Frederick National Laboratory for Cancer Research

Clinical Laboratory Support of NCI's Precision Medicine Trials

Chris Karlovich, PhD

Director of the Molecular Characterization Lab,
Frederick National Laboratory for Cancer Research (FNLCR)

March 13, 2024

MOCHA

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Overview of MDNet at FNLCR

- **MDNet Goals: Building upon NCI-MATCH/PedsMATCH experience, establish an assay network for support of NCI's Precision Medicine Trials Initiative**
  - iMATCH
  - ComboMATCH
  - MyeloMATCH
- **Utilizing:**
  - Designated Laboratory Network for standard-of-care assays (ComboMATCH)
  - Sub-contracts with external laboratories OR FNLCR laboratories for new and novel assays

MDNet Trials: Developing a biomarker plan that includes assays and their intended use

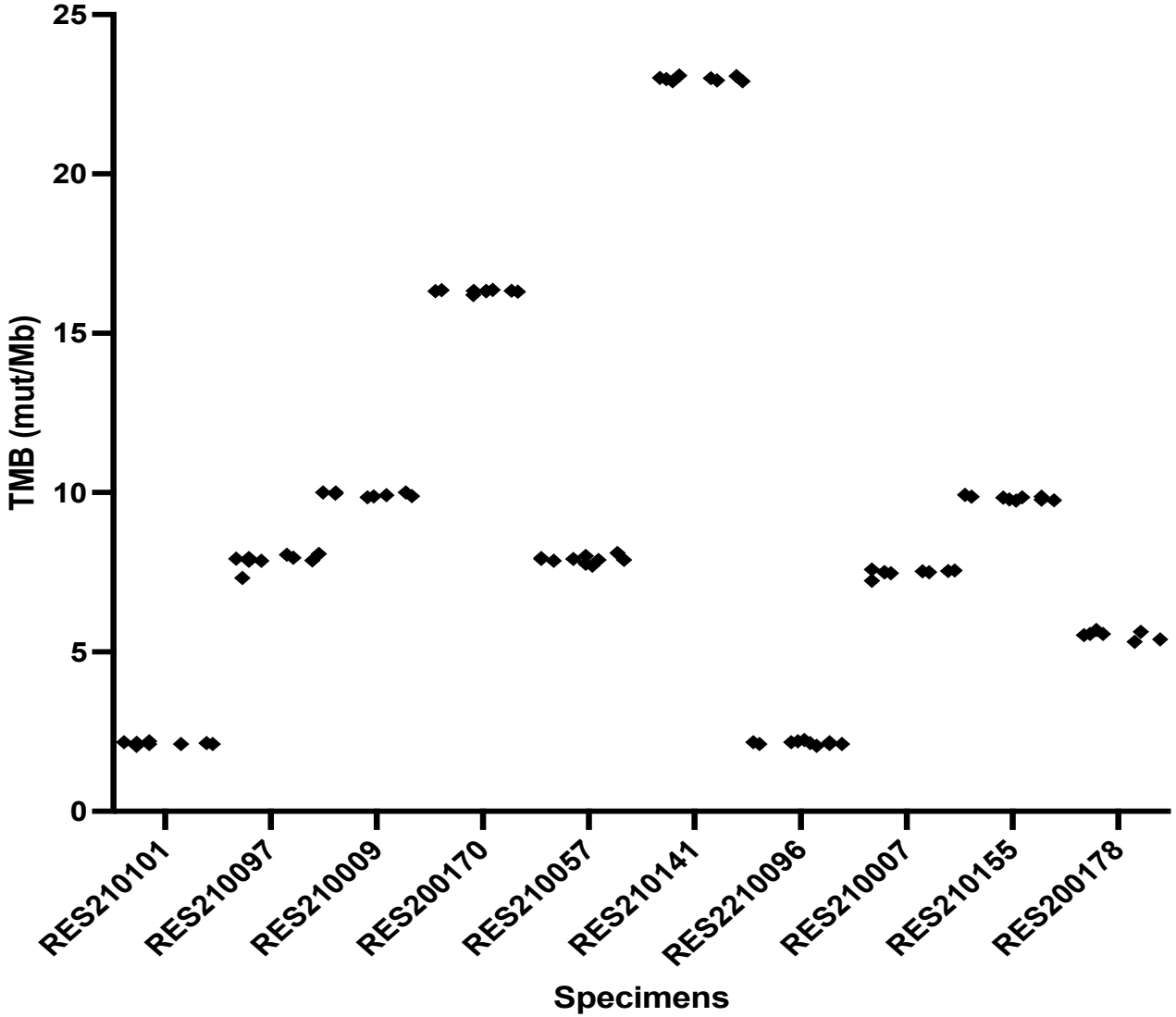
- **FNLCR staff work with NCI and trial investigators to develop a biomarker plan**
  - Central to the biomarker plan is assay intended use
    - Integral assays are performed in a CLIA lab to select or stratify patients for an NCI trial
    - Integrated assays are for Research Use Only, but still require validation and locked protocols
  - Specific biomarkers and their thresholds are defined
  - Specimen pre-analytics are defined
    - Method of collection, shipment, central pre-analytic lab versus assay lab processing, specimen processing requirements
  - Required turn-around time for results is discussed (e.g., 72 hours for MyeloMATCH)

iMATCH Assay Support

Assay	Assay Type	Laboratory	Biomarker
cWES	(1) Integral (2) Exploratory	MoCha MD Anderson	(1) Tumor Mutational Burden (TMB) (2) Mutations and complex biomarkers other than TMB (e.g., LOH, MSI)
IO360 Gene Expression Panel	(1) Integral (2) Exploratory	Almac	(1) Tumor Inflammation Score (TIS) (2) >40 Gene expression signatures from tumor and immune pathways
CD8 and PD-L1 IHC	Integrated	MD Anderson	Immune-related protein biomarkers
RNA-seq	Integrated	MoCha MD Anderson	Gene expression signatures and clinically relevant fusions
ctDNA NGS	Integrated	MoCha MD Anderson	Somatic mutation profile, correlation of ctDNA to treatment response

Precision of cWES TMB

- **Precision of TMB values across the reportable range of 5-20 mut/Mb is high (% CV <2.87)**



ComboMATCH Assay Support

Assays	Assay Type	Laboratory	Biomarker
Next Generation Sequencing	Integral	Designated Lab (DL) Network: 38 commercial and academic laboratories	Eligible actionable mutations from all treatment arms
WES	Integrated	MoCha MD Anderson	Clinically relevant mutations and complex biomarkers (e.g., LOH, MSI, TMB)
RNAseq	Integrated	MoCha MD Anderson	Gene expression signatures and clinically relevant fusions
ctDNA NGS	Integrated	MoCha MD Anderson	Somatic mutation profile, correlation of ctDNA to treatment response

Finding the Laboratories - ComboMATCH Designated Lab (DL) Network

- Finding and qualifying DL applicants
  - RFI posted in Federal Register to add labs to the DL Network
  - Assays vetted for acceptable analytical performance
  - Assay analytical validation report reviewed, and cross lab comparability studies performed
    - If approved, NCI signs a research contract for assay support
- Ongoing monitoring of DLs during the ComboMATCH trial
  - Assay performance monitored by periodic proficiency testing or comparability studies
  - CAPAs related to the trial are documented (with appropriate follow up)
  - Any major assay changes are vetted for acceptable performance
- A recent Federal Register notice will add new labs with ≥30% underserved pt population
- We are working with FDA to incorporate ctDNA tests into the DL Network

MyeloMATCH Assay Support

Assay	Assay Type	Laboratory	Biomarker
Cytogenetics/FISH*	Integral	Fred Hutchinson Cancer Center	Translocations for ELN Risk
MyeloMATCH NGS*	Integral	MoCha Fred Hutchinson Cancer Center	Somatic mutations for ELN Risk and treatment selection
FLOW*	Integral	Children's Hospital Los Angeles	Disease stratification and MRD
Duplex Sequencing (NGS)	Initially integrated; may become integral	TwinStrand MoCha	Initially research comparison to FLOW, if adequate performance is observed will be moved into MRD and treatment selection

*Integral assays require 72-hour turnaround time at diagnosis

IND and IDE Discussions with FDA

- **Assay details are included in the trial IND**
- **MoCha attends discussions with CDRH when needed to address assay-related questions**
- **Risk determination is agreed upon**
  - ComboMATCH DL Network required an abbreviated IDE; assays deemed a non-significant risk
  - MyeloMATCH assays required a full IDE; assays deemed a significant risk
- **We partner with NCI during the trial for lab monitoring and audits**

Finding the Laboratories - Highly Subjective or New & Novel Assays

- **Highly subjective assays include non-standardized LDT IHC assays**
- **New and novel examples include: 72-hour turnaround MyeloMATCH NGS, Myeloid Duplex Sequencing assay for MRD**
- **Depending on expertise and status of the technology, RFPs are opened to all applicants or focused on a few with unique expertise (TwinStrand: dsMyeloid NGS)**
- **The MoCha lab develops novel assays via CRADAs**
  - TSO 500 ctDNA (Illumina)
  - MyeloMATCH NGS (Thermo Fisher Scientific)
- **MoCha staff write the technical statements of work, evaluate the RFPs, monitor sub-contract performance, approve invoicing, participate in lab audits, monitor chain of custody and CAPAs, and work with NCI to collect and upload data to public databases**

Summary

- **We have established networks of laboratories to provide genomic assays in support of MDNet precision medicine initiatives**
- **The focus remains on providing accurate, “fit for the intended use” and well-documented assays, such that data is reproducible and available in the public domain**

Acknowledgements to MANY!!

- **NCI (Dr. Lyndsay Harris, Dr. Rich Little, Dr. Helen Chen, CTEP Regulatory and Dr. Jim Doroshow)**
- **Ralph Parchment, Christie Young and other collaborators at FNLCR**
- **Our many subcontractors and other external collaborators**
- **MoCha staff**
  - P. Mickey Williams PhD, former MoCha Director and current FNLCR Emeritus Researcher
  - Lily Chen PhD, BioInformatic/Computational Biology
  - Bishu Das PhD, Associate Director
  - DJ Jiwani MD PhD, CLIA Lab Director/Histology
  - Corrine Camalier
  - Andi Zak

- **OPEN TO COMMENTS AND QUESTIONS AT THE END OF PRESENTATION**

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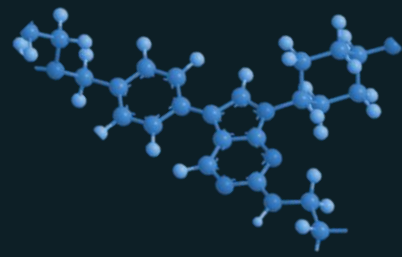
ComboMATCH

Funda Meric-Bernstam M.D.
James Ford M.D.
Lyndsay Harris, M.D.
Meg Mooney M.D.



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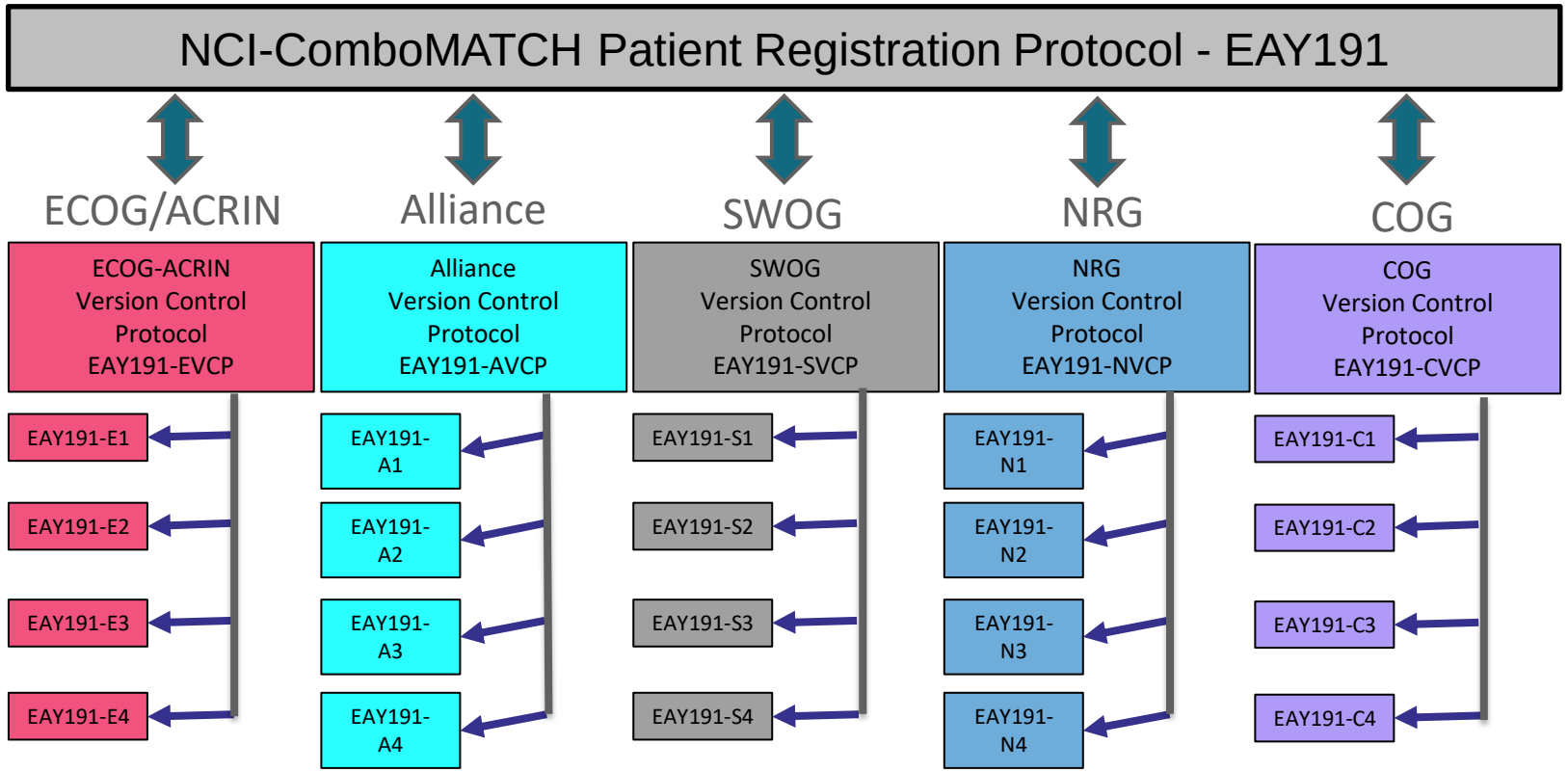
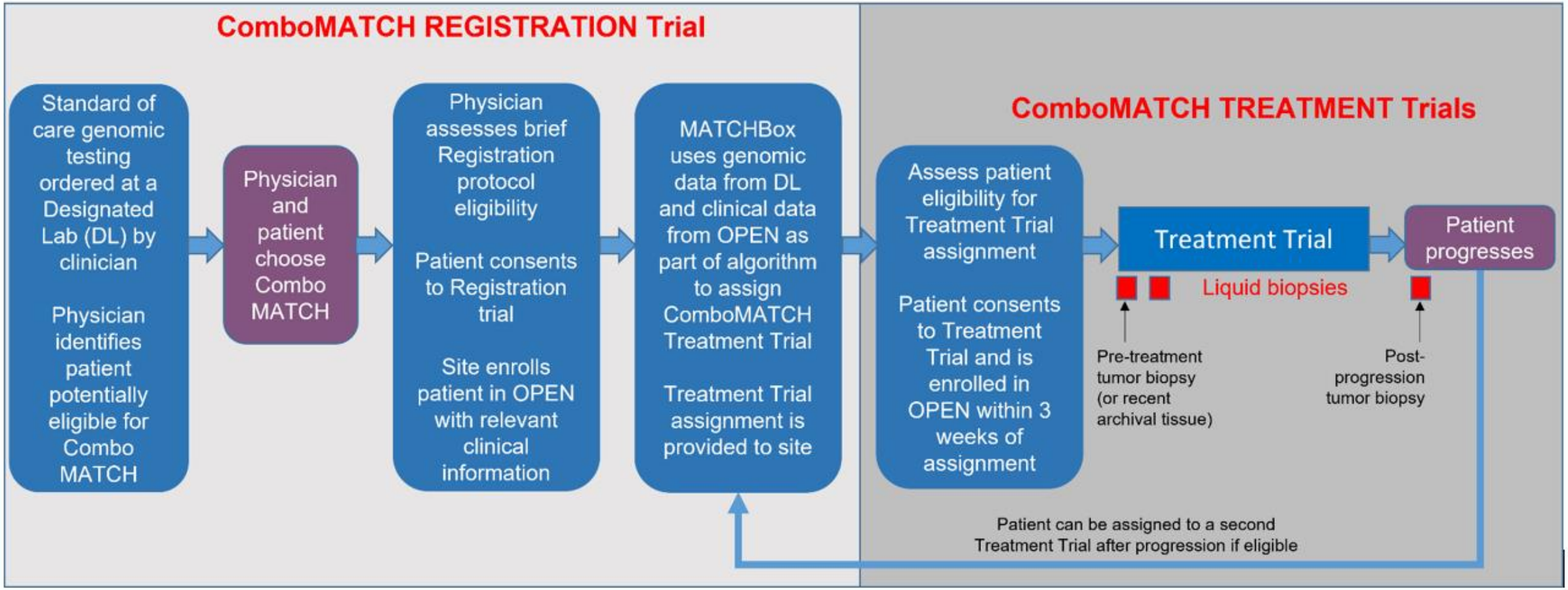
ComboMATCH

- **Premise:** Drug combinations are more likely to provide clinical benefit than single agents in most situations, so the successor trial to NCI-MATCH focuses on therapeutic combinations
- **Hypothesis:** Pre-clinical data from *in vivo* models of combinations demonstrating drug synergy and prolonged tumor regressions can predict clinical benefit in defined patient groups
- **ComboMATCH** will use both single arm studies and Phase II randomized trials in both histology-agnostic and -specific patient cohorts
- **Umbrella** screening study led by ECOG-ACRIN
- **Extramural co-leads**: Funda Meric-Bernstam, Jim Ford; **NCI co-leads**: Lyndsay Harris, Jeff Moscow
- **Requires**: Initial ComboMATCHbox algorithms for interpreting commercial NGS testing for eligibility **(Designated Lab Network)**; subsequent ctDNA assessments before, during and after treatment **(MDNet)**

ComboMATCH Protocol Organization

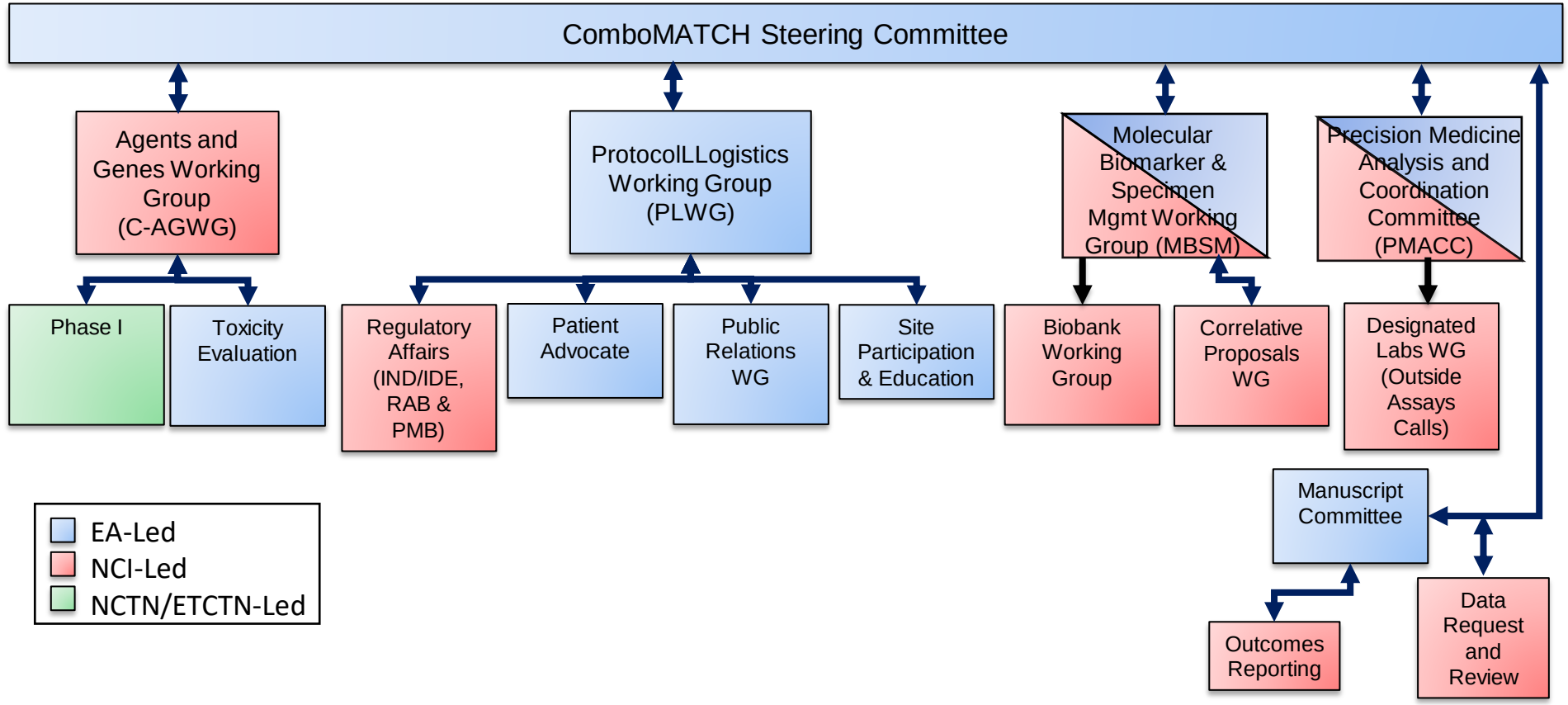


ComboMATCH Steps for Patients

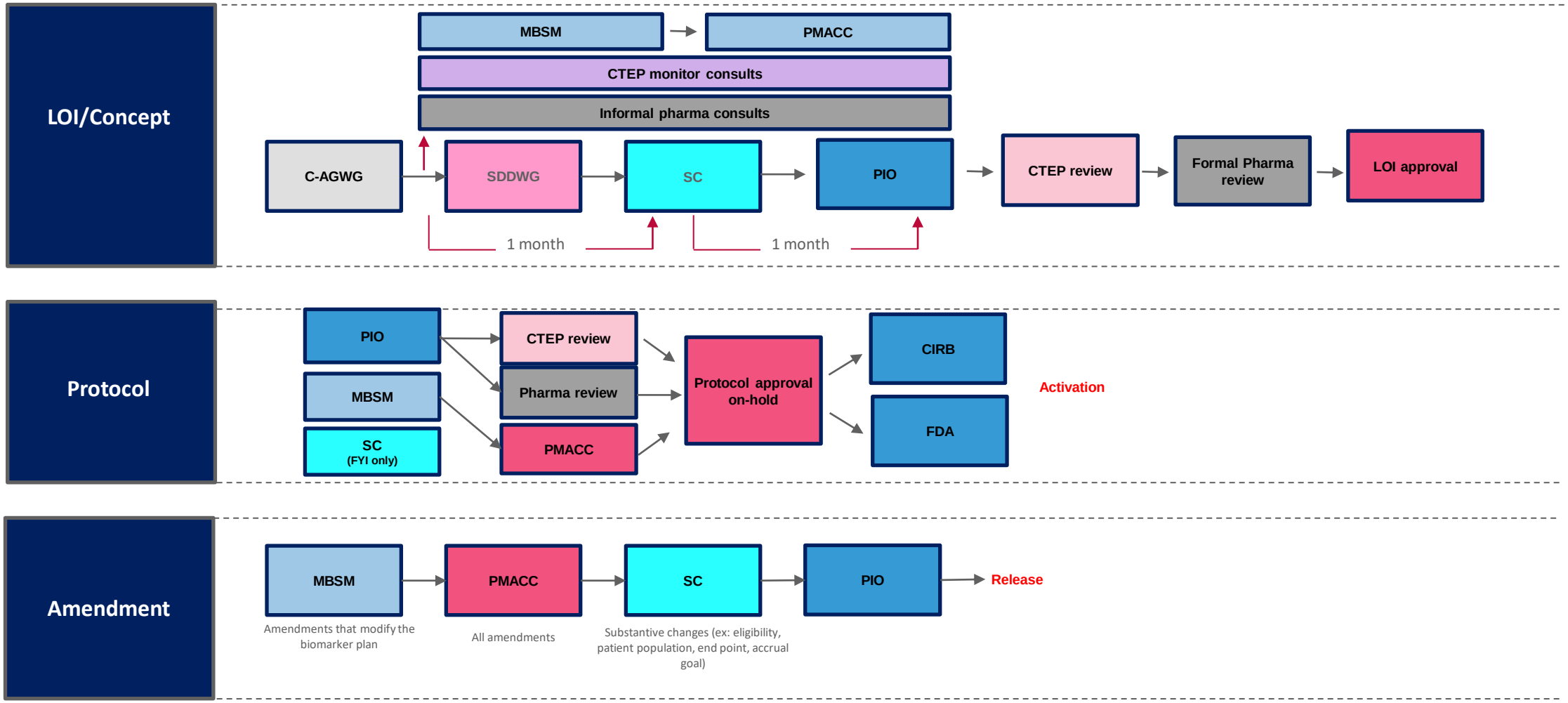


Meric-Bernstam, *CCR*, 2023

ComboMATCH Committee Structure



ComboMATCH Protocol Review



C-AGWG: ComboMATCH Agents and Genes Working Group
SDDWG: Sub-Protocol Design Development Working Group (SDDWG)
SC: Steering Committee
MBSM: Molecular Biomarker and Specimen Management Committee
PMACC: Precision Medicine Analysis and Coordination Committee

Overview of Variants and Diseases per Substudy

Protocol	Drug Combination	Inclusionary Variants	Inclusionary Variant Type(s)	Exclusionary Variants	Disease Inclusions
EAY191-E4	**Nilotinib & Paclitaxel**	None * This sub-study is interested in participants who have had previous taxane therapy	•SNVs •Inframe: INS, DEL, INDEL	Specific cKIT variants and PDGFRA variants	Solid Tumors (Excludes: Platinum-resistant epithelial serous ovarian cancer)
EAY191-E5	**Sotorasib & Panitumumab**	KRAS G12C	•KRAS G12C	N/A	Solid Tumors
EAY191-N2	**Binimetinib & Fulvestrant**	NF1 disrupting mutations	Variant categories: Nonsense or Frameshifts	None	HR+ and HER2 negative metastatic breast cancer
EAY191-N4	**Olaparib & Selumetinib**	Activating mutations in: KRAS, NRAS, HRAS, BRAF, MEK1, MEK2 Inactivating Mutations in: NF1	•SNVs •Inframe: INS, DEL, INDEL	None	Ovarian or Endometrial Cancers
EAY191-S3	**Ipatasertib & Paclitaxel**	AKT1, AKT2, or AKT3	•SNVs •Inframe: INS, DEL, INDEL	KRAS, NRAS, HRAS, or BRAF	Non-breast solid tumors
EAY191-A6	**Binimetinib & FOLFOX**	RAS/RAF/MEK/ERK pathway mutations	•SNVs •Inframe: INS, DEL, INDEL	BRAF V600E	Biliary Tract cancers (Intrahepatic cholangiocarcinoma, Extrahepatic cholangiocarcinoma, Gallbladder)
EAY191-A3	**Palbociclib & Binimetinib**	KRAS, NRAS, HRAS, or BRAF activating mutations	•SNVs •Inframe: INS, DEL, INDEL	N/A	People who have histologically confirmed cancer – cohorts have LGSOC, pancreatic cancer, and other solid tumors
EAY191-N5	**Palbociclib & Neratinib**	HER2	•Copy number amplification	RB1 copy number loss or deletion, HER2 copy number loss or	HER2 amplified solid tumors by NGS (Excludes Breast Cancer)

Designated Laboratory Network

- Screening for ComboMATCH
- Vetted network of academic and commercial CLIA labs performing NGS as part of standard of care
- Whole exome and targeted panel DNA sequencing will detect snvs, indels, CNVs and fusions
- Variants that match listed on CLIA report
- Physician can directly refer based on CLIA report

Designated Commercial Labs

- BostonGene
- Caris Life Sciences
- CellNetix
- Exact Sciences
- Foundation Medicine
- Genomic Testing Cooperative
- GenPath Diagnostics
- Neogenomics Labs
- Quest Diagnostics
- siParadigm Diagnostic Informatics
- Tempus
- The Jackson Laboratory
- Myriad Genetics

Designated Academic Labs

- Cedars-Sinai
- Children’s Hospital of Philadelphia
- City of Hope
- Columbia
- Johns Hopkins
- Knight/Oregon HSU
- Memorial Sloan-Kettering
- Molecular Characterization Lab at Frederick National Lab
- NCI
- Providence
- Stanford
- Texas Children’s Hospital
- UT MD Anderson Cancer Center
- U California San Francisco
- U Chicago
- U Colorado
- U Illinois Chicago
- U Michigan
- U Washington
- Weill Cornell

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CTAC Meeting
March 13, 2024

Immunotherapy "MATCH" - iMATCH

- A Platform for Immunotherapy Trials with Prospective Molecular Characterizations

Helen Chen, M.D.
Larissa Korde, M.D.
Magdalena Thurin, Ph.D.
On behalf of the iMATCH team (NCI, MDNet, SWOG)

Aiming for precision immunotherapy (IO) – *A step-wise approach (1)*

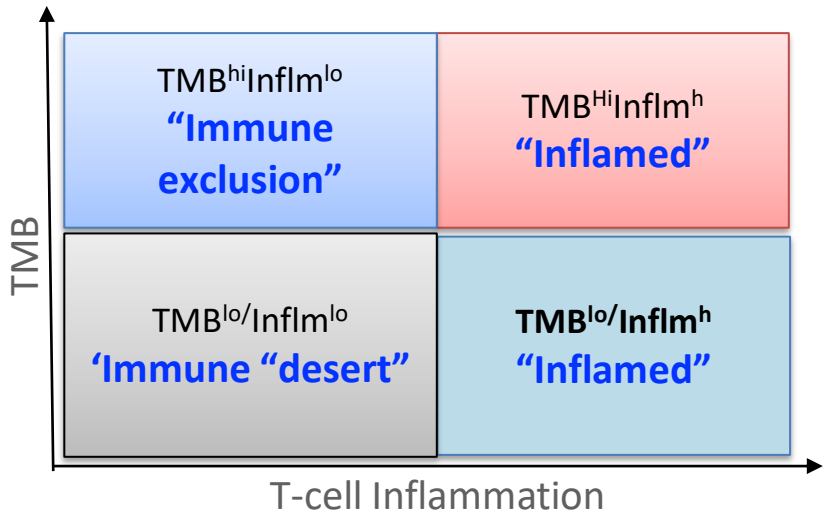
Challenge: A main challenge in IO development is the complexity of biology and lack of predictive markers for combination strategies.

- Signal seeking trials in **"all comer"** are often difficult to interpret, with potential "target" subsets too small for meaningful analysis

Hypothesis: Currently available **clinical grade markers may be used <u>prospectively</u>** to **stratify or enrich immune-based subgroups** with relevant biology for the regimens under study

Markers available in CLIA labs

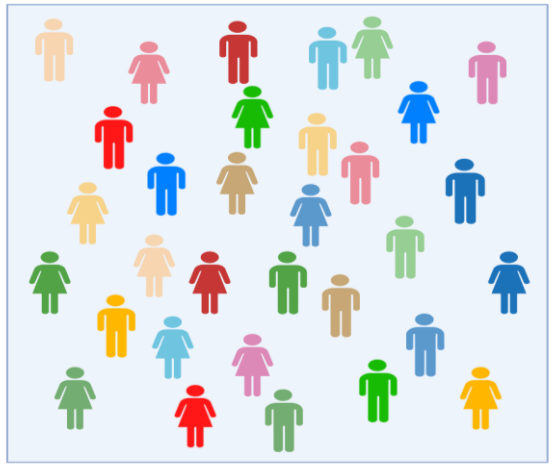
- **Tumor mutation burden** (TMB)
- **T-cell Inflammation markers**
  - TIS-Tumor Inflammation Signature;
  - CD8



Aiming for Precision Immunotherapy
– a step-wise approach (2)

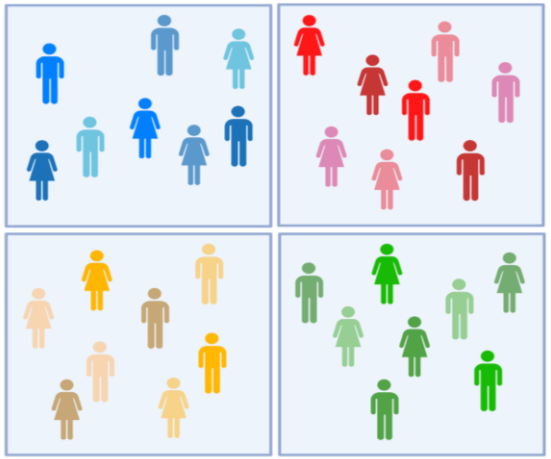
Current

Most IO combination trials in all comers



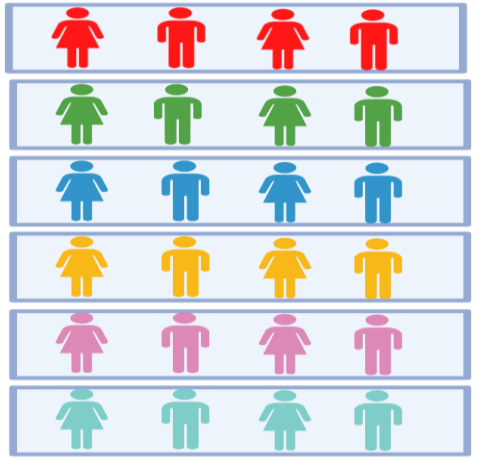
iMATCH Initiative

Prospective testing for immune-based enrichment/stratification



Future

True precision biomarkers for individual therapies



The iMATCH Concept

- **iMATCH aims to enhance clinical evaluation of novel IO agents and combinations, by providing a central assay platform for both prospective and retrospective molecular characterizations**
- **The integral markers will be used to define "immune-based subgroups"** (based on TMB, inflammation markers, and "actionable" variants)
- **Comprehensive retrospective analysis will be performed to optimize classifiers, enhance biological understanding, and explore predictive markers**
- **iMATCH will be a cross-NCTN effort. Independent therapeutic protocols can be developed under the central assay protocol, with a focus on signal seeking trials**

Selection of integral markers and assays

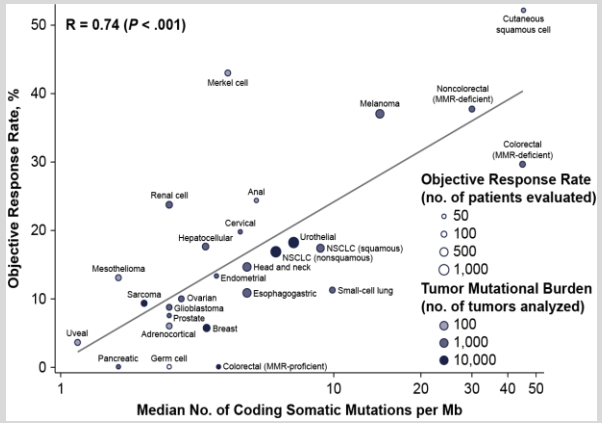
Tumor Mutation Burden

- **WES-based TMB** will be used - reference standard for TMB assays; validated at MoCha CLIA lab
  - Cut point of 10 mut/Mb, was selected for ”biological” stratification in iMATCH pilot

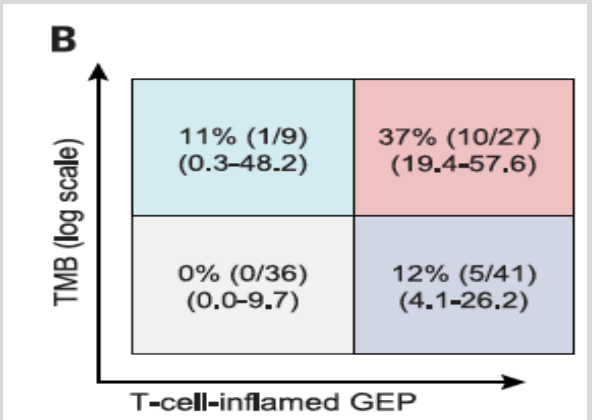
T-cell Inflammation markers

- **Tumor Inflammation Signature (TIS),** based on NanoString IO360**,** was selected for iMATCH pilot
  - Robust assay, with scores (combined with TMB) tested for correlation with response to anti-PD-1
  - Correlated closely with CD8 and an RNA-based signature
- **CD8 IHC and RNAseq** based markers are potential alternatives

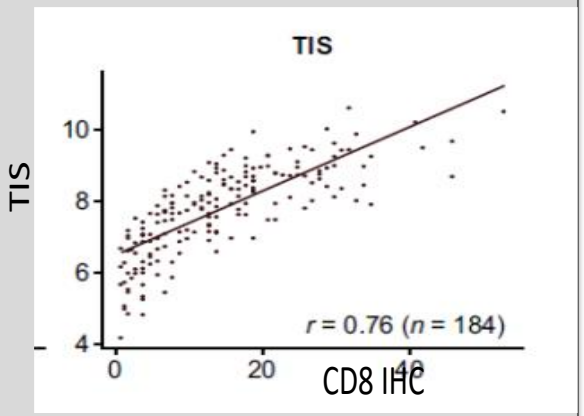
TMB by tumor types and Response to anti-PD1/L1



ORR to Anti-PD1 by TMB/TIS



TIS vs. CD8 IHC



Selected citations:
Yarchoan et al. *NEJM*, 2017
Cristescu et al, Science 2018
Ott et al, JCO 2019
Szabo et al, J Mol Diagnostic, 2022

The iMATCH Platform

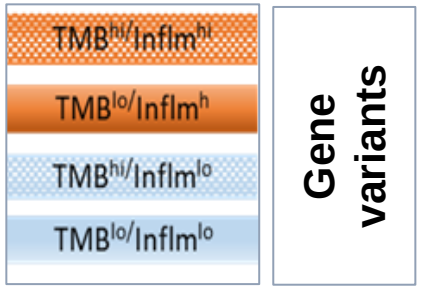
Recent biopsy or new biopsy

iMATCH Central Testing Platform
(Upfront assays **WES** AND **IO 360)**

Retrospective studies
- Integrated:
  - Deeper WES and IO360 analysis
  - RNASeq, PD-L1, CD8 IHC
  - ctDNA;
- Exploratory: mIF and others

Integral markers
- TMB
- TIS
- Actionable variants

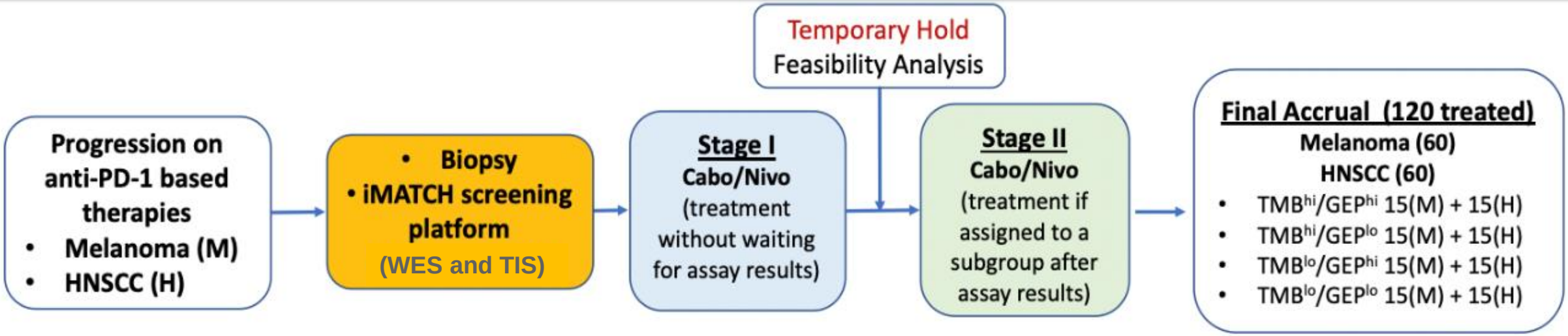
Therapeutic protocols
(Integral markers will define subgroups for enrichment or stratification)



- Cutoffs will be pre-defined based on best available data, but may be adjusted after interim data analysis
- A given regimen may be tested in all or some subgroups, but each can be enrolled for a pre-defined sample size

iMATCH Pilot Trial:

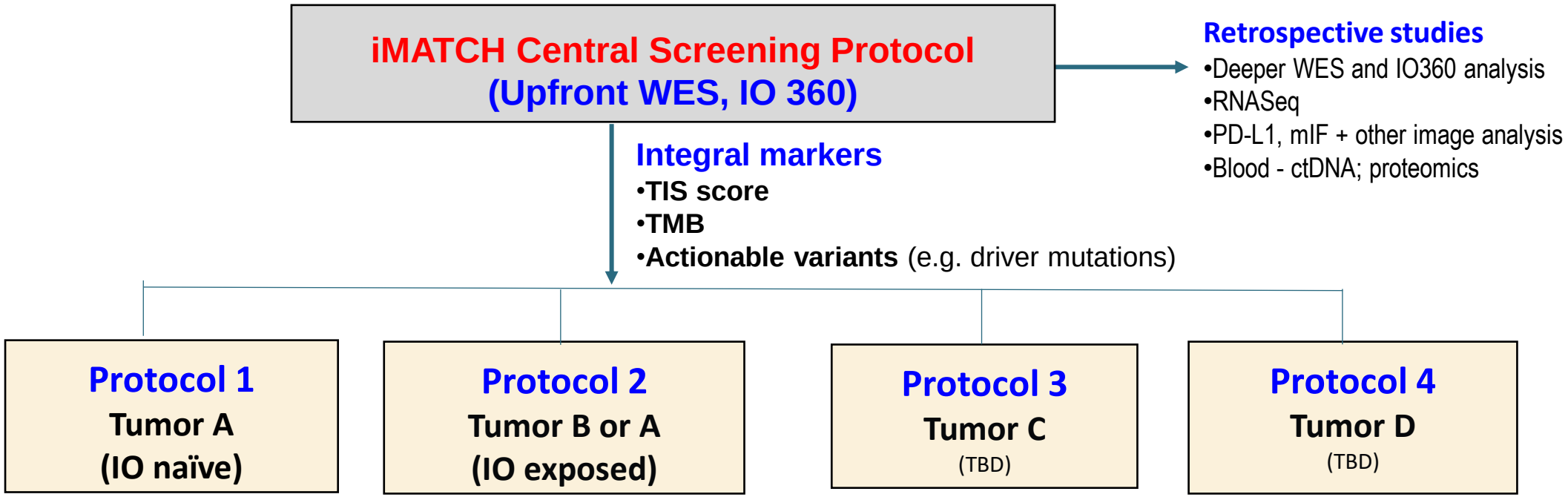
SWOG 2101: BiCaZO – (Biomarker Stratified CaboZantinib and NivOlumab in pts with CPI-refractory melanoma or HNSCC)



- **Primary Goals -**
  - Feasibility (Turnaround time for both TMB and TIS)
  - Preliminary efficacy data in subgroups
- **Design**
  - **Stage I** – All patients will have upfront testing, but can be treated before test results
  - **Stage II** – Patients will be selected to fill subgroups with pre-defined sample size
  - **Interim analysis**
    - Ensure feasible turnaround time for upfront testing
    - Inform potential need for cutoff adjustment

Status: Active, Ongoing

Potential Therapeutic Trials



- Each protocol will be standalone using the central molecular testing protocol
- Each protocol will focus on a specified clinical setting (single or limited histology, IO-naïve or exposed)
- Each protocol may use some or all of the integral markers to define subgroups, for enrichment and/or stratification as appropriate for the disease setting and agents in question
- A variety of regimens may be tested to address resistance mechanisms in different immune status (e.g. T-cell inflamed; immune-excluded; immune-desert)

iMATCH Summary

- **iMATCH will provide a central assay protocol for <u>prospective</u> patient enrichment or stratification, and <u>retrospective</u> biomarker optimization and discovery**
  - Comprehensive assay platforms and rapid turnaround time
  - Flexibility to incorporate new markers or combination of markers

- **The goal of iMATCH is to enhance clinical evaluation of novel IO agents and combinations**
  - ➢ Allow enrichment of potentially relevant subgroups for signal seeking trials
  - ➢ Enhance retrospective analysis to timely inform study design adaptations in same or subsequent trials
  - ➢ Facilitate development of clinically actionable markers for regimens beyond anti-PD-1

- **The pilot trial will assess feasibility of the platform and optimize selection of assays**

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MyeloMATCH

Myeloid Malignancies Molecular Analysis for Therapy Choice

NCI National Clinical Trials Network

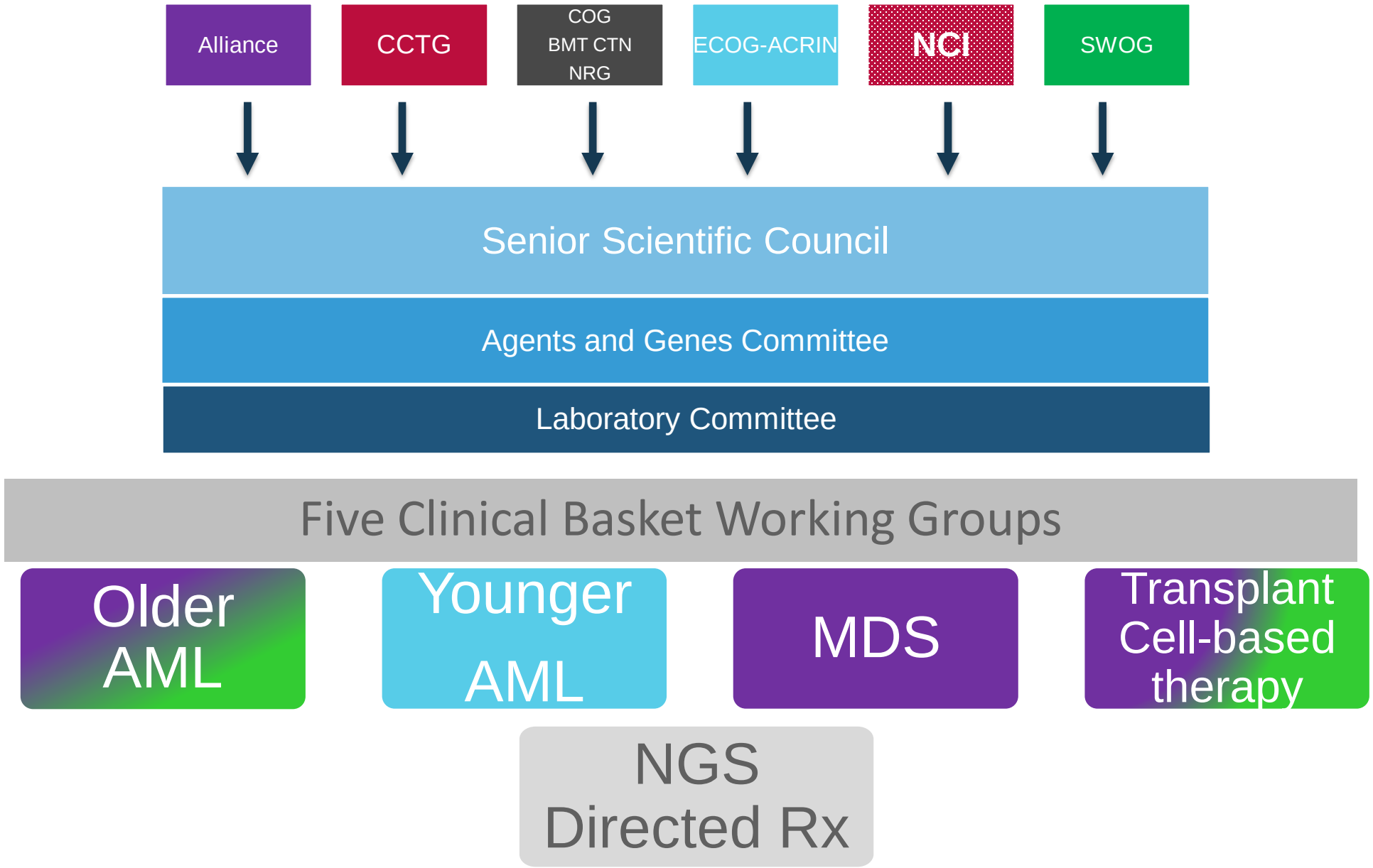
MyeloMATCH AIMS

- To create a portfolio of rationally designed treatment substudies onto which patients sequentially enroll over their entire treatment journey until progression or death. As increasingly lower remaining tumor burden is achieved, the focus will be to target residual disease more effectively.

- Create an efficient operational model attractive to industry partners and NCTN sites to accelerate therapeutic advances for myeloid malignancies.
  - One IND
  - One IDE

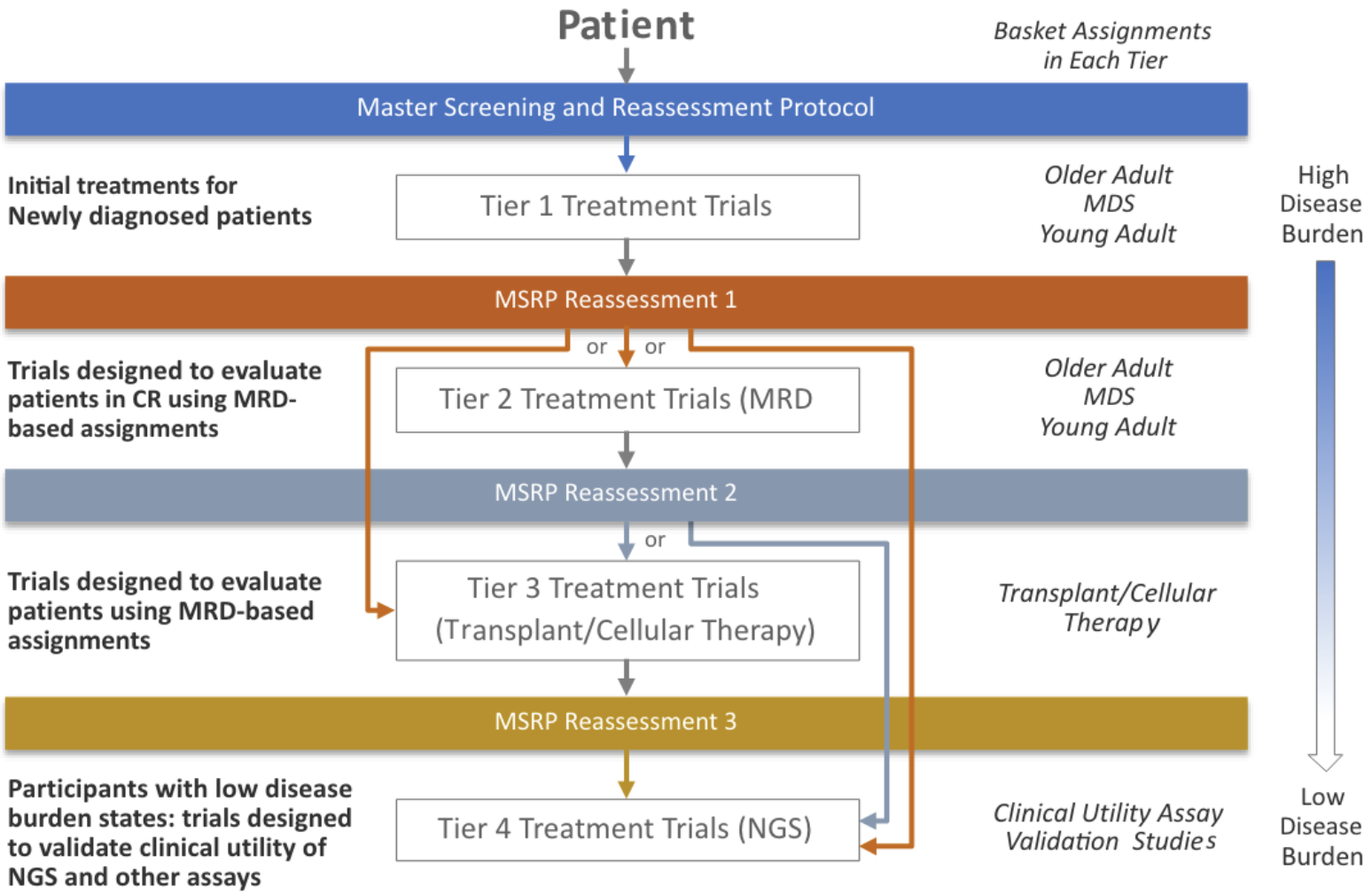
- Develop the careers of young investigators by promoting leadership throughout the clinical trial portfolio and laboratory program.

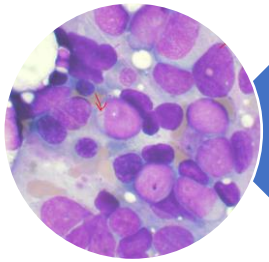
Administrative Components of MyeloMATCH Enhance Collaboration



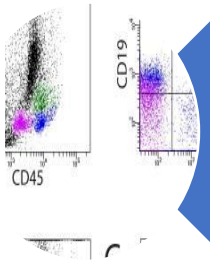
Assays for Treatment Assignment in myeloMATCH

MyeloMATCH MSRP Schema





Genexus, Cytogenetics, FISH for targeted treatments or risk based assignments



Flow MRD for response and next protocol assignment

Error Corrected Duplex Sequencing to target surviving clones

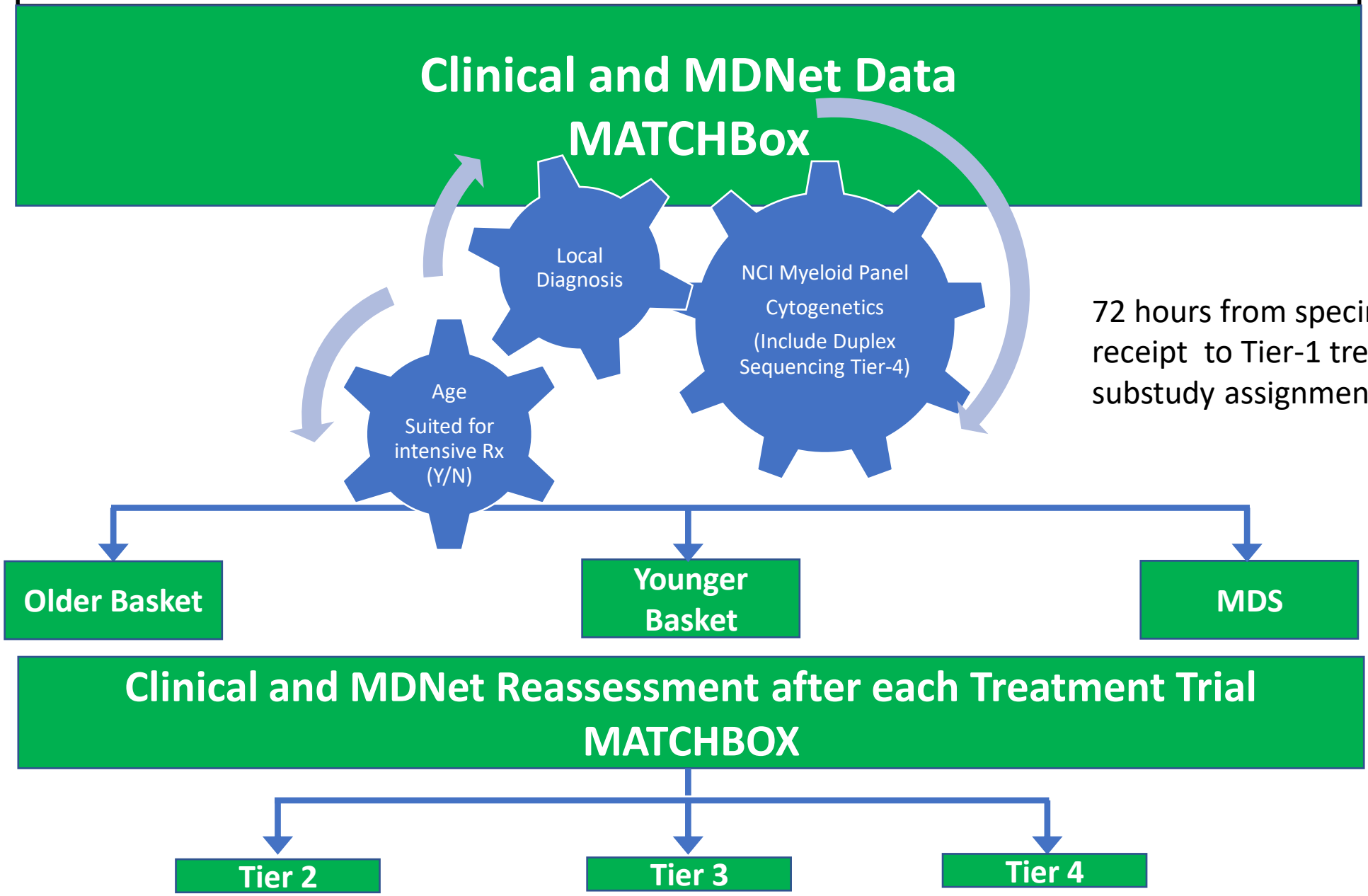
Molecular Diagnostics Laboratory Network (MDNet)
Integral Assays Under NCI IDE

72 Hours for Initial Patient Assignment and
10 Days for Subsequent Assignment

- NCI Myeloid Assay version 2
- Cytogenetics and FISH
- Flow Cytometric Analysis
- Duplex Sequencing to be added to IDE for tier 4 assignments

Integrated assays not subject to IDE include Whole Exome Sequencing, RNA Sequencing

Master Screening and Reassessment Protocol



General Structure of Tier-1 studies

Basket and Protocol Assignment by MATCHBox

Older AML

- FLT3 Mut
- TP53 Mut
- IDH1 Mut
- IDH2 Mut
- No Target

MDS

High Risk

- IDH1 Mut
- IDH2 Mut
- No Target
- TP53 Mut

Non-High Risk

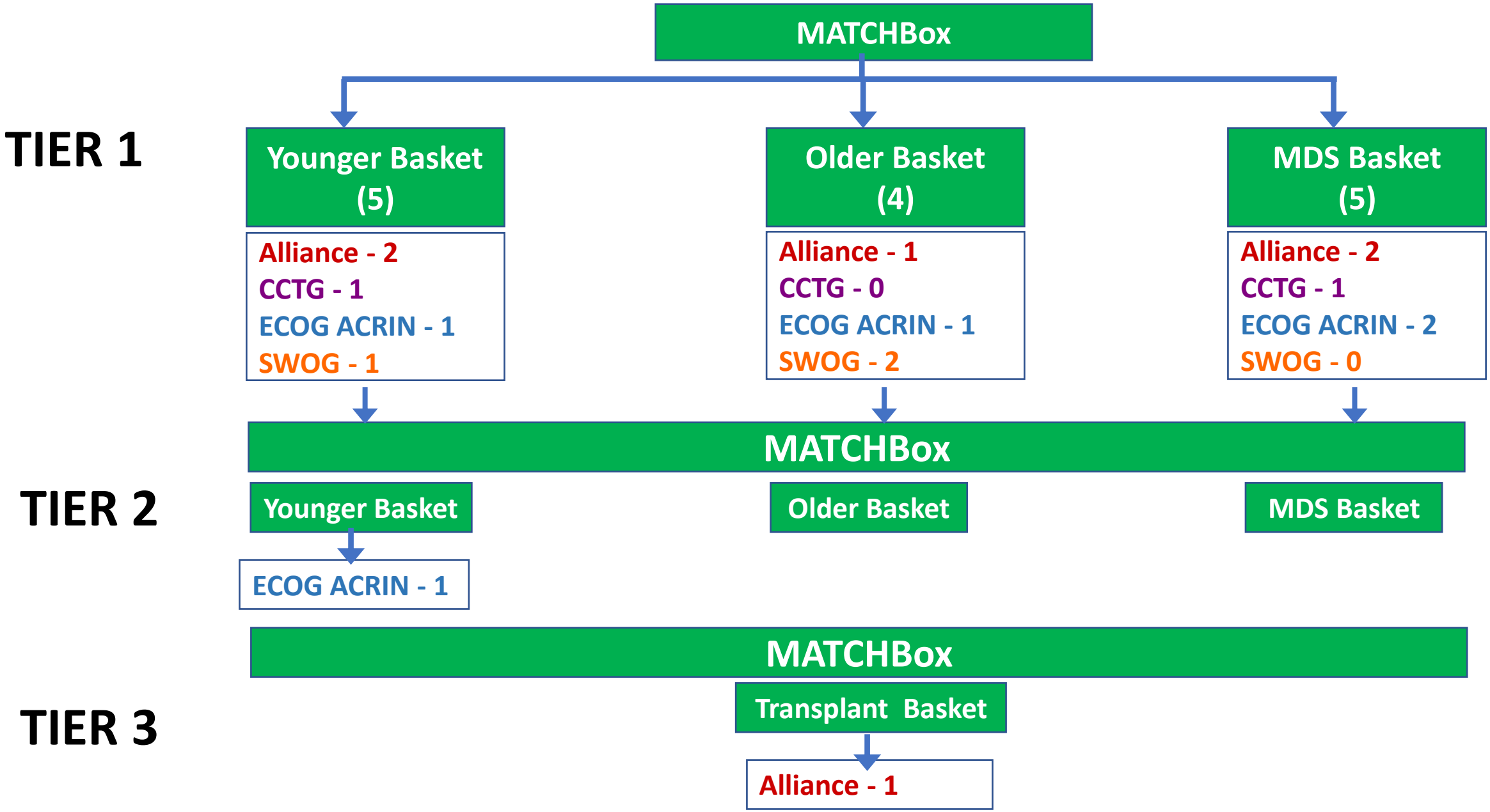
- SFB31

Younger AML

- FLT3 Mut
- TP53 Mut
- NPM1 Mut
- CBF
- Intermediate Risk
- High Risk

Most substudies are randomized phase 2 with MRD-neg CR as primary endpoint

16 MyeloMATCH Treatment Substudies in Development by NCTN Group as of March 2024



CRADA and Sub-Contract Collaborators for NCI MyeloMATCH*

- Genentech AbbVie
- BMS
- Astellas
- Blueprint Medicines
- Jazz Pharmaceuticals
- Gilead
- Astex/Taiho
- Rigel/Forma
- Actinium Pharmaceuticals
- Curis
- Syndax
- ThermoFisher
- TwinStrand Biosciences

*As of March 3, 2024
Additional collaborations under discussion

MyeloMATCH and MDNet

- DCTD's largest most complex trial in a single disease area treating patients through sequential treatment substudies from initial diagnosis until progression or death
- Active collaborations with pharma for novel-novel combinations
- Assay data will promote rapid treatment assignment and inform clonal evolution and provide insights into treatment sensitivity and resistance.
- May provide insights toward changing AML and MDS treatment paradigm
- Trial would not be feasible without DCTD infrastructure and the laboratory network
  - Leadership from Frederick National Laboratory, Fred Hutch Cancer Center, and Children's LA Cancer Center

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DISCUSSION QUESTIONS

- What challenges do you foresee for these trials and what are strategies to maximize success?
- How do we encourage sites to open master protocol treatment sub-studies when only a small number of patients will have the targeted alteration?
- How do we best engage clinical sites for biospecimen collection?