Cancer Biomarkers: Hope, Hype or Help. Does the past predict the future?

ECMC Quality Assurance & Translational Science Network Group

10th Anniversary Symposium of the ECMC QATS Network Group

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Definitions

- Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

- Clinical endpoint: A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

- Surrogate endpoint: A biomarker intended to substitute for a clinical endpoint.

(NIH recommended definitions, 2001; Controlled Clinical Trials 22:485–502 (2001))

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Types of Biomarkers

- ***Risk/Predisposition biomarkers:*** These identify individuals at increased risk of developing disease and can be identified in large population based studies, clinical trials or family studies, where examples include genetic screening for cancer pre-disposition genes such as BRCA1/2, APC or MLH1.

- ***Screening biomarkers:*** These aid in identifying disease at early stage and can be developed in large population based studies and/or clinical trials; an example being PSA for prostate cancer.

- ***Diagnostic biomarkers:*** These are used to define the presence of disease. They can be developed from large population based studies or from clinical trial data. Diagnostic biomarkers could also be used to detect recurrent disease after primary therapy. An example of this biomarker category is mammogram for breast cancer

- ***Prognostic biomarkers:*** These indicate the likely course of the disease. Prognostic biomarkers can guide treatment decisions; i.e. cancer patients with prognostic biomarkers that predict a poor outcome could be selected for aggressive treatments to increase their chance of survival, whereas patients with biomarkers predicting a good outcome could be spared unnecessary treatments. For example, intensive combination adjuvant chemotherapy is appropriate for patients with extensive lymph node involvement – a poor prognostic biomarker - as opposed to lymph node negative breast cancer.

- ***Predictive biomarkers:*** These biomarkers identify subpopulations of patients who are most likely to respond to a given therapy. For example, breast cancer patients with oestrogen receptor positive tumours are more likely to respond to anti-endocrine therapies, and only patients with HER2 amplification should be given trastuzumab (Herceptin) therapy.

- ***Pharmacological biomarkers:*** These measure the effects of a drug treatment on a specific target. Such pharmacodynamic biomarkers can only be fully interpreted with the corresponding pharmacokinetic data.

Pharmacodynamic Biomarkers: The ho(y)pe

Question	Result
Does it hit the target in man ?	Go/ No go Proof of mechanism (PoM) e.g. enzyme inhibition, receptor blockade
Does it have an effect on the disease phenotype?	Go/ No Go Proof of Principle (PoP) e.g.Increased cell death markers (apoptotic markers- eg. TuNeL),
Does this result in a beneficial clinical effect?	Go/ No Go Proof of Concept (PoC) e.g. Tumour size reduction,

Progressive reduction of uncertainty about effects

Increasing level of confidence about outcomes

No guarantee of Success: rather Staged risk management

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Pharmacodyanmic Biomarkers: Helping decision making

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Question to FDA & EMEA:

Do you agree that conceptually pharmacodynamic biomarkers offer utility to drug development decisions with respect to

-making go/no go decisions
-defining MBED
-guiding optimal schedule

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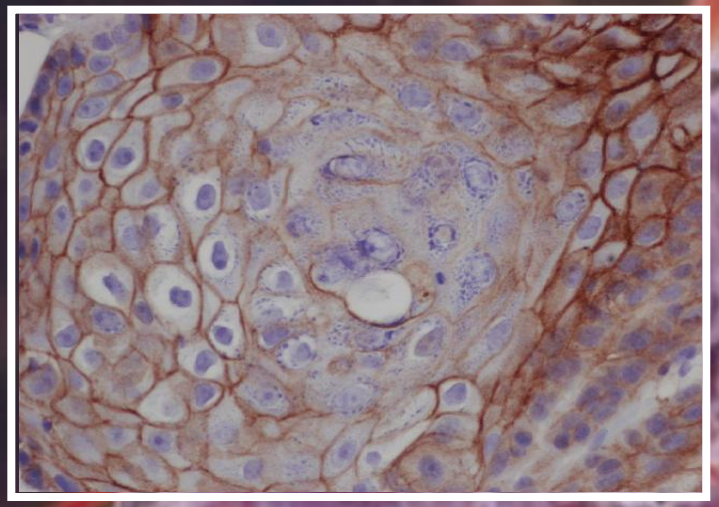
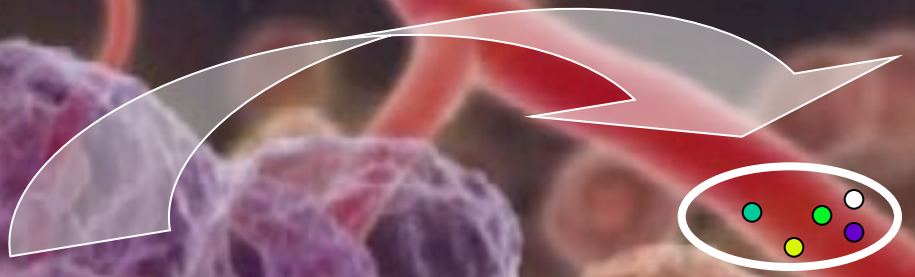
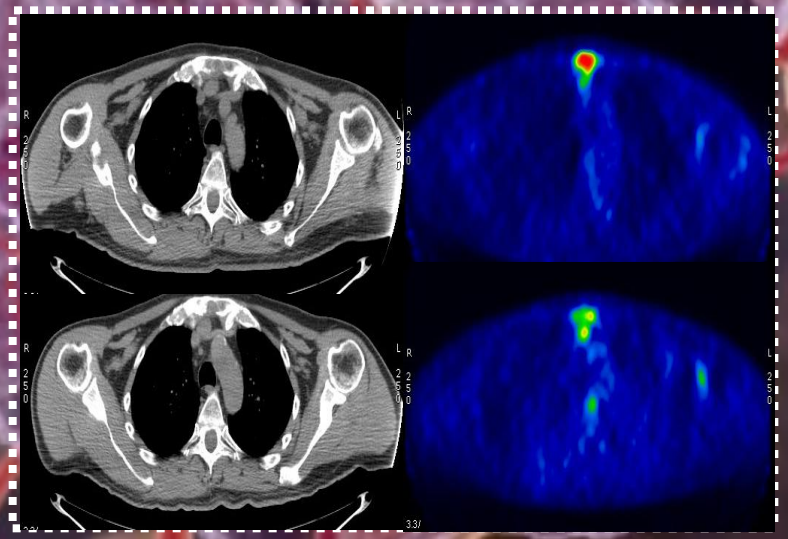
Histopathology





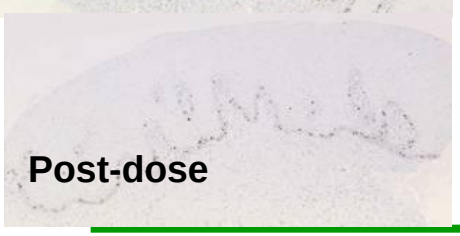
Blood Borne



Imaging

Go/No Go: Losing a loser

(AZD5438; 2005)



Convincing biological activit

Maximum Tolerated Single dose
In volunteers

Maximum Tolerated Repeat dose
In patients

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B. Vose: Annual Business Review Day: 2004, 2006

Go/No Go: Picking a winner

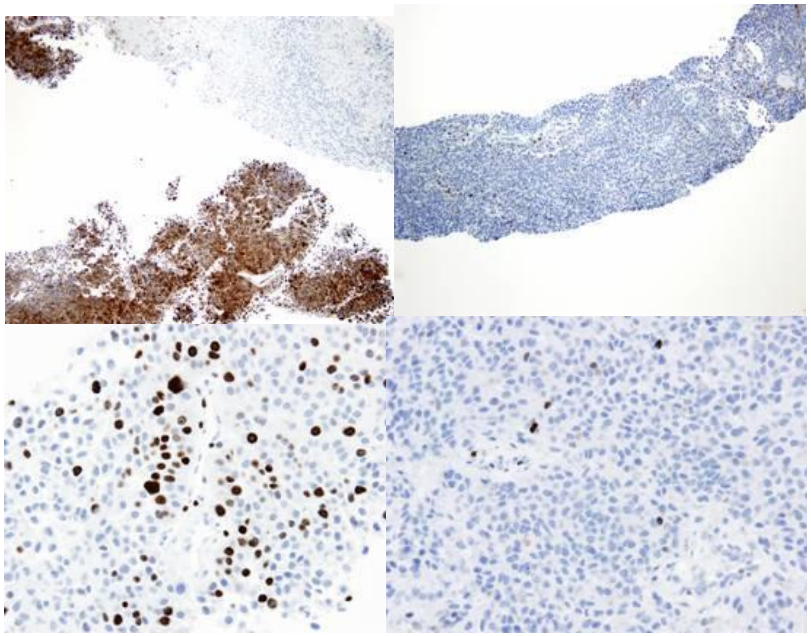
(AZD6244; 2005)

Response	Stable Disease	Progression

Pre-dose Post-dose

Drug target
-pERK

Tumour growth
-Ki67 proliferation



B.Vose: Analyst Briefing 2006

A. Adjei: NCI-EORTC-AACR 2006

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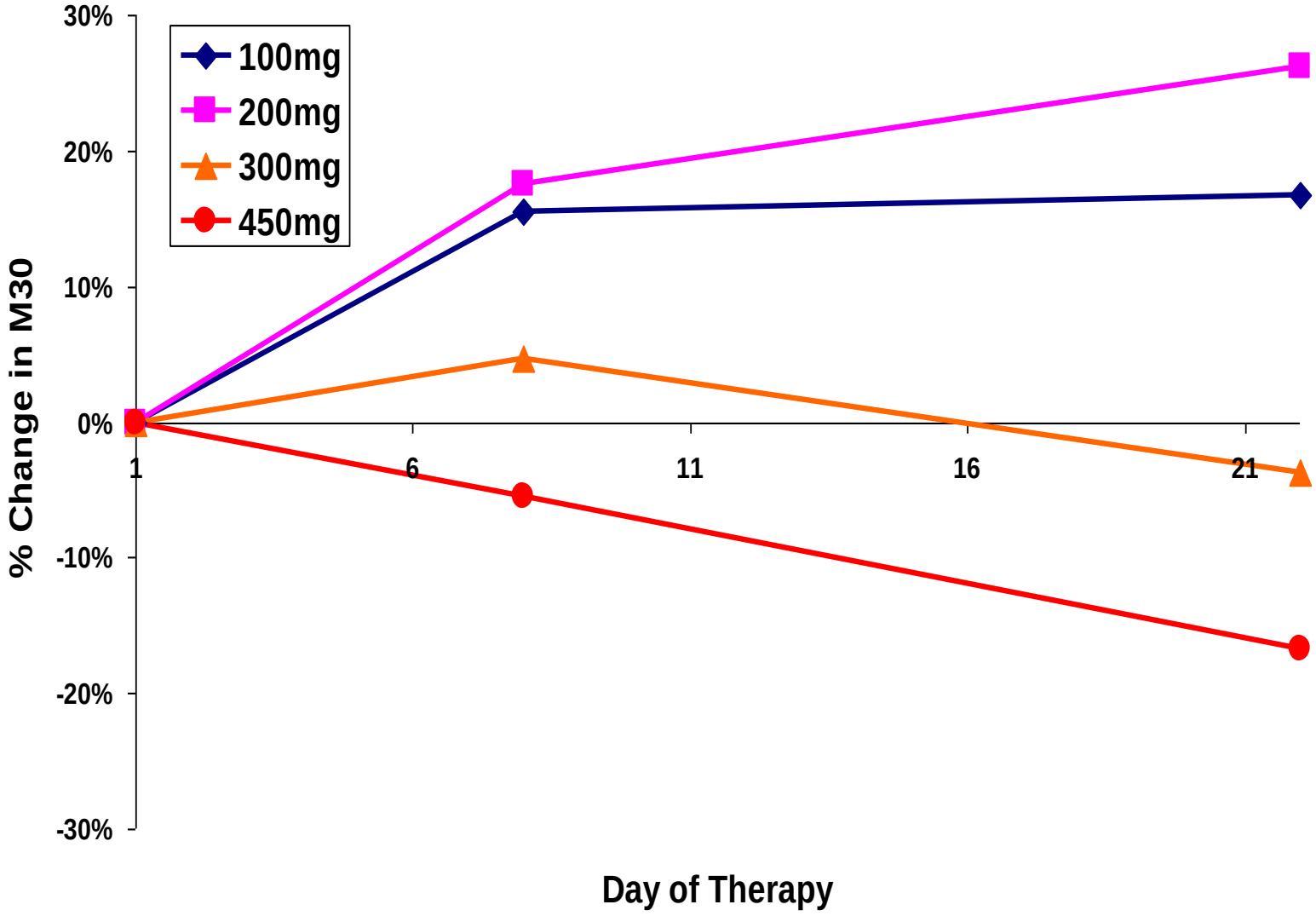
Dose response- AZD1152



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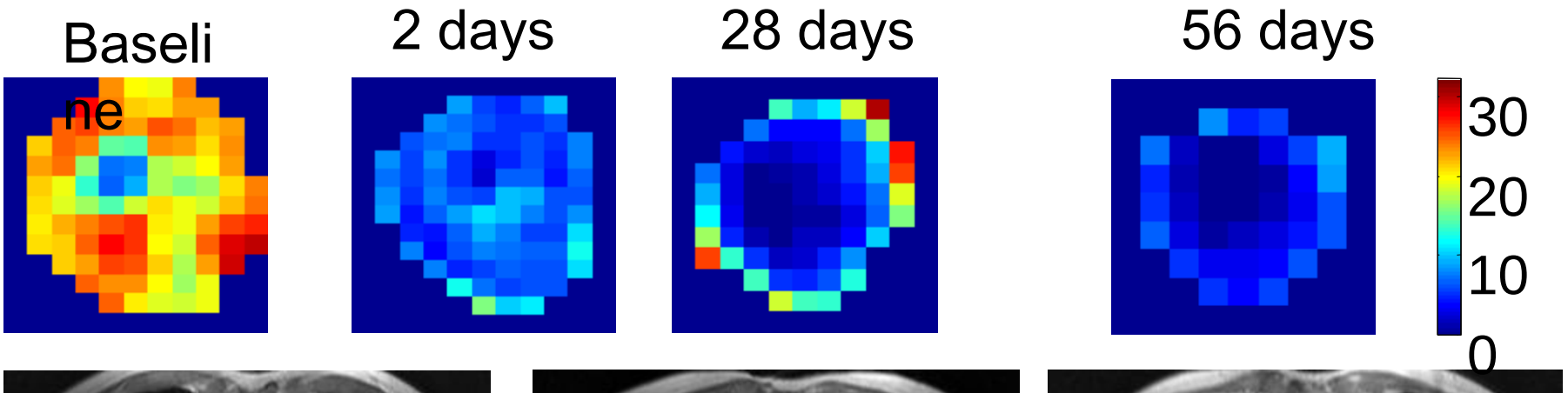
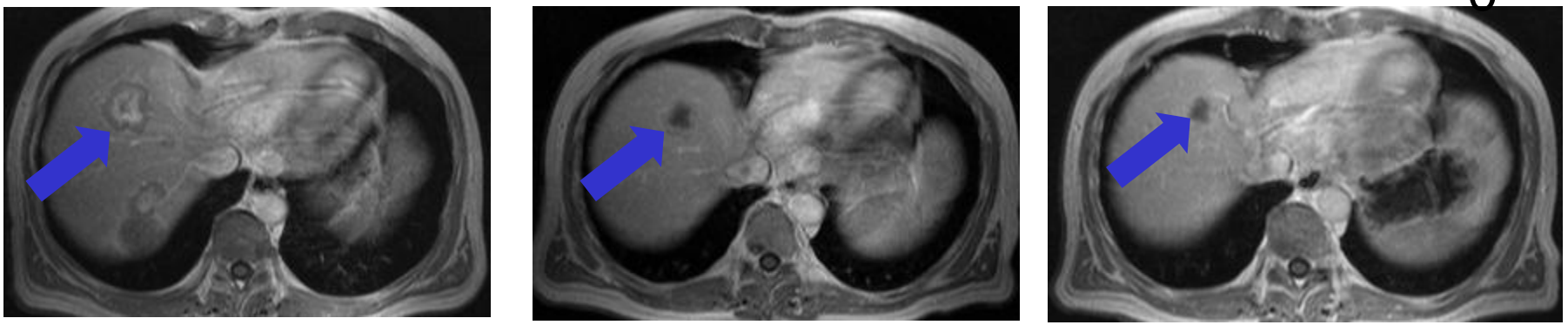
Dose and Duration: Cedirinib

Tumour blood flow & permeability – DCE-MRI





Structural imaging – MRI

Baseline 28 days 56 days

Drevs J et al. Proc ASCO 2005; Abstr 3002.

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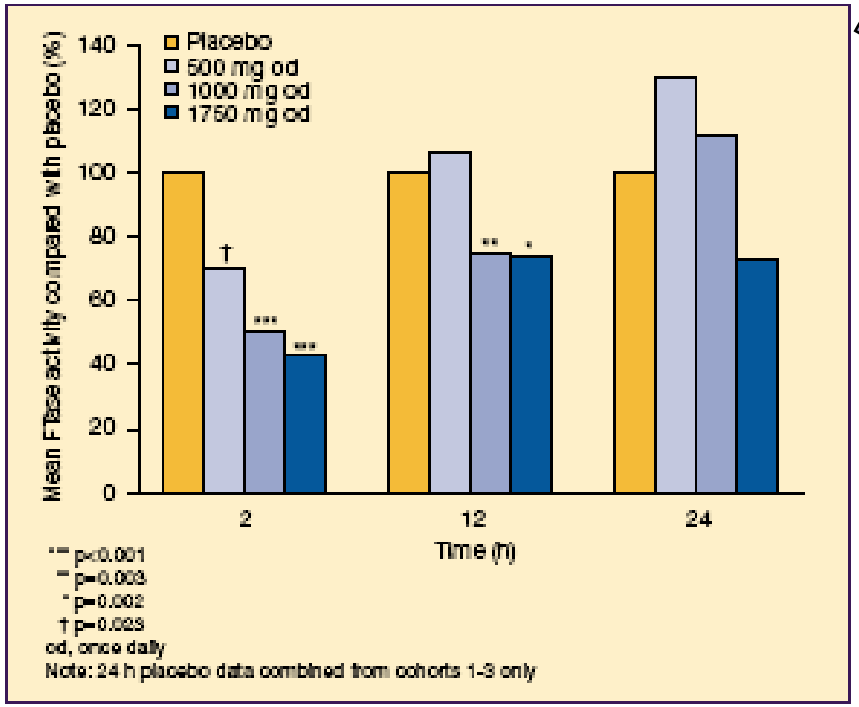
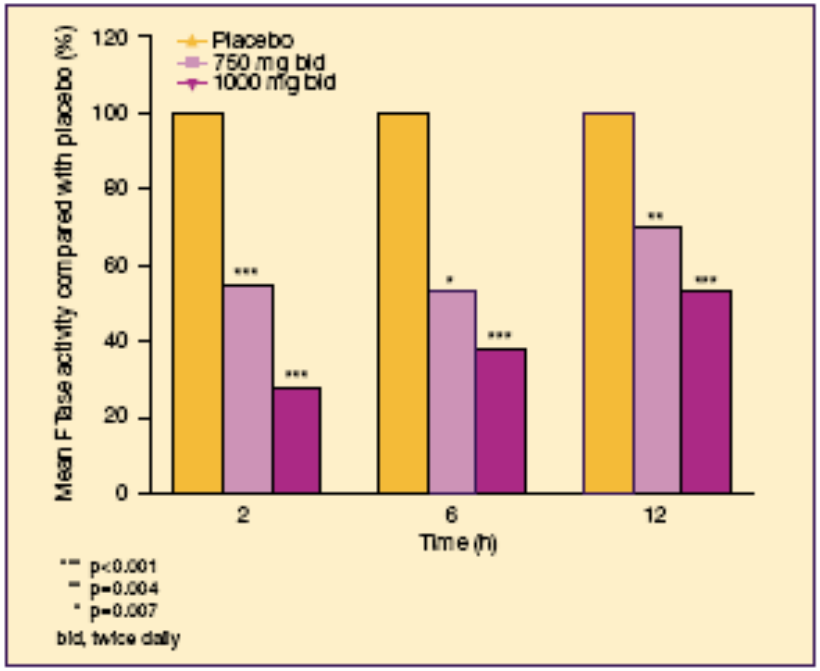
Schedule: AZD3409

Once daily insufficient coverage of target



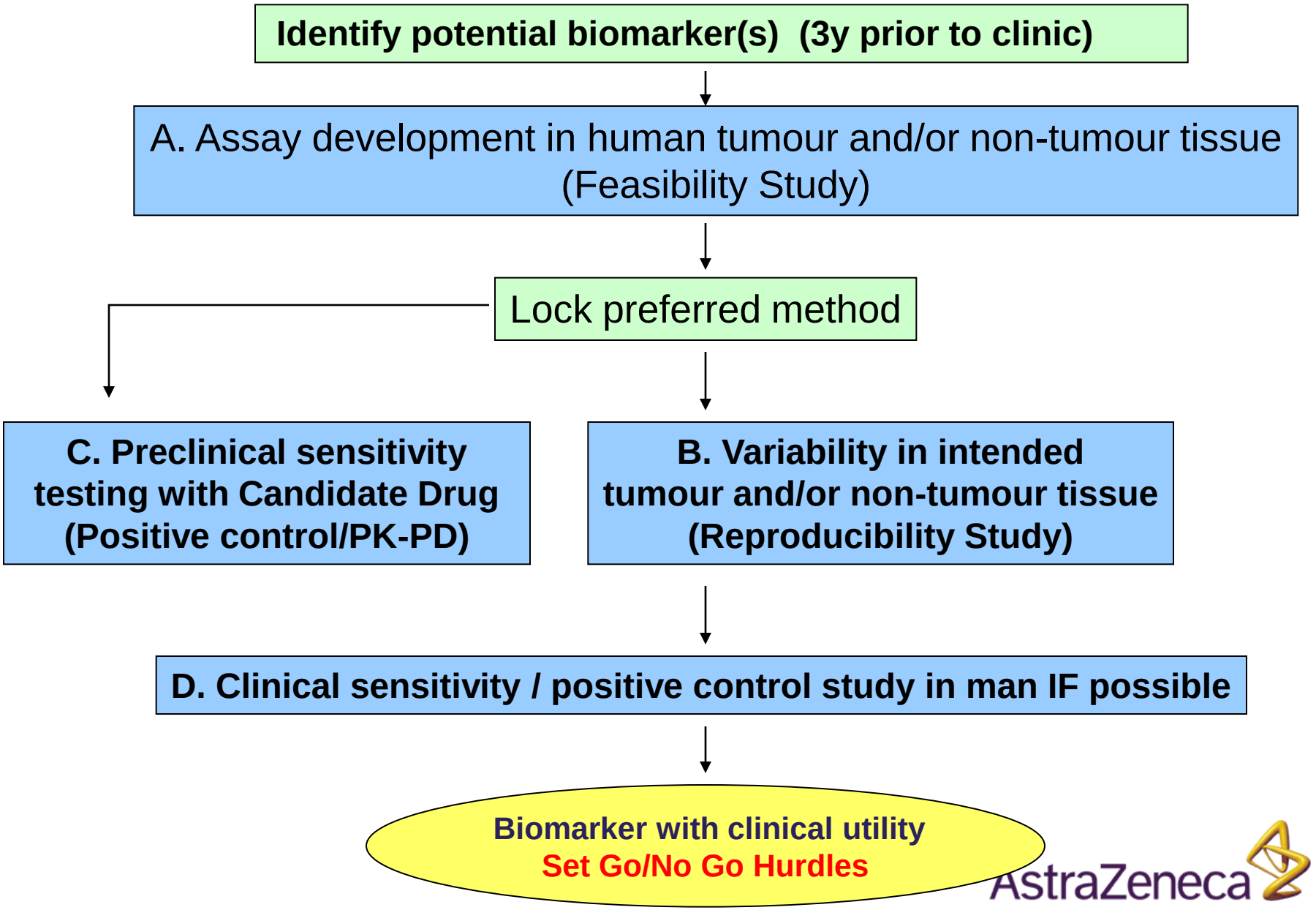
Drove decision to
alter clinical schedule

Twice daily sufficient coverage of target



Wilson, EORTC-NCI-AACR; October 2004

Business model to *"qualify"* a biomarker in Oncology



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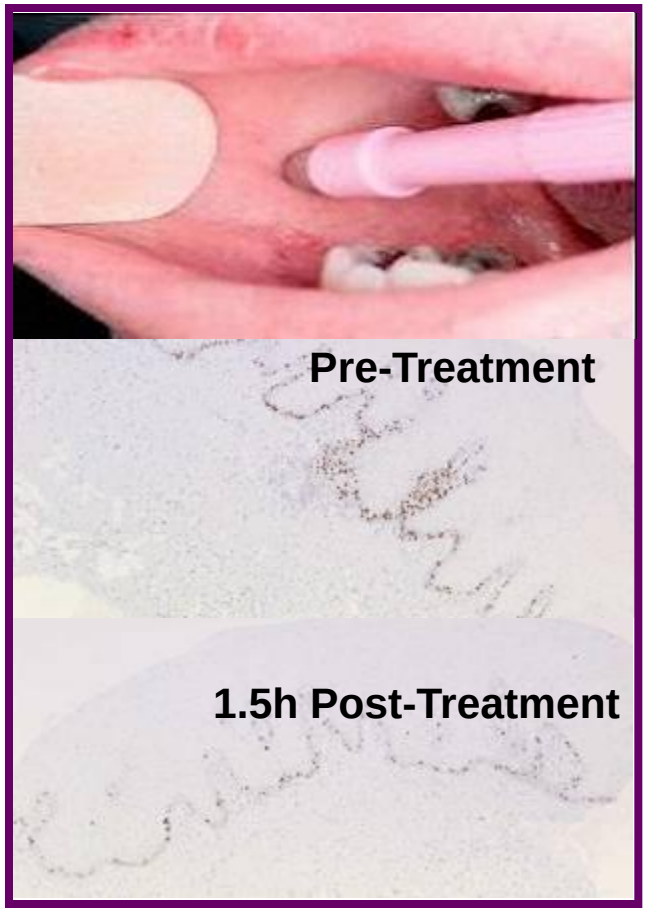
AZD5438: cyclin dependent kinase (CDK) inhibitor

Tumour cell apoptosis inducer with no effect on normal resting cells



- CD nomination to first human dose in 5 months
- Proof of mechanism in healthy volunteers within 12 months of nomination
  - AZD5438 inhibits the Phosphorylation of pRb in tissues at well tolerated doses
- Now in patient trials

Brent Vose: AstraZeneca Annual Business Review

October 2004

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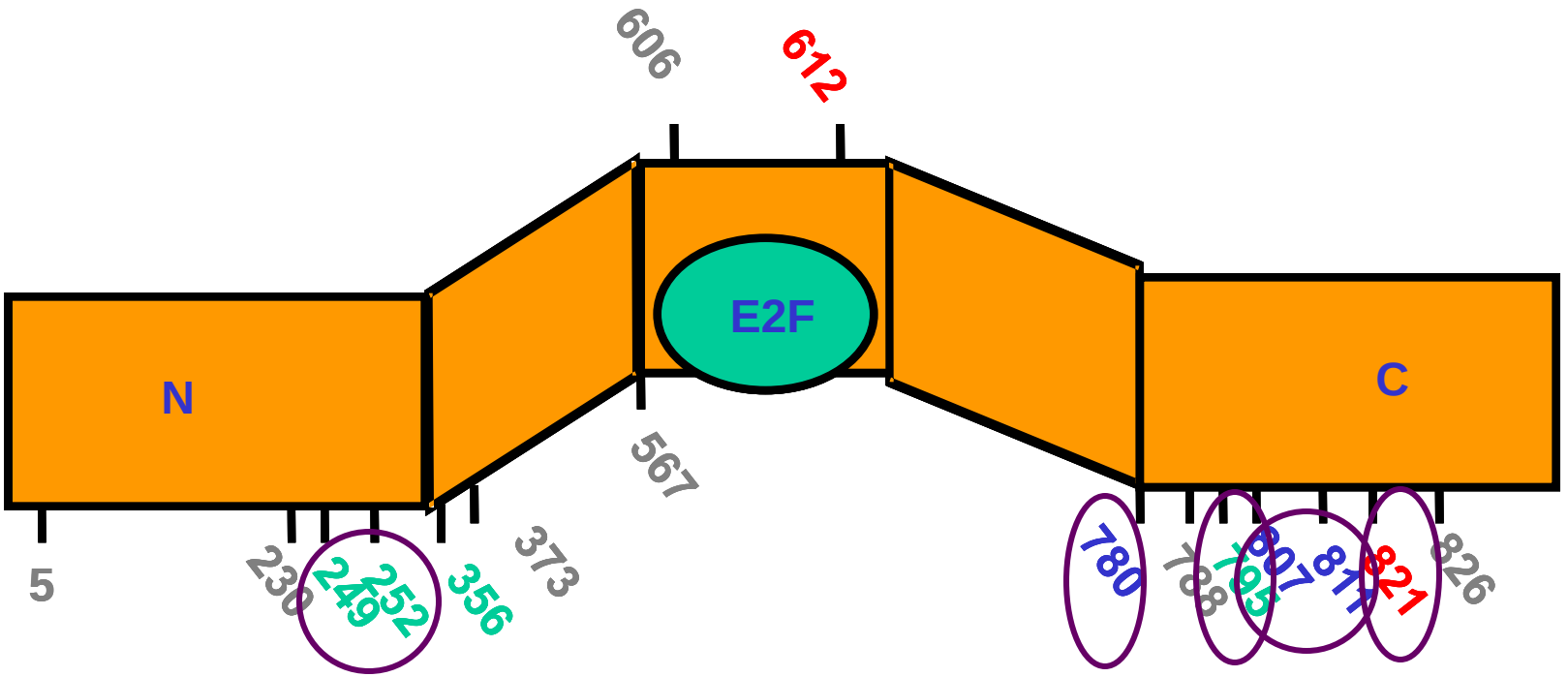
Identify Potential Biomarker



Key: No commercialy available antibody defined

cdk4/2 cdk4 cdk2

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Feasibilty

3 mm biopsy punch under local anaesthesia

Actual biopsy

Well tolerated

9/10 subjects said that they would undergo repeat biopsies

No adverse events on any real note

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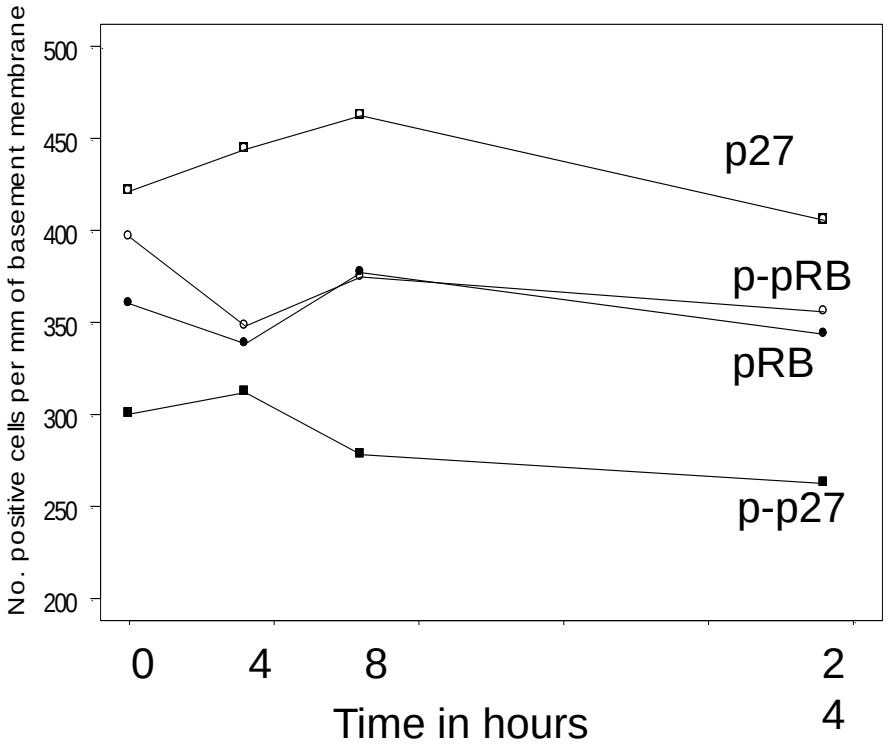
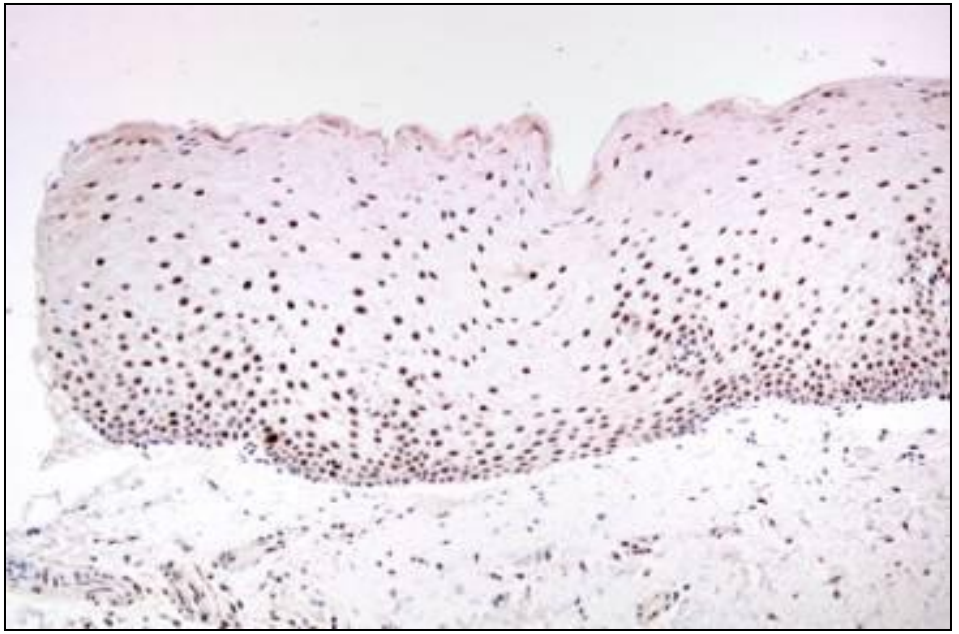
Human Buccal Tissue: Feasibility and Reproducibility results





	CV (%)	
	Between Subject	Within Subject
phospho-pRb	19.0	29.3
pRB	13.7	18.5
pRB ratio	10.6	30.2
phospho-p27	15.9	19.4
p27	17.8	24.9
p27 ratio	23.9	21.6

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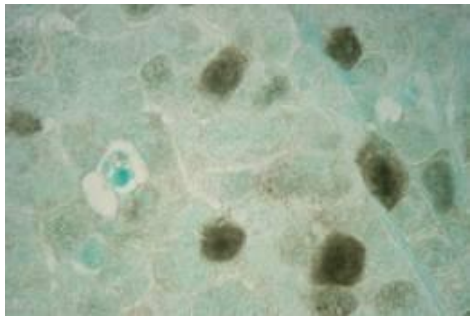
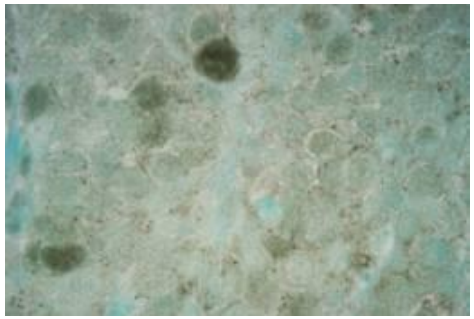
In vivo xenograft

Pre-dose



Post-dose



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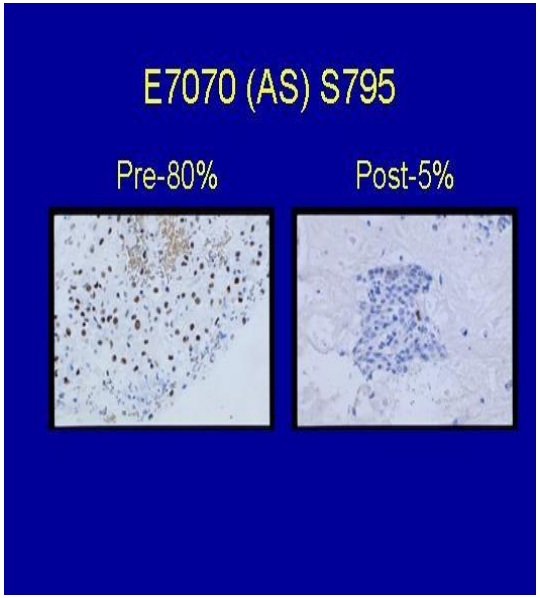
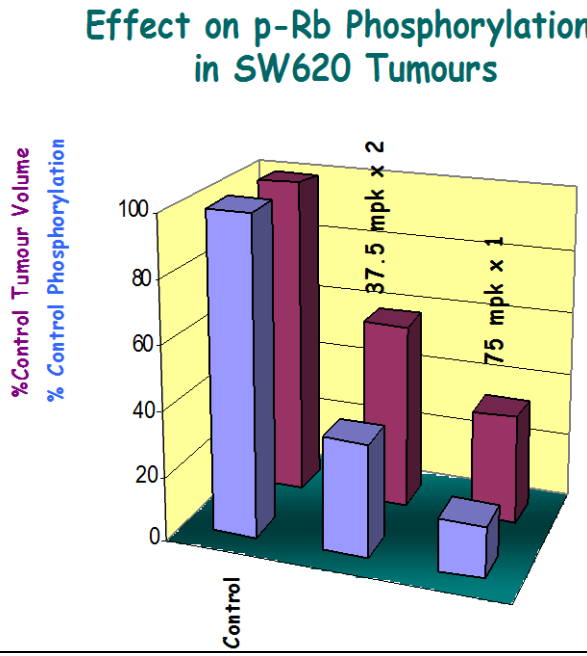
Setting your hurdle

Competitor data



Your own pre-clin data



Human variability

CV%=11%

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Now your ready to use it in anger….and if nothing happens make a kill decision with confidence

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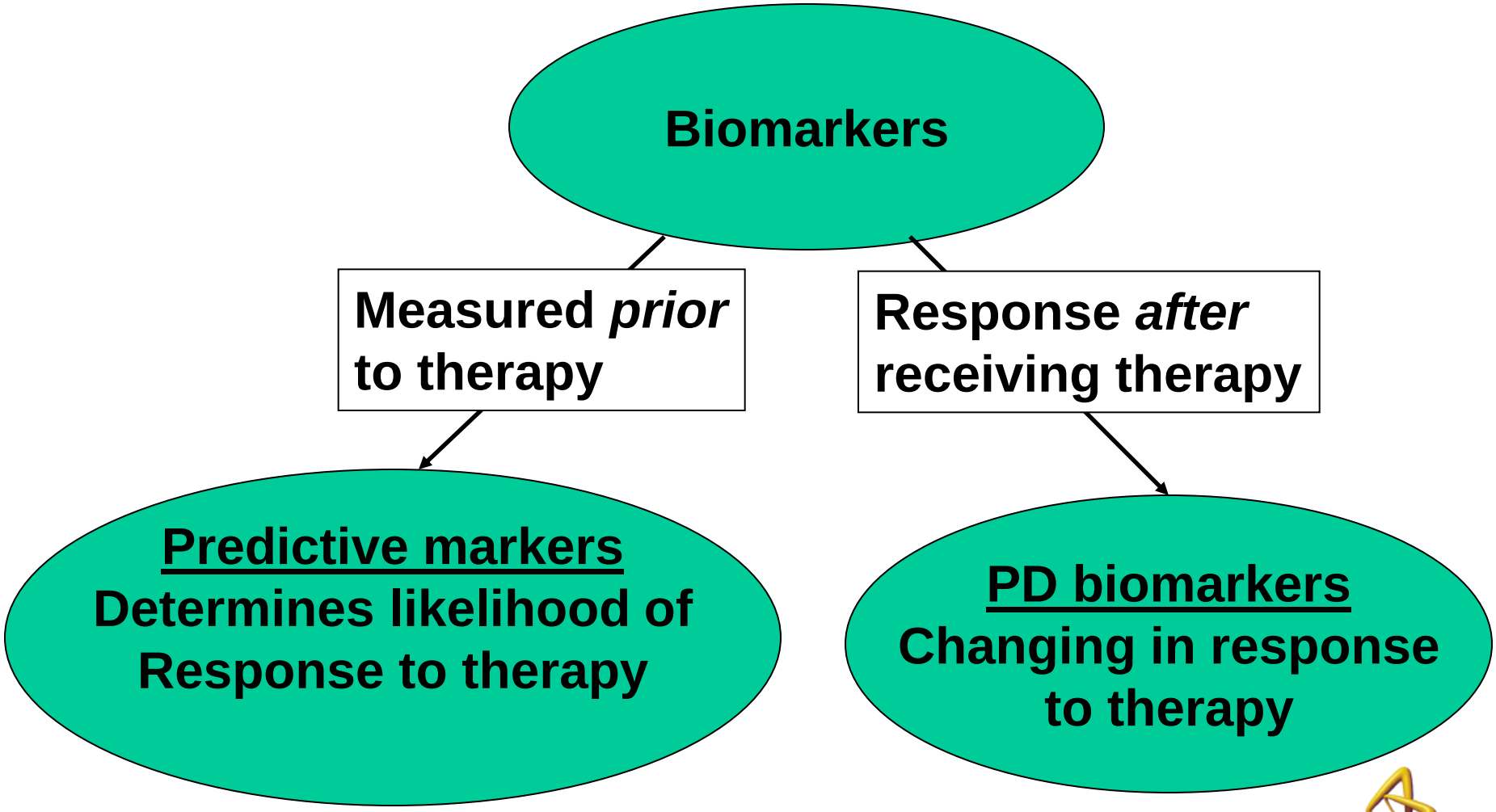
A reminder on terminology



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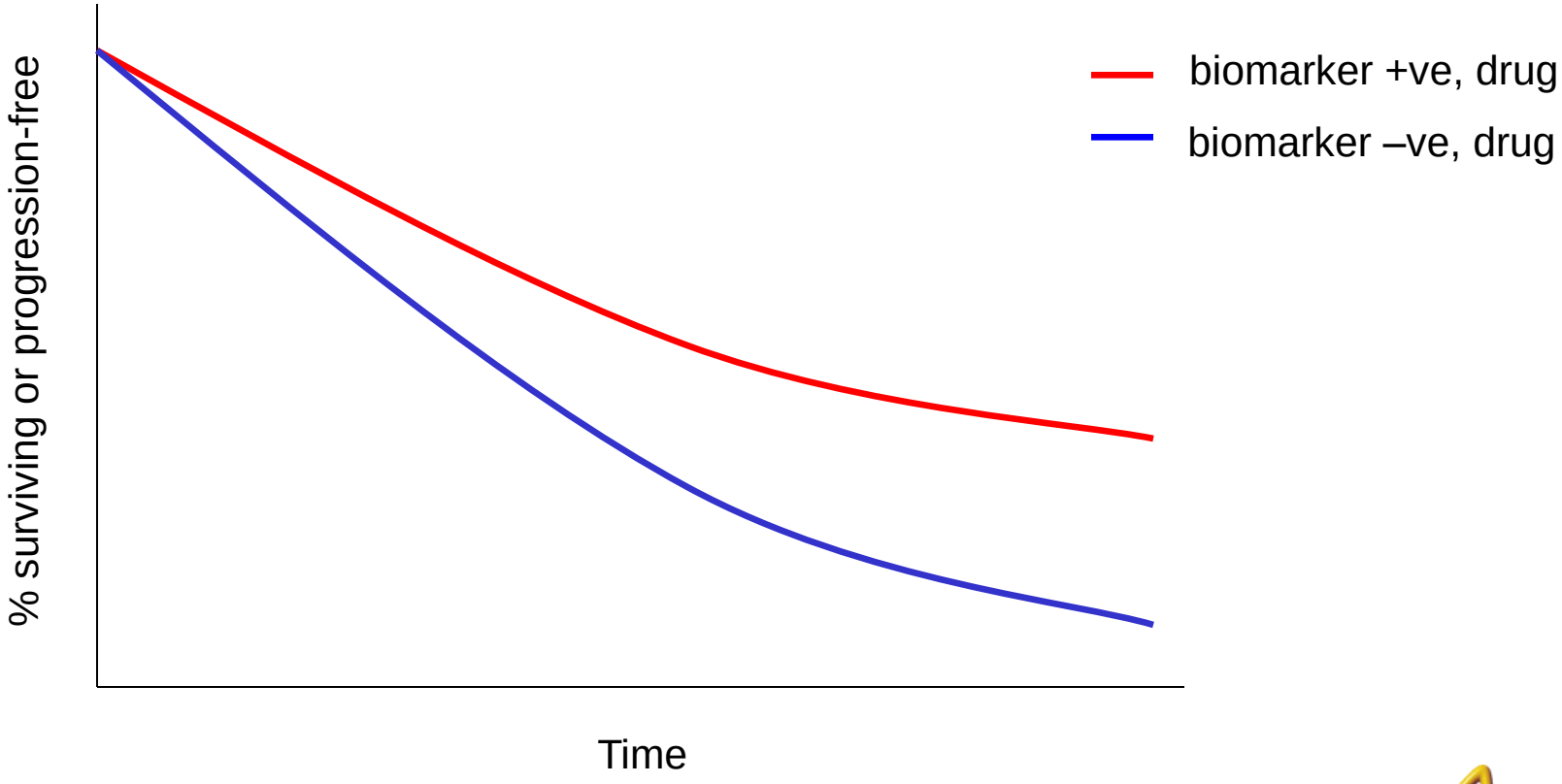
Amongst patients treated with drug, biomarker +ve patients do better than biomarker –ve patients



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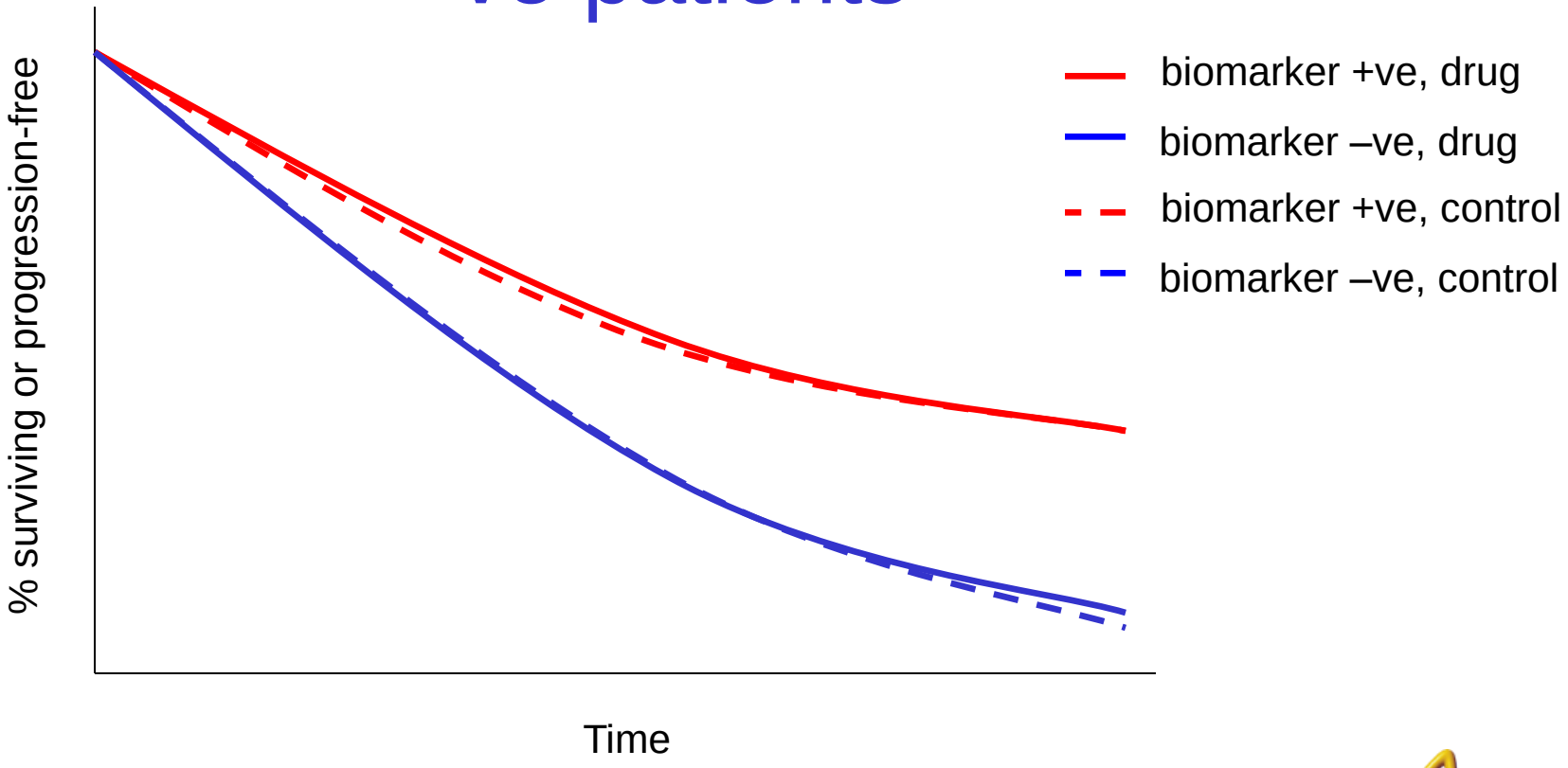
..but the same is true for patients treated with control, biomarker +ve patients do better than biomarker –ve patients



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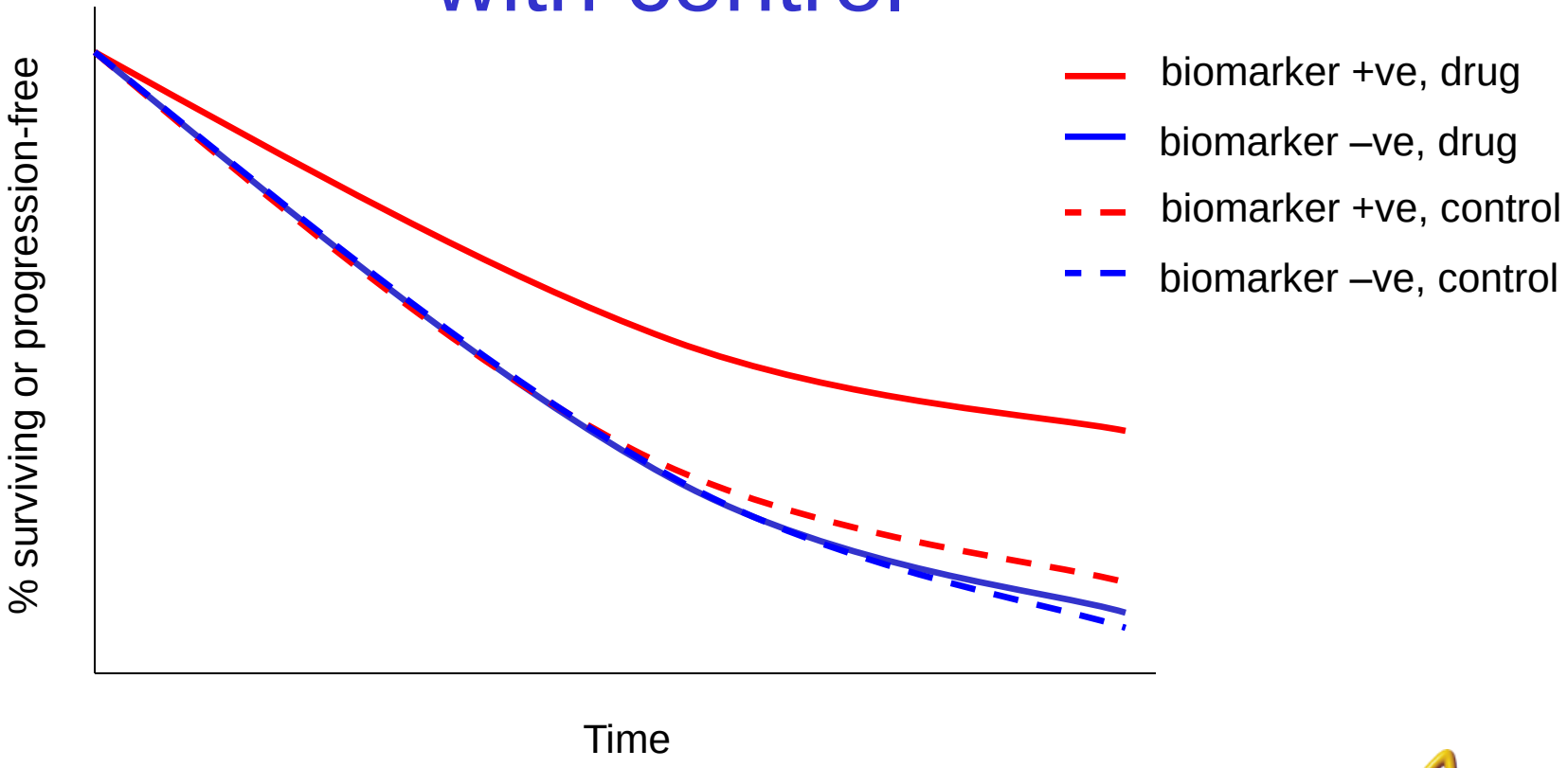
biomarker+ve patients treated with drug do better than biomarker +ve patients treated with control



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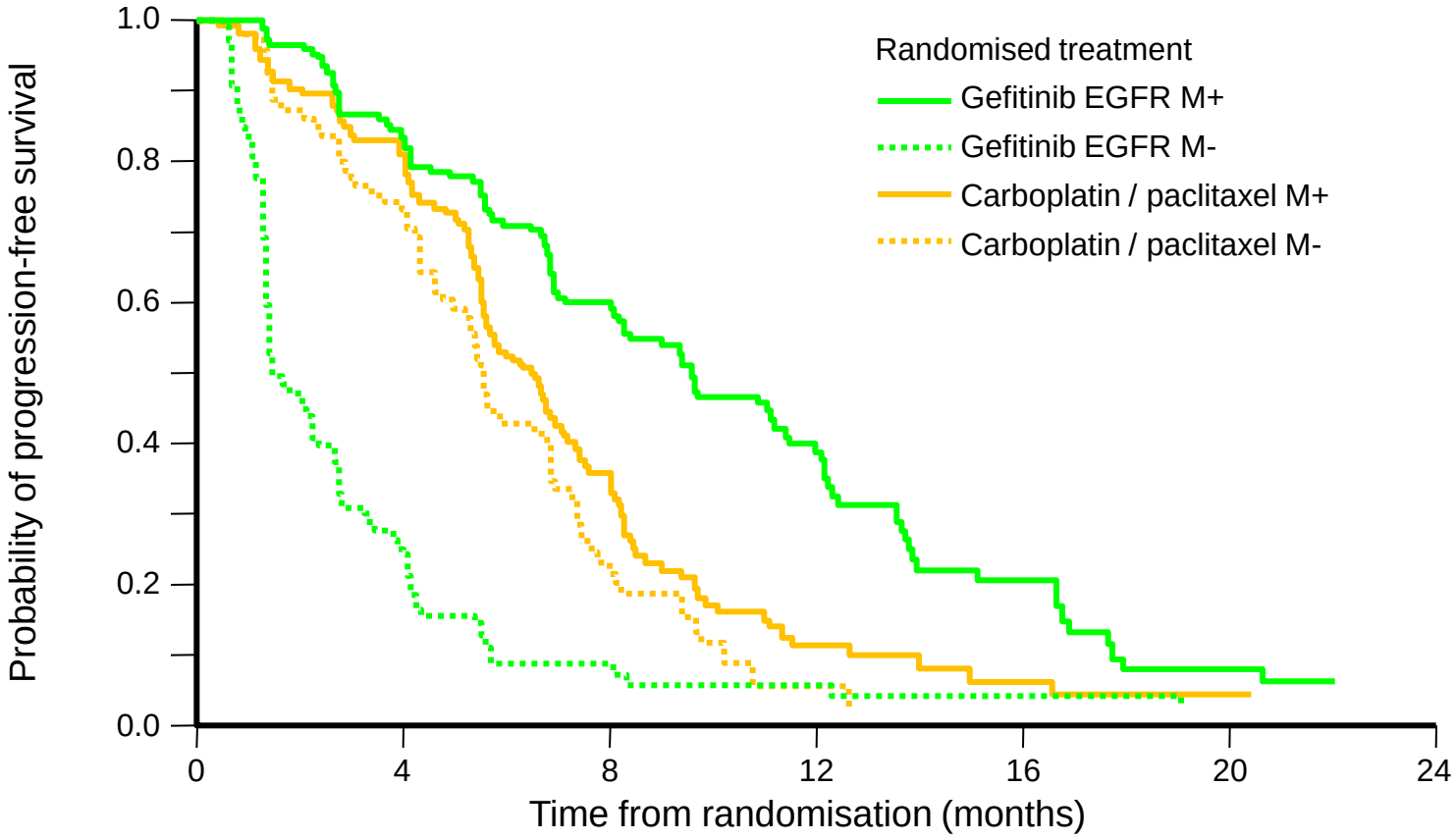
PFS by Mutation Status

– Overlaid KM Curves



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PM Trials are smaller and quicker…

…or are they?

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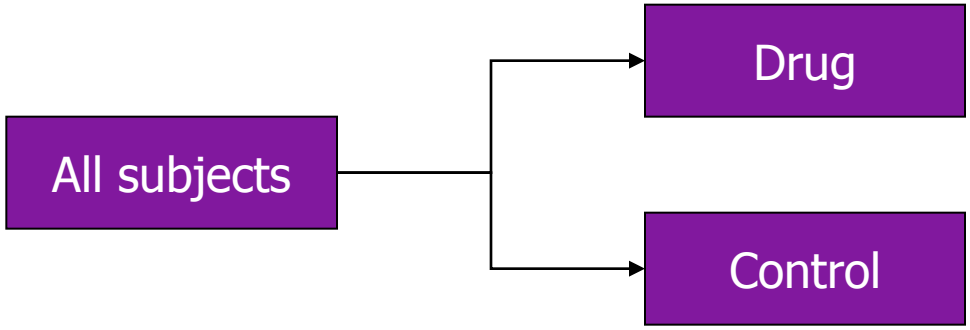
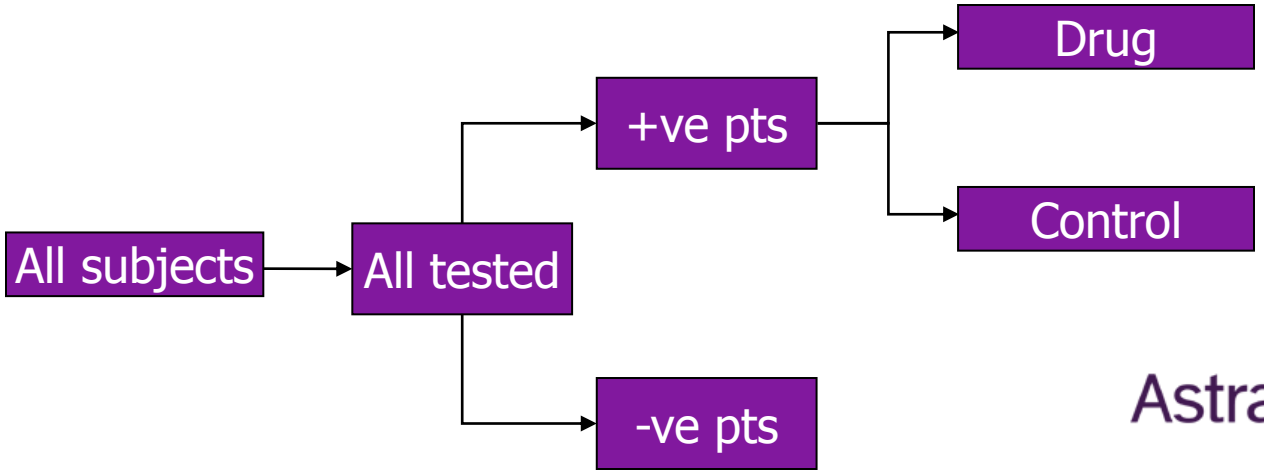
Assume you had a drug which doubled the time to progression (HR=0.5) in biomarker +ve subjects and no effect in biomarker –ve subjects and the target for the drug is only present in 25% of people

1. Unselected Design



2. Prospective selection



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No effect in –ve patients

	C	E	Effect (HR)
+ve (25%)	6 mo	12 mo	0.50
–ve (75%)	6 mo	6 mo	1.00
All patients	6 mo	7.5 mo	0.80

	N req'd to enter[1]	N req'd to screen
Unselected	1000	
Prospective selection +ve (25%)	117	468
	8.6 fold	2.1 fold

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[1]median follow-up of 18 months assumed

…but this assumes…

A. the selection test is perfect…

B. biomarker –ve patients have no effect

What happens to the numbers if this isn't the case

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An imperfect test lessens the advantage of a targeted trial

Sens, Spec	PPV	C	E	Effect size	N req'd to enter	N req'd to screen
100%,100%	100%	6 mo	12 mo	0.50	117	468
95%, 75%	56%	6 mo	9.4 mo	0.64	260	613
75%, 95%	83%	6 mo	11 mo	0.55	149	663
75%, 75%	50%	6 mo	9 mo	0.68	317	845

Remember: An Unselected trial required 1000 patients

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Anyway, assume we have the perfect test, what happens if there is some modest (~1/3 of biomarker +ve) effect in –ve pts?

Is a selected design still best?

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Even a small effect in –ve pts erodes the apparent advantage of a targeted trial

	C	E	Effect
+ve (25%)	6 mo	12 mo	0.50
–ve (75%)	6 mo	7.5 mo	0.80*
All patients	6 mo	8.7 mo	0.69

	N req'd to enter	N req'd to screen
All patients	384	
+ve (25%)	117	468
	3.3 fold	0.8 fold

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* Effect in –ve pts = 1/3 effect in +ve patients)

In a PM strategy we would need to be very confident that (i) we had a very good test and (ii) the untargeted population achieved no benefit from treatment

in order to gain clinical trial efficiency in conducting the trial in only biomarker +ve subjects

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