Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

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

CHMP draft guideline

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 detectable MRD

- Exploratory

  different cut-offs

  MRD in PR/VGPR/nCR

  PB tumour cells

  MRD at different time-points

Unknown

- 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