Regulatory Aspects - AML & CLL

Dr Beatriz Flores

November 2018

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to CDDF its directors, employees, volunteers, members, chapters, councils or any organisation with which the presenter is employed or affiliated.

Haematological malignancies

- Standard endpoints: OS, PFS, EFS, LFS, RR…
- Improved clinical outcomes with novel therapies
- Advances test identifying residual tumour cells after treatment
- Need new surrogate endpoints to faster clinical development & approval

Surrogate clinical endpoint

- Aims to predict a clinical outcome
- **Should**
  - **reliably & precisely predict effect** of the drug/intervention on long-term clinical outcome
  - **validated** in longer term trials to confirm association with clinical outcome

Minimal residual disease (MRD)

Wide potential:

- **Surrogate clinical endpoint**
- Stratification factor in CT
- Prognostic risk of relapse

MRD in Haematological Malignancies

- Heterogenous field
- Validation as surrogate per disease
- Even validation per disease subtype (AML?)
- Depends on validation of measurement tests

Guideline MRD as endpoint in CLL

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/CHMP/703715/2012 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)

Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man

Condition Specific Guidance

7. Minimal residual disease as an endpoint in chronic lymphocytic leukaemia studies

Guideline MRD as endpoint in CLL (cont.)

- Threshold 10^{-4}
- Adequate laboratory measurements available
- Sample first in PB but confirmed in bone marrow
- Timepoint ~ 3 months after end of treatment
- Endpoint MRD response rate (ITT: CR + MRD below threshold)
- Pre-specified SAP including PFS and OS

Guideline MRD as endpoint in CLL (cont.)

Previous uncertainties :

- PR but MRD undetectable
- Value other thresholds
- Correlation MRD in PB versus BM
- MRD Kinetics and relapse
- Guide for treatment

….Now?

AML complex disease

- Multiple driver mutations
- Competing co-occurring clones
- Disease evolution

AML heterogenous

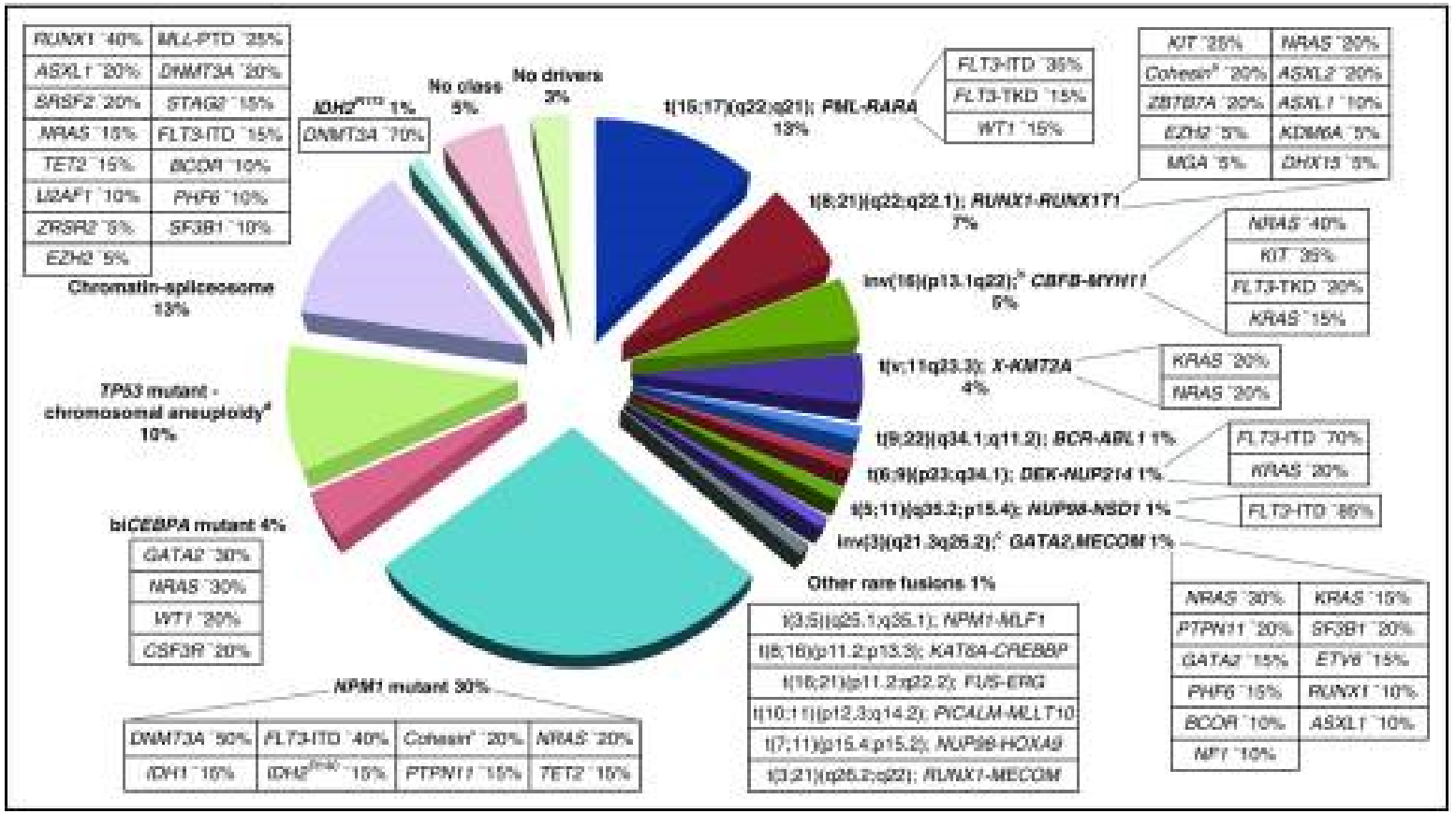

Image from *Diagnosis and management of AML in adults:2017 ELN recommendations from an international panel (Blood, 26 January 2017)*

AML- MRD

- Genetic evolution at progression
- Phenotype shift more common in some mutations
- Need broad use MRD markers
- Detection of pre-malignant clones of unknown significance
- Not all MRD positive post consolidation will relapse
- Different relapse kinetics by subtype

Uncertainties MRD in AML

- Mutations reliable for malignant clones associated with relapse?
- Best time for MRD testing?
- Threshold?
- Multicentre clinical trials need centralised lab?
- Validated tests?
- Can results be extrapolated across risk groups within a subtype?
- Can results be extrapolated across different treatments (transplant, non intensive CT etc)

Regulatory limited experience

Recent CHMP regulatory reviews:

- Mylotarg (gemtuzumab ozogamacin)
- Vyxeos (cytarabine/daunorubicin)
- Rydapt (midostaurin)
- Quinprezo (vosaroxin)

Regulatory experience: national scientific advice

Since 2015 only two SA discussed use of MRD: one in AML and one in CLL

MRD- AML

- Too early for validation of MRD as surrogate endpoint?
- Now international recommendation for assessment in clinical trials (ELN)
- Await Phase III clinical trials outcome
- Likely to evolve as surrogate by disease subtype

MRD general regulatory aspects

- Objective
- But depends on lab assays
- Ideal independent of variables
- Still need trial powered for traditional time-related endpoints
- Regulatory pathway

MRD – Benefit Risk

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
					Age groups? **Lines treatment?** **Class treatment?** **Subgroups risk?** **ITT vs PP** **Missing samples?** **Long term effects?** ….	
Unfavourable Effects						

Thank you

“Medicine is a science of uncertainty
and an art of probability “

William Osler