Tercera Reunión Anual del grupo:

GEDEFO

Grupo de Farmacia Oncológica de la SEFH

sefh
Sociedad Española de Farmacia Hospitalaria

fefh
Fundación Española de Farmacia Hospitalaria

ATENCIÓN FARMACÉUTICA
AL PACIENTE
ONCOHEMATOLÓGICO

VALUE FRAMEWORKS: ESCALA DE BENEFICIO DE LA ESMO

Álvaro Rodríguez-Lescure
Hospital General Universitario de Elche

Clinical Benefit Scales in Medical Oncology
The ESMO Magnitude of Clinical Benefit Scale

Álvaro Rodríguez-Lescure
Hospital General Universitario de Elche
Madrid, 3 de octubre de 2018

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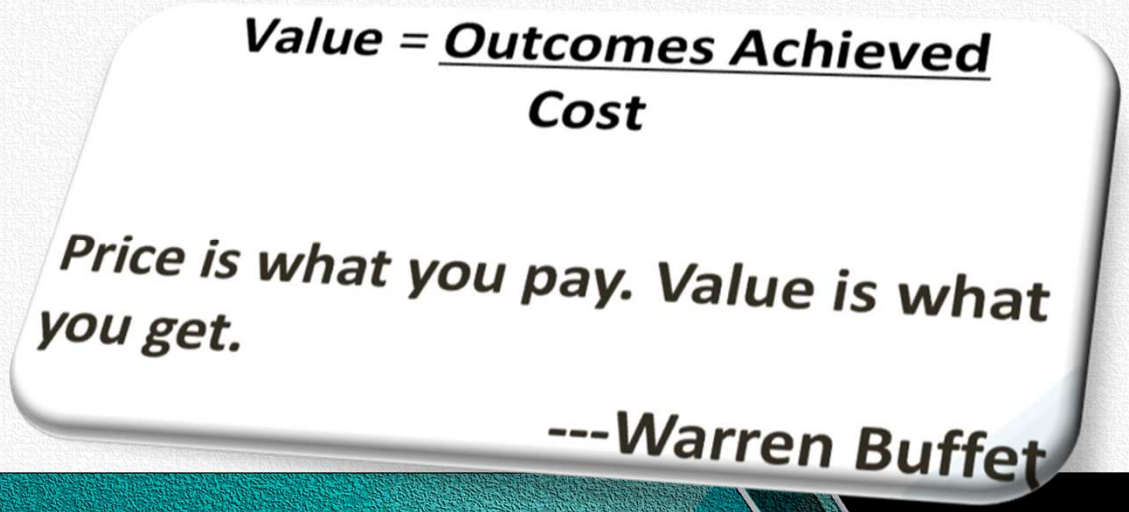
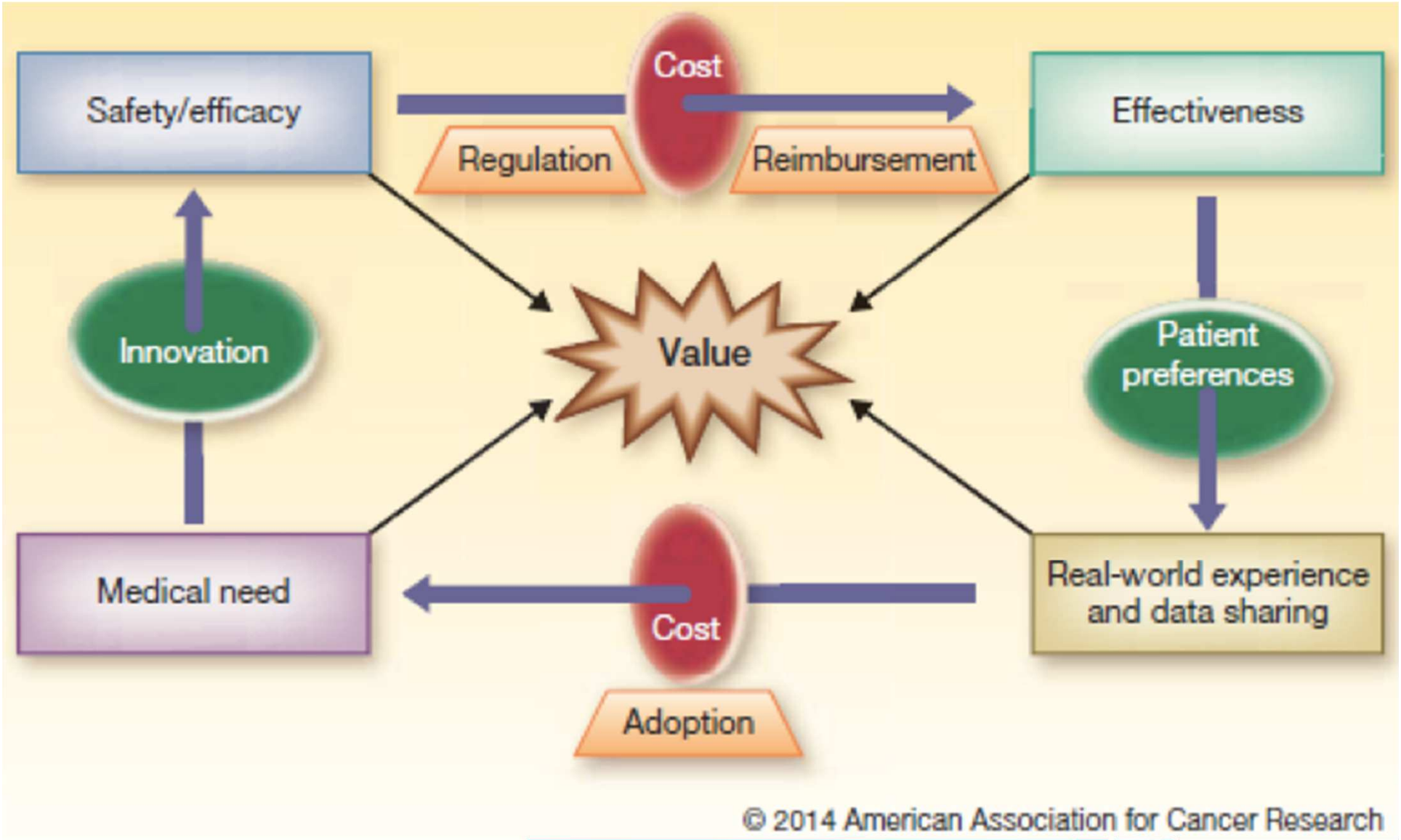
ATENCIÓN FARMACÉUTICA
AL PACIENTE ONCOHEMATOLÓGICO

Paradigm Shift

- Traditional models:
  - Based on EBM: NCCN Guidelines
  - Based on cost-effectiveness: NICE.
- New models:
  - Based on outcomes: ESMO MCBS
  - Based on value: ASCO





JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Recommendations for clinically meaningful outcomes

American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

Lee M. Ellis, David S. Bernstein, Emile E. Voest, Jordan D. Berlin, Daniel Sargent, Patricia Cortazar, Elizabeth Garrett-Mayer, Roy S. Herbst, Rogerio C. Lilenbaum, Camelia Sima, Alan P. Venook, Mithat Gonen, Richard L. Schilsky, Neal J. Meropol, and Lowell E. Schnipper

Published Ahead of Print on March 17, 2014 as 10.1200/JCO.2013.53.8009
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.53.8009

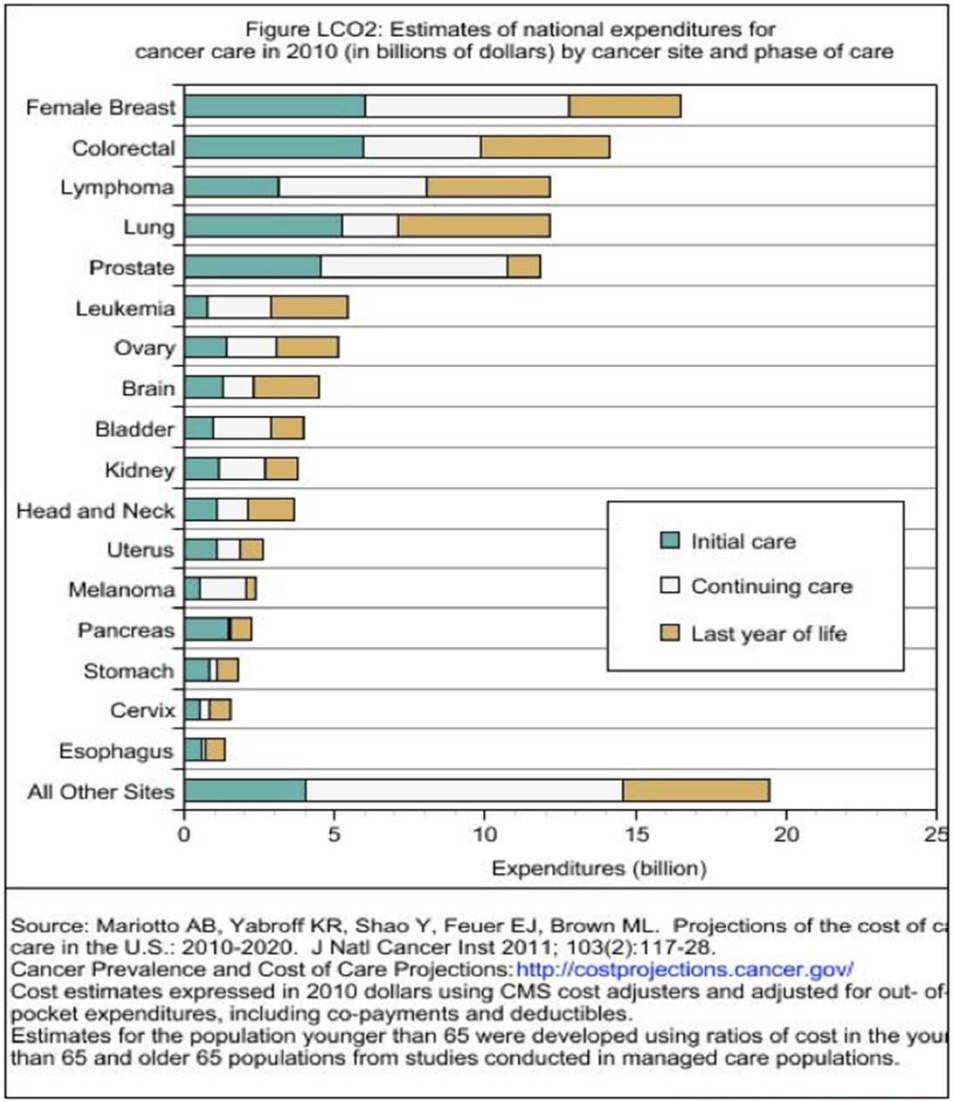
Minimum meaningful incremental improvement is an HR of ≤0.8 and median OS improvement from 2.5 to 6 months

New regimens that are substantially more toxic than current standards should also produce the greatest increments in OS

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

			Primary End Point		Secondary End Point	
Cancer Type	Patient Population	Current Baseline Median OS (months)	Improvement Over Current OS That Would Be Clinically Meaningful (months)	Target HRs	Improvement in 1-Year Survival Rate (%)*	Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Cost of Cancer Care is Rising

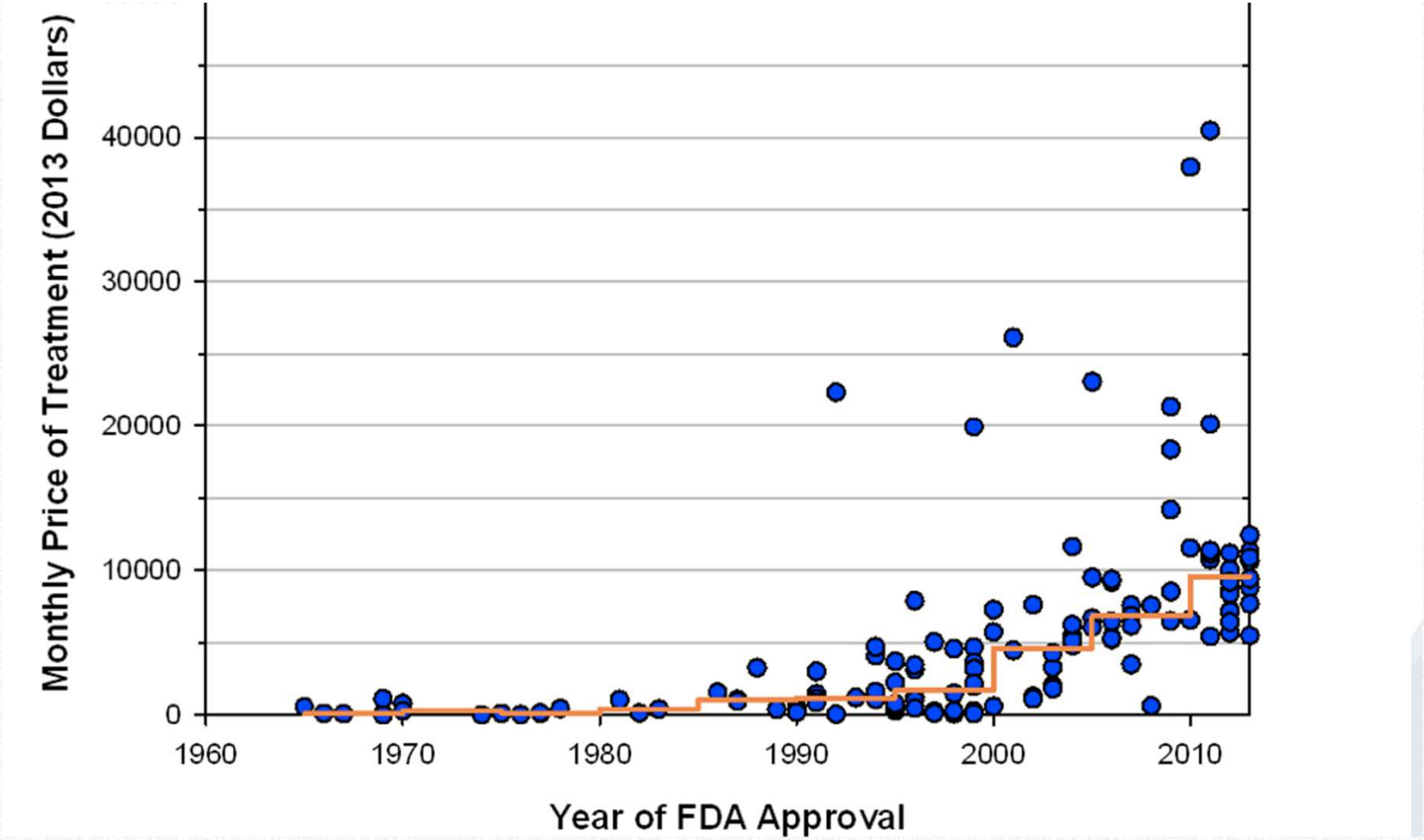


→ $125 billion in **2010**

→ $175 billion in **2020**

ASCO

Monthly and Median Costs of Cancer Drugs as the Time of FDA Approval 1965-2013



ASCO Value in Cancer Care Task Force

Established in 2007 as the Cost of Care Task Force to define the challenges related to the cost of cancer care and develop strategies to address these challenges in the context of ASCO's mission

Goals:

- Increase physician education and guidance about cost
- Increase patient education and assistance regarding cost
- Promote high-value medical decision-making
- Assess the value of cancer care

ASCO Value Framework

Within this framework, "value" will be defined by:

- **Clinical Benefit:** The treatment demonstrates an improvement in survival, compared with no therapy (when appropriate) or a known effective therapy, although this can sometimes differ (e.g., improvement in time to disease progression).
- **Toxicity:** The degree of treatment-associated adverse events, particularly those that affect QoL or the ability to complete usual activities of daily living. Many of which can be managed with supportive or additional treatments.
- **Cost:** Expenses incurred by patients, society, and insurers.

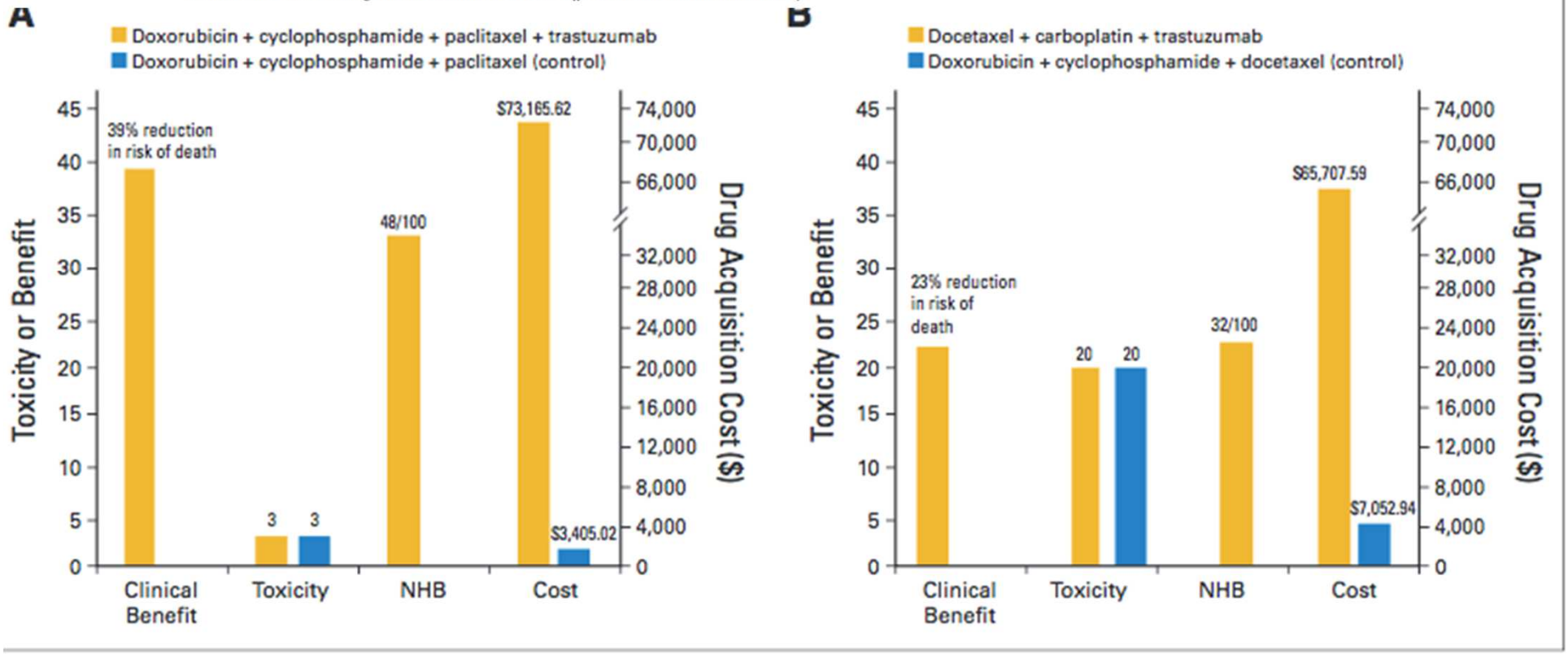
Net Health Benefit (NHB)

Points accumulated on Clinical Benefit and Toxicity (and bonus points, in the advanced disease framework) are combined to generate a net health benefit (NHB) score, which is then juxtaposed against the direct cost of the treatment, to provide an overall summary assessment.

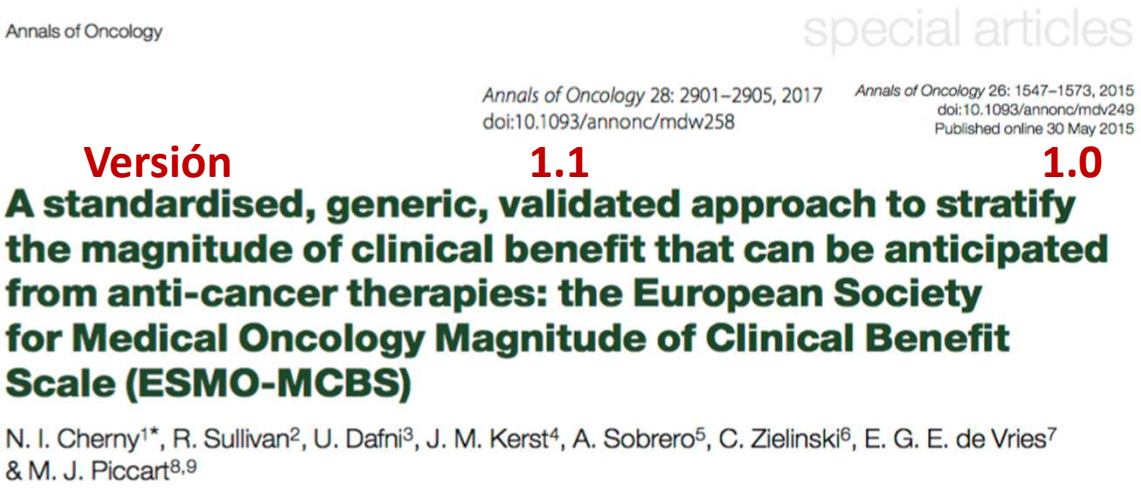
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options

Lowell E. Schnipper, Nancy E. Davidson, Dana S. Wollins, Courtney Tyne, Douglas W. Blayney, Diane Blum, Adam P. Dicker, Patricia A. Ganz, J. Russell Hoverman, Robert Langdon, Gary H. Lyman, Neal J. Meropol, Therese Mulvey, Lee Newcomer, Jeffrey Peppercorn, Blase Polite, Derek Raghavan, Gregory Rossi, Leonard Saltz, Deborah Schrag, Thomas J. Smith, Peter P. Yu, Clifford A. Hudis, and Richard L. Schilsky



ESMO-MCBS

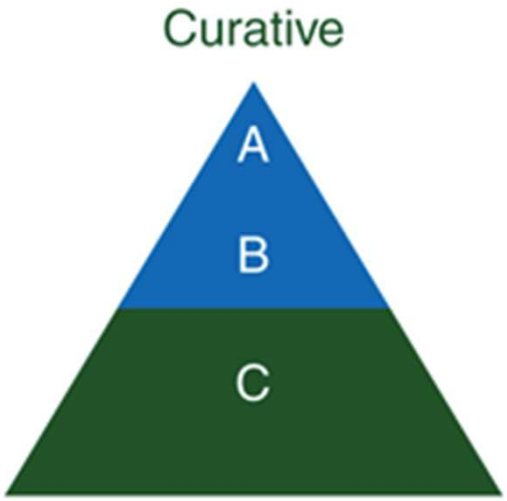


- Necesidad.
- Valor en función de eficacia, toxicidad y coste. Definir y clasificar Beneficio clínico.
- Entorno con recursos limitados y costes crecientes.
- Nacimiento con vocación de herramienta dinámica.
- Asunciones: “Vivir más y mejor”: OS y QoL
  - Escenario de curabilidad
  - Escenario de incurabilidad: Variables subrrogadas NO TAN CLARAS.
- Generación de 4 + 1 grupos diferentes según escenario, variable evaluada y su magnitud.
- Grados de beneficio: *A, B y C.

  *5, 4, 3, 2 y 1.

FORM: 1

ESMO-MCBS Adjuvant



A and B: Grades with substantial improvement

Grade A

>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)

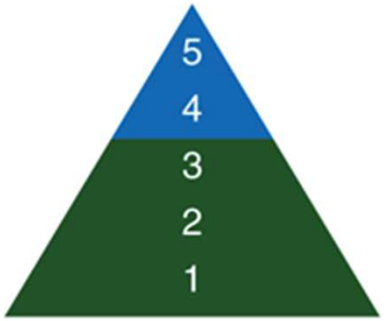
Grade C

<3% improvement of survival at ≥ 3 years follow-up
Improvement in DFS alone (primary endpoint) (HR >0.8) in studies without mature survival data
Improvements in pCR alone (primary endpoint) by ≥30% relative AND ≥15% absolute gain in studies without mature survival data

ESMO-MCBS Non-curative

FORM 2a:OS If median OS with the standard treatment is ≤ 12 months

Non-curative



5 and 4:
Grades with substantial improvement

Grade 4

HR ≤0.65 AND Gain ≥3 months

Increase in 2 year survival ≥10%

Grade 3

HR ≤0.65 AND Gain ≥2.0, <3 months

Grade 2

HR ≤0.65 AND Gain ≥1.5, <2.0 months

HR >0.65-0.70 AND Gain ≥1.5 months

Grade 1

HR >0.70 OR Gain <1.5 months

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*	

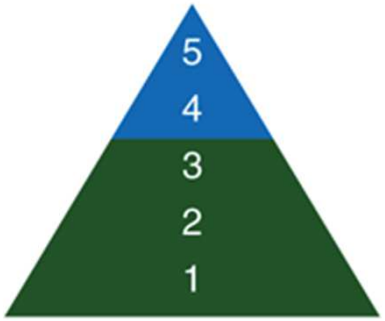
*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Adjustments

1. Upgrade 1 level if improved quality of life and/or less grade 3-4 toxicities impacting daily well-being are shown
2. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 year, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4

FORM 2a:OS If median OS with the standard treatment is > 12 months ≤ 24 months

Non-curative



5 and 4:
Grades with substantial improvement

Grade 4

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 >0.70-0.75 AND Gain ≥1.5 months

Grade 1

HR > 0.75 OR Gain <1.5 months

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.

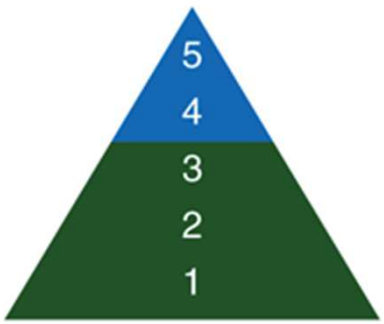
Adjustments

1. Upgrade 1 level if improved quality of life and/or less grade 3-4 toxicities impacting daily well-being are shown
2. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 year, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4

ESMO-MCBS Non-curative

ESMO-MCBS Non-curative

FORM 2a:OS If median OS with the standard treatment is > 24 months



5 and 4:
Grades with substantial improvement

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

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

1. Upgrade 1 level if improved quality of life and/or less grade 3-4 toxicities impacting daily well-being are shown
2. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 year, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4

ESMO-MCBS Non-curative

FORM 2b: PFS

IF with median PFS with standard treatment ≤6 months

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

IF median PFS with standard treatment >6 months

Grade 3

HR ≤0.65 AND Gain ≥3 months

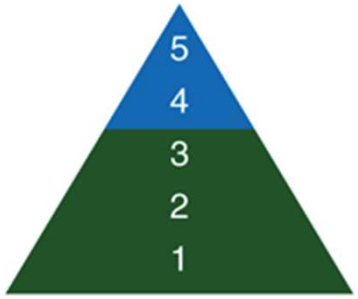
Grade 2

HR ≤0.65 BUT Gain <3 months

Grade 1

HR >0.65

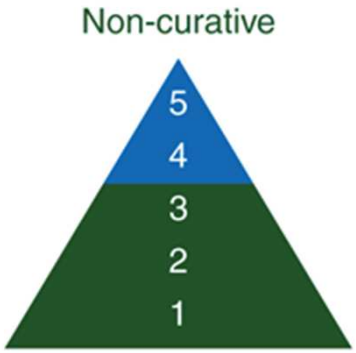
Non-curative



5 and 4: Grades with substantial improvement

FORM 2b: PFS

ESMO-MCBS Non-curative



5 and 4: Grades with substantial improvement

Early stopping or crossover

Did the study have an early stopping rule based on interim analysis of survival?
Was the randomization terminated early based on the detection of overall survival advantage at interim analysis?

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

Toxicity assessment

Is the new treatment associated with a statistically significant incremental rate of:
«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*

FORM 2b: PFS

ESMO-MCBS
Non-curative

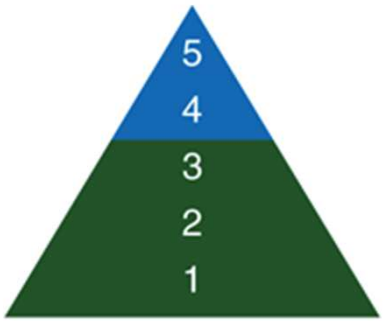
Adjustments

a) When OS as secondary endpoint shows improvement, it will prevail and the new scoring will be done according to form 2a
b) Downgrade 1 level if there is one or more of the above incremental toxicities associated with the new drug
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 improved quality of life or if less grade 3-4 toxicities that bother patients are demonstrated
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 year

FORM 2c:

ESMO-MCBS Non-

Non-curative



5 and 4:
Grades with substantial improvement

No OS nor PFS or equivalence trials

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

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

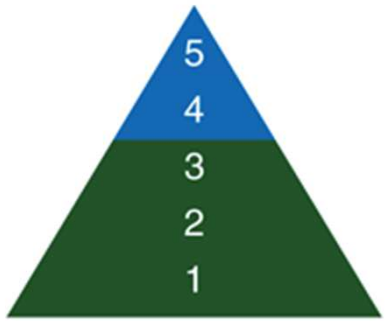
RR is increased <20% but no improvement in toxicity/QoL/PFS/OS

FORM 3: Single-arm studies in orphan diseases and for diseases with “high unmet need” when primary outcome is PFS or ORR

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

Non-curative



5 and 4:
Grades with substantial improvement

ESMO-MCBS Non-curative

Grade 3
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

- **Amendment:** New criteria for grade C have been inserted 'Improvements in **pCR (pathological complete remission)** alone (primary end point) by ≥30% relative gain AND ≥15% absolute gain in studies without mature survival data'
- **Amendment:** The prognostic stratification for form **2a** has been revised, v1.1 incorporates a **three-level prognostic stratification: ≤12 months, >12 to ≤24 months, and >24 months.** The >24-month stratification is introduced to achieve maximal score if either: HR ≤0.70 AND Gain ≥9 months or increase in 7-year survival of >10%.
- **Amendment:** There is a new adjustment to the preliminary scoring: 'If there is a long-term plateau in the survival curve, and OS advantage continues to be observed at 5 years (or 7 years for diseases with median survival >24 months), also score according to form 1 (treatments with curative potential) and present both scores, i.e. A/4'.
- ....
- ....
- ....
- ....

ESMO-MCBS: New tool at the European level

- ESMO-MCBS:

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.

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