

## ESMO Magnitude of Clinical Benefit Grading Scale (ESMO-MCBS) Instructions

### 1. There are 4 forms:

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

Hyper mature data from studies that were un-blinded after compelling early results with subsequent access to the superior arm are contaminated, subsequently late intention to treat (ITT) follow-up data are not evaluable.

- Evaluation form 2a: for therapies that are not likely to be curative with primary endpoint of OS with separate sheets for:
  - IF median OS with the standard treatment is  $\leq 1$  year
  - IF median OS with the standard treatment  $> 1$  year
- Evaluation form 2b: for therapies that are not likely to be curative with primary endpoint PFS with separate sheets for:
  - IF median PFS with standard treatment  $\leq 6$  months
  - IF median PFS with standard treatment  $> 6$  months
- Evaluation form 2c: for therapies that are not likely to be curative with primary endpoint other than OS or PFS or equivalent studies.

### 2. The highest grade of the ESMO-MCBS is A in the curative setting and this is restricted to new curative treatments; for non-curative indications 5 is the highest possible grade, yet sufficient to trigger rapid consideration for reimbursement is B and 4.

### 3. Analysis of phase III trials

- a) Priority: well powered studies showing statistically significant improvement.
- b) Careful analyses “control arm” and identification of endpoints.
- c) Check subgroup analysis. In negative phase III trials often based on emerging candidate biomarkers. They can reveal apparent benefits in the primary endpoint via a subgroup.

#### Un-planned not in ESMO-MCBS

- considered «hypothesis-generating», requires confirmation in an independent data-set

#### Pre-planned in ESMO-MCBS

- when  $\leq 3$  subgroups defined «a priori»: benefit in a subgroup for the primary endpoint can be «scaled», provided adjusted for multiple comparisons

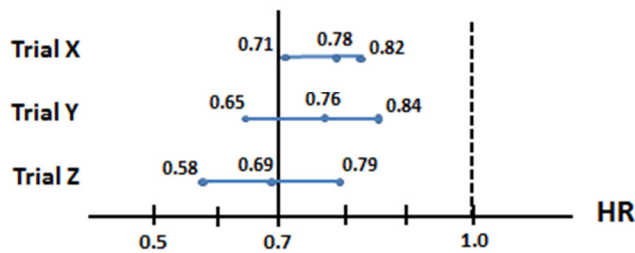
### 4. More than one outcome may be applicable

For a required HR, not the point estimate but the **lower limit of** 95% CI estimated based on the observed HR in the trial should encompass the required HR

Figure 1

Understanding the meaning of a threshold HR in the  
ESMO Magnitude of Clinical Benefit Scale

Example: threshold set at  $HR \leq 0.70$



Trial X does not qualify  
Trials Y and Z do qualify

Example: for threshold set at  $HR \leq 0.70$  it is the lower limit of the 95%CI which has to be  $\leq 0.70$

5. In the Case of OS in the non-curative setting check for

- Reduced toxicity
- Improvement in quality of life
- Report final adjusted grade taken into account toxicity, and QoL when relevant

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

- indicators of toxicity
- survival data also available
- global QoL advantage using validated scale if applicable
- report final adjusted grade taken into account toxicity, survival advantage and QoL when applicable