NCI-Molecular Analysis for Therapy Choice (NCI-MATCH or EAY131)

Interim Analysis Results

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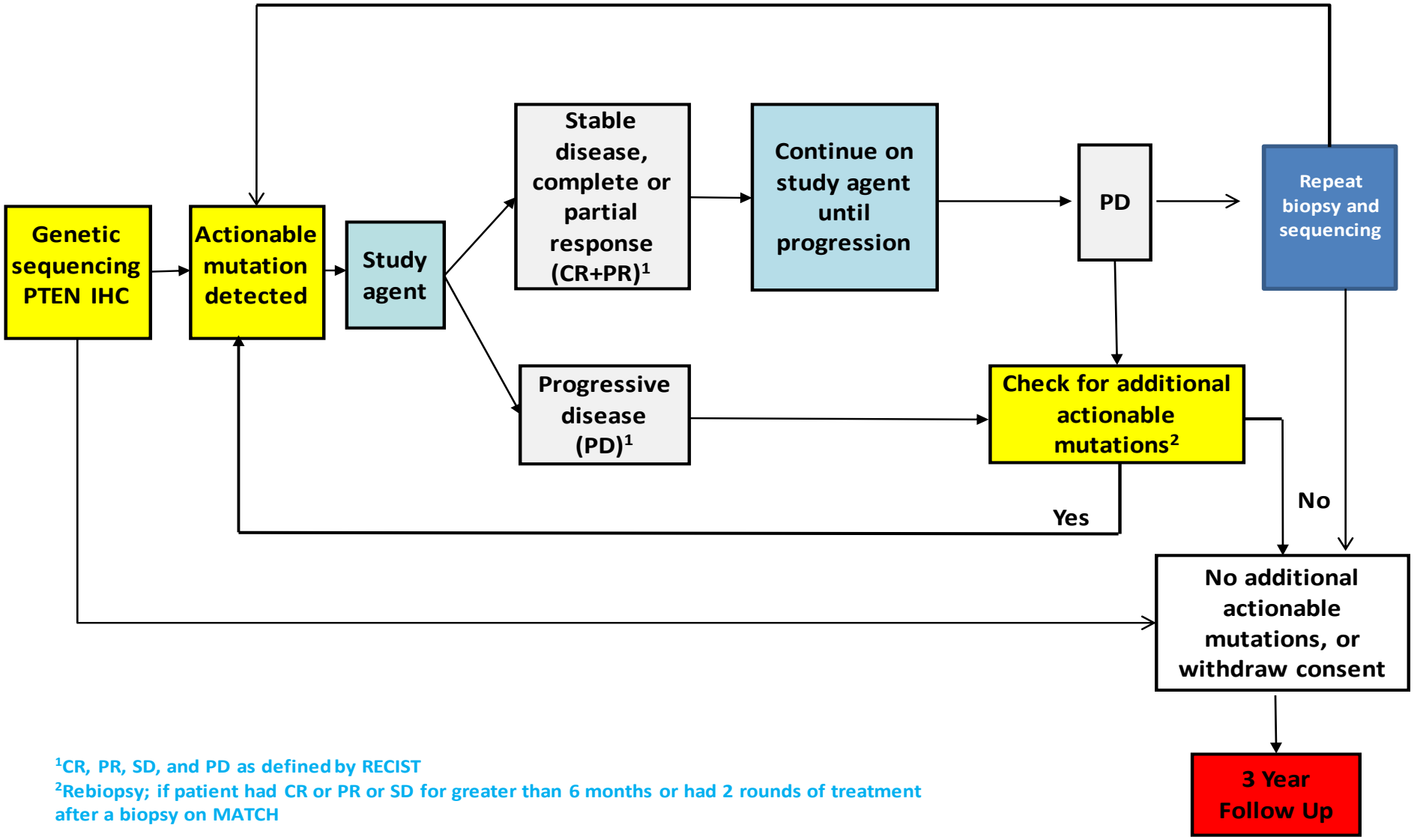
Objectives

- Describe interim analysis of NCI-MATCH
- Describe upcoming changes in NCI-MATCH

NCI-MATCH / EAY131 SCHEMA



[1]CR, PR, SD, and PD as defined by RECIST
[2]Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH

NCI-MATCH Interim Analysis

- Due to the uniqueness of the trial, early scientific review was built into the protocol design
- From the protocol:

  "Given a number of unknown aspects about this study (e.g. prevalence of specific alterations), after 500 patients are screened the design will be reassessed to assure its appropriateness. An analysis of the distributions of actionable alterations and of tumor types, both overall and within treatment subprotocols, will be performed…."

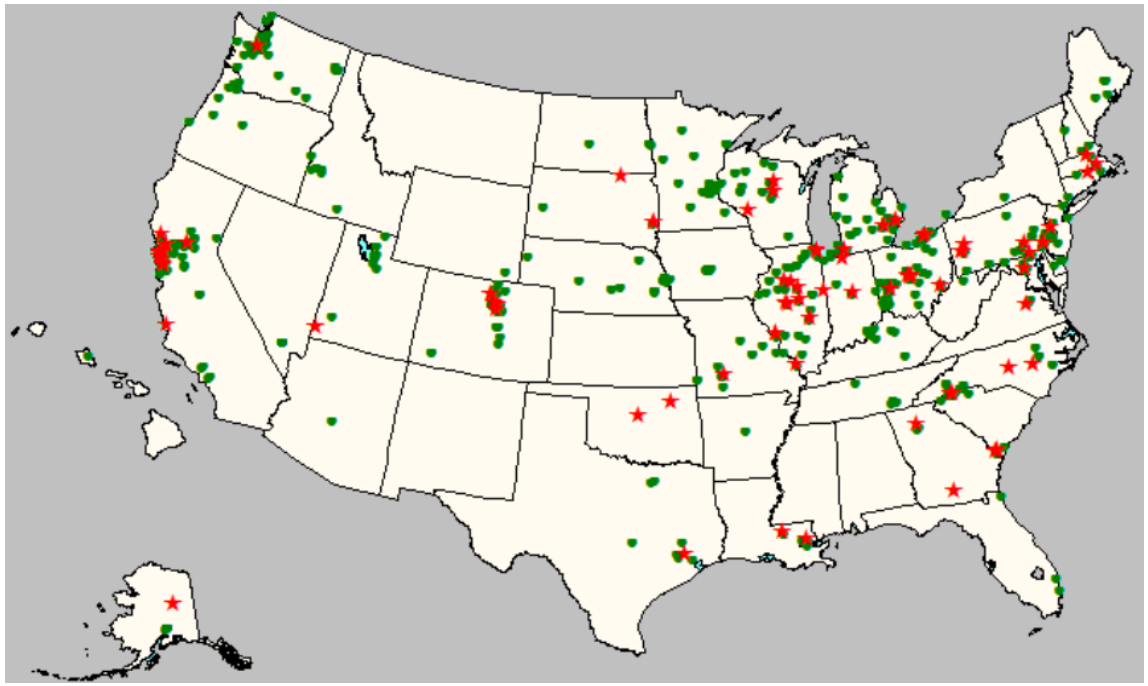
- Data as of March 9, 2016 are included in this analysis

NCI-MATCH Trial Status

- Trial opened on Aug 12, 2015, with 10 treatment arms
  - And plan to add at least 14 more arms in coming months
- Initial goal of 3000 patients for tumor gene testing
  - Estimated mutation matching rate of 30% when all arms open
  - But 10% for first 10 arms
- Registration of *new* patients was paused on Nov 11, 2015
- Pause allowed for a planned interim analysis
  - After first 500 patients had undergone tumor testing
- Due to extremely rapid pace of accrual, it was not possible to pause enrollment at a precise cut-off
- By the time 500 patients had undergone tumor testing, several hundred more had begun the initial screening process

NCI-MATCH Patients and Sites

- 795 patients enrolled for screening in the first 3 months
- Far surpassing original estimate of 50/month
- Typical registration patterns start slowly and ramp up over time



- 192 active sites (at least 1 patient)
  - 2/3 community
  - 1/3 academic
- 796 approved sites

NCI-MATCH Accrual Summary

Activated 08/12/15; paused 11/11/15: 92 days		
Patient cases registered for screening	795	
Cases with samples submitted	739	
Cases where labs were able to successfully complete tumor testing	645	87% (N=739)
Cases with mutation matching 1 of 10 available treatment arms	56	9% (N=645)
Patients matching specific eligibility criteria for, and assigned to, a treatment arm	33	5% (N=645)
Patients who entered 7 of 10 available treatment arms	16	2.5% (N=645)

Overall mutation rate of 9% for first 10 treatment arms was expected

NCI-MATCH Accrual Demographics

	Enrolled for Screening (N=795)	Assigned to Rx (N=33)
Median Age	63 (Range 24-93)	68 (Range 40-82)
Male	305 (38%)	16 (48%)
Female	490 (62%)	17 (52%)
White	646 (81%)	29 (88%)
Black	88 (11%)	1 (3%)
Asian	27 (3%)	2 (6%)
Native American	4 (1%)	--
Native Hawaiian	1 (0%)	--
Race Not Reported	29 (4%)	1 (3%)
Hispanic Ethnicity	36 (5%)	--

NCI-MATCH First Ten Arms and Mutation Prevalence Rates Per Arm (Actual vs Estimated)

- Overall 9% mutation match rate for first ten arms (56/645)
- Expected 10%

	Actual MATCH Rate (%)	Estimated Prevalence Rate (%)
Q: Ado-trastuzumab emtansine in HER2 amplifications	1.7	5
U: Defactinib in NF2 loss	1.1	2
B: Afatinib in HER2 mutations	0.8	2-6
H: Dabrefenib+Trametinib in BRAF V600	0.8	7
R: Trametinib in BRAF non-V600	0.3	2.8
E: AZD9291 in EGFR T790M	0.2	1-2
F: Crizotinib in ALK translocation	0.2	<2
V: Sunitinib in cKIT mutations	0.2	2
A: Afatinib in EGFR mutations	0	1-4
G: Crizotinib in ROS1 translocation	0	<2

NCI-MATCH Primary Disease Sites

Common Cancers	Enrolled for Screening (N=795)	Screened (N=645)	Assigned to Rx (N=33)
Colorectal	104 (13.1%)	84 (13.0%)	6 (18.2%)
Breast	96 (12.1%)	84 (13.0%)	2 (6.1%)
Non-Small Cell Lung	62 (7.8%)	48 (7.4%)	5 (15.2%)
Prostate	20 (2.5%)	17 (2.6%)	1 (3.0%)
Common Cancers Subtotal	**282 (35.47%)**	**233 (36.12%)**	**14 (42.42%)**

Uncommon Cancers			
Ovarian	89 (11.2%)	72 (11.2%)	6 (18.2%)
Pancreas (Adeno/NOS)	43 (5.4%)	34 (5.3%)	--
Head and Neck[1]	38 (4.8%)	34 (5.3%)	--
Endometrial/Uterine (Non-Sarcoma)	34 (4.3%)	27 (4.2%)	--
Esophageal/GE Junction/Gastric	31 (3.9%)	28 (4.3%)	4 (12.1%)
Neuroendocrine[2]	27 (3.4%)	20 (3.1%)	2 (6.1%)
Cholangio	24 (3.0%)	22 (3.4%)	1 (3.0%)
Bladder/Urinary Tract	21 (2.6%)	14 (2.2%)	1 (3.0%)
Endometrial/Uterine Sarcoma[3]	20 (2.5%)	16 (2.5%)	--
Small Cell Lung	16 (2.0%)	14 (2.2%)	--
Other[4]	151 (19.0%)	116 (18.0%)	3 (9.1%)
Primary Site Not Specified	19 (2.4%)	15 (2.3%)	2 (6.1%)
Uncommon Cancers Subtotal	**513 (64.53%)**	**412 (63.87%)**	**19 (57.57%)**

[1] Salivary Gland = 3
[2] NOS = 18, Pancreas = 6, Carcinoid = 3
[3] Uterine Carcinosarcoma = 7
[4] Key Other Types: Lymphoma = 9, Brain Tumor = 9, Melanoma = 9

NCI-MATCH Treatment Assignments to First Ten Arms, by Arm, Cancer Type

	Assigned to Rx	Uncommon Cancers	Common Cancers
Q: Ado-trastuzumab emtansine in HER2 amplifications	11	Adeno Esophageal (2) Ovarian (3) Cholangio (1) TCC Urothelium (1)	Colon Adeno (3) Colon NOS (1)
U: Defactinib in NF2 loss	7	Mesothelioma (2) Ovarian (2) Pancreas/Adeno NOS (1)	Colon Adeno (1) Lung Adeno (1)
B: Afatinib in HER2 mutations	5	Gastric Adeno (1) Adeno Esophageal (1)	Breast (2) Prostate (1)
H: Dabrefenib+Trametinib in BRAF V600	5	Neuroendocrine (1)	Lung Adeno (3) Lung Adeno w. BAF (1)
R: Trametinib in BRAF non-V600	2	Ovarian (1)	Colon Adeno (1)
E: AZD9291 in EGFR T790M	1	Neuroendocrine NOS (1)	--
F: Crizotinib in ALK translocations	1	Mets to Peritoneum NOS (1)	--
V: Sunitinib in cKIT mutations	1	Thymoma (1)	--
A: Afatinib in EGFR mutations		--	--
G: Crizotinib in ROS1 translocations		--	--
Total	**33**	**19 (57.57%)**	**14 (42.42%)**

NCI-MATCH Enrollment Status of Patients with Treatment Assignments to First Ten Arms

	Assigned to Rx (N-33)	No Longer Met Overall Study Eligibility	Ineligible for Arm	Progressed/ Deteriorating Condition/ Started Other Rx	Died	Enrolled for Rx (N=16)
Q: Ado-trastuzumab emtansine in HER2 amplifications	11		3		2	6
U: Defactinib in NF2 loss	7	2	1	1	1	2
B: Afatinib in HER2 mutations	5	1			1	3
H: Dabrefenib+Trametinib in BRAF V600	5	1		2		2
R: Trametinib in BRAF non-V600	2		1			1
E: AZD9291 in EGFR T790M	1					1
F: Crizotinib in ALK translocations	1					1
V: Sunitinib in cKIT mutations	1	1				
A: Afatinib in EGFR mutations						
G: Crizotinib in ROS1 translocations						
Total	**33**	**5**	**5**	**3**	**4**	**16**

NCI-MATCH Expanding to 24 Arms in Late May 2016

Arm / Target	Drugs(s)
A EGFR mut	Afatinib
B HER2 mut	Afatinib
C1 MET amp	Crizotinib*
C2 MET ex 14 sk	Crizotinib*
E EGFR T790M	AZD9291
F ALK transloc	Crizotinib
G ROS1 transloc	Crizotinib
H BRAF V600	Dabrafenib+trametinib
I PIK3CA mut	Taselisib
N PTEN mut	GSK2636771
P PTEN loss	GSK2636771
Q HER 2 amp	Ado-trastuzumab emtansine

Arm / Target	Drug(s)
R BRAF nonV600	Trametinib
S1 NF1 mut	Trametinib
S2 GNAQ/GNA11	Trametinib
T SMO/PTCH1	Vismodegib
U NF2 loss	Defactinib
V cKIT mut	Sunitinib
W FGFR1/2/3	AZD 4547*
X DDR2 mut	Dasatinib
Y AKT1 mut	AZD 5363*
Z1A NRAS mut	Binimetinib*
Z1B CCND1,2,3 amp	Palbociclib*
Z1D dMMR	Nivolumab*

*Pending approval

NCI-MATCH Assumptions for Enrollment Projections Across 24 Treatment Arms

- Trial size will increase to 5000 patients for screening
  - 795 already registered = 4205 more patients
  - Site involvement may increase threefold
- Tumor testing completion rate of 87% (645/739)
- Mutation rates same as in patients enrolled to date
- 65% of patients with treatment assignments will enroll
- One treatment arm assignment per patient (some may have more than one matching mutation)

NCI-MATCH Projected Match Rates and Enrollments for 24 Treatment Arms (N=5000 Screened)

Expected Overall Match Rate = 23%

Arm / Target	Expected Match Rate %	Expected Enroll-ment
I PIK3CA mut	4.0	89
Z1B CCND1 amp	3.6	79
W FGFR1/2/3	2.9	65
P PTEN loss	2.5	55
Q ERBB2 amp	1.7	44
S1 NF1 mut	1.9	41
Z1C CDK4/6 amp	1.7	38
Y AKT1 mut	1.2	28
Z1A NRAS mut	1.2	28
U NF2 loss	1.1	26
N PTEN mut	1.1	24
C1 MET amp	0.9	21

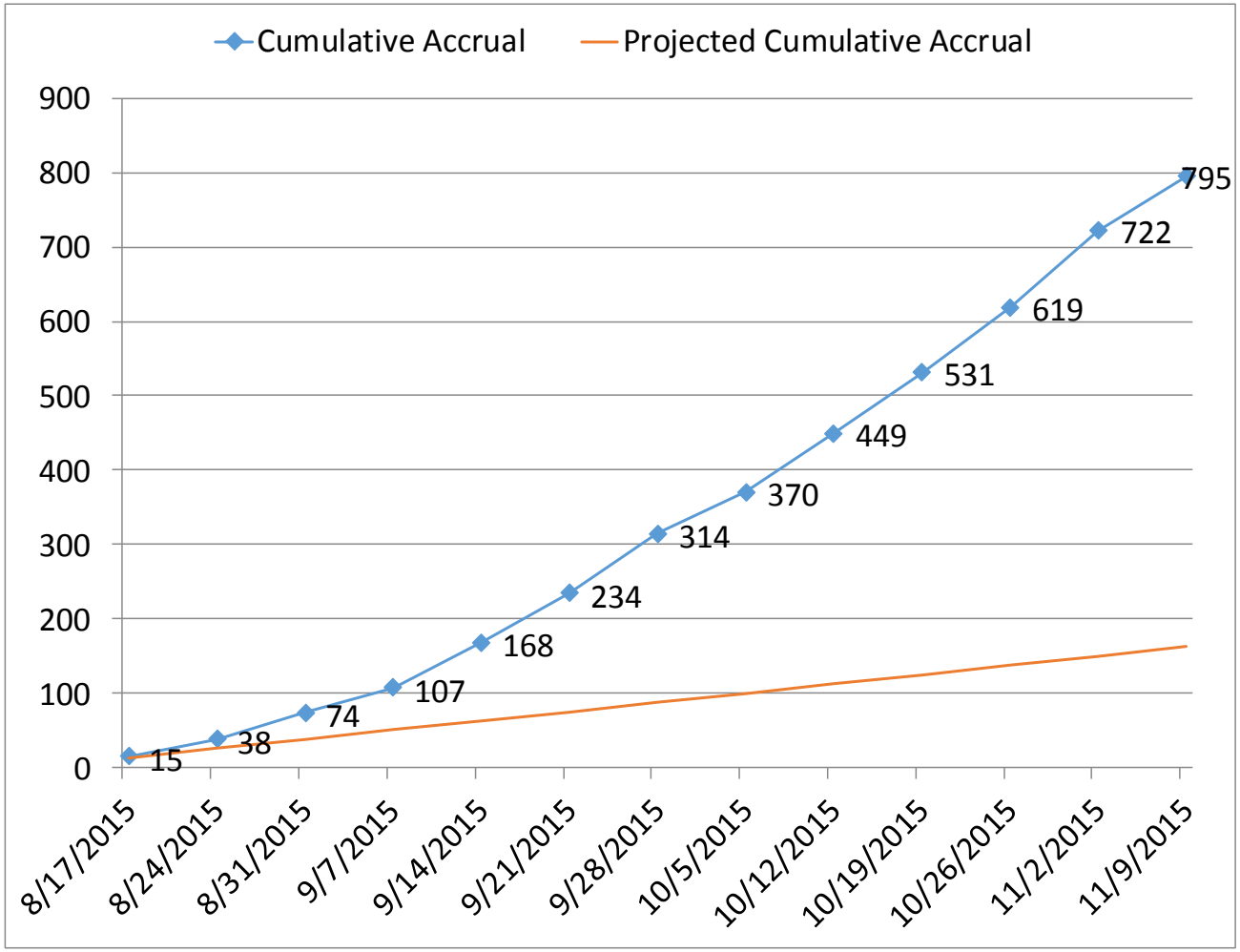
Arm / Target	Expected Match Rate %	Expected Enroll-ment
B ERBB2 mut	0.8	20
H BRAF V600	0.8	19
T SMO/PTCH1	0.6	14
R BRAF non V600	0.3	8
E EGFR T790M	0.2	4
F ALK transloc	0.2	4
V cKIT mut	0.2	3
A EGFR mut	0	0
G ROS1 transloc	0	0
S2 GNAQ/GNA11	0	0
C2 MET ex 14 sk	No Data	Not Known
Z1D dMMR	No Data	Not Known

NCI-MATCH Enrichment Strategies for Rare Mutations

Increase enrollment of pre-screened patients by:

- Increasing the participation of centers currently performing next-generation sequencing (NGS) in advanced cancer population
- Developing communication plan with commercial NGS labs to notify ordering physicians of relevant NCI-MATCH arms for actionable mutations of interest

NCI-MATCH Weekly Accrual Far Exceeded Projections



Projected 50 Cases/Month at Start

Gradual Ramp-up in Year 1

NCI-MATCH Sample Processing Turn-around Times Extended with Increased Registration Rate Over Time

Period	# Days	# Samples	Median (Days)
Aug 21 to Sep 27	38	162	14
Sep 28 to Oct 25	28	274	23
After Oct 26	--	336	36
Total		772	

- Most samples received by Nov 22
- Averaged 80 samples / week from Oct 12 to Nov 15
- Median days for sample submission from sites to central lab: 7

NCI-MATCH Successfully Analyzed 87% of Cases

- Success rate (645/739) is within industry standard (≥80%)
- Sample quality major reason for 94 cases not analyzed

Reason	# Samples Not Analyzed	% Samples (N=127)	Total % of Samples (N=772)
No Viable Tumor	61	48.0%	8.2%
Insufficient DNA/RNA	44	34.6%	5.9%
Insufficient Tumor % or No Tissue	10	7.8%	1.3%
Tumor Gene Testing QC	9	7.0%	1.2%
Sample Did Not Meet Protocol Req's	3	2.3%	0.4%
Total	127*		

* Reason linked to individual sample sets

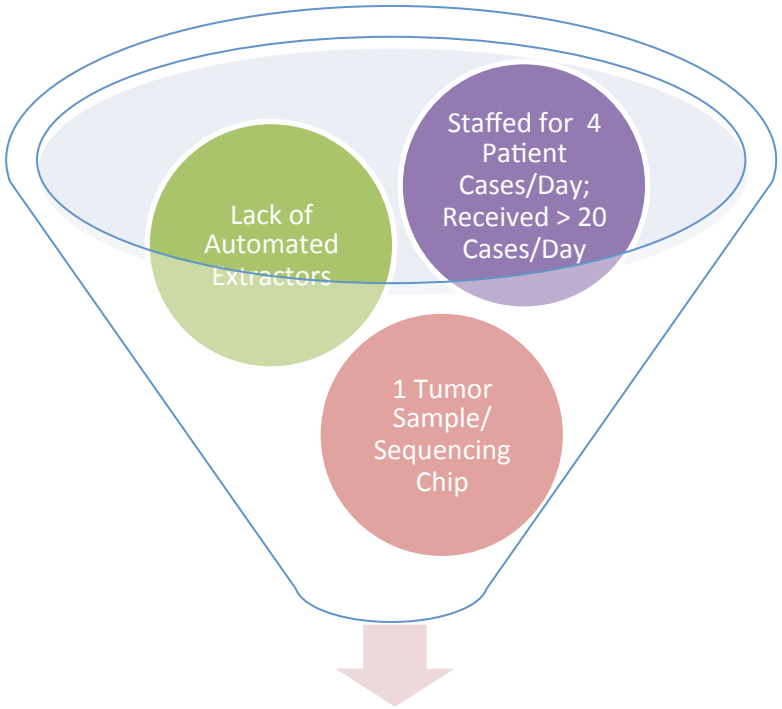
739 Cases with Samples Submitted
+33 Cases Requiring 2nd Biopsy
772 Total Samples Submitted

NCI-MATCH Samples Requiring Use of Cytology

- Optional needle aspirate specimens submitted: 179/739 (24% of patient cases with samples submitted)
- Condition of cytology specimens:
  - Tumor present: 173/179 (97%)
  - Core unusable so cytology specimen used for nucleic acid extraction: 22/173 (12%)
- Successful sequencing: 19/22 (86%)
- Cytology contribution to providing genomic results: 19/645 (3%)
- Predicted contribution if all patients had cytology exam: 84 more patients (based upon salvage of 86% of 94 cases not analyzed), overall success rate 98.6% (729/739)

NCI-MATCH Laboratory Expansion to Handle Expected Demand and Improve Turn-around Times (TAT)

Before

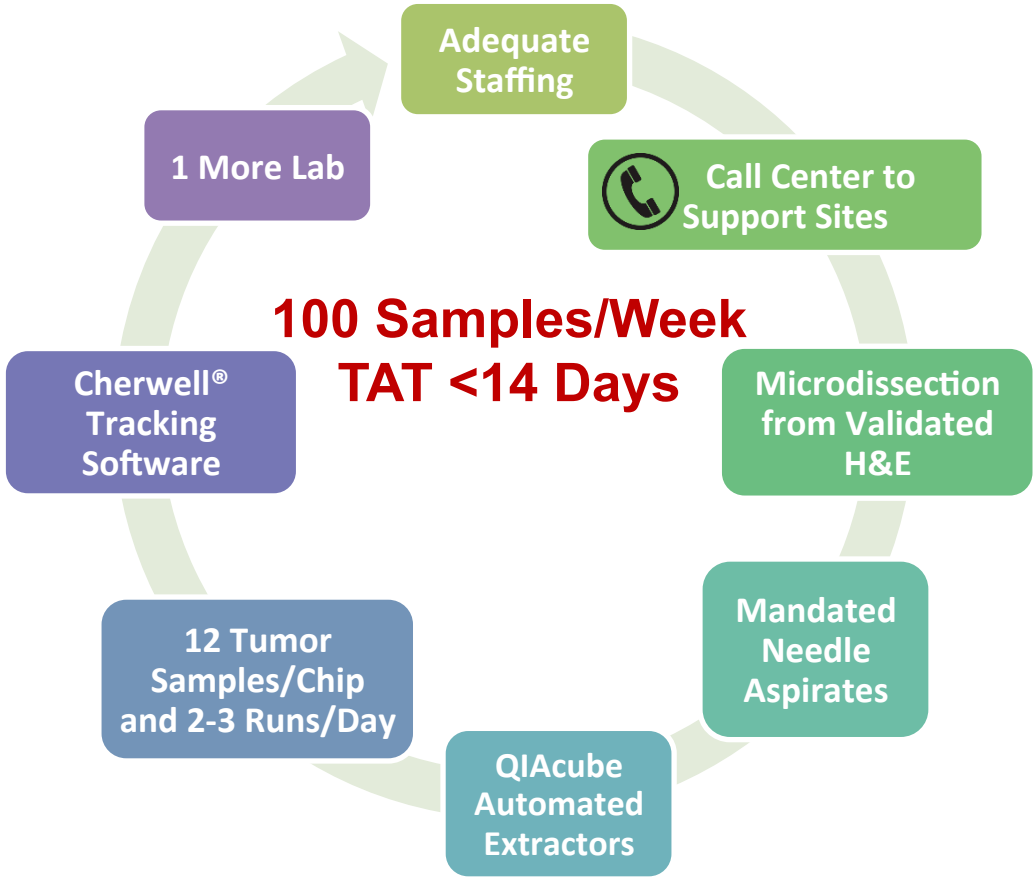


Avg 80 Samples/Week - by Week 8

Bottleneck

TAT > 14 Days

After Patient Registration Resumes



NCI-MATCH Changes Underway

- Main changes:
  - Increase in screening goal to 5000 patients
  - Increase in number of arms (24 by late May, planned already)
    - Match rate expected to be 23% overall
  - Greater focus on communication to influence patient selection
  - Expansion of analytical capacity to accelerate return of results for patients
  - Mandating needle aspiration in all cases
- Other changes:
  - Allowing tumor samples obtained up to 6 months prior to registration
  - Allowing data from other genetic platforms

NCI-MATCH Conclusions from the Interim Analysis

1. A trial of therapy based on genetic characteristics of the tumor is feasible in the institutions of the NCTN
   - Unprecedented with registration higher than for any other NCTN trial to date
2. The success rate of the whole process of tumor characterization from accrual to biology read-out was accomplished in 87% of patients
3. A high proportion of less common malignancies in this early analysis opens options for advances in these cancers

NCI-MATCH Conclusions Cont'd

4. The interim analysis that was applied early in the trial permitted implementation of several enhancements to the structure of the study
5. The analysis has also permitted planning for realistic needs of trials/drugs that can be analyzed in each molecular subset
6. This potential has been recognized by expanding the planned accrual from 3000 to 5000 patients
7. Other interim analyses are under consideration

Acknowledgements

- Patients and their physicians
- NCI National Clinical Trials Network
- NCI Community Oncology Research Program
- Network groups
  - Alliance for Clinical Trials in Oncology
  - Children's Oncology Group
  - ECOG-ACRIN Cancer Research Group
  - NRG Oncology
  - SWOG
- 150+ scientists, physicians, laboratory experts and patient advocates
  - Subprotocol PIs
  - Steering committee and working groups
    - Agents and Gene Selection
    - Correlative Proposals
    - Imaging
    - Informatics
    - Protocol Logistics
    - Samples and Sequencing
    - Site Participation & Education
    - Patient Advocate
    - Public Relations

Resources for NCI-MATCH

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
Patient Brochure:	EA website (above)
Site Process Brochure:	EA website (above)

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

NCI-MATCH Biopsy-related Adverse Events

	Grade		
	1	2	3
Abdominal pain	2	0	1
Anemia	0	0	1
Bleeding, post biopsy	1	0	0
Bloating	1	0	0
Duodenal obstruction	0	0	1
Dyspnea	0	0	1
Hematoma	1	0	0
Hepatic pain	0	1	0
Hypertension	0	0	1
Pain of skin	1	0	0
Pneumothorax	4	2	1
Postoperative hemorrhage	1	0	0
Supraventricular tachycardia	0	0	1
Worst Degree	9	3	5

Biopsy data submitted for 659 cases

AEs reported for 17 cases (2.6%)

No grade 4 or grade 5 AEs