ΚΡΙΤΗΡΙΑ ΑΞΙΟΛΟΓΗΣΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗΣ ΕΠΙΤΡΟΠΗ ΦΑΡΜΑΚΩΝ (ΣΕΦ)

Α) Εισαγωγή:

Μετά από εισήγηση του Διοικητικού Συμβουλίου ημερομηνίας 17/05/2021 , η Συμβουλευτική Επιτροπή Φαρμάκων (ΣΕΦ) προχώρησε στην περαιτέρω διευκρίνηση των κριτηρίων που λαμβάνονται υπόψη κατά την αξιολόγηση φαρμακευτικών προϊόντων για ένταξη στον Κατάλογο Φαρμακευτικών Προϊόντων που αποζημιώνονται από το ΓεΣΥ.

Τα υφιστάμενα κριτήρια περιλαμβάνονται στον περί Γενικού Συστήματος Υγείας Εσωτερικό Κανονισμό του 2019 (Συμβουλευτική Επιτροπή Φαρμάκων, Υποεπιτροπές, Καταρτισμός Καταλόγου Φαρμακευτικών Προϊόντων και Υγειονομικών Ειδών) και έχουν ως εξής:

Α. Τεκμηριωμένη κλινική πρακτική
Β. Τεκμηριωμένη επιστημονική βιβλιογραφία λαμβανομένης υπόψιν της διαβάθμισης της
Γ. Φαρμακοοικονομικές μελέτες
Δ. Αξιολογήσεις τεχνολογιών υγείας διεθνώς αναγνωρισμένων επιστημονικών οργάνων για συμπερίληψη του υπό εξέταση φαρμακευτικού προϊόντος σε συστήματα υγείας άλλων χωρών
Ε. Καθεστώς αδειοδότησης του υπό εξέταση φαρμακευτικού προϊόντος σύμφωνα με τον περί Φαρμάκων Ανθρώπινης Χρήσης (Έλεγχος, Προμήθειας και Τιμών) Νόμο
ΣΤ. Θεραπευτική θέση του υπό εξέταση φαρμακευτικού προϊόντος στη βάση των διεθνών κατευθυντήριων γραμμών
Ζ. Υφιστάμενα φαρμακευτικά προϊόντα του καταλόγου φαρμακευτικών προϊόντων για τη συγκεκριμένη ένδειξη
Η. Επιδημιολογικά στοιχεία της πάθησης για την οποία προορίζεται το υπό εξέταση φαρμακευτικό προϊόν
Θ. Ασφάλεια δικαιούχων
Ι. Σχέση κόστους/ αποτελεσματικότητας (cost-effectiveness)
ΙΑ. Ορθολογική χρήση των εν λόγω φαρμακευτικών προϊόντων
ΙΒ. Βέλτιστη διαχείριση των διαθέσιμων πόρων του Οργανισμού
ΙΓ. Ύπαρξη εναλλακτικών μη φαρμακευτικών θεραπειών

Οι νέες εισηγήσεις της ΣΕΦ που αφορούν στα κριτήρια βασίστηκαν στα πιο κάτω:

1. Expert Review Committee Deliberative Framework, Pan-Canadian Oncology Drug Review (pCODR), 2011
2. Medicines Reimbursement Policies in Europe, WHO, 2017
3. Pharmaceutical Regulation in 15 European Countries: review, LSE Research on Line

4. From efficacy to Equity: Literature Review of decision criteria for Resource allocation and healthcare decision making; Guindo et al. Cost effectiveness and Resourse allocation 2012, 10:9

Β) ΕΙΣΗΓΗΣΕΙΣ

Β.1 Πεδίο εφαρμογής:

α) νέα φαρμακευτικά προϊόντα για ένταξη στον Κατάλογο Φαρμακευτικών Προϊόντων του ΓεΣΥ

β) αποζημίωση νέων ενδείξεων για υφιστάμενα φαρμακευτικά προϊόντα

Β.2 Κριτήρια:

Criteria **Κριτήρια**	**Sub-criteria** **Επιμέρους Κριτήρια**	**Sub-Criteria definitions** **Ορισμοί/επεξηγήσεις για επιμέρους κριτήρια**
Overall Clinical Benefit	Effectiveness	The potential health impact of the drug compared to the other alternatives measured in terms of relevant patient outcomes such as mortality, morbidity, quality of life. Magnitude, direction and uncertainty of effect should be considered.
Συνολικό Κλινικό Όφελος	Αποτελεσματικότητα	Πιθανή επίπτωση του φαρμακευτικού προϊόντος στην υγεία σε σύγκριση με άλλες εναλλακτικές θεραπείες που αποζημιώνονται όσον αφορά σχετικούς δείκτες όπως: θνητότητας, νοσηρότητας, ποιότητας ζωής. Για ογκολογικά προϊόντα, μπορούν να χρησιμοποιούνται τα European Society for Medical Oncology (ESMO)-magnitude of clinical benefit scale (Συνημμένο

		IIB) or National Comprehensive cancer network (NCCN) Evidence Blocks ως ενδεικτικά για το κλινικό όφελος
	Safety Ασφάλεια	Frequency and severity of adverse effects (alone and in comparison with alternatives) Συχνότητα και σοβαρότητα των ανεπιθύμητων ενεργειών (της θεραπείας ή/και σε σύγκριση με εναλλακτικές θεραπείες που αποζημιώνονται)
	Quality of evidence Βαθμός αξιοπιστίας των δεδομένων	Clinical trial design Level of guideline recommendations Σχεδιασμός Κλινικών Δοκιμών Επίπεδο τεκμηρίωσης των συστάσεων στις κατευθυντήριες οδηγίες
	Burden of disease Φορτίο Νόσου	Incidence, prevalence or other measure of burden of disease Επίπτωση, επιπολασμός ή άλλος δείκτης μέτρησης του φορτίου της νόσου
	Need Αναγκαιότητα	Unmet medical need and/or availability of an effective alternative to the drug technology. Μη ύπαρξη εναλλακτικών θεραπειών ή ύπαρξη διαθέσιμων αποτελεσματικών εναλλακτικών

Cost effectiveness Λόγος κόστους - αποτελεσματικότητας	Economic Evaluations Φαρμακο-οικονομικές αξιολογήσεις	Cost-effectiveness studies Μελέτες κόστους-αποτελεσματικότητας
	Economic Evaluations from Health Technology Assessment (HTA) bodies Φαρμακο-οικονομικές αξιολογήσεις από αρμόδιες αρχές αξιολόγησης τεχνολογιών υγείας	Evaluations from Health Technology Assessment (HTA) bodies: For Drug Advisory Committee (DAC) recommendations regarding treatment criteria, evaluations from the following HTA bodies shall be taken into account in the following order: -NICE (National Institute for Health and Care Excellence)- England -SMC (Scottish Medicines Consortium)-Scotland and NCPE (National Center for Pharmacoeconomics)-Ireland For information only: -CADTH (Canadian Agency for Drugs and Technologies in Health)-Canada -PBAC (Pharmaceutical Benefits Advisory Committee)-Australia. Αξιολογήσεις από αρμόδιες αρχές αξιολόγησης τεχνολογιών υγείας:

		Κατά τη διαμόρφωση εισήγησης σχετικά με τα κριτήρια θεραπείας, η ΣΕΦ να λαμβάνει υπόψη τις συστάσεις των πιο κάτω φαρμακοοικονομικών φορέων (κατά σειρά προτεραιτότητας): -NICE (National Institute for Health and Care Excellence)-Αγγλία -SMC (Scottish Medicines Consortium)-Σκωτία και NCPE (National Center for Pharmacoeconomics)-Ιρλανδία Για πληροφόρηση μόνο: -CADTH (Canadian Agency for Drugs and Technologies in Health)-Καναδάς -PBAC (Pharmaceutical Benefits Advisory Committee)-Αυστραλία
Reimbursement by other European countries	European countries where the product is reimbursed after full HTA evaluation. Cyprus is a small country with limited resources that does not perform its own HTA evaluations.	Product is reimbursed in at least 5 European countries which have full HTA evaluation processes in place. The European countries which undertake full HTA evaluations are: Austria, Belgium, Croatia, Denmark, Estonia, France, Ireland, Italy, The Netherlands, Spain, Sweden, UK (Scotland), Norway*. In the case of orphan diseases, it is not mandatory to prove that the pharmaceutical product under assessment has undergone full HTA evaluation if the afford-

		mentioned countries have not performed such evaluation but nevertheless reimburse it. In exceptional cases where epidemiological data differs substantially in Cyprus it may be justified to reduce the number of European countries that perform full HTA and reimburse the product, to 3.
Αποζημίωση από άλλες Ευρωπαικές χώρες	Ευρωπαϊκές χώρες στις οποίες το φαρμακευτικό προϊόν αποζημιώνεται μετά από πλήρη αξιολόγηση τεχνολογιών υγείας. Η Κύπρος είναι μια μικρή χώρα με περιορισμένους πόρους η οποία δε διενεργεί τις δικές της αξιολογήσεις τεχνολογιών υγείας.	Φαρμακευτικό προϊόν το οποίο αποζημιώνεται σε τουλάχιστον 5 ευρωπαϊκές χώρες οι οποίες διενεργούν πλήρη αξιολόγηση τεχνολογιών υγείας (full HTA). Οι ευρωπαϊκές χώρες που διενεργούν πλήρη αξιολόγηση HTA είναι: Αυστρία, Βέλγιο, Κροατία, Δανία, Εσθονία, Γαλλία, Ιρλανδία, Ιταλία, Ολλανδία, Ισπανία, Σουηδία, Ηνωμένο Βασίλειο (Σκωτία) και Νορβηγία*. Επισημαίνεται ότι στην περίπτωση ορφανών νοσημάτων δεν είναι αναγκαία η διενέργεια πλήρους αξιολόγησης HTA για το συγκεκριμένο φαρμακευτικό προϊόν αν οι πιο πάνω χώρες δεν έχουν προβεί σε τέτοια αξιολόγηση, αλλά παρόλα αυτά το αποζημιώνουν. Σε εξαιρετικές περιπτώσεις όπως όταν τα επιδημιολογικά δεδομένα στην Κύπρο διαφέρουν σημαντικά, να είναι δυνατή

		η μείωση των ευρωπαϊκών χωρών που διενεργούν πλήρη αξιολόγηση HTA και αποζημιώνουν το φαρμακευτικό προϊόν σε 3.
Feasibility of Adoption into the Health System	Economic Feasibility (evaluation of budget impact assessment)	The budget impact of the new drug compared to the cost of other drugs, including companion testing technology.
Δυνατότητα υλοποίησης στο Σύστημα Υγείας	Οικονομική δυνατότητα (αξιολόγηση της επίπτωσης στον προϋπολογισμό)	Επίπτωση που θα επιφέρει το νέο φαρμακευτικό προϊόν στον προϋπολογισμό σε σύγκριση με το κόστος άλλων φαρμάκων συμπεριλαμβανομένων των συνοδών τεχνολογιών (companion testing technology)
	Organizational Feasibility	The ease with which the new drug can be adopted, with an assessment of health system enablers and barriers to implementation, inclusive of all elements: operational, capital, human resources, legislative and regulatory requirement
	Οργανωτική Δυνατότητα	Η ευκολία με την οποία το νέο φαρμακευτικό προϊόν μπορεί να ενταχθεί αφού αξιολογηθούν τα εμπόδια και οι δυνατότητες υλοποίησης συμπεριλαμβανομένων των πιο κάτω απαιτήσεων: επιχειρησιακών, οικονομικών, ανθρώπινου δυναμικού, νομοθετικών και κανονιστικών.

*Mapping of HTA national organisations, programmes and processes in EU and Norway, European Commission, 2017

Εξειδίκευση κριτηρίων για ογκολογικά φαρμακευτικά προϊόντα

Magnitude of clinical benefit scale (MCBS) by the European Society for Medical Oncology (ESMO)**	Positive recommendation by DAC if there is substantial benefit according to the published MCBS score from ESMO. Substantial benefit is defined by ESMO as: 1) grade A-B in the curative setting (see attachment, p13 for scaling explanations) 2) grade 4-5 in the non-curative setting (see attachment, p16-30 for scaling explanations)
Διαβάθμιση κλινικού οφέλους από ESMO**	Θετική σύσταση από τη ΣΕΦ για τα φάρμακα που προσφέρουν σημαντικό κλινικό όφελος σύμφωνα με τη δημοσιευμένη βαθμονόμηση του ESMO, δηλαδή: 1) επίπεδο Α-Β σε περίπτωση ριζικής θεραπείας με σκοπό την ίαση (βλ. επισυναπτόμενο, σελ 13, για εξηγήσεις σχετικά με την καταγοριοποίηση). 2) επίπεδο 4-5 σε περίπτωση μη ριζικής θεραπείας: (βλ. επισυναπτόμενο, σελ 16-30, για εξηγήσεις σχετικά με την καταγοριοποίηση)
National Comprehensive cancer network (NCCN) Evidence Blocks (when ESMO-MCBS not available)**	Positive recommendation by DAC if the relevant key measures by NCCN are as follows: -Efficacy: 4-5 AND -Safety: 3-5 AND -Quality Of Evidence: 4-5 (3-5 in case of orphan disease) AND -Consistency Of Evidence: 4-5 (3-5 in the case of orphan disease) <u>-Efficacy</u> **5** (Highly effective): Cure likely and often provides long-term survival advantage **4** (Very effective): Cure unlikely but sometimes provides long-term survival advantage <u>-Safety:</u> **5** (Usually no meaningful toxicity): Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)

	4 (Occasionally toxic): Rare significant toxicities or low-grade toxicities only; little interference with ADLs **3** (Mildly toxic): Mild toxicity that interferes with ADLs -<u>Quality Of Evidence:</u> **5** (High quality): Multiple well-designed randomized trials and/or meta-analyses **4** (Good quality): One or more well-designed randomized trials **3** (Average quality): Low quality randomized trial (s) or well-designed non-randomized trial(s) **-**<u>Consistency Of Evidence:</u> **5** (Highly consistent): Multiple trials with similar outcomes **4** (Mainly consistent): Multiple trials with some variability in outcome **3** (May be consistent): Few trials or only trials with few patients, whether randomized or not, with some validity in outcome.
NCCN EVIDENCE BLOCKS (Όταν δεν υπάρχει διαθέσιμη διαβάθμιση του κλινικού οφέλους από ESMO)**	Θετική σύσταση από τη ΣΕΦ για τα φάρμακα που έχουν τα πιο κάτω χαρακτηριστικά και με την αντίστοιχη διαβάθμιση σύμφωνα με το NCCN: - Αποτελεσματικοτητα:4-5 ΚΑΙ - Ασφάλεια: 3-5 ΚΑΙ - Βαθμός Αξιοπιστίας των Δεδομένων: 4-5 (3-5 στην περίπτωση ορφανών φαρμάκων) ΚΑΙ - Συνέπεια των Δεδομένων: 4-5 (3-5 στην περίπτωση ορφανών φαρμάκων) <u>Αποτελεσματικότητα:</u> **5** (Υψηλά αποτελεσματικό): Πιθανή θεραπεία και συχνά προσφέρει μακροχρόνιο πλεονέκτημα όσον αφορά στην επιβίωση **4** (Πολύ αποτελεσματικό): Μη πιθανή θεραπεία αλλά μερικές φορές προσφέρει μακροχρόνιο πλεονέκτημα όσον αφορά στην επιβίωση <u>Ασφάλεια:</u> **5** (Συνήθως μη αξιοσημείωτη τοξικότητα): Μη συχνές ή ελάχιστες τοξικότητες. Δεν παρεμβαίνουν στις δραστηριότητες της καθημερινής ζωής

	4 (Περιστασιακά τοξικό): Σπάνια εμφανίζεται σημαντική τοξικότητα ή χαμηλού βαθμού τοξικότητα. Παρεμβαίνουν στις δραστηριότητες της καθημερινής ζωής σε μικρό βαθμό **3** (Ήπια τοξικότητα): Ήπια τοξικότητα που παρεμβαίνει στις δραστηριότητες της καθημερινής ζωής <u>Ποιότητα των Δεδομένων:</u> **5** (Ψηλή Ποιότητα): Πολλαπλές, καλά σχεδιασμένες, τυχαιοποιημένες μελέτες και/ή μετα-αναλύσεις **4** (Καλή ποιότητα): Μία ή περισσότερες καλά σχεδιασμένες τυχαιοποιημένες μελέτες **3** (Μέτρια Ποιότητα): Χαμηλής ποιότητας τυχαιοποιημένη(ες) μελέτη(ες) ή καλά σχεδιασμένη(ες) μη-τυχαιοποιημενη(ες) μελέτη(ες) <u>Συνέπεια των δεδομένων:</u> **5** (Υψηλή συνέπεια): Πολλαπλές μελέτες με παρόμοια αποτελέσματα **4** (Αρκετή συνέπεια): Πολλαπλές μελέτες με κάποια μεταβλητότητα στα αποτελέσματα **3** (Μέτρια συνέπεια): Λίγες μελέτες ή μελέτες με λίγους ασθενείς, τυχαιοποιημένες ή όχι, με μερική εγκυρότητα ως προς το αποτέλεσμα.

**In the case which two or more pharmaceutical products under evaluation have equal ratings by ESMO and/or NCCN, priority will be given to the pharmaceutical product that is rated as “preferred” by NCCN.

** Στην περίπτωση που δύο ή περισσότερα φαρμακευτικά προϊόντα υπό αξιολόγηση διαβαθμίζονται ως ισότιμα από την ESMO ή/και το NCCN, προτεραιότητα θα δίνεται σε αυτό που κατονομάζεται ως «προτιμητέο» από το NCCN.

A tool to assist in the prioritisation of medicines in cancer care

Evidence-based standards for patient care

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

esmo.org

ESMO-MCBS factsheet

PROMOTING CLEAR AND EVIDENCE-BASED COMMUNICATION ABOUT THE BENEFIT OF CANCER TREATMENTS

In 2015 the European Society for Medical Oncology (ESMO) launched the **ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS)**[1,2] to facilitate improved decision-making regarding the value of anti-cancer therapies, promote the accessibility and reduce iniquity of access to high value cancer treatments. Since value is based on considerations of the magnitude of clinical benefit as well as cost, and given the challenges to understanding the actual magnitude of the clinical benefit, the ESMO-MCBS was developed as a validated and reproducible scale that is applicable across the full range of solid tumours in oncology.

It incorporates a structured, rational and valid approach to data interpretation and analysis that reduces the tendency to have judgements affected by bias or uninformed and/or idiosyncratic data interpretation that has been developed in accordance with the public policy standard of “accountability for reasonableness”.

It is a dynamic tool and its criteria are revised on a regular basis. The ESMO-MCBS is an important first step to the critical public policy issue of value in cancer care, helping to frame the appropriate use of limited public and personal resources in the delivery of cancer care.

[1] Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for medical oncology magnitude of clinical benefit scale (ESMO-MCBS). Ann Oncol2015;26:1547–73.

[2] Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol2017;28:2340–66.

ESMO-MCBS: SCORING CRITERIA ACCORDING TO CLINICAL SETTINGS

The scale considers overall survival, progression-free survival, disease free survival, hazard ratio, response rate, quality of life, prognosis of the condition and toxicity. There are 5 evaluation forms.

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

02. 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

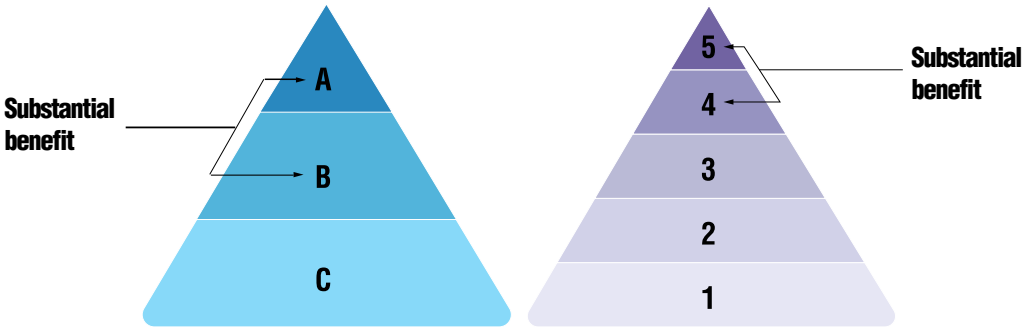
03. Evaluation form 2b: for therapies that are not likely to be curative with primary endpoint progres sion-free survival (PFS) with separate sheets for:

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

04. 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.

05. 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).

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 clinical benefit.



WHAT IS THE POTENTIAL USE AND ACCESSIBILITY OF THE ESMO-MCBS?

This structured and disciplined approach to deriving estimates of clinically meaningful benefit from published data can be used in arange of settings, including:

1. Public policy applications – Grading derived from the ESMO-MCBS provides a backbone for value evaluations of cancer medicines and can help public policy-makers in the advancement of 'accountability for reasonableness' in resource allocation deliberations.

2. Formulation of clinical guidelines – For cancer therapies, the ESMO-MCBS scale provides a clear, well-structured and validated mechanism to indicate the magnitude of clinical benefit, in addition to the level of evidence, that can inform both national and international guidelines.

3. Clinical decision making – The data enclosed in ESMO-MCBS scoring can help clinicians weigh the relative merits of competing relevant therapeutic options and may also be of benefit in explaining the relative merit of therapeutic options to patients and their families. This information may be especially helpful when treatments incorporate substantial out-of-pocket costs.

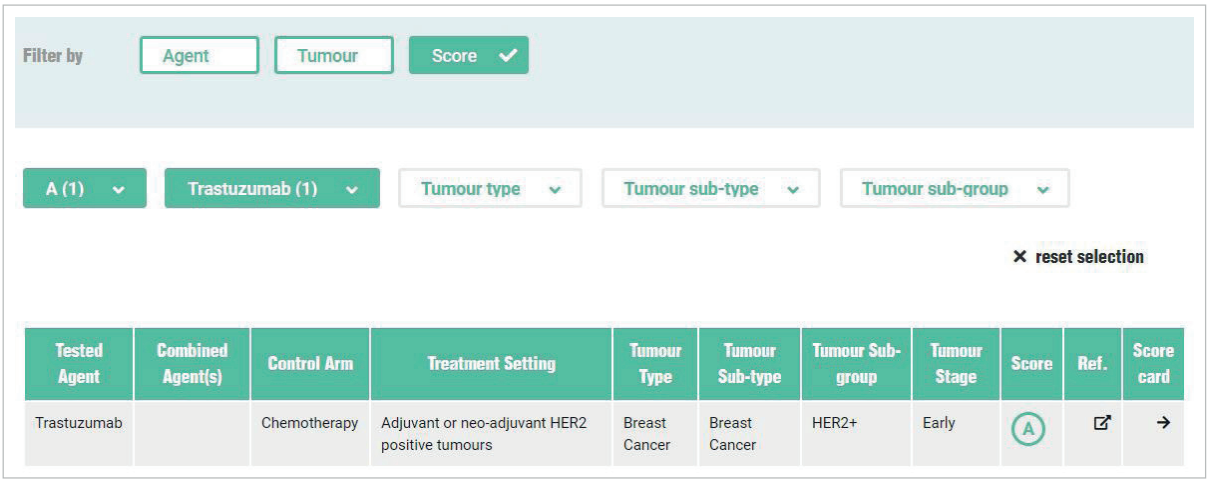
4. Editorial decisions and commentaries – The ESMO-MCBS may be of use to editors, peer reviewers and commentators in considering the clinical significance of research findings from randomised clinical studies, cohort studies and meta-analyses with statistically significant positive findings.

5. Education – The ESMO-MCBS is a powerful tool to teach a disciplined and validated approach to data interpretation. It is especially valuable for oncologists in training and for application in journal club discussion.

HOW IS THE ESMO-MCBS BEING USED?

It is incorporated in the ESMO Clinical Practice Guidelines and the Pan-Asian Adapted Guidelines, helping to provide patients with the best care options and setting the highest standards for cancer care.

- It has been acknowledged by the World Health Organisation as 'a screening tool to identify cancer treatments that have potential therapeutic value that warrants full evaluation for the Essential Medicines List listing'[3].
- It is being used as part of Health Technology Assessment (HTA) processes in a growing number of countries.
- It has been presented inside and outside Europe and in educational workshops for stakeholders, patient (advocates), pharma representatives and HTA bodies to increase knowledge sharing of the tool.
- It being used in oncology training programmes and journal club presentations, modelling a structured approach to data interpretation in the evaluation of clinical benefit.
- ESMO offers support to third parties wanting to use the scale.
- ESMO has developed a searchable portal and online tools to facilitate the use of the ESMO-MCBS.



[3] World Health Organisation. Executive Summary. The Selection and Use of Essential Medicines 2019. Report of the 22nd WHO Expert Committee on the Selection and Use of Essential Medicines, 1-5 April 2019.

ESMO-MCBS instructions and forms

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:

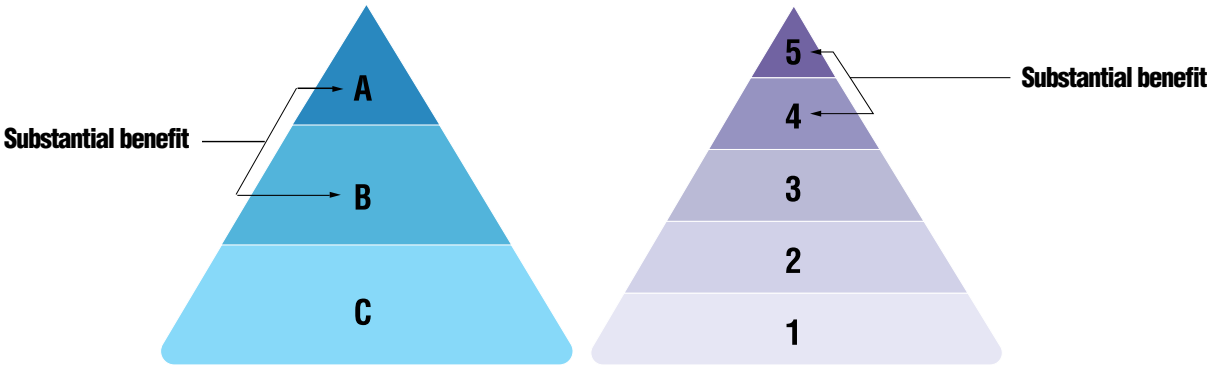
- IF median PFS with standard treatment is ≤6 months
- IF median PFS with standard treatment is >6 months

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.

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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.

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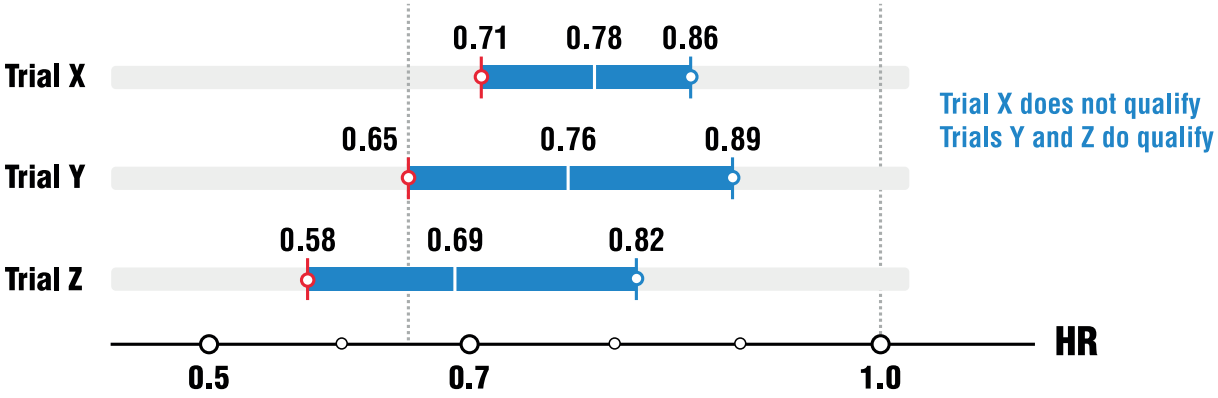
05. For a required hazard ratio (HR), not the point estimate but the lower limit of 95% confidence interval (CI) estimated based on the observed HR in the trial should encompass the required HR.



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

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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.

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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.

Curative Setting Form

EVALUATION FORM 1

For new approaches to adjuvat therapy or new potentially curative therapies

Name of study:					
Study medicine:		**Indication:**			
First author:		**Year:**		**Journal:**	
Name of evaluator:					

GRADE A	>5% improvement of survival at ≥3 years follow-up	◯
	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	◯
GRADE B	≥3% BUT ≤5% improvement at ≥3 years follow-up	◯
	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	◯
	Non inferior OS or DFS with reduced treatment toxicity or improved QoL (with validated scales)	◯
	Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	◯
GRADE C	<3% improvement of survival at ≥3 years follow-up	◯
	Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	◯
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	◯

Mark with √ if relevant

Magnitude of clinical benefit grade (highest grade scored)	**A**	**B**	**C**
	☐	☐	☐

Curative setting grading - A and B indicates a substantial magnitude of clinical benefit.

DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; QoL, quality of life.

Non-Curative Setting Forms

EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:					
Study medicine:		**Indication:**			
First author:		**Year:**		**Journal:**	
Name of evaluator:					

If median OS with the standard treatment is ≤12 months

GRADE 4	HR ≤0.65 AND gain ≥3 months	○
	Increase in 2 year survival ≥10%	○
GRADE 3	HR ≤0.65 AND gain ≥2.0-<3 months	○
GRADE 2	HR ≤0.65 AND gain ≥1.5-<2.0	○
	HR >0.65-0.70 AND gain ≥1.5 months	○
GRADE 1	HR >0.70 OR gain <1.5 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**4**	**3**	**2**	**1**
	☐	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; OS, overall survival

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	◯
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	◯

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	**5**	**4**	**3**	**2**	**1**
	☐	☐	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of Life

EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:					
Study medicine:		**Indication:**			
First author:		**Year:**		**Journal:**	
Name of evaluator:					

If median OS with the standard treatment >12 months ≤24 months

GRADE 4	HR ≤0.70 AND gain ≥5 months	○
	Increase in 3 year survival alone ≥10%	○
GRADE 3	HR ≤0.70 AND gain ≥3-<5 months	○
GRADE 2	HR ≤0.70 AND gain ≥1.5-<3 months	○
	HR >0.70-0.75 AND gain ≥1.5 months	○
GRADE 1	HR > 0.75 OR gain <1.5 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**4**	**3**	**2**	**1**
	☐	☐	☐	☐

Non-curative setting grading - 5 and 4 (substantial benefit), 3 (moderate benefit), 2 and 1 (negligible benefit)

HR, hazard ratio; OS, overall survival

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	**5**	**4**	**3**	**2**	**1**
	☐	☐	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of life

EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

Name of study:					
Study medicine:		**Indication:**			
First author:		**Year:**		**Journal:**	
Name of evaluator:					

If median OS with the standard treatment >24 months

GRADE 4	HR ≤0.70 AND gain ≥9 months	○
	Increase in 5 year survival alone ≥10%	○
GRADE 3	HR ≤0.70 AND gain ≥6-<9 months	○
GRADE 2	HR ≤0.70 AND gain ≥4-<6 months	○
	HR >0.70-0.75 AND gain ≥4 months	○
GRADE 1	HR >0.75 OR gain <4 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**4** ☐	**3** ☐	**2** ☐	**1** ☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; OS, overall survival

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement?	◯
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	◯

*This does not include alopecia, myelosuppression, but rather chronic nausea,diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown

02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 7 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Final adjusted magnitude of clinical benefit grade	**5** ☐	**4** ☐	**3** ☐	**2** ☐	**1** ☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

OS, overall survival; QoL, quality of Life

EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint of PFS

Name of study:					
Study medicine:		**Indication:**			
First author:		**Year:**		**Journal:**	
Name of evaluator:					

If median PFS with standard treatment ≤6 months

GRADE 3	HR ≤0.65 AND gain ≥1.5 months	○
GRADE 2	HR ≤0.65 BUT gain <1.5 months	○
GRADE 1	HR >0.65	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; PFS, progression-free survival

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	○
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?	○

If the answer to both is "yes", then see letter "E" in the adjustment section below

Mark with √ if relevant

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:

«Toxic» death >2%	○
Cardiovascular ischemia >2%	○
Hospitalisation for «toxicity» >10%	○
Excess rate of severe CHF >4%	○
Grade 3 neurotoxicity >10%	○
Severe other irreversible or long lasting toxicity >2% please specify:	○

(Incremental rate refers to the comparison versus standard therapy in the control arm)

Mark with √ if relevant

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

CHF, congestive heart failure; QoL, quality of Life

EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint of PFS

Adjustments

A When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a.

B Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new medicine.

C Downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.

D Upgrade 1 level if improved QoL or if less grade 3-4 toxicities that bother patients are demonstrated.

E Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis.

F Upgrade 1 level if there is a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 1 year.

Final, toxicity and QoL adjusted, magnitude of clinical benefit grade	**4** ☐	**3** ☐	**2** ☐	**1** ☐

Highest magnitude clinic benefit grade that can be achieved grade 4.

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life

EVALUATION FORM 2B

For therapies that are not likely to be curative with primary endpoint PFS

Name of study:					
Study medicine:		**Indication:**			
First author:		**Year:**		**Journal:**	
Name of evaluator:					

If median PFS with standard treatment >6 months

GRADE 3	HR ≤0.65 AND gain ≥3 months	○
GRADE 2	HR ≤0.65 BUT gain <3 months	○
GRADE 1	HR >0.65	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3**	**2**	**1**
	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

HR, hazard ratio; PFS, progression-free survival

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	○
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?	○

If the answer to both is "yes", then see letter "E" in the adjustment section below

Mark with √ if relevant

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:

«Toxic» death >2%	○
Cardiovascular ischemia >2%	○
Hospitalisation for «toxicity» >10%	○
Excess rate of severe CHF >4%	○
Grade 3 neurotoxicity >10%	○
Severe other irreversible or long lasting toxicity >2% please specify:	○

(Incremental rate refers to the comparison versus standard therapy in the control arm)

Mark with √ if relevant

Quality of life/Grade 3-4 toxicities* assessment

Was QoL eveluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

CHF, congestive heart failure; QoL, quality of Life

Adjustments

A When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a.

B Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new medicine.

C Downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.

D Upgrade 1 level if improved QoL or if less grade 3-4 toxicities that bother patients are demonstrated.

E Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis.

F Upgrade 1 level if there is a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 2 years.

Final, toxicity and QoL adjusted, magnitude of clinical benefit grade	**4** ☐	**3** ☐	**2** ☐	**1** ☐

Highest magnitude clinic benefit grade that can be achieved grade 4.

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life

EVALUATION FORM 2C

For therapies that are not likely to be curative with primary endpoint other than OS or PFS or equivalence studies

Name of study:					
Study medicine:		**Indication:**			
First author:		**Year:**		**Journal:**	
Name of evaluator:					

Primary outcome is Toxicity or Quality of Life AND Non-inferiority Studies

GRADE 4	Reduced toxicity or improved QoL (using a validated scale) with evidence for statistical non-inferiority or superiority in PFS/OS	○
GRADE 3	Improvement in some symptoms (using a validated scale) BUT without evidence of improved overall QoL	○

Primary outcome is Response Rate

GRADE 2	RR is increased ≥20% but no improvement in toxicity/QoL/PFS/OS	○
GRADE 1	RR is increased <20% but no improvement in toxicity/QoL/PFS/OS	○

Mark with √ if relevant

Final magnitude of clinical benefit grade	**4** ☐	**3** ☐	**2** ☐	**1** ☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

PFS, progression-free survival; OS, overall survival; QoL, quality of life; RR, response rate

EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:					
Study medicine:		**Indication:**			
First author:		**Year:**		**Journal:**	
Name of evaluator:					

GRADE 3	PFS ≥6 months	○
	ORR (PR+CR) ≥60%	○
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	○
GRADE 2	PFS ≥3-<6 months	○
	ORR (PR+CR) ≥40-<60%	○
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	○
GRADE 1	PFS 2-<3 months	○
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	○
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	○

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	**3** ☐	**2** ☐	**1** ☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	○
Does secondary endpoint QoL show improvement?	○
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	○

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with √ if relevant

Adjustments

A Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*

B Upgrade 1 level if improved QoL

C Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
	☐	☐	☐	☐

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

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