CDDF
Cancer Drug Development Forum

CDDF MULTI - STAKEHOLDER WORKSHOP

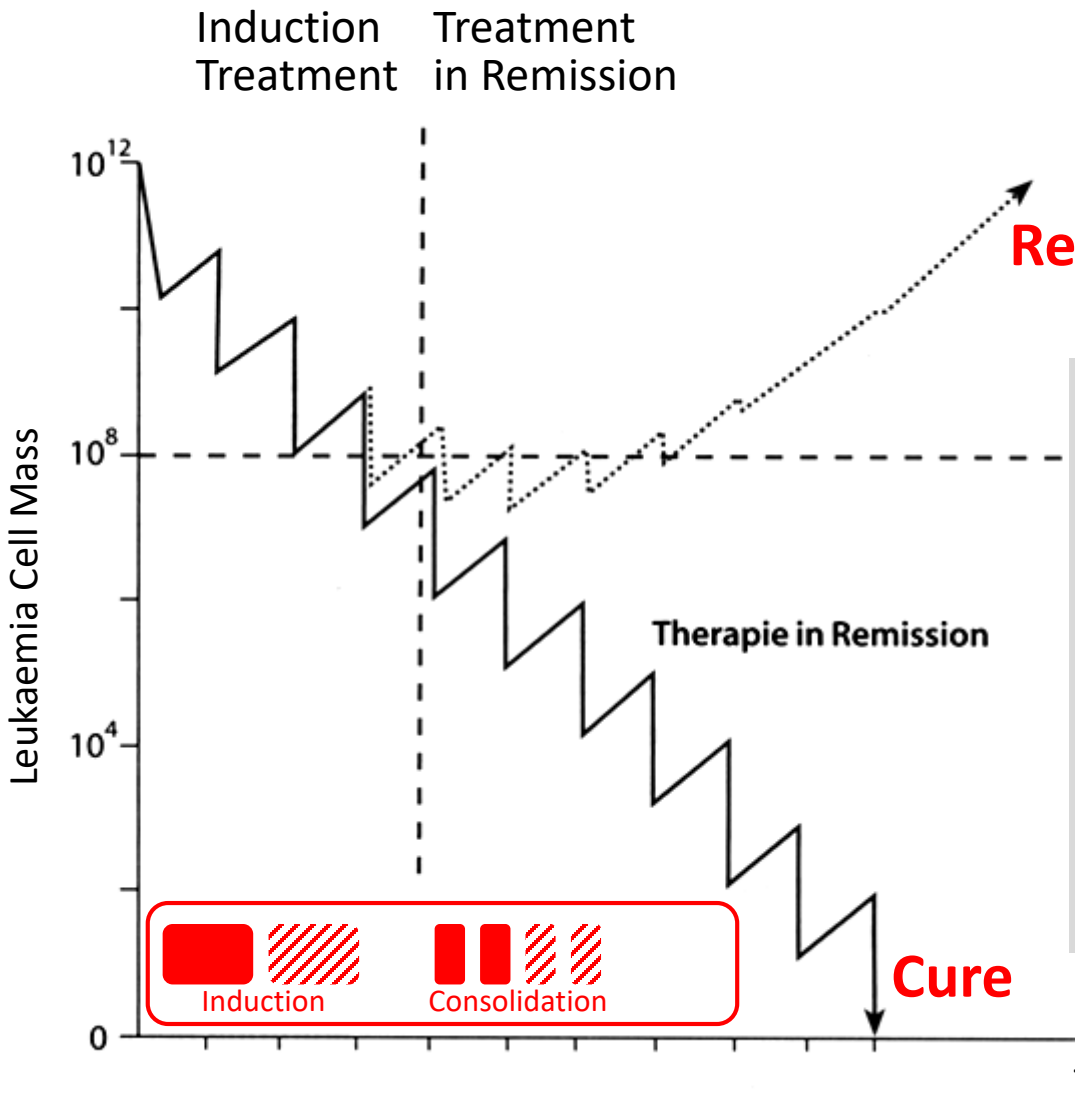
MINIMAL RESIDUAL DISEASE (AML - CLL)

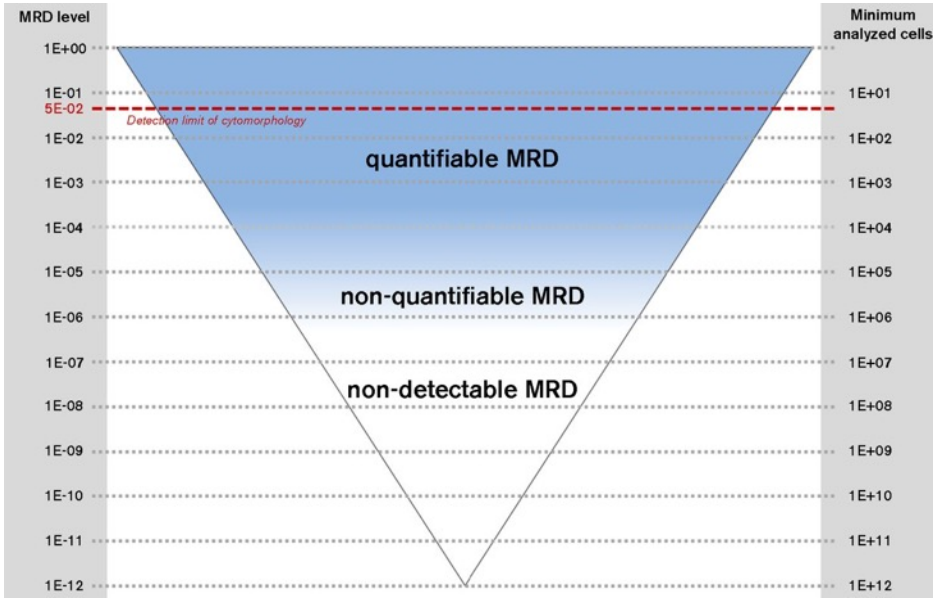
London, United-Kingdom
8 - 9 November 2018

Introduction to the Workshop

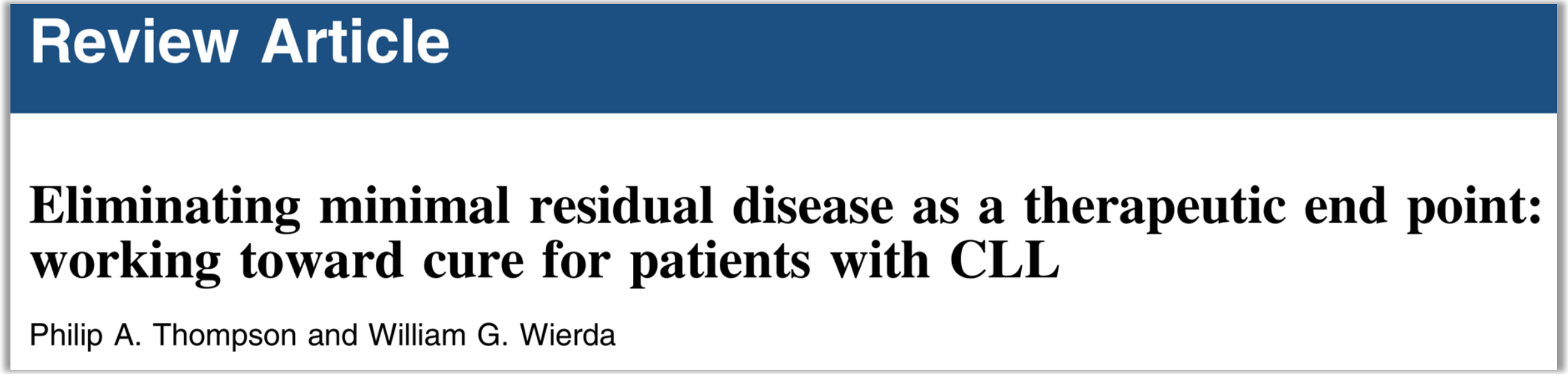
Axel Glasmacher

Leukaemia Cell Mass during Cytotoxic Treatment





Eliminating MRD as a Gateway to Cure?

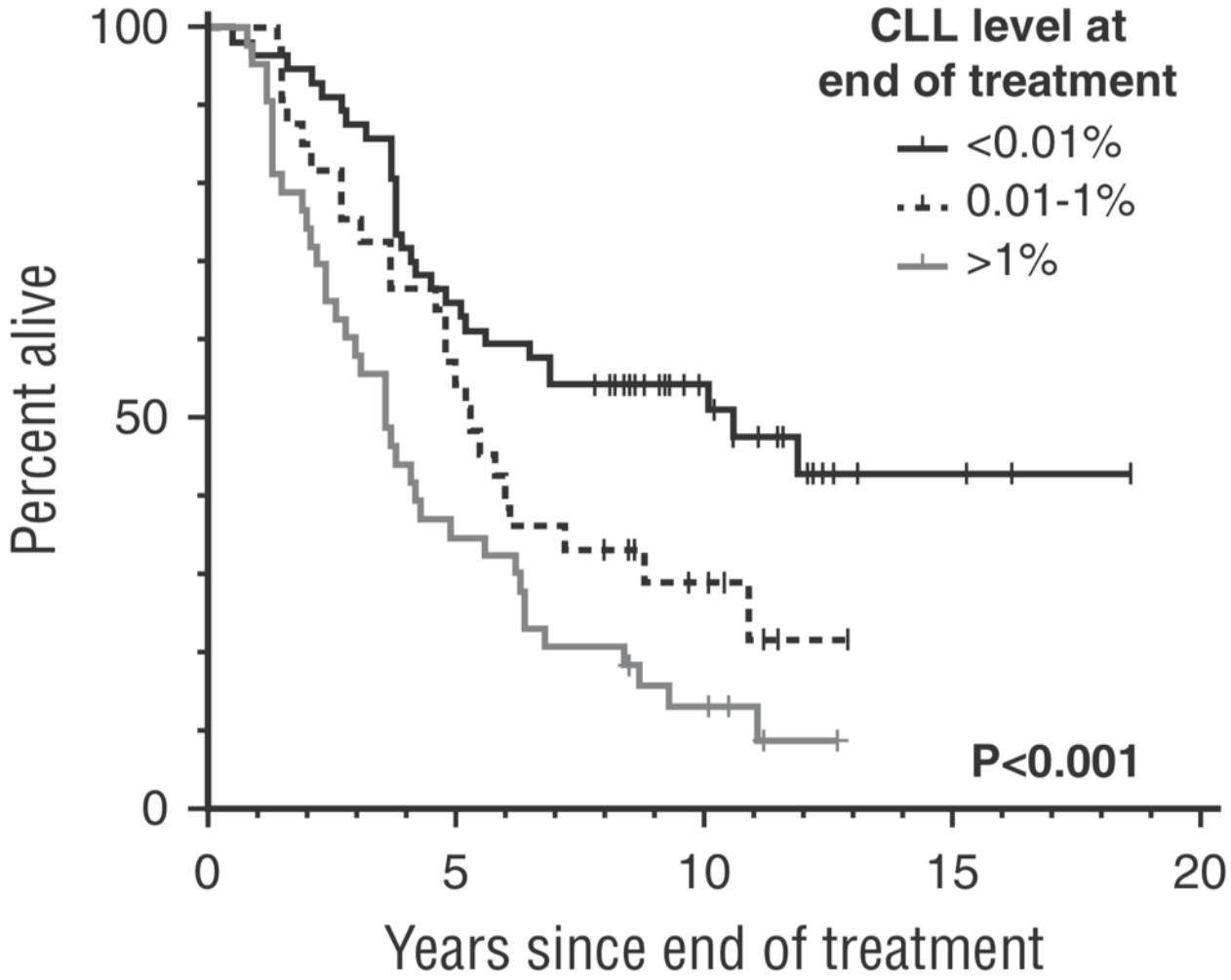

Review Article

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

Philip A. Thompson and William G. Wierda

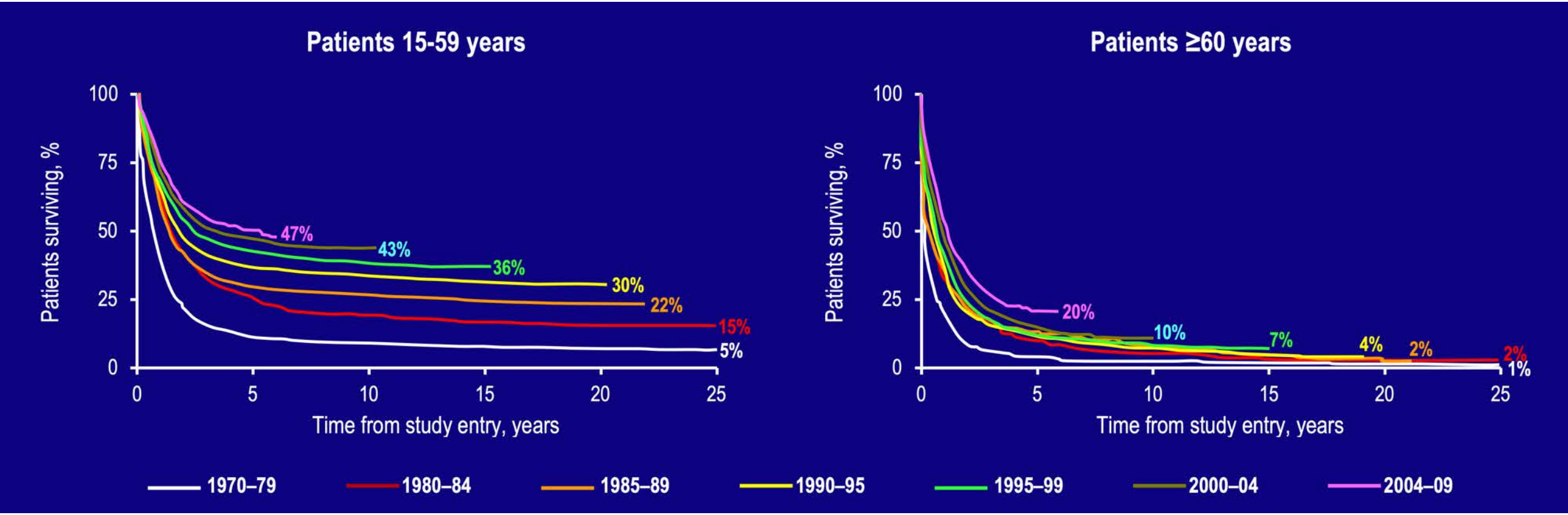
Thompson et al., Blood 2016; 127: 279

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



Burnett AK. *ASH Education Book* 2012;2012:1–6

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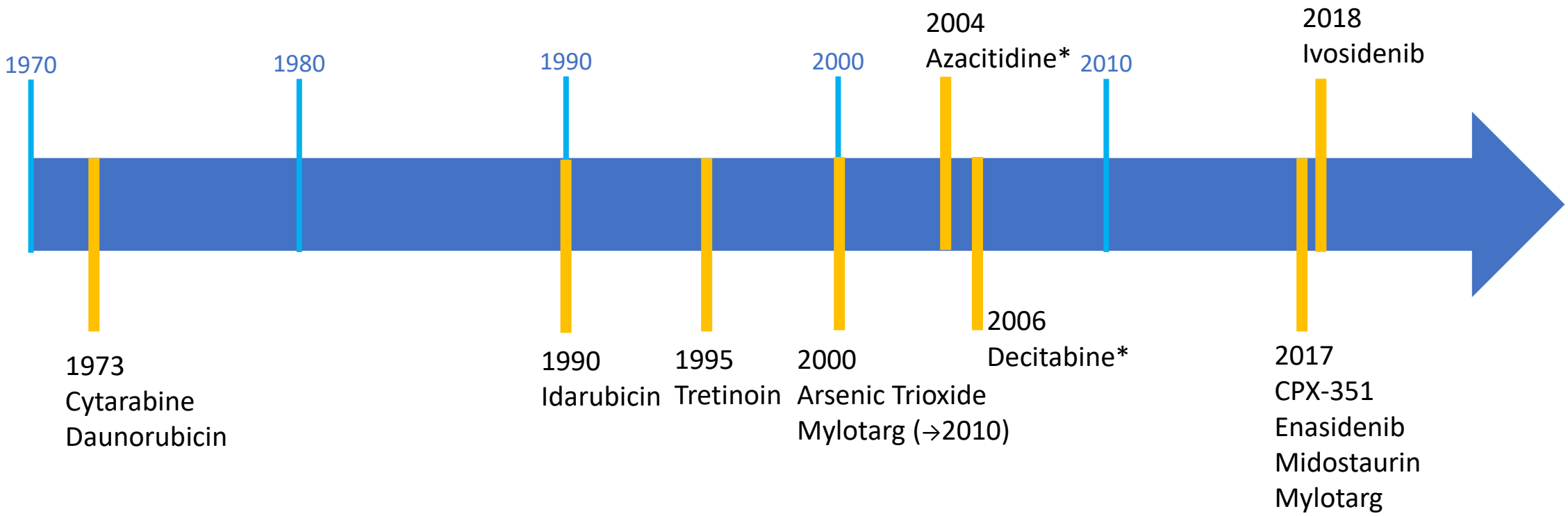
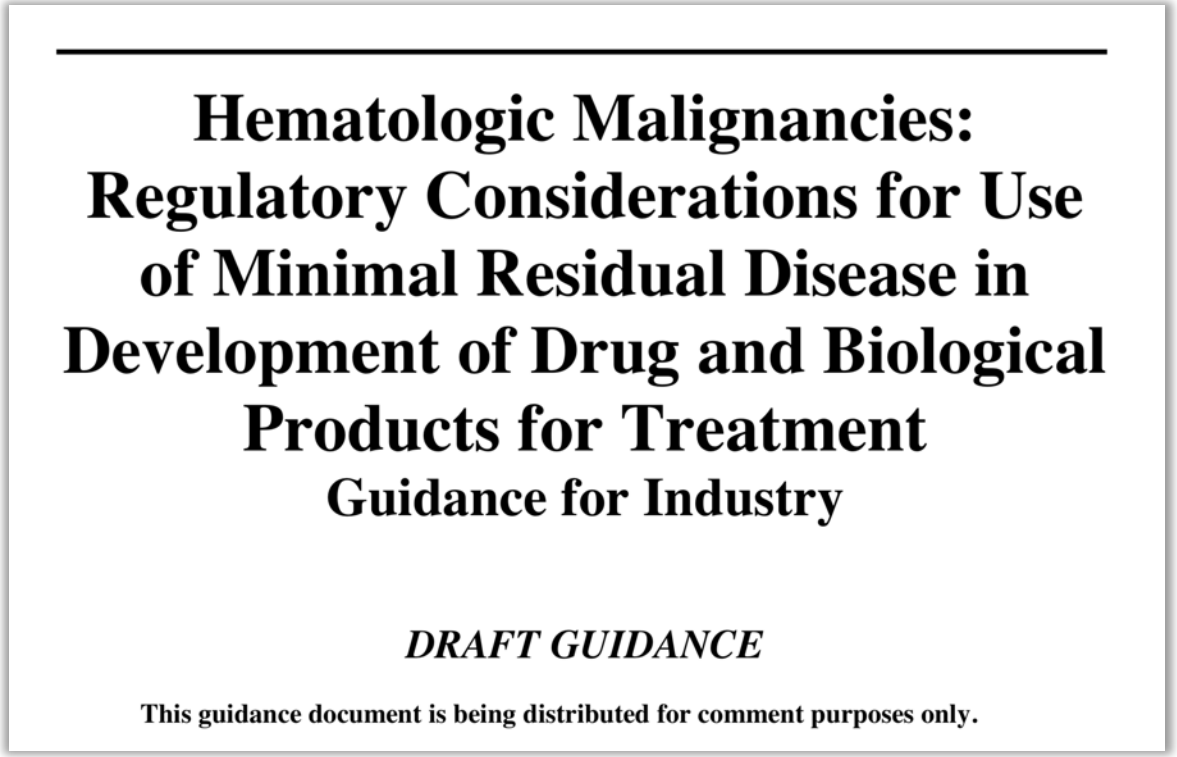
FDA Approved Drugs for AML



* 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.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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
5 clinical endpoint in multiple myeloma studies
6 Draft

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm623333.pdf

https://www.ema.europa.eu/documents/scientific-guideline/draft-guideline-use-minimal-residual-disease-clinical-endpoint-multiple-myeloma-studies_en.pdf

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FDA Analysis of MRD Data in Haematological Malignancies

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

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

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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

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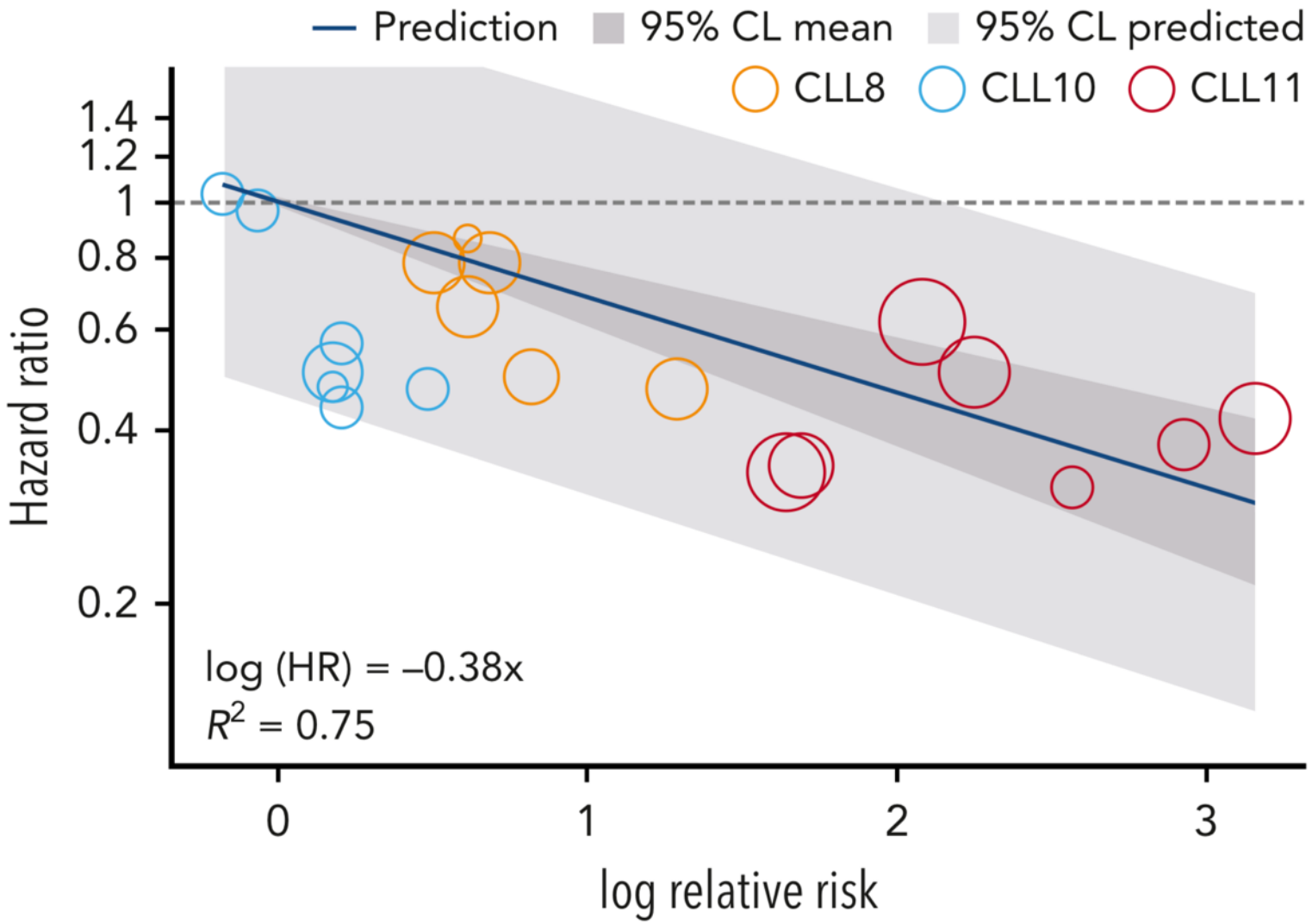
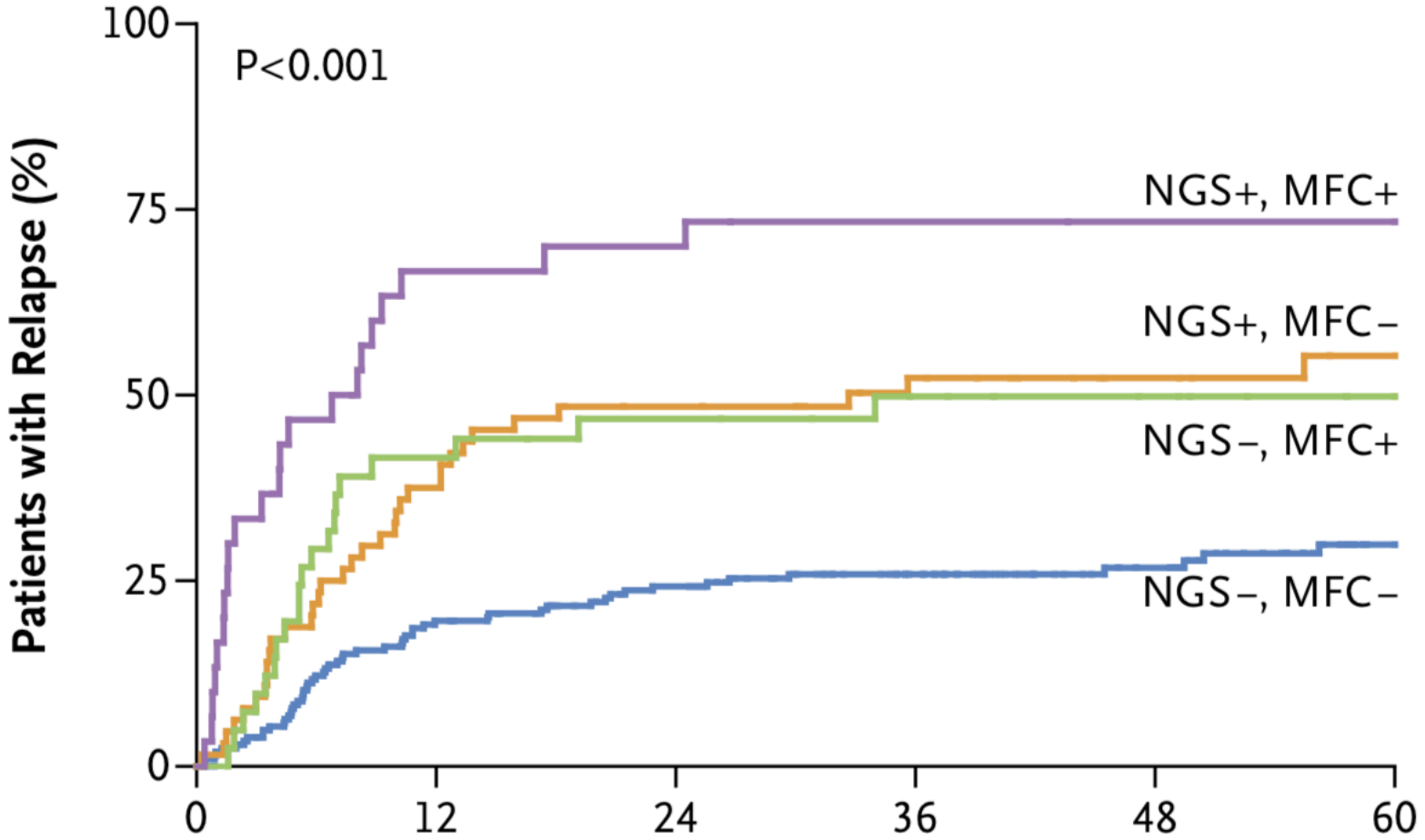
CLL: Meta-Regression Sensitivity Analysis Restricting PFS



Dimier et al., Blood 2018; 131: 955

Using different methods in AML



Jongen-Lavrencic M et al., NEJM 2018; 378: 1189

How should we call MRD?

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Special Report
Blood 2018; 131: 1275

~~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,[8] 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. Ossenkoppele[1]

Workshop Programme: Day 1 (Nov. 8)

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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

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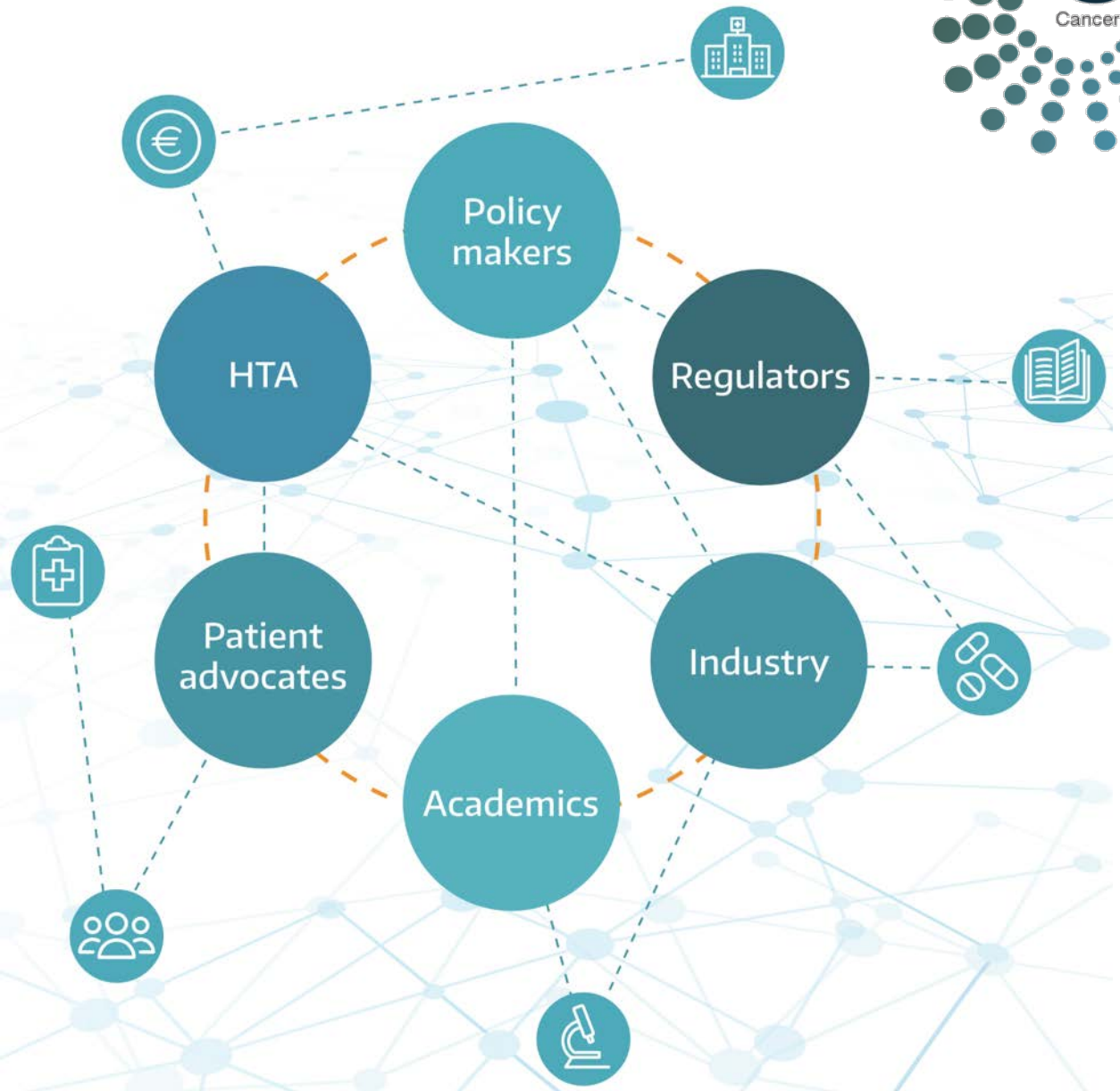
Workshop Programme: Day 2 (Nov. 9)

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



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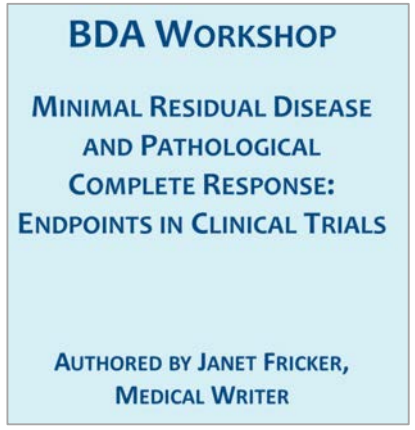
- The Cancer Drug Development Forum is an international organization providing a platform for all stakeholders involved in the development of oncology drugs.
- The aim of the not-for-profit organization is to accelerate the delivery of effective oncology agents to patients.
- Established in 2001 as Biotherapy 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



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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.

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thank you
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謝謝
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рахмат
teşekkür ederim
спасибо
gracias
dank je
tapadh leat
Баярлалаа
bedankt
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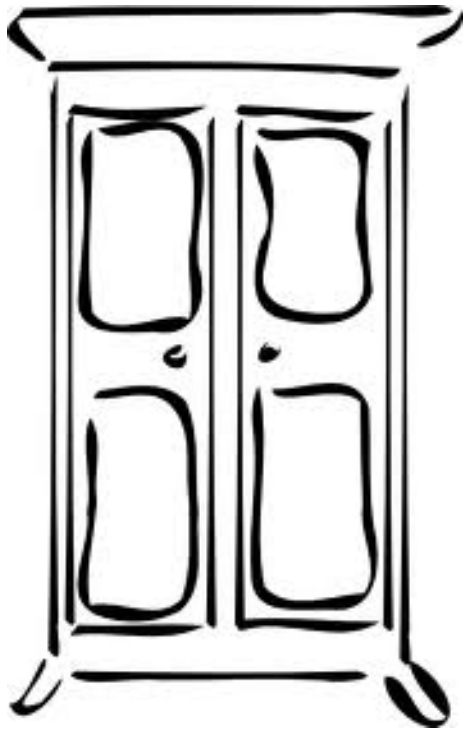
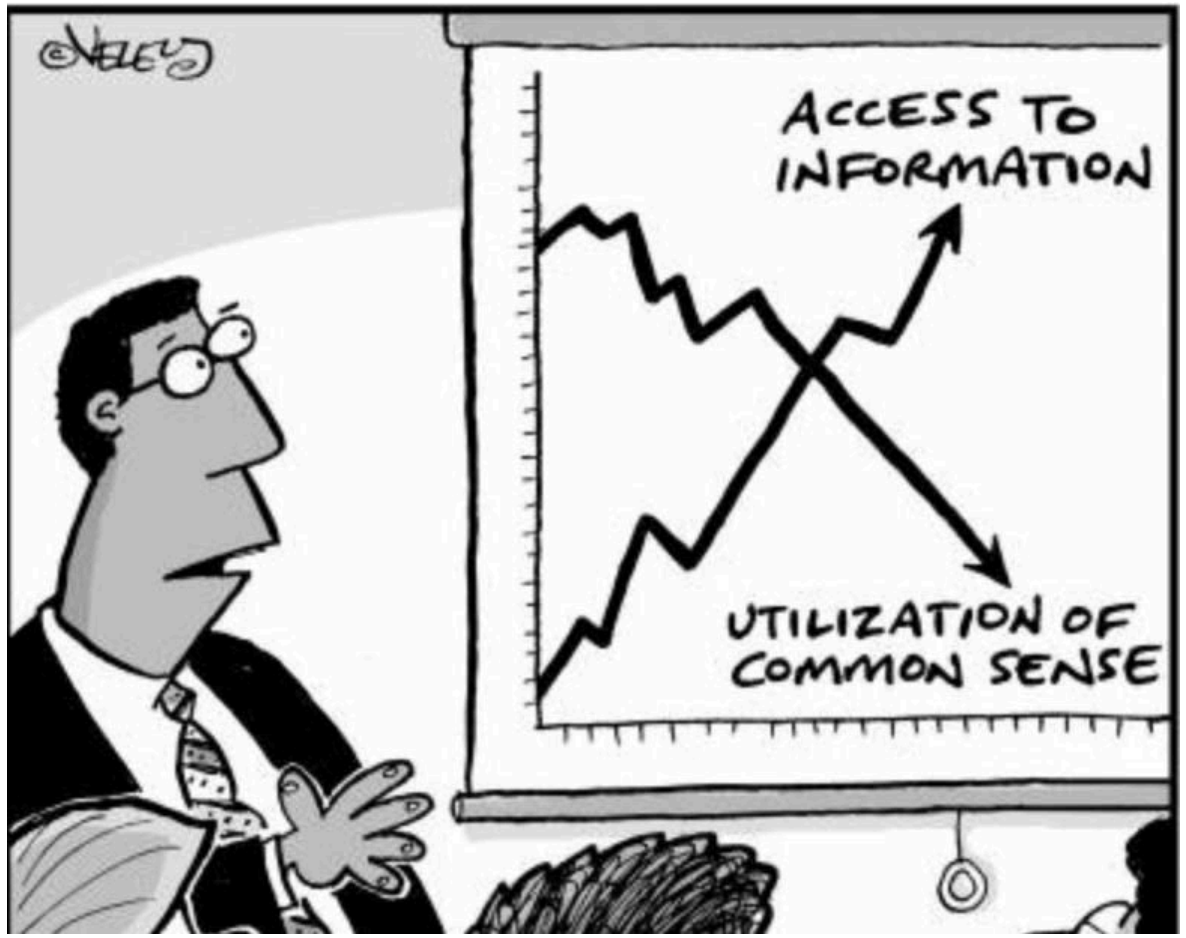


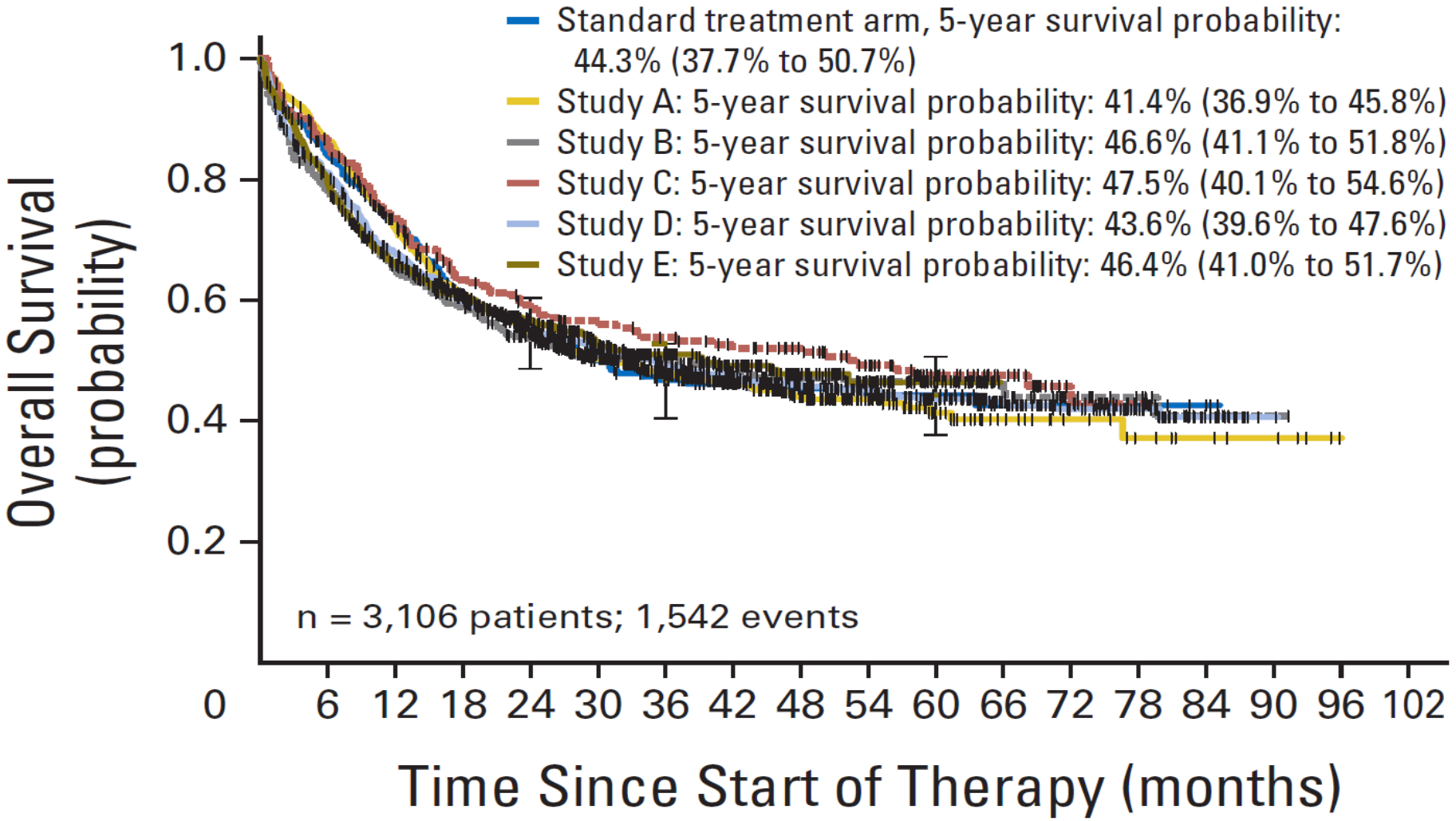
The CDDF will Publish a Meeting Report



CartoonStock.com

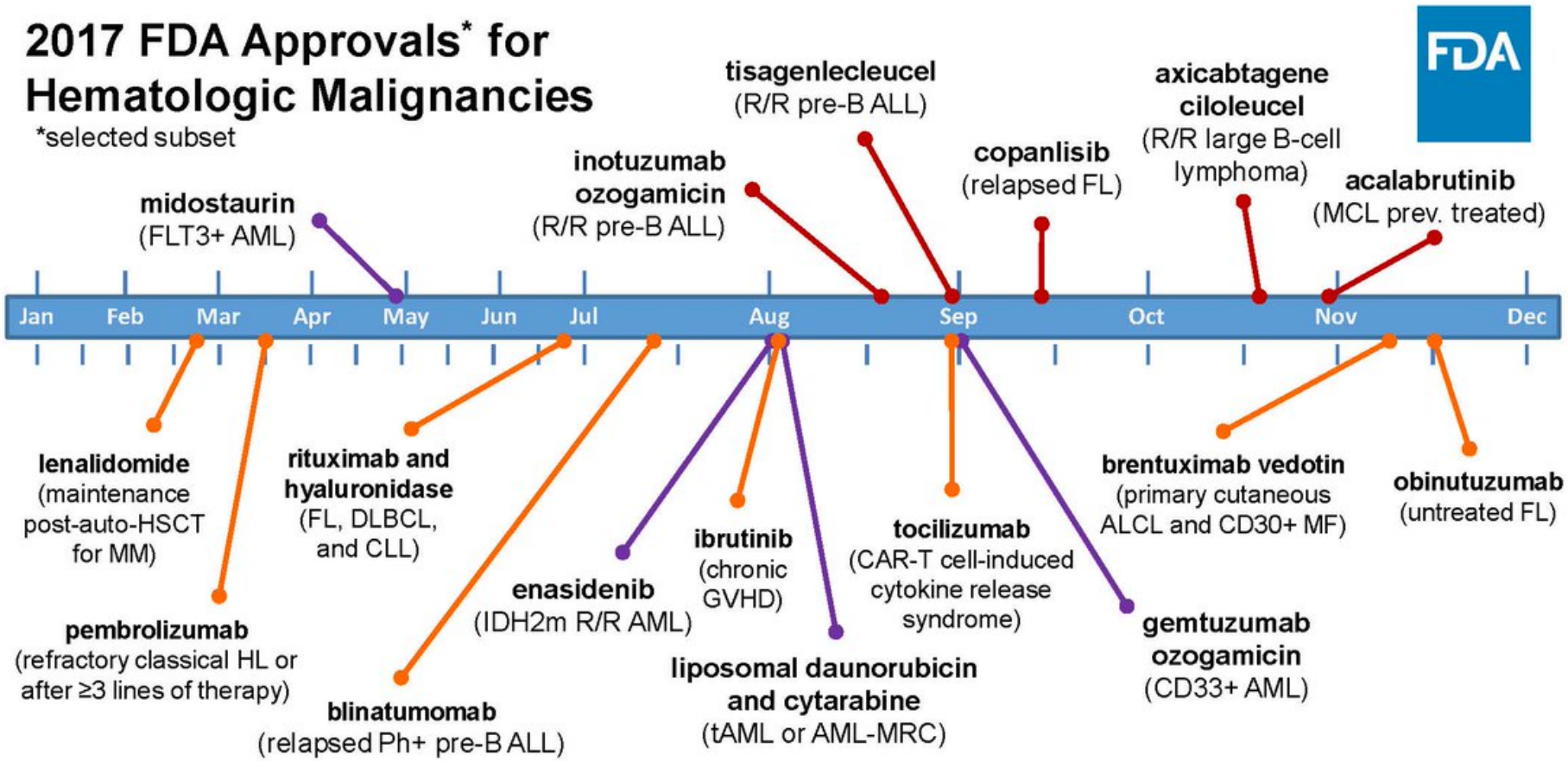
www.cddf.org

German Intergroup Study: Five Concepts and Standard Arm



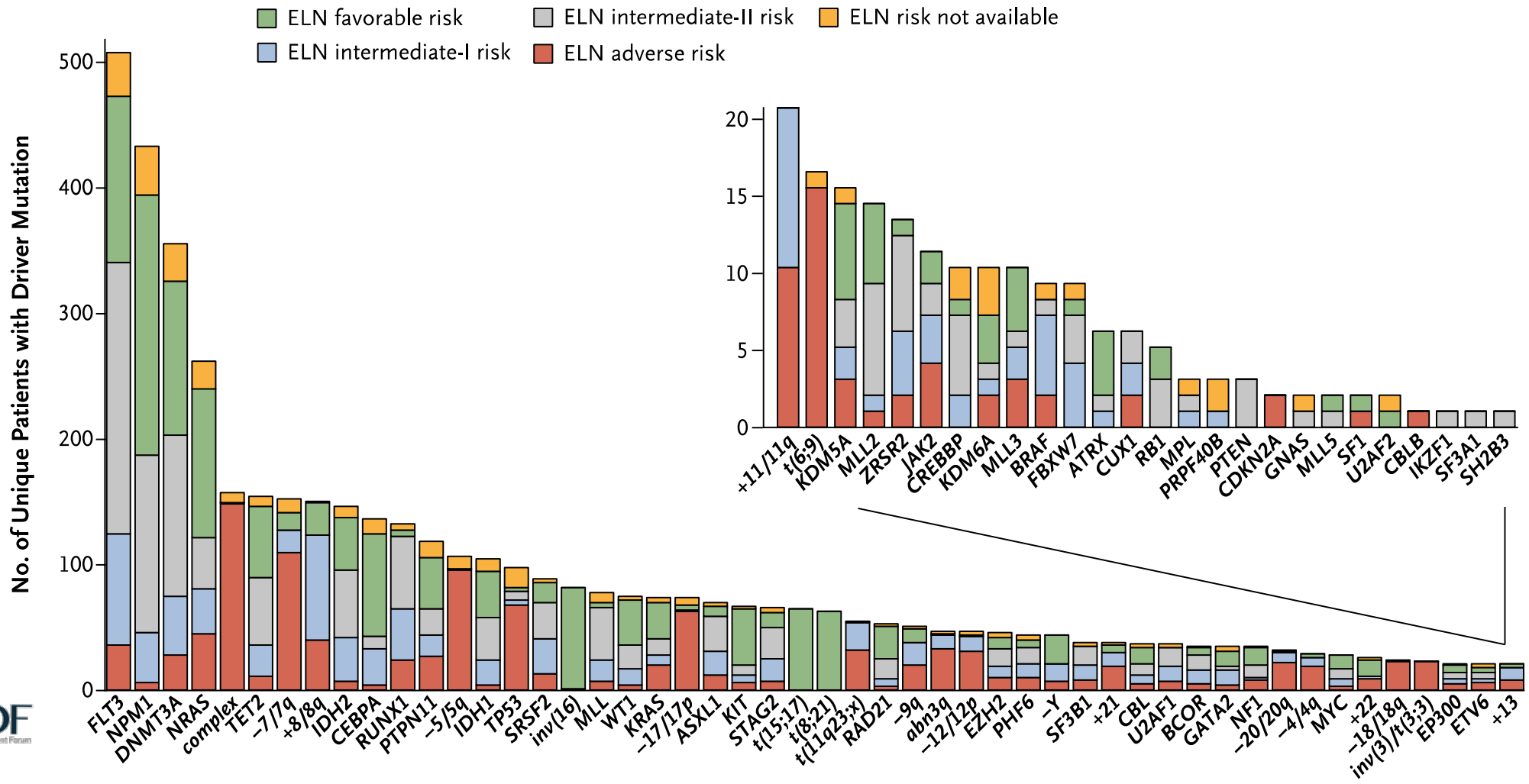
Büchner et al. JCO 2012; 30: 3604

New Approvals in AML



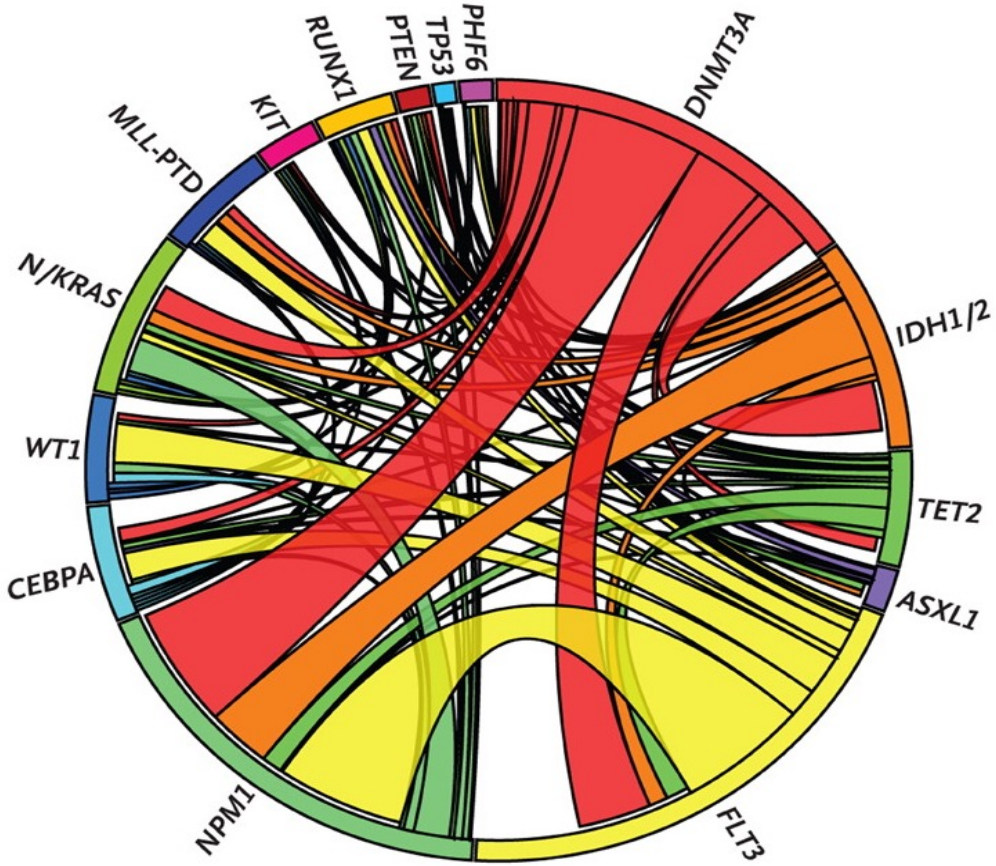
Abbreviations: ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GVHD, graft-versus-host disease; HL, Hodgkin lymphoma; IDH2m, isocitrate dehydrogenase 2 mutated; HSCT, hematopoietic stem 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

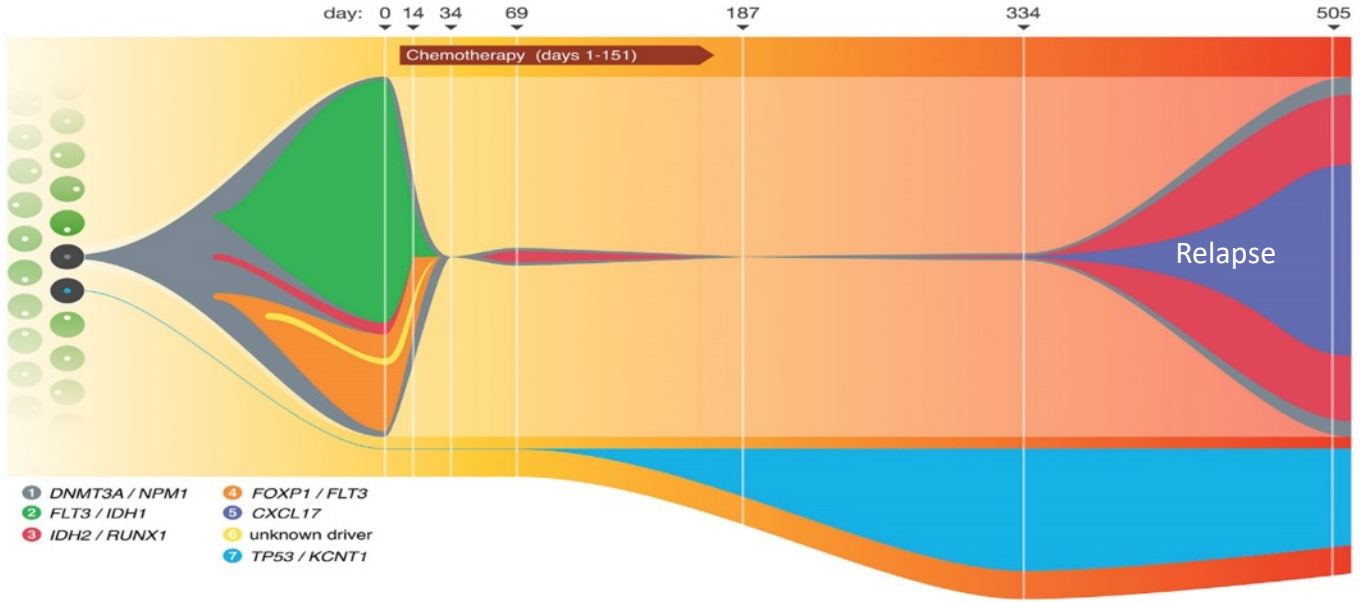


Papaemmanuil et al., N Engl J Med 2016; 374:2209

Genomic Heterogeneity and Clonal Evolution in AML



Patel JP et al. N Engl J Med 2012;366:1079-1089.

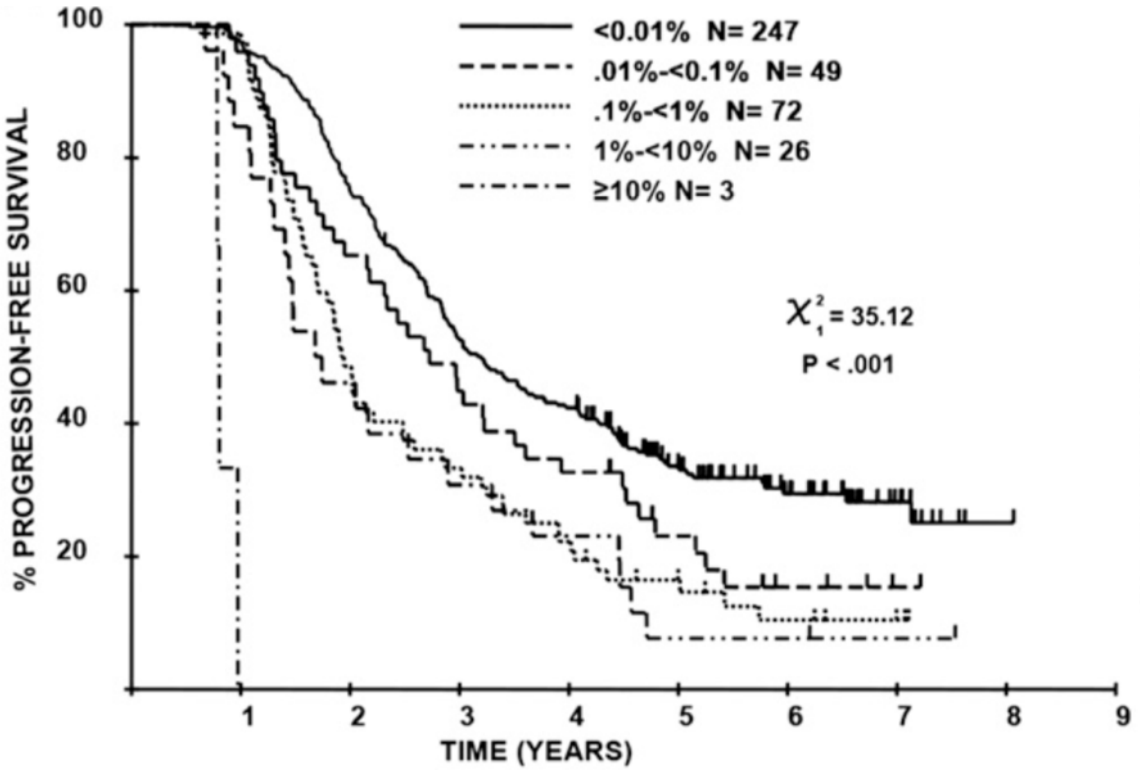


Griffith et al. *Cell Systems* 2015;1:210–23

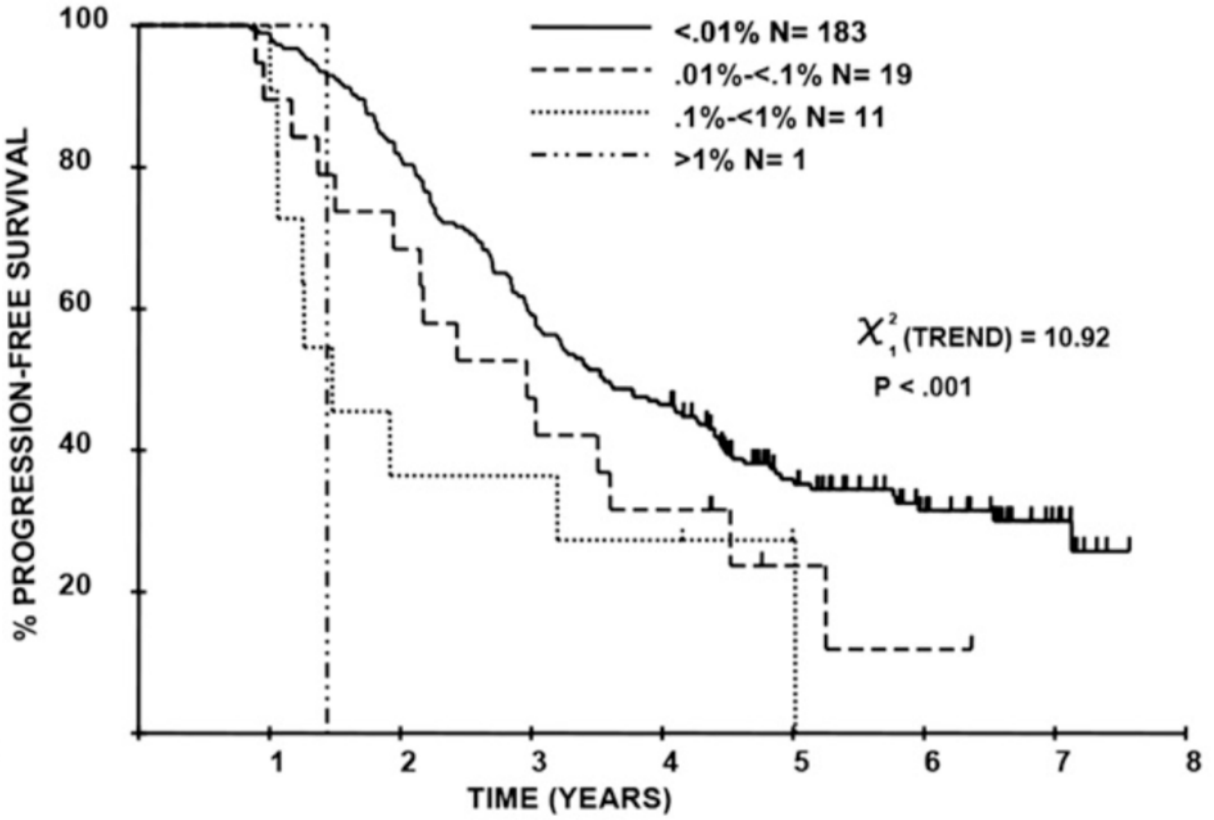
Disease continuum with Myelodysplastic Syndromes (MDS)

Quantitative Relation of MRD and Outcome

MRD Level (log depletion) and PFS in UK MM IX



All Patients

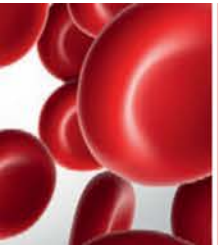


Patients in CR

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

How should we call MRD?

Blood 2018; 131: 1275



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Special Report

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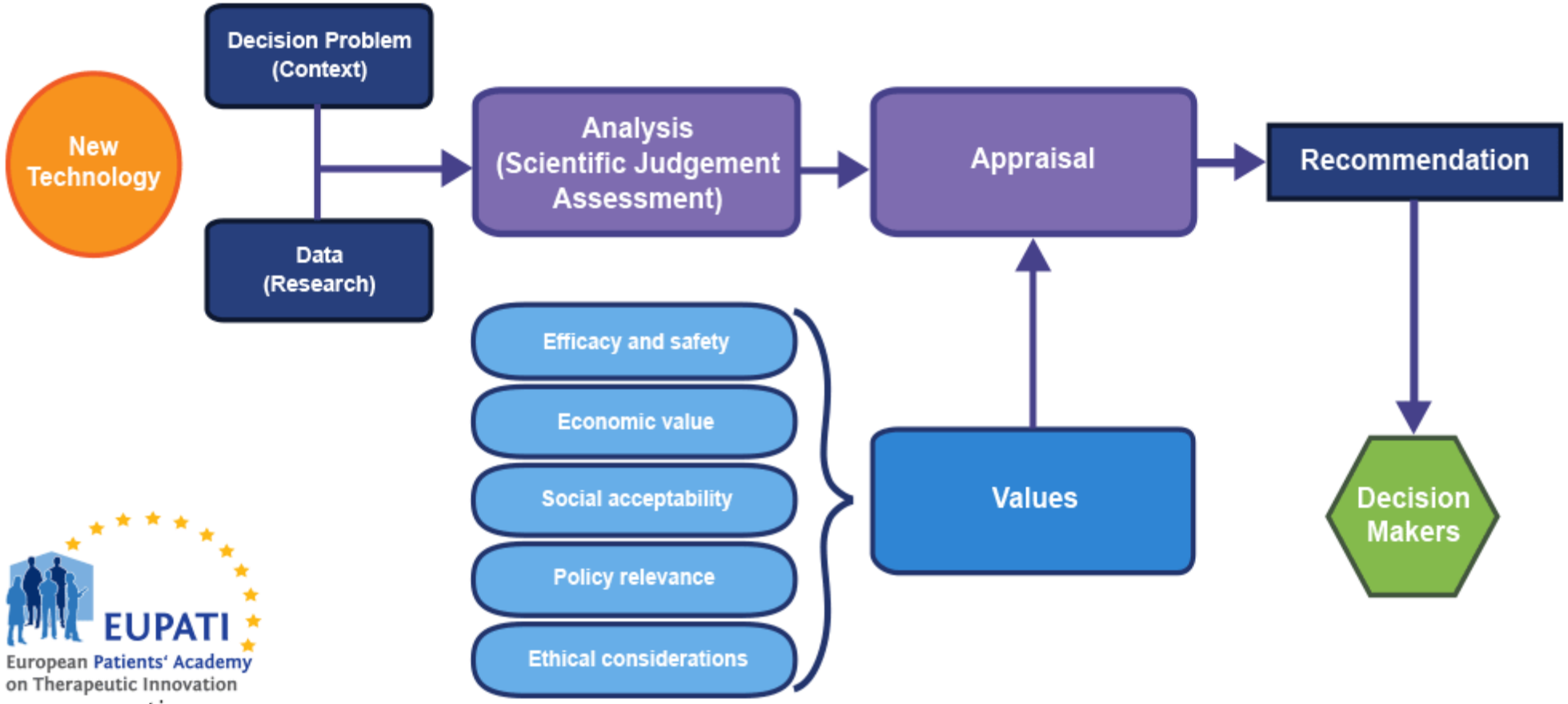
HTA Analysis and MRD Endpoints



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