Primary outcome is molecular response rate, response rate, toxicity or quality of life and non-inferiority studies

GRADE 4
Reduced toxicity* or improved quality of life (using validated scale) with evidence for statistical non-inferiority or superiority in PFS/OS/CRR/MMR

Major molecular response rate (MR 4+) increased ≥20%

GRADE 3
Improvement in some symptoms (using a validated scale) BUT without evidence of improved overall quality of life

Major molecular response rate (MR 4+) increased 10 - <20%

GRADE 2
RR is increased ≥20%

Major molecular response rate (MR 4+) increased ≥5 - <10%

GRADE 1
RR is increased <20%

Major molecular response rate (MR 4+) increased <5%

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Preliminary magnitude of clinical benefit grade (highest grade scored)

CRR, complete remission rate; MMR, major molecular response; MR, molecular response; OS, overall survival; PSF, progression-free survival; RR, response rate.
## Incremental toxicity

Is the new treatment associated with an incremental rate of:

- «Toxic» death >2% of patients [ ]
- Premature discontinuation of therapy >10% of patients [ ]
- Hospitalisation for «toxicity» >10% of patients [ ]
- Grade 3+ mucositis >10% of patients [ ]
- Grade 3+ diarrhoea >10% of patients [ ]
- Grade 3+ fatigue >10% of patients [ ]
- Grade 3+ neurotoxicity >10% of patients [ ]
- Other distressing toxicity grade 3+ >10% of patients [ ]
- Overall grade 3-4 toxicity impacting on daily well-being * or serious adverse events >20% of patients [ ]
Quality of life/ grade 3-4 toxicities assessment

Was quality of life evaluated as secondary outcome?  

Does secondary endpoint quality of life show improvement?  

Are there less grade 3-4 toxicities impacting on daily well-being*  

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Adjustments

01. When OS as secondary endpoint shows improvement, it will prevail and the scoring should be done according to form 2a

02. Upgrade 1 level if study with primary outcome of MR or RR demonstrates
   a. Improved quality of life OR
   b. Less grade 3-4 toxicities that affect well-being of patients are demonstrated

03. Downgrade 1 level if the treatment has incremental toxicity

Final magnitude of clinical benefit grade

5  4  3  2  1

Non-curative setting grading 5 and 4 indicates a substantial magnitude of clinical benefit

MR, molecular response; OS, overall survival; RR, response rate.