ESMO Open
Cancer Horizons

The European Society for Medical Oncology 'Magnitude of Clinical Benefit Scale' field-tested in infrequent tumour entities: an extended analysis of its feasibility at the Medical University of Vienna

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To cite: Kiesewetter B, Raderer M, Prager GW, *et al*. The European Society for Medical Oncology 'Magnitude of Clinical Benefit Scale' field-tested in infrequent tumour entities: an extended analysis of its feasibility at the Medical University of Vienna. *ESMO Open* 2017;**2**:e000166. doi:10.1136/esmoopen-2017-000166

Received 23 January 2017
Revised 13 April 2017
Accepted 20 April 2017

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ABSTRACT

Background The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a new tool to quantify the clinical benefit that may be anticipated from a novel anticancer treatment. We present here an analysis on the feasibility of the ESMO-MCBS in less frequent tumour entities.

Methods This study evaluates the practicability of the ESMO-MCBS for metastatic neuroendocrine tumours (NETs), soft tissue sarcomas, glioblastoma, thyroid cancer, pancreatic cancer, head/neck cancer, urothelial cancer and ovarian cancer at the Medical University Vienna. A three-step approach including data acquisition, assessment of ESMO-MCBS scores and evaluation of results with a focus on clinical feasibility was applied.

Results In NET and thyroid cancer, all analysed trials were very comparable in design and efficacy, and the ESMO-MCBS scores appeared to be consistent with the clinical benefit seen in practice. For pancreatic cancer, it was more difficult to compare first-line trials due to diverging populations included in the respective studies. Concerning soft tissue sarcomas, the ESMO-MCBS was applicable for gastrointestinal stromal tumours(GIST) and 'non-GIST' soft tissue sarcoma with respect to data deriving from randomised studies. However, due to the heterogeneity of the disease itself and a limited number of controlled trials, limitations are noted. In ovarian cancer, the ESMO-MCBS supported the use of bevacizumab in high-risk patients. To date, there are only limited data for glioblastoma, head/neck cancer and urothelial cancer but whenever randomised trials were available, the ESMO-MCBS rating supported clinical decisions. Interestingly, nivolumab for salvage treatment of head/neck cancer rated extremely high.

Conclusion The ESMO-MCBS scores supported our common treatment strategies and highlight the potential of new immunomodulatory drugs. Our results encourage further development of the ESMO-MCBS.

Key questions

What is already known about this subject?

The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) has been developed aiming to provide a standardised, generic and validated approach to stratify the potential clinical benefit that may be anticipated from a novel anticancer treatment. The score has been internally validated in a selection of trials during the initial development process and recently in a pilot field-testing on common tumour entities at our institution.

What does this study add?

We report a 'real-life' experience of the ESMO-MCBS applied for treatment decisions in metastatic neuroendocrine tumours, soft tissue sarcomas, glioblastoma, thyroid cancer, pancreatic cancer, head/neck cancer, urothelial cancer and ovarian cancer at the Medical University of Vienna. In line with our recent report on common tumour entities, most scores assessed corresponded well with the daily clinical experience at our institution. The results supported both the use of the ESMO-MCBS and our current treatment standards. Furthermore, the ESMO-MCBS highlighted the high clinical benefit to be expected from novel immunomodulatory treatment options exemplified by immune checkpoint inhibitors. However, limitations were noted in case of cascade like treatment settings, orphan diseases or scenarios in which trials of most efficacious treatments are missing (e.g., in the first-line treatment of pancreatic cancer).

How might this impact on clinical practice?

Our results encourage further development of the ESMO-MCBS and illustrate how the score may be applied in daily clinical practice. In addition, we highlight potential limitations that have to be considered.

INTRODUCTION

The European Society for Medical Oncology (ESMO) - Magnitude of Clinical Benefit Scale (MCBS) has been developed by a taskforce of renowned European medical oncologists aiming to provide a standardised, generic and validated approach to stratify the potential clinical benefit that may be anticipated from a novel anticancer treatment based on original data extracted from randomised or controlled clinical trials.[1]

While due to the enormous velocity in clinical drug development in recent months, several institutions worldwide have made strong efforts to evolve concepts, scores or scales for stratification of new treatment approaches, the ESMO-MCBS appears somehow unique as it concentrates particularly on the clinical benefit to be expected for the *individual patient* irrespective of socioeconomic factors.[1–3] In addition, it is easy to use for the qualified clinician based on forms publicly available on the ESMO homepage and allows on-time evaluation of new data on a regular basis.[4] Key points requested during assessment of the ESMO-MCBS scores include the primary endpoint of the specific study in terms of absolute gain in progression-free survival (PFS) or overall survival (OS) in months and the corresponding 95% CI of the HR; in a second step, information about toxicity and quality of life (QOL) is added if available. The concept offers different forms for curative and palliative care setting and has adapted versions with respect to duration of response in the control arm. Following this process, the user is provided with a recommendation level of '1–5' in the palliative and 'A' to 'C' in curative scenarios with '4–5' and 'A' corresponding to a high level of benefit and 'C'/'1' identifying treatment regimens that are considered non-recommended.[1]

Being introduced for the first time by the middle of 2015 by ESMO, the ESMO-MCBS has excited great public interest in the last year. However, we felt that due to the fact that the score has only been internally validated in a selection of trials during the development process, a further assessment of reproducibility under real-life conditions would be necessary prior to implementation in daily practice. Consequently, we have recently conducted a systematic field testing of the ESMO-MCBS at the Medical University of Vienna (MUV) including data on advanced breast cancer, lung cancer, colorectal cancer, prostate cancer and renal cell cancer.[5] We could demonstrate that in the majority of cases, the ESMO-MCBS scores are consistent with clinical practice at our institution and are particularly in line with our first-line standards for common tumour entities like metastatic breast cancer, colorectal cancer or lung cancer. Thus, the score appeared to be feasible and useful for daily practice in a tertiary centre.

In addition to our personal experience at the MUV, Giuliani and colleagues from Italy[6] have presented their experience with pivotal phase III randomised trials on tyrosine-kinase inhibitors (TKIs) first line for advanced lung cancer with activating epidermal growth factor receptor mutations. In line with our data, they have observed a high level of recommendation for compounds in regular use and suggested combination with pharmacological costs to gain additional socioeconomic information by use of the ESMO-MCBS.

Based on these promising results and the positive resonance we have received for our pilot trial on common tumour subtypes, we present here an extended analysis on the feasibility of the ESMO-MCBS in relatively rare tumour entities. These include our results on neuroendocrine tumours (NETs), thyroid cancer, pancreatic cancer, head and neck cancer, glioblastoma, ovarian cancer, urothelial cancer and soft tissue sarcomas (STS).

METHODS

This study evaluated the clinical applicability and practicability of the ESMO-MCBS in less frequent tumour entities in general and at the MUV, Clinical Division of Oncology and the Comprehensive Cancer Center, a tertiary referral centre for oncological diseases, in particular. Based on the concept developed for the testing of frequent tumour entities, we have used a three-step approach including data acquisition, assessment of ESMO-MCBS scores and evaluation of results with a focus on clinical feasibility.

Step one: data acquisition

A systematic data collection of intravenously and orally applied anticancer drugs in regular use at the MUV over a period of 2 months was performed. Treatment protocols and applied regimens including cytostatic agents, antibodies and immunotherapeutic compounds were extracted from CATO (computer aided therapy for oncology), a software technology routinely used for managing administration of oncological therapies at our clinic. Tumour subtypes evaluated in this study were locally advanced or metastatic NETs of the gastrointestinal (GI) tract and lung, thyroid cancer, pancreatic cancer, squamous-cell cancer of the head and neck (non-nasopharyngeal), glioblastoma, ovarian cancer, urothelial cancer and STS (all histologies, including gastrointestinal stromal tumours (GIST)). This selection of tumour entities is based on the clinical focus of our department and includes only entities accounting for less than 5% of all cancer cases in Europe.[7] Data were subdivided per treatment setting from first line to salvage therapy. (Neo-) Adjuvant treatment strategies were excluded due to strict compliance to guidelines in these settings.

Step two: ESMO-MCBS assessment

A literature search was conducted to assess source data for treatment approaches identified in step one (i.e., trials identified as reference for the established treatment protocols at our department). While we have systematically analysed and investigated data relevant to the daily routine at our department, it must be clearly stated that we aimed to provide a thorough 'one-centre' experience but not a complete work-up of oncological therapies

available. The data presented here are a selection of trials considered essential for practice at our clinic. Randomised or controlled clinical trials (comparative cohort design) were scored with the ESMO-MCBS forms for the palliative treatment setting using versions 2A, 2B or 2C based on the primary endpoint of the trial. All scores were assessed by BK and re-evaluated by the senior medical oncologists for the respective tumour entity. Results are referred to as MCBS field testing (MCBS-FT score) throughout the manuscript. In case of pre-evaluation of a trial in the internal validation cohort of the ESMO taskforce, those results were adopted and rechallenged according to local standards (referred to as ESMO-MCBS score). As outlined in the original version of the ESMO-MCBS, scores of 4 and 5 were accepted as high level of recommendation. Trials that failed to demonstrate statistical significance of evaluated outcomes are not eligible for ESMO-MCBS assessment but documented in this analysis if relevant to our practice (referred to as 'not applicable').

Step three: feasibility assessment

We have performed interviews to review data and results with the tumour entity specific programme directorships (PDs) (=senior medical oncologist) and their coworkers covering the distinct tumour entities within specialised subunits. ESMO-MCBS results and recommendation levels were reassessed and checked for completeness, significance and clinical feasibility. Each PD had to address the following points: (1) Do the ESMO-MCBS scores correlate with the clinical experience? (2) Does the ESMO-MCBS support treatment decisions in daily practice? (3) What are the potential limitations of the ESMO-MCBS? The consensus was then summarised in the conclusion section of each tumour entity.

RESULTS

Neuroendocrine tumours

Data of locally advanced/metastatic NETs were subdivided into common treatment strategies for midgut/lung NET and pancreatic NET, respectively (table 1).[8–15]

Assessment of ESMO-MCBS scores for advanced NET revealed comparable results in all available data (all trials placebo controlled). The CLARINET and the PROMID trial represent two proof of principle studies demonstrating for the first time direct antiproliferative effects of somatostatin analogues for advanced midgut and pancreatic NET irrespective of progression status.[8 9] For both, lanreotide (median PFS gain +32% at 2 years; median HR 0.47, 95% CI 0.30 to 0.73) and octreotide (PFS gain 8.3 months; HR 0.34, 95% CI 0.20 to 0.59), a significant increase in PFS was documented. QOL data confirmed maintenance of QOL in the treatment arm, but no improvement was documented (downgrade 1 point). Documented toxicity was low, and no downgrading for adverse events (AEs) was indicated resulting in a final MCBS-FT score of 2. Everolimus was equally effective in the setting of progressive GI and lung NET (PFS gain 7.1 months, HR 0.48, 95% CI 0.35 to 0.67) reaching a MCBS-FT score of 3.[10]

In non-pancreatic and pancreatic patients, the RADIANT-2 (PFS gain 5.1 months; HR 0.77, 95% CI 0.59 to 1.0) and RADIANT-3 (PFS gain 6.4 months; HR 0.35; 96% CI 0.27 to 0.45) trials showed comparable activity for everolimus in non-functioning and hormone-active NET and while the first did not meet its primary endpoint (ESMO-MCBS not applicable), the second resulted in an MCBS-FT score of 3.[11–13] Data on sunitinib for pancreatic NET were in the same range with 5.5 months PFS in the placebo arm and 11.4 months in the treatment group (HR 0.42, 95% CI 0.26 to 0.66), but the final score was downgraded for QOL results (MCBS-FT score 2).[14 15] The absolute number of AEs was increased for everolimus-treated and sunitinib-treated patients, but this did not meet criteria for downgrading by the ESMO-MCBS. Noteworthy, in none of these trials a significant OS benefit was demonstrated.[8–15]

Conclusion: To date, published trials are comparable in design and efficacy, and the corresponding MCBS-FT score of 2–3 is consistent with the moderate clinical benefit seen while treating patients with advanced or metastatic NET. The fact that all trials rated equally in quite similar clinical settings reflects however one difficulty of the scale in its current version: as only one trial may be considered at once (except for meta-analyses), there is no additional information for optimal sequencing of treatment options added by the ESMO-MCBS scoring system; this has also previously been discussed for colorectal cancer and renal cell cancer in our pilot analysis.

Thyroid cancer

Data of locally advanced/metastatic thyroid cancer were subdivided into common treatment strategies for medullary thyroid cancer and well-differentiated iodine-refractory thyroid cancer, respectively (table 2).[16–19]

In the case of medullary thyroid cancer, there are currently two TKIs of interest.[16 17] Both compounds were analysed in comparable randomised trials powered for an endpoint of PFS. For cabozantinib, the median PFS gain was 7.2 months (HR 0.28, 95% CI 0.19 to 0.40). Toxicity was high with 20% increase in serious AEs diminishing the expected clinical benefit (downgrade 1 point, MCBS-FT score 2).[16] Vandetanib showed an improvement of 11.2 months in PFS (HR 0.46, 95% CI 0.31 to 0.69).[17] Declaration of toxicities was not clear in this publication so it is debatable whether downgrading of the final ESMO-MCBS score is required (MCBS-FT score 2–3).

Lenvatinib for progressive, iodine-refractory differentiated thyroid cancer showed a high median PFS of 18.3 months versus 3.6 months in the control arm (HR 0.21, 95% CI 0.14 to 0.31), but again significantly more toxicities including toxic deaths were documented (downgrade 1 point, MCBS-FT score 2).[18] Similarly, sorafenib (PFS gain 5 months; HR 0.59; 95% CI 0.45 to 0.76) resulted in more than 10% increase in serious AEs (downgrade 1 point, MCBS-FT score 2).[19]

Table 1 FT of the ESMO-MCBS for the treatment of neuroendocrine tumours 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
Lanreotide versus placebo (CLARINET) Caplin *et al*, NEJM[8]	Ki-67<10% GI or unknown origin (non-functioning)	PFS	18 months	+32% at 2 year	0.47 (0.30–0.73)				No improvement in QOL, downgrade 1 point	–	**2**
Octreotide versus placebo (PROMID) Rinke *et al*, JCO[9]	Midgut, unknown (non-functioning and functioning)	TTP	6 months	8.3 months	0.34 (0.20–0.59)				No improvement in QOL, downgrade 1 point	–	**2**
Everolimus versus placebo (RADIANT-4) Yao *et al*, Lancet[10]	Progressive disease lung or GI (non-functioning)	PFS	3.9 months	7.1 months	0.48 (0.35–0.67)					–	**3**
Everolimus versus placebo (RADIANT-3) Yao *et al*, NEJM[11] Yao *et al*, JCO[12]	Progressive disease pancreatic NET	PFS	4.6 months	6.4 months	0.35 (0.27–0.45)	37.7m	6.3m	Non-significant		–	**3**
Octreotide ± everolimus (RADIANT-2) Pavel *et al*, Lancet[13]	Progressive disease lung, GI, unknown (functioning)	PFS	11.3 months	5.1 months	Non-significant					–	**NA**
Sunitinib versus placebo Raymond *et al*, NEJM[14] Faivre *et al*, JCO[15]	Progressive pancreatic NET	PFS	5.5 months	5.9 months	0.42 (0.26–0.66)	29.1m	9.5m	Non-significant	No improvement in QOL, downgrade 1 point	–	**2**

EP, endpoint; ESMO, European Society for Medical Oncology; FT, field testing; GI, gastrointestinal; MCBS, Magnitude of Clinical Benefit Score; NA, not applicable; NET, neuroendocrine tumour; OS, overall survival; PFS, progression-free survival; QOL, quality of life; TTP, time to progression.

Table 2 FT of the ESMO-MCBS for the treatment of thyroid 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
Cabozantinib versus placebo Elisei *et al*, JCO[16]	Progressive disease medullary thyroid cancer	PFS	4 months	7.2 months	0.28 (0.19–0.40)				42% versus 23% SAE, downgrade 1 point	–	2
Vandetanib versus placebo Wells *et al*, JCO[17]	Medullary thyroid cancer	PFS	19 months	11.2 months	0.46 (0.31–0.69)				More grade III/IV AEs	–	2–3*
Lenvatinib versus placebo (SELECT) Schlumberger *et al*, NEJM[18]	Progressive disease iodine-refractory differentiated thyroid cancer	PFS	3.6 months	14.7 months	0.21 (0.14–0.31)				Increased toxicity including toxic deaths, downgrade 1 point	–	2
Sorafenib versus placebo (DECISION) Brose *et al*, Lancet[19]	Progressive disease iodine-refractory differentiated thyroid cancer	PFS	5.8 months	5 months	0.59 (0.45–0.76)				37% versus 26% SAE, downgrade 1 point	–	2

*Unclear toxicity data.
AE, adverse event; EP, endpoint; ESMO, European Society for Medical Oncology; FT, field testing; MCBS, Magnitude of Clinical Benefit Score; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event.

Conclusion: Treatment with modern TKIs increased PFS but was usually associated with a significant gain of toxicity. In line with NET and colorectal cancer, the point of discussion not addressed by the ESMO-MCBS is the optimal sequencing and data have to be interpreted with caution concerning progression status and inclusion criteria of the respective trial. For example, in subgroup analyses lenvatinib showed a significant PFS benefit also for sorafenib pretreated patients while prior TKI treatment was not allowed in the sorafenib trial suggesting use of the first compound in this specific setting.[18 19]

Pancreatic cancer

Data of locally advanced/metastatic pancreatic ductal adenocarcinoma (mPDAC) were subdivided into common strategies for first-line and salvage treatment, respectively (table 3).[20–24]

For first-line treatment in mPDAC, a comparison between different clinical phase III trials is impossible due to the fact of different trial designs and target populations. Thus, the application of the ESMO-MCBS is complicated by methodological issues in this context. While the clinical phase III trial MPACT (add-on of nab-paclitaxel to gemcitabine) was an international trial performed in 861 patients cared for in 151 centres in 11 different countries in three continents,[20] the PRODIGE4/ACCORD11 trial (FOLFIRINOX versus gemcitabine) was designed as a clinical phase II trial, which was consecutively extended to a clinical phase III trial, but was performed only in 342 patients from 48 centres limited to France.[21] Most importantly, the latter trial had no central radiological assessment. Furthermore, the trial was limited to fit (ECOG 0–1) and younger patients, while the MPACT trial included also elderly patients and patients with moderate performance status corresponding to a population closer to a real-world clinical setting.[20] Although the PRODIGE4/ACCORD11 trial was awarded an ESMO-MCBS score of 5, the higher toxicity of the triplet combination has to be taken into account. In terms of efficacy, there is no head-to-head comparison trial favouring FOLFIRINOX over the gemcitabine plus nab-paclitaxel combination (ESMO-MCBS score 3). A bias towards the more toxic triplet-combination cannot be excluded, although FOLFIRINOX might be an effective treatment option for younger and fit patients. Thus, the adherence to the American Society of Clinical Oncology guidelines on the treatment of mPDAC considering efficacy versus toxicity is recommended.[25]

Conclusion: Because mPDAC patients have a limited prognosis of <12 months in median OS, there is an urgent need for a head-to-head comparison trial of FOLFIRINOX versus gemcitabine plus nab-paclitaxel. Thus, the ESMO-MCBS will have to be adapted to the outcome of such a head-to-head comparison. Currently, the authors suggest nab-paclitaxel/gemcitabine to be the favourable treatment option with FOLFIRINOX being an effective protocol for a certain subgroup of younger and fit patients.

Table 3 FT of the ESMO-MCBS for the treatment of pancreatic 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
Gemcitabine ± *nab*-Paclitaxel* (MPACT) Von Hoff *et al*, NEJM[20]	First-line Karnofsky index >70%	OS				6.7 months	1.8 months	0.72 (0.61–0.83)	5% OS gain at 24 months	**3**	–
FOLFIRINOX versus gemcitabine* (PRODIGE 4/ACCORD 11) Conroy *et al*, NEJM[21]	First-line ECOG performance status 0–1	OS				6.8 months	4.4 months	0.57 (0.45–0.73)	Delayed deterioration of QOL, upgrade 1 point	**5**	–
Gemcitabine ± erlotinib* Moore *et al*, JCO[22]	First-line	OS				5.9 months	0.3 months	0.82 (0.69–0.99)		**1**	–
FOLFOX versus 5FU (CONKO-003) Oettle *et al*, JCO[23]	Second-line after progress to gemcitabine	OS				3.3 months	2.6 months	0.66 (0.48–0.91)		–	**3**
Nal-irinotecan + fluorouracil versus nal-irinotecan versus fluorouracil (NAPOLI-1) Wang-Gillam *et al*[24]	Second-line after progress to gemcitabine-based therapy	OS				4.2 months	1.9 months 0.7 months	0.67 (0.49–0.92) Non-significant		2 **1**	

*Adapted according to Cherny *et al*.[1]
EP, endpoint; ESMO, European Society for Medical Oncology; FT, field testing; MCBS, Magnitude of Clinical Benefit Score; OS, overall survival; PFS, progression-free survival; nal = nanoliposomal.

Head and neck cancer

Data of recurrent or metastatic head and neck cancer were subdivided into common strategies for first-line and salvage treatment, respectively (table 4).[26–29]

A landmark study in this setting was the EXTREME trial published in 2008.[27] This randomised phase III study investigated the impact of cetuximab as add-on to standard platinum-based chemotherapy followed by a maintenance phase (OS benefit 2.7 months; HR 0.80, 95% CI 0.64 to 0.99) and has most potentially set a new standard of care (MCBS-FT score 3). In second-line afatinib showed only in a minor PFS benefit (PFS gain 0.9 months; HR 0.80; 95% CI 0.65 to 0.98) but improvement in QOL was documented resulting in a final MCBS-FT score of 3 (upgrade 1 point).[28] To date, we add data on addition of nivolumab to standard of care in second-line or recurrent squamous-cell carcinoma of head and neck (CheckMate 141 trial).[29] With an increase in OS to 7.5 months versus 5.1 months in the control arm (OS gain 2.4 months; HR 0.70, 95% CI 0.51 to 0.96), a decrease in daily relevant toxicities (upgrade 1 point) and a substantial improvement of QOL (upgrade 1 point), the assessed MCBS-FT score of 4 may be considered a striking result in terms of clinical benefit. Of note, subgroup analyses demonstrated a particular OS benefit for programmed death-ligand 1 (PD-L1) expression >1% and p16-positive patients; however, the study was not powered to detect a significant difference herein and further data need to be awaited also in terms of ESMO-MCBS assessment.

Conclusion: These data are particularly of interest as we have observed in former analysis that the ESMO-MCBS level usually decreases within subsequent treatment lines, but it appears that immune checkpoint inhibitors may counterbalance this phenomenon. This has also been shown for renal cell cancer or lung cancer previously. In addition, it is noteworthy that nivolumab resulted in a decline of side effects and a significant increase in QOL.

Glioblastoma

Data of glioblastoma were subdivided into common strategies for first-line and recurrent disease, respectively (table 5).[30–35]

While concomitant radio plus chemotherapy is gold standard for the first-line treatment of glioblastoma,[30] we have analysed two trials investigating a potential benefit by addition of bevacizumab to this routine approach.[31 32] Both studies showed no improvement in OS, but PFS was prolonged as compared with standard. However, there were controversial data regarding QOL resulting in a substantial difference of ESMO-MCBS recommendation levels. While the trial by Gilbert *et al* (PFS gain 3.4 months; HR 0.79, 95% CI 0.66 to 0.94) documented a deterioration in QOL for no measurable clinical benefit per ESMO-MCBS (MCBS-FT score 1 for PFS, but 1 point downgrade for QOL),[31] the second trial by Chinot and colleagues had slightly better PFS results (PFS gain 4.4 months; HR 0.64, 95% CI 0.55 to 0.74) and showed—despite a substantial increase in toxicity—a significant

Table 4 FT of the ESMO-MCBS for the treatment of head and neck 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
Cisplatin ± cetuximab Burtness *et al*, JCO[26]	Previously untreated	PFS	2.7 months	1.5 months	Non-significant				Increase in response rate	–	NA
Platinum-based CT±cetuximab followed by maintenance (EXTREME) Vermorken *et al*, NEJM[27]	Previously untreated	OS				7.4 months	2.7 months	0.80 (0.64–0.99)		–	3
Afatinib versus methotrexate (LUX-Head & Neck 1) Machiels *et al*, Lancet Oncol[28]	Previously treated with platin-based therapy	PFS	1.7 months	0.9 months	0.80 (0.65–0.98)				Improved QOL, upgrade 1 point	–	3
Nivolumab versus investigator's choice (CheckMate 141) Ferris *et al*, NEJM[29]	Previously treated with plating-based therapy	OS	–	–	–	5.1 months	2.4 months	0.70 (0.51–0.96)	Less toxicity, upgrade 1 point; improved QOL, upgrade 1 point	–	4*

*More mature survival data may improve outcome of MCBS.
EP, endpoint; ESMO, European Society for Medical Oncology; FT, field testing; MCBS, Magnitude of Clinical Benefit Score; OS, overall survival; PFS, progression-free survival; CT, chemotherapy; QOL, quality of life.

improvement of QOL for a final MCBS-FT score of 3 (MCBS-FT score 3 for PFS, downgrade 1 point for toxicity, but upgrade 1 point for QOL).[32]

Furthermore, we have made efforts to assess three publications on bevacizumab for recurrent disease, but none of the trials provided a clinical benefit measurable by the ESMO-MCBS.[33–35]

Conclusion: To date, usability and practicably of the ESMO-MCBS for glioblastoma is not sufficiently clear. Bevacizumab did not show a clinical benefit for recurrent disease in randomised trials according to ESMO-MCBS rating. However, our PDs feel that bevacizumab is needed in specific patients to reduce brain oedema. In a fatal disease like glioblastoma inclusion of improvement in symptoms and possible toxicity/QOL data into treatment decisions appears important and thus the ESMO-MCBS might be a useful tool for further trials and treatment decisions.

Ovarian cancer

Data of locally advanced/metastatic ovarian cancer were subdivided into common treatment strategies for first-line, maintenance and salvage treatment (see table 6).[36–44]

In the first-line setting, the benefit of add-on bevacizumab has been evaluated in the ICON7 trial (including high-risk patients) and the GOG218 trial (incompletely resected patients).[36 37] According to the ESMO-MCBS and in line with our clinical experience, the high-risk subgroup of the ICON7 collective achieved a high level of recommendation (ESMO-MCBS score 4) based on a significant OS benefit (7.8 months; HR 0.64, 95% CI 0.48 to 0.85), which was not detected for the low-risk subgroup.[36] In contrast, secondary endpoint of OS was only non-significantly improved in the GOG218 trial, thus ESMO-MCBS recommendation level remains moderate (ESMO-MCBS score 3).[37] In both trials, QOL was not addressed.

In the setting of recurrent platinum sensitive disease, the addition of bevacizumab to a standard monotherapy achieved a median PFS gain of 4 months (HR 0.48, 95% CI 0.39 to 0.61) and 3.3 months (HR 0.48; 95% CI 0.38 to 0.60), respectively, and in synopsis with an improved QOL a high level of clinical benefit was documented for the second trial (ESMO-MCBS score 4).[38–40] The ICON6 trial evaluated addition of cediranib to standard chemotherapy in relapsed, platinum sensitive disease.[41] PFS gain was moderate (2.3 months; HR 0.56, 95% CI 0.44 to 0.72) and adverse events slightly elevated (no downgrading) resulting in a MCBS-FT score of 2. In terms of salvage treatment, trabectedin plus liposomal doxorubicin showed a small PFS benefit of median 1.7 and 1.5 months for platinum sensitive and resistant patients, respectively (HR 0.73; 95% CI 0.56 to 0.95 and HR 0.79; 95% CI 0.65 to 0.96) (ESMO-MCBS score 2 and 3).[42]

Maintenance therapy is currently considered a hot topic in treating advanced ovarian cancer. The landmark trial on olaparib for breast cancer gene (BRCA)-positive ovarian cancer in remission was powered for PFS

Table 5 FT of the ESMO-MCBS for the treatment of glioblastoma 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
Radiotherapy ± temozolomide Stupp *et al*, NEJM[30]	Untreated disease	OS				12.1 months	2.5 months	0.63 (0.52–0.75)		–	**2**
Radiotherapy, temozolomide± bevacizumab Gilbert *et al*, NEJM[31]	Untreated disease	OS, PFS	7.3 months	3.4 months	0.79 (0.66–0.94)	16 months	–	Non-significant	Deterioration in QOL	–	**No clinical benefit**
Radiotherapy, temozolomide ± bevacizumab Chinot *et al*, NEJM[32]	Untreated disease	OS, PFS	6.2 months	4.4 months	0.64 (0.55–0.74)	17 months	0.1 months	Non-significant	Improved QOL, upgrade 1 point; 39% versus 26% SAEs, downgrade 1 point	–	**3**
Lomustine versus bevacizumab versus bevacizumab + lomustine (BELOB) Taal *et al*, Lancet Oncol[33]; Dirven *et al*, EJC[34]	Recurrent disease	OS 9 months				43%	– 20%	Not applicable	Combination selected for phase III trial, QOL assessed		**NA**
Lomustine ± bevacizumab (EORTC 26101) Abstract only[35]	Recurrent disease	OS				8.6 months	0.5 months	Non-significant		–	**NA**

EP, endpoint; ESMO, European Society for Medical Oncology; FT, field testing; MCBS, Magnitude of Clinical Benefit Score; OS, overall survival; PFS, progression-free survival; QOL, quality of life.

Table 6 FT of the ESMO-MCBS for the treatment of ovarian 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
Paclitaxel + carboplatin ± bevacizumab until 18 cycles (ICON7)* Perren *et al*, NEJM[36]	High risk, early stage post resection or advanced ovarian or primary peritoneal	PFS all pts	22 months	1.7 months	0.81 (0.7–0.94)	–	–	Non-significant	Improvement in survival -> form 2A	**1**	–
		PFS high risk	14.5 months	3.6 months	0.73 (0.6–0.9)	29 months	7.8 months	0.64 (0.48–0.85)		**4**	
Paclitaxel + platin ± bevacizumab until 10 months (GOG218)* Burger *et al*, NEJM[37]	Incompletely resected stages III and IV	PFS	10.3 months	3.9 months	0.72 (0.63–0.82)			Non-significant		**3**	–
Gemcitabine and carboplatin ± bevacizumab (OCEANS)* Aghajanian *et al*, NEJM[38]	Recurrent platinum sensitive	PFS	8.4 months	4 months	0.48 (0.39–0.61)					**3**	
CT ± bevacizumab (AURELIA)* Pujade-Lauraine 2014, JCO[39] Stockler *et al*, JCO[40]	Recurrent platinum sensitive	PFS	3.4 months	3.3 months	0.48 (0.38–0.60)				QOL improved, upgrade 1 point	**4**	–
Cediranib + CT+ maintenance versus CT (ICON6) Ledermann *et al*, Lancet Oncol[41]	Recurrent platinum sensitive	PFS	8.7 months	2.3 months	0.56 (0.44–0.72)	–	–	–	QOL data not mature	–	**2**
Pegylated liposomal doxorubicin ± trabectedin (OVA 301)* Monk 2010, JCO[42]	Second-line metastatic	PFS sens.	7.5 months	1.7 months	0.73 (0.56–0.95)					**2**	–
		PFS resis.	5.8 months	1.5 months	0.79 (0.65–0.96)					**3**	
Olaparib versus placebo* Ledermann 2014, Lancet Oncol[43]	BRCA ovarian cancer in remission	PFS	4.3 months	6.9 months	0.18 (0.1–0.31)			Non-significant	QOL not improved, downgrade 1 point	–	**2**
Niraparib versus placebo (ENGOT-OV16/NOVA) Mirza 2016, NEJM[44]	Maintenance for platinum-sensitive recurrent disease	PFS BRCA	5 months	15.5 months	0.27 (0.17–0.41)				QOL not improved, downgrade 1 point	–	**2**
		PFS WT	3.8 months	9.1 months	0.38 (0.24–0.59)						

BRCA, breast cancer gene; CT, chemotherapy; EP, endpoint; ESMO, European Society for Medical Oncology; FT, field testing; MCBS, Magnitude of Clinical Benefit Score; OS, overall survival; PFS, progression-free survival; resis., platinum-resistant; sens., platinum-sensitive; WT, wild type.
*Adapted according to Cherny *et al*.[1]

and resulted in a moderate clinical advantage for the patient (ESMO-MCBS grade 2).[43] Further follow-up data would be of interest. In addition, very recently, data on niraparib as maintenance treatment for recurrent, platinum sensitive ovarian cancer have been published in the *New England Journal of Medicine*.[44] While PFS gain was even more impressive in the BRCA germline-mutated cohort (5.5 vs 20.0 months; HR 0.27, 95% CI 0.17 to 0.41), it was less but still relevant in the BRCA wild-type population (3.8 vs 12.9 months; HR 0.38; 0.24–0.59). The calculated MCBS-FT score was 2 for both. Documentation of AEs was increased but mainly affecting the bone marrow.

Conclusion: Recommendations resulting of ESMO-MCBS are in line with the clinical practice for treating ovarian cancer, particularly concerning data on bevacizumab. Application of the ESMO-MCBS for maintenance treatment has not been evaluated extensively to date; however, results on poly(ADP-ribose) polymerase inhibitors (PARP inhibitors) appear realistic. Follow-up data and more clinical experience will be of interest. There exist no randomised trials comparing the different approved monotherapies in the relapsed setting.

Urothelial cancer

Data of locally advanced/metastatic urothelial cancer were subdivided into common treatment strategies for first line and salvage treatment (see table 7).[45–52]

In the first-line setting of urothelial cancer randomised trials date back more than 20 years, but there are only a couple of trials with clinical impact. Non-inferiority of cisplatin/gemcitabine in comparison with MVAC was one of the major achievements in the last decades. In 2000, a study addressing this question was published in JCO with the primary endpoint being OS.[45–47] For this study, no clear-OS benefit was demonstrated, despite two updates being published in the following. However, there was consistent non-inferiority documented with a favourable toxicity profile for cisplatin/gemcitabine. We assessed this trial with form 2C for a MCBS-FT score of 4 in terms of clinical benefit. Next, high-dose MVAC is still an option for young and fit patients. In a trial matching this regimen with MVAC standard an OS benefit was observed (>5% increase in 3 year OS; HR 0.76, 95% CI 0.58 to 0.99) (MCBS-FT score 3).[49 50] A comparison of this regimen with cisplatin/gemcitabine is not available.

The study on vinflunine by Bellmunt *et al* all addressed the key question if chemotherapy is superior to best supportive care in this setting.[51 52] Long-term results showed only a non-significant OS improvement (ESMO-MCBS not applicable), thus no further information is added by use of the scoring system in this particular setting. Randomised data on immune checkpoint inhibitors are currently not yet available but a wide range of trials testing PD-1/ PD-L1 inhibitors are ongoing.

Conclusion: ESMO-MCBS assessment of the first-line standard treatment appears reasonable and feasible. In the salvage setting, there is a lack on randomised data

Table 7 FT of the ESMO-MCBS for the treatment of urothelial 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
Cisplatin + gemcitabine versus MVAC von der Maase *et al*, JCO[45] von der Maase *et al* , JCO[46] Roberts *et al*, Ann Oncol[47]	First-line advanced or metastatic disease	Non-inferiority	–	–	Non-significant	–	–	Non-significant	Less toxicity with new combination	–	4
Cisplatin + gemcitabine ± paclitaxel (EORTC 30987) Bellmunt *et al*, JCO[48]	First-line advanced or metastatic disease	OS	7.6 months	0.7 months	0.87 (0.74–1.03)	12.7 months	3.1 months	Non-significant	Increase in response rate	–	NA
High-dose intensified MVAC versus classic MVAC Sternberg *et al*, JCO[49] Sternberg *et al* , Eur J Cancer[50]	First-line advanced or metastatic disease	OS		–		14.9 months	0.2 months	0.76 (0.58–0.99)	Score based on 3 year OS (+>5%)	–	3
Vinflunine versus best supportive care Bellmunt *et al* , JCO[51] Bellmunt *et al*, Ann Oncol[52]	Second-line treatment after platin-based treatment	OS				4.6 months	2.3 months	Non-significant		–	NA

EP, endpoint; ESMO, European Society for Medical Oncology; FT, field testing; MCBS, Magnitude of Clinical Benefit Score; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; OS, overall survival; PFS, progression-free survival.

and particularly data on checkpoint inhibitors need to be awaited.

Soft tissue sarcoma

Data of locally advanced/metastatic STS were subdivided into common treatment strategies for GIST and STS, respectively (see table 8).[53–63]

GIST: While imatinib remains the undisputable standard of care for untreated advanced/metastatic GIST with corresponding trials in the past having concentrated mainly on different dosing strategies,[64–66] there are important placebo-controlled data on sunitinib for second line and regorafenib for third line.[53 54] Both trials resulted in an ESMO-MCBS score of 3 supporting the use of these compounds in the respective setting.

STS: We have identified two trials assessing the addition of ifosfamide to doxorubicin for first-line advanced/metastatic STS. Both trials did not meet their predefined primary endpoints. Consequently, the ESMO-MCBS scoring system was not applicable und results do not support treatment intensification in this scenario in general.[55 56] However, if a response is needed, this combination is of value in selected histologies. Liposomal formulation of doxorubicin might reduce toxicity in selected patients (MCBS-FT 1–3).[57] Finally, recently promising data on addition of anti-PDGFRα antibody olaratumab to doxorubicin have been published.[58] Olaratumab/doxorubicin resulted in a significant improvement of secondary endpoint OS (+11.8 months; HR 0.46, 95% CI 0.30 to 0.71) and the corresponding MCBS-FT score of 4 reflects clearly the high clinical benefit to be expected of this combination.

In the setting of relapsed STS data of the PALETTE trial showed evidence for a benefit of pazopanib with a median PFS plus of 3.0 months (HR 0.31, 95% CI 0.24 to 0.40) (MCBS-FT score 3).[59] The combination of gemcitabine/dacarbazine versus gemcitabine monotherapy reached a high level of recommendation by means of the ESMO-MCBS due to a 8.6 months increase in median survival (HR 0.56; 95% CI 0.36 to 0.9) (MCBS-FT score 4).[60]

Trabectedin for salvage treatment in STS has been approved in Europe and the USA based on trials with a low maximum clinical benefit score of 2 (MCBS-FT).[61 62] The earlier trial compared trabectedin 3-weekly versus weekly and underlined activity of this compound in STS; however, the clinical benefit assessed by ESMO-MCBS appeared marginal (MCBS-FT score 2).[61] A subsequent randomised trial versus dacarbazine was powered for OS but did only improve PFS and was thus a negative trial per endpoint (ESMO-MCBS not applicable).[62] In 2016, first data on eribulin (versus dacarbazine) were published and followed with great interest. OS was 13.5 months in median versus 11.5 months (HR 0.77, 95% CI 0.62 to 0.95) (MCBS-FT score 2).[63] Remarkably, in a planned subgroup analysis for liposarcoma median OS was 8.4 months in the standard group versus 15.6 months in the experimental arm (OS gain 7.2 months; HR 0.51, 95% CI 0.35 to 0.75) supporting the use of eribulin in this subgroup (MCBS-FT score 4).

Conclusion: In GIST, clinical benefit as assessed by the ESMO-MCBS displays well the real-life situation. Clinical practicability of the MCBS in 'non-GIST' STS is very limited. The tumour entity 'soft tissue sarcoma' encompasses more than 50 different histologies that does not allow the application of the MCBS in this heterogeneous disease. In addition, the example of trabectedin shows that in some situations a certain control arm as 3-weekly versus weekly application might make sense in the clinical setting but undermines the result if evaluated with the ESMO-MCBS.[61] Equally, in the second study on trabectedin, ESMO-MCBS was not applicable as the study failed to meet its primary endpoint due to a PFS but not OS surplus (primary endpoint OS).[62] However, in 'real life' prolonged and sustained disease stabilisation is of definitive benefit for the individual patient.

DISCUSSION

In the past few months, we have been evaluating the feasibility and applicability of the ESMO-MCBS in the daily routine of the Clinical Division of Oncology at the MUV, a tertiary referral centre for medical oncological care. In our pilot analysis on common tumour subtypes, we have demonstrated that the ESMO-MCBS scores are consistent with our practice in the majority of malignancies and treatment settings and are particularly confirming our first-line standards for frequent tumour entities including metastatic breast cancer, colorectal cancer or lung cancer.[5] However, there were certain limitations detected including salvage treatment situations with a lack of randomised data and therapeutic decisions being mostly based on single arm phase II trials or tumour entities involving cascade like treatment settings.

In the current analysis, we report data on infrequent tumour entities. While in the early stage of development of the ESMO-MCBS by the taskforce only a careful selection of studies for a proof of principle analysis has been aimed at, we have now also included entities with basically no prior experience of usability of the ESMO-MCBS such as NET, thyroid cancer, glioblastoma, urothelial cancer, STS, and head and neck cancer.

In line with our recent experience in common tumour entities, most scores assessed by our field testing corresponded with the daily clinical practice at our institution and supported both the use of the ESMO-MCBS and our current treatment standards. Interestingly, less frequent tumour entities generally scored lower than entities analysed before, but the clinical benefit appeared to be depicted adequately whenever data from randomised studies were available. In NETs, for example, all current trials resulted in a MCBS-FT score of 2 or 3 reflecting the moderate PFS benefit aligned with a favourable toxicity profile quintessential for the treatment of this specific disease.[8–15] However, a maximum score of 3 is clearly inferior to results achieved for metastatic breast or colorectal

Table 8 FT of the ESMO-MCBS for the treatment of GIST and soft tissue sarcomas 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
Sunitinib versus placebo* Demetri *et al*[53]	Second-line advanced GIST after imatinib	TTP	6.4 weeks	16.9 weeks	0.33 (0.23–0.47)					**3**	–
Regorafenib versus Placebo (GRID)* Demetri *et al*[54]	third-line advanced GIST after imatinib and sunitinib	PFS	0.9 months	3.7 months	0.27 (0.19–0.39)					**3**	–
Doxorubicin ± ifosfamide (EORTC 62012) Judson *et al*[55]	Previously untreated soft tissue sarcoma	OS				13 months	1.5 months	Non-significant	Results do no support intensified treatment	–	**NA**
High-dose doxorubicin + ifosfamide versus doxorubicin Maurel *et al*[56]	Previously untreated soft tissue sarcoma	PFS	26 weeks		Non-significant				Results do no support intensified treatment	–	**NA**
Pegylated liposomal doxorubicin versus doxorubicin Judson *et al*[57]	Naïve or pretreated advanced soft tissue sarcoma	RR	9%	1%					Less toxicity, upgrade 1–2 points	–	**1–3**
Doxorubicin +/- olaratumab Tap *et al*[58]	Previously untreated soft tissue sarcoma	PFS	4.1 months	2.5 months	0.67 (0.44–1.02)	14.7 months	11.8 months	0.46 (0.30–0.71)	Improvement in survival -> form 2a	–	**4**
Pazopanib versus placebo (PALETTE)* van der Graaf *et al*[59]	Previously treated soft tissue sarcoma	PFS	1.6 months	3.0 months	0.31 (0.24–0.4)					**3**	–
Gemcitabine + dacarbazine versus gemcitabine García-Del-Muro *et al*[60]	Previously treated soft tissue sarcoma	PFS 3 months	2 months	2.2 months	0.58 (0.39–0.86)	8.2 months	8.6 months	0.56 (0.36–0.9)	Improvement in survival -> form 2a	–	**4**
Trabectedin q21 versus trabectedin q28 d1+8+15 Demetri *et al*[61]	Previously treated liposarcoma, leiomyosarcoma	TTP	2.3 months	1.4 months	0.73 (0.55–0.97)				Data support use of trabectedin	–	**2**
Trabectedin versus dacarbazine Demetri *et al*[62]	Previously treated liposarcoma, leiomyosarcoma	OS	1.5 months	2.7 months	0.55 (0.44–0.70)	12.4 months	0.5 months	Non-significant	PFS as second endpoint improved	–	**NA**
Eribulin versus dacarbazine Schöffski *et al* [63]	Previously treated liposarcoma, leiomyosarcoma	OS	–	–	–	11.5 months	2 months	0.77 (0.62–0.95)		–	**2**

*Aadapted according to Cherny *et al.*[1]
†Unclear toxicity data.
EP, endpoint; ESMO, European Society for Medical Oncology; FT, field testing; GIST, gastrointestinal stromal tumours; MCBS, Magnitude of Clinical Benefit Score; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

cancer.[5] This fact might possibly be related to the inferior power of trials in infrequent diseases. In addition, we could identify several trials relevant to our practice that added new data to the field but per definition did not meet their statistical endpoint. As outlined in the primary publication by the ESMO taskforce, those trials are not assessable by the ESMO-MCBS even if they result in potentially clinical relevant prolongation of PFS/OS (eg, trabectedin for STS).[62]

As of 2017 and in view with the increasing experience and knowledge on immunomodulatory treatment strategies, it appears of pre-eminent public interest to assess the applicability of the ESMO-MBCS on those particular compounds. It was thus encouraging to observe that checkpoint inhibitors seem to do extremely well in the ESMO-MCBS scoring system. In the current analysis, we have assessed new data on nivolumab for second-line head and neck cancer. Results were convincing with a MCBS-FT score of 4 (higher than the first-line data with a MCBS-FT of 3) based on an increase in PFS and superior QOL during therapy.[27 29] It appears that checkpoint inhibitors fully underline the concept of the ESMO-MCBS due to the fact that they are usually characterised by positive efficacy data paired with reduction in toxicities and consequently an improvement in QOL. Similar results were also obtained in our analysis for common entities exemplified by PD-1 inhibition in non-small cell lung cancer and renal cell cancer providing a stringent concept for the use of the ESMO-MCBS in the era of immunomodulatory treatment.[5]

The limitations of the ESMO-MCBS were clinical settings where a cascade-like treatment algorithm is standard of care. While the ESMO-MCBS in its current version allows assessment of multiple studies in form of meta-analyses, it is not possible to interconnect or combine the results of two or more distinct trials. Thus, due to a lack of proper data, the ESMO-MCBS does not support treatment decisions in these specific scenarios. While this was already obvious in our pilot trial on frequent entities including renal cell and colorectal cancers, we have observed the same phenomenon now for NET and thyroid cancer.[5 8–19] Notably, the ESMO taskforce plans to re-evaluate the ESMO-MCBS on a regular basis and this caveat is already part of current considerations underlining the importance of the ESMO-MCBS representing a dynamic tool.

In addition, the results of the ESMO-MCBS appear less useful in situations where former disease 'entities' are becoming subdivided into subsets in which certain therapies are efficacious, whereas they are not in others with STS being an excellent example. Here, the ESMO-MCBS will have to await further clarification regarding disease subsets versus treatment options. Finally, in such scenarios in which trials of most efficacious treatments are missing (eg, in the first-line treatment of pancreatic cancer), the magnitude of clinical benefit has to remain open until further trials will be performed.

To conclude, the ESMO-MCBS appears to be unique due to the fact that it is based on the *clinical* benefit to be expected for the *individual* patient. While we cannot provide a 100% complete work-up of all oncological treatment options, our data represent clearly a consistent real-life experience in a university hospital setting. Our results encourage the use of the ESMO-MCBS in clinical routine—irrespective of the specific work environment—as it is easy to use and helps to interpret and categorise original data with a focus on an individual patient's needs. In addition, ESMO plans to include ESMO-MCBS scores in all new clinical practice guidelines and assess scores of European Medicines Agency approvals. It will be interesting to learn about further amendments of the scoring systems, as by now major efforts are being made in this direction acknowledging and addressing potential caveats and points of discussions in the use of the ESMO-MCBS V1.0. The ESMO-MCBS V1.1 is currently being field tested by the taskforce and first results will be available in 2017.

Contributors All authors fulfill the criteria for authorship and have read and approved the final version of the manuscript.

Competing interests GWP has received honoraria for lectures by Merck Serono, Amgen, Bayer, Servier, Lilly, Celgene, Roche and Sanofi Aventis; TF has received honoraria or research grants from MSD, Merck, BMS, Pfizer, Sandoz and Astra Zeneca; MP has received research support from Boehringer-Ingelheim, GlaxoSmithKline, Merck Sharp & Dome and Roche and honoraria for lectures, consultation or advisory board participation from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche and Astra Zeneca; GJL has received research support from Pierre Fabre and honoraria for lectures, consultation or advisory board participation from Bristol-Myers Squibb and Roche; TB has received personal fees from Amgen (lecture fee and advisory board), personal fees from Bayer (lecture fee and advisory board), personal fees from Eisai (lecture fee and advisory board), personal fees from Eli Lilly (lecture fee and advisory board), personal fees from Novartis (lecture fee and advisory board), personal fees from PharmaMar (lecture fee) and personal fees from Roche (lecture fee) outside the submitted work. CCZ has received honoraria by Bristol Myers-Squibb, Merck Sharp Dohme, Novartis, Roche, Astra Zeneca, Ariad and Imugene. All remaining authors have declared no conflict of interest.

Provenance and peer review Not commissioned; externally peer reviewed.

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