The European Society for Medical Oncology Magnitude of Clinical Benefit Scale in daily practice: a single institution, real-life experience at the Medical University of Vienna

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ABSTRACT

Background: The European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) has been designed to stratify the therapeutic benefit of a certain drug registered for the treatment of cancer. However, though internally validated, this tool has not yet been evaluated for its feasibility in the daily practice of a major center of medical oncology.

Methods: The practicability of the MCBS for advanced oncological diseases at the Clinical Division of Oncology, Medical University of Vienna, which constitutes one of the largest oncological centres in Europe, was analysed in a three-step approach. First, retrospectively collected data were analysed to gain an overview of treatments in regular use. Second, data were scored by using the MCBS. Third, the ensuing results were evaluated within corresponding programme directorships to assess feasibility in a real-life clinical context.

Results: In the majority of tumour entities, the MCBS results reported earlier are consistent with daily clinical practice. Thus, in metastatic breast cancer or advanced lung cancer, there was a high level of clinical benefit for first-line treatment standards, and these results reflected well real-life experience. However, analyses based on the first version of the MCBS are limited if it comes to salvage treatment in tumour entities in which optimal sequencing of potential treatment options is of major importance, as in metastatic colorectal or renal cell cancer. In contrast to this, it is remarkable that certain novel therapies such as nivolumab assessed for heavily pretreated advanced renal cancer reached the highest level of clinical benefit due to prolongation in survival and a favourable toxicity profile. The MCBS clearly underlines the potential benefit of these compounds.

Conclusions: The MCBS is an excellent tool for daily clinical practice of a tertiary referral centre. It supports treatment decisions based on the clinical benefit to be expected from a novel approach such as immunotherapy in as yet untested indications.

INTRODUCTION

As of 2016, novel agents and new therapeutic approaches in oncology evolve with tremendous velocity with currently more than 770
drugs and vaccines under development only in the USA, and an increasing number of compounds being approved every year.1 However, while the quality of clinical trials and published data appears to be improving due to strong regulatory requirements, the actual selection of novel treatment options with substantial and applicable clinical benefit for the single patient remains challenging. In addition to potential side effects caused by new drugs or mistakenly overestimating treatment effects experienced by the individual patient,2 the currently exploding costs facing public and private healthcare providers promote development of strategies for objective evaluation of novel treatments.

From the 2000s on, several institutions have made efforts to develop specific tools for objectifying the actual benefit to be expected of a new therapeutic approach. However, while in the past the focus for facing this problem was put on the development of cost-effectiveness models,3–5 recent projects concentrated on quantification of the actual clinical benefit derived from a new intervention.6–8

The European Society for Medical Oncology (ESMO) has developed a standardised, generic, validated concept named the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS).8 This approach considers the predefined primary and secondary study end points (overall survival (OS) and progression-free survival (PFS) in terms of absolute gain and lower end of the 95% CI of the corresponding HR), and quality of life (QOL) or toxicity, respectively. Data of the new treatment are then analysed with respect to the duration of response or survival in the control arm, which has to be entered in corresponding forms and results in a clinical benefit ranking. One of the major advantages of this tool is its simplicity—the forms are publicly accessible at the ESMO homepage and are easy to use for the qualified clinician.9

As the Clinical Division of Oncology and the Comprehensive Cancer Center of the Medical University of Vienna—General Hospital constitutes one of the major centres for the care of patients with malignant disorders in Europe and is a tertiary reference centre for patients from within the country, and from abroad with all inherent and resulting implications, we have made efforts to evaluate systematically how the ESMO-MCBS works in advanced oncological diseases outside of clinical trials and assessed its feasibility and clinical impact on the daily routine within the context of such a major oncological centre.

METHODS

We have assessed the daily practicability of the ESMO-MCBS for advanced oncological diseases at the Clinical Division of Oncology of the Medical University of Vienna, a tertiary referral centre for medical oncological care. A three-step approach was used to address this question. First, we have retrospectively collected data of 2 months daily care at our clinic to overview treatments of daily significance. Second, we have analysed and scored data with the ESMO-MCBS. Third, we have discussed results with our programme directorships (PDs) and their coworkers covering the specific tumour entities to assess the feasibility in a real-life clinical context.

A retrospective data analysis of intravenously applied anticancer drugs including cytostatic agents, antibodies and immunotherapeutics applied from September 2015 to November 2015 at the Clinical Division of Oncology of the Medical University of Vienna was conducted. Data were extracted from CATO, a software routinely used for ordering and administration of oncological therapies at our clinic. Tumour entities evaluated for the sake of this study were metastatic/advanced breast cancer (mBC), lung cancer (mLC), colorectal cancer (mCRC), gastric and gastro-oesophageal cancer (mGEC), renal cell cancer (mRCC) and prostate cancer (mPC). Rare tumour entities will be addressed in a second evaluation. (Neo)Adjuvant data were excluded due to strong guidelines in this setting. In addition, we assessed commonly applied oral anticancer drugs.

Treatment strategies extracted in step one underwent a precise literature search in order to identify corresponding trials and data. In the following, those were analysed and scored according to the ESMO-MCBS forms 2a–c as outlined in the primary publication (1–5 for palliative strategies).8 Grades 4 and 5 were accepted as evidence for a strong clinical benefit as previously discussed. Assessed results were highlighted as ‘MCBS-field testing’ (MCBS-FT) in the current work. In the case of pre-evaluation of specific studies in the primary ESMO publication,8 those results were included in the analysis and adapted according to the local guidelines (referred to as ‘ESMO-MCBS’).

In the final phase, we have conducted interviews to review the results with the corresponding PDs and their coworkers for specific tumour entities. Results were discussed and thoroughly checked for completeness, significance, feasibility and practicability in the context of clinical routine.

RESULTS

Metastatic breast cancer (mBC)

For mBC, analysed data were subdivided into common strategies for human epidermal growth factor receptor (HER)2-positive mBC, hormone receptor (HR)-positive mBC and untargeted approaches, respectively (table 1).10–26

In HER2-positive mBC, assessed ESMO-MCBS grades were consistent with daily clinical practice. In the first-line metastatic setting, the CLEOPATRA trial defines dual HER2 blockade in combination with docetaxel as standard and with a median OS gain of 15.7 months and an HR for progress or death of 0.68 (95% CI 0.56 to 0.84) the assessed ESMO-MCBS score of 4 supports this
| Analysed treatment | Setting | Primary EP | PFS control | PFS gain | PFS HR | OS control | OS gain | OS HR | Adjustment/remark | MCBS | MCBS-FT |
|--------------------|---------|------------|-------------|----------|--------|------------|---------|-------|------------------|------|--------|
| Trastuzumab+CT ±pertuzumab (CLEOPATRA)* | First-line metastatic, HER2-positive | PFS | 12.4 m | 6 m | 0.62 (0.52 to 0.84) | 40.8 m | 15.7 m | 0.68 (0.56 to 0.84) | No improvement of QOL | 4 | NA |
| T-DM1 vs lapatinib + capecitabine (EMILIA)* | Second-line metastatic after trastuzumab failure, HER2-positive | PFS, OS | 6.4 m | 3.2 m | 0.65 (0.55 to 0.77) | 25 m | 6.8 m | 0.68 (0.55 to 0.85) | Delayed deterioration of QOL | 5 | NA |
| Capecitabine ± lapatinib* | Second-line metastatic after trastuzumab failure, HER2-positive | PFS | 4.4 m | 4 m | 0.49 (0.34 to 0.71) | – | – | Non-significant | | 3 | NA |
| Lapatinib ± trastuzumab (EFG104900)* | Third-line metastatic, HER2-positive | PFS | 2 m | 1 m | 0.73 (0.57 to 0.93) | 9.5 m | 4.5 m | 0.74 (0.57 to 0.97) | | 4 | NA |
| Capecitabine ± trastuzumab (GBG-26) | Second-line metastatic after trastuzumab-containing treatment, HER2-positive | OS | – | – | – | 20.6 m | 4.3 m | 0.94 (0.65 to 1.35) | OS predefined secondary end point | NA | 3 |
| Exemestane ± everolimus (BOLERO-2)* | HR-positive after failure of aromatase inhibitor and PFS>6 m | PFS | 4.1 m | 6.5 m | 0.43 (0.35 to 0.54) | – | – | – | No improvement of QOL | 2 | NA |
| Letrozole ± palbociclib (PALOMA-1/Trio-18) | First-line metastatic HR-positive HER2-negative | PFS | 10.2 m | 10 m | 0.49 (0.32 to 0.75) | – | – | – | QOL data pending | NA | 3 |
| Fulvestrant ± palbociclib (PALOMA-3) | HR-positive, HER2-negative with progress after endocrine therapy | PFS | 3.8 m | 5.4 m | 0.42 (0.32 to 0.56) | – | – | – | QOL improved | NA | 4 |
| Paclitaxel ± bevacizumab* | First-line metastatic | PFS | 5.9 m | 5.8 m | 0.60 (0.51 to 0.70) | – | – | Non-significant | No improvement of QOL | 2 | NA |

Continued
| Analysed treatment                                                                 | Setting                              | Primary EP       | PFS control | PFS gain | OS control | OS gain | OS HR | Adjustment/remark | MCBS | MCBS-FT |
|----------------------------------------------------------------------------------|--------------------------------------|------------------|-------------|----------|------------|---------|-------|-------------------|------|---------|
| Pegylated liposomal doxorubicin vs conventional doxorubicin                       | First-line metastatic               | Non-inferiority  | 7.8 m       | –        | Non-significant | –       | –     | –                 | NA   | 4       |
| Brien et al\(^{22}\)                                                              |                                      |                  |             |          |             |         |       | Less cardiotoxicity; less alopecia and nausea |      |         |
| Capecitabine ± bevacizumab, anthracycline-based/ taxane-based CT ± bevacizumab   | First-line metastatic, HER2-negative| PFS               | 5.7 m       | 2.9 m    | 0.69 (0.56 to 0.84) | –       | –     | Non-significant | Increased toxicity for taxane-based arm | NA   | 3       |
| (RIBBON-1) Robert et al\(^{23}\)                                                  |                                      | PFS               | 8 m        | 1.2 m    | 0.64 (0.52 to 0.80) | –       | –     | –                 | 1(-2)† |         |
| Docetaxel ± bevacizumab (7.5 mg vs 15 mg/kg) (AVADO) Miles et al\(^{24}\)       | First-line metastatic or locally recurrent | PFS (7.5 mg)     | 8.2 m       | 0.8 m    | 0.80 (0.65 to 1.0) | –       | –     | –                 | Increase in venous thromboembolism | NA   | 2       |
|                                                                                   |                                      | PFS (15 mg)       | 1.8 m      | 0.67    | 0.54 to 0.83 | –       | –     | –                 | NA   | 2       |
| Nab-paclitaxel vs conventional paclitaxel Gradishar et al\(^{25}\)               | Metastatic patients eligible for single-agent paclitaxel | Non-inferiority | 16.9 w     | 6.1 w    | 0.75        | –       | –     | RR 19% vs 33%, p=0.001 | Less clinically relevant side effects | NA   | 3       |
| Cortes et al\(^{26}\)                                                            | Third-line metastatic after anthracycline and taxane | OS               | –          | –        | –          | 10.6 m  | 2.5 m | 0.81 (0.66 to 0.99) | 2     | NA      |

Underlined words relate to the name of the trial/acronym.

*Adapted according to Cherny et al\(^{8}\).
†Unclear value of toxicities in the taxane-based arm.

CT, chemotherapy; EP, end point; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FT, field testing; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; m, months; NA, not applicable; OS, overall survival; PFS, progression-free survival; QOL, quality of life; T-DM1, trastuzumab emtansine; w, weeks.
high level of recommendation. In the second-line setting, the EMILIA trial (trastuzumab emtansine vs lapatinib plus capecitabine) achieved a score of 5 by ESMO-MCBS calculation due to improvement in QOL and an OS benefit of 6.8 months (HR 0.68, 95% CI 0.55 to 0.85). In contrast, the combination of lapatinib with capcitabine scored lower due to a significant difference in OS (ESMO-MCBS score 3), while lapatinib plus trastuzumab third line showed a median OS benefit of 4.5 months with the main benefit in HER2-positive HR-negative mBC (HR 0.74, 95% CI 0.57 to 0.97; ESMO-MCBS score 4). This was due to well-designed trials including validated QOL analysis allowing an increase in clinical benefit rating. Toxicity profiles also favoured targeted therapy with a significant reduction of serious adverse events (12–15% for erlotinib compared with standard). Furthermore, there is obviously still room for improvement as exemplified by data from the LUX LUNG-3 trial updated for OS recently increasing the MCBS-FT score to 5 for patients with EGFR exon 19 deletion (OS gain 12.2 months; HR 0.54, 95% CI 0.36 to 0.79).18

For HR-positive mBC, the BOLERO-2 trial evaluating everolimus/exemestane was downgraded 1 point irrespective of PFS benefit due to an increment in toxicity (ESMO-MCBS score 2). This appears to be in line with the clinical routine experience. In the current analysis, we assessed for the first time recent data on the cyclin-dependent kinase (CDK)/4/6 inhibitor palbociclib (PALOMA trials). Letrozole plus palbociclib first line (PALOMA-1 trial) showed a PFS gain of 10 months (HR 0.49, 95% CI 0.32 to 0.75) for an MCBS-FT score of 3.19 To date, results of the analysis of QOL assessed in this study are still pending. In contrast, QOL data are available for the PALOMA-3 trial (fulvestrant plus palbociclib), and showed a clear benefit leading to an upgrade in the MCBS-FT by 1 point to a score of 4 (PFS gain 5.4 months; HR 0.42, 95% CI 0.32 to 0.56).20 OS data for both PALOMA trials are immature and awaiting final assessment yet. Available toxicity data confirmed the justification of an MCBS-FT score 4.

For untargeted treatments in mBC, the addition of bevacizumab to taxane-based chemotherapy was given an MCBS-FT score 2 primarily, but treatment was associated with an increase of toxicity in terms of hospitalisation and febrile neutropenia (as described in the RIBBON-1 trial) resulting in a downgrade in the scale by 1 point. The combination of bevacizumab with capcitabine for first-line HER2-negative MBC reached an MCBS-FT score of 3.

Conclusion: The ESMO-MCBS was well qualified for the daily routine setting of mBC. However, it was striking that for some substances used in daily practice (eg, non-pegylated liposomal doxorubicin), no randomised data are available, making appropriate scoring impossible. Regarding palbociclib and with QOL and OS data still pending, further insights into the practicability of the ESMO-MCBS in mBC for new treatment approaches in the clinical real-life setting are eagerly awaited.

Lung Cancer (LC)

For metastatic or advanced (m)LC, analysed data were subdivided into common strategies for first-line and salvage treatment with respect to histological and molecular subtype (table 2).27-44

As platinum-based treatment in epidermal growth factor receptor (EGFR)-unmutated and anaplastic lymphoma kinase (ALK)-unmutated patients remains unquestioned standard in the first-line treatment of mLC, we have analysed particularly targeted therapies in this specific setting. Remarkably and as already highlighted in the original publication of the ESMO task force, the whole lot of data on first-line targeted treatment for stage IIIB/IV non-squamous EGFR-mutated or ALK-mutated mLC reached a high level of recommendation (ESMO-MCBS/MCBS-FT score 4) despite a lack of OS benefit in the majority of trials.27-35 This was due to well-designed trials including validated QOL analysis allowing an increase in clinical benefit rating. Toxicity profiles also favoured targeted therapy with a significant reduction of serious adverse events (12–15% for erlotinib compared with standard). Furthermore, there is obviously still room for improvement as exemplified by data from the LUX LUNG-3 trial updated for OS recently increasing the MCBS-FT score to 5 for patients with EGFR exon 19 deletion (OS gain 12.2 months; HR 0.54, 95% CI 0.36 to 0.79).18

For EGFR-mutated and ALK-unmutated adenocarcinoma, first-line data for cisplatin/pemetrexed compared with cisplatin/gemcitabine were similarly beneficial in terms of the ESMO-MCBS (score 4) as reported for tyrosine kinase inhibitors and EGFR-mutated or ALK-mutated patients. Bevacizumab as add-on is not used routinely at our institution, which was supported by evaluation of respective data resulting in an ESMO-MCBS/MCBS-FT score of 2.

When analysing maintenance therapy after response to platinum doublets, we assessed relevant data on pemetrexed and erlotinib.40-41 Due to a significant gain of OS for pemetrexed in non-squamous cell carcinoma (5.2 months; HR 0.70, 95% CI 0.58 to 0.88), which was not shown for erlotinib in the SATURN trial, only pemetrexed succeeded to achieve an MCBS-FT score of 4.

Regarding very recent data on the checkpoint inhibitor nivolumab, available data obtained in the second-line treatment were analysed, which resulted in a high scoring of MCBS-FT of 4 and 5 for non-squamous (OS gain 2.8 months; HR 0.73, 95% CI 0.59 to 0.89) and squamous mLC (OS gain 3.2 months; HR 0.56, 95% CI 0.44 to 0.79), respectively.43-44 In both trials, upgrade points for limited toxicity were allowed by the MBCS, thus underlining and expanding on the clear clinical benefit.

Conclusion: The ESMO-MCBS worked well for targeted therapy in mLC and confirmed its accuracy in the assessment of the clinical benefit of new treatment modalities such as the checkpoint inhibitor nivolumab.

Colorectal cancer (CRC)

For metastatic or advanced (m)CRC, the analysed data were subdivided into common strategies for first-line, second-line and salvage treatments (table 3).45-63

In the first-line setting, clinical phase III studies are stratified into RAS wild-type or unselcted patients. For a cross-over comparison of clinical trials, the analysis in
| Analysed treatment | Setting | Primary EP | PFS control | PFS gain | PFS HR | OS control | OS gain | OS HR | Adjustment/remark | MCBS | MCBS-FT |
|--------------------|---------|------------|-------------|----------|--------|------------|---------|-------|-------------------|------|---------|
| Erlotinib vs carboplatin (OPTIMAL, CTONG 0802)*Zhou et al | First-line IIIB or IV, non-squamous, EGFR-mutated | PFS | 4.6 m | 8.5 m | 0.16 (0.10 to 0.26) | – | – | – | 12% less serious AEs | 4 | NA |
| Erlotinib vs platinum-based CT doublet (EURTAC)*Rosell et al | First-line IIIB or IV, non-squamous, EGFR-mutated | PFS | 5.2 m | 4.5 m | 0.37 (0.25 to 0.54) | 19.5 m | – | Non-significant | 15% less serious AEs | 4 | NA |
| Gefitinib vs Carbo implant +paclitaxel (IIPASS)Mok et al | First-line IIIB or IV, non-squamous (EGFR-mutated) | PFS | 6.3 m | 3.3 m | 0.48 (0.34 to 0.67) | – | – | – | QOL improved, less toxicity | NA | NA |
| Afatinib vs cisplatin +pemetrexed (LUX Lung-3)*Sequist et al | First-line IIIB or IV adenocarcinoma, EGFR-mutated (EGFR exon 19 deletion) | PFS | 6.9 m | 4.2 m | 0.58 (0.43 to 0.78) | 28.2 m | – | Non-significant | OS improved for del19 patients | NA | 4 |
| Crizotinib vs CT*Shaw et al | First-line IIIB or IV adenocarcinoma, ALK-mutated | PFS | 3.0 m | 4.7 m | 0.49 (0.37 to 0.64) | – | – | – | +1% toxic death, QOL improved | 4 | NA |
| Crizotinib vs cisplatin +pemetrexed*Solomon et al | First-line IIIB or IV non-squamous, ALK-mutated | PFS | 7.0 m | 3.9 m | 0.45 (0.35 to 0.60) | – | – | – | QOL improved | 4 | NA |
| Cisplatin+pemetrexed vs cisplatin+gemcitabine*Scagliotti et al | First-line IIIB or IV non-squamous | Non-inferiority (OS) | – | – | – | 10.4 m | 1.4 m | 0.81 (0.70 to 0.94) | Less grade III haematologic AEs | 4 | NA |
| Paclitaxel/carboplatin ±bevacizumab*Sandler et al | First-line IIIB or IVB, non-squamous | OS | – | – | – | 10.3 m | 2.0 m | 0.79 (0.67 to 0.92) | – | 2 | NA |
| Gemcitabine+cisplatin ±bevacizumab (high/low dose) (AVAIL)Reck et al | First-line advanced, non-squamous | PFS (low) | 6.1 m | 0.6 m | 0.75 (0.62 to 0.91) | – | – | – | Survival data not mature | NA | 2 |
| CT±palliative care*Temel et al | Stage IV, ECOG<2 | QOL | – | – | – | 8.9 m | 2.7 m | HR death 1.7 | QOL improved | 4 | NA |

Continued
| Analysed treatment                        | Setting                                      | Primary EP | PFS control | PFS gain | PFS HR (0.42 to 0.61) | OS control | OS gain | OS HR (0.56 to 0.88) | Adjustment/remark | MCBS | MCBS-FT |
|-------------------------------------------|----------------------------------------------|------------|-------------|----------|-----------------------|------------|---------|-----------------------|--------------------|------|---------|
| Pemetrexed vs placebo                     | Maintenance after response to platinum doublet (non-squamous) | PFS (all)  | 2.6 m       | 1.7 m    | 0.50                  | 10.6 m     | 2.8 m   | 0.79 (0.65 to 0.95)   | NA                 | 3    |         |
| Ciuleanu et al                           |                                              | PFS (non-sq.) | 2.6 m       | 1.9 m    | 0.44 (0.36 to 0.55)   | 10.3 m     | 5.2 m   | 0.70 (0.56 to 0.88)   | NA                 | 4    |         |
| Erlotinib vs placebo                      | Maintenance after response to platinum doublet | PFS        | 11.1 w      | 1.2 w    | 0.71 (0.62 to 0.82)   | 11 m       | 1.0 m   | 0.81 (0.70 to 95)     | 1                  | NA   |         |
| (SATURN)* Capuzzo et al                   |                                              |            |             |          |                       |            |         |                       |                    |      |         |
| Docetaxel+nintedanib                     | Second line (adenocarcinoma with PD 9 m after start first line) | PFS (all)  | 2.7 m       | 0.7 m    | 0.79 (0.68 to 0.92)   | 9.1 m      | 1.0 m   | 0.94 (0.83 to 1.05)   | Uncertain significance of AEs, more diarrhoea | NA   | 1       |
| Reck et al‡                            |                                              | PFS (adeno.) | 1.5 m       | 2.1 m    | 0.63 (0.48 to 0.83)   | 7.9 m      | 3 m     | 0.75 (0.6 to 0.92)    | NA                 | 4    |         |
| Nivolumab vs docetaxel                   | Second-line non-squamous cell lung cancer   | OS         | 4.2 m       | –        | –                     | 9.4 m      | 2.8 m   | 0.73 (0.59 to 0.89)   | Significantly less grade III/IV toxicity | NA   | 4       |
| (Checkmate 057) Borghaei et al‡          |                                              |            |             |          |                       |            |         |                       |                    |      |         |
| Nivolumab vs docetaxel                   | Second-line squamous cell lung cancer       | OS         | 2.8 m       | 0.7 m    | 0.62 (0.47 to 0.81)   | 6.0 m      | 3.2 m   | 0.56 (0.44 to 0.79)   | –48% grade III/ IV AEs | NA   | 5       |
| (Checkmate 017) Brahmier et al‡          |                                              |            |             |          |                       |            |         |                       |                    |      |         |

Underlined words relate to the name of the trial/acronym.
*Adapted according to Cherny et al.8
†No quality-of-life data for overall survival available.
Adeno., adenocarcinoma only; AEs, adverse events; ALK, anaplastic lymphoma kinase; CT, chemotherapy; del, deletion; EP, end point; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ECOG, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFR+, EGFR mutated only; FT, field testing; m, months; NA, not applicable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QOL, quality of life.
| Analysed treatment | Setting | Primary EP | PFS control | PFS gain | PFS HR | OS control | OS gain | OS HR | Adjustment/remark | MCBS | MCBS-FT |
|-------------------|---------|------------|-------------|----------|--------|------------|---------|-------|------------------|-------|---------|
| FOLFIRI±cetuximab (CRYSTAL)* Van Cutsem et al<sup>45</sup> | First-line metastatic stratified for KRAS wild type | PFS | 8.4 m | 3.0 m | 0.56 (0.41 to 0.76) | 20.2 m | 8.2 m | 0.69 (0.54 to 0.88) | 4 | NA |
| FOLFOX4±panitumumab (PRIME)* Douillard et al<sup>46</sup> | First-line metastatic (post hoc KRAS, NRAS BRAF wild type) | PFS | 7.9 m | 2.3 m | 0.72 (0.58 to 0.90) | 20.2 m | 5.8 m | 0.78 (0.62 to 0.99) | 4 | NA |
| IFL±bevacizumab* Hurwitz et al<sup>47</sup> | First-line metastatic | OS | – | – | – | 15.6 m | 4.7 m | 0.66 (0.54 to 0.81) | Positive subgroup analysis for BRAF-mut. | 3 | NA |
| FOLFOXIRI±bevacizumab vs FOLFRIRI +bevacizumab * Loupakis et al<sup>48</sup> | First-line metastatic | PFS | 9.7 m | 2.4 m | 0.75 (0.62 to 0.9) | – | – | Non-significant | 2 | NA |
| XELOX/FOLFOX ±bevacizumab Saltz et al<sup>49</sup> | First-line metastatic | PFS | 8.0 m | 1.4 m | 0.83 (0.72 to 0.95) | – | – | Non-significant | NA | 1 |
| 5FU-based CT±cetuximab or bevacizumab (CALGB/SWOG-80405) Venook et al<sup>50</sup> | First-line metastatic all RAS wild type, PS 0–1 | OS | – | – | – | 29.0 m | 0.9 m | Non-significant | Published in abstract form only, immature | NA | 1 |
| FOLFIRI±cetuximab or bevacizumab (FIRE-3) Heinemann et al<sup>51</sup> | First-line metastatic KRAS wild type | ORR | 58% | 4% | OR 1.18 | 29.0 m | – | – | Form 2c due to end point ORR | NA | 1 |
| Bevacizumab +capcitabine vs capecitabine (AVEX) Cunningham et al<sup>52</sup> | First-line metastatic, elderly | PFS | 5.1 m | 4 m | 0.53 (0.41 to 0.69) | 16.8 m | 3.9 m | Non-significant | No deterioration of QOL | NA | 3 |
| Bevacizumab +capcitabine vs observation (CAIRO-3) Simkens et al<sup>53</sup> | First-line metastatic after CAPOX-B induction | PFS2 | 8.5 m | 3.2 m | 0.67 (0.56 to 0.81) | – | – | – | No deterioration of QOL | NA | 3 |
| FOLFOX±bevacizumab vs bevacizumab (E3200)* Giantonio et al<sup>54</sup> | Second-line metastatic after FOLFIRI | OS | – | – | – | 10.8 m | 2.1 m | 0.75 (0.63 to 0.89) | Second-line OS benefit | 2 | NA |
| second-line chemotherapy ±bevacizumab (ML18147)* Bennouna et al<sup>55</sup> | Second-line beyond progression on bevacizumab | OS | – | – | – | 9.6 m | 1.5 m | 0.81 (0.69 to 0.94) | Second-line OS benefit | 1 | NA |

Continued
| Analysed treatment | Setting | Primary EP | PFS control | PFS HR (or range) | OS control | OS gain (or range) | OS HR (or range) | Adjustment/remark | MCBS | MCBS-FT |
|--------------------|---------|------------|-------------|------------------|------------|-------------------|------------------|------------------|------|--------|
| FOLFIRI±afibercept (VELOUR)* | Second-line after oxaliplatin-based treatment | OS | 4.7 m | 2.2 m | 0.76 (0.66 to 0.87) | 12.1 m | 1.5 m | 0.82 (0.71 to 0.94) | Second-line OS benefit | 1 | NA |
| Van Cutsem et al | | | | | | | | | | |
| FOLFIRI±panitumumab* | Second-line metastatic KRAS wild type | PFS | 3.9 m | 2.0 m | 0.73 (0.59 to 0.90) | – | – | – | No OS benefit | 3 | NA |
| Peeters et al | | | | | | | | | | |
| FOLFIRI±panitumumab (20050181) | Second-line after 5FU-based treatment (PD during therapy or within 6 months) | PFS, OS | 4.9 m | 1.8 m | 0.82 (0.69 to 0.97) | – | – | – | Non-significant No OS benefit | NA | 1 |
| Peeters et al | | | | | | | | | | |
| FOLFIRI±ramucirumab (RAISE)* | Second-line metastatic after bevacizumab, oxaliplatin, 5FU | OS | – | – | – | 11.7 m | 1.6 m | 0.84 (0.73 to 0.97) | Second-line OS benefit | 1 | NA |
| Taberno et al | | | | | | | | | | |
| Cetuximab vs best supportive care* | Refractory metastatic KRAS wild type | OS | 1.9 m | 1.8 m | 0.40 (0.30 to 0.54) | 4.9 m | 4.7 m | 0.55 (0.41 to 0.74) | | 4 | NA |
| Karapetis et al | | | | | | | | | | |
| Panitumumab vs best supportive care* | Third-line metastatic stratified for KRAS | PFS | 7.3 w | 5 w | 0.45 (0.34 to 0.59) | – | – | – | | 2 | NA |
| Amado et al | | | | | | | | | | |
| TAS-102 vs placebo (CONCOURSE)* | Third-line or beyond metastatic | OS | – | – | – | 5.3 m | 1.8 m | 0.68 (0.58 to 0.81) | | 2 | NA |
| Mayer et al | | | | | | | | | | |
| Regorafenib vs placebo (CORRECT)* | Third-line metastatic | OS | – | – | – | 5 m | 1.4 m | 0.77 (0.64 to 0.94) | | 1 | NA |
| Grothey et al | | | | | | | | | | |

Underlined words relate to the name of the trial/acronym.
*Adapted according to Cherny et al.8 CAPOX-B, capecitabine, oxaliplatin, bevacizumab; CT, chemotherapy; EP, end point; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FT, field testing; FOLFIRI, fluorouracil, irinotecan; FOLFOXIRI, fluorouracil, oxaliplatin, irinotecan; FOLFOX, fluorouracil, irinotecan; IFL, irinotecan, bolus fluorouracil, leucovorin; m, months; mut., mutated; NA, not applicable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; QOL, quality of life; XELOX, capecitabine, oxaliplatin.
this manuscript was limited to the RAS wild-type studies. In this scenario, the CRYSTAL trial ( fluorouracil, irinotecan (FOLFIRI) plus cetuximab, OS gain 8.2 months; HR 0.69, 95% CI 0.54 to 0.88) and the PRIME trial ( fluorouracil, oxaliplatin, irinotecan (FOLFOX) plus panitumumab, OS gain 5.8 months; HR 0.78, 95% CI 0.62 to 0.99) were the only studies reaching a high level of recommendation (ESMO-MCBS score 4).45 46 However, in two phase III head-to-head trials, comparing a doublet chemotherapy plus cetuximab or plus bevacizumab, the primary end points were negative (MCBS-FT score 1).50 51 Thus, the addition of bevacizumab to a doublet chemotherapy in this specific subset of patients seems not to be inferior per definition of its respective primary end points. In a non-biomarker-selected population, the addition of bevacizumab resulted only in a high ESMO-MCBS score whenever the chemo-backbone was rather weak, as exemplified by the AVEX trial.52 In this particular trial, capcitabine plus/minus bevacizumab for the elderly was assessed. In terms of PFS, an MCBS-FT score 3 was calculated without any deterioration of QOL (PFS gain 4 months; HR 0.53, 95% CI 0.41 to 0.69). OS was improved but did not differ statistically between arms.

The impact of maintenance with capcitabine and bevacizumab after induction treatment was assessed in the CAIRO-3 trial.53 With a median PFS gain of 3.2 months (HR 0.67, 95% CI 0.56 to 0.81), the MCBS-FT achieved a score of 3, and it appeared remarkable that QOL was not affected by maintenance treatment (no deterioration of QOL).

For further line treatments, it is important to emphasise the fact that due to the variety of potential sequential combinations including options for chemotherapy, antibodies and other targeted drugs and the diversity of control arms, an assessment by the ESMO-MCBS appears very difficult and with limited applicability. Results from ongoing sequential studies will have to be assessed.

Conclusion: In contrast with mBC or mLC, the application of the ESMO-MCBS into daily routine appears to be much more complicated in mCRC due to the multitude of options for sequential therapies. Currently, there are a variety of trials ongoing to answer the very question of an optimal sequence of treatments in mCRC. Meanwhile, common guidelines, including the one from ESMO, give recommendations how to treat in a specific scenario. Particularly in the first-line setting, the predefined secondary end points such as tumour shrinkage were consistently increased by the addition of anti-EGFR treatment, which is not considered in the ESMO-MCBS but the ESMO guidelines. Moreover, it has to be taken into account that biological activity of drugs is decreased by lines of treatment in mCRC, but might be additive in sequential treatment options. Thus, OS benefit appears to be underestimated by the ESMO-MCBS particularly in the second and subsequent line settings (see table 3).

**Gastric or gastro-oesophageal cancer (GEC)**

For metastatic or advanced (m)GEC, the analysed data were subdivided into common strategies for first-line and salvage treatments (table 4)44–49 59 acknowledging the fact that an optimal first-line palliative treatment is difficult to define in this entity. Thus, recently data on a modified docetaxel, cisplatin and fluorouracil (mDCF) regimen were presented which have successfully analysed the efficacy of dose reductions within the frame of the original protocol.65 We found this trial to have potential influence on our daily clinical practice due to toxicity of the original DCF regimen. Therefore, the MCBS was calculated for the mDCF regimen. In direct comparison with standard DCF, mDCF significantly reduced toxicity and increased PFS at 6 months (+10%). As the data for mDCF are still immature, we used form 2c (non-inferiority, reduced toxicity) for its evaluation resulting in an MCBS-FT score of 4. Follow-up data need to be awaited. In HER2-overexpressing mGEC, the TOGA trial demonstrated an OS benefit (2.7 months; HR 0.74, 95% CI 0.60 to 0.91) when trastuzumab was added to chemotherapy resulting in an MCBS-FT of stage 3.56

For salvage treatment, ramucirumab (±paclitaxel) in two different settings was assessed. Owing to a non-improvement of QOL and only a slight median gain in OS of a maximum of 2.2 months, the assessment by ESMO-MCBS and MCBS-FT resulted in a score of 2.68 69 Thus, the result corresponded with an equally low scoring level as the recommendation of chemotherapy versus palliative care in this clinical setting (ESMO-MCBS score 2).70

Conclusions: The ESMO-MCBS reflects well the difficulties in the choice of treatment for gastric cancer. While the optimal first-line regimen has not been clearly defined, there exist randomised data for salvage therapy. However, the clinical benefit achieved by chemotherapy in this setting is small, as reflected by the low scoring of this treatment option in the ESMO-MCBS.

**Prostate cancer (PC)**

For metastatic or advanced prostate cancer (m)PC, the analysed data were subdivided into common strategies for hormone-sensitive and castration-refractory disease. (table 5).71–78

While the castration-refractory setting has been well analysed by the ESMO working group, we want to add recently published data on chemotherapy for early disease: the CHAARTED trial published in 2015 was the first randomised clinical study to show a gain in OS (13.6 months; HR 0.61, 95% CI 0.47 to 0.80) in patients treated with docetaxel for early disease (MCBS-FT score 4).71 Recently, another study, the STAMPEDE trial, based on an analogous concept, evaluated the impact of early docetaxel and zoledronic acid versus standard treatment in a four-arm design. This trial also showed an OS gain for docetaxel versus standard treatment of 10 months (HR 0.78, 95% CI 0.66 to 0.93), resulting in an identical MCBS-FT score of 4.72

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| Analysed treatment | Setting | Primary EP | PFS control | PFS gain | PFS HR | OS control | OS gain | OS HR | Adjustment/remark | MCBS | MCBS-FT |
|--------------------|---------|------------|-------------|----------|--------|------------|---------|------|-----------------|------|---------|
| FOLFIRI vs ECX     | advanced first-line gastric or gastro-oesophageal adenocarcinoma | TTF          | 4.2 m      | 0.9 m   | 0.77   | (0.63 to 0.93) | –       | –   | Non-significant | No benefit in QOL | NA   | 2       |
| Modified DCF vs DCF| Advanced first-line gastric or gastro-oesophageal cancer adenocarcinoma | PFS at 6 m   | 53%        | 10%     | –      | 12.6 m     | 6.2 m   | 0.74 | (0.60 to 0.91) | Reduced toxicity, increase in PFS and OS | NA   | 4*      |
| CT±trastuzumab     | Advanced first-line HER2-positive gastric or gastro-oesophageal cancer | OS          | 5.5 m      | 2.2 m   | 0.71   | (0.59 to 0.85) | 11.1 m  | 2.7 m | 0.74 | Non-inferiority criteria were met | NA   | 3       |
| ECX vs ECF and EOX | Advanced first-line gastric or gastro-oesophageal cancer | Non-inferiority (OS) | –   | – | – | 9.9 m | 0 m | 0.86 | (0.80 to 0.99) | NA   | NC      |
| Ramucirumab vs placebo† | Second-line gastric or gastro-oesophageal cancer after cisplatin/5FU | OS          | – | – | – | 3.2 m | 2.0 m | 0.78 | (0.60 to 0.99) | No difference in QOL | 2 | NA |
| Paclitaxel±ramucirumab | Second-line gastric or gastro-oesophageal cancer after cisplatin/5FU | OS          | – | – | – | 7.4 m | 2.2 m | 0.81 | (0.68 to 0.96) | Treatment: docetaxel or irinotecan | 2 | NA |
| Salvage chemotherapy vs best supportive care | Second-line or third-line gastric or gastro-oesophageal cancer after cisplatin/5FU | OS          | – | – | – | 3.8 m | 1.5 m | 0.66 | (0.49 to 0.89) | NA | 2 |

*Calculated according to form 2c due to immature data.
†Adapted according to Cherny et al.8
CT, chemotherapy; DCF, docetaxel, cisplatin, fluorouracil; EP, end point; ECF, epirubicin, cisplatin, fluorouracil; ECX, epirubicin, cisplatin, capecitabine; EOX, epirubicin, oxaliplatin, capecitabine; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FT, field testing; FOLFIRI, fluorouracil, irinotecan; m, months; NA, not applicable; NC, not calculated; OS, overall survival; PFS, progression-free survival; QOL, quality of life; TTF, time to treatment failure.
Table 5  Field testing of the ESMO-MCBS for the treatment of advanced prostate cancer at the Medical University of Vienna

| Analysed treatment | Setting                              | Primary EP | PFS control | PFS gain | PFS HR | OS control | OS gain | OS HR | Adjustment/remark | MCBS | MCBS-FT |
|--------------------|--------------------------------------|------------|-------------|----------|--------|------------|---------|-------|-------------------|------|---------|
| ADT±early docetaxel (CHAARTED) Sweeney et al<sup>71</sup> | Metastatic hormone sensitive         | OS         | 11.7 m      | 8.5 m    | 0.61 (0.51 to 0.72) | 44.0 m   | 13.6 m   | 0.61 (0.47 to 0.80) | No QOL assessment | NA    | 4       |
| SOC vs SOC+docetaxel vs SOC+zoledronic acid vs SOC+docetaxel+zoledronic Acid (STAMPEDE) James et al<sup>72</sup> | High risk locally advanced or metastatic | OS         | –          | –        | –      | 71.0 m    | 10.0 m  | 0.78 (0.66 to 0.93) | Multiarm, multistage design | NA    | 4       |
| Docetaxel+prednisone vs mitoxantrone+prednison<sup>*<sup>1</sup>Tannock et al<sup>73</sup> | Castration refractory                | OS         | –          | –        | –      | 16.5 m    | 2.4 m   | 0.76 (0.62 to 0.94) | QOL improved | 3     | NA      |
| Enzalutamide vs placebo (PREVAIL)<sup>*<sup>2</sup>Beer et al<sup>74</sup> | Castration-refractory pre-docetaxel | PFS, OS    | 3.2 m      | >12 m    | 0.19 (0.15 to 0.23) | 30.2 m   | 2.2 m    | 0.71, (0.60 to 0.84) | QOL improved | 3     | NA      |
| Standard non-CT or RT ±radium-223 (ALSYMPCA)<sup>*<sup>Parker et al<sup>75</sup> | Castration refractory and bone pain/lesions | OS         | –          | –        | –      | 11.3 m    | 3.6 m   | 0.70 (0.55 to 0.88) | QOL improved | 5     | NA      |
| Prednisone+abiraterone<sup>*<sup>De Bono et al<sup>76</sup> | Castration refractory after docetaxel | OS         | –          | –        | –      | 10.9 m    | 3.9 m   | 0.65 (0.54 to 0.77) |             | 4     | NA      |
| Enzalutamide vs placebo (AFFIRM)<sup>*<sup>Scher et al<sup>77</sup> | Castration refractory after docetaxel | OS         | –          | –        | –      | 13.6 m    | 4.8 m   | 0.63 (0.53 to 0.75) | QOL improved | 4     | NA      |
| Cabazitaxel+prednisone vs mitoxantrone+prednisone (TROPIC)<sup>*<sup>De Bono et al<sup>78</sup> | Castration refractory after docetaxel | OS         | –          | –        | –      | 12.7 m    | 2.4 m   | 0.70 (0.59 to 0.83) |             | 2     | NA      |

* Adapted according to Cherny et al.<sup>8</sup>

ADT, androgen deprivation treatment; CT, chemotherapy; EP, end point; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FT, field testing; m, months; NA, not applicable; NR, not reached; OS, overall survival; PFS, progression-free survival; QOL, quality of life; RT, radiotherapy; SOC, standard of care.

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In the castration-refractory setting, high scores were obtained for enzalutamide before (ESMO-MCBS score 3) and particularly after docetaxel (ESMO-MCBS score 4). This is in line with the benefit of abiraterone after standard docetaxel, which raises the question of reasonable sequencing, in analogy to the situation seen in mCRC. Finally, the ALSYMPCA trial showed a high clinical benefit of radium-223 treatment for castration-refractory patients with bone pain (ESMO-MCBS score 5). All of these trials could demonstrate a statistically significant OS benefit, and due to proper QOL assessment, the ESMO-MCBS was upgraded for QOL improvement.

Interestingly, salvage treatment with cabazitaxel versus mitoxantrone achieved only a minor lever of recommendation despite a comparable OS benefit (2.4 months; HR 0.70, 95% CI 0.59 to 0.83), as QOL was not assessed in this setting. Nevertheless, the results appear remarkable, as this trial was the only testing one active against another active treatment instead of placebo in mPC.

Conclusions: The ESMO-MCBS reflects well the most recent data for hormone-sensitive patients. We further analysed data from the castration-refractory setting, although chemotherapy such as cabazitaxel can obviously not compete with the next-generation antiandocrine compounds such as abiraterone and enzalutamide, which in trials were tested against placebo control arms.

Renal cell cancer (RCC)

For metastatic or advanced (m)RCC, data were subdivided into common strategies for first-line and second-line or salvage treatment (table 6).

Temsirilimus and sunitinib have been proven superior to former standard interferon. OS benefit (3.3 months; HR 0.73, 95% CI 0.58 to 0.92) was pivotal for temsirilimus reaching an MCBS-FT score of 4. For sunitinib, PFS was increased (6 months; HR 0.42, 95% CI 0.32 to 0.54), but QOL assessment demonstrated a clinical benefit (upgrade, ESMO-MCBS score 4).

For bevacizumab, the AVOREN trial was able to demonstrate a clear median PFS benefit of 4.6 months (HR 0.63, 95% CI 0.52 to 0.75; MCBS-FT score 3). In contrast, the CALBG-90206 trial achieved only an ESMO-MCBS-FT score of 1 due to only a small gain in PFS potentially explained by patient selection. None of these trials evaluating bevacizumab first line for mRCC met the predefined significance criteria for OS.

In second-line sorafenib, pazopanib, axitinib and everolimus, all achieved ESMO-MCBS scoring of 3, but again none of these trials could demonstrate a statistically significant OS benefit. Interestingly, axitinib was the only tyrosine kinase inhibitor compared with an active compound (sorafenib) and still could improve PFS by 2 months (HR 0.66, 95% CI 0.55 to 0.81). Striking are recent data on nivolumab tested versus everolimus in the CHECKMATE 025 trial. An MCBS-FT score of 5, resulting from a significant OS benefit (5.4 months; HR 0.73, 95% CI 0.57 to 0.93) and significantly reduced toxicity, underlines the high clinical benefit of this treatment. Cabozantinib succeeded particularly in the setting of sunitinib-pretreated patients (PFS gain 5.4 months; HR 0.41, 95% CI 0.28 to 0.61; MCBS-FT score 3). Survival data are immature and might improve reported results.

Conclusion: Analogous to mCRC, the ESMO-MCBS reflects the clinical benefit which is achieved by single treatment options; the question of optimal sequencing of available therapies regarding the resulting clinical benefit is left unanswered. For new treatment options such as nivolumab and cabozantinib, the ESMO-MCBS demonstrates their clinical benefit and thus might be helpful to implement such therapies in clinical practice.

DISCUSSION

The ESMO-MCBS adds a new tool into daily clinical practice for categorising and processing trial data in terms of the clinical benefit of drugs tested within the context of controlled randomised clinical trials. While the original publication by Cherny et al provides a clear insight into the development process and how to use the ESMO-MCBS including some examples by field testing, we felt that it might be interesting to further investigate clinical practicability of the ESMO-MCBS in a ‘real-life’ experience of a major center of medical oncology.

In the current study, we have thus systemically evaluated well-established oncological treatment strategies from first-line to salvage treatment throughout major tumour entities at our institution and discussed clinical impact and feasibility of the results with the PDs responsible for the various disease entities of the department. While we certainly cannot provide an end-to-end complete work-up of all oncological treatments, our data show the outcome of multiple analyses of everyday procedures regarding oncological treatment by the ESMO-MCBS in a real-life routine setting.

It appears that the ESMO-MCBS worked very reliably and reproducibly in the field of advanced or metastatic diseases throughout all treatment settings and entities. It is clear that the level of recommendation by the ESMO-MCBS becomes smaller in the subsequent numbers of treatment lines. This effect may be correlated to a usually shorter PFS – and subsequently OS – duration observed with each applied therapy. However, particularly in the setting of salvage treatment—for example eribulin for mBC—also treatments with a low level of clinical benefit based on ESMO-MCBS (eg, score 2 for eribulin) are useful, as the patient collective is highly pretreated. Thus, in the case of an acceptable toxicity profile, any OS benefit might be beneficial in this setting. In contrast, it is even more remarkable to see that certain new treatments such as checkpoint inhibitors improve outcome impressively in comparison with recent treatment standards, as assessed by the ESMO-MCBS. Thus, such remarkable compounds should be recommended for fast-track implementation in practice.
| Analysed treatment | Setting | EP | PFS control | PFS gain | PFS HR | OS control | OS gain | OS HR | Adjustment/remark | MCBS | MCBS-FT |
|--------------------|---------|----|-------------|----------|--------|------------|---------|-------|-------------------|-------|---------|
| Temsirolimus vs interferon vs combined Hudes et al| First-line metastatic (poor prognosis) | OS (tem.) | – | – | – | 7.3 m | 3.3 m | 0.73 (0.58 to 0.92) | OS gain for temsirolimus | NA | 4 |
| | | OS (comb.) | – | – | – | 1.1 m | 0.96 (0.76 to 1.2) | – | – | NA | 1 |
| Sunitinib vs interferon* Motzer et al Motzer et al | First-line metastatic | PFS | 5 m | 6 m | 0.42 (0.32 to 0.54) | 21.8 m | 4.6 m | Non-significant QOL improved | 4 | NA |
| Escudier et al Escudier et al | First-line metastatic with clear cell | PFS | 5.4 m | 4.6 m | 0.63 (0.52 to 0.75) | – | – | Non-significant Primary end point OS amended to PFS | NA | 3 |
| Interferon+bevacizumab (AVOREN) Escudier et al Escudier et al | First-line metastatic with clear cell | PFS | 5.2 m | 3.3 m | 0.71 (0.66 to 0.83) | – | – | Non-significant Primary end point OS amended to PFS | NA | 1 |
| Interferon+bevacizumab (CALBG 90206) Rini et al Rini et al | First-line metastatic with clear cell | PFS | 2.8 m | 2.7 m | 0.44 (0.35 to 0.55) | 15.9 m | 3.4 m | 0.77 (0.63 to 0.95) | 3 | NA |
| Sorafenib vs placebo (TARGET)* Escudier et al | Second-line locally advanced or metastatic | OS | 4.2 m | 5.0 m | 0.46 (0.34 to 0.62) | – | – | – | 3 | NA |
| Pazopanib vs placebo* Stemberg et al | Second-line locally advanced or metastatic | PFS | 4.7 m | 2.0 m | 0.66 (0.55 to 0.81) | – | – | – | 3 | NA |
| Axitinib vs sorafenib (AXIS)* Rini et al | Previously treated metastatic | PFS | 1.9 m | 2.1 m | 0.30 (0.22 to 0.40) | – | – | – | 3 | NA |
| Everolimus vs placebo (RECORD-1)* Motzer et al | Second-line or third-line after tyrosine kinase inhibitor metastatic | PFS | 4.4 m | 0.2 m | 0.88 (0.75 to 10.3) | 19.6 m | 5.4 m | 0.73 (0.57 to 0.93) | Significantly less grade III/IV AEs | NA | 5 |
| Nivolumab vs everolimus (Checkmate-025) Motzer et al | Advanced or metastatic with progress after at least one antiangiogenic treatment | OS | 3.8 m | 3.6 m | 0.58 (0.45 to 0.75) | – | – | – | Survival data immature but expected to be positive | NA | 3 |
| Cabozantinib vs everolimus (METEOR) Choueiri et al | Advanced or metastatic with progress after at least one antiangiogenic treatment (pretreated with sunitinib) PFS (sunitinib) | PFS (all) | 3.7 m | 5.4 m | 0.41 (0.28 to 0.61) | – | – | – | 3 | 3 |

*Adapted according to Cherny et al.8

AEs, adverse events; comb., combined; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FT, field testing; m, months; NA, not applicable; OS, overall survival; PFS, progression-free survival; EP, end point; QOL, quality of life; tem., temsirolimus.
Finally, analyses definitely become more difficult when it comes to a setting where a cascade mode of treatment is an accepted standard such as in mCRC or mRCC. It appears that the ESMO-MCBS in its current form has limited applicability in this particular situation, which might lead to the need to analyse treatment concepts or ‘packages’ rather than individual therapy options in such settings.

Taken together, the ESMO-MCBS is very much applicable for the daily clinical practice of a tertiary referral centre. It supports clinical decision-making based on the clinical benefit derived from a new treatment and reflects well the daily experience. In addition, even though the cost factor is not implemented in the scale, the ESMO-MCBS might also support decision-making within socioeconomic contexts.

Competing interests GP has received honoraria for lectures by Merck Serono, Amgen, Bayer, Servier, Lilly, Celgene, Roche and Sanofi Aventis. RP has received honoraria for lectures or advisory boards by AstraZeneca, Böhringer Ingelheim, Lilly, MSD, Pfizer, Roche and Syntelast. MP has received research support by Böhringer Ingelheim, GSK, MSD, Roche and honoraria by BMS, Novartis, CMC Contrast, GSK, Mundipharma and Roche. MS has received honoraria for lectures by Pfizer, BMS, Novartis, Roche and Astellas. CCZ has received honoraria for advisory boards by Bristol Myers-Squibb, AstraZeneca, Imugene and Roche. All remaining authors have declared no conflict of interest.

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