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BEST PRACTICE

THE ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1

User instructions and ESMO-MCBS case studies

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DISCLOSURES

- Elisabeth de Vries does not hold stock in any business. She is currently conducting research sponsored by the following companies: Amgen, Roche/Genentech, Chugai Pharma, Synthon, AstraZeneca, Radius Health, CytomX Therapeutics and Nordic Nanovector (all payments to the institution). She has a consulting or advisory role for the following company: Pfizer (all payments to the institution). She is not a member of any Speaker's Bureau.
- Nathan Cherny has reported no conflicts of interest
- Nicola Latino has reported no conflicts of interest

INSTRUCTIONS

Initial steps

- Identify control and experimental aims OR single arm
- Comparative study type: randomized phase II or III, meta-analysis, cohort
- Identify study group and specific indications
- Identify pre-specified subgroups (if any): confirm ≤3
- Identify primary outcomes: OS, DFS/PFS/TTP, QoL, Non-inferiority
- Identify secondary outcomes: OS, QoL (check that this is a valid scale), Toxicity
- Type of study/appropriate form (there are 5 forms):
  - Curative intent
    - Adjuvant/Curative therapy — Form 1
  - Non-curative intent
    - OS — Form 2a
    - PFS — Form 2b
    - Comparative: RR or QoL or Non-inferiority — Form 2c
    - Single arm — Form 3

UNDERLYING PREMISES

1. Cure takes precedence over deferral of death
2. Direct endpoints such as survival and QoL take precedence over surrogates such as PFS or RR
3. DFS in curative disease is a more valid surrogate than PFS in non-curative disease
4. Interpretation of the evidence for benefit derived from surrogate outcomes (such as PFS or RR) may be influenced by secondary outcome data
5. Tail of curve data may sometimes indicate important gain for a minority of responders
6. Data from RCTs are more credible than from single arm studies

DUAL RULE

Relative benefit rule:

- The lower limit of the 95%CI for the HR is compared with specified threshold values
- PFS: LL95%CI<0.65
- OS: LL95%CI<0.65 or LL<0.70 for median control < 12 months or >12 months, respectively

Absolute benefit rule:

- The observed absolute difference in median treatment outcomes is compared with the **minimum clinically significant absolute benefit**

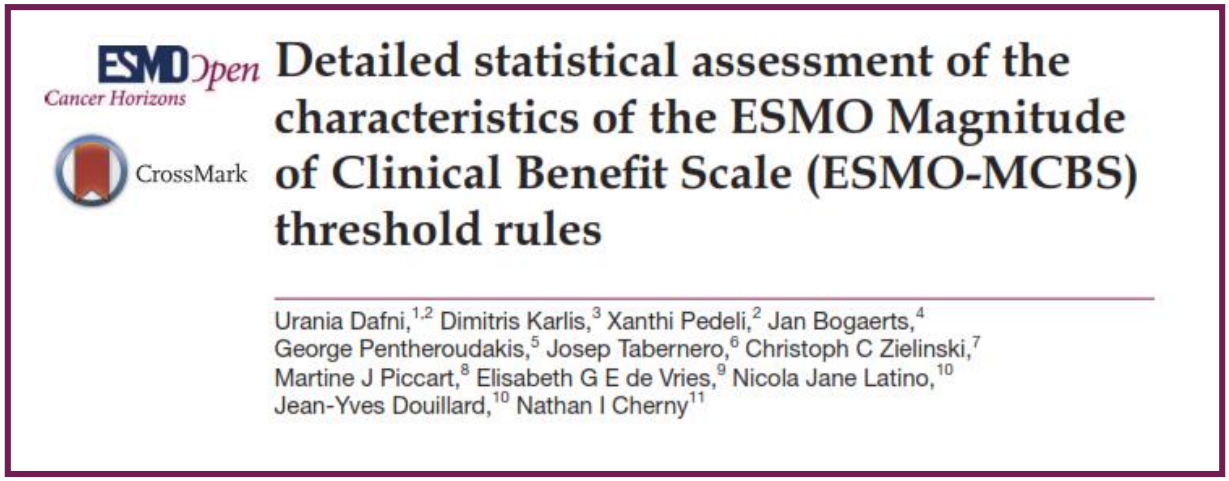
CATEGORICAL APPROACH USING LL96%CI<0.65

Avoid inaccurate claims of precision (integrity)

Robustly credits true big benefit (inclusiveness)

Avoids over crediting small benefit (discernment)

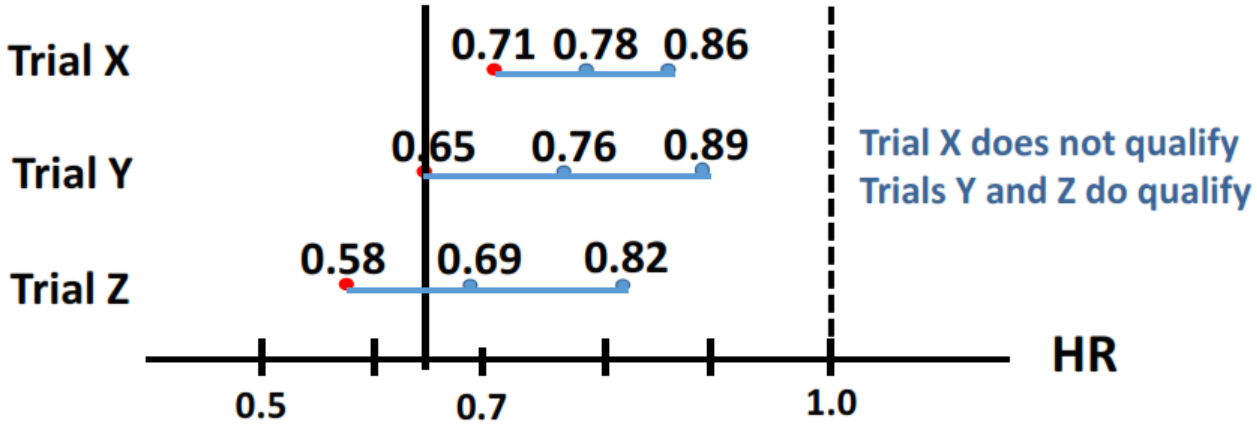
Discernment is further strengthen by dual RB+AB criteria



INSTRUCTIONS CONT.

Use of the LL 95% CI

For a required HR, not the point estimate but the lower limit of 95% CI estimated based on the observed HR in the trial should encompass the required HR



Example: for threshold set at HR <0.65 it is the lower limit of the 95%CI which has to be <0.65

FORMS ESMO-MCBS V1.1

Curative setting	→	**Evaluation form 1** **grade A, B, C**
Non-curative setting	→	**Evaluation form 2a** **grade 5, 4, 3, 2, 1** **Evaluation form 2b** **grade 4, 3, 2, 1** **Evaluation form 2c** **grade 4, 3, 2, 1**
Non-curative setting Single arm studies	→	**Evaluation form 3** **grade 4, 3, 2, 1**

FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies: **Key steps**

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

Is mature OS data available?

- Document baseline and Gain

If Not, evaluate DFS

- Gain must meet criteria for statistical significance
- Document Control, Gain, HR

Is pCR the primary outcome

- Document baseline and Gain

Evaluate toxicity data

FORM 1

For new approaches to adjuvant therapy or new potentially curative therapies

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 - 0.80) 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 >0.80) in studies without mature survival data	
Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain 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 OS: **Key steps**

Document OS of control group to select correct prognostic group

- IF median OS with the standard treatment is ≤12 months
- IF median OS with the standard treatment >12 months, ≤24 months
- IF median OS with the standard treatment >24 months

Document gain and HR including LL 95%CI

- Overall
- Each pre specified subgroup

Evaluate Kaplan-Meier curve

- For evidence of >10% benefit at 2-3 years
- For plateau with gain of >10% benefit at 5-7 years (if so score also with Form A)

Calculate preliminary score(s)

Evaluate toxicity, QoL

Apply adjustments

FORM 2A

For therapies that are not likely to be curative with primary endpoint OS: **Key steps**

IF median OS with the standard treatment ≤12 months

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 ≥ 2.0 - <3 months	
Grade 2	
HR ≤0.65 AND Gain ≥1.5 - <2 months	
HR >0.65-0.70 AND Gain ≥1.5 months	
Grade 1	
HR > 0.70 OR Gain <1.5 months	

FORM 2A

For therapies that are not likely to be curative with primary endpoint OS: **Key steps**

IF median OS with the standard treatment >12 months <24 months

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 - <5 months	
Grade 2	
HR ≤0.70 AND Gain >1.5 - <3 months	
HR >0.65-0.70 AND Gain ≥1.5 months	
Grade 1	
HR > 0.75 OR Gain <1.5 months	

FORM 2A

For therapies that are not likely to be curative with primary endpoint OS: **Key steps**

IF median OS with the standard treatment >24 months

	Mark with X if relevant
Grade 4	
HR ≤0.70 AND Gain ≥9 months	
Increase in 5 year survival alone ≥10%	
Grade 3	
HR ≤0.70 AND Gain >6 - <9 months	
Grade 2	
HR ≤0.70 AND Gain >4 - <6 months	
HR >0.70-0.75 AND Gain >4 months	
Grade 1	
HR >0.75 OR Gain <4 months	

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FORM 2A

For therapies that are not likely to be curative with primary endpoint OS:
Preliminary magnitude of clinical benefit grade

STEP 1

4	3	2	1

Assessment QoL & grade 3-4 toxicities

STEP 2

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

Upgrade 1 level if improved QoL or toxicity is shown

If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5/7 year, also score according to Form 1 (treatments with curative potential) and present both scores i.e. A/4

Final adjusted magnitude of clinical benefit grade

STEP 3

5	4	3	2	1

FORM 2B:

For therapies that are not likely to be curative with primary endpoints PFS: **Key steps (appreciate that this is more challenging)**

Document PFS of control group to select correct prognostic group

- IF median PFS with standard treatment ≤6 months
- IF median PFS with standard treatment >6 months

Scan data for information relating to:

- Crossover, subsequent treatments interim assessment and early un-blinding

Document gain and HR including LL 95%CI

- Overall
- Each pre specified subgroup

If OS data is available:

- Is it mature/immature (criteria: control arm has achieved median survival)
- Significant/non-significant
- Document OS data if significant (if significant consider using 2A if gain reaches criteria for grade 3 or 4)

Calculate Preliminary score(s)

FORM 2B:

For therapies that are not likely to be curative with primary endpoints
PFS cont.: **Key steps (appreciate that this is more challenging)**

Evaluate Kaplan Meier curves for long term plateau with >10% difference at 12+ months

Evaluate Toxicity using the criteria listed

Evaluated Global QoL:

- Improvement OR delayed deterioration

Key information for adjustments

- Plateau >10% gain
- Toxicity
- QoL
- OS
- Early un-blinding b/c OS advantage

Apply adjustments

FORM 2B:

For therapies that are not likely to be curative with primary endpoints PFS cont.

Studies with median PFS with standard treatment ≤6 months

	Mark with X if relevant
Grade 3	
HR ≤0.65 AND Gain ≥1.5 months	
Grade 2	
HR ≤0.65 BUT Gain <1.5 months	
Grade 1	
HR >0.65	

FORM 2B:

For therapies that are not likely to be curative with primary endpoints PFS cont.

Studies with median PFS with standard treatment >6 months

	Mark with X if relevant
Grade 3	
HR ≤0.65 AND Gain ≥3 months	
Grade 2	
HR <0.65 BUT Gain <3 months	
Grade 1	
HR >0.65	

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FORM 2B:

For therapies that are not likely to be curative with primary endpoints PFS cont.

Preliminary magnitude of clinical benefit grade (highest grade scored)

STEP 1

3	2	1

STEP 2

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?	
Was there early crossover because or early stopping or crossover based on detection of survival advantage at interim analysis	

(If the answer to both is “yes”, then see adjustment “a” below)

FORM 2B:

For therapies that are not likely to be curative with primary endpoints PFS cont.

Toxicity and QoL adjustment when only a PFS improvement

STEP 3

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)

FORM 2B:

For therapies that are not likely to be curative with primary endpoints PFS cont.

STEP 4

Assessment QoL & grade 3-4 toxicities

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*	

a) When OS as 2nd endpoint is improved, it prevails, score according to form 2a
b) Downgrade 1 level if ≥ 1 of above incremental toxicities
c) Downgrade 1 level if the drug ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL
d) Upgrade 1 level if > QoL or if less grade 3-4 toxicities that bother patients
e) Upgrade 1 level if study had early crossover because of early stopping or crossover based on detection of survival advantage at interim analysis
f) Upgrade 1 level if there is a long term plateau in the PFS curve, and there is ≥10% improvement in PFS at 1/2 year

STEP 5

Final, toxicity and QoL adjusted, magnitude clinical benefit grade

4	3	2	1

Highest grade that can be achieved grade 4

FORM 2C:

For therapies that are not likely to be curative with primary endpoint other than OS or PFS and or equivalent studies

Identify non OS/PFS outcomes

- Noninferiority
- RR
- QoL

Noninferiority studies

- Confirm non-inferiority
- Evaluate for data on toxicity, QoL, Cost

QoL studies

- Evaluate global *vs*. isolated symptom benefit
- Survival benefit

FORM 2C:

For therapies that are not likely to be curative with primary endpoint other than OS or PFS and or equivalent studies

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

Grade 4	Mark with X if relevant
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	
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

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FORM 3:

For single-arm studies in “orphan diseases” and for diseases with “high unmet need” when primary outcome is PFS or ORR

Confirm that there is no data from randomized study available

Key data extraction

- PFS (is it > 6 months)
- ORR (PR+CR)
- Duration of response

Calculate preliminary score

Evaluate toxicity

- >30% grade 3-4 toxicities impacting on daily well-being

QoL: Improvement

Search for Mature phase IV data

EVALUATION FORM 3:

For single-arm studies in “orphan diseases” and for diseases with “high unmet need” when primary outcome is PFS or ORR

Grade 3	Mark with X if relevant
PFS ≥6 months	
ORR (PR+CR) ≥60%	
ORR (PR+CR) ≥20, <60% AND Duration of response ≥9 months	

Grade 2	
PFS ≥3-<6 months	
ORR (PR+CR) ≥40, <60%	
ORR (PR+CR) ≥20, <40% AND Duration of response ≥6 months <9 months	

Grade 1	
PFS 2-<3 months	
ORR (PR+CR) ≥20, <40% AND Duration of response <6 months	
ORR (PR+CR) >10, <20% AND Duration of response ≥6 months	

EVALUATION FORM 3:

For single-arm studies in “orphan diseases” and for diseases with “high unmet need” when primary outcome is PFS or ORR

STEP 1

Preliminary magnitude of clinical benefit grade (highest grade scored)

3	2	1

STEP 2

Quality of life/grade 3 -4 toxicities assessment

	Mark with X if relevant
Was quality of life (QoL) evaluated as secondary outcome?	
Does secondary endpoint quality of life show improvement	
Are there ≥30% 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 are ≥30% grade 3-4 toxicities impacting on daily well-being*
b. Upgrade 1 level if improved quality of life
c. Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

STEP 3

Final adjusted magnitude of clinical benefit grade

4	3	2	1

CASE STUDIES

With illustrative points

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HERA (PICCART-GEBHART): ADJUVANT FORM 1

Illustrates form 1 for adjuvant studies

Medication	Trial Name	Setting	Primary outcome	DFS control	DFS Gain	DFS HR	OS control	OS Gain	OS HR	QoL	Toxicity	ESM0-MCBS V1.1	Tumour setting
Chemotherapy +/- trastuzumab	HERA	Adjuvant or neo-adjuvant HER2 positive tumours	DFS	2 years DFS 77.4%	8.40%	0.54 (0.43-0.67)						A	Breast

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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.

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BEV 1ST LINE (MILLER): PFS FORM 2B

Example of QoL penalty when PFS not supported by either OS or QoL gain

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS control	OS Gain	OS HR	QoL	Toxicity	ESM0-MCBS V1.1	Tumour setting
Paclitaxel +/- bevacizumab		1st line metastatic breast (no crossover)	PFS	5.9 months	5.9 months	0.60 (0.51–0.70)			NS	No improvement		2	Breast

Miller K, Wang M, Gralow J, *et al.,* Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New Engl J Med 2007; 357: 2666-2676.

CRYSTAL (VAN CUTSEM): OS FORM 2A

Example of PFS study with OS gain form 2b=>2a because of OS gain

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS control	OS Gain	OS HR	QoL	Toxicity	ESM0-MCBS V1.1	Tumour setting
FOLFIRI +/- cetuximab	CRYSTAL	1st line metastatic Colorectal stratified for KRAS-WT (post hoc KRAS, MRAS WT)	PFS	8.4 months	3 months	0.56 (0.41-0.76)	20.2 months	8.2 months	0.69 (0.54-0.88)			4	Colorectal

Van Cutsem E, Lenz HJ, Kohne CH, *et al.,* Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015; 33: 692-700.

MAGIC (CUNNINGHAM): ADJUVANT FORM 1

Example of non chemotherapy intervention in curative setting

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS Control	OS Gain	OS HR	ESMO-MCBS v1.1	Tumour Setting
Surgery +/- perioperative epirubicin, cisplatin, 5-FU	MAGIC	Gastric or distal oesophagus stage II-III	OS				5-year survival 23%	13%	0.66(0.53-0.81)	A	Gastro-oesophageal

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Cunningham D, Allum WH, Stenning SP, *et al.,* Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New Engl J Med 2006; 355: 11-20.

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RAINBOW (WILKE): OS FORM 2A

K-M plot at 2 year: gain <10%➔ no upgrade

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS control	OS Gain	OS HR	QoL	Toxicity	ESM0-MCBS V1.1	Tumour setting
Paclitaxel + ramucirumab vs paclitaxel + placebo	RAINBOW	2nd line advanced or metastatic gastric or EGJ adenocarcinoma after platinum plus fluoropyrimidine +/- anthracycline	OS				7.4 months	2.2 months	0·81 (0·68-0·96)			2	Gastro-oesophageal

Wilke H, Muro K, Van Cutsem E, *et al.,* Ramucirumab plus paclitaxel *versus* placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. The Lancet. Oncology 2014; 15: 1224-1235.

CHECKMATE 017 (BRAHMER): OS FORM 2A

Illustrates score for 2 year survival gain with toxicity bonus

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS control	OS Gain	OS HR	QoL	Toxic-ity	ESM0-MCBS V1.1	Tumour setting
Nivolumab vs docetaxel	CheckMate 017	2nd line after platinum-based therapy advanced squamous-cell NSCLC	OS	2.8 months	0.7 months	0.62 (0.47-0.81)	6 months	3.2 months 2-year survival gain >10%	0.59 (0.44-0.79)	Reduced grade 3/4 AE 7% vs 55%		5	Lung

Brahmer J, Reckamp KL, Baas P, *et al.,* Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015; 373: 123-135.

AURA-3 (MOK): PFS FORM 2B

Illustrates crossover study with PFS gain toxicity bonus

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS control	OS Gain	OS HR	QoL	Toxicity	ESM0-MCBS V1.1	Tumour setting
Osimertinib vs platinum/ pemetrexed	AURA3	2nd line for EGFR mutated NSCLC after TKI with new T790M mutation	PFS (crossover allowed)	4.4 months	5.7 months	0.30 (0.23-0.41)					Reduced toxicity	4	Lung

Mok TS, Wu YL, Ahn MJ, *et al.,* Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2016.

CHEMOTHERAPY +/- PALLIATIVE CARE (TEMEL): QOL FORM 2C

Illustrates QoL primary outcome (sole example)

Medication	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS Control	OS Gain	OS HR	QoL	ESMO-MCBS v1.1	Tumour Setting
Chemotherapy +/- palliative care	Stage IV NSCLC ECOG<2	QoL				8.9 months	2.7 months	HR for death in control arm 1.7 (1.14-2-54)	Improved	4	Lung

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.

REVEL (GARON): OS FORM 2A

Illustrates small 2 year survival advantage not credited because not significant

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS control	OS Gain	OS HR	QoL Toxicity	ESM0-MCBS V1.1	Tumour setting
Docetaxel +/- ramucirumab	REVEL	2nd line after platinum-based therapy NSCLC	OS				9.1 months	1.4 months	0·86 (0·75–0·98) 2-year survival gain 3-5%		1	Lung

Garon EB, Ciuleanu TE, Arrieta O, *et al.,* Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014; 384: 665-673.

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IPILIMUMAB 1ST LINE (ROBERT, MAIO): OS FORM 2A & FORM 1

Illustrates OS study with 5 year survival gain and plateau=> also scored with Form 1=> double score

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS Control	OS Gain	OS HR	QoL	ESMO-MCBS v1.1	Tumour Setting
Dacarbazine +/- ipilimumab		1st line metastatic melanoma	OS (crossover allowed)				5-year survival 8.8%	9.40%	2-year survival gain 11%		A/4	Melanoma

Robert C, Thomas L, Bondarenko I, *et al.,* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. New Engl J Med 2011; 364: 2517-2526.
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.

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OLARATUMAB (TAP): OS FORM 2A

Illustrates challenges with randomised phase II studies

Medication	Trial Name	Setting	Primary outcome	PFS control	PFS Gain	PFS HR	OS Control	OS Gain	OS HR	QoL	ESMO-MCBS v1.1	Tumour Setting
Doxorubicin +/- olaratumab		Advanced soft tissue sarcoma not previously treated with doxorubicin	PFS	4.1 months	2.5 months	NS	14.7 months	11.8 months	0·46 (0·30-0·71)		4*	Sarcoma

* Randomised phase II study

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Tap WD, Jones RL, Van Tine BA, *et al.,* Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016.

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OLAPARIB 4TH LINE: SINGLE ARM FORM 3

Illustrates use of form 3

Medication	Trial Name	Setting	Stratification	ORR	CR	DoR	PFS	QoL	Toxicity	ESMO-MCBS v1.1	Tumour Setting
Olaparib		After 3 lines of therapy BRCA mutated (Germline OR somatic)		31%	3%	7 months	7 months			3	Ovarian

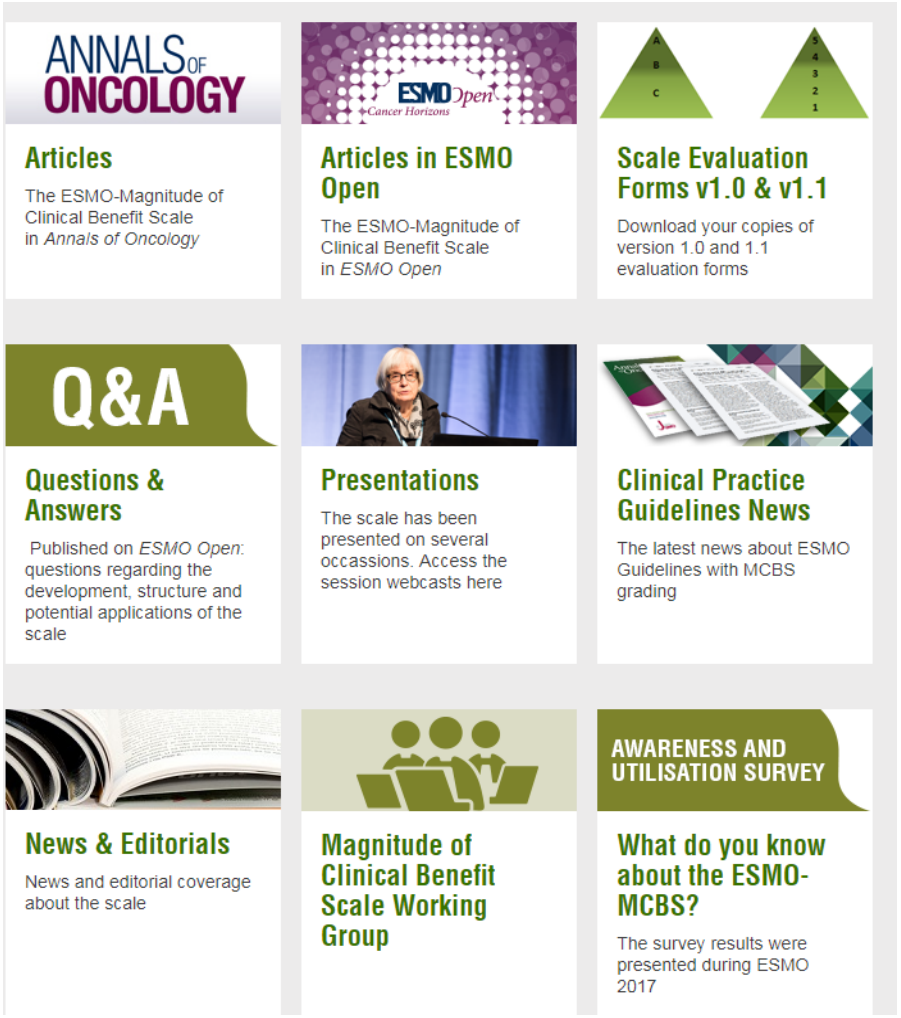
Kaufman B, Shapira-Frommer R, Schmutzler RK, *et al.,* Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. Journal of clinical oncology 2015; 33: 244-250.

ESMO WEBSITE AND INFORMATION

The ESMO-MCBS Section on the ESMO website is kept up to date

The most current evaluation Forms and instructions can be found there also the most recent articles and eUpdates of scores

If you have any questions, please contact us: mcbs@esmo.org



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