Biologic and metaphysical limits to pursuing precision oncology

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Disclosures

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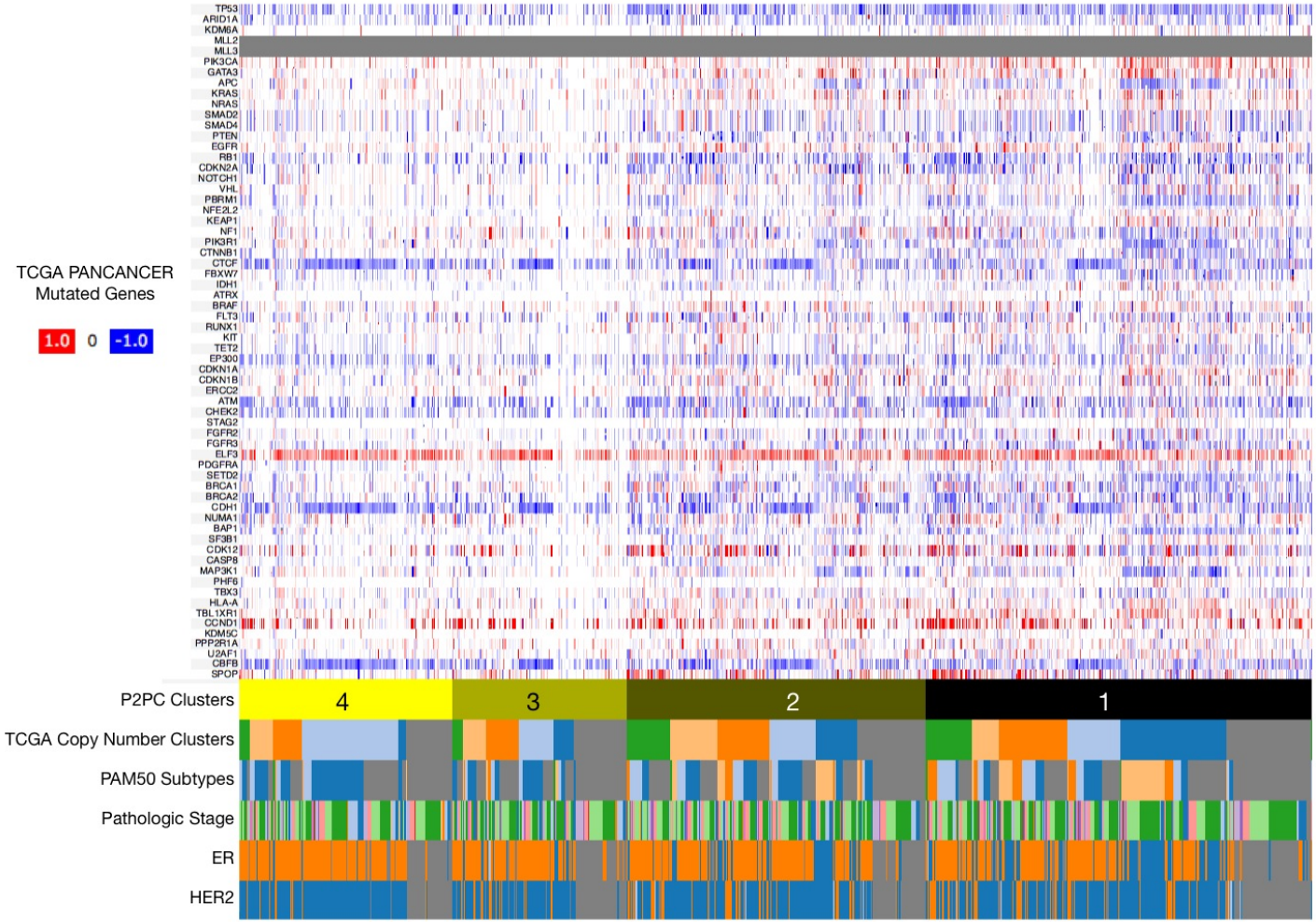
- Consultant: Novartis, Genentech, BMS, Merck, Takeda, Verastem, Checkmate, Boston Biomedical

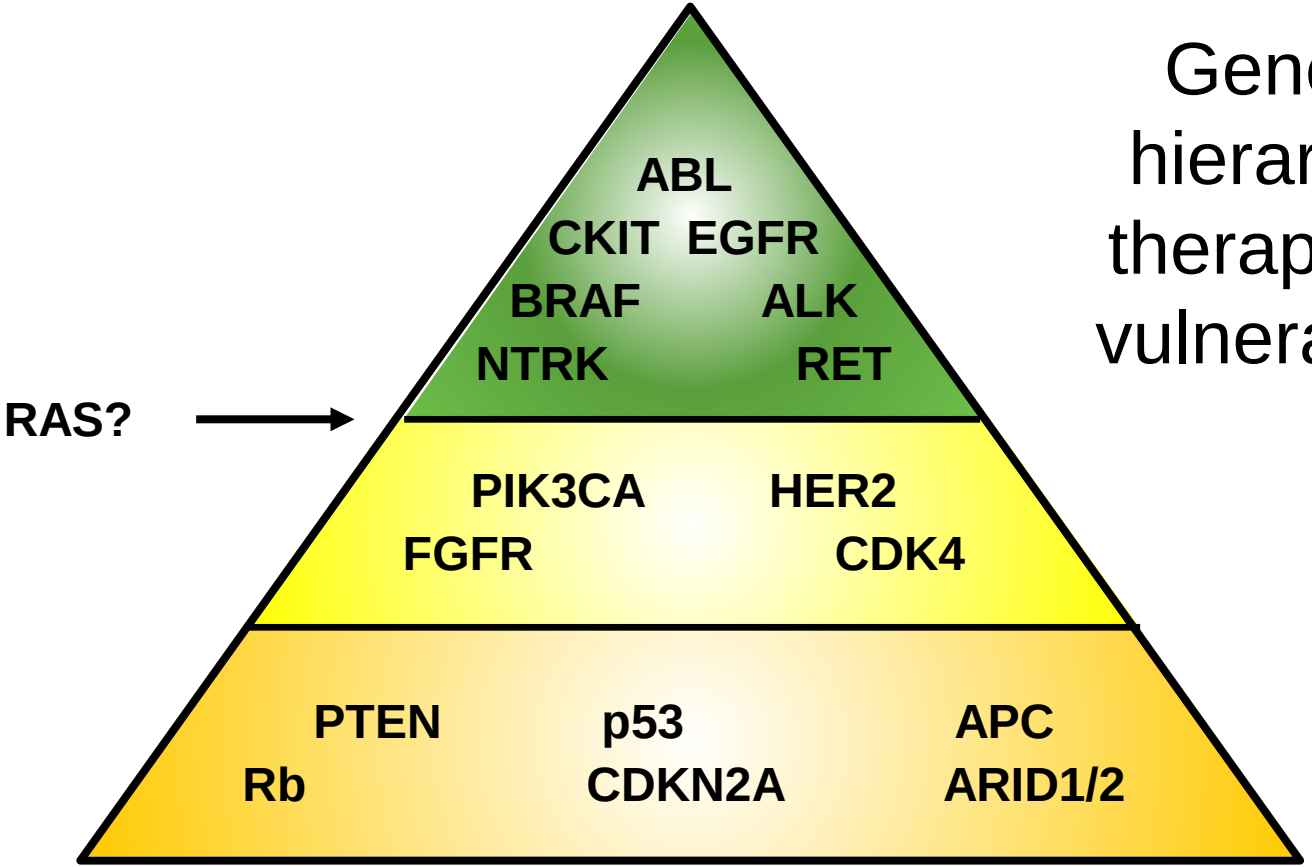
Landscape of somatic genetic alterations across cancer

6 validated targets

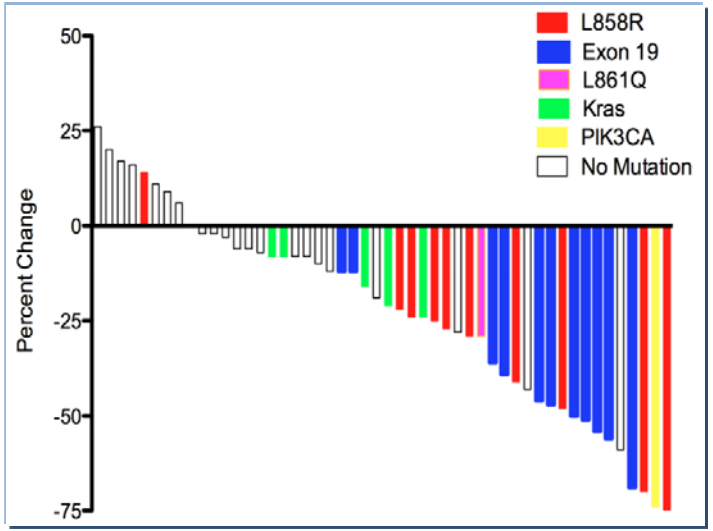


BMC Medical Genomics
https://doi.org/10.1186/s12920-017-0256-3

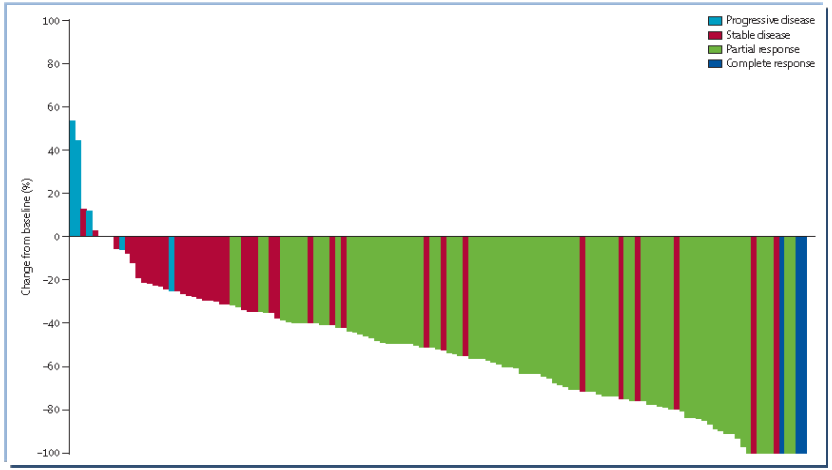
Genetic hierarchy: therapeutic vulnerability



Matching patients to therapy on the basis of genetic features: erlotinib in EGFR mutant & crizotinib in ALK translocated NSCLC

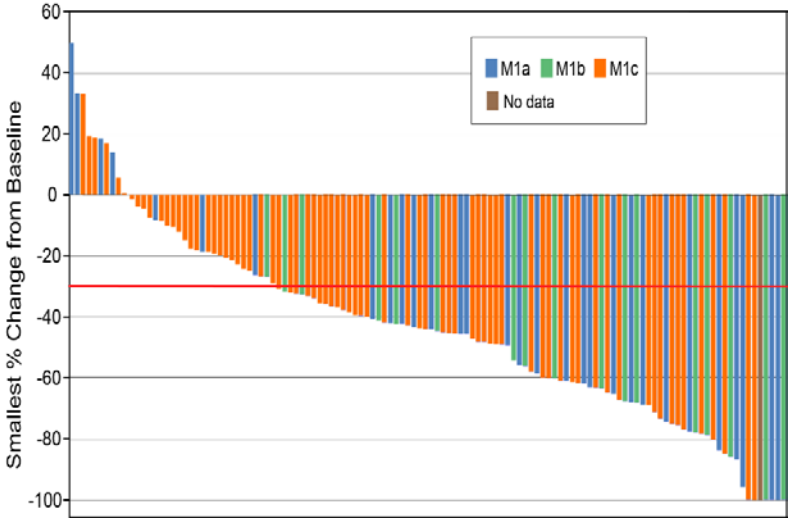


Rizvi N et al. CCR 2011

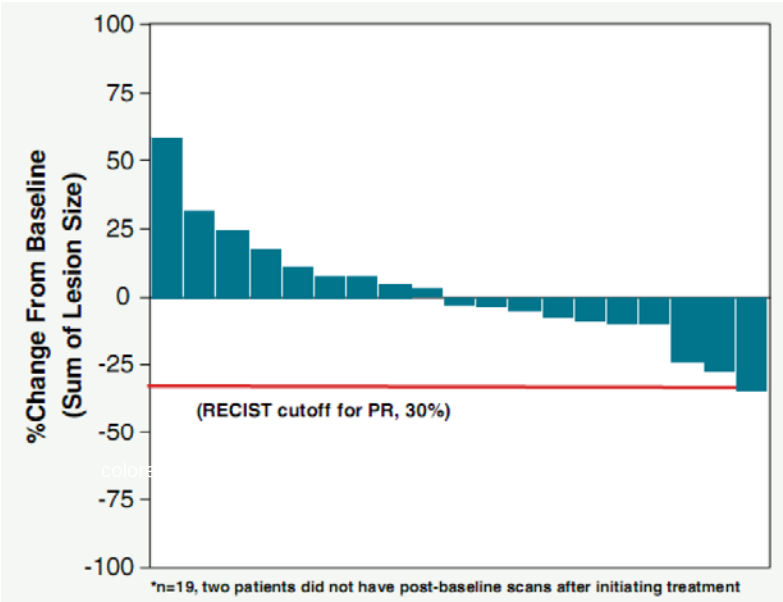


Camidge R et al. Lancet Oncol 2012

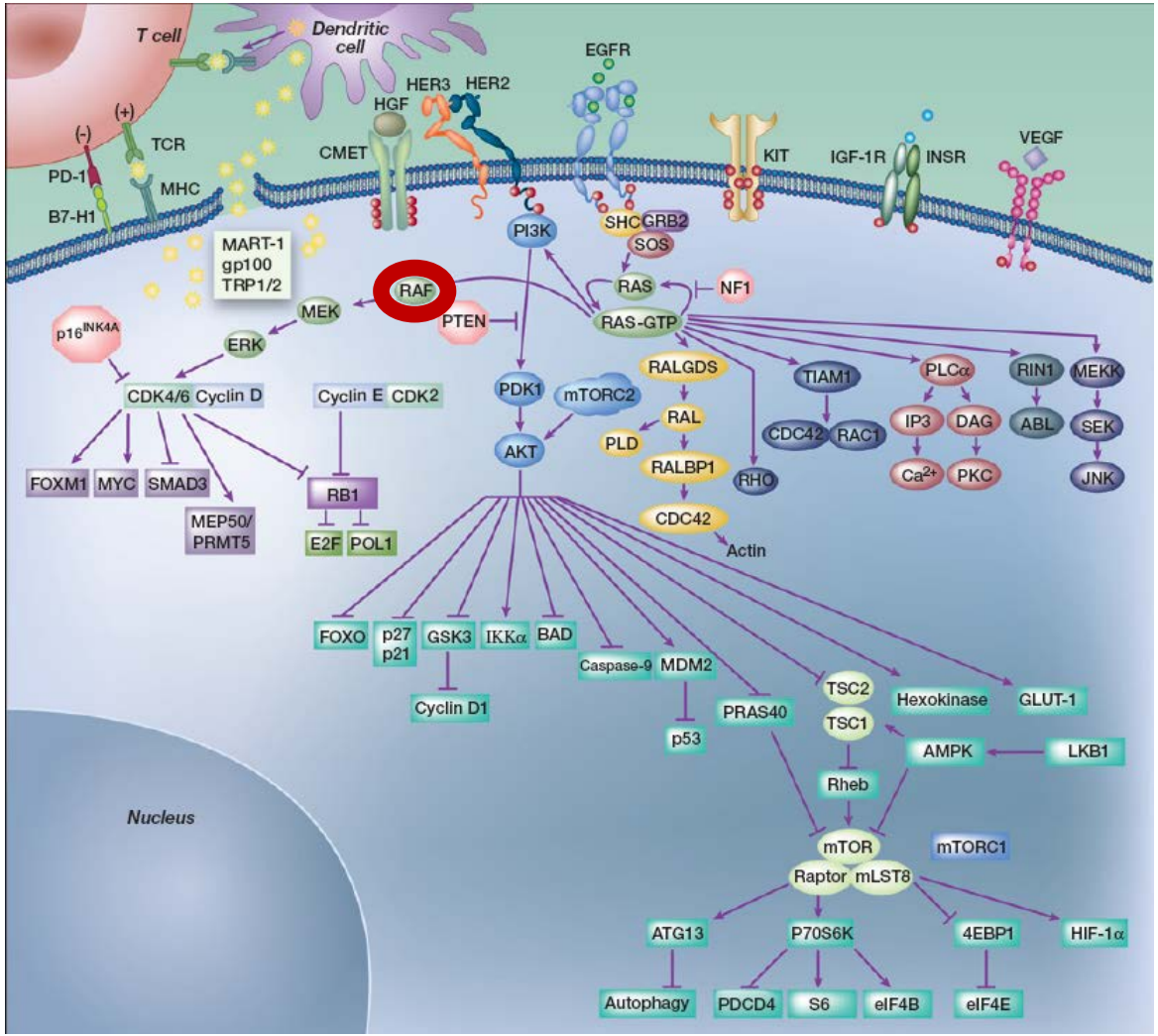
BRAF inhibitor therapy markedly more effective for ^{V600E}BRAF melanoma compared to colon cancer



Sosman J et al. NEJM 2012

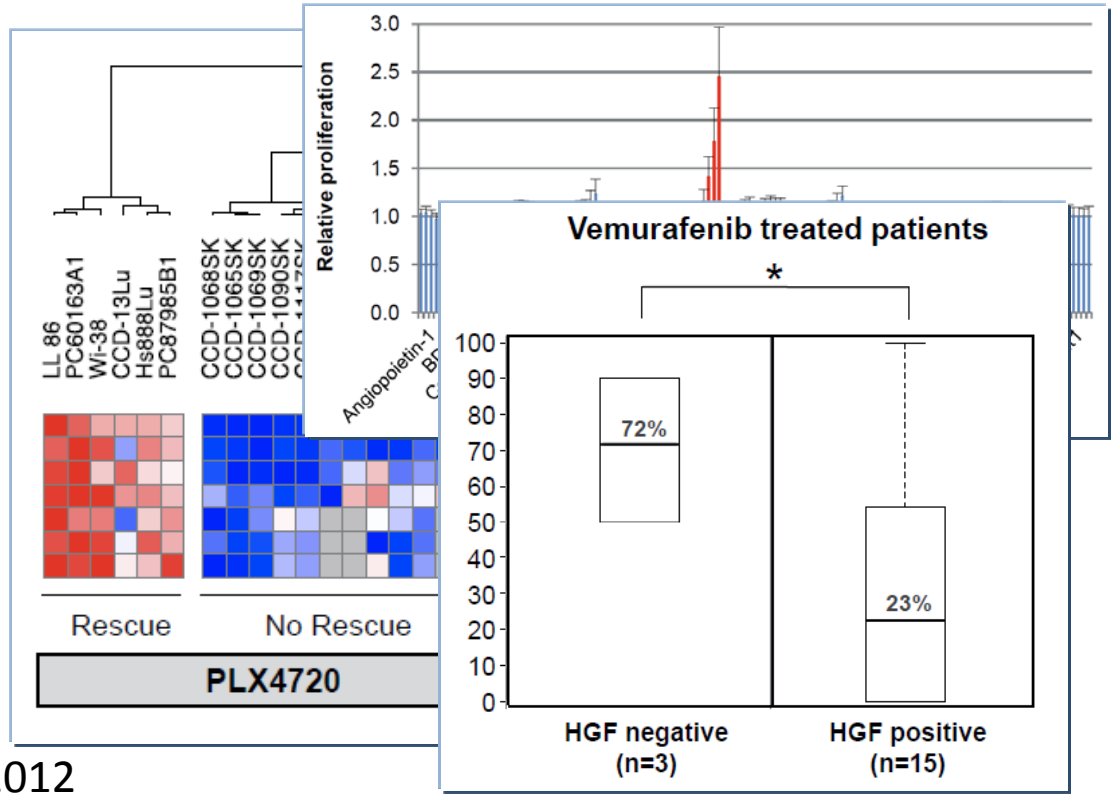


Kopetz, ASCO 2010


T cell
Dendritic cell
(+)
(-)
TCR
PD-1
MHC
B7-H1
MART-1
gp100
TRP1/2
HGF
HER3
HER2
CMET
EGFR
KIT
IGF-1R
INSR
VEGF
PI3K
SHC
GRB2
SOS
RAS
NF1
RAS-GTP
RAF
MEK
ERK
PTEN
p16INK4A
CDK4/6 Cyclin D
Cyclin E
CDK2
PDK1
mTORC2
AKT
RALGDS
RAL
PLD
RALBP1
CDC42
Actin
RHO
TIAM1
CDC42
RAC1
PLCα
IP3
DAG
Ca2+
PKC
RIN1
MEKK
ABL
SEK
JNK
FOXM1
MYC
SMAD3
MEP50/
PRMT5
RB1
E2F
POL1
FOXO
p27
p21
GSK3
IKKα
BAD
Caspase-9
MDM2
p53
Cyclin D1
PRAS40
TSC2
TSC1
Rheb
Hexokinase
GLUT-1
AMPK
LKB1
mTOR
mTORC1
Raptor
mLST8
ATG13
P70S6K
4EBP1
HIF-1α
Autophagy
PDCD4
S6
eIF4B
eIF4E
Nucleus

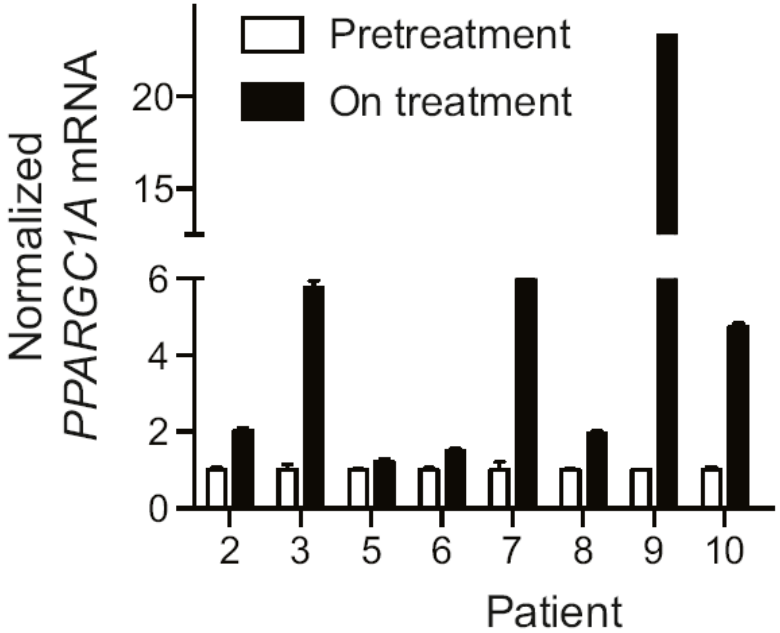
Fibroblasts conferred resistance to BRAF inhibition in melanoma via HGF/c-met

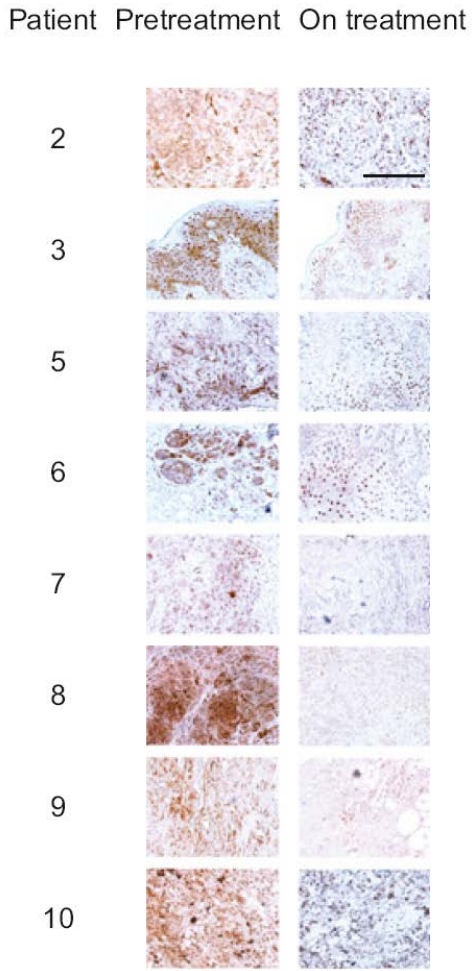
576 cytokines



Straussman et al. Nature 2012

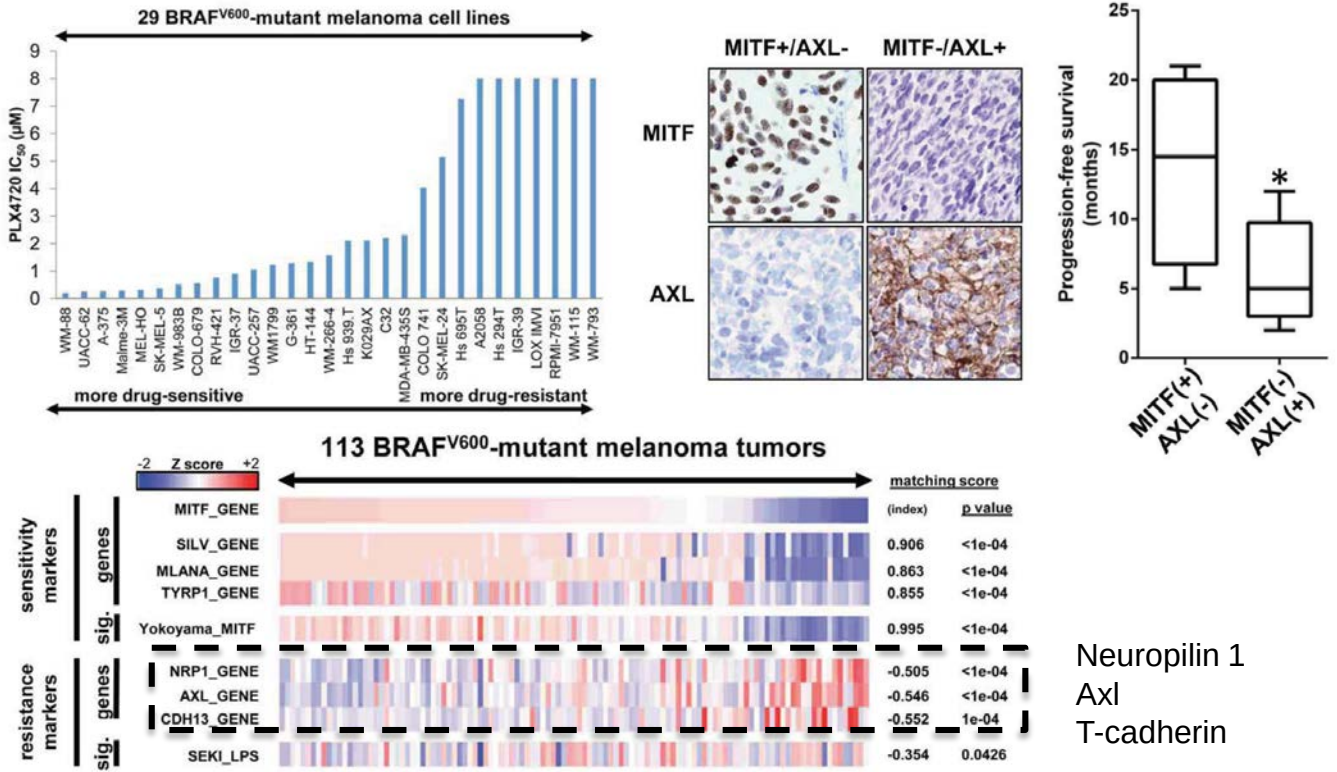
Upregulation of oxidative phosphorylation: sometimes, but not always





Haq R et al. Cancer Cell 2013

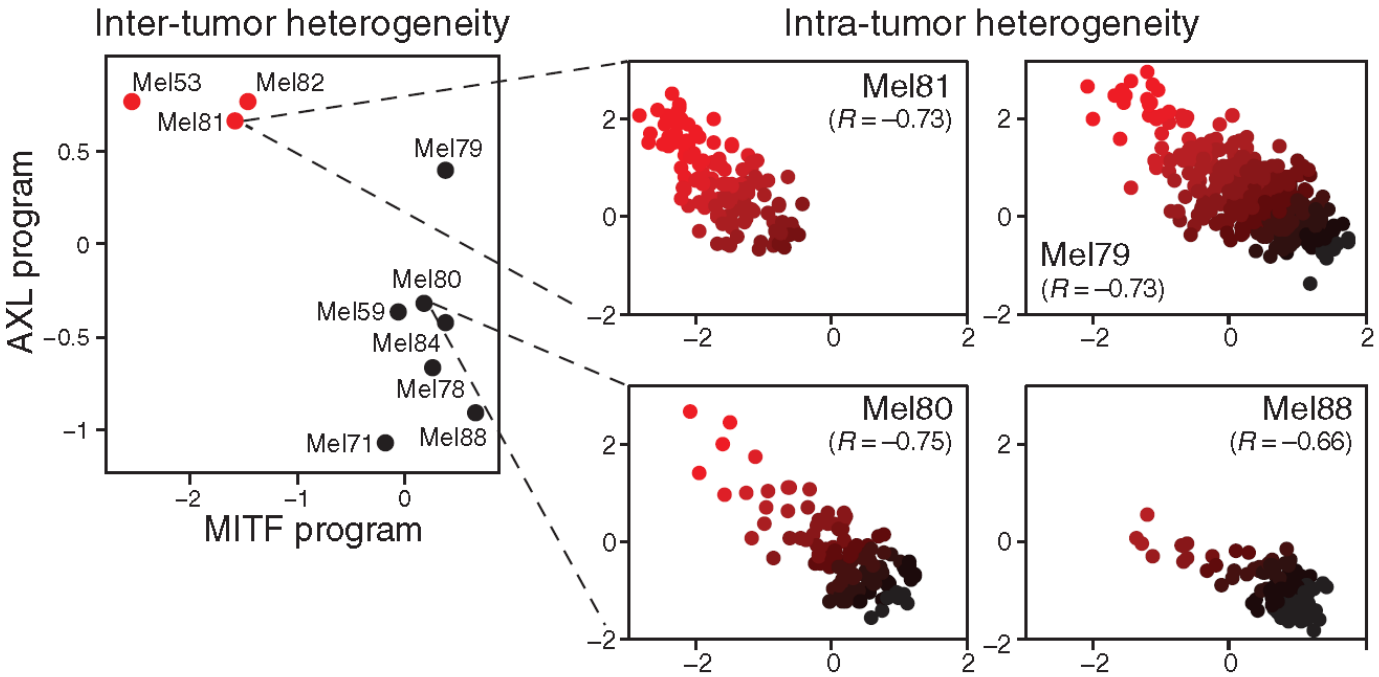
Epigenetic state & therapeutic resistance



Neuropilin 1
Axl
T-cadherin

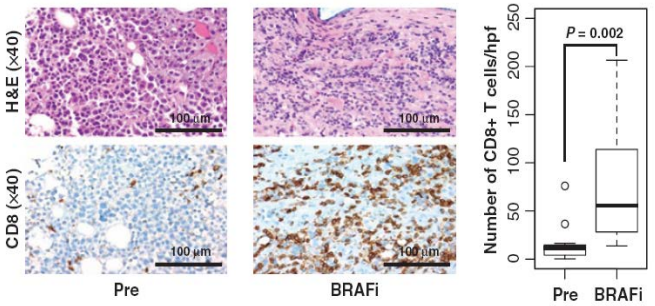
Konieczkowski et al. Cancer Discov 2014

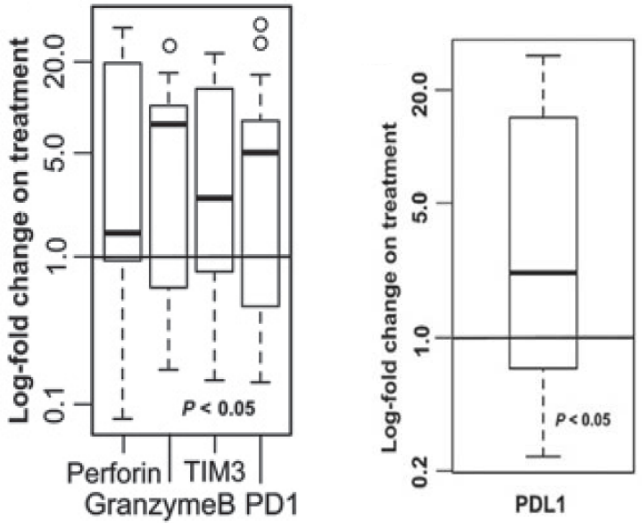
Heterogeneity in MITF expression within & across melanomas

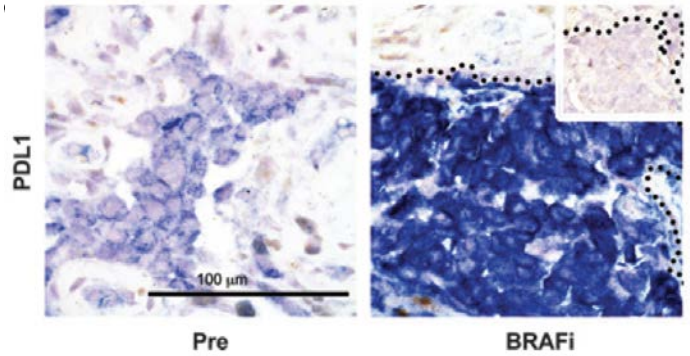


Tirosh et al. Science 2016

Immunologic consequences of BRAF inhibition







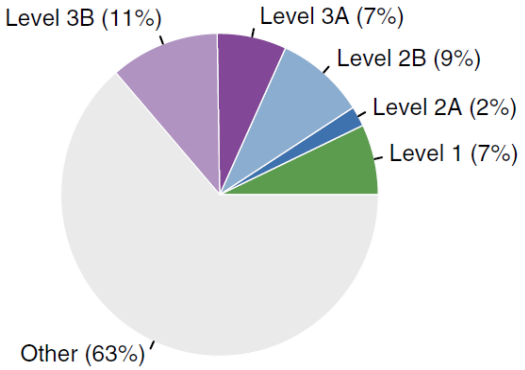
Frederick et al. Clin Cancer Res 2012

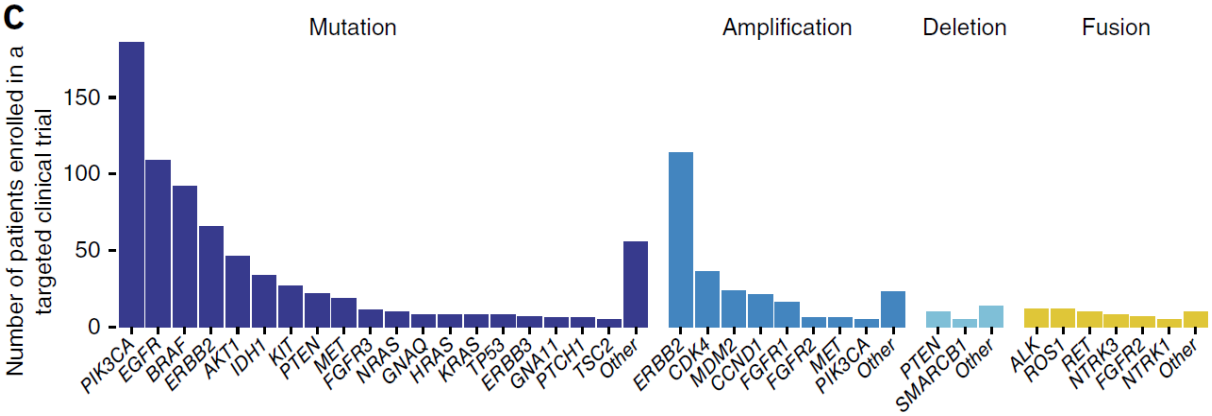
NCI-MATCH Objective

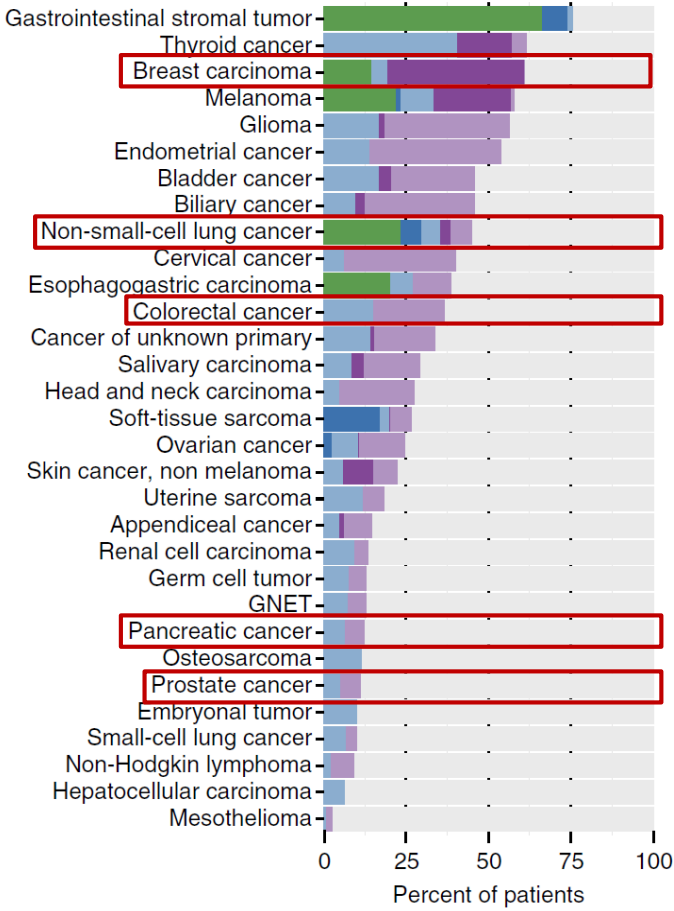
- To determine whether matching certain drugs or drug combinations in adults whose tumors have specific gene abnormalities will effectively treat their cancer, regardless of the cancer type
- This is a signal-finding trial; treatments that show promise can advance to larger, more definitive trials

Mining for the actionable in metastatic cancer patients

Level 1	FDA-recognized biomarker for an FDA-approved drug in the same indication
Level 2A	Standard of care biomarker for an FDA-approved drug in the same indication
Level 2B	Standard of care biomarker for an FDA-approved drug in another indication
Level 3A	Compelling clinical evidence supporting the biomarker as being predictive of drug response in the same indication
Level 3B	Compelling clinical evidence supporting the biomarker as being predictive of drug response in another indication







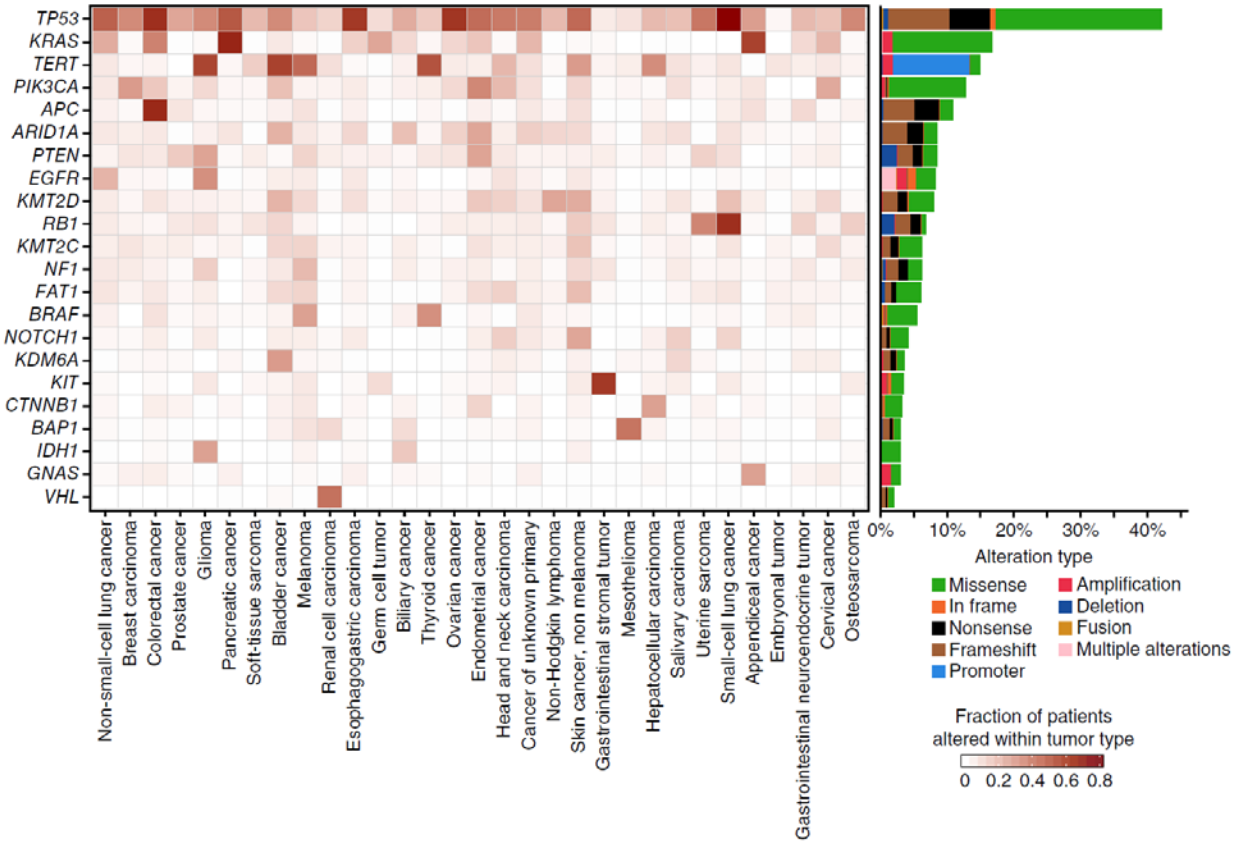
Zehir et al. *Nat Med* 2017

NCI-MATCH Central Screening Summary (cont'd)

- 35% of patients have "actionable alterations"
- Treatment assignment rate: 18%
  - Patients with a tumor gene abnormality that matched to one of the 30 treatment arms (992/5560 with testing completed)
- Enrollment rate: 69%
  - Patients with a treatment assignment who enrolled

Real-world genomic landscape

p53, KRAS & APC mutations commonly co-occur with actionable alterations



Zehir et al. *Nat Med* 2017

LoRusso et al. *Clin Cancer Res* 2012

Table 3. Suggestions on how to improve clinical trials for combination therapies

- Develop a precompetitive venue for testing drug combinations.
- Develop assays to identify patients more or less likely to respond to the drugs.
- Use adaptive trial designs.
- Use appropriate endpoints.
- Set a higher bar for effectiveness.
- Establish a single Institutional Review Board of record for multi-institutional trials.
- Deploy informed consent forms that allow for broader use of patient specimens and patient information for future studies.
- Obtain repeat biopsies of patients' tumors to assess therapeutic effectiveness.

Adapted with permission from IOM (Institute of Medicine; ref. 13).

Scarlett et al. *Cancer Discovery* 2017

"Our analysis shows that the volume of clinical trials testing multiple investigational pipeline agents ("novel–novel" combinations) is dismally low, as out of approximately **1,500** phase I to III investigational combination trials initiated in 2014–2015, only **80** were for novel–novel combinations, and only **9** of those involved more than one company."

LoRusso et al. *Clin Cancer Res* 2012

Table 4. Suggestions on overcoming challenges to collaborations

Cultural challenges

- Increase communication/transparency among collaborating partners.
- Involve patients in discussions of how tissue resources are shared and used.
- Establish a safe harbor for industry to facilitate greater availability of failed investigational compounds for research.
- Provide financial incentives to encourage more collaboration.

Legal challenges

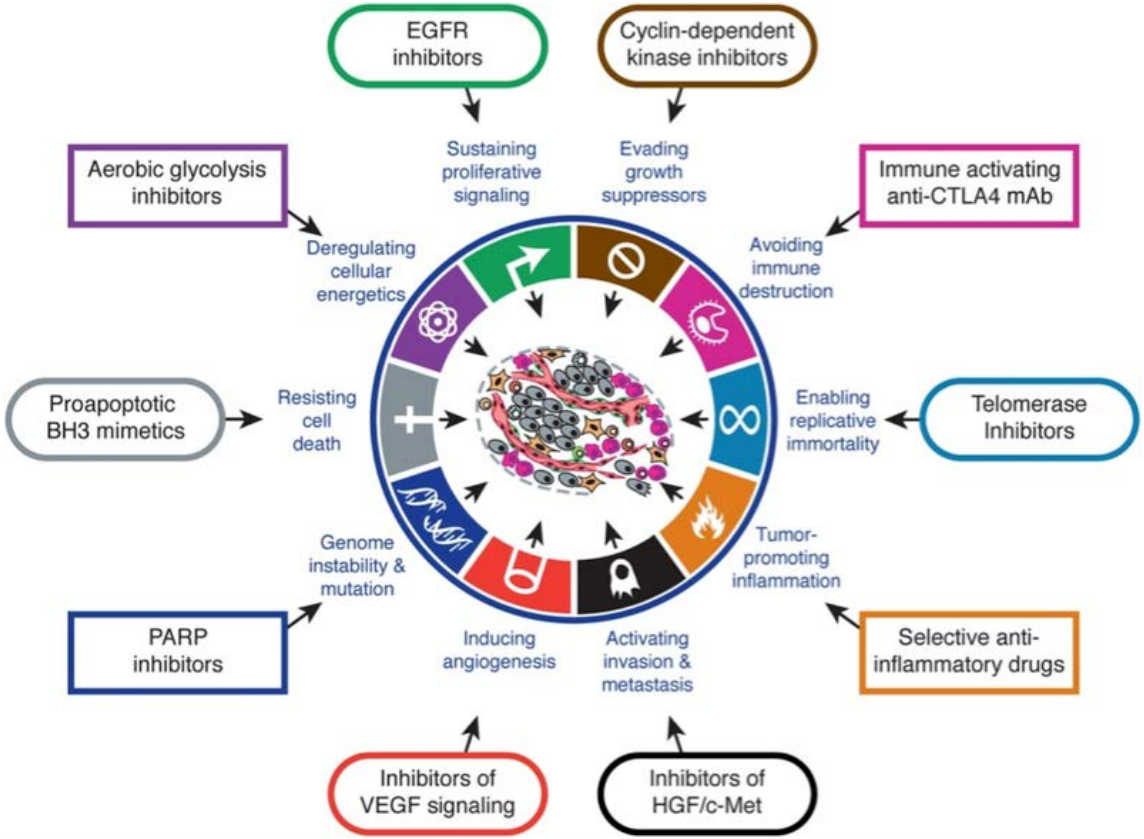
- Give patients more autonomy in deciding how much risk they are willing to take in clinical trials.
- Discuss collaboration and intellectual property at earlier stages of development.
- Reserve intellectual property protections for direct drug candidates.
- Embrace precompetitive collaborations for work upstream of specific candidates.
- Standardize material transfer agreements.
- Specify upfront the negotiable and nonnegotiable aspects of an agreement.
- Restrict collaborations to research and development to avoid antitrust violations.

Regulatory challenges

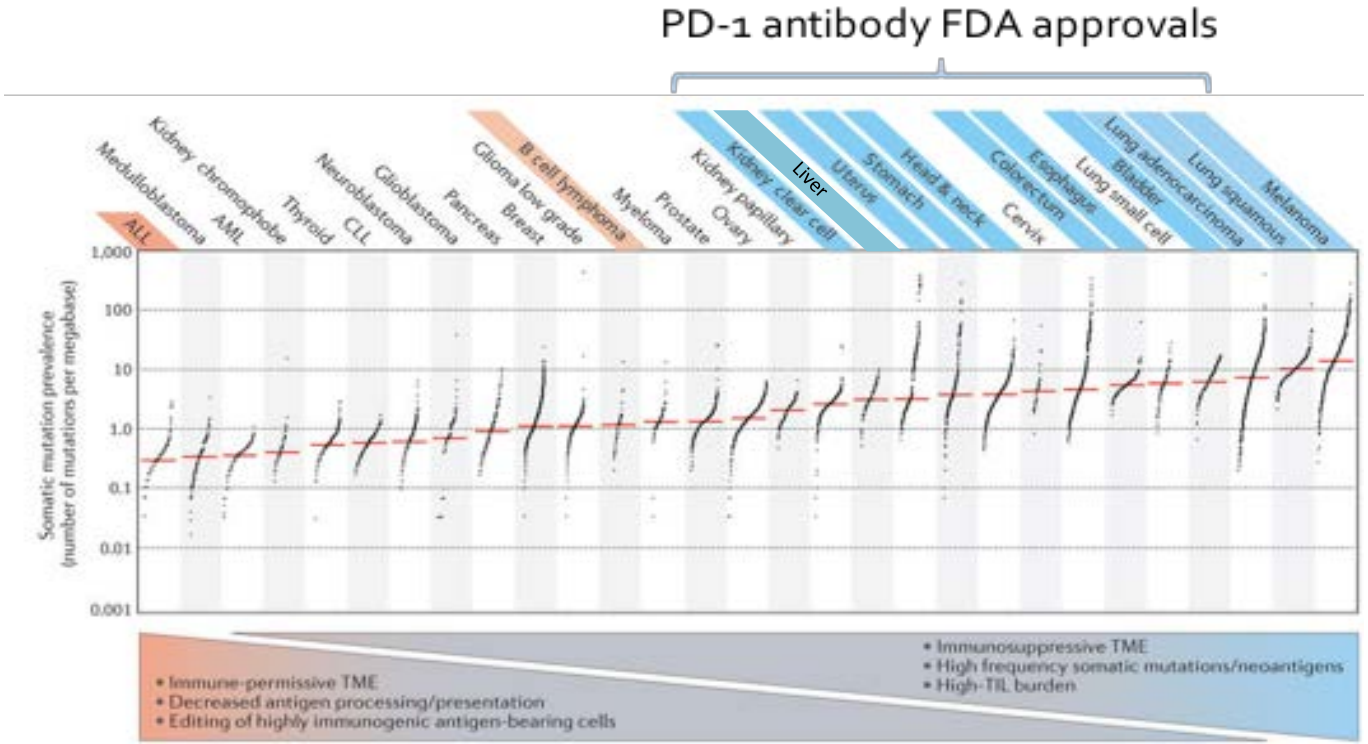
- Focus on combinations with a compelling biologic rationale and strong preclinical data.
- Seek dialogue with the U.S. Food and Drug Administration (FDA) early and often in the development process.
- Establish more dialogue between FDA and the European Medicines Agency to enhance harmonization of regulations.
- Obtain clarification from FDA about the types and strength of evidence needed for combination therapies.
- Obtain clarification from FDA on how sponsors should best interact with multiple FDA offices involved in combination product development.

NOTE: Adapted with permission from IOM (Institute of Medicine; ref. 13).

Therapeutic modality & progress with precision medicine

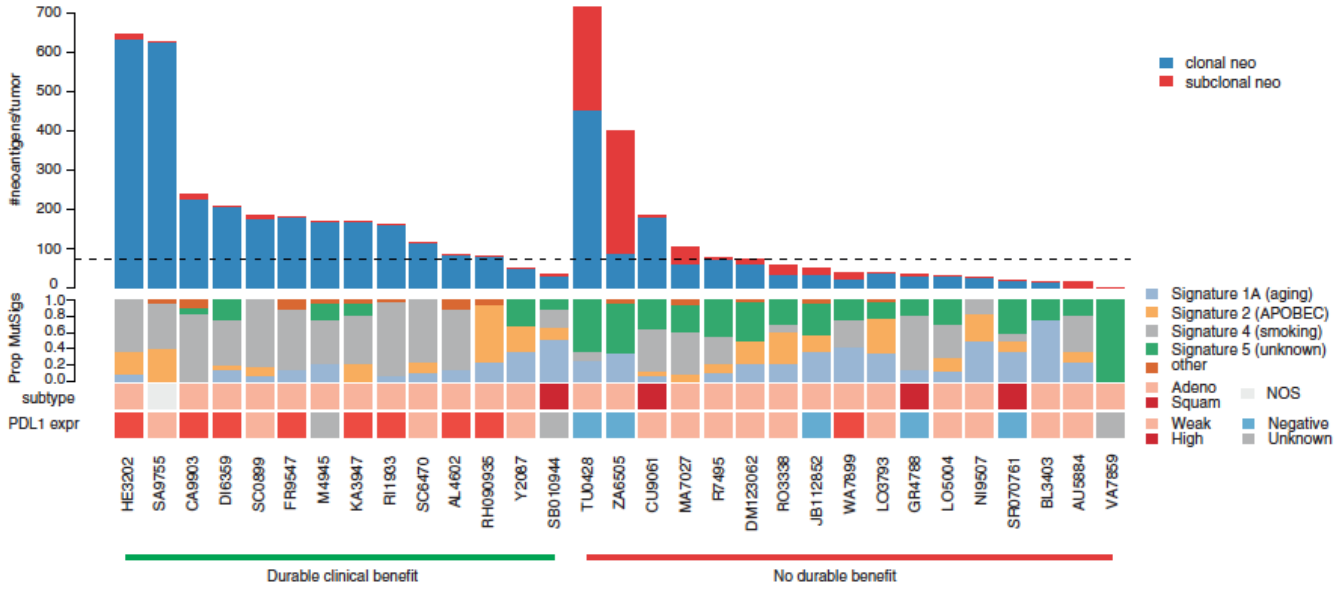


Somatic mutation burden & PD-1/PD-L1 approvals



Adapted from Alexandrov et al. Nature 2013

Clonal neoantigens and response to PD-1 or CTLA-4 antibodies in melanoma & NSCLC

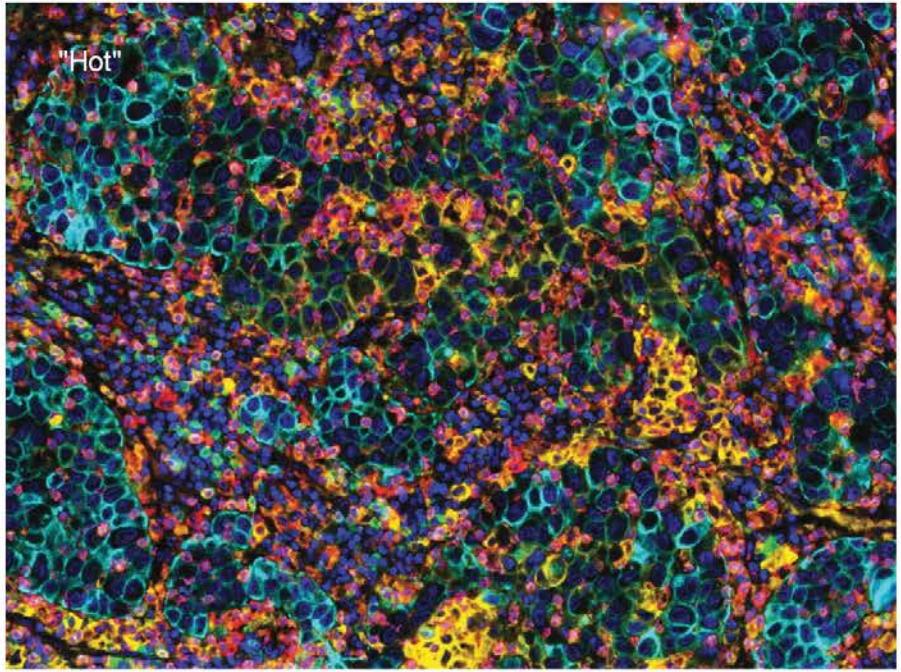


Clonal

Subclonal

McGranahan et al Science 2016; 351: 1463-9

Inflamed versus uninflamed tumors



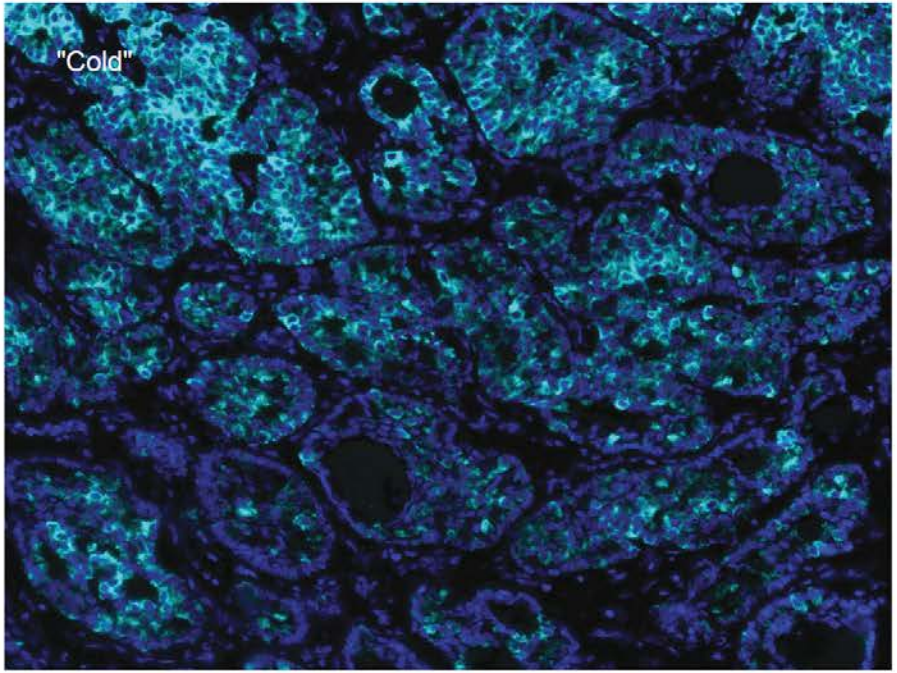
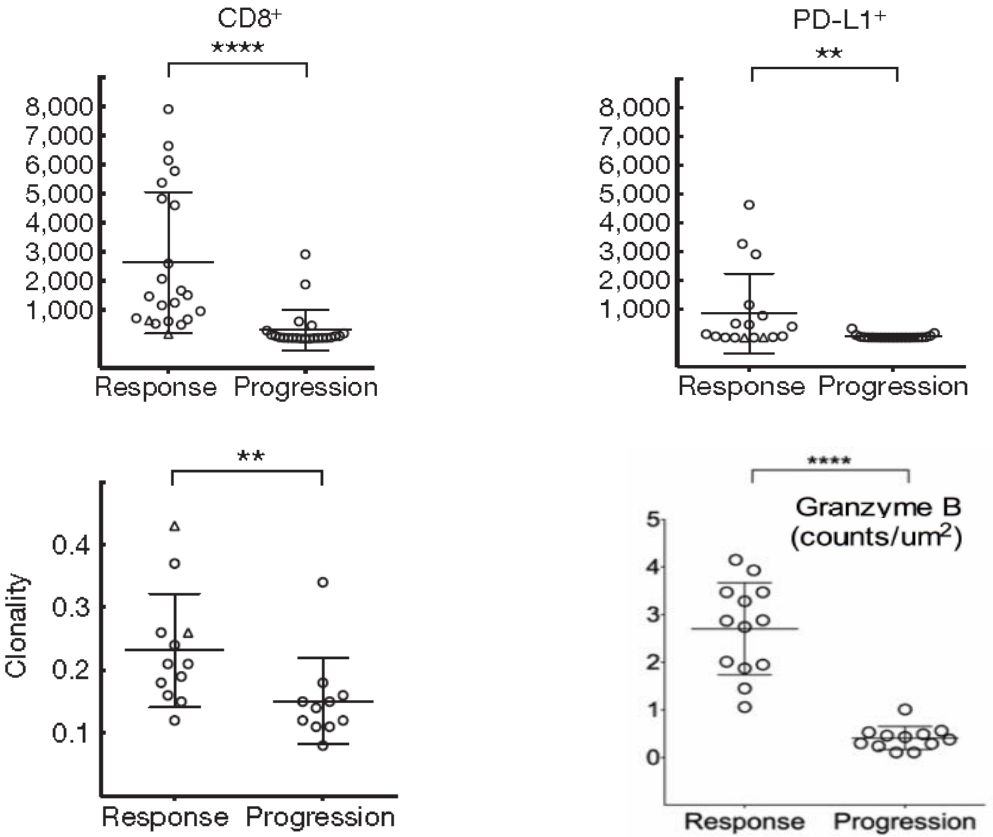


Figure 2A. Representative images of “hot” (L) and “cold” (R) non-small cell lung carcinoma (NSCLC) tumors. DAPI – Blue, CK – Cyan, PD-1 – Green, TIM-3 – Yellow, CD8 – Orange, PD-L1 – Red, LAG3 – Magenta

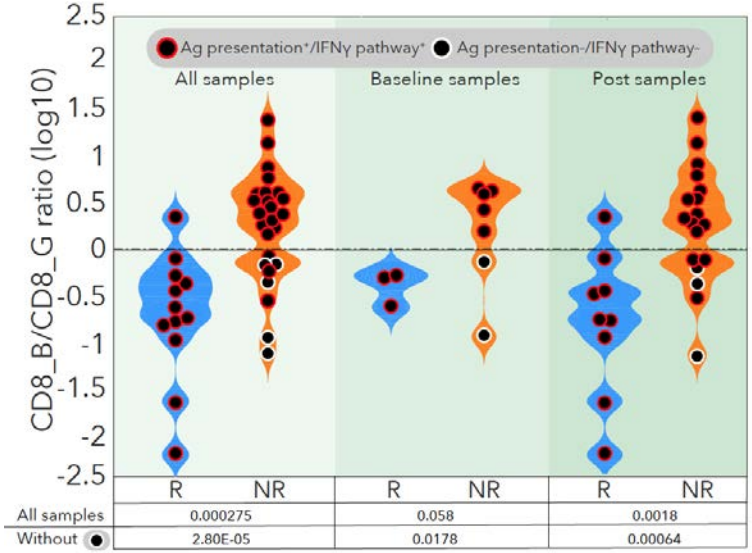
Ziello et al. AACR 2018

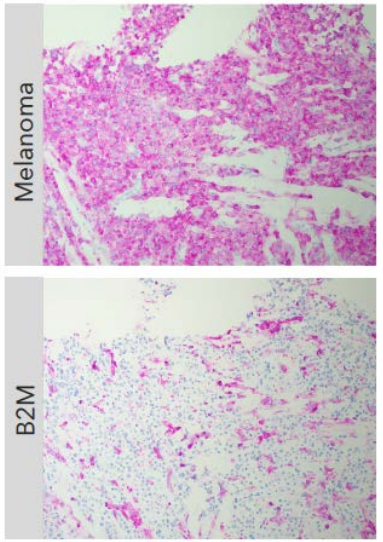
“Inflamed” tumors are more likely to respond to PD-1 antibody therapy



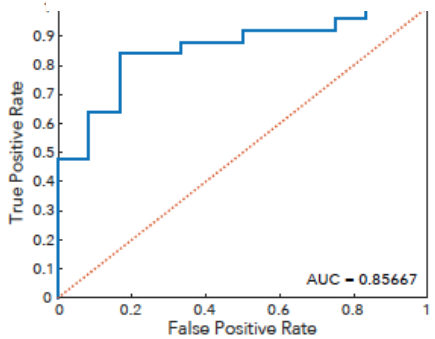
Tumeh P et al.
Nature 2014

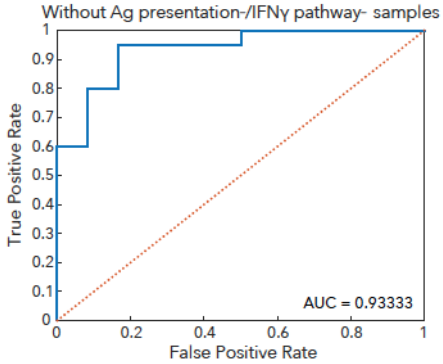
Two CD8+ T cell states associate with CPB response





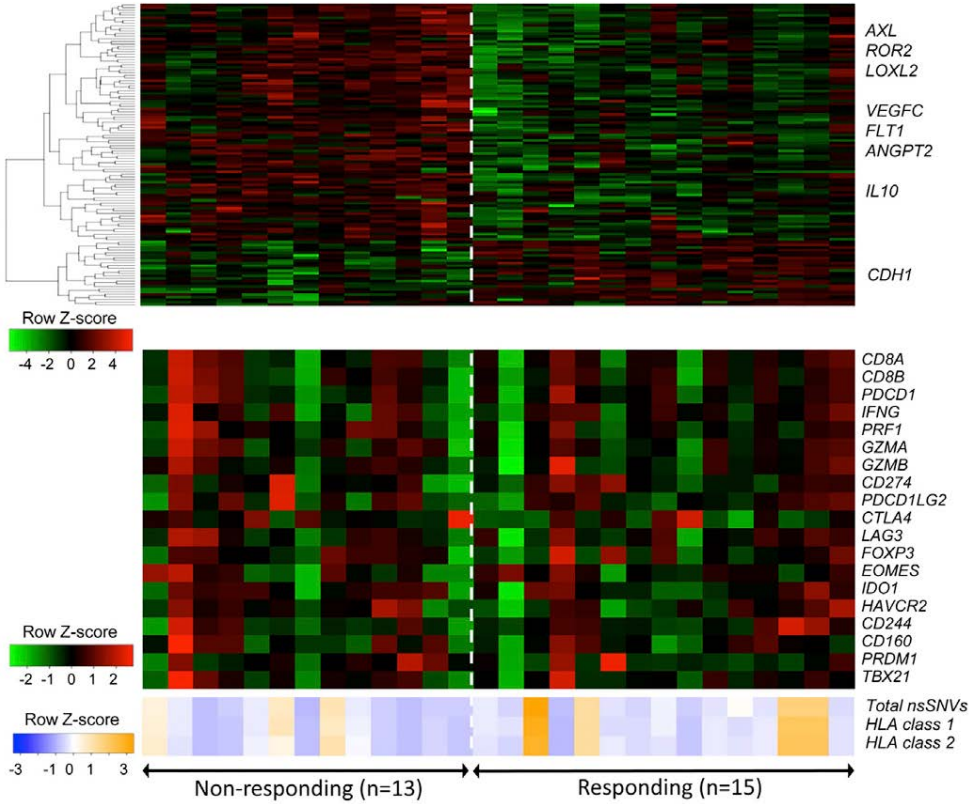
Predictive value

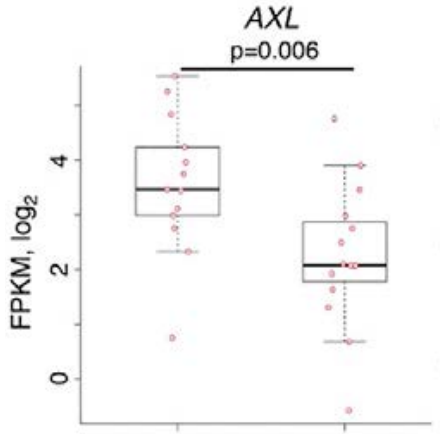




Sade-Feldman et al.
In press, *Cell*

Tumor gene expression, but not immune checkpoints sorts response/non-response





Hugo et al. Cell 2016

Conclusions

- Single-agent vulnerabilities have been pursued in largely tumor-type specific clinical development
- Broader investigation across cancer types with common molecular features to determine rules of homogeneity/heterogeneity of response
- Lineage-dependent factors appear capable of mediating therapeutic resistance: to both targeted and immunotherapy
- Precision-medicine principles are coming to immunotherapy, but who will develop markers to limit approved indications?
- Combination regimen investigation are falling further & further behind