GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

INSTITUTE OF CANCER POLICY

ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS)

for new anticancer therapies

Personal reflections

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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)

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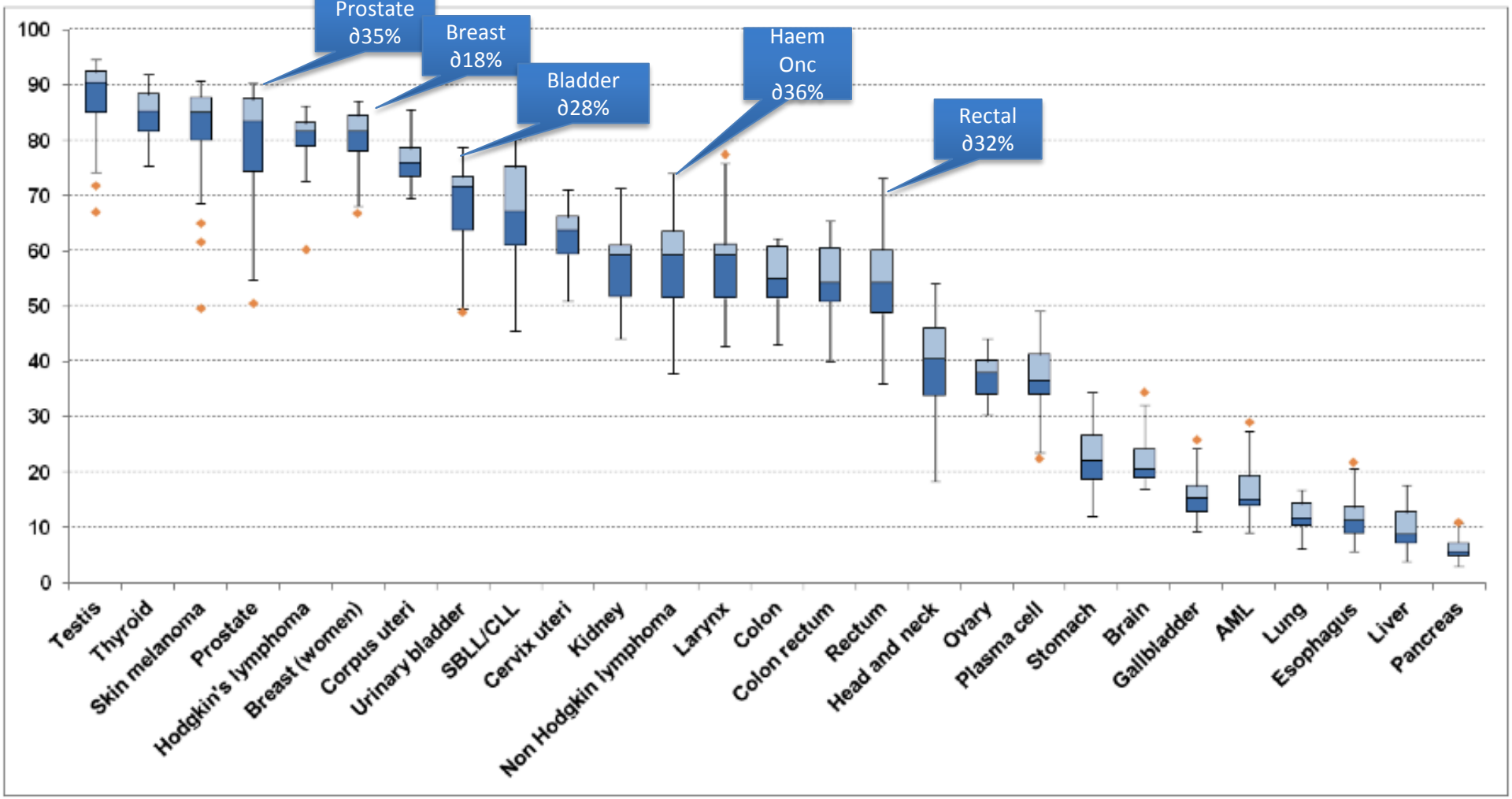
Why did we do this?

- **Affordable cancer care, particularly medicines**
- **Inequality and Access**
- **Cancer Outcomes across Europe**
- **Marketing Authorisation[a] & Health Technology Assessments**
- **Research portfolios, design of clinical trials, relevance to improving population outcomes, driving zeitgeist of research**

[a]Drugs, cancer and end of life care. Social Sci Med 2015, 131: 207-214



EUROCARE V - 5 Year Survival EU-28

Range of cancer care health expenditures (in euro) on individual site specific cancers across Europe is huge

	(Euro)			Diff
Blood cancers	7,576	-	38,595	**x5**
Prostate	6,006	-	34,474	**x6**
Colorectal	8,421	-	26,215	**x3**
Bladder	1,117	-	13,370	**x12**
Breast	5,976	-	32,237	**x5**
Lung	5,511	-	29,121	**x5**

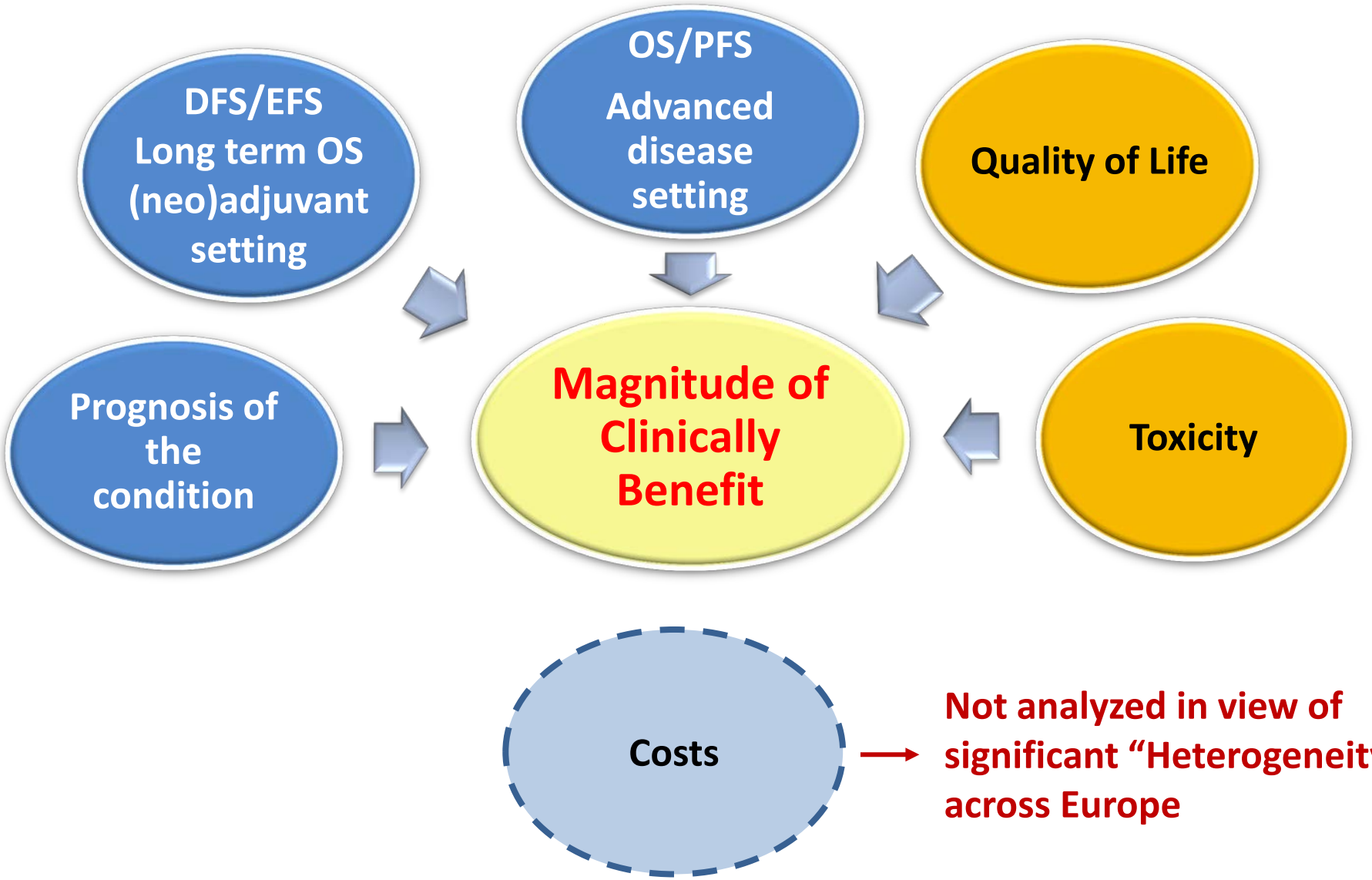
Economic burden of cancer in Europe. Lancet Oncology 2013: 14(12): 1165-1174.
Economic burden of bladder cancer across European Union. Eur Urology, 2015 (on line)

Expenditure range on medicines as a % of total is equally varied, and has NO correlation with outcomes

	% of total spend			Av
Blood cancers	5.4	-	54.8%	**44.3%**
Prostate	16	-	93.6%	**78.4%**
Colorectal	1.2	-	11.7%	**7.9%**
Bladder	6.7	-	36.3%	**29.1%**
Breast	14.2	-	83.6%	**61.3%**
Lung	0.8	-	11.1%	**4.6%**

Economic burden of cancer in Europe. Lancet Oncology 2013: 14(12): 1165-1174.
Economic burden of bladder cancer across European Union. Eur Urology, 2015 (on line)

Factors taken into account for ESMO-MCBS



Underlying Premises ESMO-MCBS

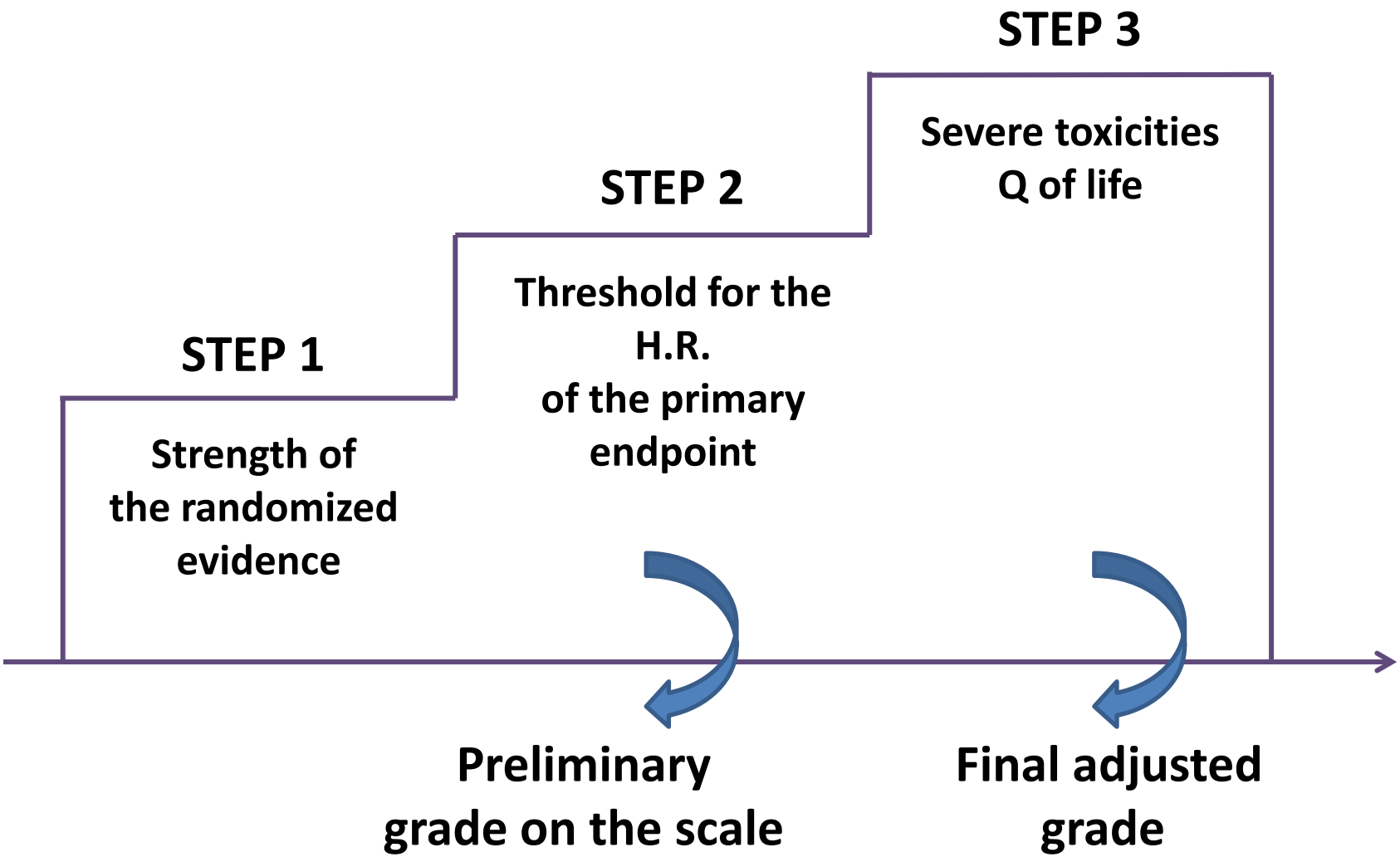
1. Cure takes precedence over deferral of death

2. Direct endpoints such as survival and QoL take precedence over surrogates such as PFS

3. DFS in curative disease is a more valid surrogate than PFS (or RR) in non-curative disease

4. Interpretation of the evidence for benefit derived from surrogate outcomes (such as PFS) may be influenced by secondary outcome data

Using the ESMO-MCBS
3 critical steps

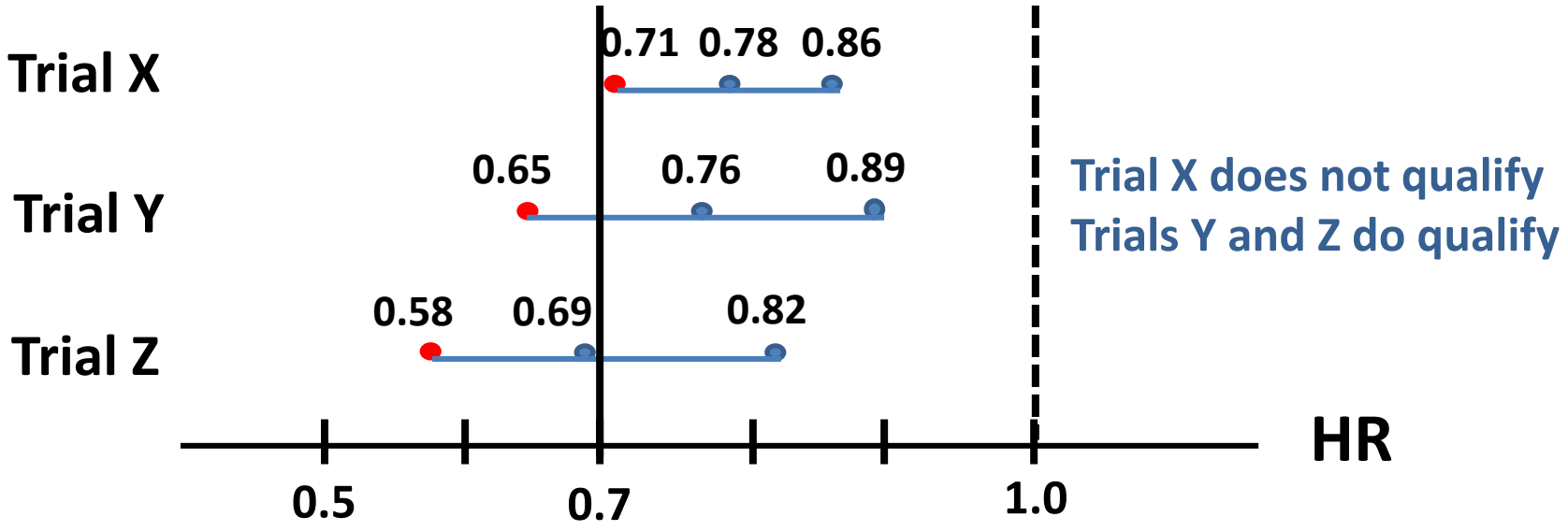


3 Rules, #2 ESMO-MCBS

a. More than one outcome may be applicable
b. For a required HR, not the point estimate but the lower limit of the 95% CI is used to take into account the variability of the estimate

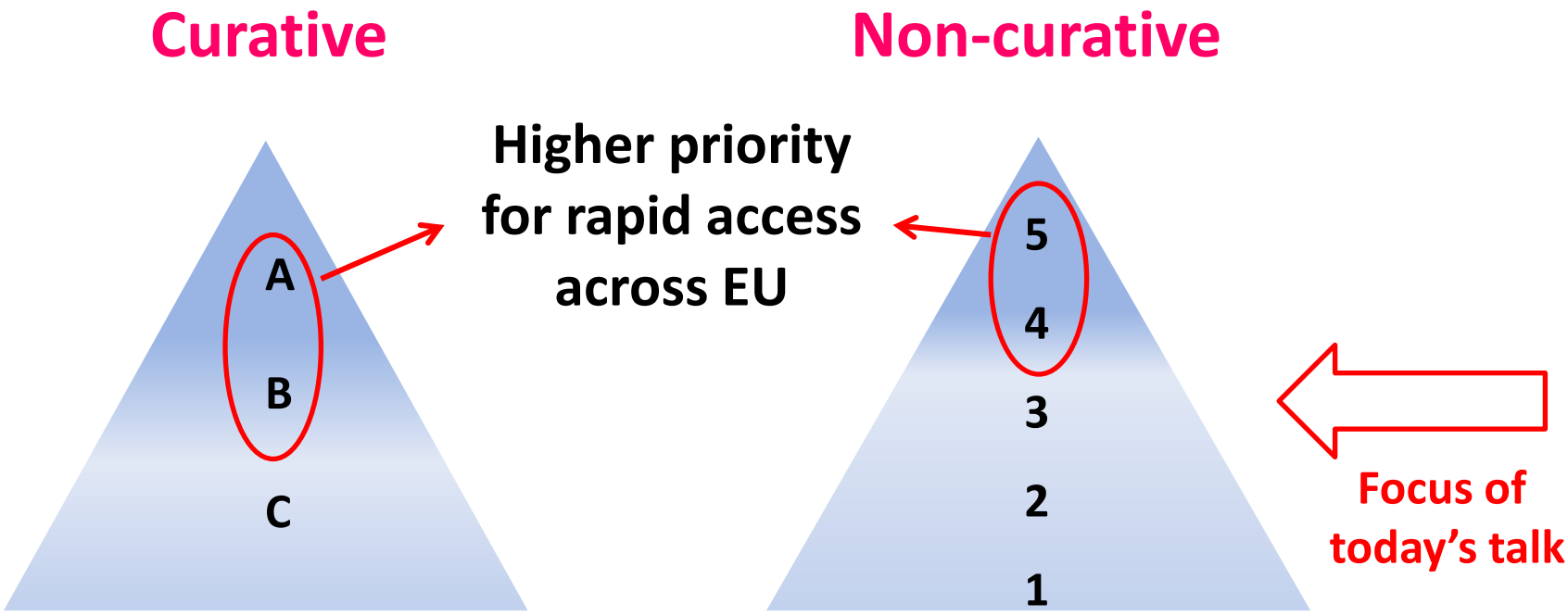
Example: for threshold set at HR ≤ 0.70

it is the lower limit of the 95%CI which has to be ≤ 0.70

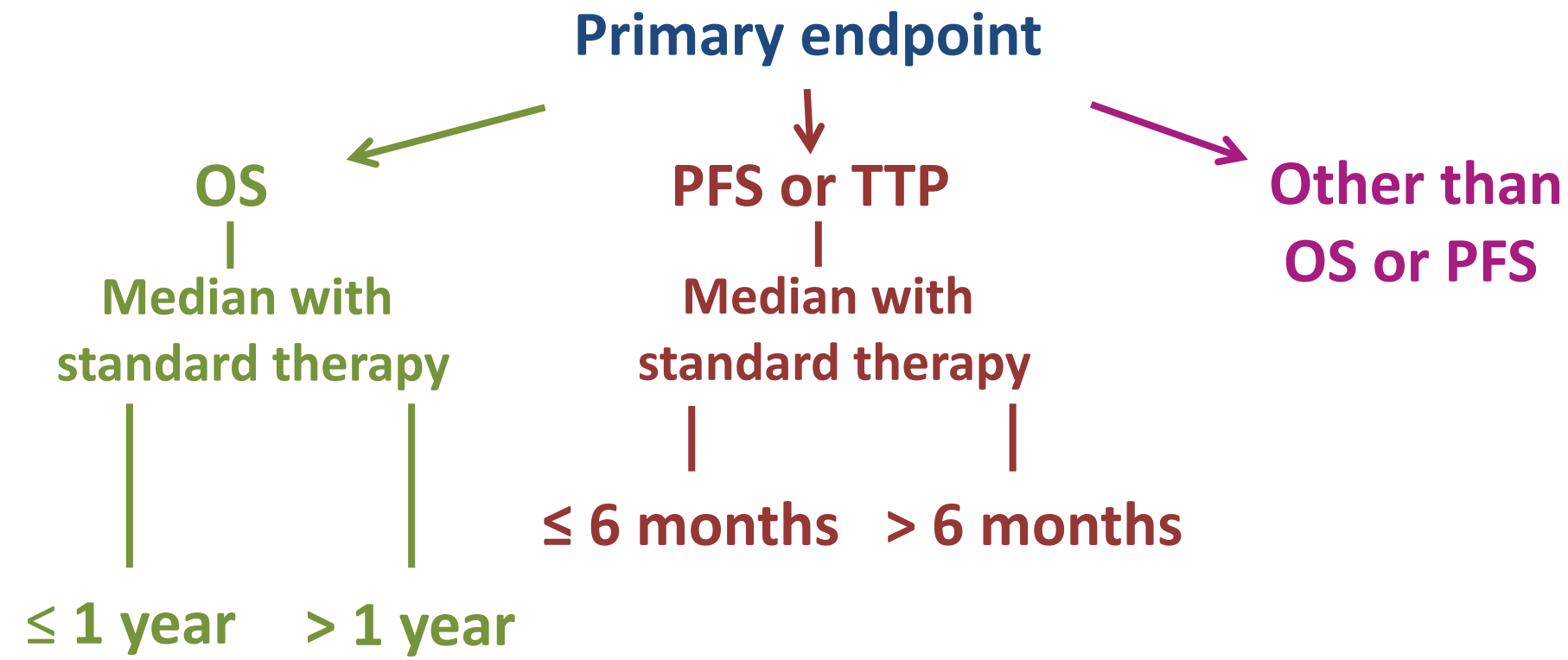


ESMO-MCBS substantial improvements

- **Curative setting A & B or non-curative setting 5 & 4**



ESMO-MCBS distinctions:
for treatment with non-curative intent



- No downgrading for gr 3-4 toxicities
- Upgrade possible if less gr 3-4 tox a/o better Q of life

- Downgrading for gr 3-4 toxicities
- Upgrade possible if less gr 3-4 tox a/o better Q of life

Evaluation form 2a: treatments with non-curative intent, primary endpoint **OS**

IF median OS with the standard treatment is ≤ 1 year

	Mark with X if relevant
Grade 4	
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 month	
Increase in 2 year survival alone < 3%	

Evaluation form 2a: treatments with non-curative intent, primary endpoint **OS**

IF median OS with the standard treatment is > 1 year

	Mark with X if relevant
Grade 4	
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 month	
Increase in 3 year survival alone <3%	

Evaluation form 2a: treatments with non-curative intent, primary endpoint **OS**

Step 1

Preliminary magnitude of clinical benefit grade
(highest grade scored)

4	3	2	1

Step 2

Assessment QoL & grade 3-4 toxicities

Does secondary endpoint QoL show improvement	
Are there statistically significantly < grade 3-4 toxicities impacting daily well-being*	

***not including alopecia, myelosuppression, but rather chronic nausea, diarrhea, fatigue, etc.**

Step 3

Adjustment: Upgrade 1 level if improved QoL or less toxicity or is shown

Final adjusted magnitude of clinical benefit grade

5	4	3	2	1

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Field testing Breast Cancer

EXAMPLE

Medication	Trial	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	ESM0 - MCBS
Chemo +/- **trastuzumab**	HERA	(Neo)Adjuvant HER-2 positive tumors	DFS	2 y DFS 77.4%	8.4%	0.54 (0.43-0.67)					**A**
T-DM1 vs capecitabine + lapatinib	EMILIA	2nd line metastatic after trastuzumab failure	PFS & OS	6.4 m	3.2 m	0.65 (0.55-0.77)	25 m	6.8 m	0.68 (0.55-0.85)	Later deterioration	**5**
Trastuzumab + chemo +/- **pertuzumab**	CLEOPATRA	1st line metastatic	PFS	12.4 m	6 m	0.62 (0.52-0.84)	40.8 m	15.7 m	0.68 (0.56-0.84)	~	**4**
Lapatinib +/- trastuzumab	EGF 104900	3rd line metastatic	PFS	2 m	1 m	0.73 (0.57-0.93)	9.5 m	4.5 m	0.74 (0.57-0.97)		**4**
Capecitabine +/- **lapatinib**	Geyer, 2006	2nd line metastatic after trastuzumab failure	PFS	4.4 m	4 m	0.49 (0.34-0.71)			NS		**3**
Eribulin vs other chemo	EMBRACE	3rd line metastatic after anthracycline & taxane	OS				10.6 m	2.5 m	0.81 (0.66-0.99)		**2**
Paclitaxel +/- **bevacizumab**	Miller, 2007	1st line metastatic	PFS	5.9 m	5.8 m	0.6 (0.51-0.70)			NS	~	**2**
Exemestane +/- **everolimus**	BOLERO-2	Metastatic after failure aromatase	PFS	4.1 m	6.5 m	0.43 (0.36-0.54)			NS	~	**2**

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Field testing Lung Cancer

Medication	Trial	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS HR	QoL	Toxicity	ESM0-MCBS
Erlotinib vs carboplatin gemcitabine	OPTIMEL, CTONG-0802	1st line stage 3b/4 non-squamous + EGFR mutation	PFS	4.6 m	8.5 m	0.16 (0.10-0.26)				12% < serious adverse events	**4**
Erlotinib vs Pt-based chemo doublet	EURTAC	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	5.2 m	4.5 m	0.37 (0.25-0.54)	19.5 m	NS		15% < severe adverse reactions	**4**
Gefitinib vs carboplatin + paclitaxel	IPASS	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	6.3 m	3.3 m	0.48 (0.34-0.67)			↑	< toxicity	**4**
Afatinib vs cisplatin + pemetrexed	LUX Lung 3	1st line stage 3b/4 non-squamous + EGFR mutation	PFS, crossover allowed	6.9 m	4.2 m	0.58 (0.43-0.78)			↑		**4**
		Del19/L858R		6.9 m	6.7 m	0.47 (0.34-0.65)			↑		**4**
Crizotinib vs chemo	Shaw 2013	1st line stage 3b/4 non-squamous + ALK mutation	PFS, crossover allowed	3.0 m	4.7 m	0.49 (0.37-0.64)			↑	1% > toxic death	**4**
Crizotinib vs cisplatin + pemetrexed	Solomon 2014	1st line stage 3b/4 non-squamous + ALK mutation	PFS	7.0 m	3.9 m	0.45 (0.35-0.60)			↑		**4**

My conclusions

1. **Tool for assessing whether a 'valid trial' has produced a 'clinically meaningly endpoint' as defined by a set of European medicial oncologists and statisticians.**

2. **Will call into question clinical trial design *et al*** (*n*=3 grade 5; *n*=29 grade 4; *n*=40 grades 3,2,1).

3. **It is not about true value. No account of price/cost is taken but it starts the debate about one half of the equation**

4. **Will call into question why certain cancer medicines 'deserved' to have been given a marketing autorisation**

4. **Unclear what interface this will have with HTA**

Acknowledgments

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