Transition from phase II to shortening treatment

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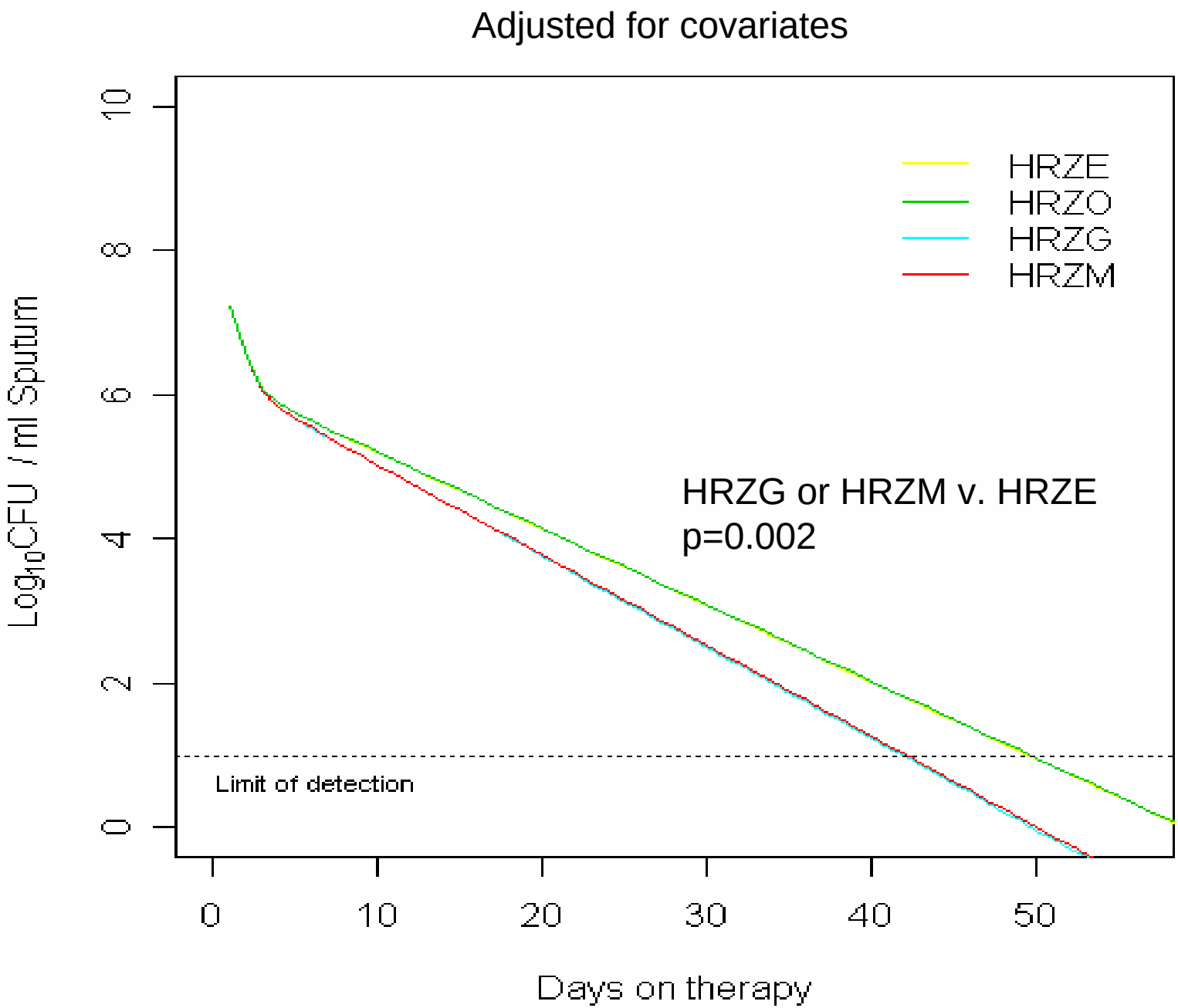
Relapse rates after short duration regimens of HRZ

Duration	No. of patients	Failure/ No.	Relapse %	95% CI
6*	347	17	5	
4.4-5**	465	17	3	2-6
4**	364	93	12	9-16
3**	307	41	13	10-18

* Jindani, Nunn & Enarson, Lancet 2004, 364, 1244.

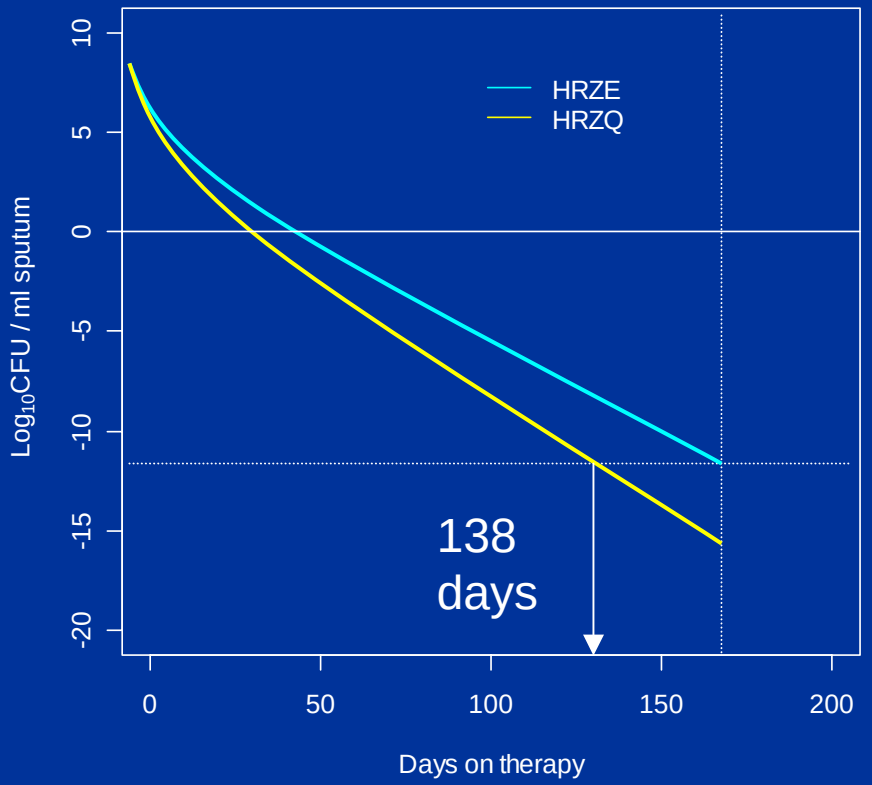
** Fox, W. Brit J Dis Chest 1981, 75, 331.


Adjusted for covariates
HRZE
HRZO
HRZG
HRZM
HRZG or HRZM v. HRZE
p=0.002
Limit of detection
Log10CFU / ml Sputum
0
2
4
6
8
10
0
10
20
30
40
50
Days on therapy

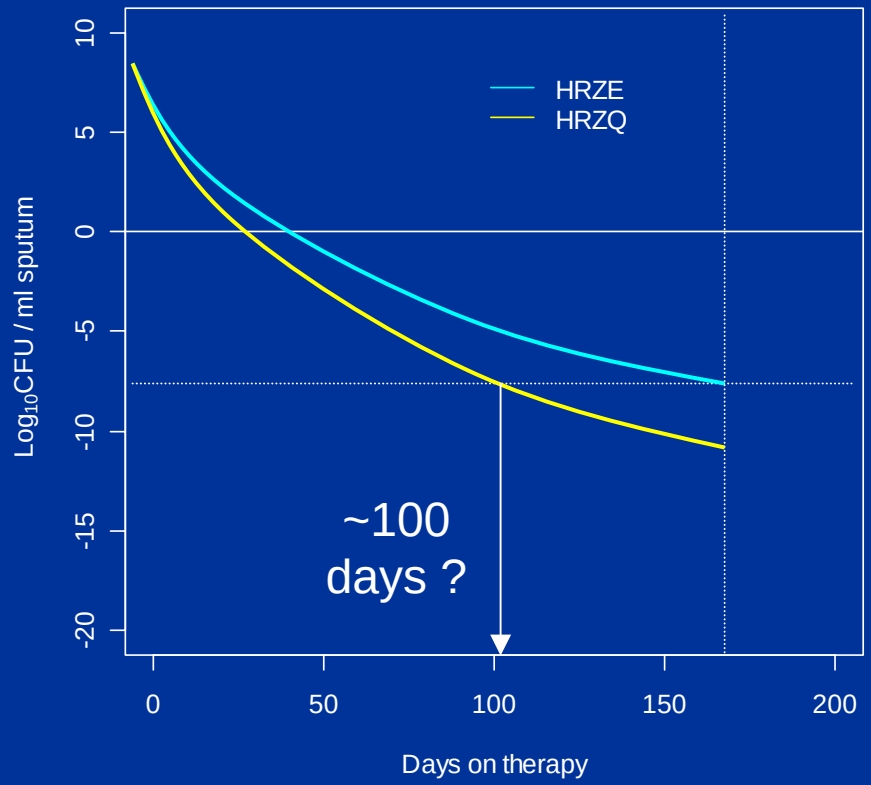
Can we extrapolate from 8 weeks onwards?

1. The linearity of the bi-exponential fit near 8 weeks is uncertain.
2. PZA does not sterilize after 8 weeks, so rate of kill is less.
3. Residual population may be more difficult to kill.

Forecasting duration of therapy by extrapolation

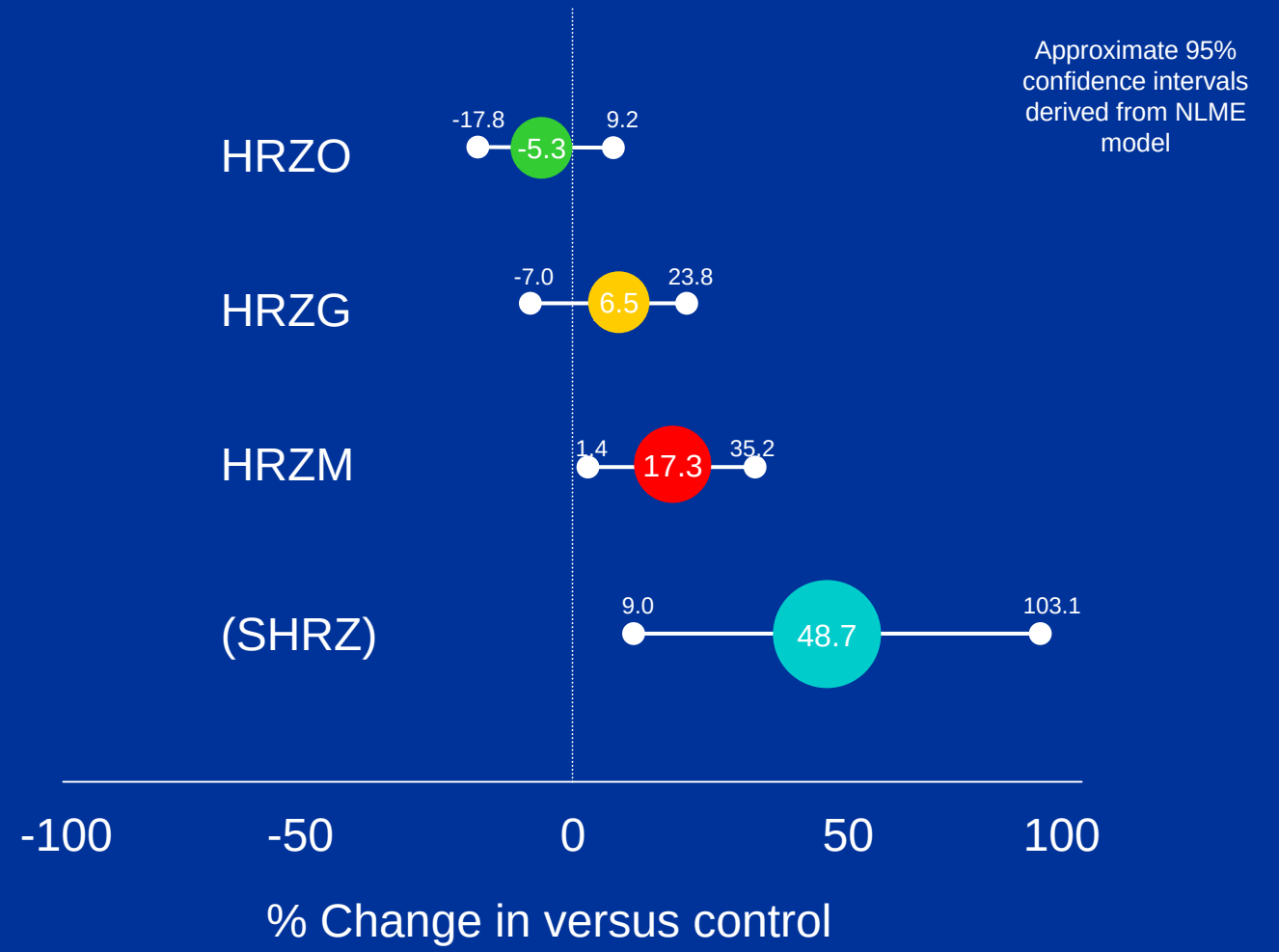


Biexponential model



Triexponential model

Forecasting duration of therapy by effect size



Measuring duration of treatment

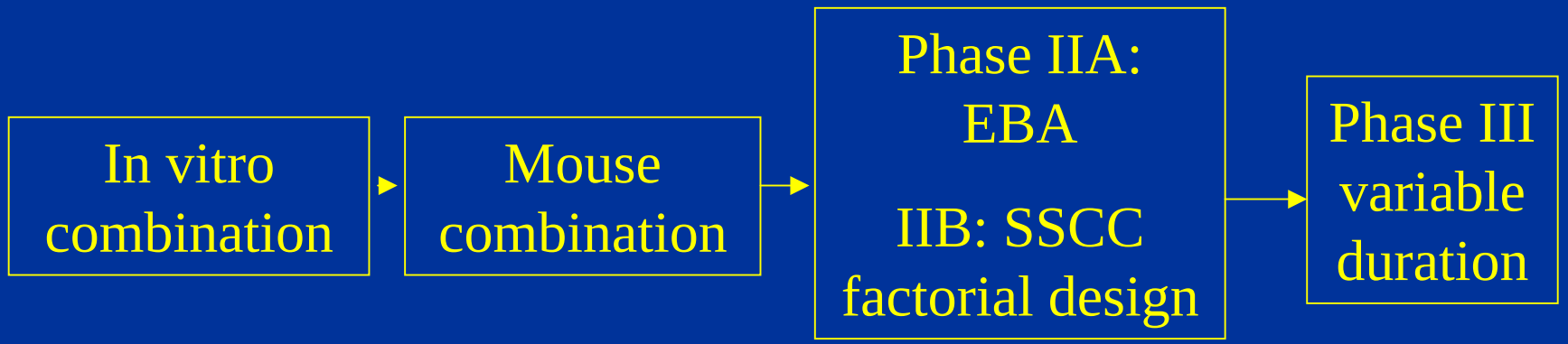
BMRC East African Studies

Study	Regimen	No. of patients	Duration (months)	Relapse rate (%)
1	2SHRZ/TH	75	6	13
		81	8	0
	1SHRZ/TH	79	6	18
		58	8	7
	1SHRZ/$(SHZ)_3$	75	6	9
		86	8	2
2	2SHRZ/H	156	6	10
		123	8	3

New Phase IIIA study design

	Duration (months)	No. of patients
New drug combinations	3	250
	4	250
	5	250
Control (2HRZE/4HR)	6	350
	Total	1100

Possible progression of drug assessments



Other biomarkers ?

As a good surrogate (i.e. able to forecast), the biomarker must:

1. Be found to correlate with relapse.
2. Not be affected by factors other than treatment (no heterogeneity).
3. Be examined in several clinical trials.