Early Drug Development

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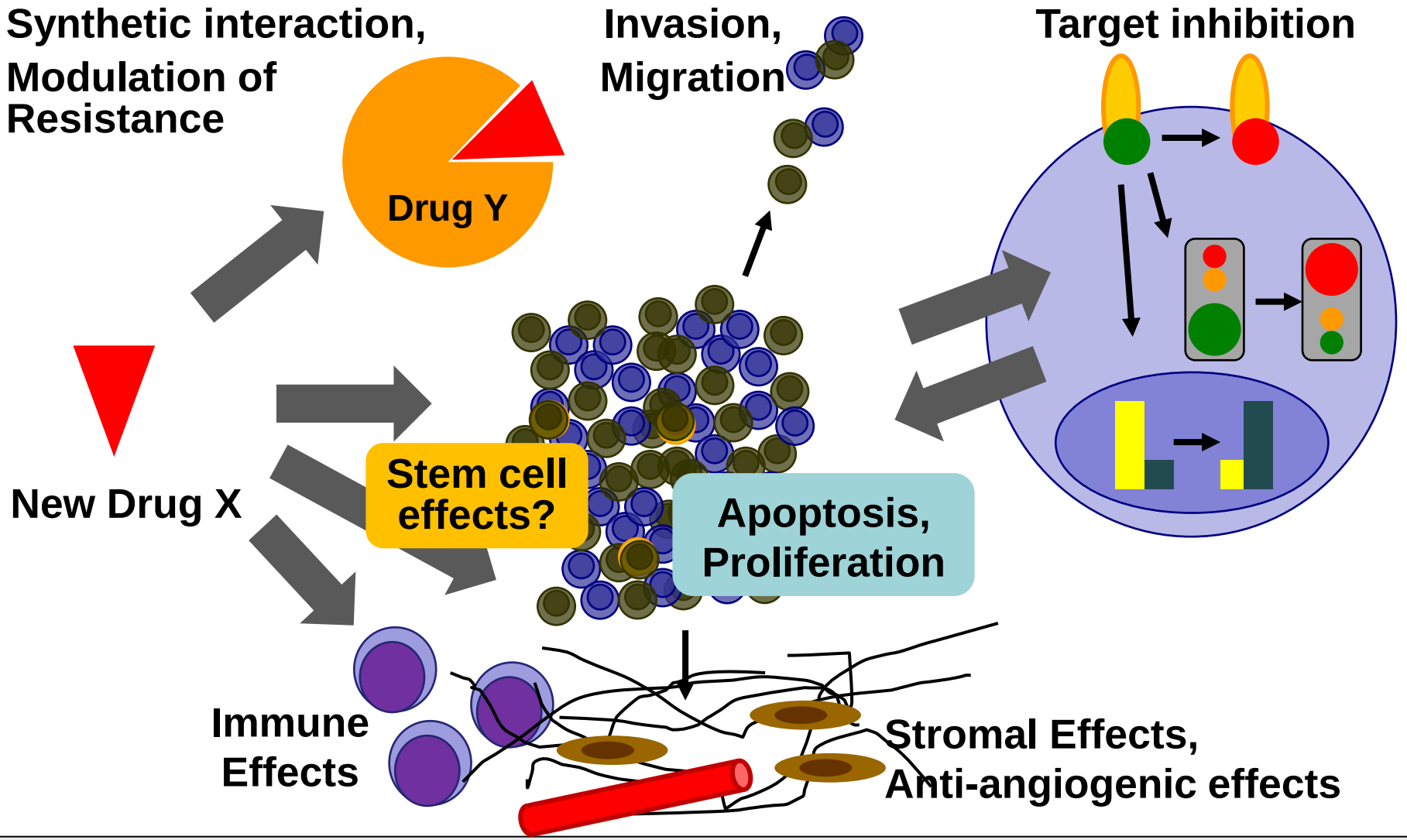
Clinical Development of Novel Drugs

What to we need to know from preclinical studies?

- Does the Drug hit the Target?
- Mode of Action (-> PD markers)
- Anti-tumour Effects
- Target Population (-> Predictive BM)
- Interactions (Combination, Schedule)

Preclinical Development of Novel Cancer Therapies
Characterisation of antitumour effects



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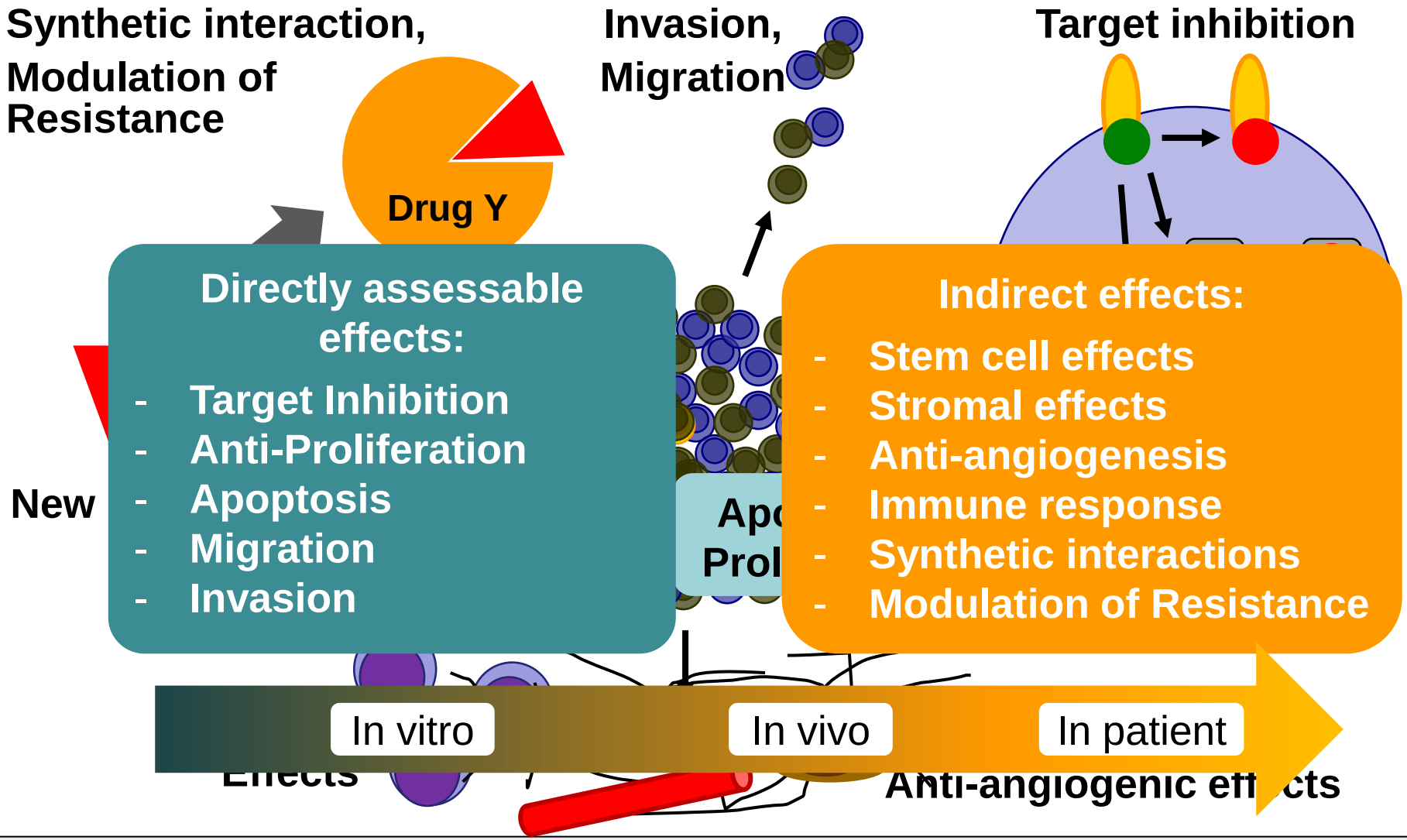
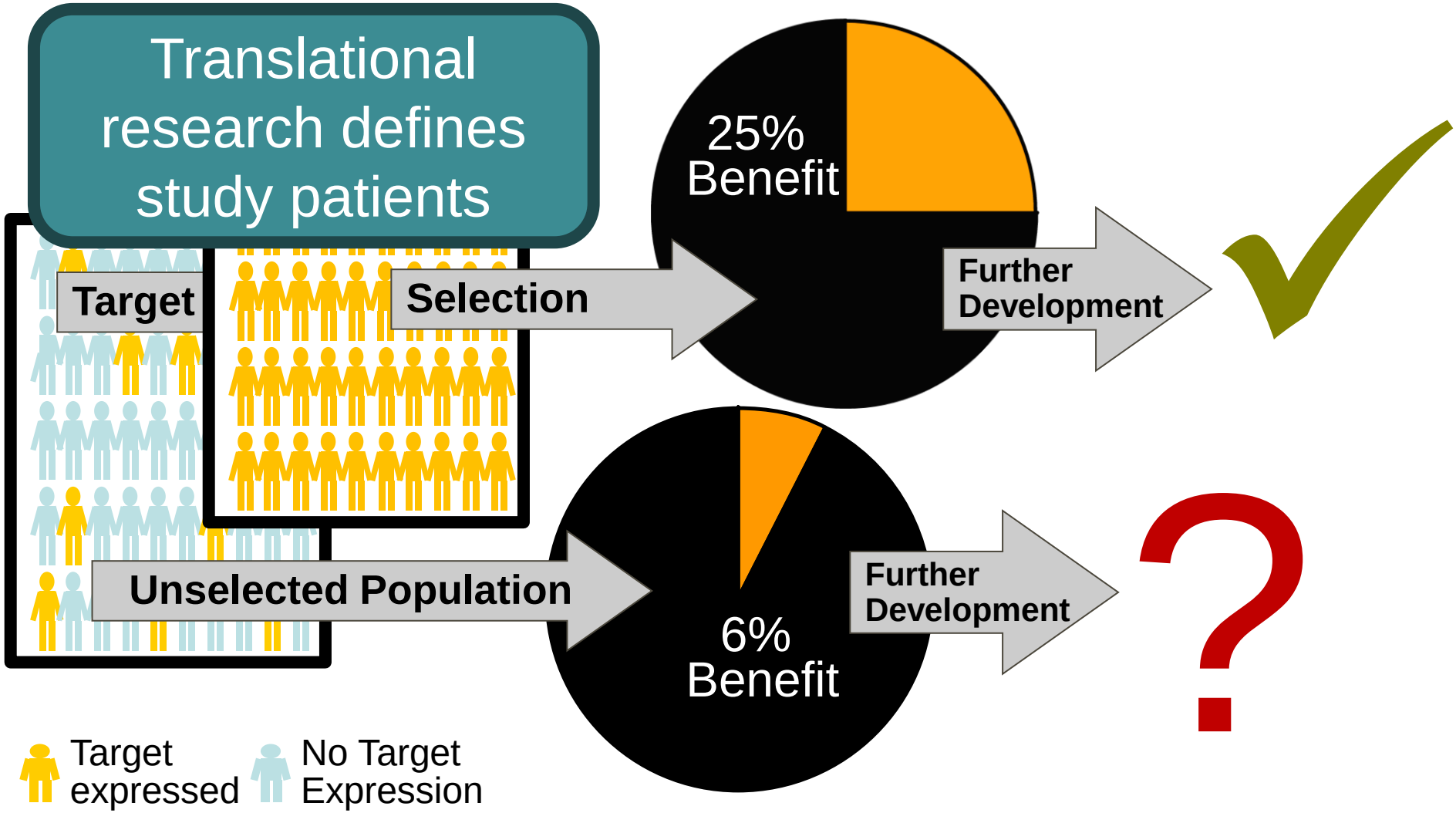


Clinical Development: Identifying the Target Population

Treating the right patients is critical



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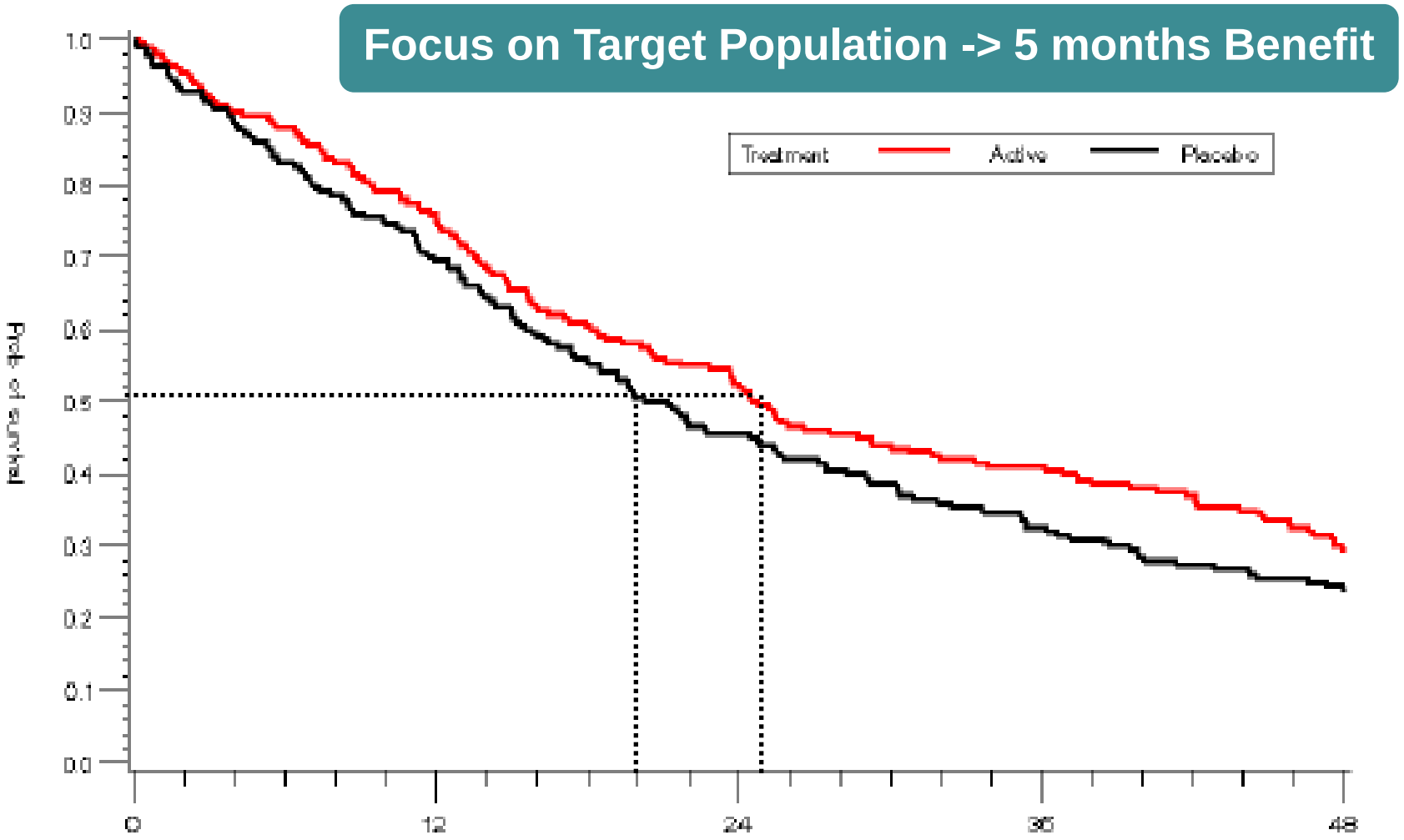

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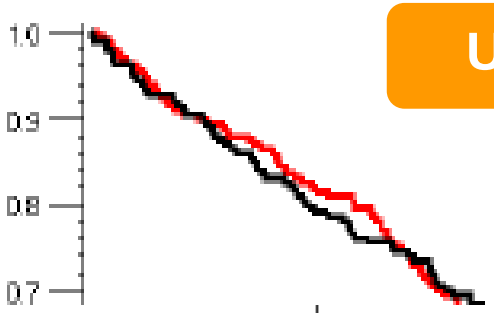
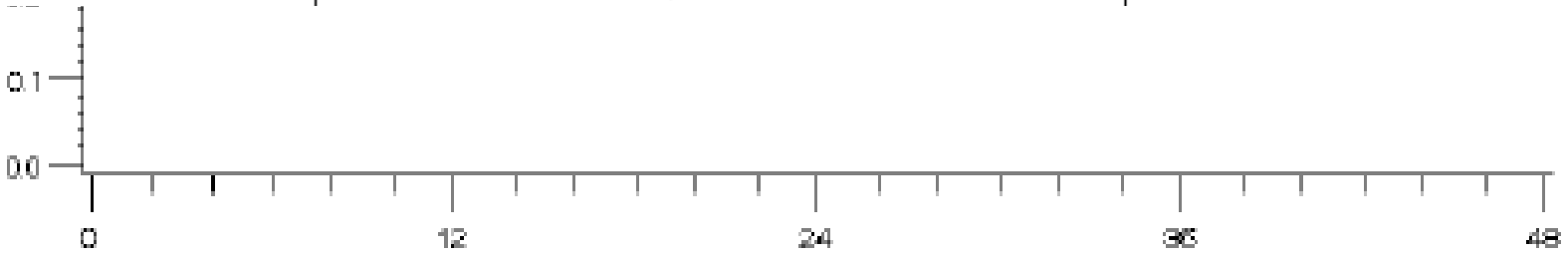


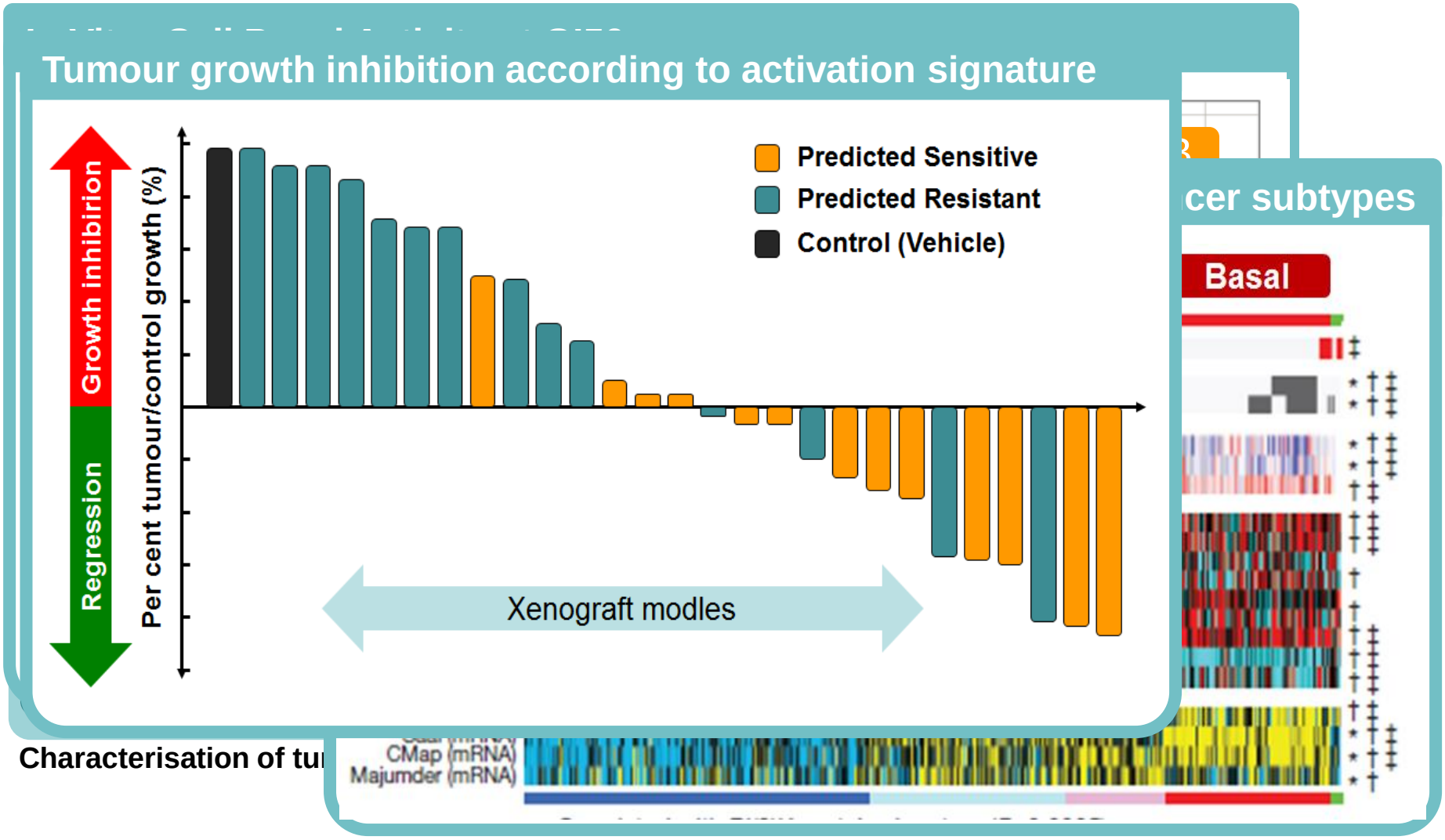
Unselected Population (25% express target)

Treatment — Active — Placebo

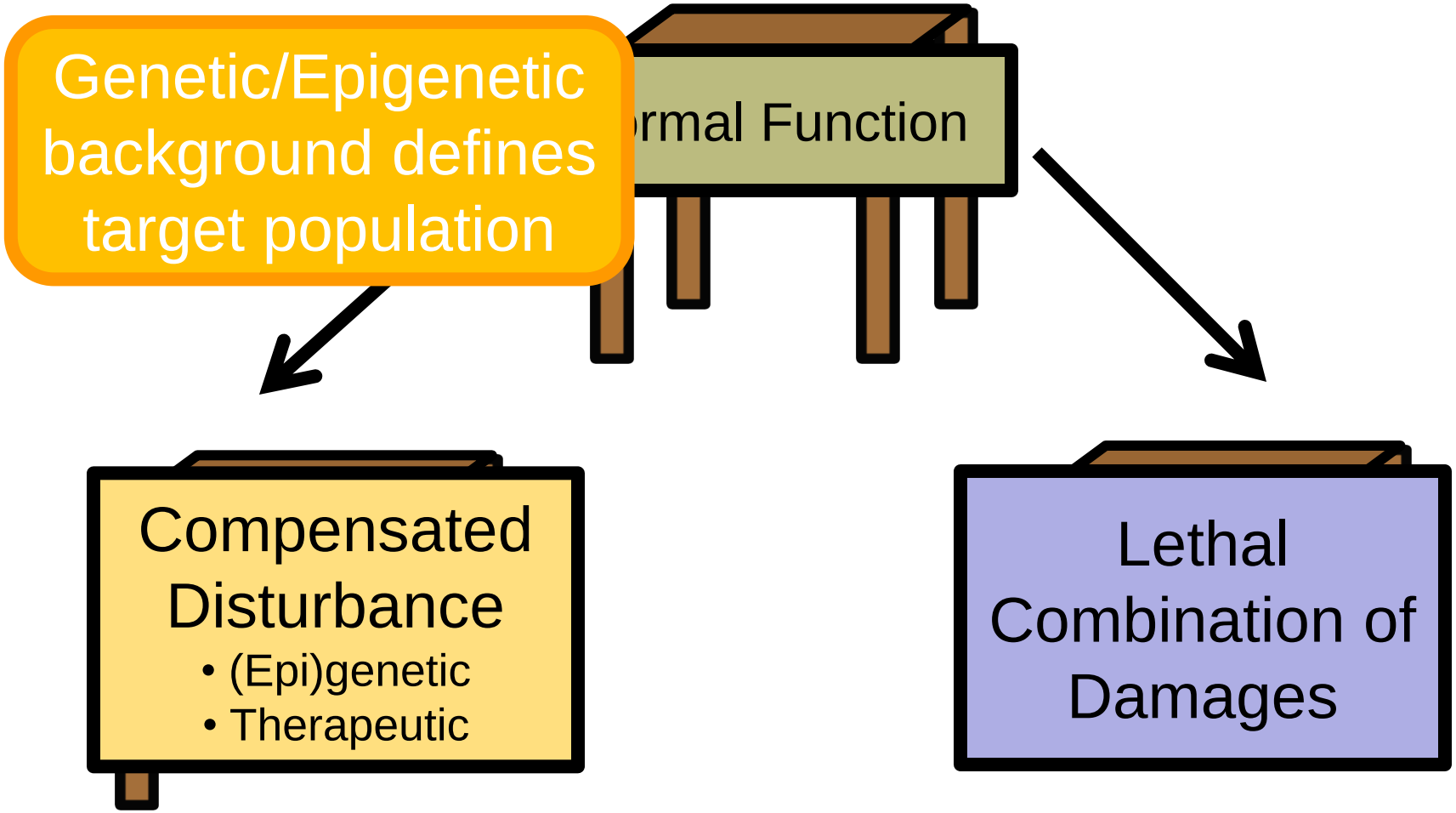
Expected Benefit	Target Prevalence	Actual Benefit (All Patients)	Required Sample Size And Study Duration
↑ 5 months (22.7%)	100%	↑ 5 mos (22.7%)	1250 → 52 mos
	50%	↑ 2.5 mos (11.4%)	3500 → 108 mos
	25%	↑ 1.25 mos (5.7%)	11000 → 349 mos



Preclinical Development of Novel Cancer Therapies
Characterisation of Target Population



New Targeted Approaches
Utilising synthetic Lethality Strategies



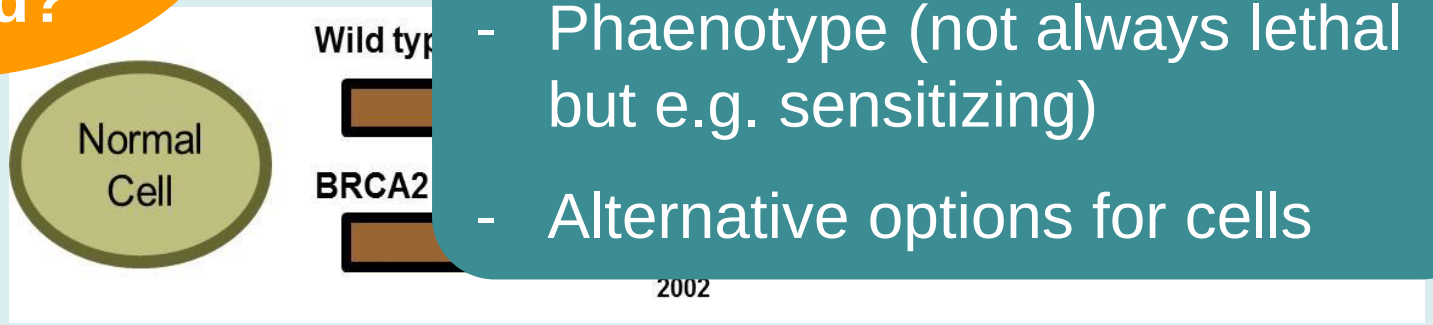
Utilising synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP

Why don't all patients respond?

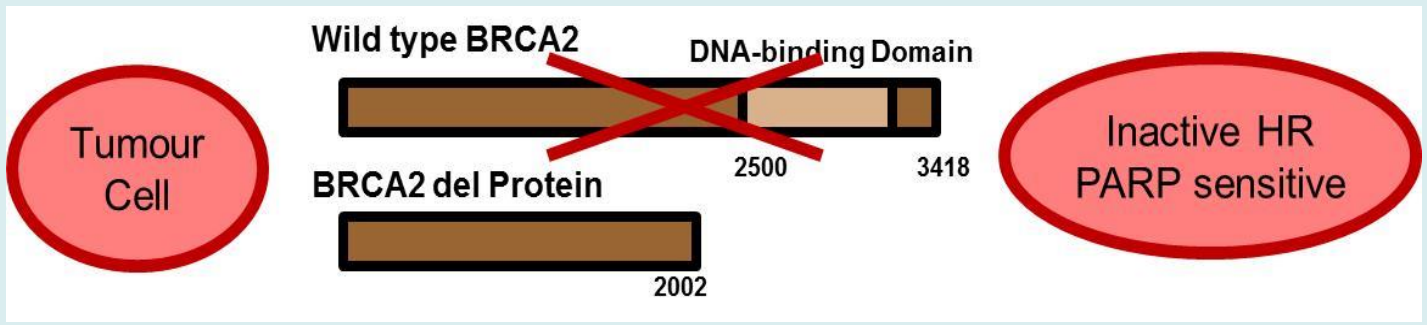
Why effect t… selec…

Critical to understand biology

- (Epi)Genetic background (e.g. total vs partial loss of function)
- Phaenotype (not always lethal but e.g. sensitizing)
- Alternative options for cells

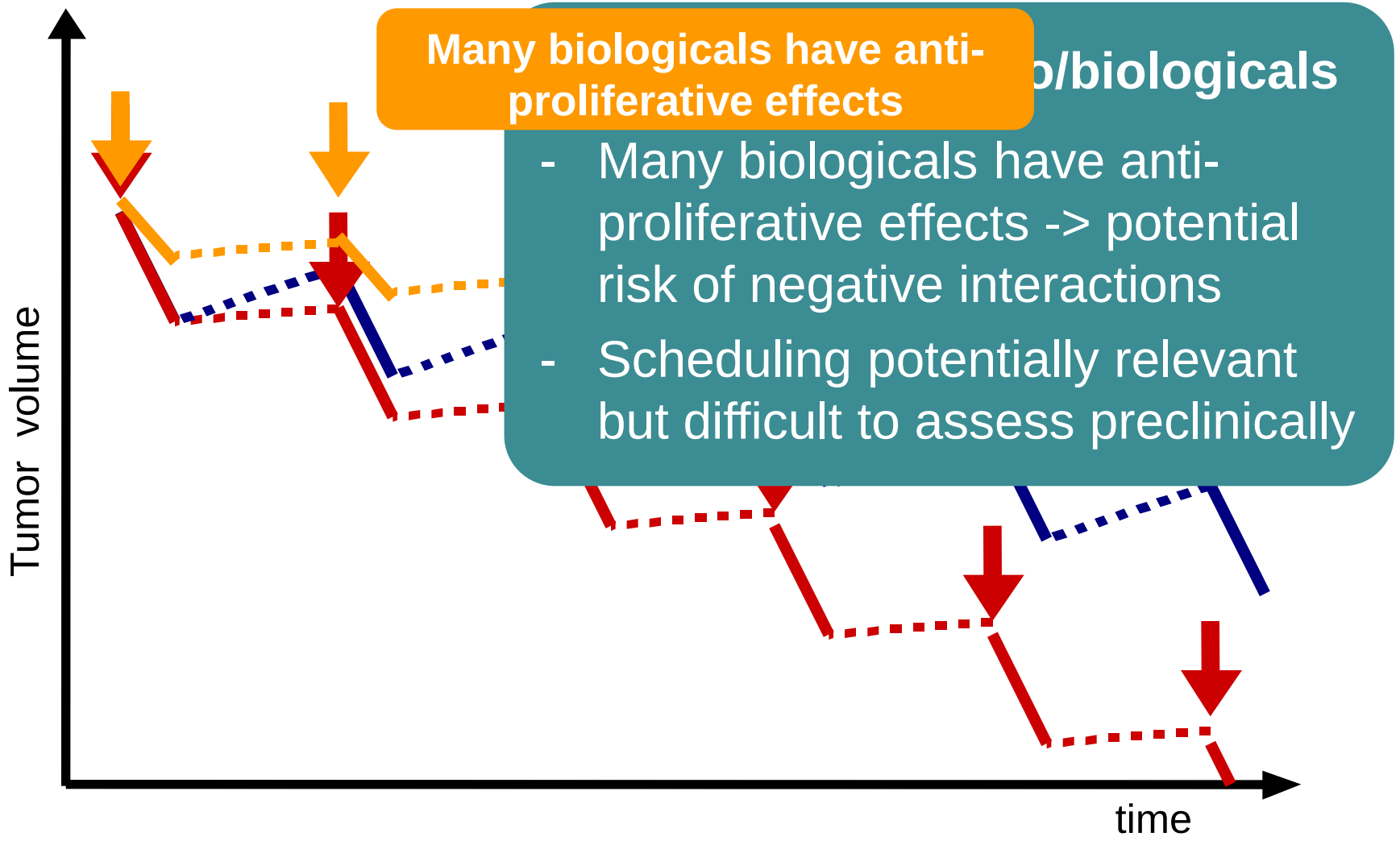


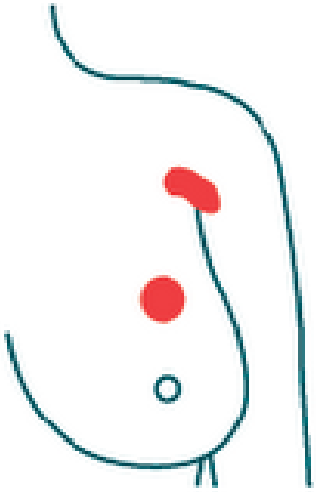
Cell death

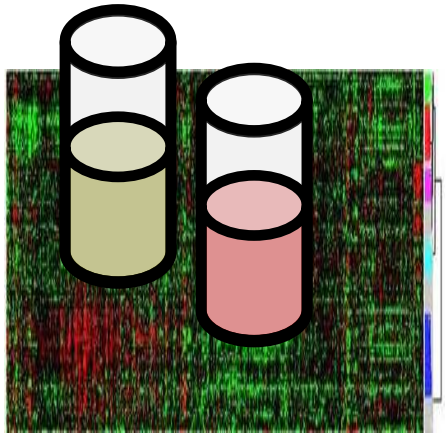


Combination of biologicals and chemotherapy

Relevance of scheduling





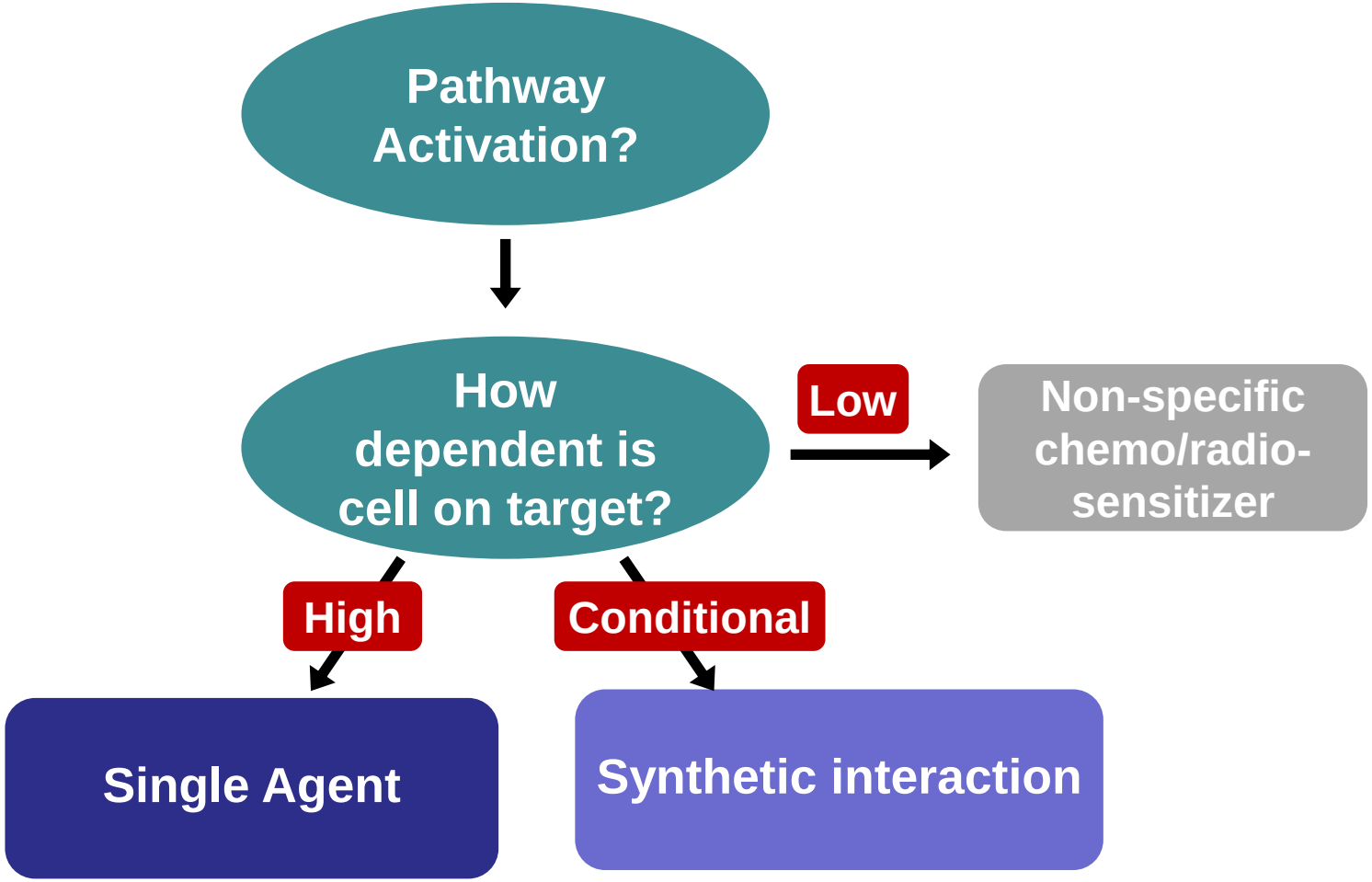


From the Lab back to the Clinic:

Challenges and new strategies

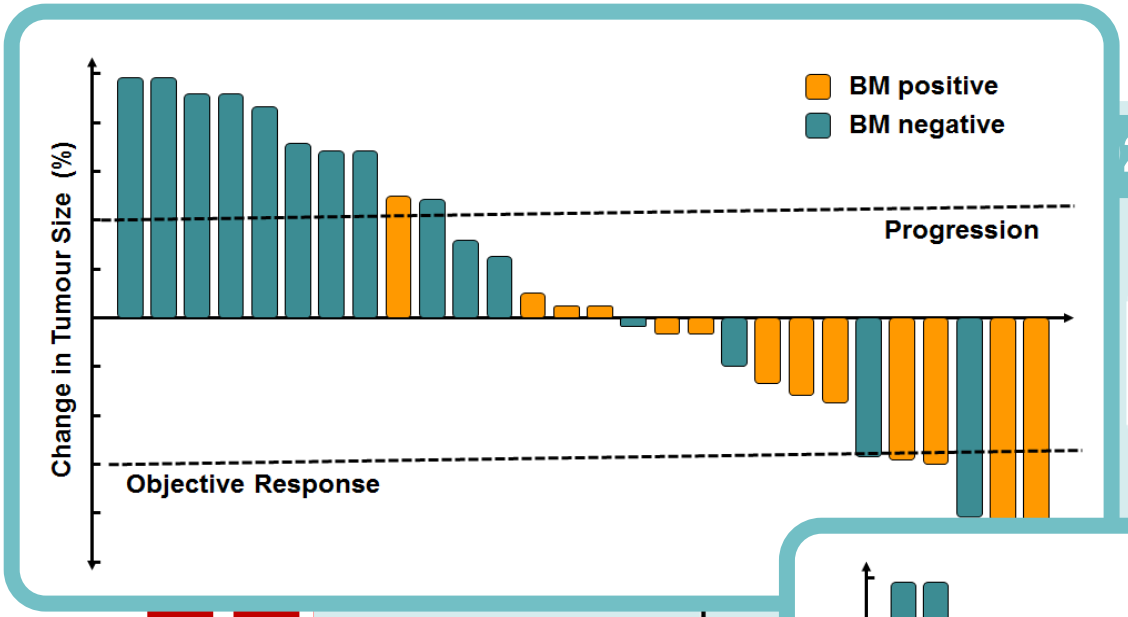
Clinical Development: Choosing the right strategy (I)

Single agent or combination?



Clinical Development: Choosing the right strategy (II)

Choosing the right endpoint



Patient dies

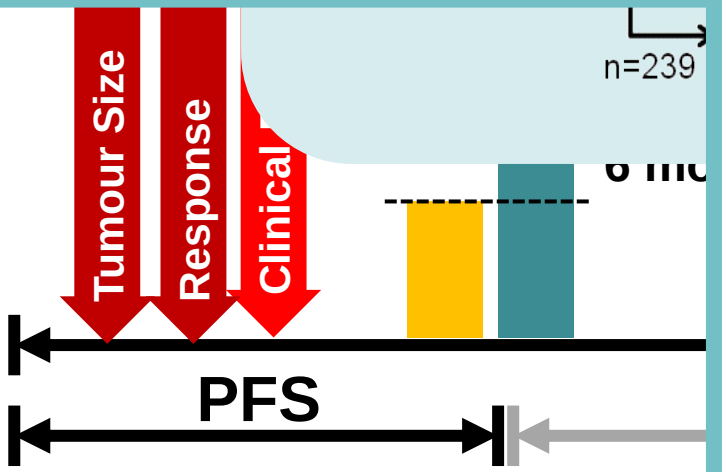
2 Trial

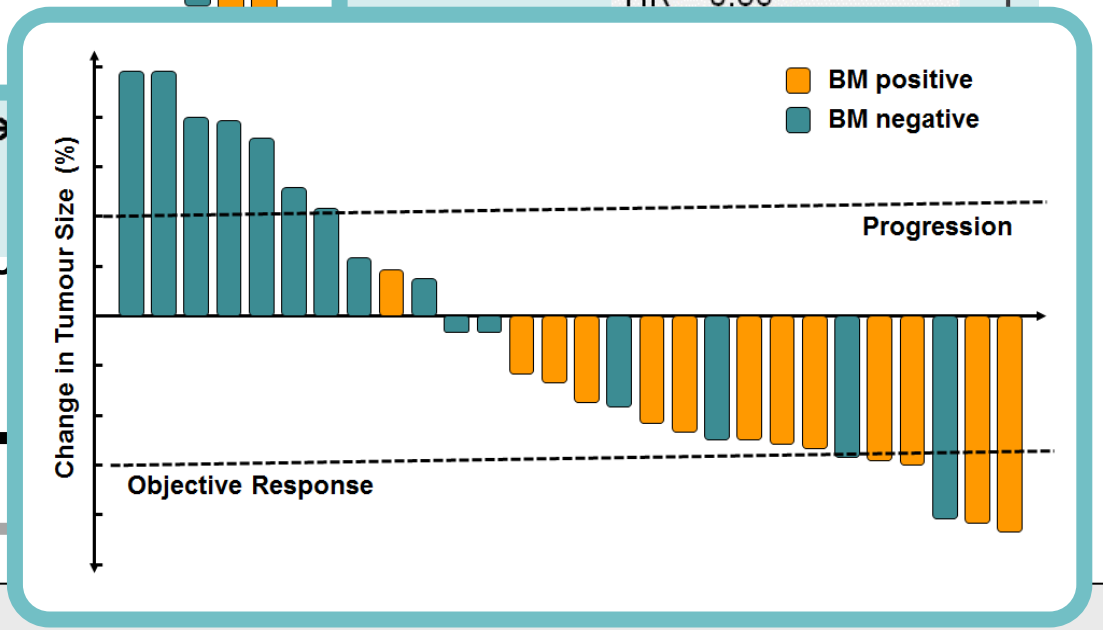
Time to Progression

11.0 months

HR = 0.36

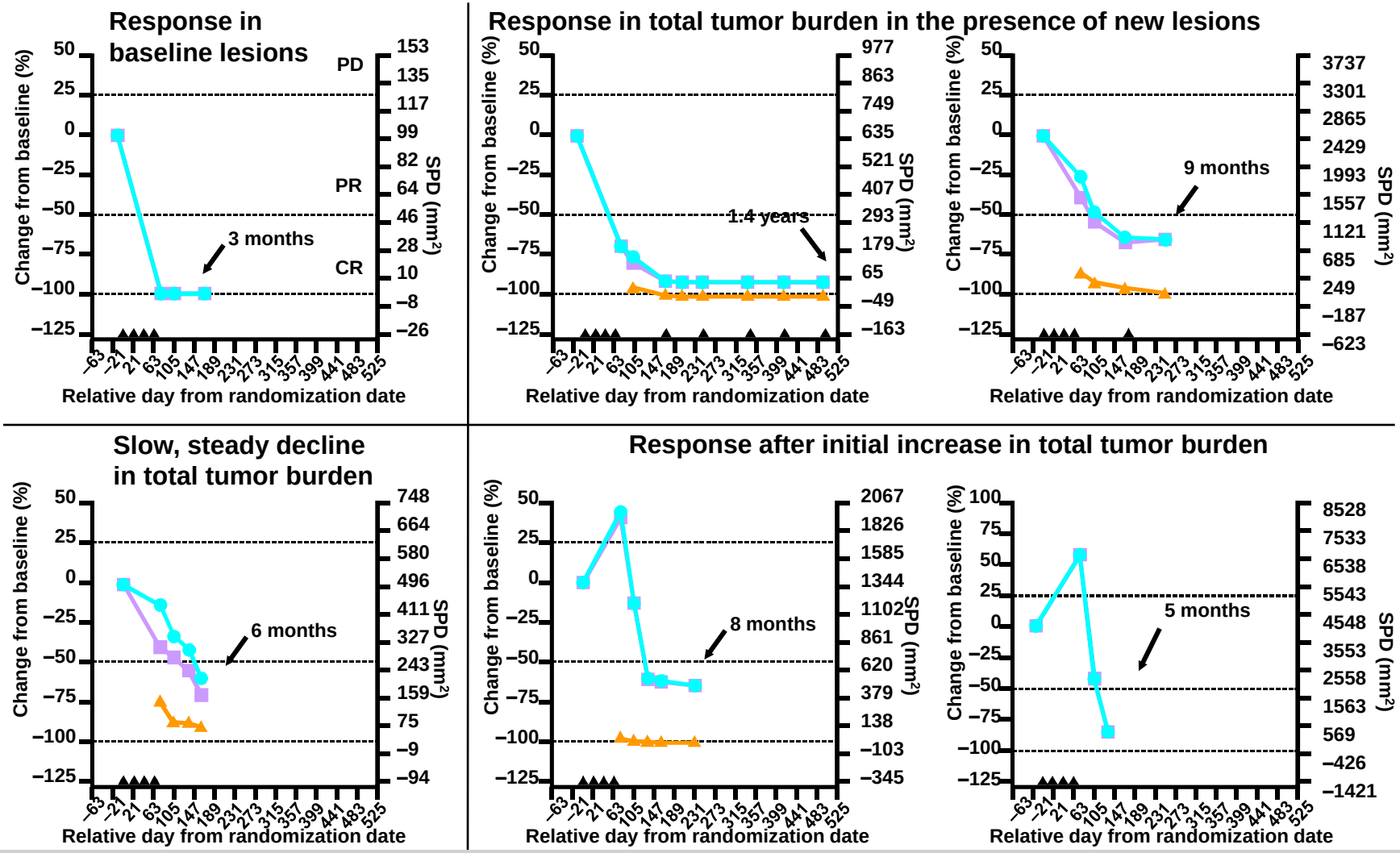
n=239





Clinical Development: Choosing the right endpoint (II)

Patterns of Response with Ipilimumab



Weber et al, 2008.

Clinical Development: Choosing the right endpoint (II)

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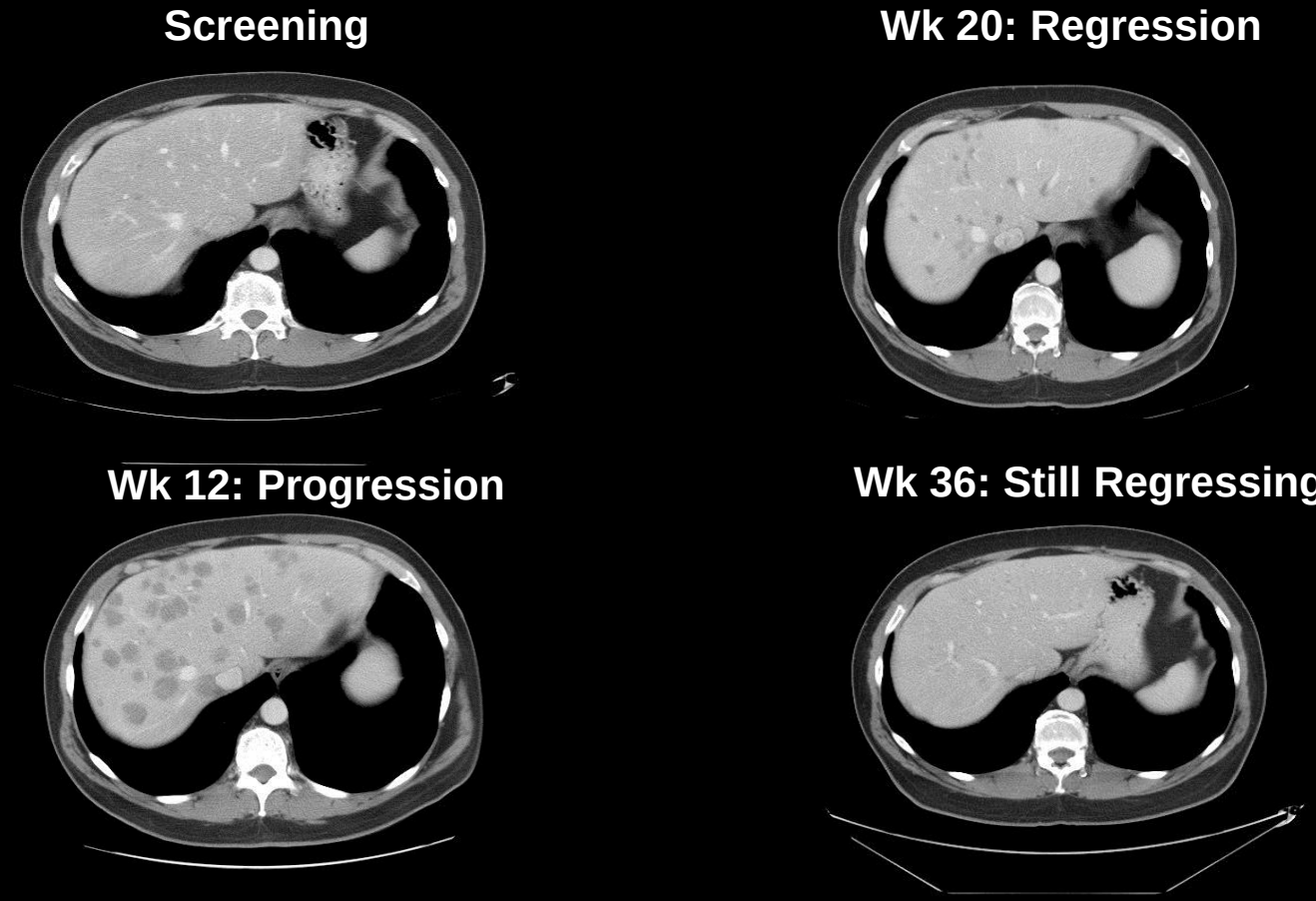
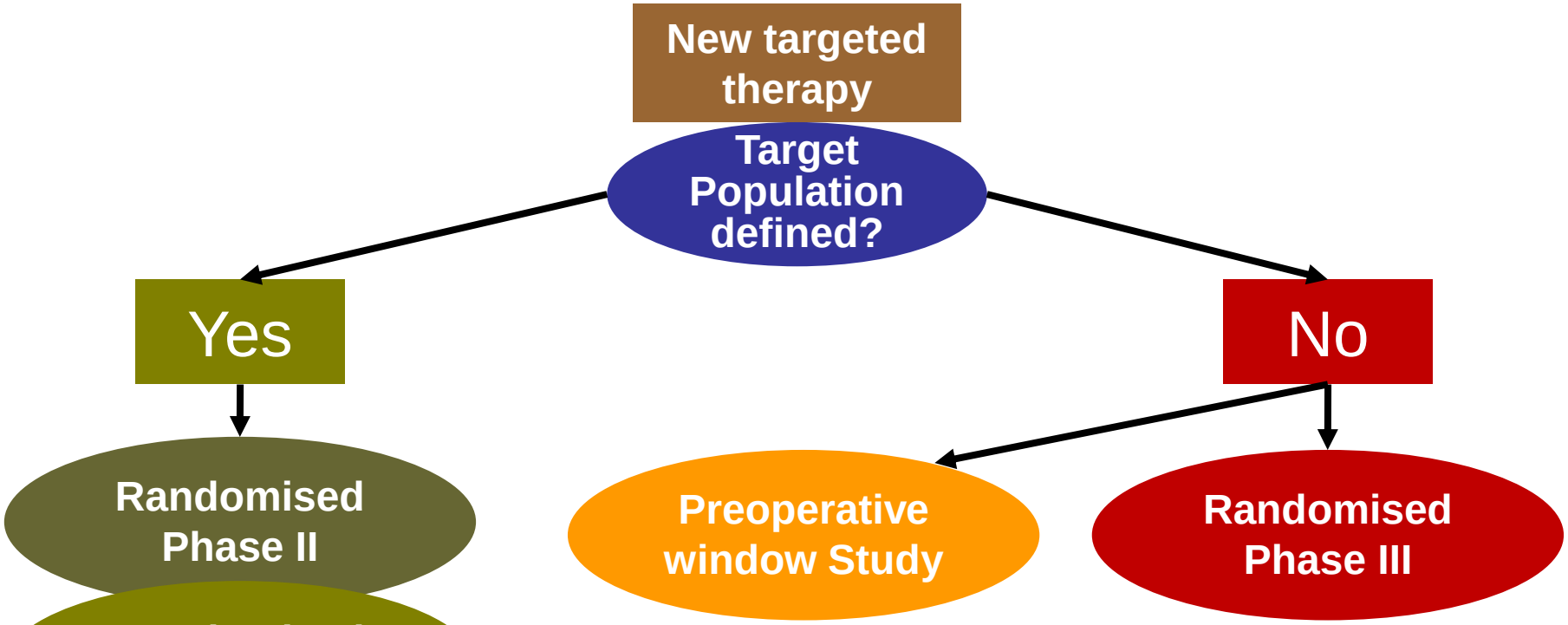


Response to Ipilimumab After Significant Progression With Tumor Volume Increase

Saenger et al, 2008.

Clinical Development: Choosing the right strategy (III)

Is the target population defined?

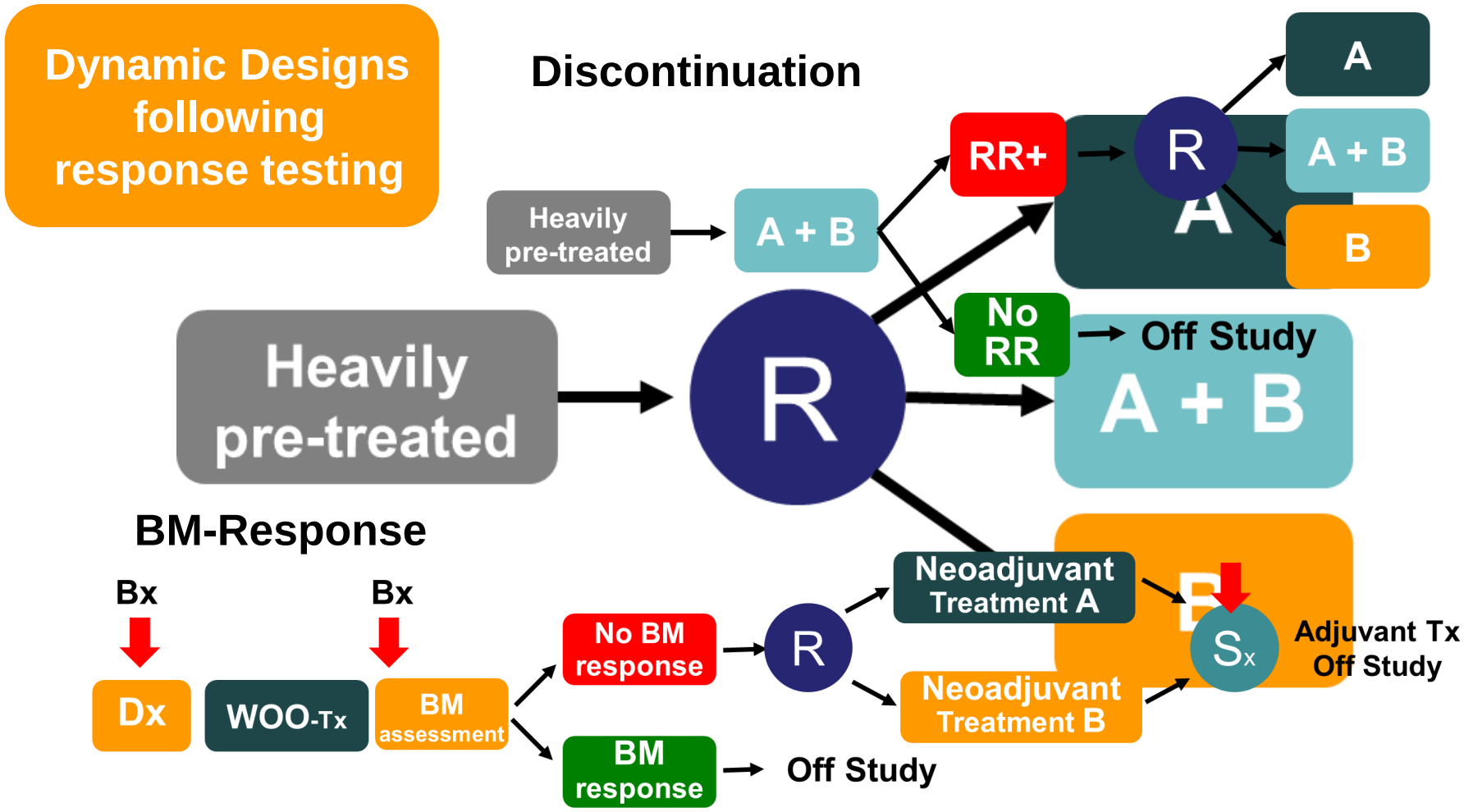


- MBC
- N ca. 150
- HR <0.7

- Preoperative
- Many Patients eligible
- Rapid Evaluation
- Easy access to Representative Tissue

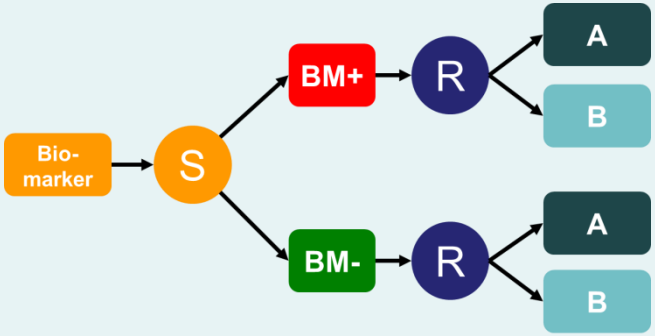
- Phase 2 insuff. powered
- No of MBC pts ↓
- Multiple centres required
- No representative Tissue
- **Slow and expensive**

If target population is defined:
Randomised Phase 2 Studies



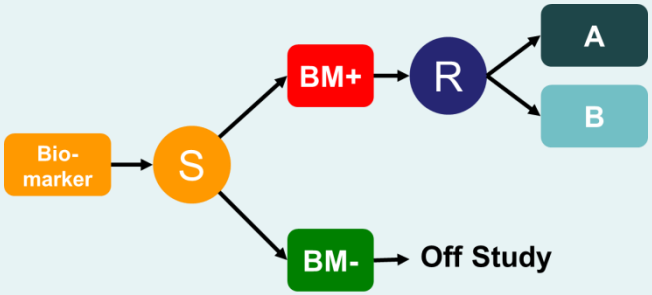
Biomarker-guided randomised trials
Biomarker-strategy Design

BM-Stratified



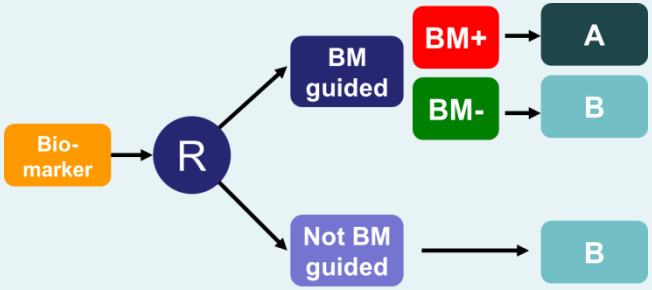
- Doesn't work for >1 options
- Most robust
- Relatively large

Enrichment



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

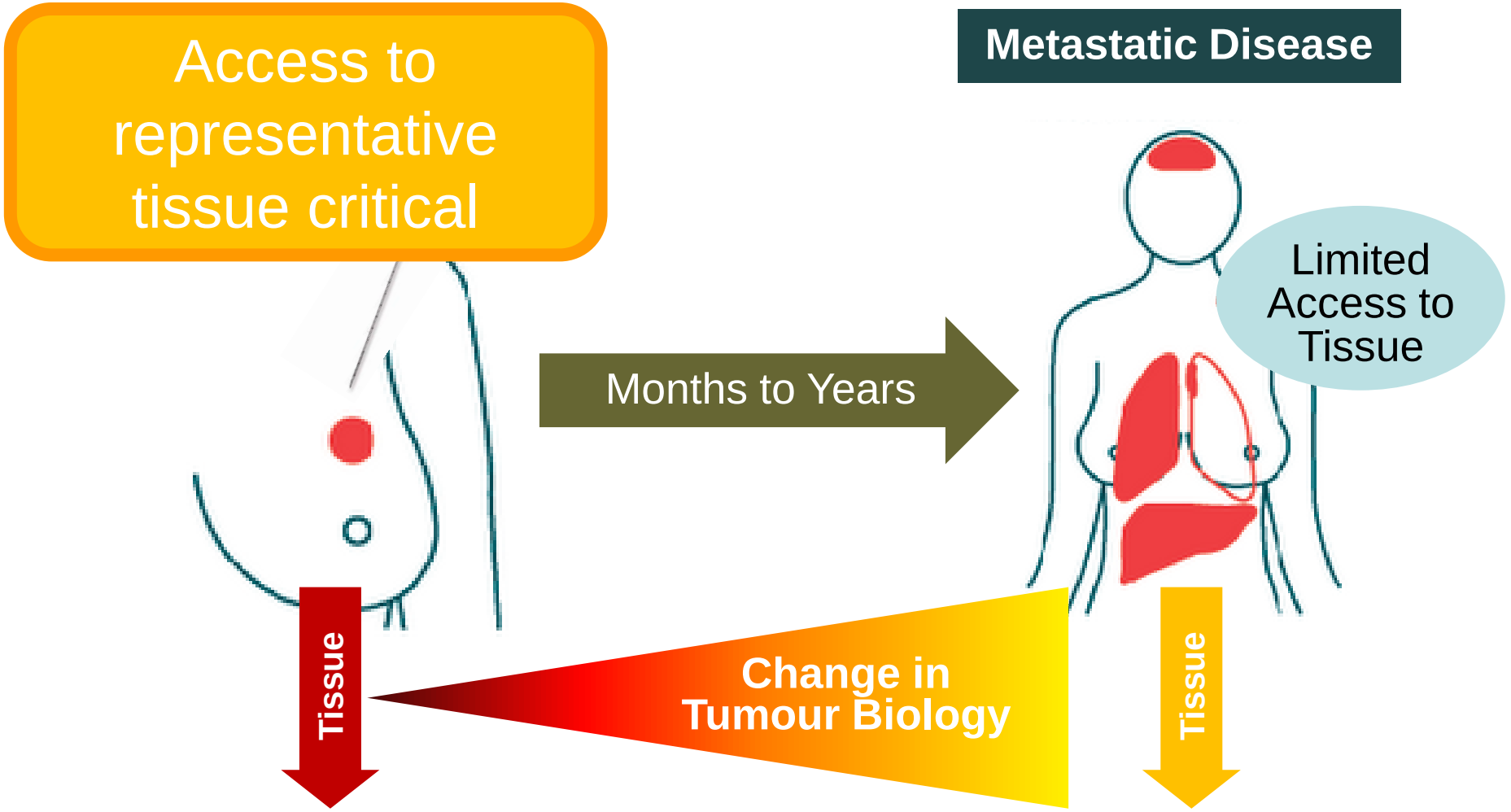
BM-Strategy



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

Novel Targeted Therapies and Patient Selection

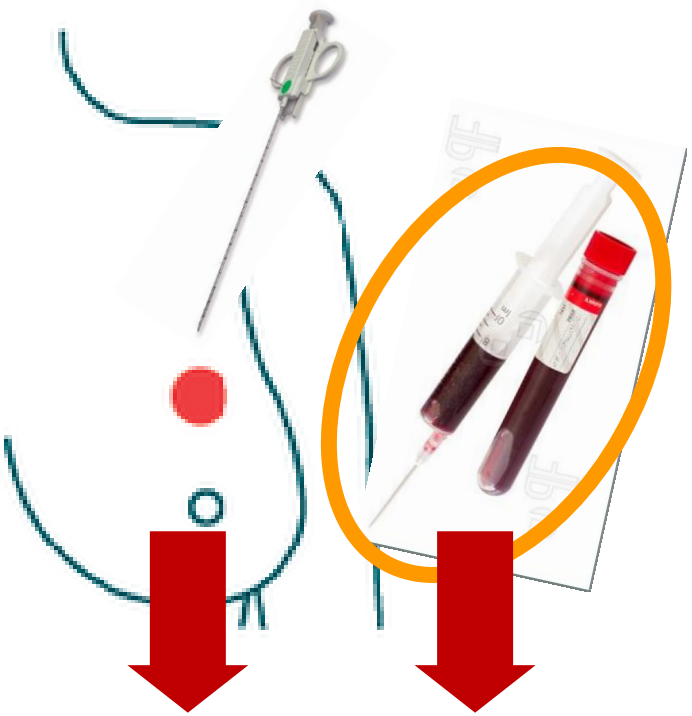
Change of Tumour Biology over Time

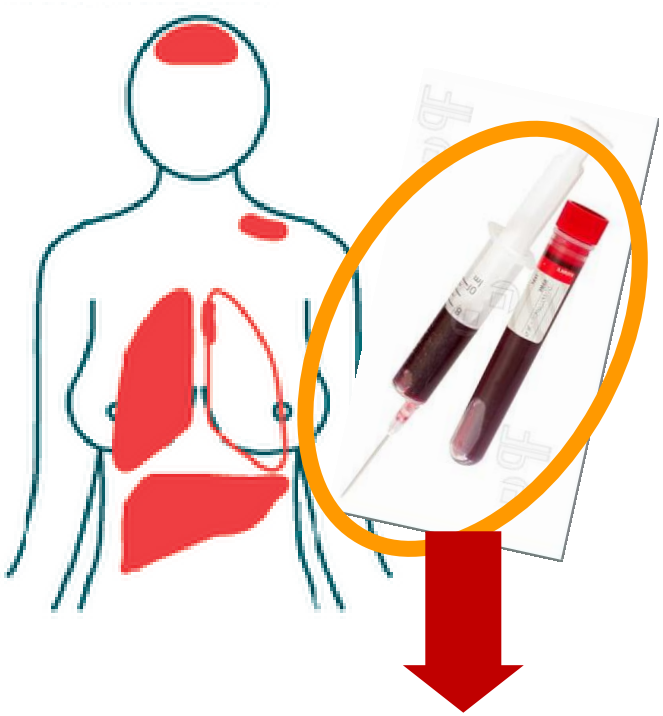


Novel Biomarkers to assess dynamic changes
(Epi)genetic profiles from Plasma DNA

Early Breast Cancer

Metastatic Disease

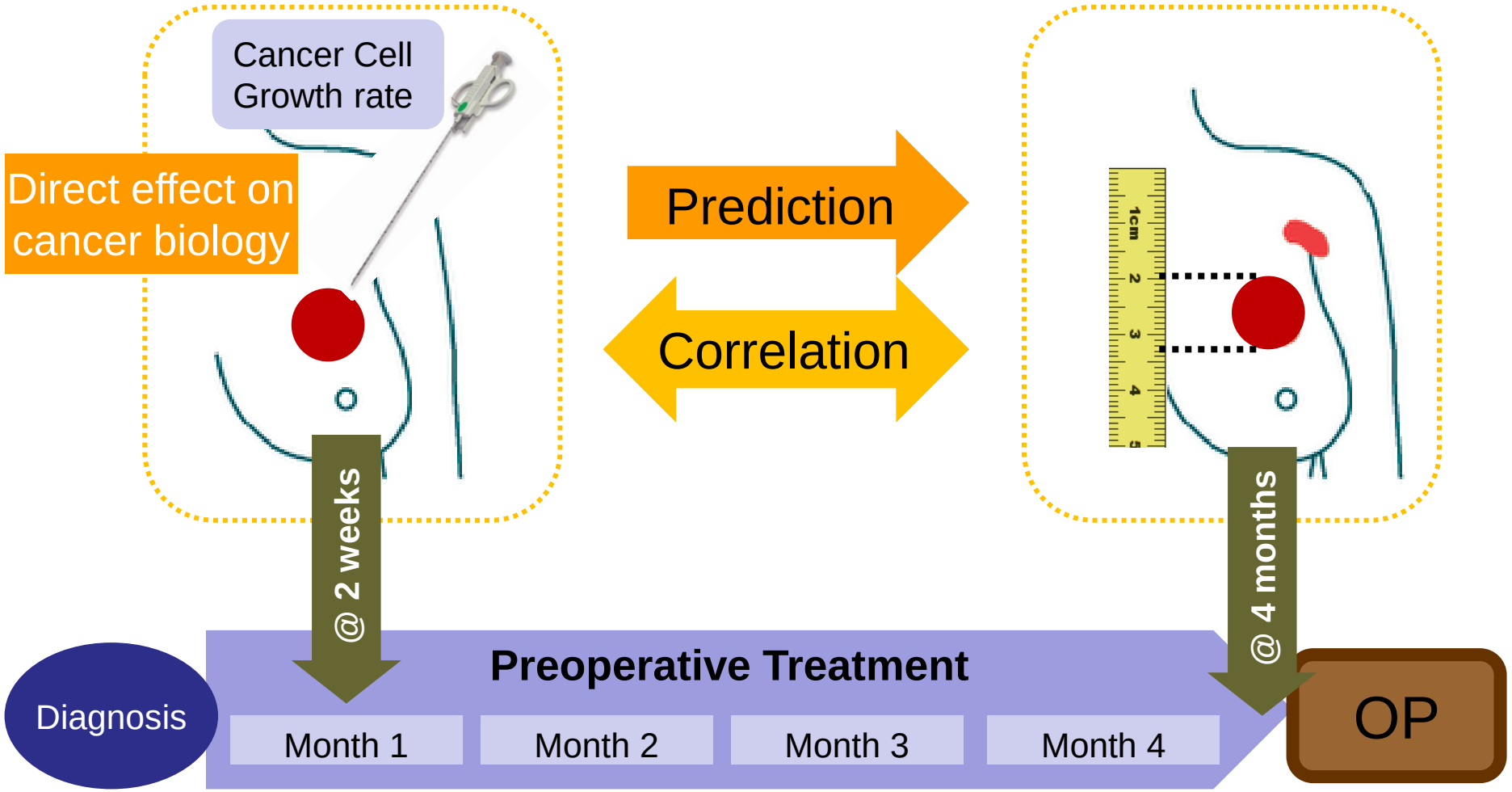




(Epi)genetic changes detectable in Blood

Simple Means for assessing changes

If target population is NOT defined:
WOO Studies



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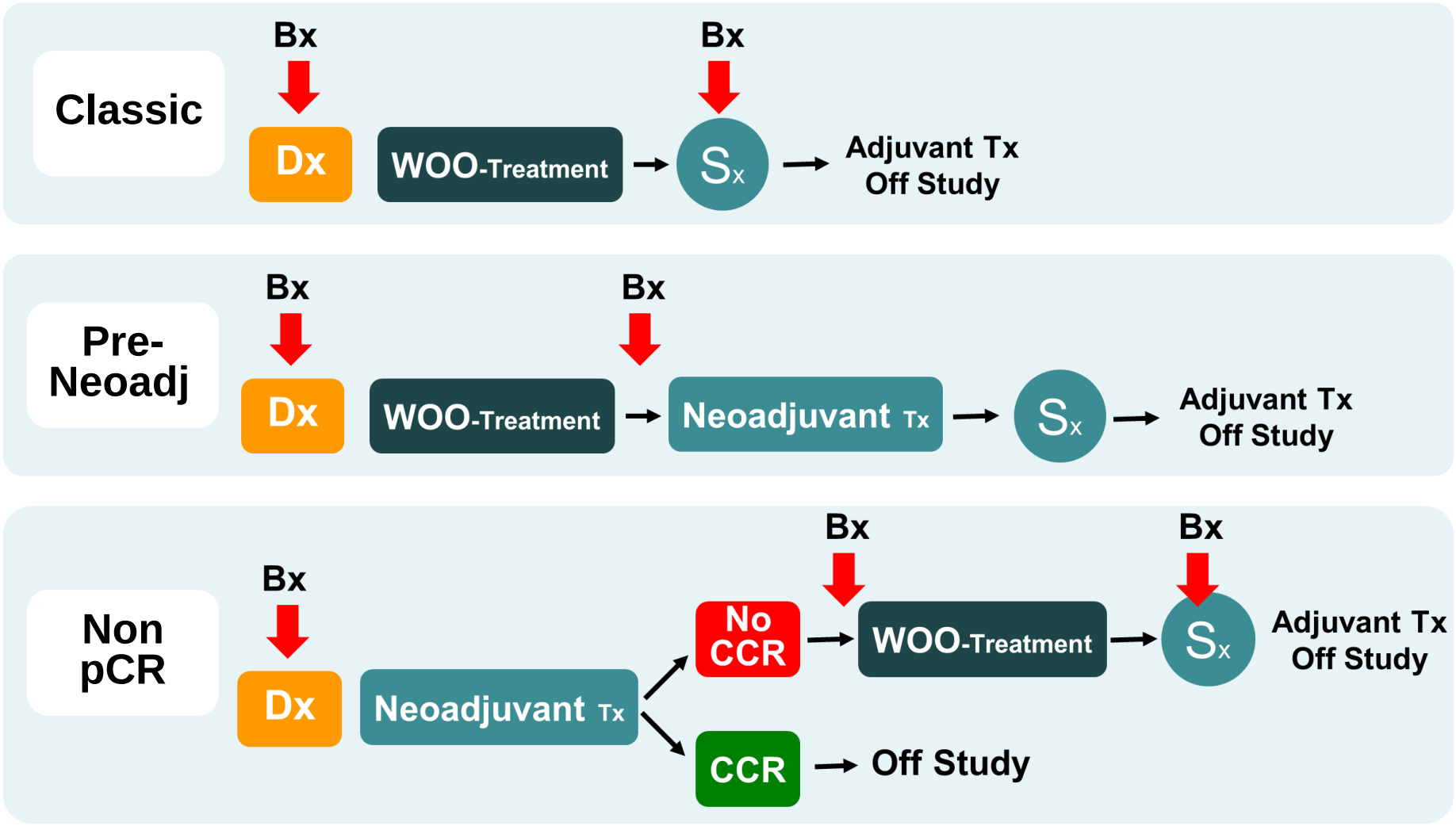

Platforms of preclinical applications:
The use in clinical study design

- Detailed understanding of MOA and tumour effects is critical
- Some aspects difficult to model preclinically (e.g. scheduling)
- Target population key to clinical development
  - If defined, randomised phase 2 study
  - If not defined, WOO study to defined target population
- BM/Clinical/Path. Response-triggered dynamic concepts open new avenues

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