Decoding the Tower of Babel

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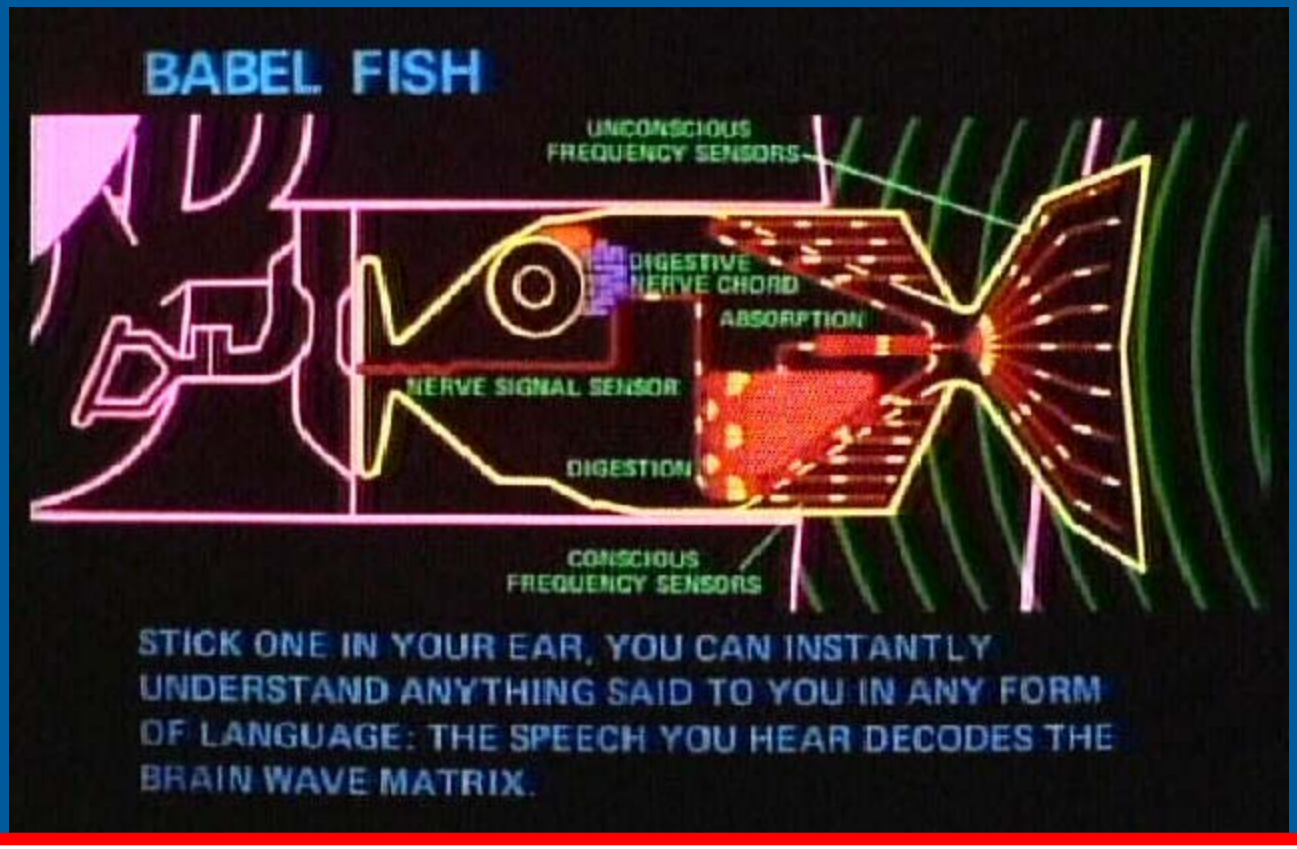
The Tower of Babel

The Tower of Babel

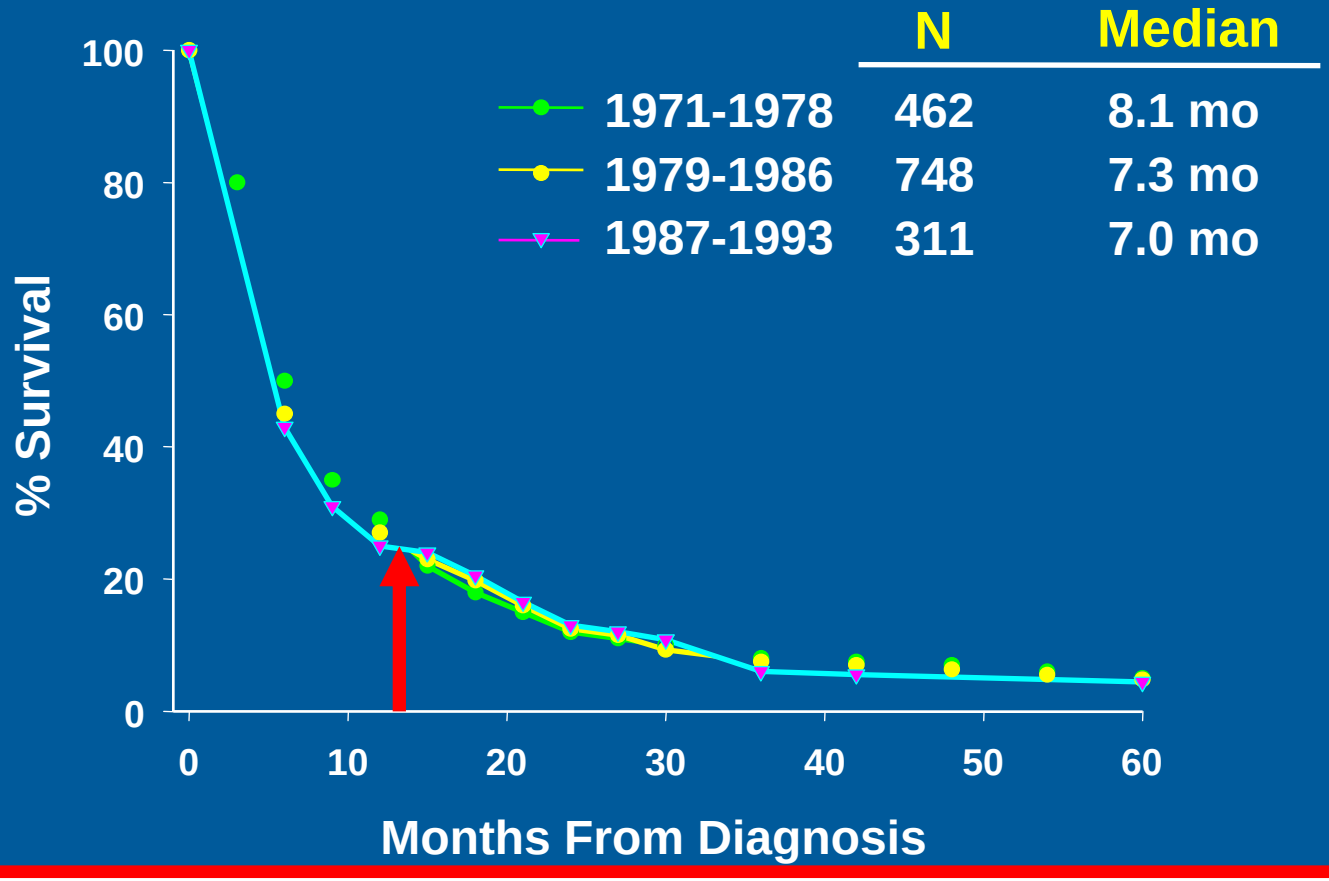
The destruction of the Tower of Babel left humanity (and especially melanoma researchers) speaking multiple languages and unable to achieve the greatness

The Babel Fish



"The most massively useful thing in the known universe"
The Hitchhikers Guide to the Galaxy
Douglas Adams

Overall Survival for Metastatic Melanoma



There has been no significant improvement in overall survival for metastatic melanoma in the past 30 years

Barth. *J Am Coll Surg* 1995;181:193.

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FDA Approved Drugs in Use for Melanoma

- **Dacarbazine (DTIC)**
  - Response rate: <10% in unselected stage IV melanoma patients
  - No proven impact on survival
  - Temozolomide, carbo-taxol frequently used instead
- **High-dose IL-2**
  - Response rate: 16% in highly selected stage IV melanoma patients
  - Durable responses: ~5%
  - Rarely used outside of a few high-volume centers
- **High-dose IFN**
  - The only approved adjuvant therapy
  - Consistent benefit on relapse-free survival, controversial survival benefit

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The New Tower of Babel?

For melanoma, there are now at least seven agents that are or potentially soon will be seeking FDA and/or European approval

1. Pegylated interferon alfa-2b
2. Delcath percutaneous hepatic perfusion chemotherapy
3. Ipilimumab (anti-CTLA4 monoclonal antibody)
4. PLX4032 (V600 mutant BRAF inhibitor)
5. Oncovex-GMCSF (oncolytic virus for intralesional treatment)
6. Nilotinib (cKIT inhibitor)
7. Tilmanocept (Lymphoseek, new radiolabelled lymphatic mapping tracer)

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The New Tower of Babel?

Agent	Endpoint	Trial Design
Peg-IFN α2b	**Relapse-free survival**	Randomized phase III adjuvant trial vs observation
Delcath	**Hepatic progression-free survival**	Randomized phase III vs "best alternative care" *crossover*
Ipilimumab	**Overall survival**	Randomized phase III vs gp100 vaccine
PLX4032	**Response rate** **Overall survival**	Phase I/II trial Randomized phase III vs DTIC *non-crossover*
Oncovex-GMCSF	**Durable (6 month) response**	Randomized phase III vs systemic GM-CSF
Nilotinib	**Progression-free survival**	Randomized phase III vs DTIC *crossover*
Tilmanocept	**% of blue lymph nodes that are also hot**	Open label single arm non-randomized phase III

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Survival – The Gold Standard

- Overall survival (or disease-specific survival) is considered the “gold standard” for accepting a new therapy

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Survival – The Gold Standard

- Once one drug improves survival, the ethics and the practicality of using survival as the primary goal changes
- In melanoma, with so few active drugs, the ethics of “non-crossover” designs that prohibit trial participants from receiving potentially active therapy have been questioned

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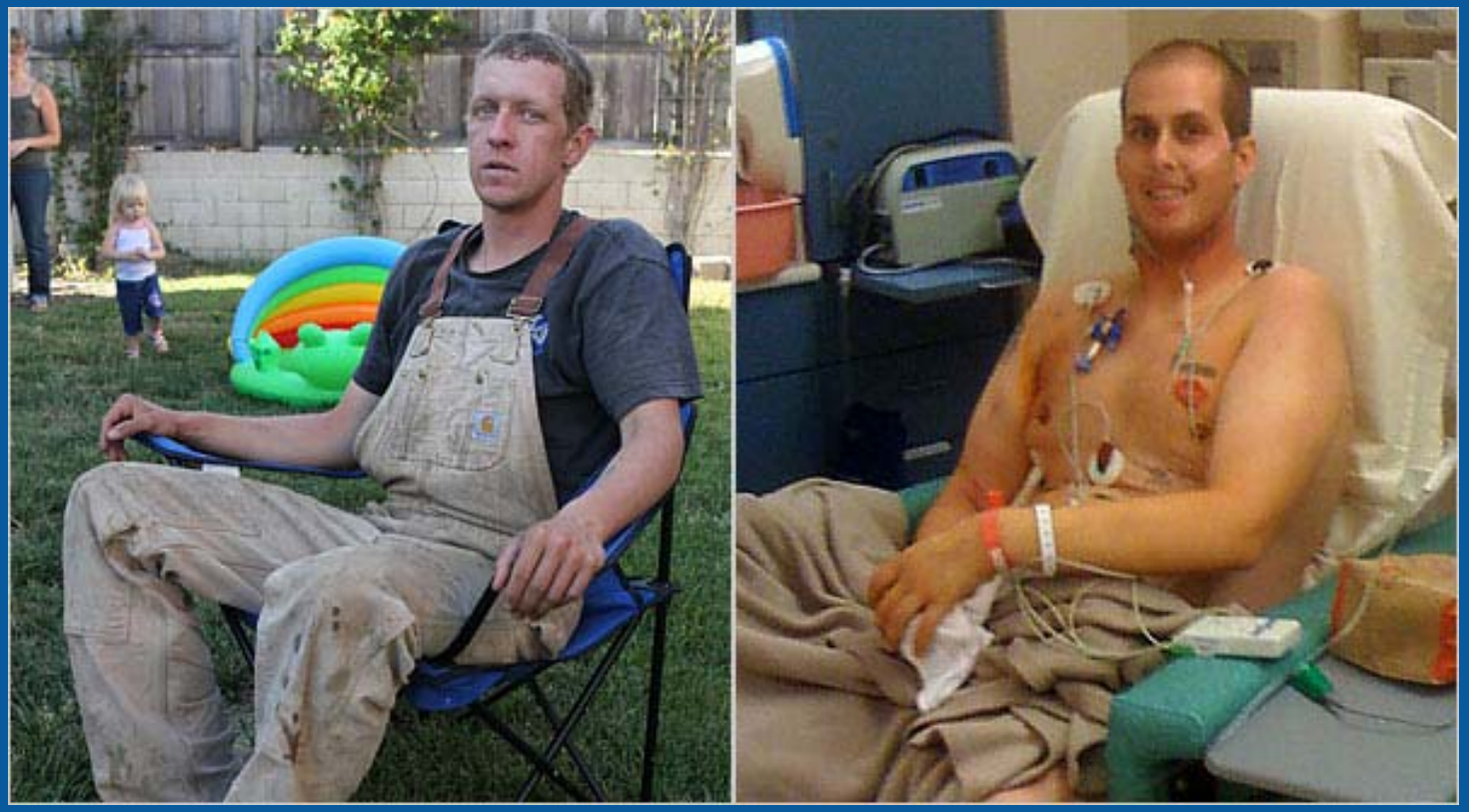
Target Cancer

New Drugs Stir Debate on Rules of Clinical Trials

New York Times September 18, 2010



Two Cousins, Two Paths Thomas McLaughlin, left, was given a promising experimental drug to treat his lethal skin cancer in a medical trial; Brandon Ryan had to go without it.

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Clinical Trial Endpoints
Issues To Consider

- We need reliable endpoints to identify active drugs early in their development so that the best drugs get tested
- We need endpoints that are meaningful to regulators, physicians and patients so that approved drugs get used
- **How reliable are progression-free survival (PFS) and overall survival (OS) in melanoma, and are there alternate endpoints based on them to use?**

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Metaanalysis of Phase II Cooperative Group Trials in Stage IV Melanoma

- 42 Phase II trials, 70 individual trial arms, conducted from 1975 to 2005
  - **2,100 patients**
  - SWOG, ECOG, CALGB, NCCTG, and NCIC-CTG
  - All trials reported as “negative”
- **Median OS: 6.2 months**
- **1-Yr survival: 25.5%**

Korn et al. *J Clin Oncol* 2008;26:527-534.

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Cooperative Group Phase II Trial Metaanalysis

Trials Included

#	Group	Study	P.I.	Arm	N	Closed	Agent
1	CALGB	C500001	Carson	1	38	2004	**Interleukin-12/Interferon_Alpha-2b**
2	CALGB	C500102	Krown	1	16	2005	**Temozolomide/Thalidomide**
3	CALGB	C500104	Gajewski	1	14	2005	**R115777**
4	CALGB	C509901	Roberts	1	26	2003	**g209-2M_peptide_vaccine/low_dose_IL-2**
5	ECOG	E1675	Guerry	A	61	1978	**MECCNU 250 MG**
6	ECOG	E1675	Guerry	B	76	1978	**Hydroxyurea+MECCNU+DTIC**
7	ECOG	E1675	Guerry	C	71	1978	**MECCNU+BCG**
8	ECOG	E1675	Guerry	D	130	1977	**MECCNU 150 MG**
9	ECOG	E1675	Guerry	E	52	1979	**Hydroxyurea+Actinomycin+Cytoxan**
10	ECOG	E1675	Guerry	F	47	1979	**Chlorozotocin**
11	ECOG	E1675	Guerry	G	48	1979	**Neocarzinostatin**
12	ECOG	E1675	Guerry	H	4	1981	**MECCNU 200MG**
13	ECOG	E1675	Guerry	I	39	1980	**Dibromodulcitol**
14	ECOG	E1675	Guerry	J	48	1981	**MGBG (Methyl Gag)**
15	ECOG	E1687	Hochster	A	17	1988	**MELPHALAN**
16	ECOG	E2681	Arseneau	A	27	1982	**Mitoxantrone**
17	ECOG	E2681	Guerry	B	26	1982	**AZQ**
18	ECOG	E2681	Gale	C	36	1983	**Demser**
19	ECOG	E2683	Parkinson	A	41	1984	**VINBLASTINE**
20	ECOG	E2683	Wolter	B	39	1984	**ACIVICIN**
21	ECOG	E2683	Hawkins	C	56	1985	**IFN-ALPHA-2**
22	ECOG	E2683	Wolter	D	50	1985	**CCNU**
23	ECOG	E2685	Chang	A	28	1988	**Carboplatin**
24	ECOG	E2685	Hochster	B	20	1990	**4-DEOXYDOXORUBICIN**

Cooperative Group Phase II Trial Metaanalysis

Trials Included

#	Group	Study	P.I.	Arm	N	Closed	Agent
25	ECOG	E4687	Schiller	A	16	1992	**IFN-γ 0.01MG**
26	ECOG	E4687	Schiller	B	15	1992	**IFN-γ 0.03MG**
27	ECOG	E4687	Schiller	C	14	1992	**IFN-γ 0.10MG**
28	ECOG	E4687	Schiller	D	14	1992	**IFN-γ 0.30MG**
29	ECOG	E4687	Schiller	E	12	1992	**IFN-γ 0.50MG**
30	ECOG	E4687	Schiller	F	11	1992	**IFN-γ 0.70MG**
31	ECOG	E4687	Schiller	G	13	1992	**IFN-γ 0.90MG**
32	ECOG	PA682	Green	A	20	1984	**4'Epiadriamycin**
33	ECOG	PA686	Einzig	I	33	1987	**TAXOL**
34	ECOG	PB687	Hochster	A	19	1990	**DIDEMNIN B**
35	ECOG	PC680	Muggia	A	16	1984	**Poly ICLC**
36	ECOG	PZ686	Harris	A	15	1991	**IFN Alpha2 + Feldene**
37	NCCTG	82-70-51	Creagan	1	35	1985	**Carmustine + 6-Thioguanine**
38	NCCTG	95-70-51	Creagan	1	15	2000	**KW2189 0.4 mg/m2**
39	NCCTG	95-70-51	Creagan	2	30	2000	**KW2189 0.5 mg/m2**
40	NCIC	I104	Seymour	A	17	1998	**Bryostatin 25 µg/m2**
41	NCIC	I104	Seymour	B	17	1998	**Bryostatin 120 µg/m2**
42	NCIC	I137	Eisenhauer	A	17	2001	**Flavopiridol**
43	NCIC	I156	Eisenhauer	A	18	2004	**Perifosine**
44	NCIC	I169	Seymour	A	17	2005	**SB-715992**
45	NCIC	I56	Eisenhauer	A	16	1992	**anthrapyrazole**
46	NCIC	I61	Eisenhauer	A	16	1992	**10-EDAM**
47	NCIC	I91	Eisenhauer	A	29	1997	**BB-2516**
48	SWOG	S8118	Alberts	1	37	1984	**Bisantrene high dose**
49	SWOG	S8118	Alberts	2	14	1984	**Bisantrene low dose**

Cooperative Group Phase II Trial Metaanalysis

Trials Included

#	Group	Study	P.I.	Arm	N	Closed	**Agent**
50	SWOG	S8240	Goodwin	1	10	1985	**Spirogermanium high dose**
51	SWOG	S8240	Goodwin	2	10	1985	**Spirogermanium low dose**
52	SWOG	S8324	Kish	1	20	1987	**Fludarabine Phos, high dose**
53	SWOG	S8324	Kish	2	7	1987	**Fludarabine Phos, low dose**
54	SWOG	S8562	Mortimer	1	15	1987	**CDDP**
55	SWOG	S8569	Whitehead	1	42	1987	**Interleukin**
56	SWOG	S8723	Slavik	1	20	1989	**Amonafide**
57	SWOG	S8754	Harvey	1	11	1989	**Didemnin B**
58	SWOG	S8804	Fletcher	1	59	1989	**CDDP + DTIC**
59	SWOG	S8913	Slavik	1	36	1993	**Merbarone**
60	SWOG	S8921	Flaherty	1	11	1991	**CTX + IL-2**
61	SWOG	S8921	Flaherty	2	12	1991	**DTIC + IL-2**
62	SWOG	S8921	Flaherty	3	55	1991	**DTIC + CDDP + Tamoxifen**
63	SWOG	S9116	Sosman	1	48	1993	**Piroxantrone**
64	SWOG	S9223	Meyskens	1	52	1995	**α-IFN + tRA**
65	SWOG	S9228	Whitehead	1	34	1995	**IL-4**
66	SWOG	S9348	Margolin	1	79	1995	**BCNU/DTIC/CDDP/Tam**
67	SWOG	S9350	Margolin	1	25	1996	**α-IFN/DTIC/CDDP/Tam**
68	SWOG	S9505	Whitehead	1	23	1997	**PZDH**
69	SWOG	S9622	Whitehead	1	24	1997	**CI-980**
70	SWOG	S9804	Whitehead	1	21	2001	**Navelbine**

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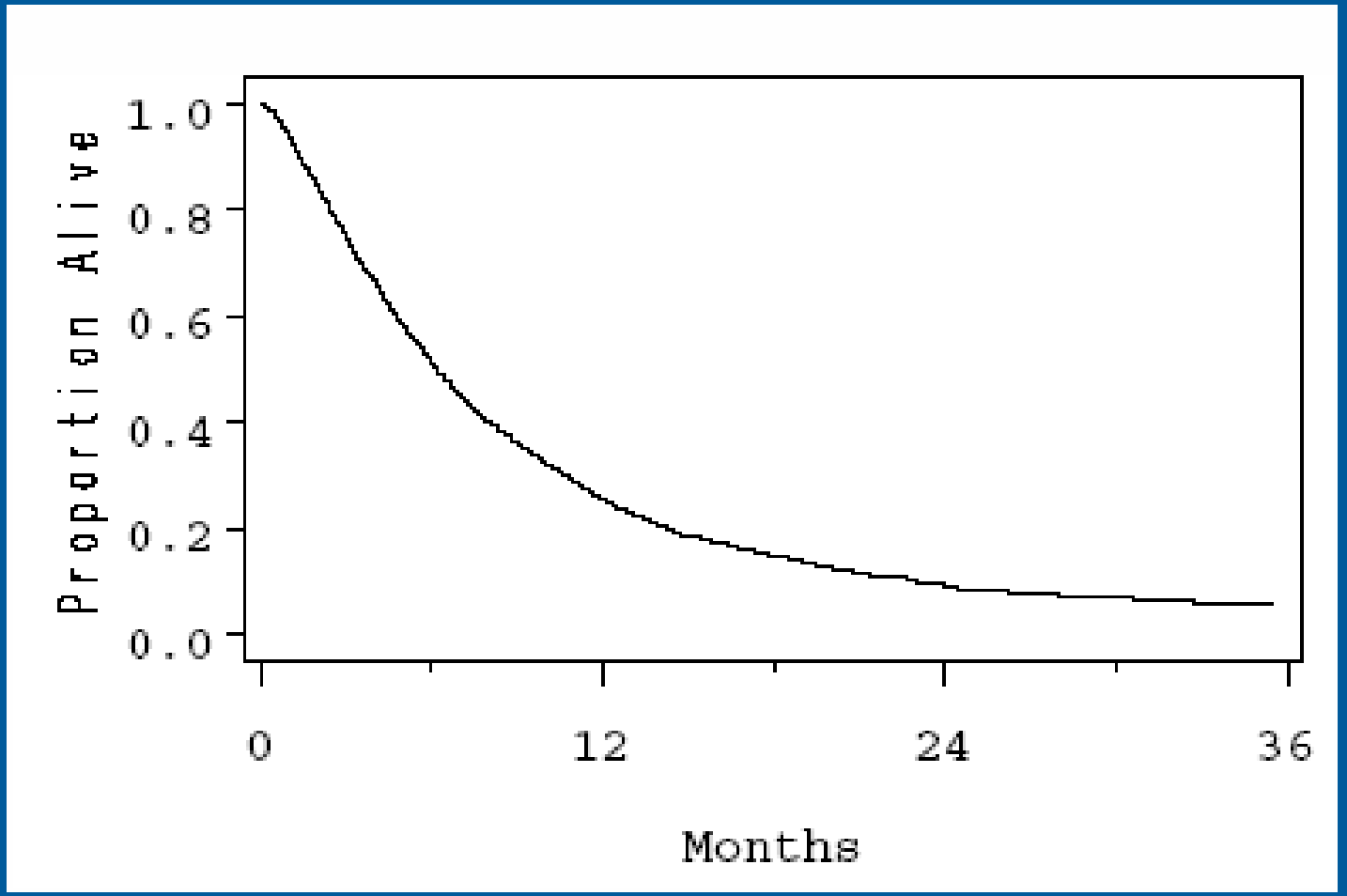
Cooperative Group Phase II Trial Metaanalysis

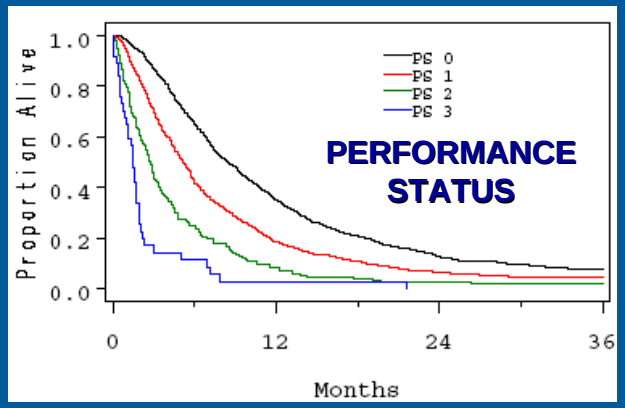
Overall Survival Results

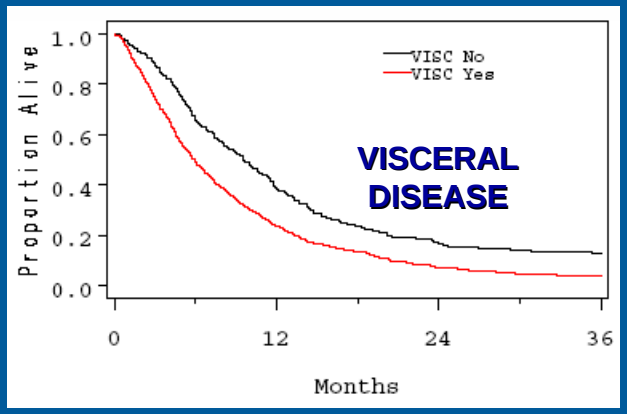


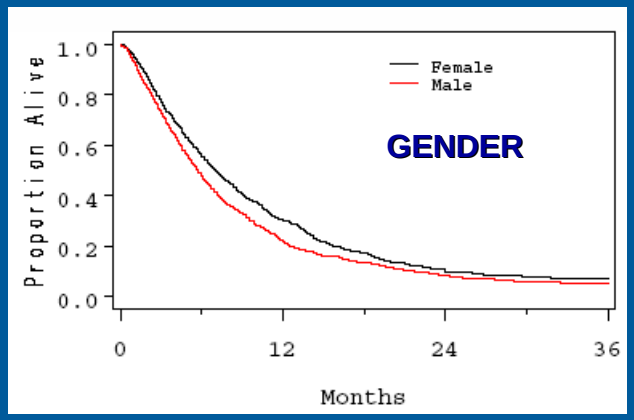
Korn et al. *J Clin Oncol* 2008;26:527-534

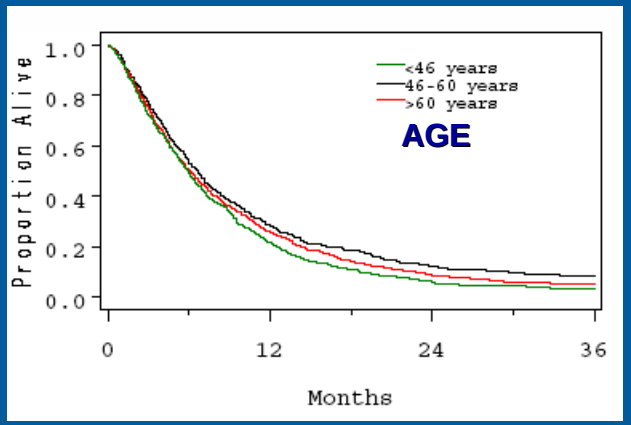
Cooperative Group Phase II Trial Metaanalysis

Factors Influencing Overall Survival









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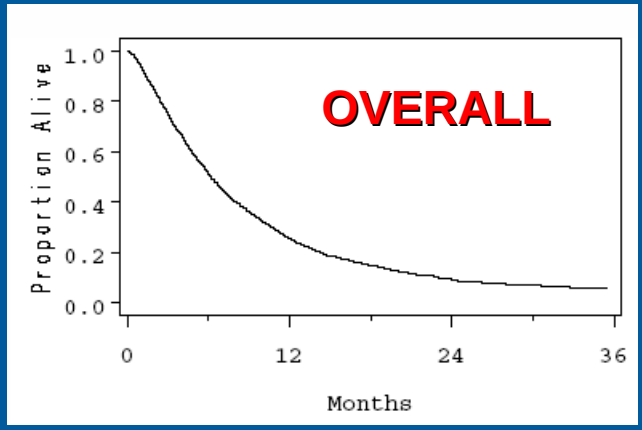

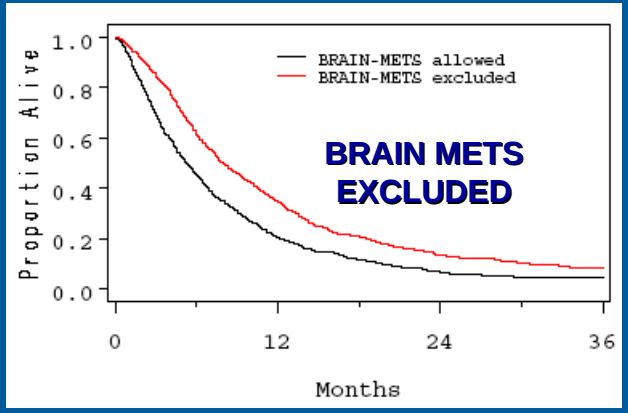

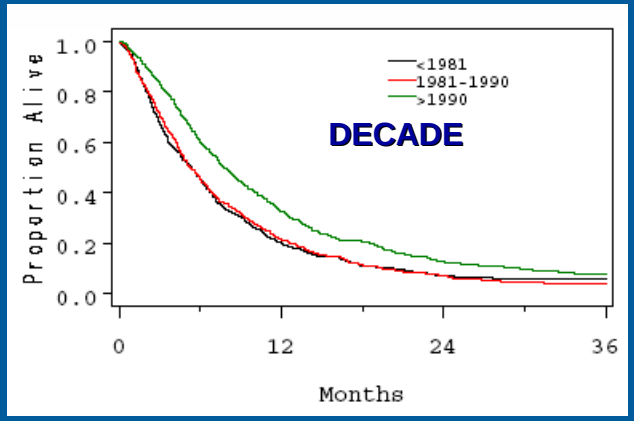

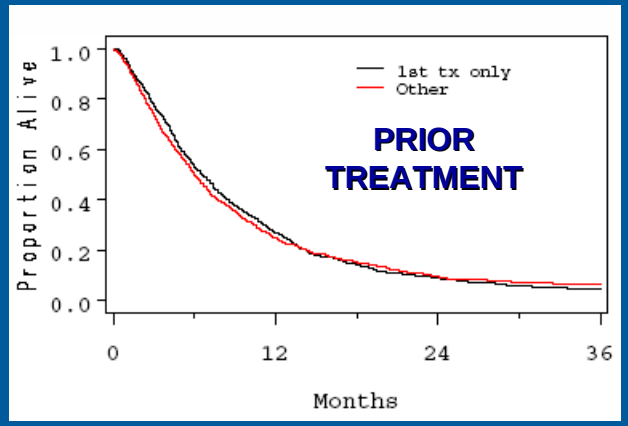

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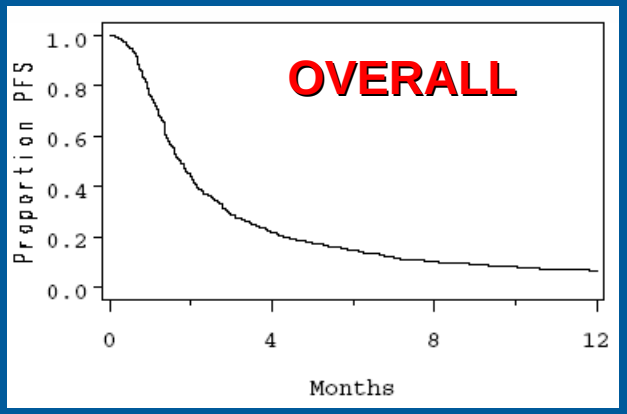
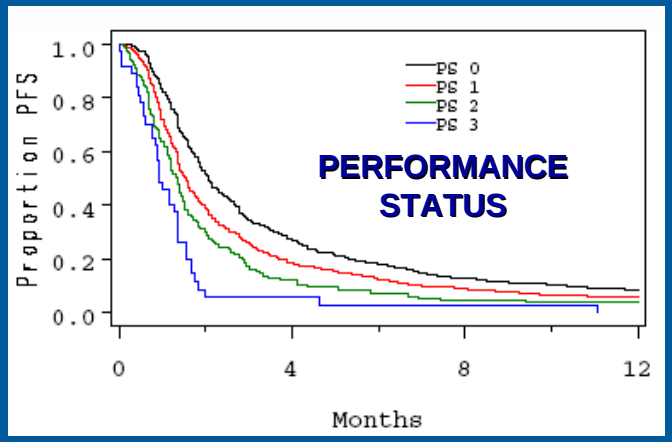
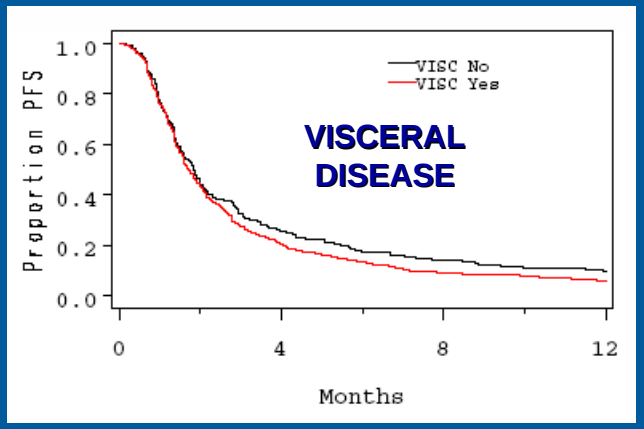
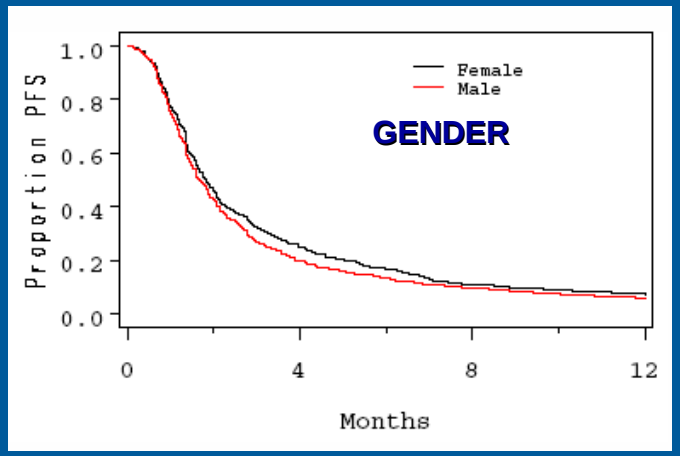
Cooperative Group Phase II Trial Metaanalysis

Progression-Free Survival Results









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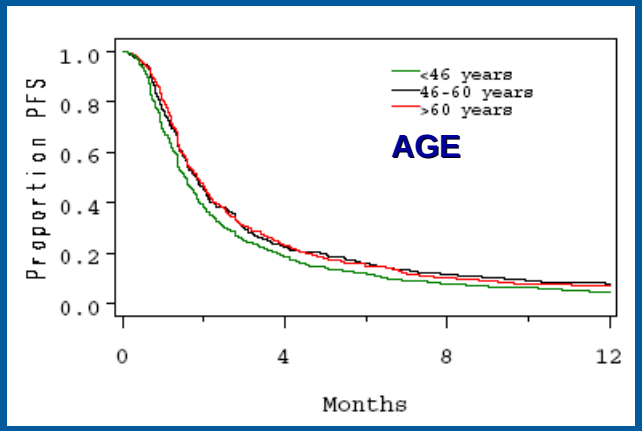
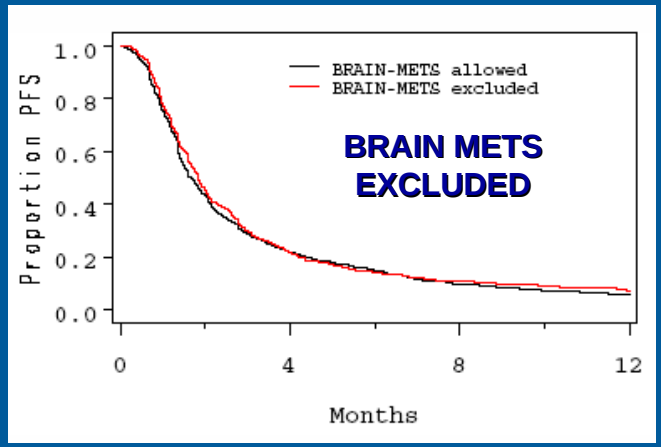
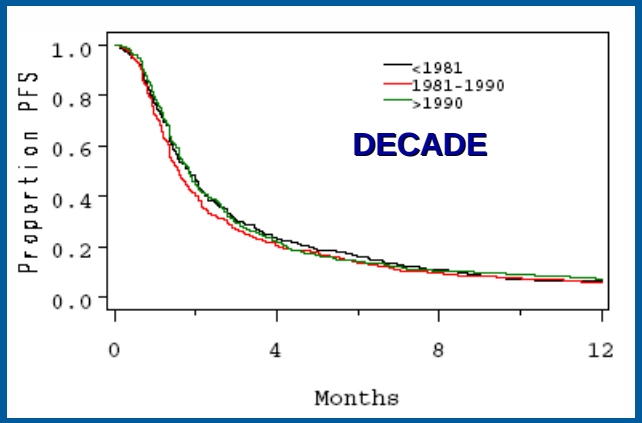
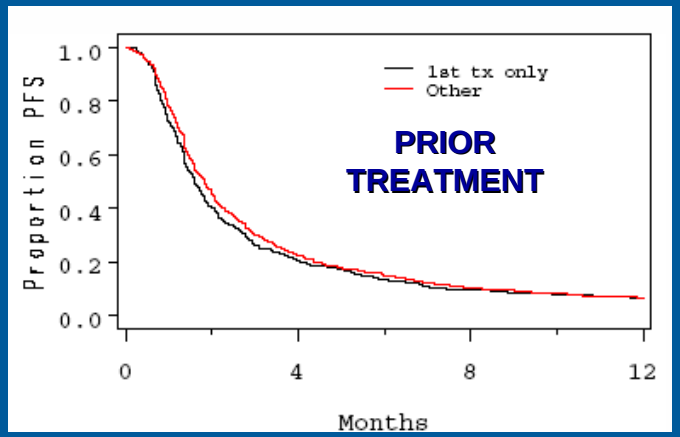
Cooperative Group Phase II Trial Metaanalysis

Progression-Free Survival Results









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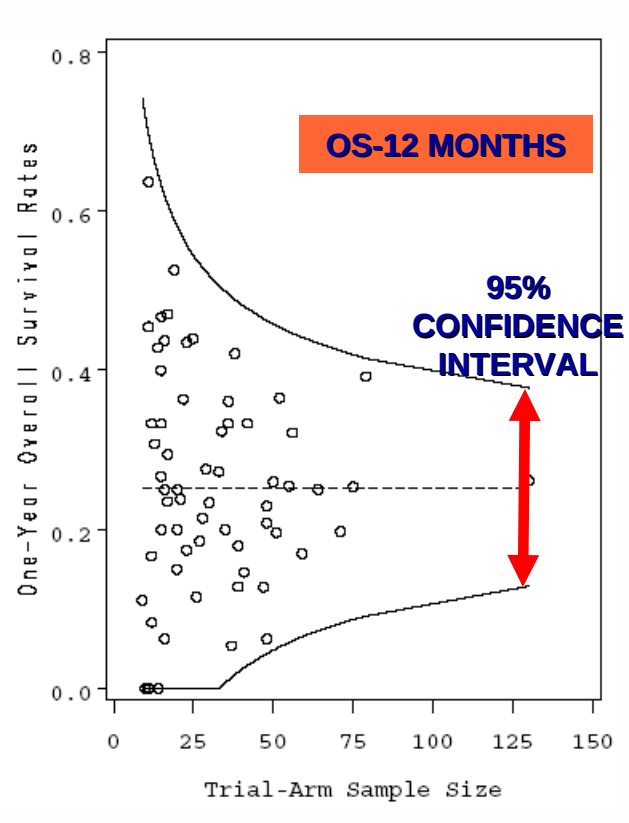
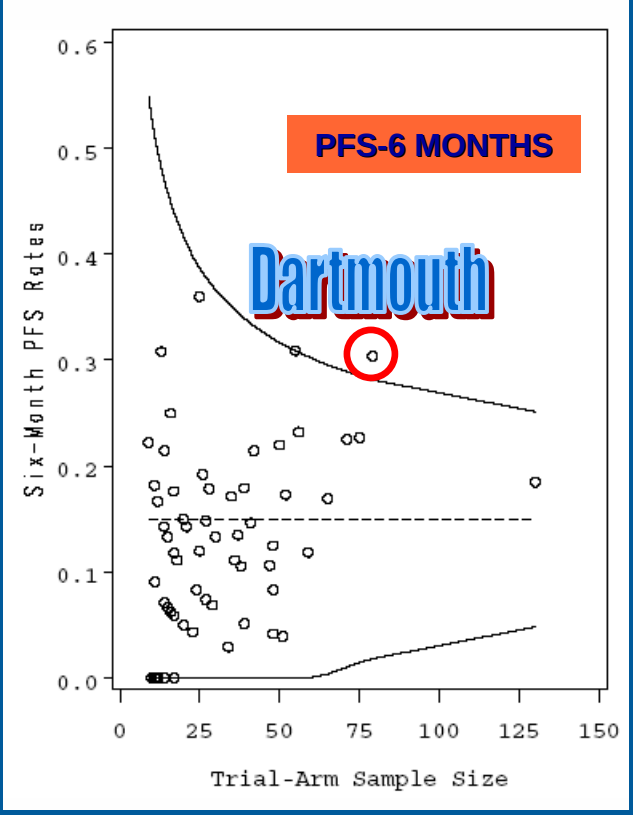
“Benchmarks” Provide Statistical Consistency of Endpoints Across Trials





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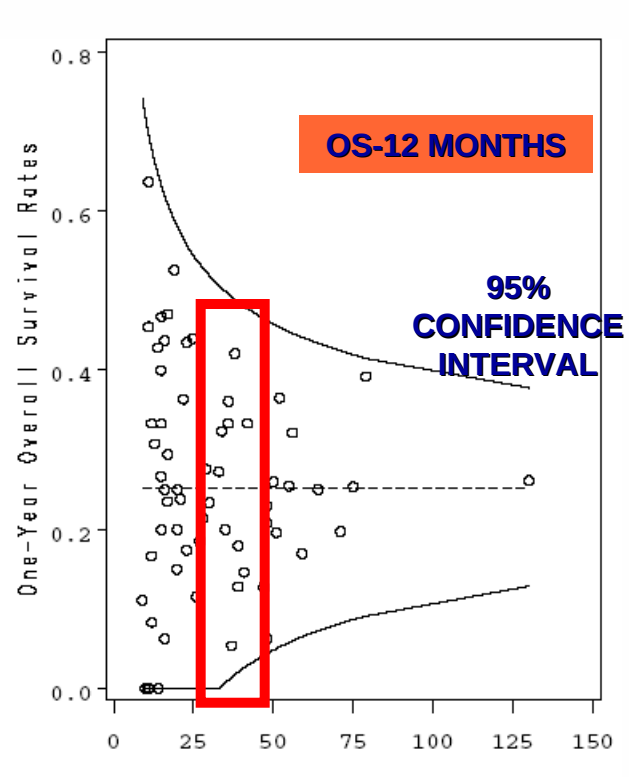
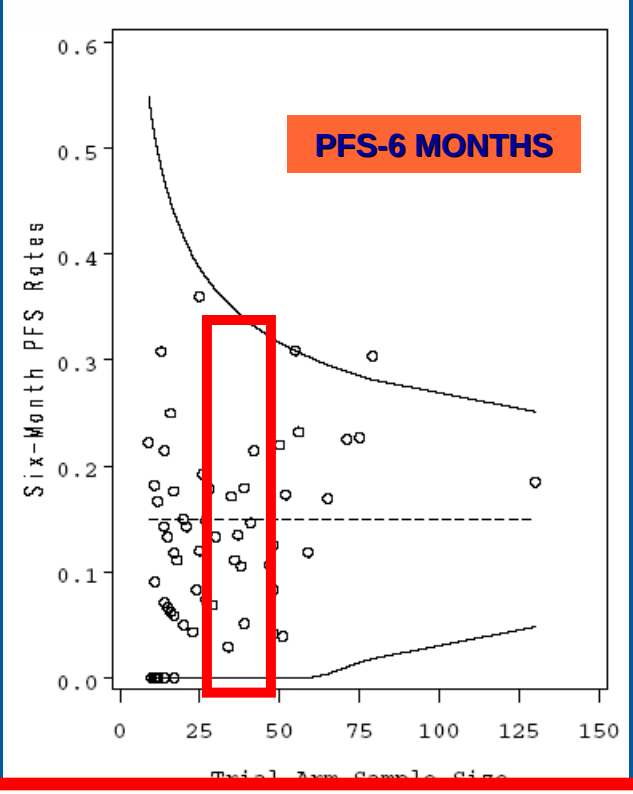
Statistical but Not Clinical Consistency of Endpoints





With multiple phase II evaluations of the same INACTIVE agent involving only ~37 patients per arm, we would expect a broad range of outcomes by chance alone

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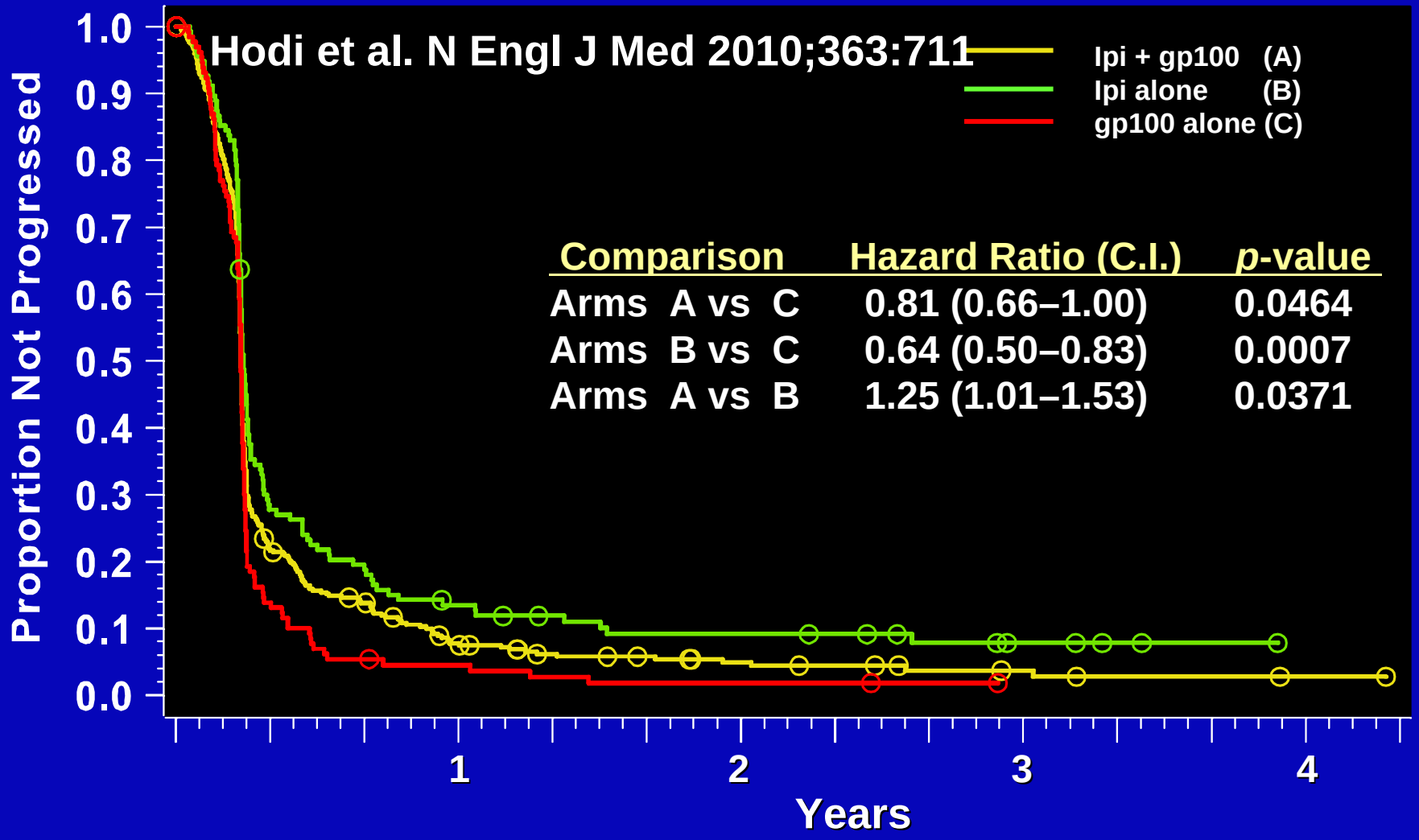
Cooperative Group Phase II Trial Metaanalysis

Applying the Results

- In the Korn metaanalysis, patients with PS 0 (n=938), OS at 1 year was 35.2%, with PFS at 6 months 18%
- Given a study with at least 50 PS 0 patients, >45% survival at 1 year or >30% progression free at 6 months are probably useful endpoints for selecting regimens for testing in phase III trials
- In recent single institution phase II trials, unequivocally negative trials had 11-22% PFS at 6 months

Anti-CTLA4 Antibody Treatment Improves Progression-Free Survival in Adults with Previously Treated Stage IV Melanoma



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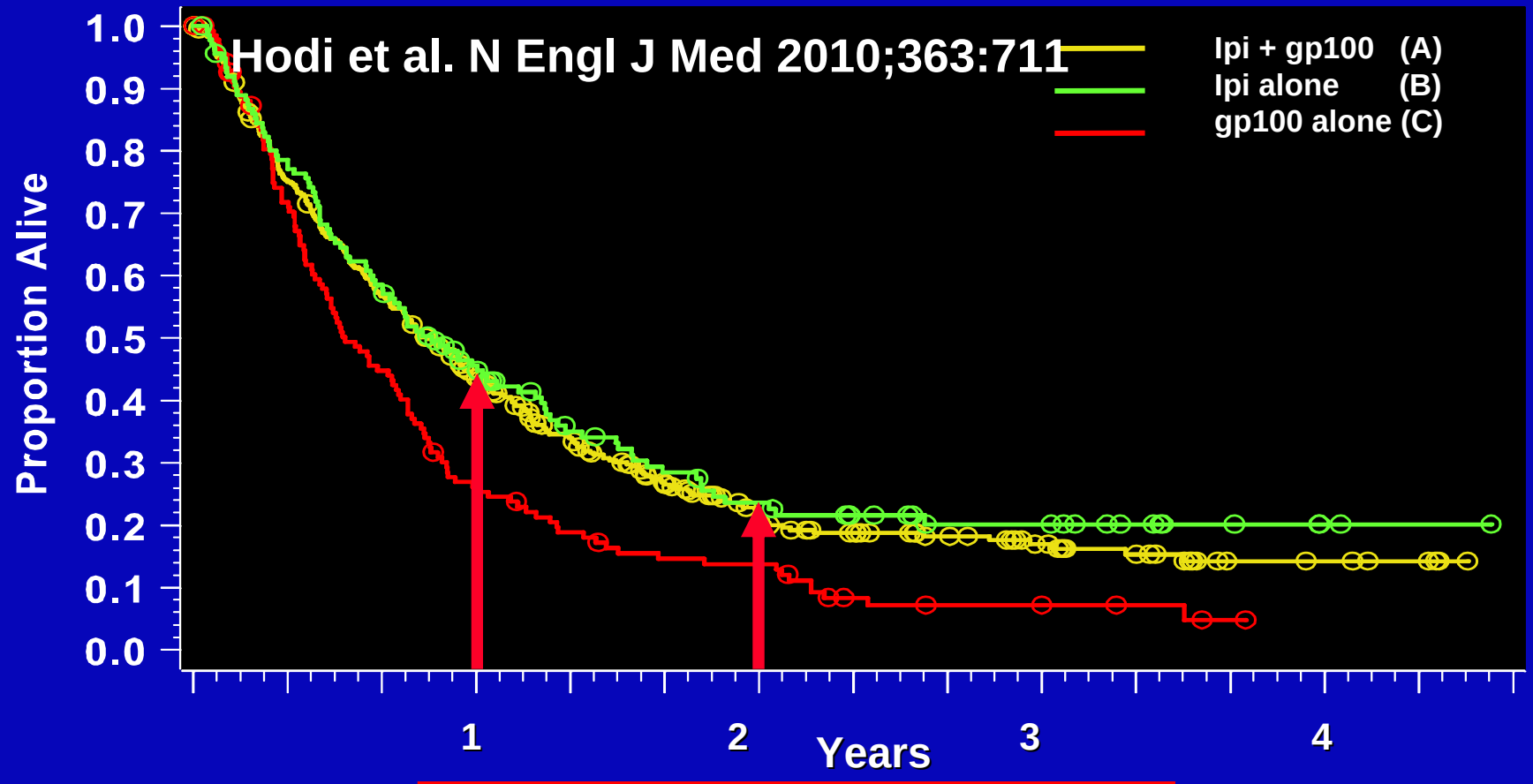
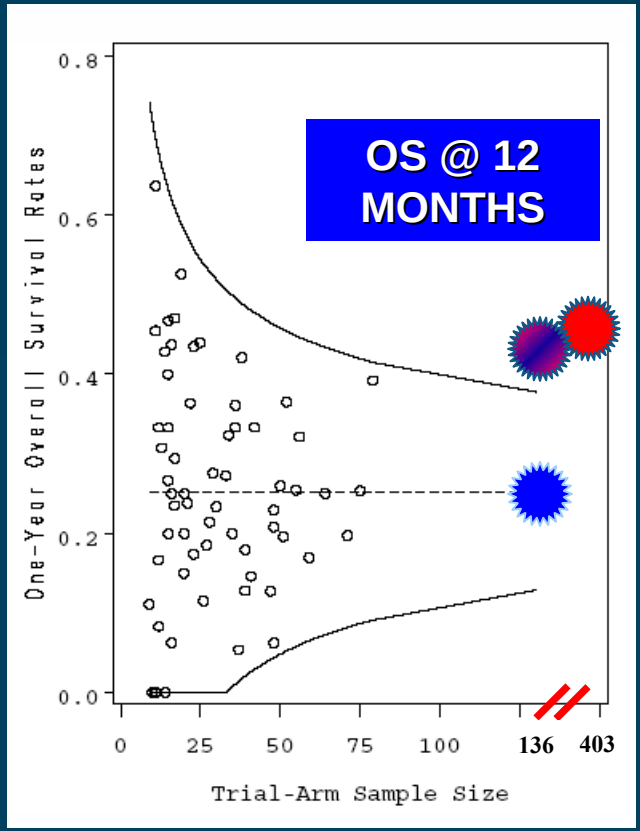


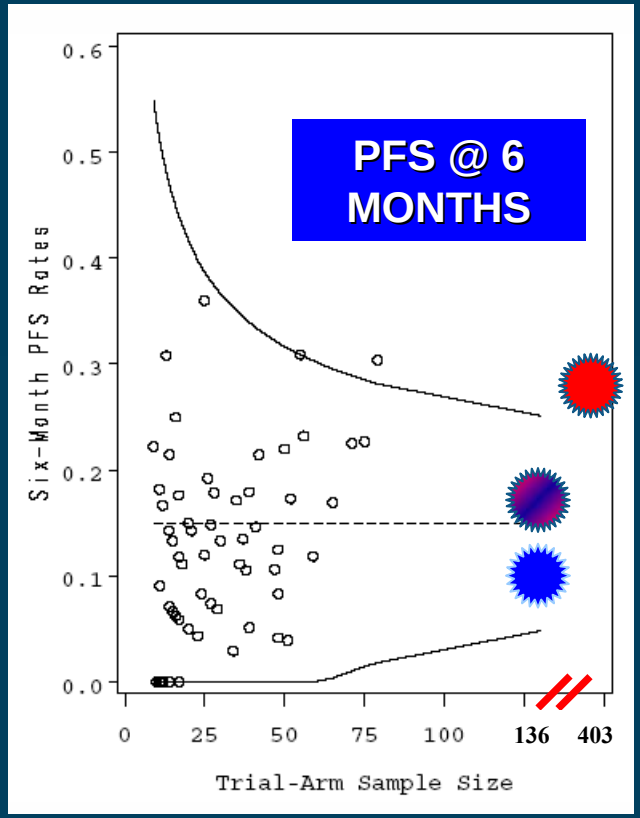
Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

IPILIMUMAB ± gp100 VS gp100 ALONE

How Do These Results Compare?

gp100/placebo Ipi/placebo Ipi/gp100

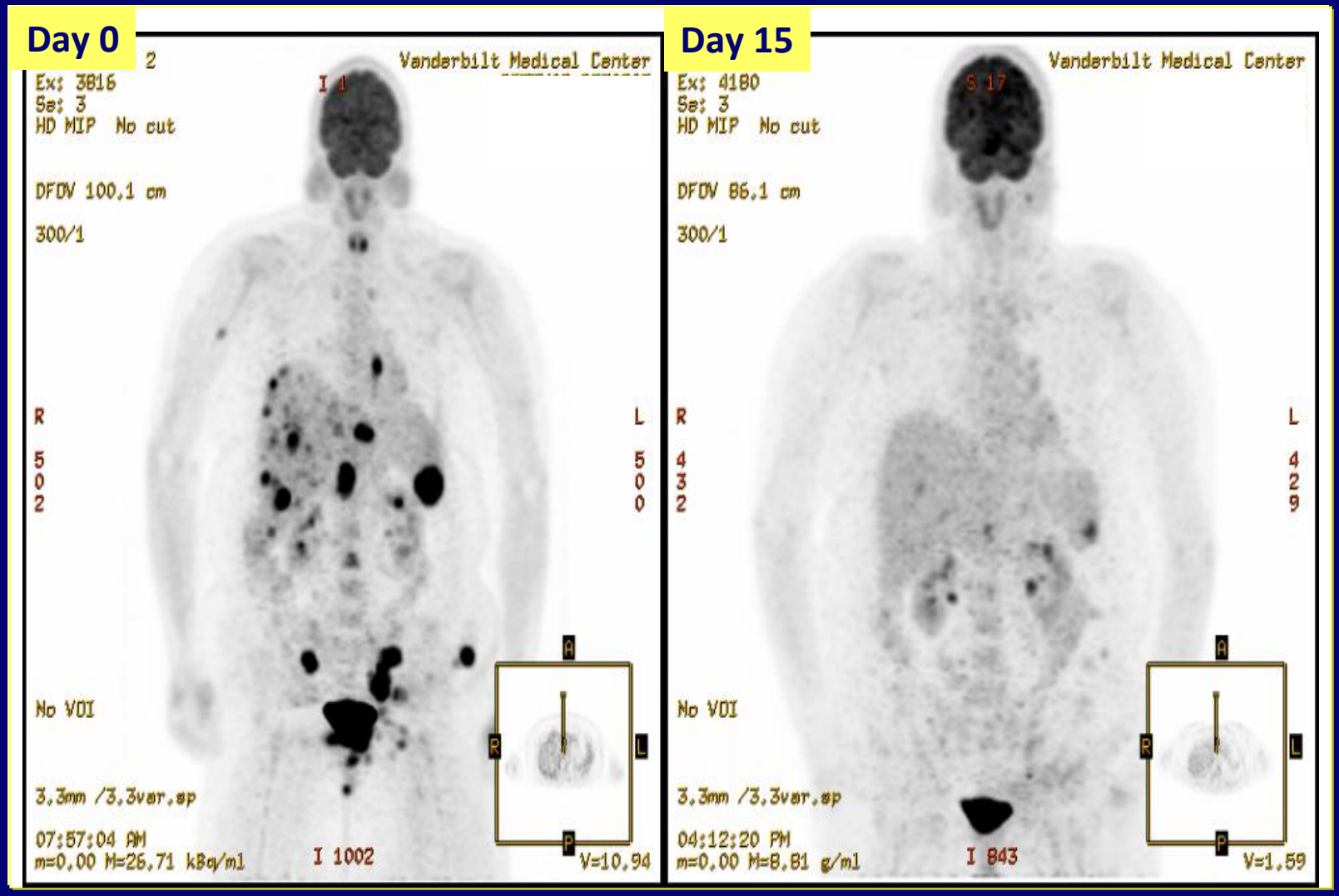




ASCO Annual '10 Meeting

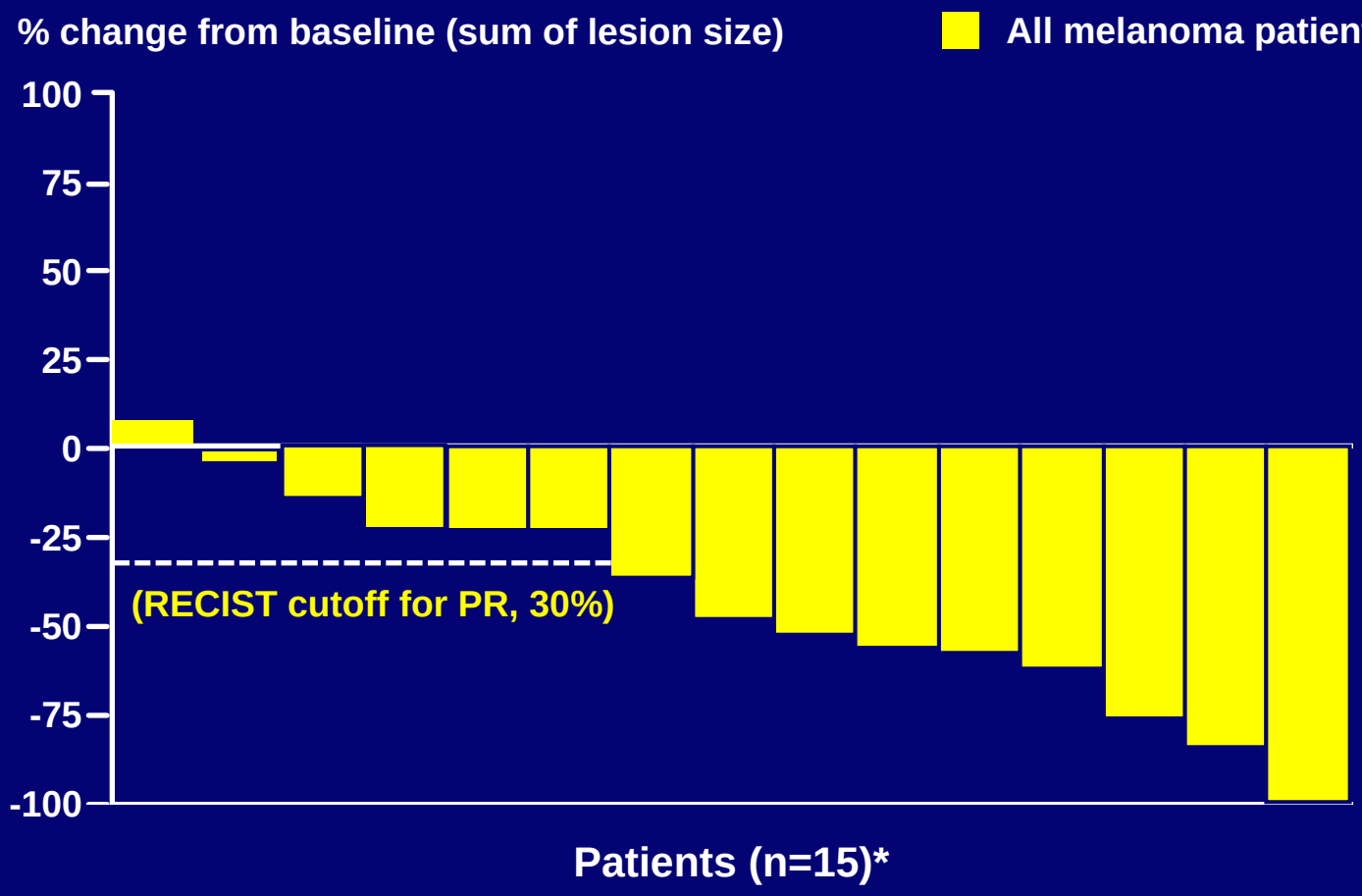
O'Day et al. *Proc ASCO 2010* abstract 4

$BRAF^{V600E}$ melanoma patient PET scan at baseline and day 15 after PLX4032 treatment at 720 mg BID



Flaherty K et al. N Engl J Med 2010;363:809

Tumor response for $BRAF^{V600E}$ melanoma patients treated with PLX4032 ≥240 mg BID



Flaherty K et al. N Engl J Med 2010;363:809

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Targeted Therapy Phase II Trials Metaanalysis

PFS vs Response

- 89 phase II trials involving targeted therapies tested in 6 different solid tumor types
  - Breast, lung, colorectal, prostate, ovarian, renal carcinomas
  - No melanoma patients
- Evaluated relationship between overall response rates and progression-free survival, and also looked at whether the agent received eventual regulatory approval

El-Maraghi et al. *J Clin Oncol* 2008;26:1356.

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Targeted Therapy Phase II Trials Metaanalysis

PFS vs Response

Table 5. Overall Single-Agent Phase II Response Rates and Regulatory Approval* for Tumor Types Included in Review

Overall Response Rate†	No. of Agents	No. of Agents Approved by FDA	Comments
0%	9	0	Note: one of these agents, imatinib was approved in indications (CML, GIST) not included in this review
> 0% to ≤ 10%	6	4	Sorafenib; bevacizumab; cetuximab; temsirolimus
> 10% to ≤ 20%	3	2 (3)	Trastuzumab; erlotinib (gefitinib: accelerated approval only)
> 20%	1	1	Sunitinib
Total	19	7 (8)	P = .005 excluding gefitinib; P = < .0001 including gefitinib

Abbreviation: FDA, US Food and Drug Administration; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor.
*Regulatory approval at FDA by June 2007.
†Overall response rate calculated for each agent by pooling results of all trials across all tumor types included in the review. One agent (marimastat) did not have response outcomes reported in any of the three publications and is included as 0%.

- **No agent with 0% response rate approved**
- **"Significant association between increasing response rate and likelihood of approval," but 4 of 6 agents with response rates of 10% or less were approved!**

El-Maraghi et al. *J Clin Oncol* 2008;26:1356.

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Cooperative Group Phase II Trial Metaanalysis

What lessons have we learned?

- Progress in the systemic therapy of metastatic melanoma requires well designed, well executed phase III trials using agents appropriately selected in phase II studies
- Eligibility criteria, patient selection and study size account for a large percentage of the variation in outcomes in phase II trials

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Cooperative Group Phase II Trial Metaanalysis

What lessons have we learned?

- Six-month PFS and 12-month OS may be better “selection” endpoint for phase II trials in melanoma than objective response or median survival
- New trial designs, such as adaptive randomization, and careful and individualized selection of endpoints are going to be necessary to evaluate the increasing number of promising agents in melanoma and other malignancies

The Tower of Babel

BUT WE CAN'T JUST BUILD A SHINY NEW TOWER OF BABEL ALL OVER AGAIN