CDDF MULTI - STAKEHOLDER WORKSHOP

MINIMAL RESIDUAL DISEASE (AML - CLL)

London, United-Kingdom
8 - 9 November 2018
Introduction to the Workshop

Axel Glasmacher
Leukaemia Cell Mass during Cytotoxic Treatment

Induction Treatment

Treatment in Remission

Relapse

Therapie in Remission

Cure

Leukaemia Cell Mass

Time

Cure

Induction

Consolidation

MRD level

1E-01
1E-02
1E-03
1E-04
1E-05
1E-06
1E-07
1E-08
1E-09
1E-10
1E-11
1E-12

1E+00
1E+01
1E+02
1E+03
1E+04
1E+05
1E+06
1E+07
1E+08
1E+09
1E+10
1E+11
1E+12

quantifiable MRD

non-quantifiable MRD

non-detectable MRD

Minimum analyzed cells
Eliminating MRD as a Gateway to Cure?

Review Article

Eliminating minimal residual disease as a therapeutic end point: working toward cure for patients with CLL

Philip A. Thompson and William G. Wierda

Thompson et al., Blood 2016; 127: 279
Unmet Need in CLL

Minimal residual disease is an independent predictor for 10-year survival in CLL

Kwok M et al., Blood 2016; 128: 2770
Overall Survival in MRC Studies 1970-2009
FDA Approved Drugs for AML

1970
1980
1990
2000
2010

1973
Cytarabine
Daunorubicin

1990
Idarubicin

1995
Tretinoin

2000
Arsenic Trioxide
Mylotarg (→2010)

2004
Azacitidine*

2006
Decitabine*

2010

2017
CPX-351
Enasidenib
Midostaurin
Mylotarg

2018
Ivosidenib

* For MDS only; Azacitidine approved in 2015 for AML in the EU
Mylotarg: Gemtuzumab ozogamicin approved in 2000, withdrawn in 2010, (re-)approved in 2017
www.hemonc.org; O. Abdel-Wahab, The Hematologist 2018, 17 (Jan-Feb)
EMA and FDA develop the field intensively

Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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1 26 July 2018
2 EMA/CHMP/459559/2018
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on the use of minimal residual disease as a clinical endpoint in multiple myeloma studies
5 Draft


## FDA Analysis of MRD Data in Haematological Malignancies

<table>
<thead>
<tr>
<th>NDA or BLA submitted with MRD data</th>
<th>34; <strong>13 in haematological malignancies</strong> (CML, CLL, ALL, MM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD included in Product Information</td>
<td>6 (46%): Testing PCR (5), Flow Cytometry (1)</td>
</tr>
<tr>
<td>MRD not included in Product Information</td>
<td>4: declined by FDA. Issues identified:</td>
</tr>
<tr>
<td></td>
<td>- Missing data of pts. in CR</td>
</tr>
<tr>
<td></td>
<td>- Incomplete test performance data</td>
</tr>
<tr>
<td></td>
<td>- Disparate sample sources (blood vs bone marrow)</td>
</tr>
<tr>
<td></td>
<td>- High amount of test failure</td>
</tr>
<tr>
<td></td>
<td>- Lack of test validation</td>
</tr>
<tr>
<td></td>
<td>- Inappropriate planned statistical analyses</td>
</tr>
<tr>
<td></td>
<td>3: not proposed by applicant</td>
</tr>
</tbody>
</table>

Gormley N et al., JCO 2017; 35: 2541 (suppl)
Open Questions

? MRD as surrogate or intermediary endpoint
  • Accepted as intermediary endpoint
    ? What is needed to validate a surrogate endpoint?

? How many methods are necessary?
  ? Two or one – how deal with mismatched results?

? When and how often to measure?
  ? Early and prolonged MRD negativity is better. How is that relevant?

? Health Technology Assessment
  ? How to deal with MRD endpoints?

? Validation of peripheral blood sampling
  • Patient perspective
CLL: Meta-Regression Sensitivity Analysis Restricting PFS

\[
\log (HR) = -0.38x \\
R^2 = 0.75
\]
Using different methods in AML

Jongen-Lavrencic M et al., NEJM 2018; 378: 1189
How should we call MRD?

Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party

Gerrit J. Schuurhuis,1 Michael Heuser,2,* Sylvie Freeman,3,* Marie-Christine Béné,4 Francesco Buccisano,5 Jacqueline Cloos,1,6 David Grimwade,7 Torsten Haferlach,6 Robert K. Hills,9 Christopher S. Hourigan,10 Jeffrey L. Jorgensen,11 Wolfgang Kern,8 Francis Lacombe,12 Luca Maurillo,5 Claude Preudhomme,13 Bert A. van der Reijden,14 Christian Thiede,15 Adriano Venditti,5 Paresh Vyas,16 Brent L. Wood,17,18 Roland B. Walter,17,19 Konstanze Döhner,20,† Gail J. Roboz,21,† and Gert J. Ossenkoppele1
Workshop Programme: Day 1 (Nov. 8)
Workshop Programme: Day 1 (Nov. 8)
Workshop Programme: Day 2 (Nov. 9)

08:00  Regulatory Aspects AML & CLL  
Nicole Gormley (FDA, USA)

WORKSHOP PROGRESS ON MRD IN CLL

Co-chairs: Robert Gale (Celgene, USA) & Andy Rawstron (Leeds Teaching Hospitals NHS Trust, UK)

08:30  Clinical Overview: MRD in CLL  
Matthias Ritgen (University Medical Center Schleswig-Holstein, DE)

09:15  Methodological Overview: MRD in CLL  
Andy Rawstron (Leeds Teaching Hospitals NHS Trust, UK)

10:00  Industry Perspective  
Davy Chiodin (Acerta/AstraZeneca, USA)

10:30  Coffee break
Workshop Programme: Day 2 (Nov. 9)

ROUNDTABLE: LESSONS LEARNED AND OPEN QUESTIONS FOR AML & CLL, NEXT STEPS

**Moderator:** John Smyth (CDDF/University of Edinburgh, UK)

11:00 **Regulators** (B. Flores, N. Gormley), **Academia** (K. Döhner, A. Rawstron),
**Industry** (C. Pallaud, I. Radtke)

12:30 End of workshop
• The Cancer Drug Development Forum is an international organization providing a platform for all stakeholders involved in the development of oncology drugs.

• The aim of the not-for-profit organization is to accelerate the delivery of effective oncology agents to patients.

• Established in 2001 as Biotherapy Development Association (BDA), in 2014 the name was changed to Cancer Drug Development Forum.

• The CDDF, based in Brussels, unites experts from academia, the pharmaceutical industry, regulatory authorities (including the EMA and FDA), payers (health technology assessors) and patient advocates.
Previous CDDF Multi-Stakeholder-Workshops on MRD

www.cddf.org
Chatham House Rule applies

“When a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed.

This includes social media.

www.chathamhouse.org
backup
The CDDF will Publish a Meeting Report

www.cddf.org
German Intergroup Study: Five Concepts and Standard Arm

Overall Survival (probability)

- Standard treatment arm, 5-year survival probability: 44.3% (37.7% to 50.7%)
- Study A: 5-year survival probability: 41.4% (36.9% to 45.8%)
- Study B: 5-year survival probability: 46.6% (41.1% to 51.8%)
- Study C: 5-year survival probability: 47.5% (40.1% to 54.6%)
- Study D: 5-year survival probability: 43.6% (39.6% to 47.6%)
- Study E: 5-year survival probability: 46.4% (41.0% to 51.7%)

n = 3,106 patients; 1,542 events
New Approvals in AML

2017 FDA Approvals* for Hematologic Malignancies

*selected subset

- midostaurin (FLT3+ AML)
- inotuzumab ozogamicin (R/R pre-B ALL)
- tisagenlecleucel (R/R pre-B ALL)
- copanlisib (relapsed FL)
- axicabtagene ciloleucel (R/R large B-cell lymphoma)
- acalabrutinib (MCL prev. treated)

- lenalidomide (maintenance post-auto-HSCT for MM)
- rituximab and hyaluronidase (FL, DLBCL, and CLL)
- enasidenib (IDH2m R/R AML)
- ibrutinib (chronic GVHD)
- tocilizumab (CAR-T cell-induced cytokine release syndrome)
- brentuximab vedotin (primary cutaneous ALC and CD30+ MF)
- obinutuzumab (untreated FL)

- pembrolizumab (refractory classical HL or after ≥3 lines of therapy)
- blinatumomab (relapsed Ph+ pre-B ALL)
- liposomal daunorubicin and cytarabine (tAML or AML-MRC)
- gemtuzumab ozogamicin (CD33+ AML)

Abbreviations: ALC, anaplastic large cell lymphoma; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GVHD, graft-versus-host disease; HL, Hodgkin lymphoma; IDH2m, isocitrate dehydrogenase 2 mutated; HSCT, hematopoietic stem cell transplantation; MCL, mantle cell lymphoma; MF, mycosis fungoides; MM, multiple myeloma; MRC, myelodysplasia-related changes; pre-B ALL, B-cell precursor acute lymphoblastic leukemia; R/R, relapsed or refractory; tAML, therapy-related AML
AML: Genomic Heterogeneity

Genomic Heterogeneity and Clonal Evolution in AML

Disease continuum with Myelodysplastic Syndromes (MDS)


Quantitative Relation of MRD and Outcome
MRD Level (log depletion) and PFS in UK MM IX

All Patients

Patients in CR

Rawstron et al., Blood. 2015; 125: 1932

\[ \chi^2 = 35.12 \]

\( P < .001 \)

\[ \chi^2 (TREND) = 10.92 \]

\( P < .001 \)
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HTA Analysis and MRD Endpoints