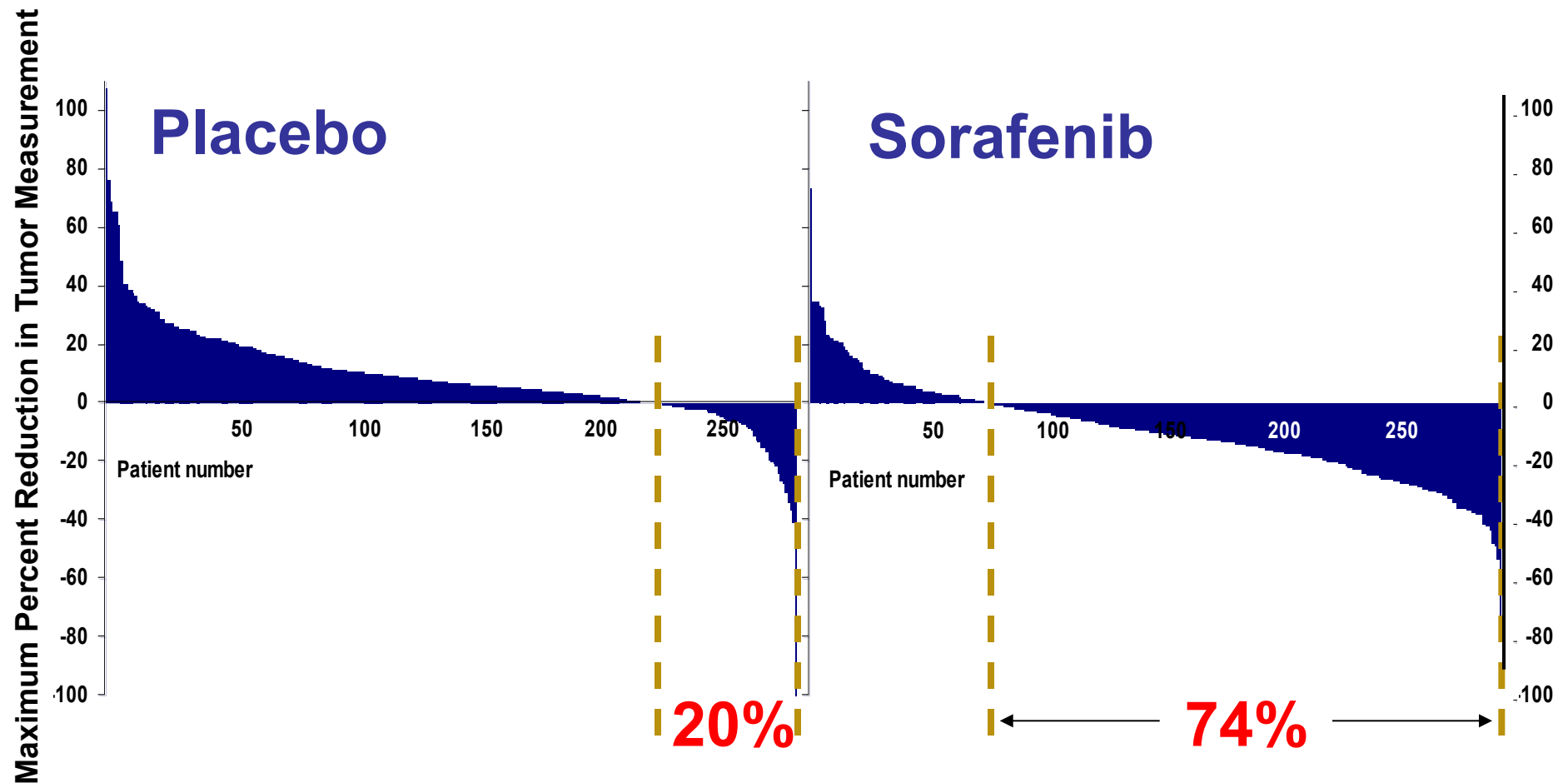


Sorafenib in RCC (TARGET Trial)

A Disease-Stabilizing Agent?



*Independently assessed measurements available for 574 patients

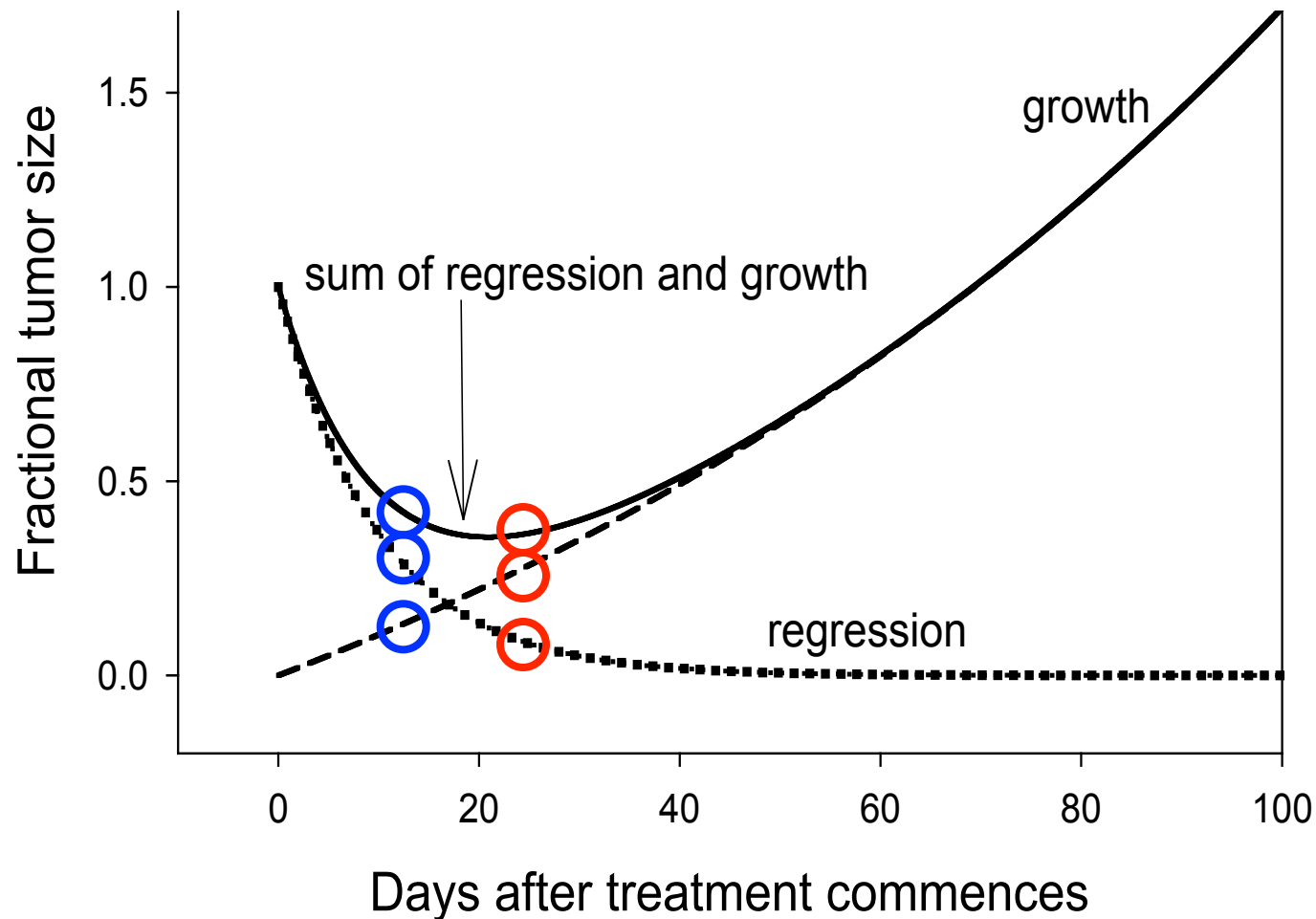
Phase of Study / Drug / Dose	# Patients	RAI-R ^A	ORR ^B	PFS ^C	Duration Rx ^D	Discontinued ^E	Reduced ^F	Reference
Well-differentiated Thyroid Cancers								
P2 Sorafenib 400 mg bid	27	Yes	26%	19.4	6.2	20%	47%	Gupta-Abramson, 2008
P2 Sorafenib 400 mg bid	52	Yes	11%	< 16	≈11	26%	55.8%	Kloos, 2009
P2 Sorafenib 400 mg bid	31	yes	25%	13.4	NR	19%	56%	Hoflizer, 2009
P2 Sorafenib 400 mg bid	13	Yes	15%	19	NR	NR	NR	Cabanillas, 2010
P2 Sorafenib 400 mg bid	19	Yes	18%	>19	16.5 ^G	NR	79% ^G	Ahmed, 2011
P2 Sorafenib 400 mg bid	16	Yes	19%	13.5	NR	NR	35% ^G	Capdevila, 2012
P1 Sorafenib 400 mg AM/200mg PM ^H	22	Yes	4.5%	20	NR	14-23% ^G	40% ^G	Hong, 2011
P2 Sunitinib 50 mg qd 4/6 wks	13	Yes	7.7%	NR	2.9	NR	23.5%	Ravaud, 2008
P2 Sunitinib 50 mg qd 4/6 wks	37	Yes	10.8%	NR	NR	NR	NR	Cohen, 2008
P2 Sunitinib 37.5 mg daily	29	Yes	24%	12.8 ^{ITT^P}	8.5 ^G	11.4% ^G	60%	Carr, 2010
P2 Pazopanib 800 mg qd	39	Yes	46%	11.7	≈11	7.7%	43%	Bible, 2010
P2 Motesanib 125 mg qd	93	Yes	14%	9.2	8.1	13%	NR	Sherman, 2008
P2 Selumetinib	39	Yes	2.6%	7.4	3	15.4%	30.8%	Hayes, 2012
P2 Axitinib 5 mg bid	45	Yes	31%	18.1 ^G	4.8 ^G	13-30% ^G	38% ^G	Cohen, 2008
P2 Levantinib 24 mg qd	58	Yes	50%	12.6	NR	23%	35%	Sherman, 2011
P2 Vandetanib 300 mg qd	72	Yes	1.4-8%	11.1	6.3	33%	38%	Leboulleux, 2010
Medullary Thyroid Cancer								
P2 Axitinib 5 mg bid	11	NR	18%	18.1 ^G	4.8 ^G	13-30% ^G	38% ^G	Cohen, 2008
P2 Sorafenib 400 mg bid	21	-	9.5%	17.9	15	23.8%	76%	Lam, 2010
P2 Sorafenib 400 mg bid	15	NR	25%	>12	16.5 ^G	NR	79% ^G	Ahmed, 2011
P2 Sorafenib 400 mg bid	15	-	47%	10.5	NR	NR	35% ^G	Capdevila, 2012
P1 Sorafenib 400 mg AM/200 mg PM ^H	13	-	38%	15	NR	14-23% ^G	40% ^G	Hong, 2011
P2 Sunitinib 37.5 mg daily	6	-	50%	12.8 ^{ITT^P}	8.5 ^G	11.4% ^G	60%	Carr, 2010
P2 Sunitinib 50 mg qd 4/6 weeks	15	-	13.3%		NR	NR	60%	Ravaud, 2010
P2 Sunitinib 50 mg qd 4/6 weeks	25	Yes	32%	12	NR	NR	NR	DeSouza, 2010
P2 Motesanib 125 mg qd	91	-	2%	11.1	8.8	17.6%	NR ^I	Schiumberger, 2009
P3 Vandetanib 300 mg qd	231	-	45%	≈30.5	20.8	12.1%	35%	Wells, 2010
P1 Cabozantinib, various doses	37	-	27%	NR	NR	NR	NR	Kurzrock, 2010
P3 Cabozantinib 140 mg qd	220	-	28%	11.2	NR	High	High	Schoffski et al, 2012
	28		21.5%	13.1	8.3	20%	40%	

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Theory for regression and growth



$$f = \exp(-d \cdot t) + \exp(g \cdot t) - 1$$

Where f = tumor measurement in t days

d = regression rate constant; g = growth rate constant

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JULY 31, 2003

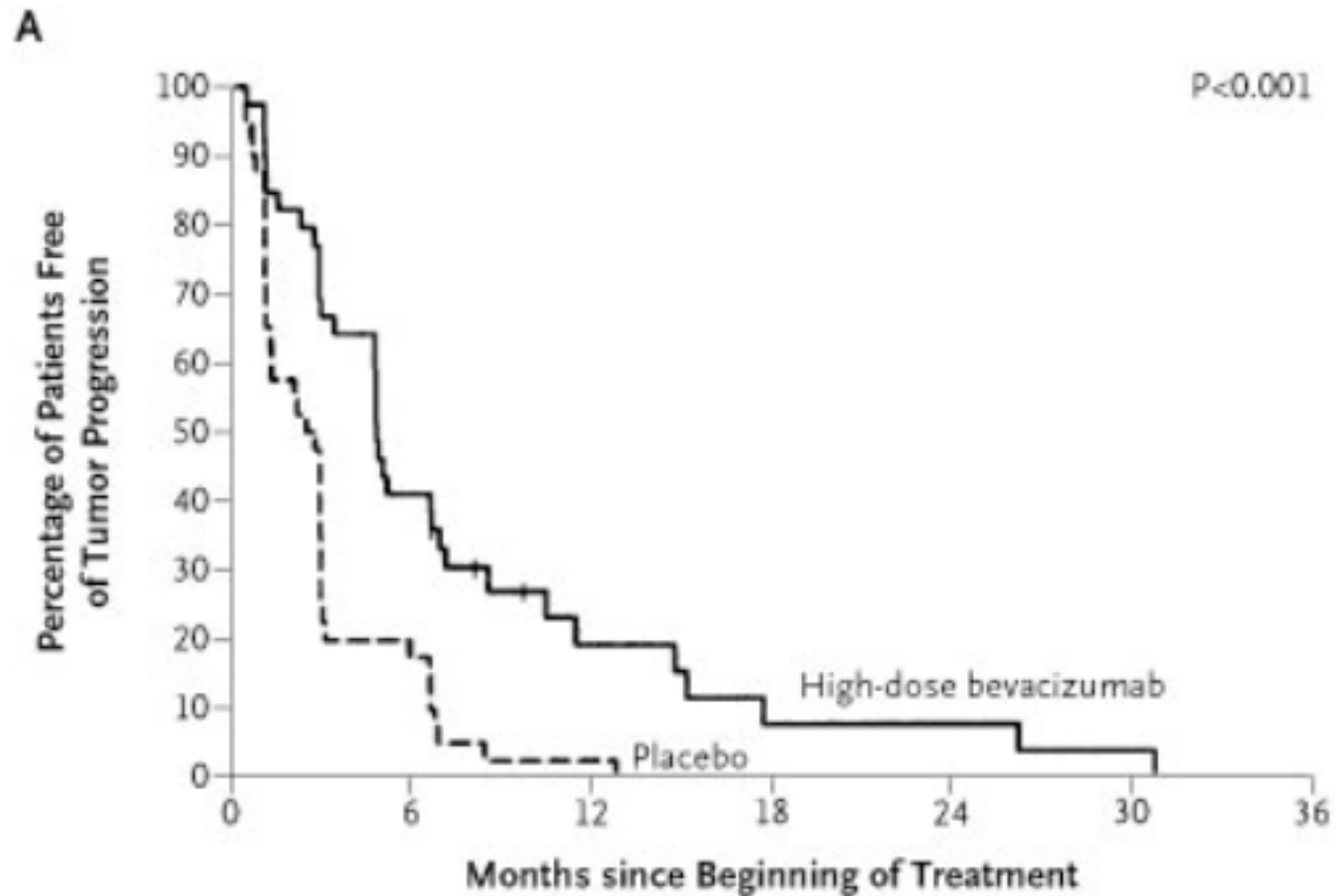
VOL. 349 NO. 5

A Randomized Trial of Bevacizumab, an Anti-Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer

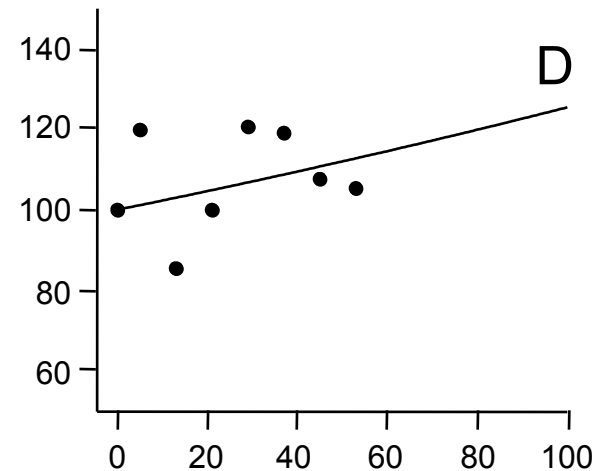
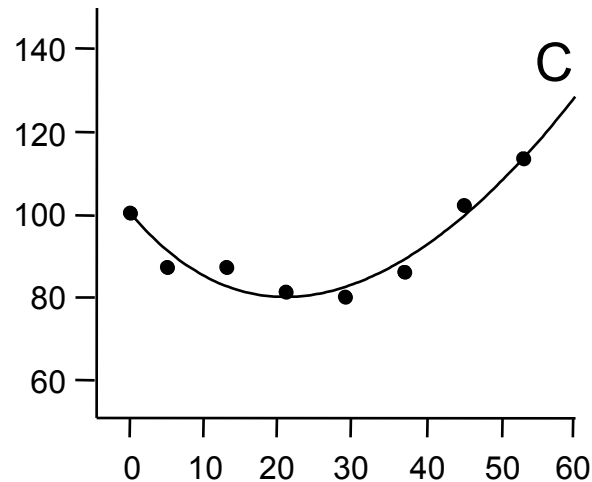
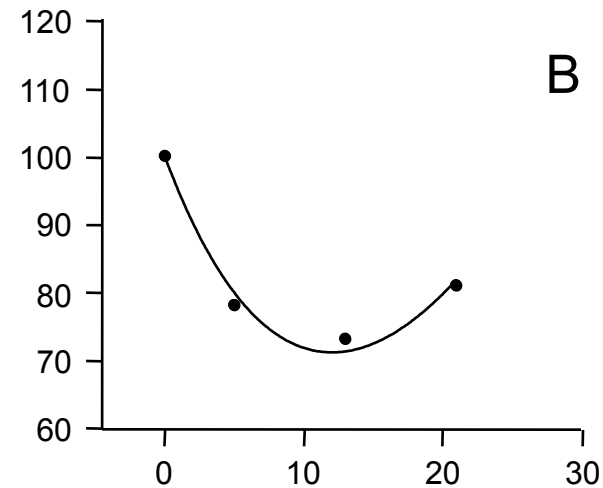
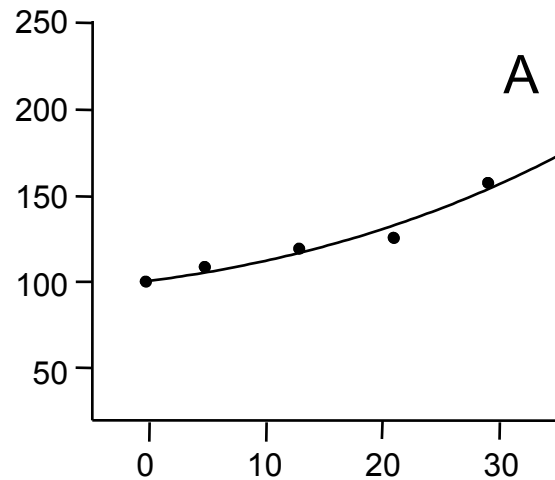
James C. Yang, M.D., Leah Haworth, B.S.N., Richard M. Sherry, M.D., Patrick Hwu, M.D.,
Douglas J. Schwartzentruber, M.D., Suzanne L. Topalian, M.D., Seth M. Steinberg, Ph.D., Helen X. Chen, M.D.,
and Steven A. Rosenberg, M.D., Ph.D.

Kaplan-Meier Plot: PFS

High-Dose Bevacizumab in RCC



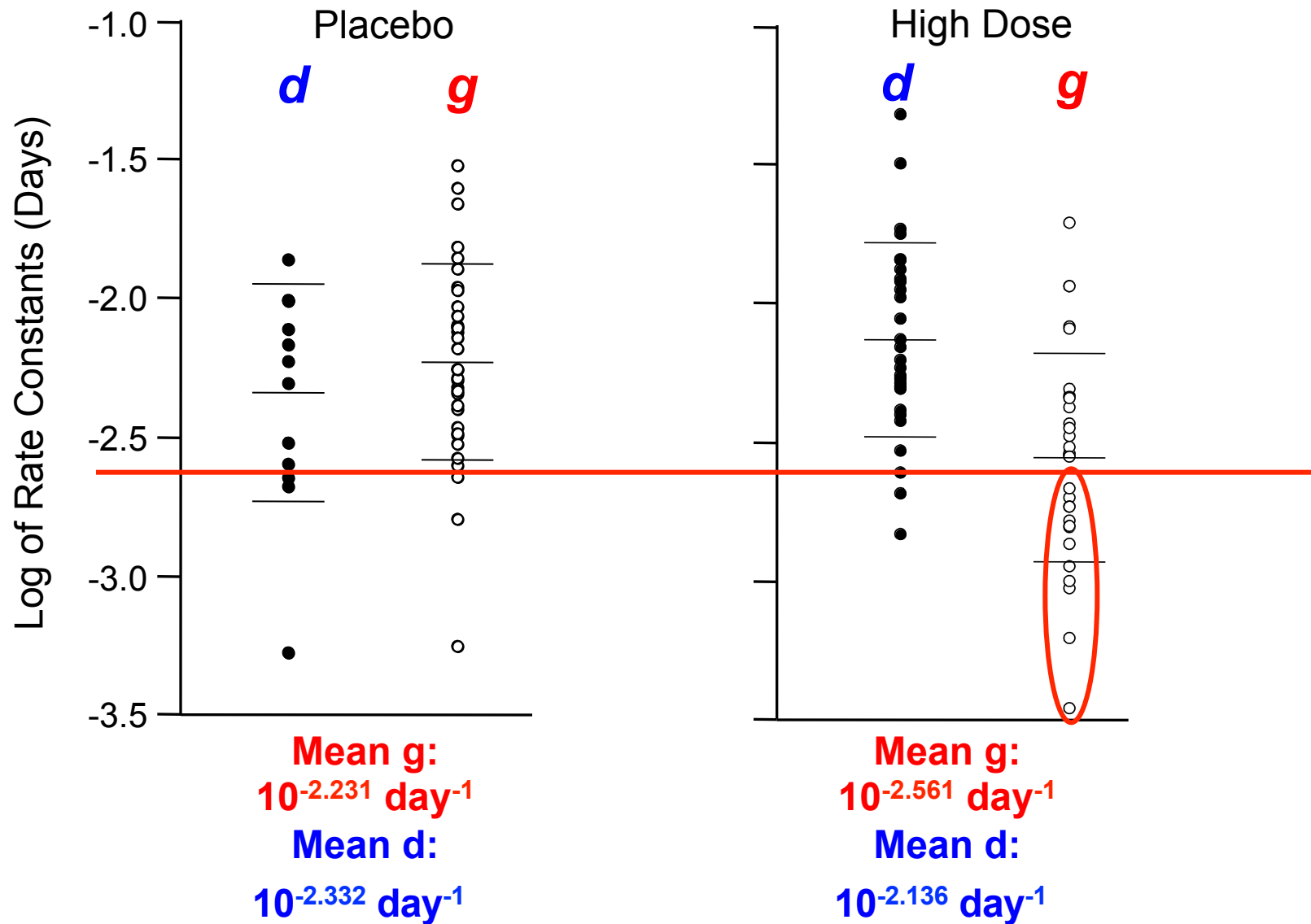
Sigmaplot Curve Fits: Renal Cell Carcinoma



$$f = \exp(-d \cdot t) + \exp(g \cdot t) - 1$$

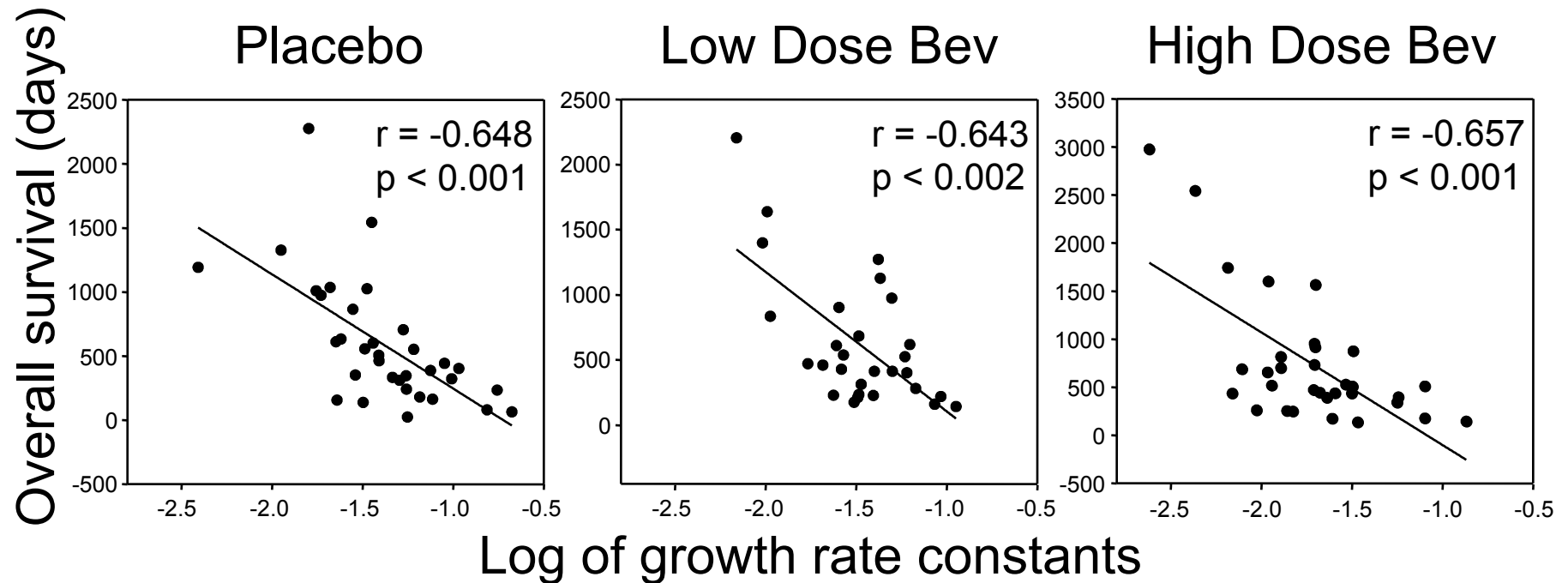
d = regression rate constant; g = growth rate constant

Dot Plot of Regression and Growth Rate Constants



Regression rate constants (\bullet) / Growth rate constants (\circ) / Horizontal lines are mean \pm SD

Growth Rate Constants Correlate with Survival in Renal Cell Carcinoma



In g we thus had an excellent surrogate for the FDA gold standard - OS - a surrogate that could help us discern effective versus non-effective therapies

Prostate Cancer

Patients with metastatic CRPC

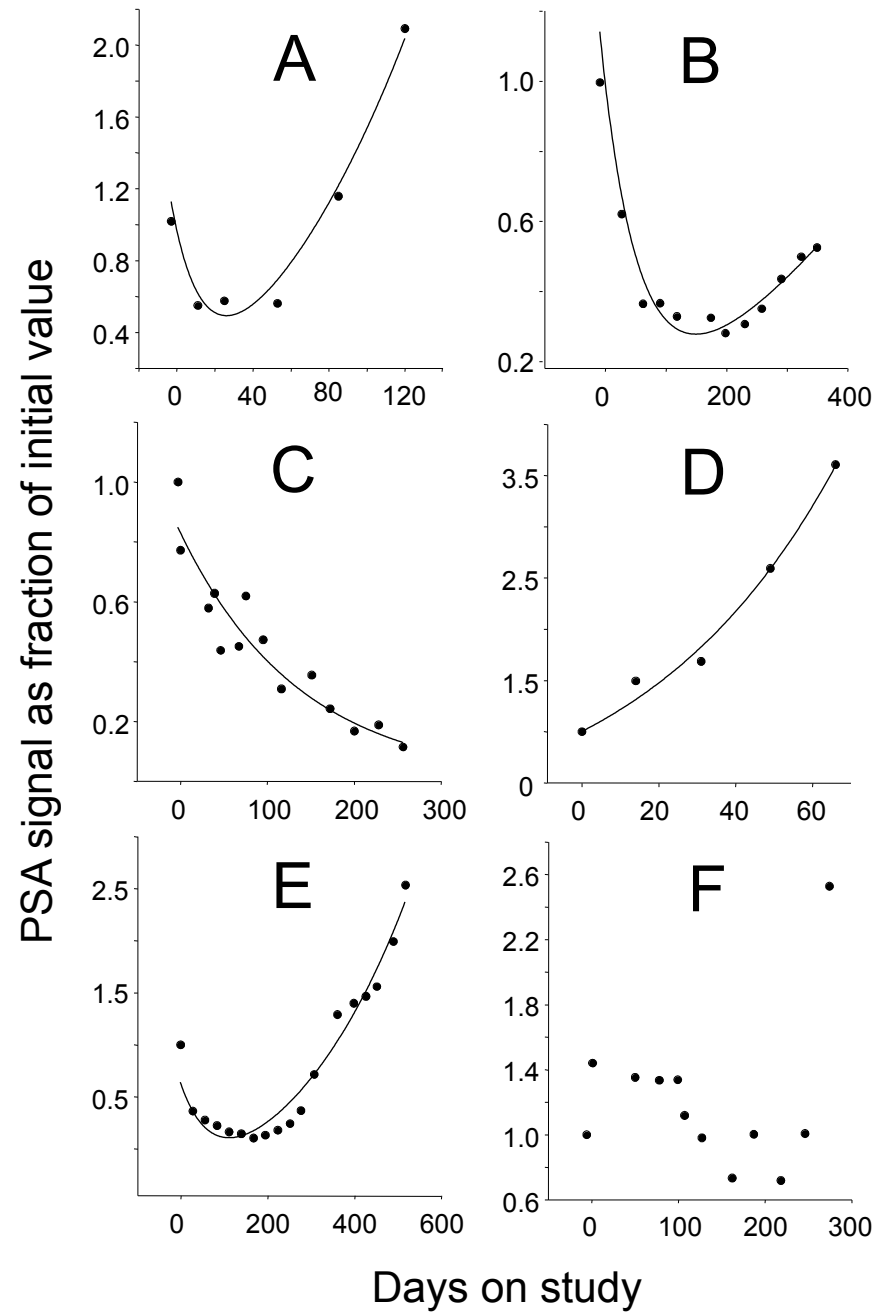
Did not benefit from:

1. Combined androgen blockade
2. Anti-androgen withdrawal

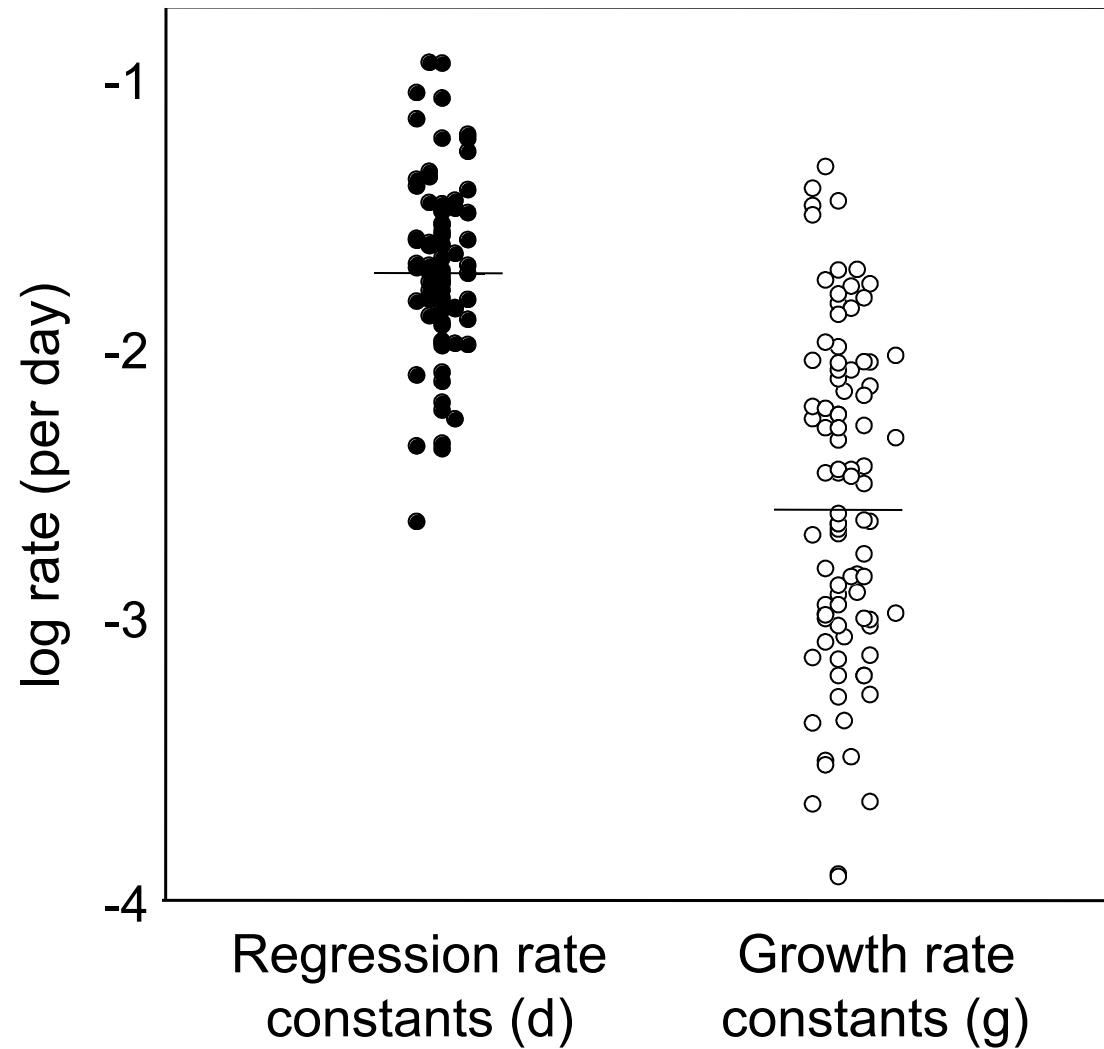
Chemotherapy:

1. Thalidomide
2. Docetaxel + Thalidomide
3. Ketoconazole + Alendronate
4. ATTP (Avastin + Thalidomide + Taxotere + Prednisone)

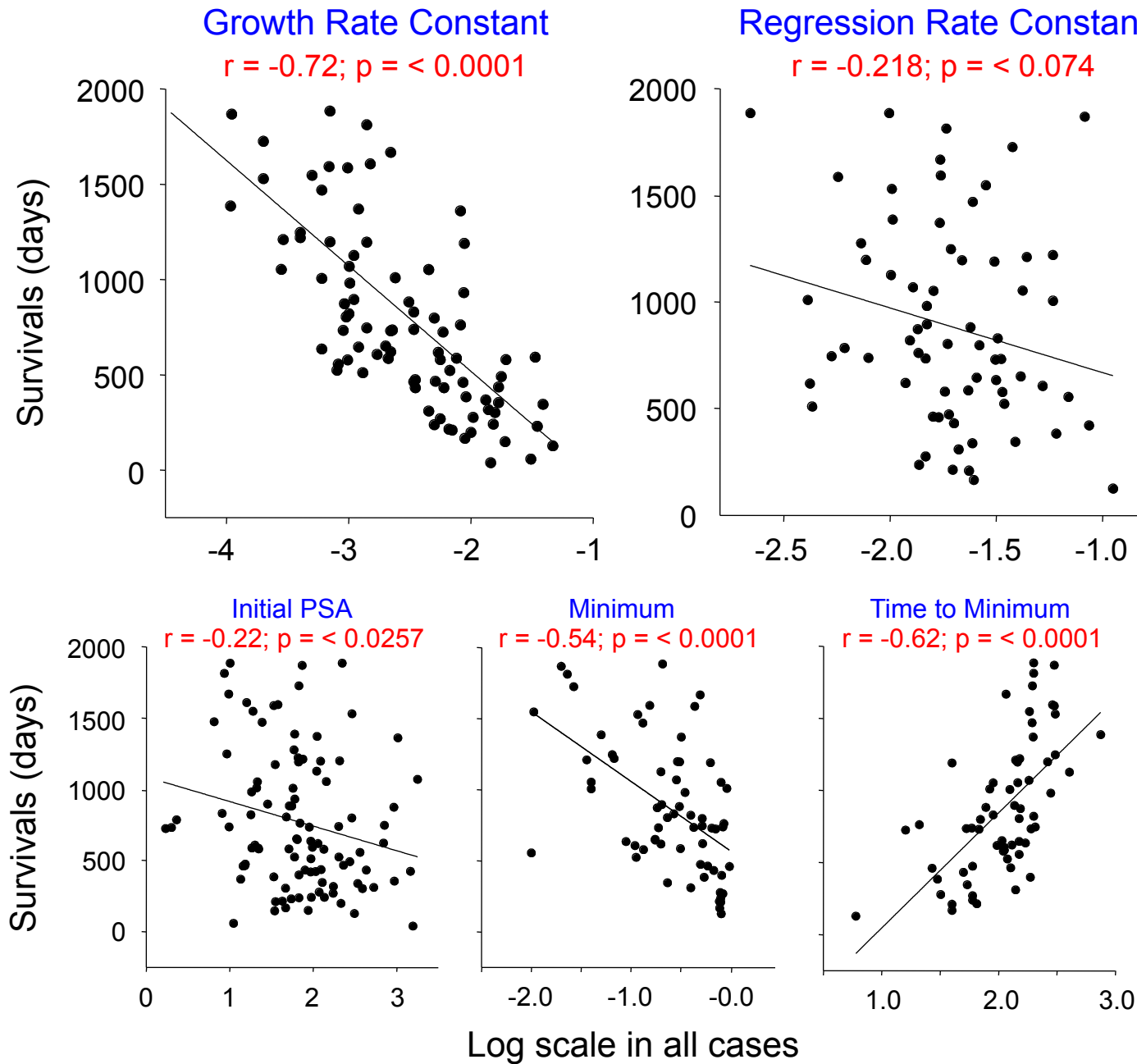
Sigmaplot Curve Fits: Prostate Cancer



Prostate Cancer Regression and Growth Rate Constants

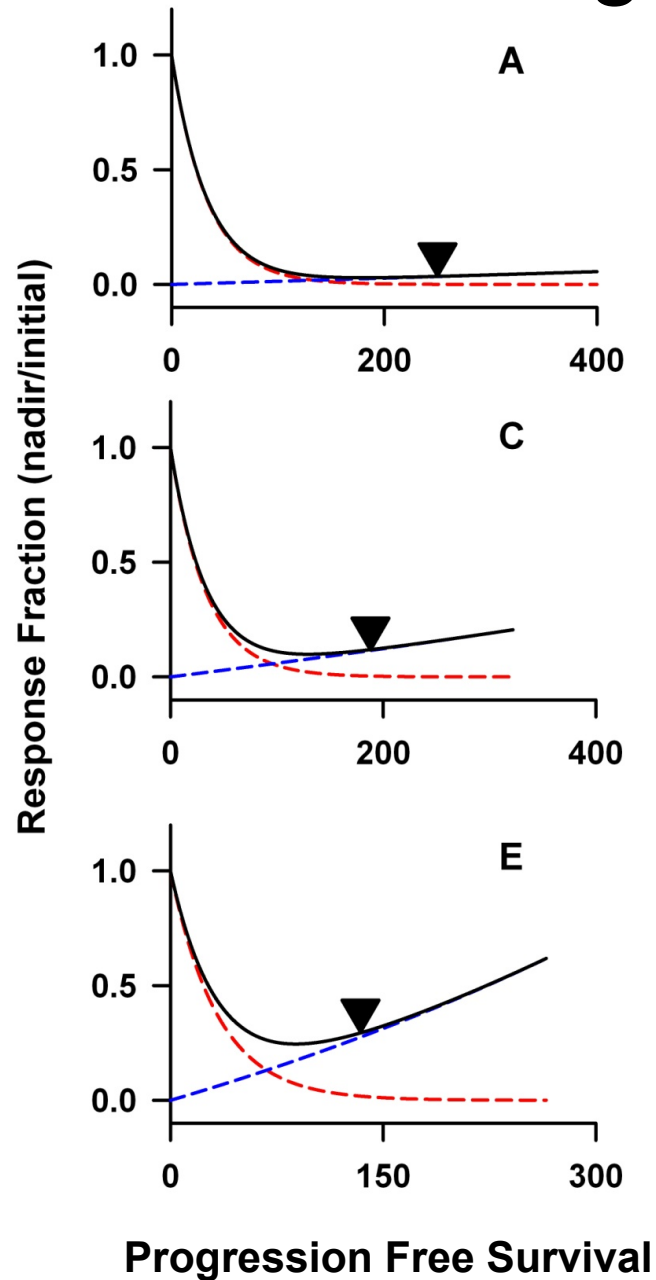


Prostate Cancer: Correlation of Parameters with Survival

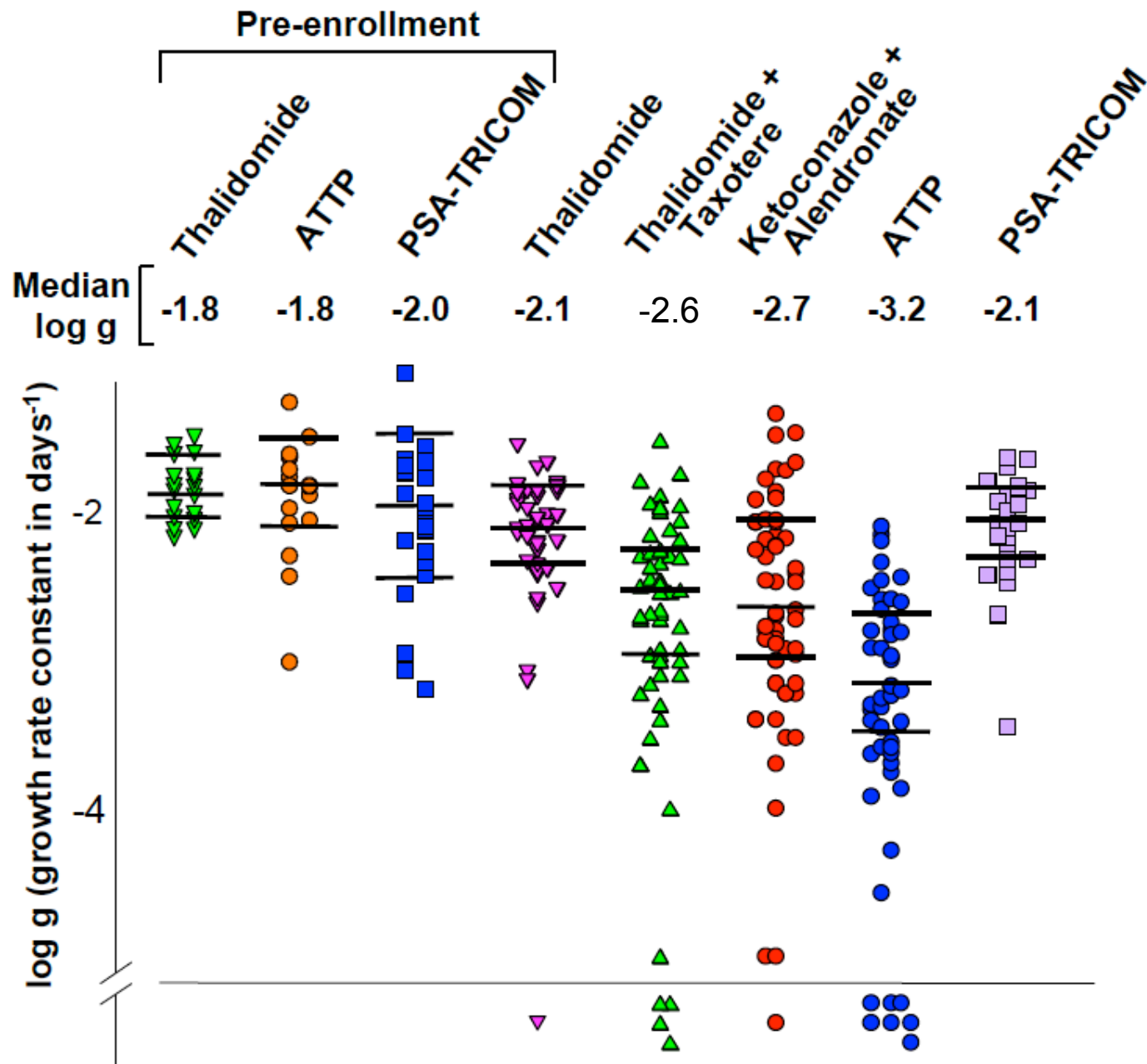


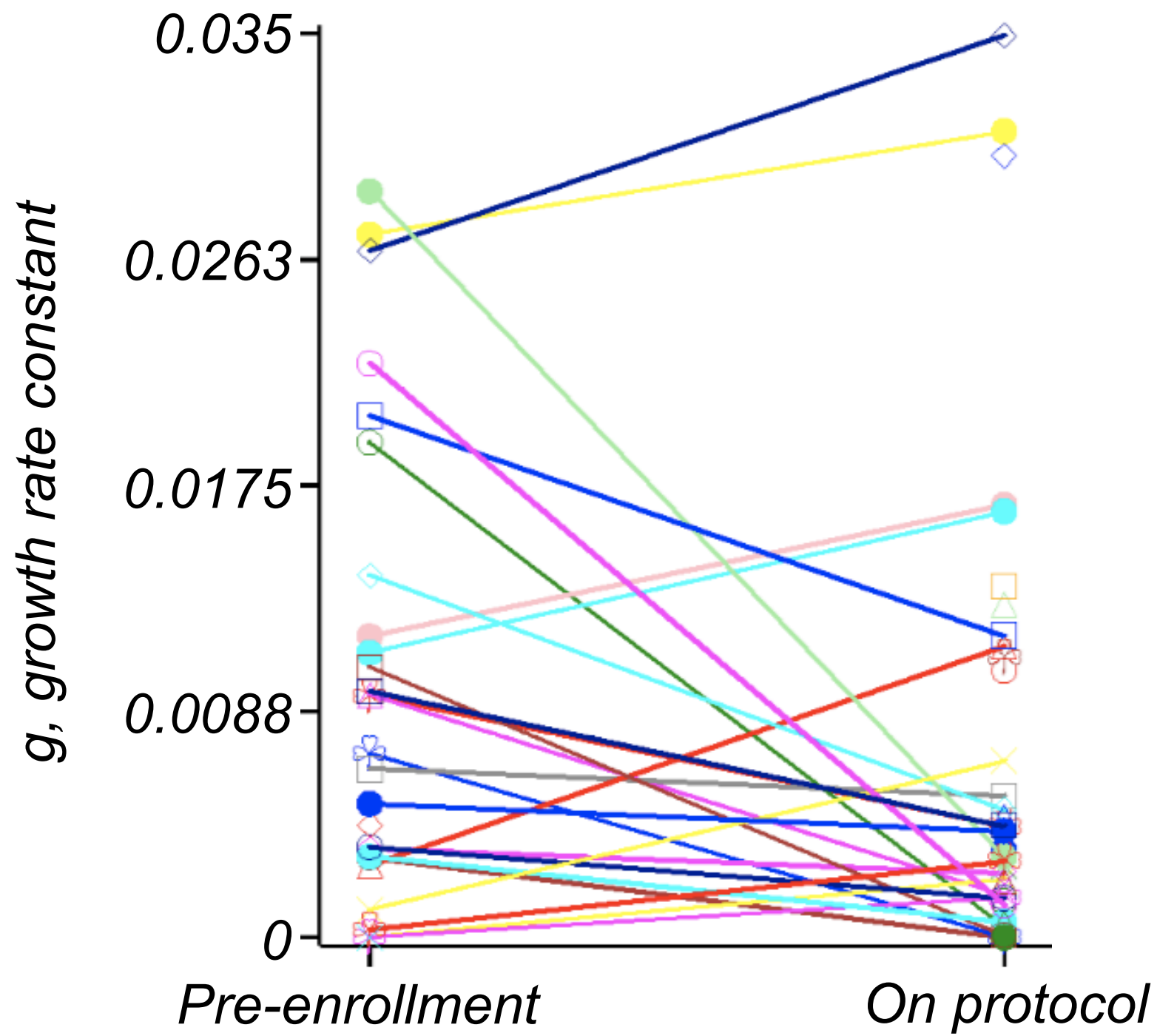
Nadir and PFS are surrogates for g

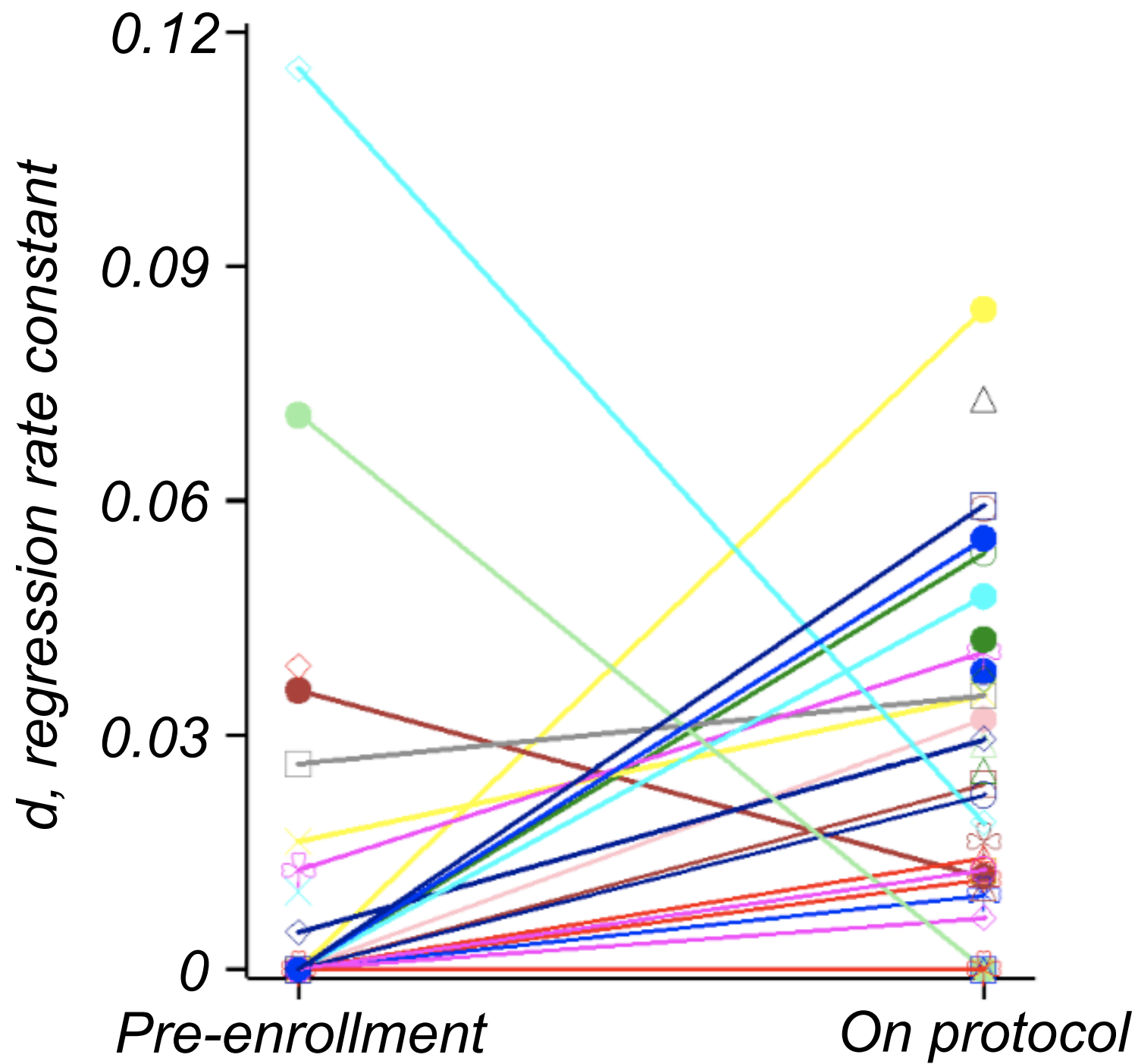
*As g increases,
the nadir (▼) rises
and comes sooner*

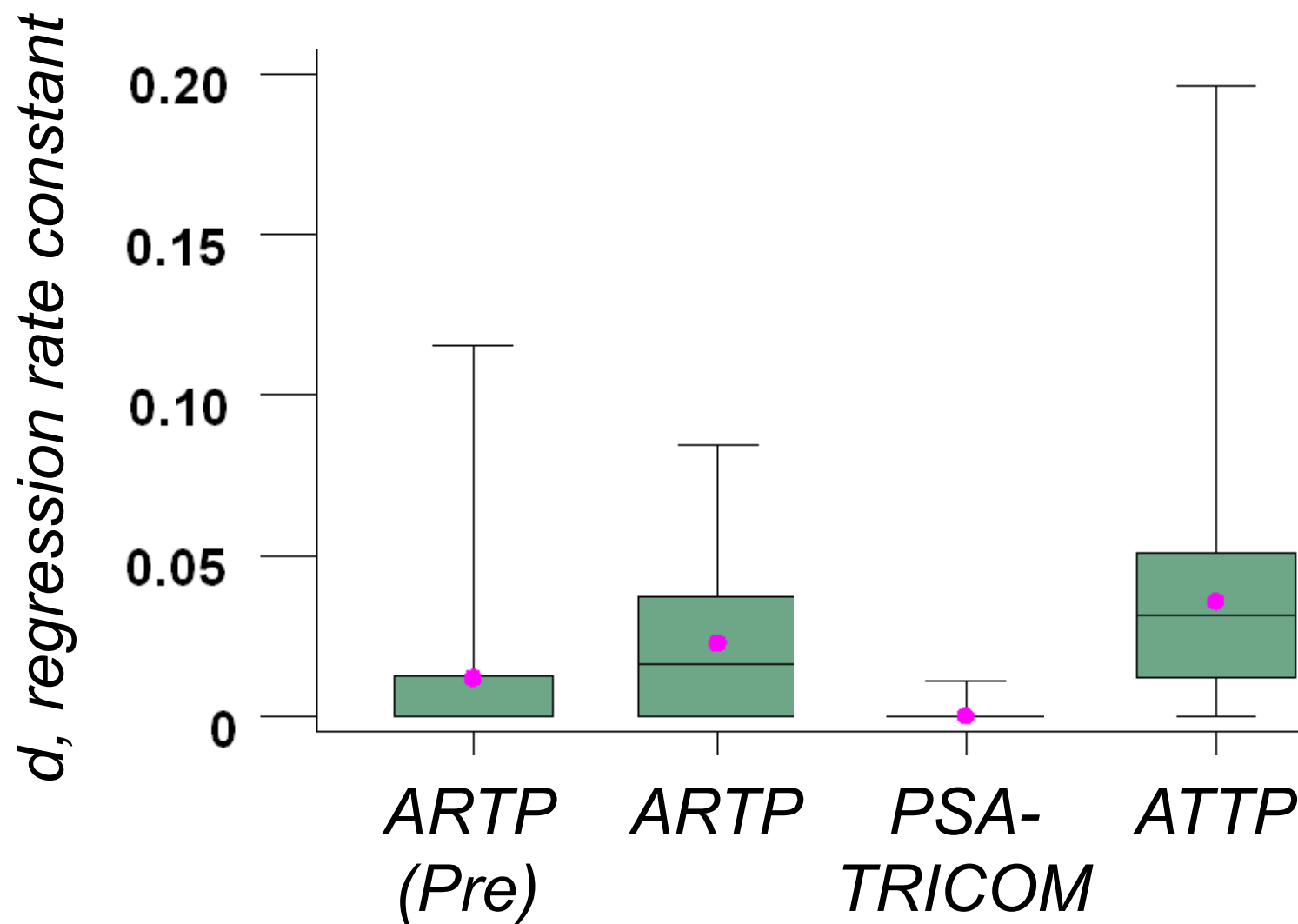


12 Years of Prostate Cancer Trials at the NCI



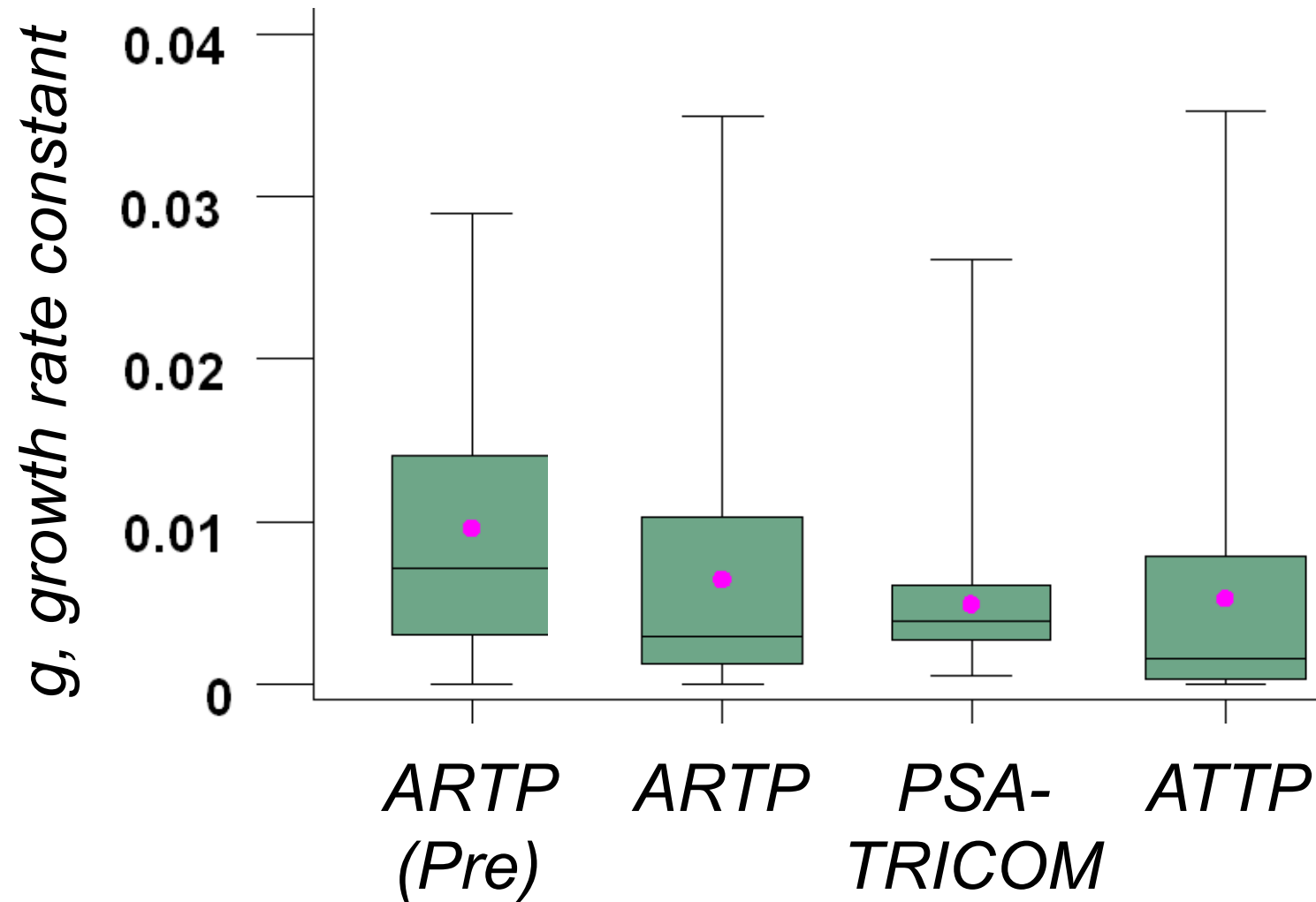






Median *d*: .0000 .0016 .0000 .0032

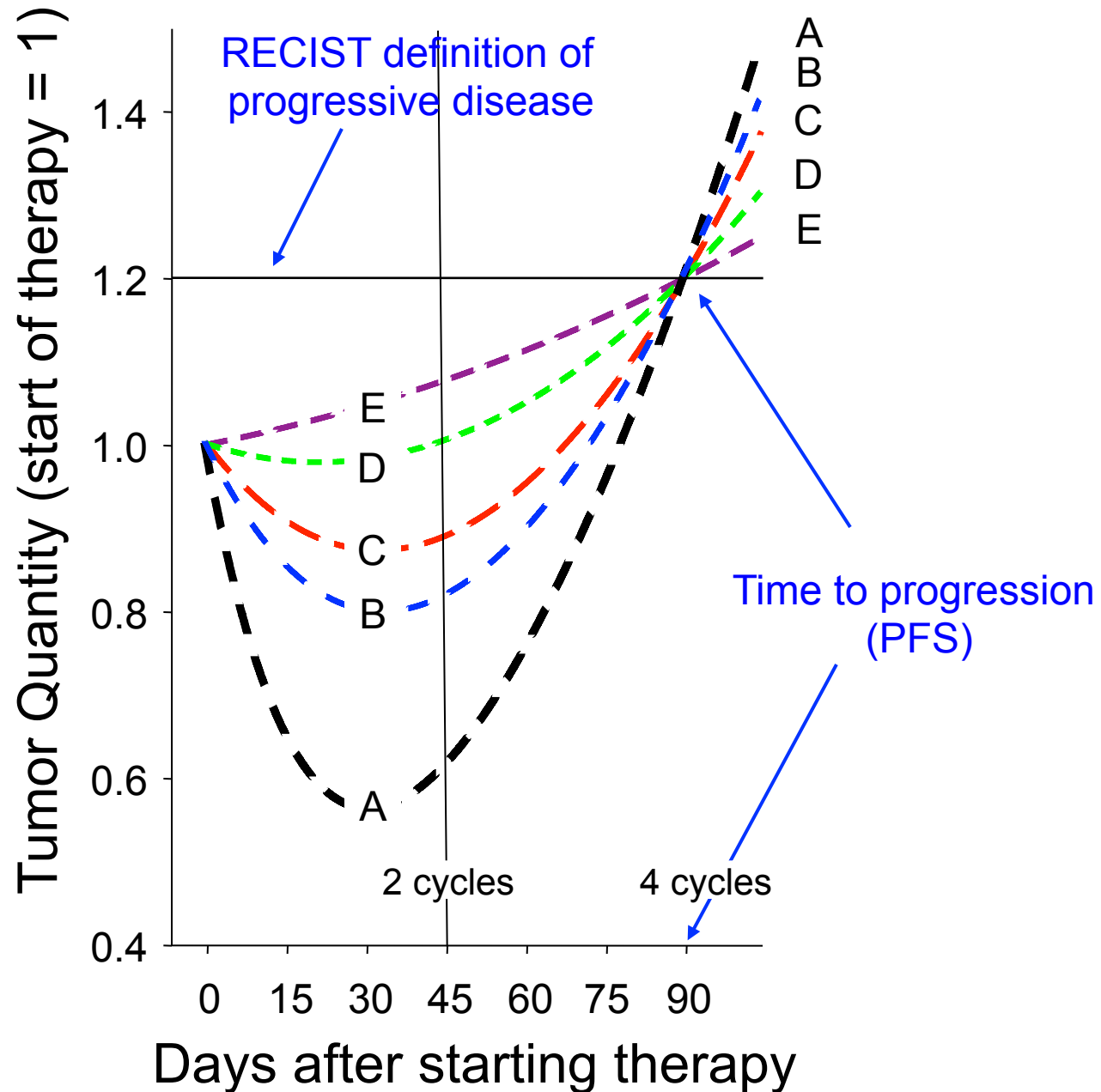
P value: L .005 J L .025 J



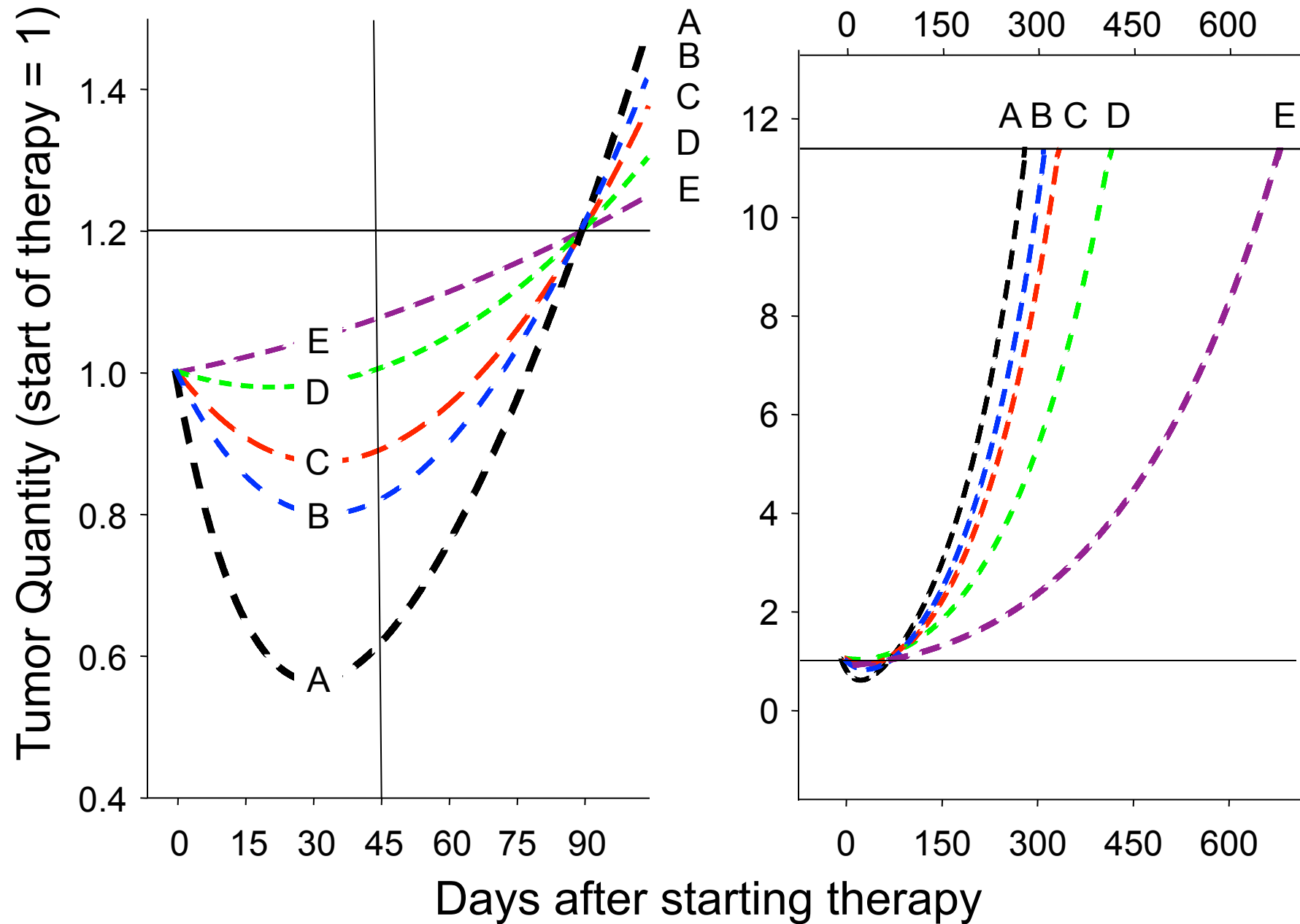
Median g : .0071 .0030 .0038 .0016

P value: .008 .291

Modeling Tumor Growth: Effect of Growth Rate on Survival



Growth Rate Not Nadir or Time to Progression Influence Survival

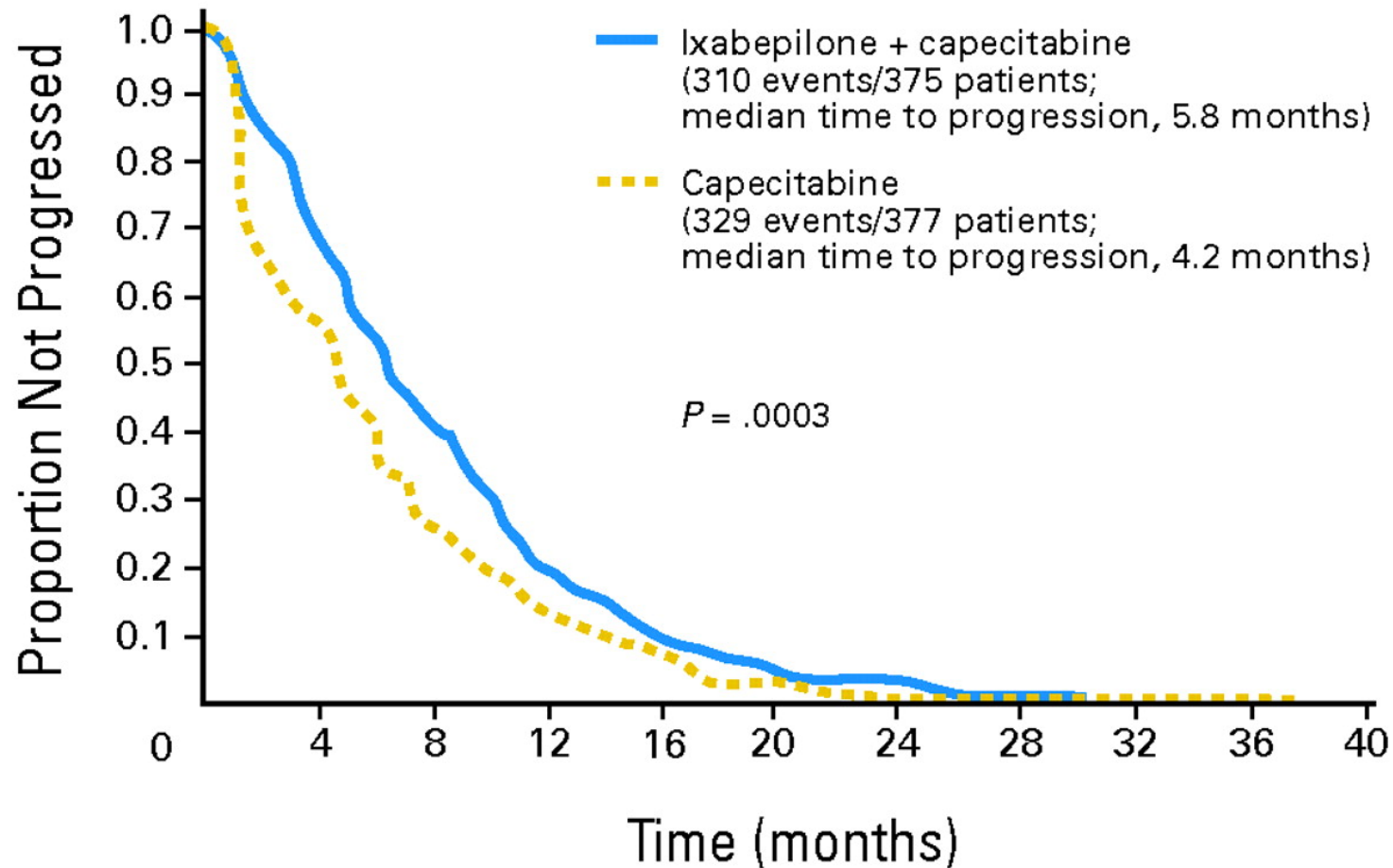


Ixabepilone Plus Capecitabine for Metastatic Breast Cancer Progressing After Anthracycline and Taxane Treatment

Eva S. Thomas, Henry L. Gomez, Rubi K. Li, Hyun-Cheol Chung, Luis E. Fein, Valorie F. Chan, Jacek Jassem, Xavier B. Pivot, Judith V. Klimovsky, Fernando Hurtado de Mendoza, Binghe Xu, Mario Campone, Guillermo L. Lerzo, Ronald A. Peck, Pralay Mukhopadhyay, Linda T. Vahdat, and Henri H. Roché

Second Line: Metastatic Breast Cancer

Capecitabine vs Capecitabine + Ixabepilone



Second Line: Metastatic Breast Cancer

Capecitabine vs Capecitabine + Ixabepilone

Table 2. Objective Tumor Responses in Randomly Assigned Patients (independent radiology review)

	Ixabepilone Plus Capecitabine (n = 375)		Capecitabine (n = 377)	
Response	No. of Patients	%	No. of Patients	%
Objective response rate	130	34.7	54	14.3
95% CI	29.9 to 39.7		10.9 to 18.3	
Difference in response rates (%)	19.5			
95% CI for difference	13.6 to 25.3			
Complete response	1	< 1	0	
Partial response	129*	34	54	14
Stable disease	155	41	175	46
Progressive disease	58	15	102	27
Not determined	32	9	46	12
Clinical benefit†	190	51	113	30

*Includes one patient with a partial response who was assigned to the ixabepilone + capecitabine group but received capecitabine only.

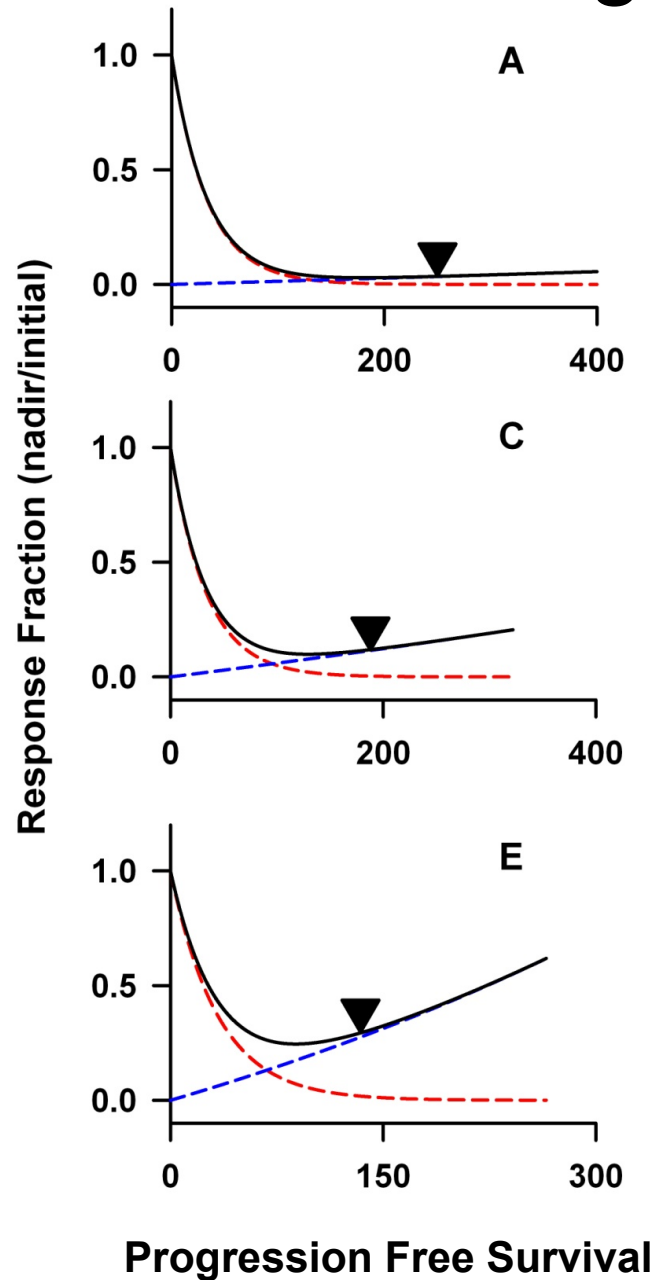
†Complete response + partial response + stable disease \geq 6 months.

Second Line: Metastatic Breast Cancer Capecitabine vs Capecitabine + Ixabepilone

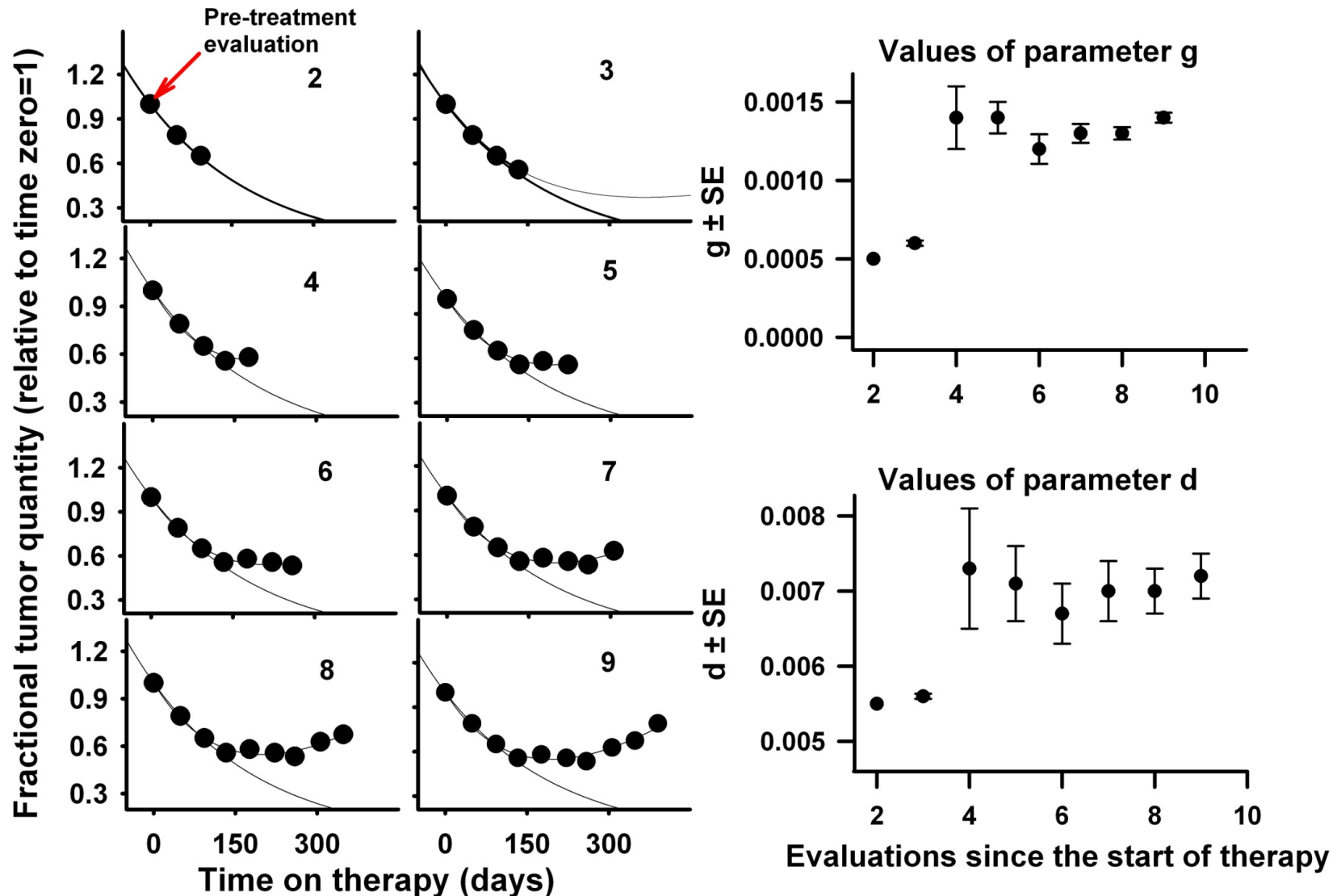
Treatment Arm	Median g [days-1]	Median d [days-1]
Capecitabine	0.00288	0.00840
Ixabepilone + Capecitabine	0.00191	0.00863
	p < 0.001	p = 0.400 NS

Nadir and PFS are surrogates for g

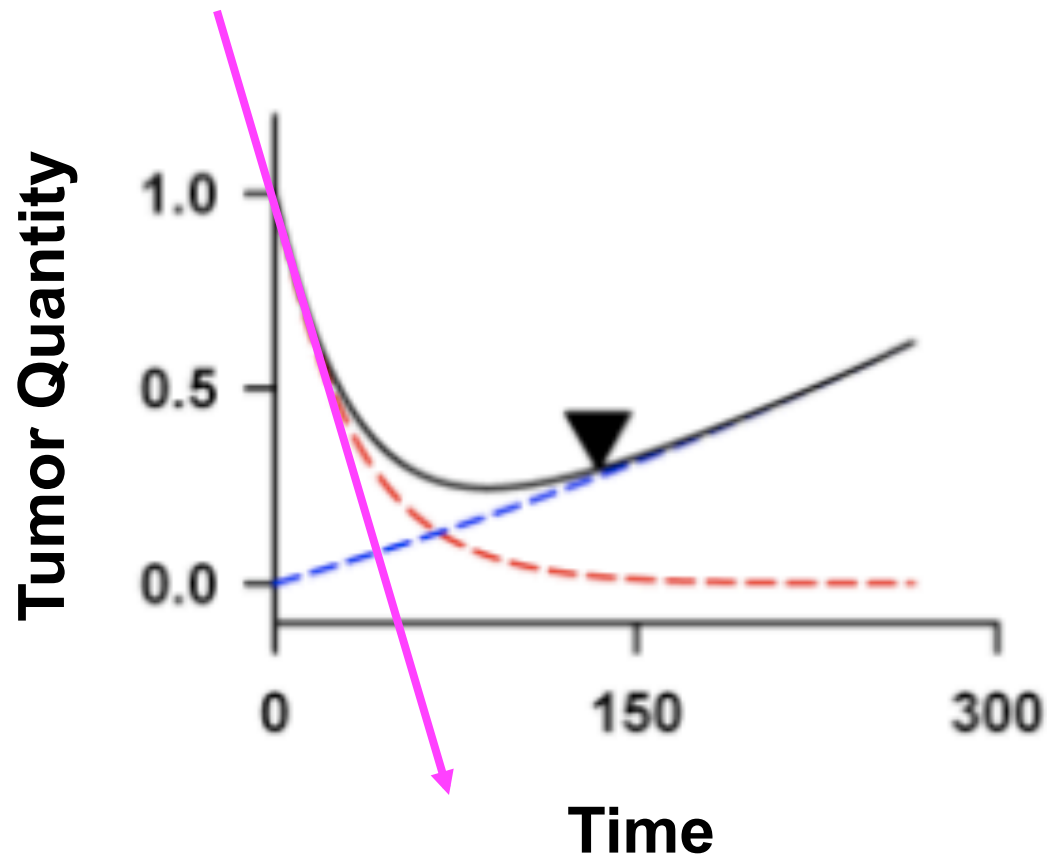
*As g increases,
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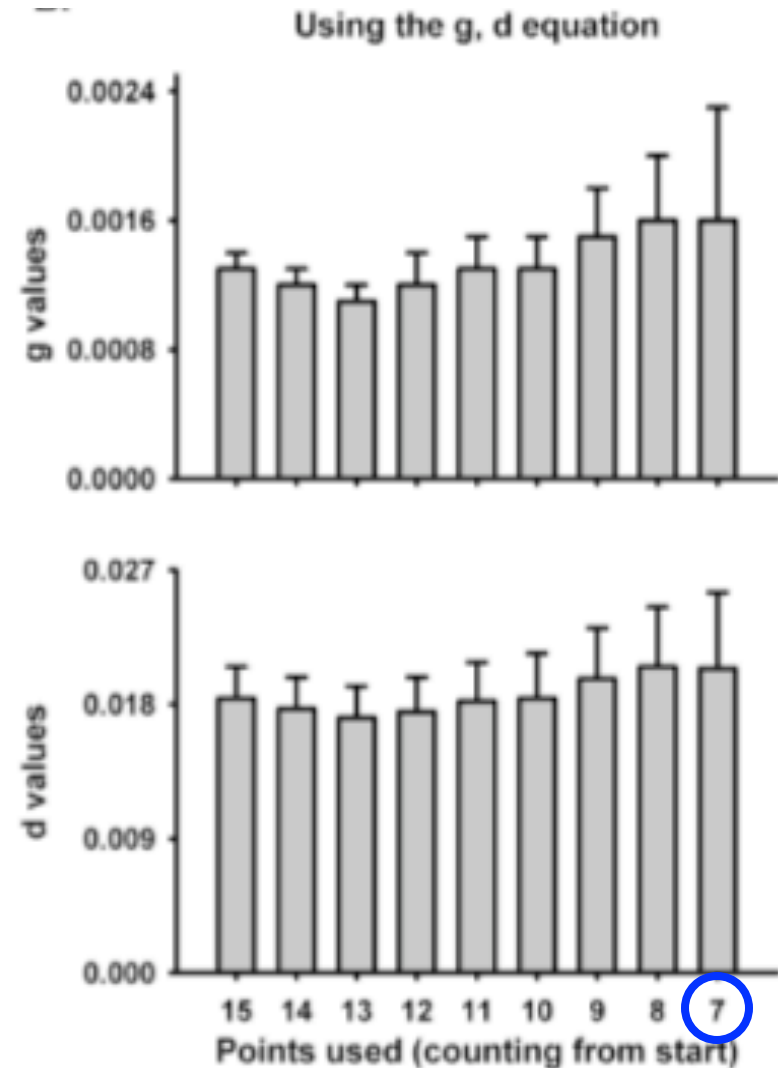
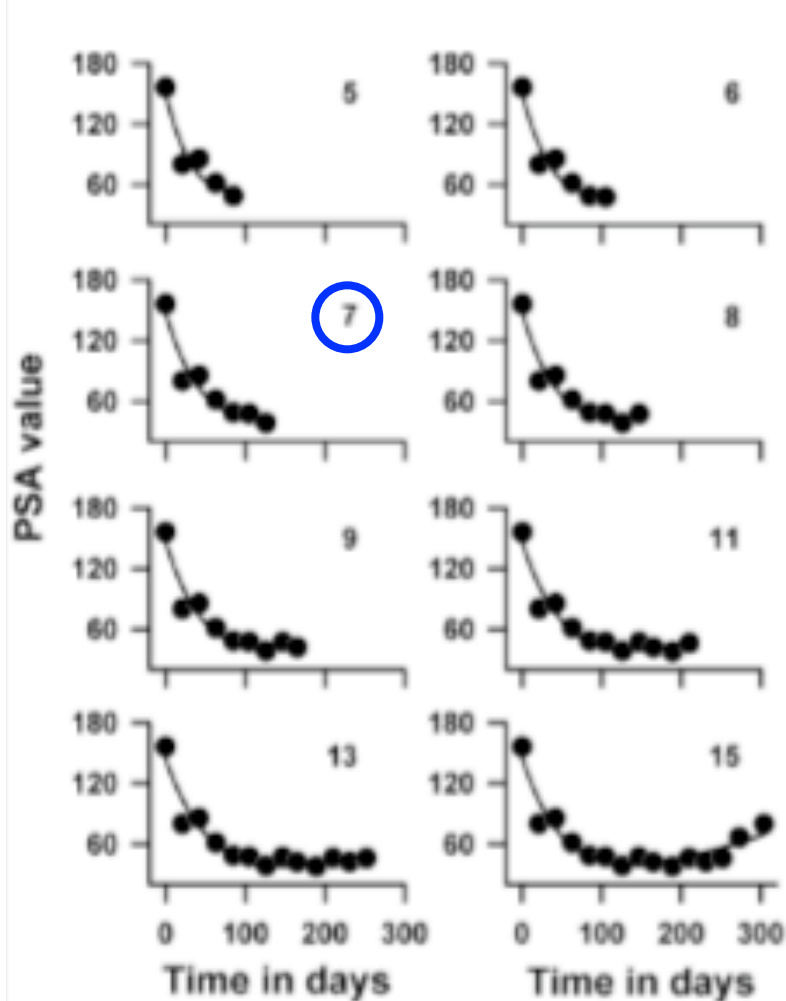
Breast cancer: g and d can be extracted accurately before the nadir is reached



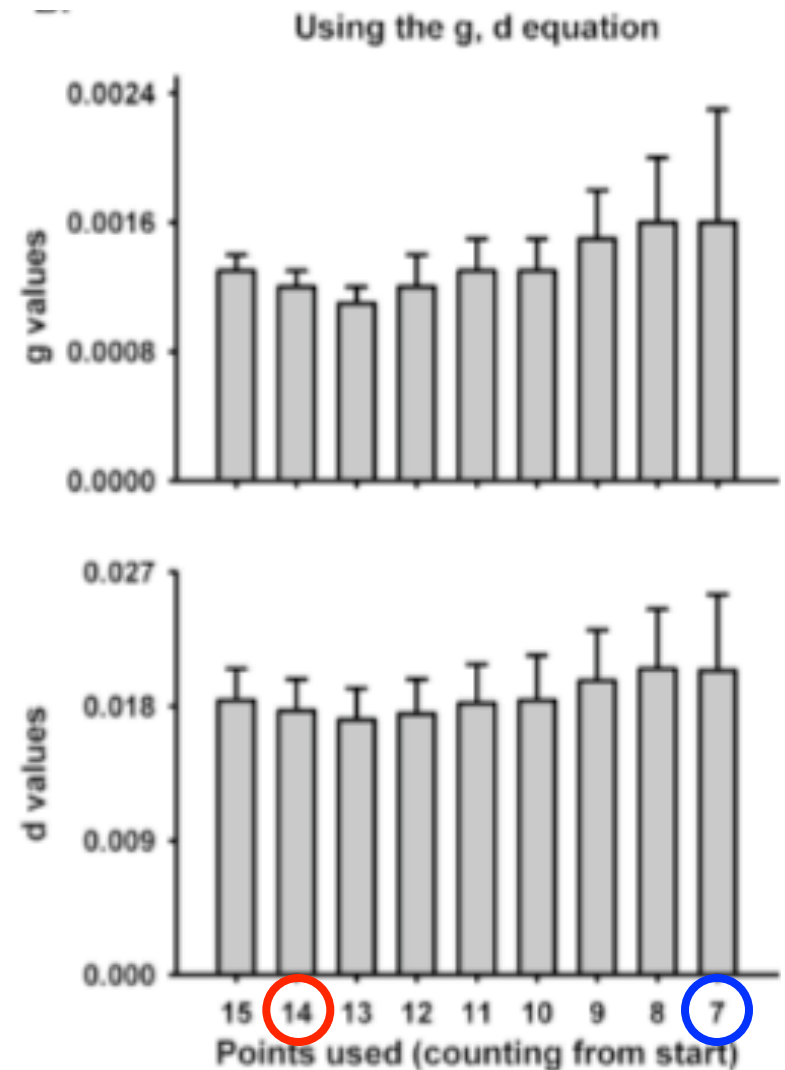
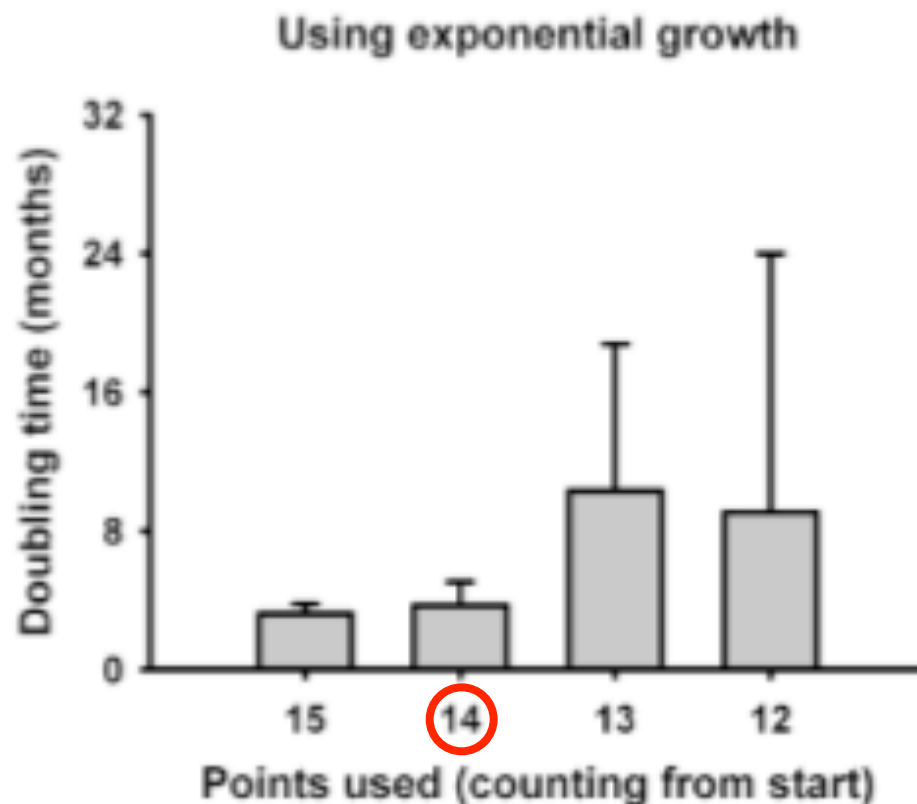
The “unseen” growing fraction
“deviates” the tumor’s regression
from its downward trajectory



Prostate cancer: g and d can be extracted accurately before the nadir is reached - long before a PSA-DT can be calculated



Prostate cancer: g and d can be extracted accurately before the nadir is reached - long before a PSA-DT can be calculated

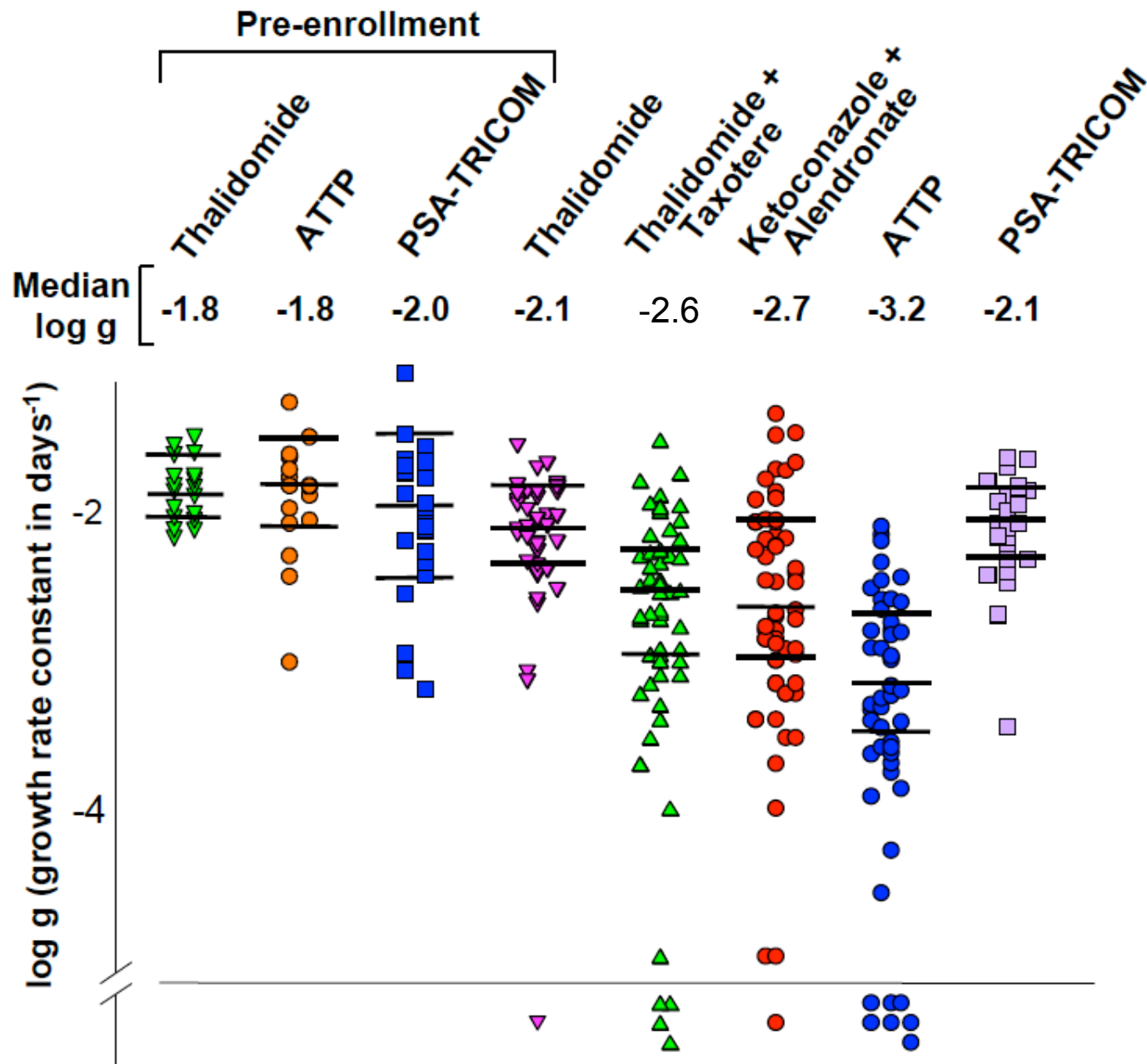


Superiority of g over PSA-DT

An accurate g can be calculated a median of 13 weeks earlier

Patient no.	Date of Nadir	Date g/d determined (g-nadir, wks)	Date PSA-DT determined	Difference in weeks (PSA-DT - g)
1	10/3/2005	10/3/2005 (0)	12/12/2005	10
4	4/24/2006	4/3/2006 (3)	6/26/2006	12
9	1/23/2006	12/22/2005 (5)	3/6/2006	11
10	1/30/2006	1/9/2006 (3)	3/13/2006	9
11	5/26/2006	5/8/2006 (3)	9/18/2006	19
16	5/15/2006	5/15/2006 (0)	8/7/2006	12
17	7/17/2006	6/26/2006 (3)	9/1/2006	10
19	9/5/2006	9/25/2006 (-3)	10/16/2006	3
21	12/4/2006	10/23/2006 (6)	1/29/2007	14
22	6/26/2006	6/26/2006 (0)	3/26/2007	39
23	2/17/2006	11/28/2005 (12)	6/12/2006	28
30	6/19/2006	12/12/2005 (27)	10/30/2006	46
41	11/5/2007	9/24/2007 (6)	10/15/2007	3

12 Years of Prostate Cancer Trials at the NCI



Dependence of patient survival on the log of the growth rate constants

Thalidomide

$R = 0.38$

$p = 0.027$

**Ketoconazole +
Alendronate**

$R = 0.69$

$p < 0.0001$

**Thalidomide +
Docetaxel**

$R = 0.74$

$p < 0.0001$

ATTP

$R = 0.42$

$p = 0.005$

PSA-TRICOM

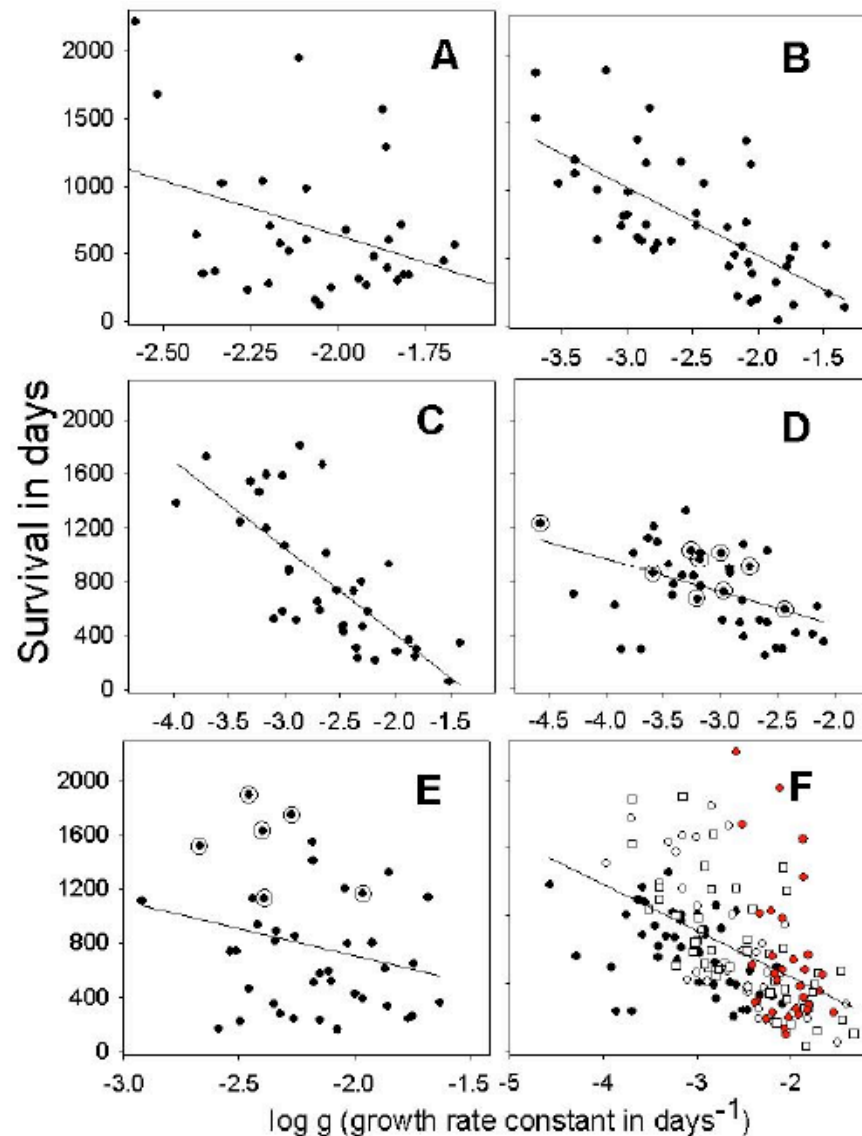
$R = 0.25$

$p = 0.13$

Combined data set

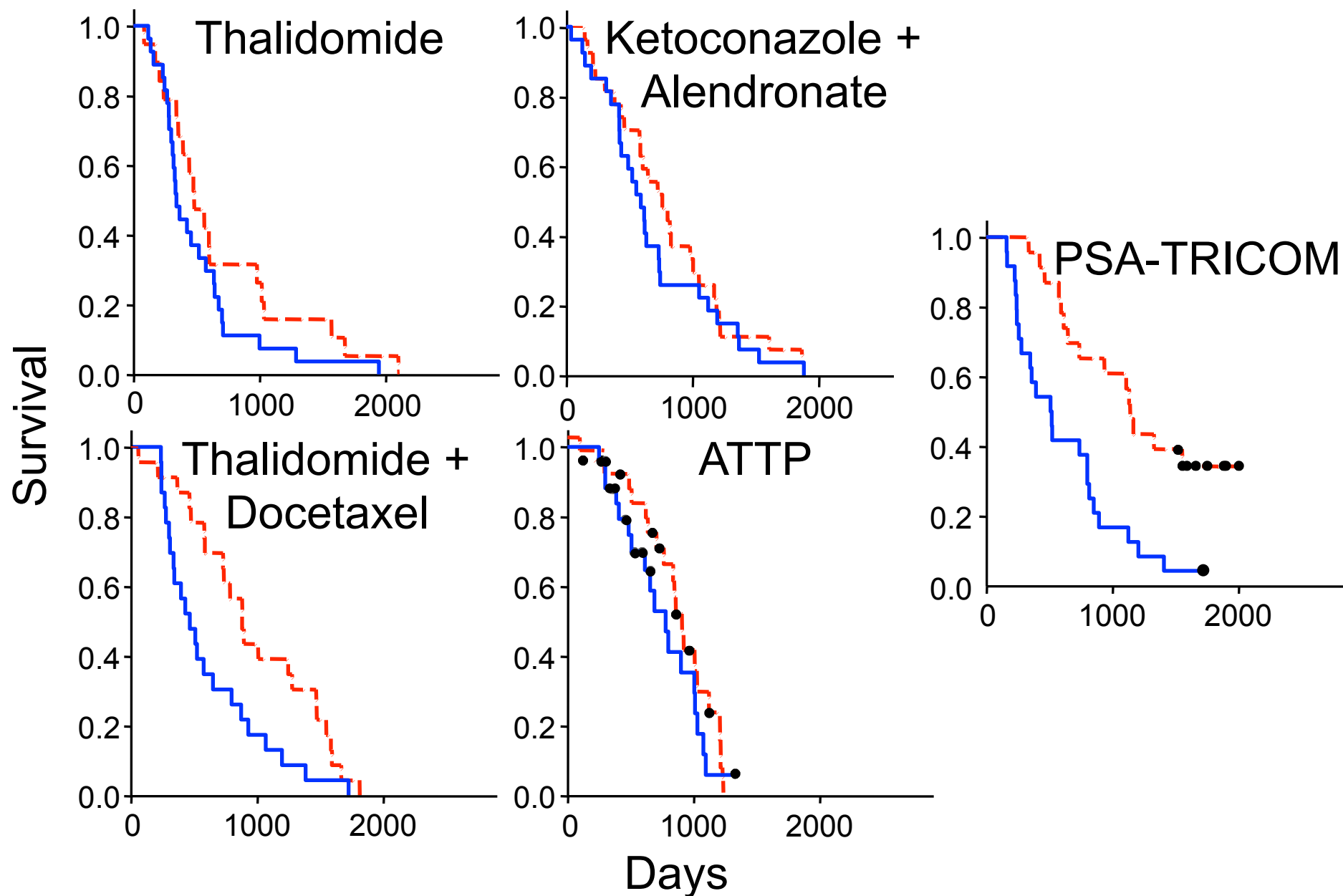
$R = 0.50$

$p < 0.0001$

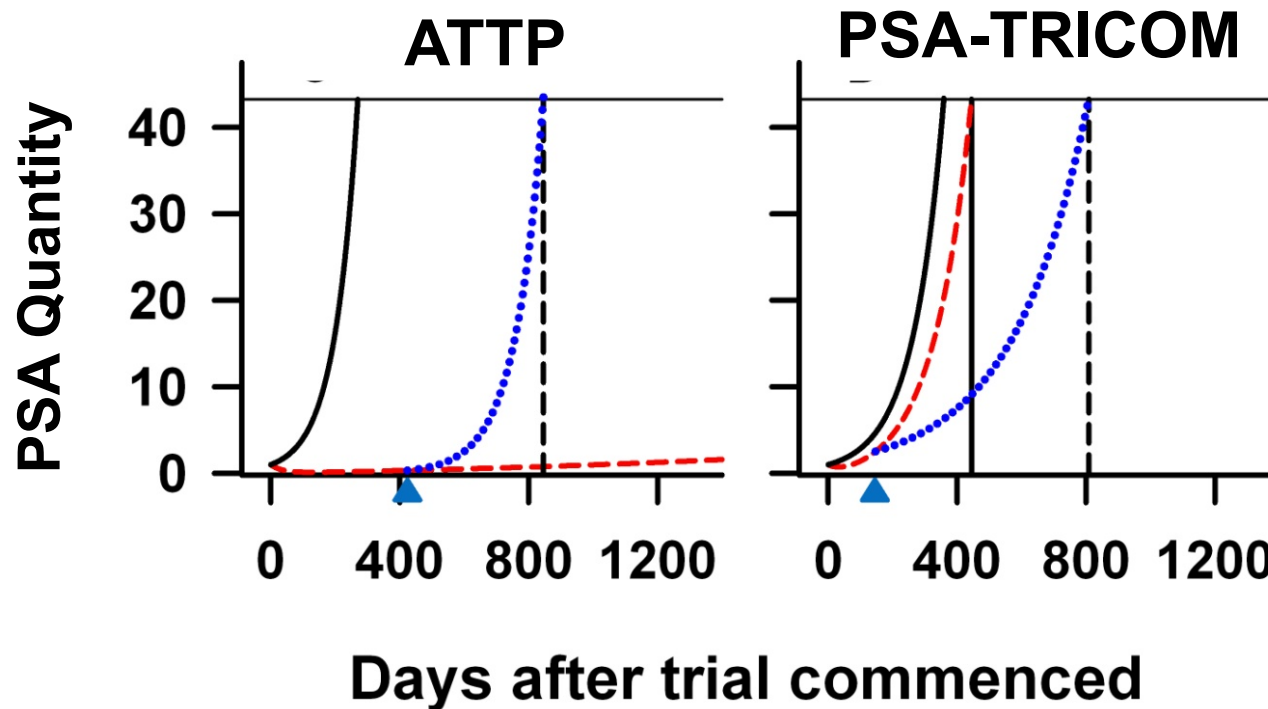


Prostate Cancer Trials at NCI: Kaplan Meier Survival Analyses

Stratified by initial PSA signal **above** and **below** median



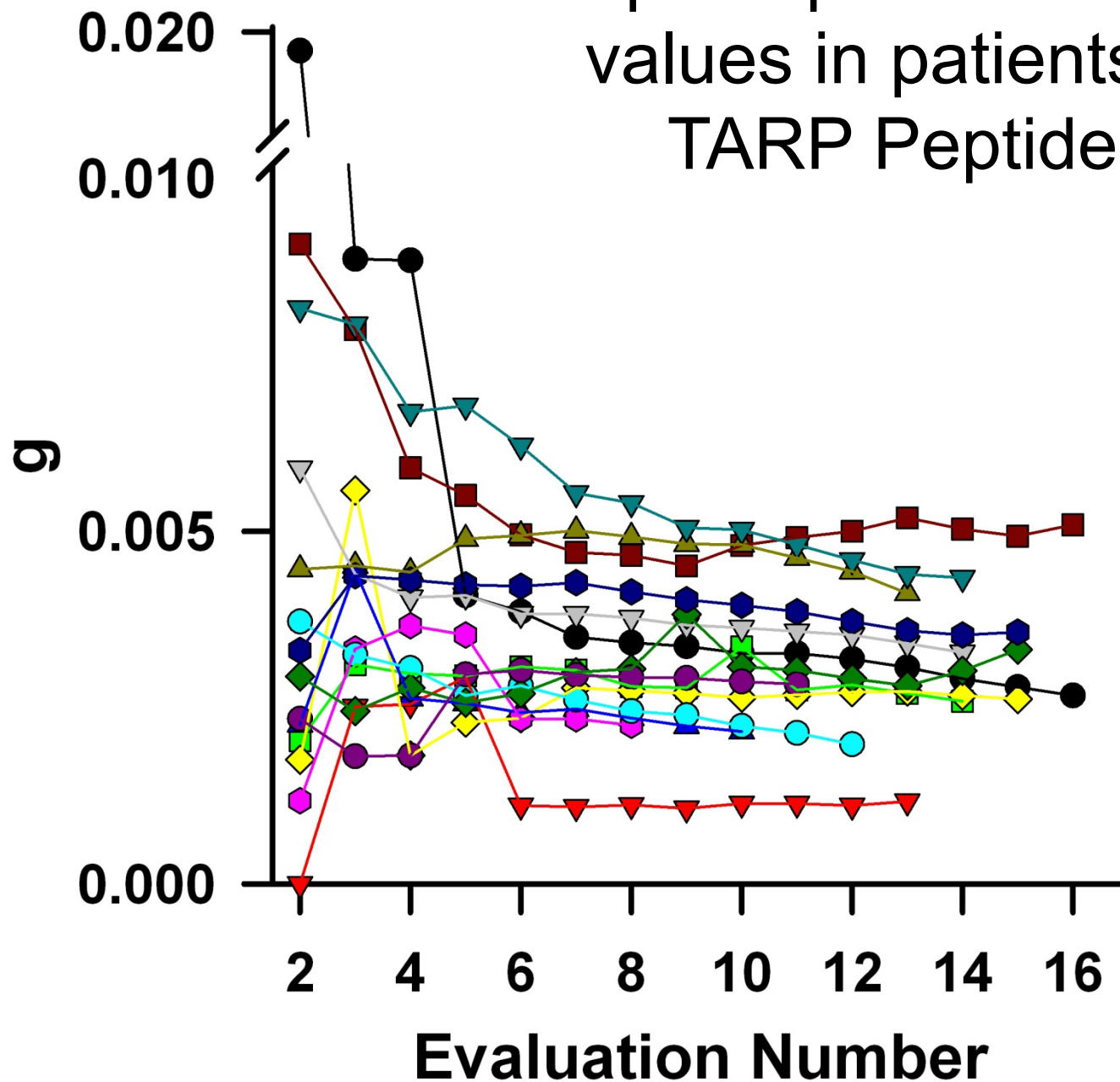
How can we account for the efficacy of the PSA-TRICOM vaccine?

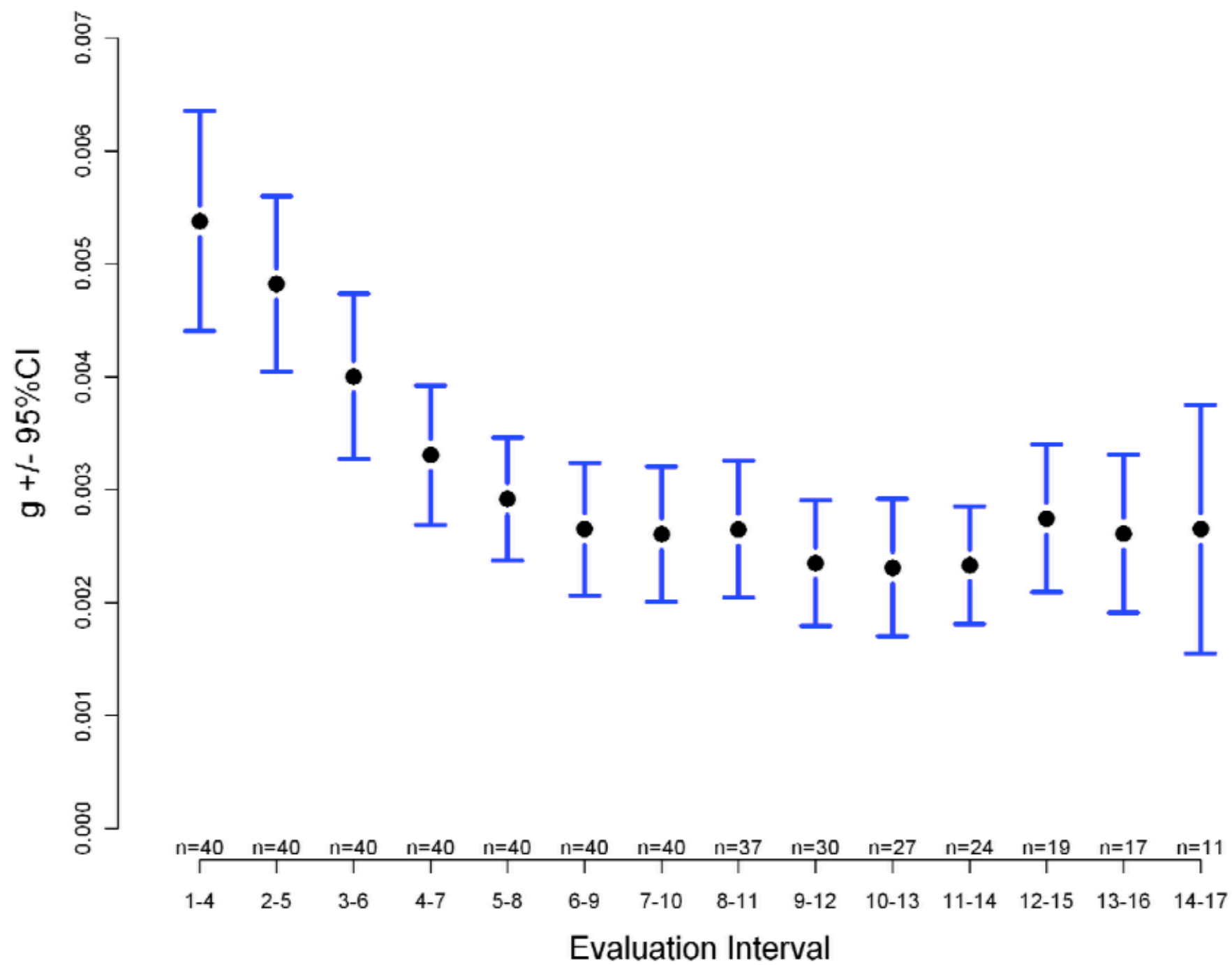


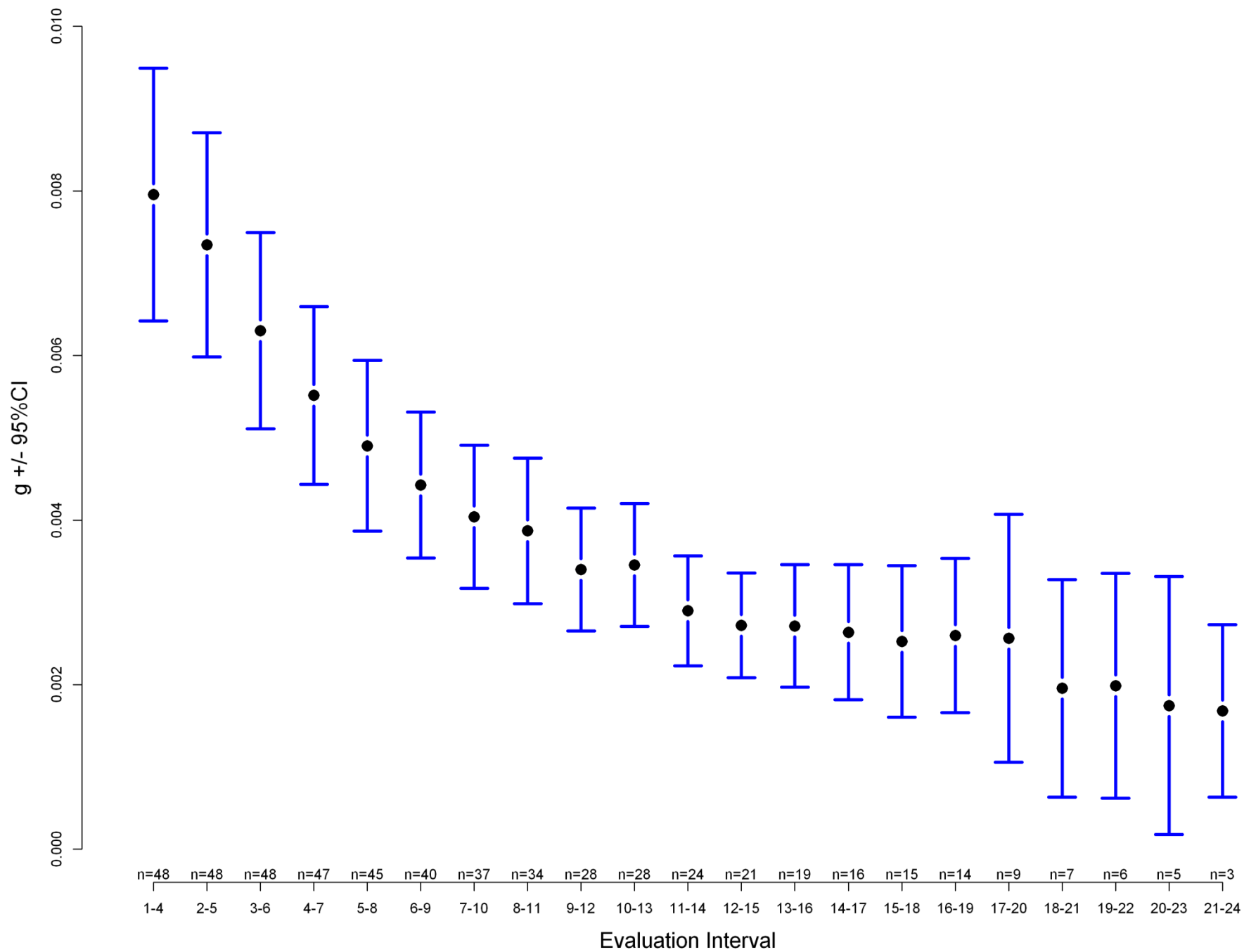
To accurately predict **survival**, the models require a marked slowing in the **measured** growth rate constant **after** PSA-TRICOM has been administered

Spider plot showing serial g values in patients receiving TARP Peptide Vaccine

Jay Berzofsky
Lauren Wood







Recap of Lessons Learned and Intuitions Gained from Applying Wilfred Stein's Analysis to Tumor Growth and Regression

- We can calculate a growth rate constant, g , and a regression constant, d , from data routinely obtained on a clinical trial
- Tumor quantity depends on time and g and d
- Effective therapies reduce the growth rate constant g
- g correlates with the FDA gold standard overall survival (**OS**)
- g is a better measure of therapeutic efficacy than response or stable disease rates

Stein's Analysis of Tumor Growth and Regression

- **d** does not correlate with **OS**
- As a continuous variable, **g** is better than **PFS**
- **g** can be determined over time, independent of trial design
- **Slowing g** is the most important factor in improving survival
- **g** can be measured before there is clinical evidence of tumor growth
- **g** can be determined in censored patients – in contrast to **PFS** – reducing bias
- The data suggest resistance is intrinsic

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Herb Kotz

Sam Wells

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Jeff Schlom

Ravi Madan

Yang-min Ning

Doug Price

Jay Berzofksy

Lauren Wood