Pre-IMPAKT Training Course

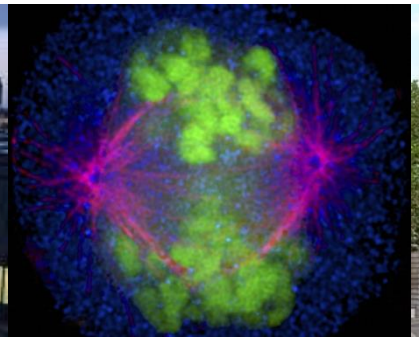
Early Drug Development

Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine

Barts Cancer Institute, St Bartholomew's Hospital

Queen Mary University of London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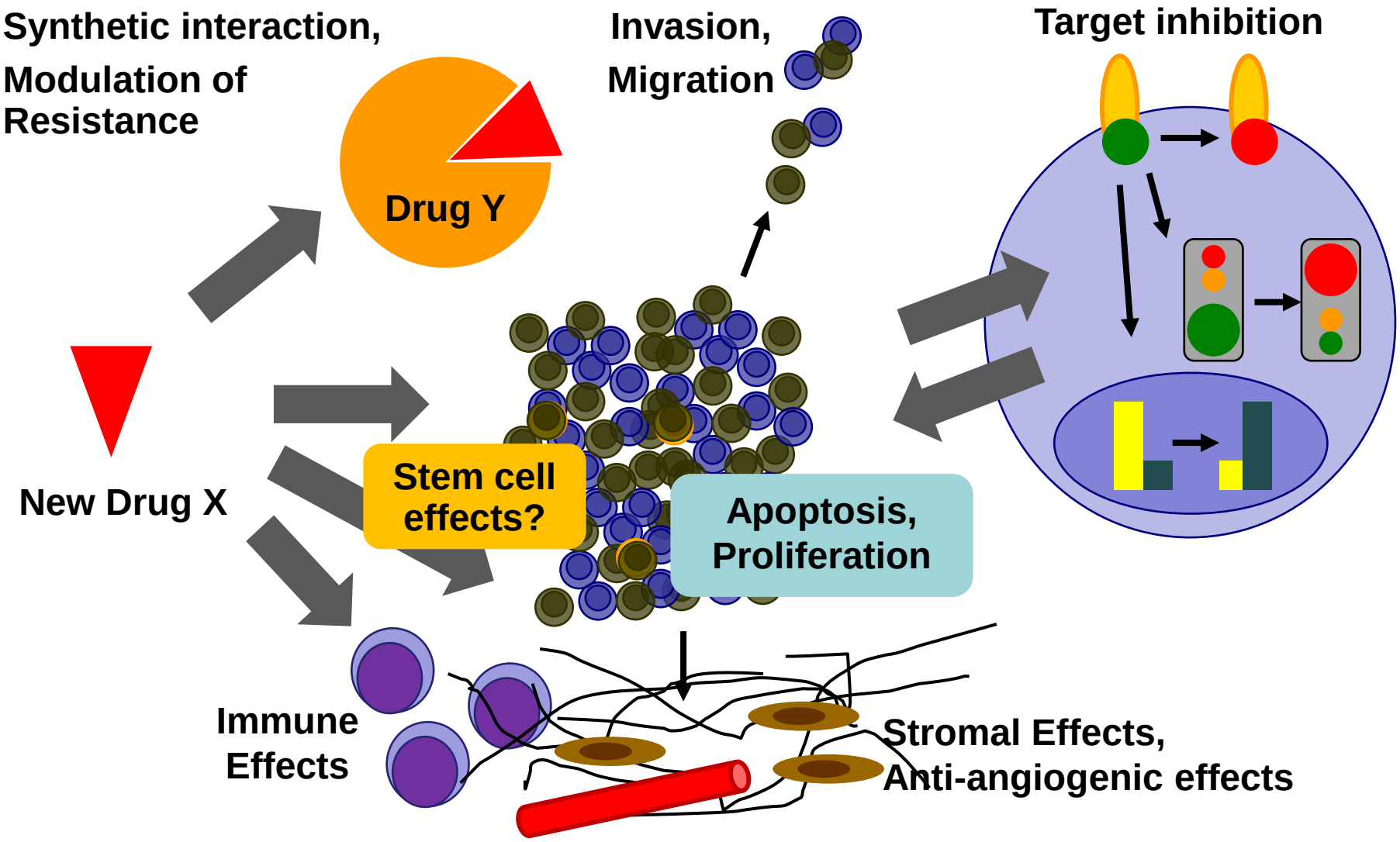
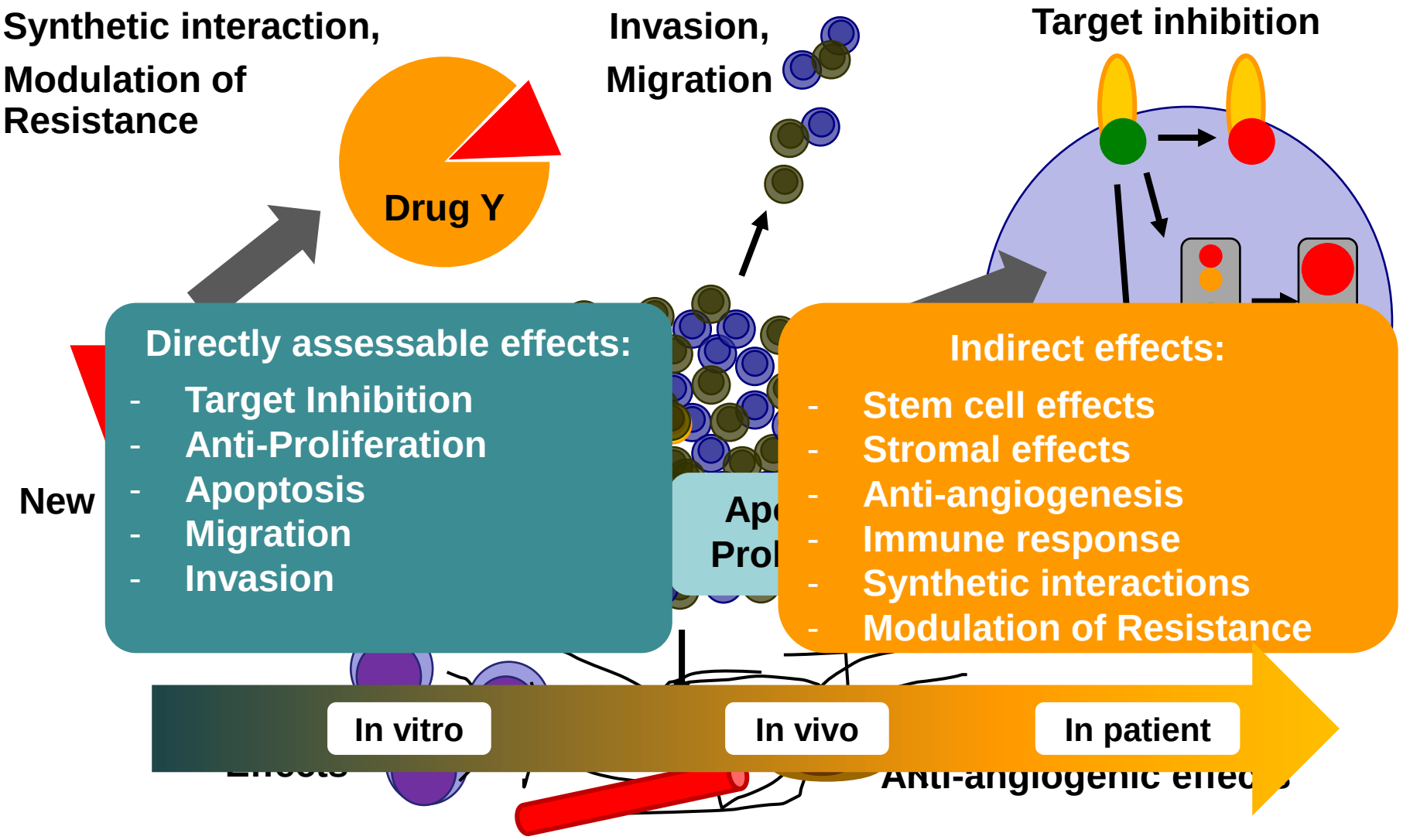
Preclinical Characterisation of antitumour effects



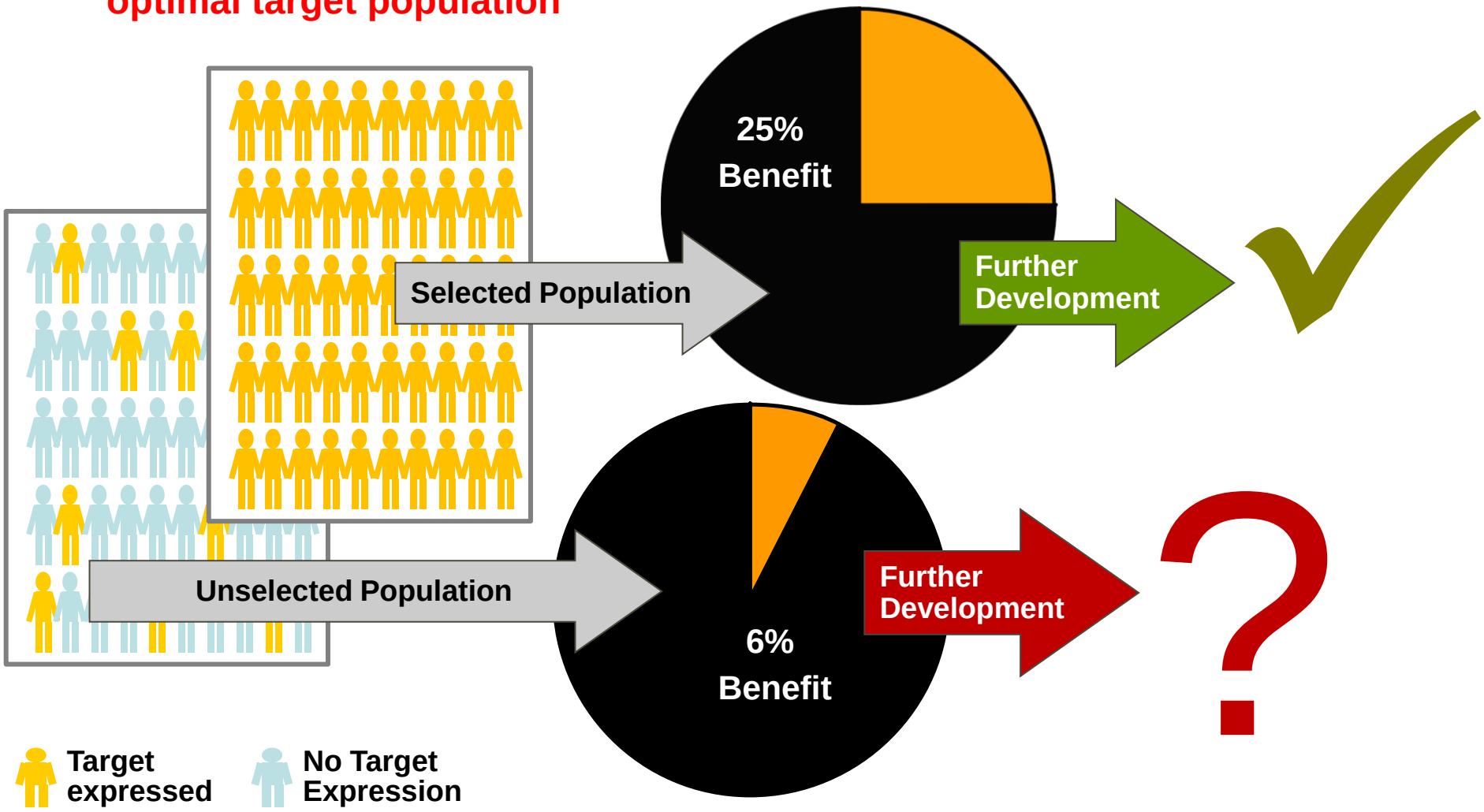
Preclinical Characterisation of antitumour effects



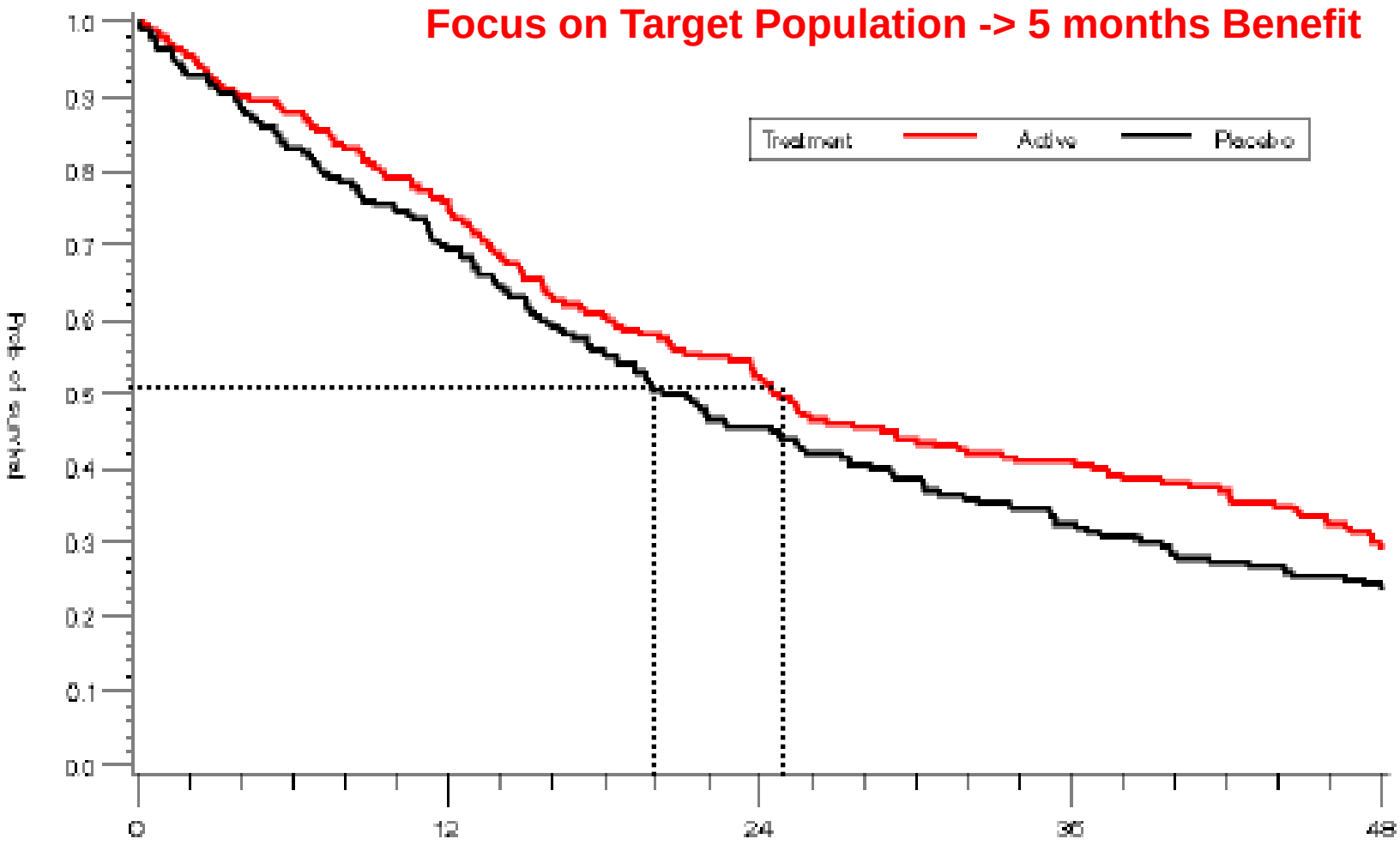
- Who should we treat?
- How to measure the effect of the drug?
- What’s the best strategy (eg combination, schedule)?

Treating the right patients is critical

Translational research defines optimal target population



Treating the right patients is critical for randomised trials



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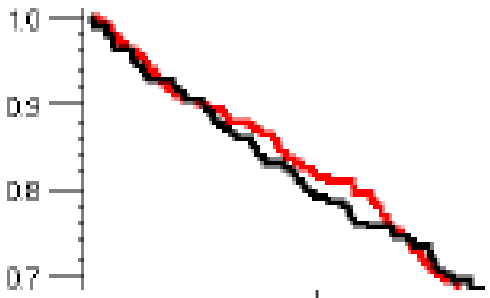
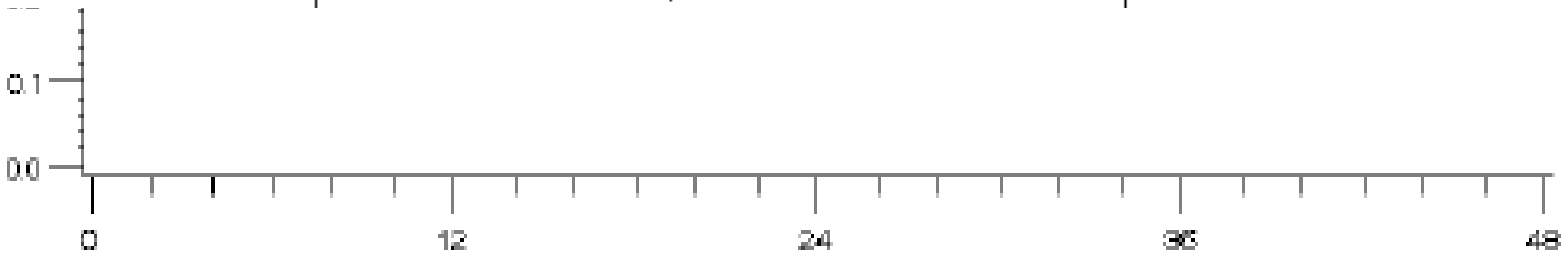


Unselected Population (25% express target)

Expected Benefit	Target Prevalence	Actual Benefit (All Patients)	Required Sample Size And Study Duration
↑ 5 months (22.7%)	100%	↑ 5 mos (22.7%)	1250 → 52 mos
	50%	↑ 2.5 mos (11.4%)	3500 → 108 mos
	25%	↑ 1.25 mos (5.7%)	11000 → 349 mos



Preclinical Characterisation of Target Population

Target Activation
(eg. Amplification, Mutation, Expression, Activation signature)

Synthetic Interaction
(eg. Secondary resistance, Sensitizing Gene defect)

Target → **MOA** → **Target Effects**

Characterisation of tumour effects

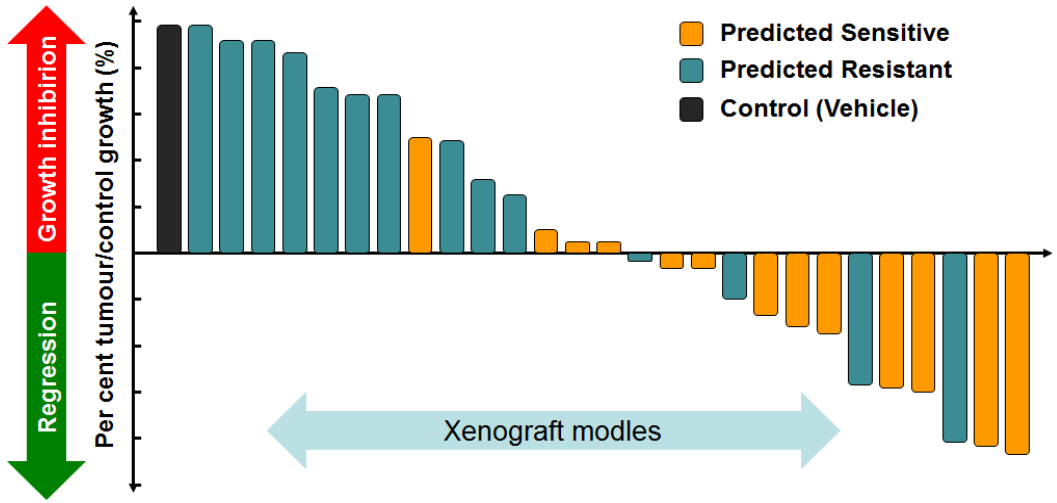
Indirect → **Activity in panel of xenografts**

Direct → **Activity in cell line panel**

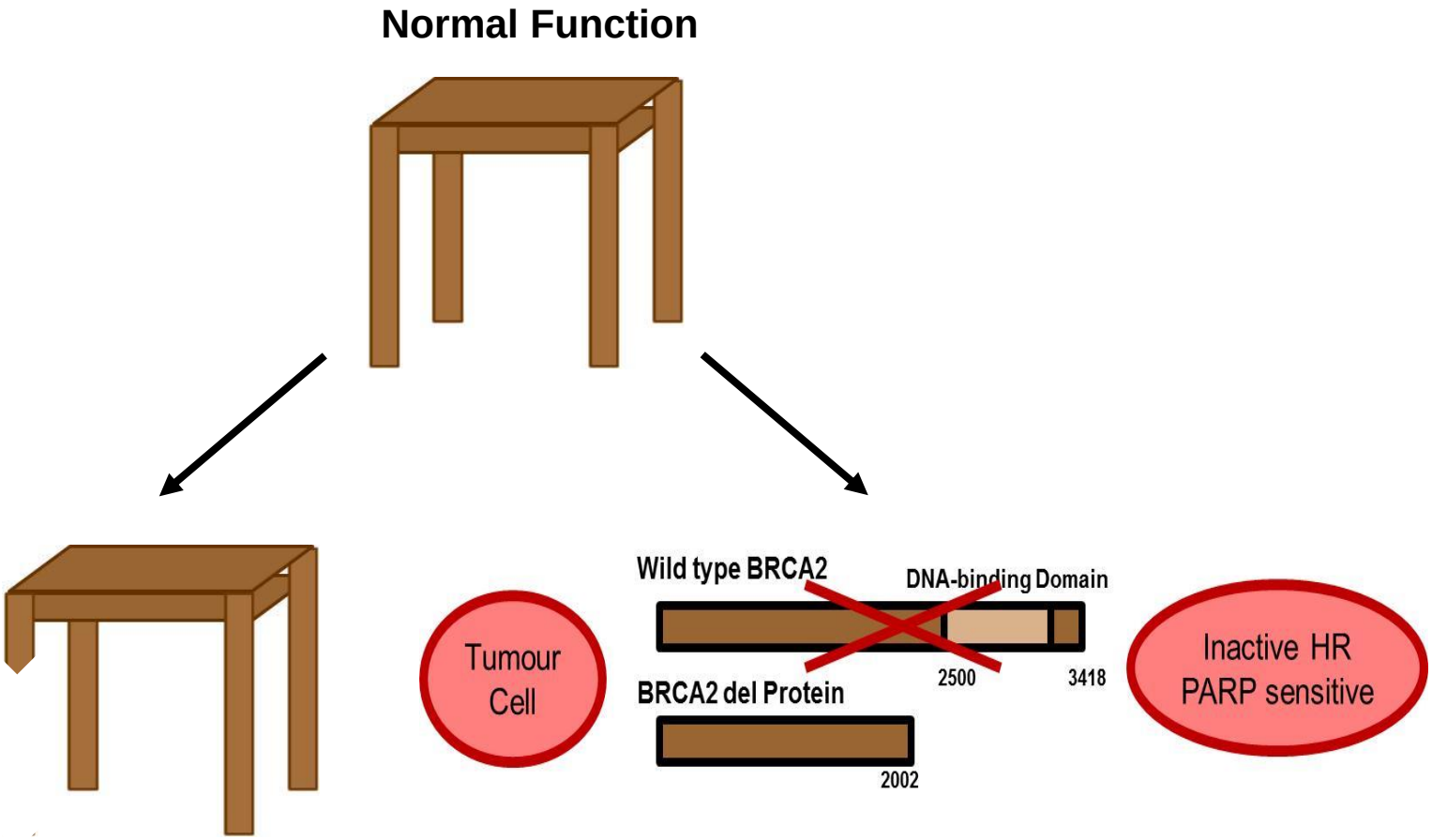
Validation

Identify predictors of response through molecular profiling
(eg activat. signature)

Tumour growth inhibition by activation signature



Synthetic Lethality Strategies

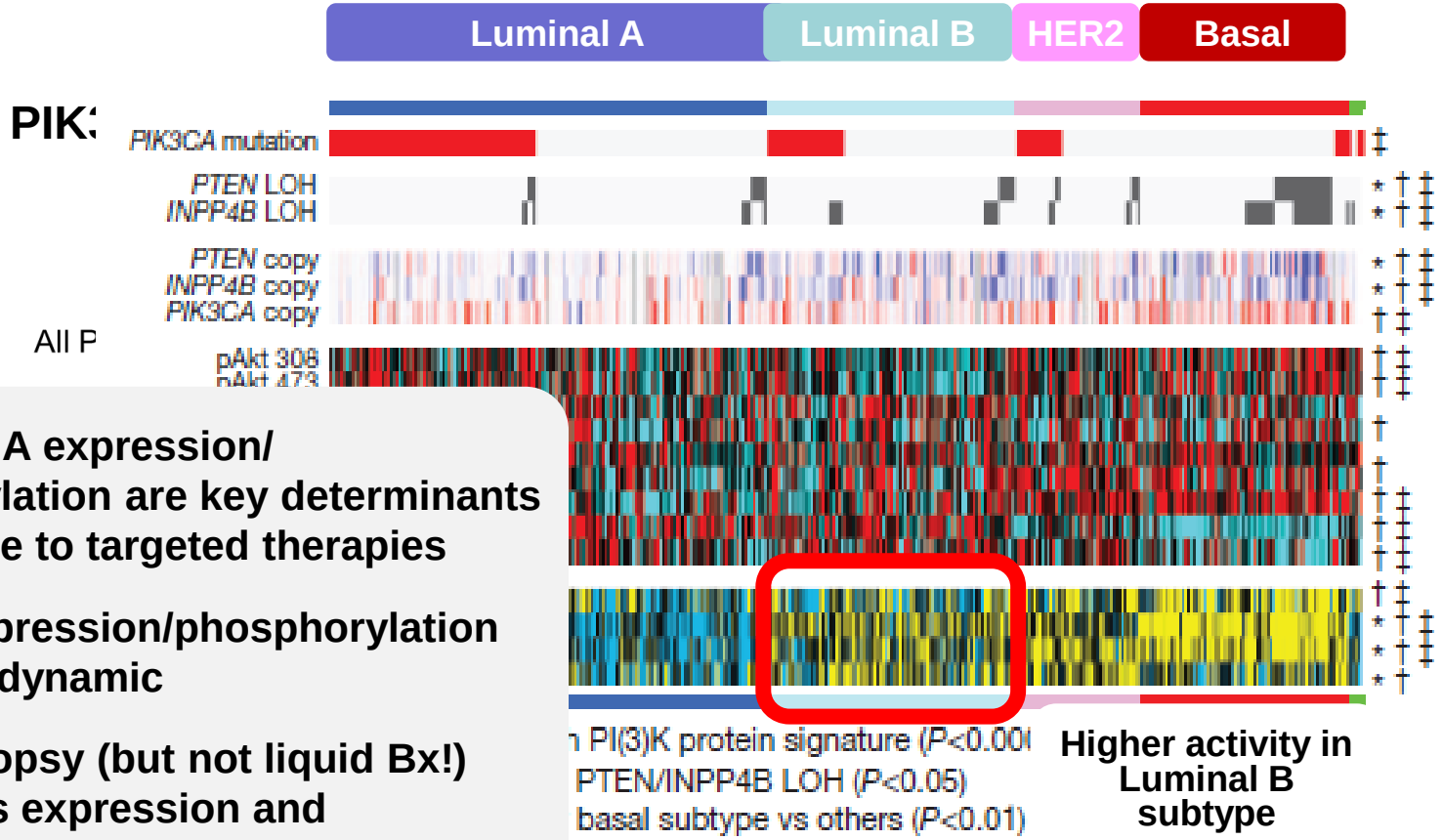


Compensated Disturbance (Genetic, epigenetic)

Lethal Combination of Damages

Do we need to go beyond genomic analyses?

Isolated genetic analysis fails to define cellular dependence of aberrant target



1. **Protein/RNA expression/ phosphorylation are key determinants of response to targeted therapies**
2. **Protein expression/phosphorylation are highly dynamic**
3. **Tumour biopsy (but not liquid Bx!) can assess expression and phosphorylation**

Curtis et al, Nature 2012; Schmid P et al, SABCS 2014

Neoantigen expression and immune therapy

RCC patients treated with CTLA-4 antibodies → WES, neoantigen analysis & HLA typing

Mutational load → **Mutant peptides** → **MHC binding**

Mutational burden associated with response but insufficient to predict benefit

Non-mutant peptides

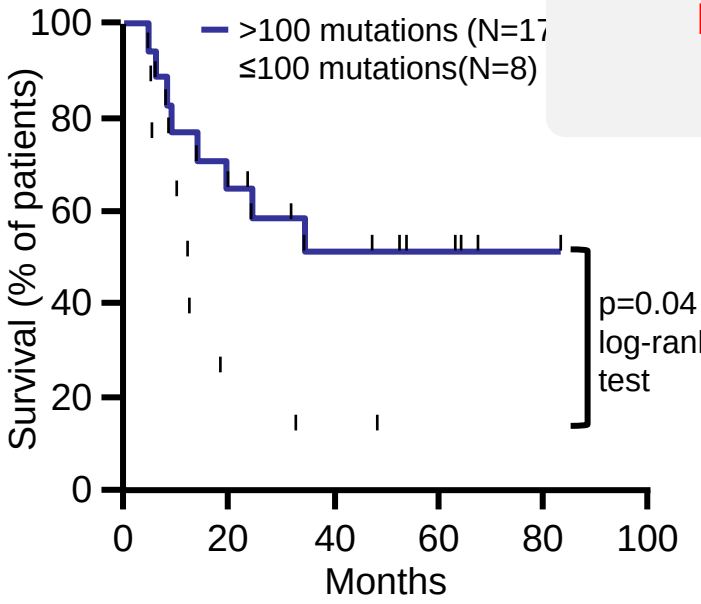
Neoepitopes in discovery set

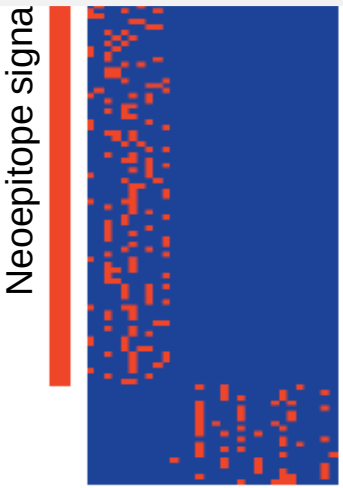
Long- Minimal

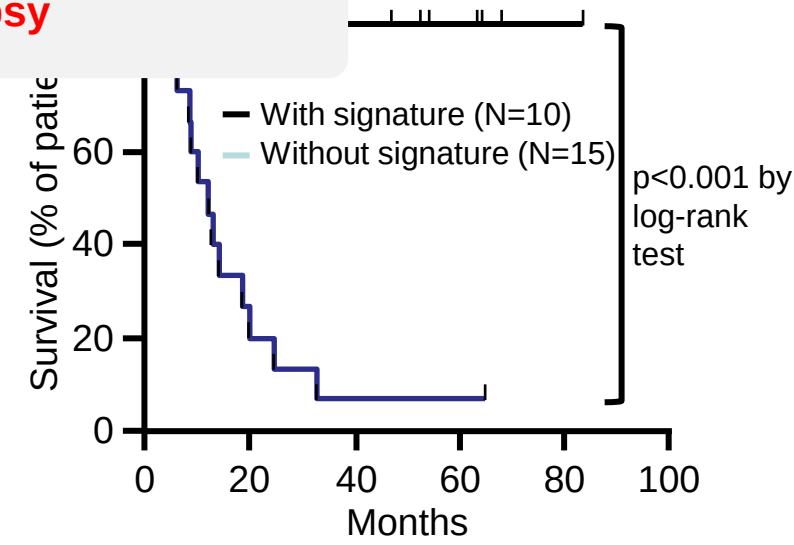
Tetrapeptide signature identified.

Homology with viral / bacterial antigens associated with increased response

Changes of the immune component are highly dynamic and require a tumour biopsy

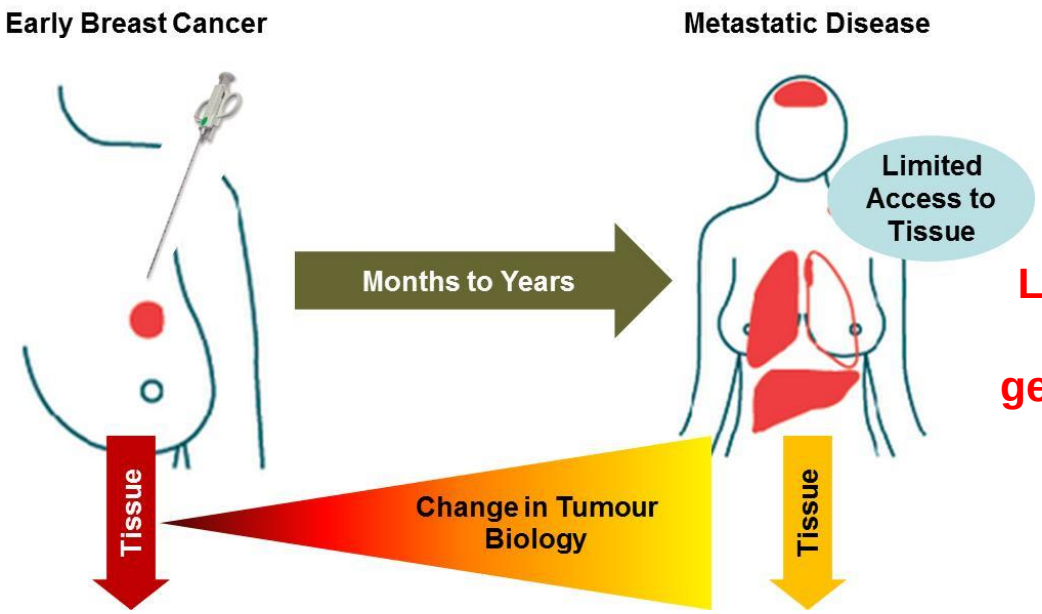






Snyder, et al. NEJM 2014

How do changes in biomarkers occur over time?



Liquid Biopsy can only assess genomic alterations

Timescale for changes

Genomic alterations	Months - years
Expression (RNA/protein)	Hours - Days
Protein Phosphorylation	mins - hours
Stroma and Immune system	?

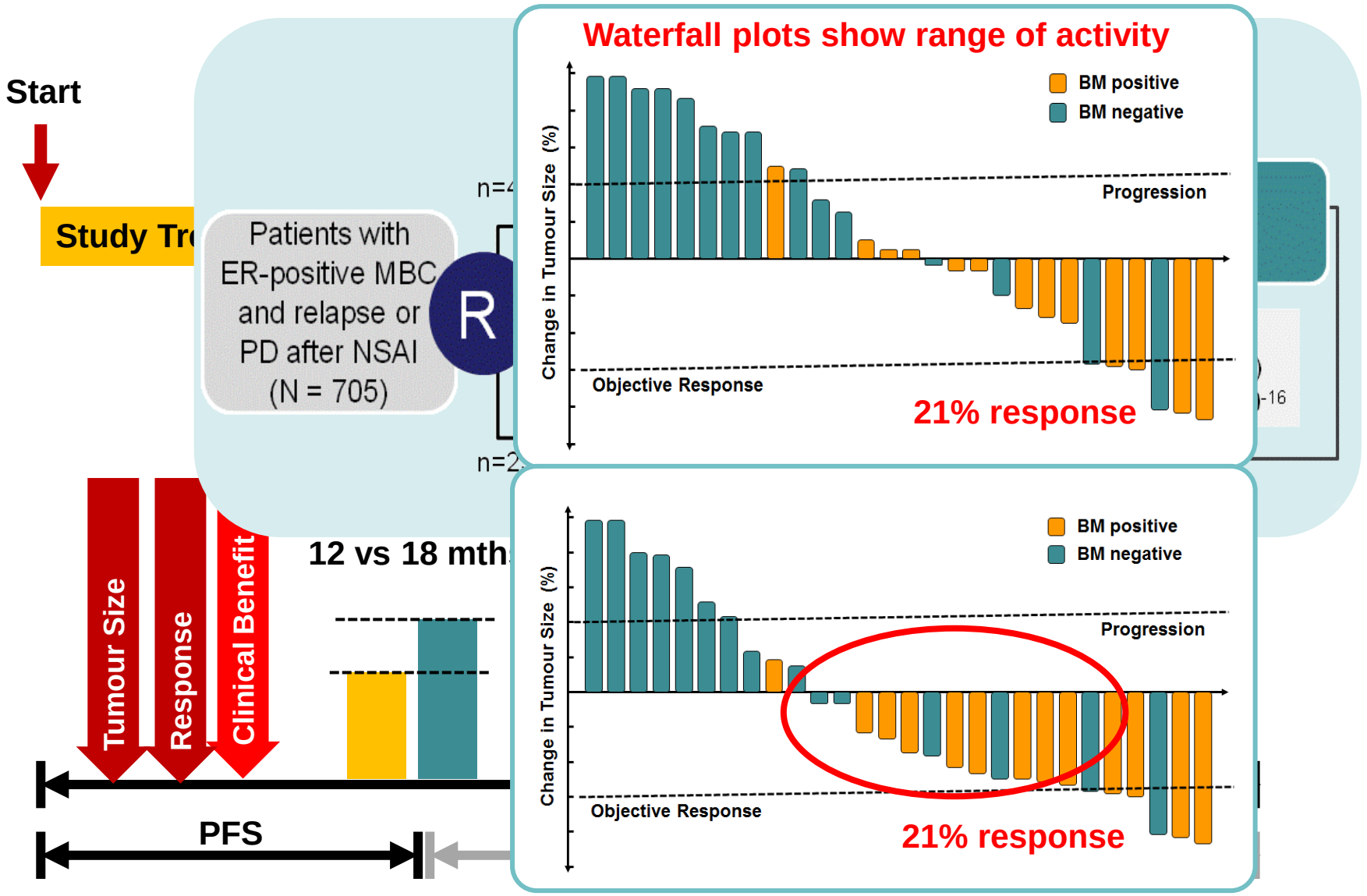
Differences between subtype (genetic stability)

Selection

Adaptation

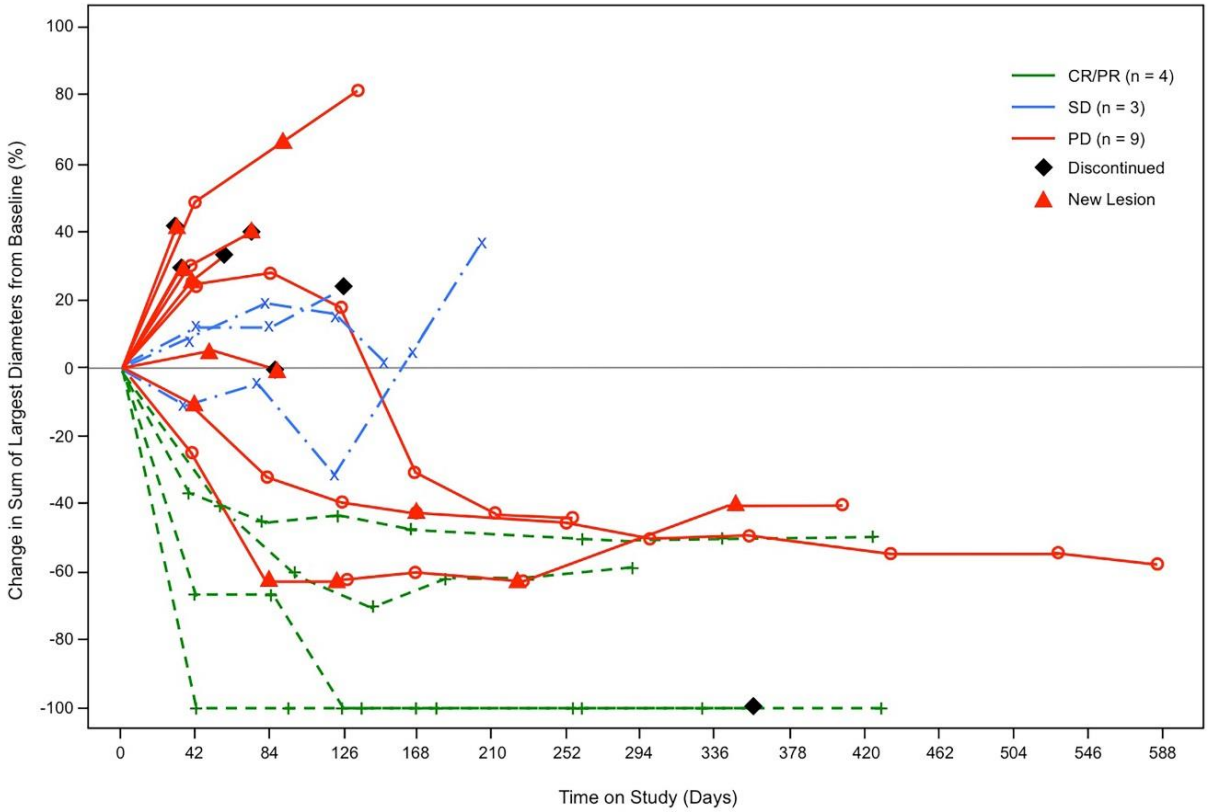
- Who should we treat?
- How to measure the effect of the drug?
- What’s the best strategy (eg combination, schedule)

Selecting the right endpoint for advanced disease



Challenges with immune checkpoint inhibitors

Anti-PD-L1 antibody (MPDL3280A) in TNBC (efficacy-evaluable population)

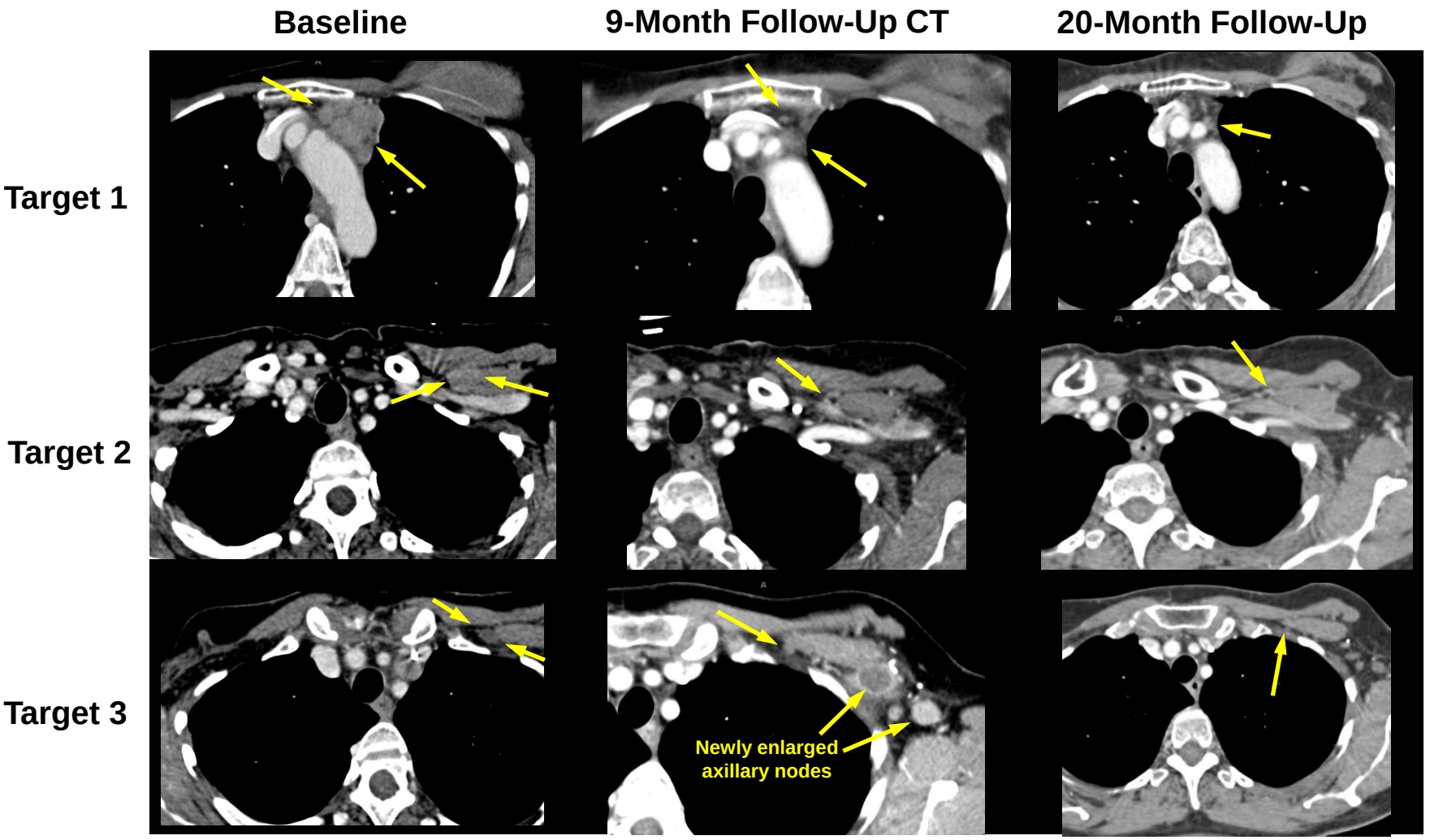


- **Median duration of response has not yet been reached (range: 18 to 56+ wks)**
- **Median duration of survival follow-up is 40 wks (range: 2+ to 85+ wks)**

Investigator-assessed confirmed ORRs per RECIST v1.1.
Efficacy population includes patients dosed by July 21, 2014; clinical data cutoff, December 2, 2014.
New lesions at consecutive visits for the same patient might be the same lesion.

Emens et al. AACR 2015

Activity of MPDL3280A after Pseudo-progression

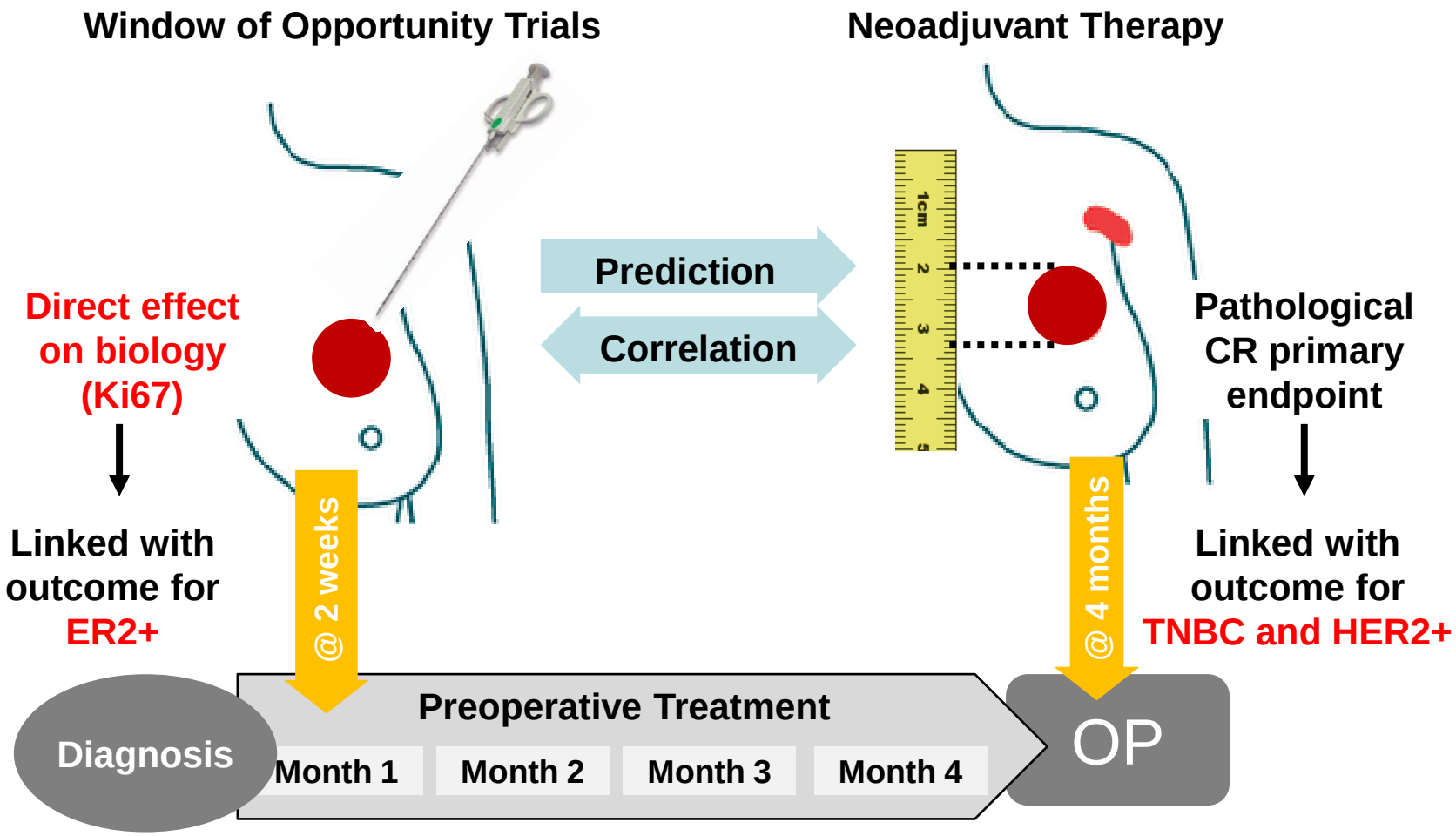


- TNBC; s/p salvage chemotherapy (× 3), trial vaccine; MPDL3280A (Mar 2013 to Feb 2014)
- Target lesions responded, and new lesions developed; new lesions eventually responded

Emens et al. AACR 2015

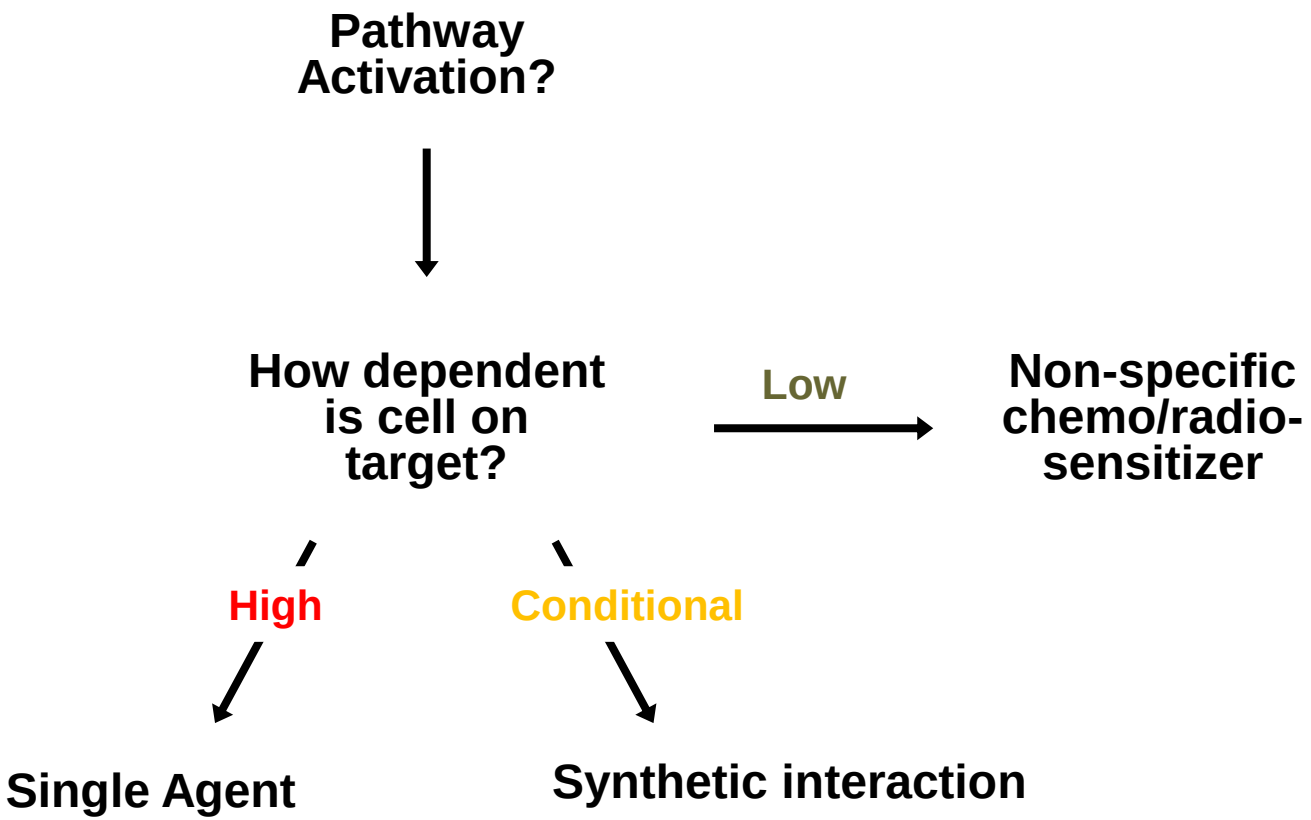
Selecting the right endpoint for early disease

Postoperative therapy not suited for early drug development due to long F/U time

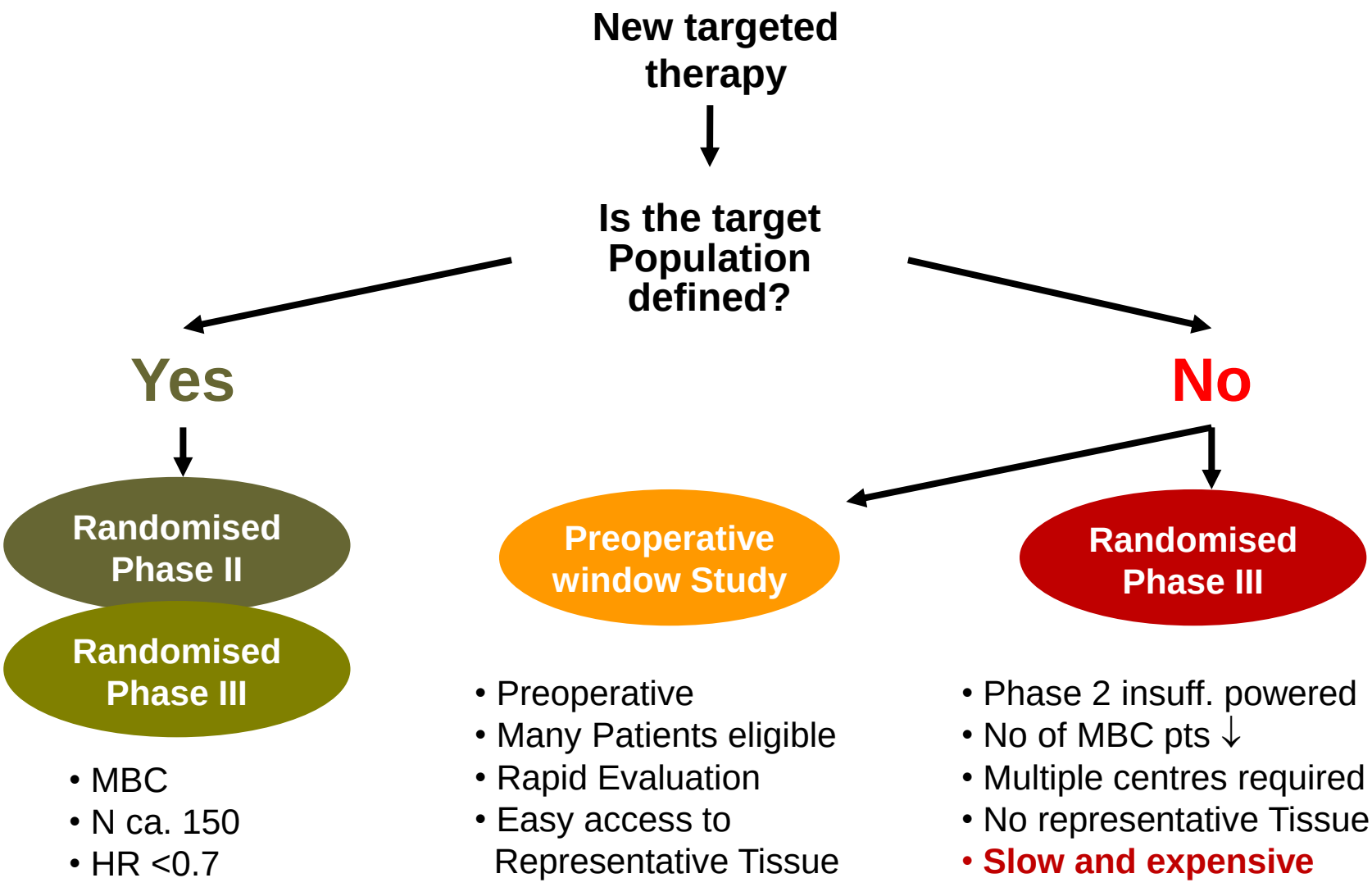


- Who should we treat?
- How to measure the effect of the drug?
- What's the best strategy (eg combination, schedule)?

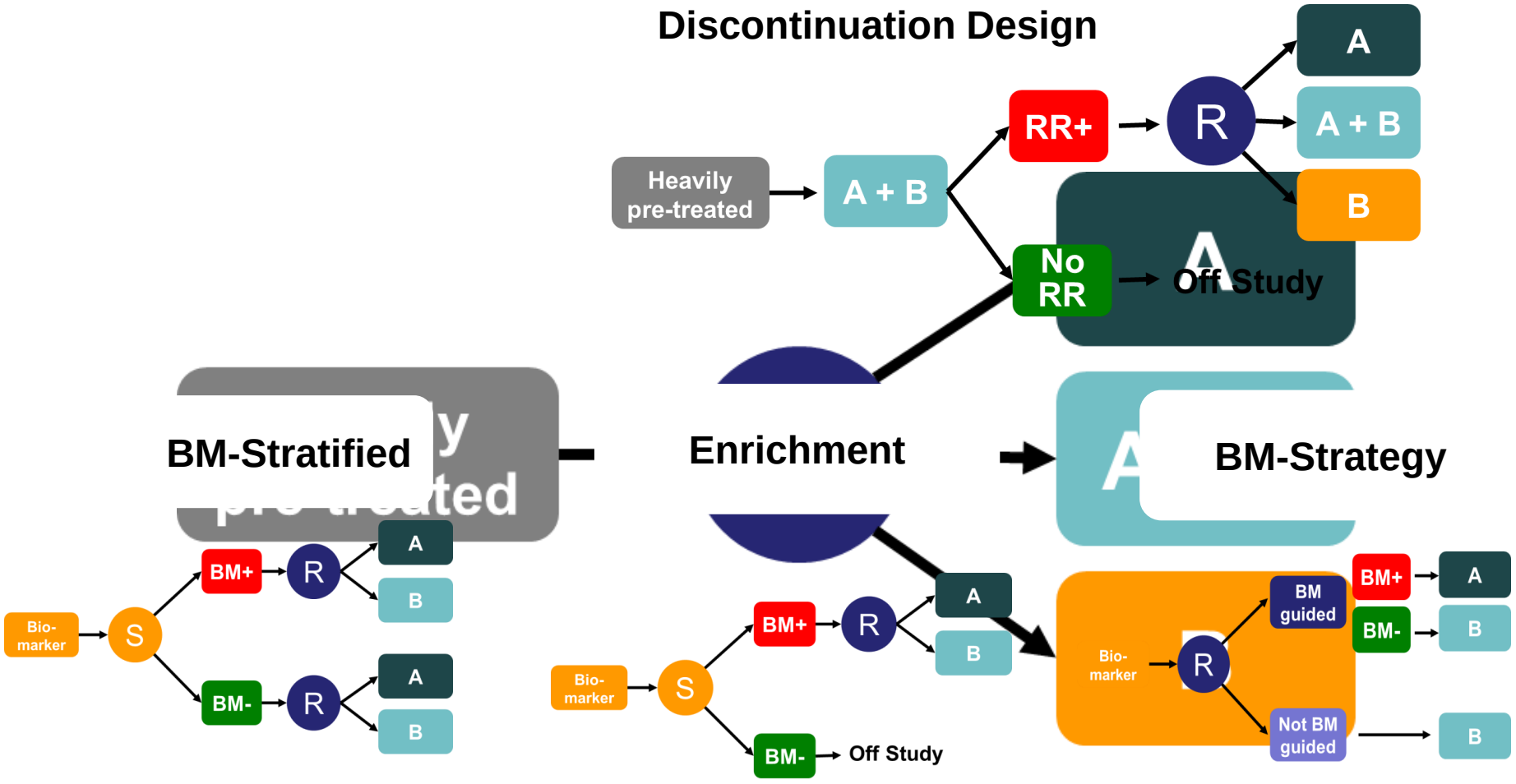
Single agent or combination?



Is the target population defined?



If target population is defined -> rand. Phase 2 Study

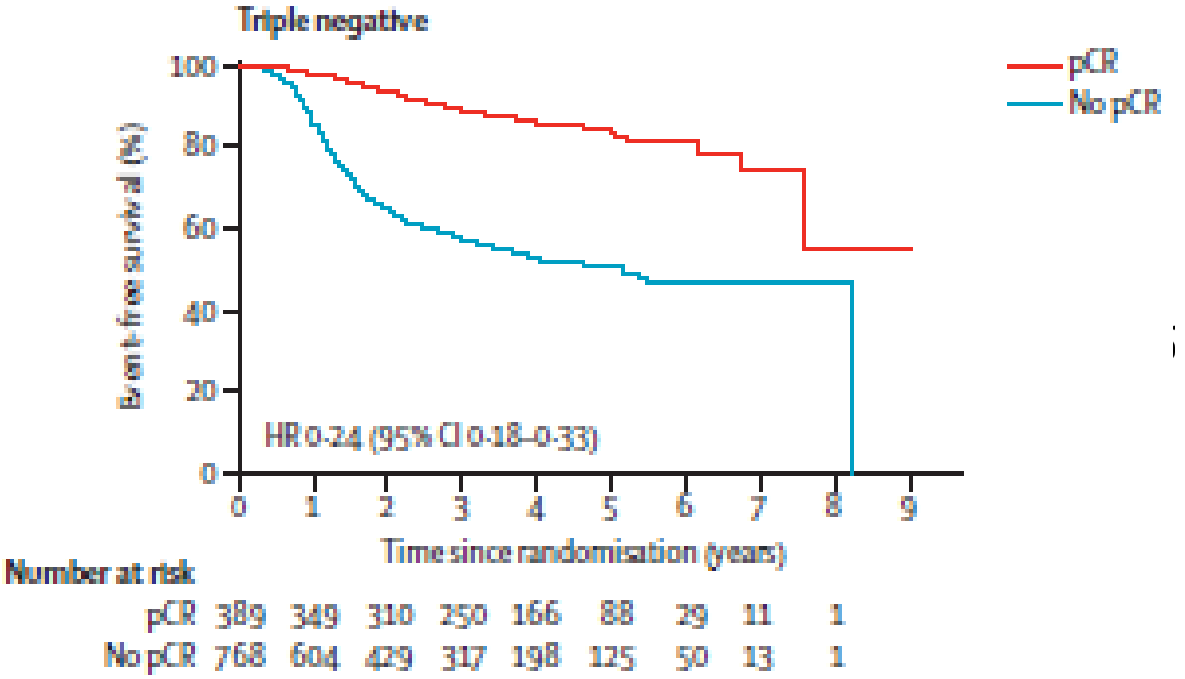


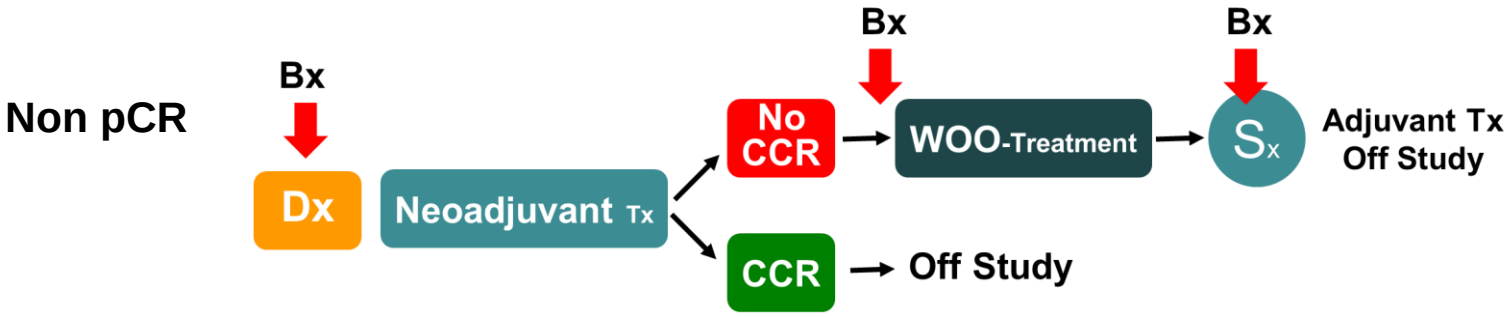
- Doesn't work for >1 options
- Most robust
- Relatively large

- Efficient
- Reliant on BM
- Trial+ not proof of BM validity

- Works for >1 options
- Inefficient
- Trial+ not proof of BM validity

Dynamic preoperative Designs





[1] Cortazar, Lancet 2014

Summary and Conclusions

- Detailed understanding of mode of action and tumour effects is critical for effective clinical development
- Preclinical characterization can guide selection of optimal clinical endpoints
- New strategies bring new challenges (pseudo-progression)
- Target population key to clinical development
  - If defined, randomised phase 2 study
  - If not defined, WOO study to defined target population
- Biomarkers or clinical/pathological response-triggered dynamic concepts open new avenues

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Lead, Centre for Experimental Cancer Medicine

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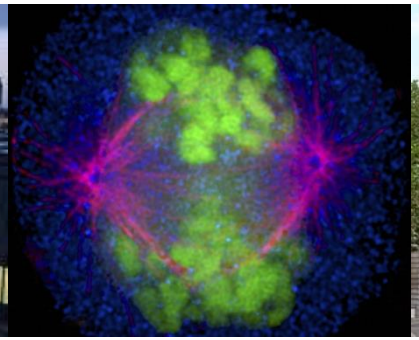


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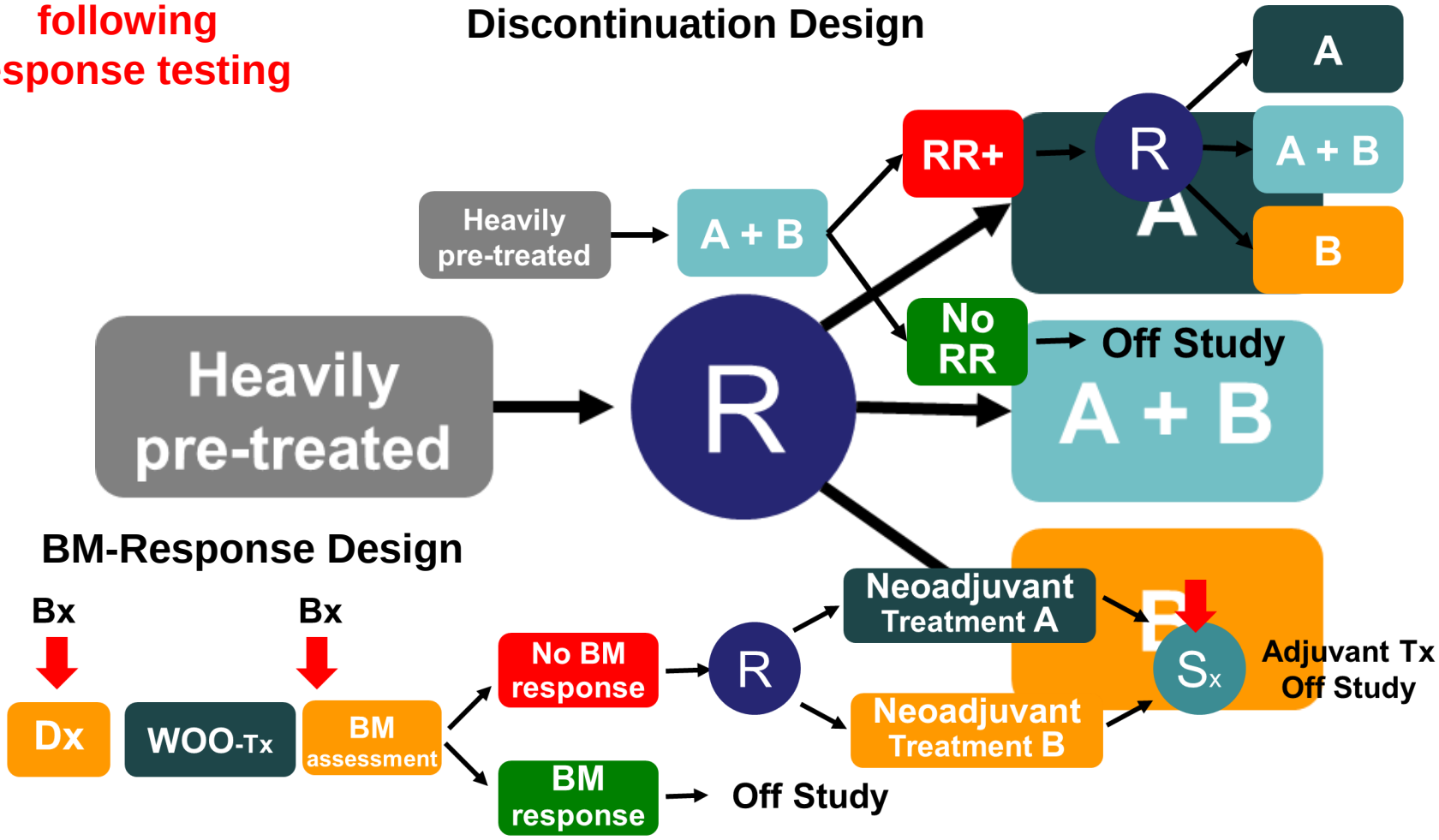
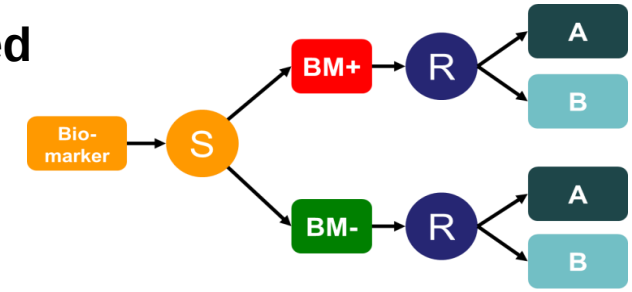
If target population is defined -> rand. Phase 2 Study

Dynamic Designs following response testing



Biomarker-guided randomised trials

BM-Stratified



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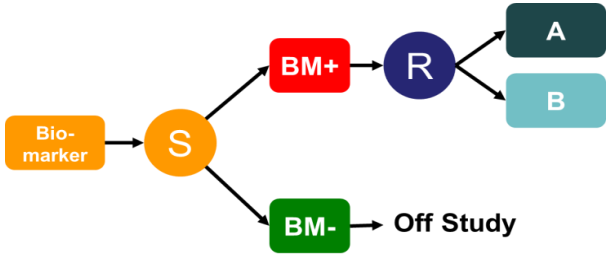
Enrichment



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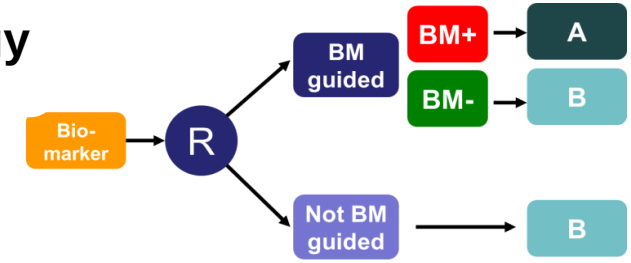
BM-Strategy



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