Expected Impact of the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) on Health Technology Assessment

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BACKGROUND
• European Society For Medical Oncology (ESMO) published in 2015 the Magnitude of Clinical Benefit Scale (MCBS) to support European health authorities’ decisions and recommending therapies with the highest scores in their guidelines [1].

OBJECTIVES
• The objective of this research was to analyse how ESMO-MCBS fits the health technology assessment (HTA) framework in oncology.

METHODS
• ESMO-MCBS [1] was reviewed to identify dimensions taken into account and compared to three different HTA frameworks:
  ▪ Clinically driven – France and Germany
  ▪ Cost-effectiveness driven – United Kingdom
  ▪ In addition, a comprehensive literature review related to the use of ESMO-MCBS in HTA practice was performed.

RESULTS
• ESMO-MCBS (Figure 1) has been developed for solid cancers and is applied to comparative studies (randomised, comparative cohort studies and meta-analysis).
  - It does not allow assessing products with single-arm studies.
  - The scale includes 2 parts:
    Form 1 for therapies likely to be curative.
    Form 2 for therapies not likely to be curative.
  - Being sub-divided depending on primary endpoints: overall survival (OS), progression-free survival (PFS) or others.
  - Magnitude of clinical benefit grade is driven by hazard ratio (HR) (referring to the lower extreme of the 95% confidence interval (CI)) and minimum observed benefit.
  - For non-curative therapies, this benefit is modulated according to the background risk (OS or PFS in the control arm); quality of life (QoL) and grade 3-4 toxicities contribute to upgrade or downgrade the benefit score.

Figure 1. Illustration of ESMO-MCBS [1]

Table 1. Studies comparing ESMO-MCBS scores to HTA bodies’ real-life decisions

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| Hammerness et al. [3] | Comparison of ESMO-MCBS scores and actual reimbursement decisions in trials for 34 cancer drugs that were candidates for reimbursement in 2013-2015 | 87% (17/19) of the approved drugs gained a high score (≥4) | Analyzed reimbursement decisions demonstrated concordance with ESMO scores (≥3).
| Lindgren et al. [4] | Comparison of ESMO-MCBS scores based on drug pilot testing used for development of the scale and real-life outcomes of HTA assessments in France, Sweden and Germany | ESMO-MCBS scores were: in reasonable agreement with the additional benefit scores in Germany • Significantly correlated with improvement in actual benefit (AVM) scores in France (with some disagreement in the middle of the scale) • Very weakly correlated with Quality-Adjusted Life Years (QALY) gained assessed in Sweden. | ESMO-MCBS purports to be useful for reimbursement decisions • Usefulness of ESMO-MCBS for pricing and reimbursement decisions remain questionable considering the big gap between relative effectiveness and cost-effectiveness.
| Ryan et al. [5] | Comparison of ESMO-MCBS scores and real-life outcomes of HTA assessments in the United Kingdom, France and Germany | Quantification of clinical benefit differed between HTA bodies and recommendations of ESMO-MCBS • Assessment of clinical benefit particularly in terms of OS improvement differed between HTA bodies. | Head of consistent and representative assessment of clinical benefit of new cancer drugs is recognised by oncology societies • Due to the use of generic approach across therapy areas, assessment of clinical benefit by HTA bodies in oncology remains inconsistent.
| Wild et al. [6] | Comparison of ESMO-MCBS scores and actual outcomes of HTA assessments in France of a large programme (n=11) | HOS scores derive from ESMO-MCBS scores (1-2 scores lower in average) • Deviation of scores from ESMO due to using the point estimate instead of using the lower limit of CI and degrading because of adverse events or if only PFS data available; rather than upgrading because of improvement in QoL. | The authors suggested some adaptations to ESMO-MCBS tool.

CONCLUSIONS
• ESMO-MCBS applies only to comparative research.
  - Even if oncologists agree that the framework is a gold standard for HTA submissions, additional evidence might be considered by HTA bodies such as deriving from single-arm studies (especially when there is no therapeutic alternative) or observational studies other than comparative cohort design.
  - For example, in France, vemurafenib indications were based on phase II data for first-line treatment for unresectable metastatic melanoma (8). ESMO agreed with their decision arguing that it would underestimate the substantially significant potential benefit of the treatment (9).
  - However, in Germany, it will conflict with existing standardised clinical assessment driven by CI upper limit.

Criticism about the use of the lower limit of CI:
• The use of the lower limit of the CI other than the point estimate has been discussed as introducing an optimistic bias in the estimation of the scale.
• Need of consistent and representative assessment of clinical benefit of new cancer drugs is recognised by oncology societies.

Reported bias toward an optimistic perspective concentrating on efficacy:
• This was acknowledged by ESMO, while no penalty has been included for increased toxicity for score based on OS (but this feature is under review) (10).

Lock of patient perspective:
• It has been reported that patient perspective was not enough taken into account in terms of patient /family preferences of significant clinical improvements and how they may translate in real life (e.g. return to work) (4).

ESMO-MCBS does not incorporate any cost data in relation to the additional benefit.
• ESMO-MCBS is not expected to impact countries using health economics evidence.
• An additional scoring system for economic assessment of which is translated in QALY gain, in other countries with less standardised clinical assessment, it may provide subjective guidance.

REFERENCES