Annals of Oncology 26: 1547–1573, 2015
doi:10.1093/annonc/mdv249
Published online 30 May 2015

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

[1]Cancer Pain and Palliative Medicine Service, Department of Medical Oncology, Shaare Zedek Medical Center, Jerusalem, Israel; [2]Kings Health Partners Integrated Cancer Centre, King's College London, Institute of Cancer Policy, London, UK; [3]University of Athens and Frontiers of Science Foundation-Hellas, Athens, Greece; [4]Department of Medical Oncology, Antoni van Leeuwenhoek Hospital; [5]Department of Medical Oncology, IRCCS San Martino IST, Genova, Italy; [6]Division of Oncology, Medical University Vienna, Vienna, Austria; [7]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [8]Jules Bordet Institute, UniversitéLibre de Bruxelles, Brussels, Belgium; [9]Netherlands Cancer Institute, Amsterdam, The Netherlands

Received 22 May 2015; accepted 22 May 2015

The value of any new therapeutic strategy or treatment is determined by the magnitude of its clinical benefit balanced against its cost. Evidence for clinical benefit from new treatment options is derived from clinical research, in particular phase III randomised trials, which generate unbiased data regarding the efficacy, benefit and safety of new therapeutic approaches. To date, there is no standard tool for grading the magnitude of clinical benefit of cancer therapies, which may range from trivial (median progression-free survival advantage of only a few weeks) to substantial (improved long-term survival). Indeed, in the absence of a standardised approach for grading the magnitude of clinical benefit, conclusions and recommendations derived from studies are often hotly disputed and very modest incremental advances have often been presented, discussed and promoted as major advances or 'breakthroughs'. Recognising the importance of presenting clear and unbiased statements regarding the magnitude of the clinical benefit from new therapeutic approaches derived from high-quality clinical trials, the European Society for Medical Oncology (ESMO) has developed a validated and reproducible tool to assess the magnitude of clinical benefit for cancer medicines, the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). This tool uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment. The ESMO-MCBS is an important first step to the critical public policy issue of value in cancer care, helping to frame the appropriate use of limited public and personal resources to deliver cost-effective and affordable cancer care. The ESMO-MCBS will be a dynamic tool and its criteria will be revised on a regular basis.

Key words: ESMO, clinical benefit, tool

introduction

The value of any new therapeutic strategy or treatment is determined by the magnitude of its clinical benefit balanced against its cost [1]. Value considerations have become increasingly important in an era of rapid expansion of new, expensive cancer medicines and other technologies such as advanced radiotherapy techniques or robotic surgery which provide small incremental benefits [2–5] within the context of cost-constrained health care systems [6]. This is especially true in Europe where the costs of care delivery [6] and cancer outcomes [7–9] vary substantially across Europe with the latter being influenced by the level of economic development [9, 10]. In some instances, discrepant outcomes between countries in Europe can be attributed to inordinate delays, sometimes of years, in making highly effective treatments available at an affordable cost to the patient [11, 12].

Whereas costs of procurement and out of pocket expenditures vary from country to country, the magnitude of clinical benefit, as derived from well-designed clinical trials, is a relative constant. Consequently, meaningful discussion of value and relative

*Correspondence to: Prof. Nathan I. Cherny, Cancer Pain and Palliative Medicine Service, Department of Medical Oncology, Shaare Zedek Medical Center, Jerusalem 91031, Israel. Tel: +972-68-685780; E-mail: mcbs@esmo.org

value are predicated on an understanding of the magnitude of clinical benefit [1]. Clinical benefit in this context refers to the added benefit compared with a control which, in most cases, is the best current standard care.

Evidence for clinical benefit from new treatment approaches is derived from comparative outcome studies, most commonly phase III randomised clinical trials, which generate ostensibly unbiased data regarding the efficacy, benefit and safety of new therapeutic approaches. The potential benefits of a new treatment can be summarised as either living longer and/or living better, evaluated in clinical studies through the treatment effect on overall survival (OS) and/or quality of life (QoL), and their surrogates (Table 1). In studies of interventions with curative intent in which mature survival data are not yet available disease-free survival (DFS), recurrence-free survival (RFS), event-free survival (EFS), distant disease-free survival and time to recurrence (TTR), are used as surrogate measures. The validity of this approach, though not uncontroversial [13], is relatively well supported by data derived from a wide range of solid tumour settings including in colon [14], gastric [15], lung [16] and breast [17] cancers. In studies evaluating therapies in non-curative settings, progression-free survival (PFS), and time to progression (TTP) provide information about biological activity and may indicate benefit for some patients [18, 19]; however, they are not reliable surrogates for improved survival [18, 20–23] or QoL [23, 24].

To date, there is no standard tool for grading the magnitude of clinical benefit of cancer therapies [25, 26], which may range from trivial (median PFS advantage of only a few weeks) to substantial (improved long-term survival). Indeed, in the absence of a standardised approach for grading, the magnitude of clinical benefit, conclusions and recommendations derived from studies are often hotly disputed [25] and very modest incremental advances have often been presented, discussed and promoted as major advances or 'breakthroughs' [5, 25–29]. Overestimating or overstating the benefits from new intervention can cause harm: it confounds public policy decision making [29], undermines the credibility of oncology research reporting [26, 29, 30], harms patients who choose to undertake treatments based on exaggerated expectations that may subject them to either risk of adverse effects, inconvenience or substantial personal costs [26, 28] and, in the public domain, they fuel sometimes inappropriate hype or disproportionate expectations about novel treatments [31, 32] and the need to allocate public or personal funds to provide them.

It is important for the Oncology Community to present clear and unbiased statements regarding the magnitude of clinical benefit from new therapeutic approaches supported by credible research. ESMO aims to emphasize those treatments which bring substantial improvements to the duration of survival and/or the QoL of cancer patients which need to be distinguished from those whose benefits are more modest, limited or even marginal. To this end, ESMO has undertaken the development of a validated and reproducible tool to assess the magnitude of clinical benefit of anti-cancer interventions, the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). ESMO intends to apply this scale prospectively to each new anti-cancer drug/intervention that will be European Medicines Agency (EMA) approved. Drugs or treatment interventions that obtain the highest scores on the scale will be emphasized in the ESMO guidelines, with the hope that they will be rapidly endorsed by health authorities across the European Union.

Table 1. Potential benefits of a new treatment

Living longer
Improved OS
Improved surrogate of OS
DFS (when OS data are immature in adjuvant setting)
Improved PFS
Living better
Improved quality of life
Improved surrogate of quality of life
Improved PFS
Reduced toxicity

background and methodology

An ESMO Task Force to guide the development of the grading scale was established in March 2013. The members of the Task Force co-chaired by Elisabeth de Vries and Martine Piccart are Richard Sullivan, Nathan Cherny, Urania Dafni, Martijn Kerst, Alberto Sobrero and Christoph Zielinski. A first-generation draft scale was developed and adapted through a 'snowball' method based upon previous work of Task Force members who had independently developed preliminary models of clinical benefit grading. The first-generation scale was sent for review by 276 members of the ESMO faculty and a team of 51 expert biostatisticians.

The second-generation draft was formulated based on the feedback from faculty and biostatisticians and the conceptual work of Alberto Sobrero regarding the integration of both hazard ratio (HR), prognosis and absolute differences in data interpretation [33, 34]. The second-generation draft was applied in a wide range of contemporary and historical disease settings by members of the ESMO-MCBS Task Force, the ESMO Guidelines Committee and a range of invited experts. Results were scrutinised for face validity, coherence and consistency. Where deficiencies were observed or reported, targeted modifications were implemented and the process of field testing and review was repeated. This process was repeated through 13 redrafts of the scale preceding the current one (ESMO-MCBS v1.0). The final version and fielded testing results were reviewed by selected members of the ESMO faculty and the ESMO Executive Board.

The goal of the ESMO-MCBS evaluation was to assign the highest grade to trials having adequate power for a relevant magnitude of benefit, and to make appropriate grade adjustment to reflect the observed magnitude of benefit. To achieve this goal, a dual rule was implemented; first, taking into account the variability of the estimated HR from a study, the lower limit of the 95% confidence interval (CI) for the HR is compared with specified threshold values; and secondly the observed absolute difference in treatment outcomes is compared with the minimum absolute gain considered as beneficial. Different candidate threshold values for HR and absolute gains for survival, DFS and PFS, adjusted to represent as accurately as possible the expert opinion of the oncology community, have been explored through extensive simulations. The finally implemented combined thresholds for the HR

Table 2. Maximal preliminary scores

Treatments with curative intent (form 1)
>5% improvement of survival at ≥3-year follow-up
Improvements in DFS alone HR <0.60 (primary end point) in studies without mature survival data
Treatments with non-curative intent (form 2)
Primary outcome OS (form 2a)
Control ≤12 months
HR ≤0.65 *AND* gain ≥3 months *OR*
Increase *in* 2-year survival alone ≥10%
Control >12 months
HR ≤0.70 *AND* gain ≥5 months *OR*
Increase *in* 3-year survival alone ≥10%
Primary outcome PFS (form 2b)
Control ≤6 months
HR ≤0.65 *AND* gain ≥1.5 months
Control >6 months
HR ≤0.65 *AND* gain ≥3 months

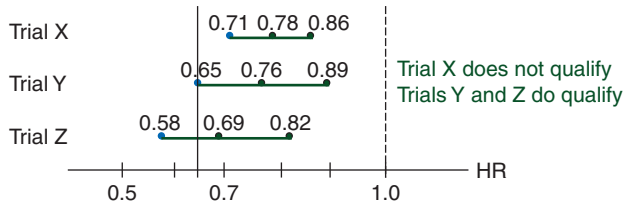

Figure 1. Use of threshold HR in the ESMO-MCBS exemplified for HR threshold of 0.65.

and the minimum observed benefit that could be considered as deserving the highest grade in both the curative and non-curative setting are outlined in Table 2.

In all forms, HR thresholds refer to the lower extreme of the 95% CI (Figure 1). The performance of the evaluation rule based on the lower limit of the 95% CI of HR, was compared with the simpler rule of using a cut-off for the point estimate of HR, in conjunction with the additional rule on the minimum absolute gain in treatment outcome. The simulation results under different HR values and corresponding power, favoured the proposed approach to use the lower limit of the 95% CI which takes into account the variability of the estimate. The correspondence between an HR value and the minimum absolute gain considered as beneficial according to the ESMO-MCBS, is presented by median survival (OS or PFS) for standard treatment, in Figure 2. For example, for a standard treatment median survival of 6 months, an absolute gain of 3 months corresponds to an HR = 0.67, while a gain of 1.5 months corresponds to an HR = 0.8.

the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS v1.0)

The ESMO Magnitude of Clinical Benefit Scale version 1 (ESMO-MCBS v1.0) (Appendix 1) has been developed only for solid cancers. Given the profound differences between the curative and palliative settings, the tool is presented in two parts. Form 1 is used to evaluate adjuvant and other treatments with curative intent. Form 2 (a, b or c) is used to evaluate non-

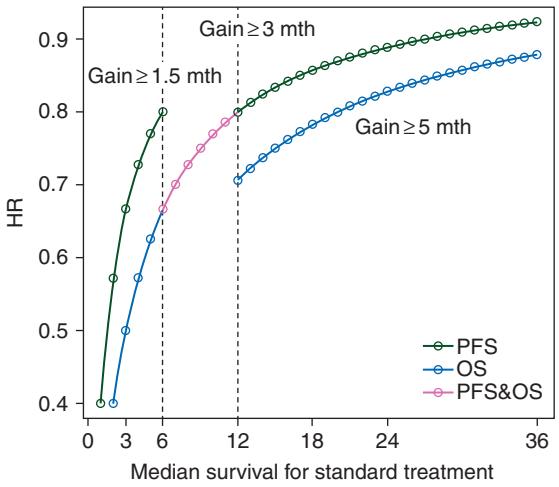

Figure 2. The correspondence between an HR value and the minimum absolute gain in months considered as beneficial according to the ESMO-MCBS by median survival (OS or PFS) for control.

curative interventions, with form 2a for studies with OS as the primary outcome, form 2b for studies with PFS or TTP as primary outcomes, 2c for studies with QoL, toxicity or response rate (RR) as primary outcomes and for non-inferiority studies. Form 2a is prognostically sub-stratified for studies where the control arm produced OS greater or less than or equal to 1 year and form 2b for studies where the control arm produced PFS greater or less than or equal to 6 months.

eligibility for application of the ESMO-MCBS

The ESMO-MCBS can be applied to comparative outcome studies evaluating the relative benefit of treatments using outcomes of survival, QoL, surrogate outcomes for survival or QoL (DFI, EFS, TTR, PFS and TTP) or treatment toxicity in solid cancers. Eligible studies can have either a randomised or comparative cohort design [35, 36] or a meta-analysis which report statistically significant benefit from any one, or more of the evaluated outcomes. When more than one study has evaluated a single clinical question, results derived from well-powered registration trials should be given priority.

Studies with pre-planned subgroup analyses with a maximum of three subgroups can be scored. When statistically significant results are reported for more than one subgroup, then each of these should be evaluated separately. Subgroups not showing statistically significant results are not graded. Except for studies that incorporate collection of tissue samples to enable re-stratification based on new genetic or other biomarkers, findings from un-planned (*post hoc*) subgroup analysis cannot be graded and they can only be used as foundation for hypothesis generation.

form 1

This form is used for adjuvant and neoadjuvant therapies and for localised or metastatic diseases being treated with curative intent. This scale is graded A, B or C. Grades A and B represent a high level of clinical benefit (Figure 3). The scale makes allowance for early data demonstrating high DFS without mature survival data. Studies initially evaluated based on DFS criteria

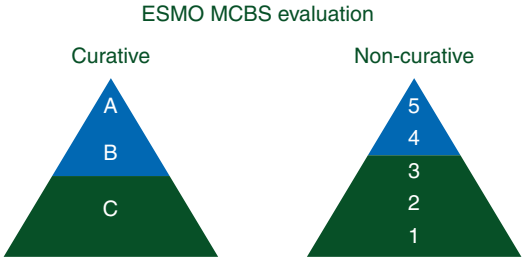

Figure 3. Visualisation of ESMO-MCB scores for curative and non-curative setting. A & B and 5 and 4 represent the grades with substantial improvement.

alone will need to be revaluated when mature survival data is available. Hyper-mature data from studies that were un-blinded after compelling early results with subsequent access to the superior arm are contaminated, subsequently late intention-to-treat (ITT) follow-up data are not evaluable [37, 38]. Pathological complete remission from neoadjuvant therapies is not included as a criteria for clinical benefit because of lack of consistent evidence that it is a valid surrogate for survival in clinical studies [39–42].

forms 2

These forms are used for studies of new agents or approaches in the management of cancers without curative intent. This scale is graded 5, 4, 3, 2, 1, where grades 5 and 4 represent a high level of proven clinical benefit (Figure 3).

form 2a. This version is used for therapies evaluated using a primary outcome of OS. The form is stratified by median OS of the control arm ≤12 and >12 months. Preliminary grading takes into consideration HR and median survival gain as well as late survival advantage and is reported on a 4-point scale. When there is differential grading between the median and late survival gain, the higher score prevails. Preliminary scores can be upgraded by 1 point when the experimental arm demonstrates improved QoL or delayed deterioration in QoL using a validated scale or substantial reduction in grade 3 or 4 toxicity. A score of 5 can only be achieved when optimal survival outcomes are further enhanced by data indicating reduced toxicity or improved QoL.

form 2b. This version is used for therapies evaluated using a primary end point of PFS or TTP. The form is stratified by median duration of PFS of the control arm ≤6 and >6 months. The maximal preliminary score is discounted to 3 because PFS and TTP are surrogate outcomes with a less reliable relationship to improved survival or QoL [18, 20–23]. In studies that allow crossover on subsequent therapy, this may be the best available evidence of activity since subsequent therapies may reduce the likelihood of observing survival benefit.

Preliminary scores derived from PFS studies can be upgraded or downgraded depending on secondary outcomes such as toxicity data, improvement in OS or data derived from QoL evaluation. This form incorporates an adverse effect criterion for down-grading in cases of severe toxicity compared with the control arm. If an OS advantage is observed as a secondary outcome, scores are upgraded using the scale on form 2a. In PFS studies that evaluate global QoL, positive findings (as evidenced by statistically significant improvement in global QoL or delayed deterioration in QoL) will upgrade the evaluation by 1 point and, in the absence of survival advantage, the absence of QoL advantage will result in a down-grading by 1 point.

form 2c. This form is used for therapies evaluated in non-inferiority (equivalence) studies and for studies in which the primary outcomes are QoL, toxicity or RR.

field testing of ESMO-MCBS

ESMO-MCBS has been applied in a wide range of solid tumours by members of the ESMO-MCBS Task Force, the ESMO Guidelines Committee and a range of invited experts (Tables 3–12).

When discrepancies between graders were observed, this was generally related to either inaccurate data extraction, variable interpretation of the significance and severity of toxicity data, or errors in applying the data to the correct grading criteria.

discussion

inherent challenges in developing standard Clinical Benefit Scale

The substantial variability of study designs (crossover, non-crossover and partial crossover), planned outcomes and reported outcomes inherently challenge the process of developing a unified scale of clinical benefit. This challenge is all the greater in an era in which both researchers and regulatory authorities are employing surrogate outcome indicators as primary end points for both research and registration criteria [5]. A unified scaling approach requires a process of relative weighting of evidence that demands conceptual rigor, careful reviews of the validity and strength of surrogate end points and clinical nuance.

validity of the ESMO-MCBS

The ESMO-MCBS version 1 (ESMO-MCBS v1.0) provides an objective and reproducible approach that allows comparisons of the magnitude of benefit between studies that incorporate different primary outcomes (OS, PFS, QoL) and different designs through a process of variable weighting of primary outcomes and adjustments for significant secondary outcomes and toxicity.

The development process has been compliant with the criteria for 'accountability for reasonableness' which represent the ethical gold-standard for a fair priority setting process in public policy [134, 135]. The validity of the ESMO-MCBS is derived from (i) clinically relevant and reasonable criteria for prioritisation of different types of benefit, i.e. that cure takes precedence over deferral of death, direct end points such as survival and QoL take precedence over less reliable surrogates such as PFS or RR and that the interpretation of the evidence for benefit derived from indirect primary outcomes (such as PFS or RR) may be influenced by secondary outcome data, (ii) coherence: procedural agreements regarding the evidence to be used/not

Table 3. Field testing ESMO-MCBS v1.0: lung cancer

Lung cancer													
Medication (new versus control)	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESM0-MCBS	Ref.
Erlotinib versus carboplatin gemcitabine	OPTIMAL, CTONG-0802	First-line stage IIIb or IV non-squamous, with EGFR mutation	PFS	4.6 months	8.5 months	0.16 (0.10–0.26)					12% less serious adverse events	4	[43]
Erlotinib versus platinum-based chemotherapy doublet	EURTAC	First-line stage IIIb or IV non-squamous, with EGFR mutation	PFS (crossover allowed)	5.2 months	4.5 months	0.37 (0.25–0.54)	19.5 months		NS		15% less severe adverse reactions	4	[44]
Gefitinib versus carboplatin + paclitaxel	IPASS	First-line stage IIIb or IV adenocarcinoma, with EGFR mutation	PFS (crossover allowed)	6.3 months	3.3 months	0.48 (0.34–0.67)				Improved	Reduced toxicity	4	[45, 46]
Afatinib versus Cisplatin + pemetrexed	LUX—Lung 3	First-line stage IIIb or IV adenocarcinoma with EGFR mutation (Del19/ L858R)	PFS (crossover allowed)	6.9 months	4.2 months	0.58 (0.43–0.78)				Improved		4	[47, 48]
				6.9 months	6.7 months	0.47 (0.34–0.65)				Improved			
Crizotinib versus chemotherapy		First-line stage IIIb or IV non-squamous, with ALK mutation	PFS (crossover allowed)	3.0 months	4.7 months	0.49 (0.37–0.64)				Improved	1% increased toxic death	4	[49]
Crizotinib versus cisplatin + pemetrexed		First-line stage IIIb or IV non-squamous, with ALK mutation	PFS	7.0 months	3.9 months	0.45 (0.35–0.60)				Improved		4	[50]
Pemetrexed versus placebo		Stage IIIb or IV disease maintenance after responding to four cycles platinum doublet	PFS stratified for histology (non-squamous)	2.6 months	1.9 months	0.47 (0.37–0.60)	10.3 months	5.2 months	0.70 (0.56–0.88)			4	[51]
Cisplatin pemetrexed versus cisplatin gemcitabine		First-line stage IIIb or IV (non-squamous)	OS (non-inferiority)				10.4 months	1.4 months	0.81 (0.70–0.94)		Less grade 3 + toxicity neutropenia anaemia thrombocytopenia	4	[52]
Chemotherapy ± palliative care		Stage IV non-small-cell ECOG <2	QoL				8.9 months	2.7 months	HR for death in control arm 1.7 (1.14–2.54)	Improved		4	[53]
Paclitaxel/ carboplatin ± bevacizumab		First-line stage IIIb or IV, non-squamous	OS				10.3 months	2.0 months	0.79 (0.67–0.92)			2	[54]
Erlotinib versus placebo	SATURN	Stage IIIb or IV disease maintenance after responding to four to six cycles platinum doublet	PFS	11.1 weeks	1.2 weeks	0.71 (0.62–0.82)	11.0 months	1.0 months	0.81 (0.70–0.95)			1	[55]

Table 4. Field testing ESMO-MCBS v1.0: breast cancer

Breast cancer												
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESM0-MCBS	Ref.
Chemotherapy ± trastuzumab	HERA	(Neo)adjuvant HER-2-positive tumours	DFS	2-year DFS 77.4%	8.40%	0.54 (0.43–0.67)						A	[56]
T-DM1 versus lapatinib + capecitabine	EMILIA	Second-line metastatic after trastuzumab failure	PFS and OS	6.4 months	3.2 months	0.65 (0.55–0.77)	25 months	6.8 months	0.68 (0.55–0.85)	Delayed deterioration		5	[57, 58]
Trastuzumab + chemotherapy ± pertuzumab	CLEOPATRA	First-line metastatic	PFS	12.4 months	6 months	0.62 (0.52–0.84)	40.8 months	15.7 months	0.68 (0.56–0.84)	No improvement		4	[59–62]
Lapatinib ± trastuzumab	EGF104900	Third-line metastatic	PFS	2 months	1 months	0.73 (0.57–0.93)	9.5 months	4.5 months	0.74 (0.57–0.97)			4	[63, 64]
Capecitabine ± lapatinib		Second-line metastatic after trastuzumab failure	PFS	4.4 months	4 months	0.49 (0.34–0.71)			NS			3	[65]
Eribulin versus other chemotherapy	EMBRACE	Third-line metastatic after anthracycline and taxane	OS				10.6 months	2.5 months	0.81 (0.66–0.99)			2	[66]
Paclitaxel ± bevacizumab		First-line metastatic	PFS	5.9 months	5.8 months	0.60 (0.51–0.70)			NS	No improvement		2	[24]
Exemestane ± everolimus	BOLERO-2	Metastatic after failure of aromatase inhibitor (with PFS >6 months)	PFS	4.1 months	6.5 months	0.43 (0.35–0.54)			NS	No improvement		2	[67]

Table 5. Field testing ESMO-MCBS v1.0: prostate cancer

Prostate cancer												
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESM0-MCBS	Ref.
Best standard non-chemotherapy or radiotherapy treatment ± radium-223	ALSYMPCA	Castration refractory and bone pain	OS				11.3 months	3.6 months	0.70 (0.55–0.88)	Improved		5	[68]
Prednisone ± abiraterone		Castration refractory after docetaxel	OS				10.9 months	3.9 months	0.65 (0.54–0.77)			4	[69]
Enzalutamide versus placebo	AFFIRM	Castration refractory after docetaxel	OS				13.6 months	4.8 months	0.63 (0.53–0.75)	Improved		4	[70]
Enzalutamide versus placebo	PREVAIL	Castration refractory pre-docetaxel	PFS and OS	3.2 months	>12 months	0.19 (0.15–0.23)	30.2 months	2.2 months	0.71 (0.60–0.84)	Improved		3	[71]
Docetaxel(Q7 or Q21) prednisone versus mitoxantrone + prednisone		Castration refractory	OS				16.5 months	2.4 months (Q21) 0.9 months (Q7)	0.76 (0.62–0.94) 0.83 (0.70–0.99)	Improved Improved		3	[72]
Cabazitaxel + prednisone versus mitoxantrone + prednisone	TROPIC	Castration refractory after docetaxel	OS				12.7 months	2.4 months	0.70 (0.59–0.83)			2	[73]

Table 6. Field testing ESMO-MCBS v1.0: colorectal cancer

Colorectal cancer												
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL Toxicity	ESM0-MCBS	Ref.
FOLFOX4 ± panitumumab	PRIME	First-line metastatic (*post hoc* KRAS, NRAS BRAF WT)	PFS	7.9 months	2.3 months	0.72 (0.58–0.90)	20.2 months	5.8 months	0.78 (0.62–0.99)		4	[74]
Panitumumab + mFOLFOX6 versus bevacizumab + mFOLFOX6	PEAK	First-line metastatic (KRAS-WT)	PFS			NS	24.3 months	9.9 months	0.62 (0.44–0.89)		4[a]	[75]
FOLFIRI ± cetuximab	CRYSTAL	First-line metastatic stratified for KRAS-WT (*post hoc* KRAS, NRAS WT)	PFS	8.4 months	3.0 months	0.56 (0.41–0.76)	20.2 months	8.2 months	0.69 (0.54–0.88)		4	[76]
Cetuximab versus best supportive care		Refractory metastatic KRAS-WT	OS	1.9 months	1.8 months	0.4 (0.30–0.54)	4.8 months	4.7 months	0.55 (0.41–0.740		4	[77]
FOLFOX4 ± panitumumab	PRIME	First-line metastatic KRAS-WT	PFS	8 months	1.6 months	0.80 (0.66–0.97)	19.4 months	4.4 months	0.83 (0.70–0.98)		3	[78, 79]
FOLFIRI ± cetuximab	CRYSTAL	First-line metastatic stratified for KRAS-WT	PFS	8.4 months	1.5 months	0.70 (0.56–0.87)	20 months	3.5 months	0.80 (0.67–0.95)		3	[80, 81]
ILF ± bevacizumab		First-line metastatic	OS				15.6 months	4.7 months	0.66 (0.54–0.81)		3	[82]
FOLFIRI ± panitumumab		Second-line metastatic KRAS-WT	PFS	3.9 months	2 months	0.73 (0.59–0.90)					3	[83]
FOLFOX ± bevacizumab versus bevacizumab alone	E3200	Second-line metastatic after FOLFIRI	OS				10.8 months	2.1 months	0.75 (0.63–0.89)		2	[84]
Panitumumab, versus best supportive care		Third-line metastatic stratified for KRAS	PFS	7.3 weeks	5 weeks	0.45 (0.34–0.59)					2	[85]
FOLFIRI bevacizumab versus FOLFOXIRI bevacizumab		First-line metastatic	PFS	9.7 months	2.4 months	0.75 (0.62–0.90)			NS		2	[86]
TAS-102 versus placebo	CONCOURSE	Third-line or beyond metastatic	OS				5.3 months	1.8 months	0.68 (0.058–0.81)		2	[87]
Regorafenib versus placebo	CORRECT	Third-line metastatic	OS				5 months	1.4 months	077 (0.64–0.94)		1	[88]
Second-line chemotherapy ± bevacizumab	ML18147	Second line beyond progression on bevacizumab	OS				9.6 months	1.5 months	0.81 (0.69–0.94)		1	[89]
FOLFIRI ± aflibercept	VELOUR	Second line after oxaliplatin-based treatment	OS	4.7 months	2.2 months	0.76 (0.66–0.87)	12.1 months	1.5 months	0.82 (0.71–0.94)		1	[90]
FOLFIRI ± Ramucirumab	RAISE	Second-line metastatic after bevacizumab, oxaliplatin, fluoropyrimidine	OS				11.7 months	1.6 months	0.84 (0.73–0.97)		1	[91]

[a]Unbalanced crossover.

doi:10.1093/annonc/mdv249 | 1553

Table 7. Field testing ESMO-MCBS v1.0: ovarian cancer

Ovarian cancer												
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESMO-MCBS	Ref.
Paclitaxel or topotecanor liposomal doxorubicin ± bevacizumab	AURELIA	Recurrent platinum resistant	PFS (crossover allowed)	3.4 months	3.3 months	0.48 (0.38–0.60)				Improved		4	[92, 93]
Paclitaxel and carboplatin (five or six cycles) ± bevacizumab till 18 cycles or progression	ICON7	High-risk, early-stage post-resection or advanced ovarian or primary peritoneal	PFS stratified for stage and risk of progression	(All) 22.4 months (high risk) 14.5 months	1.7 months 3.6 months	0.81 (0.70–0.94) 0.73 (0.60–0.90)	28.8 months	7.8 months	NS 0.64 (0.48–0.85)			1 4	[94]
Gemcitabine and carboplatin ± bevacizumab	OCEANS	Recurrent platinum sensitive	PFS (crossover allowed)	8.4 months	4 months	0.48 (0.39–0.61)						3	[95]
Paclitaxel and carboplatin (6 cycles) ± bevacizumab continual till 10 months or progression	GOG 218	Incompletely resected stage III and stage IV	PFS (crossover allowed)	10.3 months	Bevacizumab continual 3.9 months	0.72 (0.63–0.82)			NS			3	[96]
Liposomal doxorubicin ± trabectedin	OVA-301	Second-line metastatic	PFS stratified for platinum sensitivity/ resistance	(sensitive) 7.5 months (resistant) 5.8 months	1.7 months 1.5 months	0.73 (0.56–0.95) 0.79 (0.65–0.96)						2	[97]
Olaparib versus placebo		BRCA ovarian cancer in remission	PFS	4.3 months	6.9 months	0.18 (0.10–0.31)			NS	Not improved		2	[98]

used, how it will be analysed and evaluated, and precautions to minimising bias (including conflict of interest issues) based upon an understanding of the relative strengths and weaknesses of the usual measured outcomes OS and QoL, and their surrogates [13–23, 136] and rigorous bio statistical review, (iii) wide applicability over a range of solid cancers and a range of prognoses that have been rigorously tested (iv) statistical validity and (v) a transparent process of development with scope for peer review, appeal and revision.

ESMO-MCBS scores for a specific therapy are not generalisable to indications outside the confines of the context in which they have been evaluated. Consequently, the ESMO-MCBS score for a particular medication or therapeutic approach may vary depending on the specifics of the indication and may vary between studies.

limitations of the ESMO-MCBS v1.0

The ESMO-MCBS can only be applied to comparative research outcomes; it is therefore not applicable when evidence of benefit derives from single-arm studies. This limits its utility in the uncommon situation in which registration is granted on the basis of outcomes reported from single-arm studies.

The process of relative weighting of evidence and the thresholds for HR and absolute gains involves judgements and subjective considerations which are amenable to dispute and challenge and indeed, this is invited as part of the dynamic process of peer review and further development.

factors that may skew or alter ESMO-MCBS scores

control arm evaluation. The ESMO-MCBS evaluates data derived from comparative research, either randomised phase II [137] or phase III studies or cohort studies. The validity of the results may be influenced by the quality and design of the study. Design issues are critical insofar as studies that incorporate a relatively weak control arm may generate the impression of exaggerated benefit. This was manifest in studies evaluating treatment options for hormone refractory prostate cancer where one study used mitoxantrone/prednisone as the control arm [73] based on the findings of a phase III study comparing prednisone versus the combination of prednisone and mitoxantrone which demonstrated improved QoL but no survival advantage for the combination therapy [138] and others used prednisone alone [69] or placebo [70].

crossover. Crossover, or subsequent treatment of control arm patients with biologically similar agent, severely compromises the ability to derive reliable data regarding the survival advantage of treatments in phase III studies. This factor may impact on OS results as illustrated by the study of dacarbazine versus ipilimumab in metastatic melanoma [126] in which the evidence for survival advantage was diluted by the crossover provision in the study. In some instances in which strong PFS advantage is seen, crossover of this type will obscure the potential survival benefit of the new treatment. Statistical approaches to estimate longer term clinical outcomes despite substantial treatment crossover have been developed [139, 140], and applied [141–144]. While these approaches are encouraging, they incorporate a range of assumptions and are not universally accepted [145].

Table 8. Field testing ESMO-MCBS v1.0: renal cell cancer

Renal cell cancer													
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESM0-MCBS	Ref.
Pazopanib versus sunitinib	COMPARZ	First-line metastatic RCC with clear-cell component	PFS non-inferiority	9.5 months		NS					Reduced	4	[99]
Temsirolimus versus interferon versus combined		First-line poor-prognosis metastatic RCC	OS				7.3 months	(TEM alone) 3.3 months	0.73 (0.58–0.92)			4	[100]
Sunitinib versus interferon		First-line metastatic	PFS crossover allowed	5 months	6 months	0.42 (0.32–0.054)	21.8 months	4.6 months	NS	Improved		4	[101, 102]
Axitinib versus sorafenib	AXIS	Previously treated metastatic RCC	PFS	4.7 months	2.0 months	0.66 (0.55–0.81)						3	[103]
Sorafenib versus placebo	TARGET	Second line locally advanced or metastatic	OS	2.8 months	2.7 months	0.44 (0.35–0.55)	15.9 months	3.4 months	0.77 (0.63–0.95)			3	[104]
Everolimus versus placebo	RECORD1	Second or third line after TKI metastatic RCC	PFS crossover allowed	1.9 months	2.1 months	0.30 (0.22–0.40)						3	[105]
Pazopanib versus placebo		Second line locally advanced or metastatic	PFS crossover allowed	4.2 months	5 months	0.46 (0.34–0.62)						3	[106]
Interferon ± bevacizumab	AVOREN	First-line metastatic RCC with clear cell	PFS	5.4 months	4.6 months	0.63 (0.52–0.75)						3	[107]
Interferon ± bevacizumab	CALGB 90206	First-line metastatic RCC with clear cell	OS amended to PFS	5.2 months	3.3 months	0.71 (0.66–0.83)						1	[108]

doi:10.1093/annonc/mdv249 | 1555

Table 9. Field testing ESMO-MCBS v1.0: Sarcoma

Sarcoma													
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESM0-MCBS	Ref.
Imatinib 1 year versus placebo	ACOSOG Z9001	Adjuvant for GIST	RFS stratified for risk	1-year RFS 83%	13%	0.35 (0.22–0.53)						A	[109]
3 versus 1 year imatinib	SSG XVIII	Adjuvant for high-risk GIST	5-year RFS	48%	18%	0.46 (0.32–0.65)						A	[110]
Sunitinib versus placebo		Advanced GIST second line after imatinib	TTP crossover allowed	6.4 weeks	16.9 weeks	0.33 (0.23–0.47)						3	[111]
Regorafenib versus placebo	GRID	Third line after imatinib and sunitinib	PFS crossover allowed	0.9 months	3.7 months	0.27 (0.19–0.39)						3	[112]
Pazopanib versus placebo	PALETTE	Previously treated non-GIST metastatic soft tissue sarcoma	PFS	1.6 months	3 months	0.31 (0.24–0.40)						3	[113]
Ridaforolimus versus placebo	SUCCEED	Sarcoma after response or stable disease with first-line treatment	PFS	14.6 weeks	3.1 weeks	0.72 (0.61–0.85)						1	[114]

Table 10. Field testing ESMO-MCBS v1.0: melanoma

Melanoma													
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESM0-MCBS	Ref.
Ipilimumab ± glycoprotein 100 vaccine versus vaccine alone		Previously treated metastatic	OS				6.4 months	3.7 months	0.69 (0.56–0.85)			4	[115]
Vemurafenib versus dacarbazine	BRIM-3	First line or second line after IL-2 metastatic with BRAF V600E mutation	PFS and OS	1.6 months	4.7 months	0.26 (0.20–0.33)	9.7 months	3.9 months	0.70 (0.57–0.87)			4	[116, 117]
Trametinib versus dacarbazine or paclitaxel	METRIC	Unresectable or metastatic with BRAF V600E mutation	PFS (crossover allowed)	1.5 months	3.3 months	0.45 (0.33–0.63)	6 months: 67%	14%		Improved		4[a]	[118, 119]
Dabrafenib ± trametinib		First line unresectable or metastatic with BRAF V600E mutation	Toxicity, PFS	5.8 months	3.6 months	0.30 (0.25–0.62)					12% reduction skin cancer	4	[120]
Dabrafenib versus dacarbazine		First line unresectable or metastatic with BRAF V600E mutation	PFS (crossover allowed)	2.7 months	2.1 months	0.30 (0.18–0.51)				Improved		4	[121, 122]
Dabrafenib + trametinib versus vemurafenib		First line unresectable or metastatic with BRAF V600E mutation	OS	7.3 months	4.1 months	0.69 (0.53–0.89)	1 year: 65%	7%	0.69 (0.53–0.89)		17% reduction skin cancer	4*	[123]
Vemurafenib ± cobimetinib		First line unresectable or metastatic with BRAF V600E mutation	PFS	6.2 months	3.7 months	0.51 (0.39–0.68)	9 months: 73%	8%			9% reduction skin cancer	4*	[124]
Dacarbazine ± nivolumab		First line unresectable or metastatic BRAF V600-WT	OS	2.2 months	2.9 months	0.43 (0.34–0.56)	10.8 months	6+ months	0.42 (0.25–0.73)			4*	[125]
Dacarbazine ± ipilimumab		First-line metastatic	OS (crossover allowed)				3-year survival 12.2% 9.1 months	8.60% 2.1 months	0.33 (0.24–0.53			3	[126, 127]

[a]Immature survival data.

doi:10.1093/annonc/mdv249 | 1557

Table 11. Field testing ESMO-MCBS v1.0: pancreatic cancer

Pancreatic cancer												
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESM0-MCBS	Ref.
FOLFIRINOX versus gemcitabine		First line advanced or metastatic, good PS	OS (crossover allowed)				6.8 months	4.4 months	0.57 (0.45–0.73)	Delayed deterioration		5	[128]
Gemcitabine ± nab-paclitaxel		First line advanced or metastatic, good PS	OS				6.7 months	1.8 months	0.72 (0.61–0.83) 5% gain at 24 months			3	[129]
Gemcitabine ± erlotinib		First line advanced or metastatic	OS				5.9 months	0.3 months	0.82 (0.69–0.99)			1	[130]

Table 12. Field testing ESMO-MCBS v1.0: gastro-oesophageal cancer

Gastro-oesophageal cancer												
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESM0-MCBS	Ref.
Surgery ± perioperative epirubicin, cisplatin, 5-FU	ISRCTN 93793971	Gastric or distal oesophagus stage II–III	OS				5 years: 23%	13%	0.66 (0.53–0.81)			A	[131]
Surgery ± perioperative cisplatin/5-FU		Gastric or distal oesophagus stage II–III	OS				5 years: 24%	14%	0.69 (0.50–0.95)			A	[132]
Ramucirumab versus placebo	REGARD	Second-line gastro-oesophageal or gastric cancer after cisplatin/5-FU	OS				3.2 months	2 months	0.78 (0.60–0.99)			2	[133]

unbalanced crossover. In other instances, unbalanced crossover may exaggerate differences in survival. For instance, in the PEAK study comparing FOLFOX6 with either bevacizumab or panitumumab among the patients with KRAS wild-type tumours, only 38% of those in the bevacizumab arm received any EGFR antibody in subsequent therapy [146]. Although this study showed a survival advantage of 9.9 months over a baseline of 24.3 months for patient initiated on treatment with panitumumab, it remains unclear as to whether this was affected by the sequence of treatments or if it was the result that more than half of the patients in the bevacizumab arm were never exposed to an EGFR antibody.

follow-up reports. In some studies, first reports are followed up with subsequent further relevant data analysis. This is particularly true when mature survival data were not available in studies with a primary outcome of PFS or DFS and in studies that have incorporated *post hoc* stratification based on refined appreciation of tumour biology that may impact on outcome evaluation.

Both of these phenomena were observed in the three publications reporting the findings from the same study on FOLFOX4 ± panitumumab for the first-line treatment of KRAS wild-type colorectal cancer [74, 78, 79]. The study, which did allow for crossover to other EGFR antibodies, had PFS as a primary end point. The initial publication demonstrated a modest PFS advantage with non-significant median OS gain [78]. The subsequent publication of mature data demonstrated a significant OS gain [79] with the greatest benefit restricted to patients with KRAS, NRAS, BRAF wild-type tumours [74]. Almost identical data maturation was observed in the CRYSTAL study evaluating FOLFIRI ± cetuxumab in the same clinical setting [76, 80, 81].

Maturation of survival data also increased the ESMO-MCBS score of vemurafenib in the treatment of metastatic melanoma [116, 117] from ESMO-MCBS 3 based on PFS to 4, based on OS.

using data from the ESMO-MCBS

The ESMO-MCBS incorporates a structured, rational and valid approach to data interpretation and analysis that reduces the tendency to have judgements affected by bias or uninformed and/or idiosyncratic data interpretation. Consequently, application of the scale reduces the likelihood that statements of clinical benefit will be distorted by either overestimation or overstatement on one extreme or, nihilism at the other. This structured and disciplined approach to deriving estimates of clinically meaningful benefit from published data can be used in a range of settings.

public policy applications. Grading derived from the ESMO-MCBS provides a backbone for value evaluations for cancer medicines. Medicines and therapies that fall into the ESMO-MCBS A + B for curative therapies and 4 + 5 for non-curative therapies should be emphasized for accelerated assessment of value and cost-effectiveness. While a high ESMO-MCBS score does not automatically imply high value (that depends on the price), the scale can be utilised by to frame such considerations [147] and can help public policy-makers advance 'accountability for reasonableness' in resource allocation deliberations [134, 135].

formulation of clinical guidelines. The prevailing current practice of the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), ESMO and the National Cancer Institute (NCI) in their guidelines is to grade the 'level of evidence' supporting the efficacy of therapeutic interventions; grading the evidence as very high when derived from meta-analyses of well-conducted phase III studies, or from large well-conducted phase III studies relative to lower levels such as that derived from non-randomised studies, anecdote or expert clinical opinion. A major shortcoming of this approach is that it may result in a high level of evidence irrespective of the actual magnitude of the benefit observed, even if the magnitude of the benefit is very limited [148]. This discrepancy has been emphasized by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group which was formed in 2000 to improve the quality of guideline formulation. The GRADE working group emphasised that a particular quality of evidence does not necessarily imply a particular strength of recommendation [149, 150]. They have developed and championed a widely endorsed approach emphasising appropriate framing of research and guideline questions [151], evaluation of the strength of recommendations that incorporates evaluation of the balance between desirable and undesirable outcomes (estimated effects), and the confidence in the magnitude effect of the interventions on important outcomes [152].

This recommendation can be accomplished by describing both the level of benefit and the level of evidence for recommended therapeutic interventions. For cancer therapies, the ESMO-MCBS scale provides a clear, well-structured and validated mechanism to indicate the magnitude of benefit in addition to the level of evidence that can inform both national and international (e.g. ESMO) guidelines.

clinical decision making. The data encapsulated in ESMO-MCBS scoring can help clinicians to weigh the relative merits of competing relevant therapeutic options in situations in which there is no direct comparative data comparing the available therapeutic options. The grading may also be of benefit in explaining the relative merit of therapeutic options to patients and their families. This information may be especially helpful when treatments incorporate substantial out of pocket costs and the real 'value' of the treatment needs to be candidly addressed to avoid over investment or sacrifice of limited financial resources to pay for treatments that have only limited magnitude of benefit.

editorial decisions and commentaries. The ESMO-MCBS may be of use to editors, peer reviewers and commentators in considering the clinical significance of research findings from randomised clinical studies, cohort studies and meta-analyses with statistically significant positive findings.

relevance to the ASCO initiatives

ASCO has undertaken two initiatives to help promote the value in cancer care. The first was a working group to propose new thresholds for the approval of cancer medications [153]. For each of four conditions (metastatic colon cancer, metastatic breast cancer, non-small-cell lung cancer and pancreatic cancer), they have proposed thresholds for meaningful clinical benefit improvement defined in terms of minimal increases

in OS (absolute and HR) and also thresholds for minimal increases in surrogate indicators including 1-year survival and PFS. Interestingly, in non-curative therapies, the ASCO recommended thresholds for survival benefit correlate very closely to the thresholds for ESMO-MCBS score of 4–5 (in form 2a) and the recommended thresholds for PFS correlate closely with the thresholds for ESMO-MCBS score of 3–4 which is the highest attainable when the primary outcome is PFS (in form 2b). Secondly, ASCO has developed a Value in Cancer Care Task Force that has been charged with the challenge of developing a framework for evaluating value in oncology. While concurring with ESMO that the evaluation of net clinical benefit is key element in the evaluation of value, ASCO has not yet described their proposed approach to evaluate the magnitude of clinical benefit. A key challenge for the future will be to establish whether there can be harmonisation between the different approaches to value in Europe and the United States.

conclusion

ESMO is committed to promoting rational, responsible and affordable cancer care, the importance of organisational integrity, and the promotion of best use of limited health care resources. The ESMO-MCBS v1.0 was born out of these considerations. It represents a first version of a well-validated tool to stratify the magnitude of clinical benefit for new anti-cancer treatments and is applicable over a full range of solid tumours. Based on the data derived from well-structured phase III clinical trials or meta-analyses, the tool uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of benefit that can be anticipated from any new treatment. The ESMO-MCBS is an important first step to the major ongoing task of evaluating value in cancer care which is essential for appropriate uses of limited public and personal resources for affordable cancer care. The ESMO-MCBS will be a dynamic tool and its criteria will be revised on a regular basis pending peer reviewed feedback and developments in cancer research and therapies.

acknowledgements

The authors wish to acknowledge the support and contribution of the ESMO Executive Board, the ESMO Faculty, Members of the ESMO Guidelines Committee, and the logistic and organisational support provided by ESMO Staff and in particular Nicola Latino. Appendix 2 lists biostatistics and oncology colleagues who provided feedback on earlier versions of the scale and the manuscript.

funding

This project was funded by ESMO.

disclosure

The authors have declared the following: UD: lecture fees—Amgen. EGEV: research grants from Roche/Genentech, Amgen, Novartis, Pieris and Servier to the institute, data monitoring committee Biomarin, advisory board Synthon. MJP: board member—PharmaMar; Consultant (honoraria)—Amgen, Astellas, AstraZeneca, Eli Lilly, GSK, Invivis, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi Aventis, Symphogen, Synthon, Verastem; Research grants to Institute: most companies; Speakers bureau/stock ownership: none. AS: advisory Board and Symposia Satellite with; Amgen, Bayer, Celgene, Merck, Roche and Sanofi. CZ: advisory Boards—Roche, Celgene, Bristol Myers-Squibb; lecture fees—Amgen, Bristol Myers-Squibb. All remaining authors have declared no conflicts of interest.

references

1. Porter ME. What is value in health care? N Engl J Med 2010; 363: 2477–2481.
2. Hoffman A, Pearson SD. 'Marginal medicine': targeting comparative effectiveness research to reduce waste. Health Aff (Millwood) 2009; 28: w710–w718.
3. Emanuel EJ. The cost of marginal medicine is too high. MedGenMed 2005; 7: 67.
4. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. JAMA Otolaryngol Head Neck Surg 2014; 140: 1225–1236.
5. Davis C. Drugs, cancer and end-of-life care: a case study of pharmaceuticalization? Soc Sci Med 2014; http://www.sciencedirect.com/science/article/pii/S0277953614007965 (3 June 2015, date last accessed).
6. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol 2013; 14: 1165–1174.
7. De Angelis R, Sant M, Coleman MP et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. Lancet Oncol 2014; 15: 23–34.
8. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374–1403.
9. Munro AJ. Comparative cancer survival in European countries. Br Med Bull 2014; 110: 5–22.
10. Gatta G, Trama A, Capocaccia R. Variations in cancer survival and patterns of care across Europe: roles of wealth and health-care organization. J Natl Cancer Inst Monogr 2013; 2013: 79–87.
11. Ades F, Senterre C, Zardavas D et al. An exploratory analysis of the factors leading to delays in cancer drug reimbursement in the European Union: the trastuzumab case. Eur J Cancer 2014; 50: 3089–3097.
12. Ades F, Zardavas D, Senterre C et al. Hurdles and delays in access to anti-cancer drugs in Europe. Ecancermedicalscience 2014; 8: 482.
13. Seruga B, Tannock IF. Up-front use of aromatase inhibitors as adjuvant therapy for breast cancer: the emperor has no clothes. J Clin Oncol 2009; 27: 840–842.
14. Sargent DJ, Wieand HS, Haller DG et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2005; 23: 8664–8670.
15. Oba K, Paoletti X, Alberts S et al. Disease-free survival as a surrogate for overall survival in adjuvant trials of gastric cancer: a meta-analysis. J Natl Cancer Inst 2013; 105: 1600–1607.
16. Mauguen A, Pignon J-P, Burdett S et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. Lancet Oncol 2013; 14: 619–626.
17. Gill S, Sargent D. End points for adjuvant therapy trials: has the time come to accept disease-free survival as a surrogate end point for overall survival? Oncologist 2006; 11: 624–629.
18. Saad ED, Katz A, Hoff PM, Buyse M. Progression-free survival as surrogate and as true end point: insights from the breast and colorectal cancer literature. Ann Oncol 2010; 21: 7–12.
19. Shi Q, Sargent DJ. Meta-analysis for the evaluation of surrogate endpoints in cancer clinical trials. Int J Clin Oncol 2009; 14: 102–111.
20. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol 2012; 30: 1030–1033.

21. Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. J Clin Oncol 2010; 28: 1958–1962.
22. Wilkerson J, Fojo T. Progression-free survival is simply a measure of a drug's effect while administered and is not a surrogate for overall survival. Cancer J 2009; 15: 379–385.
23. Amir E, Seruga B, Kwong R et al. Poor correlation between progression-free and overall survival in modern clinical trials: are composite endpoints the answer? Eur J Cancer 2012; 48: 385–388.
24. Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357: 2666–2676.
25. Ocana A, Tannock IF. When are 'positive' clinical trials in oncology truly positive? J Natl Cancer Inst 2011; 103: 16–20.
26. Vera-Badillo FE, Al-Mubarak M, Templeton AJ, Amir E. Benefit and harms of new anti-cancer drugs. Curr Oncol Rep 2013; 15: 270–275.
27. Saltz LB. Progress in cancer care: the hope, the hype, and the gap between reality and perception. J Clin Oncol 2008; 26: 5020–5021.
28. Smith TJ, Hillner BE. Concrete options and ideas for increasing value in oncology care: the view from one trench. Oncologist 2010; 15(Suppl 1): 65–72.
29. Fojo T, Grady C. How much is life worth: cetuximab, non–small cell lung cancer, and the $440 billion question. J Natl Cancer Inst 2009; 101: 1044–1048.
30. Vera-Badillo F, Shapiro R, Ocana A et al. Bias in reporting of end points of efficacy and toxicity in randomized, clinical trials for women with breast cancer. Ann Oncol 2013; 24: 1238–1244.
31. Lewison G, Tootell S, Roe P, Sullivan R. How do the media report cancer research? A study of the UK's BBC website. Br J Cancer 2008; 99: 569–576.
32. Ooi ES, Chapman S. An analysis of newspaper reports of cancer breakthroughs: hope or hype? Med J Aust 2003; 179: 639–643.
33. Sobrero A, Bruzzi P. Incremental advance or seismic shift? The need to raise the bar of efficacy for drug approval. J Clin Oncol 2009; 27: 5868–5873.
34. Sobrero AF, Pastorino A, Sargent DJ, Bruzzi P. Raising the bar for antineoplastic agents: how to choose threshold values for superiority trials in advanced solid tumors. Clin Cancer Res 2015; 21: 1036–1043.
35. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000; 342: 1887–1892.
36. Berger ML, Dreyer N, Anderson F et al. Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task force report. Value Health 2012; 15: 217–230.
37. Joensuu H. HERA crosses over. Lancet Oncol 2011; 12: 203–204.
38. Gianni L, Dafni U, Gelber RD et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol 2011; 12: 236–244.
39. Bianchini G, Gianni L. Surrogate markers for targeted therapy-based treatment activity and efficacy. J Natl Cancer Inst Monogr 2011; 2011: 91–94.
40. Burki TK. Pathological complete response is no surrogate for survival. Lancet Oncol 2014; 15: e111.
41. Glynne-Jones R, Mawdsley S, Pearce T, Buyse M. Alternative clinical end points in rectal cancer—are we getting closer? Ann Oncol 2006; 17: 1239–1248.
42. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164–172.
43. Zhou C, Wu Y-L, Chen G et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12: 735–742.
44. Rosell R, Carcereny E, Gervais R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13: 239–246.
45. Fukuoka M, Wu Y-L, Thongprasert S et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011; 29: 2866–2874.
46. Mok TS, Wu Y-L, Thongprasert S et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361: 947–957.
47. Sequist LV, Yang JC-H, Yamamoto N et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31: 3327–3334.
48. Yang JC-H, Hirsh V, Schuler M et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31: 3342–3350.
49. Shaw AT, Kim D-W, Nakagawa K et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368: 2385–2394.
50. Solomon BJ, Mok T, Kim DW et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014; 371: 2167–2177.
51. Ciuleanu T, Brodowicz T, Zielinski C et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009; 374: 1432–1440.
52. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non–small-cell lung cancer. J Clin Oncol 2008; 26: 3543–3551.
53. Temel JS, Greer JA, Muzikansky A et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010; 363: 733–742.
54. Sandler A, Gray R, Perry MC et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 2006; 355: 2542–2550.
55. Cappuzzo F, Ciuleanu T, Stelmakh L et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010; 11: 521–529.
56. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659–1672.
57. Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367: 1783–1791.
58. Welslau M, Dieras V, Sohn JH et al. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. Cancer 2014; 120: 642–651.
59. Swain SM, Kim S-B, Cortés J et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013; 14: 461–471.
60. Baselga J, Cortés J, Kim S-B et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012; 366: 109–119.
61. Swain SM, Baselga J, Kim S-B et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015; 372: 724–734.
62. Cortes J, Baselga J, Im YH et al. Health-related quality-of-life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer. Ann Oncol 2013; 24: 2630–2635.
63. Blackwell KL, Burstein HJ, Storniolo AM et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 study. J Clin Oncol 2012; 30: 2585–2592.
64. Blackwell KL, Burstein HJ, Storniolo AM et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010; 28: 1124–1130.
65. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2733–2743.
66. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011; 377: 914–923.

67. Baselga J, Campone M, Piccart M et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012; 366: 520–529.
68. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213–223.
69. De Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995–2005.
70. Cabot RC, Harris NL, Rosenberg ES et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187–1197.
71. Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–433.
72. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502–1512.
73. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376: 1147–1154.
74. Douillard J-Y, Oliner KS, Siena S et al. Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013; 369: 1023–1034.
75. Schwartzberg LS, Rivera F, Karthaus M et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014; 32: 2240–2247.
76. Van Cutsem E, Lenz HJ, Kohne CH et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J Clin Oncol 2015; 33: 692–700.
77. Karapetis CS, Khambata-Ford S, Jonker DJ et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008; 359: 1757–1765.
78. Douillard J-Y, Siena S, Cassidy J et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010; 28: 4697–4705.
79. Douillard J, Siena S, Cassidy J et al. Final results from PRIME: randomized phase 3 study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 2014; 25: 1346–1355.
80. Van Cutsem E, Köhne C-H, Hitre E et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009; 360: 1408–1417.
81. Van Cutsem E, Köhne C-H, Láng I et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011; 29: 2011–2019.
82. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335–2342.
83. Peeters M, Price TJ, Cervantes A et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010; 28: 4706–4713.
84. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007; 25: 1539–1544.
85. Amado RG, Wolf M, Peeters M et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26: 1626–1634.
86. Loupakis F, Cremolini C, Masi G et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 2014; 371: 1609–1618.
87. Mayer RJ, Van Cutsem E, Falcone A et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015; 372: 1909–1919.
88. Grothey A, Cutsem EV, Sobrero A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381: 303–312.
89. Bennouna J, Sastre J, Arnold D et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013; 14: 29–37.
90. Van Cutsem E, Tabernero J, Lakomy R et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012; 30: 3499–3506.
91. Tabernero J, Yoshino T, Cohn AL et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 2015; 16: 499–508.
92. Naumann RW, Coleman RL. Management strategies for recurrent platinum-resistant ovarian cancer. Drugs 2011; 71: 1397–1412.
93. Stockler MR, Hilpert F, Friedlander M et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. J Clin Oncol 2014; 32: 1309–1316.
94. Perren TJ, Swart AM, Pfisterer J et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011; 365: 2484–2496.
95. Aghajanian C, Blank SV, Goff BA et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or Fallopian tube cancer. J Clin Oncol 2012; 30: 2039–2045.
96. Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011; 365: 2473–2483.
97. Monk BJ, Herzog TJ, Kaye SB et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010; 28: 3107–3114.
98. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014; 15: 852–861.
99. Motzer RJ, Hutson TE, Cella D et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013; 369: 722–731.
100. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356: 2271–2281.
101. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356: 115–124.
102. Motzer RJ, Hutson TE, Tomczak P et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 3584–3590.
103. Rini B, Escudier B, Tomczak P et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011; 378: 1931–1939.
104. Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007; 356: 125–134.
105. Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008; 372: 449–456.
106. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28: 1061–1068.
107. Escudier B, Pluzanska A, Koralewski P et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2008; 370: 2103–2111.
108. Rini BI, Halabi S, Rosenberg JE et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008; 26: 5422–5428.
109. DeMatteo RP, Ballman KV, Antonescu CR et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009; 373: 1097–1104.

110. Joensuu H, Eriksson M, Hall KS et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012; 307: 1265–1272.
111. Demetri GD, van Oosterom AT, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329–1338.
112. Demetri GD, Reichardt P, Kang Y-K et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381: 295–302.
113. van der Graaf WT, Blay J-Y, Chawla SP et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379: 1879–1886.
114. Demetri GD, Chawla SP, Ray-Coquard I et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. J Clin Oncol 2013; 31: 2485–2492.
115. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711–723.
116. Chapman PB, Hauschild A, Robert C et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364: 2507–2516.
117. McArthur GA, Chapman PB, Robert C et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014; 15: 323–332.
118. Flaherty KT, Robert C, Hersey P et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012; 367: 107–114.
119. Schadendorf D, Amonkar M, Milhem M et al. Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. Ann Oncol 2014; 25: 700–706.
120. Flaherty KT, Infante JR, Daud A et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012; 367: 1694–1703.
121. Hauschild A, Grob J-J, Demidov LV et al. Dabrafenib in BRAF mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380: 358–365.
122. Grob J-J, Amonkar M, Martin-Algarra S et al. Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality of life analyses of the BREAK-3 study comparing dabrafenib with DTIC. Ann Oncol 2014; 25: 1428–1436.
123. Robert C, Karaszewska B, Schachter J et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015; 372: 30–39.
124. Larkin J, Ascierto PA, Dreno B et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014; 371: 1867–1876.
125. Robert C, Long GV, Brady B et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372: 320–330.
126. Robert C, Thomas L, Bondarenko I et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364: 2517–2526.
127. Maio M, Grob JJ, Aamdal S et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III Trial. J Clin Oncol 2015; 33: 1191–1196.
128. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817–1825.
129. Von Hoff DD, Ervin T, Arena FP et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013; 369: 1691–1703.
130. Moore MJ, Goldstein D, Hamm J et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007; 25: 1960–1966.
131. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11–20.
132. Ychou M, Boige V, Pignon J-P et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29: 1715–1721.
133. Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014; 383: 31–39.
134. Gruskin S, Daniels N. Process is the point: justice and human rights: priority setting and fair deliberative process. Am J Public Health 2008; 98: 1573–1577.
135. Daniels N. Accountability for reasonableness. BMJ 2000; 321: 1300–1301.
136. Berruti A, Amoroso V, Gallo F et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014; 32: 3883–3891.
137. Gan HK, Grothey A, Pond GR et al. Randomized phase II trials: inevitable or inadvisable? J Clin Oncol 2010; 28: 2641–2647.
138. Tannock IF, Osoba D, Stockler MR et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996; 14: 1756–1764.
139. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS clinical trial with Inverse Probability of Censoring Weighted (IPCW) Log-Rank Tests. Biometrics 2000; 56: 779–788.
140. Shao J, Chang M, Chow SC. Statistical inference for cancer trials with treatment switching. Stat Med 2005; 24: 1783–1790.
141. Jin H, Tu D, Zhao N et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. J Clin Oncol 2012; 30: 718–721.
142. Colleoni M, Giobbie-Hurder A, Regan MM et al. Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1–98 study. J Clin Oncol 2011; 29: 1117–1124.
143. Finkelstein DM, Schoenfeld DA. Correcting for discretionary treatment crossover in an analysis of survival in the Breast International Group BIG 1–98 trial by using the inverse probability of censoring weighted method. J Clin Oncol 2011; 29: 1093–1095.
144. Rimawi M, Hilsenbeck SG. Making sense of clinical trial data: is inverse probability of censoring weighted analysis the answer to crossover bias? J Clin Oncol 2012; 30: 453–458.
145. Prasad V, Grady C. The misguided ethics of crossover trials. Contemp Clin Trials 2014; 37: 167–169.
146. Stintzing S, Jung A, Modest D et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE- 3: a randomized phase III study of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS (exon 2) metastatic colorectal cancer patients. 2013 European Cancer Congress, 2013. Abstract 17; 1693–1699.
147. Shih YC, Ganz PA, Aberle D et al. Delivering high-quality and affordable care throughout the cancer care continuum. J Clin Oncol 2013; 31: 4151–4157.
148. Petticrew M, Roberts H. Evidence, hierarchies, and typologies: horses for courses. J Epidemiol Community Health 2003; 57: 527–529.
149. Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924–926.
150. Balshem H, Helfand M, Schunemann HJ et al. GRADE guidelines: 3. rating the quality of evidence. J Clin Epidemiol 2011; 64: 401–406.
151. Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 2. framing the question and deciding on important outcomes. J Clin Epidemiol 2011; 64: 395–400.
152. Andrews JC, Schunemann HJ, Oxman AD et al. GRADE guidelines: 15. going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013; 66: 726–735.
153. Ellis LM, Bernstein DS, Voest EE et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014; 32: 1277–1280.

appendix 1

ESMO magnitude of Clinical Benefit Scale v1.0

Form 1: for new approaches to adjuvant therapy or new potentially curative therapies

Name of study:			
Study drug:	Indication:		
First author:	Year:	Journal:	
Name of evaluator:			

Grade A	*Mark with X if relevant*
>5% improvement of survival at ≥3 years follow-up	
Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	

Grade B	
≥3% but ≤5% improvement at ≥3 years follow-up	
Improvement in DFS alone (primary endpoint) (HR 0.65–0.8) without mature survival data	
Non inferior OS or DFS with reduced treatment toxicity or improved Quality of Life (with validated scales)	
Non inferior OS or DFS with reduced treatment cost as reported study outcome (with equivalent outcomes and risks)	

Grade C	
<3% improvement of survival at ≥3 years follow-up	
Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data	

Magnitude of clinical benefit grade (highest grade scored)

A	B	C

Form 2a: for therapies that are not likely to be curative with primary endpoint of OS

Name of study:			
Study drug:	Indication:		
First author:	Year:	Journal:	
Name of evaluator:			

IF median OS with the standard treatment is ≤1 year

Grade 4	*Mark with X if relevant*
HR ≤0.65 AND Gain ≥3 months	
Increase in 2 year survival alone ≥10%	

Grade 3	
HR ≤0.65 AND Gain 2.5–2.9 months	
Increase in 2 year survival alone 5 - <10%	

Grade 2	
HR >0.65–0.70 OR Gain 1.5–2.4 months	
Increase in 2 year survival alone 3 - <5%	

Grade 1	
HR >0.70 OR Gain <1.5 months	
Increase in 2 year survival alone <3%	

Preliminary magnitude of clinical benefit grade (highest grade scored)

4	**3**	**2**	**1**

Quality of Life assessment /grade 3–4 toxicities assessment*

Does secondary endpoint quality of life show improvement	
Are there statistically significantly less grade 3–4 toxicities impacting on daily well-being*	

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

Adjustments

Upgrade 1 level if improved quality of life and/or less grade 3–4 toxicities impacting daily well-being are shown

Final adjusted magnitude of clinical benefit grade

5	4	3	2	1

IF median OS with the standard treatment >1 year

Grade 4	*Mark with X if relevant*
HR ≤0.70 AND Gain ≥5 months	
Increase in 3 year survival alone ≥10%	

Grade 3

HR ≤0.70 AND Gain 3–4.9 months	
Increase in 3 year survival alone 5 - <10%	

Grade 2

HR >0.70–0.75 OR Gain 1.5–2.9 months	
Increase in 3 year survival alone 3 - <5%	

Grade 1

HR >0.75 OR Gain <1.5 months	
Increase in 3 year survival alone <3%	

Preliminary magnitude of clinical benefit grade (highest grade scored)

4	3	2	1

Quality of Life assessment /grade 3–4 toxicities assessment*

Does secondary endpoint quality of life show improvement	
Are there statistically significantly less grade 3–4 toxicities impacting on daily well-being*	

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

Adjustments

Upgrade 1 level if improved quality of life and/or less grade 3–4 toxicities impacting daily well-being are shown

Final adjusted magnitude of clinical benefit grade

5	4	3	2	1

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

Name of study:			
Study drug:	Indication:		
First author:	Year:	Journal:	
Name of evaluator:			

IF with median PFS with standard treatment ≤6 months

Grade 3	*Mark with X if relevant*
HR ≤0.65 AND Gain ≥1.5 months	

Grade 2	
HR ≤0.65 BUT Gain <1.5 months	

Grade 1	
HR >0.65	

Preliminary magnitude of clinical benefit grade (highest grade scored)

3	2	1

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:	*Mark with X if relevant*
«toxic» death >2%	
cardiovascular Ischemia >2%	
hospitalization for «toxicity» >10%	

excess rate of severe CHF >4%	
grade 3 neurotoxicity >10%	
severe other irreversible or long lasting toxicity >2% please specify:	

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

Quality of life/ grade3–4 toxicities assessment

Was quality of life (QoL) evaluated as secondary outcome?	
Does secondary endpoint quality of life show improvement	
Are there statistically significantly less grade 3–4 toxicities impacting on daily well-being*	

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

Adjustments

a) Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new drug

b) Upgrade 1 level if improved quality of life or if less grade 3–4 toxicities that bother patients are demonstrated

c) When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a

d) Downgrade 1 level if the drug ONLY leads to improved PFS and QOL assessment does not demonstrate improved QoL

Final, toxicity and QoL adjusted, magnitude clinical benefit grade

4	3	2	1

Highest magnitude clinic benefit grade that can be achieved Grade 4.

IF median PFS with standard treatment >6 months

Grade 3	*Mark with X if relevant*
HR ≤0.65 AND Gain ≥3 months	

Grade 2	
HR ≤0.65 BUT Gain <3 months	

Grade 1	
HR >0.65	

Preliminary magnitude of clinical benefit grade (highest grade scored)

3	2	1

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:	*Mark with X if relevant*
«toxic» death >2%	
cardiovascular Ischemia >2%	
hospitalization for «toxicity» >10%	
excess rate of severe CHF >4%	
grade 3 neurotoxicity >10%	
severe other irreversible or long lasting toxicity >2% please specify:	

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

Quality of life/ grade3–4 toxicities assessment

Was quality of life (QoL) evaluated as secondary outcome?	
Does secondary endpoint quality of life show improvement	
Are there statistically significantly less grade 3–4 toxicities impacting on daily well-being*	

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

Adjustments

a) Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new drug

b) Upgrade 1 level if improved quality of life or if less grade 3–4 toxicities that bother patients are demonstrated

c) When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a

d) Downgrade 1 level if the drug ONLY leads to improved PFS and QOL assessment does not demonstrate improved QoL

Final, toxicity and QoL adjusted, magnitude clinical benefit grade

4	3	2	1

Highest magnitude clinical benefit grade that can be achieved Grade 4.

Evaluation form 2c: for therapies that are not likely to be curative with primary endpoint other than OS or PFS or equivalence studies

Name of study:		
Study drug:	Indication:	
First author:	Year:	Journal:
Name of evaluator:		

Primary outcome is Toxicity or Quality of life AND Non-inferiority Studies

	Mark with X if relevant
Grade 4	
Reduced toxicity or improved QoL (using validated scale) with evidence for statistical non inferiority or superiority in PFS/OS	
Grade 3	
Improvement in some symptoms (using a validated scale) BUT without evidence of improved overall QoL	

Primary outcome is Response Rate

Grade 2	
RR is increased ≥20% but no improvement in toxicity/QoL/PFS/OS	
Grade 1	
RR is increased <20% but no improvement in toxicity/QoL/PFS/OS	

Final magnitude of clinical benefit grade

4	3	2	1

appendix 2

Fabrice Andre, France; Dirk Arnold, Germany; Paolo A. Ascierto, Italy; Stefan Bielack, Germany; Jean Yves Blay, France; Federico Cappuzzo, Italy; Fatima Cardoso, Portugal; Andrés Cervantes, Spain; Fortunato Ciardiello, Italy; Alan Stuart Coates, Australia; Karina Dahl Steffensen, Denmark; Theo M. De Reijke, The Netherlands; Jean Yves Douillard, France; Reinhard Dummer, Switzerland; Tim Eisen, UK; Enriqueta Felip, Spain; Constantine Gatsonis, USA; Heikki Joensuu, Finland; Ian Judson, UK; Vesa Kataja, Finland; Roberto Labianca, Italy; Jonathan A. Ledermann, UK; Sumithra J. Mandrekar, USA; Stefan Michiels, France; Mansoor Raza Mirza, Denmark; Mustafa Özgüroğlu, Turkey; Chris Parker, UK; Camillo Porta, Italy; Noemi Reguart, Spain; Daniel J. Sargent, USA; Elżbieta Senkus, Poland; Cristiana Sessa, Switzerland; Kirsten Sundby Hall, Norway; JosepTabernero, Spain; Dongsheng Tu, Canada; Johan Vansteenkiste, Belgium.

Annals of Oncology 26: 1573–1588, 2015
doi:10.1093/annonc/mdv187
Published online 20 April 2015

2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

W. E. E. Eberhardt[1], D. De Ruysscher[2], W. Weder[3], C. Le Péchoux[4], P. De Leyn[5], H. Hoffmann[6], V. Westeel[7], R. Stahel[8], E. Felip[9], S. Peters[10] & Panel Members[†]

[1]Department of Medical Oncology, West German Cancer Centre, University Hospital, University Duisburg-Essen, Ruhrlandklinik, Essen, Germany; [2]Department of Radiation Oncology, KU Leuven–University of Leuven, University Hospitals Leuven, Leuven, Belgium; [3]Division of Thoracic Surgery, University Hospital Zürich, Zürich, Switzerland; [4]Department of Radiation Oncology, Gustave Roussy Cancer Institute, Villejuif, France; [5]Department of Thoracic Surgery, University Hospitals, KU Leuven, Leuven, Belgium; [6]Department of Thoracic Surgery, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; [7]Department of Chest Disease, University Hospital, Besançon, France; [8]Clinic of Oncology, University Hospital Zürich, Zürich, Switzerland; [9]Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; [10]Département d'Oncologie, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Received 6 August 2014; revised 24 March 2015; accepted 9 April 2015

To complement the existing treatment guidelines for all tumour types, ESMO organises consensus conferences to focus on specific issues in each type of tumour. The 2nd ESMO Consensus Conference on Lung Cancer was held on 11–12 May 2013 in Lugano. A total of 35 experts met to address several questions on non-small-cell lung cancer (NSCLC) in each of four areas: pathology and molecular biomarkers, first-line/second and further lines of treatment in advanced disease, early-stage disease and locally advanced disease. For each question, recommendations were made including reference to the grade of recommendation and level of evidence. This consensus paper focuses on locally advanced disease.
Key words: non-small-cell lung cancer, locally advanced, stage III, recommendations, ESMO

methods

A detailed literature review was done by the writing group for this manuscript and was extended after sending out the preliminary paper to all other Panel Members (see Appendix). All available meta-analysis, randomized phase III trials and phase II trials considered by the panel as of key importance were put forward for the scoring of the guidelines. The scores for level of evidence and grade of recommendation were proposed and fully consented within the writing committee that met at the Consensus Conference in Lugano. In an initial summary discussion meeting at the Consensus Conference, these scores were already presented to the full Consensus Panel and evaluated and amended whenever necessary. During the final writing process, these scores were further consented within the writing group together with the full consensus panel. Final given levels of evidence and grades of recommendation in this manuscript were consented without significant divergence between the different panel members if not otherwise openly specified in the text (Table 1). Statements without grading were considered standard clinical practice by the experts. The methods both for the conference and the writing process for this topic were as those for the other three manuscripts produced from this conference [2–4]. To minimise

Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

[†]See Appendix for Panel Members.