Developing rational systemic therapies for patients with bladder cancer

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Memorial Sloan-Kettering Cancer Center

Disclosures

- I will discuss off-label use of everolimus.
- I have served as a consultant for Pfizer, Novartis, Loxo Oncology.

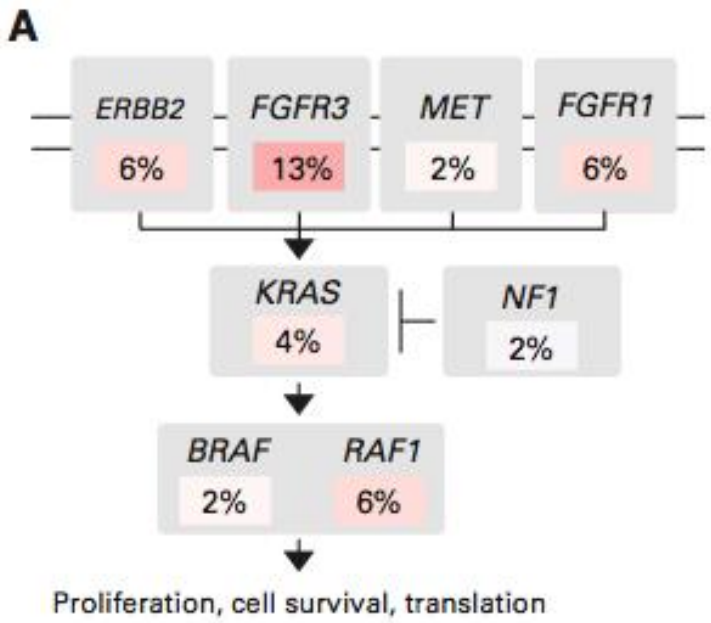
How do we accelerate drug discovery?

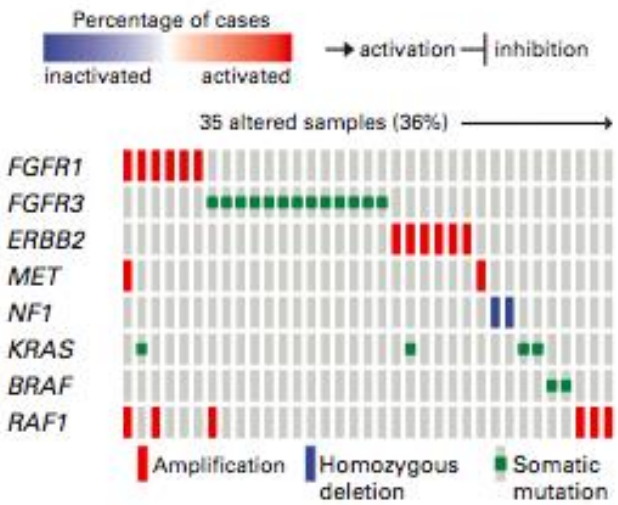
1. Define the Targets
2. Identify a “drug”
3. Identify the Patients

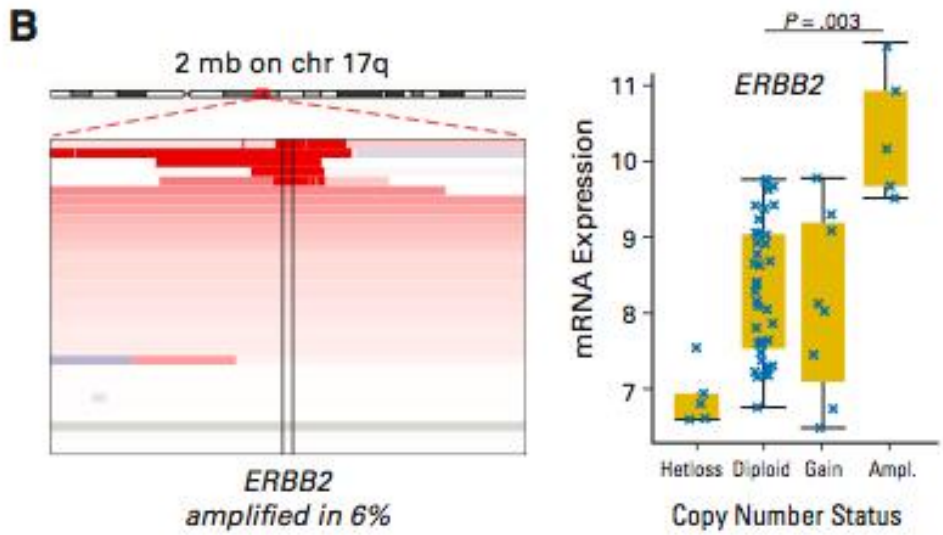
How do we define the targets?

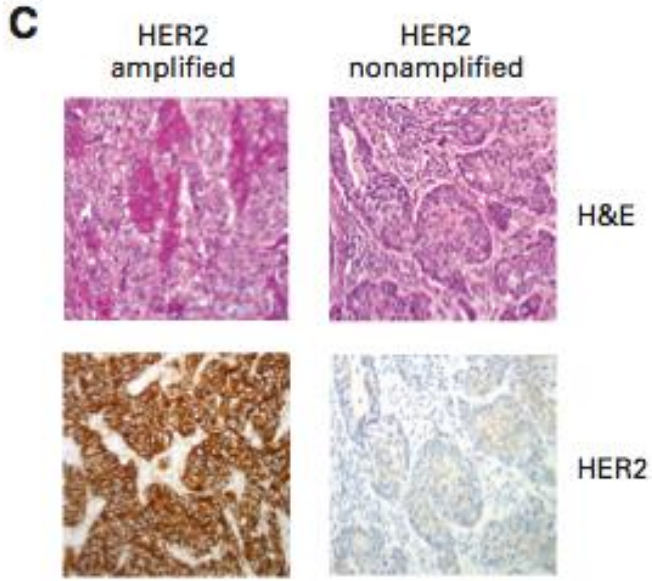
Genotype to Phenotype (G2P):

- Targets initially identified by retrospectively characterizing cohorts of tumors and cell lines.
- Recent success with inhibitors of BRAF, KIT, ALK, etc.

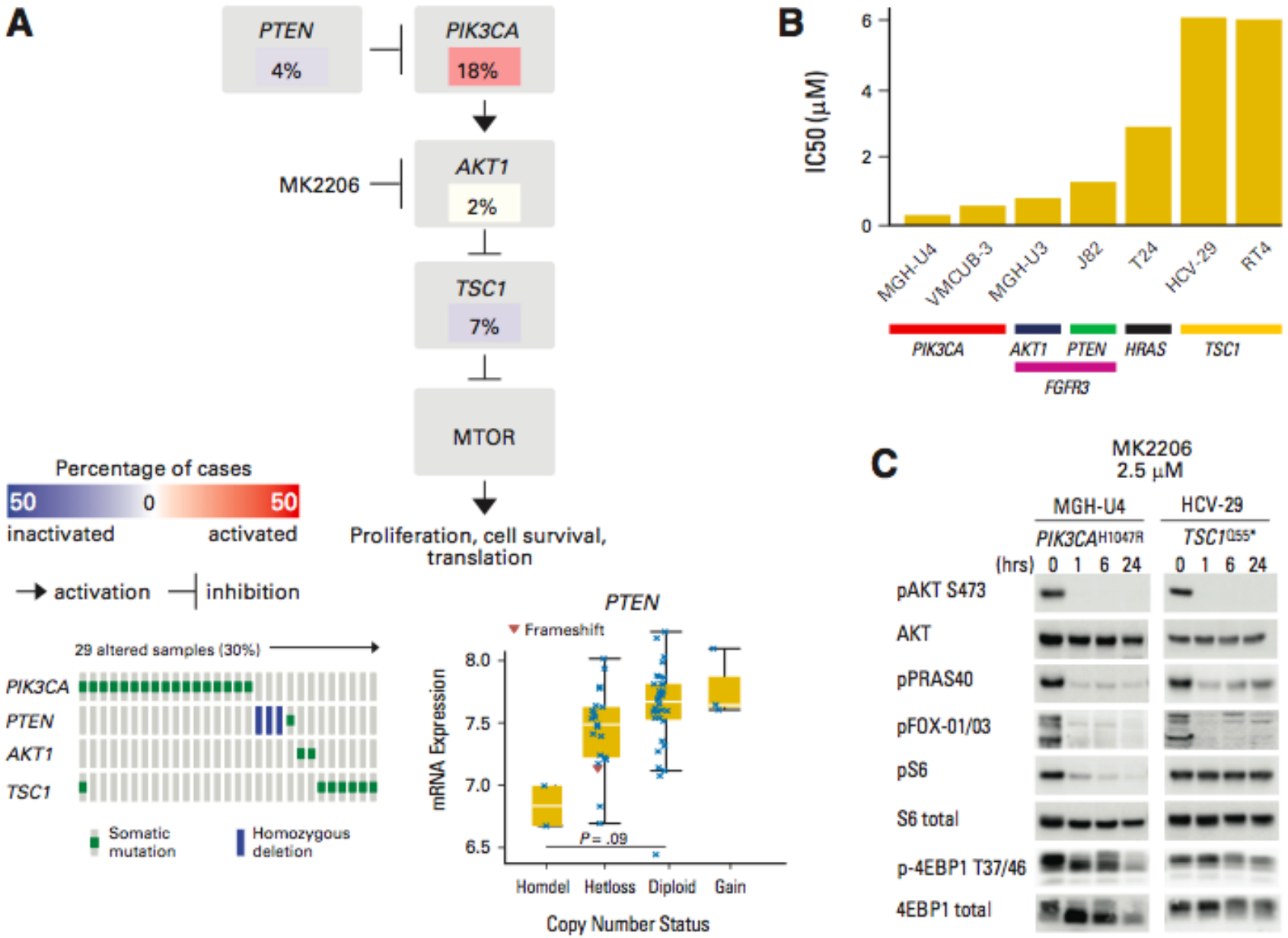








Iyer et al., JCO, 2013



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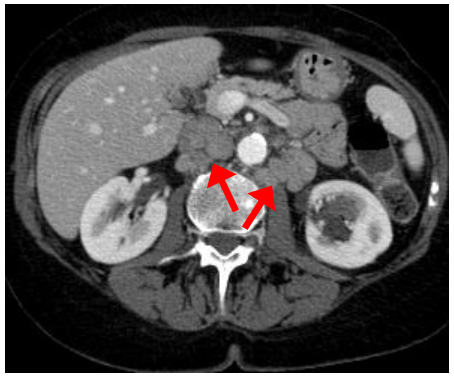
Phenotype to Genotype (P2G):

- Can we identify the genetic basis for rare, extraordinary clinical responses?
- Would this then guide trials in select subpopulations.

Response to everolimus on MSKCC IRB protocol 08-123.

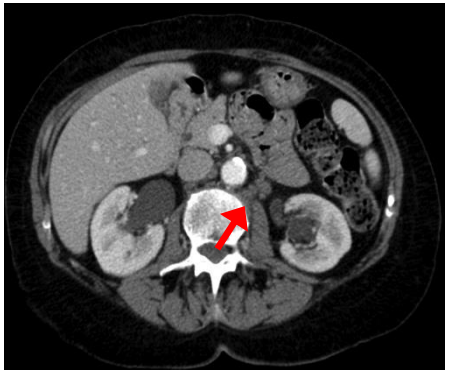
- 73 year old women with metastatic bladder cancer.
- Achieved a complete response to everolimus (mTORC1 inhibitor) on MSKCC protocol 08-123.
- The patient remains on drug with no evidence of disease 24 months after starting treatment.
- This patient was one of only 2 of 45 patients who responded to drug.

Pre-Treatment



January 2010

3 month interval

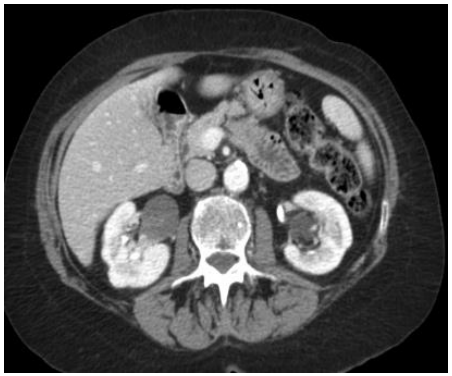


April 2010

6 month interval

July 2010

18 month interval

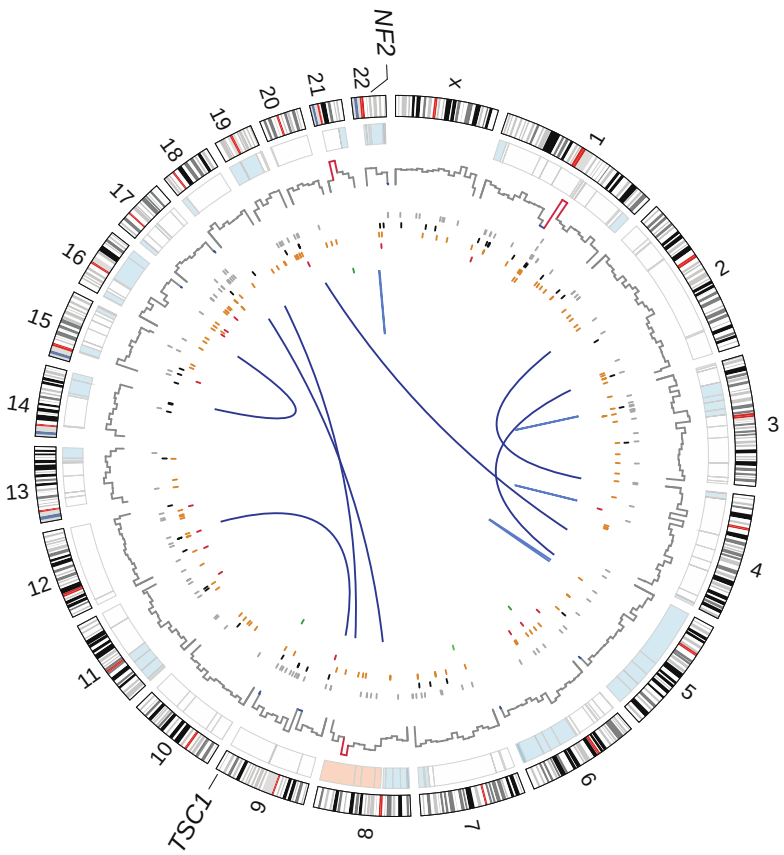


July 2011

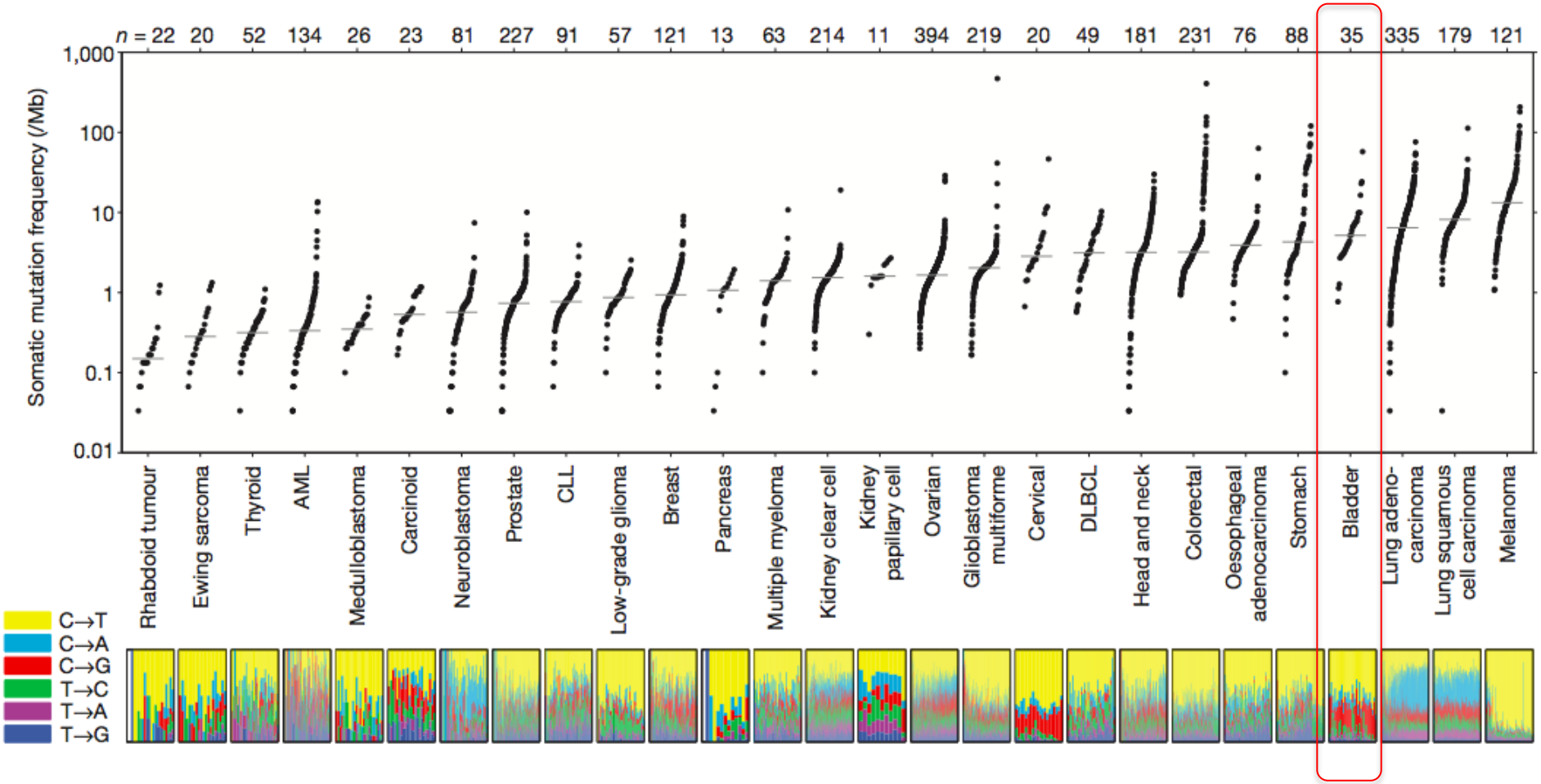
Why did this patient respond so dramatically to mTORC1 inhibition?

First Cancer Genome at MSKCC

- 17,000+ somatic mutations
- 140 NS coding mutations



Iyer et al., Science, 2012



Lawrence et al., Nature, 2013

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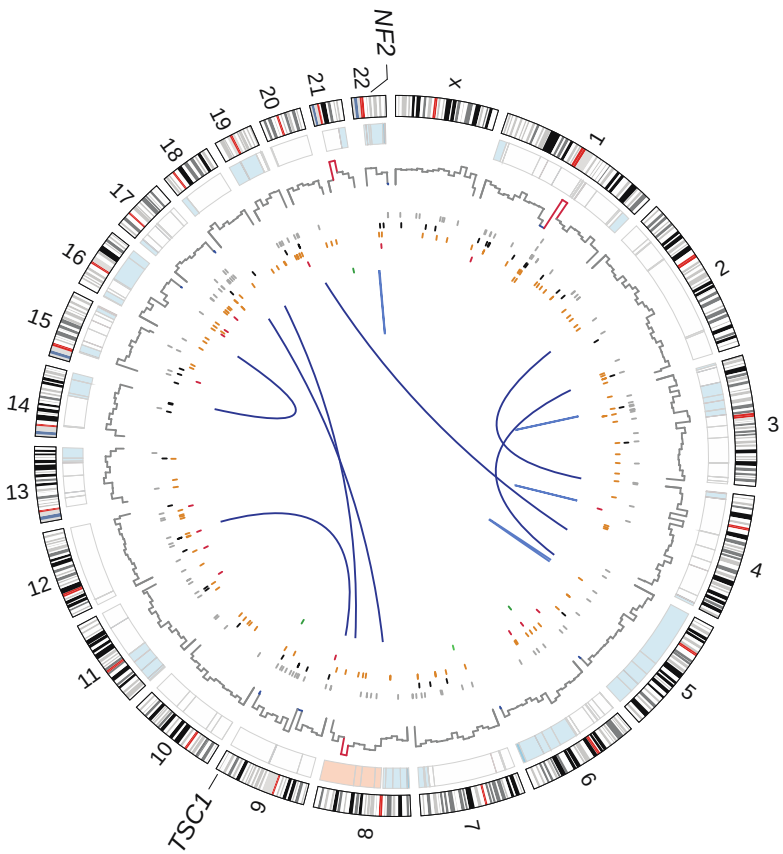
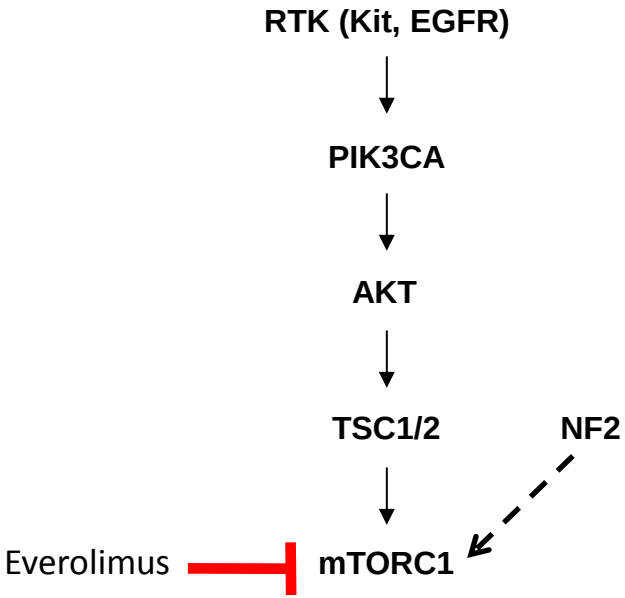
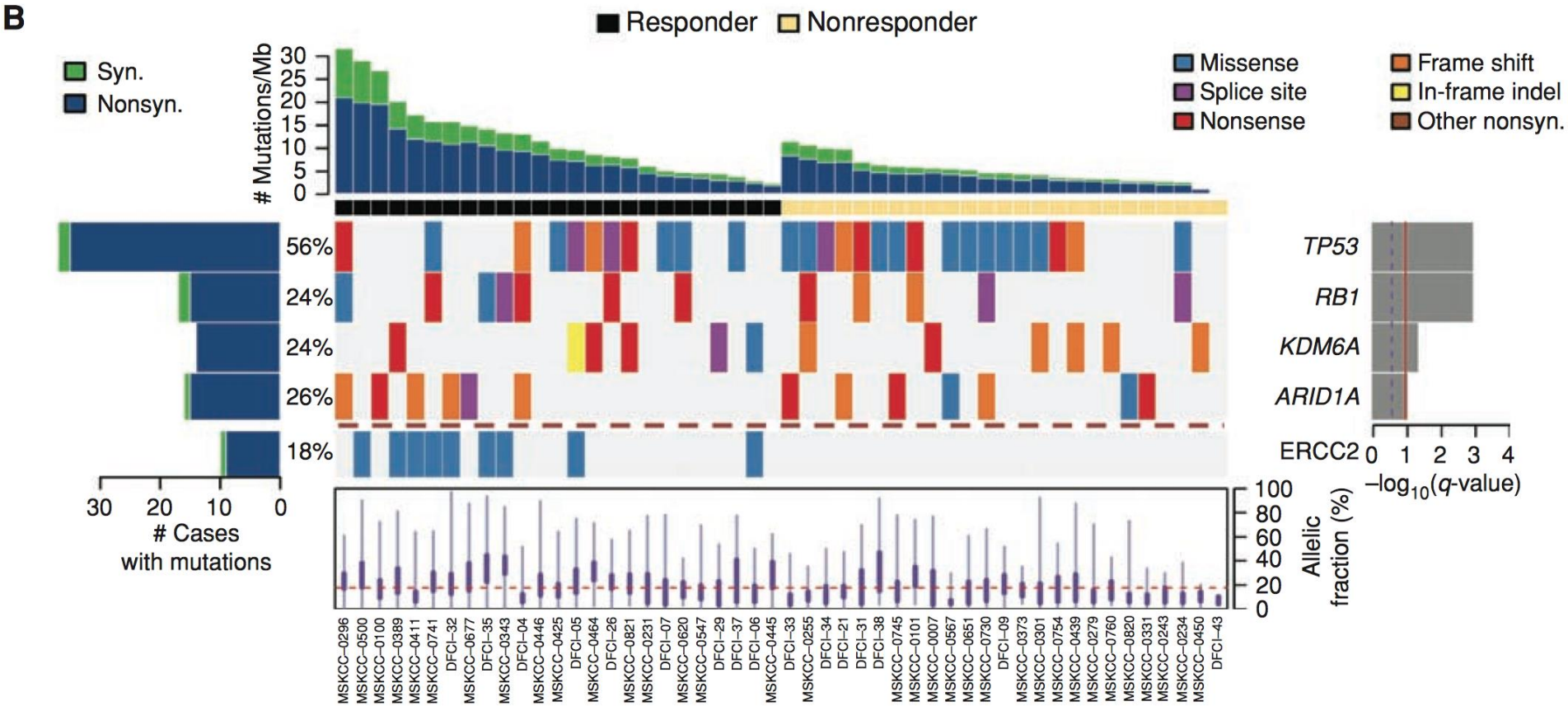




Iyer et al., Science, 2012

ERCC mutation correlates with response to neo-adjuvant platinum-based chemotherapy



Van Allen et al., Cancer Discovery, 2014

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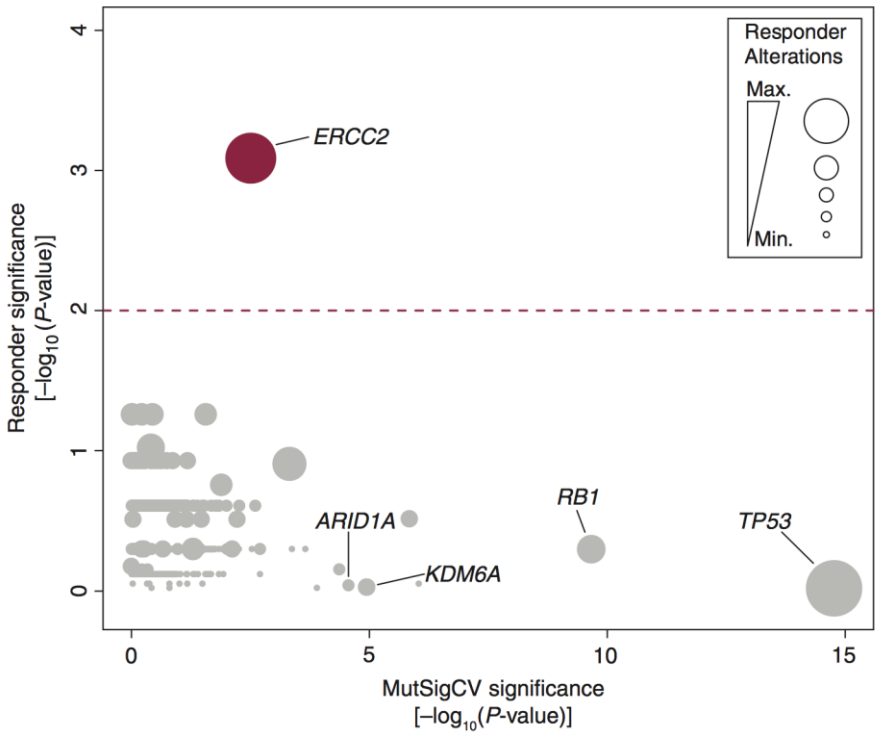
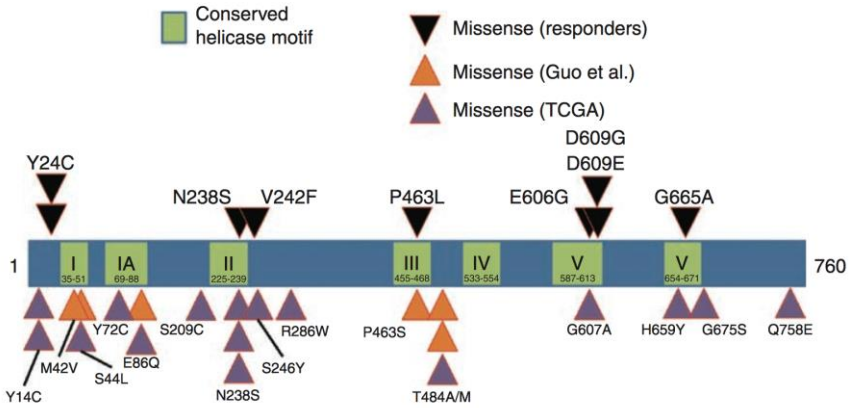
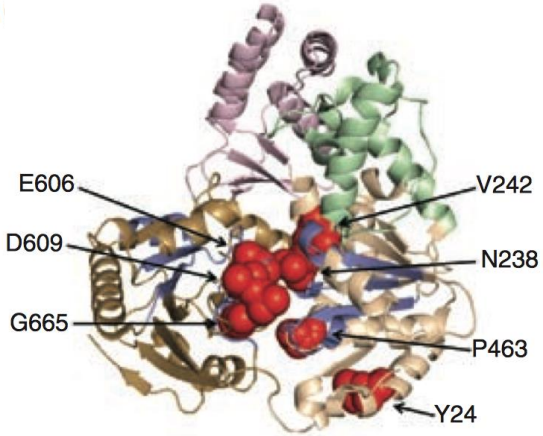


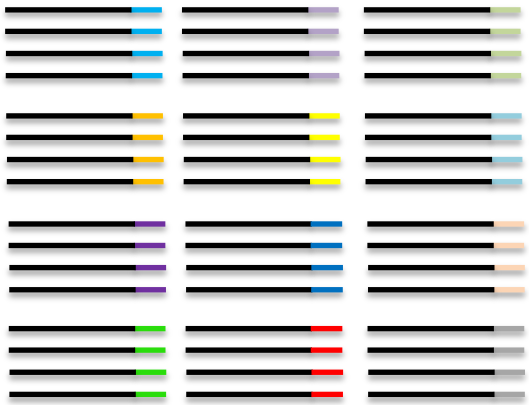




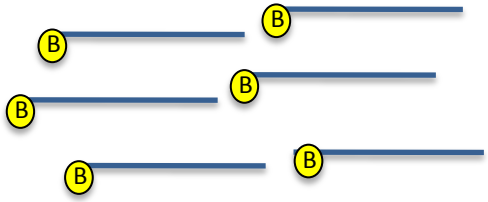
Responders

MSK-IMPACT: Integrated Mutation Profiling of Actionable Cancer Targets

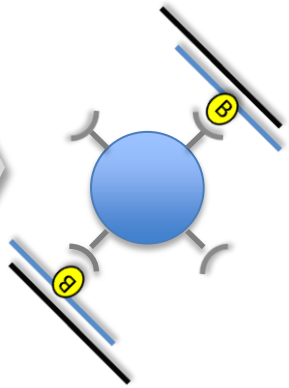
Prepare **24-48 libraries**



Probes for **341 cancer genes**

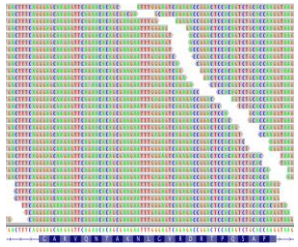


Hybridize and select
(NimbleGen SeqCap)



Sequence to 500-1000X
(HiSeq 2500)

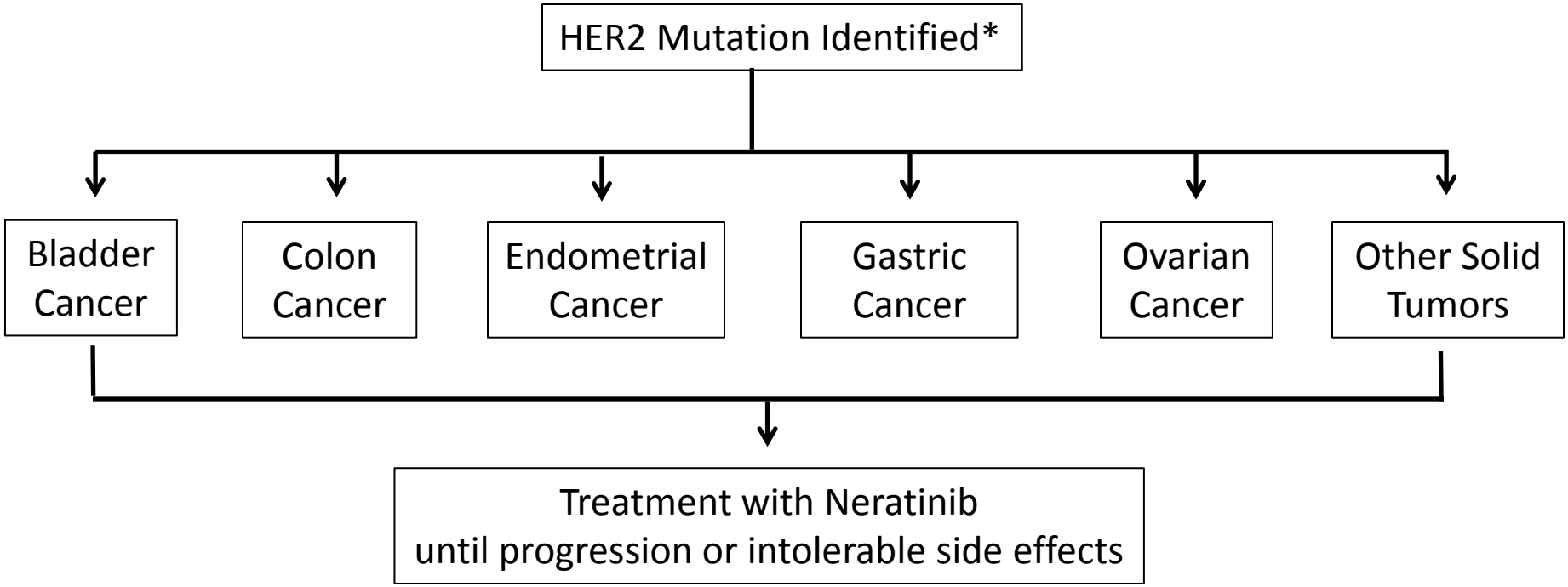
Align to genome
and analyze



Current List of 341 Cancer Genes

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

IRB# 13-140: HER2 Mutation Basket Study Schema

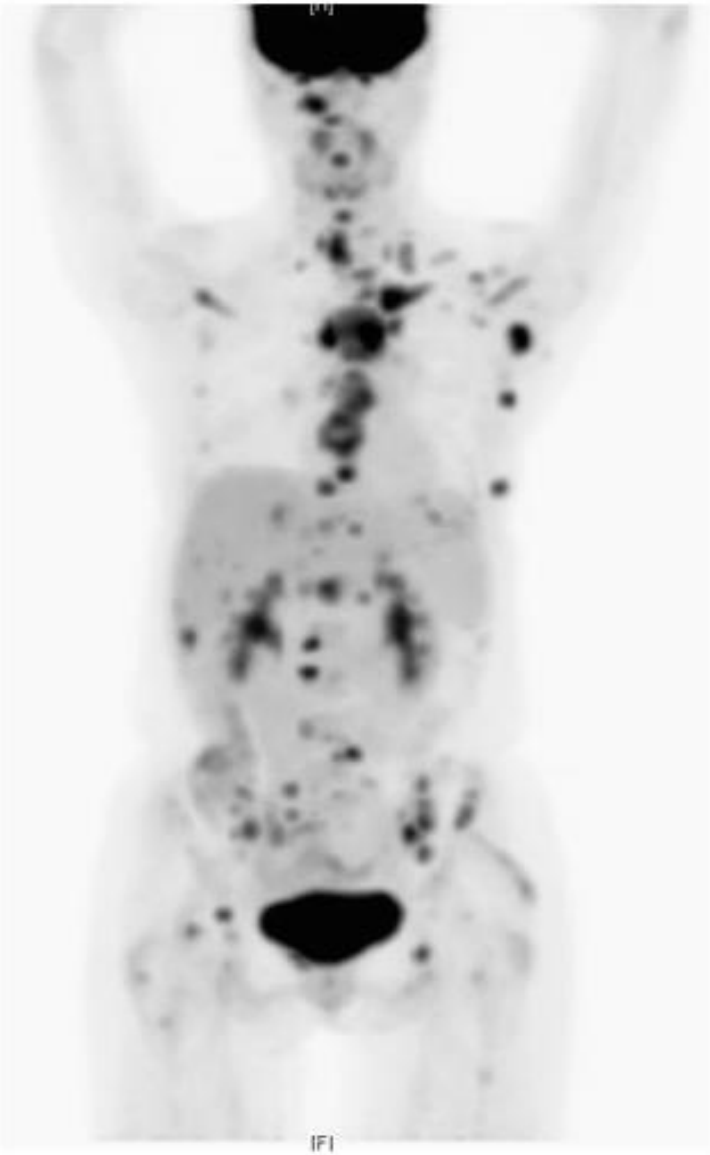


Primary Endpoint: Overall response rate (at 8 weeks)
Secondary Endpoints: PFS, OS

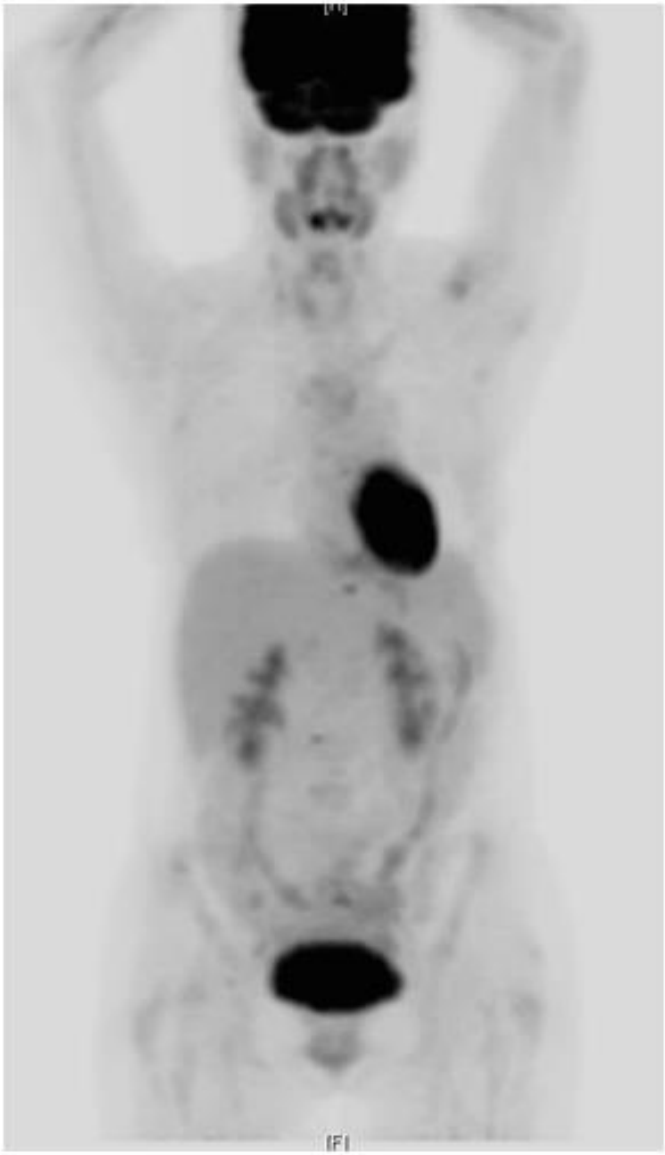
Multinational Study, MSKCC Lead Site
MSKCC Central Repository for All Biospecimens

*- Not limited to previously characterized activating mutations

Patient with a V777L ERBB2 mutation



July 2014



Sept 2014

Summary

- Bladder cancer is genomically complex
- Potential targetable driver alterations are common but none are found in a majority of a patients.
- Prospective molecular profiling will be needed to successfully develop targeted therapies for patients with bladder cancer.
- ERCC2 mutation predicts for response to neoadjuvant cisplatin-based chemotherapy.