



SOPs/Instructions for Authors and templates for standard ESMO Clinical Practice Guidelines (CPGs), eUpdates and ESMO-MCBS Scores

ESMO Guidelines Committee, October 2015, latest revision October 2016

Introduction

- ✓ The CPGs should be updated when there is need for such as judged by the Guidelines Committee (GLC). Each updated CPG will be published online once finalised and subsequently in the next dedicated CPG supplement of Annals of Oncology (published annually).
- ✓ An electronic update (eUpdate) will be produced in the following instances:
 - When important breakthroughs need to be rapidly communicated.
 - When only few updates are needed for a CPG instead of producing a revised version.
 - When a Magnitude of Clinical Benefit Scale (ESMO-MCBS) score has been produced for a new therapy or a new indication of existing therapy by the EMA in the context of the relevant CPG.

Production of an eUpdate will be proposed by the Subject Editor (SE) or GLC Steering Committee (GLC-SC) and approved by the GLC-SC.

Drafting of the eUpdate is done by the SE and/or CPG coordinating author, reviewed by both and approved by the GLC-SC.

When the eUpdate refers to an ESMO-MCBS score of a new therapy/indication, it will be drafted by the Subject Editor +/- the lead author of the CPG, reviewed by the MCBS WG and approved by the GLC-SC and the ESMO President's Council. The need for such an eUpdate should be monitored by the SE, lead author and MCBS Working Group. Such eUpdates should be produced within one month.

The eUpdate will be published online and linked to the Guideline pages on esmo.org and OncologyPRO. It will also be incorporated into the CPG when a revised version is produced.

Template for an eUpdate in Appendix A.

- ✓ The standard CPGs should take into account and be in agreement with the content from the recent **ESMO Consensus Statements** when available (these are two separate products that are complementary).
- ✓ ESMO will produce pocket versions of standard CPGs as «hands-on» booklets with Tables, Flow Charts and 'bullet point' recommendations for daily use: Pocket Guidelines. The corresponding author of each CPG will be asked to review and comment on the relevant chapter of the Pocket Guidelines.
- ✓ The target audience for the CPGs is health professionals working in the field of oncology across Europe and other parts of the world, with an emphasis on Medical Oncology.

Structure

✓ **Structure of the text in thematic sections:**

1. Incidence and epidemiology
2. Diagnosis and pathology/molecular biology
3. Staging and risk assessment
4. Management of local/locoregional disease
5. Management of advanced/metastatic disease
6. Personalised Medicine Synopsis Table
7. Follow-up, Long-term implications and Survivorship
8. Bullet point Table with all recommendations
9. MCBS Table
10. References

✓ Some ESMO CPGs (specifically those focused on cancer genetics and palliative/supportive care) may not be compatible with the Thematic Section Structure above. These may follow a more «individualised» structure, though it is advised to adhere to the following general format:

1. Incidence
2. Assessment/Diagnosis
3. Management and Monitoring
4. Follow-up

✓ **Title:**

The title should be formatted according to the following example:

Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

For the titles that do not include diagnosis, treatment and follow-up, the title should be formatted according to the following example:

Central venous access in oncology: ESMO Clinical Practice Guidelines

✓ **Authorship:**

Authorship should consist of a minimum of 4 authors including the Subject Editor. The coordinating author appears as first author, followed by the other contributors and the SE as last. The coordinating author is responsible for coordination of authorship and submission of the CPG draft.

The authorship should be multidisciplinary. Thus authors should include Medical oncologists, a Surgical oncologist and a Radiation Oncology specialist as far as possible (and/or other disciplines if appropriate).

The authors should include experts from different institutions and different countries in Europe and abroad to ensure recognition as European and global guidelines.

✓ **Extent (pages):**

The manuscript should cover 8-20 pages (Arial 12 points, 1.5-line spacing) and ***particularly focus on the therapeutic recommendations.***

✓ **Personalised medicine:**

Information relating to personalised medicine should be included throughout the CPG text in the various sections where relevant and appropriate.

At the end of the CPG, before the Follow-up final section, a Personalised Medicine Synopsis table will provide summary information on **validated** biomarkers used for any of the following: a) disease classification, b) prognostic relevance, c) predictive relevance, d) used for medical treatment decisions, e) currently actionable/targetable.

See Appendix B.

If no such Table is feasible, provide a brief statement on research and potential biomarkers.

✓ **Follow-up, long-term implications and survivorship:**

This section will focus on recommendations for patient follow-up and will also include information on long-term toxicities of treatment, second tumours, psychosocial implications, rehabilitation and any other issues related to survivorship.

✓ **Tables/algorithms:**

The CPG text should be supplemented by Tables. Preferred tables are shown below and should appear in the following order:

1. Table with diagnostic work-up
2. Table with staging system (preferably TNM) and stage groups
3. ESMO-standardised Algorithm or Flow Chart with management or therapeutic strategy according to risk factors or stage
4. Optional tables on therapeutic regimens or prognosis
5. A Personalised Medicine Synopsis Table
6. Table with bullet point summary of all recommendations
7. An MCBS table with ESMO-MCBS Score for new therapies/indications approved by EMA
8. Table of Levels of Evidence and Grades of Recommendation (provided at the end of this document)

It is very important that authors produce an ESMO-Standardised Algorithm/Flow Chart on therapeutic strategy or management according to stage, risk factors and disease/molecular characteristics. This is a priority issue for ESMO.

Examples of such an Algorithm/Flow Chart are provided in Appendix C.

✓ **Levels of Evidence (LOE) and Grades of Recommendation (GOR), ESMO-MCBS score:**

Evidence levels are mandatory. Recommendations should be accompanied by proper evidence level and grade of recommendation according to the adapted Infectious Diseases Society of America-United States Public Health Service Grading System (Appendix D).

The Level of Evidence (LOE) mainly describes the quality of existing evidence (trials, cohort studies, case-control studies, expert opinion) that address a specific clinical question. The quality of evidence is assessed in terms of number of trials, sample size, methodology, bias, heterogeneity.

The Grade of Recommendation (GOR) is a composite parameter, as it incorporates both the quality of evidence (as in LOE) as well as the clinical significance/magnitude of benefit or harm given by a novel therapy.

Any therapy can be assigned a GOR which varies from positive (recommended) to negative (not recommended).

In order to avoid confusion, please refer to the Therapy being evaluated as a logically positive definition and then assign the appropriate GOR (which can be positive or negative).

Accordingly, always use the GOR in the following template manner:

Administration of Therapy A (logically positive definition) > GOR assigned (positive: Recommended or negative: Not Recommended).

Please avoid doing the opposite.

EXAMPLES:

Correct:

Administration of anti-EGFR antibodies does not result in survival improvement in patients with RAS-mutated advanced colon cancer and is not recommended (GOR E).

To be avoided:

Non-administration of anti-EGFR antibodies is the correct clinical strategy for patients with RAS-mutated advanced colon cancer and is strongly recommended (GOR A).

✓ **Magnitude of Clinical Benefit Scale (ESMO-MCBS) score:**

MCBS calculations will be performed by the Subject Editor, who should involve the CPG lead author to check and validate the score(s) produced. The scores will be reviewed and approved by the GL-SC, the MCBS Working Group and the ESMO President's Council.

When an ESMO-MCBS score has been produced for a new therapy or a new indication of existing therapy by the EMA, it should appear next to LOE, GOR in the text whenever a recommendation on the therapy is formulated.

Moreover, all ESMO-MCBS scores should be summarised in a Table at the end of the CPG, after the Table Summary of all recommendations.

This table is to be used as a tool providing easily communicable, basic information on the new therapy rather than the formal tool producing the ESMO-MCBS Score (Appendix E).

✓ **References:**

Refer to up to 20-30 citations of the most recently published randomised controlled trials (RCT), meta-analyses and/or systematic reviews. Review articles may be used as citations in order to summarise data; however, it is preferable that pivotal RCT or meta-analyses are cited in order to support a recommendation. Trials used for ESMO-MCBS score calculation should also appear in the reference list.

✓ **Declaration of interest:**

Each author must provide a disclosure of interest statement. Examples are noted below:

Dr XX has reported honoraria from Roche. Dr. XY has reported research grants from Pfizer, AstraZeneca, GlaxoSmithKline, Celgene and is a member of speaker's bureau for Novartis, Janssen. The other authors have declared no potential conflicts of interest.

CHECKLIST FOR SIGN-OFF BY CPG AUTHORS

- Coordinating author to interact with a multidisciplinary team of experts (minimum of 4 in total)
- Manuscript length 8 - 20 pages (Arial 12 points, 1.5-line spacing), *particularly focus on the therapeutic recommendations.*
- Up to 20-30 references, citations of the most recent randomised controlled trials (RCT), meta-analyses and/or systematic reviews. Include MCBS references.
- **CPG sections:**
 1. Incidence and Epidemiology
 2. Diagnosis and pathology/molecular biology
 3. Staging and Risk assessment
 4. Management of local/locoregional disease
 5. Management of advanced/metastatic disease
 6. Personalised Medicine
 7. Follow-up, Long-term implications and Survivorship
 8. Bullet point Table with all recommendations
 9. MCBS Table
 10. References

Or (in specific cases)

 1. Incidence
 2. Assessment/Diagnosis
 3. Management and Monitoring
 4. Follow-up
- **Tables/Algorithms to be included in this order:**
 1. Table with diagnostic work up
 2. Staging system (preferably TNM) and Stage Groups
 3. Algorithm or Flow Chart with risk factor or stage-matched therapeutic strategy/management
 4. Optional Tables on therapeutic regimens or prognosis
 5. A Personalised Medicine Synopsis Table
 6. Table with bullet point summary of all recommendations
 7. MCBS Table for new therapies/indications approved by EMA
 8. Table of Levels of Evidence and Grades of Recommendation
- Agreement with the content from recent *Consensus Conference CPG* when available.
- Following publication, alert for need of eUpdates and ESMO-MCBS scores of new therapies/indications, interact with Subject Editor or GLC-SC.

APPENDIX A.

Template for eUpdate

CPG. State the CPG to which the eUpdate applies.

Section and Text. Provide description of the ESMO CPG section to which the eUpdate applies.

Summarily describe the topic, the new evidence that has emerged along with the impact on current practice.

Recommendation. Provide a clear recommendation statement with LOE, GOR and ESMO-MCBS (when applicable) scores.

MCBS Table. When an ESMO-MCBS score is calculated, add a summary MCBS Table (appendix E).

APPENDIX B.

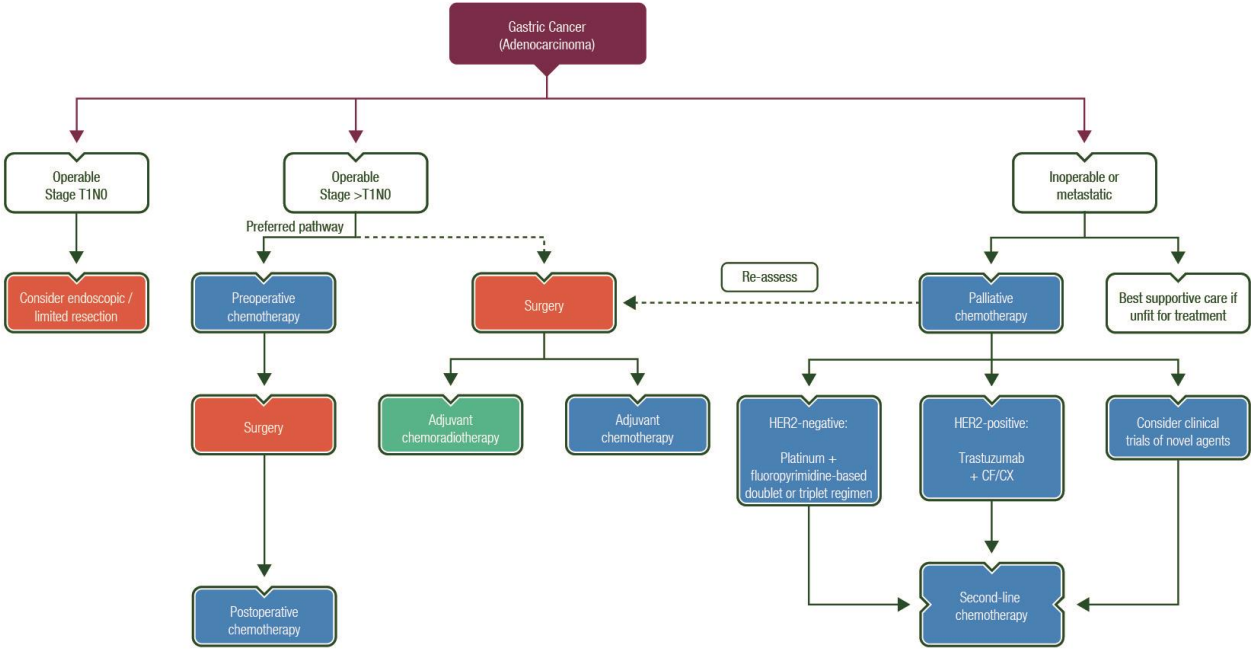
Template for a Personalised Medicine Synopsis table.

At the end of the CPG, before the Follow-up final section, a Personalised Medicine Synopsis table will provide summary information on **validated** biomarkers used for any of the following: a) disease classification, b) prognostic relevance, c) predictive relevance, d) used for medical treatment decisions, e) currently actionable/targetable.

Biomarker	Method	Use	LOE, GOR
Describe the biomarker	Describe the methodology or assay used to measure biomarker	Describe the biomarkers use/significance: (a) disease classification, b) prognostic relevance, c) predictive relevance, d) used for medical treatment decisions, e) currently actionable/targetable.	Provide level of evidence and grade of recommendation

APPENDIX C.

Example of Algorithm for Management/Therapeutic Strategy by stage/risk factors (from the 2016 ESMO CPGs on gastric cancer).



APPENDIX D.

Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aDykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

APPENDIX E.

Template for an MCBS Table

Table X. Magnitude of Clinical Benefit Scale (ESMO-MCBS) table for new therapies/indications in **X cancer**, as approved by the European Medicines Agency^a

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/Toxicity	MCBS Score^b
Describe the new therapy	(Neo)adjuvant or Advanced	Name, phase of trial	Describe the control arm	Median, in months (OS, PFS or both)	Median and 95% CI	Improved or Deteriorated or Similar or Not Available	Score X (Form X)

^aEMA approvals in 2016 to end **MONTH YEAR**.

^bESMO-MCBS version 1.0 [**ref# for Cherny manuscript cited below**]

References: trials used for ESMO-MCBS score calculation should appear in the manuscript reference list, as well as the following reference for the ESMO-MCBS study:

Ref#. 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 Oncol* 2015; 26: 1547–1573.

MCBS GRADING PROCESS

