The NCI-MATCH (EAY131) Precision Medicine Trial: Lessons Learned and Status Update

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

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Oslo Cancer Cluster
Cancer Crosslinks 2016

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

Study Leadership

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NCI-MATCH Rationale

Molecular targeted therapy has improved outcomes

- Within individual tumor types
  - Imatinib in CML (bcr-abl)
  - Imatinib in GIST (CKIT & PDGFRα)
  - Erlotinib in NSCLC (EGFR)
  - Crizotinib in NSCLC (EML4-ALK)
- And across tumor types
  - Trastuzumab in breast and gastric (HER2)
  - Vemurafenib in melanoma, thyroid & NSCLC, but not colon cancer (BRAF)

NCI-MATCH Objective

- To understand the relative effects of the same therapy applied to oncogene-defined subsets across different tumor histologies, we initiated a broad-based genomic prescreening study to assign patients whose tumors harbor specific molecular abnormalities to relevant targeted treatments, regardless of tumor histology type
- NCI-MATCH is a signal-finding trial
- Treatments that show promise can advance to larger, more definitive trials

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 Customized Tumor Gene Profiling

- Assay is in use across all labs using same SOPs
  - Was validated prior to implementation, with high rate of concordance
- Utilizes the Thermo Fischer Scientific platform
  - Ion Personal Genome Machine® and Ion Torrent™ Server
  - Ion Ampliseq™ custom DNA panel
- Screens 143 tumor genes and reports actionable mutations of interest (aMOIs)
- Labs perform immunohistochemistry in selected mutations
- Patients with aMOIs matching an available treatment arm are further evaluated for the specific eligibility criteria

Levels of Evidence for Target Selection in NCI-MATCH

- Level 1: Gene variant credentialed for selection of an approved drug
- Level 2a: Variant is eligibility criteria for an ongoing clinical trial for that drug
- Level 2b: Variant identified in an N of one response(s)
- 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 Design Features

- Test many patients to find widely distributed tumor gene abnormalities
- Biopsies needed at time of study entry (cost covered by NCI)
- Response rate (tumor regression) primary efficacy measure
- Across treatment arms, PIs drawn from the National Cancer Institute clinical trials network groups
  - Alliance, ECOG-ACRIN, NRG, and SWOG
- Contribution of expertise is tremendous
  - 150+ experts participating in specialized working groups
  - Advocates involved in trial design and helping to oversee conduct

NCI-MATCH Treatment Eligibility Defined by Molecular Characteristics

- Initial tumor biopsy to identify gene abnormalities
- Patients can be screened with local NGS but results must be confirmed on NCI-MATCH assay
- Patient assignment to relevant treatment arm
- Perform tumor biopsies and sequencing at progression to illuminate resistance mechanisms
  - Submit de-identified samples to central labs
  - Conduct whole-exome, mRNA sequencing
    - For research purposes

Tumor Biopsy in NCI-MATCH

- Upon entry to initial screening, a biopsy (four cores) in formalin, shipped to central lab for processing to FFPE blocks
- H&E sections examined by pathologist for tumor type, tumor content, % necrosis, and inflammation, and scanned into high-resolution image database
- Block selected, slides cut for IHC and nucleic acid extraction; RNA and DNA extracted from the same tissue section(s)

NCI-MATCH Structure

- Master protocol with multiple phase II treatment arms
- IND for protocol template
  - Treatment arms open and close without affecting others
- Single agents or combinations with recommended phase II dosage(s) known
- FDA-approved for a different indication or investigational agents/ combinations
- Central IRB required as the IRB of record
- US-based sites involved with the National Cancer Institute
- CLIA lab network using validated and FDA-passed assays

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

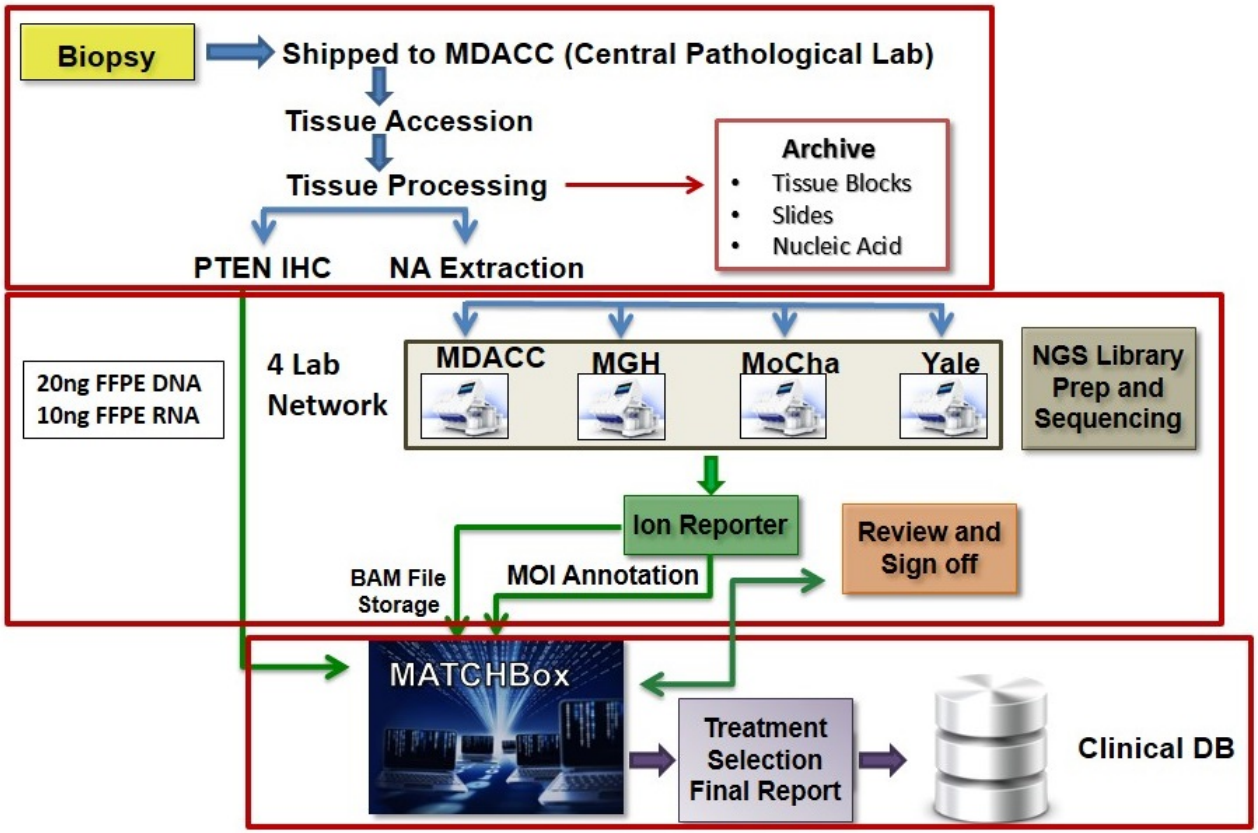
NCI-MATCH Statistical Considerations for Each Treatment Arm

- 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
  - Biomarker
- One-stage design
  - 35 patients per arm (31 evaluable)

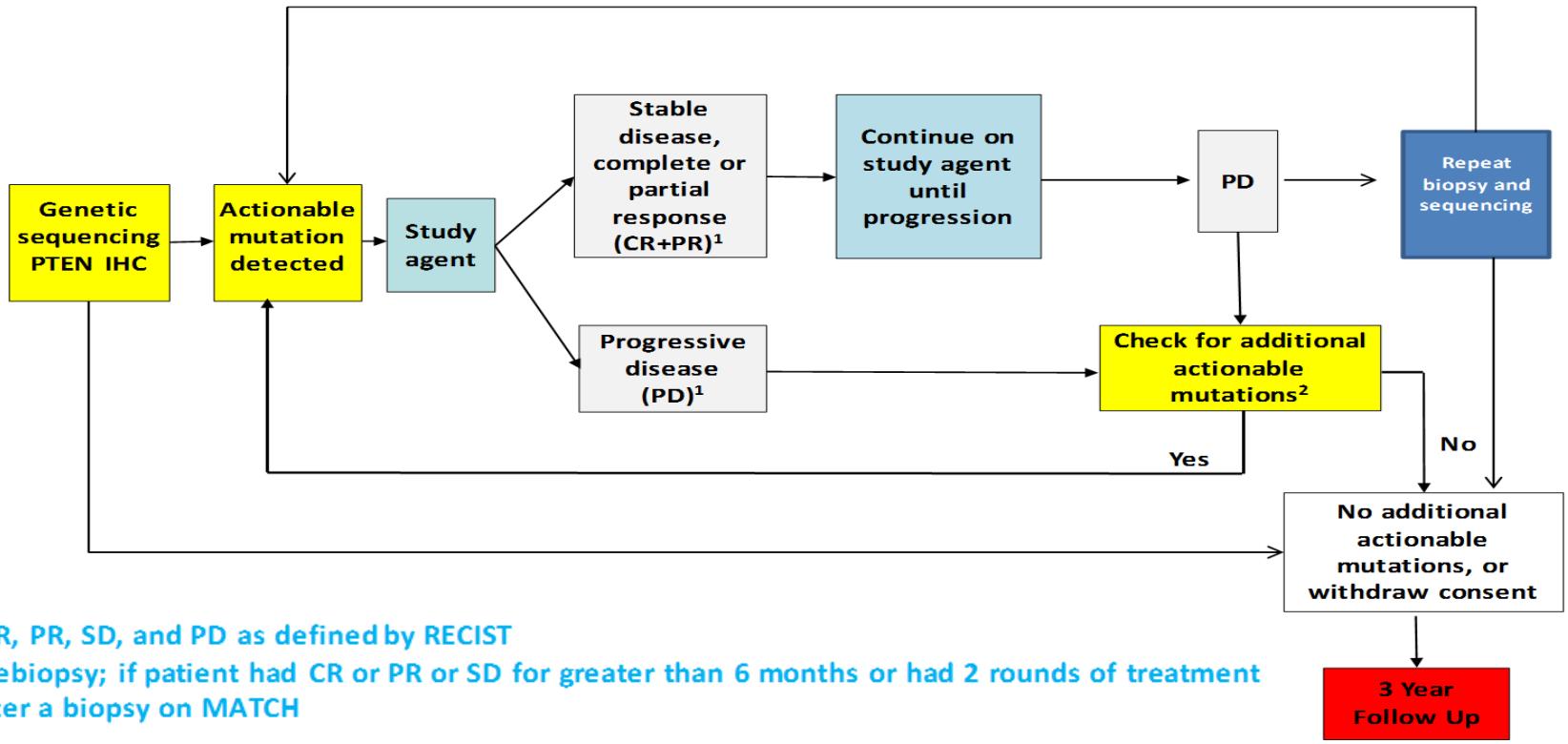
NCI-MATCH Patient Eligibility for Genetic Screening

- Adults ≥ 18 years of age
- Solid tumor or lymphoma whose disease has progressed following at least one line of standard systemic therapy
  - Or with a rare tumor that does not have standard therapy
  - Myeloma eligible if tumor tissue available – those with bone marrow aspirates will be eligible once assay is validated
- ECOG performance status zero or one
- Adequate organ function
- **Physicians are encouraged to select only those patients able to withstand being off treatment up to six weeks**

NCI-MATCH Assay Workflow



NCI-MATCH Schema



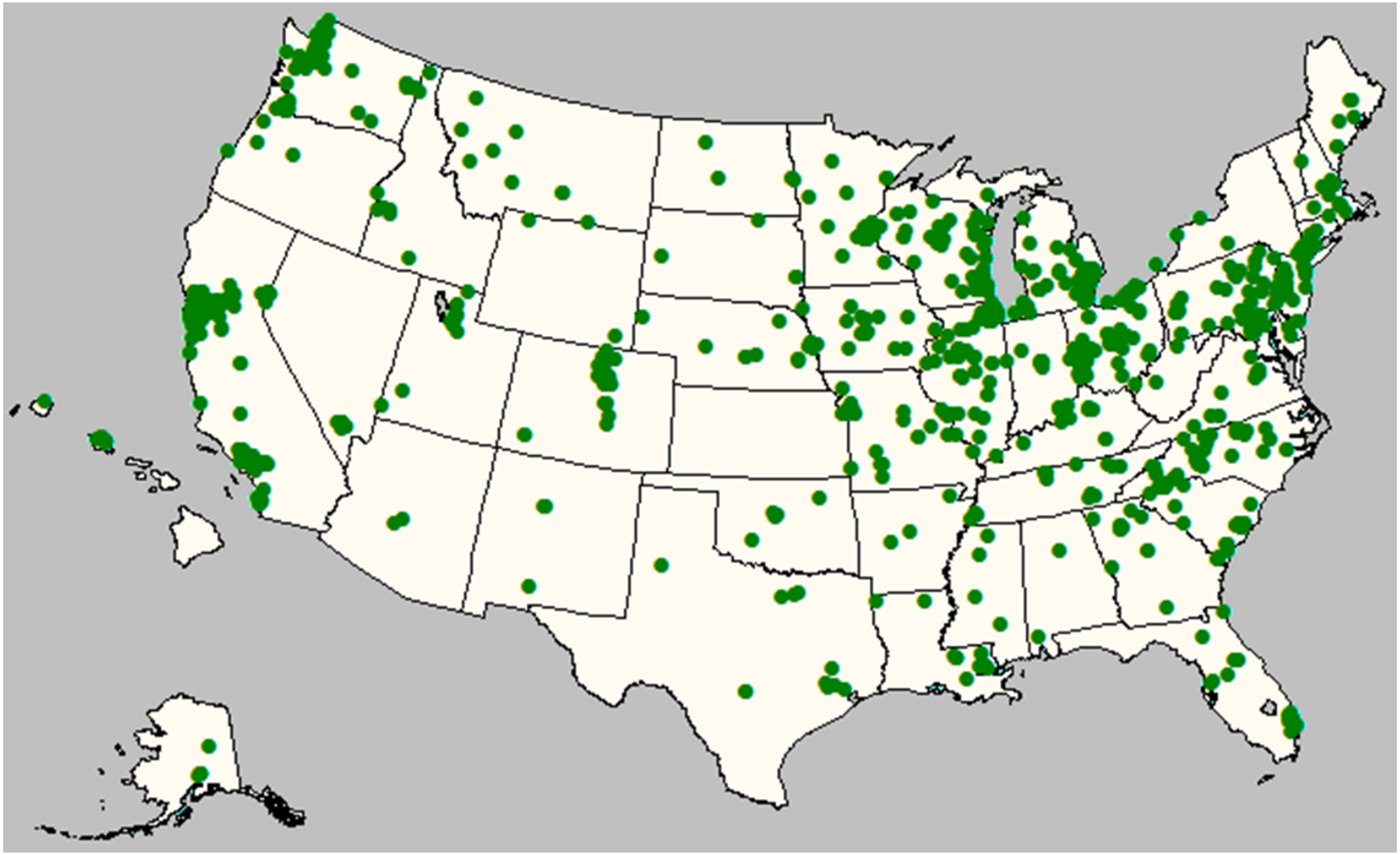
[1]CR, PR, SD, and PD as defined by RECIST

[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

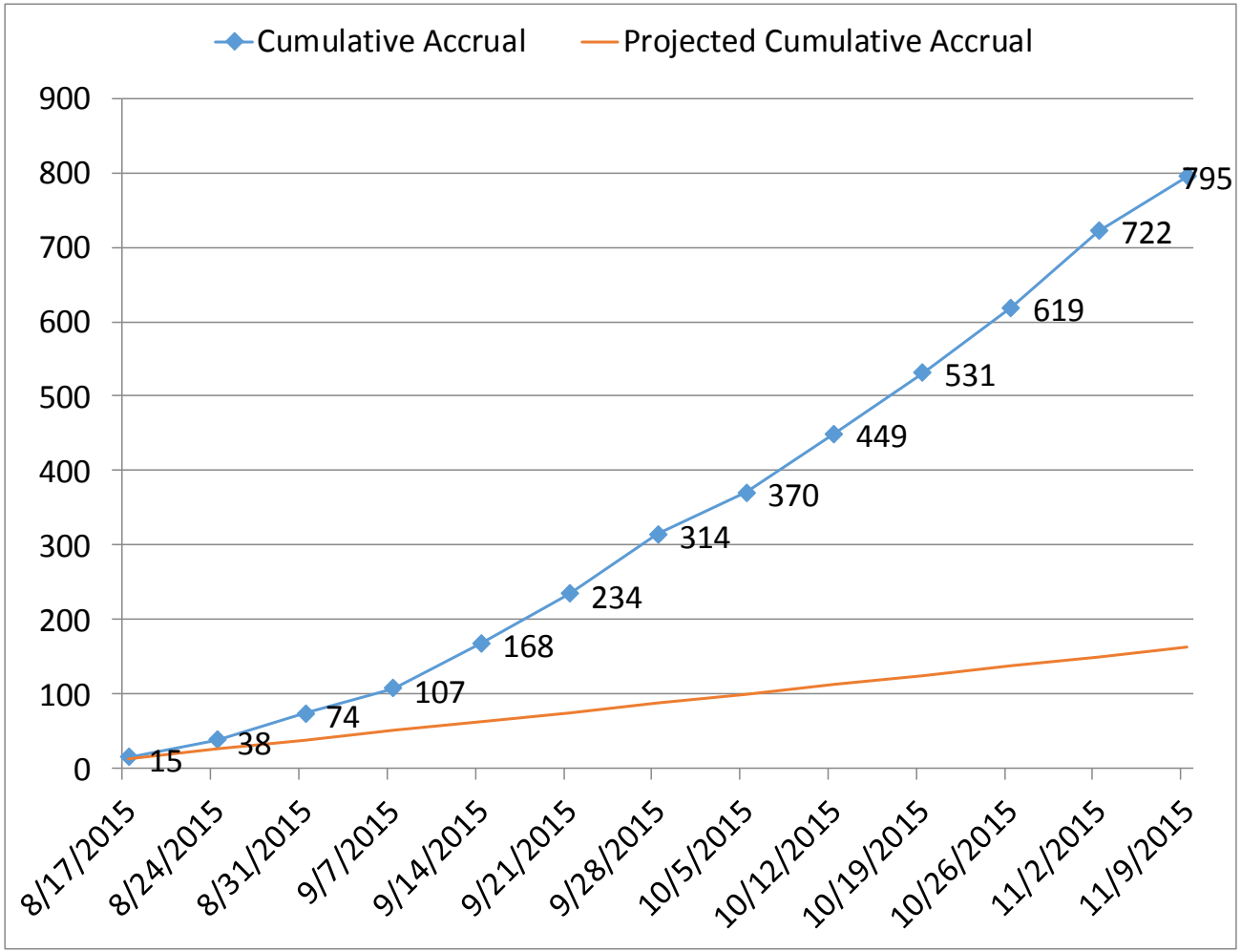
NCI-MATCH Trial Milestones

- Opened trial on August 12, 2015, with 10 treatment arms
- Paused screening of *new* patients on November 11, 2015 for planned interim analysis
- Continued development of treatment arms during pause
- Expanded to 17 arms on February 25, 2016, and re-evaluated patients with matching tumor gene abnormalities
- Resumed registration of *new* patients on May 31, 2016, with 24 treatment arms
- Completed 24 weeks of accrual activity through August 14, 2016

NCI-MATCH Participation from Nearly 1K US Sites



NCI-MATCH Weekly Accrual Far Exceeded Projections



Projected 50 Cases/Month at Start

Gradual Ramp-up in Year 1

NCI-MATCH Primary Disease Sites of Patients Enrolled in First 24 Weeks

Disease Site	Enrolled a/o 08-14-16	% (N=1702)
Colorectal	236	13.8
Breast	222	13.0
Non-Small Cell Lung	127	7.4
Prostate	40	2.3
Common Cancers Subtotal	**625**	**36.5**

Ovarian	178	10.4
Pancreas (Adeno/NOS)	100	5.8
Head and Neck[1]	78	4.5
Endometrial/Uterine (Non-Sarcoma)	68	3.9
Esophageal/GE Junction/Gastric	58	3.4
Neuroendocrine[2]	50	2.9
Cholangio	47	2.7
Bladder/Urinary Tract	40	2.3
Endometrial/Uterine Sarcoma[3]	43	2.5
Small Cell Lung	32	1.8
Other	333	19.5
Primary Site Not Specified	53	3.1
Uncommon Cancers Subtotal	**1,077**	**63.5**

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

	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: Dabrafenib+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

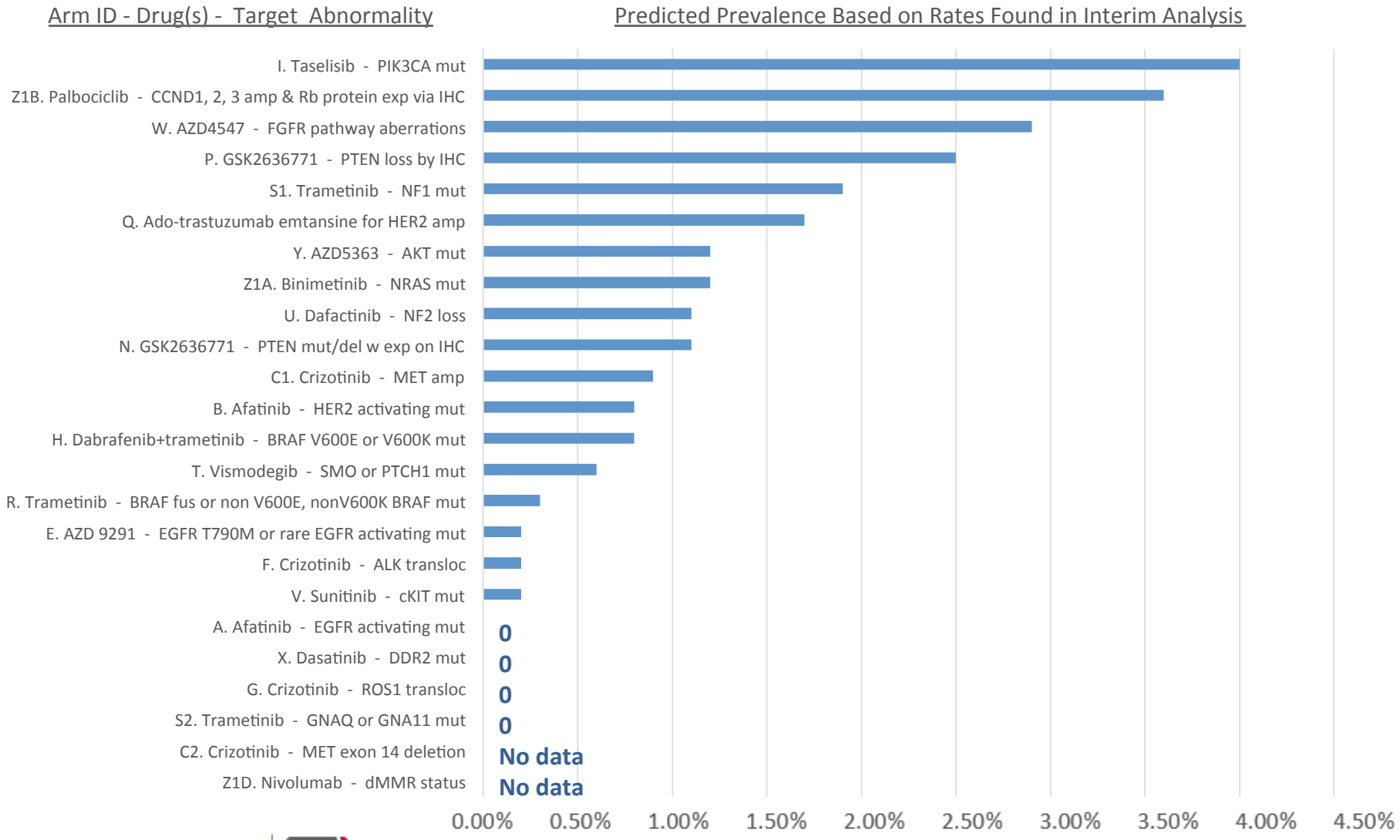
NCI-MATCH Projected Match Rates and Enrollments for 24 Treatment Arms (N=5,000 Screened)

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 24 Treatment Arms



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NCI-MATCH Laboratories Analyzed 87% of Cases

- Rate is well 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 Patient Cases Benefiting from Cytology

- Optional needle aspirate specimens submitted: 179/739 (24%)
- Cytology specimens with tumor present: 173/179 (97%)
- Patient cases where cytology was used for analysis when core was unusable: 19
- Predicted contribution if all patients had cytology exam:
  - 84 more patients (based upon salvage of 86% of 94 cases not able to be analyzed)
  - Complete tumor testing for 729/739 (98.6%)
    - Rather than 645/739 (87%)

NCI-MATCH Wait Times for Patients

Processing Step	Median Business 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	13
Further eligibility evaluation for patients assigned to a treatment arm	14

NCI-MATCH Summary of Accrual in First 24 Weeks

- Current screening goal = 5000 patients (need to screen a large number of patients to identify a small percentage with one of the gene abnormalities being studied)
- Over the first 24 weeks of accrual activity:
  - 1,434 patients registered and received tumor gene testing results
    - 245 had a gene abnormality that matched to an available treatment arm (17%)
    - 170 ultimately enrolled for treatment (70%)
  - 90% tumor gene testing completion rate (1,434 of 1,582 patient cases with samples submitted)

NCI-MATCH Accrual Comparison - Patients Screened for 17 Arms vs 24 Arms

	Weeks 1-13 08/12 - 11/11/2015 17 Treatment Arms	Weeks 14-24 05/31 - 08/14/2016 24 Treatment Arms
# of patients with tumor samples	739	843
% of patients with samples successfully tested by labs	87% (645/739)	94% (789/843)
% of patients assigned to an available treatment arm and meeting its specific eligibility criteria	8% (54/645)	24% (191/789)
From total cases with treatment assignments, % of patients who entered treatment	50% (27/54)	79% (143/191)
From total cases successfully tested, % of patients who entered treatment	4% (27/645)	18% (143/789)

NCI-MATCH Summary Statements

- Rapid pace of accrual continued, with a plateau of about 130 patients per week registering and submitting samples
- Many existing and planned treatment arms target gene abnormalities with prevalence rates lower than the literature indicated; thus, accrual strategies are being developed for arms with rates of 2% or less

Resources for NCI-MATCH

ecog-acrin.org/nci-match-eay131

cancer.gov/nci-match

Spanish: cancer.gov/espanol/nci-match

Thank you for your attention.