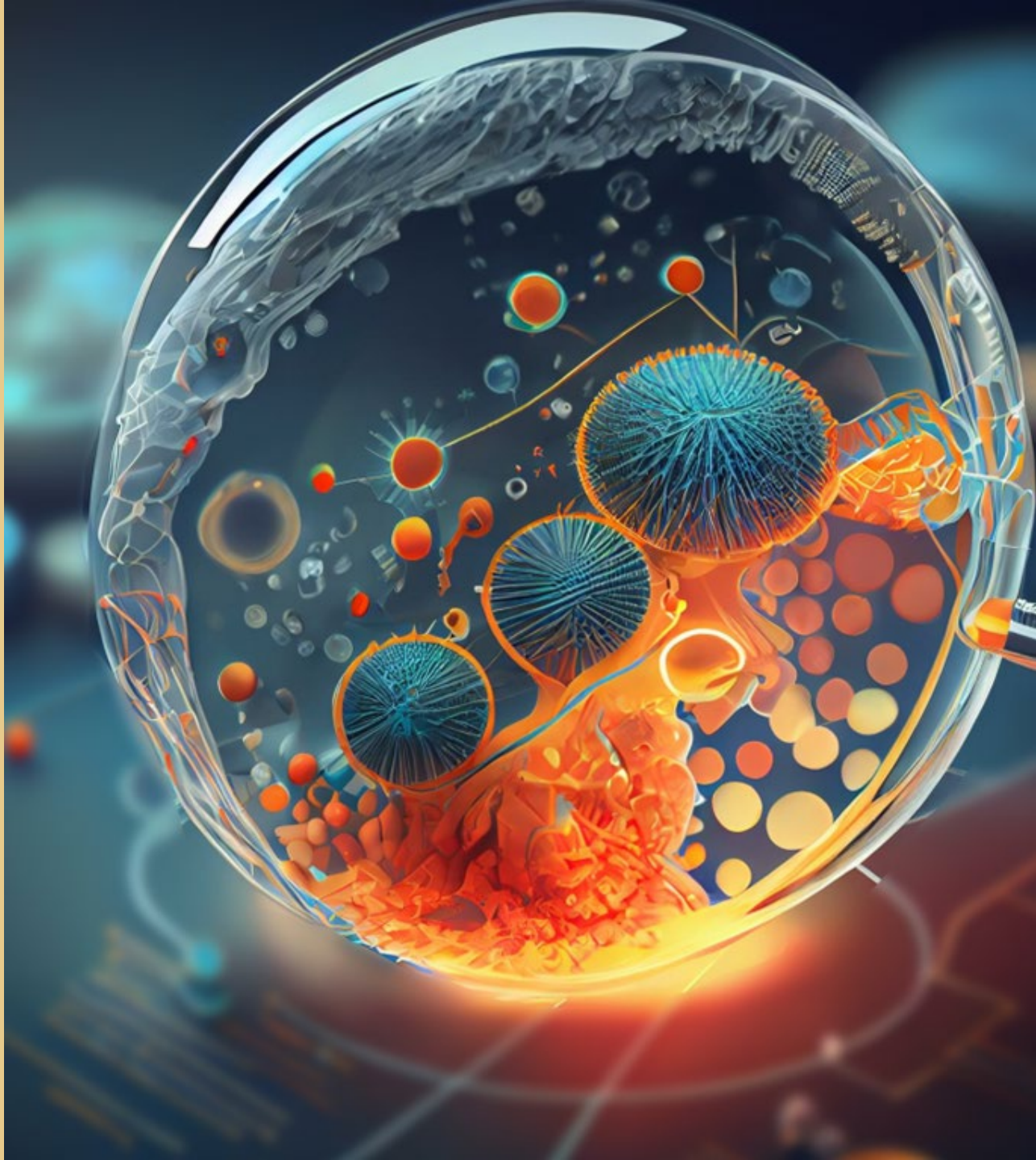
eha Sf(PM)

NCI-MATCH: the end of an era in precision medicine or just the start?



Keith T. Flaherty, MD
Massachusetts General Hospital Cancer Center

Disclosures

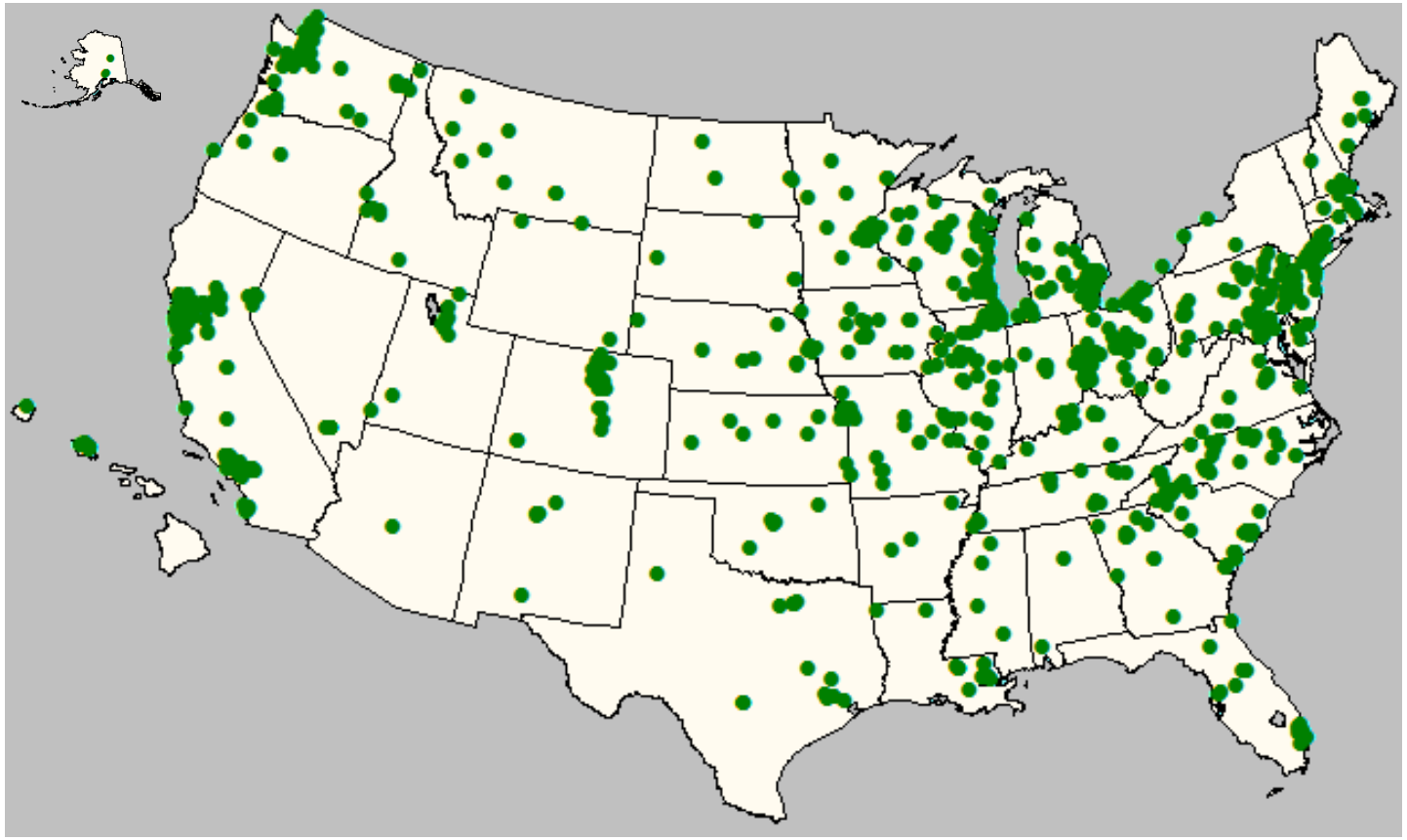
Board of Directors: Strata Oncology¥, Scorpion Therapeutics¥
Scientific Advisory Board: Apricity¥, PIC Therapeutics, Tvardi, xCures, Monopteros, Vibliome, ALX Oncology, Fog Pharma, Soley Therapeutics, Alterome, intrECate, Immagene
Consultant: Gyges¥, Nextech, Takeda*, Transcode Therapeutics, Novartis*, Roche/Genentech*

¥ Founder

* NO equity

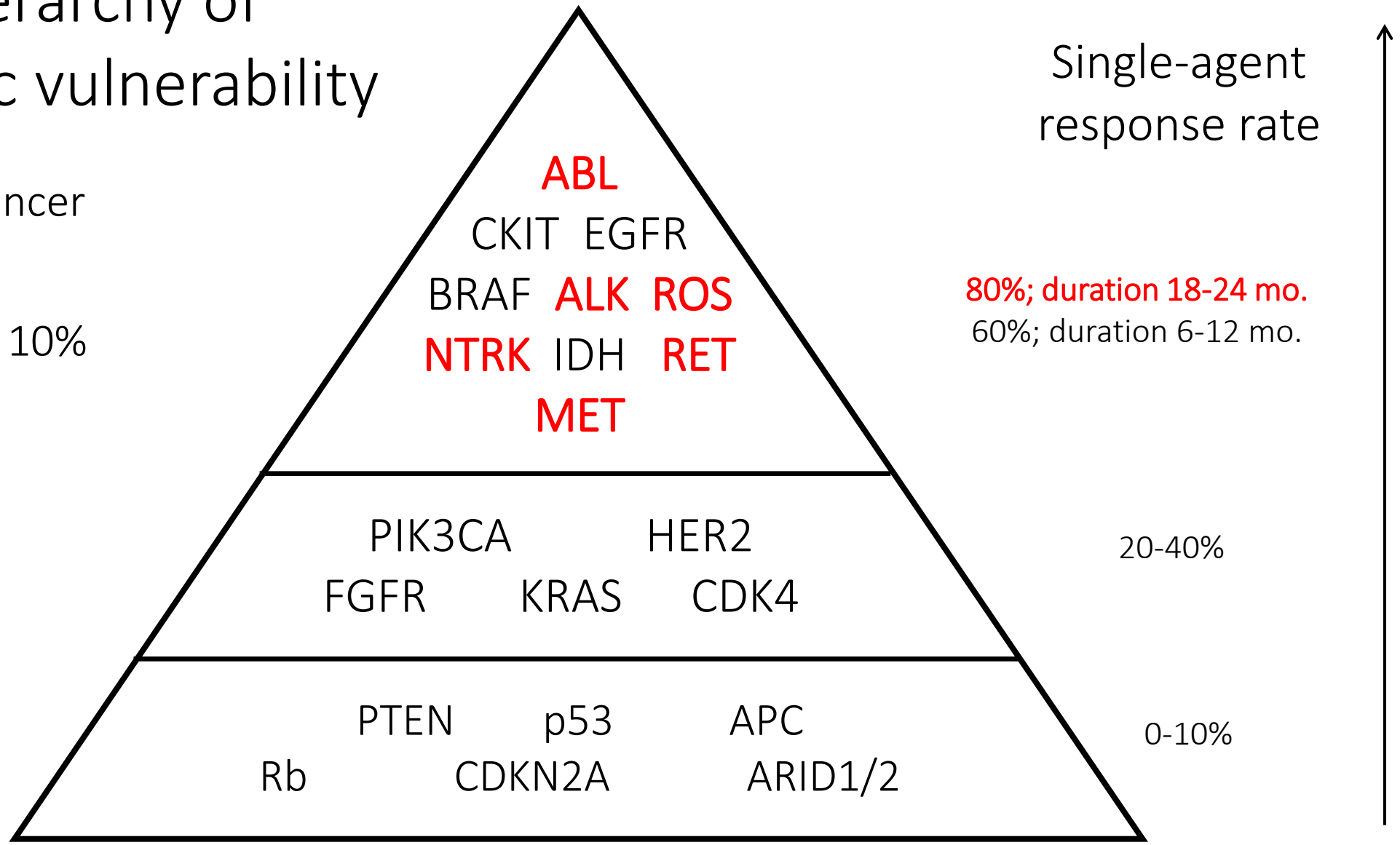
NCI-MATCH brought NGS guided investigational therapy to the community

- Availability at over 1100 sites
- 56% of accrual in community



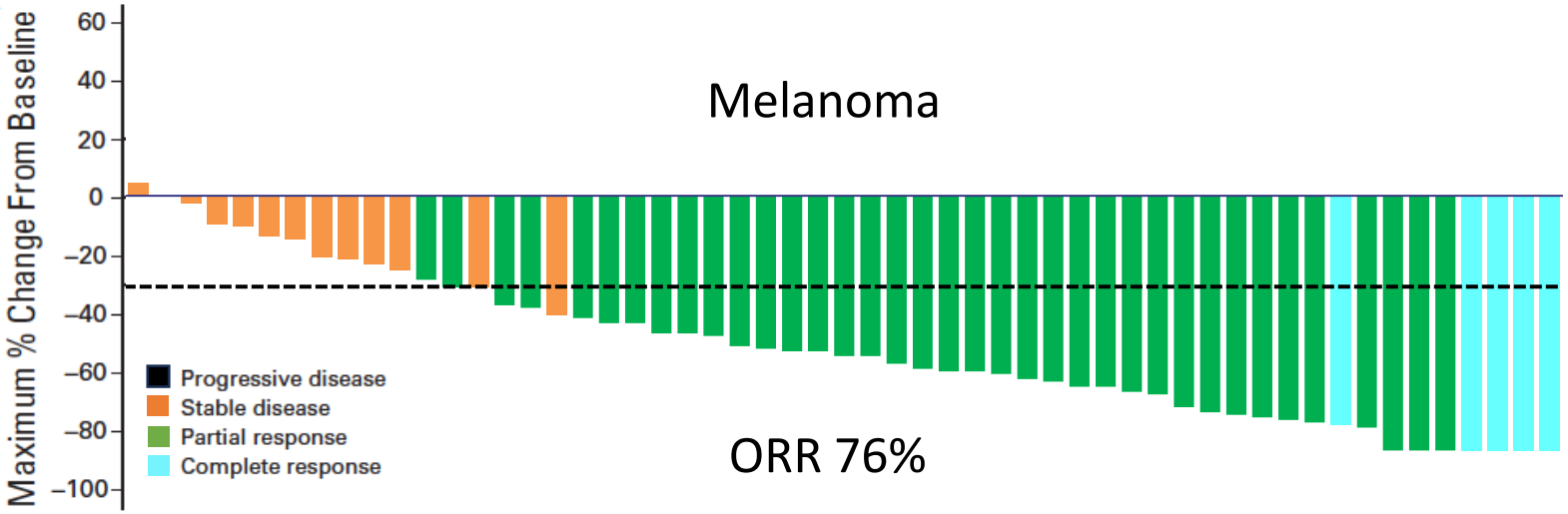
Open in every state, the District of Columbia, and Puerto Rico

Genetic hierarchy of therapeutic vulnerability

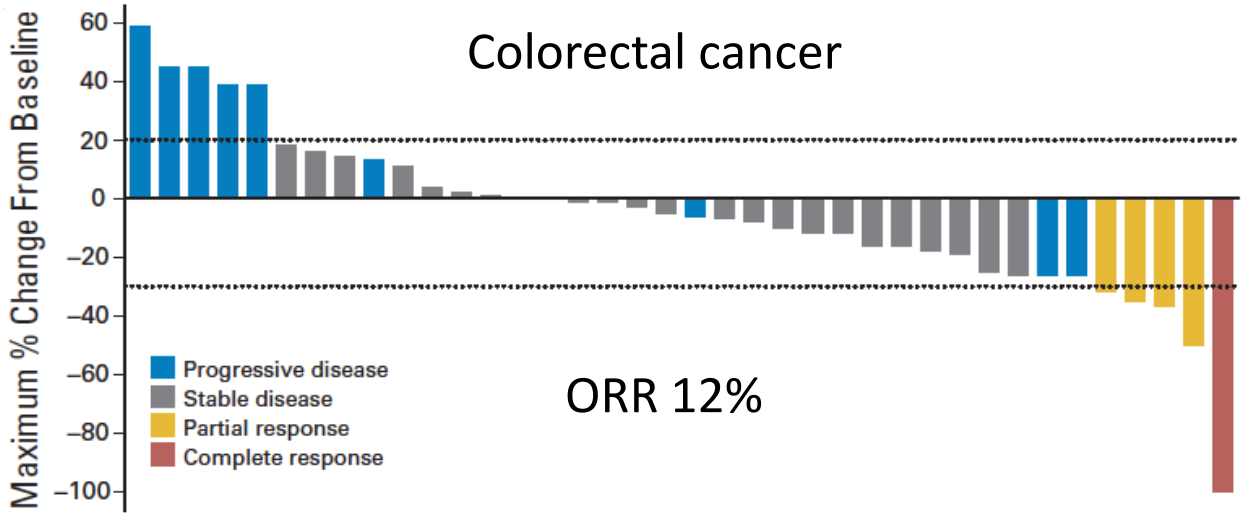


Heterogeneity of response

BRAF/MEK combination: dabrafenib/trametinib

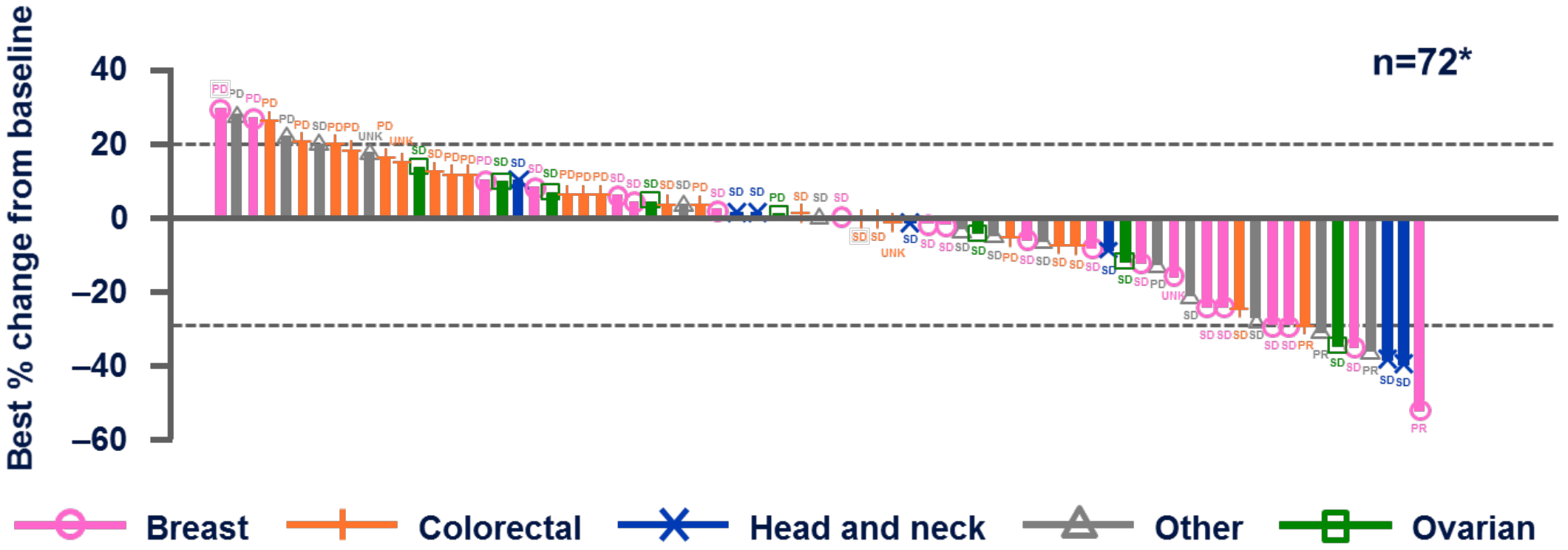


Long G et al. ESMO 2012



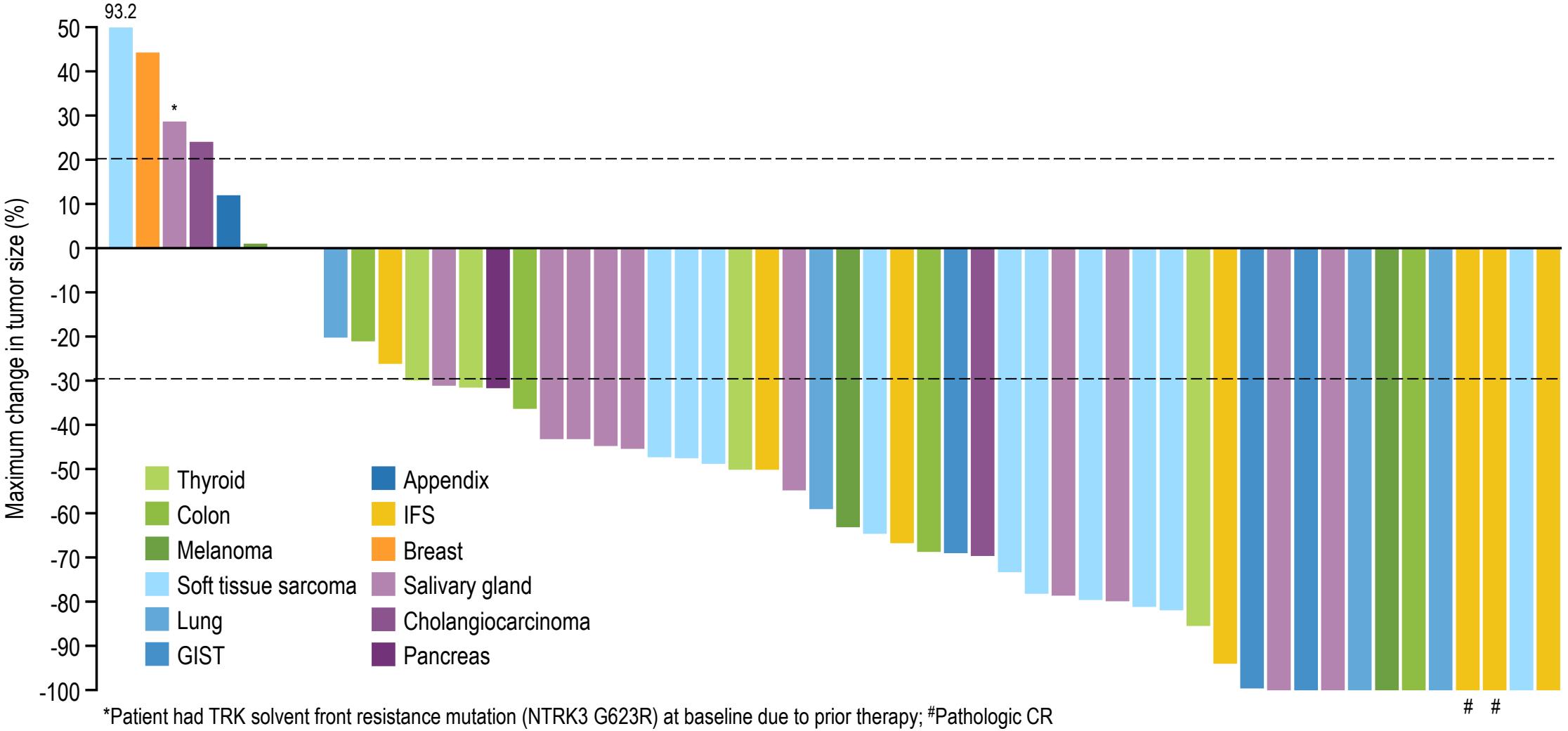
Corcoran et al. JCO 2015

PI3Kα-selective inhibitor in PIK3CA mutant cancers: Responses by tumor type



Juric, AACR 2012; Rodon, AACR 2013

Larotrectinib in TRK fusion cancers: the first targeted therapy/tumor agnostic approval

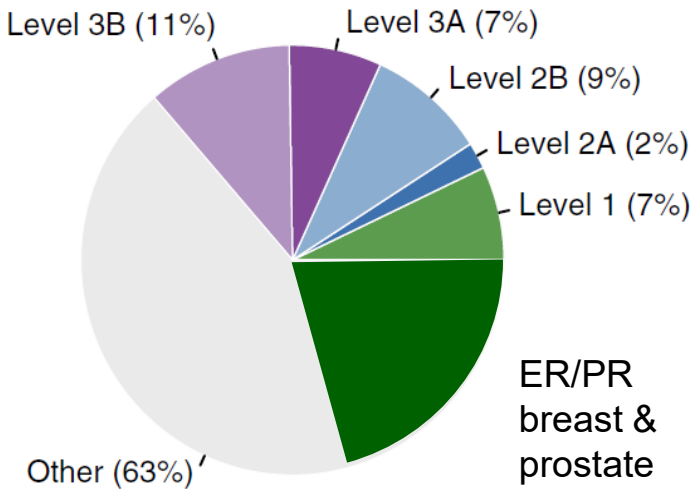


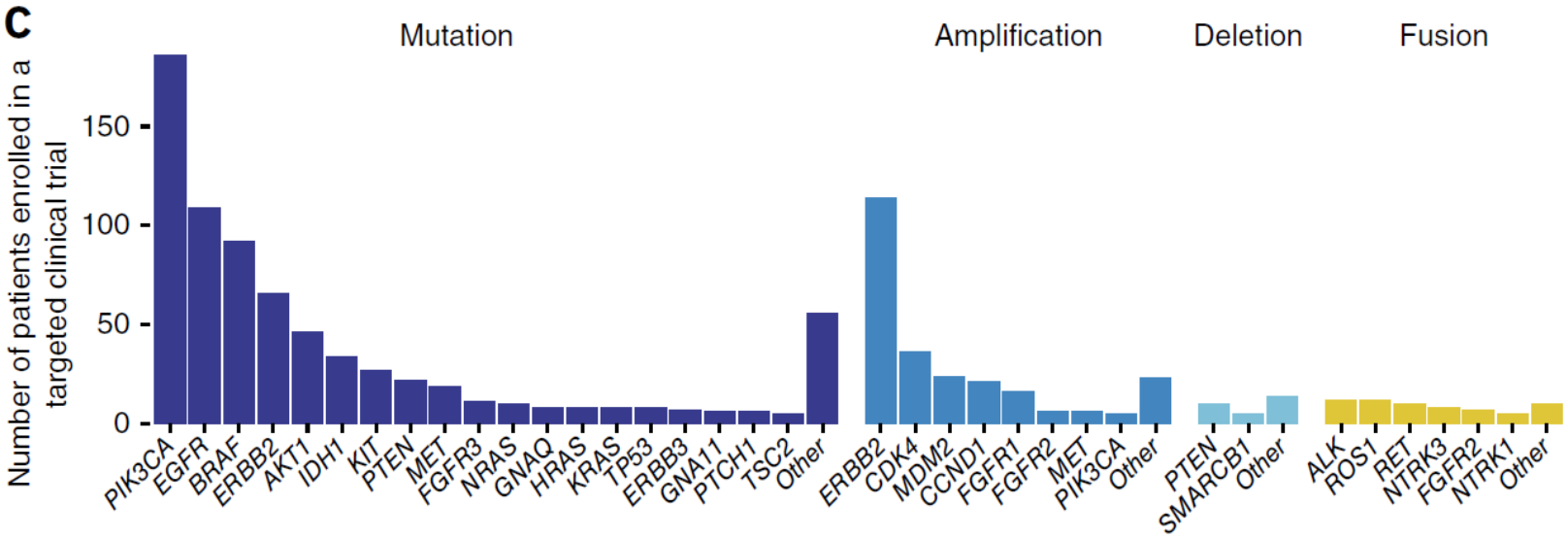
*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

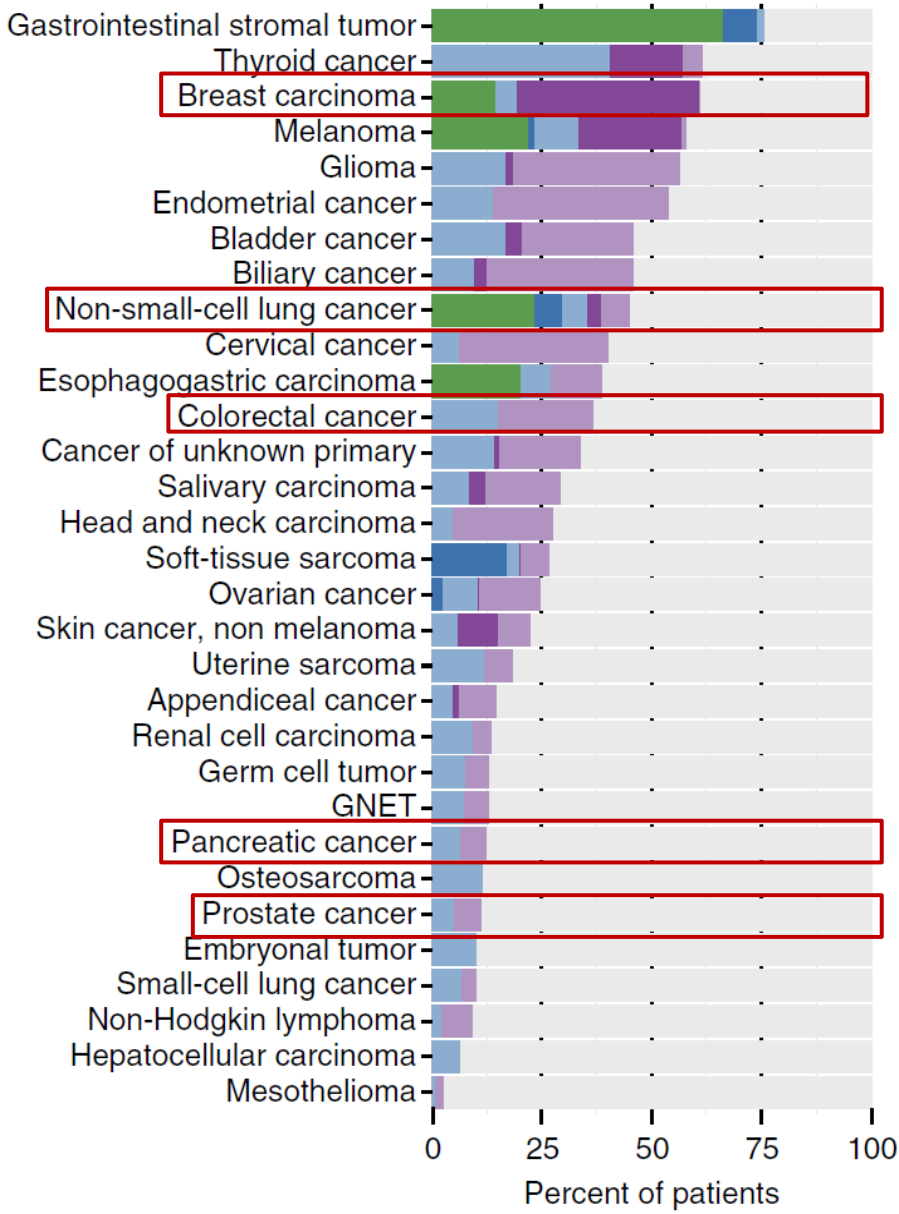
Hyman et al. ASCO 2017

Actionable alteration by cancer type

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

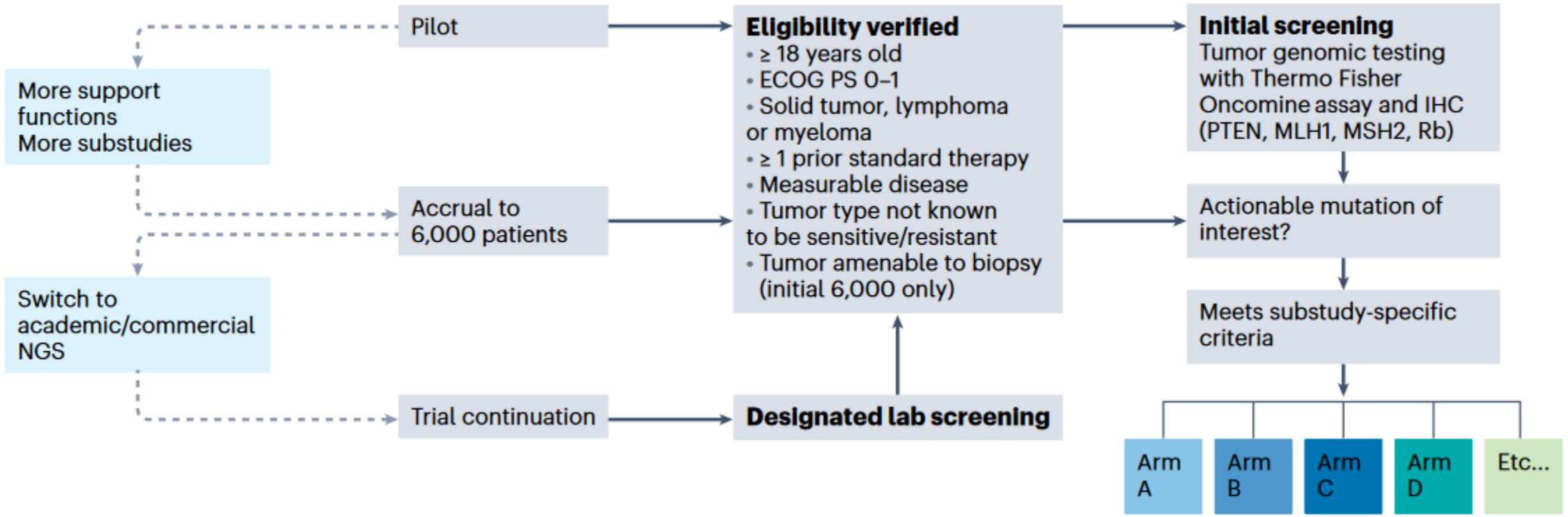
NCI-MATCH Objective

- 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

Credentialing Drugs for NCI-MATCH

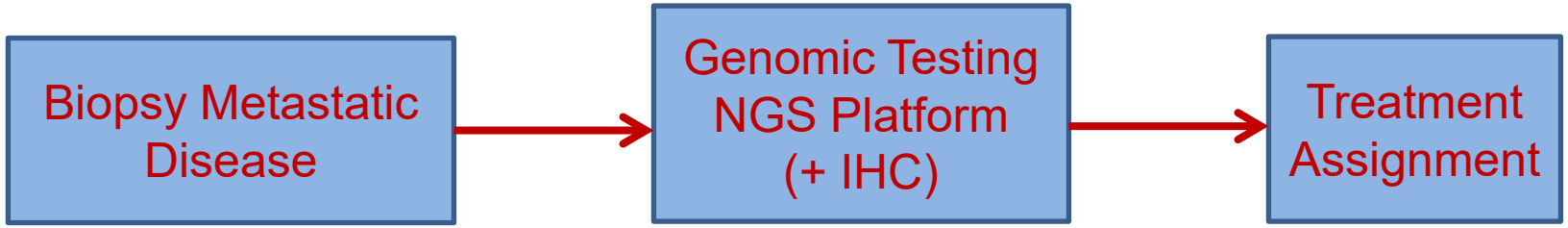
Level of Evidence	Definition
Level 1	FDA-approved for any indication for that target
Level 2	Agent met a clinical endpoint (objective response, PFS, or OS) with evidence of target inhibition
Level 3	Agent demonstrated evidence of clinical activity with evidence of target inhibition at some level

NCI-MATCH: investigating therapies beyond tumor types with known benefit



O'Dwyer PJ et al. *Nat Med* 2023

NCI-MATCH Design



- Metastasis biopsy addresses concern of heterogeneity between primary and metastatic disease
- Uniform diagnostic platform applied across all patient samples
- Imperative to have treatment allocation for as many as possible

Success in screening & ability to assign to treatment

- Profiling was successful in **93.0%** of specimens
- An actionable alteration was found in **37.6%**
- After applying clinical and molecular exclusion criteria, **17.8%** were assigned (**26.4%** could have been assigned if all subprotocols were available simultaneously)

Broad representation of cancer types

Cancer type	Screening cohort *N*=6,390	Outside assay *N*=762
Colorectal	963 (15.1%)	76 (10%)
Breast	764 (12%)	85 (11.2%)
Ovarian	610 (9.5%)	38 (5.0%)
Lung (non-small cell)	485 (7.6%)	53 (7.0%)
Pancreas	413 (6.5%)	25 (3.3%)
Uterine	402 (6.3%)	70 (9.2%)
Liver and hepatobiliary	290 (4.5%)	39 (5.1%)
Sarcoma	288 (4.5%)	29 (3.8%)
Head and neck	239 (3.7%)	34 (4.5%)
Neuroendocrine	214 (3.3%)	11 (1.4%)
Gastroesophageal	211 (3.3%)	34 (4.5%)
Prostate	157 (2.5%)	33 (4.3%)
Bladder/urothelial	108 (1.7%)	17 (2.2%)
Cervical	103 (1.6%)	9 (1.2%)
Central nervous system	103 (1.6%)	106 (13.9%)
Lung (small cell)	90 (1.4%)	4 (0.5%)
Melanoma	85 (1.3%)	14 (1.8%)
Kidney	83 (1.3%)	12 (1.6%)
Lymphoma	55 (0.9%)	1 (0.1%)
Mesothelioma	55 (0.9%)	2 (0.3%)
Anal	52 (0.8%)	6 (0.8%)
Myeloma	1 (<0.1%)	1 (0.1%)
Other	619 (9.7%)	63 (8.3%)

O'Dwyer PJ et al. *Nat Med* 2023

Results by treatment arm

Arm	Molecular aberration	Treatment	*N* enrolled	*N* evaluable†	Number of responses (%)	6-month PFS	Ref.	Met endpoint?[a]
A	EGFR-activating mutations	Afatinib	19	14	1 (7.1%)	8.9%	40	No
B	HER2-activating mutations	Afatinib	40	37	1 (2.7%)	12.0%	41	No
F	**ALK fusions**	**Crizotinib**	**5**	**4**	**2 (50.0%)**	**25%**	42	**Yes**
G	ROS1 fusions	Crizotinib	4	4	1 (25.0%)	50%	42	No
H	**p.Val600Glu or p.Val600Lys mutations**	**Dabrafenib/ trametinib**	**35**	**29**	**11 (37.9%)**	**68.4%**	17	**Yes**
I	*PIK3CA* mutation without *RAS* mutation or PTEN loss	Taselisib	70	61	0.0%	19.9%	43	No
J	*HER2* amplification	Trastuzumab/pertuzumab	35	25	3 (12%)	25.3%	44	No
K2	**FGFR mutation/fusion**	**Erdafitinib**	**35**	**21**	**3 (14.3%)**	**36.8%**	45	**Yes**
M	*TSC1* or *TSC2* mutations	TAK-228	49	34	5 (14.7%)	28.7%	46	No
N	PTEN aberration, with positive IHC expression	GSK2636771	24	22	0.0%	4.8%	47	No
P	PTEN loss by IHC	GSK2636771	35	32	0.0%	3.3%	47	No
Q	*HER2* amplification	Ado-trastuzumab emtansine	38	36	2 (5.6%)	23.6%	48	No
R	*BRAF* fusions/non-V600 mutations	Trametinib	35	32	1 (3.0%)	17%	49	No

O'Dwyer PJ et al. *Nat Med* 2023

Results by treatment arm

Arm	Molecular aberration	Treatment	*N* enrolled	*N* evaluable†	Number of responses (%)	6-month PFS	Ref.	Met endpoint?[a]
S1	*NF1* mutation	Trametinib	50	46	2 (4.3%)	20.5%	50	No
S2	*GNAQ* or *GNA11* mutation	Trametinib	4	4	1 (25%)	50%	50	No
T	*SMO* or *PTCH1* mutations	Vismodegib	34	22	2 (9.1%)	22.4%	51	No
U	*NF2* mutation	Defactinib	35	30	1 (3.3%)	22.8%	52	No
V	C-kit mutations	Sunitinib	10	8	2 (25%)	25%	53	No
W	FGFR pathway aberrations	AZD4547	52	48	4 (8.3%)	15.0%	54	No
Y	***AKT* mutations**	**Capivasertib**	**35**	**35**	**10 (28.6%)**	**50.0%**	19	**Yes**
Z1A	*NRAS* mutations	Binimetinib	53	47	1 (2.1%)	29.2%	55	No
Z1B	*CCND1/2/3* amp and Rb positive	Palbociclib	40	32	0.0%	16.0%	56	No
Z1D	**dMMR status**	**Nivolumab**	**47**	**42**	**15 (35.7%)**	**51.3%**	18	**Yes**
Z1F	**PIK3CA mutation**	**Copanlisib**	**35**	**25**	**4 (16.0%)**	**38%**	21	**Yes**
Z1H	*PTEN* mutation without PTEN protein loss	Copanlisib	35	23	1 (4.3%)	14.3%	57	No
Z1K	***AKT* mutation**	**Ipatasertib**	**35**	**26**	**6 (23.1%)**	**52.4%**	20	**Yes**
Z1L	*BRAF* fusions or non-p.Val600Glu, non-p.Val600Lys *BRAF* mutations	Ulixertinib	35	26	0.0%	5%	58	No

O'Dwyer PJ et al. *Nat Med* 2023

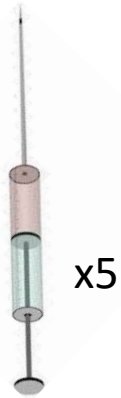
Unique approach: tumor & blood-based biomarker investigations to understand mechanisms of action & resistance

Circulating tumor cells
ctDNA
Exosomes

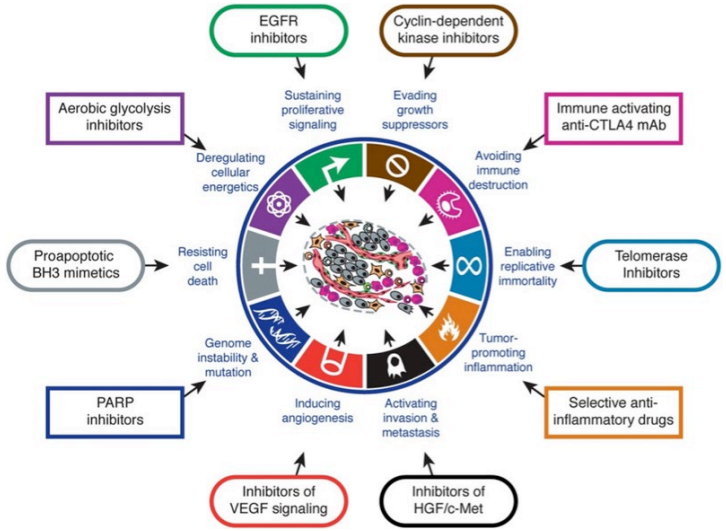
Investigational therapy

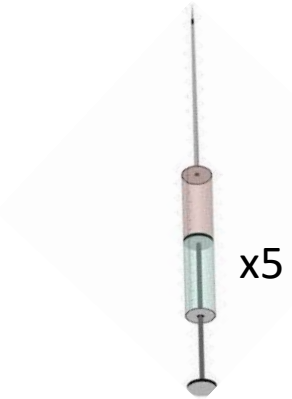
Serial Tumor Biopsy Program

x5



x5





x5

Rapid Autopsy Program

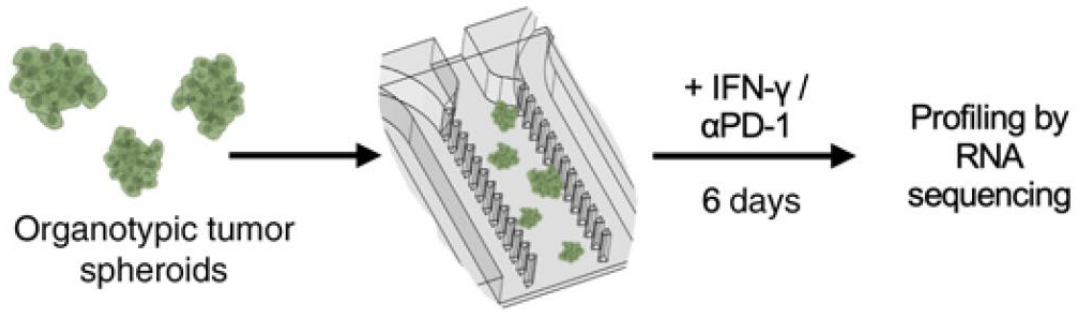
Mass General Brigham
Mass General Cancer Center

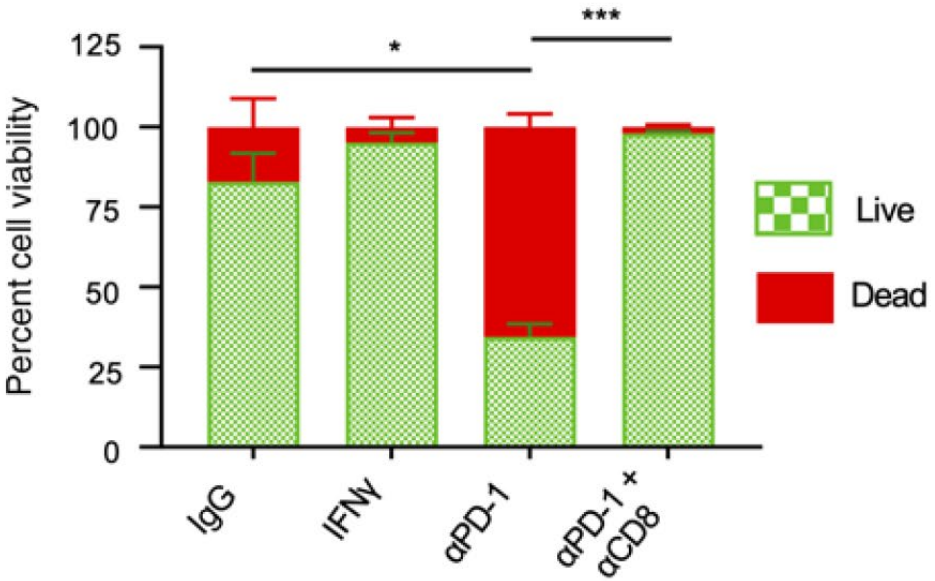
Standard "–omic" analysis of serial biopsies have driven important discoveries in resistance mechanisms & rational combinations

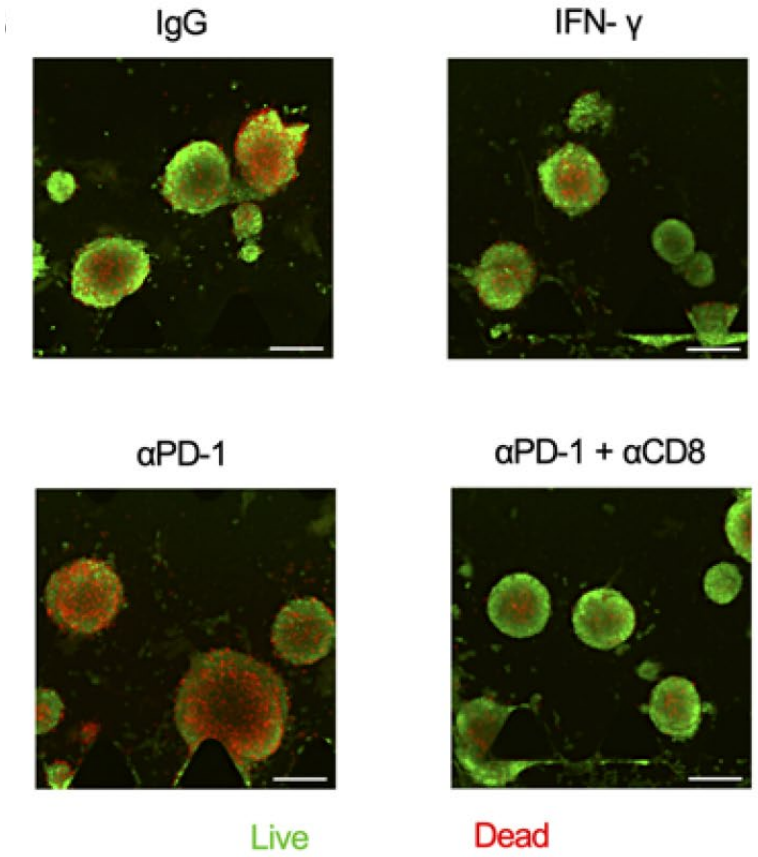
- Resistance mutations in truncal drivers:
  - 1st, 2nd & 3rd generation EGFR inhibitors in NSCLC
  - ALK, ROS, RET, KRAS in NSCLC
  - FGFR inhibitors in cholangiocarcinoma
- Compensatory signaling through genetic & epigenetic alterations
  - BRAF → BRAF/MEK across cancer; EGFR mediated resistance in colorectal
  - cMET in EGFR mutant NSCLC
  - Convergent evolution of PTEN loss to PI3Kalpha selective inhibitors
  - Dedifferentation through epigenetic changes in
    - ER+ breast cancer CTCs
    - EMT in oncogene driven NSCLC
    - Neural crest phenotype in BRAF/MEK and PD-1 resistant melanoma

Ex vivo organotypic model for drug screening

Russ Jenkins

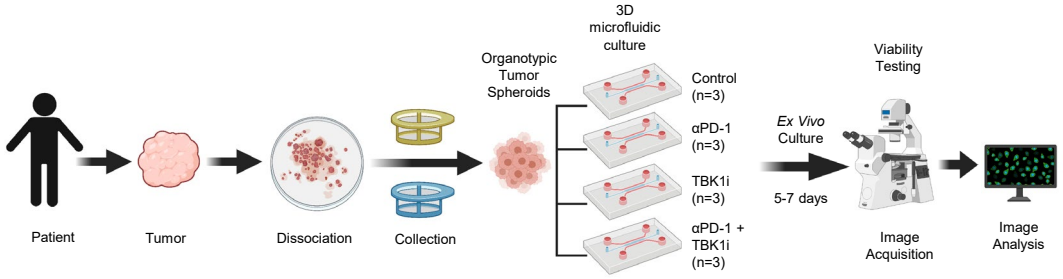


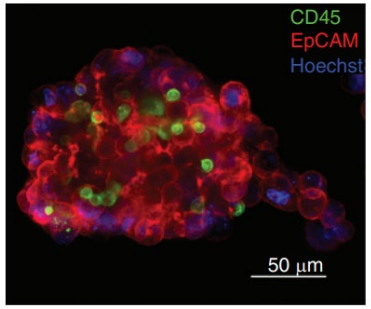


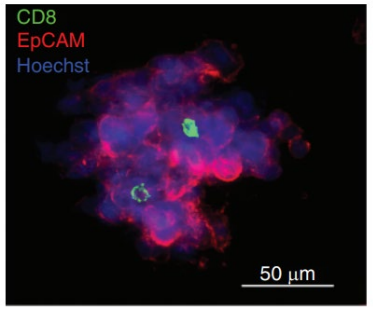


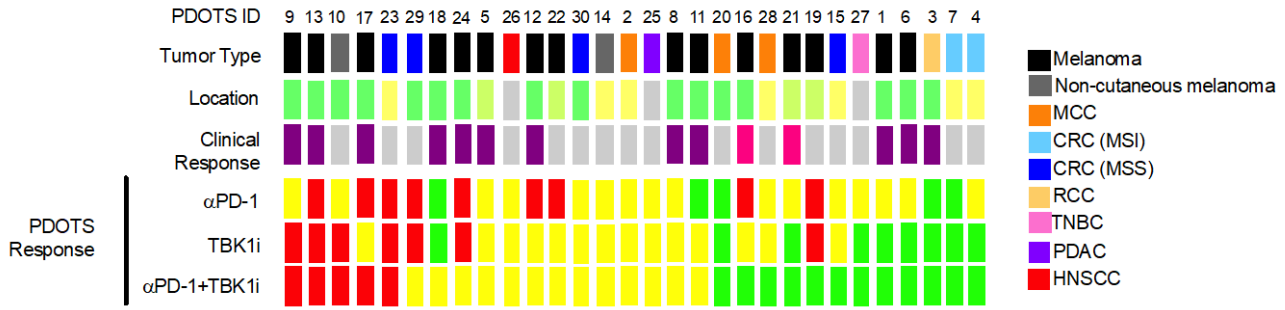
Sehgal et al. JCI 2021

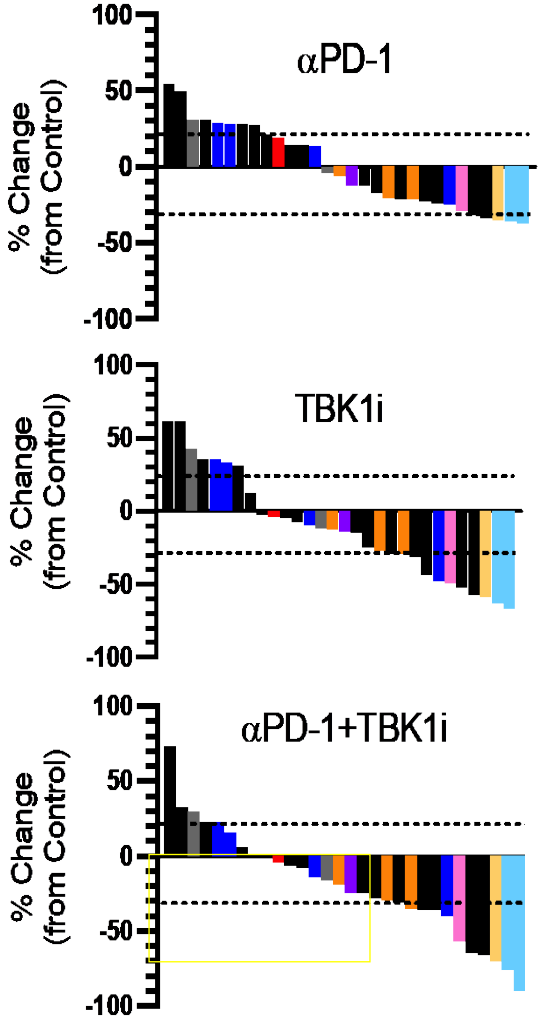
Ex Vivo Screening of Novel Immunotherapies











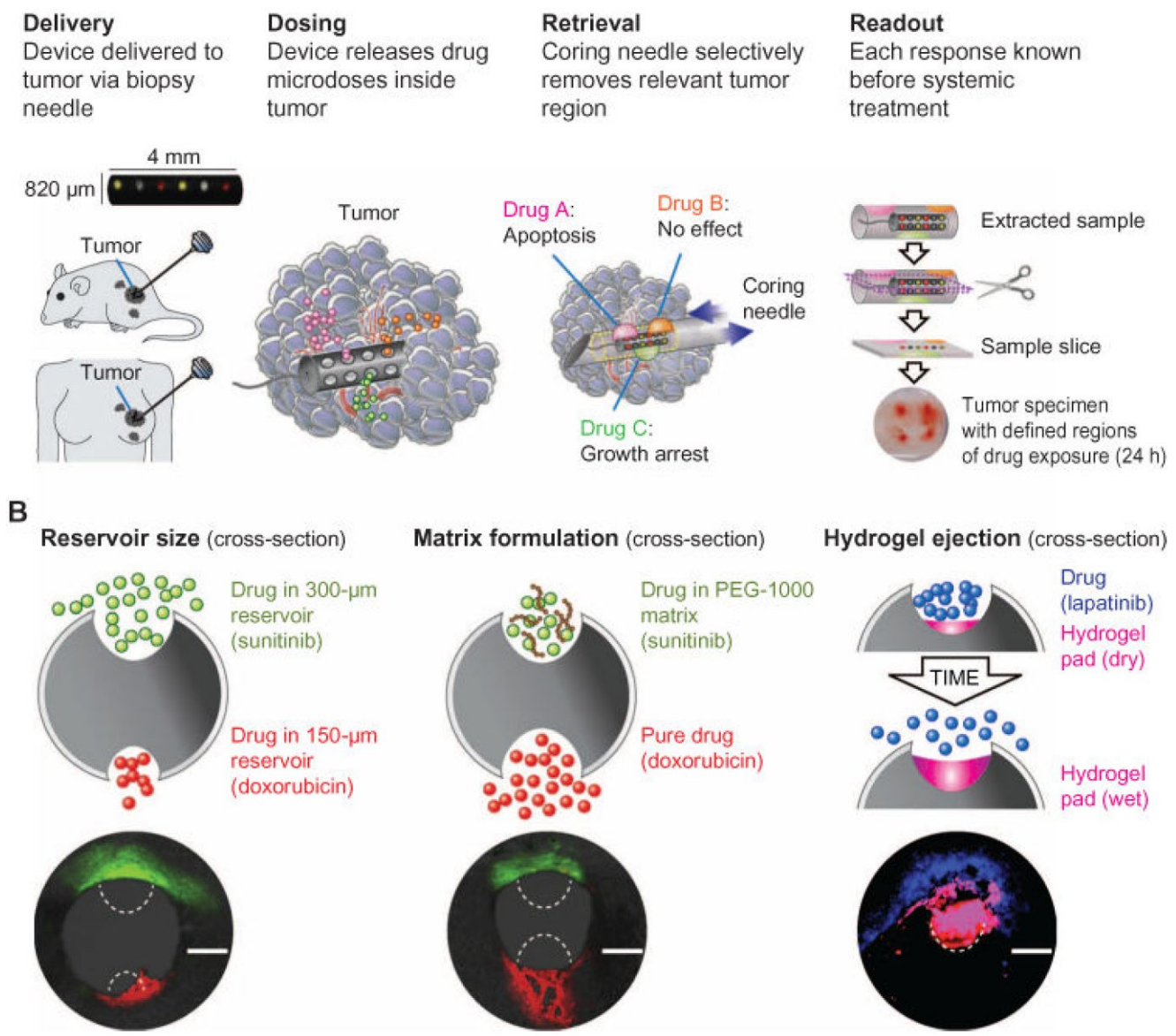
Russ Jenkins

Sun et al. *Nature* 2023

Mass General Brigham
Mass General Cancer Center

In vivo testing of novel agents & combinations

Ollie Jonas



Jonas et al. Sci Transl Med 2015

Biomarker-guided addition of 2nd agent

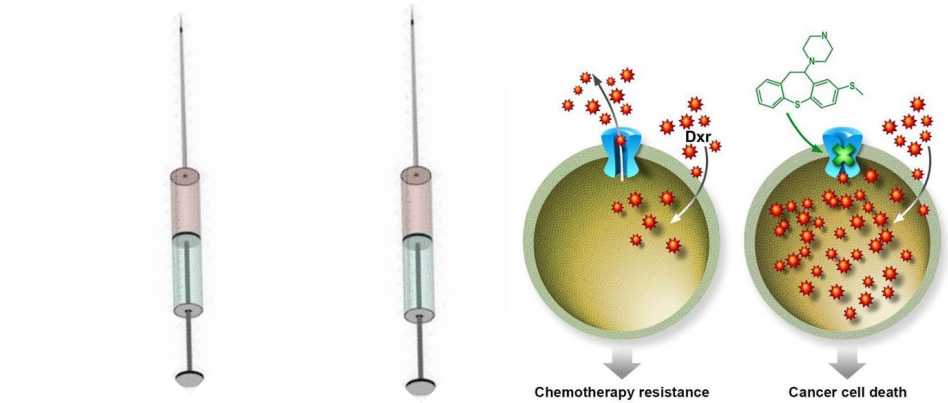
Serial blood samples

Circulating tumor cells
ctDNA
Exosomes
Proteomics

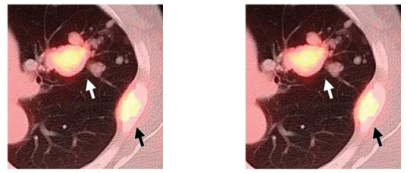
Add 2nd agent

Backbone therapy

Serial tumor biopsy

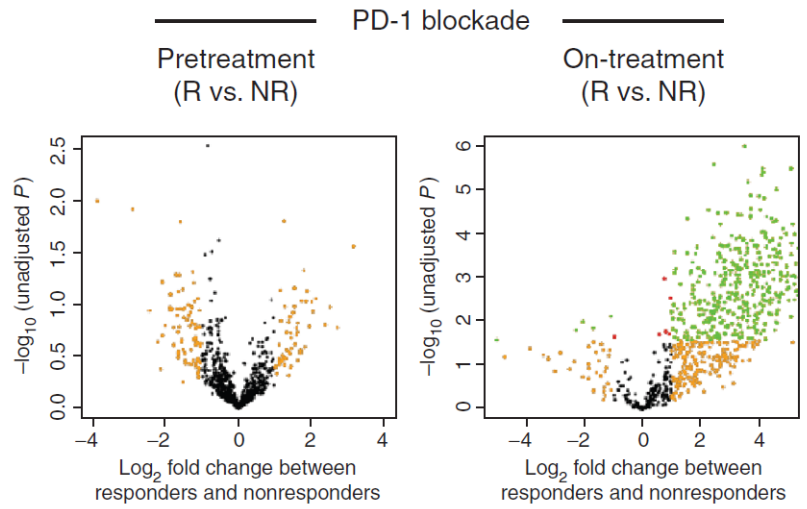


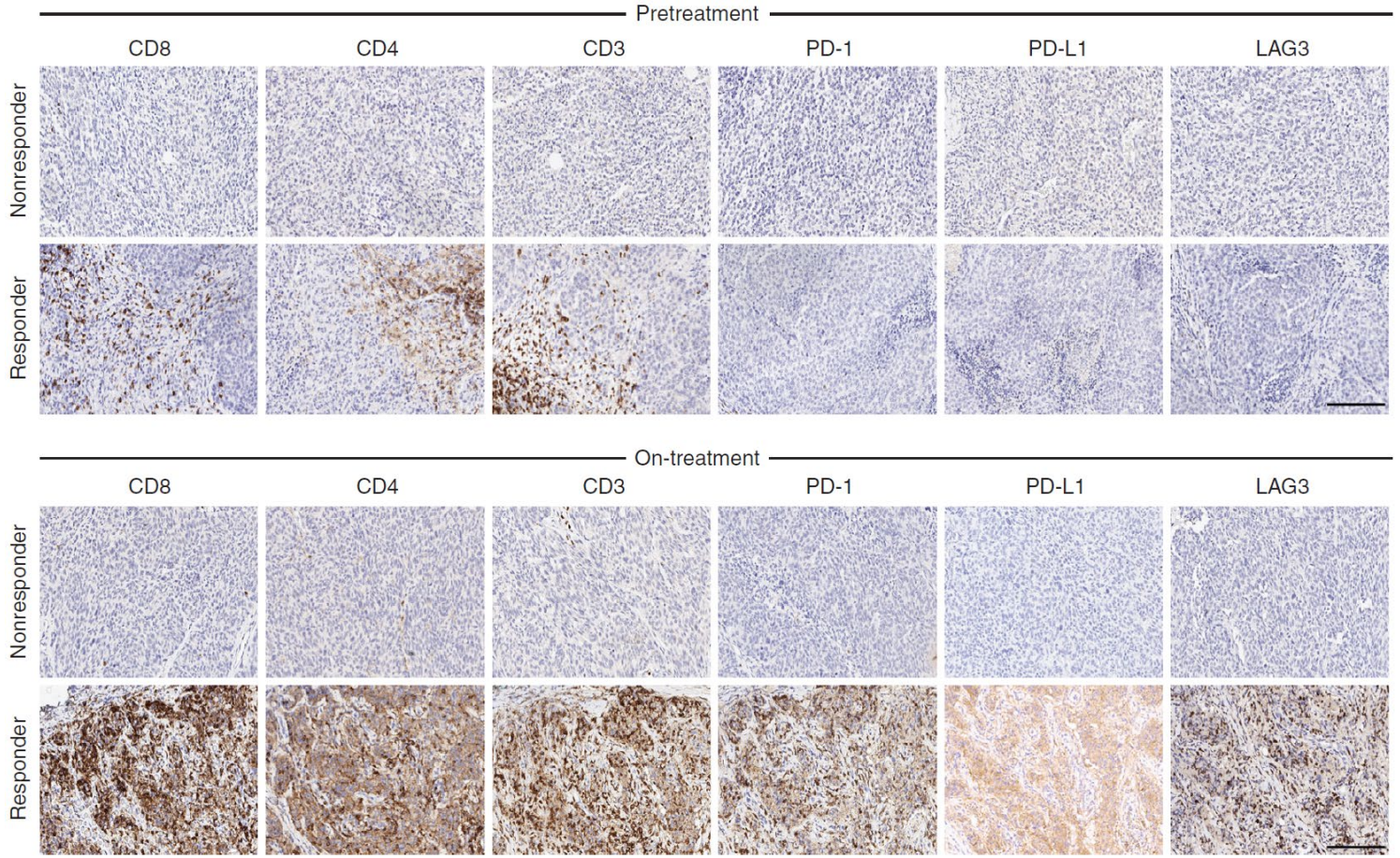
Imaging



Mass General Brigham
Mass General Cancer Center

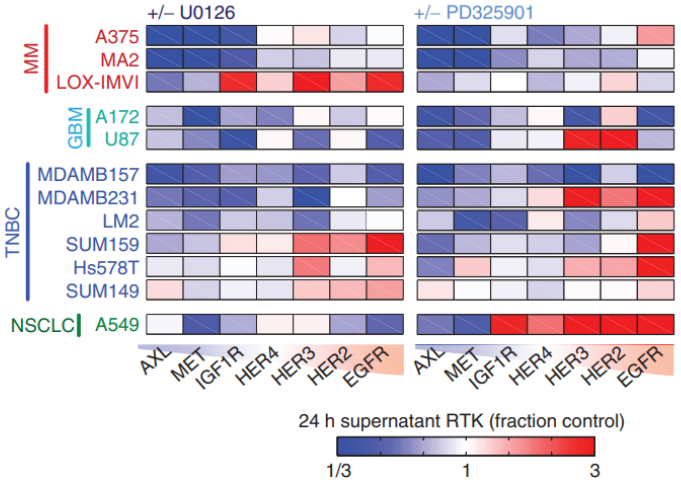
Early on-therapy biopsy much more predictive of subsequent response with PD-1 monotherapy in melanoma

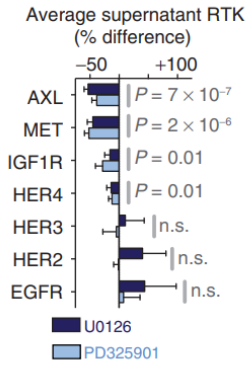


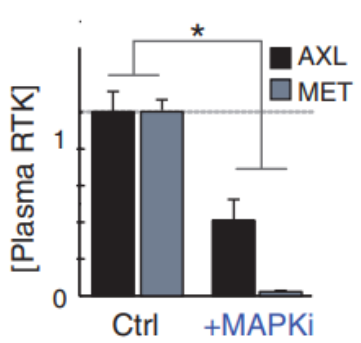


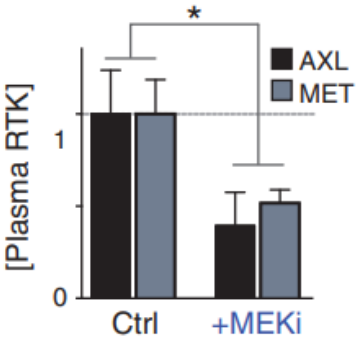
Chen et al. Cancer Discovery 2016

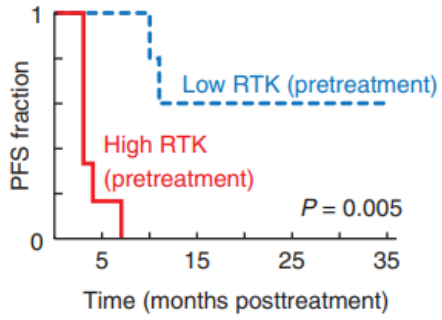
A useful correlative result:
Shed receptors pre- and on-therapy

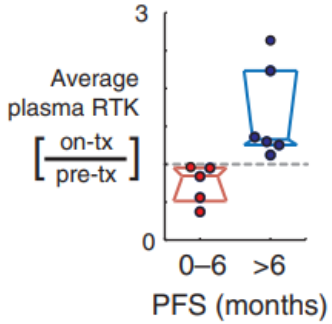


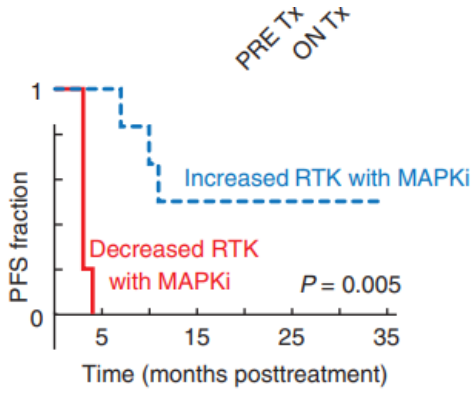












Miller et al. Cancer Discov 2016

Mass General Brigham
Mass General Cancer Center

Conclusions

- At a time when routine clinical use of next-generation sequencing was still in early adoption, NCI-MATCH provided a stream-lined, single process for performing sequencing, providing simple interpretation, and providing investigational options
- Accrual rate set record in NCI National Clinical Trial Network
- Hunting for activity outside of known indications for a broad spectrum of “credentialed” targeted therapy produced results ranging from no responses to ~40% response rates across the varied population of advanced cancer patients
- NCI-MATCH established the feasibility of a centralized screening diagnostic amongst relapsed/refractory patients
- Functional approaches could be used in place of or on top of routine DNA and RNA sequencing