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Application of the ESMO-Magnitude of Clinical Benefit Scale (V.1.1) to the field of early breast cancer therapies

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ABSTRACT

Background The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a validated value scale for solid tumour anticancer treatments. Form 1 of the ESMO-MCBS, used to grade therapies with curative intent including adjuvant therapies, has only been evaluated for a limited number of studies. This is the first large-scale field testing in early breast cancer to assess the applicability of the scale to this data set and the reasonableness of derived scores and to identify any shortcomings to be addressed in future modifications of the scale.

Method Representative key studies and meta-analyses of the major modalities of adjuvant systemic therapy of breast cancer were identified for each of the major clinical scenarios (HER2-positive, HER2-negative, endocrine-responsive) and were graded with form 1 of the ESMO-MCBS. These generated scores were reviewed by a panel of experts for reasonableness. Shortcomings and issues related to the application of the scale and interpretation of results were identified and critically evaluated.

Results Sixty-five studies were eligible for evaluation: 59 individual studies and 6 meta-analyses. These studies incorporated 101 therapeutic comparisons, 61 of which were scorable. Review of the generated scores indicated that, with few exceptions, they generally reflected contemporary standards of practice. Six shortcomings were identified related to grading based on disease-free survival (DFS), lack of information regarding acute and long-term toxicity and an inability to grade single-arm de-escalation scales.

Conclusions Form 1 of the ESMO-MCBS is a robust tool for the evaluation of the magnitude of benefit studies in early breast cancer. The scale can be further improved by addressing issues related to grading based on DFS, annotating grades with information regarding acute and long-term toxicity and developing an approach to grade single-arm de-escalation studies.

Key questions

What is already known about this subject?

► Form 1 of the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) serves to score therapies with curative intent. To date, very limited field testing has been performed to assess the scale in the curative setting.

What does this study add?

► We evaluated the applicability of the scale and assessed the reasonableness of the generated scores in early breast cancer. Form 1 of the ESMO-MCBS V.1.1 provided a generally robust tool for scoring of adjuvant breast cancer studies. Six shortcomings were identified including lack of information regarding acute and long-term toxicity, an inability to grade single-arm de-escalation scales and limitations related to grading based on disease-free survival.

How might this impact on clinical practice?

► The identified shortcomings in form 1 of the ESMO-MCBS V.1.1 will be rectified in the upcoming version 2.0 of the scale to strengthen the validity of that scale and its generated results. These developments have important implications for data interpretation, public health and clinical decision-making.

INTRODUCTION

As the population ages, the incidence and prevalence of cancer are expected to continue to rise both in developed[1] and developing countries.[2] The estimated total annual economic cost of cancer was US$1.16 trillion in 2010, about 2% of global gross domestic product[3] and is continuing to rise exponentially. Breast cancer remains the leading cause of cancer among women[2] and the ongoing care of breast cancer patients is estimated to be one of the most significant contributors to growing cancer care expenditure.[4]

These considerations underscore the need for validated tools to evaluate value of care, where value is recognised as a balance between clinical benefit and cost. With this in mind, both the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) established

Working Groups to address these issues and they have developed and published a platform for evaluating new anticancer therapeutics—the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS)[5] and the ASCO Framework for assessing value of cancer care.[6]

The ESMO-MCBS was initially launched and published in 2015[5] and revised in 2017 with version 1.1.[7] The scale aims to provide a validated and rational stratification process for oncology therapies, and its development process has been predicated on 'accountability for reasonableness' which incorporated extensive field testing and the peer review of results for 'reasonableness'.[7] Form 1 of the ESMO-MCBS, which is used to grade therapies with curative intent including adjuvant therapies, hitherto, has only been applied in a limited number of studies. Form 1 of the ESMO-MCBS grades therapies with curative intent on a three-point scale A, B and C where scores of A and B represent substantial improvement.

This is the first large-scale field testing of form 1 in early breast cancer to assess the applicability of the ESMO-MCBS in this setting, to determine whether the scoring reflected clinical practice (reasonableness) and to identify shortcomings to be addressed in future versions of the scale. It also provides an overview of the magnitude of benefit for the most common therapies/therapeutic strategies in the field of breast cancer, allowing for a critical reassessment of available options.

METHODOLOGY

ESMO-MCBS V.1.1 form 1, designed to evaluate adjuvant and neoadjuvant studies, was applied to all the selected studies (online supplementary data).

Representative key studies and meta-analyses of the major modalities of adjuvant systemic therapy of breast cancer (chemotherapy or endocrine therapy or anti-HER2 therapy) were identified for each of the major clinical scenarios (HER2-positive, HER2-negative, endocrine-responsive). Studies were identified through PubMed, Food and Drug Administration (FDA) and European Medicines Agency (EMA) registration sites. Pivotal phase 3 studies that have formed the basis for contemporary treatment practice and a randomised phase 2 study that resulted in preliminary drug registration[8] were scored.

To identify the pivotal phase 3 studies, a PubMed search was performed with the following search criteria: "breast cancer"[Title] AND breast[Title] AND cancer[Title] AND adjuvant[Title] OR neo-adjuvant AND "2002"[Date—Publication] : "2019"[Date—Publication] AND English[Language] AND "randomized controlled trial" OR "phase 3" OR "randomized phase 2" NOT retrospective[Title/Abstract] NOT historical[Title/Abstract] NOT "systematic review"[Title] NOT advanced[Title] NOT metastatic[Title] NOT irradiation[Title] NOT safety[Title] NOT insights[Title] NOT observations[Title] NOT "quality of life"[Title] NOT biosimilar[Title] NOT analysis[Title] NOT analyses[Title] NOT radiation[Title]. There were 597 studies identified from the search. Relevant studies that were comparative phase 3 randomised controlled studies were identified and subsequently cross-referenced with the FDA and EMA registration sites and ESMO[9] and National Comprehensive Cancer Network (NCCN)[10] guidelines to identify pivotal and practice changing studies. Key meta-analyses referenced by ESMO[9] and NCCN[10] guidelines were identified.

Studies were eligible for scoring if they were randomised comparative studies comparing new therapies to standard of care or meta-analyses of those studies. Studies were scored if they met the scoring criteria defined by the ESMO-MCBS guideline according to the criteria in form 1. Where missing data impeded scoring, the corresponding author was contacted with a request for data or clarification. If no response was received, the study was either marked as not scorable (this occurred for only one study[11] and one meta-analysis[12]) or excluded (if there was inadequate data reported). All scoring was reviewed for accuracy by members of the Magnitude of Clinical Benefit Working Group and the generated scores were reviewed by the ESMO Breast Cancer Faculty for reasonableness.

Scoring was performed in accordance with the rules for application of the ESMO-MCBS.[5 7] Studies initially evaluated based on disease-free survival (DFS) criteria alone or pathological complete remission (pCR) rate were re-evaluated when mature overall survival (OS) data are available and a final score was determined based on these OS results. The only exception was for studies that were un-blinded after compelling early DFS results with subsequent access to the superior arm, whereby OS results were contaminated by the crossover and therefore were not evaluable.

Studies that could not be scored were classified into one of three groups: (1) studies that did not achieve statistical significance, designated 'no evaluable benefit' (NEB), (2) non-inferiority studies in which non-inferiority was not verified, designated 'negative non-inferiority' (NNI), (3) studies that could not be scored because required data were not included in the publication, designated 'scoring not applicable' (SNA) and (4) not-scorable subgroup data

RESULTS

Sixty-five studies were eligible for evaluation: 59 individual studies and 6 meta-analyses (5 of which were individual patient-level data meta-analyses), which yielded data relevant to 101 therapeutic comparisons, 61 of which demonstrated significant benefit or non-inferiority and could be scored.

Adjuvant chemotherapy

Polychemotherapy versus no chemotherapy

Both cyclophosphamide methotrexate and 5-fluorouracil (CMF) and anthracycline-based therapy were found to be superior to no chemotherapy (in a predominantly node-positive population), both scoring an A compared with no treatment in the meta-analysis, with a 15-year gain

in breast cancer mortality of 6.2% and 6.5%, respectively(table 1).[13]

CMF versus anthracyclines

Four cycles of doxorubicin and cyclophosphamide (AC×4) were not found to be superior to CMF×6 in the meta-analysis.[13] Benefit of CAF (cyclophosphamide/doxorubicin/fluorouracil)/FEC×6 (fluorouracil/epirubicin/cyclophosphamide) over CMF×6 was not reported in individual studies,[14 15] but was demonstrated in a meta-analysis, with a 10-year OS gain of approximately 4% (grade B) (table 1).[13]

Taxanes

The three studies that evaluated the addition of a taxane to an anthracycline-based regimen all demonstrated gains in DFS, but mature survival data was available for only one of these studies with no significant survival advantage and therefore classified as NEB.[16–18] The MA-21 study compared AC×4 followed by paclitaxel to both cyclophosphamide/epirubicin/fluorouracil (CEF) and dose-dense (dd) epirubicin/cyclophosphamide followed by paclitaxel in patients with node-positive and high-risk node-negative disease.[19] Both study regimens demonstrated superiority to AC×4 followed by paclitaxel based on 30-month DFS gain with no OS data available (grade A) (table 2).

In a meta-analysis, the addition of a taxane to an anthracycline demonstrated a small survival advantage at 8 years follow-up (grade C).[13] In this meta-analysis, the assessed cohorts consisted predominantly of patients with node-positive disease.

Docetaxel and cyclophosphamide (TC) ×4 was superior to AC×4, demonstrating a 6% gain in OS at 7-year median follow-up (grade A).[20 21] However, a joint analysis of three trials comparing TC×6 to combinations including AC and a taxane did not establish non-inferiority of TC×6 when compared with a combined taxane–anthracycline regimens.[22]

Other chemotherapy regimens

In all the dose-dense(dd) regimen trials, the high-risk, node-positive population demonstrated OS advantage (two studies in grade B, one study in grade C).[23–25] The two studies with longest median follow-up achieved the highest grades.[24 25] Two meta-analyses confirmed the superiority of dd regimens over standard scheduling (table 3).[26 27]

Post-neoadjuvant capecitabine for patients with incomplete pathological response after neoadjuvant therapy demonstrated survival benefit of more than 5%, at a median of 3.6-year follow-up for the intention-to-treat (ITT) population and for the triple negative subgroup (grade A).[28]

The addition of neoadjuvant carboplatin for patients with triple negative breast cancer demonstrated a benefit in the GeparSixto study for both pCR and DFS with an absolute DFS gain of 9.6%[29] and a benefit in pCR in the

Table 1 First-generation adjuvant chemotherapy

Tested agent	Trial name	Setting	Primary outcome	Median follow-up (years)	DFS control (%)	DFS gain (%)	DFS HR*	OS control	OS gain (%)	OS HR*	pCR	ESMO-MCBS V.1.1	Reference
Polychemotherapy vs none (meta-analysis)	EBCTCG	Anthracycline vs nil 82% Node+	OS	15	47.4	8.0	0.73 (0.68–0.79)	Breast cancer mortality 35.8%	6.5	0.79 (0.72–0.85)		A	13
Polychemotherapy vs none (meta-analysis)	EBCTCG	CMF vs nil 34% Node+	OS	15	39.8	10.2	0.70 (0.63–0.77)	Breast cancer mortality 27.6%	6.2	0.76 (0.68–0.84)		A	13
CMF×6 vs CAF×6	INT 0102	High-risk Node–	DFS	10	75.0	2.0	1.05 (0.94–1.27)	82.0%	3.0	1.19 (0.99–1.43)		NEB	14
CMF×6 vs CEF×6	MA5	Node+	RFS	10	45.0	7.0	1.31 (1.06–1.61)	58.0%	4.0	1.18 (0.94–1.49)		NEB	15
CMF vs AC ×4 (meta-analysis)	EBCTCG	61% Node+	OS	10	42.1	1.1	0.99 (0.90–1.08)	Breast cancer mortality 32.5%	0.9	0.98 (0.89–1.08)		NEB	13
CMF vs 4 AC×4 (meta-analysis)	EBCTCG	61% Node+	OS	10				Overall mortality 34.6%	1.2	0.97 (0.89–1.07)		NEB	13
CMF vs CAF/FEC (meta-analysis)	EBCTCG	53% Node+	OS	10	33.8	2.6	0.89 (0.82–0.96)	Breast cancer mortality 24.1%	4.1	0.80 (0.72–0.88)		B	13
CMF vs CAF/FEC (meta-analysis)	EBCTCG	53% Node+	OS	10	33.8	2.6	0.89 (0.82–0.96)	Overall mortality 27.1%	3.9	0.84 (0.76–0.92)		B	13

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
A, doxorubicin; C, cyclophosphamide; DFS, disease-free survival; E, epirubicin; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; F, fluorouracil; M, methotrexate; NEB, no evaluable benefit; Node+, node-positive; Node–, node-negative; OS, overall survival; RFS, relapse-free survival.

Table 2 Adjuvant chemotherapy with the addition of taxane

Study	Trial name	Setting	Primary outcome	Median follow-up	DFS control (%)	DFS gain (%)	DFS HR*	OS control (%)	OS gain (%)	OS HR*	ESMO-MCBS V.1.1	Reference
TAC vs FAC	GEICAM 9805	High-risk Node–	DFS	77 months	81.8	6.0	0.68 (0.49–0.93)	93.5%	1.7	0.76 (0.45–1.26)	NEB	16
FEC-P vs FEC	GEICAM 9906	Node+	DFS	66 months	72.1	6.4	0.74 (0.60–0.92)	87.1%	2.8	0.78 (0.57–1.06)	NEB	17
AC×4 vs AC-P	NSABP-B28	Node+	DFS and OS	64.6 months	72.0	4.0	0.83 (0.72–0.95)	85.0%	0	0.93 (0.78–1.12)	NEB	18
AC-P vs CEF×6	MA-21	High-risk Node– and +	RFS	30 months	85.0†	5.1	1.49 (1.12–1.99)‡				A§	19
AC-P vs dose dense EC×6 >P×4 q21	MA-21	High-risk Node– and +	RFS	30 months	85.0†	4.5	1.68 (1.25–2.27)‡				A§	19
Paclitaxel q21 d vs q7 day	E1199	High-risk LN–/LN+	DFS	12 years	65.5‡	5.2	0.84 (0.73–0.96)	75.3%‡	2.4	1.02 (0.88–1.18)	NEB	79 80
Paclitaxel q21 d vs docetaxel q21 day	E1199	High-risk LN–/LN+	DFS	12 years	65.5‡	6.4	0.79 (0.68–0.90)	75.3%‡	3.2	0.86 (0.73–1.00)	NEB	79 80
TAC vs AC-T	BCIRG 005	Node+	DFS	65 months	79.0	0	1.0 (0.86–1.16)	88.0%	1.0	0.91 (0.75–1.11)	NEB	81
TAC vs dd AC-P	NSABP-B38	Node+	DFS	64 months	80.1	2.1	NS	89.6%	–0.5	NS	NEB	82
TAC vs dd AC-PG	NSABP-B38	Node+	DFS	64 months	80.1	0.5	NS	89.6%	0.8	NS	NEB	82
TC vs AC	US Oncology 9735	High-risk Node– and 1–3+nodes	DFS	7 years	75.0	6.0	0.74 (0.56–0.98)	84.0%	6.0	0.69 (0.50–0.97)	A	20 21
TC×6 vs Tax AC	ABC Trials—joint analysis		iDFS non-inferiority	3.3 years	88.2¶	2.5	1.2 (0.97–1.49)				NNI	22
TC×6 vs Tax AC Chemo±Taxane (meta-analysis)	EBCTCG	Chemo±Tax-(Node+100%)	iDFS non-inferiority OS	8 years	34.8	4.6	0.84 (0.78–0.91)	Breast cancer mortality 23.9%	2.8	0.86 (0.79–0.93)	C	13
								Overall mortality 26.7%	3.2	0.86 (0.79–0.93)	B	13
Chemo±Tax (meta-analysis)	EBCTCG	Tax/chemo vs different non-Tax regimen (Node+82%)	OS	8 years	22.0	2.9	0.86 (0.82–0.91)	Breast cancer mortality 11.5%	1.4	0.88 (0.81–0.95)	C	13
								Overall mortality 12.4%	1.2	0.90 (0.84–0.97)	C	13

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
†AC-T6 arm.
‡Three weekly paclitaxel arm.
§No OS data published.
¶TC×6 arm.
A, doxorubicin; C, cyclophosphamide; Chemo, chemotherapy; dd, dose dense; DFS, disease-free survival; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; F, fluorouracil; G, gemcitabine; iDFS, invasive disease-free survival; NEB, no evaluable benefit; NNI, negative non-inferiority; Node+, node-positive; Node–, node-negative; OS, overall survival; P, paclitaxel; RFS, relapse-free survival; T, docetaxel; Tax, taxane.

Table 3 Chemotherapy approaches: dose density, neoadjuvant approaches, post-neoadjuvant

Study	Trial name	Setting	Primary outcome	Median follow-up	DFS control	DFS gain	DFS HR*	OS control	OS gain (%)	OS HR*	pCR	ESMO-MCBS V.1.1	Reference
dd studies													
AC-P q21 vs q14	INT C9741/ CALGB 9741	Node+	DFS	36 months	75.00%	7.00%	0.74 (0.59–0.93)	90.00%	2.00	0.69 (0.50–0.93)		C	23
EC-P q21 vs q14	AGO	Node+	EFS	62 months	62.00%	8.00%	0.72 (0.59–0.87)	77.00%	5.00	0.76 (0.59– 0.97)		B	24
(F)EC-P q21 vs q14	GIM	Node+	DFS	7 years	76.00%	5.00%	0.77 (0.65–0.92)	89.00%	5.00	0.65 (0.51– 0.84)		B	25
Meta-analysis—dd vs regular schedule		2 weekly vs 3 weekly (same regimen)	DFS and OS	10 years	28.30%	4.30%	0.83 (0.76–0.91)	Breast cancer mortality 19.6%	1.80	0.86 (0.77–0.95)		C	26
Meta-analysis—dd vs regular schedule		Pooled-analysis—all dd and sequential	DFS and OS	10 years	32.00%	3.60%	0.65 (0.81–0.89)	Breast cancer mortality 19.6%	2.70	0.87 (0.82–0.92)		C	26
Meta-analysis—dd vs regular schedule		Pooled analysis—all dd and sequential	DFS and OS	10 years				All-cause mortality 25.5%	3.00	0.87 (0.82–0.91)		B	26
dd vs regular schedule		Stratified for HR status	DFS and OS	Variable 2–10 years		All	0.84 (0.77–0.91)			0.85 (0.79–0.93)		B	27
dd vs regular schedule		Stratified for HR status	DFS and OS	Variable 2–10 years		HR–ve				0.80 (0.69–0.92)		B	27
dd vs regular schedule		Stratified for HR status	DFS and OS	Variable 2–10 years		HR+ve				0.93 (0.82–1.05)		NEB	27
Post-neoadjuvant chemotherapy													
Capecitabine vs placebo	CREATE—X	Residual disease after neoadjuvant therapy	DFS	3.6 years	All 67.6%	6.50%	0.70 (0.53–0.92)	83.60%	5.60	0.59 (0.39–0.90)*		A	28
Capecitabine vs placebo	CREATE—X	Residual disease after neoadjuvant therapy	DFS	3.6 years	Triple negative 56.1%	13.70%	0.58 (0.39–0.87)	70.30%	8.50	0.52 (0.30–0.90)		A	28
Capecitabine vs placebo	CREATE—X	Residual disease after neoadjuvant therapy	DFS	3.6 years	HR + / HER2-neg 73.4%	3.00%	0.81 (0.55–1.17)	90.00%	3.40	0.73 (0.38–1.14)		NEB	28
Neoadjuvant carboplatin													
Neoadjuvant Peg-A+P+Bev vs Peg-A+P+Bev+Carbo	GeparSixto	Triple negative	pCR	35 months	76.10%	9.70%	0.56 (0.33–0.96)				41% vs 56.8% (ss)	A	29
P vs P + carboplatin	BRIGHTNESS	Triple negative	pCR								41% vs 56.8%	C	30
P + carboplatin vs P + carboplatin + veliparib	BRIGHTNESS	Triple negative	pCR								58% vs 53% (ns)	NEB	30
Neoadjuvant AC+P ± carboplatin	CALBG 40603	Triple negative	pCR	3 years	71.00%	5.00%	0.84 (0.58–1.22)	85.00%	–4.00	1.15 (0.74–1.79)	41% vs 54% (ss)	NEB	31
Neoadjuvant AC-P ± bevacizumab	CALBG 40603	Triple negative	pCR	3 years	72.00%	3.00%	0.80 (0.55–1.17)	81.00%	4.00	0.76 (0.49–1.19)	44% vs 52% (ss)	NEB	31

Continued

Table 3 Continued

Study	Trial name	Setting	Primary outcome	Median follow-up	DFS control	DFS gain	DFS HR*	OS control	OS gain (%)	OS HR*	pCR	ESMO-MCBS V.1.1	Reference
Neoadjuvant other agents													
D+AC vs DG+AC	NSABP-B40	HER2-negative	pCR	4.7 years	72.80%	1.10%	0.90 (0.67–1.19)	80.90%	4.80	0.73 (0.51–1.04)	32.7% vs 31.8% (ns)	NEB	11
D+AC vs DX+AC	NSABP-B40	HER2-negative	pCR	4.7 years	72.80%	–0.20%	1.01 (0.77–1.33)	80.90%	0.60	0.96 (0.68–1.32)	32.7% vs 29.7% (ns)	NEB	11
Above regimens ± Bev	NSABP-B40	HER2-negative	pCR	4.7 years	72.80%	4.00%	0.80 (0.63–1.01)	80.90%		0.65 (0.49–0.88)	28.2 vs 34.5% (ss)	B/C	11
EC+D vs EC+D+Bev	GeparQuinto	Neoadjuvant —all subtypes	pCR	3.8 years	81.50%	–2.00%	1.03 (0.84–1.25)	88.70%	2.00	0.97 (0.75–1.26)	14.9 vs 18.4% (ss)	NEB	83
P-EC vs Nab-P-EC	GeparSepto	Neoadjuvant —all subtypes	pCR								29% vs 38.4% (ss)	NEB	33

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
A, doxorubicin; Bev, bevacizumab; C, cyclophosphamide; Carbo, carboplatin; D, docetaxel; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; F, fluorouracil; G, gemcitabine; HER2-neg, HER2-negative; HR+, hormone-positive; iDFS, invasive disease-free survival; Nab-P, Nab-paclitaxel; nc, not statistically significant; NEB, no evaluable benefit; OS, overall survival; P, paclitaxel; pCR, pathological complete response; Peg-A, pegylated doxorubicin; q21, every 21 days; ss, statistically significant; V, veliparib; X, capecitabine.

BRIGHTNESS study of 15.8% compared with the non-carboplatin arm.[30] The CALGB 40603 did not demonstrate an outcome benefit from the addition of neoadjuvant carboplatin or bevacizumab despite improvements in pCR and was categorised as NEB.[31]

In the NSABP B40 study, there was no benefit of the addition of gemcitabine or capecitabine to standard neoadjuvant chemotherapy regimens.[11 32] This study reported an OS benefit from the addition of neoadjuvant bevacizumab with a HR of 0.65 (95% CI 0.49–0.88); however, since the absolute survival benefit was not published, this was not evaluable (SNA).[11]

In the GeparSepto study, neoadjuvant nab-paclitaxel demonstrated a limited improvement in pCR rate compared with paclitaxel, however the gain was below the ESMO-MCBS threshold for scoring the ≥30% relative and >15% absolute pCR gain).[33]

Anti-HER2 therapies

Trastuzumab

All the 12-month adjuvant trastuzumab studies demonstrated substantial benefit (grade A or B).[34–36] Two years of trastuzumab was not superior to 12 months.[34] While several studies failed to demonstrate non-inferiority of shorter duration of trastuzumab therapy,[37–39] the PERSEPHONE study demonstrated non-inferiority for 6 months versus 12 months of trastuzumab and scored a B based on non-inferiority and reduced cost (table 4).[40]

Dual blockade

Four of the five studies testing double blockade with trastuzumab plus a second anti-HER2 agent derived scores based on surrogate outcomes of pCR for neoadjuvant studies or DFS (table 5).

In the APHINITY study, evaluating the addition of pertuzumab to trastuzumab, the ITT population scored grade B.[41] The node-positive subgroup was not scorable since this was 1 of 12 evaluated subgroups in an exploratory analysis and was, therefore, not eligible for grading (of note, the ESMO-MCBS allows only for scoring of subgroups only if there were up to three planned subgroups in the study design).[41]

Based on pCR criteria, the NeoSphere study (without published OS data) was graded C[8] in contrast to the NeoALTTO study, which had a similar pCR gain but no OS benefit.[42 43]

Second-generation anti-HER2 therapies

In the ExteNET study, the addition of neratinib for node-positive or locally advanced breast cancer after completion of adjuvant trastuzumab scored a grade A (table 5).[44]

In patients with residual disease after neoadjuvant anti-HER2-based therapy, completing 1 year of trastuzumab emtansine (T-DM1) demonstrated large improvement in DFS compared with trastuzumab (grade A).[45]

Table 4 Anti-HER2 therapies: adjuvant trastuzumab

Study	Trial name	Setting	Primary outcome	Median follow-up	DFS control	DFS gain	DFS HR*	OS control	OS gain	OS HR*	ESMO-MCBS V.1.1	Reference
Chemotherapy±trastuzumab	HERA	Adjuvant or neoadjuvant HER2+tumours	DFS	2 years	DFS 77.4%	8.4%	0.54 (0.43–67)		–	Early crossover at interim analysis	A	34
AC-P vs AC-PH or TCaH	BCIRG006	Adjuvant HER2+tumours	DFS	65 months	75.0%	AC-PH-9%	0.63	87.0%	AC-PH-5%	0.75	A	[36]
AC-P vs AC-PH or TCaH	BCIRG006	Adjuvant HER2+tumours	DFS	65 months	75.0%	TCH-6%	0.75		TCaH-4%	0.77	B	{Slamon, 2011 #1663;Slamon, 2011 #1663[36] }
AC-P vs AC-PH	NSABP B31-NCCTG	Adjuvant HER2+ tumours	DFS	8.4 years	10 years DFS 62.2	11.5%	0.60 (0.53–0.68)	10 years OS 75.2%	8.80%	0.63 (0.54–0.73)	A	{Perez, 2014 #1668[35] }
Adjuvant chemo±trastuzumab	Meta-analysis	HER2+, <2 cm stratified for HR and nodal status	DFS and OS HR+all	8 years	75.7%	7.0%	0.70 (0.59–0.85)	88.4%	3.8%	0.68 (0.52–0.89)	B	{O'Sullivan, 2015 #1811[84] }
Adjuvant chemo±trastuzumab	Meta-analysis	HER2+, <2 cm stratified for HR and nodal status	DFS and OS HR+<1 node	8 years	81.6%	3.8%	0.64 (0.47–0.83)	92.6%	2.1%	0.68 (0.42–1.10)	NEB	{O'Sullivan, 2015 #1811}
Adjuvant chemo±trastuzumab	Meta-analysis	HER2+, <2 cm stratified for HR and nodal status	DFS and OS HR– all	8 years	66.4%	9.4%	0.66 (0.49–0.88)	78.8%	8.8%	0.59 (0.47–0.74)	A	{O'Sullivan, 2015 #1811}
Adjuvant chemo±trastuzumab	Meta-analysis	HER2+, <2 cm stratified for HR and nodal status	DFS and OS HR– <1 node	8 years	73.7%	5.9%	0.77 (0.59–1.00)	87.8%	4.0%	0.69 (0.66–1.04)	NEB	{O'Sullivan, 2015 #1811}

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
A, doxorubicin; C, cyclophosphamide; Ca, carboplatin; chemo, chemotherapy; DFS, disease-free survival; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; H, trastuzumab; HER2+, HER2 overexpression; HR+, hormone receptor-positive; NEB, no evaluable benefit; OS, overall survival; P, paclitaxel; T, docetaxel.

Table 5 HER2 double blockade and second-generation anti-HER2 therapies

Study	Trial name	Setting	Primary outcome	Median follow-up	DFS control (%)	DFS gain (%)	DFS HR*	OS control (%)	OS gain (%)	OS HR*	pCR	QoL	Toxicity	ESMO-MCBS V.1.1	Reference
Neratinib vs placebo	ExteNET	Stage 2–3 HER2+ after 12 months trastuzumab, stratified for HR status	iDFS all	5.2 years	87.7	2.5	0.73 (0.57–0.92)					After first month similar for both arms	40% grade 3 diarrhoea	A	44
Neratinib vs placebo	ExteNET	Stage 2–3 HER2+ after 12 months trastuzumab, stratified for HR status	iDFSHR+	5.2 years	86.8	4.4	0.60 (0.43–0.83)					After first month similar for both arms	40% grade 3 diarrhoea	A	44
Neratinib vs placebo	ExteNET	Stage 2–3 HER2+ after 12 months trastuzumab, stratified for HR status	iDFS HR–ve	5.2 years	88.8	0.1	0.95 (0.66–1.35)					After first month similar for both arms	40% grade 3 diarrhoea	NEB	44
AC-PH vs AC-PHPz	APHINITY	HER2+, stratified for nodal status	iDFS all	45.4 months	93.2	0.9	0.81 (0.66–1.00)							B	41
AC-PH vs AC-PHPz	APHINITY	HER2+, stratified for nodal status	iDFS Node+	44.5 months	90.2	1.8	0.77 (0.62–0.96)							Not scorable†	41
TDM1 vs H	KATHERINE	HER2+ residual disease after neoadjuvant therapy	iDFS	3 years	77.0	11.3	0.50 (0.39–0.64)							A	45
TH±Pz	NeoSphere	HER2+ (phase 2)	pCR								29.0% vs 45.8%			C	8
H vs LH	NeoALTTO	Neoadjuvant	pCR	3.77 years	76.0	8.0	0.78 (0.47–1.28)	85.0	6.0	0.62 (0.3–1.25)	24.7% vs 29.5% vs 51.3%			NEB	42 43
H vs LH	ALTTO	Adjuvant	DFS	4.5 years	86.0	2.0	0.84 (0.70–1.02)	94.0	1.0	0.80 (0.62–1.03)				NEB	85
H 6 vs 12 months	PERSEPHONE	HER2+	DFS (non-inferiority)	4 years	89.8	89.4	1.07 (0.93–1.24)							B	40

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
†More than three prespecified subgroups violates scoring rules.
A, doxorubicin; C, cyclophosphamide; chemo, chemotherapy; DFS, disease-free survival; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; H, trastuzumab; HER2+, HER2 overexpressed; HR+, hormone-positive; HR-neg, hormone-negative; iDFS, invasive disease-free survival; L, lapatinib; NEB, no evaluable benefit; OS, overall survival; P, paclitaxel; pCR, pathological complete response; Pz, pertuzumab; RFS, relapse-free survival; T, docetaxel.

Adjuvant endocrine therapy

Tamoxifen

The addition of 5 years of tamoxifen compared with placebo was graded an A based on increased long-term OS by 6% and 9% at the individual trial level and in the meta-analysis level, respectively (table 6).[46 47]

Aromatase Inhibitors

The aromatase inhibitor studies to score an A were the Intergroup Exemestane(IES) study and the Italian Tamoxifen Anastrozole (ITA) study. The ITA study score was credited based on DFS results alone in the absence of mature OS data.[48] Among the five studies with mature OS data, the data in two did not meet significance thresholds[49–52] and the OS gain merited scores of B[53–55] or C in the other three.[56–58] Comparison aromatase inhibitor alone for 5 years with a switch regimen including tamoxifen and an aromatase inhibitor (2.5 years each) were credited on the basis of non-inferiority in OS and reduced toxicity compared with aromatase inhibitor alone (table 7).[52 55 59 60]

Meta-analysis data resulted in a C score for the use of an aromatase inhibitor alone in the adjuvant setting, and a C when used a part of a switch after tamoxifen.[60]

In the premenopausal population, the addition of an aromatase inhibitor (with ovarian function suppression) scored a C when compared with tamoxifen with ovarian function suppression, in the combined SOFT-TEXT study,[61–63] but it did not score in the ABCSG-12 study.[64]

Extended endocrine therapy

In the MA-17 study of 5 years letrozole or placebo after 5 years tamoxifen, the node-positive subgroup scored A based on DFS criteria.[65 66] Other studies of extended aromatase inhibitor failed to demonstrate improvement in OS.[67–69] The ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) study of 5 years versus 10 years of adjuvant tamoxifen demonstrated a 2.8% reduction in breast cancer mortality (grade C) (table 8).[70]

Ovarian function suppression in premenopausal women

Three studies were evaluated. Two mature studies did not demonstrate significant OS gain.[61 64 71 72] In the SOFT study, a 1.8% OS advantage was observed in the tamoxifen with ovarian function suppression (OFS) arm, scoring a C, and in the subgroup of patients who had received prior chemotherapy the observed gain in OS was 4.3% (grade B) (table 9).[63]

Adjuvant bone-modifying agents

None of the six individual studies demonstrated a survival advantage. A meta-analysis identified a reduction in breast cancer mortality of 1.8% (grade C), largely derived from the benefit observed in postmenopausal subgroup where the benefit was 3.3% (grade B) (table 10).[73]

Expert peer review of the generated results

The scores generated in this field testing were reviewed by the ESMO Breast Cancer Faculty for reasonableness.

Table 6 Tamoxifen

Study	Trial name	Setting	Primary outcome	Median follow-up (years)	DFS control (%)	DFS gain (%)	DFS HR*	OS control	OS gain (%)	OS HR*	ESMO-MCBS V.1.1	Reference
Tamoxifen 5 years vs placebo	NSABP B14	Node– HR+	RFS	15	65.0	13.0	0.58 (0.50–0.67)	65.0%	6.0	0.80 (0.71–0.91)	A	46
Tamoxifen 5 years vs placebo (meta-analysis)	EBCTCG	HR+	DFS and OS	15	46.2	13.2	0.61 (0.57–0.65)	Breast cancer mortality 33.1%	9.2	0.70 (0.64–0.75)	A	47

*HR values in parentheses refer to 95% CI.
DFS, disease-free survival; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HR+, hormone receptor-positive; Node–, node negative; OS, overall survival; RFS, relapse-free survival.

Table 7 Aromatase inhibitors

Study	Trial name	Setting	Primary outcome	Median follow-up	DFS control (%)	DFS gain	DFS HR*	OS control	OS gain (%)	OS HR*	ESMO-MCBS V.1.1	Reference
A 5 years vs Tam 5 years	ATAC	Postmenopausal HR+	DFS	120 months	76.0	4.30%	0.86 (0.78–0.95)	77.5%	1.0	0.95 (0.84–1.06)	NEB	49–51
L vs Tam (5 years)	BIG 1–98	Postmenopausal HR+	DFS	97.2 months	72.0	4.4%	0.82 (0.74–0.92)	81.4%	4.0	0.79 (0.69–0.90)	B	53–55
L vs Tam→L vs L→Tam	BIG 1–98	Postmenopausal HR+	DFS (Tam→L)	71 months	87.9	–1.7	1.05 (0.84–1.32)	93.4%	–1.0	1.13 (0.83–1.53)	B	55 59
L vs Tam→L vs L→Tam	BIG 1–98	Postmenopausal HR+	DFS (L→Tam)	71 months	87.9	–0.3%	0.96 (0.76–1.21)	93.4%	–0.3	0.90 (0.65–1.24)	B	55 59
Tam 2–3→E 2–3 vs Tam 5 years	IES	Postmenopausal HR+ and unknown	DFS	55.7 months	–	All 3.3%	0.76 (0.66–0.88)	88.0%	1.3	0.85 (0.71–1.02)	B	56 57
Tam 2–3→E 2–3 vs Tam 5 years	IES	Postmenopausal HR+	DFS	55.7 months	–	HR+ 3.5%	0.75 (0.65–0.87)	87.9%	1.8	0.83 (0.69–0.99)	A	56 57
Tam 2→A 3 years vs Tam 5 year	ARNO-95	Tam 2→A 3 years vs Tam 5 years	DFS	30.1 months	89.3	4.2%	0.66 (0.44–1.00) p=0.049	94.3%	2.6	0.53 (0.28–0.99)	C	58
E vs Tam->E	TEAM	E 5 years vs Tam 2–3 years →E 5 years	DFS	5.1 years	85.0**	1.0%	0.97 (0.88–1.08)	91.0%	0	1.00 (0.89–1.14)	B	52
Tam vs Tam→A	ITA	Postmenopausal HR+ Node+	DFS	36 months	85.8	8.8%	0.35 (0.18–0.68)				A	48
5 years Tam vs 5 years AI (meta-analysis)	EBCTCG	Postmenopausal HR+	DFS and OS	10 years	22.7	3.6%	0.80 (0.73–0.88)	Breast cancer mortality 14.2%	2.1	0.85 (0.75–0.96)	C	60
5 years Tam vs 5 years AI (meta-analysis)	EBCTCG	Postmenopausal HR+	DFS and OS	10 years	22.7	3.6%	0.80 (0.73–0.88)	Overall mortality 24%	2.7	0.89 (0.8–0.97)	C	60
5 years Tam vs Tam→AI (meta-analysis)	EBCTCG	Postmenopausal HR+	DFS and OS	10 years	19.0	2.0%	0.82 (0.75–0.91)	Breast cancer mortality 10%	1.5	0.84 (0.72–0.96)	C	60
5 years Tam vs Tam→AI (meta-analysis)	EBCTCG	Postmenopausal HR+	DFS and OS	10 years	19.0	2.0%	0.82 (0.75–0.91)	Overall mortality 17.5%	2.9	0.82 (0.73–0.91)	C	60
Tam→AI vs upfront AI (meta- analysis)	EBCTCG	Postmenopausal HR+	DFS and OS	7 years	14.5	0.7%	0.9 (0.81–0.99)	Breast cancer mortality 9.3%	1.1	0.89 (0.78–1.03)	NEB	60
Tam→AI vs upfront AI (meta- analysis)	EBCTCG	Postmenopausal HR+	DFS and OS	7 years	14.5	0.7%	0.9 (0.81–0.99)	Overall mortality 14.5%	0.9	0.96 (0.86–1.07)	NEB	60

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
A, anastrozole; AI, aromatase inhibitor; DFS, disease-free survival; E, exemestane; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HR+, hormone receptor-positive; L, letrozole; NEB, no evaluable benefit; Node+, node-positive; OS, overall survival; Tam, tamoxifen.

Table 8 Extended endocrine therapy

Study	Trial name	Setting	Primary outcome	Median follow-up	DFS control	DFS gain (%)	DFS HR*	OS control	OS gain (%)	OS HR*	ESM0-MCBS V.1.1	Reference
Letrozole 5 years vs placebo	MA-17	Postmenopausal HR+ after 5 years tamoxifen (all)	DFS	30 months	89.8%	4.6	0.58 (0.45–0.76)	95.0%	0.4	0.82 (0.57–1.19)	A	65 66
Letrozole 5 years vs placebo	MA-17	Postmenopausal HR+ after 5 years tamoxifen (Node+)	DFS	30 months			0.61 (0.45–0.84)			0.61 (0.38–0.98)	A	65 66
Letrozole 5 years vs placebo	MA-17R	Postmenopausal HR+ after 5 years tamoxifen	DFS	6.3 years	91.0%	4.0	0.66 (0.48–0.91)	94.0%	1.0	0.97 (0.73–1.28)	NEB	67
Anastrozole for 3 years vs placebo	ABCSG6a	Postmenopausal HR+ after 5 years tamoxifen	RFS	>5 years	7.1%	4.7	0.62 (0.40–0.96)	88.3%	1.4	0.98 (0.59–1.34)	NEB	68
Exemestane vs placebo	NSABP-B33	Postmenopausal HR+ after 5 years tamoxifen	DFS	30 months	89.0%	2.0	0.68 p=0.07				NEB	69
Tamoxifen	ATLAS	Postmenopausal HR+ after 5 years tamoxifen	BC recurrence and BC mortality	7.6 years	Risk of recurrence at ≥10 years 25.1%	3.7	0.75 (0.62–0.90)	BC mortality 15%	2.8	0.71 (0.58–0.88)	C	70

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
BC, breast cancer; DFS, disease-free survival; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HR+, hormone receptor-positive; NEB, no evaluable benefit; Node+, node-positive; OS, overall survival; RFS, relapse free survival.

Table 9 Ovarian function suppression in premenopausal women

Study	Trial name	Setting	Primary outcome	Median follow-up (months)	DFS control (%)	DFS gain (%)	DFS HR*	OS control (%)	OS gain (%)	OS HR*	ESMO-MCBS V.1.1	Reference
Exemestane+OFS vs Tam+OFS	SOFT-TEXT	All	DFS	96	82.8	4.0	0.77 (0.67–0.90)	91.8	2.1	0.80 (0.66–0.96)	C	62 86
Tam vs Tam+OFS vs exemestane+OFS	SOFT	All	DFS Tam+OFS	96	78.9	4.3	0.76 (0.62–0.93)	91.5	1.8	0.67 (0.48–0.92)	C	62 87
Tam vs Tam+OFS vs exemestane+OFS	SOFT	All	DFS E+OFS	96	78.9	7.0%	0.65 (0.53–0.81)	91.5	0.6	0.85 (0.62–1.15)	NEB	62 87
Tam vs Tam+OFS vs exemestane+OFS	SOFT	No chemo	DFS Tam+OFS	96	87.4	3.2	0.76 (0.52–1.12)		1.6	0.74 (0.51–1.09)	NEB	62 87
Tam vs Tam+OFS vs exemestane+OFS	SOFT	No chemo	DFS E+OFS	96	87.4	5.2	0.58 (0.38–0.88)				NEB	62 87
Tam vs Tam+OFS vs exemestane+OFS	SOFT	Past- chemo	DFS Tam+OFS	96	71.4	5.3	0.76 (0.60–0.97)	85.1	4.3	0.59 (0.42–0.84)	B	62 87
Tam vs Tam+OFS vs exemestane+OFS	SOFT	Past- chemo	DFS E+OFS	96	71.4	9.0	0.82 (0.64–1.07)	85.1	2.1	0.79 (0.57–1.09)	NEB	62 87
Anastrozole+OFS vs Tam+OFS	ABCSG-12	Premenopausal HR+	DFS	94.4	NA	–	1.08 (0.81–1.44)	96.3	–2.1	1.63 (1.05–2.52)	NEB	64 71 72

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
chemo, chemotherapy; DFS, disease-free survival; E, exemestane; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; OFS, ovarian function suppression; OS, overall survival; Tam, tamoxifen.

Table 10 Adjuvant bone-modifying agents

Study	Trial name	Setting	Primary outcome	Median follow-up	DFS control (%)	DFS gain (%)	DFS HR*	OS control	OS gain (%)	OS HR*	ESMO-MCBS V.1.1	Reference
Clodronate vs placebo	NSABP-B34	Adjuvant clodronate	DFS	90.7 months	NA	Nil	0.91 (0.78–1.07)	NA	Nil	0.84 (0.65–1.05)	NEB	88
Ibandronate vs placebo	GAIN	HR+ Node+	DFS	38.7 months	NA	Nil	0.94 (0.77–1.16)	NA	Nil	0.96 (0.71–1.31)	NEB	89
Denosumab vs placebo	ABCSG-18	Postmenopausal women on AI	Time-to-first clinical fracture		NA		NA	NA		NA	SNA	90
Clodronate vs placebo	Adjuvant clodronate	Adjuvant clodronate	Time-to-first bone metastases	5.6 years	NA	NA	NA	79.3%	3.6	0.77 (0.56–1.00) NS	NEB	91 92
Zoledronate vs placebo	ABCSG-12	Premenopausal with OFS	DFS	94.4 months	85	3.40	0.77 (0.60–0.99)	94.5%	2.2	0.66 (0.43–1.02)	NEB	64 71 72
Zoledronate vs placebo	AZURE/BIG01-04		DFS (all patients)	84 months	NA		0.94 (0.82–1.06)	NA		0.93 (0.81–1.07)	NEB	93 94
Zoledronate vs placebo	AZURE/BIG01-04		DFS 5 years+menopausal at diagnosis		NA	–	0.77 (0.63–0.96)	NA	–	0.81 (0.63–1.04)	NEB	93 94
Adjuvant bisphosphonate (meta-analysis)	EBCTCG	With hormonal therapy	DFS and OS	5.6 years			All	Breast cancer mortality 18.4%	1.8	0.91 (0.83–0.99)	C	60
Adjuvant bisphosphonate (meta-analysis)	EBCTCG	With hormonal therapy	DFS and OS	5.6 years				All-cause mortality 22.3%	1.5	0.92 (0.85–1.00) p=0.06	NEB	60
Adjuvant bisphosphonate (meta-analysis)	EBCTCG	With hormonal therapy	DFS and OS	5.6 years			Postmenopausal	Breast cancer mortality 18%	3.3	0.82 (0.73–0.93)	B	60
Adjuvant bisphosphonates (meta-analysis)	EBCTCG	With hormonal therapy	DFS and OS	5.6 woman years			Premenopausal	Breast cancer mortality 20.7%	–0.1		NEB	60

Chart blanks—relevant variables not available in manuscript.
*HR values in parentheses refer to 95% CI.
AI, aromatase inhibitors; DFS, disease-free survival; ESMO-MCBS, The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HR+, hormone receptor-positive; NA, not applicable; NEB, No evaluable benefit; Node+, node-positive; NS, not statistically significant; OFS, ovarian function suppression; OS, overall survival; SNA, scoring not applicable.

Apart from the scores for double HER2 blockade, the derived scores were more commonly endorsed as reasonable than unreasonable. There was no consensus about the grading for double HER2 blockade (unreasonable 32%; reasonable 29%): many respondents expounded that the scores for the APHINITY and ExteNET studies, derived from the relative benefit gain in DFS but with very small absolute benefit, were excessively high. In situations when the primary outcome of the study was DFS, and a robust DFS benefit was observed (in terms of both relative and absolute benefits) but without significant OS benefit, a proportion of reviewers expressed that a grade of NEB under represented the clinical value of prolonged interim time without disease, treatment and toxicity.

DISCUSSION

The validity of the ESMO-MCBS is predicated on adherence to the public policy ethical standard of 'accountability for reasonableness' and the field testing of the scale over a large range of clinical trials is an important part of the development process. This study, applying the ESMO-MCBS V.1.1 to 59 individual trials and 6 meta-analyses, has demonstrated that form 1 of the ESMO-MCBS can be applied to systemic adjuvant therapy trials. Moreover, apart from a few specific exceptions, the generated grades were considered reasonable by experts in the ESMO Breast Cancer Faculty, largely reflecting standard clinical practice.

Applying the scale and interpreting the results was, in most instances, straightforward. A small number of studies did not incorporate all critical data in accordance with CONSORT standards. In some instances HRs were published without CIs, some meta-analyses did not include absolute gain data for OS[12] and some studies report the HR to reflect increased recurrence risk (eg, MA-21).[19] Furthermore, even with long-term follow-up, some studies never published follow-up of their mature survival data. Since magnitude of benefit grades derived from OS gain at maturity is often less than that derived from DFS, the non-publication of mature OS results occasionally resulted in disproportionally high scores in some studies. This is well illustrated in two examples: no mature survival data were ever published for the ITA study by Boccardo *et al* which evaluated switching from tamoxifen to an aromatase inhibitor[48] and the MA21 study that evaluated the addition of paclitaxel to an anthracycline.[19] Consequently, these were among the few studies in their respective classes to score an A, while all others for which mature survival data were available scored C or NEB. We note that this anomaly could be misinterpreted to suggest superiority, or even manipulated with delays or even non-reporting of mature OS data to avoid downgrading.

We note that the ESMO-MCBS is agnostic to DFS type and does not distinguish between DFS, invasive DFS (iDFS) and distant DFS (DDFS) that is also called 'distant metastasis-free survival'. In recent years, there has been a shift to more accurate end points such as invasive iDFS or DDFS, which are better surrogates for OS benefit,[74] since they emphasise events that are more closely related to cancer mortality (ie, invasive relapse or distant metastases). This underscores the importance of new initiatives to introduce standardisation in the definitions and application of these end points.[74 75]

A key aim of this study was to identify shortcomings in the current version of form 1 which will be addressed in future versions of the scale. This field testing and peer-review process identified six shortcomings in form 1. All of these shortcomings have been reviewed by the ESMO-MCBS Working Group and initiatives are underway to address each of them as part of the forthcoming revisions to be incorporated in the next version of the scale (V.2.0).

1. *HR thresholds for DFS are excessively lenient*: The experience of this field testing indicates that trials initially graded on the basis of DFS in initial publications, commonly attained lower scores when mature OS data were available and that in many cases the OS gains were not significant. This indicates that the relative benefit thresholds for grade B and C (lower limit of the 95% CI of the HR 0.65–0.85 and >0.85, respectively) are excessively lenient. Consequently, we recommend lowering of the HR thresholds for grades B and C.

2. *Lack of absolute gain constraint on DFS scoring can generate inappropriately high scores when absolute gain is very small*: Expert peer reviewers concerned that grades accrued on the basis of relative benefit when the observed absolute benefit is very small were unreasonably high. This was highlighted in their critique of scores generated in the APHINITY[41] and ExteNET[44] trials. This could be corrected by applying the 'dual rule' whereby grade criteria include both relative and absolute benefit thresholds in a manner that is constant with all other forms of the ESMO-MCBS V.1.1.

3. *The clinical benefit derived from DFS gain is not credited when OS gain is not verified. In many instances, gains derived from DFS were not credited when there was no significant gain in mature OS*. When substantially improved DFS does not result in improved OS, the grading of NEB undervalued the time gained without need for medical treatment, which may itself be a valued outcome independent of OS.[76]

4. *Need to define OS maturity in adjuvant studies*: According to the ESMO-MCBS V.1.1, surrogate scores prevail if mature OS data are not yet available. Maturity is generally defined as the time point where most of the anticipated events will have occurred. In a non-curative setting, when all patients are expected to die, conventionally it is when the median survival of both arms is reached. However, in the adjuvant setting, when the number of anticipated events may vary according to the tumour type and stage, this convention does not apply.

Consequently, evaluating maturity of survival data in this setting requires familiarity with the specific clinical scenario and it is conceivable that in some instances this may be source of reasonable disagreement even between experts. ESMO-MCBS instructions for use

should include guidelines for OS maturity. For example, 5 years for subtypes at high risk for earlier recurrence (such as triple negative and HER2-positive/endocrine unresponsive subtypes) and at least 8 years for endocrine responsive tumours (including HER2-positive/endocrine-responsive).[77]

5. *Lack of capacity to grade single-arm de-escalation studies in the curative setting*: A recent single-arm phase 2 study reported excellent outcomes for node-negative HER2-positive breast cancers smaller than 2 cm treated with the combination of paclitaxel and trastuzumab (without an anthracycline).[78] These type of studies are often used to evaluate de-escalation strategies. Form 1 is unable to grade these studies.

6. *Lack of consideration of toxicity in the curative setting*: The current version of form 1 does not consider toxicity. The shortcoming of this approach is illustrated by the ExteNET study that scores an 'A' for the hormone-positive subgroup despite very substantial toxicity secondary to the neratinib, which resulted in a 27.6% discontinuation rate.[44] While we appreciate that patients may be willing to make short-term toxicity trade-off to improve cure rate, it is not clear that this approach applies also for long-term toxicity such as peripheral neuropathy or secondary cancers (especially when improvement in cure rate may be small). We support the proposition, initially made by patient advocacy groups, that ESMO-MCBS scores in form 1 should be annotated to indicate acute and/or long-term toxicities.

CONCLUSIONS

In a time of exponential growth in the costs of cancer care, tools to assist physicians and regulatory bodies in evaluating new therapeutic options are critical. This study reinforces the validity of the ESMO-MCBS approach to adjuvant therapies insofar as the scoring of adjuvant approaches in early breast cancer largely reflects standard clinical practice. This field testing has identified six shortcomings that have been reviewed by the ESMO-MCBS Working Group and that form the foundation for amendments to be incorporated into future iterations of the ESMO-MCBS.

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