ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1

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 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.

   ![ESMO-MCBS scores diagram]

   - Major benefit
   - Important benefit
   - Moderate benefit
   - Substantial 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 $\leq 0.65$.

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.