NCI-Molecular Analysis for Therapy Choice (MATCH)

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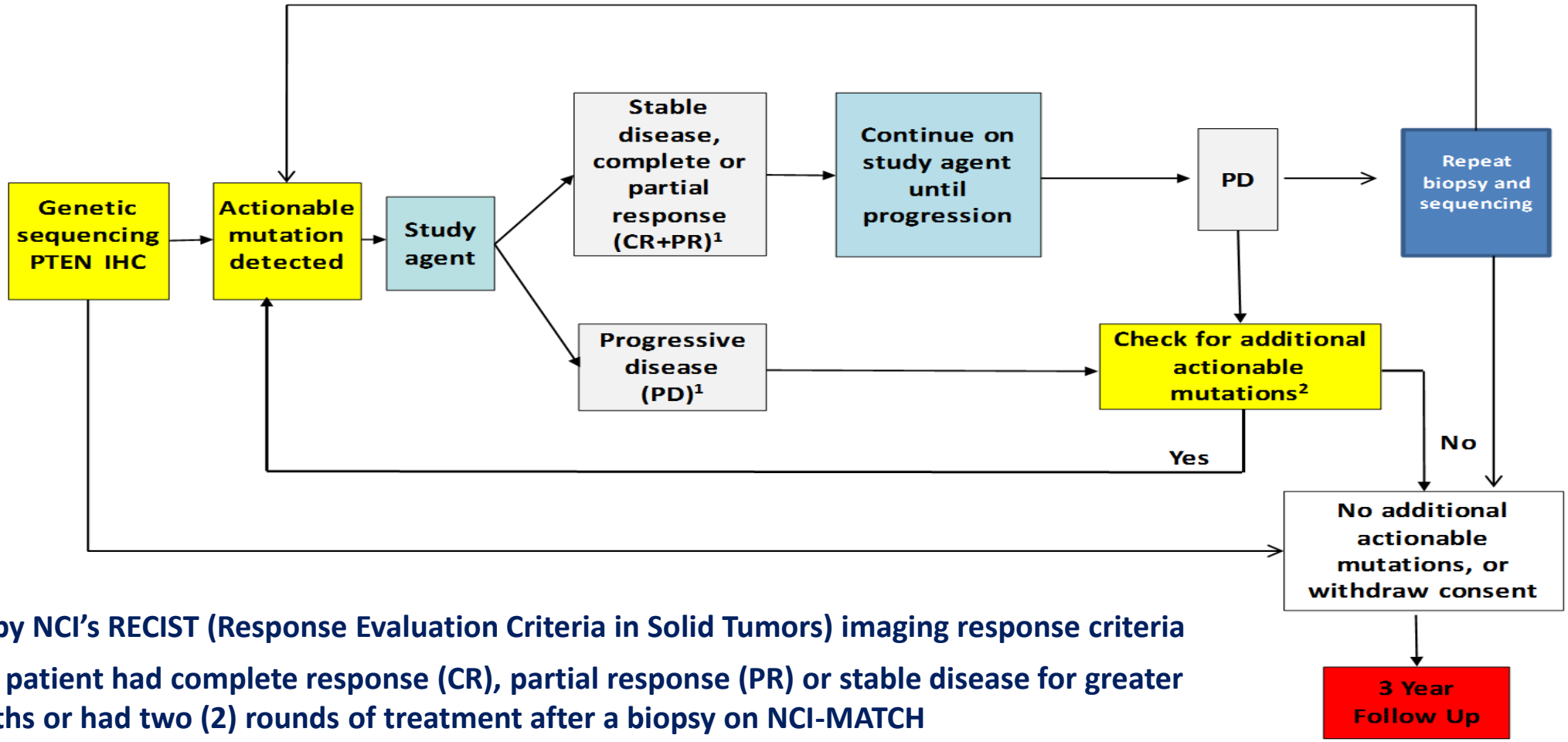
ECOG-ACRIN cancer research group | NIH NATIONAL CANCER INSTITUTE

Version Date: 11/07/2017

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
- This is a signal-finding trial—treatments that show promise can advance to larger, more definitive trials

NCI-MATCH Step-by-Step Diagram



[1]As defined by NCI's RECIST (Response Evaluation Criteria in Solid Tumors) imaging response criteria

[2]Rebiopsy; if patient had complete response (CR), partial response (PR) or stable disease for greater than 6 months or had two (2) rounds of treatment after a biopsy on NCI-MATCH

NCI-MATCH Structure

- Master protocol with multiple phase II treatment arms
  - Eligibility defined by molecular characteristics
- Single agents or combinations with recommended phase II dosage(s) known
  - FDA-approved for another indication or investigational
- IND for protocol template
  - Treatment arms open and close without affecting others
- Central IRB required as the IRB of record
- Open at US-based sites across NCTN and NCORPs

NCI-MATCH Statistical Considerations for Each Treatment Arm

- One-stage design
- Primary endpoint
  - Overall response rate 5% vs 25%
- Secondary endpoints
  - Progression free survival (PFS) 6 months 15% (median PFS 2.2 m) vs 35% (median PFS 4 m)
  - Time to progression, Toxicity, Biomarkers
- Accrual goal: 35 patients per arm

NCI-MATCH Trial Milestones

- Opened on August 12, 2015, with **10 treatments**
  - And goal to have **3000** patients submit tumor samples for testing
- Paused enrollment of *new* patients on November 11, 2015, for planned interim analysis
- Fastest accruing trial in NCI cooperative group history
  - Open at nearly 1100 sites across the U.S.
  - 795 patients screened between August and November 2015 (3 month period)
  - Original estimate of 50 screens/month greatly surpassed (>100/week)
- Expanded to **17 treatments** on February 25, 2016
- Presented interim analysis on April 18, 2016, to the American Association for Cancer Research

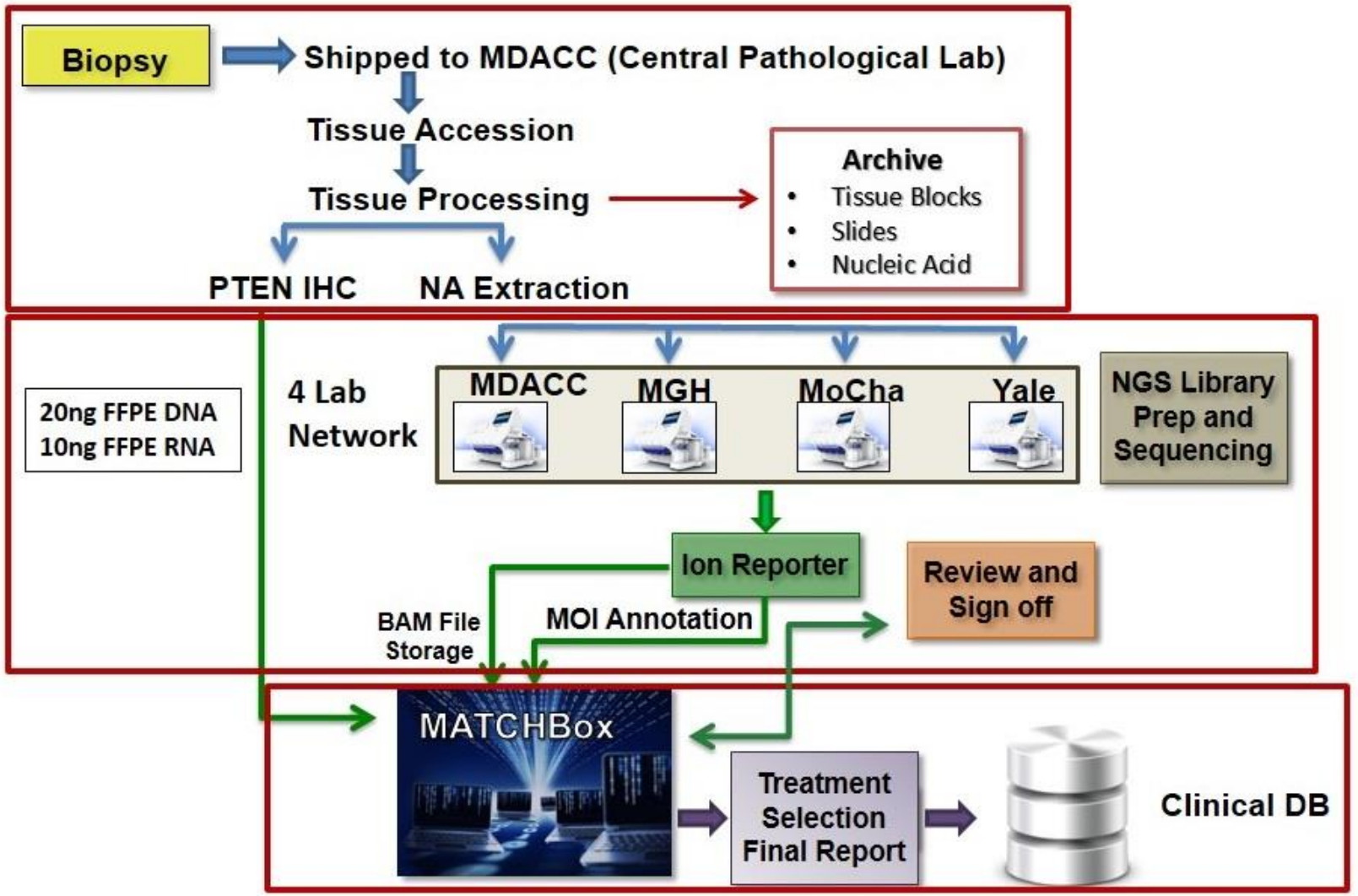
NCI-MATCH Trial Milestones (cont'd)

- Expanded to **24 treatments** and resumed enrollment of *new* patients on May 31, 2016
  - With more laboratory capacity to handle rapid pace of enrollment
- Increased 3000-patient sequencing goal to **6000** in fall of 2016
- Expanded to **30 treatments** on March 13, 2017
- *Screen rate for fresh biopsies*
  - 100-120 registrations/week
  - 100 biopsies received/week (94% assay completion)
  - 20 assigned (72% enter arm)
  - 10-15 enter/week

Levels of Evidence for Target Selection in NCI-MATCH

- Level 1: Gene variant credentialed for selection of an approved drug
- Level 2: Variant is eligibility criterion for an ongoing clinical trial for that drug OR variant identified in an N of one response
- Level 3: Preclinical inferential data
  - Models with variant respond; without variant do not
  - Gain of function mutation demonstrated in preclinical model
  - Loss of function (tumor suppressor genes or pathway inhibitor e.g. NF1); stop codon or demonstrated loss of function in pre-clinical model

NCI-MATCH Assay Workflow



NCI-MATCH's Customized Thermo Fisher Oncomine™ Assay

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**

NCI-MATCH Patient Accrual Thru 04/23/2017

	Screened	% of Total
Less Common Cancers	2885	61.5%
Common Cancers*	1809	38.5%
Total	**4694**	

The trial has far exceeded the goal that 25% of the patients screened have rare or less common types of cancer

*Common cancers screened:
Colorectal 15.5%, Breast 12.8%, NSCLC 7.6%, Prostate 2.6%

NCI MATCH RESULTS

- Results on the sequencing of 6000 patients will be tabulated
  - Tumor histology
  - Frequency of mutations overall and by tumor type
  - Percentage assigned to treatment, percentage accrued to a treatment, reasons why patients assigned did not go on to treatment
  - Demographics
- WES and RNAseq on each patient (with enough tumor) who entered a trial
- Correlate with response
  - Co-mutations
  - Requesting specimens on progression to inform on resistance mechanisms

NCI-MATCH Next Steps

- Goal to complete tumor testing on 6000 patients was completed in June 2017
- **But the trial is not ending**
- Just over half the possible accrual
  - 10 arms have accrued at least 35 patients
  - One arm administratively closed (N)
  - 19 arms have yet to accrue 35 patients (including recently added arms)
- Need to sequence many more tumors to accrue patients with rare variants
- **Open to other labs to find patients with rare variants: confirm with MATCH assay**

NCI-MATCH Effect on Analysis of Outside Assays

- Patients confirmed by NCI-MATCH assay will be included in primary outcome analysis
- All patients treated on the arm will be evaluable for toxicity
- Patients without confirmation may continue treatment, but will not be included in the primary outcome analysis

NCI-MATCH Efficacy of Individual Treatments

- For planning follow-up for any signals:
  - Plan in place for a preliminary and confidential analysis once at least 15 patients on an arm have completed enough follow-up to assess 6 month progression free survival
- Expansion of arm accrual was allowed when patients were being biopsied and tumors analyzed specifically for NCI MATCH, but only 35 patients will be necessary for signal

NCI-MATCH Designated Outside Labs Started May 11, 2017

- NCI agreements with two CLIA-accredited commercial labs allow assay results for patients in CIRB-approved trial sites
  - Foundation Medicine, Inc.
  - Caris Life Sciences
- NCI agreements with two CLIA-accredited academic labs allow assay results for their own patients
  - MD Anderson Cancer Center
  - Memorial Sloan-Kettering Cancer Center
    - Both are CIRB-approved trial sites already

NCI-MATCH Requirements for Designated “Outside” Labs

- CLIA certified lab
- Must assay required eligibility molecular variants AND
- Must assay molecular variants that would exclude patients from a study
- Notify ordering physician that patient may be eligible for NCI MATCH
- Sites must have CIRB approval for NCI MATCH
- Sites present study to patient (if deemed otherwise eligible) and send report to NCI MATCH on registration
- Need to work with labs in order to get the results into MATCHbox for treatment assignment

NCI-MATCH's 30 Current Arms/Gene Abnormalities

Arm	Drug(s)	Abnormality	Accrual Goal (Actual as of 08/27/2017)
A	afatinib	EGFR mut	35 (0)
B	afatinib	HER2 mut	70* (40)
C1	crizotinib	MET amp	35 (14)
C2	crizotinib	MET exon 14 sk	35 (16)
E	AZD9291	EGFR T790M	35 (4)
F	crizotinib	ALK transloc	35 (2)
G	crizotinib	ROS1 transloc	35 (1)
H	dabrafenib and trametinib	BRAF V600E or V600K	35 (25)
I	taselisib	PIK3CA mut	70* (70) COMPLETE
J	trastuzumab and pertuzumab	HER2 amp	35 (11)

* Accrual goal expanded

Outside Assay Required

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NCI-MATCH's 30 Current Arms Cont'd

Arm	Drug(s)	Abnormality	Accrual Goal (Actual as of 08/27/2017)
L	TAK-228	mTOR mut	35 (5)
M	TAK-228	TSC1 or TSC2 mut	35 (8)
N	GSK2636771	PTEN mut	35 (24) CLOSED
P	GSK2636771	PTEN loss	35 (35) COMPLETE
Q	ado-trastuzumab emtansine	HER2 amp	35 (38) COMPLETE
R	trametinib	BRAF nonV600	35 (35)
S1	trametinib	NF1 mut	70* (50)
S2	trametinib	GNAQ or GNA11	35 (3)
T	vismodegib	SMO or PTCH1	35 (16)
U	defactinib	NF2 loss	35 (28)

* Accrual goal expanded

Outside Assay Required

Continued on next slide

NCI-MATCH's 30 Current Arms Cont'd

Arm	Drug(s)	Abnormality	Accrual Goal (Actual as of 08/27/2017)
V	sunitinib malate	cKIT mut	35 (6)
W	AZD4547	FGFR pathway aberrations	70* (52)
X	dasatinib	DDR2 mut	35 (0)
Y	AZD5363	AKT1 mut	35 (35) COMPLETE
Z1A	binimetinib	NRAS mut	70* (53) SUSPENDED
Z1B	palbociclib	CCND1, 2, or 3 amp	70* (37)
Z1C	palbociclib	CDK4 or CDK6 amp	35 (17)
Z1D	nivolumab	dMMR status	70* (47) SUSPENDED
Z1E	larotrectinib (LOXO-101)	NTRK fusions	35 (1)
Z1I	AZD1775	BRCA1 or BRCA2 mut	35 (33)
			TOTAL: 1295 (706)

* Accrual goal expanded

Outside Assay Required

NCI-MATCH Treatment Arms Open But Not Yet Included in Outside Assay Demonstration Project

Arm	Mutation	Mutation Prevalence Rate %	Accrual Goal (Actual as of 08/30/2017)	Opened	Reason Not Included
S1	NF1	1.77	70* (50)	Feb ’16	The potential inclusion of these arms will be considered if there are treatment slots remaining after all 6k+ registered patients are through the screening process
W	FGFR	2.86	70 *(52)	May ’16	
B	HER2 activating	1.04	70* (40)	Aug ’15	
Z1I	BRCA1 or BRCA2	2.79	35 (33)	Mar ’17	Due to mutations’ higher prevalence rates, will hold for addition later after project ramps up
J	HER2 amplifying	1.49	35 (11)	Mar ‘17	

* Accrual goal expanded

NCI-MATCH Resources

Main Webpages:	cancer.gov/nci-match
	ecog-acrin.org/nci-match-eay131
Protocol Documents:	ctsu.org (password required)
Spanish:	cancer.gov/espanol/nci-match
Email Inquiries:	match@jimmy.harvard.edu

NCI's Cancer Information Service:
1-800-4-CANCER and cancer.gov/contact

This slide presentation is updated regularly. For the latest version, visit ecog-acrin.org.

Pediatric MATCH

Pediatric MATCH

NATIONAL CANCER INSTITUTE

NCI-Children's Oncology Group Pediatric MATCH Trial*

This precision medicine clinical trial, funded by NCI and conducted by COG, matches children and adolescents with treatment based on genetic changes in their tumors.

Pediatric MATCH is for patients ages 1 to 21 who have both:

- Solid tumors, including lymphomas and brain tumors, or histiocytoses
- Tumors that no longer respond to standard treatment or that have come back after treatment

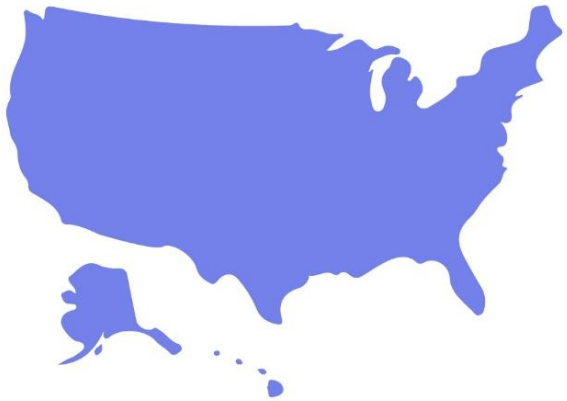
TUMOR TISSUE WILL UNDERGO TESTING FOR CHANGES IN MORE THAN 160 GENES

ABOUT **200-300** PEDIATRIC PATIENTS ARE EXPECTED TO BE SCREENED EACH YEAR

If a patient's tumor has a genetic change that matches one targeted by a drug used in the trial, the patient may be eligible to join the treatment arm targeting that genetic change.

Talk with your pediatric oncologist about whether this trial would be an option for your child.

THE TRIAL IS OFFERED IN THE U.S. AT ABOUT **—200—** CHILDREN'S ONCOLOGY GROUP SITES



Pediatric MATCH

- Opened July 24, 2017
- Enrolling children and adolescents (1-21 years of age)
- Eligible: Recurrent or refractory solid tumors, including non-Hodgkin lymphomas, brain tumors and histiocytoses
- Open at around 200 sites across the U.S. that are part of the Children's Oncology Group
- Screening goal: 1000 patients
- Estimate: 1 in 10 screened will have a match

Pediatric MATCH

- Each arm = independent, single-arm phase II trial
  - Accrual goal = at least 20 patients/arm
- Primary outcome measure: Objective response rate
- Secondary outcome measures:
  - Progression free survival
  - Pharmacokinetics
  - Toxicity
- Additional outcome measures
  - Genomic landscape of advanced pediatric cancers
  - Diagnostic and genomic profiling through circulating tumor DNA

Pediatric MATCH

- Current version of MATCH sequencing panel tests for >4000 annotated genomic variants

- Drugs are all experimental in children and adolescents, but have been tested or in some cases approved for adults and have shown activity against tumors with specific activity against tumors with specific genetic changes.

Pediatric MATCH

ARM	TARGET	DRUG
A	Pan-TRK	larotrectinib
C	EZH2	tazemetostat
D	PI3K/mTOR	LY3023414
E	MEK	selumetinib
F	ALK	ensartinib
G	BRAF	vemurafenib
H	PARP	olaparib

Pediatric MATCH

- http://pediatricmatch.org/
  - COG Protocol APEC1621
- http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match
- http://clinicaltrials.gov
  - NCT03155620

- ADDITIONAL MATCH SLIDES

Presented on Behalf of Study Chairs

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No conflicts of interest

The opinions expressed in this presentation are my own, and not necessarily
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Of the ECOG-ACRIN Cancer Research Group

Precision Medicine

- *BRAFV600E* melanoma responds to BRAF inhibitors or BRAF inhibitors combined with MEK inhibitors; but colorectal cancers with the same mutations appear not to respond
- Various tumors with *NTRK* fusions appear to respond to NTRK inhibitors (ASCO 2017)
- We need to know more about which tumors will respond to agents targeted to “driver” mutations
- Most driver mutations are relatively rare

What is NCI-MATCH?

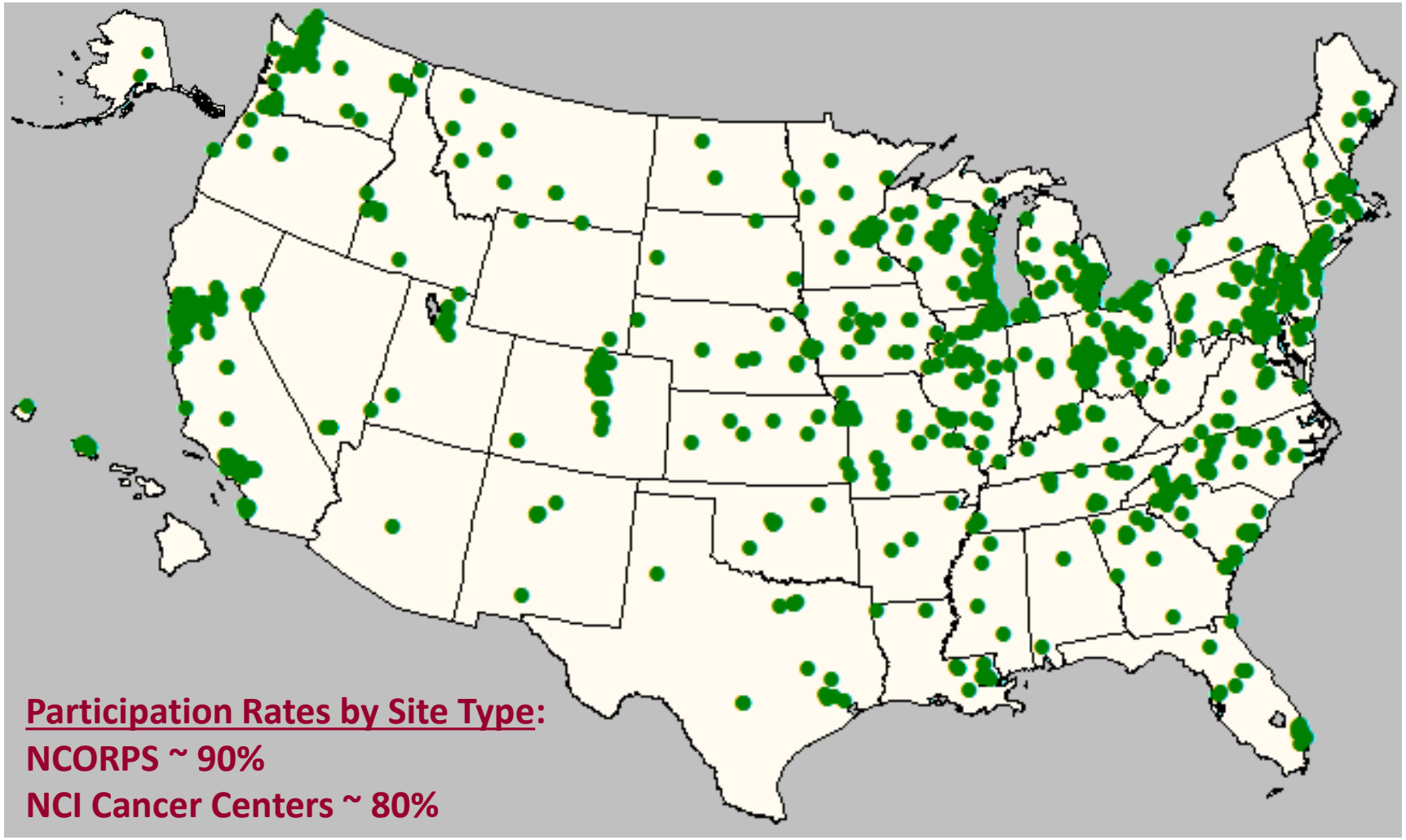
THIS PRECISION MEDICINE TRIAL EXPLORES TREATING PATIENTS BASED ON THE MOLECULAR PROFILES OF THEIR TUMORS

NCI-MATCH* IS FOR ADULTS WITH:

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

ABOUT 6,000 CANCER PATIENTS WILL BE SCREENED WITH A TUMOR BIOPSY

NCI-MATCH Distribution of Nearly 1100 Trial Sites



Levels of Evidence for Drugs in NCI-MATCH

- 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 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)

NCI-MATCH Publication of Customized Assay

"…the assay tailored for this trial is highly sensitive for detecting genetic mutations from a variety of tumor tissue and, for the first time, has been reproduced with accuracy by multiple clinical laboratories, laying the groundwork for future clinical utility."

Chih-Jian Lih et al, *The Journal of Molecular Diagnostics,* Vol 19, Issue 2, March 2017

NCI-MATCH Wait Times for Patients as of 04/23/2017

Processing Step	Median Calendar Days
Tumor sample submission from sites to EA central lab at MD Anderson Cancer Center	7
Completion of tumor testing by lab network and return of results to site	15
Further eligibility evaluation for patients assigned to a treatment arm	14

NCI-MATCH Less Common Cancers Thru 04/23/2017

Disease Site	Screened	% of Total Screened (N=4694)	Assigned to Rx	% of Screened
Ovarian	466	9.9	62	13.3%
Uterine	300	6.4	79	26.3%
Pancreas	293	6.2	16	5.5%
Sarcoma	214	4.6	29	13.6%
Liver and Hepatobiliary	202	4.3	43	21.3%
Head and Neck	174	3.7	40	23.0%
Neuroendocrine	149	3.2	22	14.8%
Gastroesophageal	147	3.1	40	27.2%
Bladder/Urinary Tract	79	1.7	28	35.4%
Small Cell Lung	73	1.6	4	5.5%
Cervical	70	1.5	19	27.1%
Central Nervous System	69	1.5	21	30.4%
Melanoma	65	1.4	19	29.2%
Kidney	55	1.2	10	18.2%
Anal	40	0.9	10	25.0%
Mesothelioma	38	0.8	8	21.1%
Lymphoma	33	0.7	1	3.0%
Myeloma	0	0	0	--
Other	418	8.9	79	18.9%
Less Common Cancers	**2885**	**61.5%**	**530**	**18.4%**

NCI-MATCH Accrual Status After 6000 Patients Screened

- Just over half the possible accrual
- 10 arms have accrued at least 35 patients
- One arm administratively closed (N)
- 19 arms have yet to accrue 35 patients (including recently added arms)

- Need to sequence many more tumors to accrue patients with rare variants
- Open to other labs to find patients with rare variants: confirm with MATCH assay

NCI-MATCH Changes

- **How will reaching the 6000 goal change the study?**
- Biggest change – the trial lab network will no longer collect and test biopsy materials for the purpose of assigning patients to treatments
- NCI reimbursement for biopsy procedures will end

NCI-MATCH Addendum #10

- Includes changes to Section 3.1 – Eligibility Criteria for Screening Biopsy
  - Section 3.1.6.4
    - Requires genetic sequencing assays by designated private-sector and academic laboratories outside the NCI-funded trial lab network
    - Outside assays must be used to identify potential candidates
    - In lieu of a fresh biopsy
    - Sites requested to send tissue for NCI MATCH assay for correlation

NCI-MATCH Addendum #10 (cont'd)

- Includes a new Appendix XIV – Screening Assessments for Designated Outside Assays
  - Names the designated laboratories
    - Caris Life Sciences, Foundation Medicine, Inc.
    - MDACC, MSKCC
  - Lists which subprotocols are affected
  - Provides guidelines to all data and forms submissions that will be necessary following patient registration to screening Step 0

NCI-MATCH Shift to Outside Assays

- This is a demonstration project
- Aimed at moving NCI-MATCH towards real-world genetic analysis of tumors
  - And aligning the trial with current practice
    - Physicians order sequencing on their patients to guide treatment
- Physicians' increasing use of assays for clinical reasons allows us to apply this approach to NCI-MATCH
  - Rather than continuing to require patients to have a fresh biopsy to determine eligibility for a single clinical trial
- Outside assays are broader than just NCI-MATCH

NCI-MATCH Shift to Outside Assays (cont'd)

- Engagement with vetted labs outside the trial network
  - Should result in access to large numbers of patients
  - To identify very small subsets
    - With qualifying genetic and disease characteristics
    - That may qualify them for the trial
- Results of outside assays should meet the standards of the trial
  - And will be confirmed by the NCI-MATCH trial labs
  - Using archived tissue
- First attempt ever, in any NCTN clinical trial

NCI-MATCH Solicitation to Add Additional Interested Labs

- Request for Letters of Interest for NCI-MATCH Laboratories
- Via Federal Register Vol. 82, No. 147pgs 35976-35978
- URL: **https://www.federalregister.gov/documents/2017/08/02/2017-16203/request-for-letters-of-interest-for-nci-match-laboratories**

NCI-MATCH Effect on Patients of Outside Assays

- Patients will enroll to arm based on outside assay result
- Patients do not need a fresh biopsy for entry into NCI-MATCH or for correlation of assay results by trial labs
- Outside assay result will be confirmed by NCI-MATCH assay on archived tissue
  - Both outside-assay lab AND the site are possible sources of the samples
- Patient treatment will not be delayed for confirmation

NCI-MATCH Reimbursement Status

- The NCI no longer pays for the biopsies
- OR the costs associated with the outside assay being performed for clinical purposes
- Assays done on the blocks submitted for concordance purposes are being done free of charge
- NCI continues to reimburse in the customary way for block submission and the reimbursement for patients entering the therapeutic arms

Correlative Study

- WES and RNAseq on each patient (with enough tumor) who entered a trial
- Correlate with response
  - Co-mutations
  - Requesting specimens on progression to inform on resistance mechanisms