ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1

ESMO-MCBS
ESMO-Magnitude of Clinical Benefit Scale

INSTRUCTIONS

01. There are 5 forms

Evaluation form 1: for new approaches to adjuvant therapy or new potentially curative therapies.

Evaluation form 2a: for therapies that are not likely to be curative with primary endpoint of overall survival (OS) with separate sheets for:

- IF median OS with the standard treatment is ≤12 months
- IF median OS with the standard treatment is >12 months, ≤24 months
- IF median OS with the standard treatment is >24 months

Evaluation form 2b: for therapies that are not likely to be curative with primary endpoint progression-free survival (PFS) with separate sheets for:

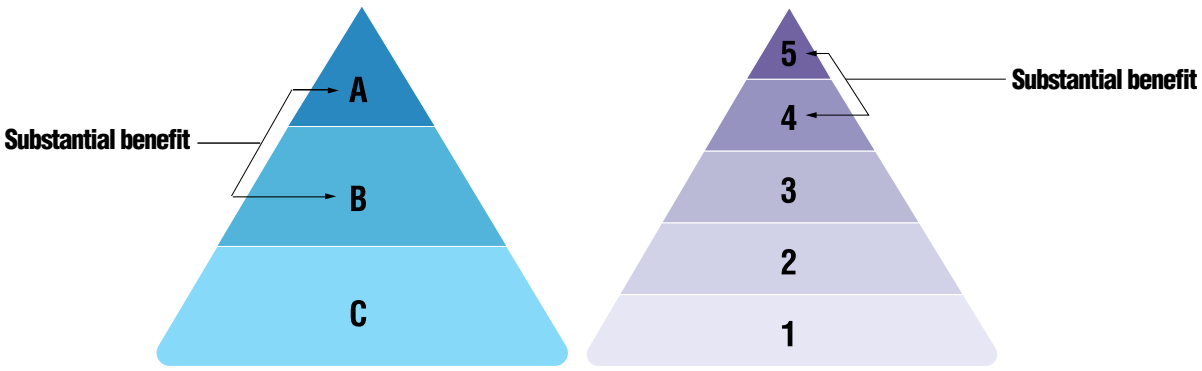
- IF median PFS with standard treatment is ≤6 months
- IF median PFS with standard treatment is >6 months

Evaluation form 2c: for therapies that are not likely to be curative with primary endpoint other than OS or PFS or equivalent (non-inferiority) studies.

Evaluation form 3: for single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or overall response rate (ORR).

02. ESMO-MCBS scores

The highest grades of the ESMO-MCBS in the curative setting are A and B and in the non-curative setting 5 and 4, which indicate a substantial magnitude of benefit.



03. Analysis of phase III trials

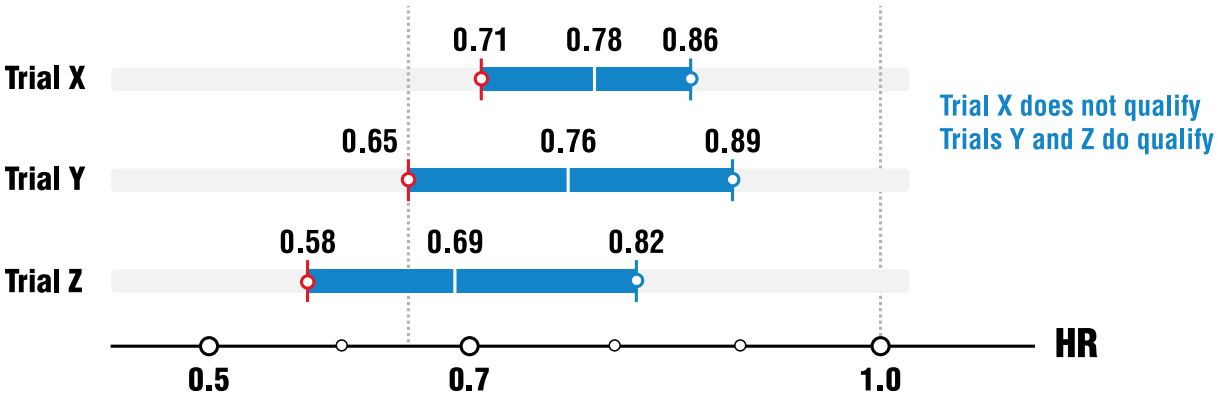
- Adequately powered studies showing statistically significant improvement in the primary outcome (defined by *P*<0.050).
- Careful analyses "control arm" and identification of endpoints.

- **Check subgroup analysis**
  a. Studies with pre-planned subgroup analyses with a maximum of 3 subgroups can be graded (provided there is adjustment for multiple comparisons).
  b. When statistically significant results are reported for any subgroup, then each of these should be graded separately.
  c. Subgroups not showing statistically significant results are not graded.
  d. Except for studies that incorporate collection of tissue samples to enable re-stratification based on new genetic or other biomarkers, findings from un-planned (post-hoc) subgroup analysis cannot be graded and they can only be used as foundation for hypothesis generation.

04. More than one outcome may be applicable

The statistical significance of secondary outcomes are determined by the same criteria as for primary outcomes i.e. defined by $P<0.050$.

05. For a required hazard ratio (HR), not the point estimate but the lower limit of 95% confidence interval (CI) estimated based on the observed HR in the trial should encompass the required HR.



Example: for threshold set at HR <0.65 it is the lower limit of the 95%CI which has to be ≤0.65

06. In the case of OS in the non-curative setting check for:

- Reduced toxicity
- Improvement in quality of life (QoL)
- Report final adjusted grade taking into account toxicity, and QoL when relevant.

07. In the case of PFS in the non-curative setting check for:

- Indicators of toxicity
- Survival data also available
- Early termination with crossover based on planned interim survival analysis
- Global QoL advantage using validated scale if applicable
- Report final adjusted grade taking into account toxicity, survival advantage and QoL when applicable.