Clinical/Translational Update

James H. Doroshow, M.D.
Deputy Director for Clinical and Translational Research
National Cancer Institute, NIH

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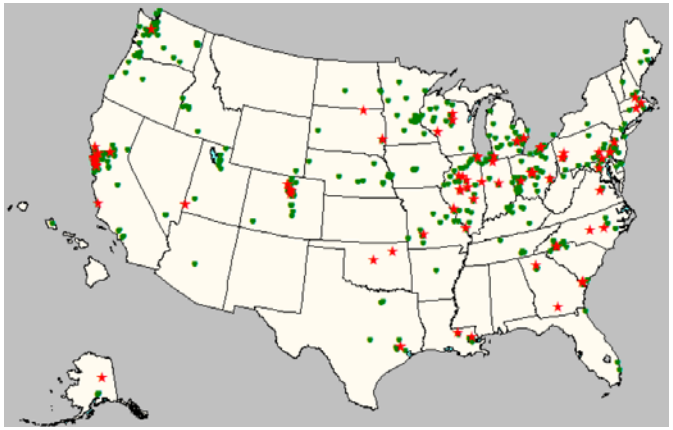
FNLCR Advisory Committee

Topics for Discussion

- Status of First Phase of NCI-MATCH
- Accrual to the Rare Variants Initiative of NCI-MATCH
- Plans for Follow-Up Trials Under the NCI-MATCH Umbrella
  - ✓ Phase II Trials
  - ✓ Additional NCI-MATCH Arms
- Cancer Immune Monitoring and Analysis Centers

Status and History of NCI-MATCH Trial

- **Trial opened August 12, 2015, with 10 treatment arms.**
- **Trial temporarily closed to new accrual November 11, 2015 for built-in interim analysis.**
- **795 patients screened between August 2015 opening and November 2015 temporary closure (3 month period).**
- **Original estimate of 50 screens per month greatly surpassed (>100/week during latter period).**
- **Over 1100 approved sites**
- **Trial re-opened May 31, 2016, with 24 treatment arms.**
- **5/17: Closed to accrual requiring bx's**



Participation Rates by Site Type:
NCORPS ~ 90%
NCI Cancer Centers & LAPS ~ 80%

NCI-MATCH Accrual Status 10/20/17

Time period	# enrolled	# first samples submitted	# first sample fail	# assay complete	# assigned to Rx	# enrolled on Rx
Total Pre Pause	794	739	116	645	54	27
Most Recent Week	0	0	0	1	0	0
Total Post Pause	5603	5223	425	4912	937	660
Overall Total Screening Cohort	**6397**	5962	541	5557	991	**687**
Total Outside Assay	62	29	2	56	51	36

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Current Status

- 30 treatment arms; ≈ 50% fully accrued; ≈ 25% well on the way;
  ≈ 25% will need additional accrual from ‘rare variant study’
- 6 more treatment arms approved for subsequent studies
- Assay success rate 94%
- Median assay turnaround time 16 days
- Toxicity acceptable
- Objective responses have been observed in 3 of the initial arms so far

Analysis Plan

- ORR, TTP, OS , toxicity in patients who received protocol therapy
- If the ORR is ≥ 5/31 (16%) the agent will be worthy of further study: Protocol Defined
- 35 patients will need to be accrued to each arm to obtain 31 for each arm (with 10% ineligibility rate)
- Need ≈8 mos median f/u to assess response

Rare Variant/ Outside Assay Initiative

NCI-MATCH Remaining 15 of 30 Current Treatment Arms, By Prevalence Rate of Gene Abnormality

Arm	Variant	Prevalence Rate %	Drug	Opened	Accrual Goal
Y	AKT	0.77	AZD5363	May ‘16	35
H	BRAF V600 E/K	0.69	Taflinar® Mekinist™	Aug ‘15	35
U	NF2 loss	0.69	Defactinib (VS-6063)	Aug ‘15	35
C2	MET exon 14	0.61	Xalkori®	May ‘16	35
C1	MET amplif.	0.51	Xalkori®	May ‘16	35
T	SMO/PTCH1	0.42	Erivedge®	Feb ‘16	35
L	mTOR	0.31	TAK-228	Mar ‘17	35
S2	GNAQ/GNA11	0.16	Mekinist™	Feb ‘16	35
E	EGFR T790M	0.11	AZD9291	Aug ‘15	35
V	cKIT	0.11	Sutent®	Aug ‘15	35
Z1E	NTRK	0.10	Larotrectinib	Mar ‘17	35
G	ROS1	0.05	Xalkori®	Aug ‘15	35
A	EGFR activating	0.05	Gilotrif®	Aug ‘15	35
F	ALK	0.03	Xalkori®	Aug ‘15	35
X	DDR2	0.00	Sprycel®	Feb ‘16	35

Rationale for Rare Variant/ Outside Assay Initiative

- About 60% of screened patients on NCI-MATCH had less common/rare cancers (not colorectal, breast, NSCLC, prostate)
- Many of these arms have not completed accrual given the low frequency of certain mutations
- Tumor gene variants in less common cancers lower than expected (3.47 percent to 0)
- Need to accrue to these arms if possible
- NCI-MATCH provides treatment options for these patients

NCI-MATCH Collaboration with Commercial Labs

- Caris Life Sciences® and Foundation Medicine, Inc. will notify the treating physician at any one of the ~1100 sites when the results of their assay could make a patient eligible for a MATCH treatment arm
- The labs *do not* specifically screen for the NCI-MATCH trial; it is only when the test is done for the purposes of clinical care.
- The results must be verified centrally by the NCI-MATCH Oncomine ® assay

NCI-MATCH Academic Laboratories

- In addition, we have engaged two academic labs that are already involved in the trial
  - MD Anderson Cancer Center
  - Memorial Sloan Kettering Cancer Center
- These labs will perform testing on their own patients, using their institutional assays
- MD Anderson uses the Oncomine® assay used in NCI-MATCH
- MSKCC uses a screening assay developed at their institution
- Patients will be considered for NCI-MATCH based on these results
- *Request for proposals from other NGS providers posted in Federal Register in July 2017 to broaden patient base for completion of ongoing arms:* **Critical for Future Precision Oncology Studies**

Future of MATCH: Considerations

Responsive Phenotypes

- For patients with the aMOI and evidence of a response (ORR>16% per study definition): Phase II trial for that drug to determine its true activity under NCI-MATCH umbrella

New Treatment Arms

- Activate 6 additional NCI-MATCH Arms (beyond Rare Variant Initiative) that have been approved by Pharma collaborators, and meet appropriate level of evidence, *IF* sufficient referral base of patients established using academic and commercial laboratories

NCI-MATCH New Treatment Arms in Development for Addendum #11 – Possible Fall 2017 Activation

Mutation	Mutation Prevalence Rate in NCI-MATCH	Arm	Drug
PIK3CA	3.47%	Z1F Follows arm I	copanlisib
PTEN loss by IHC	1.93%	Z1G Follows arm P	copanlisib
FGFR amplif.	1.86%	K1 Follows arm W	erdafitinib
PTEN	1.75%	Z1H Follows arm N	copanlisib
FGFR mut. or fusion	1.00%	K2 Follows arm W	erdafitinib
p53 and MYC	unavailable	Z1J	AZ1775

CIMAC:
Cancer Immune Monitoring & Analysis Centers

National Cancer Institute

Cancer Immune Monitoring and Analysis Centers (CIMACs)
Cancer Immunologic Data Commons (CIDC)

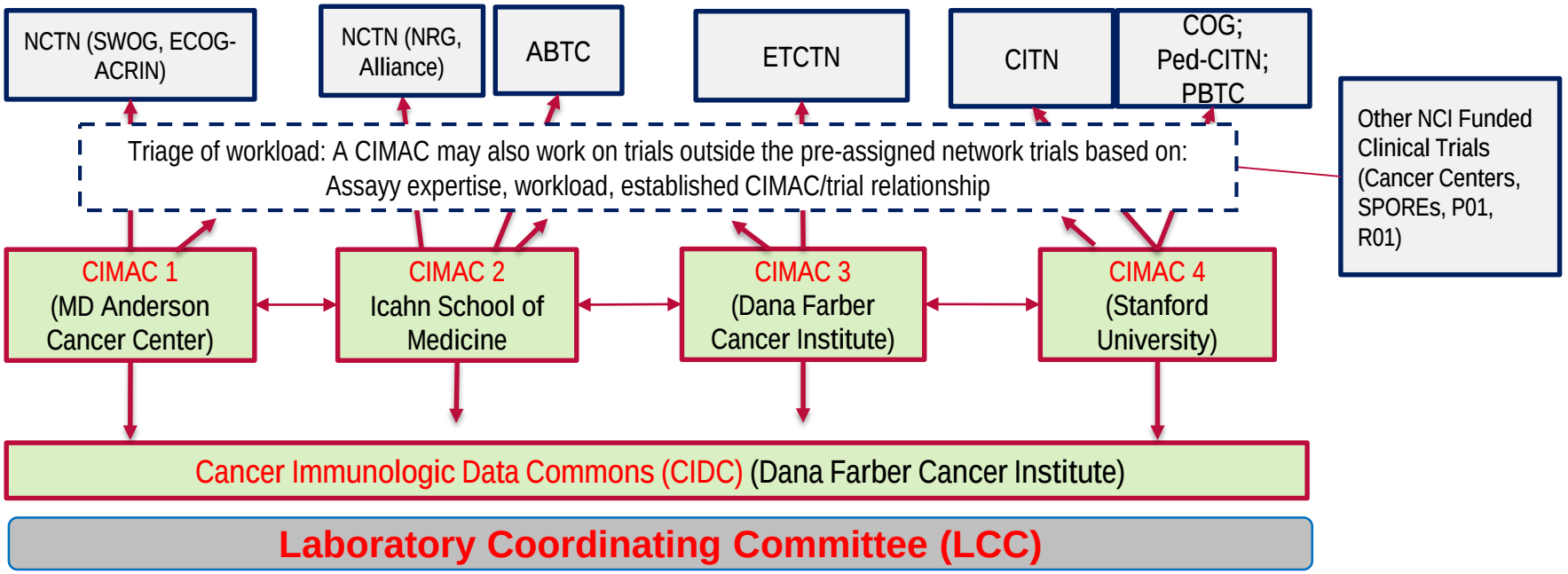
- Why CIMAC-CIDC network
  - To provide a standing, prefunded network of laboratories, along with a common data center, to perform biomarker assays and analysis for NCI-funded, early phase 1/2 clinical trials with immunotherapies, using standardized and state of the art assays
  - Data repository/center for biomarker results from CIMACs will foster a data integration/analysis platform for correlative studies within and across trials

- Funded under cooperative grant mechanisms (U24)
  - Current funding limited to early immunotherapy trials (phase I and phase II) under the NCI clinical trial networks or NCI grants (R01, SPORES, etc)
  - Covers comprehensive profiling for approximately 400 patient–timepoint per year

- Utilization of the CIMAC-CIDC resource is voluntary, but desired studies will require collaboration with CIMAC and approval by CTEP.

- FNLCR PD lab will collaborate with UCSF, Stanford, Mt. Sinai, MD Anderson, DFCI for assay development

Proposed CIMACs-CIDC Network Structure (Tentative)



- Each CIMAC is a multidisciplinary team (bioassays, statisticians, informatician, translational scientists, pathologists)
- Will be aligned with Clinical Trial Networks and Clinical trials – Collaboration in scientific planning, tissue accession, data analysis, and publication
- Triage of the work will be based on: Assay expertise; Overall workload; Established relationship with specific trials
- A given CIMAC may perform a specific assay for all CIMACs, depending on resource prioritization and expertise