Supplemental Materials

Glossary

- **Clinical added benefit/value:** conclusion on the relative value of a particular health technology compared to a comparator technology, which is relevant in the local healthcare system. It is strictly based on the available scientific evidence, does not contain modelled/extrapolated elements.
- **Critical appraisal:** the inseparable part of the reimbursement process resulting in a local assessment report, conducted by the National Institute of Pharmacy and Nutrition. Primarily consists of the systematic evaluation of the submitted dossier, which includes evidence on clinical- and cost-effectiveness.
- **Incremental health gain:** Important aspect studied during the critical appraisal, result of a health-economic model. It is based on the scientific evidence derived from clinical trials and other sources but contains modelled/extrapolated parts as well. In cost-utility analyses it can be measured in QALYs.
- **PICO:** mosaic term for defining the scope of HTA, consisting of the population of interest, claimed intervention, relevant comparator and outcomes measured.
- **Reimbursement *process*:** totality of actions performed by public and private stakeholders resulting in decision on the reimbursement of a particular health technology by the National Health Insurance Fund of Hungary.
- ***Procedure* of formulating a conclusion on clinical added benefit:** part of the critical appraisal. Using the developed framework provides information on the clinical added value of the health technology of interest in the reimbursement process, based on the submitted clinical evidence.
  In our case, the conclusion has four equally important major domains, which is described in detail in the main text.

Table S1. Mapping the ESMO-MCBS scores to the extent of CAB categories

EXTENT OF CAB (CATEGORIES)	ESMO-MCBS CURATIVE SETTING SCORES	ESMO-MCBS NON-CURATIVE SETTING SCORES
Major	A*	5*
Important	B*	4*, 3
Minor	C	2, 1
No proof of benefit / Not quantifiable	No statistically significant difference on a relevant endpoint in the PICO of the reimbursement submission	

*Scores A, B, 5 and 4 are considered as substantial benefit according to ESMO.

CAB: clinical added benefit; ESMO-MCBS: European Society for Medical Oncology – Magnitude of Clinical Benefit Scale; PICO: population-intervention-comparator-outcome.

Table S2. Stakeholder questionnaire

A	REGARDING THE PROCEDURE OF DRAWING CONCLUSION ON THE CLINICAL ADDED BENEFIT, IT...	Answers*
A1	Might improve transparency during the reimbursement process	Choose an item.
A2	Specifies and simplifies the content of the dossiers submitted for critical appraisal	Choose an item.
A3	Might improve the quality of the submitted dossiers	Choose an item.
A4	Might improve the quality of HTA reports	Choose an item.
A5	Might validate and standardize the critical appraisal process	Choose an item.
A6	Might make the HTA reports more ready-to-use	Choose an item.
A7	Might support the reimbursement process and price negotiations	Choose an item.
A8	Serves as a feasible alternative (taking into account the human resource capacities and legal frameworks) for drawing conclusion on the clinical added benefit	Choose an item.
A9	Might facilitate the learning process of new clinical assessors of the HTA department of NIPN	Choose an item.
A10	Might facilitate the learning process of new employees of companies preparing dossiers for reimbursement	Choose an item.
A11	Might validate the rightness of the method chosen for health economic analyses (mostly the type of the analysis)	Choose an item.
	Comments on questions A1-A11:	
B	**REGARDING THE SCORING SYSTEM USED IN THE PROCEDURE FOR DESCRIBING THE QUALITY OF CLINICAL EVIDENCE, IT...**	
B1	Might lead to a more uniform way of presenting scientific evidences in HTA reports	Choose an item.
B2	Separation of the level of evidence from the risk of bias might facilitate identification of new limitations	Choose an item.
B3	Its inclusion in HTA reports might further elucidate the generalizability of the presented results	Choose an item.
B4	In a situation where the extent of clinical added benefit appears to be the same, it might serve as guide to choose that therapeutic option which is supported by higher quality of evidences, therefore in general might be more useful for patients	Choose an item.
	Comments on questions B1-B4:	
C	**REGARDING THE SCALE USED FOR SCORING THE EXTENT OF CLINICAL ADDED BENEFIT, IT...**	
C1	In local circumstances a 3+1 grade scale should be enough to differentiate between therapies (extent categories: major, important, minor and no proof of benefit/not quantifiable)	Choose an item.
C2	The ESMO MCBS is a broadly accepted measure for oncological therapies	Choose an item.
C3	The ESMO MCBS considers several aspects which are meaningful for patients besides survival gain (e.g. adverse events, quality of life, patient-relevant endpoints)	Choose an item.
	Comments on questions C1-C3:	
D	**REGARDING THE FIELD CHOSEN FOR INTRODUCTION (ONCOLOGY), IT...**	
D1	It is an appropriate starting point for further development of the procedure.	Choose an item.
D2	The implementation of an internationally accepted scale (ESMO MCBS) into the local reimbursement process is acceptable.	Choose an item.
	Comments on questions D1-D2:	

All subjects could choose from the following answer options: I fully disagree / I rather disagree / I rather agree / I fully agree with the proposed statement.

Table S3. Levels of evidence

Evidence level	Evidence level by ESMO	Direct comparative trial(s) are available		Indirect comparison (lack of direct comparative clinical trial)
		One comparative clinical trial	Meta-analysis of several direct comparative trials	
High	I	Evidence from at least one large randomized, controlled phase 3 trial of good methodological quality (low potential for bias)*	Meta-analyses of well-conducted randomized trials (low potential for bias), without significant inconsistency and without significant differences within the PICO, supported by an SLR and grading of evidence or RoB assessment**.	
Moderate	II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality)*.	Meta-analyses of trials representing moderate level of evidence, or meta-analysis of trials with significant differences within the PICO frame / inconsistency with its appropriate correction. Meta-analyses not supported by an SLR or without grading of evidence or RoB assessment.	Indirect comparisons and network meta-analyses of randomized, controlled trials of good methodological quality, adjusted for differences in PICO if there are (with MAIC, STC or other suitable method) supported by an SLR and grading of evidence or RoB assessment**.
Low	III	Prospective cohort studies	Meta-analyses of low evidence level trials or meta-analysis of such moderate or high evidence level trials with significant differences within the PICO frame.	Naïve indirect comparisons. Indirect comparisons with significant differences within the PICO frame / network meta-analyses with inconsistency without corrections or where the methodology is not well-documented in the reimbursement dossier. Indirect comparisons not supported by an SLR or without grading of evidence or RoB assessment.
	IV	Retrospective cohort studies or case-control studies		
	V	Studies without control group, case reports, expert opinions		

* Categories based on a use of an internationally accepted tool (e.g. GRADE, Cochrane RoB2 or reference from a peer-reviewed paper or a publicly available HTA report (e.g. IQWiG)

**e.g. GRADE, Cochrane RoB2

RoB: Risk of Bias; SLR: systematic literature review; MAIC: Matching-Adjusted Indirect Comparison; PICO: Population-Intervention-Comparator-Outcome; STC: Simulated Treatment Comparison.

Table S4. The Results of the retrospective testing according to the dossiers, percentages represent concordance between assessors.

Test round	Endpoint relevance	Extent of CAB			Level of evidence	Risk of Bias
		CAB category	Baseline score with ESMO MCBS	Adjusted score with ESMO MCBS		
Round #2 n=7	100.0%	85.7%	100.0%	71.4%	85.7%	57.1%
	100.0%	85.7%	100.0%	100.0%	85.7%	57.1%
	57.1%	78.5%	100.0%	57.1%	85.7%	57.1%
Average	**85.7%**	**83.3%**	**100.0%**	**76.2%**	**85.7%**	**57.1%**
Round #3 n=9	100.0%	88.9%	100.0%	100.0%	88.9%	88.9%
	55.6%	66.7%	100.0%	44.4%	88.9%	77.8%
	77.8%	75.0%	100.0%	88.9%	88.9%	88.9%
Average	**77.8%**	**76.9%**	**100.0%**	**77.8%**	**88.9%**	**85.2%**
Round #4 n=7	71.4%	100.0%	100.0%	100.0%	100.0%	100.0%
	57.1%	85.7%	71.4%	57.1%	85.7%	85.7%
	57.1%	85.7%	57.1%	71.4%	85.7%	85.7%
Average	**61.9%**	**90.5%**	**76.2%**	**76.2%**	**90.5%**	**90.5%**
Average (mean)	**75.1%**	**83.5%**	**92.1%**	**76.7%**	**88.4%**	**77.6%**
SD	***15.1%***	***6.2%***	***11.9%***	***13.8%***	***2.7%***	***13.6%***

The rows in the table indicate a specific dossier in each round.

n: number of participating medical assessors; CAB: clinical added benefit; ESMO-MCBS: European Society for Medical Oncology – Magnitude of Clinical Benefit Scale