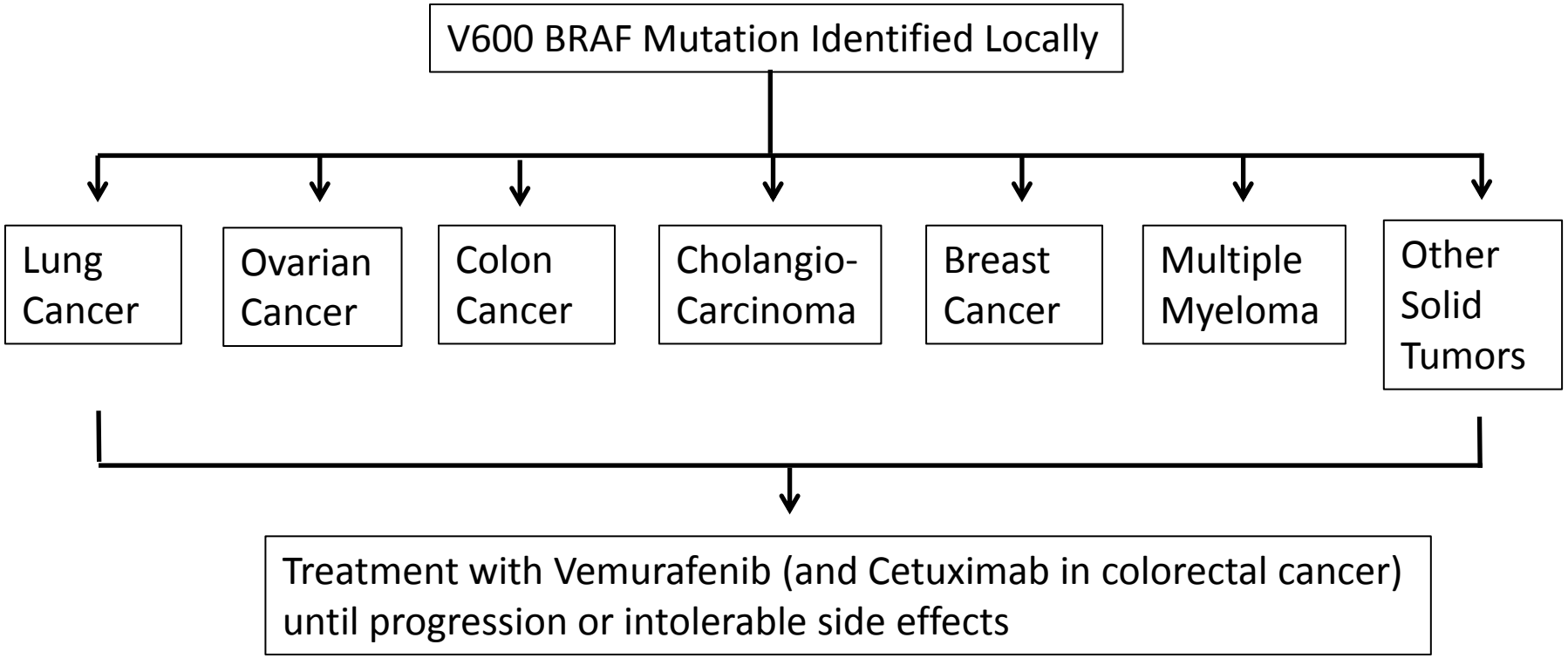
Pazdur agrees. "There's nothing in the regulations that says a drug has to be approved in breast cancer or colon cancer," he says.

In 2006, the FDA approved Novartis's targeted tyrosine kinase inhibitor Gleevec (imatinib) for five types of cancer at once, including several rare malignancies. But whether any targeted medications will have broad enough activity to warrant more sweeping approval remains to be seen. As the case of Zelboraf in colorectal cancer shows, just because a single mutation occurs in more than one type of cancer doesn't necessarily mean that a medication that targets it will work in both. "It's not just the mutation that's important. The type of cancer you have is important also," says Solit.

Teasing apart the interactions between mutational profiles and tumor types is now a top priority for the cancer field. Like many things in medicine, conquering the biology is often more challenging than clearing the regulatory hurdles.

Cassandra Willyard

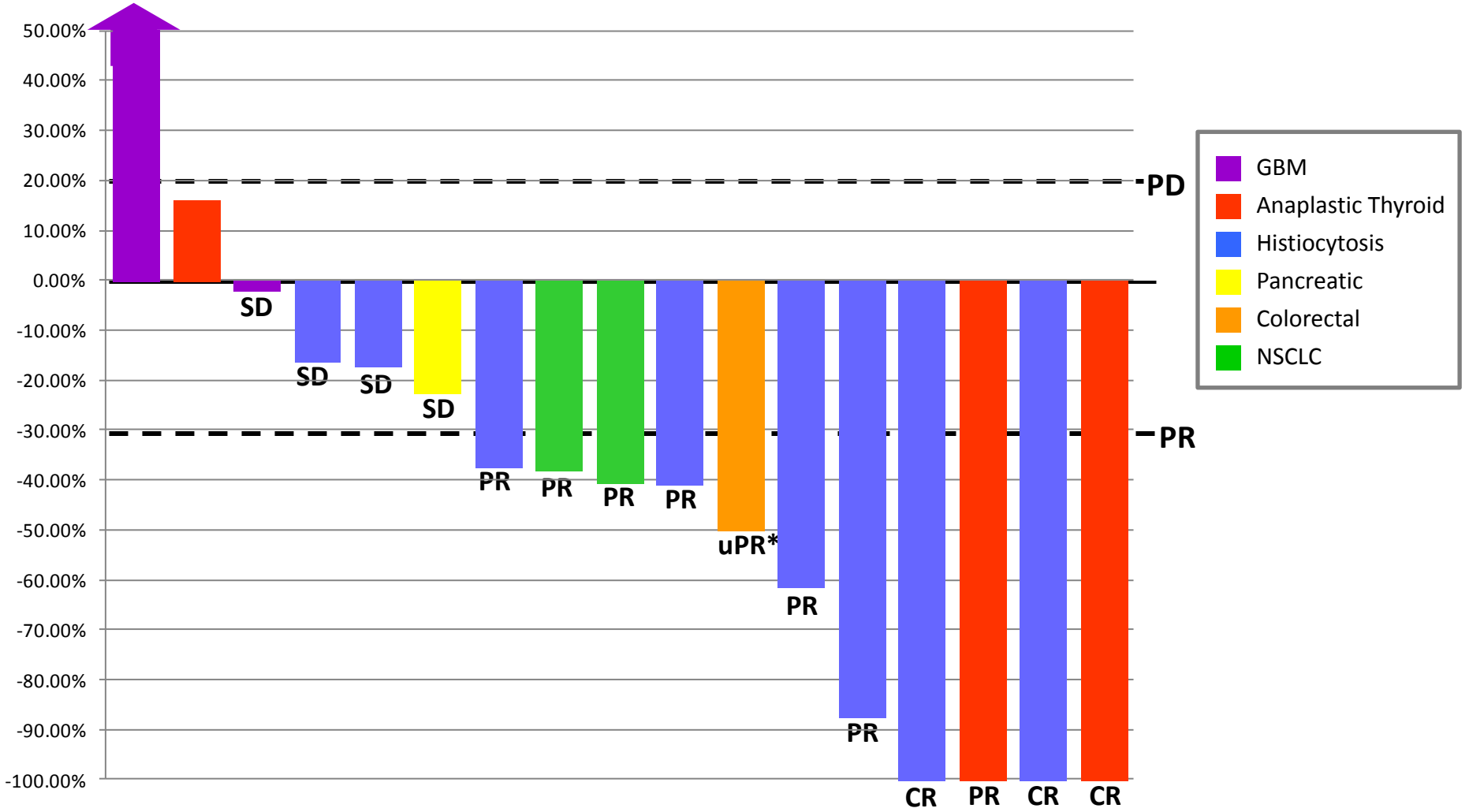
Vemurafenib Basket Study Schema



Primary Endpoint: Overall response rate (at 8 weeks)
Secondary Endpoint: Progression Free Survival

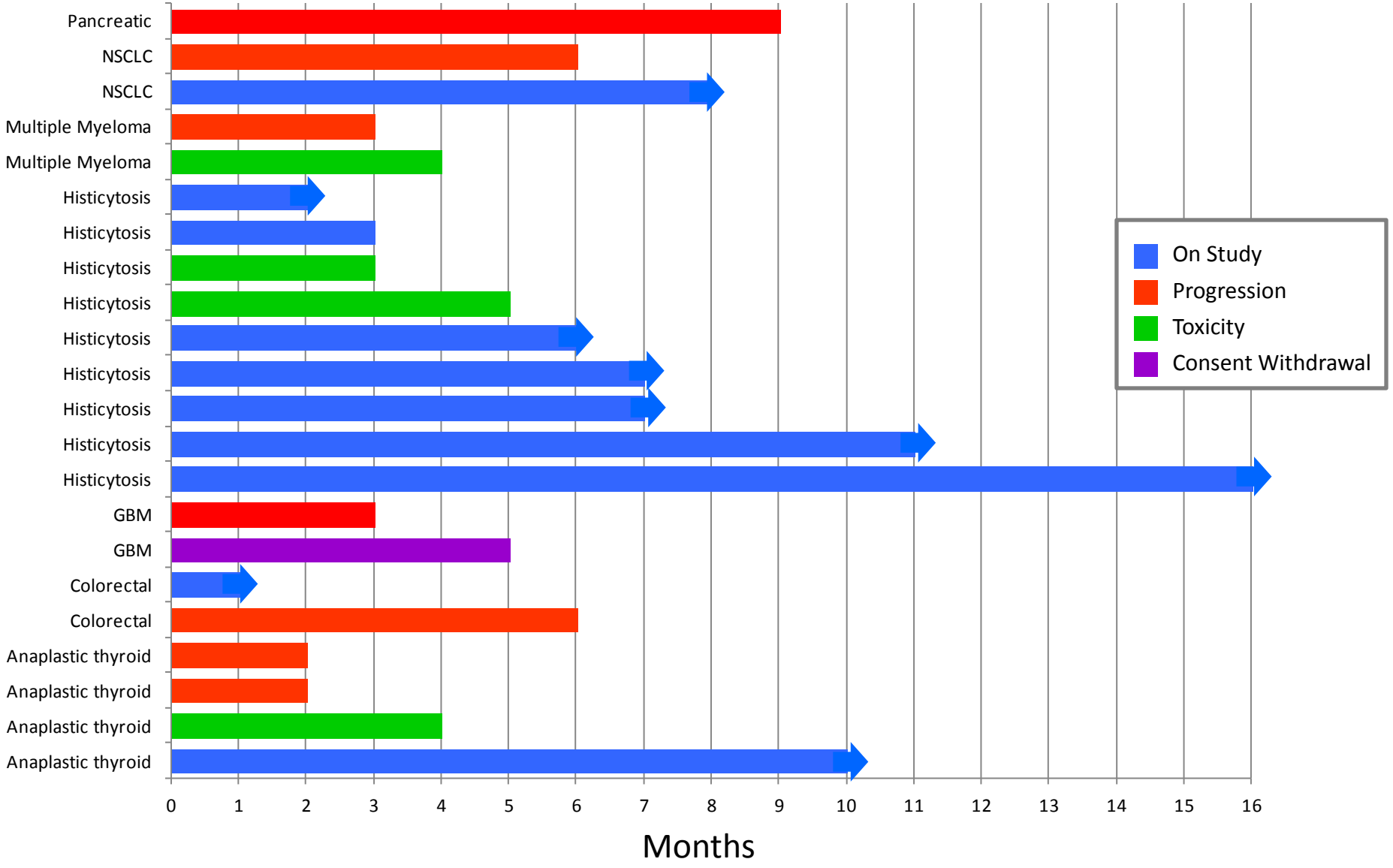
Centralized retrospective testing of all tumors to confirm V600 BRAF mutation

Vemurafenib Waterfall Plot (D. Hyman, MSKCC)

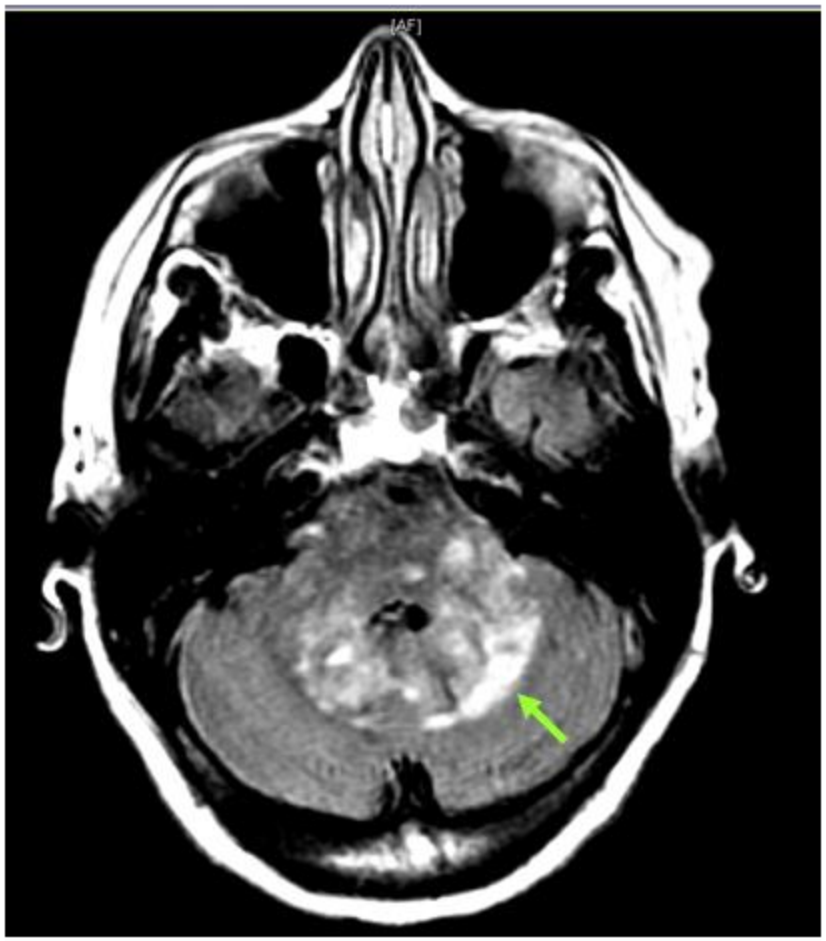


*-Vem+Cetux

Vemurafenib Time on Study (D. Hyman, MSKCC)



Erdheim Chester Disease



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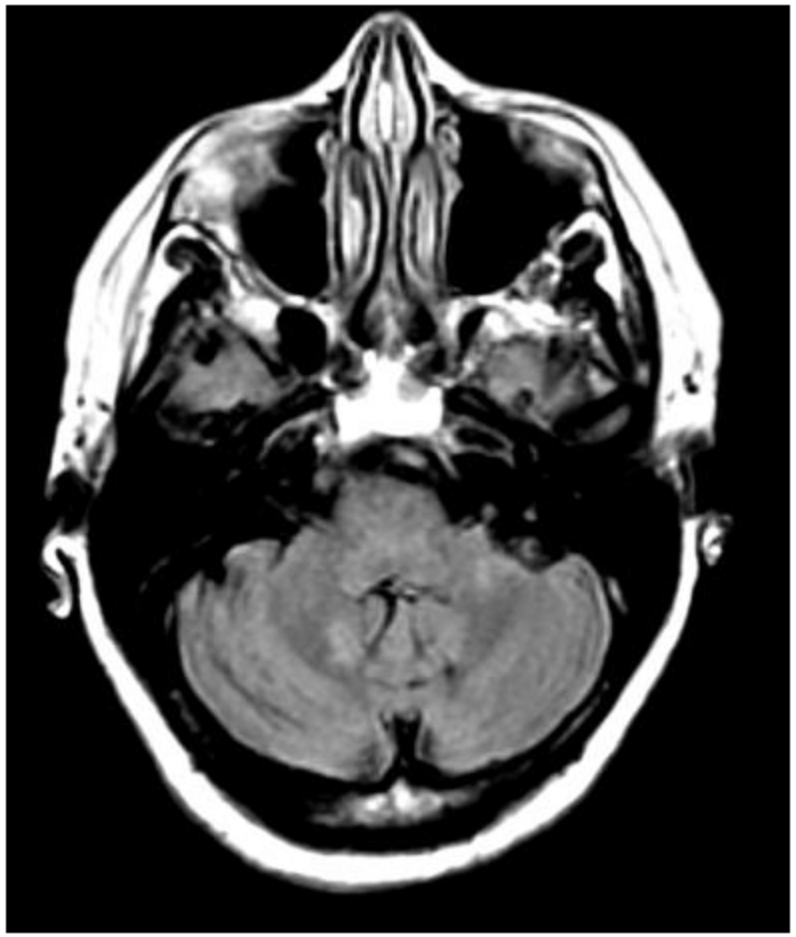
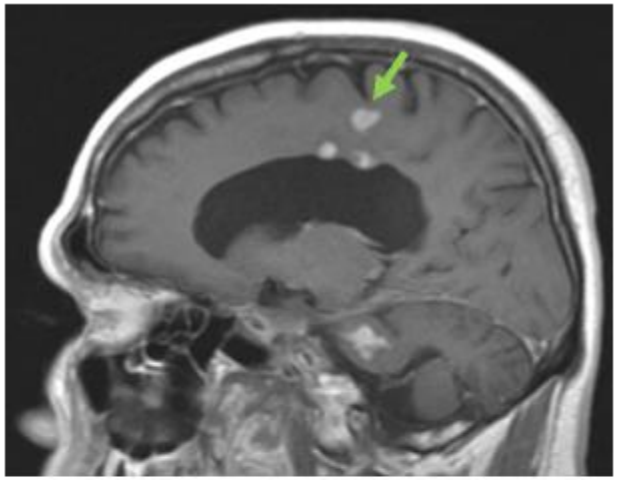


16 Months

Erdheim Chester Disease



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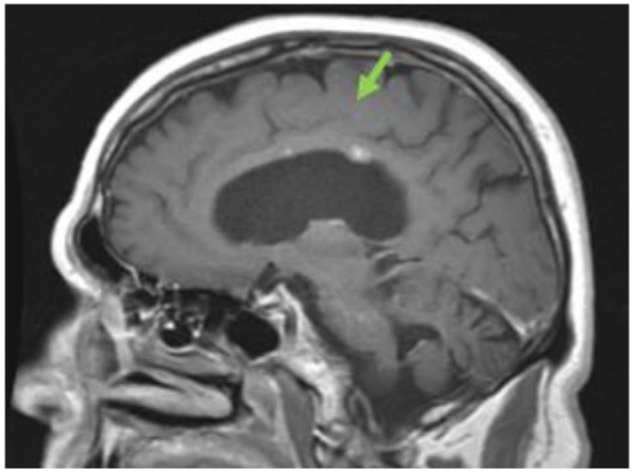
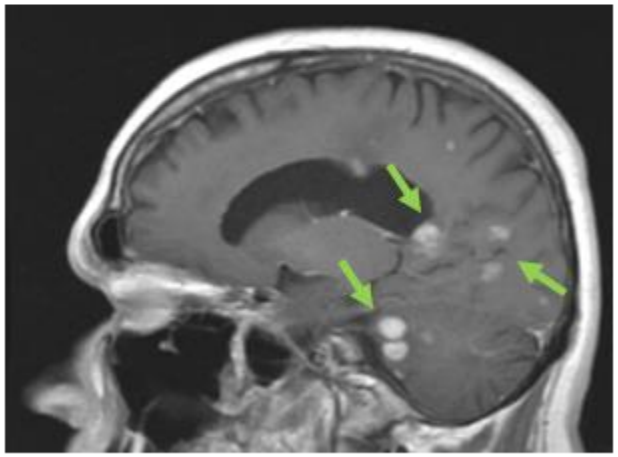
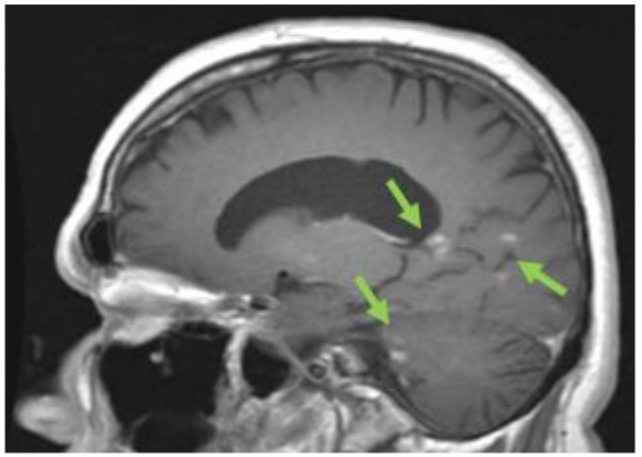
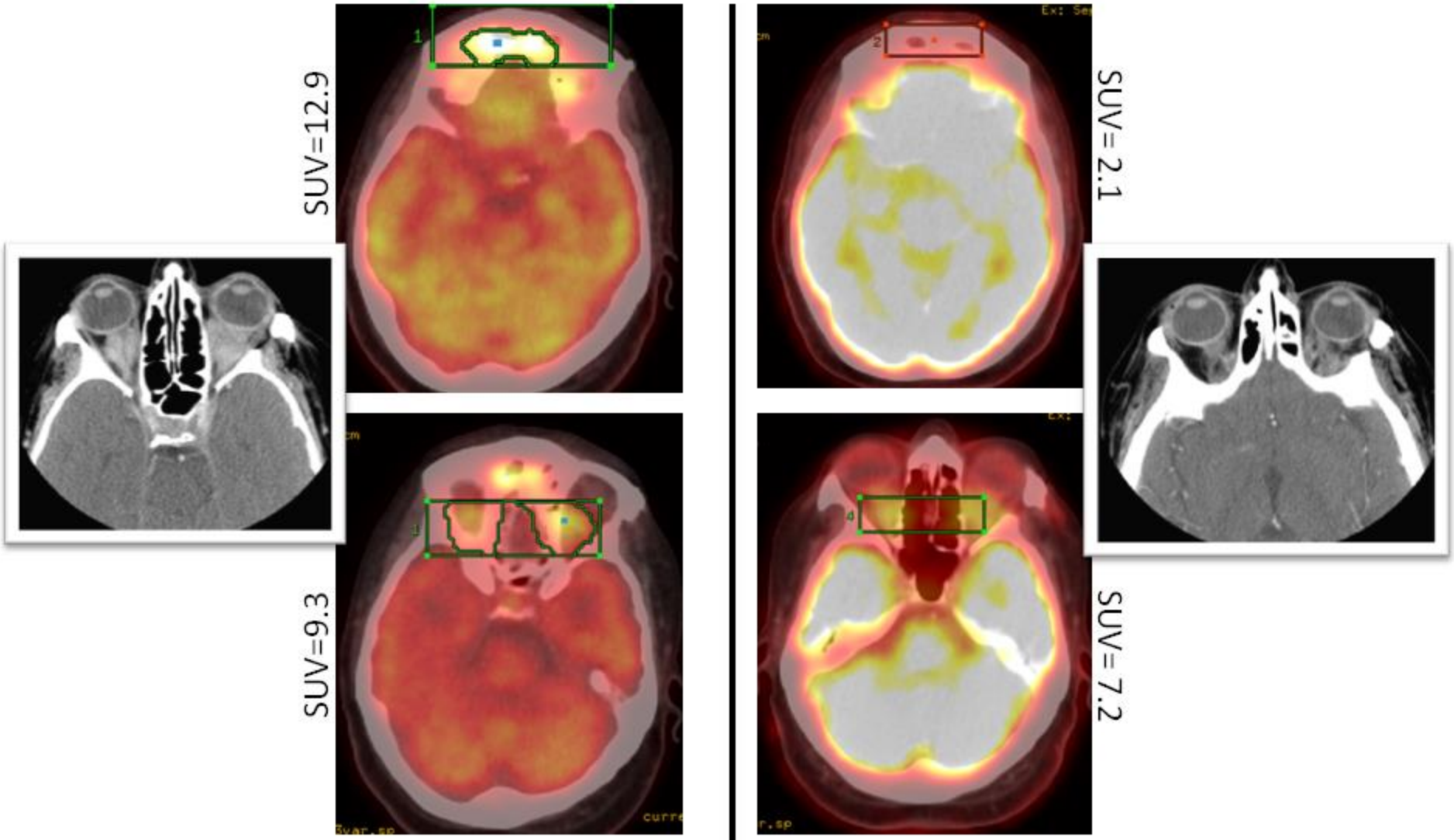


2 months





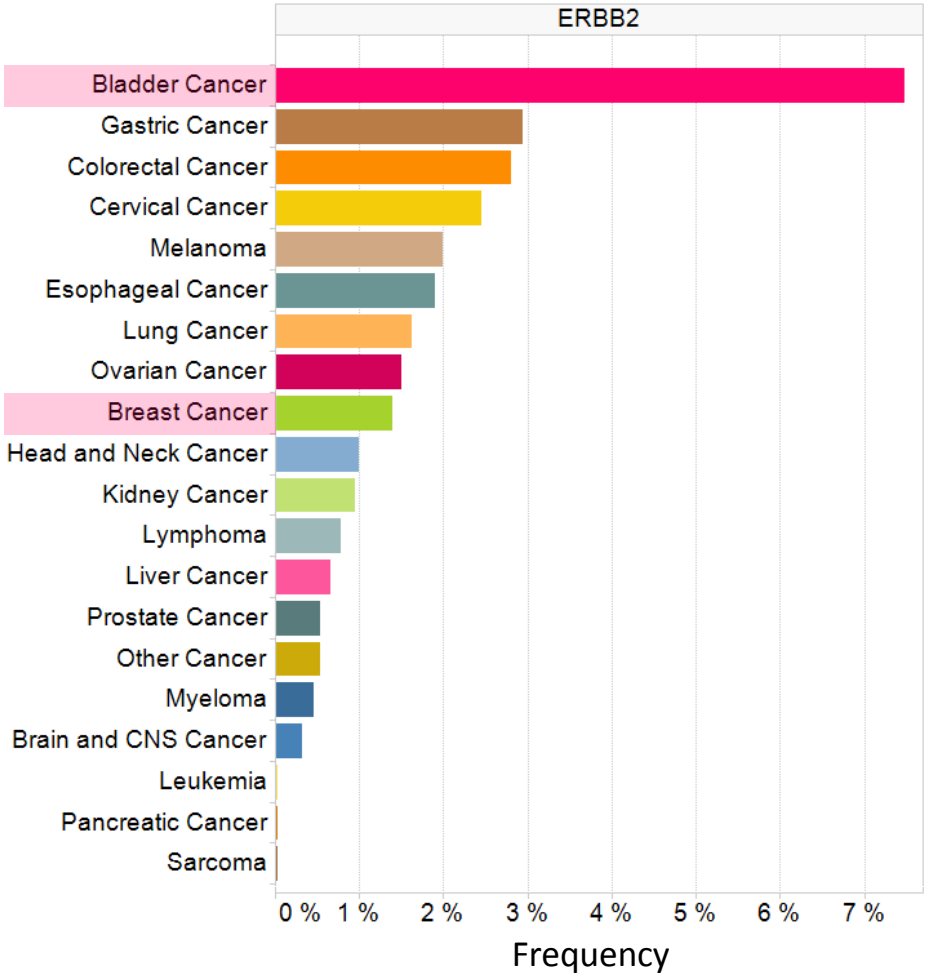
BRAF V600E ECD on Vemurafenib



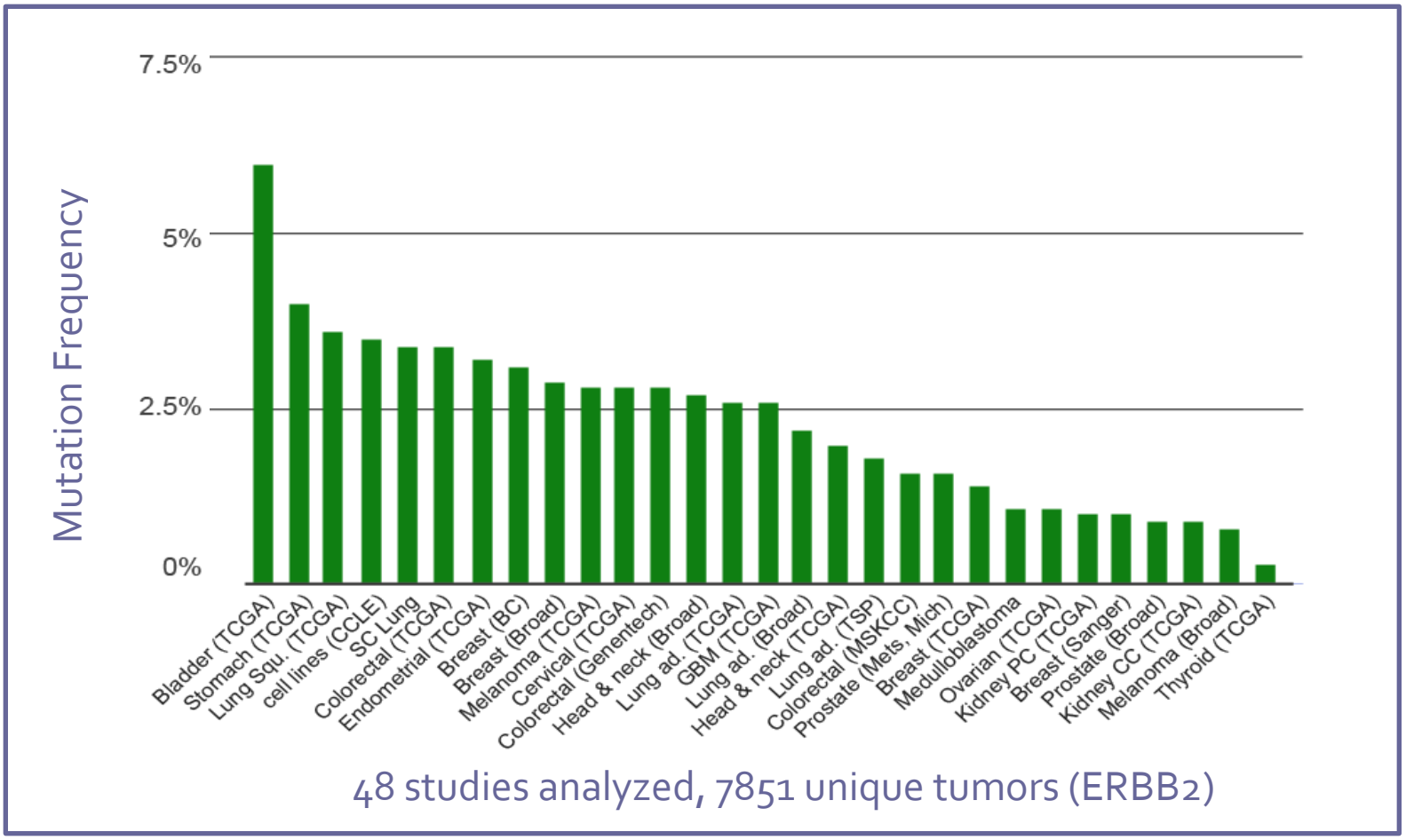
Frequency of *ERBB2* Mutations Across Cancer Types

General Cancer Type	ERBB2		
	Frequency	Count	Total
Bladder Cancer	7.5 %	28	375
Gastric Cancer	2.9 %	27	923
Colorectal Cancer	2.8 %	28	1005
Cervical Cancer	2.4 %	1	41
Melanoma	2.0 %	19	960
Esophageal Cancer	1.9 %	6	317
Lung Cancer	1.6 %	185	11464
Ovarian Cancer	1.5 %	16	1073
Breast Cancer	1.4 %	36	2611
Head and Neck Cancer	1.0 %	18	1834
Kidney Cancer	0.9 %	9	959
Lymphoma	0.8 %	2	259
Liver Cancer	0.6 %	4	622
Prostate Cancer	0.5 %	5	949
Other Cancer	0.5 %	8	1553
Myeloma	0.4 %	1	225
Brain and CNS Cancer	0.3 %	6	1987
Leukemia	0.0 %	0	753
Pancreatic Cancer	0.0 %	0	412
Sarcoma	0.0 %	0	481

Data is taken from Oncomine® Gene Browser and includes >28,800 patient samples subjected to whole exome sequencing.



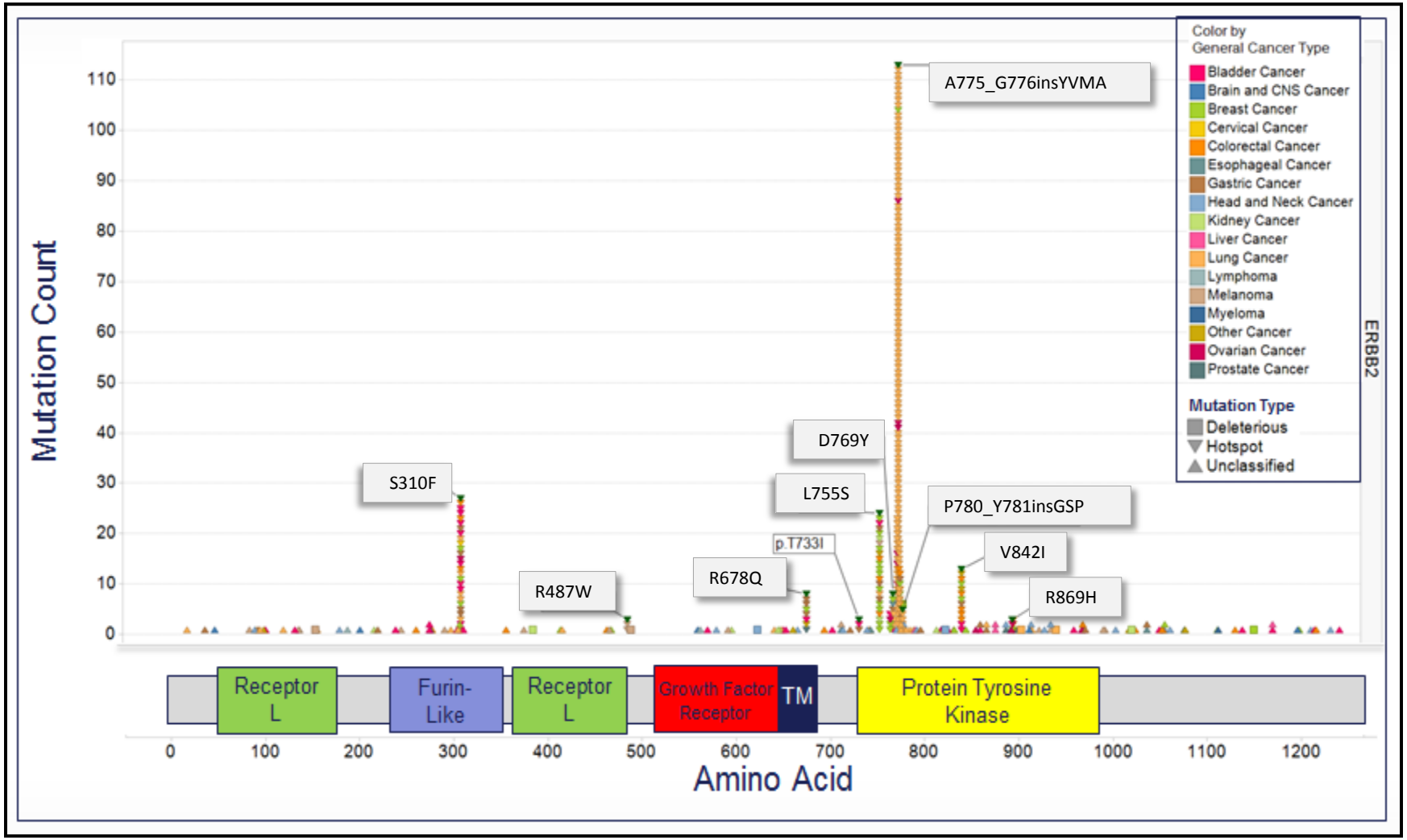
A Case for Basket Trials: Mutations are Infrequent



- Low prevalence (<5%) of mutation of interest across tumor types
- Single-histology studies with prospective centralized screening are impractical

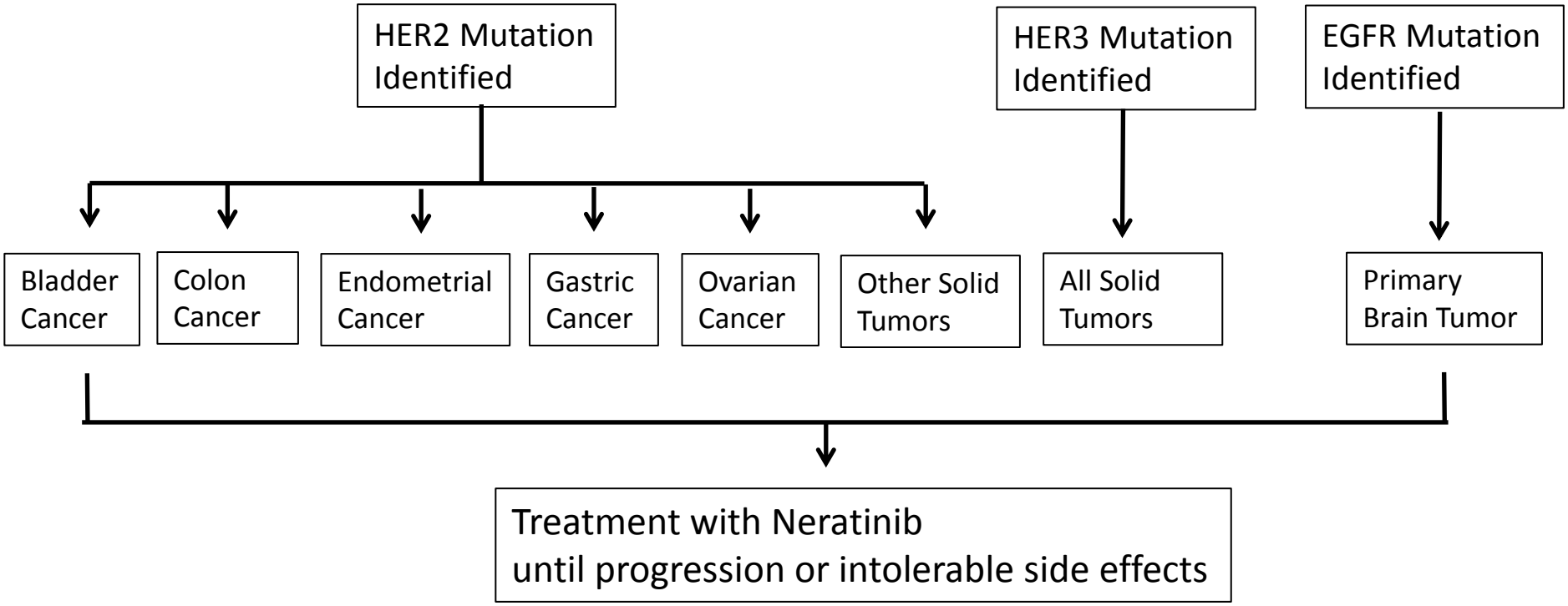
Data from MSK cBio.org

Distribution of *ERBB2* Mutations Across Cancer Types



Source: Life Technologies/Compendia Bioscience™. Data is taken from Oncomine® Gene Browser and includes >28,800 patient samples subjected to whole exome sequencing.

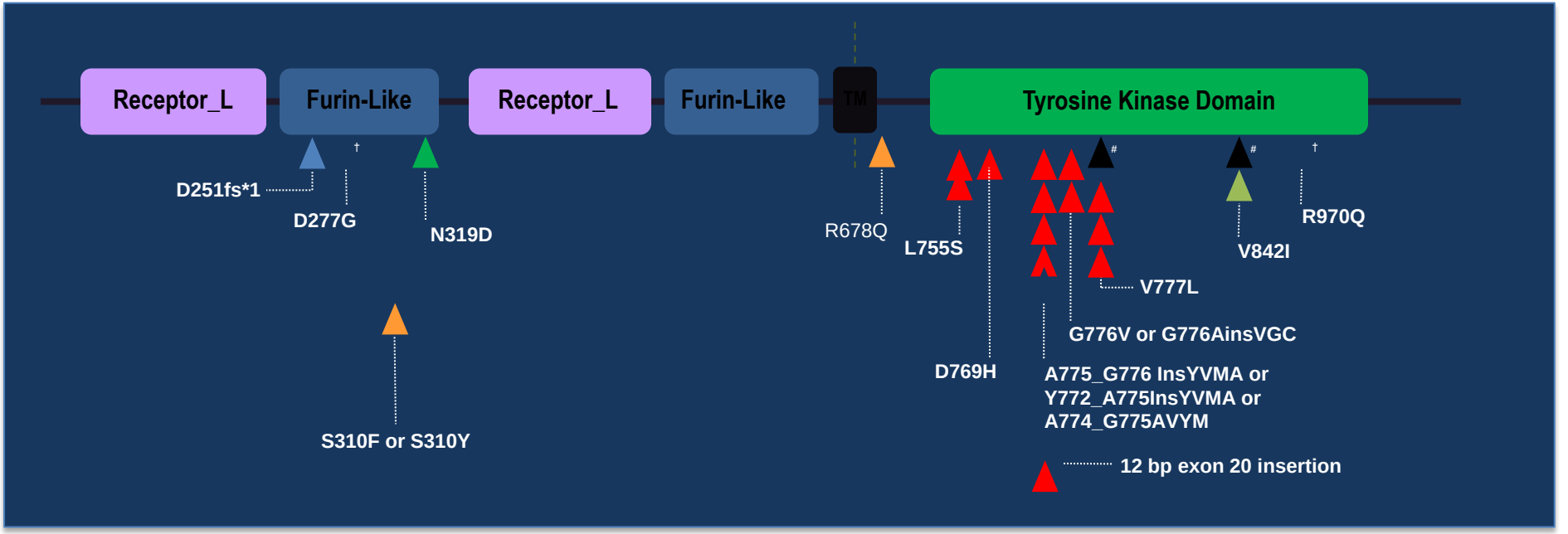
Neratinib Basket Study Schema



Primary Endpoint: Overall response rate (at 8 weeks)
Secondary Endpoints: PFS, OS

Multinational Study, MSKCC Lead Site
MSKCC Central Repository for All Biospecimens

Distribution of *ERBB2* Mutations in Patients Enrolled in Neratinib Basket Study



Tumor Legend

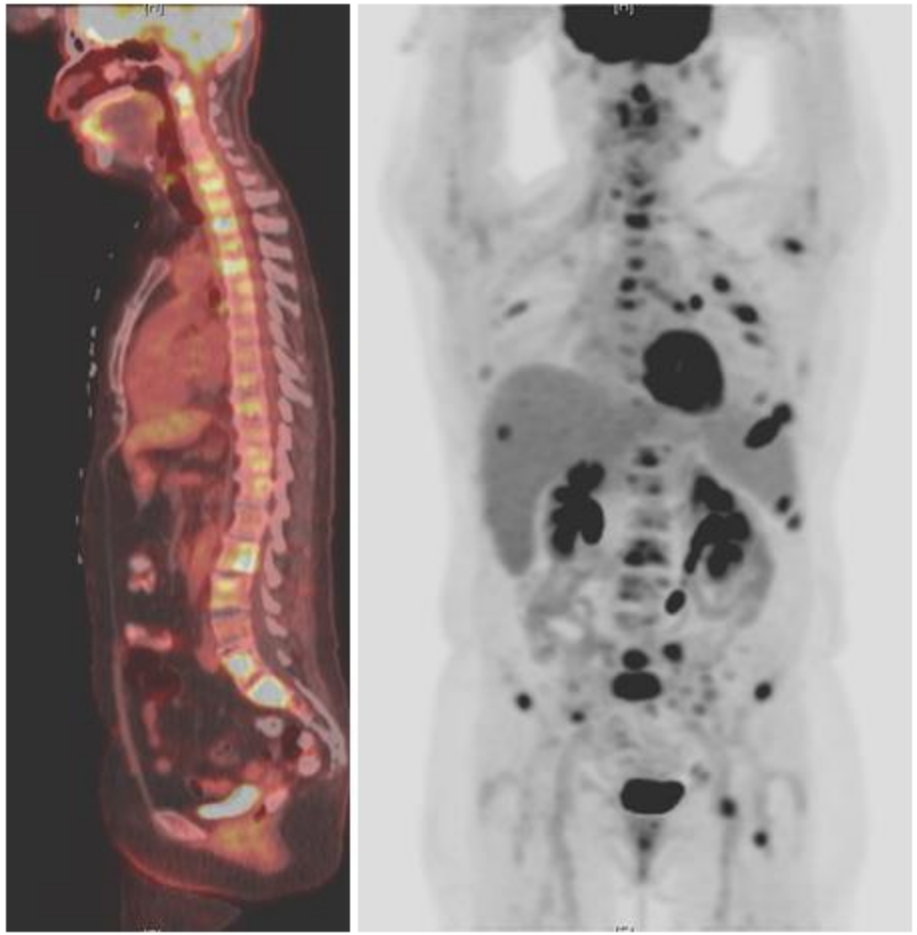
- Bladder
- CRC
- Ovarian
- Breast
- NSCLC
- Kidney
- Ampullary
- Gastroesophageal

Coexisting mutations in same patient

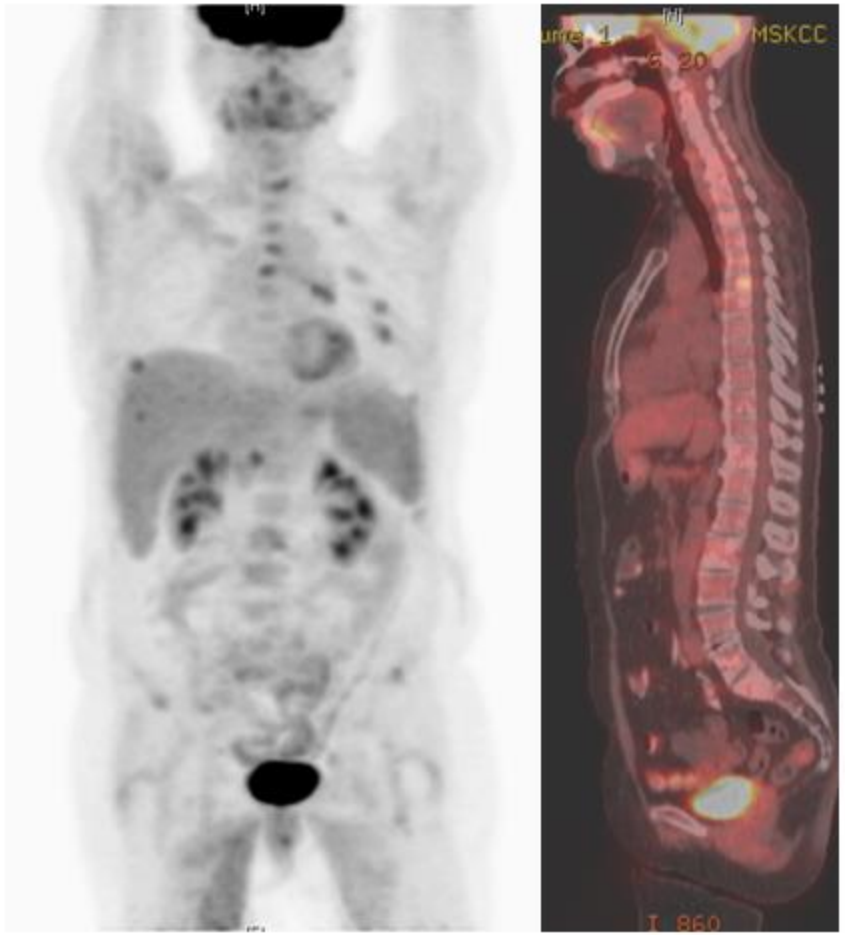
Data cutoff 26-AUG-2014

ERBB2 Mutation Type	Incidence
Missense Substitutions	69.2% (18/26)
Insertions / Deletions	26.9% (7/26)
Frameshift	3.8% (1/26)

ER/PR+, HER2 non-amplified, ERBB2 V777L Breast Cancer

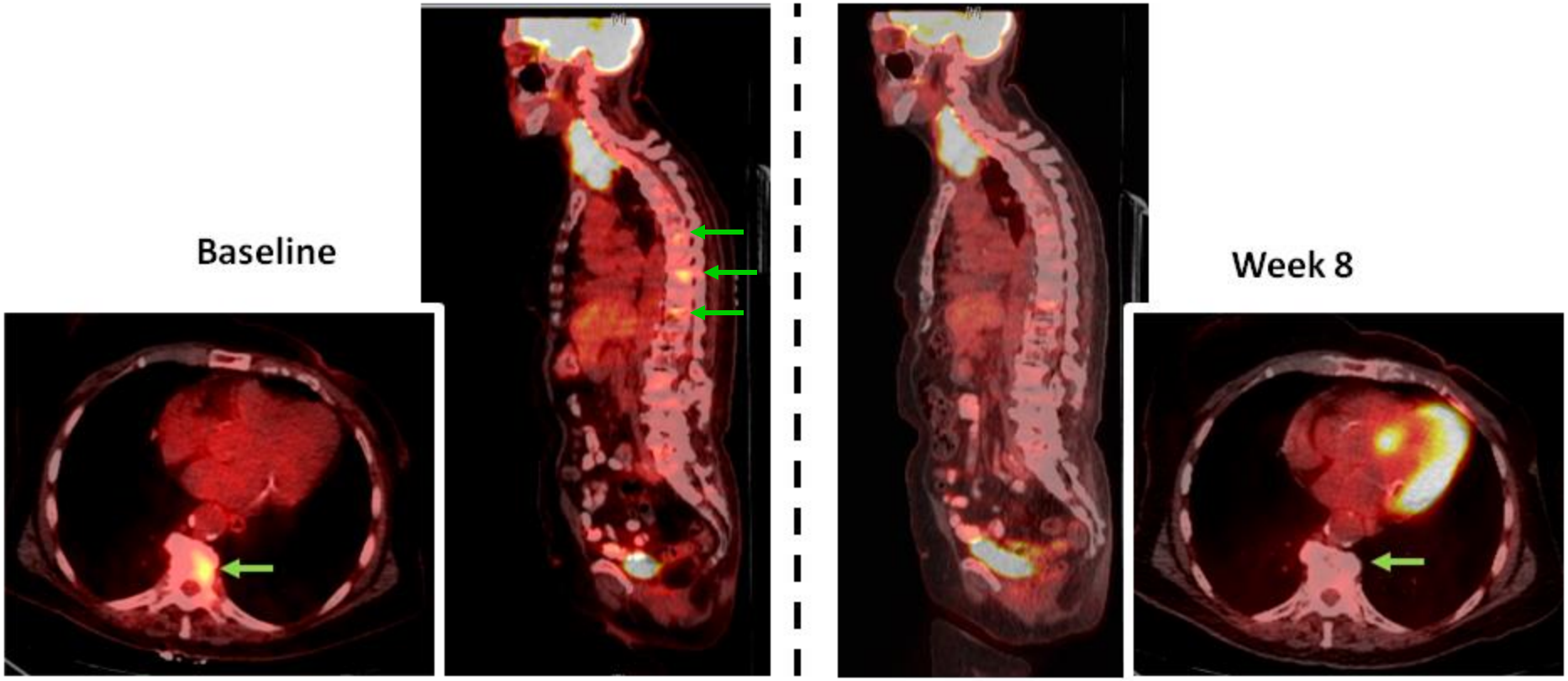


Baseline

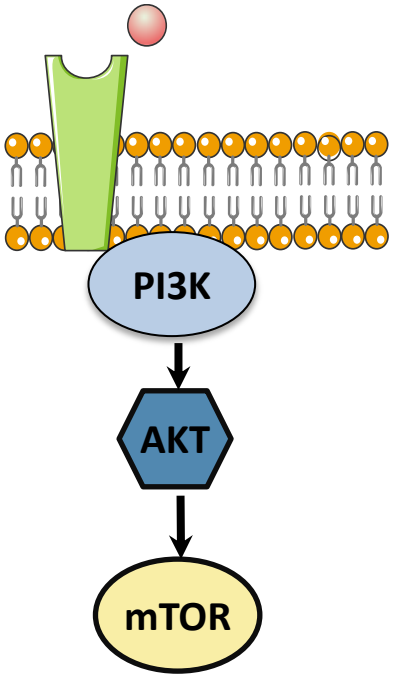


8 Weeks

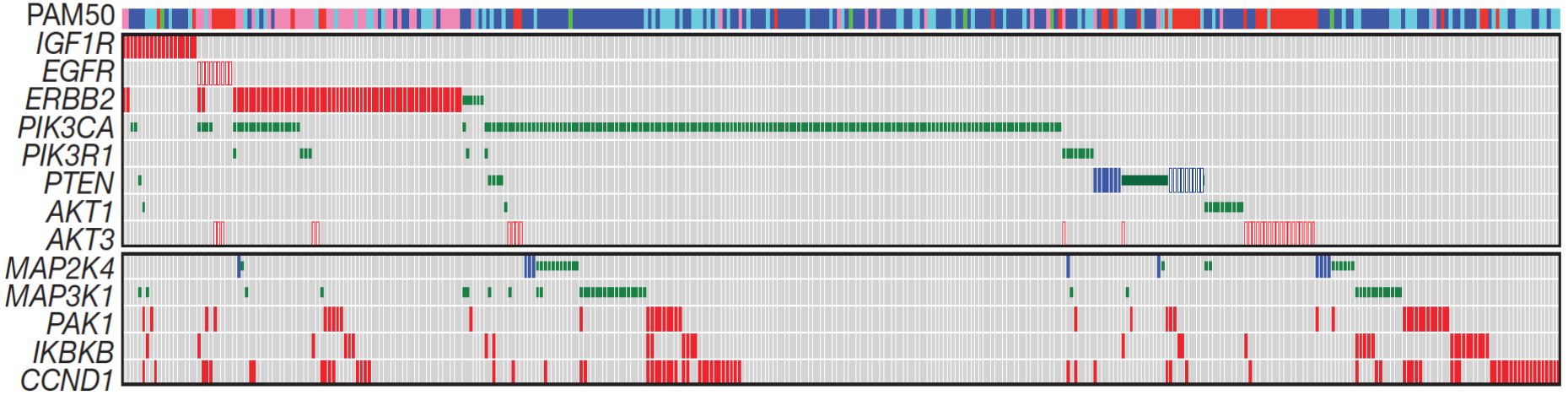
ER/PR+, HER non-amplified, ERBB2 L755S Breast Cancer



PI3K pathway in Breast Cancer

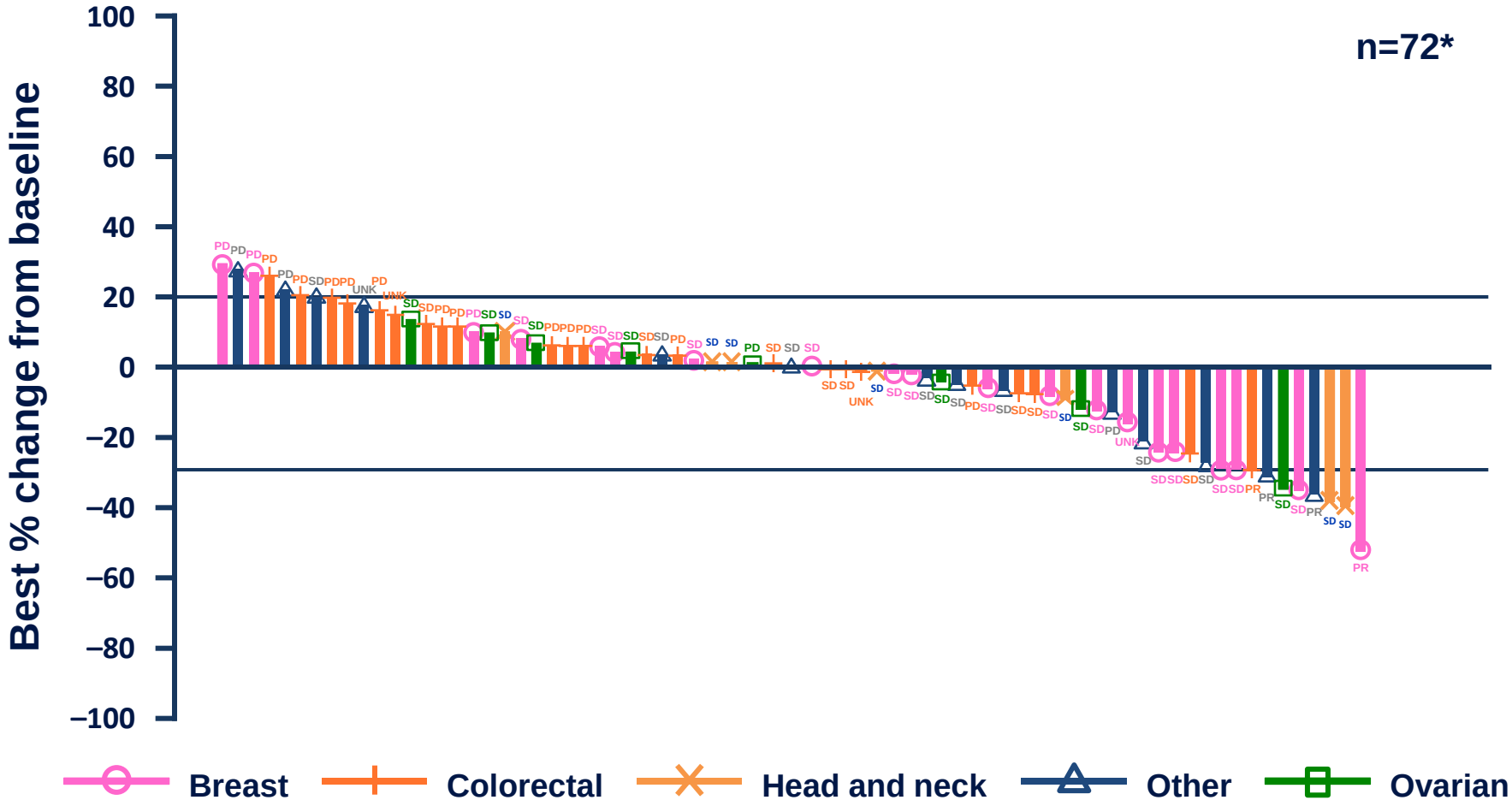


- Most frequent activating gene mutation in breast cancer
- ER + and HER2 +
- PI3K inhibitors in clinical development



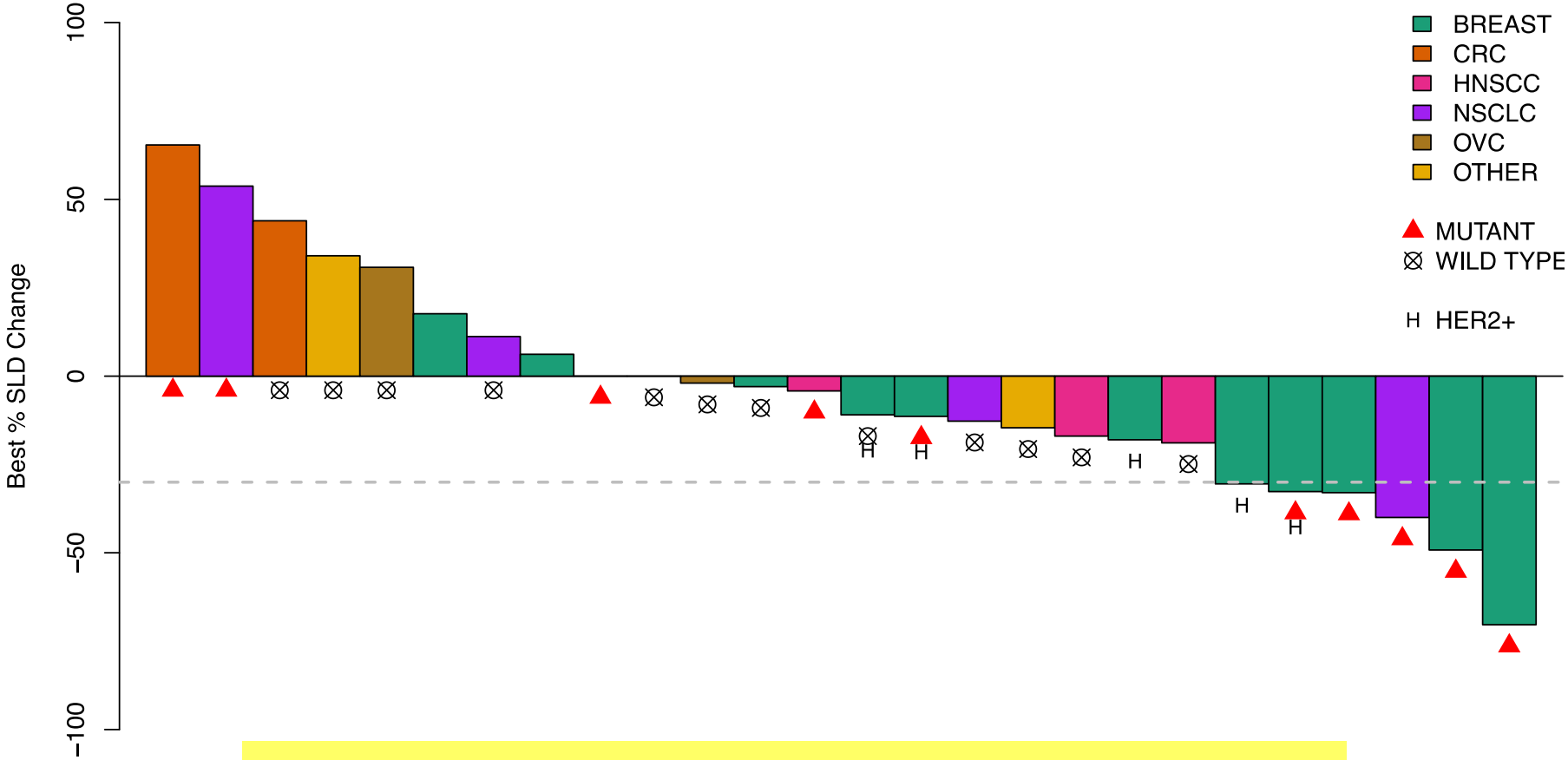
TCGA consortium, Nature, 2012

Clinical activity of BYL719 in patients with *PIK3CA* mut.



*Patients with missing best percentage from baseline and unknown best overall response are not included.
PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.

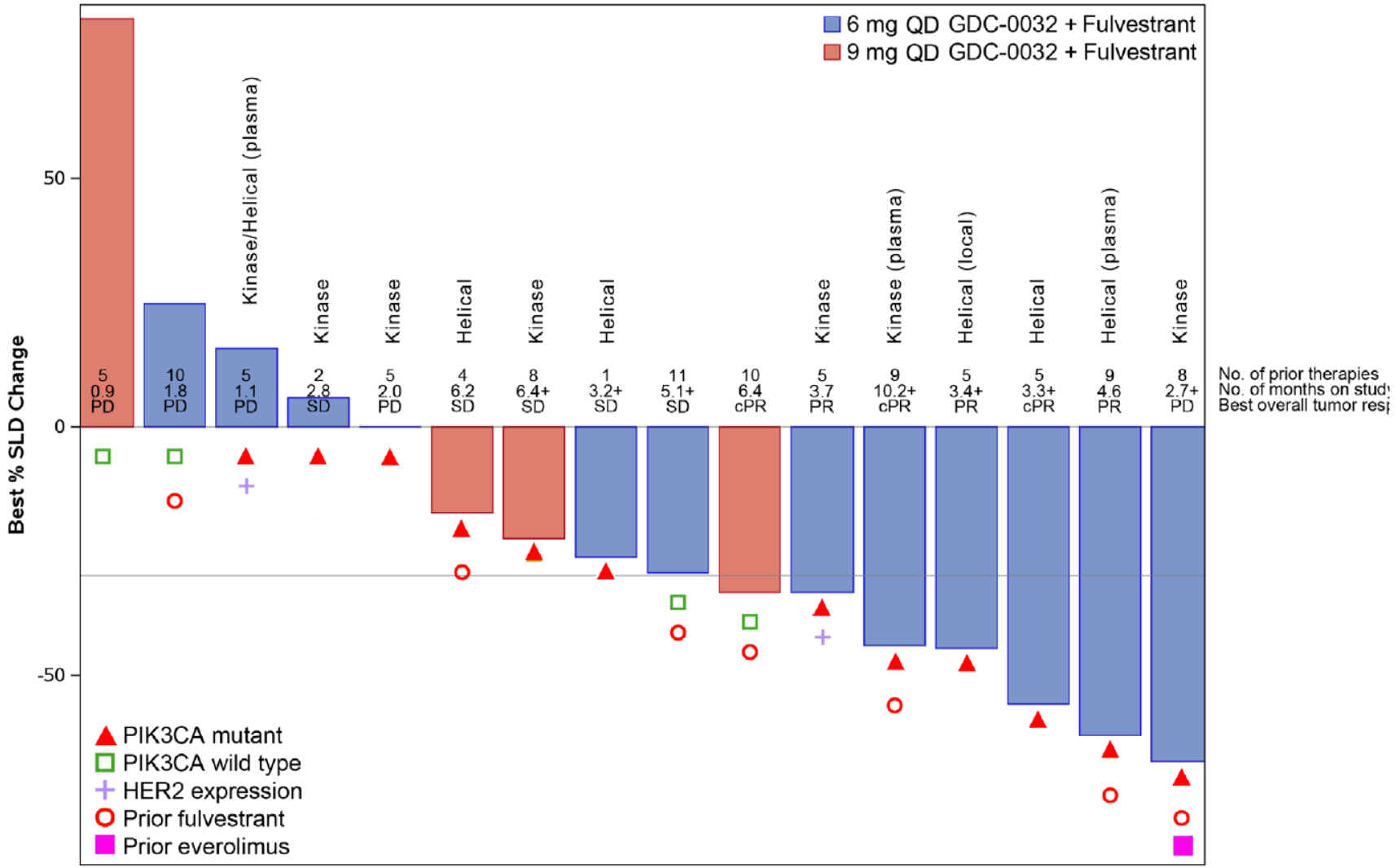
Preliminary efficacy with GDC-0032 treatment



- Trend for increased GDC-0032 anti-tumor activity in patients with *PIK3CA*^{mut} tumors

Data as of 30 Nov 2012

Anti-tumor Activity of GDC-0032 and Fulvestrant Combination

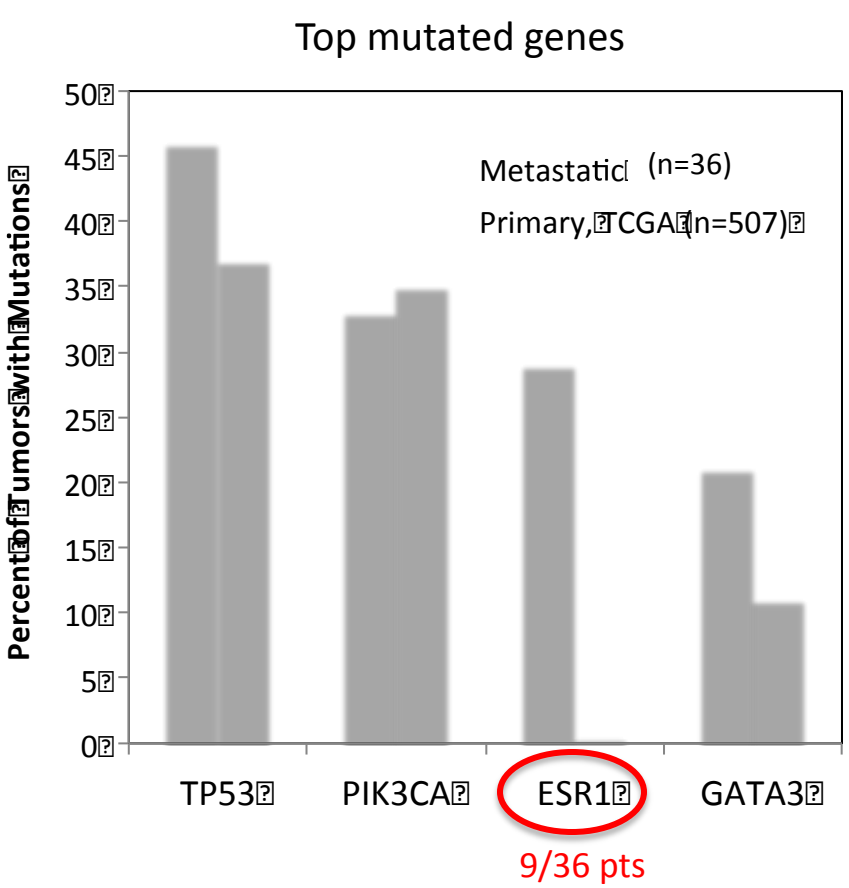


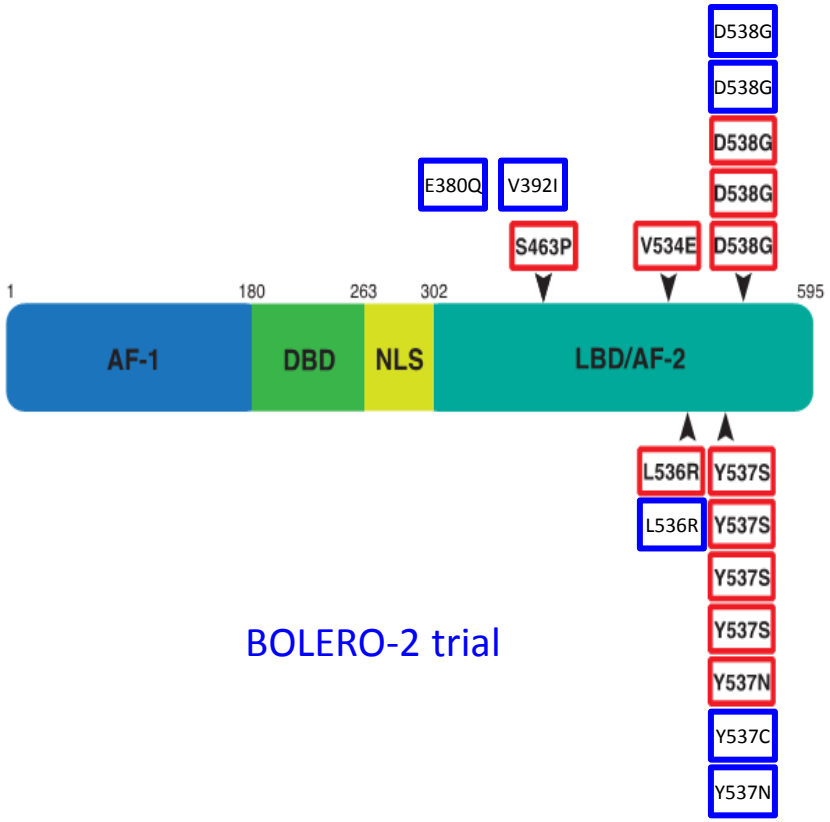
SABC 2013

ER+ Metastatic Breast Cancer: Resistance to Hormonal Therapy

Sequenced 36 ER+ metastatic breast tumors

Treated with multiple lines of hormonal therapies (average >4 years)

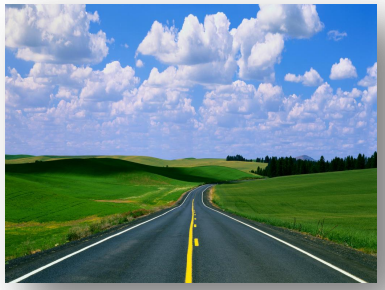




Toy *et al., Nature Genetics 2014*

Registration Road Map

- Identify functional mutations
  - Transforming and sensitive to study agent
- Define molecular tumor subtypes
  - Co-mutations
  - Identify potential combination therapies
- Develop diagnostic platform(s)
- Regulatory considerations for statistical approaches



Registration Road Map

- Approval of “low hanging fruit” indications
  - Very rare mutations with high clinical activity of study agent
    - Rare mutation defined as either frequent mutation in rare disease (*BRAF* in ECD) or rare mutation in frequent tumor (*erbb2* in breast cancer, BRAF in NSCLC)
- Address combinatorial approaches
  - Building backbone therapies and adding additional agents
    - PI3Kα inhibitor + SERD in *PIK3CA* mutant breast cancer
  - They will need to be compared to SOC

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