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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.

Key questions

What is already known about this subject?

The European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) has been designed to assess the therapeutic benefit of a certain drug registered for the treatment of cancer and has been tested in a range of solid tumours during the initial development process. However, though internally validated, this tool has not yet been evaluated in daily practice.

What does this study add?

This is the first study assessing the clinical impact and feasibility of the ESMO-MCBS in a real-life context of a major center of medical oncology. We have systemically evaluated well-established oncological treatment strategies from first-line to salvage treatment throughout major tumour entities at our institution. While we 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.

How might this impact on clinical practice?

Our results show that the ESMO-MCBS worked very reliably and reproducibly in the field of advanced or metastatic diseases and encourage its use in daily routine. 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.

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

Table 1 Field testing of the ESMO-MCBS for the treatment of advanced breast 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
Trastuzumab+CT ±pertuzumab (CLEOPATRA)* Swain *et al*[10] Swain *et al*[11]	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)* Verma *et al*[12] Weslau *et al*[13]	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* Geyer *et al*[14]	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 (EGF104900)* Blackwell *et al*[15] Blackwell *et al*[16]	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) Minckwitz *et al*[17]	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)* Baselga *et al*[18]	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) Finn *et al*[19]	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) Turner *et al*[20]	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* Miller *et al*[21]	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

Table 1 Continued

Analysed treatment	Setting	Primary EP	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	Adjustment/remark	MCBS	MCBS-FT
Pegylated liposomal doxorubicin vs conventional doxorubicin Brien *et al*[22]	First-line metastatic	Non-inferiority	7.8 m	–	Non-significant	–	–	–	Less cardiotoxicity; less alopecia and nausea	NA	4
Capecitabine ±bevacizumab, anthracycline-based/ taxane-based CT ±bevacizumab (RIBBON-1) Robert *et al*[23]	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
		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
Eribulin vs other CT (EMBRACE)* 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.[10 11] 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).[12 13] In contrast, the combination of lapatinib with capecitabine scored lower due to an insignificant difference in OS (ESMO-MCBS score 3),[14] 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).[15 16]

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).[18] 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.[23] The combination of bevacizumab with capecitabine 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 platin-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).[31–33]

For EGFR-unmutated 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.[36] 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.[37 38]

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 unselected patients. For a cross-over comparison of clinical trials, the analysis in

Table 2 Field testing of the ESMO-MCBS for the treatment of advanced lung 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
Erlotinib vs carboplatin (OPTIMAL, CTONG 0802)* Zhou *et al*[27]	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*[28]	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 Carboplatin +paclitaxel (IPASS) Mok *et al*[29] Fukuoka *et al*[30]	First-line IIIB or IV, non-squamous *(EGFR-mutated)*	PFS (all)	NA	NA	0.74 (*0.65 to 0.85*)	–	–	–	QOL improved, less toxicity	NA	NA
		PFS (EGFR+)	*6.3 m*	*3.3 m*	*0.48 (0.34 to 0.67)*	–	–	–		NA	*4*
Afatinib vs cisplatin +pemetrexed (LUX Lung-3)* Sequist *et al*[31] Yang *et al*[32] Yang *et al*[33]	First-line IIIB or IV adenocarcinoma, EGFR-mutated *(EGFR exon 19 deletion)*	PFS (all)	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
		PFS (del19)	*6.9 m*	*6.7 m*	*0.47 (0.34 to 0.65)*	*21.1 m*	*12.2 m*	*0.54 (0.36 to 0.79)*		*NA*	*(4-)5*†
Crizotinib vs CT* Shaw *et al*[34]	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*[35]	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* Scagliotiti *et al*[36]	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*[37]	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*[38]	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
		PFS (high)		0.4 m	0.82 (0.68 to 0.98)					NA	1
CT±palliative care* Temel *et al*[39]	Stage IV, ECOG<2	QOL	–	–	–	8.9 m	2.7 m	HR death 1.7	QOL improved	4	NA

Continued

Table 2 Continued

Analysed treatment	Setting	Primary EP	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	Adjustment/ remark	MCBS	MCBS-FT
Pemetrexed vs placebo Ciuleanu *et al*[40]	Maintenance after response to platinum doublet	PFS (all)	2.6 m	1.7 m	0.50 (0.42 to 0,61)	10.6 m	2.8 m	0.79 (0.65 to 0.95)		NA	3
	(non-squamous)	*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 (SATURN)* Capuzzo *et al*[41]	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
Docetaxel±nintedanib (LUME-Lung1) Reck *et al*[42]	Second 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
	(adenocarcinoma with PD 9 m after start first line)	*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 (Checkmate 057) Borghaei *et al*[43]	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
Nivolumab vs docetaxel (Checkmate 017) Brahmer *et al*[44]	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

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.

Table 3 Field-testing of the ESMO-MCBS for the treatment of advanced colorectal 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
FOLFIRI±cetuximab (CRYSTAL)* Van Cutsem *et al*[45]	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*[46]	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*[47]	First-line metastatic	OS	–	–	–	15.6 m	4.7 m	0.66 (0.54 to 0.81)		3	NA
FOLFOXIRI+bevacizumab vs FOLFRIRI +bevacizumab * Loupakis *et al*[48]	First-line metastatic	PFS	9.7 m	2.4 m	0.75 (0.62 to 0.9)	–	–	Non-significant	Positive subgroup analysis for BRAF-mut.	2	NA
XELOX/FOLFOX ±bevacizumab Saltz *et al*[49]	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 (CALBG/ SWOG-80405) Venook *et al*[50]	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*[51]	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 +capecitabine vs capecitabine (AVEX) Cunningham *et al*[52]	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 +capecitabine vs observation (CAIRO-3) Simkens *et al*[53]	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*[54]	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*[55]	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

Table 3 Continued

Analysed treatment	Setting	Primary EP	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	Adjustment/ remark	MCBS	MCBS-FT
FOLFIRI±aflibercept (VELOUR)* Van Cutsem *et al*[56]	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
FOLFIRI±panitumumab* Peeters *et al*[57]	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
FOLFIRI±panitumumab (20050181) Peeters *et al*[58]	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
FOLFIRI+ramucirumab (RAISE)* Taberno *et al*[59]	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
Cetuximab vs best supportive care* Karapetis *et al*[60]	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
Panitumumab vs best supportive care* Amado *et al*[61]	Third-line metastatic stratified for KRAS	PFS	7.3 w	5 w	0.45 (0.34 to 0.59)	–	–	–		2	NA
TAS-102 vs placebo (CONCOURSE)* Mayer *et al*[62]	Third-line or beyond metastatic	OS	–	–	–	5.3 m	1.8 m	0.68 (0.58 to 0.81)		2	NA
Regorafenib vs placebo (CORRECT)* Grothey *et al*[63]	Third-line metastatic	OS	–	–	–	5 m	1.4 m	0.77 (0.64 to 0.94)		1	NA

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; FOLOFX, fluorouracil, oxaliplatin; 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, capecitabine plus/minus bevacizumab for the elderly was assessed. In terms of PFS, an MCBS-FT score 3 was calculated without any deterioration in 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 capecitabine 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)[64–70] 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.[66]

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±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]

Table 4 Field testing of the ESMO-MCBS for the treatment of advanced gastric 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
FOLFIRI vs ECX Guimbaud *et al*[64]	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 Shah *et al*[65]	Advanced first-line gastric or gastro-oesophageal cancer adenocarcinoma	PFS at 6 m	53%	10%	–	12.6 m	6.2 m	P=0.07	Reduced toxicity, increase in PFS and OS	NA	4*
CT±trastuzumab (TOGA) Bang *et al*[66]	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 (0.60 to 0.91)		NA	3
ECX vs ECF and EOX vs EOF Cunningham *et al*[67]	Advanced first-line gastric or gastro-oesophageal cancer	Non-inferiority (OS)	–	–	–	9.9 m 9.3 m	0 m 1.9 m	0.86 (0.80 to 0.99) 0.92 (0.80 to 1.1)	Non-inferiority criteria were met	NA	NC
Ramucirumab vs placebo† (REGARD) Fuchs *et al*[68]	Second-line gastric or gastro-oesophageal cancer after cisplatin/ 5FU	OS	–	–	–	3.2 m	2.0 m	0.78 (0.60 to 0.99)		2	NA
Paclitaxel±ramucirumab (RAINBOW) Wilke *et al*[69]	Second-line gastric or gastro-oesophageal cancer after cisplatin/ 5FU	OS	–	–	–	7.4 m	2.2 m	0.81 (0.68 to 0.96)	No difference in QOL	NA	2
Salvage chemotherapy vs best supportive care Kang *et al*[70]	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)	Treatment: docetaxel or irinotecan	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; EOF, epirubicin, oxaliplatin, fluorouracil; 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*[71]	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*[72]	High risk locally advanced or metastatic	OS	– – –	– – –	– – –	71.0 m	10.0 m NR 5.0 m	0.78 (0.66 to 0.93) 0.94 (0.79 to 1.11) 0.82 (0.69 to 0.97)	Multiarm, multistage design	NA NA NA	4 – 4
Docetaxel+prednisone vs mitoxantrone+prednisone* Tannock *et al*[73]	Castration refractory	OS	–	–	–	16.5 m	2.4 m	0.76 (0.62 to 0.94)	QOL improved	3	NA
Enzalutamide vs placebo (PREVAIL)* Beer *et al*[74]	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)* Parker *et al*[75]	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* De Bono *et al*[76]	Castration refractory after docetaxel	OS	–	–	–	10.9 m	3.9 m	0.65 (0.54 to 0.77)		4	NA
Enzalutamide vs placebo (AFFIRM)* Scher *et al*[77]	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)* De Bono *et al*[78]	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*.[8]
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.

In the castration-refractory setting, high scores were obtained for enzalutamide before (ESMO-MCBS score 3) and particularly after docetaxel (ESMO-MCBS score 4).[74 77] This is in line with the benefit of abiraterone after standard docetaxel,[76] 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).[75] All of these trials proved a slight 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.[78] 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 antiendocrine 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).[79–91]

Temsirolimus 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 temsirolimus reaching an MCBS-FT score of 4.[79] 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).[80 81]

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).[82 83] 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.[84 85] 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.[86–89] 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.[90] 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).[91] 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*[8] 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[26]—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.

Table 6 Field testing of the ESMO-MCBS for the treatment of advanced renal cell carcinoma 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
Temsirolimus vs interferon vs combined Hudes *et al*[79]	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*[80] Motzer *et al*[81]	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
Interferon±bevacizumab (AVOREN) Escudier *et al*[82] Escudier *et al*[83]	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 (CALBG 90206) Rini *et al*[84] Rini *et al*[85]	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
Sorafenib vs placebo (TARGET)* Escudier *et al*[86]	Second-line locally advanced or metastatic	OS	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
Pazopanib vs placebo* Sternberg *et al*[87]	Second-line locally advanced or metastatic	PFS	4.2 m	5.0 m	0.46 (0.34 to 0.62)	–	–	–		3	NA
Axitinib vs sorafenib (AXIS)* Rini *et al*[88]	Previously treated metastatic	PFS	4.7 m	2.0 m	0.66 (0.55 to 0.81)	–	–	–		3	NA
Everolimus vs placebo (RECORD-1)* Motzer *et al*[89]	Second-line or third-line after tyrosine kinase inhibitor metastatic	PFS	1.9 m	2.1 m	0.30 (0.22 to 0.40)	–	–	–		3	NA
Nivolumab vs everolimus (Checkmate-025) Motzer *et al*[90]	Advanced or metastatic with progress after at least one antiangiogenic treatment	OS	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
Cabozantinib vs everolimus (METEOR) Choueiri *et al*[91]	Advanced or metastatic with progress after at least one antiangiogenic treatment	PFS (all)	3.8 m	3.6 m	0.58 (0.45 to 75)	–	–	–	Survival data immature but expected to be positive	NA	3
	(pretreated with sunitinib)	*PFS (sunitinib)*	3.7 m	*5.4 m*	*0.41 (0.28 to 0.61)*	–	–	–		*NA*	*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 Synta. 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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