TO-PARP - CRUK/11/029
Olaparib in Castration Resistant Prostate Cancer
Adaptive Phase II design

Roger A'Hern

ICR Clinical Trials and Statistics Unit (ICR-CTSU)
Institute of Cancer Research

TO-PARP CI: Johann de Bono; Scientific Lead : Emma Hall

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- Olaparib (Astra-Zeneca) – PARP inhibitor
- Exploits synthetic lethality in Cancers with DNA repair defects
- Need to identify a group of patients likely to have a survival benefit from olaparib to be assessed in an RCT at Phase III
- Only a high response rate (50%+) thought to be associated with a survival benefit

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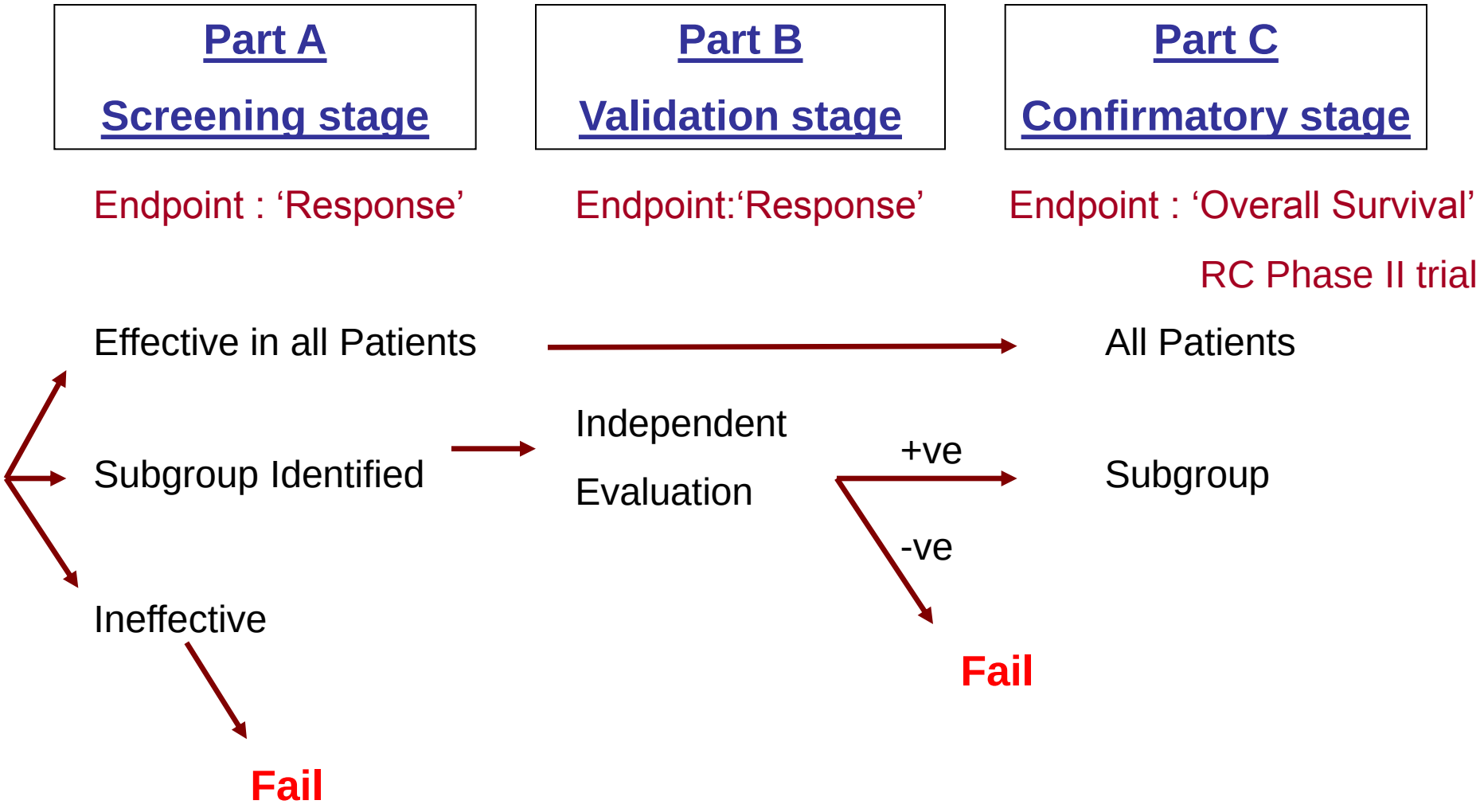

Part A
Screening stage
Part B
Validation stage
Part C
Confirmatory stage
Endpoint : 'Response'
Endpoint:'Response'
Endpoint : 'Overall Survival'
RC Phase II trial
Effective in all Patients
All Patients
Subgroup Identified
Independent
Evaluation
+ve
Subgroup
-ve
Ineffective
Fail
Fail

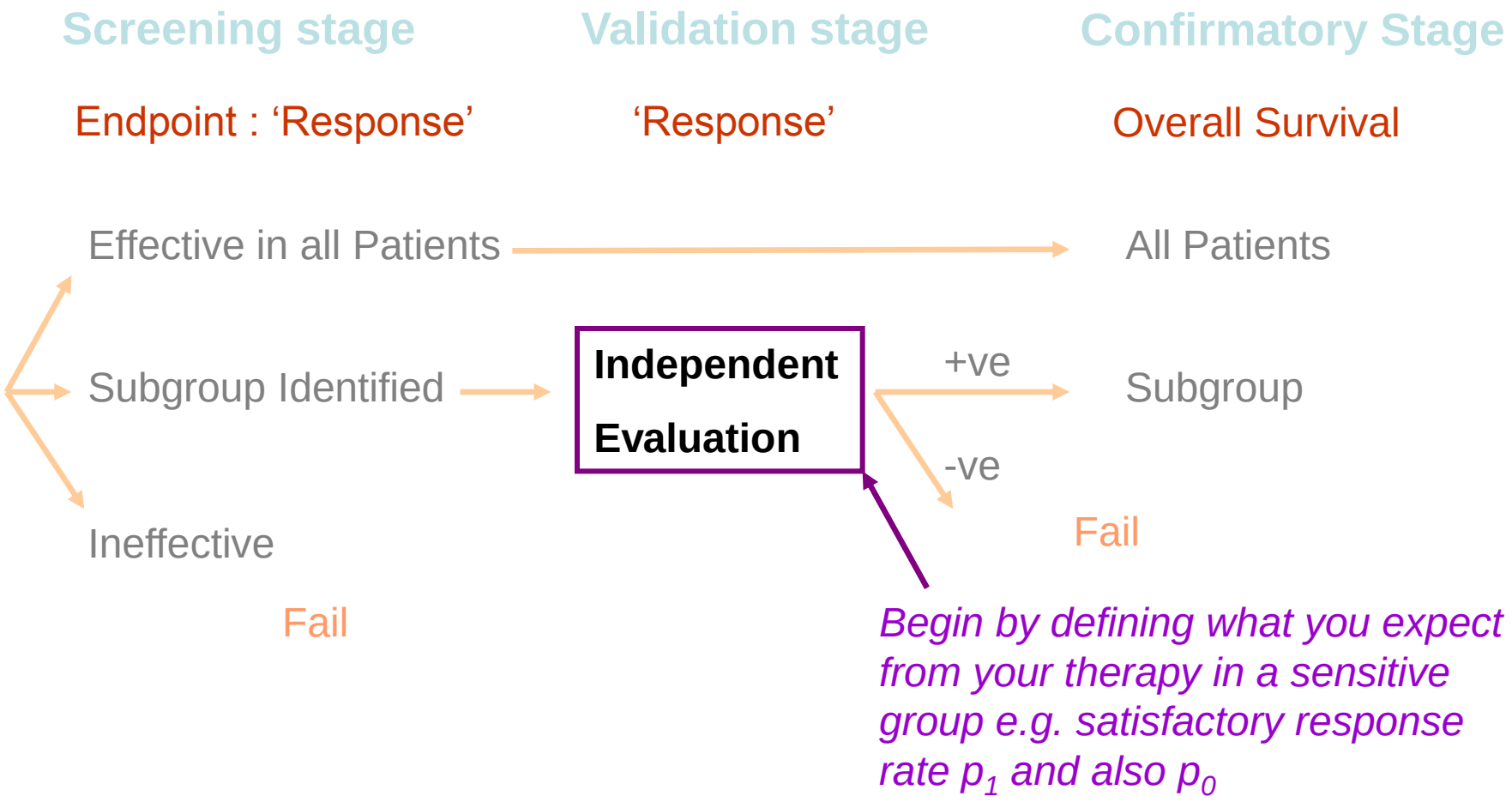
Definition of response

- Phase II rationale – *response likely to be due to therapy*
- Response by RECIST (decrease in measurable lesion size(s)) or
- Response by PSA fall (50% for 28d min) or
- Response by CTC fall (≥5 to <5 per ml of blood)

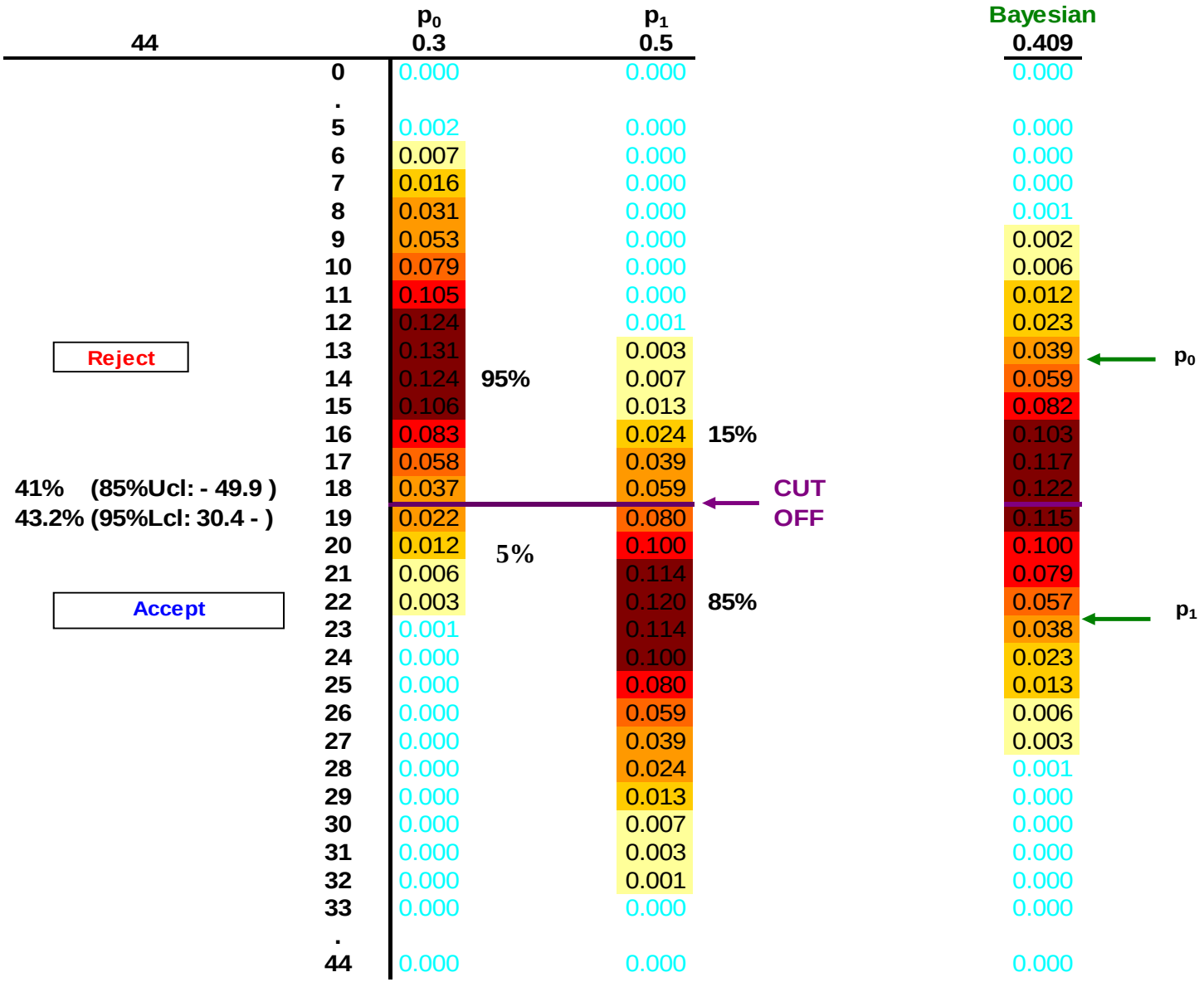
FAILURE :

- Progression by RECIST - increase in measurable lesion size(s) or new lesion

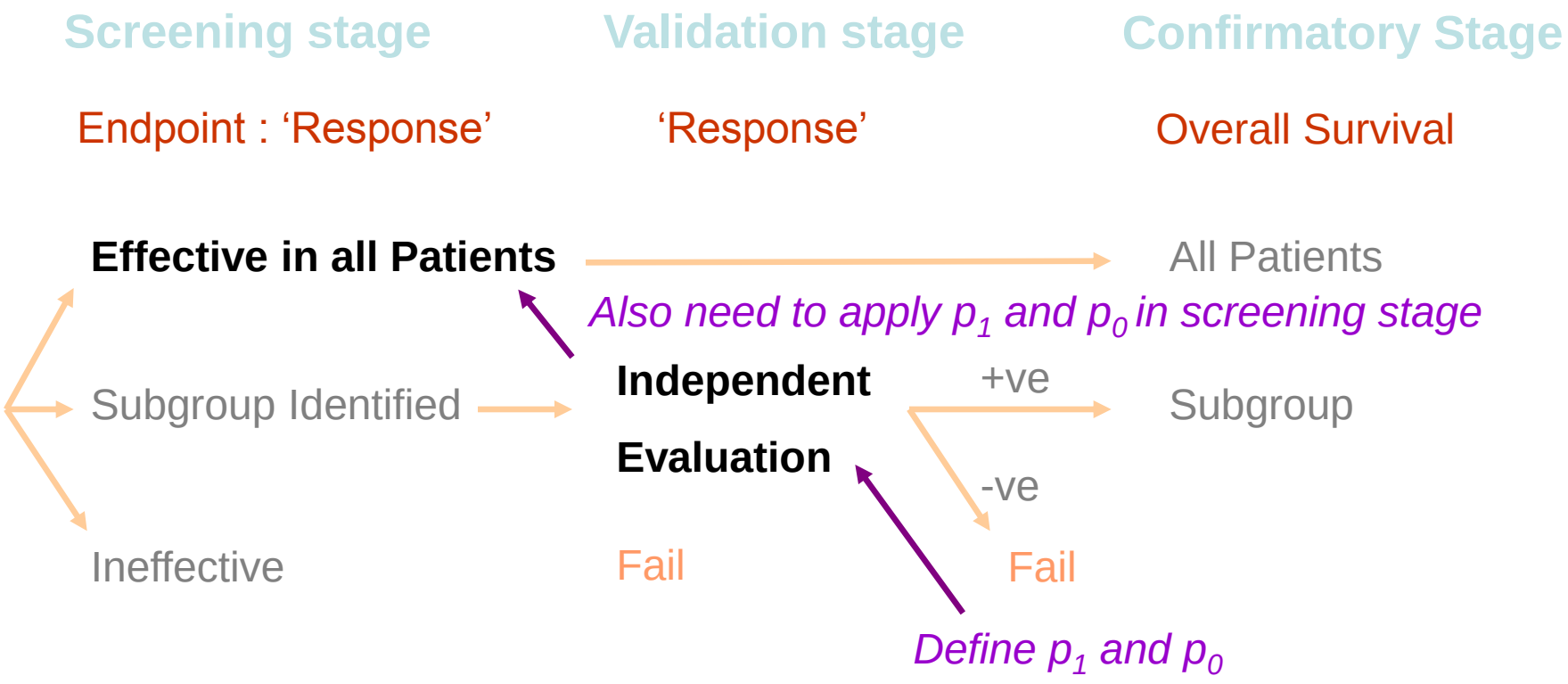
Selection of p_1 and p_0



Validation Stage



Screening Stage



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Screening Stage choice of basal p_1

If the sensitive subgroup, with a response rate of 50%, comprised 20% of patients and the remaining patients had a response rate of 30%, then the overall response rate would be 34%

$$0.2 \times 0.5 + 0.8 \times 0.3 = 34\%$$

$$0.4 \times 0.5 + 0.6 \times 0.1 = 26\%$$

$$0.1 \times 0.5 + 0.9 \times 0.05 = 9.5\%$$

$$0.3 \times 0.5 + 0.7 \times 0.1 = 22\%$$

Screening Stage choice of basal p_1 and p_0

	p_1	p_0
0.2 x 0.5 + 0.8 x 0.3	= 34%	---- 0.2 x 0.3 + 0.8 x 0.3 = 30%
0.4 x 0.5 + 0.6 x 0.1	= 26%	---- 0.4 x 0.3 + 0.6 x 0.1 = 18%
0.1 x 0.5 + 0.9 x 0.05	= 9.5%	---- 0.1 x 0.3 + 0.9 x 0.05 = 7.5%
0.3 x 0.5 + 0.7 x 0.1	= 22%	---- 0.3 x 0.3 + 0.7 x 0.1 = 16%

Difficult! Solution - do best possible : p_1=20%, p_0=5%

Making p_1 as low as possible and p_0 as high as possible

(also not interested in subgroups of size 10%)

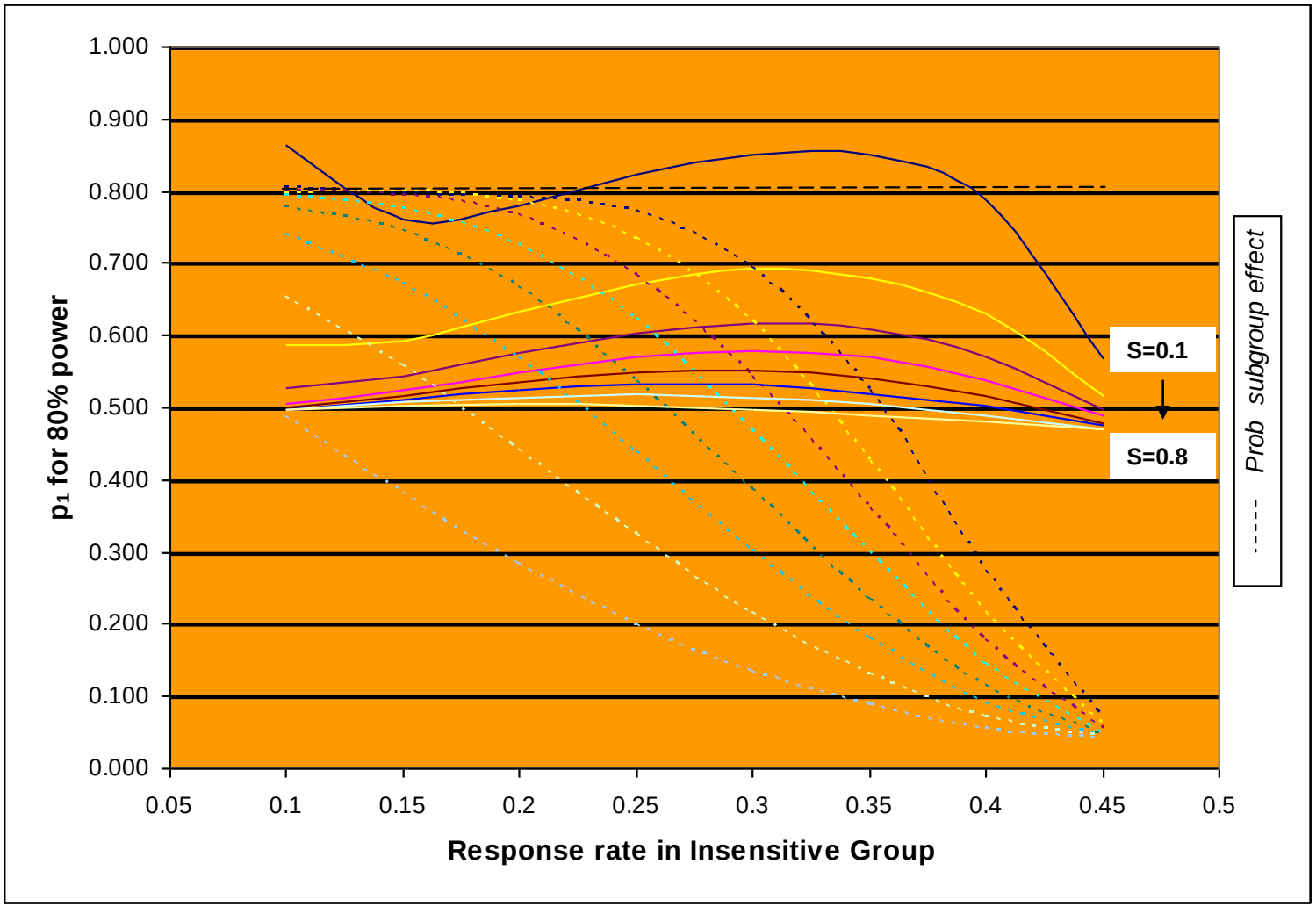
Use a two stage design to allow early rejection for inefficacy

Part A, Screening Stage : Outcome Space

	15		s1	0.6	s0	0.3	s	0.3	p	0.39						
0.39	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	R1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
3	R2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
4		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
5	0.000	0.000	0.000	0.000	0.001	0.001	0.001	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000
6	0.000	0.000	0.000	0.001	0.002	0.003	0.003	0.002	0.002	0.001	0.000	0.000	0.000	0.000	0.000	0.000
7	0.000	0.000	0.001	0.002	0.004	0.006	0.007	0.005	0.003	0.002	0.001	0.000	0.000	0.000	0.000	0.000
8	0.000	0.000	0.002	0.004	0.008	0.011	0.012	0.010	0.006	0.003	0.001	0.000	0.000	0.000	0.000	0.000
9	0.000	0.001	0.002	0.007	0.013	0.018	0.019	0.016	0.010	0.005	0.002	0.001	0.000	0.000	0.000	0.000
10	0.000	0.001	0.003	0.009	0.017	0.024	0.026	0.021	0.013	0.007	0.003	0.001	0.000	0.000	0.000	0.000
11	0.000	0.001	0.004	0.010	0.020	0.028	0.030	0.024	0.016	0.008	0.003	0.001	0.000	0.000	0.000	0.000
12	0.000	0.001	0.004	0.010	0.020	0.028	0.030	0.025	0.016	0.008	0.003	0.001	0.000	A2	0.000	0.000
13	0.000	0.001	0.003	0.009	0.018	0.025	0.027	0.022	0.014	0.007	0.003	0.001	0.000	0.000	0.000	0.000
14	0.000	0.001	0.003	0.007	0.014	0.019	0.021	0.017	0.011	0.005	0.002	0.001	0.000	0.000	0.000	0.000
15	0.000	0.000	0.002	0.005	0.009	0.013	0.014	0.012	0.007	0.004	0.001	0.000	0.000	0.000	0.000	0.000
16	0.000	0.000	0.001	0.003	0.006	0.008	0.008	0.007	0.004	0.002	0.001	0.000	0.000	0.000	0.000	0.000
17	0.000	0.000	0.001	0.002	0.003	0.004	0.004	0.004	0.002	0.001	0.000	0.000	0.000	0.000	0.000	0.000
18	0.000	0.000	0.000	0.001	0.001	0.002	0.002	0.002	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.000
19	0.000	0.000	0.000	0.000	0.001	0.001	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
20	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
21	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
22	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
23	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
24	0.000	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
25	0.000	0.000	0.000	0.000	0.000	0.000	0.000	A1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
26	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
27	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
28	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
29	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
30	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

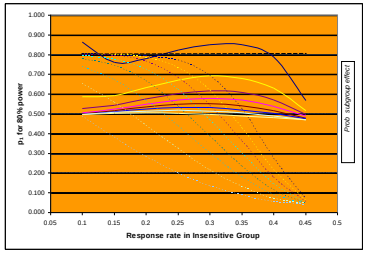
Detectable Effects

P-value ≤ 0.10, Fisher's Exact, s= sensitive proportion



Steps involved

- Decide on p_1 and p_0 in validation stage
- Make screening stage of similar size or larger
- Choose basal p_1 and p_0 for screening stage
- Look at overall performance
- No good? Reiterate



Selection of biomarkers

- In current context well defined
- Generally would use a false discovery rate (p=10%) for state of ‘ignorance’
- Size of screening stage would be dependent on information available from other sources
- Cancer : Move to treating the biological defect not the specific tumour type ‘Predictive Medicine’ - can use information from other cancer types

Selection of biomarkers

- Backward selection (45/10 ~ 5)
- Informal meta-analytic (Bayesian?) approach

Sensitivity may be too rare to detect in Phase II trials e.g. Imatinib in c-Kit mutated metastatic melanoma

- First two trials unselected n=41, found no responses, poor OS
- Case report of responding Patient with mutation in Exon 11

Correlations of Response and *c-Kit* Aberrations

c-Kit status	No. of Patients	PR		SD		PR + SD	
		No.	%	No.	%	No.	%
c-Kit amplification	3	1	33.3	0		1	33.3
c-Kit mutation							
Exon 9	3	0		2	66.7	2	66.7
Exon 11	17	6	35.3	5	29.4	11	64.7
Exon 13	9	3	33.3	1	11.1	4	44.4
Exon 17	5	0		2	40.0	2	40.0
Exon 18	6	0		3	50.0	3	50.0
Multiple aberrations*	5	3	60.0	2	40.0	4	100.0

Guo et al, J Clin Oncol 29:2904-2909

Thanks

Clinical – Experimental Cancer Medicine

- Johann De Bono
- Shahneen Sandhu

ICR-CTSU

- Emma Hall
- Ria Kalaitzaki
- Martine Usdin

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