CENTER OUTCOMES FORUM WORK GROUP #2

OCTOBER 18, 2023
KEY QUESTIONS TO ADDRESS

- What additional information currently collected by the CIBMTR should be used for disease-based risk adjustment for AML, ALL, and MDS?

- What changes in data collection are recommended soon to improve risk adjustment for AML, ALL, and MDS in the future?

- Members included Kwang Ahn, Yi-Ben Chen, Stella Davies, Firas El Chaer, Selina Lugar, Kristin Page, Wael Saber, Bart Scott
OVERVIEW OF WHAT WE CURRENTLY COLLECT FOR AML

- Disease subtype based on WHO (2016) ** ELN risk category (2017)
- Transform from MDS (Y/N) **
- Therapy related (Y/N) **
- Predisposing conditions (Bloom/Down/Fanconi/DKC/Other)
- Disease-specific labs (FISH, Karyo, Flow, PCR)
  - Three time points: diagnosis, in between, before prep
  - Used to confirm disease classification and MRD status
- CNS leukemia (Y/N)
- Disease status (PIF, CR1, CR2, CR3+, in relapse (#)) **
- How many induction cycles were required to achieve 1st CR? **
  - Time from CR1 to HCT for patients in CR2+ or relapse (AML/ALL) ** (surrogate for time in CR1)
- Measurable Residual Disease (MRD) questions

Recommendations:
- Transition to WHO 2022/ELN 2022, ICC when possible
- Update forms to collect needed data
- Update MRD questions
- Likely that several variables will be less relevant in future:
  - Transformation/Therapy-related (per WHO 2022)
  - # Induction cycles

** In CSA Model
Including these baseline characteristics would help classify AML in a clinically relevant categories

Dohner H. et al. Blood 2022

Khoury JD. et al. Leukemia 2022
IMPACT OF MRD ON LEUKEMIA-FREE SURVIVAL

Regardless of test used:

AML MRD in CR before Allo-HCT = worse survival after transplant.

Buckley et al. Haematologica, 2017
ESTIMATED SURVIVAL CURVES IN AML STRATIFIED BY MRD STATUS

Short N. et al. JAMA Onc 2020
MRD TESTING MODALITIES

Hourigan and Karp, Nature Reviews Clinical Oncology, 2013
**METHODS FOR DETECTION OF MRD IN AML**

<table>
<thead>
<tr>
<th>Method</th>
<th>Target</th>
<th>Sensitivity</th>
<th>Applicable in % of AML</th>
<th>Turn-around time (days)</th>
<th>Limitations/Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established Multi-parameter flow cytometry (MFC)</td>
<td>Leukemia-associated immunophenotype (LAIP) or different from normal (DіN)</td>
<td>$10^{-3}$ to $10^{-4}$</td>
<td>85-90</td>
<td>2</td>
<td>Less sensitive, more subjective analysis</td>
</tr>
<tr>
<td>Established Real-time quantitative PCR (RT-qPCR)</td>
<td>Robust data: NPM1, CBFB::MYH11, RUNX1::RUNX1T1 Less validated: KMT2A::MLLT3, DEK::NUP214, BCR::ABL1, WT1</td>
<td>$10^{-4}$ to $10^{-5}$</td>
<td>40-50*</td>
<td>3-5</td>
<td>Limited applicability</td>
</tr>
<tr>
<td>Exploratory Next-generation sequencing (NGS)†,‡</td>
<td>Potentially any somatic mutation†</td>
<td>$10^{-2}$ to $10^{-4}$</td>
<td>~100</td>
<td>5-10</td>
<td>Less sensitive, costly, technically challenging</td>
</tr>
<tr>
<td>Exploratory Digital PCR (dPCR)</td>
<td>Specific targeted mutations</td>
<td>$10^{-3}$ to $10^{-4}$</td>
<td>~70</td>
<td>3-5</td>
<td>Specific assay necessary for every mutation, limited sensitivity</td>
</tr>
</tbody>
</table>

Dohner H. et al. Blood 2022
### HR FOR AML MRD-TESTING SUBTYPES

#### A) Overall survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Favors no MRD</th>
<th>Favors MRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>0.38 (0.33-0.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric</td>
<td>0.30 (0.20-0.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>0.22 (0.07-0.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MRD time point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>0.40 (0.35-0.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During consolidation</td>
<td>0.37 (0.29-0.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After consolidation</td>
<td>0.30 (0.23-0.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MRD detection method</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFC</td>
<td>0.47 (0.39-0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR (WT1)</td>
<td>0.30 (0.19-0.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR (gene)</td>
<td>0.25 (0.20-0.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGS</td>
<td>0.43 (0.24-0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics/FISH</td>
<td>0.89 (0.43-1.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0.43 (0.20-0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AML subtype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBF</td>
<td>0.20 (0.13-0.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CBF</td>
<td>0.40 (0.36-0.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specimen source</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0.37 (0.33-0.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>0.27 (0.16-0.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>0.37 (0.16-0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA-bayesian</td>
<td>0.37 (0.33-0.42)</td>
<td></td>
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</tr>
</tbody>
</table>

#### B) Disease-free survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Favors no MRD</th>
<th>Favors MRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>0.40 (0.33-0.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric</td>
<td>0.38 (0.26-0.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>0.42 (0.18-0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MRD time point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>0.44 (0.35-0.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During consolidation</td>
<td>0.41 (0.31-0.56)</td>
<td></td>
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<td></td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>PCR (gene)</td>
<td>0.34 (0.25-0.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGS</td>
<td>0.45 (0.25-0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics/FISH</td>
<td>0.75 (0.39-1.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0.48 (0.28-0.81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AML subtype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBF</td>
<td>0.26 (0.18-0.38)</td>
<td></td>
<td></td>
</tr>
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<td>Non-CBF</td>
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Short N. et al. JAMA Onc 2020
OVERVIEW OF WHAT WE CURRENTLY COLLECT FOR AML

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- Transform from MDS (Y/N) **
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Recommendations:
- Transition to WHO 2022/ELN 2022, ICC when possible
- Update forms to collect needed data
- Update MRD questions
- Likely that several variables will be less relevant in future:
  - Transformation/Therapy-related (per WHO 2022)
  - # Induction cycles

** In CSA Model
OVERVIEW OF WHAT WE CURRENTLY COLLECT FOR ALL

- Disease subtype using WHO 2016 ** Risk stratification (Lazaryan)
  - T-cell and Ph+ status
- Predisposing conditions (SAA, Bloom, Down, Fanconi, Other)
- Prior TKI use (Y/N)
- Disease-specific labs (FISH, Karyo, Flow, PCR)
  - Three time points: diagnosis, in between, before prep
  - Used to confirm disease classification and MRD status
- CNS leukemia (Y/N)
- Disease status (PIF, CR1, CR2, CR3+, in relapse (#)) **
- How many induction cycles were required to achieve 1st CR? **
  - Time from CR1 to HCT (if AML/ALL and in CR2+ or relapse) **
- MRD questions

Recommendations:
- Transition to WHO 2022
- Update forms to collect needed data including expanding Ph-like ALL and Early T-cell precursor
- Update MRD questions, role in ALL is clear

** In CSA Model
### CLINICAL RISK STRATIFICATION FOR ALL

<table>
<thead>
<tr>
<th></th>
<th>B-ALL</th>
<th>T-ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&gt;35 years</td>
<td>&gt;35 years</td>
</tr>
<tr>
<td><strong>White blood cell (WBC) count</strong></td>
<td>&gt;30 x 10⁹/L</td>
<td>&gt;100 x 10⁹/L</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>N/A</td>
<td>ETP-ALL</td>
</tr>
<tr>
<td><strong>Cytogenetics/Molecular risk group</strong></td>
<td>See Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL (<a href="#">ALL-3</a>)</td>
<td><em>RAS/PTEN</em> mutation and/or <em>NOTCH1/FBXW7</em> wild type</td>
</tr>
</tbody>
</table>

NCCN Guidelines version 3.2023
# CYTOGENETIC AND MOLECULAR PROGNOSTIC RISK STRATIFICATION FOR B-ALL

<table>
<thead>
<tr>
<th>RISK GROUPS</th>
<th>CYTOGENETIC AND MOLECULAR ALTERATIONS</th>
</tr>
</thead>
</table>
| Standard risk | • Hyperdiploidy (51–65 chromosomes)  
   ▶ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome  
   ▶ t(12;21)(p13;q22): **ETV6-RUNX1**  
   ▶ t(1;19)(q23;p13.3): **TCF3-PBX1**  
   ▶ **DUX4** rearranged  
   ▶ **PAX5** P80R  
   ▶ t(9;22)(q34;q11.2): **BCR-ABL1** without **IKZF1** plus^k and without antecedent chronic myeloid leukemia (CML) |
| Poor risk | • Hyperdiploidy^L (≤44 chromosomes)  
   ▶ **TP53** mutation  
   ▶ KMT2A rearranged ([t;4;11] or others)  
   ▶ **IgH** rearranged^L  
   ▶ **HLF** rearranged  
   ▶ ZNF384 rearranged  
   ▶ **MEF2D** rearranged  
   ▶ **MYC** rearranged  
   ▶ **BCR-ABL1**-like (Philadelphia chromosome [Ph]-like) **ALL**  
   ▶ JAK-STAT (CRLF2, EPOR, JAK1/2/3, TYK2, mutations of SH2B3, IL7R, JAK1/2/3)  
   ▶ ABL class (rearrangements of ABL1, ABL2, PDGFRα, PDGFRβ, FGFR)  
   ▶ Other (NTRK1, FLT3, LYN, PTK2B)  
   ▶ **PAX5alt**  
   ▶ t(9;22)(q34;q11.2): **BCR-ABL1** with **IKZF1** plus^k and/or antecedent CML  
   ▶ Intrachromosomal amplification of chromosome 21 (iAMP21)  
   ▶ Alterations of **IKZF1**^k,i,p,q  
   ▶ Complex karyotype (5 or more chromosomal abnormalities) |

NCCN Guidelines version 3.2023
The ClonoSEQ assay is an in vitro diagnostic that uses multiplex PCR and NGS to identify and quantify certain gene sequences in DNA extracted from bone marrow from patients with ALL or multiple myeloma.

The ClonoSEQ assay measures the amount of MRD and is capable of detecting MRD at levels below 1 in 1 million cells.

Wood B. et al. Blood 2018
NGS-MRD PRE- AND EARLY POST-ALLO-BMT FOR ALL

Pulsipher et al. Blood 2015
NGS-MRD PRE- AND EARLY POST-ALLO-BMT FOR ALL

Pulsipher et al. Blood 2015
NGS-MRD PRE- AND EARLY POST-ALLO-BMT FOR ALL

Pulsipher et al. Blood 2015
OVERVIEW OF WHAT WE CURRENTLY COLLECT FOR ALL

- Disease subtype using WHO 2016 ** Risk stratification (Lazaryan)
  - T-cell and Ph+ status
- Predisposing conditions (SAA, Bloom, Down, Fanconi, Other)
- Prior TKI use (Y/N)
- Disease-specific labs (FISH, Karyo, Flow, PCR)
  - Three time points: diagnosis, in between, before prep
  - Used to confirm disease classification and MRD status
- CNS leukemia (Y/N)
- Disease status (PIF, CR1, CR2, CR3+, in relapse (#)) **
- How many induction cycles were required to achieve 1st CR? **
  - Time from CR1 to HCT (if AML/ALL and in CR2+ or relapse) **
- MRD questions

Recommendations:
- Transition to WHO 2022
- Update forms to collect needed data including expanding Ph-like ALL and Early T-cell precursor
- Update MRD questions, role in ALL is clear

** In CSA Model
OVERVIEW OF DATA WE CURRENTLY COLLECT FOR MDS

- Disease subtype at diagnosis using WHO 2016
  - Therapy related (Y/N)
  - Predisposing condition
    - SAA/DDX41/Diamond Blackfan/ Fanconi/ GATA2/
      - Li-Fraumeni/ PNH/ RUNX1/ SAMD9/ Shwachman/ Telomere/Other
  - CBC results
  - Disease specific labs (FISH, Karyo):
    - Two time points
    - Did the recipient transform to a different subtype or AML?
  - IPSS-R risk score at HCT

Recommendations:
- Transition to WHO 2022
- Update forms to collect needed data
- Consider IPSS-M
## Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.

<table>
<thead>
<tr>
<th>Category and Variable</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>Model Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow blasts — %</td>
<td>1.07 (1.05–1.09)</td>
<td>0.0704</td>
</tr>
<tr>
<td>min(Patients,250) — x10^9/l</td>
<td>0.998 (0.997–0.999)</td>
<td>-0.00222</td>
</tr>
<tr>
<td>Hemoglobin — g/dl</td>
<td>0.84 (0.81–0.88)</td>
<td>-0.171</td>
</tr>
<tr>
<td><strong>Cyto genetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS-R cytogenetic category</td>
<td>1.33 (1.12–1.47)</td>
<td>0.287</td>
</tr>
</tbody>
</table>

Gene main effects (17 variables, 16 genes§)

- TP53
- MCL1
- FLT3
- SF3B1
- NPM1
- RUNX1
- NRAS
- ETV6
- IDH2
- CBL
- EZH2
- U2AF3
- SRSF2
- DNMT3A
- ASXL1
- KRA5
- SF3B1

- Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)||
- min(Nres,2) | 1.26 (1.12–1.42) | 0.231

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IPSS-M RISK SCORE CONSTRUCTION FROM AN ADJUSTED COX MULTIVARIABLE REGRESSION FOR LEUKEMIA-FREE SURVIVAL

* CI denotes confidence interval; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, International Prognostic Scoring System–Revised; ITD, internal tandem duplication; min, minimum; PTD, partial tandem duplication; and TKD tyrosine kinase domain.

† Hazard ratio is for the risk of leukemic transformation or death, adjusted for age, sex, and secondary/therapy-related versus primary myelodysplastic syndrome. Cox regression was performed for 2428 patients with available covariates and leukemia-free survival data.

‡ Model weights were derived from the logarithm of the raw hazard ratios up to three significant digits. The following formula applies: IPSS-M score = $1.35467 + \sum_{j=1}^{16} w_j \log(2)$, where $w_j$ denotes the weight of variable $j$, and $\log(2)$ is the value of the variable $j$ observed in a given patient.

§ IPSS-R cytogenetic categories were as follows: 0 denotes very good, 1 good, 2 intermediate, 3 poor, and 4 very poor.

¶ SF3B1 is the SF3B1 mutation in the presence of isolated del(5q)—that is, del(5q) only or with one additional aberration excluding -7/del(7q). SF3B1 is the SF3B1 mutation without comutations in BCOR, BCL11A, RUNX1, NRAS, STAG2, SRSF2, and del(5q).

|| N inters is defined as the number of mutated genes within the following list: BCOR, BCL11A, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF2, PHF6, PPM1D, PRF1, PTPN11, SETBP1, STAG2, and WT1: The variable min(Nres,2) can therefore take the value 0, 1, or 2.
OVERVIEW OF DATA WE CURRENTLY COLLECT FOR MDS

- Disease subtype at diagnosis using WHO 2016 **
  - Therapy related (Y/N)
  - Predisposing condition
    - SAA/DDX41/Diamond Blackfan/ Fanconi/ GATA2/
    - Li-Fraumeni/ PNH/ RUNX1/ SAMD9/ Shwachman/ Telomere/Other
- CBC results
- Disease specific labs (FISH, Karyo):
  - Two time points
  - Did the recipient transform to a different subtype or AML?
- IPSS-R risk score at HCT

Recommendations:
- Transition to WHO 2022
- Update forms to collect needed data
- Consider IPSS-M
MRD QUESTIONS FOR AML / ALL (TED LEVEL DATA)

- Forms currently ask the following MRD questions:
  - Specify method(s) that was used to assess measurable residual disease status (check all that apply)
    - FISH/Karyotyping/Flow/PCR/NGS/Not assessed
  - Was measurable residual disease detected by…
    - FISH (Y/N)
    - Karyo (Y/N)
    - Flow (Y/N)
    - NGS (Y/N)

Concerns raised that:
1. Cytogenetic data likely represents gross levels of disease as opposed to MRD
2. Consider capturing VAF
3. What do we need for research purposes?
4. What are data managers accurately able to report?
WHEN CONSIDERING MRD TESTING, SEVERAL KEY QUESTIONS NEED TO BE ADDRESSED:

- **Patient's Disease Status:**
  - Was the patient's disease considered to be MRD positive, MRD negative, or was it not assessed? This question helps establish the baseline MRD status and informs subsequent monitoring strategies.

- **Testing Methods and Practices:**
  - What MRD testing methods were employed? Different laboratories and institutions may use varying techniques, such as flow cytometry, polymerase chain reaction (PCR), or next-generation sequencing (NGS). Understanding the specific method is crucial for comparing results.
  - Are these tests performed at fixed intervals or triggered by specific clinical events? Defining the frequency of MRD testing is important for tracking disease progression.

- **Sensitivity of MRD Testing:**
  - What is the sensitivity of the MRD testing used at each center? Sensitivity refers to the ability of a test to detect very low levels of disease. Sensitivity can vary widely, from 1 in 1,000 cells to 1 in 1,000,000 cells.
  - How do we reconcile differences in sensitivity between academic center A and community center B, which detects 1 in 10,000 cells? It's crucial to acknowledge these variations and consider them when interpreting results.