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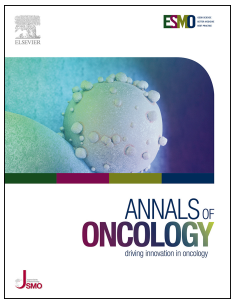

ESMO-Magnitude of Clinical Benefit Scale for Haematological Malignancies (ESMO-MCBS:H) Version 1.0

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ESMO-Magnitude of Clinical Benefit Scale for Haematological Malignancies (ESMO-MCBS:H) Version 1.0

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Running title: ESMO-MCBS:H Version 1.0

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ABSTRACT

Background: The European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) has been accepted as a robust tool to evaluate the magnitude of clinical benefit reported in trials for oncological therapies. However, the ESMO-MCBS hitherto has only been validated for solid tumours. With the rapid development of novel therapies for haematological malignancies, we aimed to develop an ESMO-MCBS version that is specifically designed and validated for haematological malignancies.

Methods: ESMO and the European Hematology Association (EHA) initiated a collaboration to develop a version for haematological malignancies (ESMO-MCBS:H). The process incorporated five landmarks: field-testing of the ESMO-MCBS v1.1 to identify shortcomings specific to haematological diseases, drafting of the ESMO-MCBS:H forms, peer review and revision of the draft based on re-scoring (resulting in a second draft), assessment of reasonableness of the scores generated, final review and approval by ESMO and EHA including executive boards.

Results: Based on the field-testing results of 80 haematological trials and extensive review for feasibility and reasonableness, five amendments to ESMO-MCBS were incorporated in the ESMO-MCBS:H addressing the identified shortcomings. These concerned mainly clinical trial endpoints that differ in haematology versus solid oncology and the very indolent nature of nevertheless incurable diseases such as follicular lymphoma, which hampers presentation of mature data. In addition, general changes incorporated in the draft version of the ESMO-MCBS v2 were included, and specific forms for haematological malignancies generated. Here we present the final approved forms of the ESMO-MCBS:H, including instructions.

Conclusion: The haematology-specific version ESMO-MCBS:H, allows now full applicability of the scale for evaluating the magnitude of clinical benefit derived from clinical studies in haematological malignancies.

Keywords:

ESMO-MCBS, value frameworks, clinical benefit, clinical trials, haematological malignancies, quality of life.

HIGHLIGHTS

- The ESMO-MCBS:H is the first version of the ESMO-MCBS designed specifically for haematological malignancies.
- The scale has been developed in a joint project of ESMO and EHA following all the validation steps of the solid tumour version.
- The ESMO-MCBS:H is ready to use hand-in-hand with the solid tumour version.
- The ESMO-MCBS:H will support the shared mission of ESMO and EHA to identify novel treatments that bring a substantial clinical benefit to the patient.

INTRODUCTION

The European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCSB), first published in 2015, represents a standardized, reproducible, and repeatedly validated tool to quantify the clinical benefit expected from a novel oncological treatment [1]. The development process was based on the increasing pace of oncological drug approvals in the 2010s [2], and the need to distinguish between therapies delivering a high level of benefit to patients (which needed prioritisation in the HTA process) from those in which benefits were small or marginal.

The ESMO-MCBS assesses the magnitude of clinical benefit of new cancer drugs through a validated algorithm for clinical benefit scoring, which considers therapies' prognostically weighted relative and absolute benefits against pre-specified thresholds, adverse effects, and impact on quality of life (QOL) [1]. Treatments with curative intent are graded with a 3-level scale (A, B, C), and treatments in the non-curative setting are graded on a descending 5-point scale (5-1). Scores of A and B in the curative setting and 5 and 4 in the non-curative setting represent substantial benefit, and scores of C, 2, and 1 indicate low benefit.

The ESMO-MCBS has been developed as a dynamic tool with a commitment to address identified shortcomings and new developments in regulatory standards for the approval of new therapies. Accordingly, version 1.1 (v1.1), published in 2017, incorporated 10 revisions based on identified shortcomings and accommodated the increasing use of evidence from single arm studies by the regulatory bodies [3]. This continual quality improvement process is part of the commitment to “accountability of reasonableness” in all aspects of the ESMO-MCBS development process that requires transparency, accountability, and responsiveness in all workflows.

The versions of the ESMO-MCBS hitherto available have only been validated for solid tumours. With the very rapid development of multiple new therapies for the management of haematological malignancies [4], there is a recognised need to develop a version of the scale that is validated specifically for haematological malignancies.

The need for an independent validation process and possibly a separate version of the ESMO-MCBS for haematological malignancies derives from the appreciation that there are several major differences in the behaviour of haematological as compared to solid tumour malignancies [5]. Haematological malignancies are

characterized by a more variable natural history which can range from fulminant (acute leukaemia and high-grade lymphomas) to almost benign (low-grade myelodysplastic syndromes (MDS)). Unlike solid tumours, many malignant haematological diseases, even when not cured, are characterized by very long progression-free (PFS) and overall survival (OS) times that are rarely seen among incurable solid tumour malignancies. Finally, the end points used in the studies of treatments for haematological malignancies are sometimes different from those used in solid tumours and in some instances, such as chronic myeloid leukaemia (CML), they are even disease-specific [6].

In 2017, the European Hematology Association (EHA) and ESMO started a joint initiative to develop a version of the ESMO-MCBS validated for haematological malignancies. As a first step in this process ESMO-MCBS (version 1.1) was field tested in 80 studies, including the following haematological malignancies: acute leukaemia (myeloid - AML, lymphoblastic - ALL) and chronic leukaemia (myeloid - CML, lymphocytic - CLL), multiple myeloma (MM), indolent and aggressive lymphomas and MDS [5]. This evaluation found that 90% of studies were scoreable and results were judged reasonable in most cases by the experts. The score was not applicable in 5/80 (6%), and in three other studies (4%) it could not be applied to all endpoints. This study identified six shortcomings in ESMO-MCBS v1.1 requiring specific amendments to improve the applicability and reasonableness of ESMO-MCBS scoring for malignant haematological conditions.

Based on this experience, the joint initiative has developed a version of the ESMO-MCBS that has been validated specifically for haematological malignancies; ESMO-MCBS:H v1.0. This version addresses the identified shortcomings in ESMO-MCBS v1.1 and incorporates other amendments being made for upcoming revision of the solid tumour version of the scale. This paper presents the development and validation of the ESMO-MCBS:H v1.0, including instructions and forms (Figure 1).

METHODS

The development process of the ESMO-MCBS:H incorporated five predefined landmarks:

1. Field testing of the ESMO-MCBS v1.1 forms for clinical trials in the field of haematological malignancies to assess applicability, feasibility, and reasonableness and to identify shortcomings specific to haematological malignancies. The details of the field testing have been previously published and the identified shortcomings are included in Table 1 [5].

2. Drafting of ESMO-MCBS:H. Amendments to ESMO-MCBS v1.1 for solid tumours were drafted to address the previously identified shortcomings to make the scale more widely applicable to haematological malignancies [5]. The 1st draft of the ESMO-MCBS:H was constructed incorporating these amendments as well as other general, not haematology-specific changes that are planned to be included in the forthcoming revision of the solid tumour version of the scale.

3. Peer review and revision of the 1st draft of the ESMO-MCBS:H. This was a 2-step process. The 80 studies previously scored in the pilot testing were re-scored applying the draft version of the ESMO-MCBS:H. The development team reviewed the generated scores and, when ongoing shortcomings were observed, further adjustments were adopted to address them. A 2nd draft version was developed, and the studies were again rescored applying the 2nd draft. This draft was deemed satisfactory to the core development team and was submitted for an evaluation of reasonableness.

4. The reasonableness of the scores generated by the 2nd draft was evaluated by a group of international experts from EHA and ESMO faculty with specific expertise in each of the eight settings. Reviewers evaluated the reasonableness of each score using a verbal rating scale: strongly agree, agree, disagree. When reviewers indicated that they disagreed they were asked to elaborate in free text. This was in accordance with the methodology applied to the development of previous versions of the ESMO-MCBS [7, 8].

5. This was followed by final review and approval of the ESMO-MCBS working group, the EHA task force for the ESMO-MCBS:H and the EHA and ESMO executive boards.

Study selection:

The field testing included mainly but not only pivotal studies, aiming to provide a broad overview on the current and upcoming trial landscape and its ESMO-MCBS applicability. These studies were selected in 2018 at the time of initiation of this project. For methodological purposes and comparability, the same studies were used for the re-testing.

RESULTS

Design issues in the development of the ESMO MBCS:H

The drafting of the ESMO-MCBS:H was based on ESMO-MCBS v1.1 with amendments in response to the shortcomings previously identified as well as other general, not haematology specific, changes that are being incorporated into the forthcoming revision of the solid tumour version of the scale.

Amendments incorporated into ESMO-MCBS:H addressing the identified shortcomings:

Shortcoming 1: ESMO-MCBS v1.1 does not have a form to grade single-arm treatments with curative intent.

Amendment: The ESMO-MCBS:H entails a new form 1b to score single arm studies with curative intent and studies addressing de-escalation in this setting.

*Type***:** Structural amendment.

*Rationale***:** In aggressive haematological malignancies such as acute leukaemia, high-dose chemotherapy-based treatment regimens are applied with curative intent. Recently, add-on of molecular-driven targets to standard treatment has resulted in promising outcomes based on single-arm studies. Similarly, CAR-T-cell therapies have been approved based on single arm studies [9-11]. These were previously not scoreable with curative intent in the ESMO-MCBS v1.1.

Additionally, the term adjuvant is not used for haematological malignancies and has been withdrawn from the ESMO-MCBS:H forms.

*Index case***:** Add-on of the tyrosine kinase inhibitor (TKI) ponatinib to standard high-dose chemotherapy in the up-front treatment of Philadelphia positive ALL was tested in a single-arm phase II study [12]. For patients achieving remission, ponatinib was continued as maintenance therapy. The integration of ponatinib into the treatment protocol resulted in a high 3-year event-free survival (EFS) rate of 70%. This was previously not scoreable with the

MCBS v1.1. Applying the new form 1b for the MCBS:H, this trial scores now B based on the results generated of this single-centre trial. The observed EFS is within the prespecified targets, with the documented 3-year EFS for the standard of care set at 60%.

Shortcoming 2: ESMO-MCBS v1.1 did not include standard molecular surrogate endpoints used for CML.

Amendment: ESMO-MCBS:H includes major molecular response (MMR) and molecular response greater or equal to log 4 (MR4+) on the international reporting scale in addition to the conventional surrogate outcomes. This appears in Form 2c, which is used for therapies that are not likely to be curative with a primary endpoint other than OS or PFS, and non-inferiority studies, where the primary endpoint is response rate.

Type: Nuanced amendment.

Rationale: In addition to (complete) cytogenetic response, molecular responses are the current gold standard to classify treatment outcome in CML [6]. This is of potential relevance for all leukemic diseases. The importance of deep molecular remission was initially explored in the IRIS study and was then accepted as a milestone for treatment response measurement and a prerequisite for exploring TKI discontinuation, which is another relevant factor for patient's QOL [13].

MMR is defined as BCR-ABL transcript levels below 0.1% on the international scale [14-16]. The term deep molecular response is defined as an at least MR4 reduction of the target (4-log reduction from IRIS baseline; = BCR-ABL ≤ 0.01% on the international reporting scale), MR4.5 reduction (4.5-log reduction; = BCR-ABL ≤ 0.0032% on the international reporting scale) is associated with an even better prognosis equivalent to a complete molecular response.

Index case: In the DASISION trial, the second generation BCR-ABL kinase inhibitor dasatinib was tested against imatinib as standard arm for chronic phase newly diagnosed CML [17, 18]. Based on the only moderate increase in the complete cytological response rate at 12 months from 66% to 77% with an absolute increase of 11%, this study scored 1 in the pilot testing [5], while the more clinically important increase in MR4.5 at 5-years from 33% to 42% was not measurable with MCBS v1.1.

Applying the adapted ESMO-MCBS:H, this outcome fulfils the criteria for grade 2 with an increase of MR4+ ≥ 5 - <10%. This more adequately reflects the clinical benefit for this patient collective.

Shortcomings 3: ESMO-MCBS v1.1 did not have a mechanism to credit indolent non curable conditions with very long median PFS or to appropriately grade conditions with a very long median OS. This was a critical shortcoming for scoring clinical benefit for relatively indolent conditions with a long median PFS or OS, such as CLL, CML, indolent lymphomas and MM.

Amendment: The ESMO-MCBS:H includes new sub-forms for studies in which the median PFS for the control arm is ≥12 months and for studies with a median control OS ≥ 36 months or not reached with ≥ 36 months follow-up. In these new sub-forms pre-specified interim gains, when the median of the control arm has not been reached, are scoreable if they are statistically significant and the observed lower limit of the 95% confidence interval (95%CI) of the hazard ratio (HR) is ≤ 0.65.

Type: Nuanced and structural.

Rationale: Indolent haematological malignant diseases, including certain lymphomas, CML and MM, often have very long median PFS and OS times. It nevertheless remains common consensus that these malignancies are regarded as chronic and treatments non-curative [5]. These PFS- or OS-gains may be evaluated at pre-specified time points even when the median for the control arm, which may be very long, has not yet been reached.

Index case: The phase III GALLIUM-trial evaluated the second generation anti-CD20-antibody obinutuzumab versus standard rituximab (R) plus chemotherapy in the first line setting of follicular lymphoma [19]. The trial showed a significant increase in EFS with an HR of 0.66 (95%CI 0.51-0.85) and a 7% gain in median EFS rate at 3 years (73% for R-chemo versus 80% for obinutuzumab-chemo). While these outcomes resulted in FDA and EMA approval of obinutuzumab for up-front therapy of follicular lymphoma, because the median EFS was not reached in either arm, the observed benefit was not scoreable by the ESMO-MBCS v1.1.

Using ESMO-MCBS:H the GALLIUM 7% interim gain at 3-year EFS and HR ≤ 0.65 is now scoreable. Applying form 2b for diseases where the primary outcome is PFS with a median PFS of the control arm > 12 months, its ESMO-MCBS:H score is 1.

Shortcoming 4: ESMO-MCBS v1.1 did not make provision for the grading of non-inferiority studies based on response rate criteria.

Amendment: ESMO-MCBS:H form 2c which is used for evaluating non-inferiority studies incorporates an amendment to credit studies where non-inferiority is based on response rate or MMR. Studies with non-inferior response rate or MMR are eligible for credit if they demonstrate reduced toxicity and/or improved QOL (using a validated scale).

Type: Nuanced amendment

Rationale: Non-inferiority trials with a primary endpoint of complete remission rate (CRR) have previously supported establishment of standard regimens in lymphoma studies.

Index case: The combination regimen R-bendamustine was evaluated in the non-inferiority trial BRIGHT for untreated indolent and mantle cell lymphoma [20, 21]. In this study, R-bendamustine was randomised versus standard R-chemotherapy and met the non-inferiority threshold for CRR with evidence of fewer adverse effects and improved QOL. These results support use of R-bendamustine but were previously not scoreable using ESMO-MCBS v1.1 due the primary endpoint of CRR.

Applying ESMO-MCBS:H, which credits evidence for non-inferiority in the primary endpoint CRR, the BRIGHT study, which was previously not eligible for scoring, achieves a score of 4 using the revised form 2c criteria.

Shortcoming 5: In ESMO-MCBS v1.1 for studies evaluating response rate as a primary endpoint, there is no provision of QOL bonus if improved QOL is demonstrated as a secondary outcome.

Amendment: For studies where the primary outcome is response rate or MMR, ESMO-MCBS:H incorporates an upgrade of 1 point if the study also demonstrated improved QOL or a downgrade if excess toxicity thresholds are crossed.

Type: Nuanced.

Rationale: MDS is a bone marrow disease with heterogeneous clinical settings and distinct disease-specific outcomes defined over the years [22, 23]. While the disease course is variable, ranging from indolent to acute

leukemic, trials addressing MDS, usually include specific predefined risk groups and aim for improvement in response rates of endpoints such as transfusion dependency which is a surrogate for improved QOL. Verification of this benefit can be established by measuring QOL outcomes as a secondary endpoint.

Index case: In the phase III randomized study LEN-MDS-004, lenalidomide (10 mg) was compared to standard of care using the endpoint of transfusion independency in low-intermediate risk MDS patients with del5q [24]. Lenalidomide resulted in a 50% gain in transfusion independence from 6% to 56% with a health-related quality of life benefit that was statistically and clinically significant. This was rated as 2 in form 2c of MBCS v1.1 (response rate increase ≥20%). Using ESMO-MCBS v1.1 the significant QOL gain demonstrated in this study would not have been creditable.

Applying ESMO-MCBS:H, which incorporates a toxicity and QOL adjustment in this setting, the QOL gain demonstrated in this study is creditable with 1 point bonus and the final score is 3 based on form 2c.

Previously identified shortcomings not incorporated in ESMO-MCBS:H

At the initial field-testing a concern was raised that the scale may undervalue treatments with substantial late PFS gain but with no plateauing of the curves. Using ESMO-MCBS v1.1 credit for PFS was capped at a maximal preliminary grade of 3, with provision for an upgrade based on tail of the curve only when there is a plateau in the arm with the experimental treatment. However, the other amendments for crediting PFS in the ESMO-MCBS:H adequately facilitates reasonable scoring for the range of PFS scenarios observed in haematological malignancies, without need to revise this separately (see Table 1).

General (not haematology-specific) changes that are being incorporated into the forthcoming revision of the solid tumour version of the scale

These revisions refer to the scoring of studies in the curative setting including: 1) the addition of absolute gain criteria for disease-free survival (DFS) gain, 2) revision of the relative benefit criteria for DFS, 3) reduced but on-

going credit for DFS gain in the absence of mature OS benefit, 4) credit for single arm de-escalation studies in the curative setting and 5) annotation for acute and persistent toxicity. For the forms evaluating randomized controlled trials in a non-curative setting and when the evidence of benefit is derived from surrogate endpoints (Form 2b and 2c), criteria for toxicity penalties have been revised.

Field testing and final forms

All amendments were incorporated in the first final version of the ESMO-MCBS:H. This version was applied to all 80 studies previously selected for the pilot study [5]. Re-scoring resulted in alteration of scores due to the haematology-specific adaptations for 16/80 (20%) studies.

In summary, scores were changed due to the following reasons: new form 1b (n=1), new endpoints in form 2c (n=5), new PFS/OS intervals and definitions (n=6), and the adapted toxicity classification (n=4). In addition, acute toxicity annotations were added where necessary (e.g., first-line therapy for acute leukaemia). Only one study remained “non-scoreable” due to not meeting its endpoint [25]. All final scorings were evaluated and reapproved by the initial experts involved in the pilot study.

Tabulated results from 85 scoreable scenarios in 76 studies that remained relevant to contemporary practice were sent out to an extended group of 51 experts from the EHA and ESMO faculty with a response rate of 76.5% (39/51). Four small single arm studies were considered no longer relevant to current standards of practice, these were not included in the evaluation of reasonableness [26-29].

In 81/85 of the scenarios evaluated (95%), more than 80% of reviewers judged the score reasonable. Consensus regarding the reasonableness of the score was less than 80% in only 4 cases: In two of these scenarios (both part of one myeloma trial) [30], the disagreement between expert evaluation and the grade derived from failure of the trials to present all data requirements. In the other two studies initial scores based on first published data were considered low, however subsequent revised scores with long term data were deemed reasonable [31, 32].

Full field testing tables are presented with the supplementary files (Supplementary Table 1). The final forms of the ESMO-MCBS:H including instructions are presented in Figure 1.

DISCUSSION

The ESMO-MCBS has been widely recognised as the most robustly validated tool for the evaluation of the magnitude of clinical benefit reported in studies for the treatment of solid tumours in adults. It has been used to benchmark the benefit of approved treatments [33-36], it is widely applied in HTA process [37-39], it is used to screen candidate medication for the WHO essential medicines list [40, 41], it is used in the ESMO guidelines [42], it facilitates teaching of a structured approach to study evaluation and it has been implemented in clinical routine at many oncological centres across Europe.

Hitherto, neither the ESMO-MCBS nor any other comparable frameworks have been explicitly developed to evaluate the magnitude of clinical benefit from treatments for haematological malignancies. This has been recognised as a major deficiency, particularly since the behaviour and natural history of haematological malignancies differs significantly from solid tumours [5].

This manuscript presents the first mature validated version of the ESMO-MCBS for haematological malignancies, the ESMO-MCBS:H v1.0. The ESMO-MCBS:H v1.0 now enables the evaluation of the magnitude of clinical benefit derived from clinical research studies in a wide spectrum of haematological malignancies. This version addresses all of the shortcomings identified from applying ESMO-MCBS v1.1 to haematological malignancies [5]. It has been developed using the structured processes of the ESMO-MCBS working group for revision, and validation of any adaptions to the scale. In accordance with standard operating procedures of the ESMO-MCBS working group, all development procedures for the ESMO-MCBS:H were compliant with standards for "accountability for reasonableness" such as relevance, coherence, statistical validity, field testing, transparency, expert peer review and continuous revisability [7, 8].

We anticipate several important consequences from the development of an objective validated approach to the evaluation of the magnitude of clinical benefit from new treatments in malignant haematology. For clinicians, the ESMO-MCBS:H will aid in their clinical deliberations and in the development of evidence-based practice and

guidelines. For trainees, application of the ESMO-MCBS:H teaches a structured approach to evaluating clinical research studies. For health care systems application the ESMO-MCBS:H will assist in the process of distinguishing high benefit therapies form those with low or marginal clinical benefit for the purposes of resource allocation decision making that is essential to sustainability.

The ESMO-MCBS:H will facilitate unbiased evaluation of the magnitude of clinical benefit from cancer therapies for haematological malignancies, but it does not obviate the need to think critically about cancer medicine trial designs. The appropriate interpretation of the ESMO-MCBS scores requires the critical appraisal of trials to understand issues in trial design, implementation, and data analysis that may have biased the results and conclusions [43].

The published tables (Supplementary Table 1) in this report do not comprise a complete and contemporary list of drugs used in clinical practice but a selection for methodological purposes. The ESMO-MCBS working group in cooperation with the EHA will develop and maintain an online library of score cards for all FDA and EMA approved treatments in malignant haematology in parallel to the library already available for solid tumour treatments (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards). ESMO-MCBS:H scores will be incorporated into clinical practice guidelines by the ESMO-guideline committee.

We believe that the ESMO-MCBS:H will support the shared mission of ESMO and the EHA to identify novel treatments that bring a substantial clinical benefit to the individual patient and to fight against disparities in the treatment of cancer patients across Europe.

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Appendix B lists the names of the members of the ESMO-MCBS Working Group and Extended Working Group who are not listed as authors.

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RW reports honoraria Sanofi and Janssen.

EM reports being a member of the European Hematology Association and its president from 2021-23.

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TABLES AND FIGURES

Table 1. Shortcomings previously identified in the ESMO-MCBSv1.1 for the assessment of haematological malignancies [5] and their resolution in ESMO-MBCS:H.

Figure 1. Final forms of the ESMO-MCBS:H including instructions.

	Shortcoming	Relevant to form	Resolved in ESMO-MCBS:H
1	Regarding single-arm studies with curative intent, such as CAR T-cell salvage therapies, the ESMO-MCBS v1.1 does not have a form to grade single-arm treatments with curative intent.	1b	☑
2	Regarding relatively indolent conditions with a very long PFS (or EFS) or OS such as CLL, CML, indolent lymphoma and MM, there is no mechanism to credit strong interim gains when the median of the control arm has not yet been reached.	2a/b	☑
3	The capitation of PFS at a maximal preliminary grade of 3, with provision for an upgrade based on tail of the curve only when there is a plateau in the arm with the study medication, may undervalue treatments with substantial late PFS gain but with no plateauing of the curves.	2b	Integrated in shortcoming 2
4	Regarding the standard molecular surrogate endpoints used for CML, the surrogacy of molecular response rates must be acknowledged and incorporated.	2c	☑
5	The scale does not make provision for the grading of non-inferiority studies based on response rate criteria.	2c	☑
6	In studies evaluating response rate as a primary endpoint, there is no provision of QOL bonus if improved QOL is demonstrated as a secondary outcome.	2c	☑

01. There are 6 forms

Evaluation form 1a: for RCTs evaluating new approaches to 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 1b: for single arm therapies with curative intent and de-escalation studies

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 <12 months
- IF median OS with the standard treatment ≥12 - <24 months
- IF median OS with the standard treatment ≥24 - <36 months
- IF median OS with the standard treatment ≥36 months

Evaluation form 2b: for therapies that are not likely to be curative with primary endpoint PFS with separate sheets for:

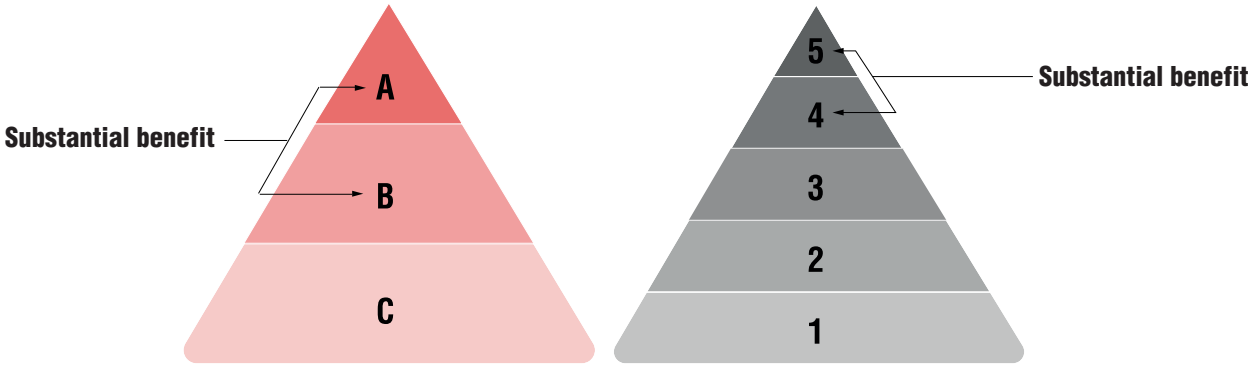
- IF median PFS with standard treatment <6 months
- IF median PFS with standard treatment ≥6 – <12 months
- IF median PFS with standard treatment ≥12 months

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 ORR.

02. ESMO-MCBS scores

The highest grades of the ESMO-MCBS:H 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:H, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale for Haematological Malignancies; ORR, overall response rate; OS, overall survival; PSF, progression-free survival.

03. Eligibility for application of the ESMO-MCBS:H

The ESMO-MCBS:H can be applied to comparative outcome studies evaluating in haematological malignancies the relative benefit of treatments using endpoints of survival, QoL and conventional surrogate endpoints (for example, DFS, DFI, RFS, EFS, PFS, RFS, TTR, TTP) or treatment toxicity.

- Eligible studies can have either a randomised or comparative cohort design or a meta-analysis which report statistically significant benefit from any one, or more of the evaluated outcomes.
- Single arm studies with curative intent, including de-escalation studies, and studies in non-curative settings that have resulted in licensing can be evaluated.
- When more than one study has evaluated a single clinical question, results derived from well powered registration trials should be given priority.
- Evidence of benefit derived from meta-analyses can be graded only for meta-analyses and systemic reviews compliant with PRISMA standards[1]. These includes requirements for:
    a. Plausible question based on randomised evidence using an exhaustive review of relevant studies
    b. Evaluation of consistency across studies regarding population of interest
    c. Relevant patient characteristics and control arm, coupled with lack of bias (publication, selective reporting)
    d. Exploration of heterogeneity and clear description of limitations.

04. Analysis of phase III trials

- Adequately powered studies showing statistically significant improvement in the primary outcome (defined by $P < 0.050$ or less if that is a predefined threshold).
- Careful analysis of the "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 biologic 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.
    e. Claims of benefit based on analyses contravening these statistical constraints are not scoreable (even when they are the basis of regulatory authority approval).

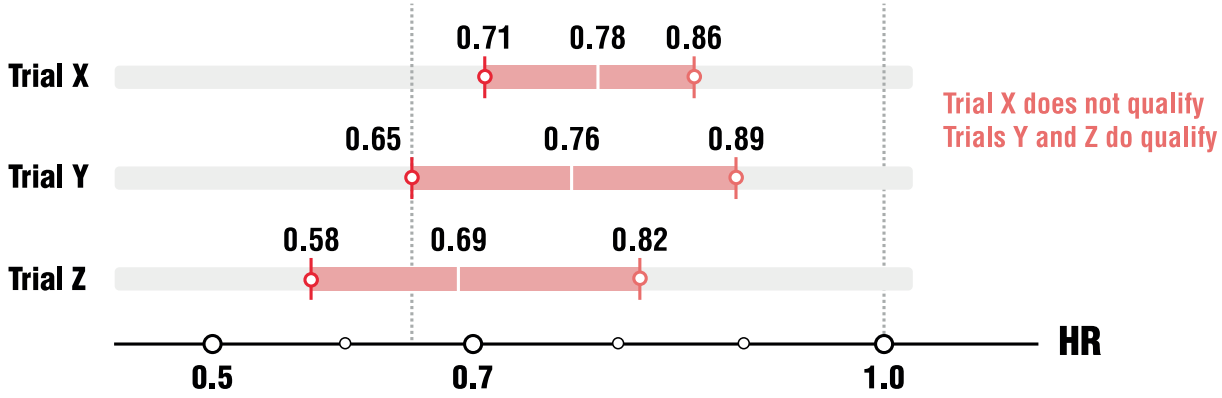
05. More than one outcome may be applicable

The statistical significance of secondary outcomes are determined by the same criteria as for primary outcomes i.e. defined by $P<0.050$ or less if that is a predefined threshold.

DFI, disease free interval; DFS, disease-free survival; EFS, event free survival; ESMO-MCBS:H, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale for Haematological Malignancies; ORR, overall response rate; OS, overall survival; PSF, progression-free survival; QoL, quality of Life; RFS, relapse free survival; TTP, time to progression; TTR, time to relapse.

1 Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009; 6(7): e1000097.

06. 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

07. In studies with curative intent

- In evaluation of DFS (or RFS, TTP and EFS)
  - Note time point of evaluation (in months or years)
  - Indicate if specific outcome TTP, DFS, iDFS (invasive DFS)
  - Maturity of survival data may be protocol defined or, if not defined, determined by the specific clinical entity. Examples:

Disease	Follow-up for OS data maturity
AML, ALL, high grade lymphoma	5 years
MM, follicular lymphoma	8-10 years

- In cases where OS data maturity has not yet been reached and both OS and DFS are potentially scoreable, the higher score prevails
- Scores are annotated for toxicity
  - AT: indicates high prevalence of acute transient side effects impacting daily well-being. All curative therapies incorporating autologous or allogeneic bone marrow or stem cell transplant are annotated AT.
  - PT: indicates high prevalence of persistent and chronic side effects and late side effects that impact QoL. All curative therapies incorporating allogeneic bone marrow or stem cell transplant are annotated PT due to graft vs host disease

08. In instances when the median of the control arm is reached and the relative benefit gain (HR) is significant, the median of the experimental arm is estimated on the basis of control arm (months) divided by the point estimate of the HR

AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; AT, acute toxicity; CI, confidence interval; DFS, disease-free survival; HR, hazard ration; iDFS, invasive disease-free survival; EFS, event free survival; MM, multiple myeloma; OS, overall survival; PT, persistent toxicity; QoL, Quality of Life; RFS, relapse free survival; TTP, time to progression.

09. **In the case of OS in the non-curative setting check for:**

a. Reduced toxicity
b. Improvement in quality of life
c. Report final adjusted grade taken into account toxicity, and QoL when relevant.

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

a. Indicators of toxicity
b. Survival data when also available
c. Early termination with crossover based on planned interim survival analysis
d. Global QoL advantage using validated scale if applicable
e. Report final adjusted grade taken into account toxicity, survival advantage and QoL when applicable

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11. **Studies violating the statistical constraints of the ESMO-MCBS:H are not eligible for grading even in circumstances where they are the basis for regulatory body (EMA, FDA, etc) approval: they may be indicated as statistical violations**

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12. **Studies using parameters that are not evaluable using the ESMO-MCBS:H are indicated not scoreable**

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

EVALUATION FORM 1A

For new potentially curative therapies

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

		Mark with X if relevant
GRADE A	≥5% improvement of survival gain	○
	Improvements in DFS alone (primary endpoint) HR ≤0.65 AND absolute gain ≥3% in studies without mature survival data	○
GRADE B	3 - <5% improvement of overall survival gain	○
	Improvements in DFS (primary endpoint) HR ≤0.65 AND absolute gain 1% - <3% in studies without mature survival data	○
	Improvement in DFS (primary endpoint) HR >0.65 - 0.70 AND absolute gain ≥3% without mature survival data	○
	Non inferior OS or DFS with reduced treatment toxicity or improved Quality of Life (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 gain	○
	Improvement in DFS (primary endpoint) HR ≤0.65 AND absolute gain <1% in studies without mature* survival data	○
	Improvement in DFS (primary endpoint) HR >0.65-0.75 AND absolute gain <3% in studies without mature* survival data	○
	Improvement in DFS (primary endpoint) HR >0.75	○
	Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data	○

Preliminary magnitude of clinical benefit grade (highest grade scored)	**A** ○	**B** ○	**C** ○

*Note: For guidelines regarding maturity of survival data see instructions point 7

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

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

TOXICITY ANNOTATION

Acute Transient Toxicity (AT)

Mark with X if relevant

Is the new treatment associated with a rate of:

Grade 3+ side effects impacting well-being >30% of patients	○
Premature discontinuation of therapy due to adverse effects >10% of patients	○
Hospitalisation for «toxicity» >10% of patients	○

Persistent Toxicity (PT)

Mark with X if relevant

Is the new treatment associated with a rate of:

Chronic neuropathy >20% of the patients*	○
Other grade 3+ chronic toxicity adversely impacting well-being >20% of patients	○
Curative therapies incorporating allogeneic bone marrow or stem cell transplant	○

*Note: For guidelines regarding maturity of survival data see instructions point 7

Adjustments

Downgrade 1 level if mature OS does not demonstrate significant benefit

Note: See instructions for use for guidelines regarding maturity of OS

Final magnitude of clinical benefit grade (highest grade scored) with toxicity annotation	**A**	**B**	**C**
	☐ (AT) ☐ (PT)	☐ (AT) ☐ (PT)	☐ (AT) ☐ (PT)

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

Note: Studies in which the goal of treatment is both cure AND prolongation of survival, if cure is not achievable, can also be graded using form 2a (using HR and median survival benefit criteria) and grades for both curative intent and non-curative intentshould be presented (i.e. A/4)

AC, acute toxicity; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; PT, persistent toxicity.

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

EVALUATION FORM 1B

Single arm studies and de-escalation studies in the curative setting

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

Mark with X if relevant

GRADE A	Multicenter trial with observed DFS or mature OS are within 2% of the pre-specified target DFS or OS (at pre-specified relevant time point, derived from the standard of care)	○
GRADE B	Single-center trial with observed DFS or mature OS are within 2% of the pre-specified target DFS or OS (at pre-specified relevant time point, derived from the standard of care)	○
GRADE C	Trial with observed DFS or mature OS within more than 2% but less than 5% of the pre-specified target DFS or OS (at pre-specified relevant time point, derived from the standard of care)	○

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

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

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

TOXICITY ANNOTATION

Acute Transient Toxicity (AT)

Mark with X if relevant

Is the new treatment associated with a rate of:

Grade 3+ side effects impacting well-being >30% of patients ○

Premature discontinuation of therapy due to adverse effects >10% of patients ○

Hospitalisation for «toxicity» >10% of patients ○

Persistent Toxicity (PT)

Mark with X if relevant

Is the new treatment associated with a rate of:

Chronic neuropathy >20% of the patients* ○

Other grade 3+ chronic toxicity adversely impacting well-being >20% of patients ○

*Note: For guidelines regarding persistent toxicity see instructions point 7

Final magnitude of clinical benefit grade (highest grade scored) with toxicity annotation	**A**		**B**		**C**	
	(AT) ☐	(PT) ☐	(AT) ☐	(PT) ☐	(AT) ☐	(PT) ☐

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

AC, acute toxicity; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response/remission; PT, persistent toxicity.

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

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

Mark with X if relevant

GRADE 4	HR ≤0.65 AND gain ≥3 months	○
	Increase in 2-year survival ≥10% (if >20% patients have reached 2 years OS)	○
GRADE 3	HR ≤0.65 AND gain ≥2 - <3 months	○
GRADE 2	HR ≤0.65 AND gain ≥1.5 - <2 months	○
	HR >0.65 - 0.70 AND gain ≥1.5 months	○
GRADE 1	HR >0.70 OR gain <1.5 months	○

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

HR, hazard ratio; OS, overall survival

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

Quality of Life assessment

Mark with X if relevant

Does secondary endpoint quality of life show improvement or delayed deterioration in quality of life	○

Adjustments

01. Upgrade 1 level if improved quality of life 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 1a (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.

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

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 - <24 months

Mark with X if relevant

GRADE 4	HR ≤0.70 AND gain ≥5 months	○
	Increase in 3-year survival alone ≥10% (if >20% patients have reached 3 years OS)	○
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	○

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

HR, hazard ratio; OS, overall survival

ESMO-Magnitude of Clinical Benefit Scale
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Quality of Life assessment

Mark with X if relevant

Does secondary endpoint quality of life show improvement or delayed deterioration in quality of life ○

Adjustments

01. Upgrade 1 level if improved quality of life 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 1a (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.

ESMO-Magnitude of Clinical Benefit Scale
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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 ≥24 - <36 months

Mark with X if relevant

GRADE 4	HR ≤0.70 AND gain ≥9 months	○
	Increase in 5-year survival ≥10% (if >20% patients have reached 5 years OS)	○
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	○

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

HR, hazard ratio; OS, overall survival

ESMO-Magnitude of Clinical Benefit Scale
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Quality of Life assessment

Mark with X if relevant

Does secondary endpoint quality of life show improvement or delayed deterioration in quality of life ○

Adjustments

01. Upgrade 1 level if improved quality of life 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 1a (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.

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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 ≥36 months or not reached with ≥36 months follow-up

Mark with X if relevant

GRADE 4	HR ≤0.70 AND gain ≥12 months	○
	HR ≤0.65 AND interim OS gain ≥20% (if OS is not mature)	○
	Increase in 7-year survival alone ≥10% (if >20% patients have reached 7 years OS)	○
GRADE 3	HR ≤0.70 AND gain ≥8 - <12 months	○
	HR ≤0.65 AND interim OS gain 10-20% (if OS is not mature)	○
GRADE 2	HR ≤0.70 AND gain ≥6 - <8 months	○
	HR >0.70-≤0.75 AND gain ≥6 months	○
	HR ≤0.65 AND interim OS gain <10% (if OS is not mature)	○
GRADE 1	HR >0.75 OR gain <6 months	○

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

HR, hazard ratio; OS, overall survival

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

Quality of Life assessment

Mark with X if relevant

Does secondary endpoint quality of life show improvement or delayed deterioration in quality of life ○

Adjustments

01. Upgrade 1 level if improved quality of life 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 10 years, also score according to form 1a (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.

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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

Mark with X if relevant

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	○

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

HR, hazard ratio; PFS, progression-free survival.

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Early stopping or crossover

Mark with X if relevant

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

Note: If the answer to both is "yes" see adjustment "3b" below

Incremental toxicity

Mark with X if relevant

Is the new treatment associated with an incremental rate of:

«Toxic» death >2% of patients	○
Premature discontinuation of therapy >10% of patients	○
Hospitalisation for «toxicity» >10% of patients	○
Grade 3+ mucositis >10% of patients	○
Grade 3+ diarrhoea >10% of patients	○
Grade 3+ fatigue >10% of patients	○
Grade 3+ neurotoxicity >10% of patients	○
Other distressing toxicity grade 3+ >10% of patients	○
Overall grade 3-4 toxicity impacting on daily well-being* or serious adverse events >20% of patients	○

Note: Incremental rate refers to the comparison versus standard therapy in the control arm

Reduced grade 3-4 toxicity

Mark with X if relevant

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.

Note: If the answer to both is "yes" see adjustment "3a" below

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Quality of Life

Mark with X if relevant

Was quality of life evaluated as secondary outcome? ○

Does quality of life assessment show improvement or delayed deterioration? ○

Note: If the answer to both is "yes" see adjustment "3a" below

Adjustments

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

02. Downgrade 1 level if:
- a. The treatment ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL
- b. The treatment has incremental toxicity

03. Upgrade 1 level if:
- a. Improved quality of life or if less grade 3-4 toxicities that bother patients are demonstrated
- b. Study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis
- c. If there is a long-term plateau in the PFS curve, and there is ≥10% improvement in PFS at 1 year

Note: no more than 1 upgrade is possible

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

Note: Highest magnitude clinical benefit grade that can be achieved in form 2b is grade 4.

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

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

ESMO-Magnitude of Clinical Benefit Scale
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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 the standard treatment ≥6 - <12 months

Mark with X if relevant

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

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

HR, hazard ratio; PFS, progression-free survival.

ESMO-Magnitude of Clinical Benefit Scale
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Early stopping or crossover

Mark with X if relevant

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

Note: If the answer to both is "yes" see adjustment "3b" below

Incremental toxicity

Mark with X if relevant

Is the new treatment associated with an incremental rate of:

«Toxic» death >2% of patients	○
Premature discontinuation of therapy >10% of patients	○
Hospitalisation for «toxicity» >10% of patients	○
Grade 3+ mucositis >10% of patients	○
Grade 3+ diarrhoea >10% of patients	○
Grade 3+ fatigue >10% of patients	○
Grade 3+ neurotoxicity >10% of patients	○
Other distressing toxicity grade 3+ >10% of patients	○
Overall grade 3-4 toxicity impacting on daily well-being* or serious adverse events >20% of patients	○

Note: Incremental rate refers to the comparison versus standard therapy in the control arm

Reduced grade 3-4 toxicity

Mark with X if relevant

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.

Note: If the answer to both is "yes" see adjustment "3a" below

ESMO-Magnitude of Clinical Benefit Scale
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Quality of Life

Mark with X if relevant

Was quality of life evaluated as secondary outcome? ○

Does quality of life assessment show improvement or delayed deterioration? ○

Note: If the answer to both is "yes" see adjustment "3a" below

Adjustments

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

02. Downgrade 1 level if:
- a. The treatment ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL
- b. The treatment has incremental toxicity

03. Upgrade 1 level if:
- a. Improved quality of life or if less grade 3-4 toxicities that bother patients are demonstrated
- b. Study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis
- c. If there is a long-term plateau in the PFS curve, and there is ≥ 10% improvement in PFS at 2 years

Note: no more than 1 upgrade is possible

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

Note: Highest magnitude clinical benefit grade that can be achieved in form 2b is grade 4.

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

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

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

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 ≥12 months

Mark with X if relevant

GRADE 3	HR ≤0.65 AND gain ≥5 months	○
	HR ≤0.65 AND Interim PFS gain ≥20% (if PFS is not mature)	○
GRADE 2	HR ≤0.65 BUT gain <5 months	○
	HR ≤0.65 AND Interim PFS gain ≥10-<20% (if PFS is not mature)	
GRADE 1	HR >0.65	○
	HR ≤0.65 AND Interim PFS gain <10% (if PFS is not mature)	○

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

HR, hazard ratio; PFS, progression-free survival.

ESMO-Magnitude of Clinical Benefit Scale
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Reduced grade 3-4 toxicity

Mark with X if relevant

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.**

Note: If the answer to both is "yes" see adjustment "3a" below

Quality of Life

Mark with X if relevant

Was quality of life evaluated as secondary outcome? ○

Does quality of life assessment show improvement or delayed deterioration? ○

Note: If the answer to both is "yes" see adjustment "3a" below

Adjustments

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

B Downgrade 1 level if
- a. The treatment ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL
- b. The treatment has incremental toxicity

C Upgrade 1 level if
- a. Improved quality of life or if less grade 3-4 toxicities that bother patients are demonstrated
- b. Study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis
- c. There is a long-term plateau in the PFS curve, and there is ≥10% improvement in PFS at 3 years

Note: no more than 1 upgrade is possible

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

Note: Highest magnitude clinical benefit grade that can be achieved in form 2b is grade 4.

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

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

ESMO-Magnitude of Clinical Benefit Scale
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Early stopping or crossover

Mark with X if relevant

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

Note: If the answer to both is "yes" see adjustment "3b" below

Incremental toxicity

Mark with X if relevant

Is the new treatment associated with an incremental rate of:

«Toxic» death >2% of patients	○
Premature discontinuation of therapy >10% of patients	○
Hospitalisation for «toxicity» >10% of patients	○
Grade 3+ mucositis >10% of patients	○
Grade 3+ diarrhoea >10% of patients	○
Grade 3+ fatigue >10% of patients	○
Grade 3+ neurotoxicity >10% of patients	○
Other distressing toxicity grade 3+ >10% of patients	○
Overall grade 3-4 toxicity impacting on daily well-being* or serious adverse events >20% of patients	○

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

ESMO-Magnitude of Clinical Benefit Scale
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EVALUATION FORM 2C

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

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

Primary outcome is molecular response rate, response rate, toxicity or quality of life and non-inferiority studies

Mark with X if relevant

GRADE 4	Reduced toxicity* or improved quality of life (using validated scale) with evidence for statistical non-inferiority or superiority in PFS/OS/CRR/MMR	○
	Major molecular response rate (MR 4+) increased ≥20%	○
GRADE 3	Improvement in some symptoms (using a validated scale) BUT without evidence of improved overall quality of life	○
	Major molecular response rate (MR 4+) increased 10 - <20%	
GRADE 2	RR is increased ≥20%	○
	Major molecular response rate (MR 4+) increased ≥5 - <10%	○
GRADE 1	RR is increased <20%	○
	Major molecular response rate (MR 4+) increased <5%	○

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

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

CRR, complete remission rate; MMR, major molecular response; MR, molecular response; OS, overall survival; PSF, progression-free survival; RR, response rate.

ESMO-Magnitude of Clinical Benefit Scale
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Incremental toxicity

Mark with X if relevant

Is the new treatment associated with an incremental rate of:

«Toxic» death >2% of patients	○
Premature discontinuation of therapy >10% of patients	○
Hospitalisation for «toxicity» >10% of patients	○
Grade 3+ mucositis >10% of patients	○
Grade 3+ diarrhoea >10% of patients	○
Grade 3+ fatigue >10% of patients	○
Grade 3+ neurotoxicity >10% of patients	○
Other distressing toxicity grade 3+ >10% of patients	○
Overall grade 3-4 toxicity impacting on daily well-being* or serious adverse events >20% of patients	○

ESMO-Magnitude of Clinical Benefit Scale
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Quality of life/ grade 3-4 toxicities assessment

Mark with X if relevant

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

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

Adjustments

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

02. Upgrade 1 level if study with primary outcome of MR or RR demonstrates
a. Improved quality of life OR
b. Less grade 3-4 toxicities that affect well-being of patients are demonstrated

03. Downgrade 1 level if the treatment has incremental toxicity

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

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

MR, molecular response; OS, overall survival; RR, response rate.

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

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:					

Mark with X if relevant

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

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

CR, complete remission; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

ESMO-Magnitude of Clinical Benefit Scale
for Haematological Malignancies

Quality of life/ grade 3-4 toxicities assessment

Mark with X if relevant

Was quality of life evaluated as secondary outcome?	○
Does secondary endpoint quality of life 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.

Adjustments

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

B Upgrade 1 level if improved quality of life

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

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