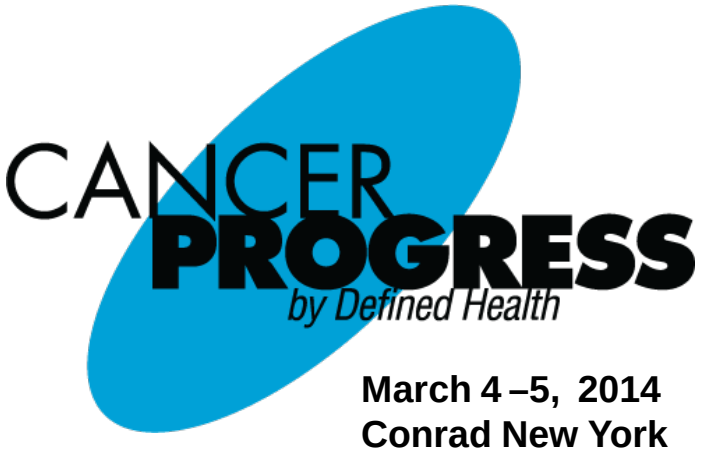
Intrinsic and Acquired Resistance in Cancer: Getting Smarter About Combinations and Sequencing



March 4 –5, 2014
Conrad New York

Intrinsic and Acquired Resistance in Cancer: Getting Smarter About Combinations and Sequencing

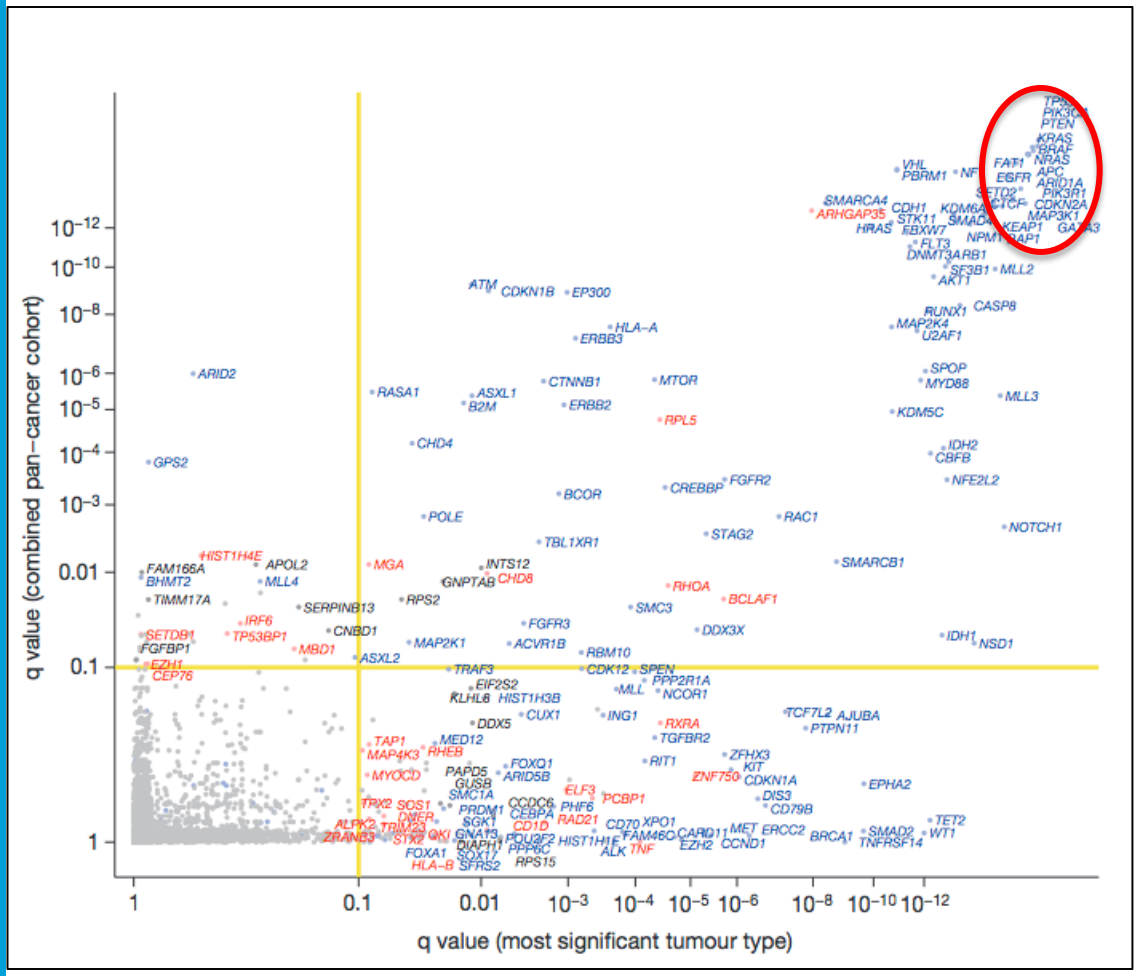
Moderator:

- Neal Rosen, MD, PhD, Director, Center for Mechanism-Based Therapeutics, Memorial Sloan-Kettering Cancer Center

Panelists:

- Jeffrey A. Engelman, MD, PhD, Director of Thoracic Oncology and Director of Molecular Therapeutics, Massachusetts General Hospital Cancer Center
- Greg Plowman, MD, PhD, VP, Oncology Research Eli Lilly and Company
- David Solit, MD, Director, Developmental Therapeutics, Memorial Sloan-Kettering Cancer Center

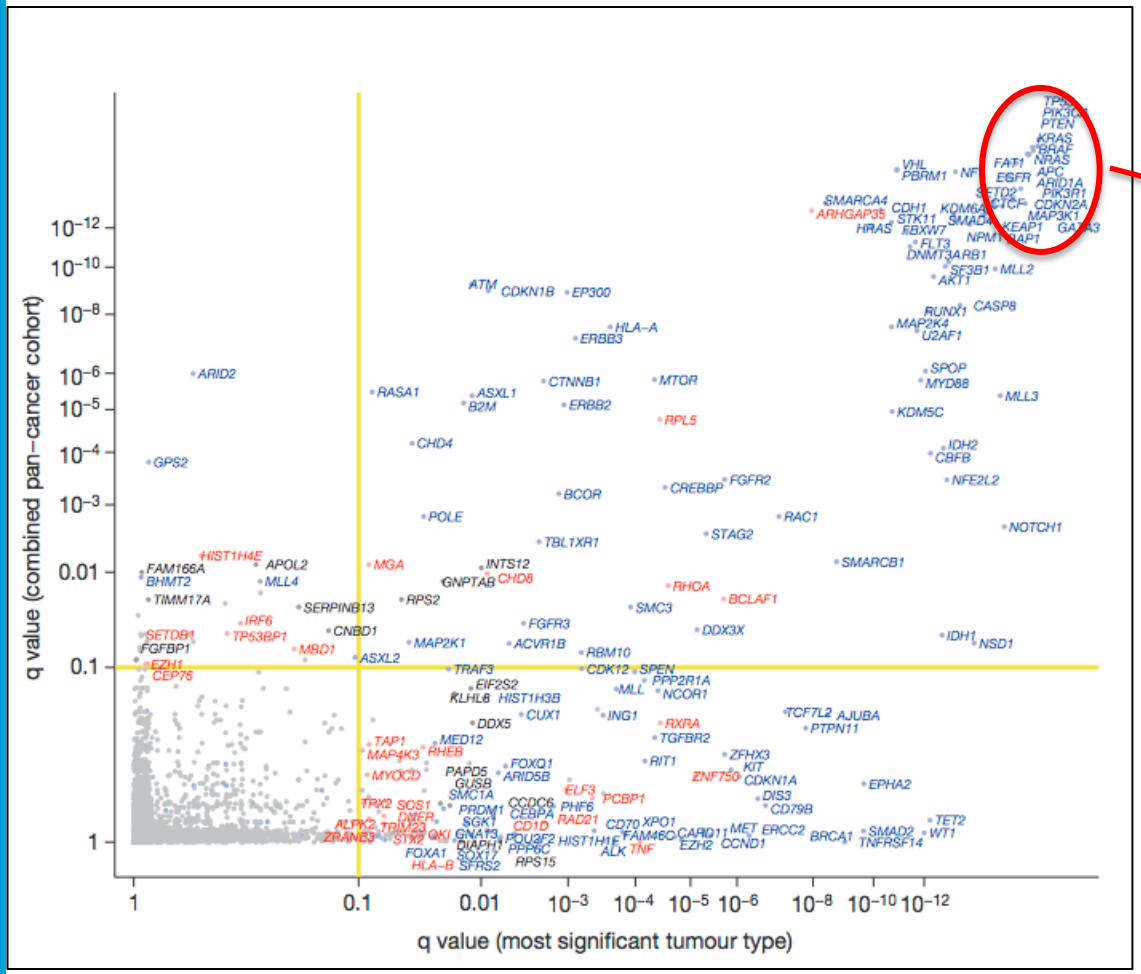
Prevalent Cancer Genes



Lawrence, M.S., Nature (2014)

Prevalent Cancer Genes

RAS/RAF, PI3K and CDK4 Pathways



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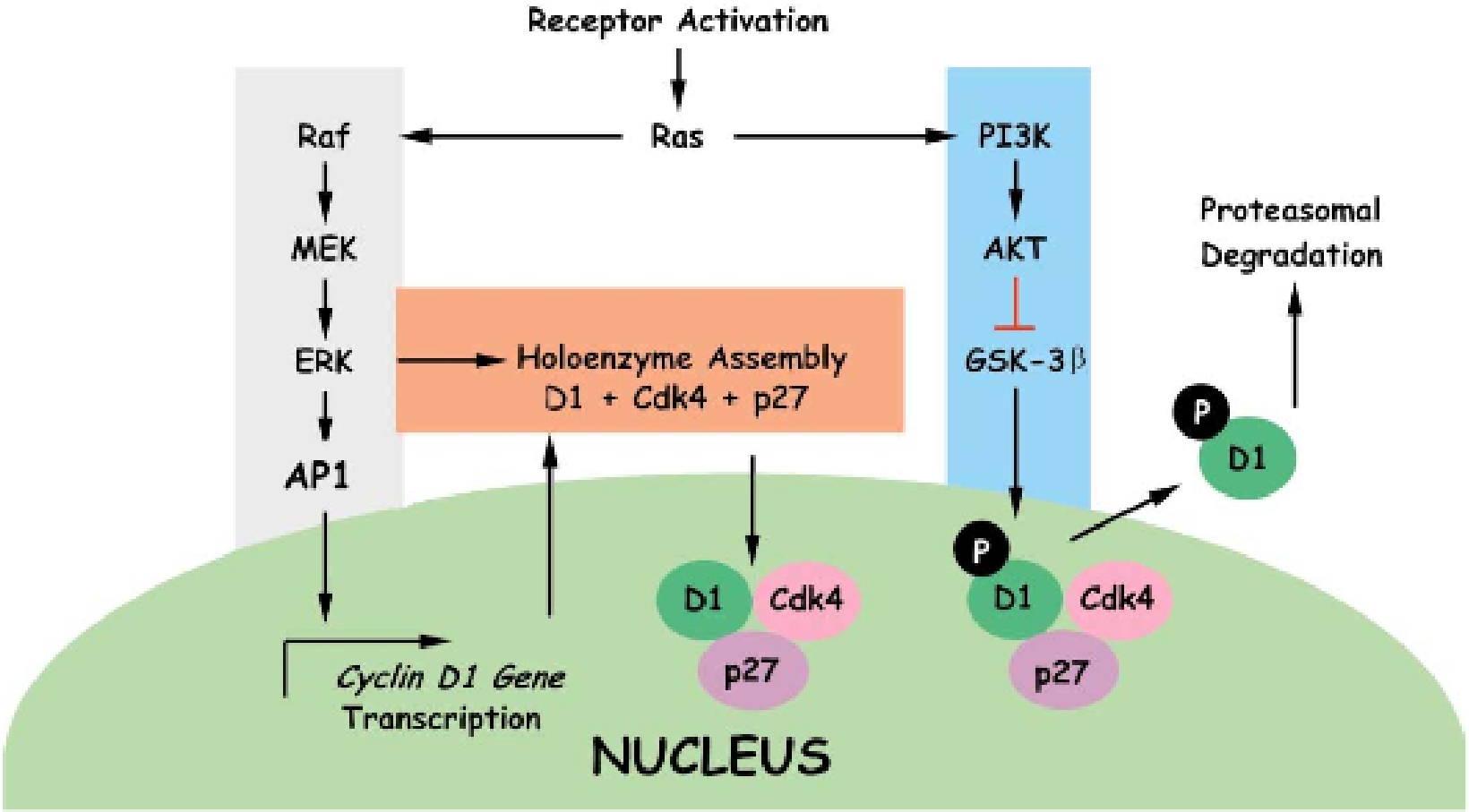
RAS/RAF, PI3K and CDK4 Pathways in Cancer



Sherr, C & McCormick, F, Cancer Cell, 2002

Application of Cancer Genomics to Routine Cancer Care

David B. Solit, MD

Geoffrey Beene Chair

Director, Center for Molecular Oncology

Memorial Sloan-Kettering Cancer Center

Cancer Progress Conference – March 5, 2014

THERAPEUTIC INSIGHT by Defined Health

DefinedHealth unconventional insight

CA Memorial Sloan-Kettering Cancer Center

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):

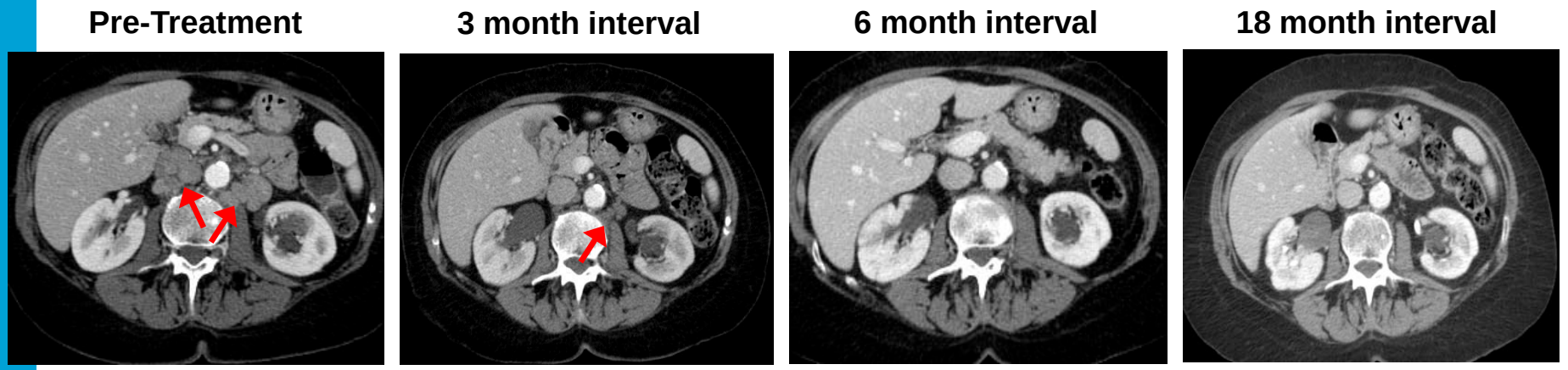
- Targets initially identified by genomically characterizing cohorts of tumors and cell lines.
- Recent success with inhibitors of BRAF, KIT, ALK, etc.

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.

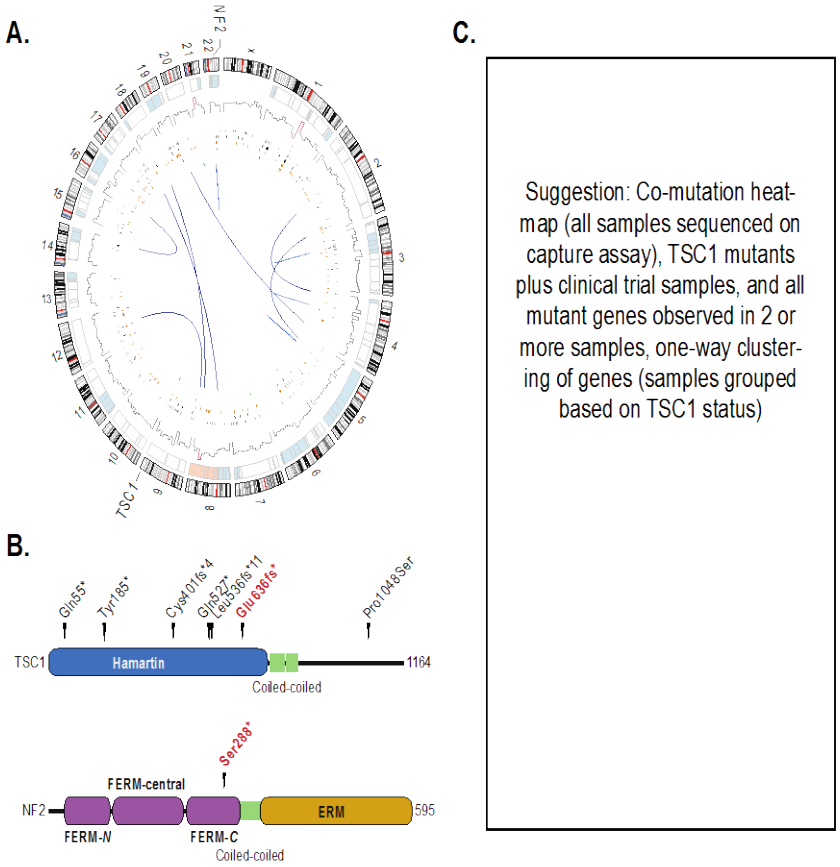
- 73 year old women with metastatic bladder cancer.
- Achieved a complete response to everolimus (mTORC1 inhibitor) on MSKCC protocol 08-123.
- The patient remains on drug with no evidence of disease 24 months after starting treatment.
- This patient was one of only 2 of 45 patients who responded to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

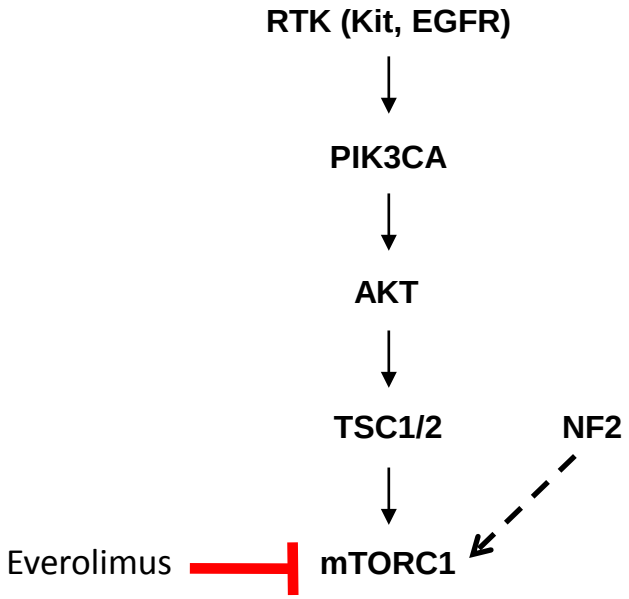


Why did this patient respond so dramatically to mTORC1 inhibition?

First Cancer Genome at MSKCC

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

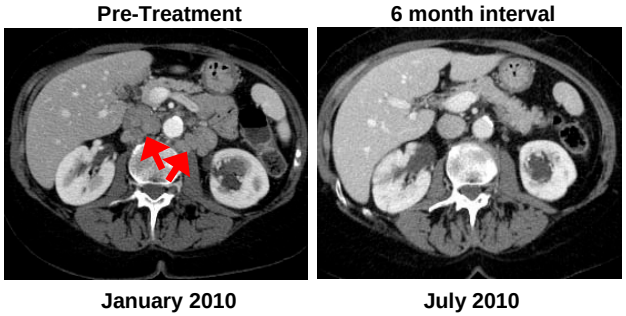


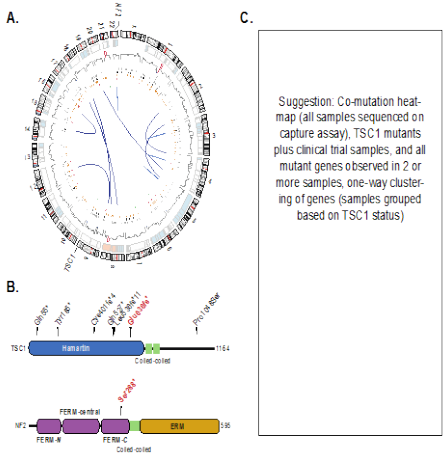


Use of whole genome outlier analysis to salvage drugs with a low response rate

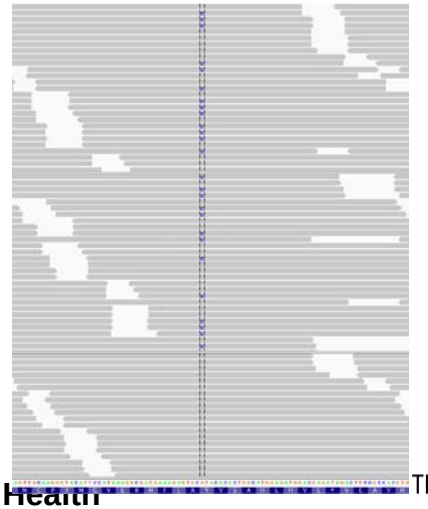
Phase 2 trial of everolimus in an unselected population.

- 2/45 responders.
- 1 with an ongoing durable CR of 22 mos





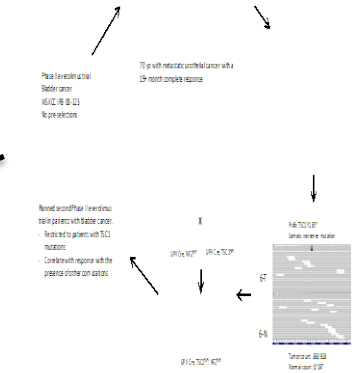
Repeat Phase 2 trial of everolimus in which study entry is restricted to patients with TSC1/2 and/or NF2 mutant/deleted pts



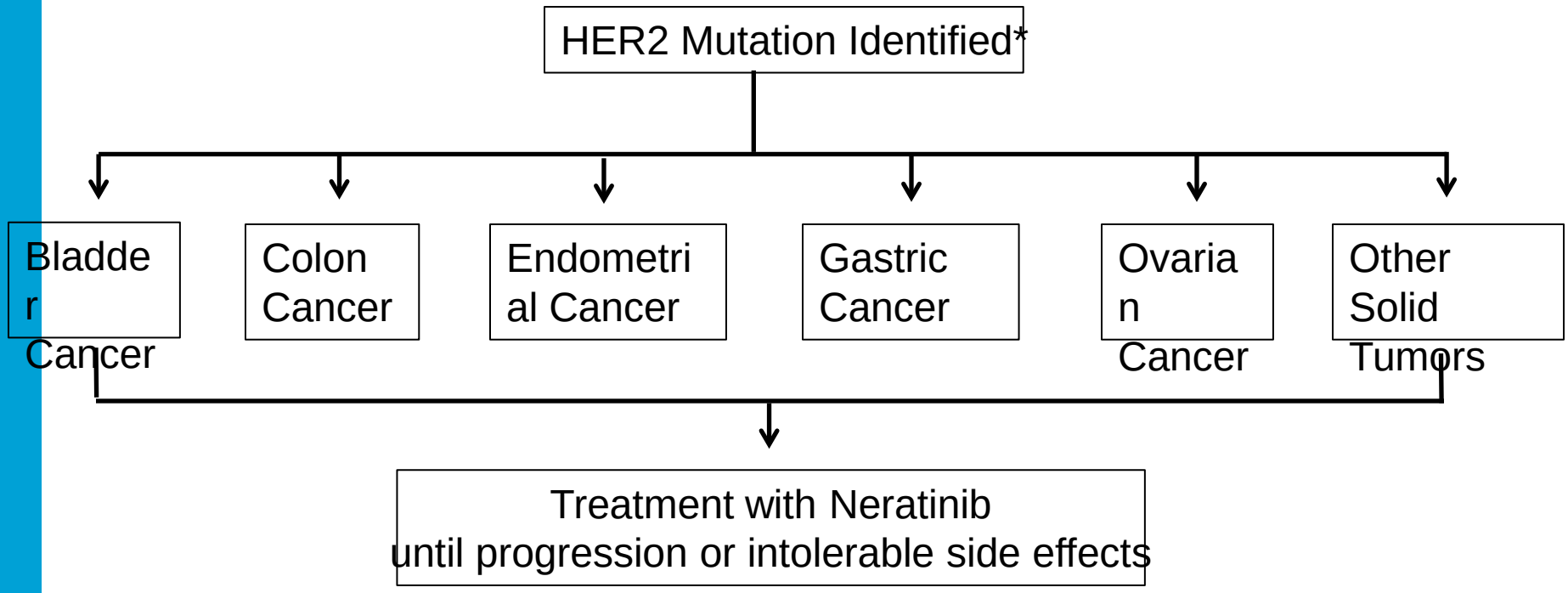
Frozen Tumor
Y185* (G>C)
445/1081 reads

Paraffin Sample
Y185* (G>C)
131/344 reads

Normal Tissue
Y185* (G>C)
0/187 reads



13-140: HER2 Mutation Basket Study Schema

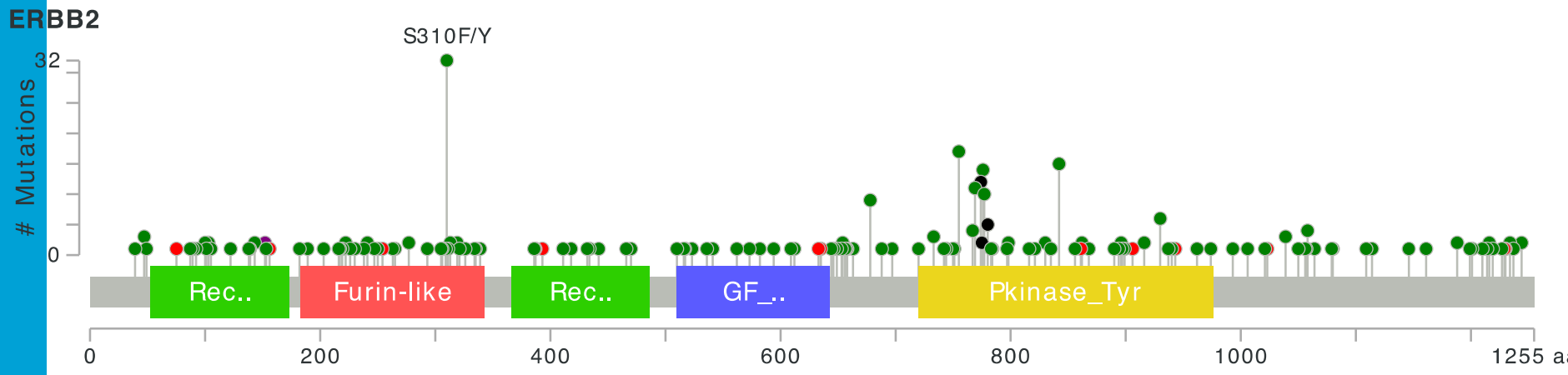


Primary Endpoint: Overall response rate (at 8 weeks)
Secondary Endpoints: PFS, OS

Multinational Study, MSKCC Lead Site

*- Not limited to previously characterized activating mutation

ERBB2 mutations identified across all cancers



- Data from 82 cancer studies
- 19,000+ tumors
- Source: MSKCC cBio Portal
- Updated March 5, 2014 @ 9:00 AM

Center for Molecular Oncology Genotyping initiative

- Molecular genotyping is only “standard of care” for select solid tumors (Lung, Colorectal, Melanoma, GIST, ?Thyroid).
- IRB protocol 12-245 (PI David Hyman) allows for prospective molecular characterization.
- Plan to perform IMPACT on a large cohort of patients from each RNB cancer type. There will be no limit to the number of breast patients that can be sent. This will be RNB but we will be working with payers to make additional cancer billable over time. Patients must be consented to 12-245 to be eligible. Results will be reported in the chart.
- Primary endpoint will be to determine whether treatment was impacted by the genotyping results. If not why (no driver identified vs. appropriate trials unavailable – KRAS, RB1, etc).

Current List of 341 Cancer Genes

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

Need to generate a more comprehensive knowledge base?

- Mutation is not a binary variable. Not all mutations in a particular gene have overlapping biologic effects.
- The pattern of co-mutation may dictate drug sensitivity.
- Should we annotate the clinical reports?
  - Alternatively, should the data simply be reported.
  - Who would generate/maintain this knowledge base given the ongoing flow of new (sometime contradictory) data.
  - Could it be crowd sourced using a Wikipedia type model.