The Evolution of NCI-MATCH: What's Next for SWOG and the NCTN

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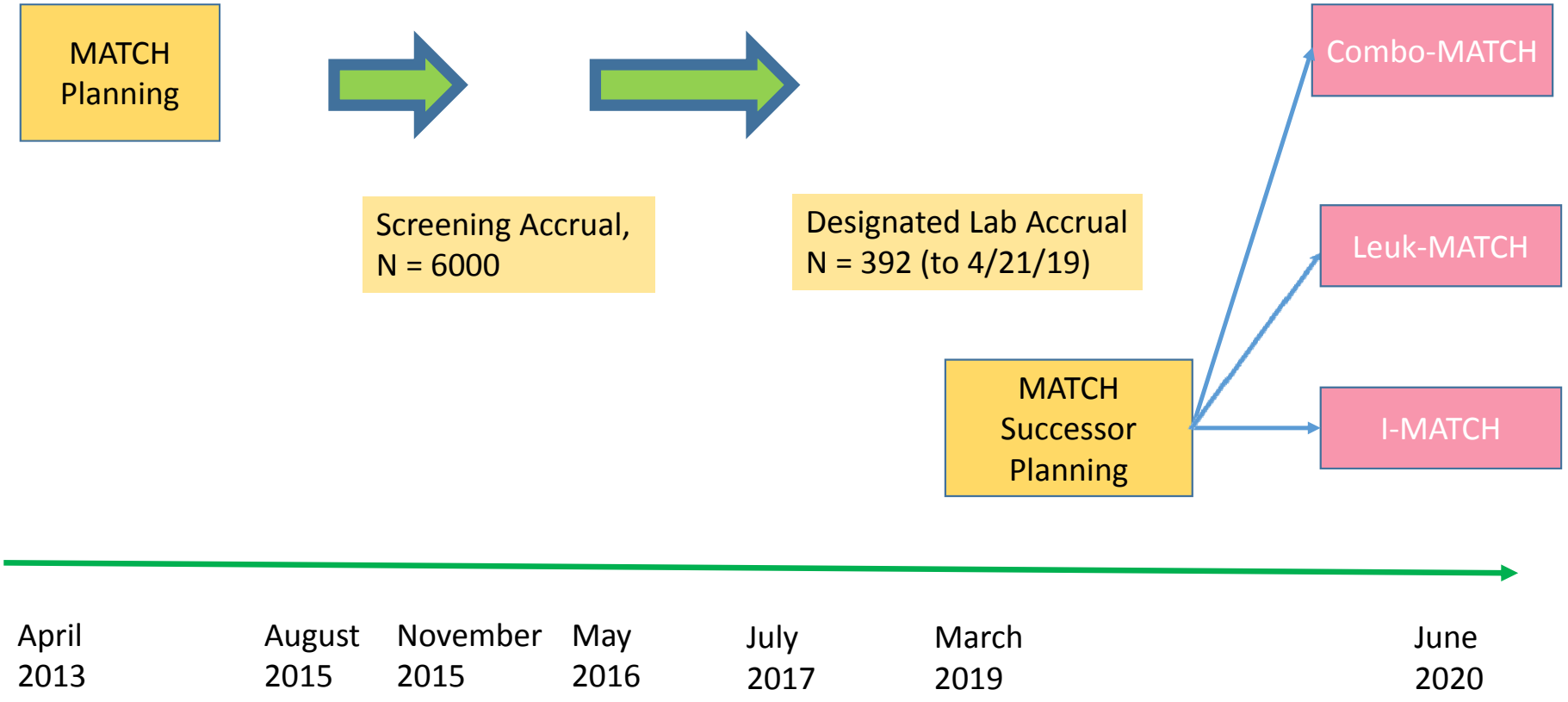
Conflict of Interest Disclosure

- Advisory: Genentech, BMS, Boehringer

- Clinical Trials support: Genentech, BMS, AZ, Celgene, Merck, Syndax, GSK, Abbvie, Incyte, Minneamrata, Pharmacyclics, Five Prime, Fortyseven

NCI-MATCH Timeline



Getting to There

- NCI-MATCH – design and structure
- MATCH with commercial and academic lab network to identify patients – “outside assay”
- Preliminary Results Summary
- Daughters of MATCH

NCI-MATCH – Design and Structure

A Disease Agnostic Basket Trial: NCI-MATCH

THIS PRECISION MEDICINE TRIAL EXPLORES TREATING PATIENTS BASED ON THE MOLECULAR PROFILES OF THEIR TUMORS

NCI-MATCH IS FOR ADULTS WITH:

- solid tumors (including rare tumors), lymphomas, and myeloma
- tumors that no longer respond to standard treatment

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Hypothetical Framework for a Genomically-Driven Trial 2013

- Derived from early successes of targeted drugs:
  - Imatinib in CML, GIST
  - RAFi in BRAF-mutated melanoma
  - ALKi in Non-small cell lung cancer
- But also from failures
  - RAFi in BRAF-mutated colon cancer
  - MEKi in all KRAS-mutated cancers
- Begs questions
  - What is utility of targeted therapy broadly
  - Feasibility of addressing that issue
  - Does matching drug-mutation outweigh tissue of origin?

Key Considerations in Molecular Triage Trial Design

Tumor biopsy

- Archival tissue vs. fresh tumor biopsy
- Primary lesion vs. metastatic site
- Biopsy while on treatment or at progression for biomarkers of response and resistance

Biomarker platform

- Multiple institutional platforms or single platform
- Reproducible and reliable

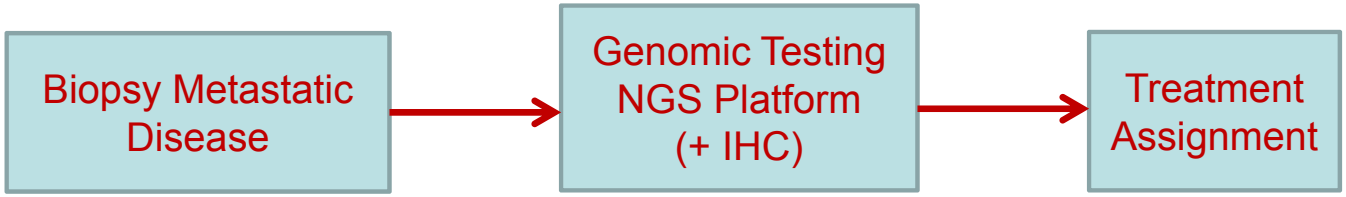
Availability of drugs

- Are drugs available for the most frequent aberrations expected
- Are mutations found frequently enough to warrant testing in this setting

Treatment setting

- Early vs. late stage
- First vs. subsequent lines of therapy

Design



- Metastasis biopsy addresses concern of heterogeneity
- Uniform platform applied across all patient samples
- Desirable to have treatment allocation for as many as possible

Customized Thermo Fisher Oncomine™ Assay

Reproduced with accuracy by MATCH laboratory network

Hotspot Genes, N=73

ABL1	GNA11	MYD88
AKT1	GNAQ	NFE2L2
ALK	GNAS	NPM1
AR	HNF1A	NRAS
ARAF	HRAS	PAX5
BRAF	IDH1	PDGFRA
BTK	IDH2	PIK3CA
CBL	IFITM1	PPP2R1A
CDK4	IFITM3	PTPN11
CHEK2	JAK1	RAC1
CSF1R	JAK2	RAF1
CTNNB1	JAK3	RET
DDR2	KDR	RHEB
DNMT3A	KIT	RHOA
EGFR	KNSTRN	SF3B1
ERBB2	KRAS	SMO
ERBB3	MAGOH	SPOP
ERBB4	MAP2K1	SRC
ESR1	MAP2K2	STAT3
EZH2	MAPK1	U2AF1
FGFR1	MAX	XPO1
FGFR2	MED12	
FGFR3	MET	
FLT3	MLH1	
FOXL2	MPL	
GATA2	MTOR	

Full-Gene Coverage, N=26

APC
ATM
BAP1
BRCA1
BRCA2
CDH1
CDKN2A
FBXW7
GATA3
MSH2
NF1
NF2
NOTCH1
PIK3R1
PTCH1
PTEN
RB1
SMAD4
SMARCB1
STK11
TET2
TP53
TSC1
TSC2
VHL
WT1

Copy Number Variants, N=49

ACVRL1	IGF1R
AKT1	IL6
APEX1	KIT
AR	KRAS
ATP11B	MCL1
BCL2L1	MDM2
BCL9	MDM4
BIRC2	MET
BIRC3	MYC
CCND1	MYCL
CCNE1	MYCN
CD274	MYO18A
CD44	NKX2-1
CDK4	NKX2-8
CDK6	PDCD1LG2
CSNK2A1	PDGFRA
DCUN1D1	PIK3CA
EGFR	PNP
ERBB2	PPARG
FGFR1	RPS6KB1
FGFR2	SOX2
FGFR3	TERT
FGFR4	TIAF1
FLT3	ZNF217
GAS6	

Fusion Drivers, N=22

ALK
RET
ROS1
NTRK1
NTRK3
FGFR1
FGFR2
FGFR3
BRAF
RAF1
ERG
ETV1
ETV4
ETV5
ABL1
AKT3
AXL
EGFR
ERBB2
PDGFRA
PPARG

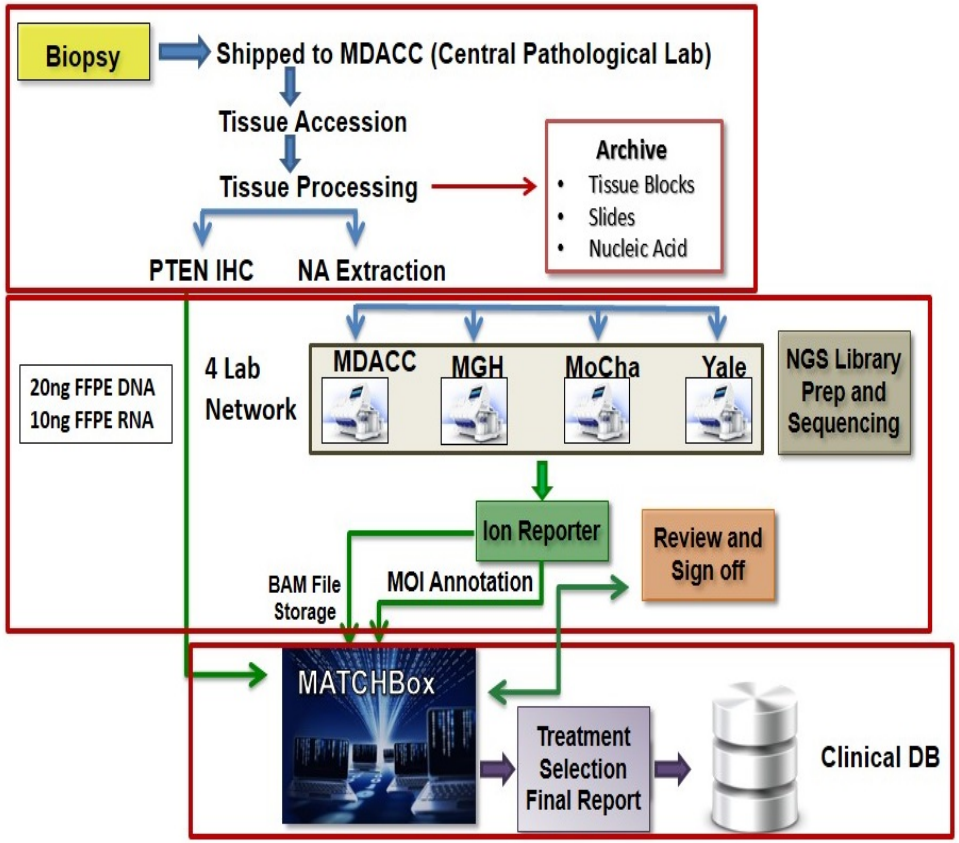
- **143 genes**
- **2530 amplicons in DNA panel**
- **207 amplicons in RNA panel**

Lih et al, *The Journal of Molecular Diagnostics* 2017

Each mutation/variant was credentialed

NCI-MATCH Laboratory Network

- ECOG-ACRIN Central Biorepository and Pathology Facility at MD Anderson Cancer Center (Stan Hamilton)
  - Intake of biospecimens and accompanying documentation
- Network of four CLIA-approved molecular diagnostics laboratories provides capacity
  - NCI Molecular Characterization Laboratory (Mickey Williams)
  - Massachusetts General (John Iafrate)
  - MD Anderson (Stan Hamilton)
  - Yale (Jeffrey Sklar)



Screening (Step 0) Overall Design

- ≥ 18 y.o.
- ECOG PS 0-1
- Solid tumor, Lymphoma or Myeloma
- ≥ 1 prior standard therapy
- Measurable disease
- Tumor amenable to biopsy OR

FFPE obtained within 6mo

→ Tumor genomic testing with Thermo Fisher Oncomine™ Assay & IHC (PTEN, MLH1, MSH2, Rb)

→ Actionable Mutation of Interest (aMOI)?

- Yes = Treatment assignment
- No = Off study

Yes = Treatment assignment →

- Arm A
- Arm B
- Arm C
- Arm D
- Etc…

Each drug-target couple was credentialed

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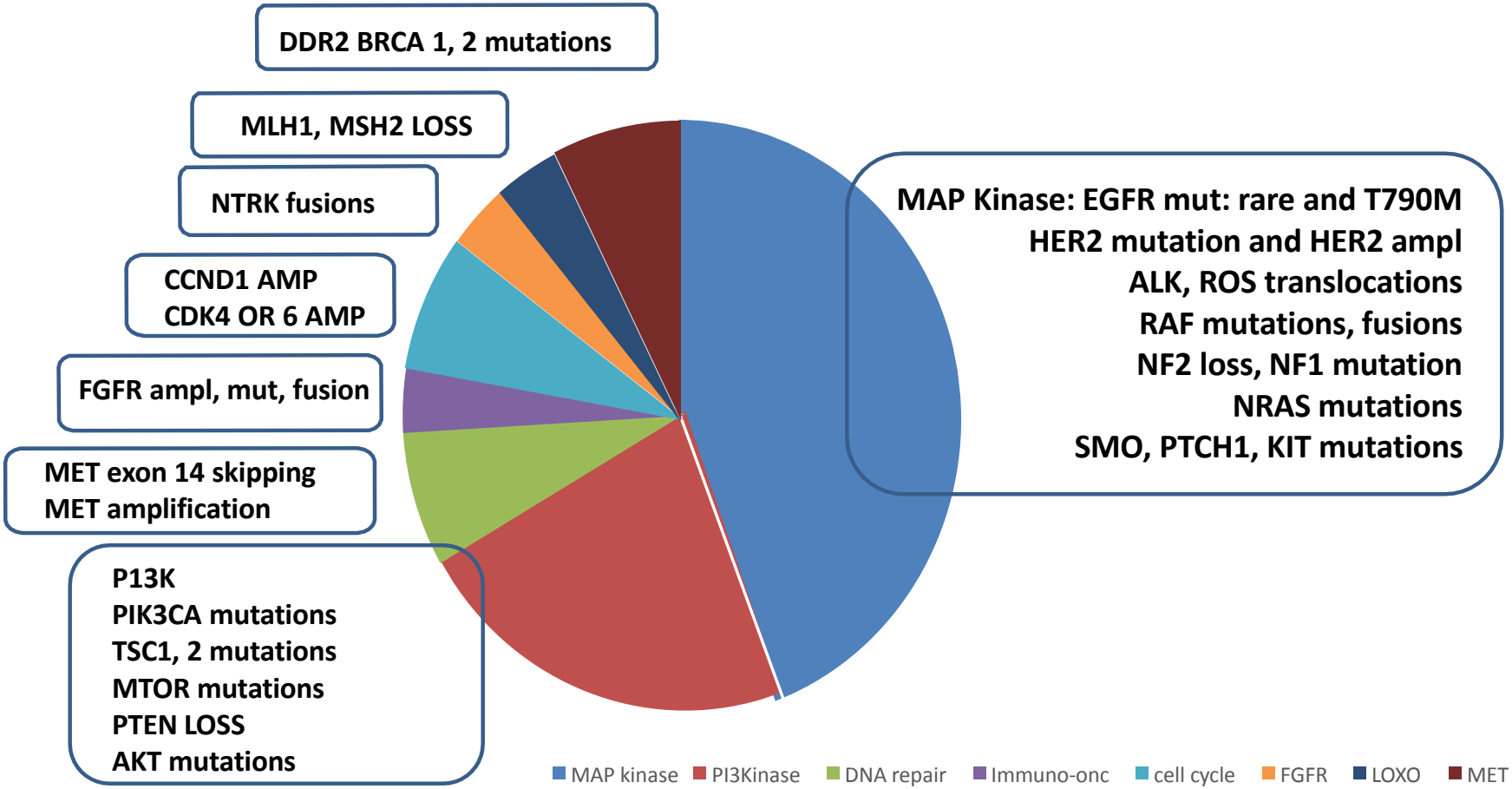
NCI-MATCH Treatment Arm Objectives

- Primary:
  - Estimate the proportion of patients with refractory solid tumor, lymphoma or myeloma who had an objective response (OR)
- Secondary:
  - Progression-free survival (PFS)
  - PFS at 6 months (PFS6)
  - Time to progression/death
  - Toxicity
  - Potential predictive biomarkers

NCI-MATCH Statistical Assumptions for Individual Arms

- Accrual goal per arm: 35
  - Some arms targeting more common gene variants were expanded to accommodate the higher numbers of patients with matches who came into the trial through central screening
- Reporting of primary and secondary endpoints to occur once there is complete response and toxicity data for at least 31 patients per arm
  - Accrue at least 35 to obtain at least 31 evaluable (10% ineligibility rate)
  - Need ~8 months of follow-up after accrual is complete
- If the OR is ≥ 5/31 (16%), agent worthy of further study
- Secondary analyses will examine response by a variety of factors

Treatment Arms in NCI-MATCH by Molecular Pathway

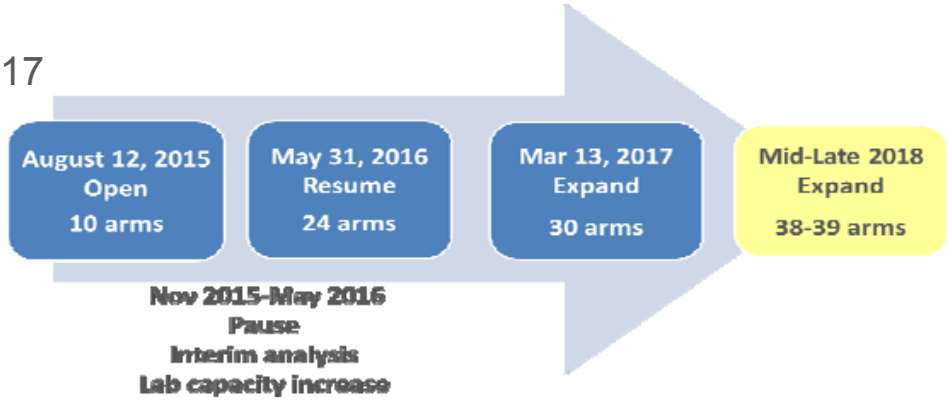


Brief History of NCI-MATCH

- Opened on August 12, 2015, with **10 treatment arms** and a goal to have **3000 patients** submit tumor samples for central testing
- 795 patients were screened in the first three months
  - Screening reached >100/week by the end of this period
  - Far surpassed original estimate of 50 screens/month
- Paused enrollment on November 11, 2015, for a planned interim analysis
- Resumed enrollment of *new* patients on May 31, 2016, with **24 treatment arms** and more laboratory capacity to handle rapid pace of enrollment, and new goal of **6000 patients for central testing**
- Expanded to **30 treatment arms** on March 13, 2017
- Completed central screening of ~6000 patients

in July 2017, nearly two years ahead of schedule

- Continued accrual since then using outside labs



Enrollment and Screening Activity – Screening Cohort

	Step 0/1
Patients Enrolled	6391
Cases with Samples Submitted	5961 (93.3%)
1st Sample Analyzed	5407
1st Sample Fail	554
2nd Sample Submitted	170
2nd Sample Analyzed	141
Total Cases Analyzed for Match Assay	5548
Patients Assigned to Rx	987(17.8%)
Patients Enrolled on Arm	686(69.5%)

NCI-MATCH –with commercial and academic lab network to identify patients – “outside assay”

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10 Commercial Labs Referring Patients to NCI-MATCH

Inquire with the lab directly –- no need to contact ECOG-ACRIN or NCI

Caris Life Sciences®	NCIMATCHTrial@CarisLS.com
CellNetix Pathology and Laboratories	cnx-trials@cellnetix.com
Foundation Medicine, Inc.	smarttrials@foundationmedicine.com
GenPath (BioReference Laboratories, Inc.)	Kbarber@bioreference.com
OmniSeq, Inc. (*not referring until further notice*)	trials@omniseq.com
The Jackson Laboratory	CGL_NCI-MATCH@jax.org
NeoGenomics Laboratories, Inc.	NCI-MATCH@neogenomics.com
PathGroup	oncologysupport@pathgroup.com
Strata Oncology, Inc.	ncimatch@strataoncology.com
Tempus Labs, Inc.	nci-match@tempus.com

16 Academic Labs Referring Patients to NCI-MATCH

Generally, cancer center labs test their own patients

Augusta University	Memorial Sloan Kettering Cancer Center
Brigham and Women's Hospital	MD Anderson Cancer Center
City of Hope	Stanford
Cedars-Sinai Medical Center	University of Chicago
Columbia University	University of Colorado
Frederick National Laboratory for Cancer Research (MoCha)	University of Michigan
Johns Hopkins University	Weill Cornell Medicine
Massachusetts General Hospital	Yale University

Enrollment and Screening Activity – Outside Assay

	Total	Last Week	Weekly Average 1/7/18 to 6/16/18	Weekly Average Since 7/28/18
Patients Enrolled	392	5	1.96	6.45
Outside Assay Processing Complete	382	5		
Patients Assigned to Rx	338(88%)	5		
Eligibility Review Pending	5			
Eligibility Evaluation Complete	333	2		
Patients Enrolled on Arm	273(82%)	2	1.65	4.45

New NCI-MATCH Arms in Development

Tumor Gene Abnormality	Prevalence Rate %	Drug	Arm ID	Opens (Pending Approval)
AKT mutations	0.77	Ipatasertib	Z1K	Late Spring 2019
Non-V600 BRAF mutations	0.80	Ulixertinib (BVD-523)	Z1L	
dMMR status and LAG-3 expression	1.51	Nivolumab + relatlimab (BMS-986016)	Z1M	Fall 2019
TP53 mutations and MYC amplification	Not available	AZD1775	Z1J	

NCI-MATCH – Preliminary Results

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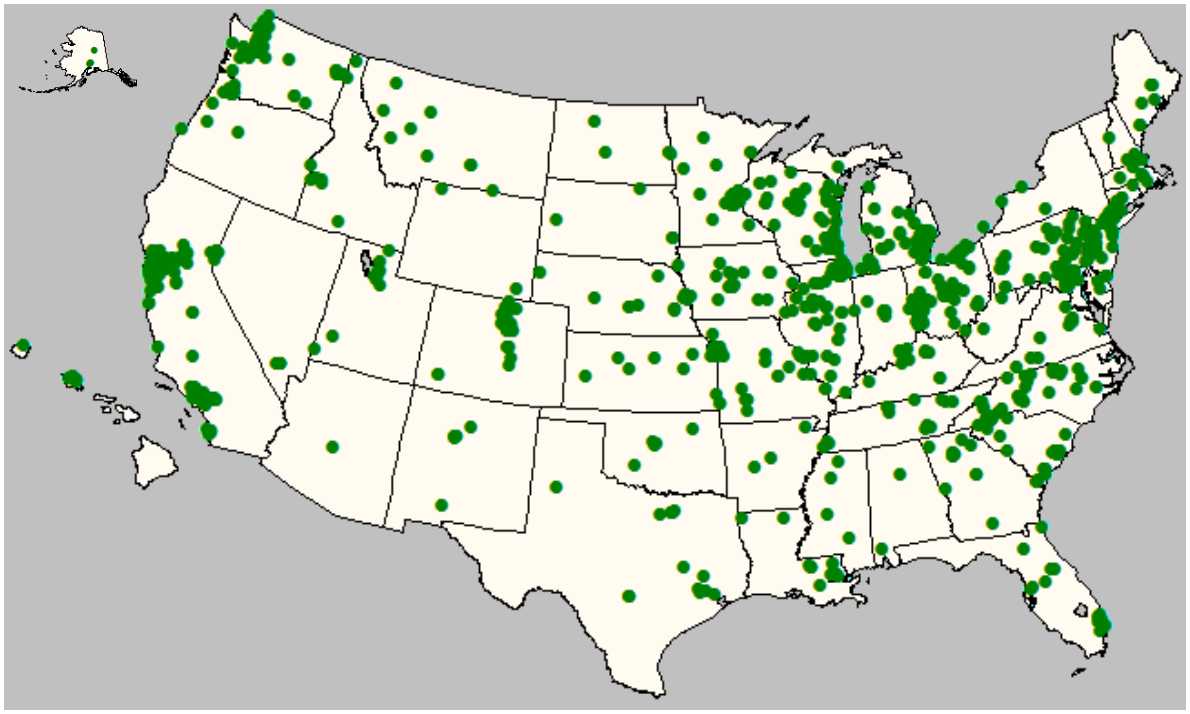
NCI-MATCH Brings Genomics to the Community

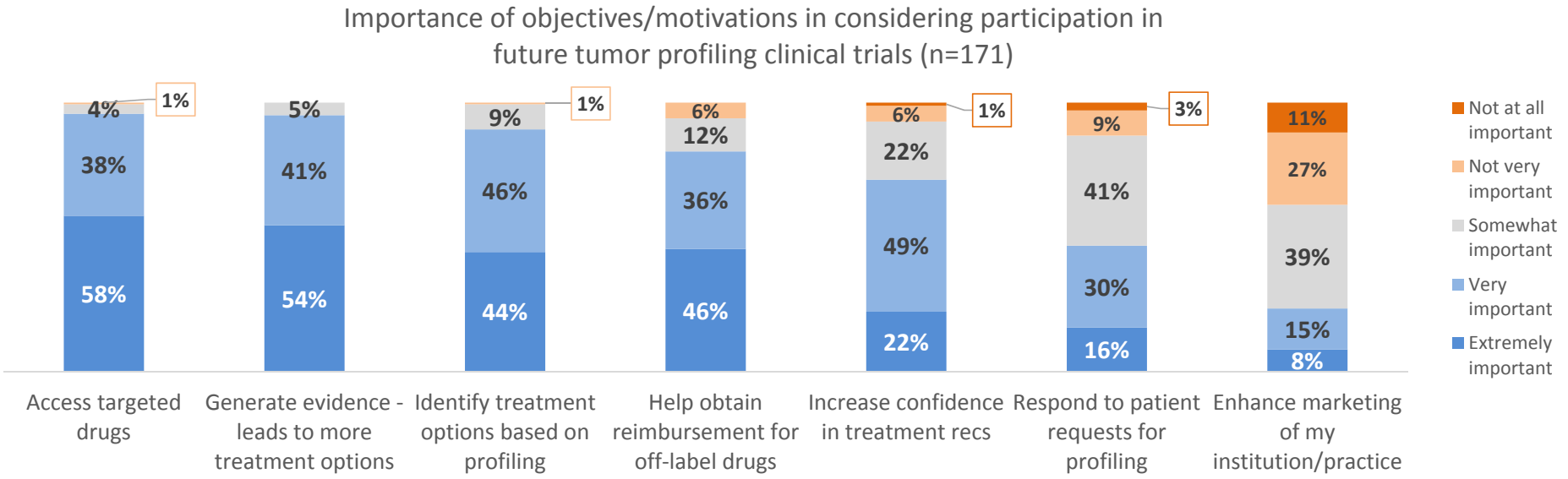
- Availability at over 1100 sites
- 56% of accrual in community
- Broad general interest in the promise of genomics



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

Accessing targeted drugs and developing treatment options were the most salient motivations for participating in future trials

- Very/extremely important for 90% or more of respondents:
  - Access to targeted drugs
  - Generating evidence that leads to treatment options
  - Identifying treatment options based on profiling
- Very/extremely important to 70-80% of respondents
  - Help getting reimbursement for off-label drugs
  - Increasing confidence in treatment recommendations (even more important to non-AMC with 83% very/extremely, vs 64% of AMC)



NCI-MATCH Central Screening by Cancer Type

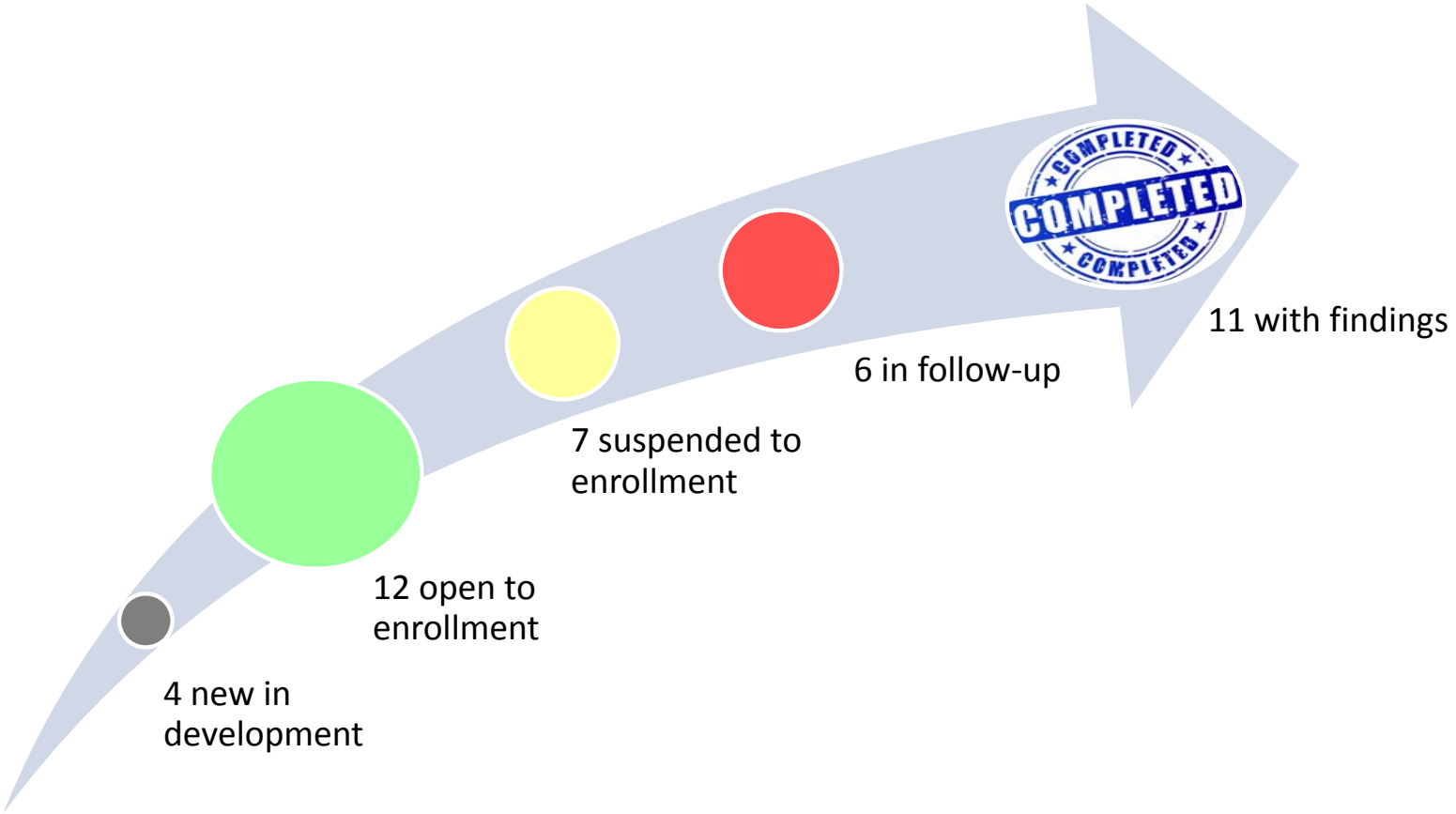
Less Common Disease Type	% of Total Screened (N=5560)
Ovarian	9.5
Uterine	6.2
Pancreas	6.1
Sarcoma	4.6
Head and Neck	3.9
Neuroendocrine	3.3
Gastroesophageal	3.2
Cholangiocarcinoma	2.8
Liver and Hepatobiliary other than Cholangio.	1.9
Central Nervous System	1.7
Bladder/Urinary Tract	1.6
Cervical	1.6
Small Cell Lung	1.4
Melanoma	1.4
Kidney	1.2
Anal	0.8
Mesothelioma	0.8
Lymphoma	0.7
Myeloma	0
Other	9.7
Less Common Cancers	**62.5%**

Common Disease Type	% of Total Screened (N=5560)
Colorectal	15.3
Breast	12.4
Non-Small Cell Lung	7.3
Prostate	2.5
Common Cancers	37.5%

Goal: 25%

Far exceeded

NCI-MATCH – Status of 39 Treatment Arms



Eleven of the 35 subprotocols have reported out: 3/11 positive (27%)

Subprotocol	Drug/molecular	Reported out	Result
Z1D	Nivolumab for MMRd	SITC 2017; manuscript pending	Positive
Y	Capivasertib/AKT mutations	Nov 2018	Positive
H	Trametinib/Dabrafenib/BRAFV600	June 2019	Positive
I	Taselisib/PIK3CA mutations	June 2018 (ASCO)	Neg
Q	Ado-trastuzumab emtansine/ERRB2 amplification	June 2018 (ASCO)	Neg (8% RR)
W	AZD4547/FGFR amplification, mutation, fusion	June 2018 (ASCO)	Neg (8% RR)
N/P	GSK2636771/PTEN mut or loss	October 2018 (ESMO)	Neg
B	Afatinib/ERRB2 activating mutations	April 2019 (AACR)	Neg (2.7%)
Z1-B	Palbociclib/CCND1, 2, or 3 amplifications	April 2019 (AACR)	Neg
Z1-I	AZD1775/BRCA 1 or BRCA2 mutations	April 2019 (AACR)	Neg (3.2%)

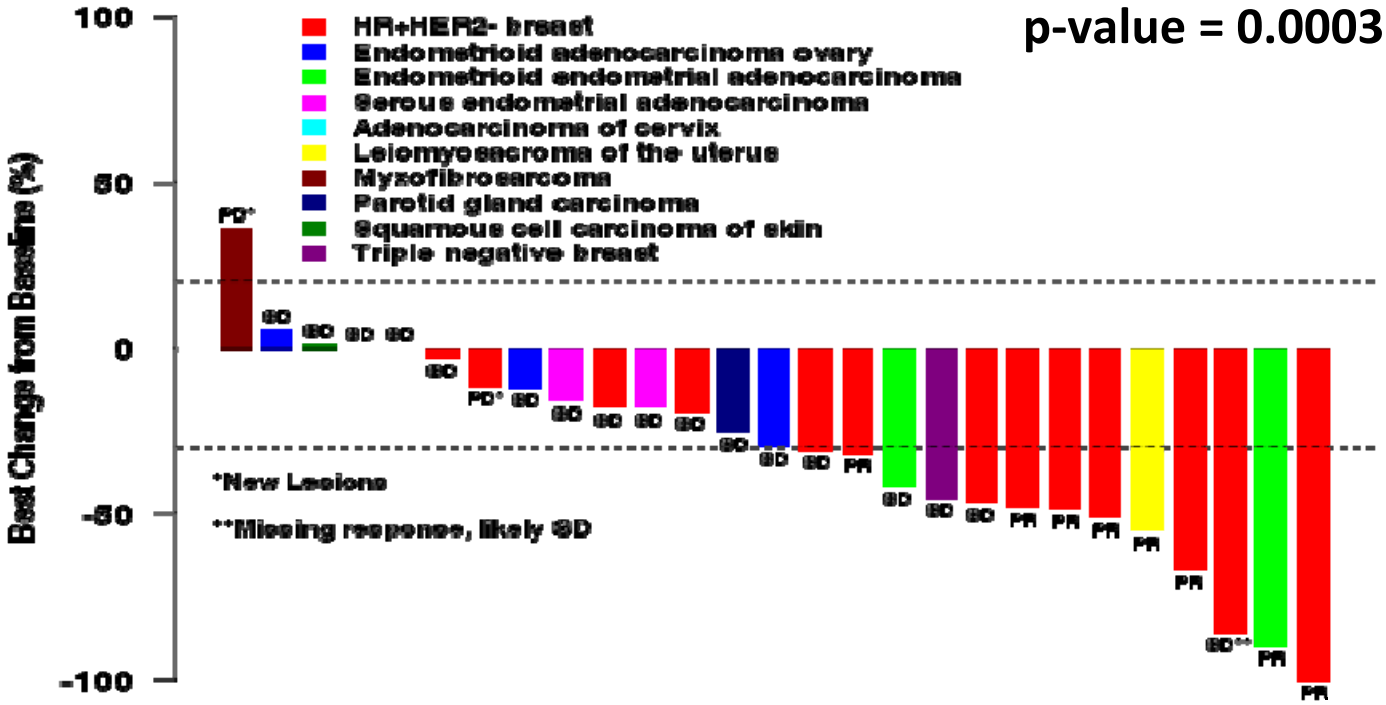
Capivasertib in Patients with Tumors with *AKT* Mutations: NCI-MATCH Subprotocol EAY131-Y: Kevin Kalinsky, Fangxin Hong, Carolyn K McCourt, Jasgit C Sachdev et al.

- Oral presentation EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics November 2018.
- Concurrent fulvestrant or aromatase inhibitor allowed for hormone receptor (HR+)/HER2- breast cancer, if last metastatic regimen included that hormonal therapy (capivasertib 400 mg)
- Excluded *KRAS*, *NRAS*, *HRAS*, or *BRAF* mutations
- No prior PI3K, AKT or mTOR inhibitor

Capivasertib: in 27 patients evaluable, positive study

Confirmed PR rate (n=35): 23% (90% CI 12-38%)

p-value = 0.0003 (<0.018)



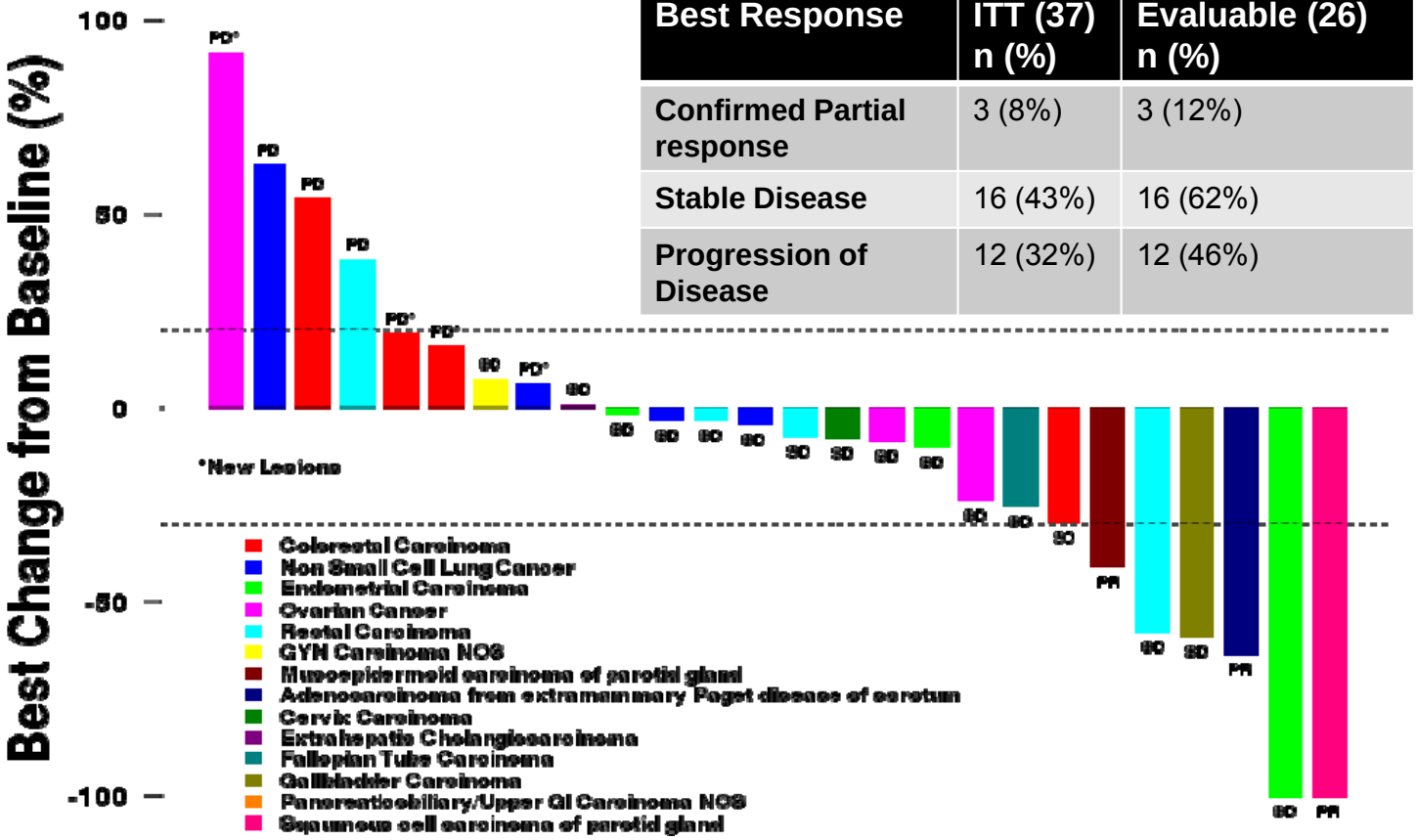
Ado-trastuzumab emtansine (T-DM1) in patients with HER2 amplified tumors excluding breast and gastric/gastro-esophageal junction (GEJ) adenocarcinomas: Results from the National Cancer Institute (NCI) - Molecular Analysis for Therapy Choice (MATCH) trial.

Komal L. Jhaveri, Vicky Makker, Xin Victoria Wang, Alice P. Chen, Keith Flaherty, Barbara A. Conley, Peter J. O'Dwyer, Paul M. Williams, Stanley R. Hamilton, Lyndsay Harris, Lisa McShane, Lawrence Rubinstein, Robert James Gray, Shuli Li, Edith P. Mitchell, David Patton, Jeffrey Moscow, James A. Zwiebel, Carlos L. Arteaga, Shiuh-Wen Luoh

Oral presentation at ASCO 2018

Arm Q Efficacy: Best % Change from Baseline (n=26)

Best Response	ITT (37) n (%)	Evaluable (26) n (%)
Confirmed Partial response	3 (8%)	3 (12%)
Stable Disease	16 (43%)	16 (62%)
Progression of Disease	12 (32%)	12 (46%)



Arm Q: ADO-TRASTUZUMAB EMTANSINE IN PATIENTS WITH *ERBB2* amplification (K. Javeri, V. Makker, S-W Luoh, et al. ASCO ORAL 2018)

- Excluded breast, gastric, GEJ cancers
- ERBB2 AMPL $\geq$ 7 per NCI –MATCH NGS assay (2%)
- 37 patients, 65% female,50% $\geq$ 3 prior treatments
- Confirmed PR in 3 patients: 8% (95% CI 2-20%)
- Responses were in rare tumors: mucoepidermoid carcinoma of salivary gland (2) and Pagets disease scrotum (1).
- 6 months PFS 25.4% (95% CI 16-41%)
- 1 patient lost *ERBB2* amplification on progression (salivary gland)

Arm W: AZD4547 IN PATIENTS WITH *FGFR* ABNORMALITIES

YK Chae, C Vaklavas, H Cheng, F Hong et al. ASCO oral 2018

- 1.3% of screened patients
- Exclusions: patients with gastric or NSCLC cancer and *FGFR* amplifications
- 50 patient treated; 50% had $\geq$ 3 prior treatments
- *FGFR1* ampl: 18; *FGFR2* ampl: 3, mutations: 20; fusions 9
- PR in 4/42 patients (9.5%): 2 with *FGFR3* fusions (urothelial cancer and SCC cervix, and 2 with mutations (extrahepatic cholangiocarcinoma and urothelial carcinoma bladder)
- PRs were long lasting: 156-334 days

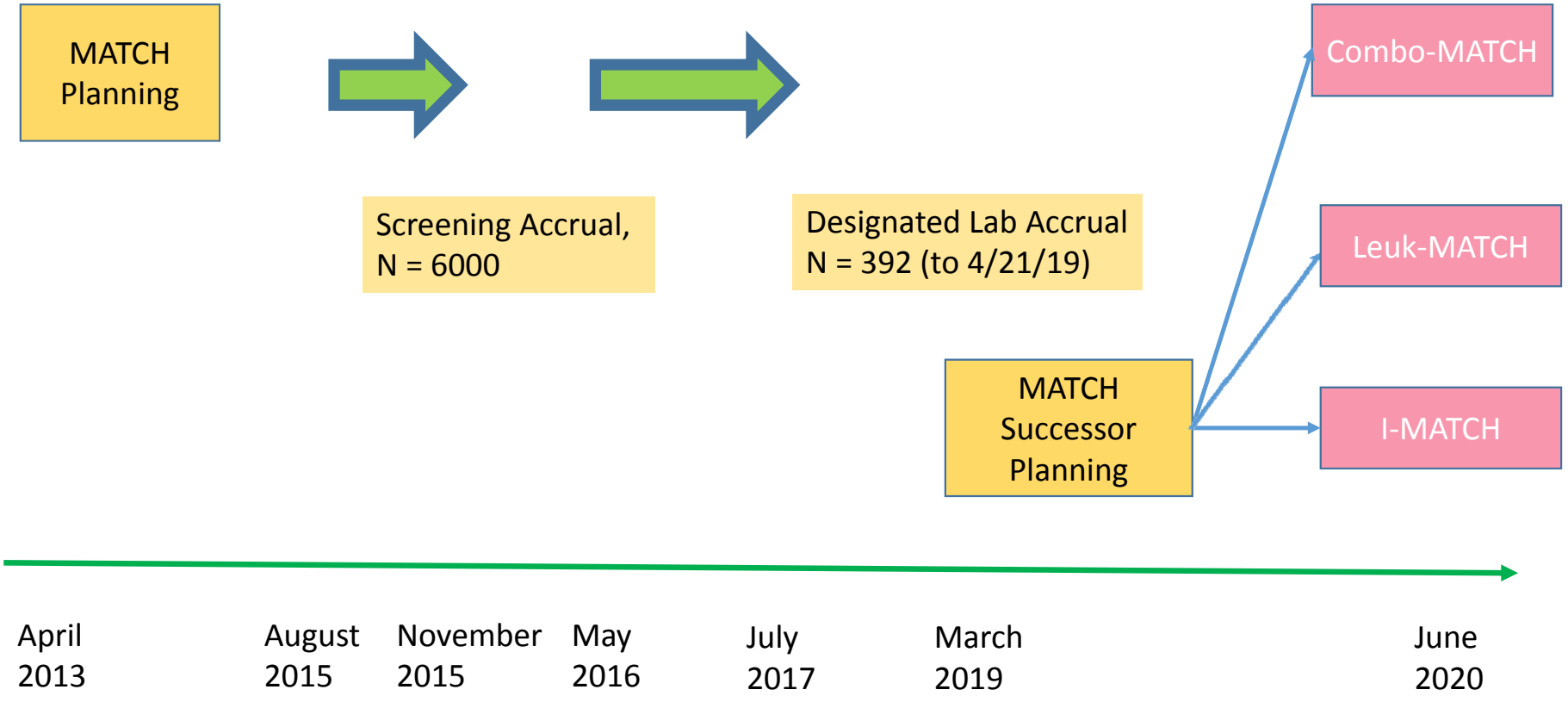
NCI-MATCH Treatment Arms Open and Enrolling

Variant	Prevalence Rate %	Drug(s)	Arm	Accrual As of 04/21/19
PTEN loss	1.93	Copanlisib	Z1G	4
PTEN (deleterious) seq. result + expr.	1.75	Copanlisib	Z1H	10
HER2 amplif.	1.49	Trastuzumab + pertuzumab	J	31
TSC1 or TSC2	1.11	TAK-228	M	33
FGFR	1.00	Erdafitinib	K2	22
MET exon 14 del.	0.61	Crizotinib	C2	18
SMO/PTCH1	0.42	Vismodegib	T	27
mTOR	0.31	TAK-228	L	15
EGFR T790M	0.11	AZD9291	E	7
cKIT	0.11	Sunitinib malate	V	9
NTRK	0.10	Larotrectinib	Z1E	7
EGFR activating	0.05	Afatinib	A	6

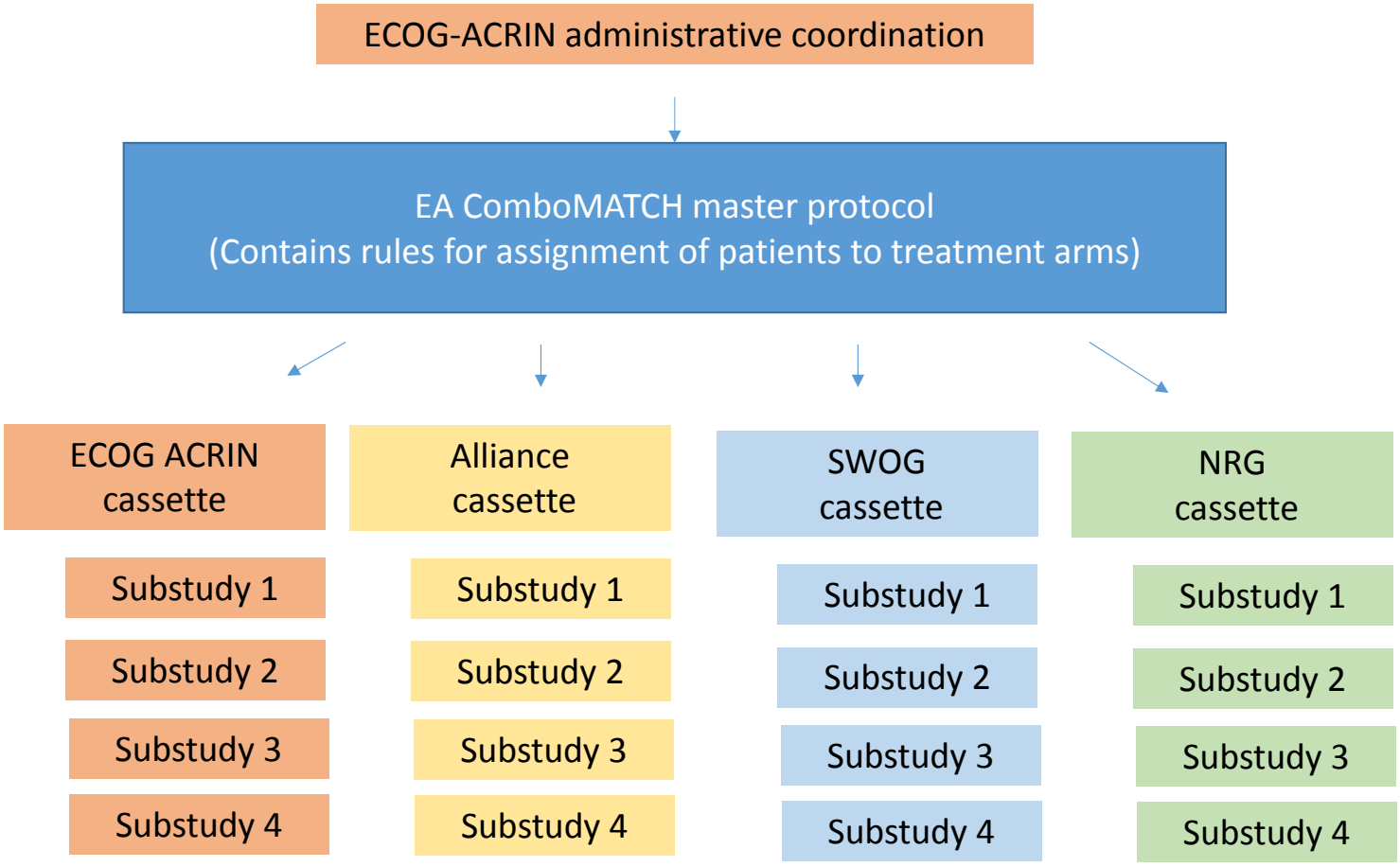
- Since end of screening, accrual based on outside lab results
- Confirmation of results using MATCH platform
- 6 new arms

Daughters of MATCH

NCI-MATCH Timeline



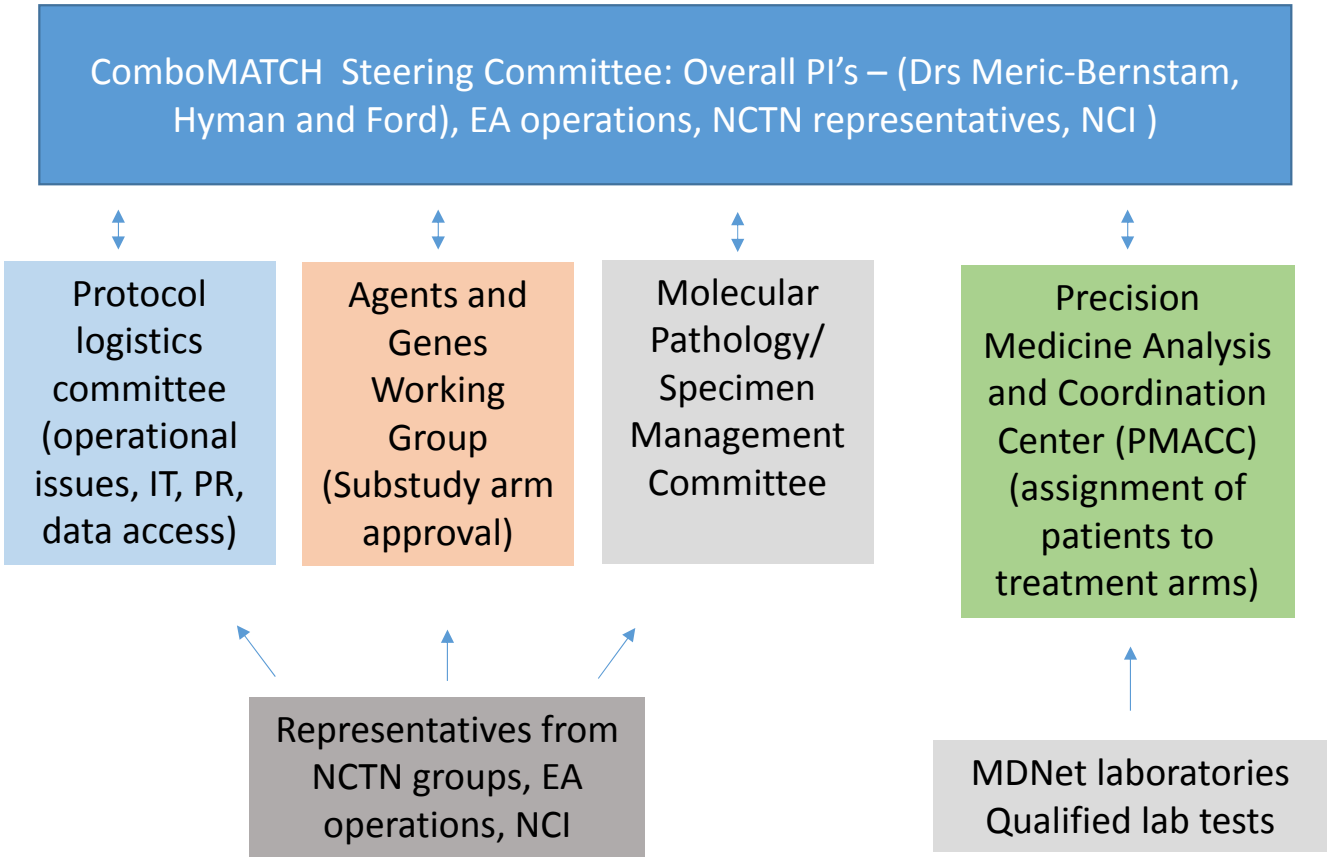
ComboMATCH protocol organization



ComboMATCH treatment arm development

- **Premise:** Drug combinations are more likely to provide clinical benefit than single agents in most scenarios, so the successor trial to MATCH will focus on drug combinations
- **Hypothesis:** Pre-clinical data from *in vivo* models of drug combinations can predict clinical benefit in defined patient groups
- C-AGWG will review drug combination data presented by investigators and Pharma, prioritize substudies for development, and work with NCTN groups to distribute substudies for incorporation into cassettes
- Drug combinations without RP2D will be assigned to ETCTN for phase 1 study
- Drug combinations with promising but inconclusive data will be assigned for further study to PDXNet

ComboMATCH administrative organization



What have we learned….

- Feasibility established, especially at the scale needed, protocol structure works
- Robust platform and pathology analysis
- Established a different and highly collaborative way of working together between EA/NCTN and NCI, especially CTEP
- Too early to judge benefit of approach, but there are “hits” that suggest disease-agnostic activity
- Trials needed to understand both tissue-specific and tumor microenvironment influences in targeted therapy
- Combi-MATCH, Leukemia-MATCH, I-MATCH – early in development, broad Group involvement, scientific opportunity
- Reach into the community, great enthusiasm

Credit…

- Colleagues at ECOG-ACRIN who have given boundless energy to thinking then doing – especially Stan Hamilton, Keith Flaherty, Bob Comis, Bob Gray, Edith Mitchell, Mary Lou Smith, Donna Marinucci, Pam Cogliano
- Colleagues at NCI who have worked closely on MATCH: Barb Conley, Alice Chen, Jeff Abrams, Lyndsay Harris, Mickey Williams, Lisa McShane, and whole MATCHBOX team
- Individuals thinking about next iteration: Jim Doroshow, Ignacio Wistuba, Mitch Schnall