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MPAACT

MRD Partnership and Alliance in AML Clinical Treatments

MPAACT Consortium to Establish Measurable Residual Disease as a Surrogate Endpoint in Acute Myeloid Leukemia Drug Development

Key Milestones to Date

2016

Duke-Margolis/FDA Public Meeting on MRD

Janssen invited to present plans to evaluate MRD as an endpoint in AML; other companies invited to create a collaborative program

2018

Alliance formed with two goals:
- Establish MRD as surrogate endpoint for AML
- Harmonise MRD testing

2019

Engagement with Health Authorities to design surrogacy analysis and discuss assay methodology

Initial discussions with the Agencies provided important feedback to help MPAACT design a meta-analysis for surrogacy

2020-2021

Substantial progress made towards MPAACT goals

- Validation of a flow MRD assay
- Advisory boards held to discuss pediatric and market access considerations
- Third-party statistical Vendor, Mayo Clinic, selected to start data collection

2022 (so far)

Inclusion of three new companies to the MPAACT Alliance

Systematic literature review completed to identify clinical trials to include in the meta-analysis

Overall Goals of MPAACT

- Establish MRD as a surrogate endpoint for overall survival in clinical trials of treatment for patients with AML
- Validate MRD assays to support a primary endpoint, which can be easily incorporated into clinical trials and clinical practice
- Proactively engage with regulators and HTAs to shape HA & HTA policies
- Mission: Accelerate the development and delivery of novel life-extending therapies to patients with AML, using MRD as a surrogate endpoint for OS

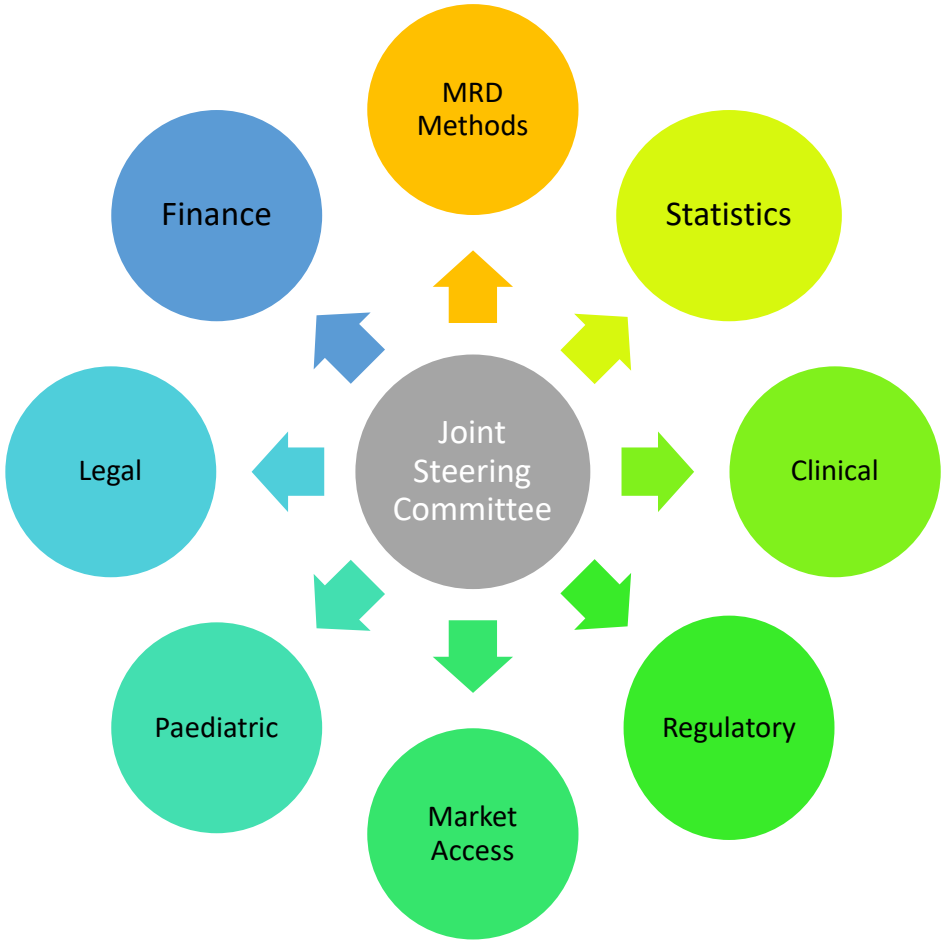
Strategic Intent: MPAACT Mission is to establish MRD as a Surrogate Endpoint for OS in AML

- MPAACT strives to define an MRD-based endpoint that:
  - Is clinically meaningful for all intended applications in future clinical trials
  - Can be measured objectively and consistently
  - Incorporates data that is already routinely collected from patients
  - Can provide an estimate of treatment effect much earlier than OS
- MPAACT acknowledges that there is heterogeneity in how MRD is currently evaluated in AML, and intends to consolidate all available data in order to define a single MRD-based endpoint to evaluate as a potential surrogate
  - In parallel, we are validating new assays to support consistency of testing in future clinical trials

MPAACT Stepwise Approach to Realize Objectives

- Surrogacy
  - Conduct an initial retrospective meta-analysis to evaluate how well treatment effect on MRD can predict treatment effect on OS, using patient-level data
  - Continue to collect additional patient-level data from ongoing clinical trials to update the initial retrospective meta-analysis and reflect the most recent treatment practice
  - The Mayo Clinic Statistics and Data Management Center, an independent statistical partner led by Dr Qian Shi, will perform the meta-analysis to assess association of MRD with OS
- MRD Testing
  - Harmonize and validate assay methodology for the assessment of MRD using multiparameter flow cytometry (MFC) and next-generation sequencing (NGS), to be used in prospective AML clinical trials conducted within clinical drug development programs retrospectively collected samples, if available
  - Collect prospective MRD datasets using harmonized and validated assays, which may be added to a potential subsequent meta-analysis
- Engaging with regulators and HTAs
  - Interactions planned for 3-4Q2022 with FDA/EMA to discuss the analysis design and strategy

MPAACT operating principles



ONE GOAL, ONE VOICE

MPAACT has an aligned and consistent approach to communications, working together to benefit AML patients

COORDINATED APPROACH

8 work streams:

Clinical, MRD Method, Stats, Pediatrics, Regulatory, Market Access, Legal, Finance and execute operational activities.

PARTNERS IN LEADERSHIP

A Joint Steering Committee (JSC) provides oversight and direction for MRD activities and establishes relationships with external collaborators

COLLABORATION

Collaborative efforts with academic groups and key opinion leaders is critical to drive the conversation on MRD and help achieve our goals

Strategy for the Retrospective Meta-analysis

- A widely accepted meta-analytic approach will be utilised
  - Data from multiple randomised clinical trials will be pooled together to assess two levels of surrogacy:
  1. **Individual-level surrogacy:** Prognostic value of achieving MRD negativity for a particular patient
  2. **Trial-level surrogacy:** Ability of the treatment effect on MRD to predict treatment effect on OS
- Major challenges will be data heterogeneity across trials, including:
  - Patient population (newly diagnosed, maintenance, relapsed/refractory)
  - Treatment MoA
  - Timing of MRD assessments per protocol
  - MRD testing methodology and threshold for negativity
- Single-arm studies will also be used to help identify the optimal MRD- threshold to be used to test surrogacy
- Paediatric studies are also being considered for inclusion in the analysis
- Statistical analysis plan will be reviewed with Health Authorities prior to any surrogacy analysis

MRD Testing Methodologies are Evolving

To be useful, MRD Methods should:

- Be standardized & validated (flow, PCR, NGS, etc.) to support context of use
  - Validation should encompass end to end process: from sample collection to results reporting
- Have a clearly defined clinical threshold
- Be robust and reproducible
- Be correlated with clinically meaningful outcomes (CR, EFS, OS)

MPAACT Methods Status & Next Steps

- Flow assay fully validated for investigational use (protocol & report available)
  - Provider has multiple sites to support global clinical trials
  - Validation suitable to support multiple context of use cases
- Second flow assay validation nearing completion at a vendor with multiple sites globally. Anticipated completion Q4 2022
- Collaboration with Invitae to develop a targeted NGS panel for AML MRD
  - Feasibility demonstrated, on-going work to assess mechanisms to further optimize NGS sensitivity
  - Targeting ability to track ≥ 90% of clinical trial participants
- Continually exploring/assessing new technologies for suitability in supporting MRD testing
- Develop mechanisms for standardisation & bringing additional providers online

FDA and EMA Meetings

Both Agencies very keen to see such an initiative and offered to work with us to help us progress

FDA (meeting 2019)

- Advice: include 10 RCTs in 1L setting, with patient-level OS and MRD data
- FDA was open to seeing analyses of MRD data that might change the definition of CR
- FDA statistical group have agreed to meet with statisticians to discuss SAP
- FDA recommended Alliance return with more information for further discussion and feedback on methodology

EMA (meeting 2020)

- CHMP supports the proposed meta-analyses on the proposed trials
- Primary surrogacy analysis should be based on achievement of MRD threshold at time of CR in BM
- Encouraged to explore sensitivity analyses
- Studies in MRD in childhood AML supported but should be performed separately
- Much is to be learned on MRD in AML by this project
  - Translating information in the implementation in clinical trial practice
  - Management in marketing authorisation of novel medications for the benefit of patients with AML
- For regulatory approval one could eventually envision MRD assessment at time of CR supported by EFS/PFS results as ground for efficacy assessment
- The Industry Alliance invited to come back for follow-up advice

Summary

- Many key academic investigators and industry collaborators in the AML field have been able to come together to pool data, resources, creativity, and intellectual strength to investigate the role of MRD as a surrogate endpoint
- The robustness of the statistical analysis and resulting evaluation of MRD as a potential surrogate endpoint will be drastically improved through inclusion of all relevant randomised clinical trials
- MPAACT aim to address heterogeneity and improve consistency in MRD testing by developing harmonised assays for use in future clinical trials with partners in the field
- Engagement with regulatory authorities and HTAs is critical for the project's success and for implementation of MRD as a future endpoint in clinical trials of new treatments for patients with AML
- **MPAACT was founded to establish surrogacy of MRD in AML which cannot be done without collaboration and data**

QUESTIONS ARE WELCOME!