CARCINOMA DEL POLMONE NON MICROCITOMA: QUALI NOVITA' PER IL 2016?

TERZA SESSIONE

L'IMMUNOTERAPIA NEL NSCLC

Commento sulla metodologia

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  - I.A.S.L.C. (International Association for the Study of Lung Cancer)
  - Fondazione *Cariverona*

FONDAZIONE *Cariverona*

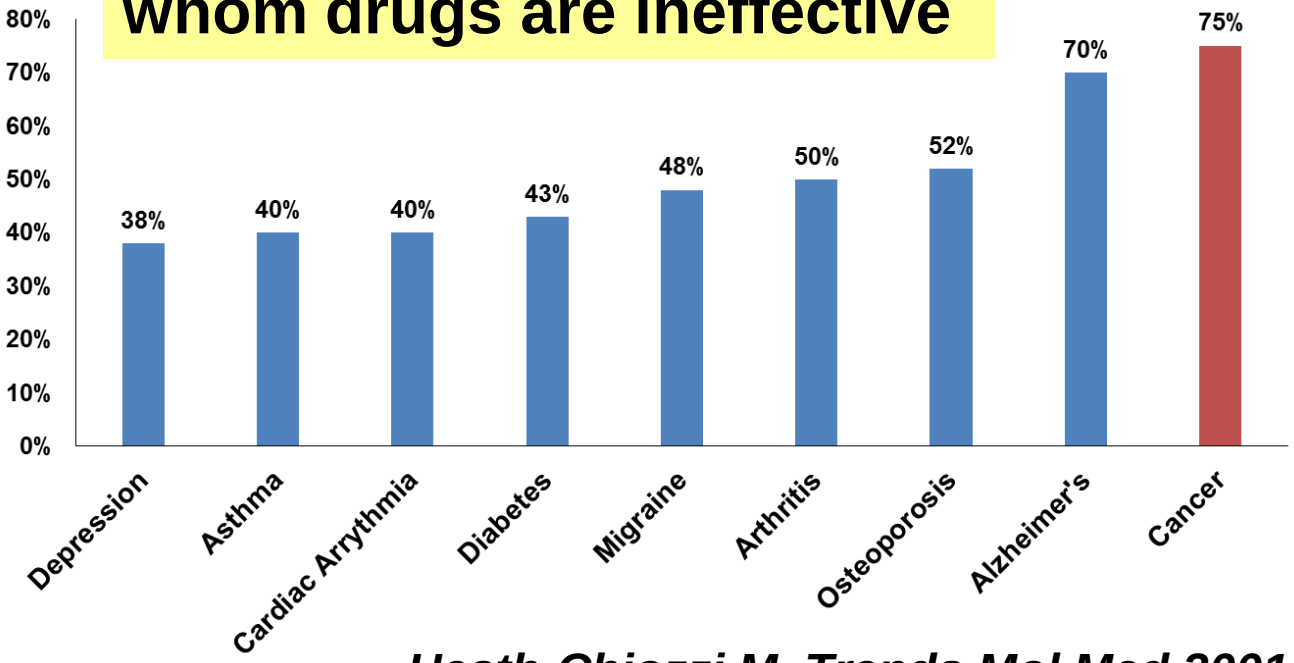
AIRC

IASLC
International Association for the Study of Lung Cancer

Immunotherapy for NSCLC

Why do we need a Methodology speech?

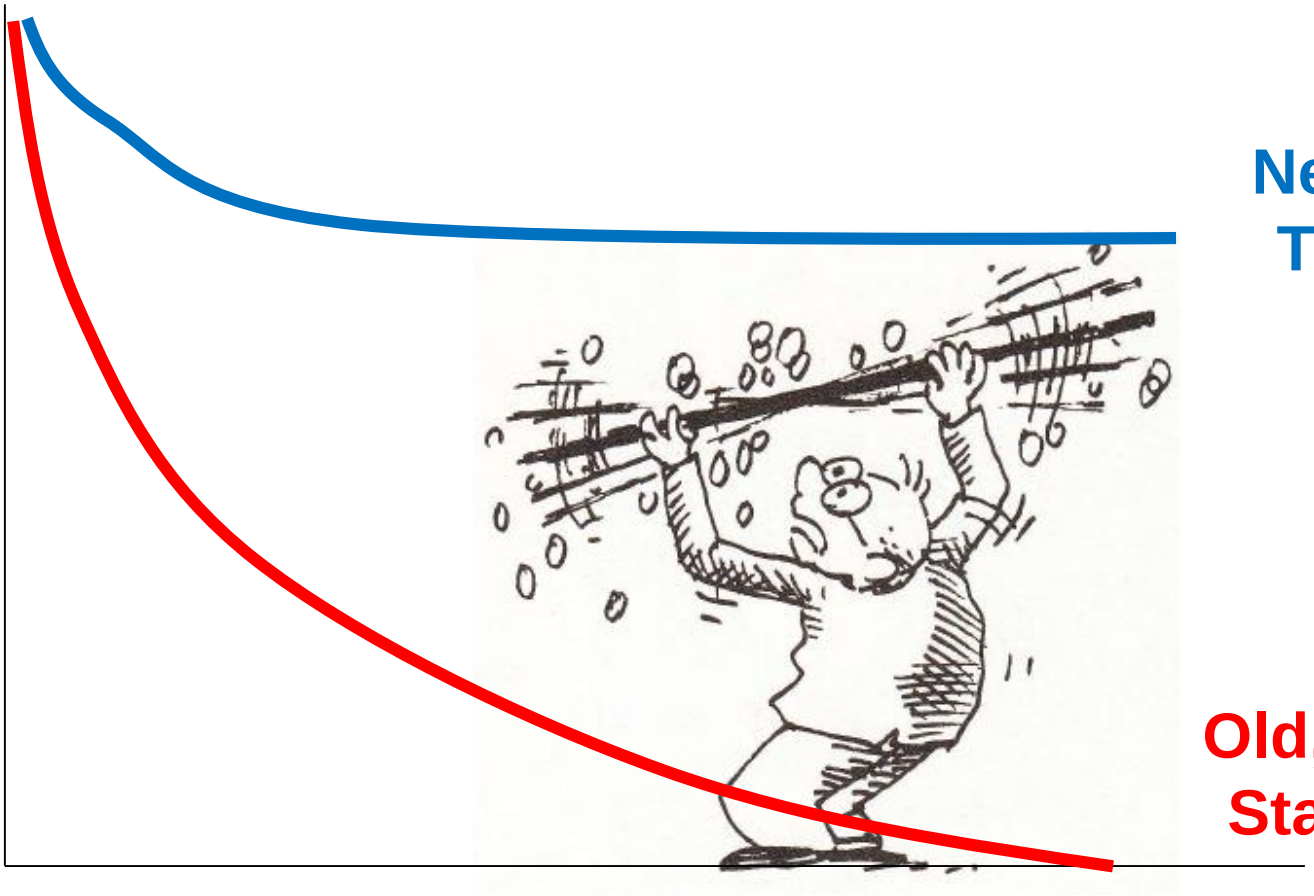
Percentage of patients for whom drugs are ineffective



Heath-Chiozzi M, Trends Mol Med 2001.

Immunotherapy for NSCLC
‘Comments’ upon Methodology

Hazard Ratio, Medians, other, *who cares if…*



New, Safe, Targeted

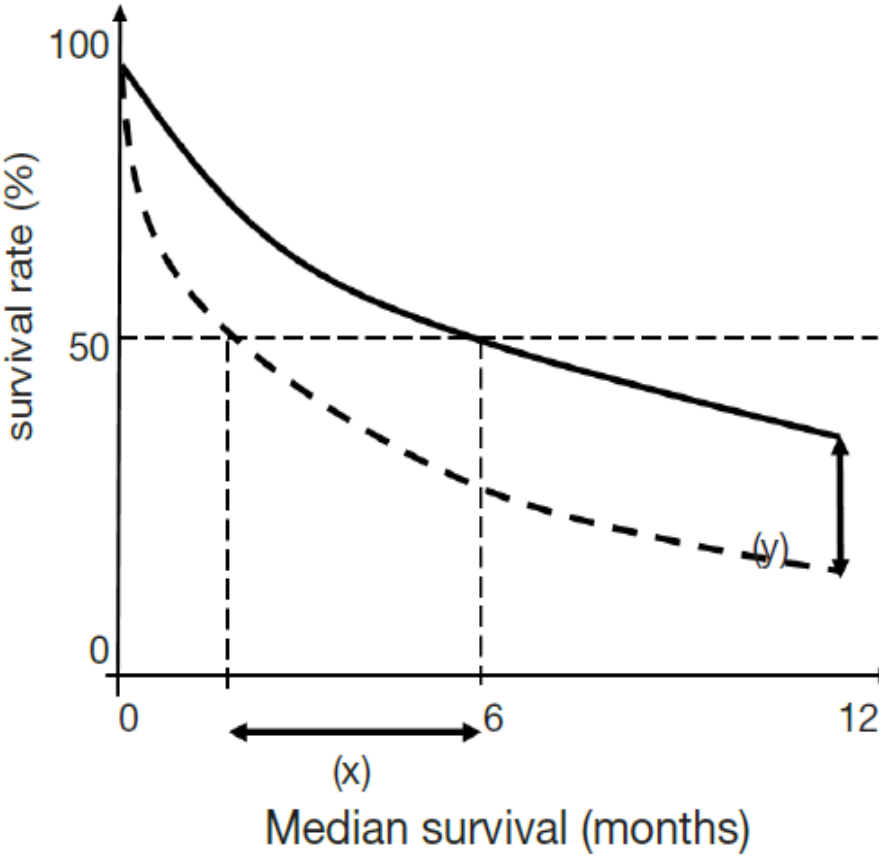
Old, Toxic, Standard

Immunotherapy for NSCLC
'Comments' upon Methodology

- **Hazard Ratio (HR)**
  - Which model for survival analysis?
  - HR: Principles, Assumptions and Limitations
- **Curves' Models**
  - Median survivals and Late rates
  - 'Adjusted' Data
- **'Visual' Maturity**
- **'Tricks' to enlarge HRs……..**
- **Correlation & Surrogates**
- **Implications for clinical trials' design**
- **The '*Two-Fingers*' Rule i.e. the '*quantity*' or ……**

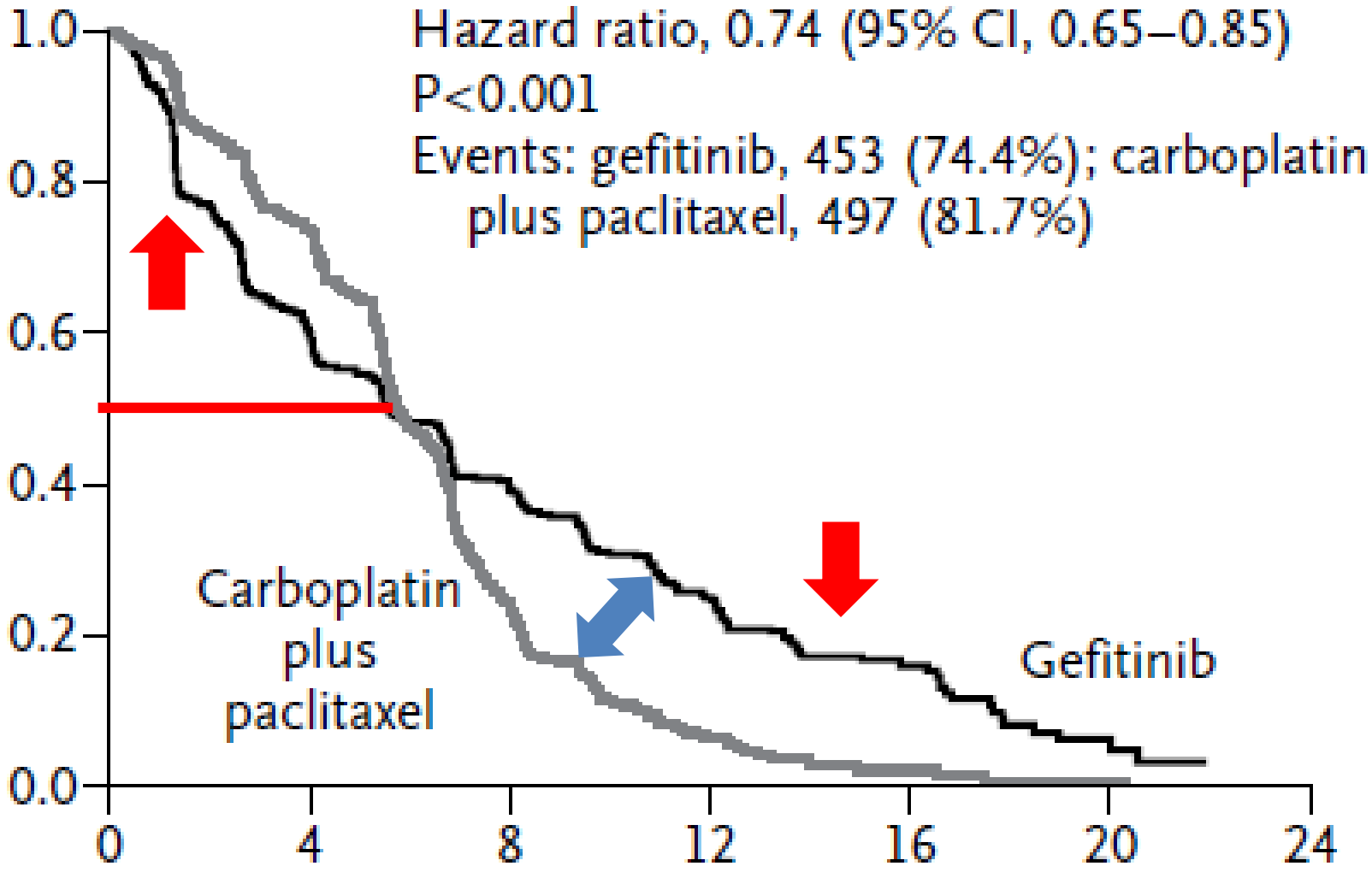
Hazard Ratio (HR)

- When **HR** is adopted, it is assumed that:
  - **Difference between groups was proportional;**
  - **Graphically the K-M survival curves displayed a constant distance apart.**
- **HR BECOMES MEANINGLESS WHEN THIS ASSUMPTION OF PROPORTIONALITY IS NOT MET!!!!!!**



[Ref. Brody, T. (2011). Clinical Trials: Study Design, Endpoints and Biomarkers, Drug Safety, and FDA and ICH Guidelines]

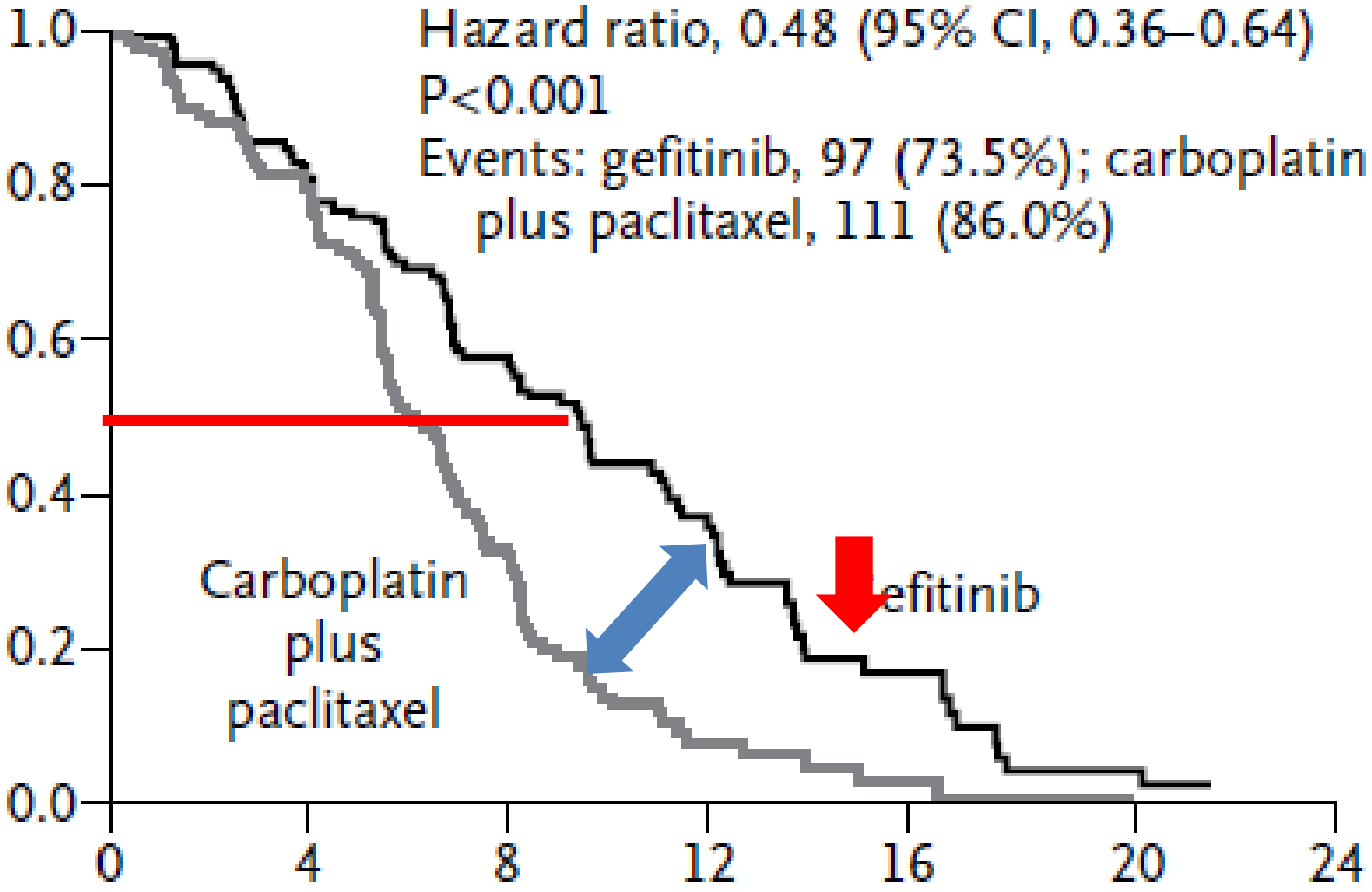
Curves' Crossing



Overall population

Source: Mok et al, NEJM 2009

Curves' Crossing… *anymore*



EGFR-Mutant

Source: Mok et al, NEJM 2009

Immunotherapy for NSCLC
'Comments' upon Methodology

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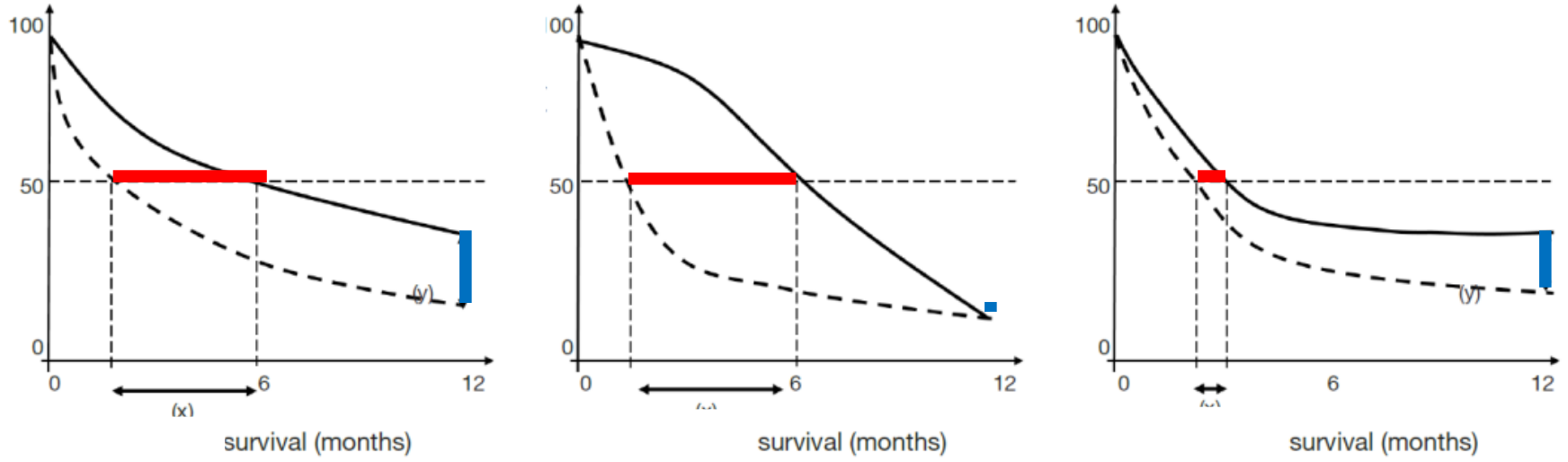
Immunotherapy for NSCLC
‘Comments’ upon Methodology: CURVES

Typical survival curves (Kaplan-Meier model) observed in clinical trials

(x) difference in median survival;
(y) 12-month difference in survival rate.

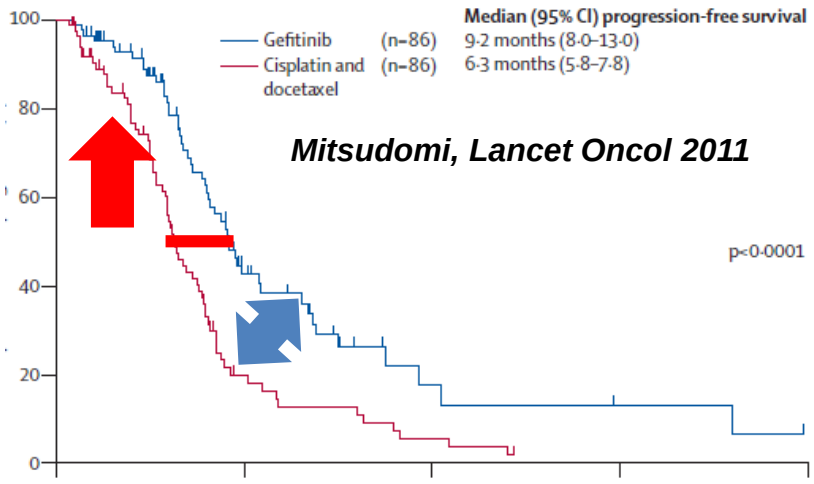


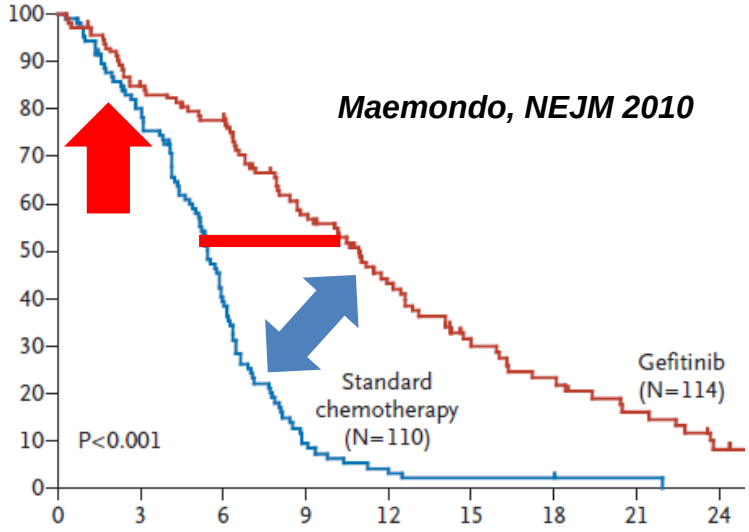
Early Stop for Futility	**YES**	**YES**	**NO**
Correlation with late benefit	**YES**	**NO**	**NO**

Pilotto S et al, TLCR 2015

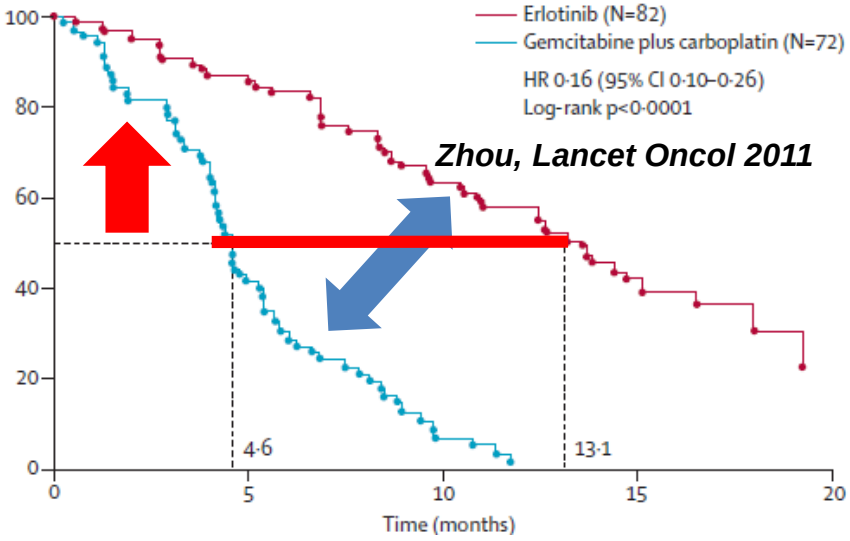
EGFR TKIs versus chemotherapy as 1st-line therapy for EGFR mutant

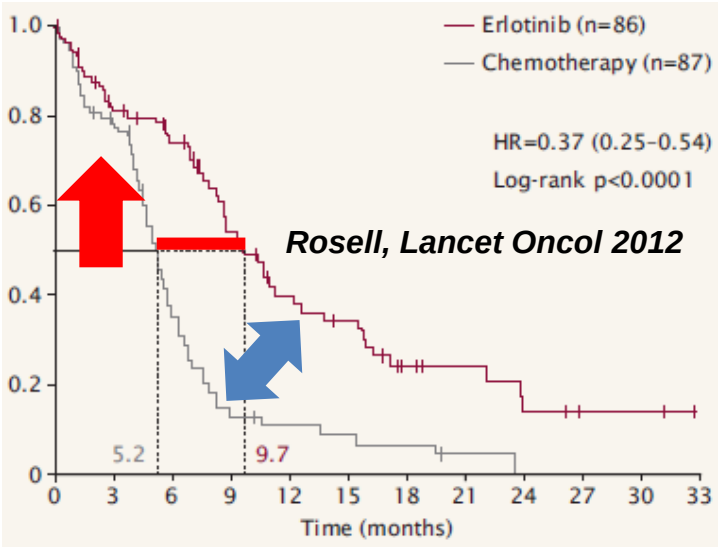
Gefitinib





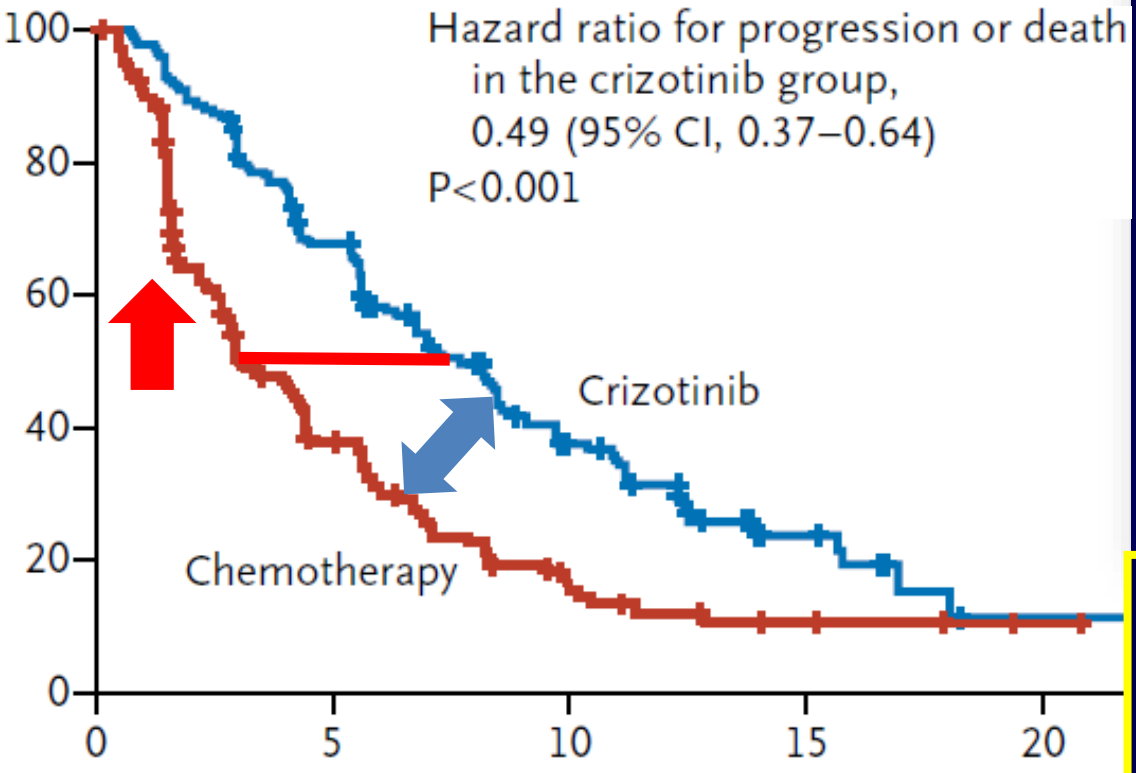
Erlotinib

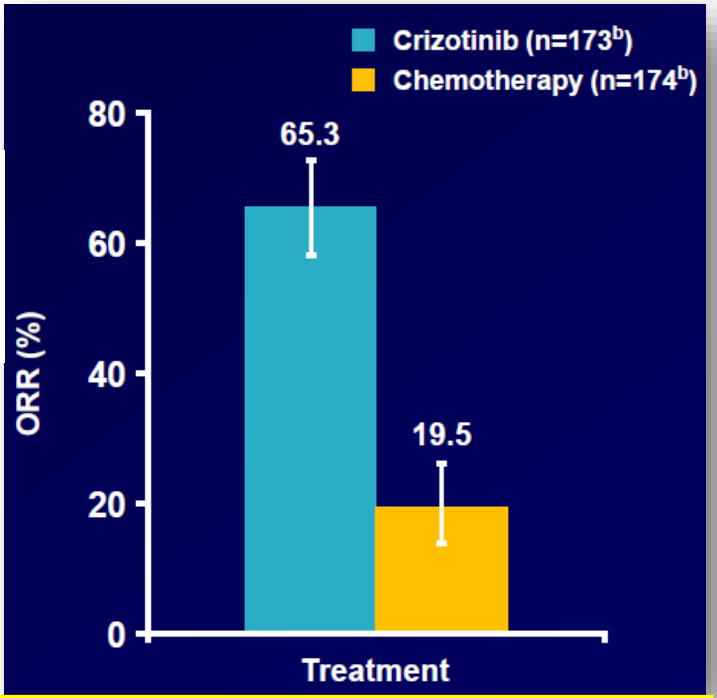




Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

The NEW ENGLAND JOURNAL of MEDICINE





Statistical Design

- **Primary endpoint: PFS per independent radiology review**
  - **Sample size: 217 events (PD or death) needed to detect HR of 0.64 (or increase in median PFS from 4.5 to 7 months) at one-sided 2.5% significance level with 90% power**

Clear and strong signal of activity

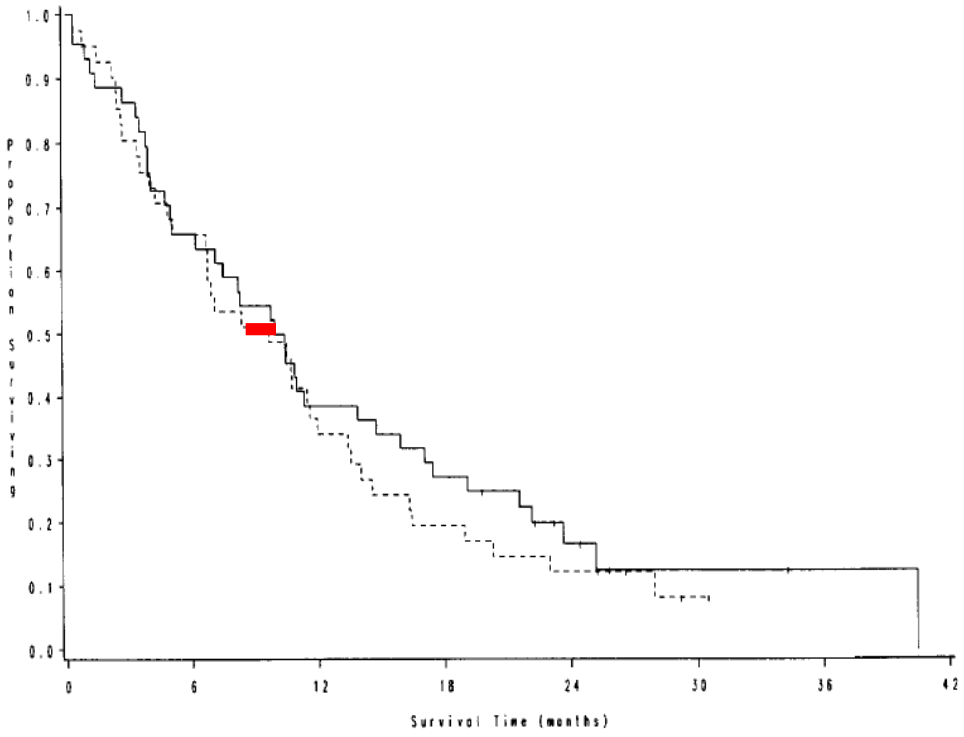
- → Objective response **is tripled**
- → PFS is improved by **4,7 months** (**HR of 0,49**)
- → Improvement of PFS in almost all subgroups
- → Improvement of lung cancer-related symptoms and global QOL

Shaw A et al [PROFILE 007] NEJM 2012

HR or Medians? Curves' Shapes

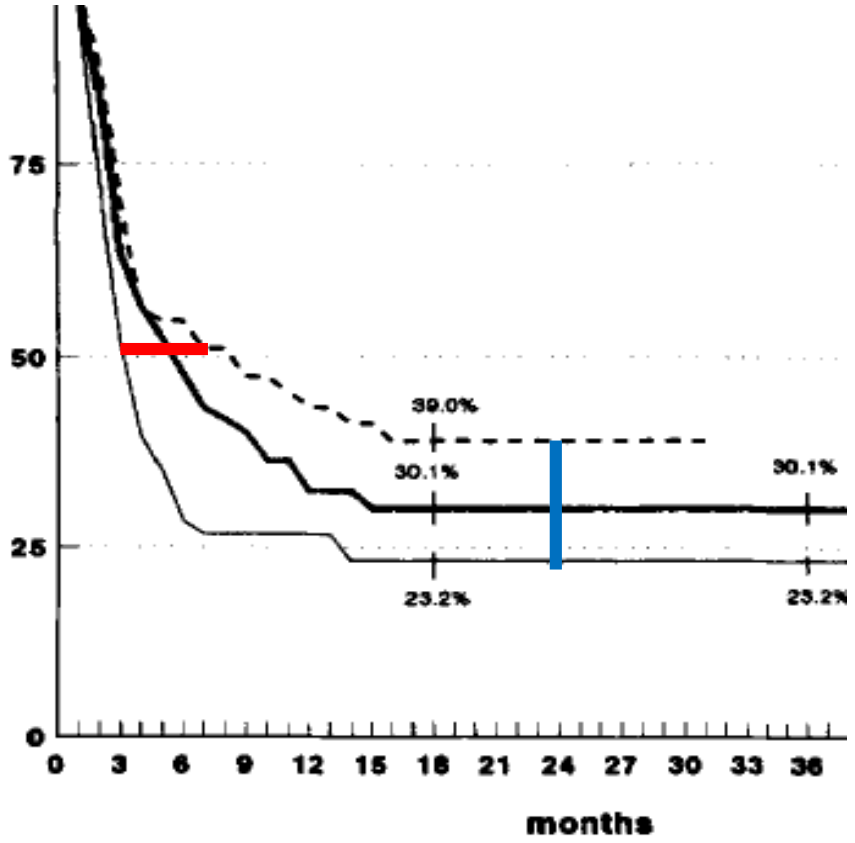
Is that a modern issue?

IL-2 + IFN-α *vs.* IL-2



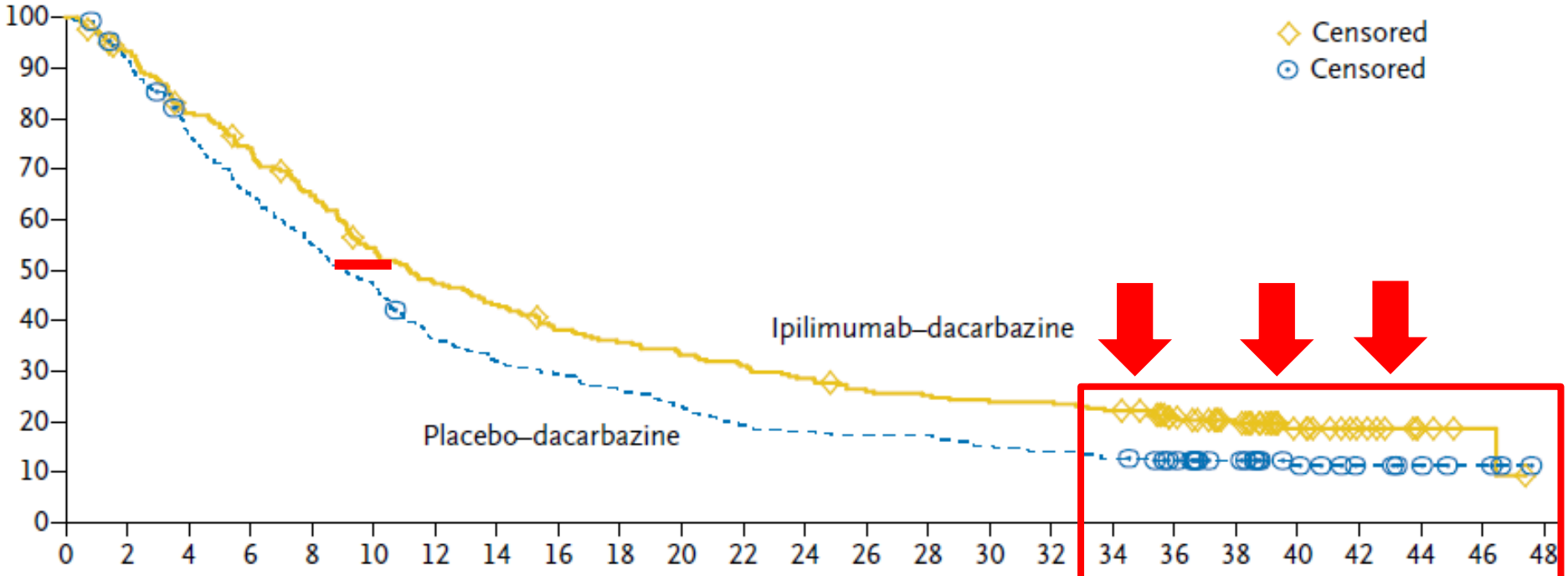
Sparano JA et al, JCO 1993

DTIC+rIFN (9mU) *vs.* DTIC+rIFN (3mU) *vs.* DTIC+rIFN



Baietta E et al, JCO 1994

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma



- **Late 'rates' better than HRs**
- **Absolute differences at specific time-points**
- **NNT**

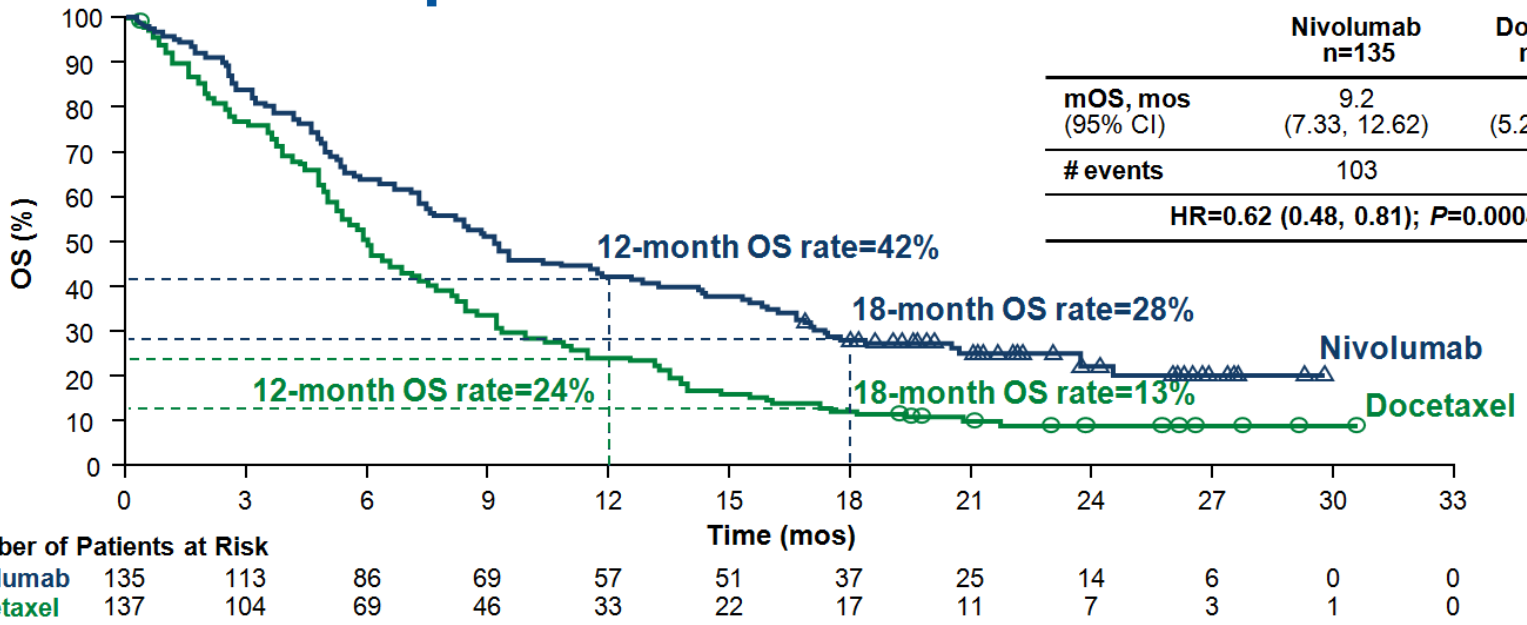
Events on the '*right*' side

The NEW ENGLAND JOURNAL of MEDICINE

Robert et al NEJM 2011

CheckMate 017: Updated OS Data

Updated Overall Survival



	Nivolumab n=135	Docetaxel n=137
mOS, mos (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR=0.62 (0.48, 0.81); *P*=0.0004		

Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	3	1	0

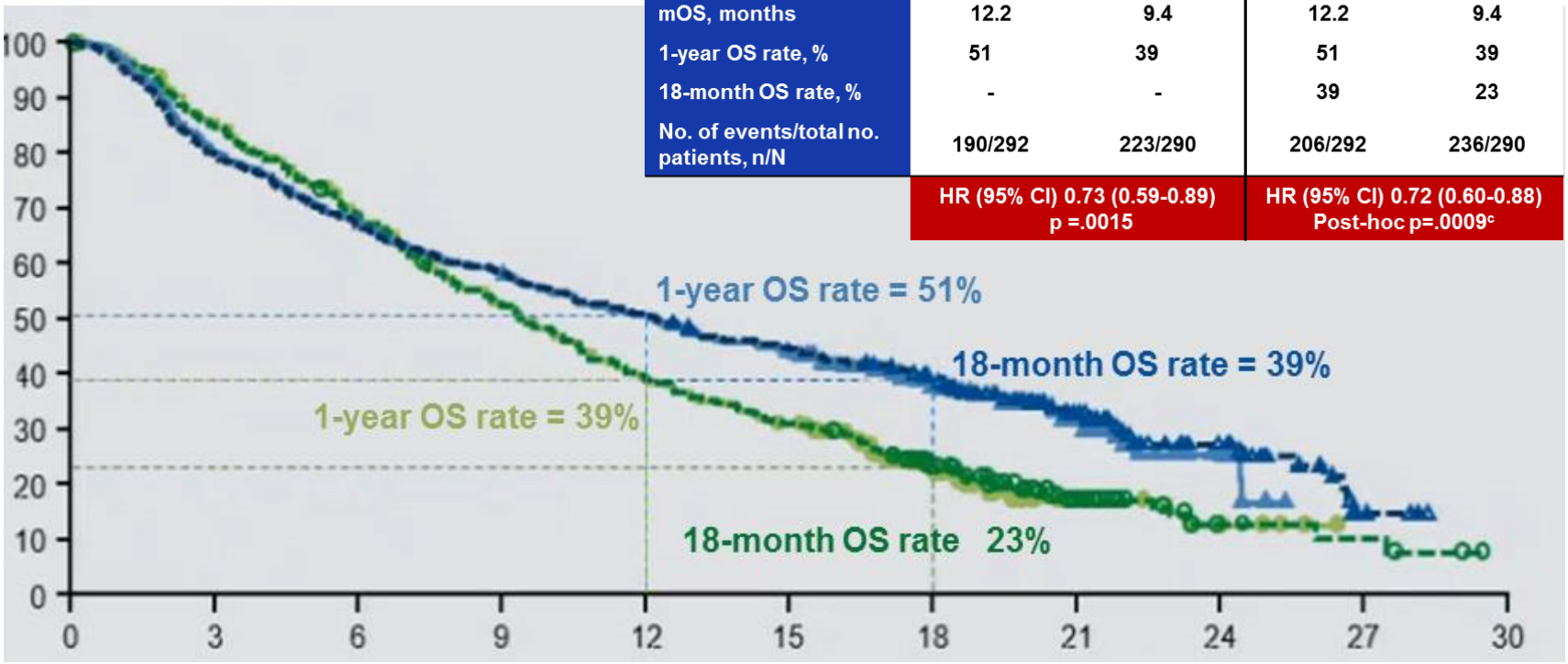
Minimum follow-up for survival: 18 months

Based on August 2015 DBL.
Symbols refer to censored observations.

Reckamp K et al, WCLC 2015

CheckMate 057: Updated OS Data

	12-month OS[a]		18-month OS[b]	
	Nivo (n=292)	Doc (n=290)	Nivo (n=292)	Doc (n=290)
mOS, months	12.2	9.4	12.2	9.4
1-year OS rate, %	51	39	51	39
18-month OS rate, %	-	-	39	23
No. of events/total no. patients, n/N	190/292	223/290	206/292	236/290
	HR (95% CI) 0.73 (0.59-0.89) p =.0015		HR (95% CI) 0.72 (0.60-0.88) Post-hoc p=.0009[c]	



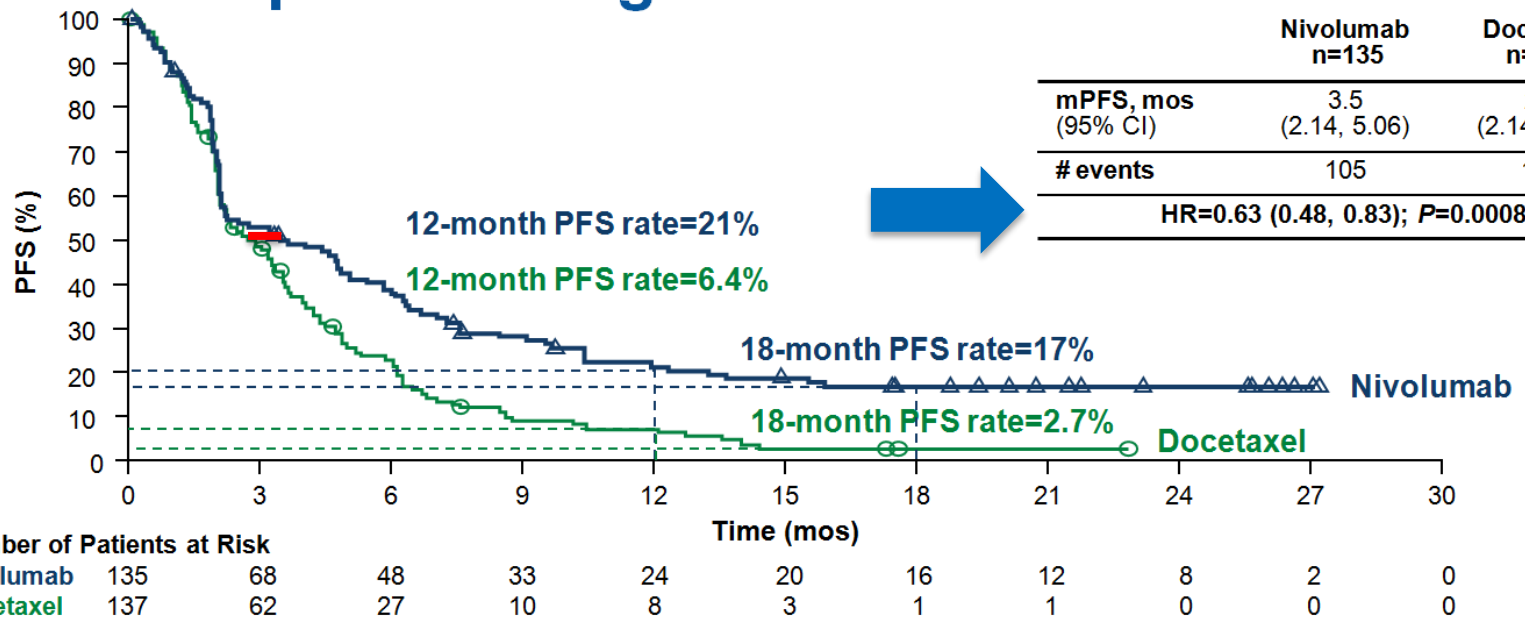
No. at risk (12-month OS)[a]											
Nivolumab	292	232	194	169	146	123	62	32	9	0	0
Docetaxel	290	244	194	150	111	88	34	10	5	0	0
No. at risk (18-month OS)[b]											
Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

Minimum F.U. for 12-month OS rate, 13.2 months; for 18-month OS rate, 17.1 months

Horn L, et al, ECC 2015

CheckMate 017: Updated PFS Data

Updated Progression-free Survival



	Nivolumab n=135	Docetaxel n=137
mPFS, mos (95% CI)	3.5 (2.14, 5.06)	2.8 (2.14, 3.52)
# events	105	122
HR=0.63 (0.48, 0.83); *P*=0.0008		

Number of Patients at Risk

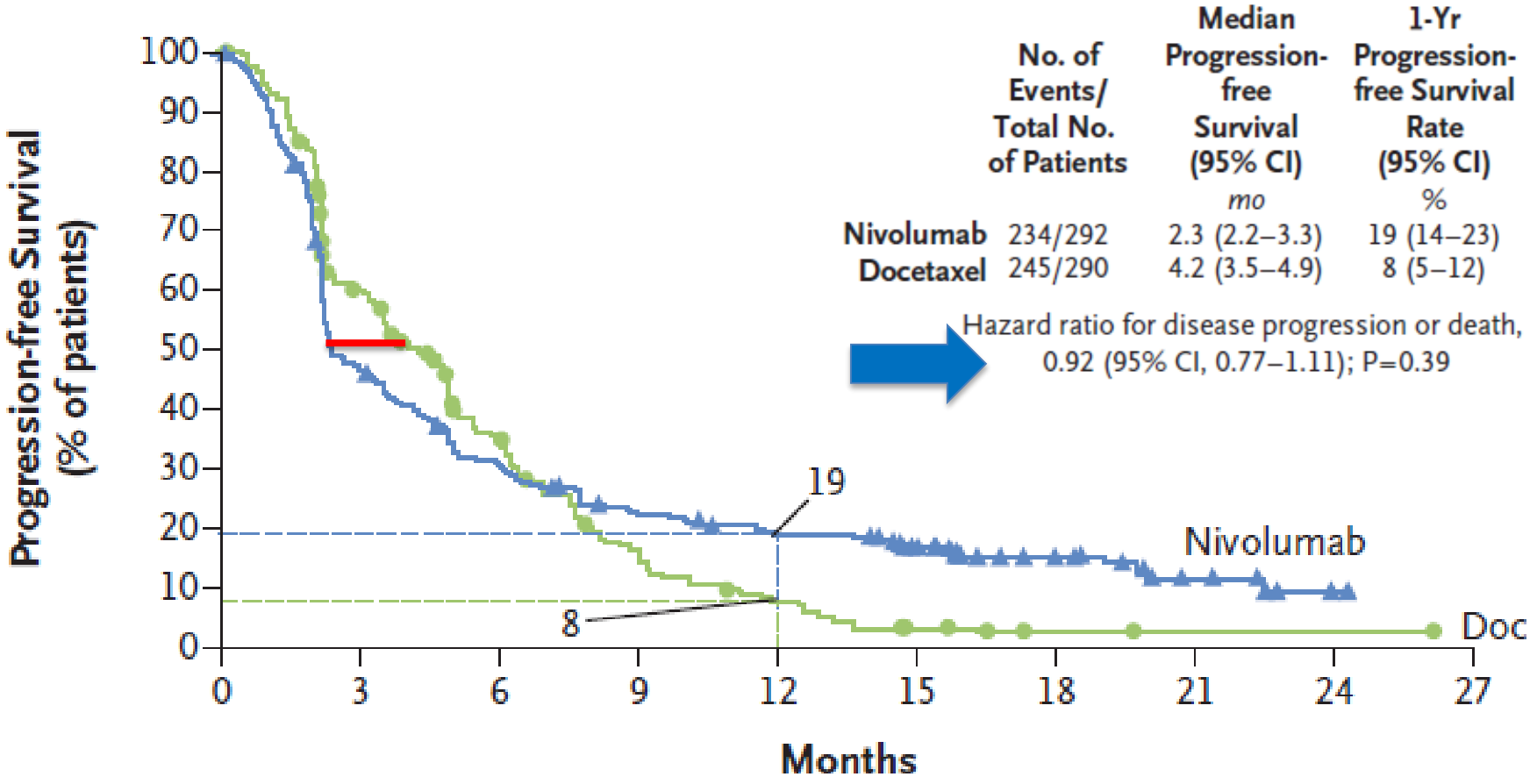
Nivolumab	135	68	48	33	24	20	16	12	8	2	0
Docetaxel	137	62	27	10	8	3	1	1	0	0	0

Minimum follow-up for survival: 18 months

Based on August 2015 DBL.
Symbols refer to censored observations.

Reckamp K et al, WCLC 2015

CheckMate 057: PFS Data



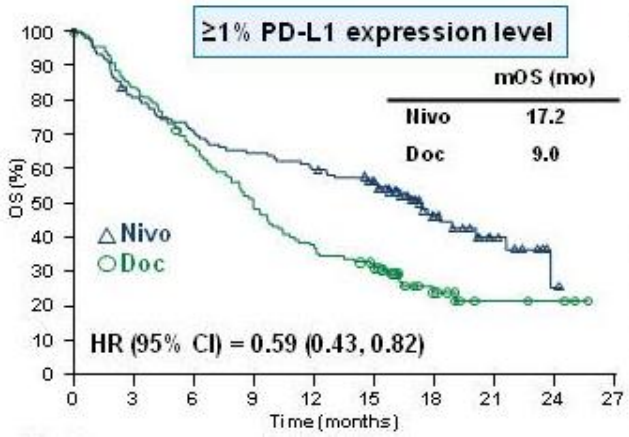
	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate (95% CI)
		mo	%
Nivolumab	234/292	2.3 (2.2–3.3)	19 (14–23)
Docetaxel	245/290	4.2 (3.5–4.9)	8 (5–12)

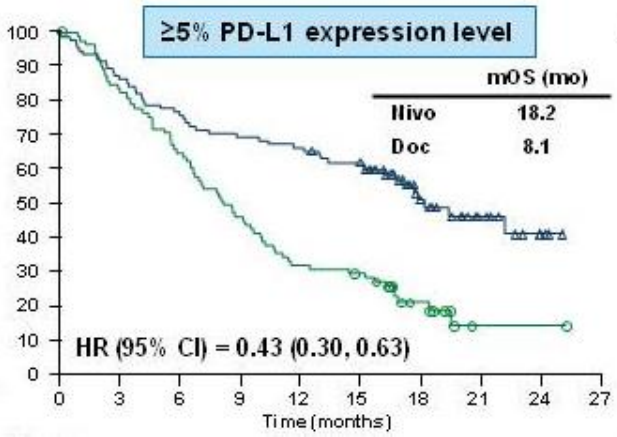
Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39

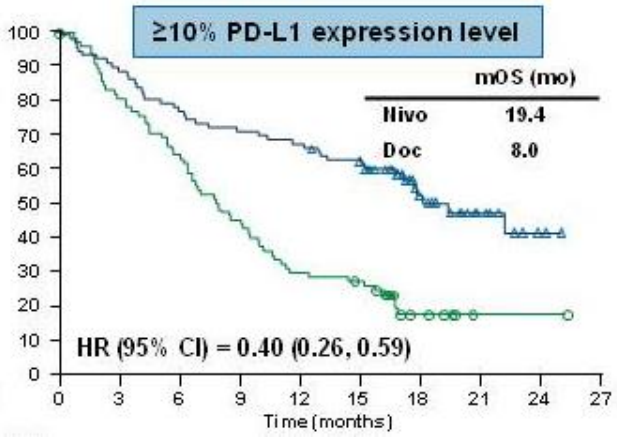
No. at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Borgheai H et al, NEJM 2015

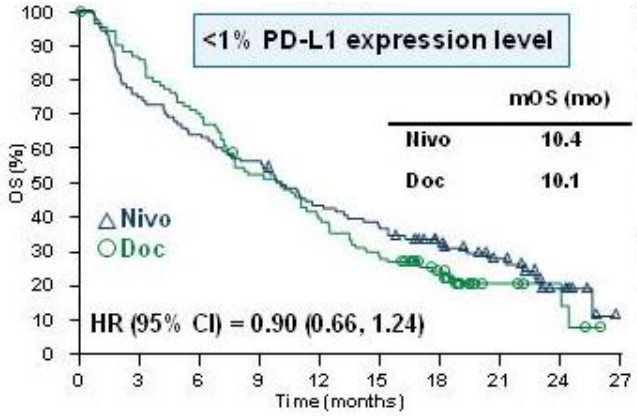
CheckMate 057: OS According to PD-L1

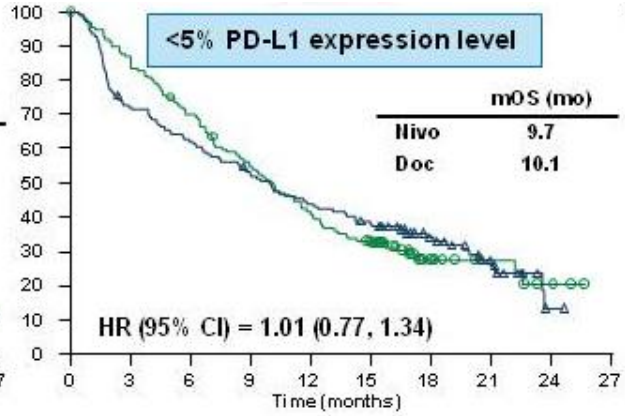


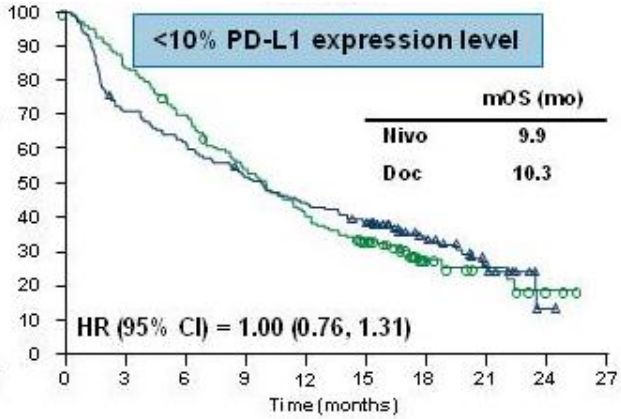




HR 0.59 **HR 0.43** **HR 0.40**







HR 0.90 **HR 1.01** **HR 1.00**

Paz-Ares L et al, ASCO 2015

Immunotherapy for NSCLC
'Comments' upon Methodology

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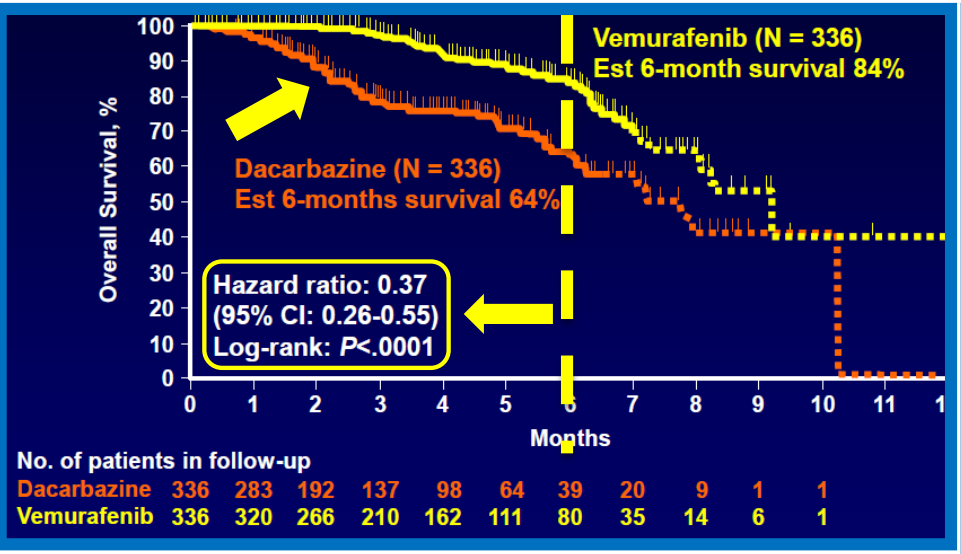
Cancer Survival Analysis

- Thus, patients should be considered:
  - **Uncensored:**
    - Subjects who are observed until they reach the endpoint of interest (i.e. recurrence or death).
  - **Censored :**
    - Those patients who survived beyond the end of the follow-up or who are lost to follow-up at some point.
      - **Censoring: the loss of subjects from a study before the events of interest has occurred.**

Source: AJCC Cancer Staging Manual, 7th Edition 2010; Everitt BS, Medical Statistics from A to Z, Ed. 2003

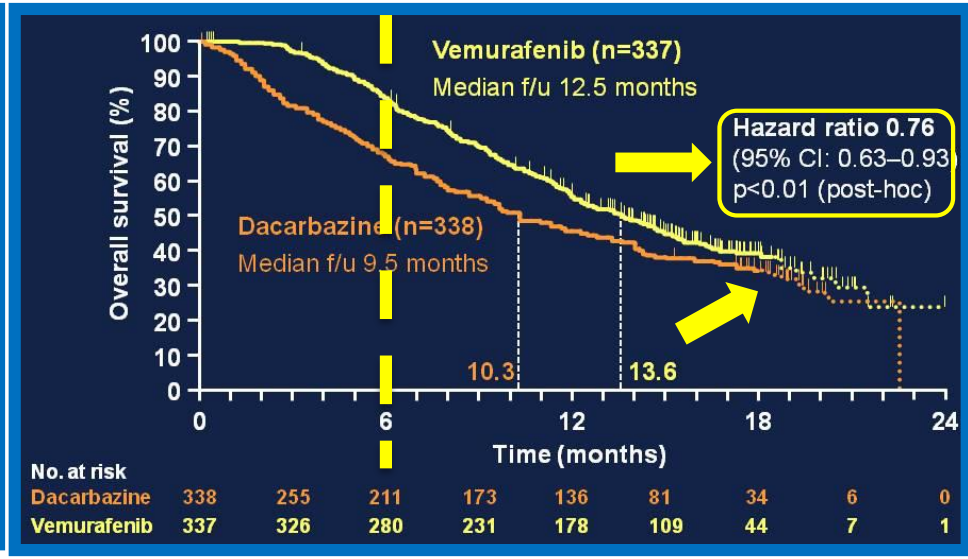
Immunotherapy for NSCLC
'Comments' upon Methodology: MATURITY

Data Cut-Off: Dec 2010



- HR 0.37
- Majority of Censored <u>WITHIN</u> 6 months (Left Side)
- Majority of Censored in the <u>Experimental Arm</u>

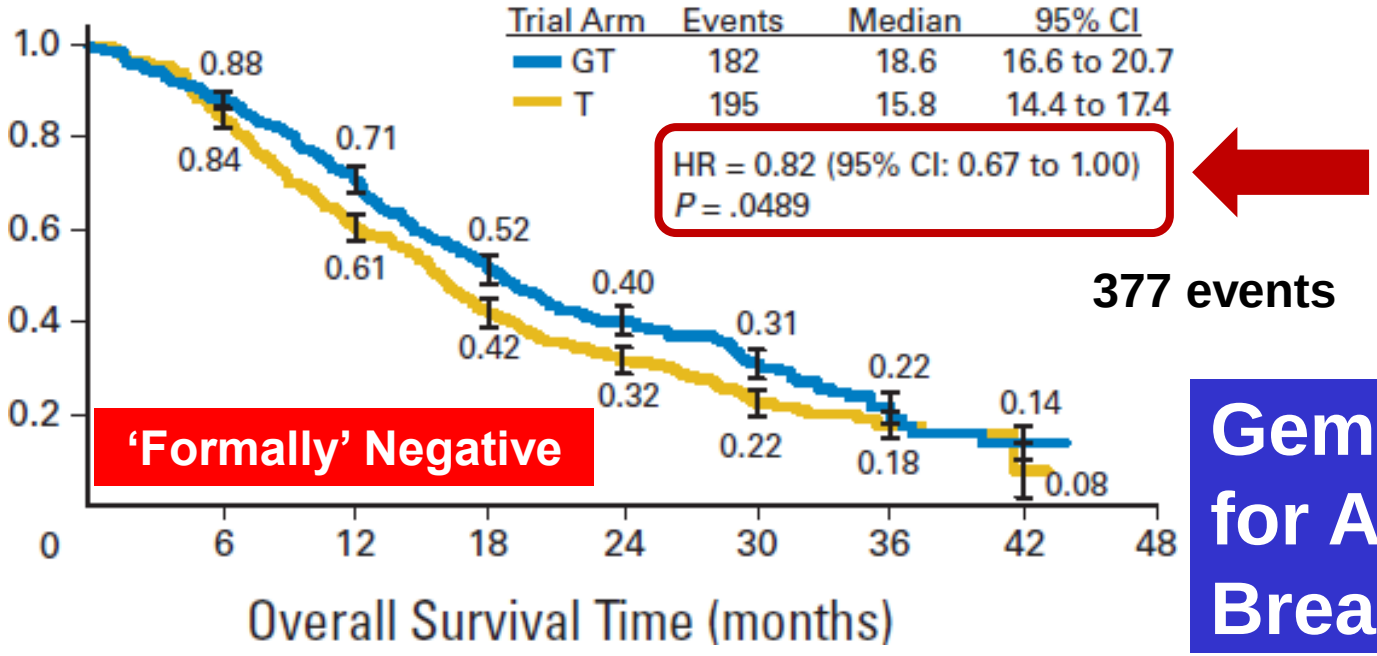
Data Cut-Off: Feb 2012



- HR 0.76
- Majority of Censored <u>AFTER</u> 12 months (Right Side)
- Majority of Censored in the <u>Experimental Arm</u>

Data Maturity: CRUCIAL FOR: AGENCIES' APPROVAL

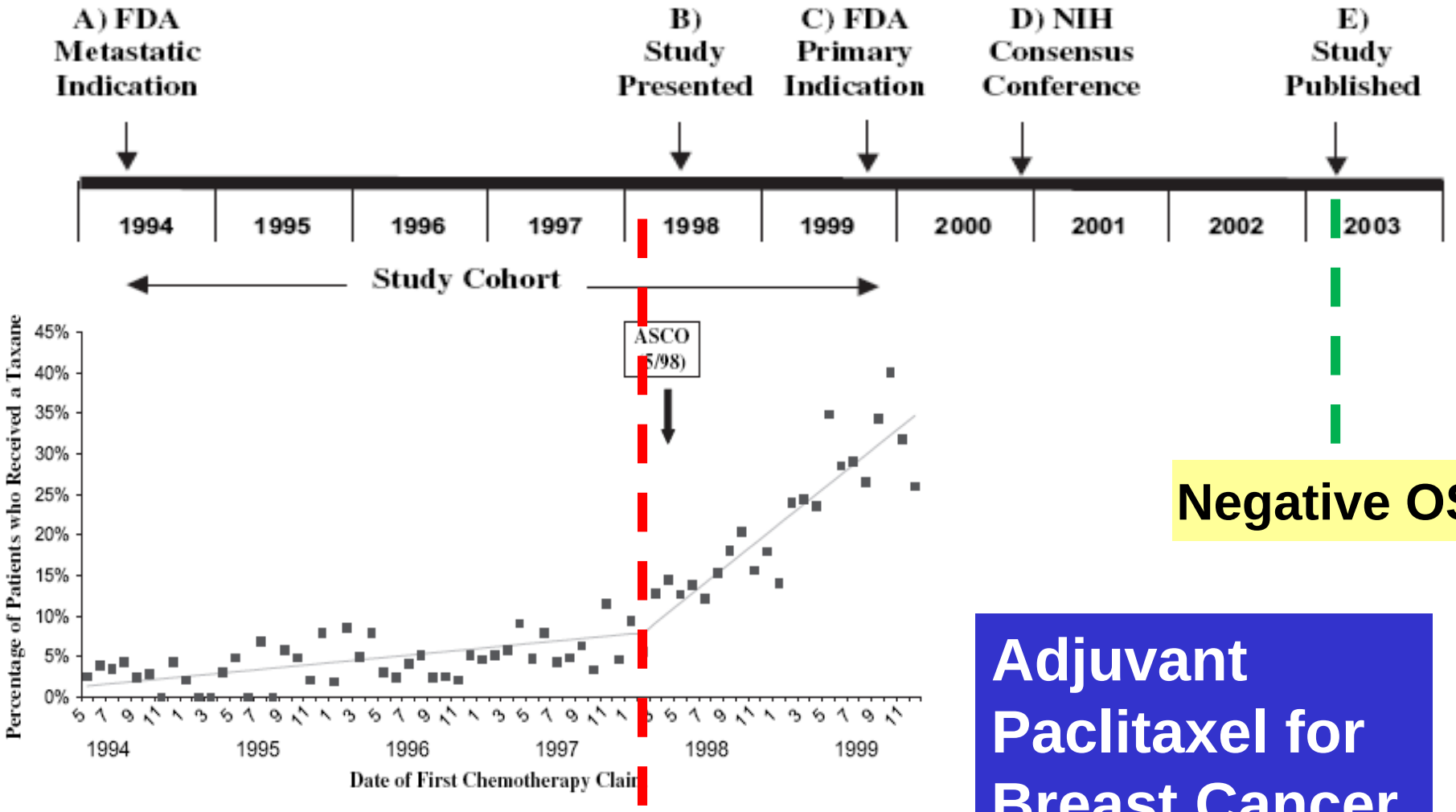
- Designed for HR 0.75 (for PFS and OS), power 80%
- First Analysis: p=0.028 (PFS) and p=0.03 (OS) BUT power 75%
  - **Nevertheless, FDA Fast Track APPROVAL (2004)**
- Finally, FDA requires only OS (HR 0.75), censoring rate <30% (<158 censored)



Gemcitabine for Advanced Breast Cancer

Albain K et al, JCO 2008

Data Maturity: CRUCIAL FOR:
DRUGS' MARKETING



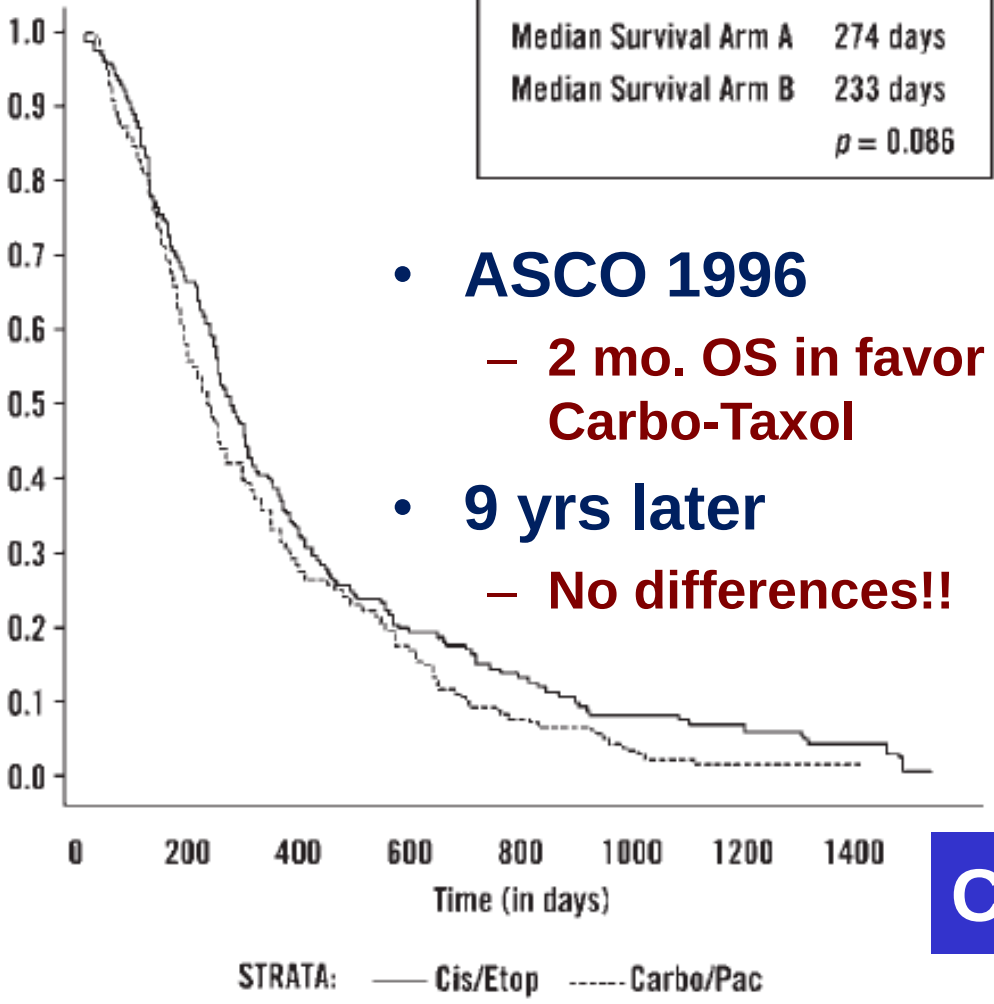
Negative OS

Positive OS

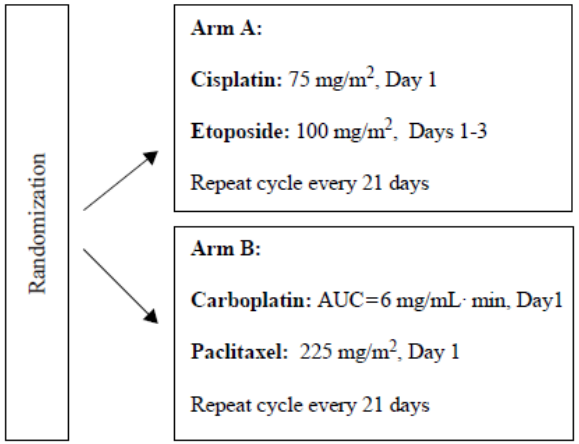
Adjuvant Paclitaxel for Breast Cancer

Giordano S et al, JNCI 2006

Data Maturity: CRUCIAL FOR: DEFINITION OF STANDARDS & CONTROL ARMS



- **ASCO 1996**
  - **2 mo. OS in favor of Carbo-Taxol**
- **9 yrs later**
  - **No differences!!**



Carbo-Taxol for NSCLC

Belani C et al, Ann Oncol 2006

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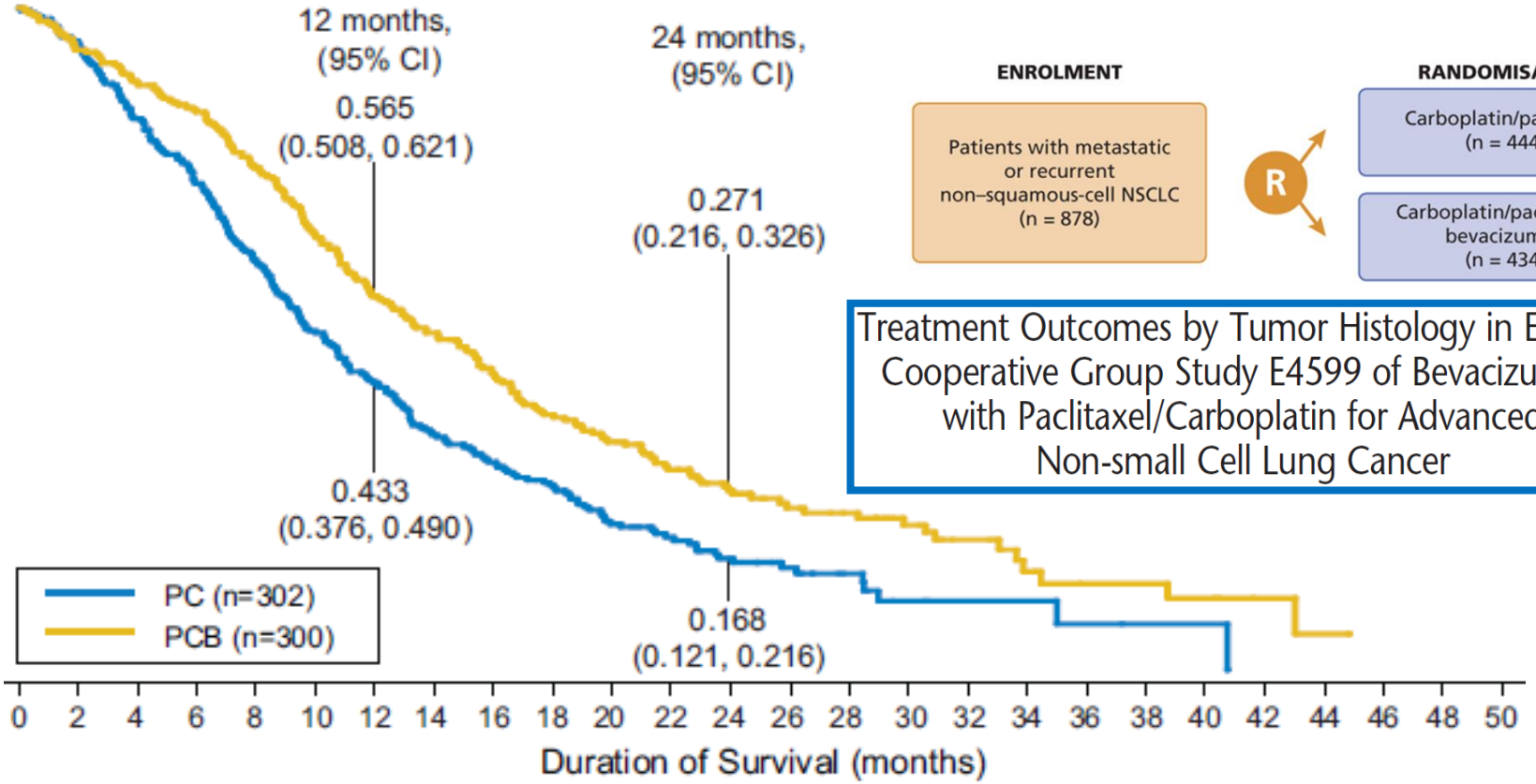
DO YOU HAVE ADEQUATE STATISTICAL MALPRACTICE INSURANCE?

‘Seeking’ for a Larger benefit

Subgroup Analysis



Treatment Outcomes by Tumor Histology in Eastern Cooperative Group Study E4599 of Bevacizumab with Paclitaxel/Carboplatin for Advanced Non-small Cell Lung Cancer

Larger HR……but no significant interaction according to Histology!

Sandler A et al, JTO 2010

Immunotherapy for NSCLC
'Comments' upon Methodology

- **Hazard Ratio (HR)**
  - Which model for survival analysis?
  - HR: Principles, Assumptions and Limitations
- **Curves' Models**
  - Median survivals and Late rates
  - 'Adjusted' Data
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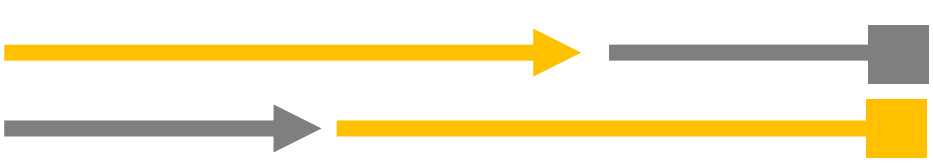
Immunotherapy for NSCLC
'Comments' upon Methodology: CORRELATION

What if this model?



Large PFS

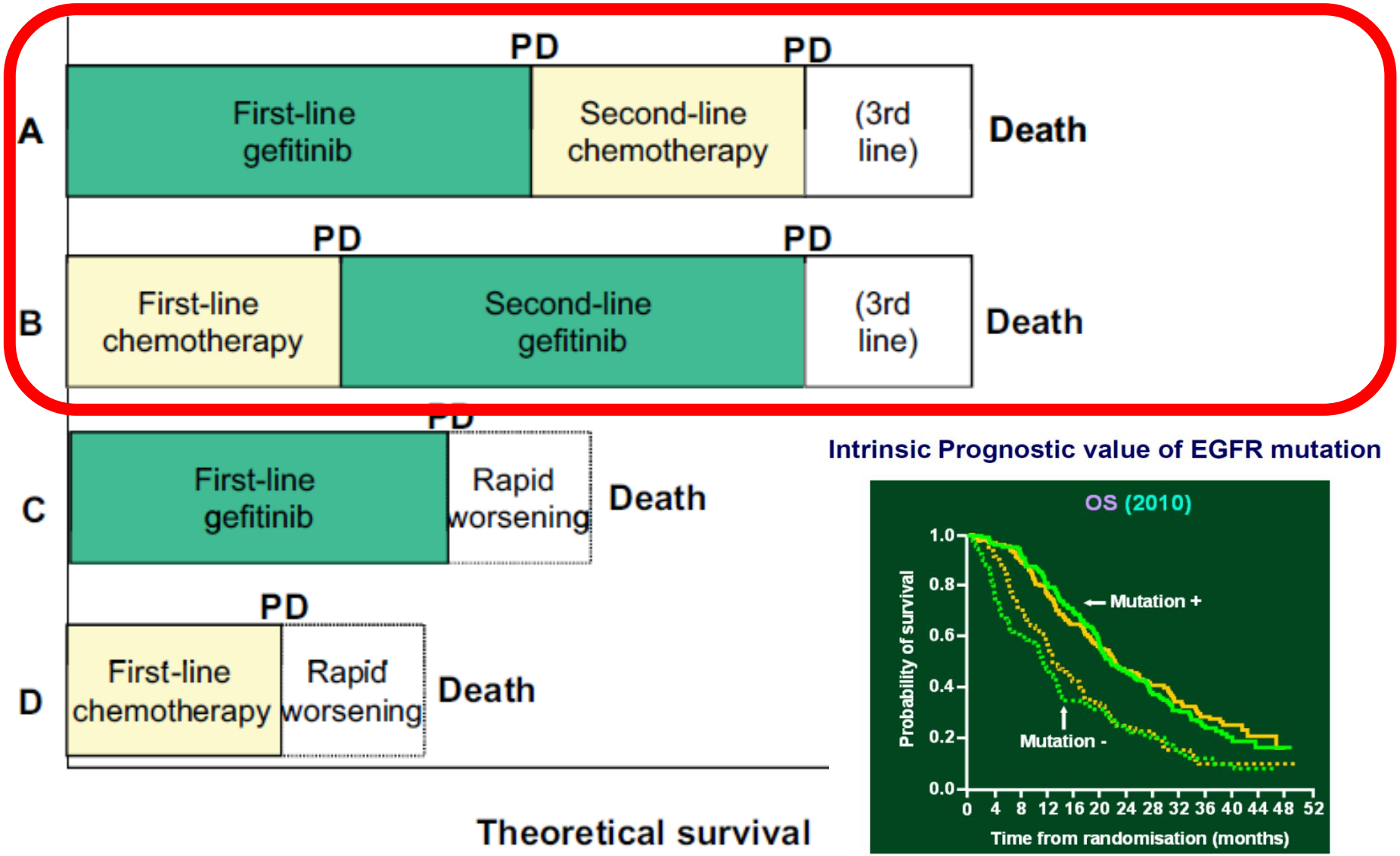
Possible OS Impact

Crossover between treatment groups allowed!

Experimental treatment
Standard treatment
Other treatment for relapse
Progression
Death

MODIFIED - Booth CM, et al, JCO 2011

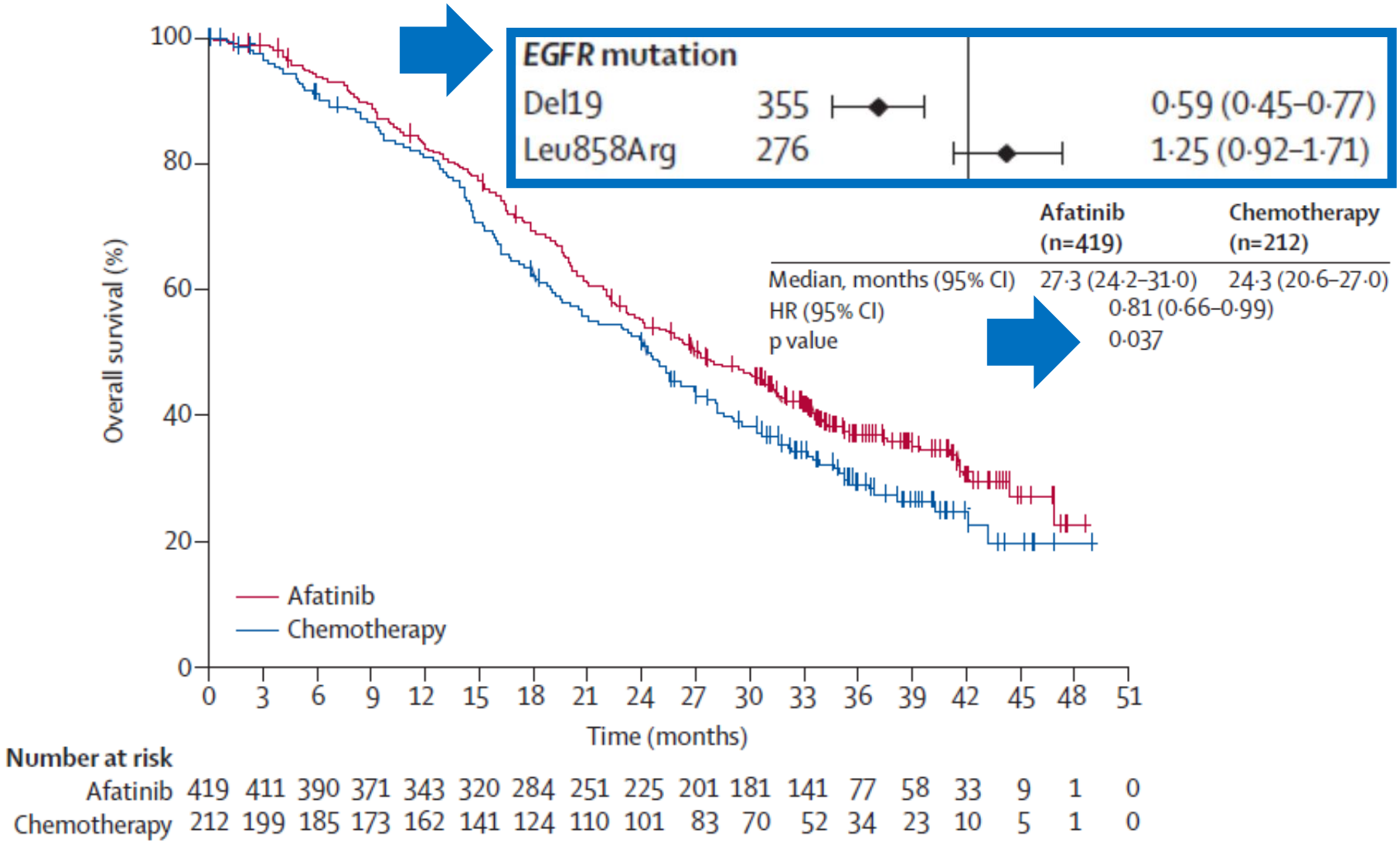
Gefitinib as first-line treatment for patients with advanced non-small-cell lung cancer with activating epidermal growth factor receptor mutation: Review of the evidence



Intrinsic Prognostic value of EGFR mutation

Lung Cancer 71 (2011) 249–257

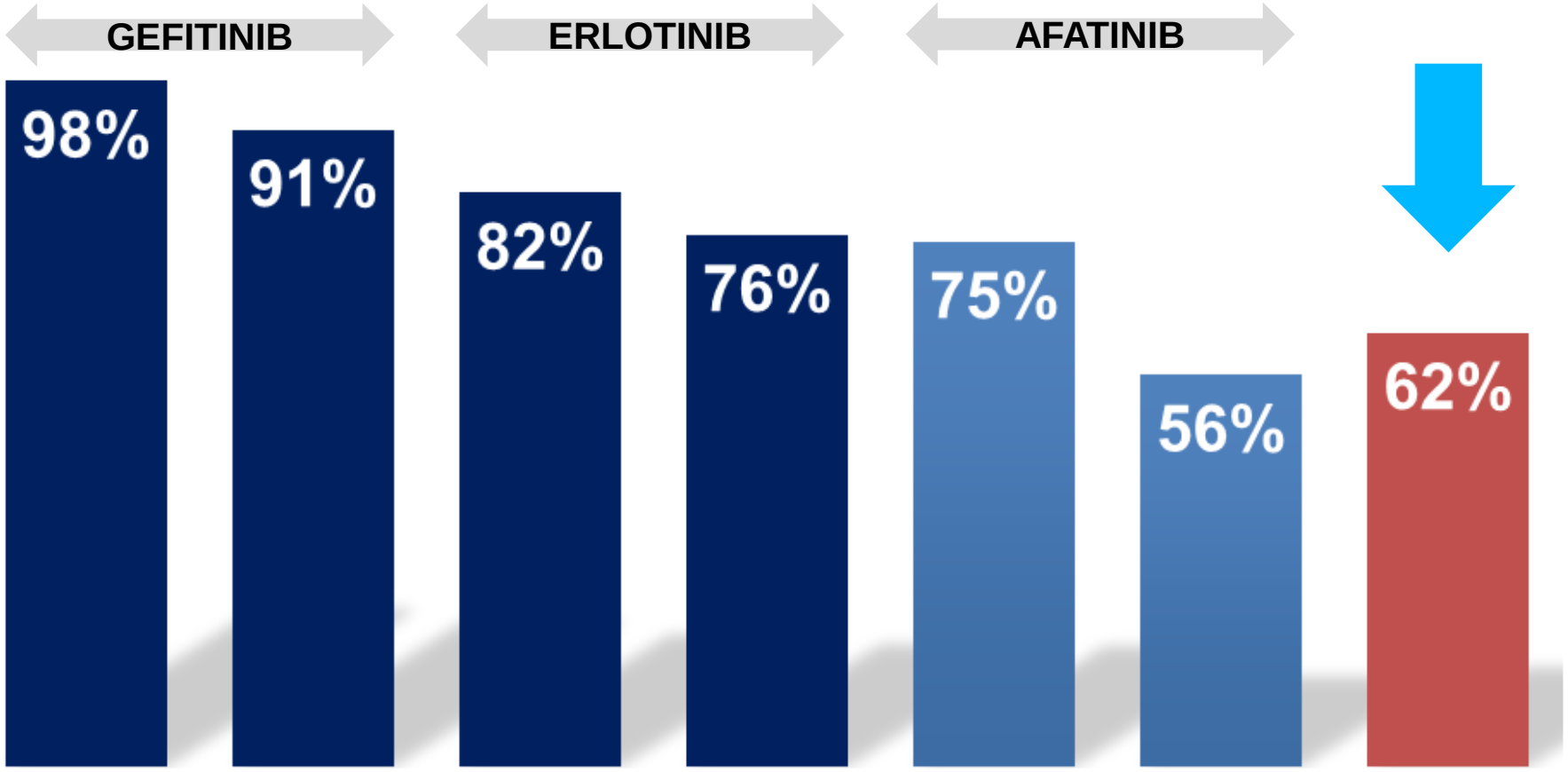
‘Combining’ LUX-Lung 3 + 6: Overall Survival [Common EGFR mutation population]



Yanj J et al, Lancet Oncol 2015

[Prospective RCTs with EGFR-TKIs]

Cross-Over Rates

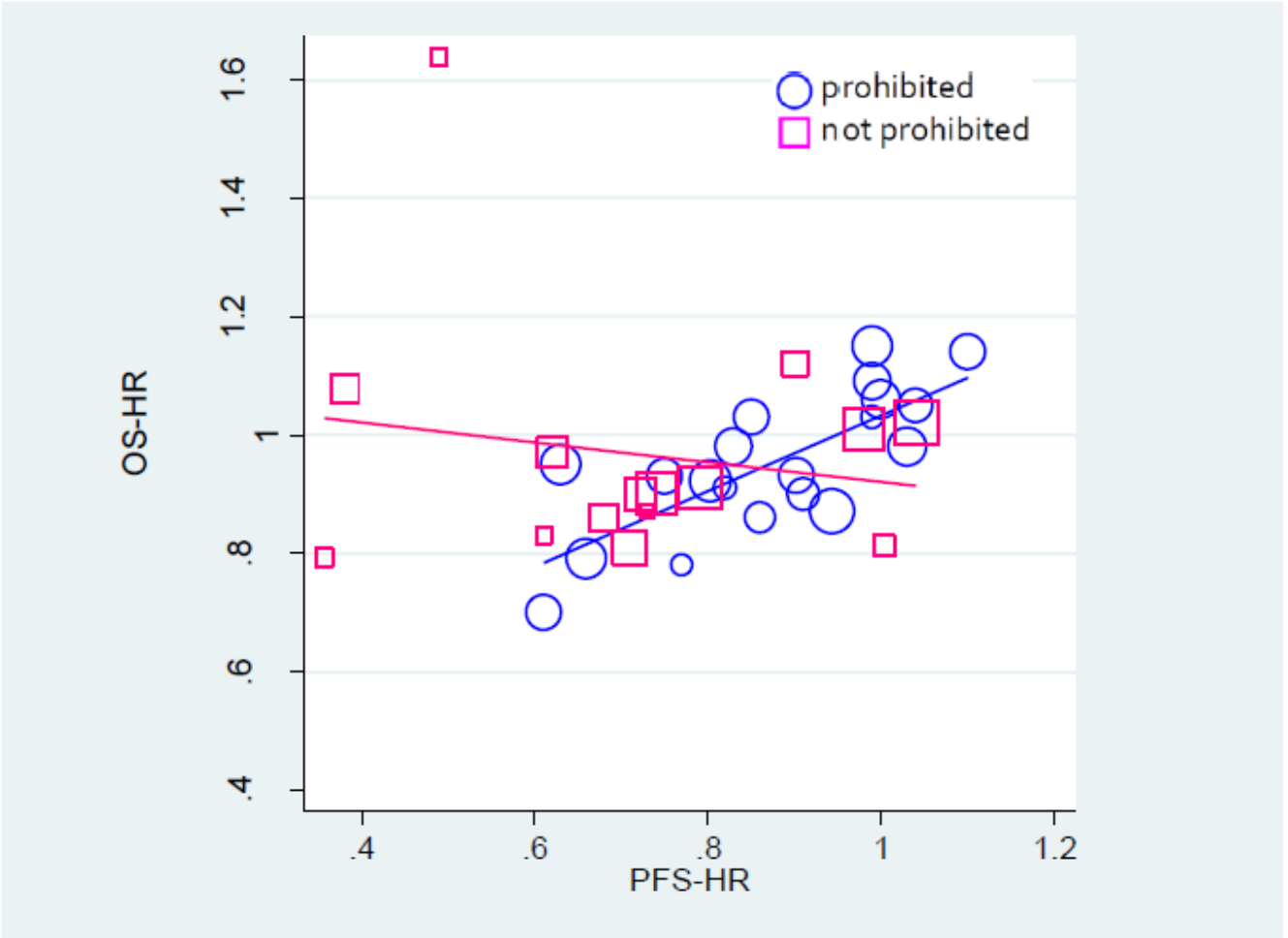


N = 115	N = 86	N = 87	N = 82	N = 230	N = 241	N = 419

Modified from West J, ASCO 2014

Impact of cross-over on correlation between PFS and OS

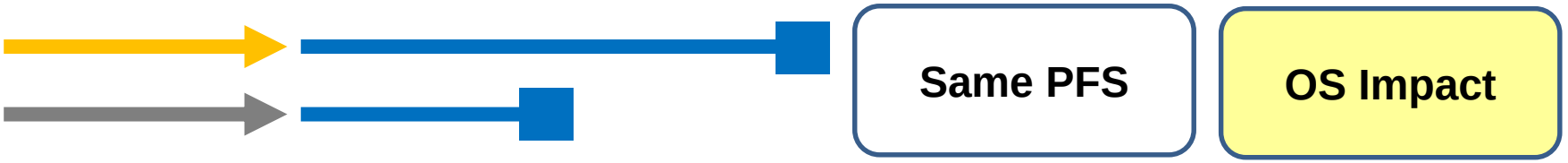
Trials of targeted agents in advanced NSCLC



Hotta K et al, Lung Cancer 2010

Immunotherapy for NSCLC
'Comments' upon Methodology: CORRELATION

What if this model?

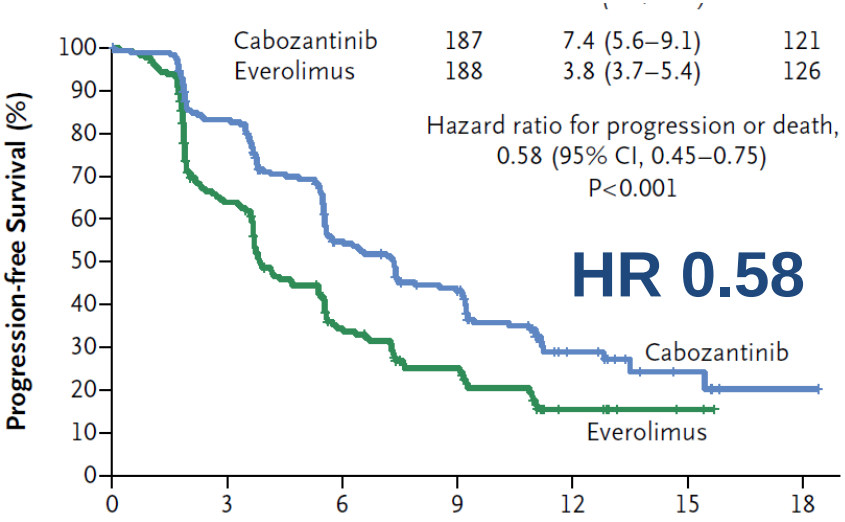


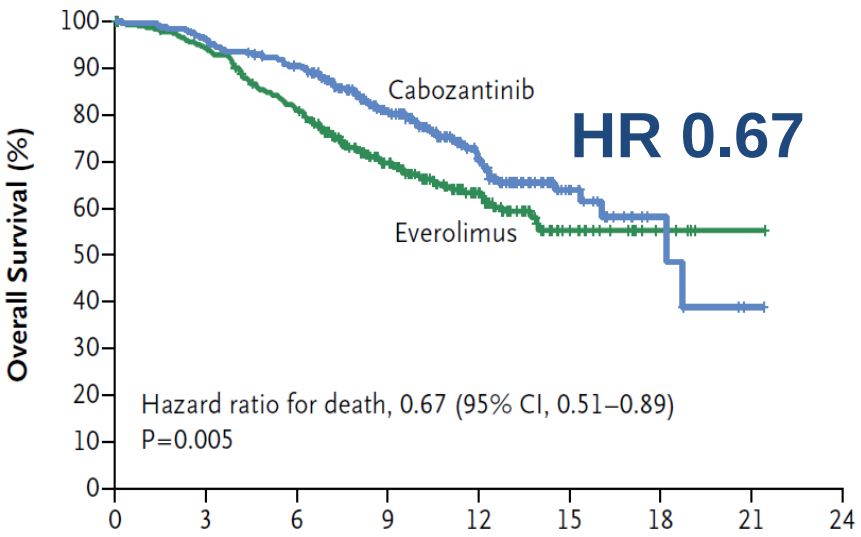
Crossover between treatment groups not allowed!

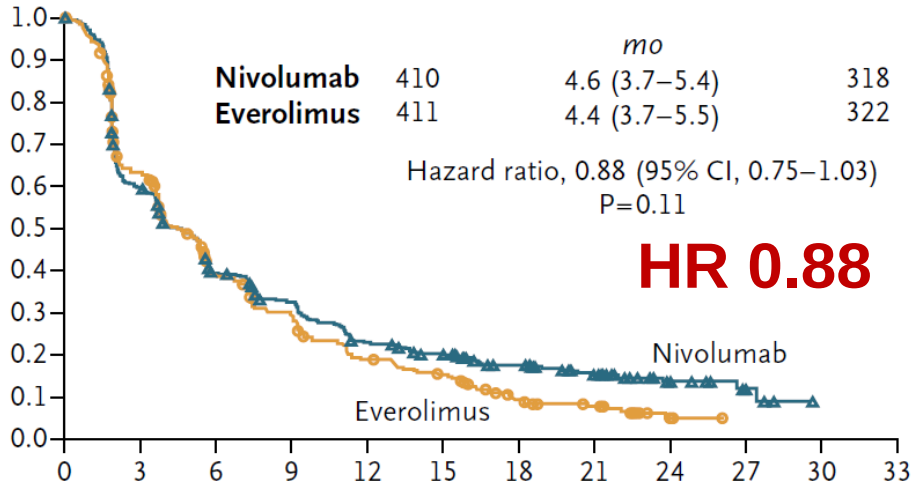
Experimental treatment
Standard treatment
Other treatment for relapse
Progression
Death

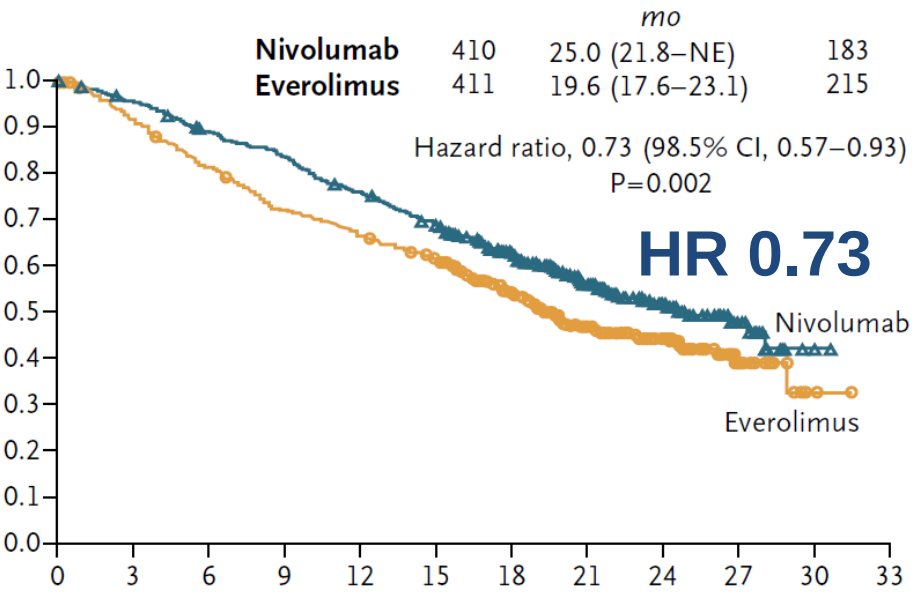
MODIFIED - Booth CM, et al, JCO 2011

Same disease [RCC], same OS benefit, same NEJM issue!









Choueiri T et al, NEJM 2015

Motzer R et al, NEJM 2015

Immunotherapy for NSCLC
'Comments' upon Methodology

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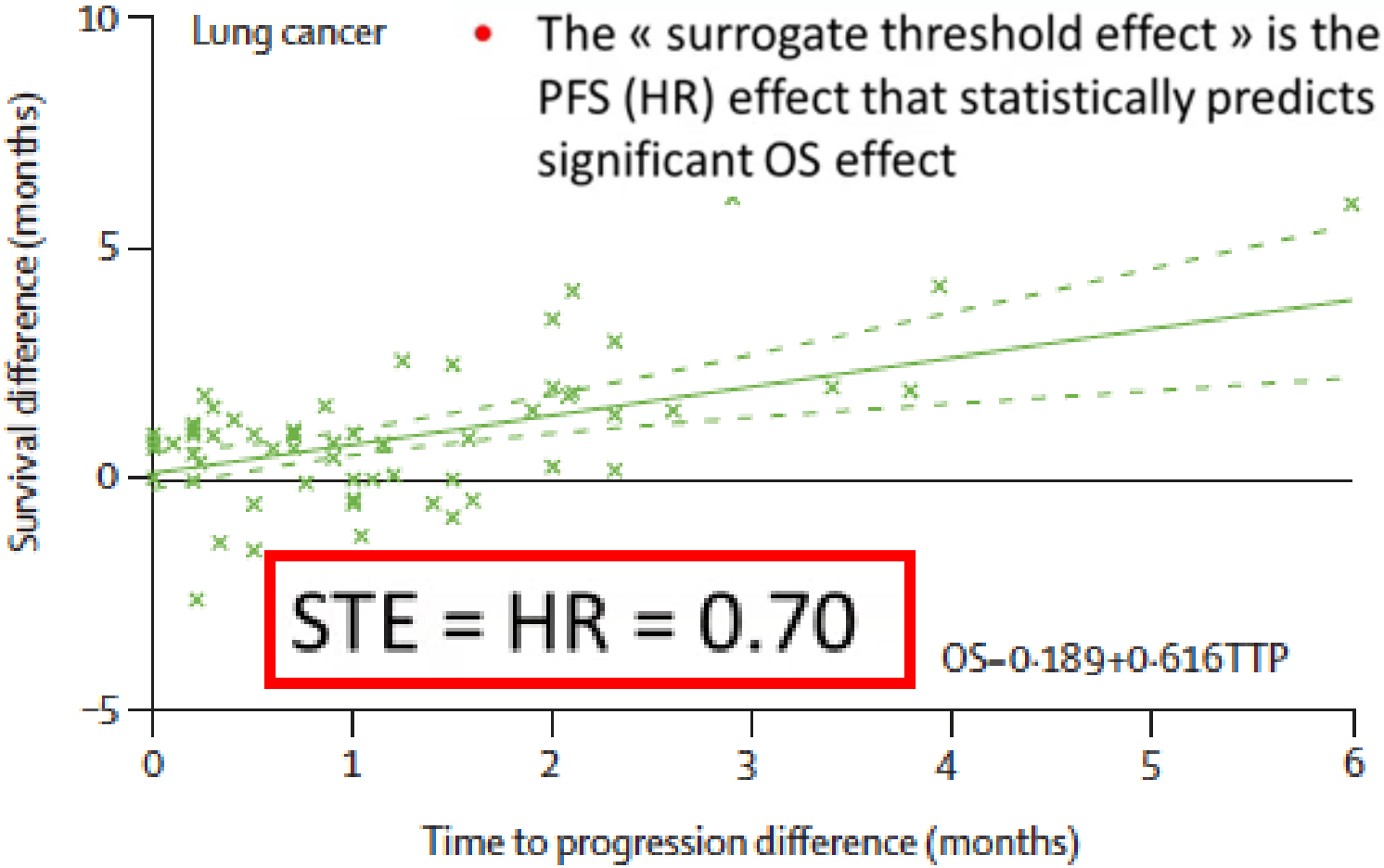
How much PFS gain do we need to impact upon OS?



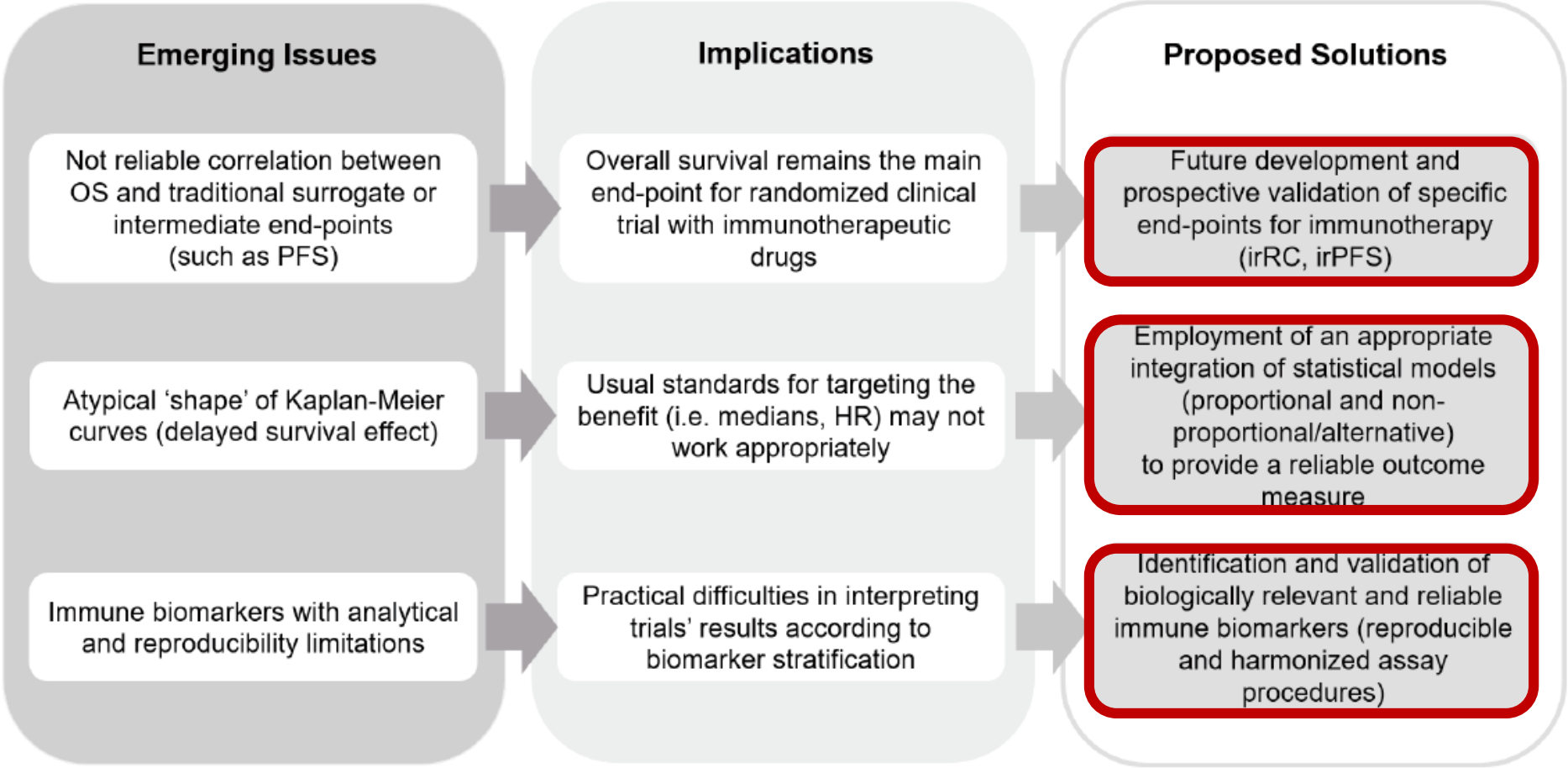
- The « surrogate threshold effect » is the minimum PFS (HR) effect that statistically predicts for a significant OS effect

- Hence, in future trials, a reduction of at least 30% in the risk of progression (or death) would predict a significant effect on survival

Lancet Oncol 2006;7:741–46

Burzykowski and Buyse, Pharmaceutical Statist 2006; 5: 173

Immunotherapy for NSCLC
'Comments' upon Methodology:
PERSPECTIVES for Clinical Trial Design



Pilotto S et al, TLCR 2015

Immunotherapy for NSCLC
'Comments' upon Methodology

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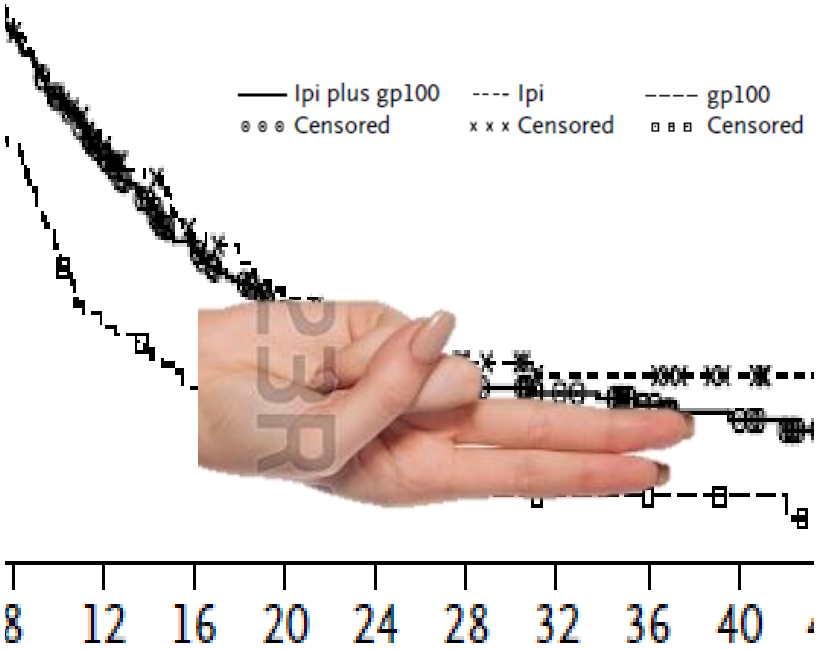
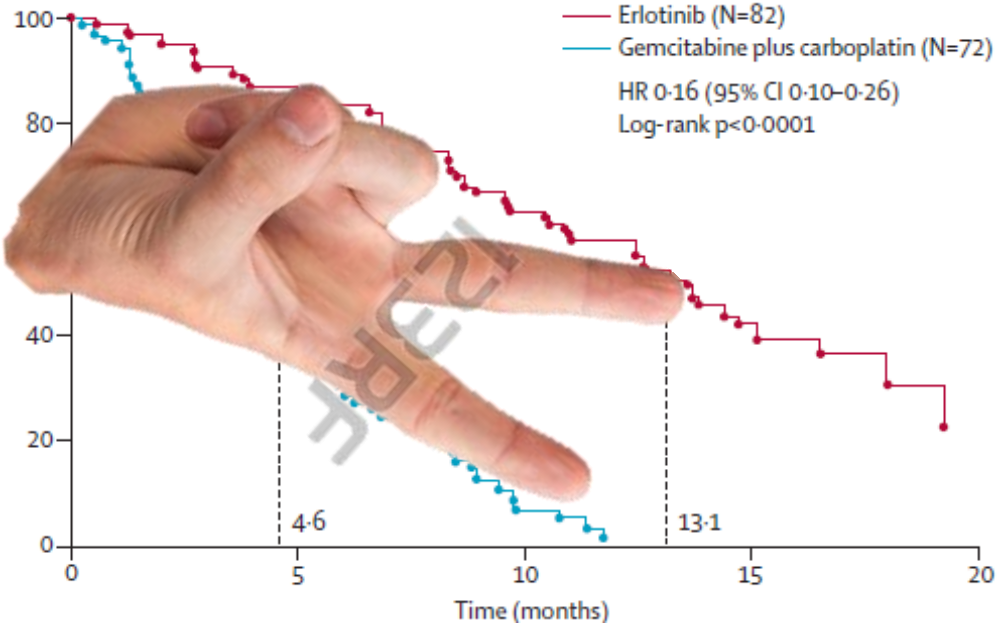
- **The '*Two-Fingers*' Rule i.e. the '*quantity*' or ……**

The NEW ENGLAND JOURNAL of MEDICINE

The '*Two-Fingers*' Rule

- **Clinically Meaningful Data if '*at least*' two fingers separates curves!**



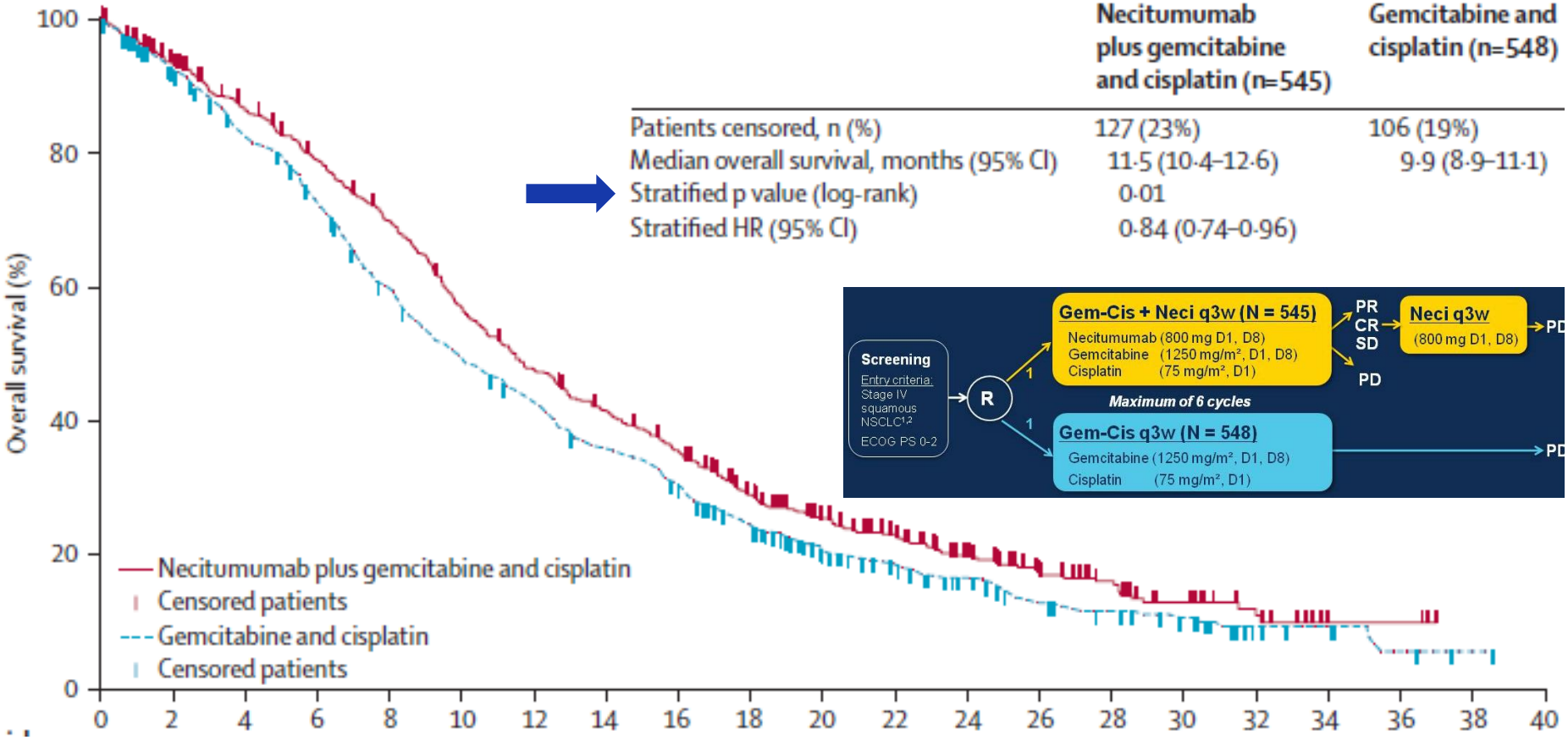


Hodi et al, NEJM 2010

Zhou et al [OPTIMAL], Lancet Oncol 2011

HR or Median? Curves' Shapes

What if statistically significant but…….



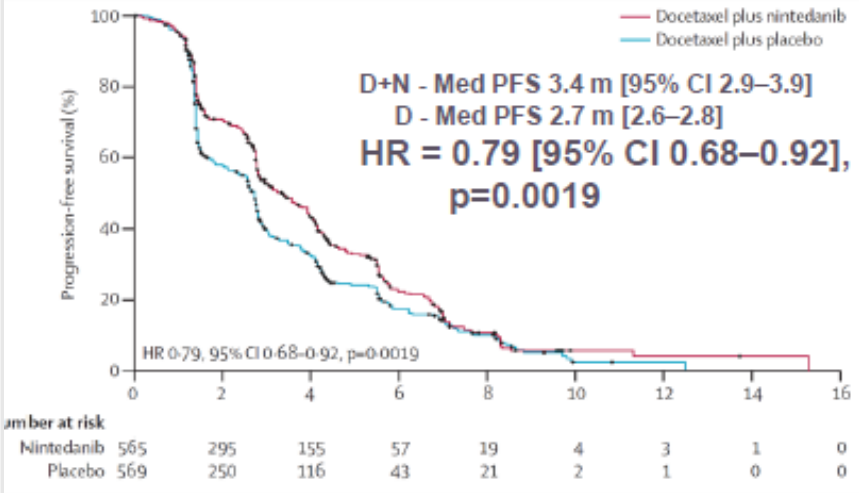
	Necitumumab plus gemcitabine and cisplatin (n=545)	Gemcitabine and cisplatin (n=548)
Patients censored, n (%)	127 (23%)	106 (19%)
Median overall survival, months (95% CI)	11·5 (10·4–12·6)	9·9 (8·9–11·1)
Stratified p value (log-rank)	0·01	
Stratified HR (95% CI)	0·84 (0·74–0·96)	

Thatcher N et al, Lancet Oncol 2015

Anti-angiogenic agents in 2nd line?

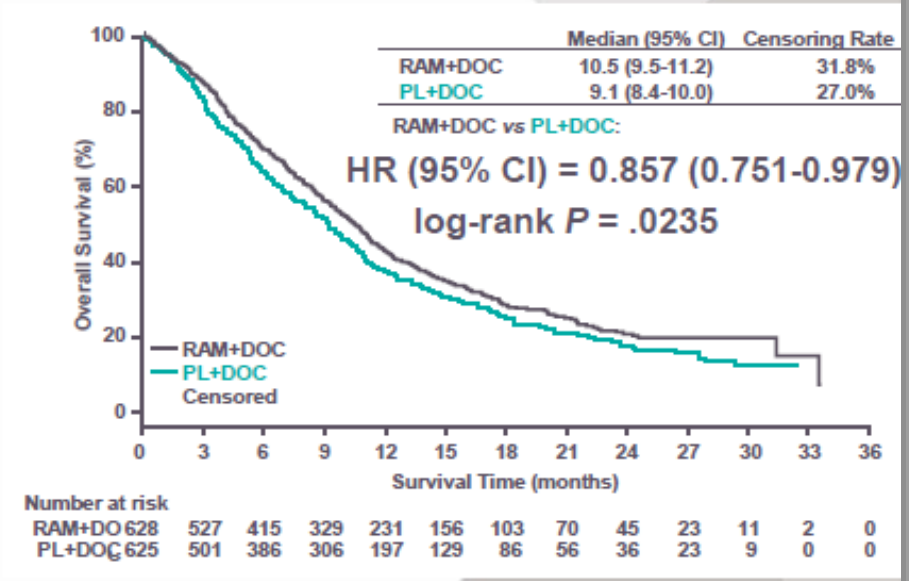
MADRID 2014 ESMO congress

PFS - Docetaxel +/- nindetanib (VEGFR TKI)



OS benefit in adenocarcinoma
PFS benefit in refractory pts
(HR= 0.67 (0.43-1.04,p=0.0725).

OS - Docetaxel +/- ramucirumab (VEGFR2 Ab)



OS benefit in SCC and non SCC

Perol ASCO 14, Reck Lancet Oncol 14

Courtesy of Besse B, ESMO 2014

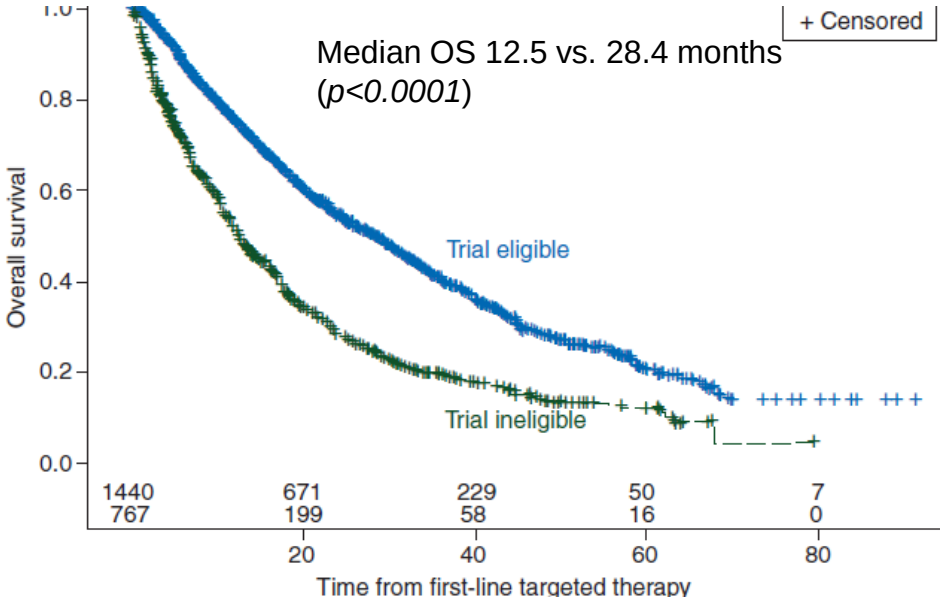
Targeted Therapy Performance in the '*Real World*'

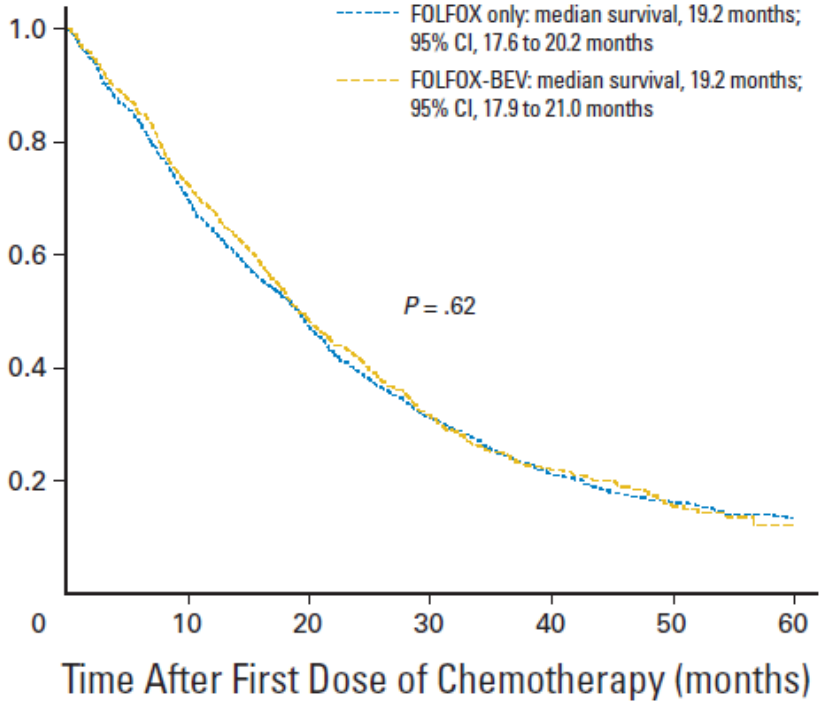
Outcomes of patients with metastatic renal cell carcinoma that do not meet eligibility criteria for clinical trials

Effectiveness of Bevacizumab With First-Line Combination Chemotherapy for Medicare Patients With Stage IV Colorectal Cancer

Trials' *Ineligible* Pts vs. *Eligible* (all receiving targeted agents)

Addition of Bevacizumab to FOLFOX, '*Registry*' Context





Deng DY et al, Ann Oncol 2014

Meyerhardt T et al, JCO 2012

Key-Concepts for Clinical Trials

What do we assess in clinical trials?

- **Activity:**
  - ability of the treatment to induce modifications of the disease thanks to which it is assumed that the patient may have a benefit **[Phase II]**
- **Efficacy:**
  - ability of the treatment to induce a clinical benefit in patients who are administered ***in an experimental context*** **[Phase III]**
- **Effectiveness:**
  - ability of a treatment to be effective in a ***non-experimental, concrete and coincident with the clinical practice*** **[are Phase IV, 'Real World' Data]**

Key Elements of Quality Health Care Delivery

- **Safety**
- **Effectiveness**
- **Cost**
- **Patient centeredness**
- **Timeliness**
- **Efficiency**
- **Equity**

- **Readily measured, ascertainable from high-quality medical evidence, and central to the mission of the clinical oncologist.**
- **Not as easily measured and are only rarely reported as outcomes of clinical trials.**

ASCO [Value in Cancer Care Task Force] JCO 2015

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

Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)	Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: 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

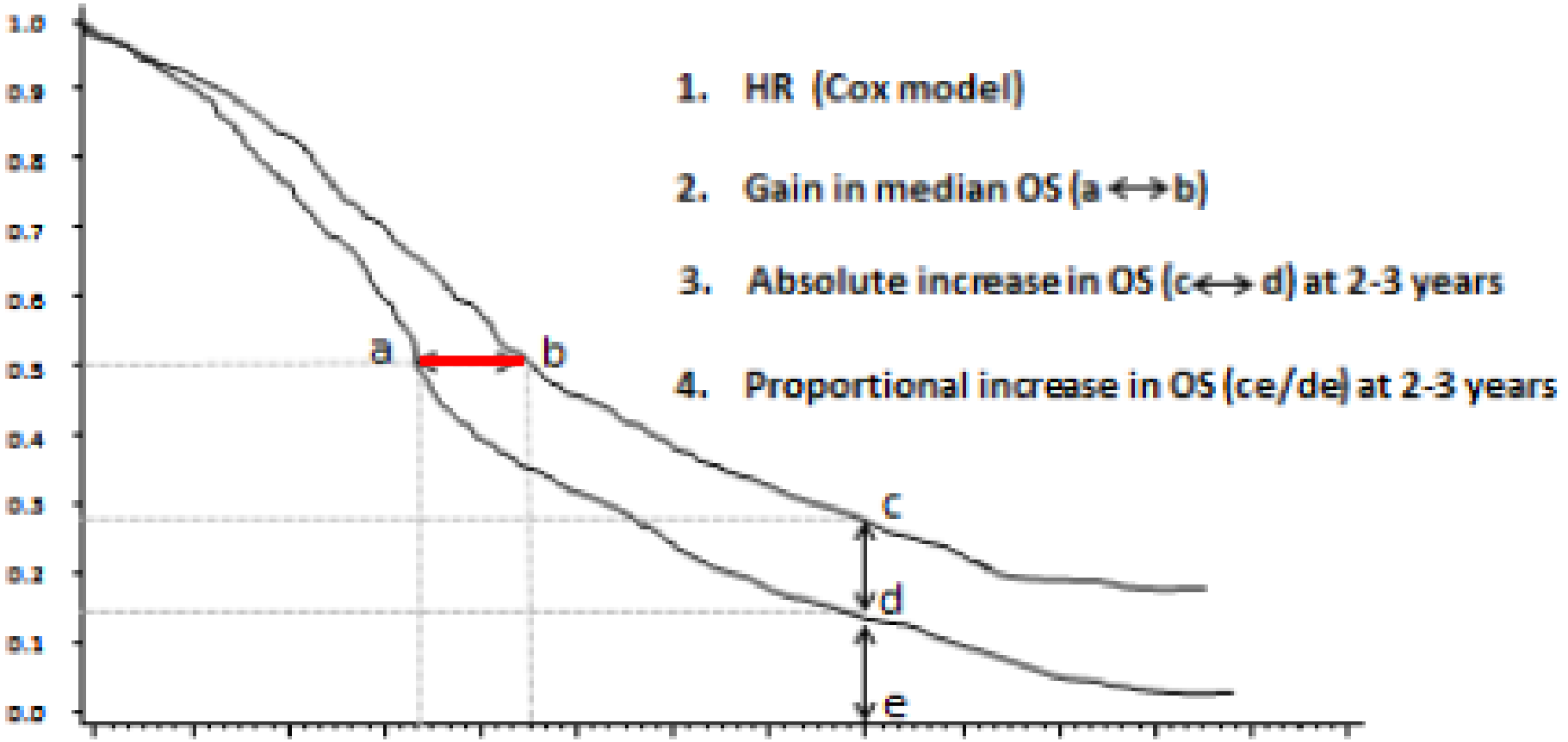
On the basis of HR and Medians, and correlation between PFS and OS!!!!

Ellis LM et al, JCO 2014

Raising the bar for antineoplastic agents: how to choose threshold values for superiority trials in advanced solid tumors

Alberto F Sobrero, Alessandro Pastorino, Daniel J. Sargent, et al.

To establish the concept of minimum ***clinically meaningful outcome (mCMO)*** of treatment in advanced solid tumors, to establish its threshold and evaluate how many superiority trials of new antineoplastic agents pass this threshold.



Sobrero A et al, CCR 2014

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

THE ASCO VALUE FRAMEWORK: ADVANCED DISEASE

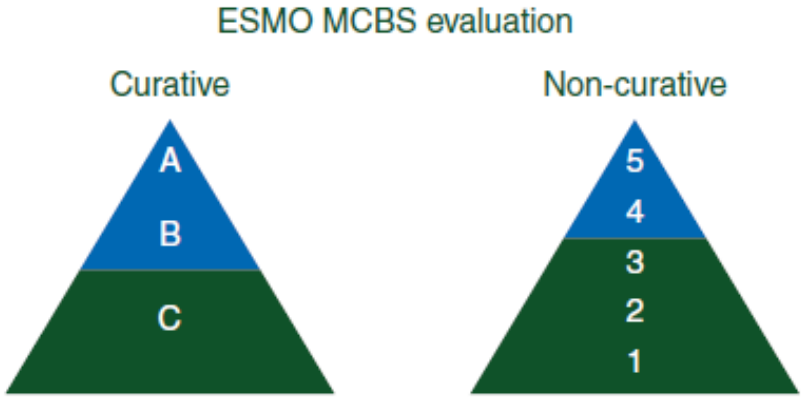
Step 1: Determine the regimen's CLINICAL BENEFIT							
1.A. Is Overall Survival (OS) reported?	**YES.** Assign an OS Score (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." **Proceed to 1.D.**						**OS Score**
	OS Score	1	2	3	4	5	
	Improvement in median OS (% change in median OS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median OS of new regimen, there is a 50% improvement in the fraction of patients surviving	
	NO. Proceed to 1.B.						
1.B. If OS is not reported, is Progression-Free Survival (PFS) reported?	**YES.** Assign a PFS Score (1 through 5 as shown below) and multiply by 11. Write this number in the box labeled, "PFS Score." **Proceed to 1.D.**						**PFS Score**
	PFS Score	1	2	3	4	5	
	Improvement in median PFS (% change in median PFS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median PFS of new regimen, there is a 50% improvement in the fraction of patients without progression or death	
	NO. Proceed to 1.C.						
1.C. If neither OS nor PFS is reported, is Response Rate (RR) reported?	**YES.** Assign an RR Score (1 through 5 as shown below) and multiply by 8. RR should be calculated by adding the complete response (CR) and partial response (PR) rates. Write this number in the box labeled, "RR Score." Proceed to 1.D.						**RR Score**
	RR Score	1	2	3	4	5	
	What was the reported response rate (CR + PR)?	> 0%-20%	21%-40%	41%-60%	61%-80%	81%-100%	
1.D. Calculate the Clinical Benefit Score	Insert the OS, PFS, or RR Score. **Note: You should have EITHER an OS Score OR a PFS score OR an RR score, NOT MORE THAN ONE.** Write the total in the box labeled "Clinical Benefit Score." The maximum allowable points are 80. **Proceed to Step 2.**						**Clinical Benefit Score**

Schnipper LE, et al, JCO 2015

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

Table 2. Maximal preliminary scores

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



Curative-Evaluation form 1: for new approaches to adjuvant therapy or new potentially curative therapies

Non-curative-Evaluation forms 2a, b or c: for therapies that are not likely to be curative

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

Cherny NI, et al, Ann Oncol 2015

Conclusions

- Immunotherapy (given the peculiar mechanism) requires a specific methodology for trial design and data analysis:
  - **HR and Medians may not entirely capture the benefit of such drugs.**
  - **Converserly, outcome differences as landmark analysis (either as absolute of relative measurements) seem more appropriate.**
- The choice of the ‘best’ way to capture outcome differences is of paramount importance, given the end-point confers ‘*quality*’ to the evidence
- Health care steps forward require minimal standards to be satisfied
  - **The QUALITY of the evidence, should be weighted with the QUANTITY of the benefit**
- Health care comparative effectiveness research is moving towards assigning ‘values’, taking into account (at least) as a objective way as possible, safety and costs as well.

Varmus's Second Act

"There's an imbalance between the money available, the work that needs to be done, and the number of people who would need to be supported to make the world feel like a more comfortable place."

Varmus H, Science 2013