Design Considerations in Studies of Rare Cancers

Mark F. Brady
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Warning, choices ahead

The 3-outcome design

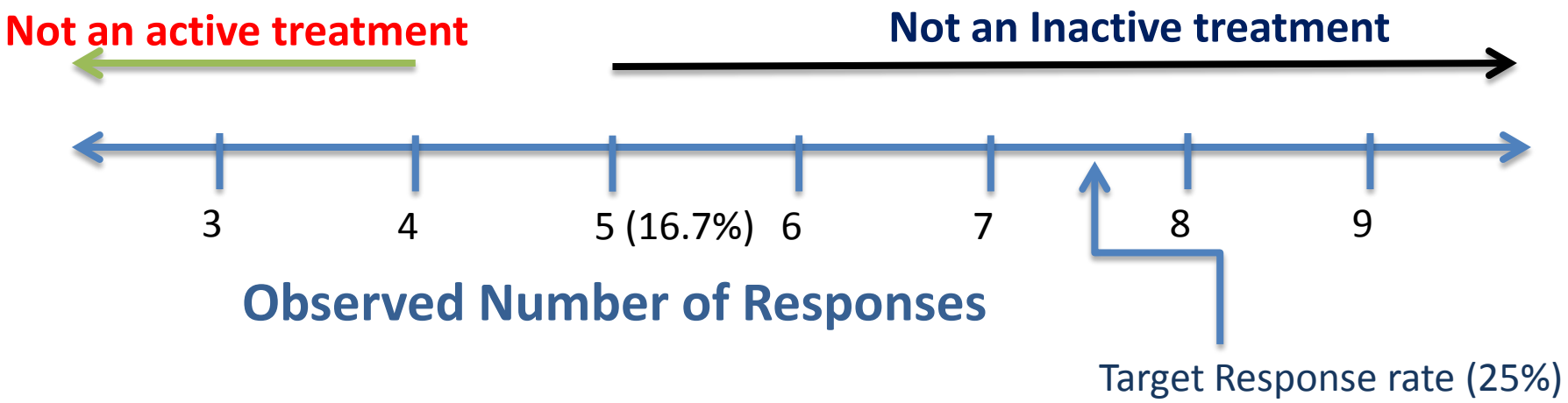
Assume we are planning a single-arm phase II study for a rare cancer

- **Probability of response for an inactive treatment = 10%**
- **Desire 90% power for detecting treatments with a response rate = 25%**

Standard two outcome design

Design option Type I error (α)	Minimum Sample Size (N)	Active Treatment Region R (% of responses)
0.10	40	≥ 7 (≥ 17.5%)
0.20	30	≥ 5 (≥ 16.6%)

Standard Two Outcome Design
Type I error = 0.20, Power=0.90, N=30



Assume we plan to conduct a clinical trial where

- **12% of new agents in the phase II setting are truly active.**

	Actual Activity of a New Agents		
	Active Agents	Inactive Agents	Total
Total	12	88	100

True Activity vs Expected Study Results

	Actual Activity of a New Agents		
Expected Study Finding	Active Agents	Inactive Agents	**Total**
Active		18	
Inactive		70	
Total	12	88	100

Assume the clinical trial is designed with

- **Type I error 20%**
- **Type II error 20%**

True Activity vs Expected Study Results

	Actual Activity of a New Agents		
Expected Study Finding	Active Agents	Inactive Agents	**Total**
Active	10	18	28
Inactive	2	70	72
Total	12	88	100

Assume the clinical trial is designed with

- **Type I error 20%**
- **Type II error 20%**

True Activity vs Expected Study Results

False Positive Rate when type I error is 0.20

	Actual Activity of a New Agents		
Study Finding	Active Agents	Inactive Agents	Total
Active	10	18	28
Inactive	2	70	72
Total	12	88	100

Assume the clinical trial is designed with

- **Type I error 20%**
- **Type II error 20%**

False positive rate: 18/28= 64% !!

Nearly 2 out of 3 treatments deemed active are expected to be NOT active.

True Activity vs Expected Study Results

False Positive Rate when type I error is 0.10

	Actual Activity of a New Agents		
Study Finding	Active Agents	Inactive Agents	Total
Active	10	9	19
Inactive	2	79	81
Total	12	88	100

Assume a single-arm phase II study with

- **Type I error 10%**
- **Type II error 20%**

False positive rate: 9/19= 47%

Less than 1 out of 2 treatments deemed active is expect to be not active.

Assume we are planning a single-arm phase II study

- **Response rate for an inactive treatment = 0.10**
- **Desire 90% power for detecting treatments with a response rate = 0.25**

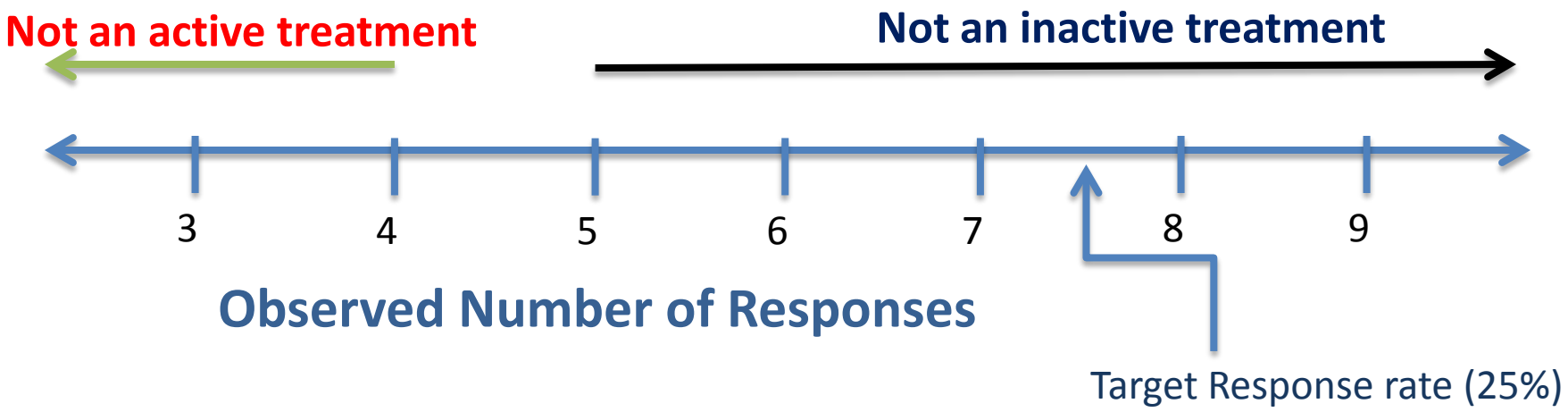
Standard two outcome design

Design option Type I error (α)	Minimum Sample Size	Active Treatment Region (N of responses)
0.10	40	≥ 7 (≥ 17.5%)
0.20	30	≥ 5 (≥ 16.6%)

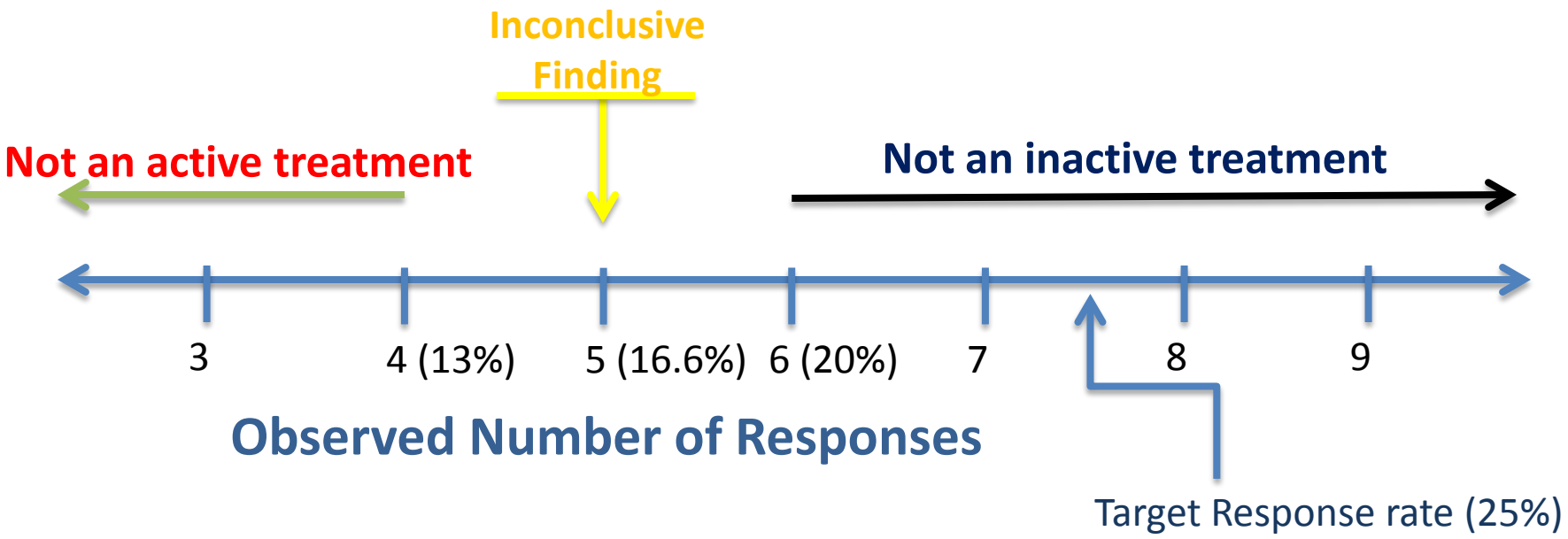
Three outcome design

Design option Type I error (α)	Minimum Sample Size	Active Treatment Region (N of responses)
0.10	30	≥ 6 (≥ 20%)

Standard Two Outcome Design
Type I error = 0.20, β=0.10, N=30



Three Outcome Design
Type I error = 0.10, β =0.10, N=30



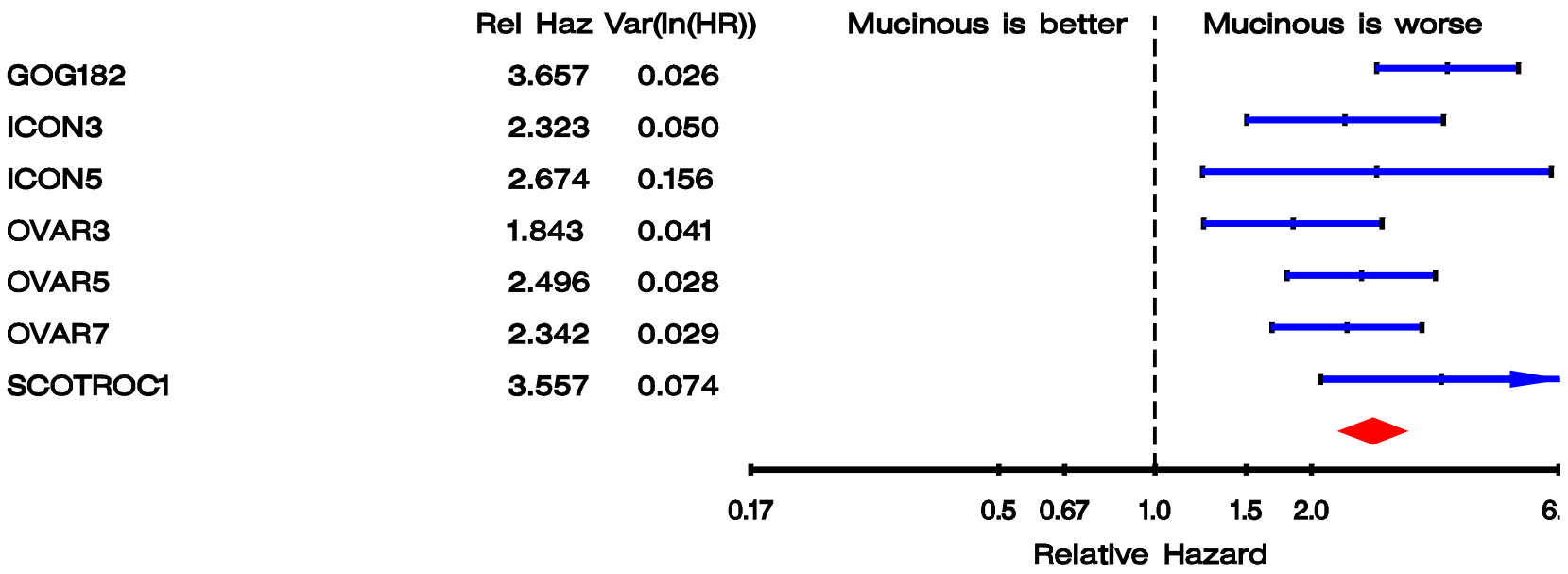
Prob (Inconclusive finding | Ha) = 0.10

Is there a place for single-arm phase II trials in rare Gynecologic cancers?

Proportion of patients with Mucinous adenocarcinoma in GCIG Trials

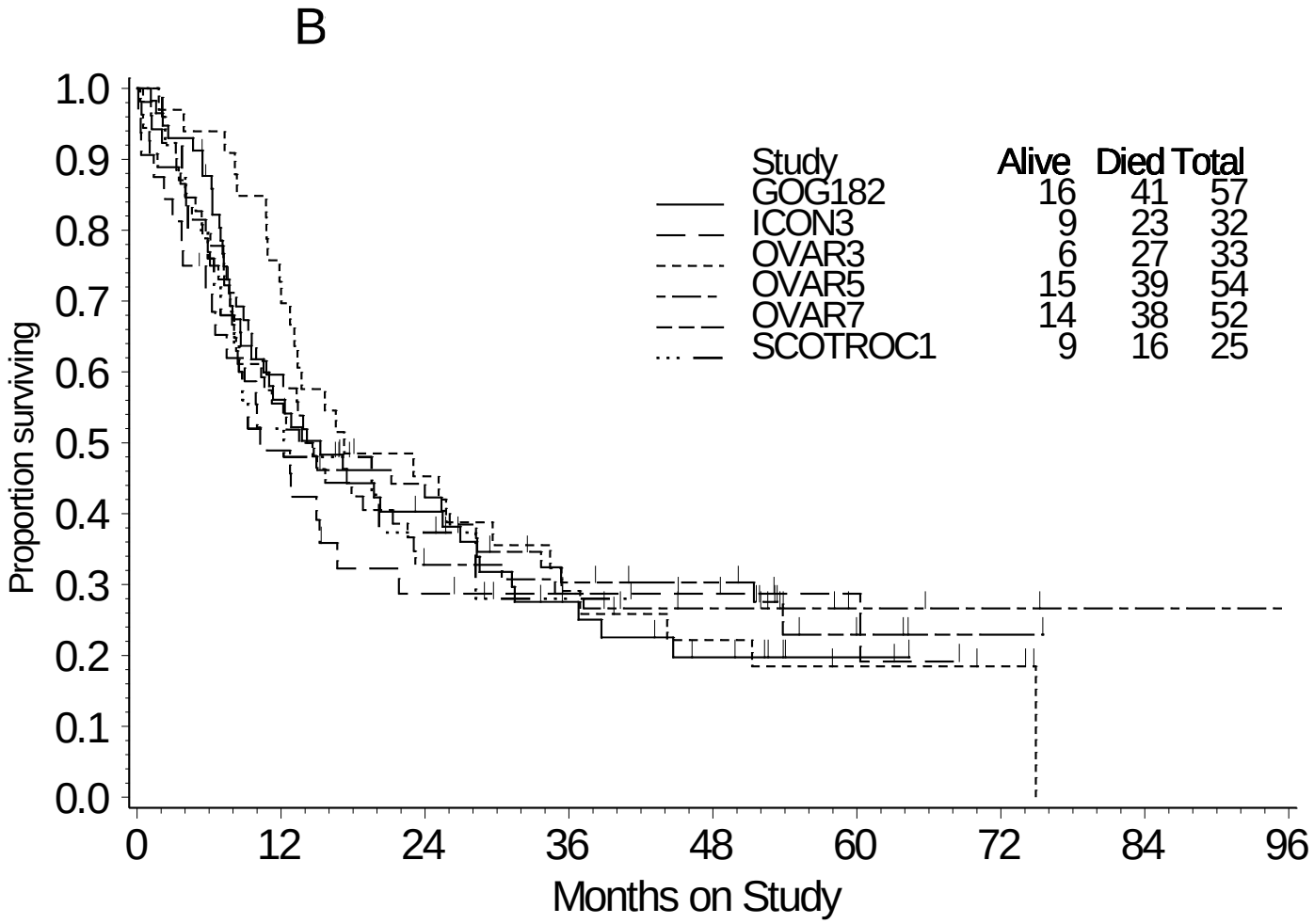
GCIG Group	Study	Total N of patients	% with Mucinous
AGO	OVAR3	705	4.7
AGO/GINECO	OVAR5	1136	4.7
AGO/GINECO	OVAR7	1170	4.4
GOG/ANZGOG	GOG-182	3882	1.5
MRC/Mango/IMN/NSGO	ICON3	567	5.6
MRC/IMN	ICON5	363	3.0
SGCTG	SCOTROC-1	881	2.8
Total Number		8704	3.0

OS Hazard Ratios by Study – Mucinous vs Serous adenocarcinoma of Ovary



Estimated relative hazard is adjusted for residual disease, stage and age.

Overall Survival by Study – Mucinous adenocarcinoma of Ovary



Thank you

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