Overview of requirements for surrogate endpoint adoption by CHMP: a regulatory perspective

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Background

• App. 4 Guideline on the evaluation of anticancer medicinal products in man- MRD as an endpoint in CLL studies (EMA/CHMP/703715/2012 Rev. 2)

• IMWG consensus criteria for response and MRD assessment in MM (2016)

• Sufficient clinical data available showing correlation between MRD after treatment and PFS/OS
EMA/283093/2016
Committee for Medicinal Products for Human Use (CHMP)

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

• **Patient-relevant (final):** the outcome by which the efficacy of treatment in CT is evaluated. A patient-relevant endpoint (PFS/OS)

• **Intermediate:** measure of a therapeutic effect that is reasonably likely to predict the clinical benefit. It does not represent the final patient-relevant outcome.

• **Surrogate:** measure of effect of a specific treatment that may correlate with a patient-relevant clinical endpoint but does not necessarily have a guaranteed relationship.
Validation of a surrogate endpoint

Regulatory requirements

1. Treatment effect on surrogate corresponds to treatment effect on the final outcome - need of RCT - specific to the treatment and indication

2. Consistent association

3. Biological plausibility
Current limitations

- We have “estimates” of the expected effect of MRD after treatment on the final outcome (PFS/OS)
- “Estimates” based on clinical studies with important differences (e.g. study population, different treatments, different assays, different MRD cut-off etc.)
- Results in the same direction: lower MRD predicts longer PFS/OS
- Level of MRD has prognostic value
- Unknown what differences in MRD between arms in a RCT can accurately predict differences in PFS/OS
MRD a surrogate endpoint?

• Not validated yet

• Accepted as an intermediate endpoint

• The effect of the treatment on a surrogate needs to be large enough to predict a clinically meaningful benefit in the final outcome

• Early approval based on MRD needs confirmatory PFS/OS analysis within an agreed timeframe

• And there is no surrogate endpoint for safety…..
MRD as intermediate clinical endpoint

- RCT
- Powered for PFS (may need OS)
- All patients follow up for OS
- Pre-specify a difference in MRD between arms post treatment sufficient to predict a meaningful benefit on PFS/OS
- Undetectable MRD RR endpoint: proportion of patients in ITT population who achieve CR and undetectable MRD in BM at pre-specified time-point after treatment
Measuring MRD

• Cut-off: <1 in $10^5$ residual tumour cells

• Sample: Bone marrow

• Assays: Standardised methods (like NG sequencing or flow)

• Timing: After each treatment stage (induction, consolidation, ASCT, maintenance)
Timing of MRD assessments

• Unknown significance achieving undetectable MRD earlier vs later

• Unknown best duration of some treatments

• Depend on type of treatment and study objectives

  ➢ Transplant NE: expected best response after induction

  ➢ Transplant E: expected best response after induction and day 100 post transplant

  ➢ Maintenance: before start maintenance and regular justified timepoints after (e.g. 1 year if standard risk)
Other endpoints

- Sustained undetectable MRD
  
  undetectable MRD in patients in CR and with normal imaging for at least 1 year

- DFP
  
  duration from start undetectable MRD until reappearance of detectable MRD

- Exploratory
  
  different cut-offs
  
  MRD in PR/VGPR/nCR
  
  PB tumour cells
  
  MRD at different time-points
• Need to use two different assays

• Undetectable MRD RR only if in CR

• Need to exclude eradication of tumour in extramedullary as part of MRD RR endpoint

• Need of normal SFC ratio to be part of MRD RR endpoint

• Immune-based therapies and MRD