Minimal Residual Disease (MRD): a potential surrogate endpoint in AML

An industry perspective

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Disclaimer

This presentation is intended for information sharing and discussion purposes, and any views or opinions expressed do not necessarily represent those of Janssen Research and Development LLC, or those of the companies participating in the MRD in AML industry alliance

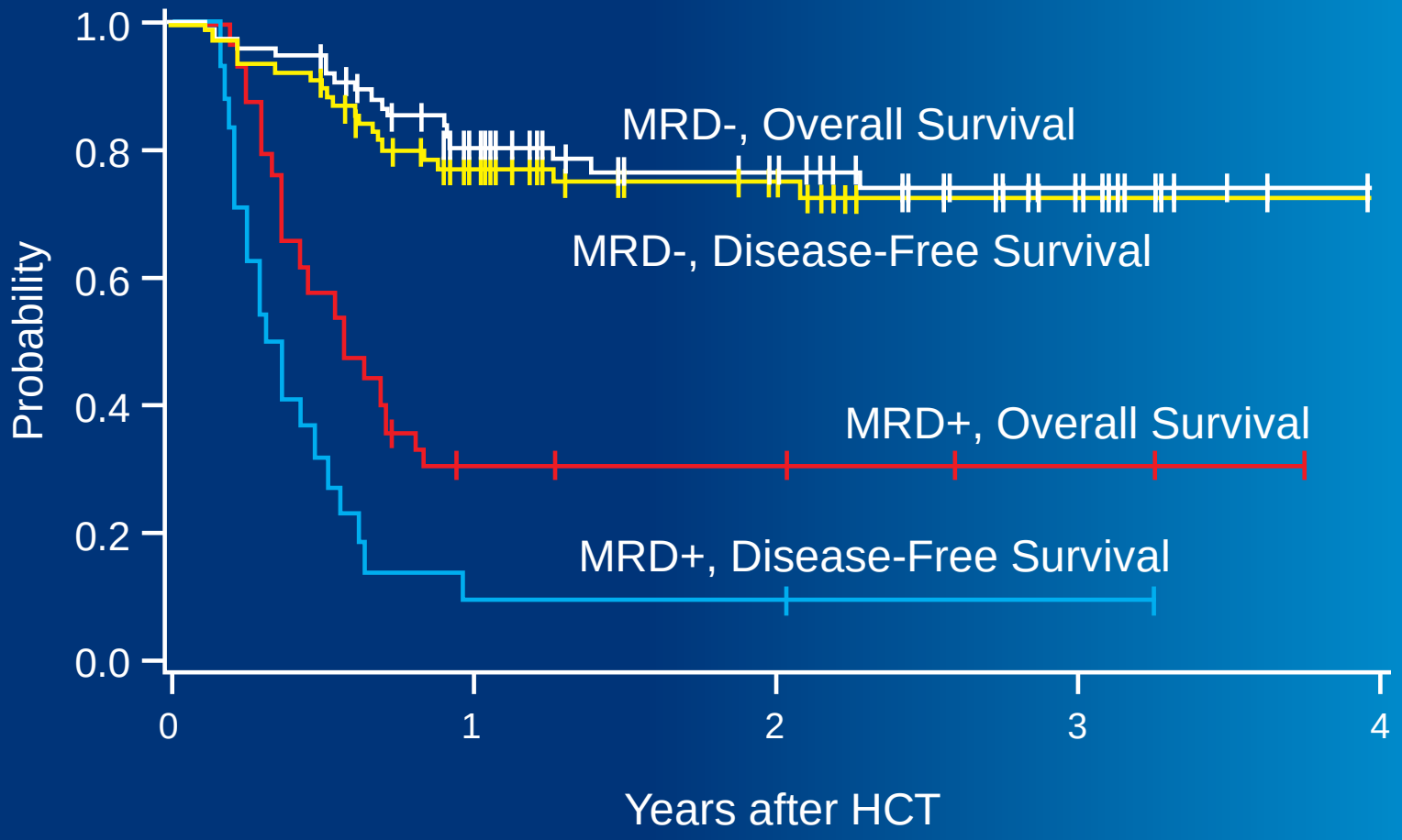
Topics

- Increasing interest in MRD over past 5 years
  - Academic/industry focus
  - Regulatory focus
- Looking forward: path to surrogacy?
  - Early Janssen activities
  - Industry alliance
    - Progress so far
    - Next Steps

MRD

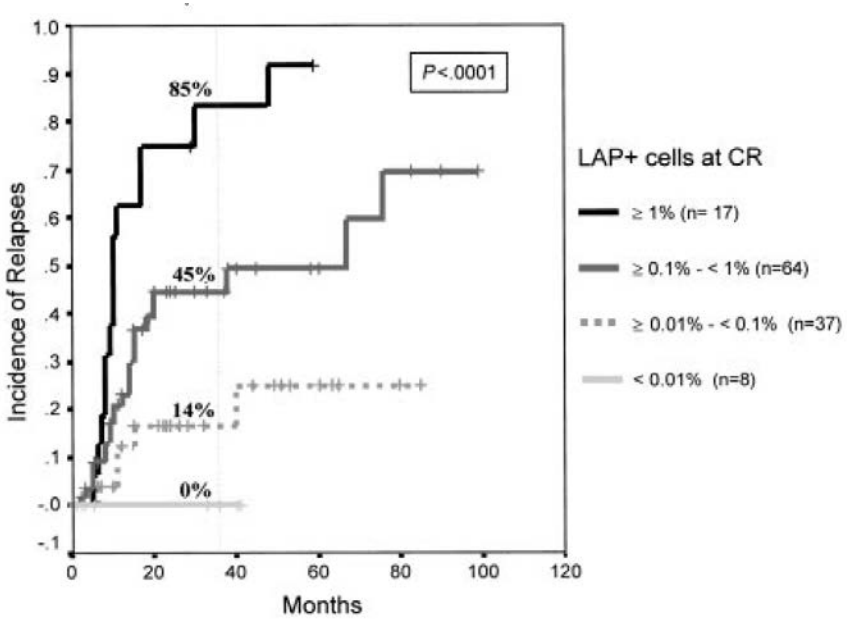
Is it a thing???

OS and DFS according to MRD by Flow status pre-transplant

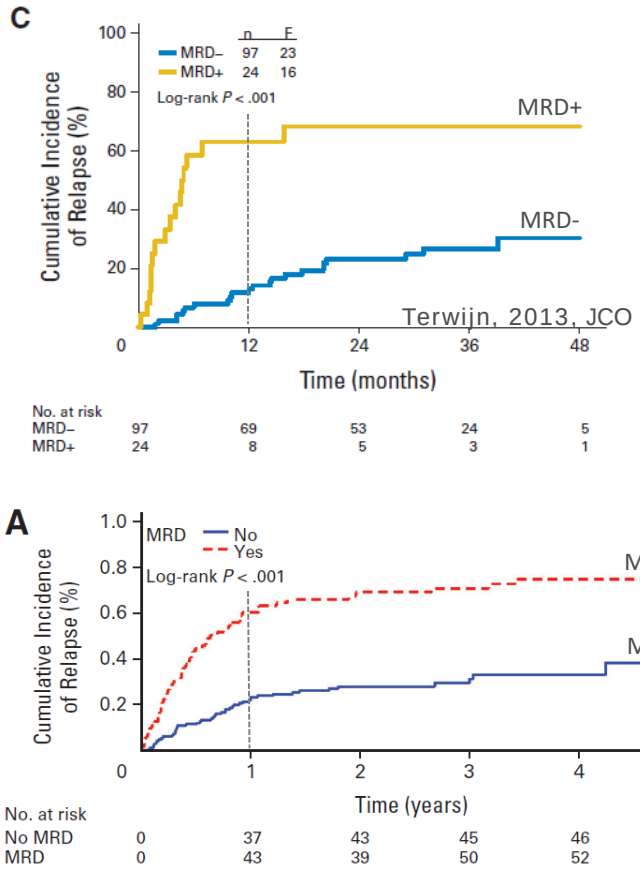


Walter RB, et al. *J Clin Oncol.* 2011 Mar 20;29(9):1190-7.

MRD- status by MFC repeatedly shown to be an independent predictor of relapse and outcomes



San Miguel, 2001, Blood



Chen, 2015, JCO

highly confidential – draft for internal use only

Prospective Molecular MRD Detection By NGS: A Powerful Independent Predictor for Relapse and Survival in Adults with Newly Diagnosed AML

Figure 1:

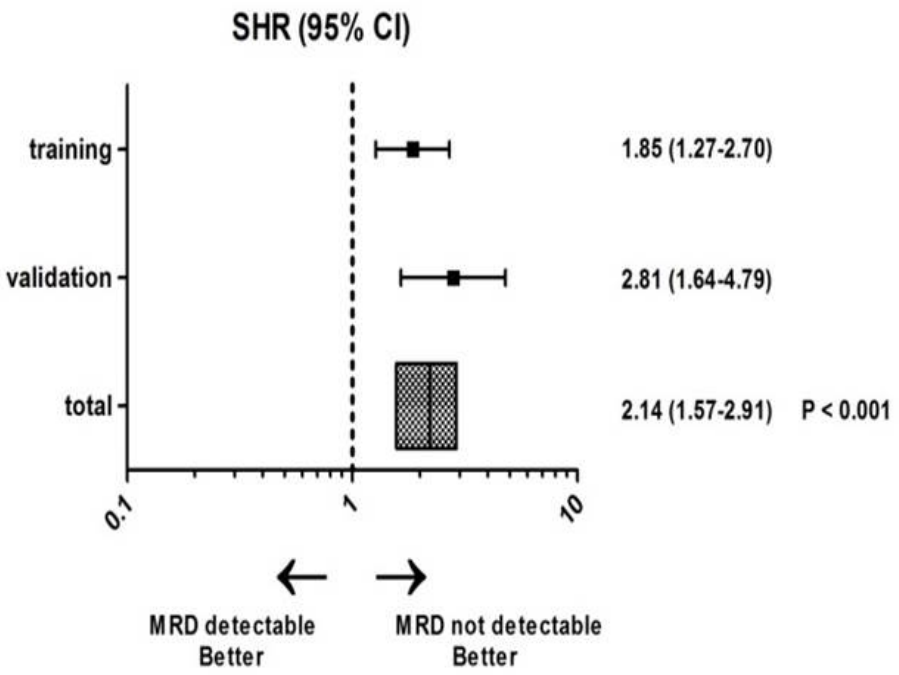
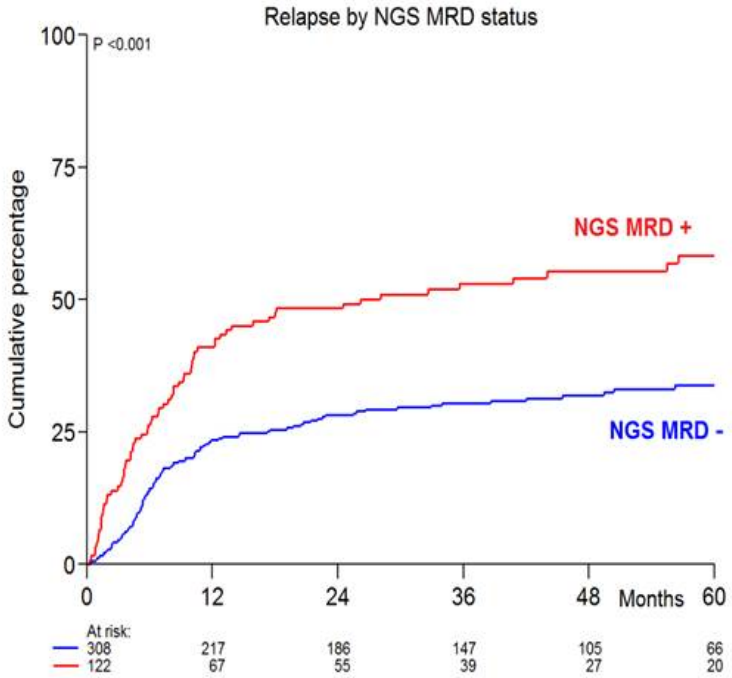


Figure 2:



Mojca Jongen-Lavrencic, MD, PhD[1], Tim Grob, MD[1*], Francois G. Kavelaars[1*], Adil S.A. Al Hinai[1*], Annelieke Zeilemaker[1*], Claudia A.J. Erpelinck-Verschueren[1*], Yvette Norden[2*], Rosa Meijer, PhD[2*], Bart J. Biemond, MD, PhD[3*], Carlos Graux[4*], Marinus van Marwijk Kooij, MD, PhD[5*], Markus G. Manz, MD[6], Thomas Pabst, MD, PhD[7], Violaine Havelange, MD, PhD[8*], Jakob R. Passweg, MD, PhD[9*], Gert J. Ossenkoppele, MD, PhD[10], Gerrit Jan Schuurhuis, PhD[10*], Mathijs A. Sanders, PhD[1*], Bob Löwenberg, MD, PhD[1] and Peter J.M. Valk, PhD[1]. ASH Dec 2017

MRD- CR as a newly recommended response criterion in 2017

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel

Hartmut Döhner,[1] Elihu Estey,[2] David Grimwade,[3] Sergio Amadori,[4] Frederick R. Appelbaum,[2] Thomas Büchner,[5] Hervé Dombret,[6] Benjamin L. Ebert,[7] Pierre Fenaux,[8] Richard A. Larson,[9] Ross L. Levine,[10] Francesco Lo-Coco,[4] Tomoki Naoe,[11] Dietger Niederwieser,[12] Gert J. Ossenkoppele,[13] Miguel Sanz,[14] Jorge Sierra,[15] Martin S. Tallman,[10] Hwei-Fang Tien,[16] Andrew H. Wei,[17,18] Bob Löwenberg,[19] and Clara D. Bloomfield[20]

BLOOD, 26 JANUARY 2017 • VOLUME 129, NUMBER 4

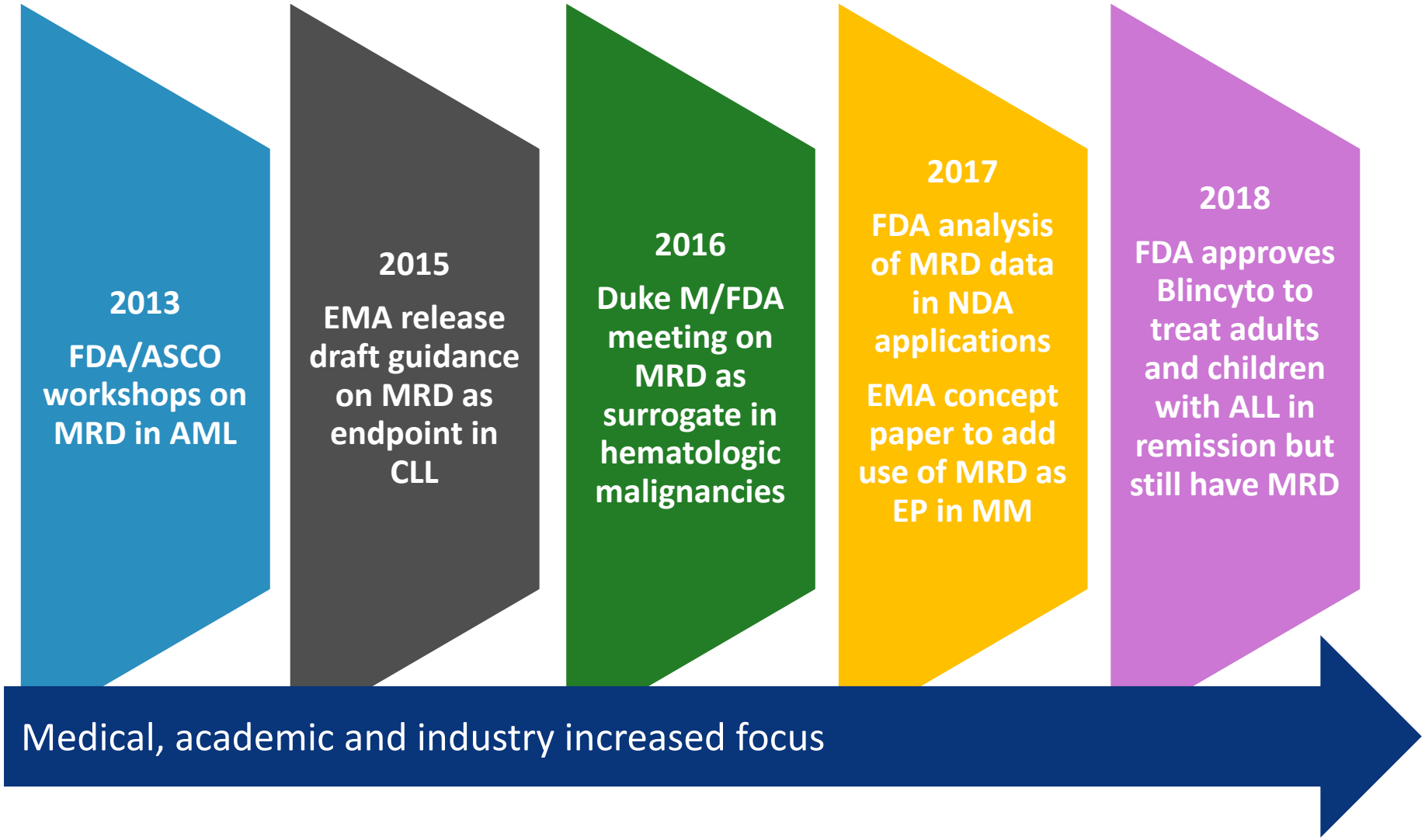
Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party

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]

Schuurhuis et. al., 2018, Blood 131(12):1275-1291

highly confidential – draft for internal use only

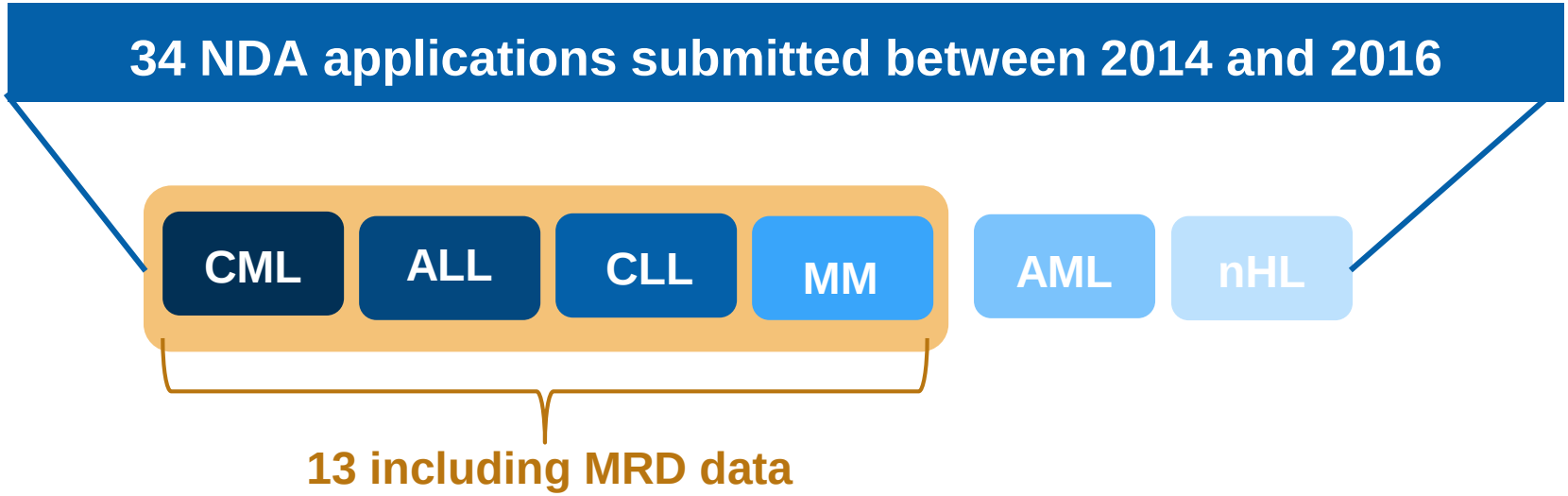
Key regulatory milestones for MRD 2012-2018



FDA analysis of MRD data in hematologic malignancy applications.

Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 2541-2541.

Nicole Gormley, Vishal Bhatnagar, Lori A. Ehrlich, Bindu Kanapuru, Hyon-Zu Lee, Amy E. McKee.



Conclusions: Nearly 40% of applications submitted to DHP between 2014 and 2016 included MRD data. While the data submitted was deemed adequate for inclusion in the PI in 46% of cases, 31% of applications contained MRD data that the Agency deemed un-interpretable. Data collection and assay performance characteristics should be of significant rigor and completeness to allow for comprehensive review.

FDA draft guidance MRD Oct2018.pdf - Adobe Reader
File Edit View Window Help
4 / 21 137% Fill & Sign Comment

15th Oct 2018

Contains Nonbinding Recommendations

Draft — Not for Implementation

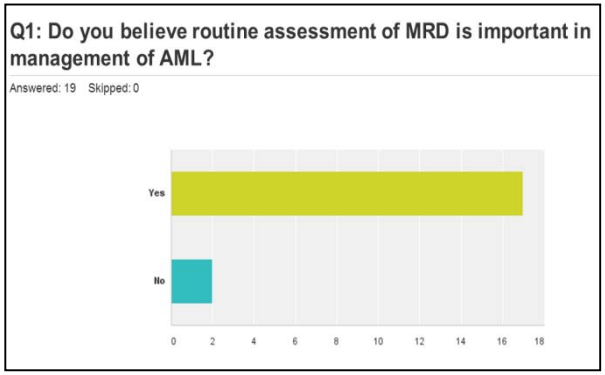
Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry[1]

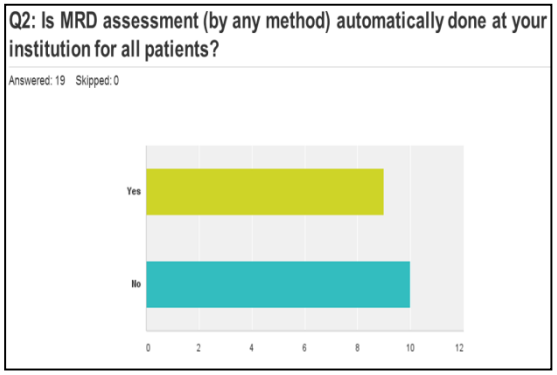
This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

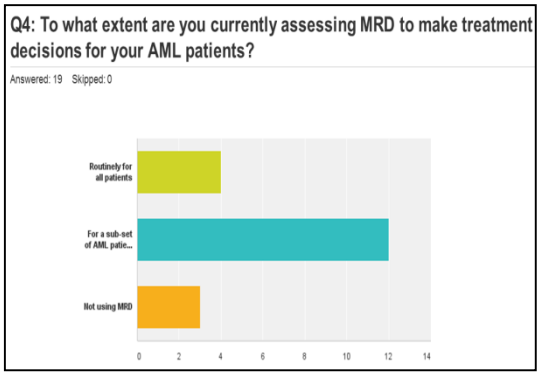
Janssen early activities for MRD in AML

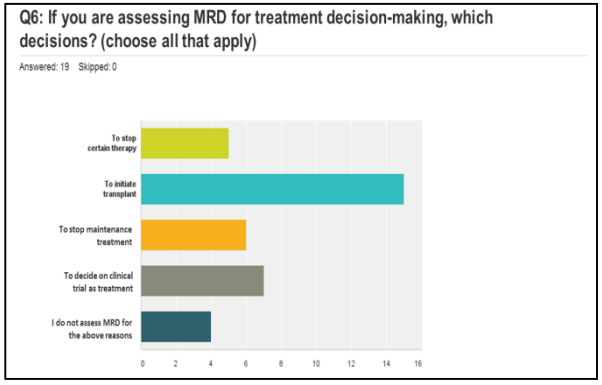
AML Ad Board Oct 2015	• Understand current applicability of MRD in clinical practise (e-questionnaire) • Future utility through standardised methods
MRD Ad Board Dec 2015	• Outline conceptual plan for pathway to surrogacy • Focus on methods, patient settings and CT designs
FDA meeting : April 2016 MHRA, DKMA : April 2017	• Collaborative effort with Gail Roboz and Gert Ossenkoppele • Review conceptual plan for pathway to surrogacy • Follow-up discussions for SAP and consider partnering
Duke M/FDA Public meeting Sept 2016	• Janssen invited to participate in panel discussion • 'Call to arms' for industry collaboration
MRD Ad Board Dec 2016-2017	• Ongoing refinement with focus on strength of existing evidence and pathway to surrogacy

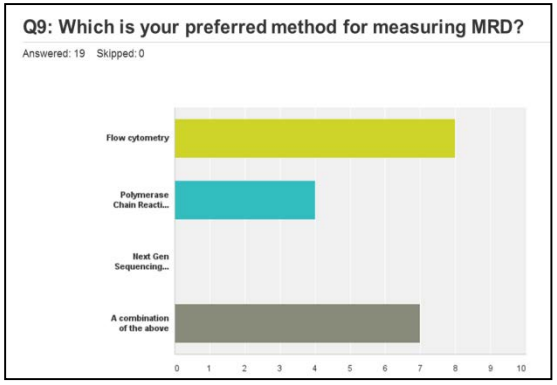
AML Ad Board: Oct 2015

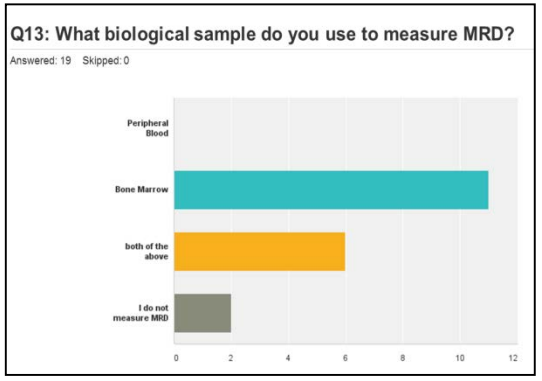






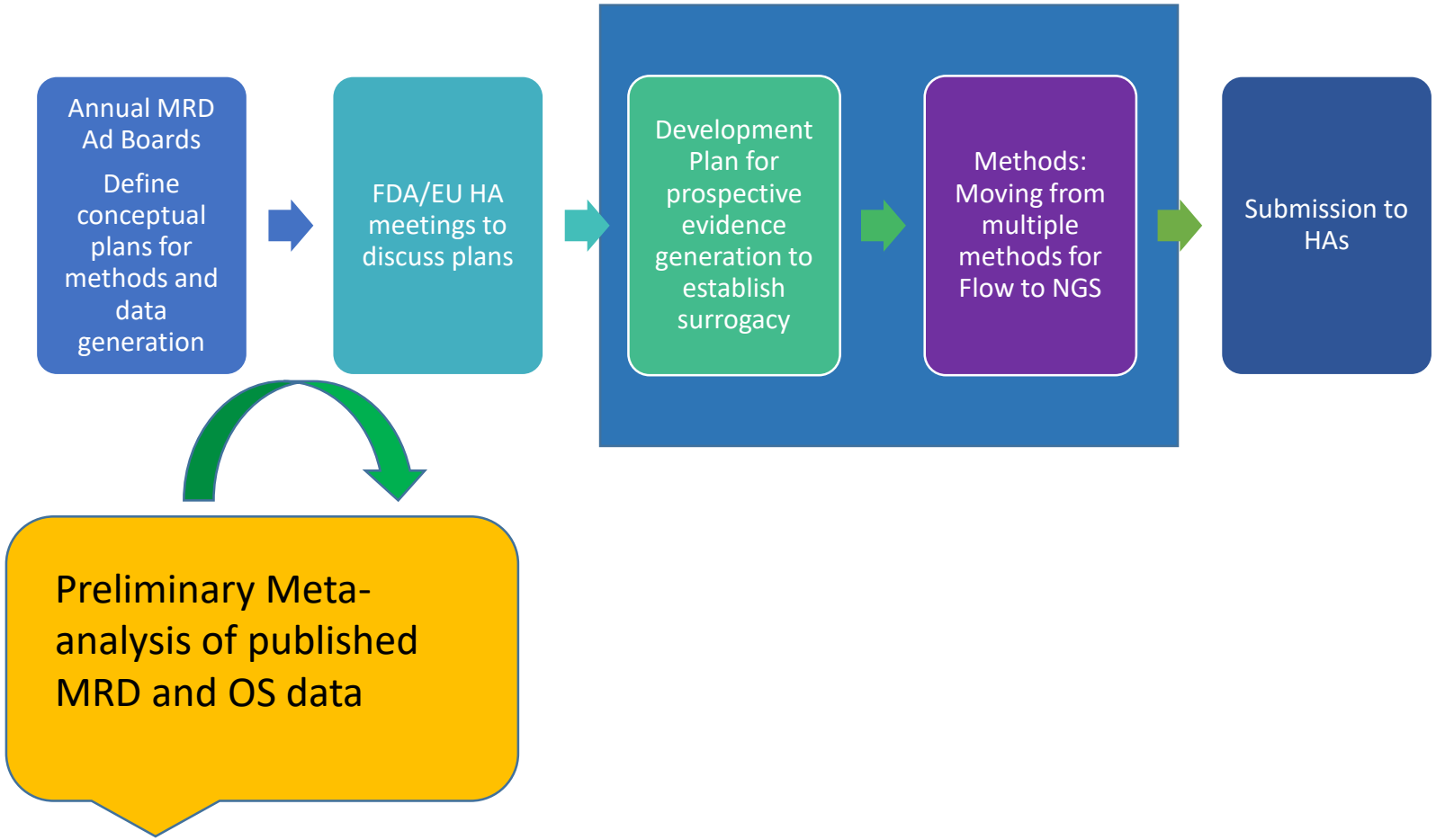






Appreciation of importance of testing MRD, but with great heterogeneity around current utility in clinical practice

Janssen Pathway to determine MRD as a surrogate for OS in AML



Preliminary Meta-Analysis of Published Data

- Objective to systematically evaluate strength of ‘signal’ widely reported in the literature
  - Janssen previously conducted targeted literature review Nov 16
  - Prognostic association between MRD and OS
  - Learning exercise for future meta-analysis

- Vendor conducted targeted literature review to cross-check previously identified literature and to update the review with recently released literature
  - Protocol pre-specified selection criteria for studies to be included, statistical methods etc

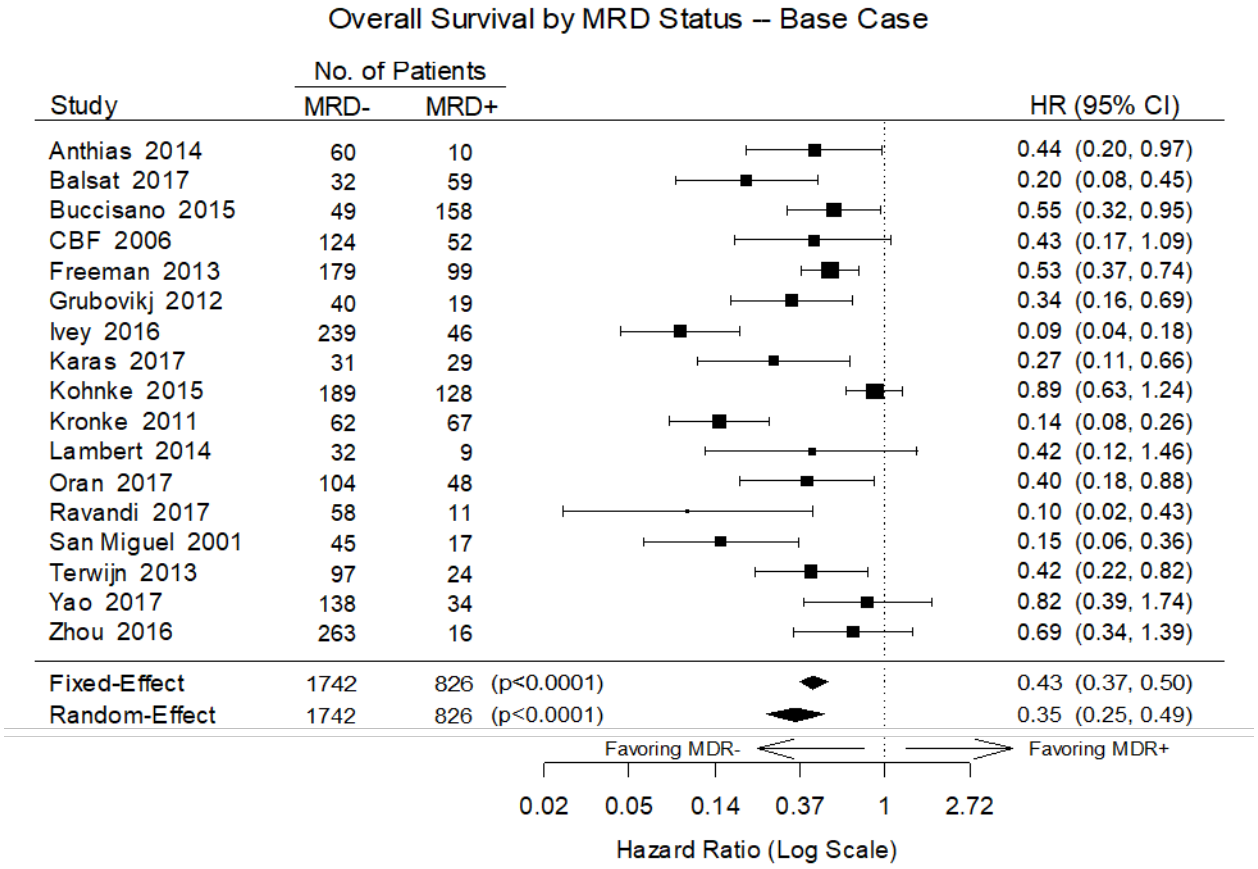
Study Selection Criteria

Parameter	Selection criteria*
Population	16+ years
Disease characteristics	AML only
AML Setting (FL, Induction, Maintenance, Other)	All settings
Endpoints	Study must report MRD negativity May also report: CR, OS, EFS, RFS, DFS
Study design	RCTs NRS
Method of MRD detection	All
Number of MRD measurements	At least one MRD measurement
Sample size	≥50 participants

* Selection Criteria agreed with KOLs at ASH Ad Board Dec 17

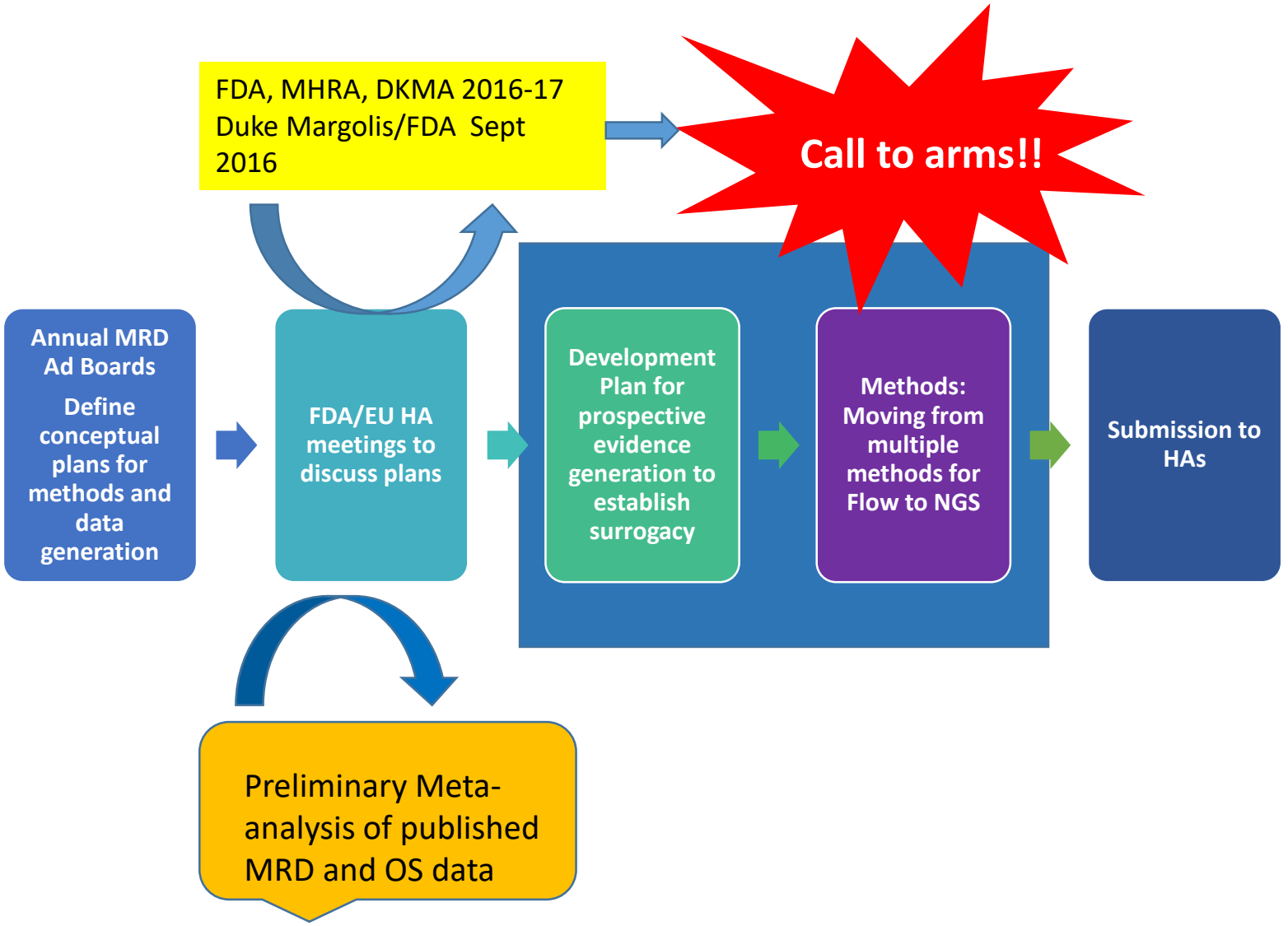
Output: 32 publications identified: 31 full papers and 1 conference proceeding

Meta-Analysis MRD studies: preliminary results



Significantly lower hazard rate of death for MRD- vs. MRD+ patients

Janssen Pathway to determine MRD as a surrogate for OS in AML



MRD in AML
Industry Alliance

Partner Industry Stakeholders

Integrated MRD strategy to support surrogacy: 3 Focus Areas

Methods

- Actively collaborate to evaluate potential for core NGS platform as possible future primary method
- Share expertise and resources to optimise and harmonise current flow methods

1

Data

- Harmonise generation of MRD data across portfolios: agree cut-off and schedule/timing of MRD assessments
- Build consolidated plan for MRD data read-outs across 4 companies
- Determine submission strategy

2

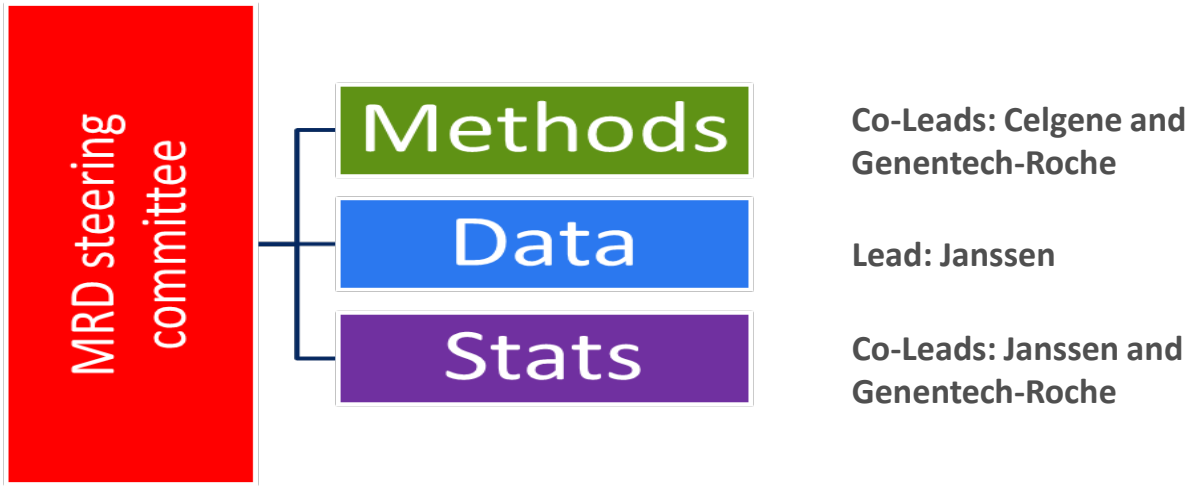
Stats

- Agree on content of SAP for meta-analysis
- Identify 3rd party data gate-keeper and agree scope of work and funding

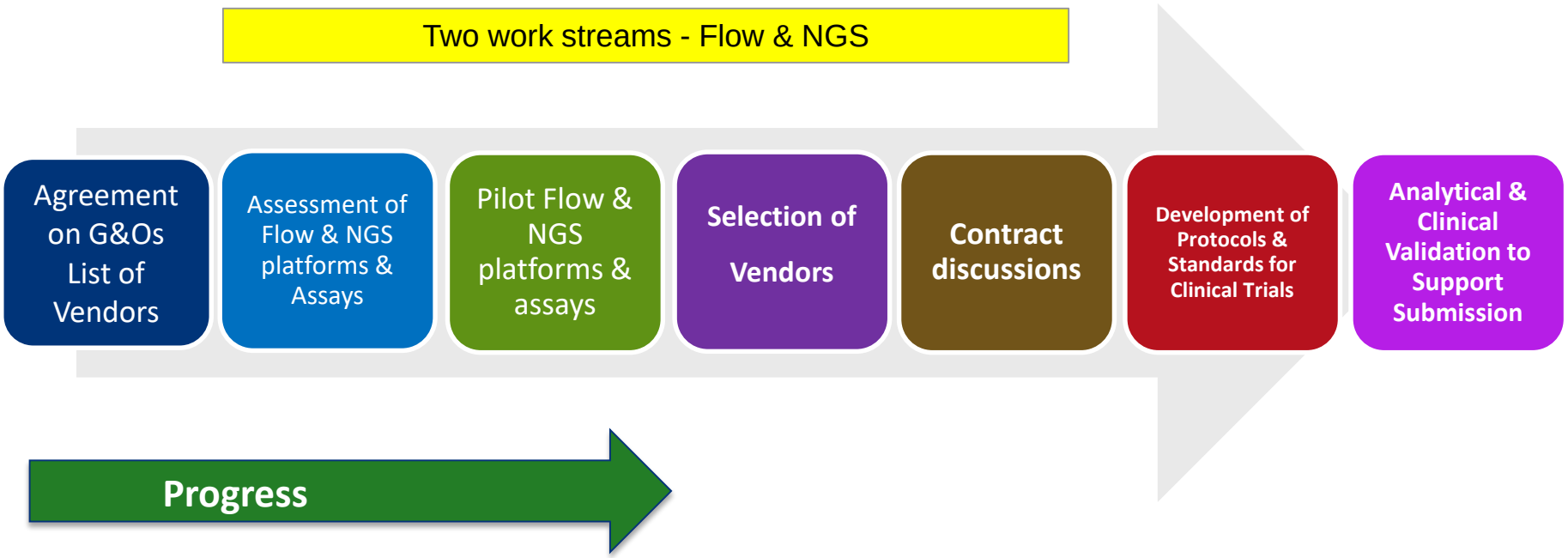
3

MRD Industry Alliance: Operational Aspects

1. Form MRD Joint Steering Committee (JSC) to define goals, deliverables and timelines
2. JSC to consider key potential confounders (e.g. legal, confidentiality issues, finances, broader collaborations)
3. Assign goals/deliverables to specialist working groups to advance Methods; Data; Stats
4. Meet F2F at least twice yearly (EHA, ASH), and bi-monthly in between as needed.

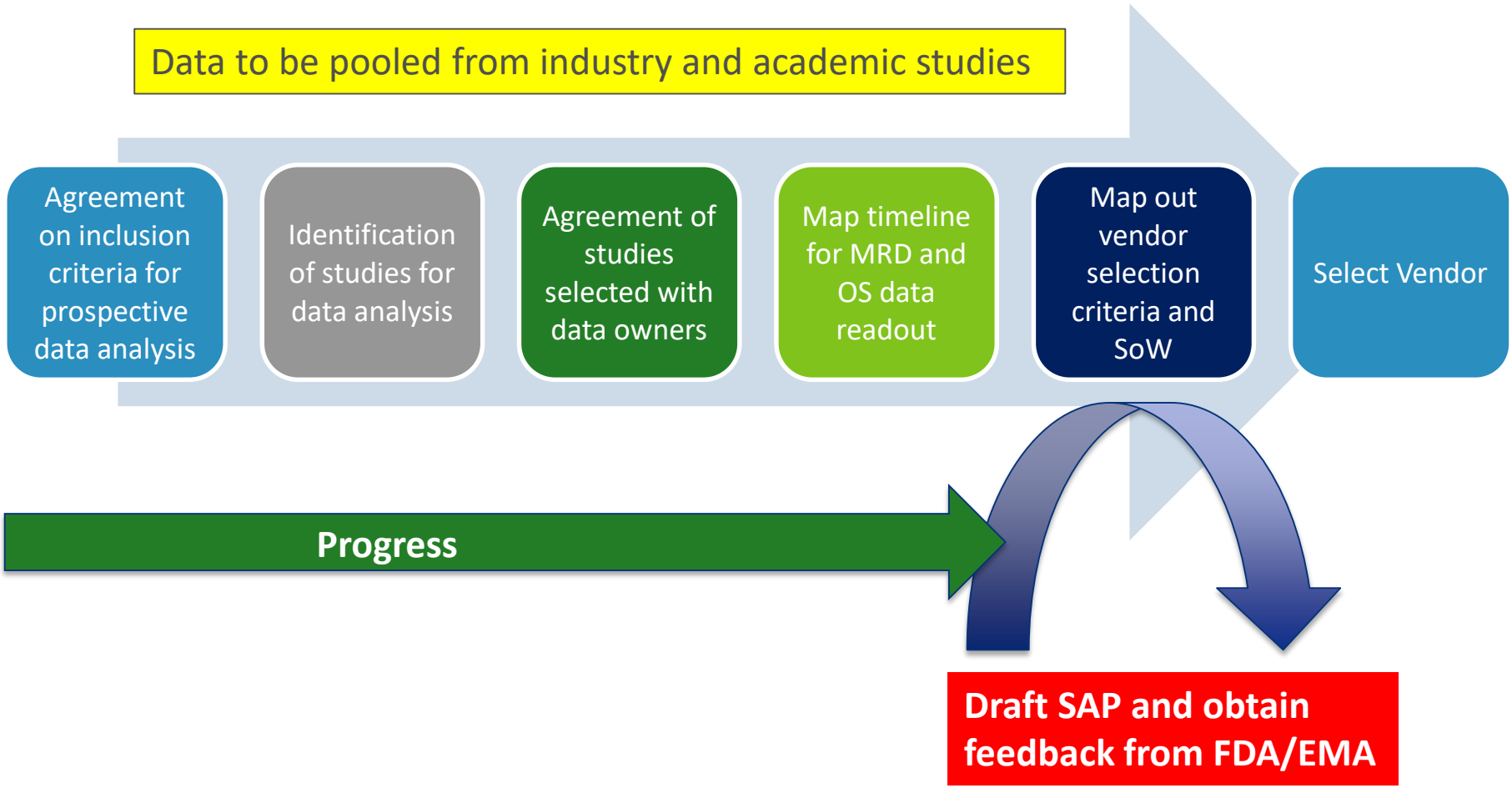


MRD Methods Work-stream



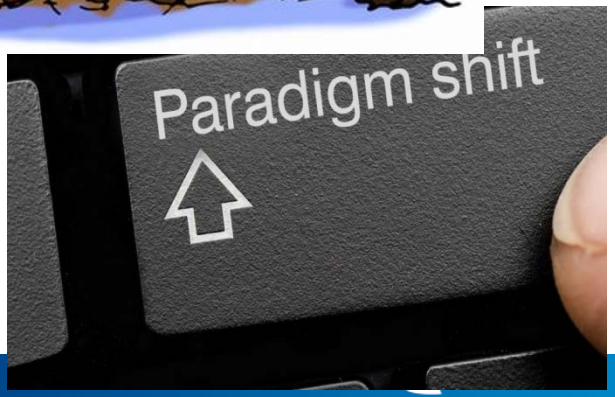
janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Data and Stats Work-Stream



Will there be a paradigm shift toward MRD as a surrogate?

By kind permission of Dr G Ossenkoppele

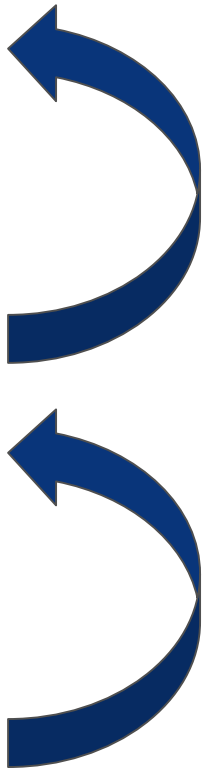


Surrogate endpoint definitions:

1) A **validated surrogate endpoint** is one that is supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate predicts a clinical benefit; therefore, such endpoints can be used to support traditional approval without the need for additional efficacy information

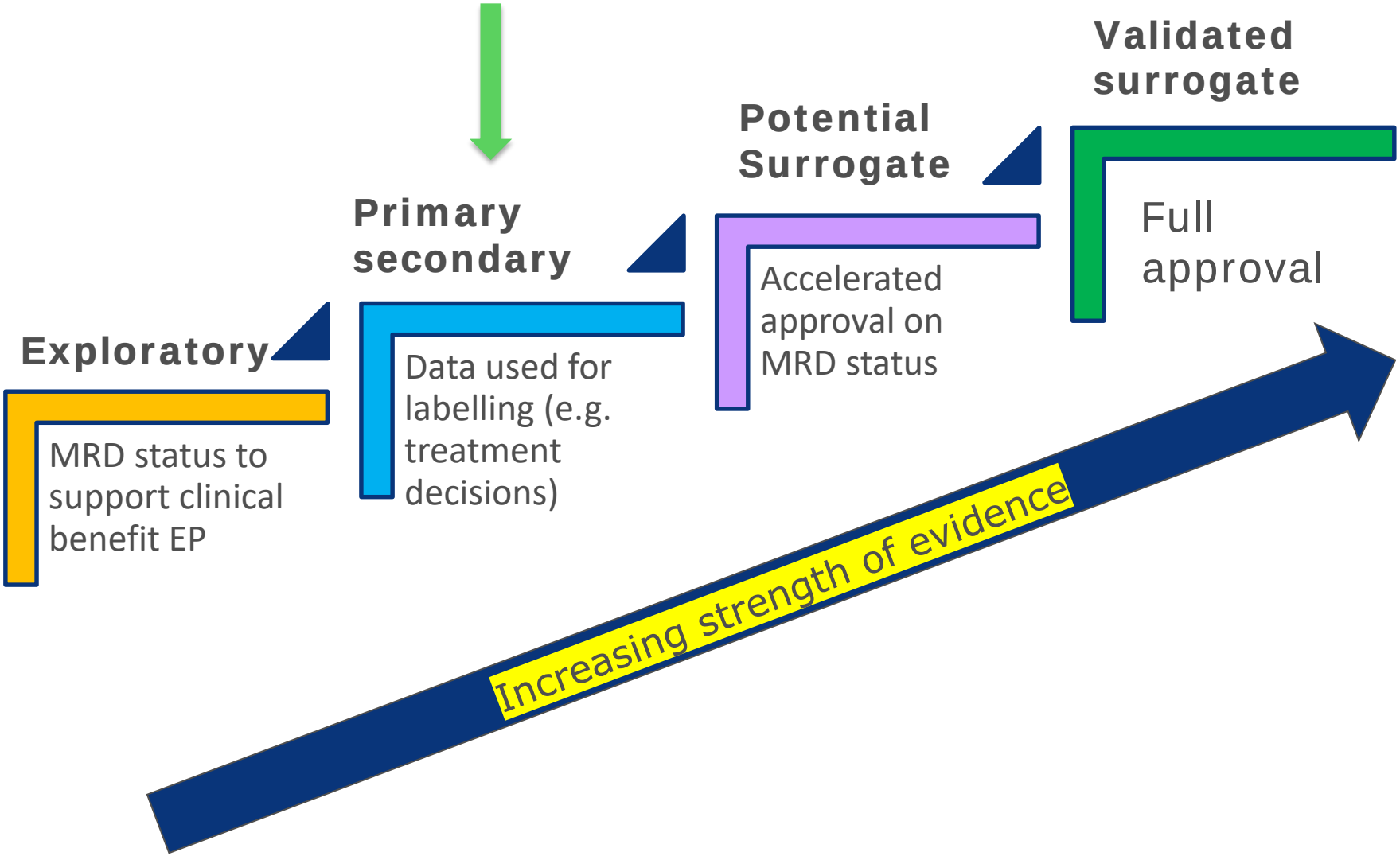
2) A **reasonably likely surrogate endpoint** is supported by clear mechanistic and/or epidemiologic rationale but insufficient clinical data to show that it is a validated surrogate endpoint; such endpoints can be used for accelerated approval for drugs or expedited access for medical devices

3) A **candidate surrogate endpoint** is still under evaluation for its ability to predict clinical benefit

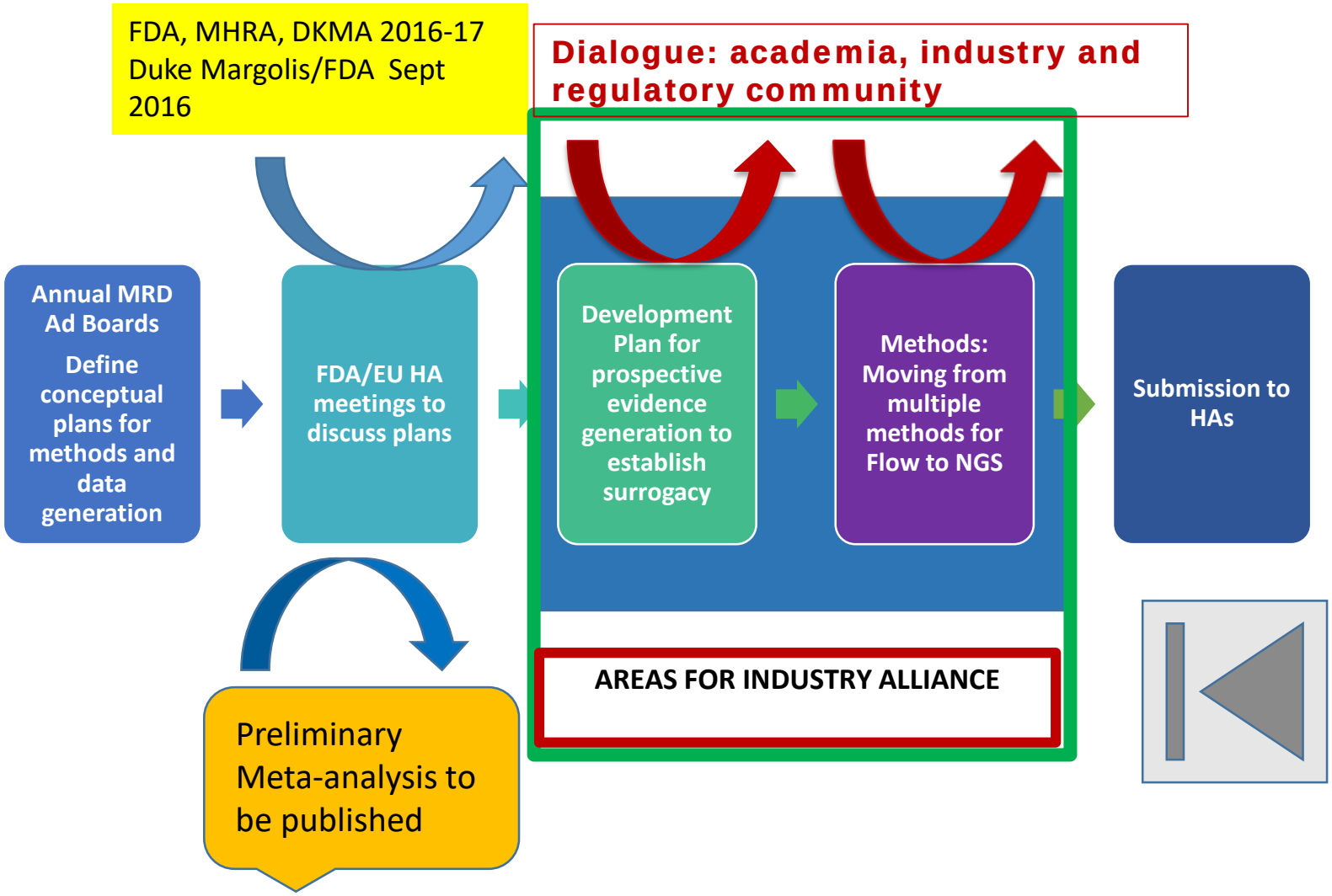


NIH-FDA joint BM team 2015 [2]

MRD as endpoint in clinical trials



Pathway to determine MRD as a surrogate for OS in AML



Lessons from the ledge: Alison Levine at TEDxMidwest
TEDxMidwest
x=independently organized TED event
ALISON LEVINE
Team Captain, First American
Women's Everest Expedition
0:02 / 18:07

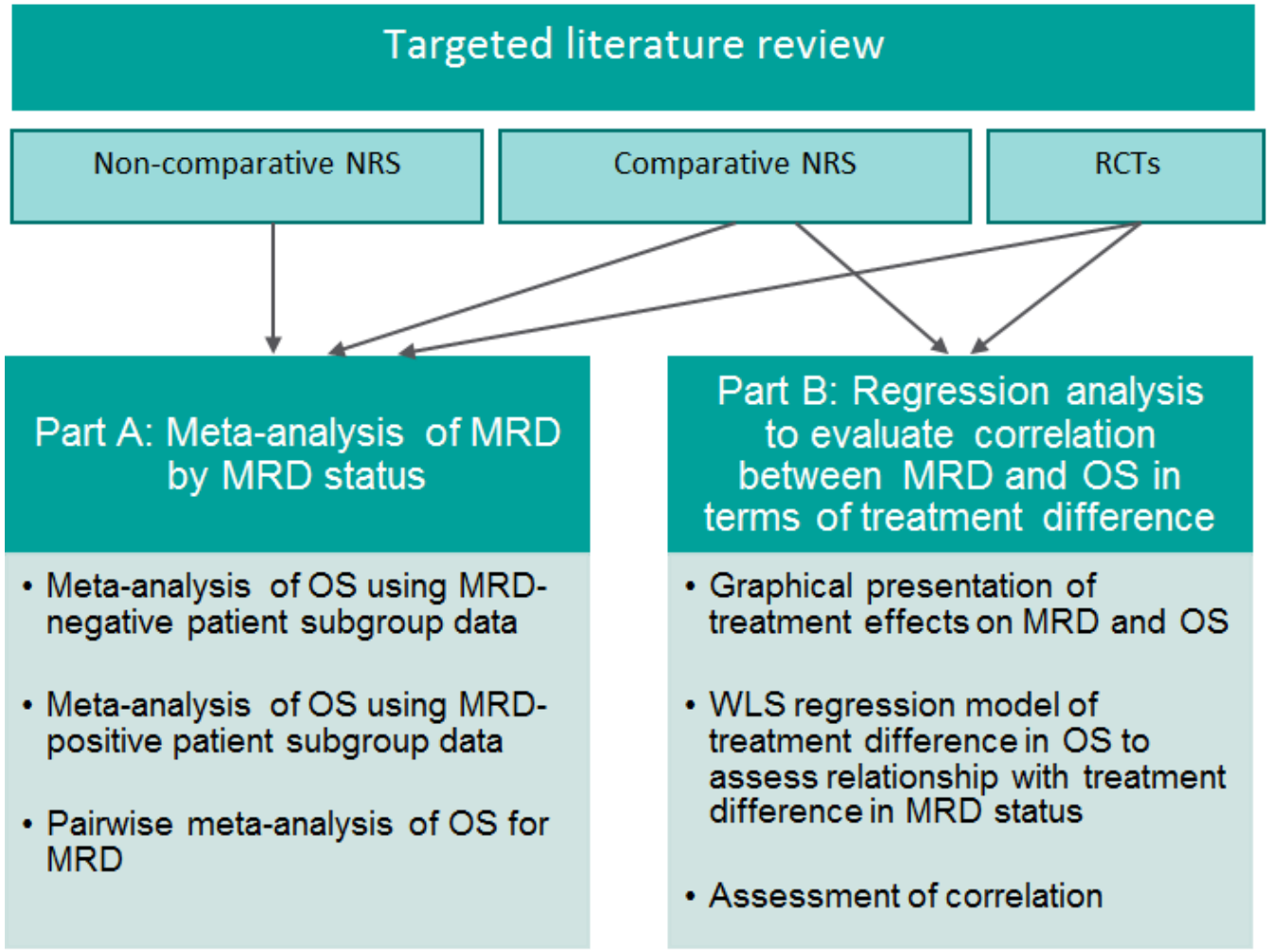
MT. EVEREST SUMMIT
8,848 metres
CAMP 4 SOUTH COL
8,000 metres
DEATH ZONE:
The lack of oxygen above 8000 metres can be fatal to climbers.
8,000 metres
CAMP 3
7,162 metres
CAMP 2
6,400 metres
CAMP 1
5,943 metres
BASE CAMP
5,334 metres
Google

Summary and Next Steps

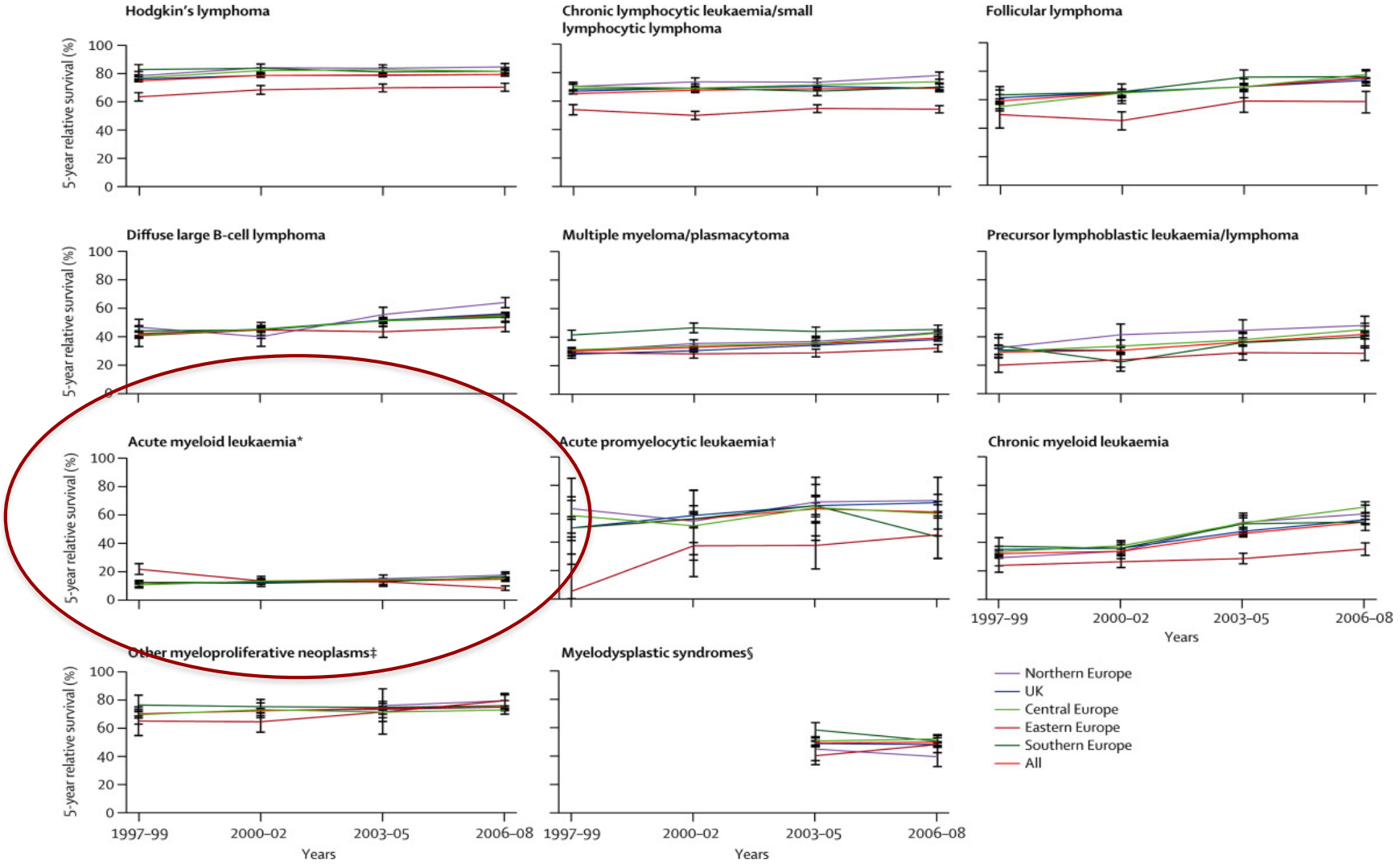
- Growing evidence of the prognostic utility of MRD status in AML between MRD negativity and improved outcome (OS)
- Good engagement with regulators with FDA/EMA meetings planned 2019
- Moving towards harmonised prospective generation of MRD data
- Industry and academic partners in active collaboration to generate and pool patient-level MRD and OS data into meta-analysis assessing predictive nature of correlation

Questions

Statistical analysis overview



5-year survival rates across haematology malignancies



Milena Sant , Pamela Minicozzi , Morgane Mounier , Lesley A Anderson , Hermann Brenner , Bernd Holleczek , Rafael ... Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. The Lancet Oncology, Volume 15, Issue 9, 2014, 931 – 942. http://dx.doi.org/10.1016/S1470-2045(14)70282-7