Can neo-adjuvant breast cancer treatment data be used to accelerate drug approval?

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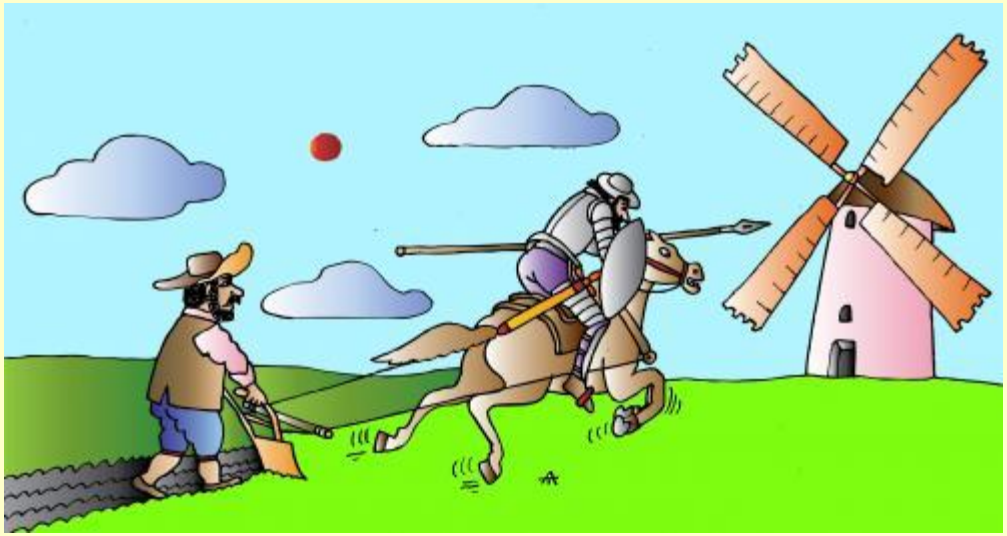
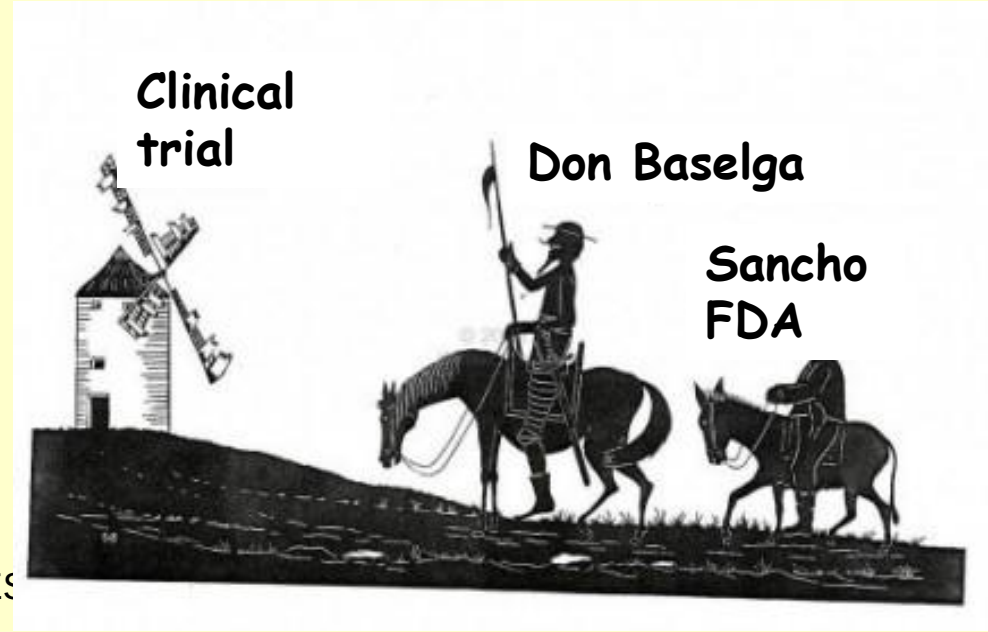
Potential conflicts of interest

I have advised multiple companies about design of trials for for which I have received contributions to my research fund.

I do not accept personal remuneration from companies



Tilting at windmills



What do we want from drug development?

There are only two goals of any new treatment:

To allow the patient to live longer

and/or

To allow the patient to live better

Hence, there are only two important endpoints of a drug registration trial:

1. Overall Survival

2. Quality of Survival

Anything else is a surrogate endpoint

We do want:

- New drugs that produce a meaningful impact on survival
- New drugs that decrease symptoms and improve quality of life

We do not need:

- Drugs that have a trivial impact on survival with high cost and toxicity

The classical route to drug approval

- Phase I trial to demonstrate safety and establish the MTD
- Phase II trial to show activity in patients with metastatic cancer
  - N.B. Drug activity ≠ patient benefit
- Phase III trial comparing addition of new agent to standard therapy in patients with advanced cancer
  - Endpoints must reflect patient benefit
- Phase III trials evaluating new agent in the adjuvant setting

Drugs approved for breast cancer in last 5 years

Drug	Date	Condition	Trial	Endpoint
Lapatinib	Mar 2007	HER2+ with capecitabine after trastuzumab, anthra, taxane	RCT N = 399	TTP (6.0 vs. 4.5)
	Jan 2010	HR+ HER2+ with letrozole	RCT: HER2+ N = 219	PFS (8.9 vs. 3.3)
Ixabepilone	Oct 2007	With capecitabine in pts resistant to anthra, taxanes	RCT N=752	PFS (5.7 vs. 4.1)
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Everolimus	July 2012	HR+, HER2- with exemestane after progression on other AI	RCT N =724	PFS (7.8 vs. 3.2)

All of these drugs were approved for advanced breast cancer

FDA draft document May 2012

Guidance for Industry

Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

"FDA may grant marketing approval for a new drug... .on the basis of well-controlled trials establishing that it has an effect on a surrogate endpoint that is reasonably likely.....to predict clinical benefit"

"Approval....will be subject to the requirement that the drug be studied further....to verify its clinical benefit"

The FDA is proposing that neoadjuvant trials in women with high-risk breast cancer might be used for accelerated approval of new drugs

Neoadjuvant trials for accelerated approval?

I accept that in neoadjuvant trials:

1. Patients who achieve pCR have better survival
2. Tissue at surgery allows study of target inhibition

The main problems are:

1. Giving a new drug with unknown safety to women with potentially curable disease
2. Is the surrogate endpoint (response) **"reasonably likely to predict clinical benefit"**

Even large RCTs are insufficient to disclose serious toxicity when new agents are prescribed

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Reporting of Serious Adverse Drug Reactions of Targeted Anticancer Agents in Pivotal Phase III Clinical Trials

Bostjan Seruga, Lynn Sterling, Lisa Wang, and Ian F. Tannock *J Clin Oncol 29:174-185. © 2010*

58% of potentially fatal adverse events are not in the initial FDA drug label, and 39% are not reported in any published randomized trial

There are ethical concerns about prescribing a new drug to patients after accelerated approval based on a small neoadjuvant trial

And if the confirmatory trial is an adjuvant trial, there are ethical concerns...

...about selling a drug to women who can afford it while recruiting others to a controlled trial

Also, women will perceive benefit because of the conditional approval and will be reluctant to take part in a controlled trial..

So the whole process may be RETARDED rather than accelerated!

The key question: Is the surrogate endpoint (response) "reasonably likely to predict clinical benefit"

VOLUME 26 · NUMBER 24 · AUGUST 20 2008

JOURNAL OF CLINICAL ONCOLOGY

CELEBRATING 25 YEARS

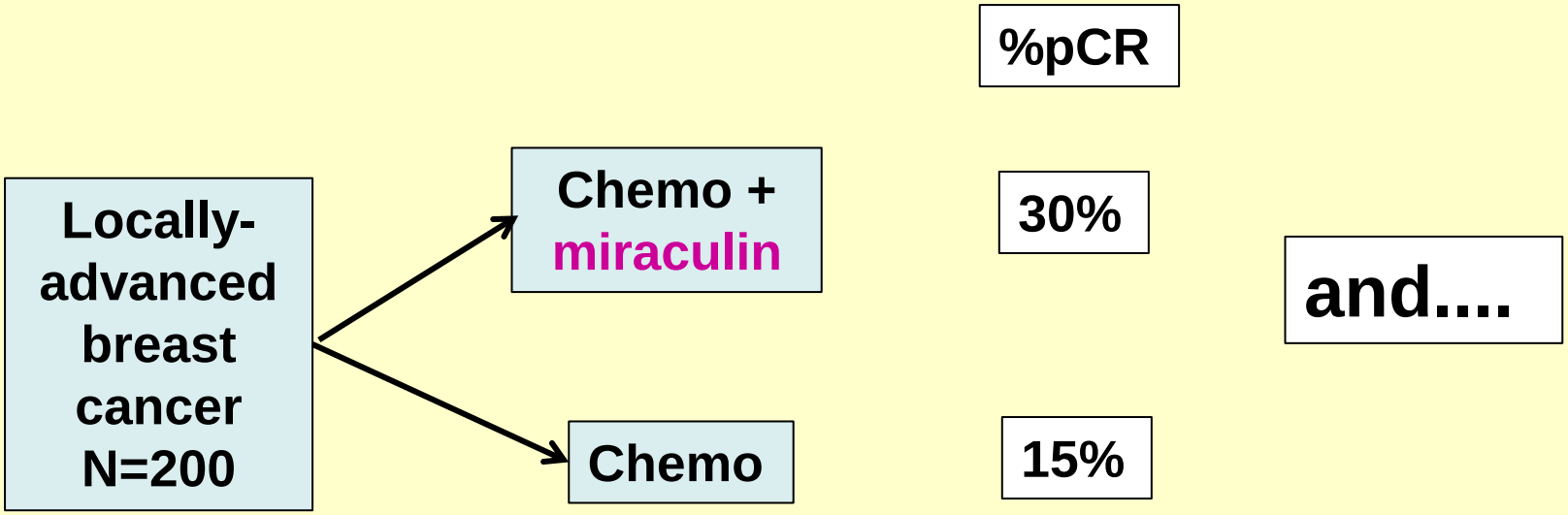
Analysis of Survival by Tumor Response and Other Comparisons of Time-to-Event by Outcome Variables

James R. Anderson, *University of Nebraska College of Public Health, Omaha, NE*
Kevin C. Cain, *University of Washington, Seattle, WA*
Richard D. Gelber, *Dana-Farber Cancer Institute and Harvard School of Public Health, Boston, MA*

Achieving CR in a neoadjuvant trial is an imperfect predictor of subsequent longer survival

Analysis of survival by tumor response .....is statistically invalid

Consider results of a neoadjuvant trial evaluating the new drug miraculin



	with pCR	without pCR
5-year survival	80%	60%

This does NOT imply better overall survival in the group receiving miraculin

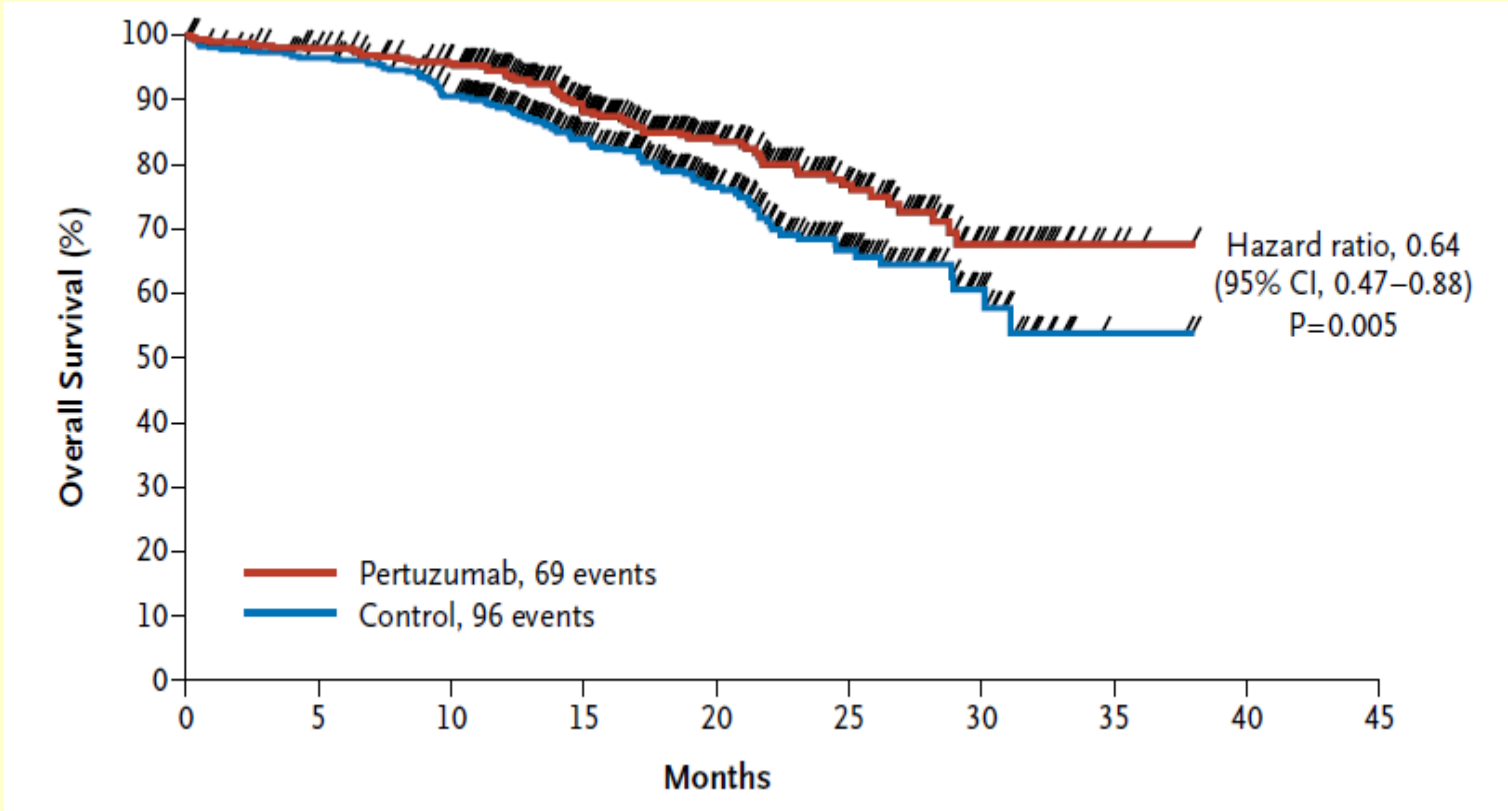
The key question: Is the surrogate endpoint (response) "reasonably likely to predict clinical benefit"

Let's look at some examples....

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

N Engl J Med 2012;366:109-19.

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*



Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

Lancet Oncol 2012; 13: 25–32

Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Laslo Roman, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elżbieta Staroslawska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Bianchi, Tania Szado, Jayantha Ratnayake, Graham Ross, Pinuccia Valagussa

Group:	N	pCR (%)	P
Trastuzumab + docetaxel	107	29.0 [20.6-38.5]	.014
Pertuzumab + trastuzumab + docetaxel	107	45.8 [36.1-55.7]	
Pertzumab + trastuzumab	107	16.8 [10.3-25.3]	
Pertuzumab + docetaxel	96	24.0 [15.8-33.7]	

There were no significant differences in toxicity

So we might be tempted to conclude....

... that we could have used the results of a 214 patient neoadjuvant trial to support registration of pertuzumab (with docetaxel + trastuzumab)

... and that the results would be confirmed in a larger RCT which recruited 808 women with metastatic breast cancer

BUT...

Finding that the results of one neoadjuvant trial is concordant with results of a large trial for metastatic disease....

....does not imply that there will be similar concordance of results of other neoadjuvant trials and large RCTs

...even if you are comfortable with giving a new and untried agent to women with potentially curable localised breast cancer...

N=270

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D.,

N Engl J Med 2012;366:520-9.

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Conclusion
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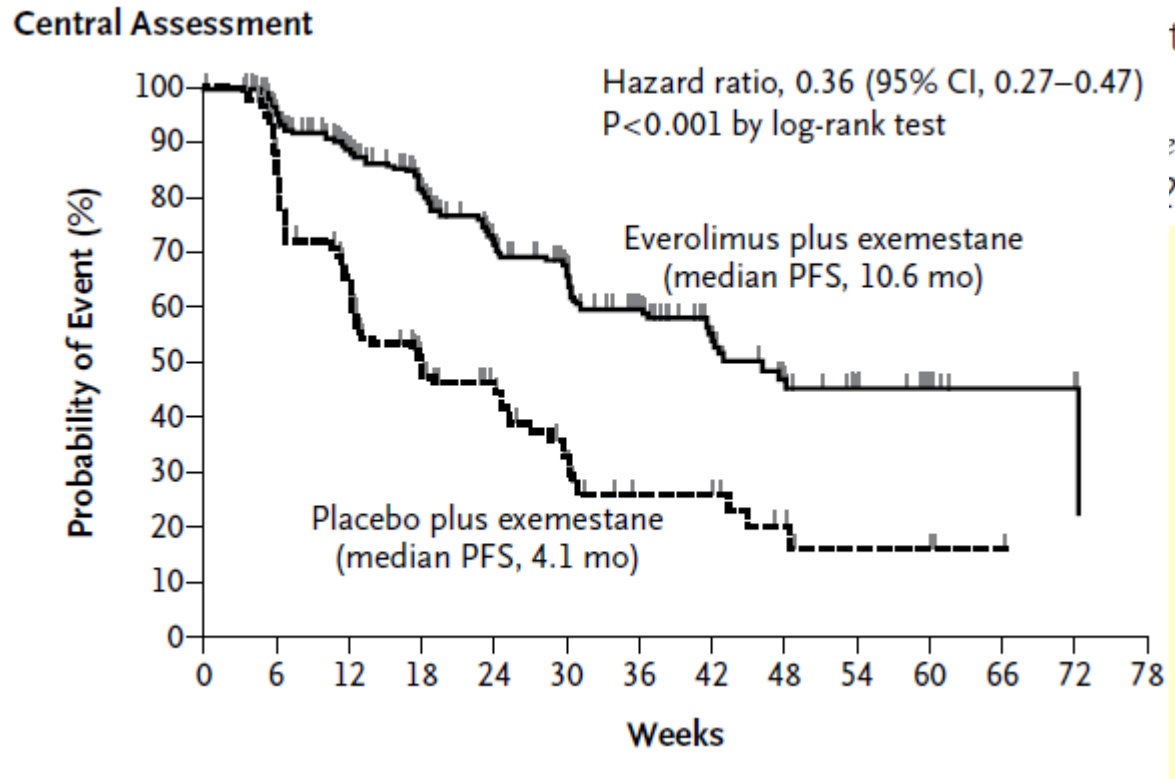
7:2630-2637. © 2009



N=270

Results

Response rate by clinical palpation in the everolimus arm was higher than that with letrozole alone (ie, placebo; 68.1% *v* 59.1%), which was statistically significant at the preplanned, one-sided, $\alpha = 0.1$ level ($P = .062$).

grades 3 to 4 adverse events occurred in 22.6% of patients who received everolimus and in 3.8% of patients who received placebo.

Conclusion

Everolimus significantly increased letrozole efficacy in neoadjuvant therapy of patients with ER-positive breast cancer.

Would any person in this room favour approval of a drug on the basis of:

1. **A difference in response rate of 68% vs. 59%, with a 2-sided p=value of 0.124**
2. **A difference in grade 3-4 toxicity of 23% vs. 4%, with 2-sided p-value of <0.0001? (my calculation)**

JOURNAL OF CLINICAL ONCOLOGY COMMENTS AND CONTROVERSIES

Addition of Bevacizumab to Chemotherapy for Treatment of Solid Tumors: Similar Results but Different Conclusions

Journal of Clinical Oncology, Vol 29, No 3 (January 20), 2011: pp 254-256

Alberto Ocaña and Eitan Amir, *Princess Margaret Hospital and University of Toronto, Toronto, Canada*
Francisco Vera, *Centro Universitario Contra el Cáncer, Hospital Universitario Universidad Autónoma de Nuevo León, Monterrey, México*
Elizabeth A. Eisenhauer, *National Cancer Institute of Canada Clinical Trials Group, Queen's University, Kingston, Canada*
Ian F. Tannock, *Princess Margaret Hospital and University of Toronto, Toronto, Canada*

Trial	N	PFS			OS			Reported as
		Diff (mo)	HR	*P*	Diff (mo)	HR	*P*	
ECOG	722	+5.9	0.60	.0001	+1.5	0.88	.16	positive
AVADO	736	+0.8	0.86	.12	-1.1	1.05	.72	positive
		+1.9	0.77	.006	-1.7	1.03	.85	
RIBBON-1	1237	+2.9	0.69	.0002	+1.4	0.85	.27	positive
		+1.2	0.64	<.001	+0.3	1.03	.83	
Meta-analysis	2447	+2.5	0.64	.0001	+0.3	0.97	.56	

Inhibiting VEGF with a monoclonal antibody was a great idea....

.... that unfortunately didn't work!

I'm not convinced that it has added much benefit in any area of oncology

Yet we oncologists made it the most profitable drug in 2010 (world sales of ~$6 billion)

What a waste of resources - and poor choice of treatment

We must learn earlier from our mistakes

The FDA (Feb 2008) and subsequently EMA approved paclitaxel +bevacizumab for treatment of metastatic breast cancer based on a trial showing ↑PFS but no difference in OS

The FDA reversed that approval in Nov 2011 **"the drug was not helping breast cancer patients to live longer or to meaningfully control their tumors, but did expose them to potentially serious side effects like severe high blood pressure and hemorrhaging.**

But how does bevacizumab perform in neoadjuvant trials?

Bevacizumab Added to Neoadjuvant Chemotherapy for Breast Cancer

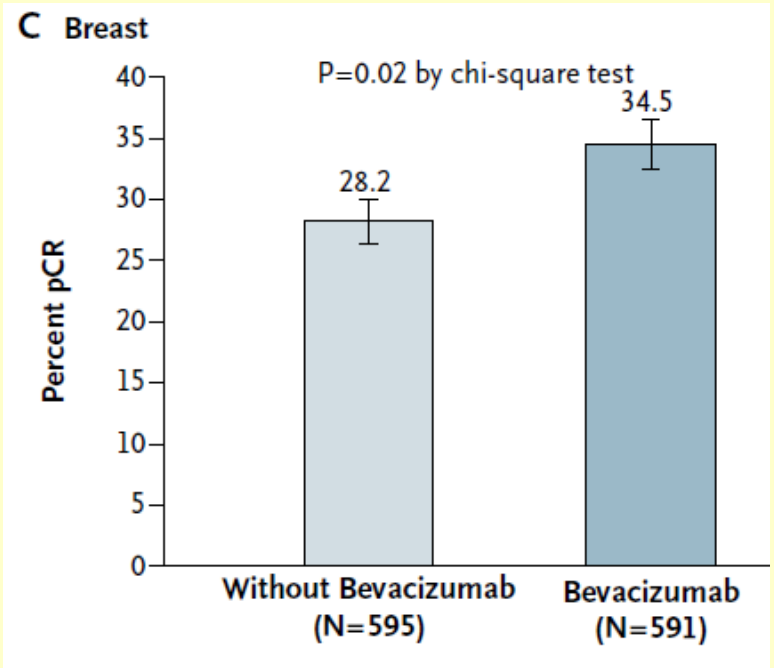
N Engl J Med 2012;366:310-20.

Harry D. Bear, M.D., Ph.D., Gong Tang, Ph.D., Priya Rastogi, M.D.,

Neoadjuvant Chemotherapy and Bevacizumab for HER2-Negative Breast Cancer

N Engl J Med 2012;366:299-309.

Gunter von Minckwitz, M.D., Holger Eidtmann, M.D., Mahdi Rezai, M.D., Peter A. Fasching, M.D.,



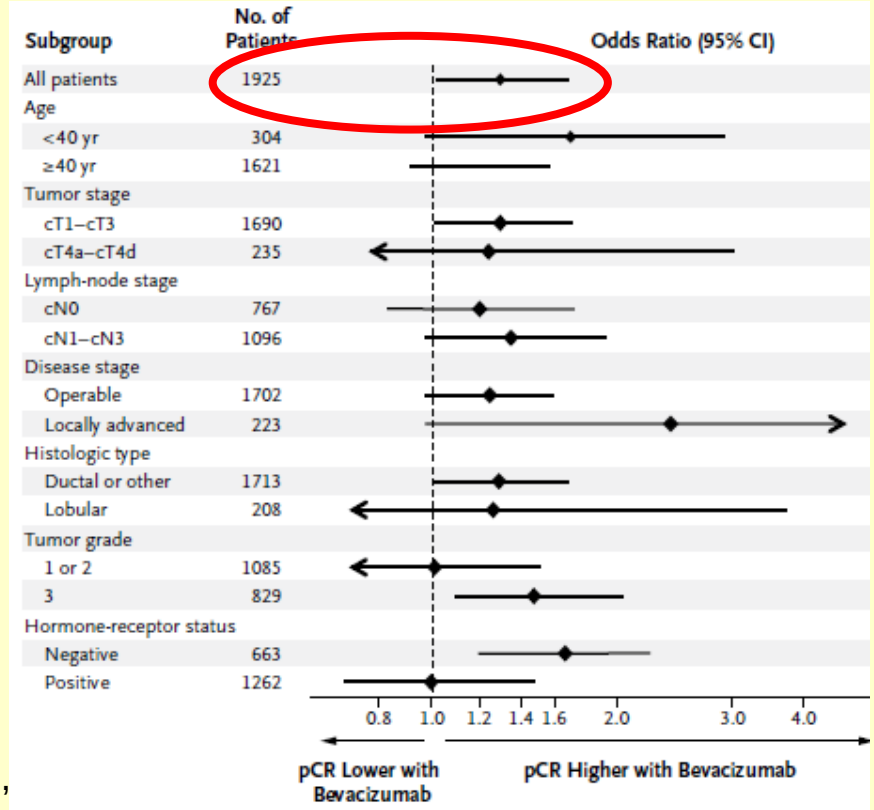
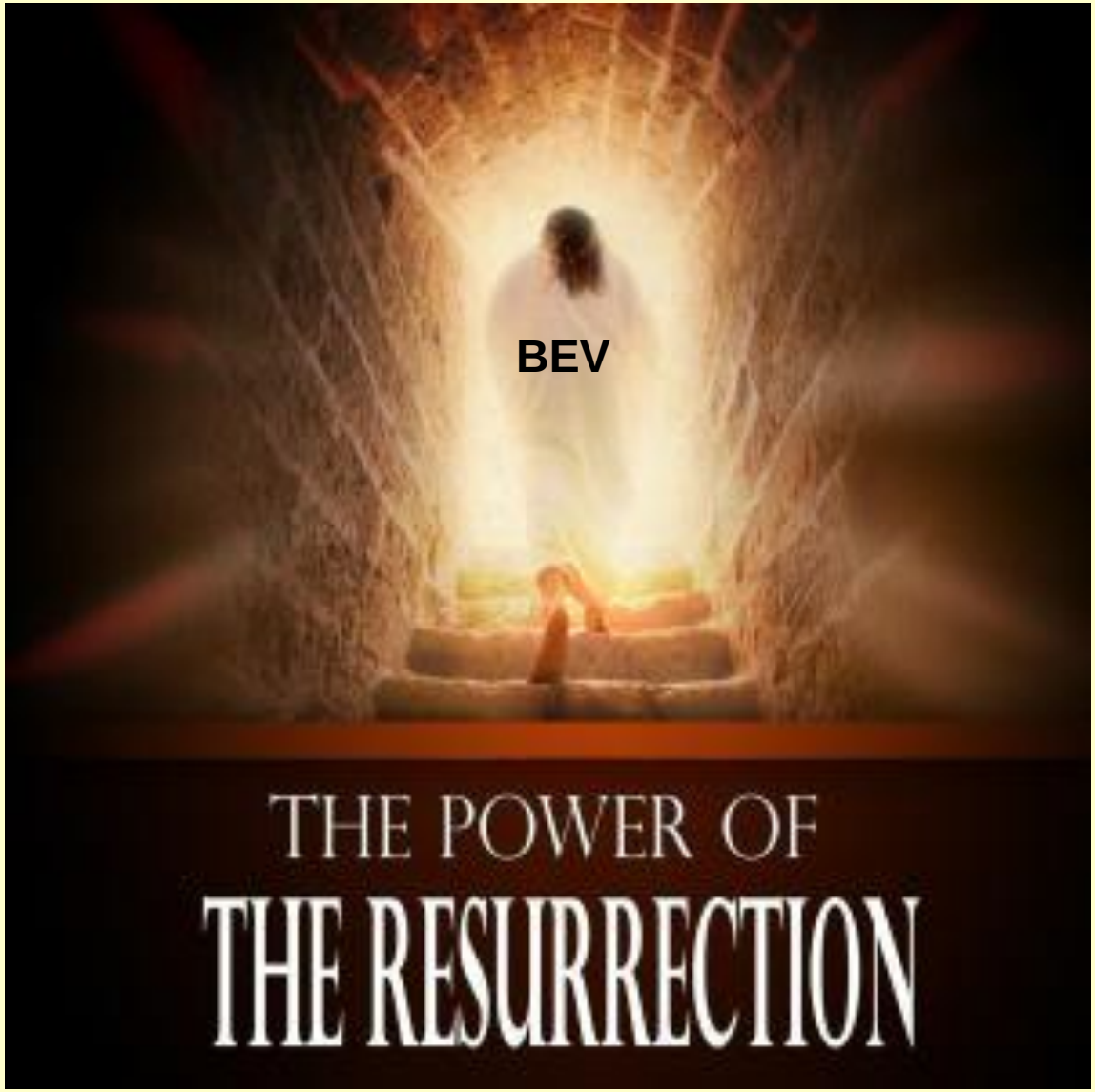


Figure 2. Pathological Complete Response (pCR), According to Subgroup.

Bevacizumab "works" in neoadjuvant trials. Perhaps they have...



FDA/EMA approved 4 new drugs to treat breast cancer in the last 5 years.

Drug	Date	Condition	Trial	Endpoint
Lapatinib	Mar 2007	HER2+ with capecitabine after trastuzumab, anthra, taxane	RCT: N = 399	TTP (6.0 vs. 4.5)
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If the system is broken, how should we improve it?

In my view, there are two problems

1. The lack of good drugs in development
   - We do not need a process that increases the approval of marginal drugs

2. The slow speed at which the few good drugs are brought to market
   - We do need to develop the effective drugs more quickly

These problems are due in part to FDA/EMA policy of approving any new drug that gives a significant improvement in OS or PFS

This policy encourages Big Pharma to pursue large trials to detect trivial differences in outcome that allow drug registration....

...and then to market these drugs at an obscene price

Oncogenic Targets, Magnitude of Benefit, and Market Pricing of Antineoplastic Drugs

J Clin Oncol 29. © 2011

Eitan Amir, Bostjan Seruga, Joaquin Martinez-Lopez, Ryan Kwong, Atanasio Pandiella, Ian F. Tannock, and Alberto Ocaña

Three groups of agents FDA approved since 2000:

(A) Targeted agents where population is selected by a biomarker

(B) Less specific biological targeted agents

(C) Chemotherapy

Group	No of drugs/ trials	HR for OS	Median monthly cost (in USA)
A	6/7	0.69	$5,375
B	7/14	0.78	$5,644
C	8/12	0.84	$6,584

Only 37% of new cancer drugs were cost effective by standard criteria

When we are prescribing new drugs we are buying a....

Ford

But we are paying for a...

Ferrari

A potential answer to the problems of unwanted marginal drugs and waste of resources on large trials to develop them....

... is NOT approval based on results of neoadjuvant trials

... it is the requirement for value-based pricing as a condition of approval – so that the price of new drugs is related to their effectiveness

If FDA and EMA changed policy to require cost-effectiveness for drug approval……

…with the caveat that it would have to allow companies to recover the real costs of research:

1. Trials for effective drugs would be smaller
   - since sample size depends on the effect size that the trial is designed to detect or exclude

2. Companies would be discouraged from developing drugs where early trials suggest marginal effectiveness

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In summary, neoadjuvant trials involving new agents...

1. Require the new drug to be given to women with potentially curable disease – not always a good strategy for potentially toxic new drugs
2. Are NOT reliable predictors of clinical benefit in larger trials

Can this house *really* believe that…

Neo-adjuvant breast cancer treatment data can be used to accelerate drug approval?

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No!

Are you crazy?

You must be joking

Get out of here

Only if you believe in fairies

Nein

Nej

Non

Nee

Não

Ei

Niet

Nei

Οχι

No way, José

..and returning to my opponent's Spanish heritage