

# PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

## Appropriate Endpoints in Clinical Trials and Markers for Long-Term Clinical Outcome

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# Alternative Title

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"How to Upset Statisticians  
and Methodologists in Less  
Than 20 Minutes"

# Goals of Preoperative Systemic Therapy in Operable Breast Cancer

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- To improve odds of breast conservation surgery  
→ *YES, BCS rates improved by 5-10%*
- To allow early assessment of treatment effect  
→ *YES, but what does it truly mean in the long run?*  
*What are the optimal markers for various phenotypes?*  
*What is the true outcome of interest?*
- To allow therapy adjustments to improve outcome  
→ *NOT THERE YET ...*  
*When to do it, how to determine the need, and change to what?*

**What Is The Clinical Utility of PST?**

# Goals of Preoperative Systemic Therapy in Operable Breast Cancer

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- PST may allow trials that target various breast cancer subtypes and that rely on robust surrogate markers for the outcome of interest
  - *Smaller, faster, and more informative trials*
  - More efficient use of resources ...*

**That's What Ultimately  
Brought Us Here Today!**

# What is a Surrogate Outcome?

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- A surrogate outcome should be in the causal pathway of true outcome
  - Replaces a distal endpoint (e.g., survival) by a proxy endpoint (e.g., clinical or pathologic response, imaging, gene expression, ...)
- Surrogate marker
  - A measure of the surrogate outcome

# What is a Reliable (Robust) Measure?

## *Basic Assumptions*

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- A method or assay used to measure a surrogate marker has been standardized
  - Including pre-analytical variables
- A method or assay is reproducible whenever/wherever used
  - Central site → gene expression profiles
  - Locally → pathology assessment  
ER/PR and HER2

# What is a Surrogate Marker?

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- Defining Characteristic:
  - A marker must predict clinical outcome, in addition to predicting the effect of treatment on clinical outcome



# What is a Surrogate Marker?

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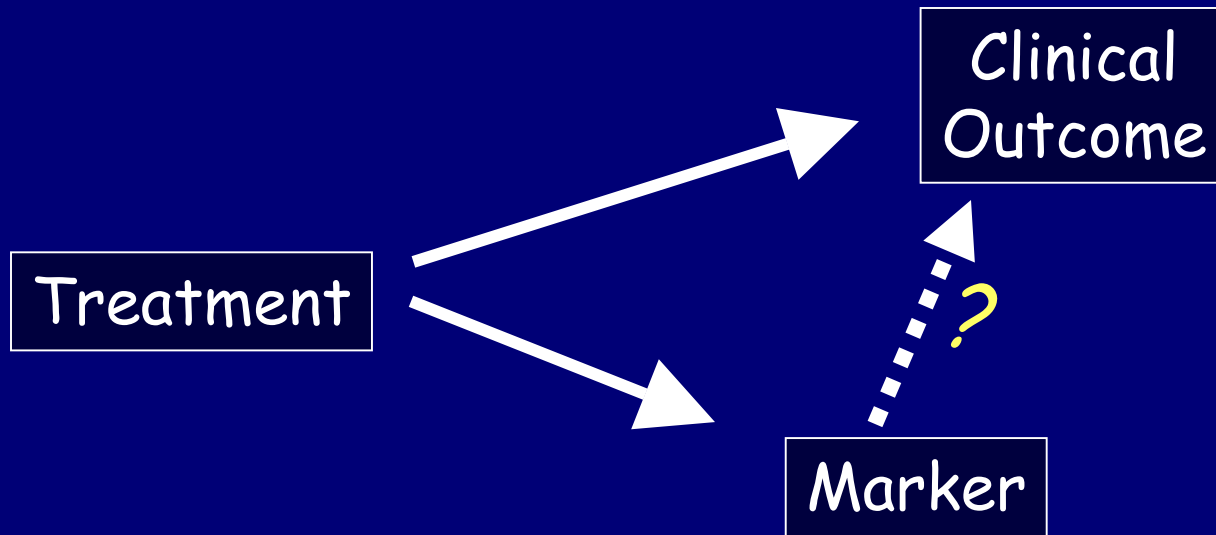
- Operational Definition:
  - Establish an association between marker and clinical outcome
  - Establish an association between marker, treatment, and clinical outcome, in which marker mediates relationship between clinical outcome and treatment





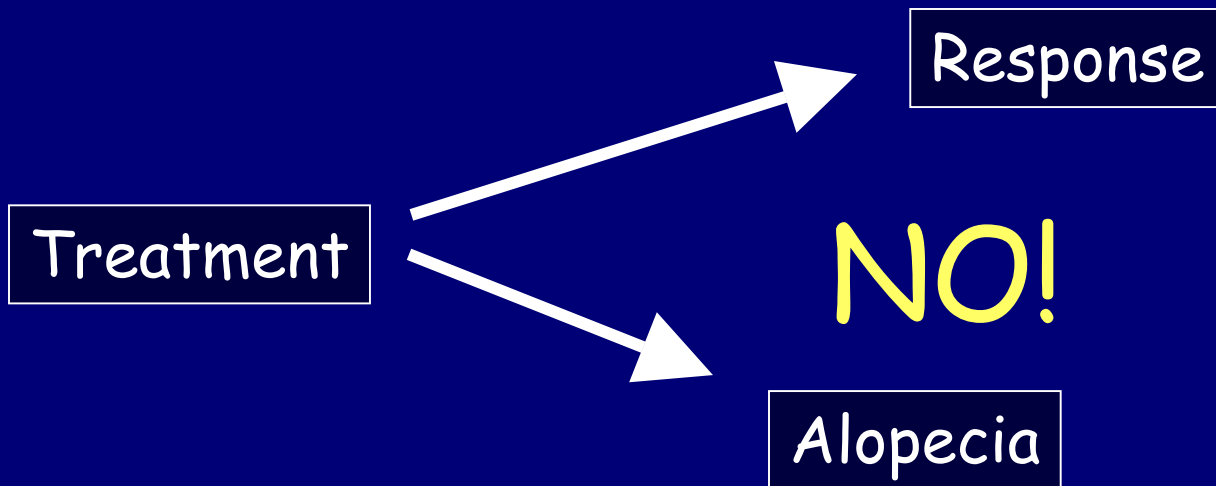
# Is a Correlate Marker Also a Surrogate Marker?

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# Not all Markers Are Appropriate for This Role ...

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# Surrogate Markers and PST

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.CHEMO

.ENDOCRINE

.ANTI-HER2, ...

.RESPONSE

- clinical or path

.MOLECULAR

- proliferation, cell death, gene expression, epigenetics, circulating tumor cells, etc ...

.IMAGING

- US, PET, MRI

.LOCAL CONTROL

.SURVIVAL

# Surrogate Markers and PST



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# Is pCR a Surrogate for Survival?

Anthracycline  
± taxane PST

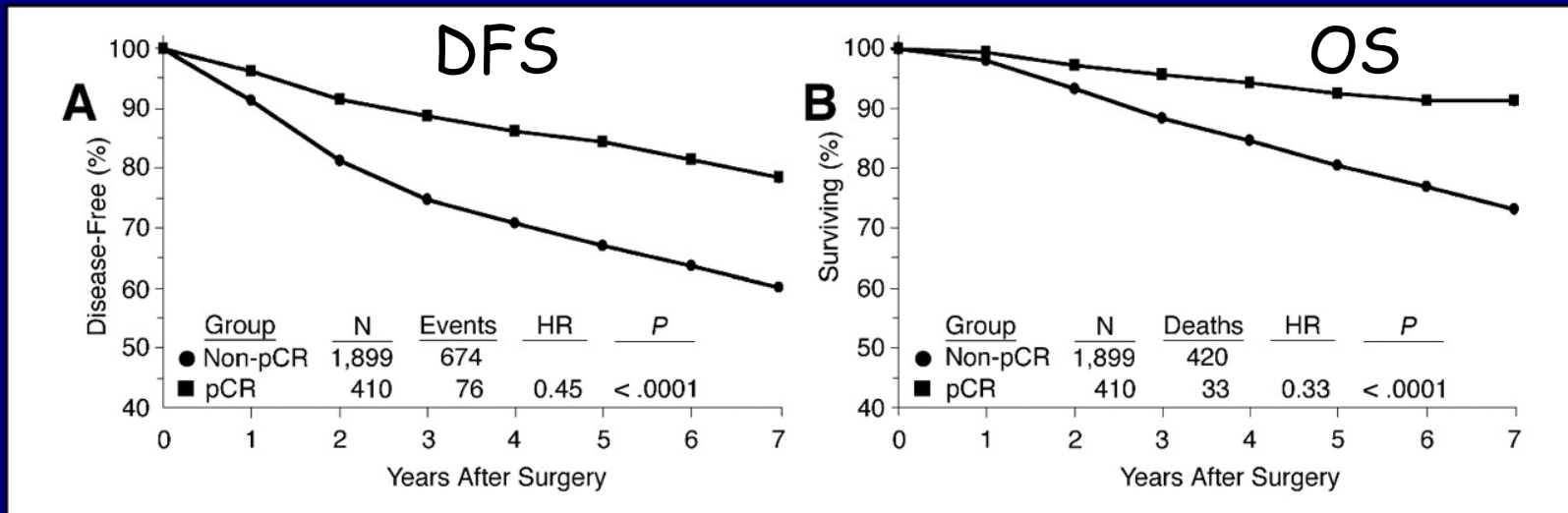


pCR



Survival

NSABP B-27



Kaplan-Meier survival curves according to pathologic response in the breast at surgery

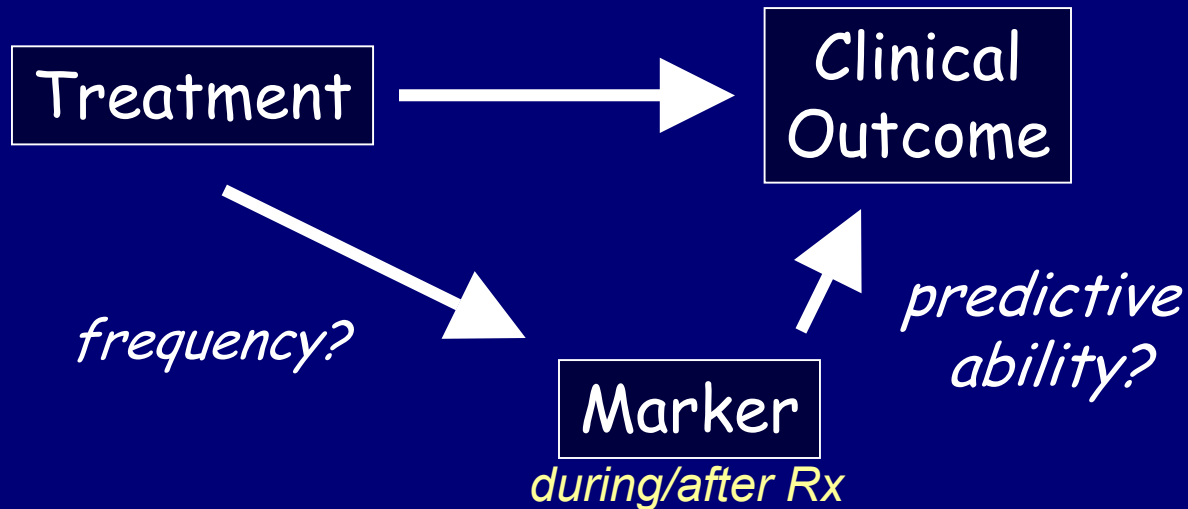
# PST, pCR, and Survival

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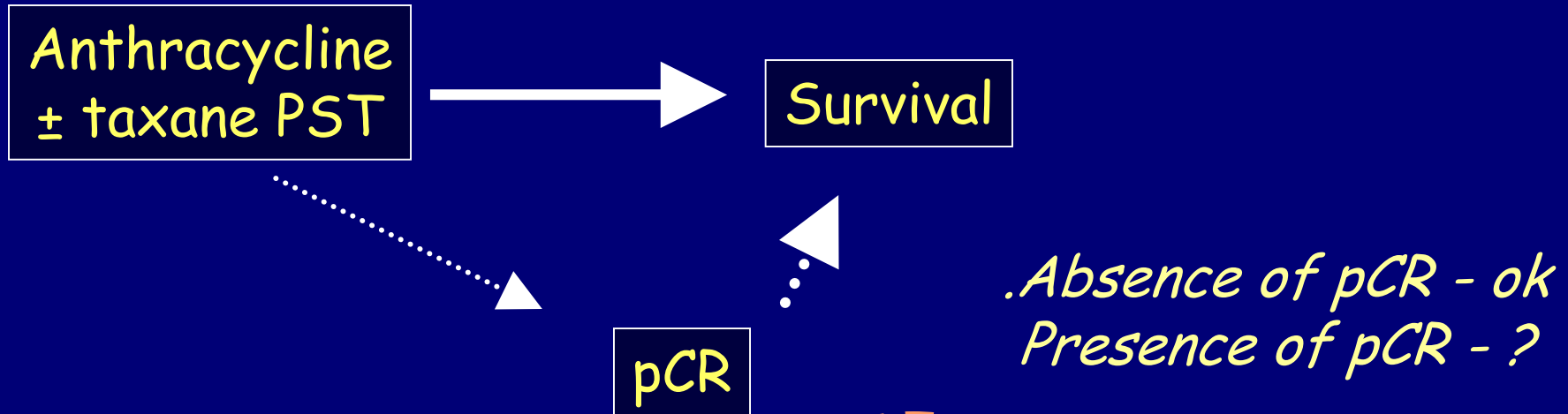
- Doubling of pCR with addition of docetaxel in NSABP B-27 did not result in improved survival
  - At least, not until this morning!
- Improved survival not limited to a pCR subset
  - Path response is a continuous variable, not "all or none"
  - The role of pathology response as a surrogate for survival can be refined by the use of standardized pathology measures after PST
    - E.g., Residual Cancer Burden (*Symmans, ASCO 2006*)
    - AJCC TNM after PST (*Carey, JNCI 2005*)

# How to Determine if a Marker is Useful as a Surrogate?

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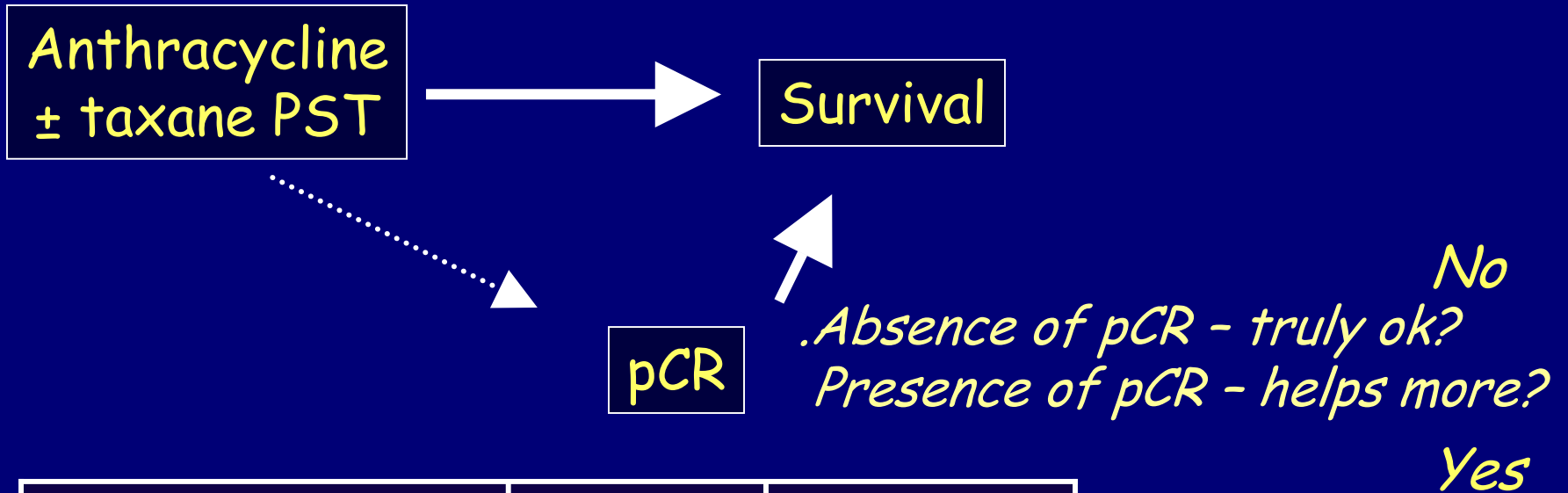
# Is pCR a Useful Surrogate in Invasive Lobular Cancer After Chemo?



| <i>Cristofanilli, JCO 2005</i> | Inv Ductal<br>(n = 770) | Inv Lobular<br>(n = 118) |
|--------------------------------|-------------------------|--------------------------|
| pCR                            | 15%                     | 3%                       |
| 5y OS                          | 70%                     | 93%                      |



# Is pCR a Useful Surrogate in ER-Positive Disease After Chemo?



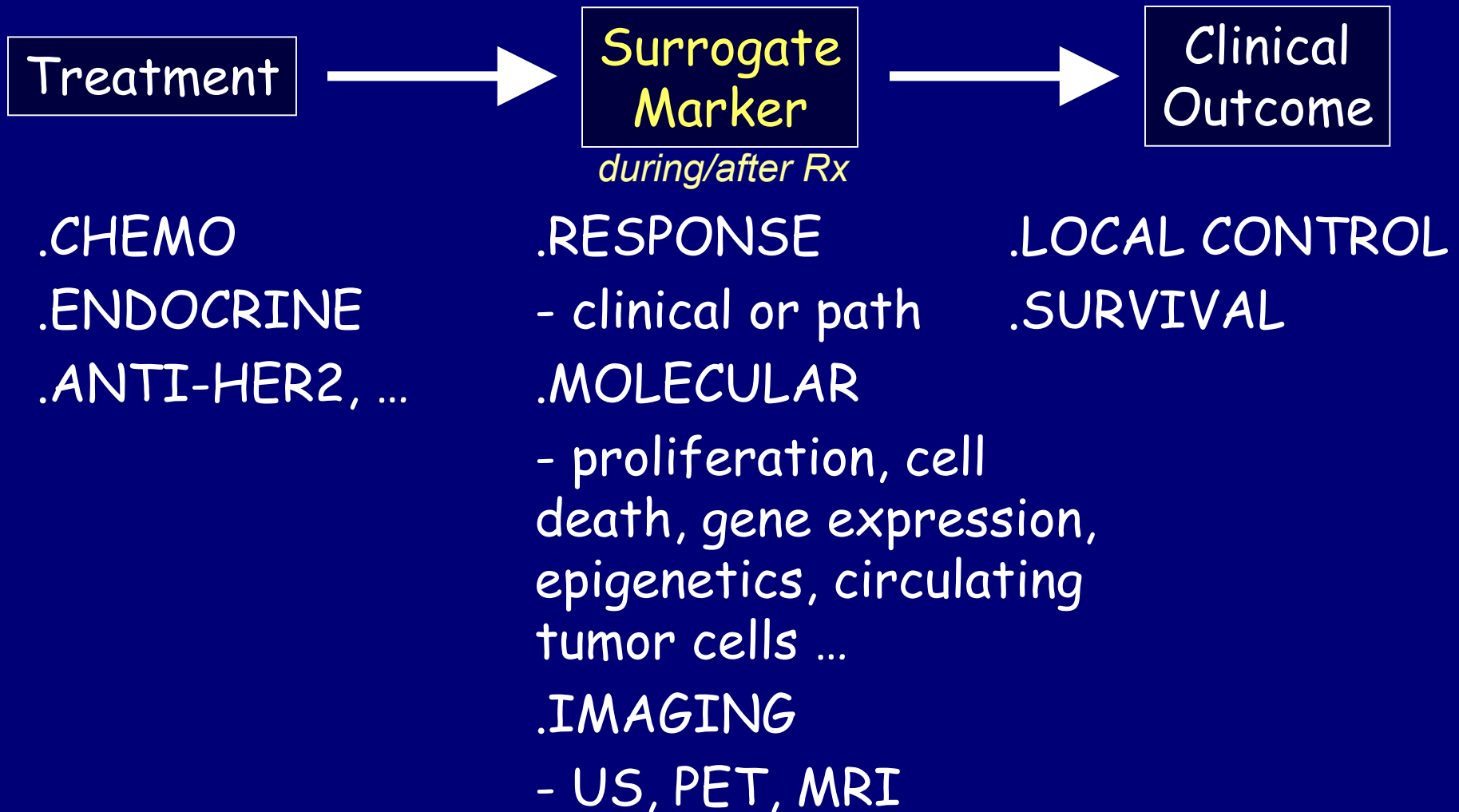
| <i>Guarneri, JCO 2006</i> | ER-neg | ER-pos |
|---------------------------|--------|--------|
| pCR                       | 24%    | 8%     |
| 5y OS                     | 84%    | 96%    |

# Is pCR a Surrogate for Survival in ER-pos Versus ER-neg Disease?

| n = 1731<br>Stage I-III<br>Anthracycline-<br>based PST<br>(66% had taxane) | ER neg        |            | ER pos        |           |
|--|---------------|------------|---------------|-----------|
|  | No pCR<br>76% | pCR<br>24% | No pCR<br>92% | pCR<br>8% |
| 5y PFS   | 50%           | 83%        | 65%           | 91%       |
| 5y OS<br>(HR 0.36)   | 67%           | 84%        | 84%           | 96%       |

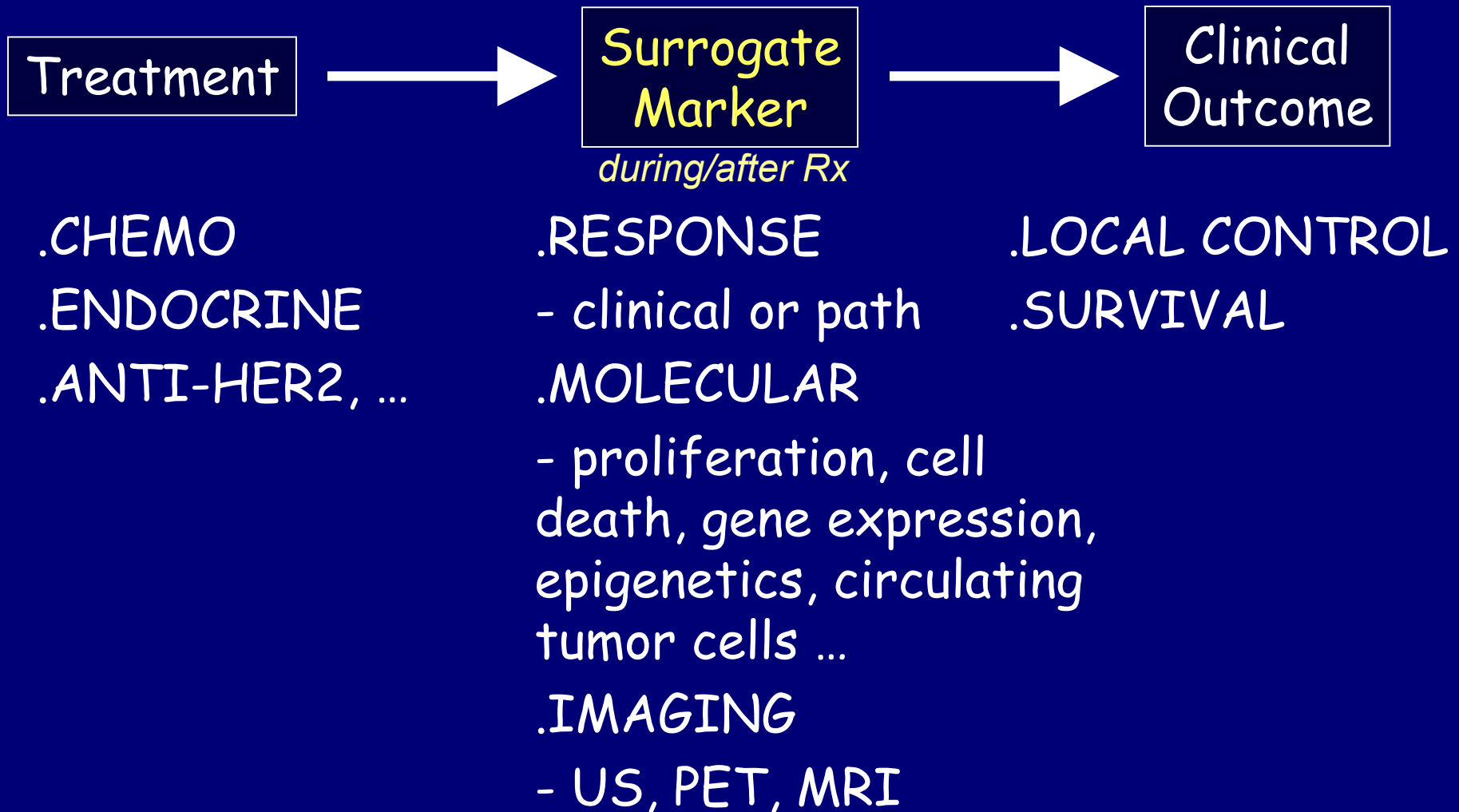
# Surrogate Markers and PST

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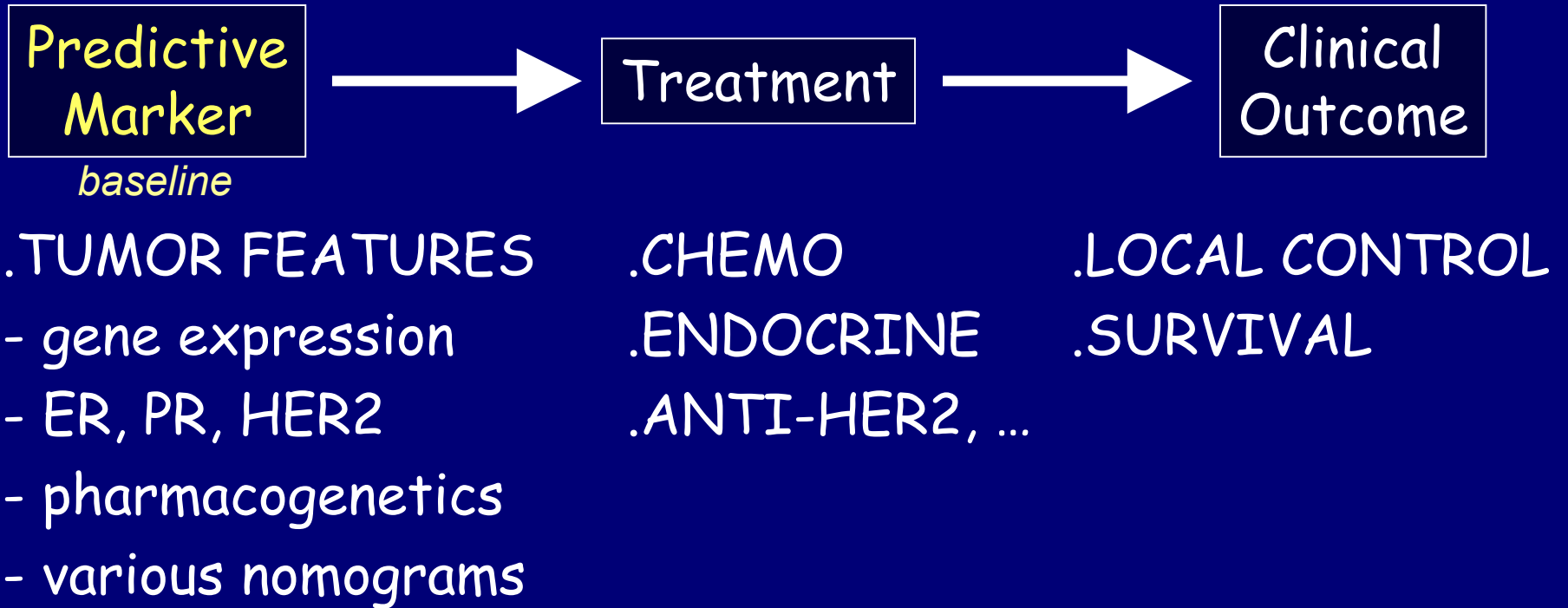
# Lessons from the Adjuvant Setting?

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# Breast Cancer is a Mosaic!

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# Identification of Tumor Subtypes

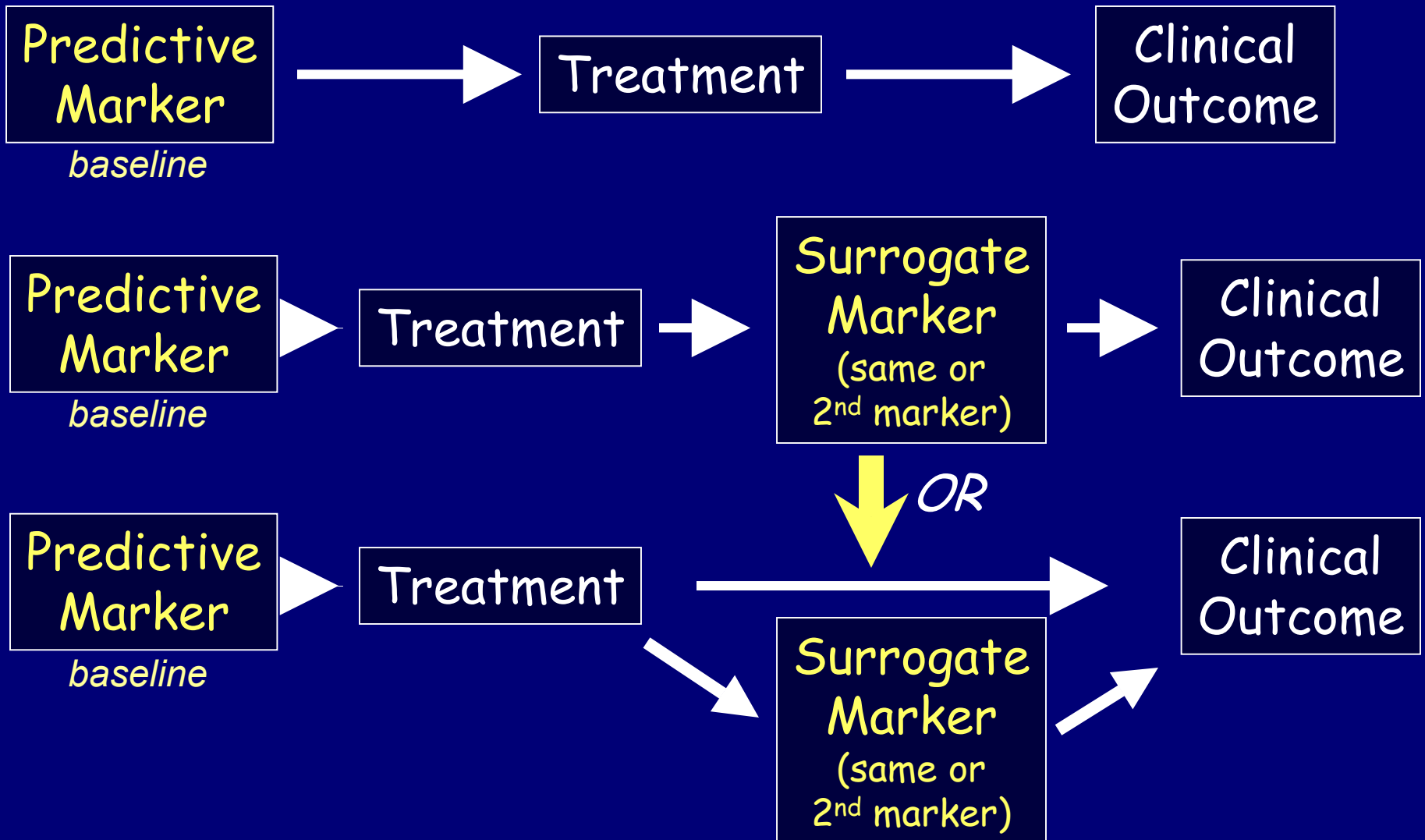
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**Selection of Patient Population  
for Various Therapy Options is Key!**

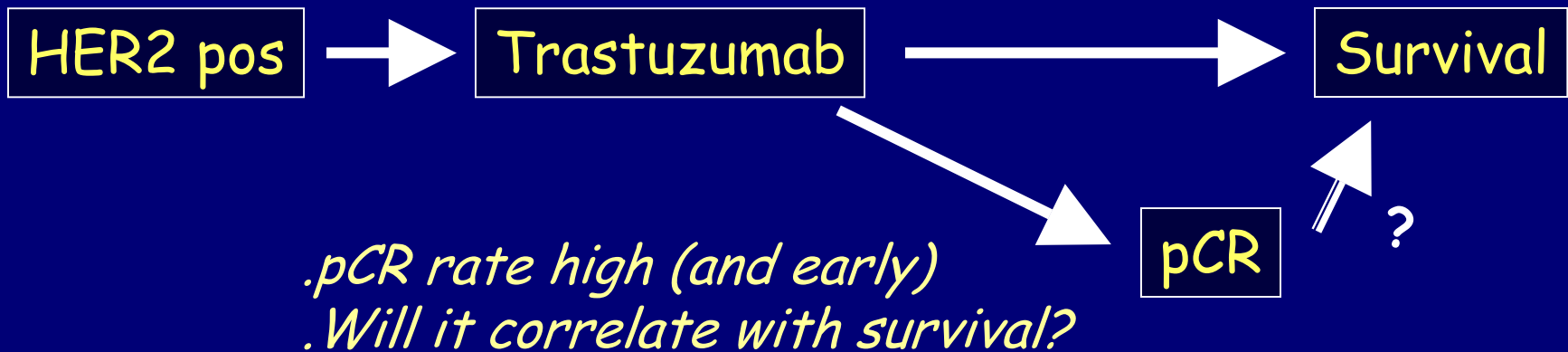
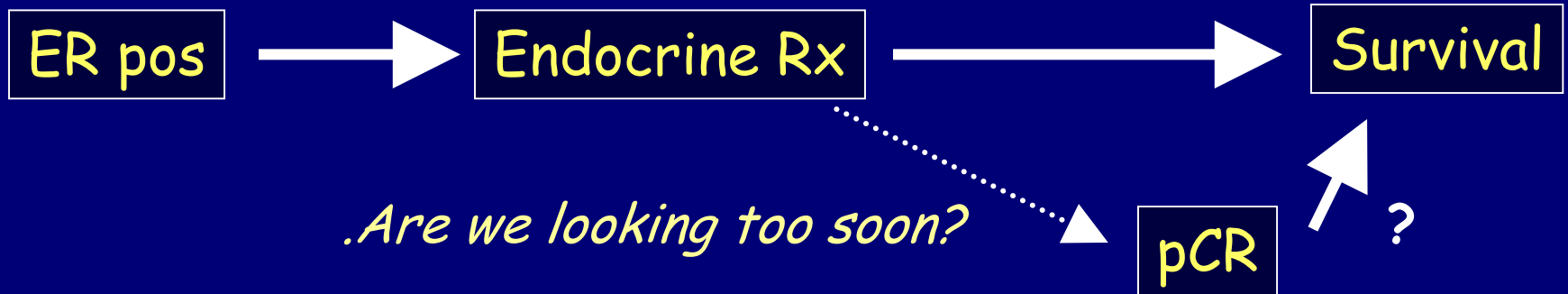
# Marker for Therapy Selection

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# Timing of Observation Matters!

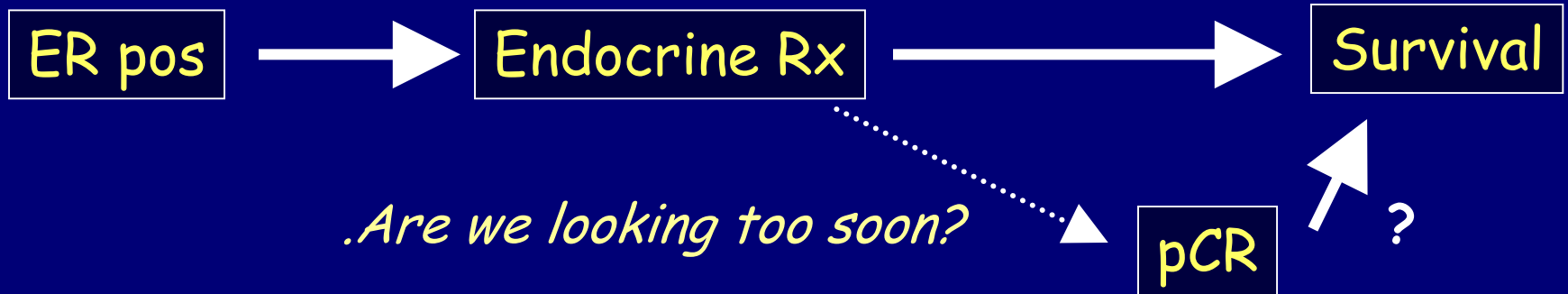
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# Timing of Observation Matters!

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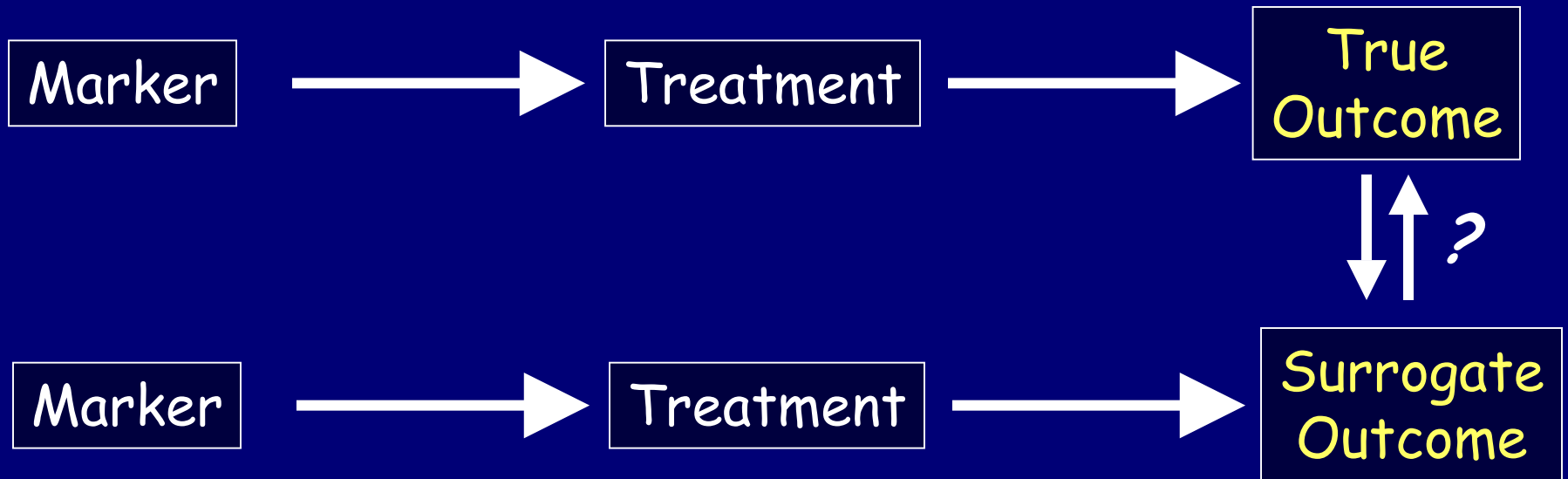


*.pCR rate high (and early)*

*.Will it correlate with survival? It may ...*

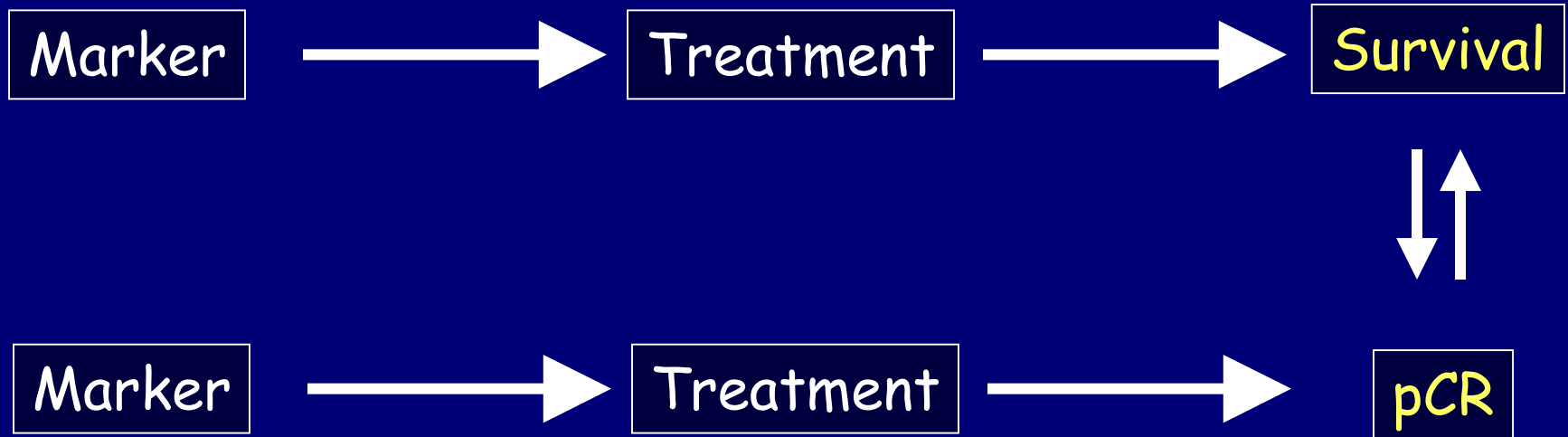
# What if Surrogate Outcome Truly Correlates with True Outcome?

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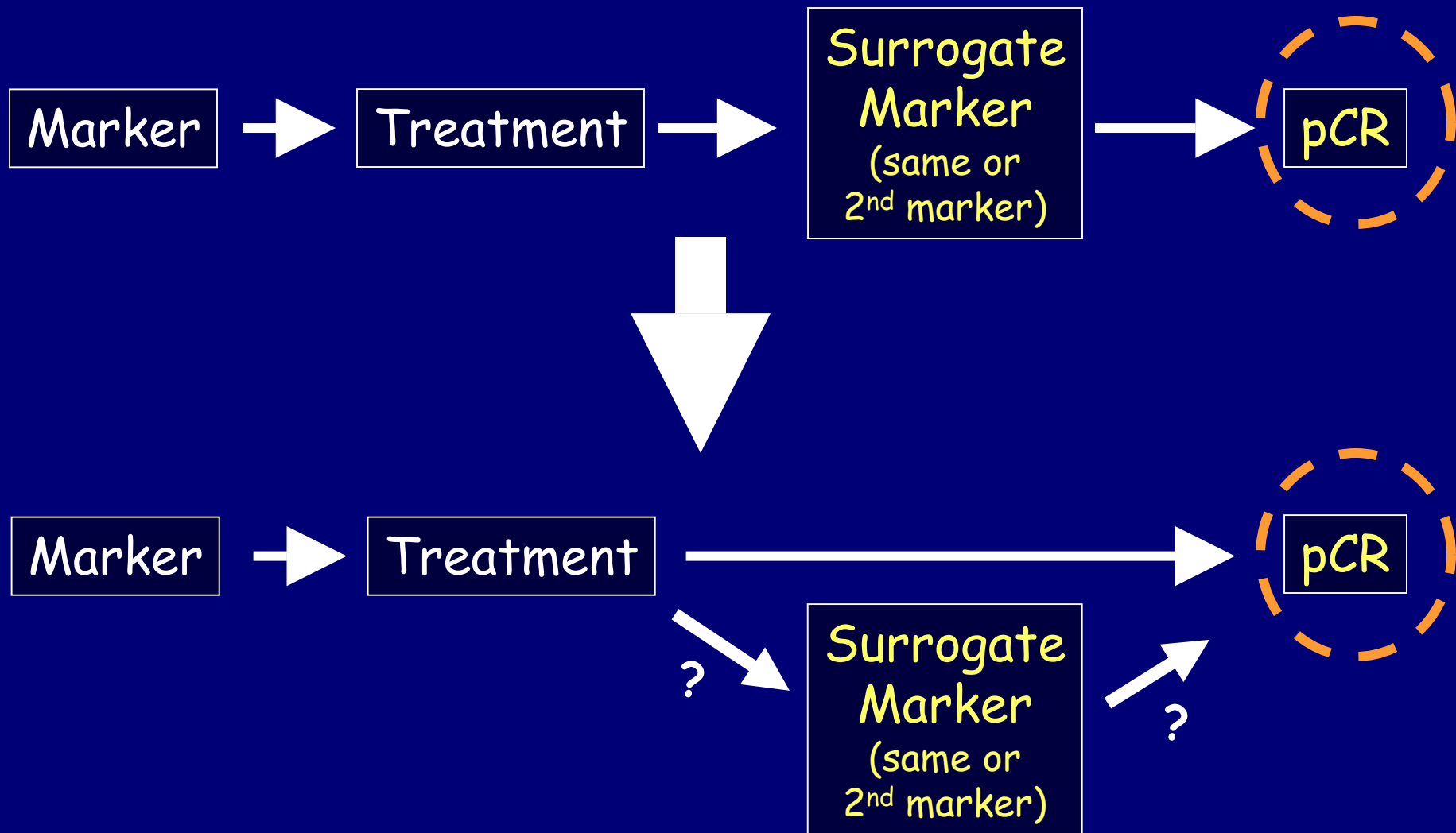
# Surrogate Itself Then Becomes the "Endpoint" ...

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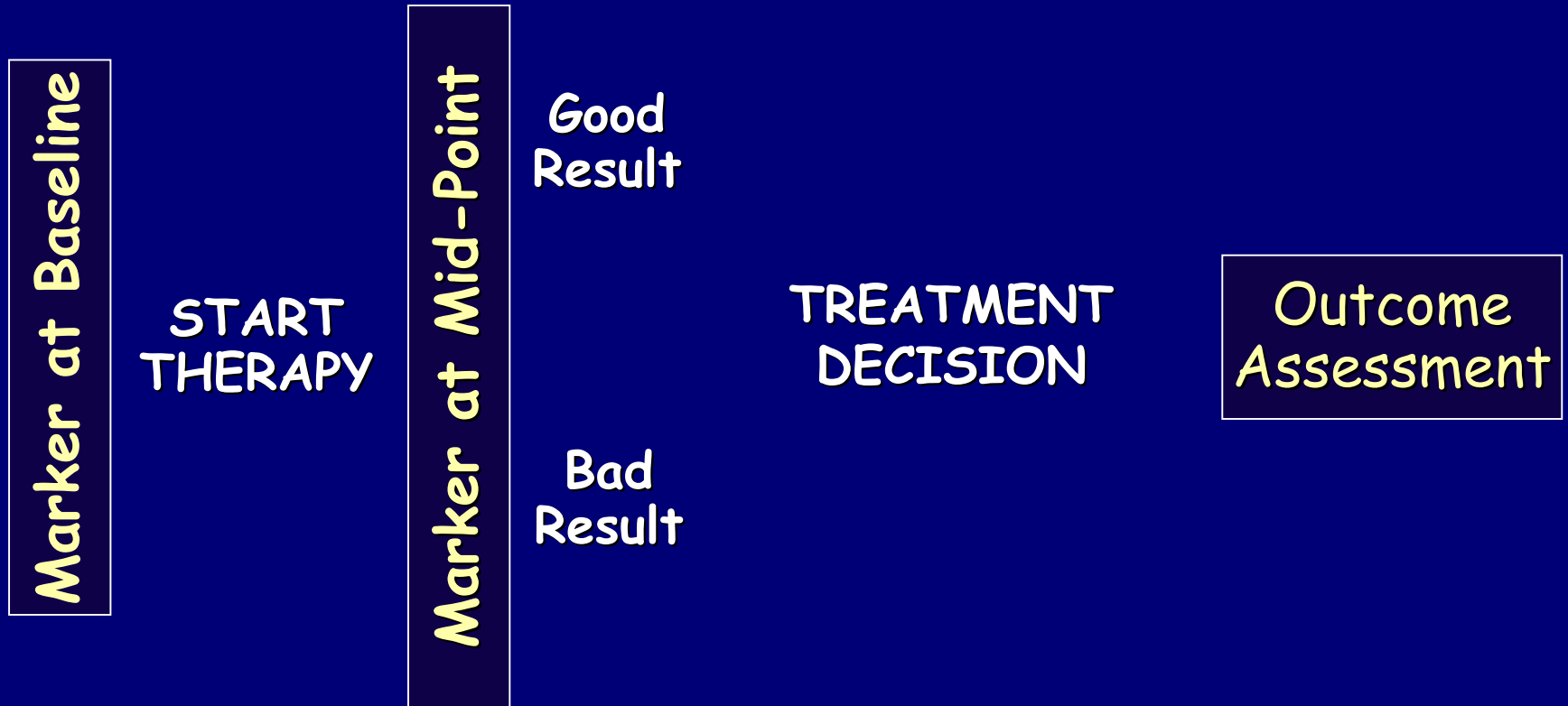
# ... And The Search Then Begins for a "Surrogate" for the Surrogate!

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# Marker Utility Trial Design

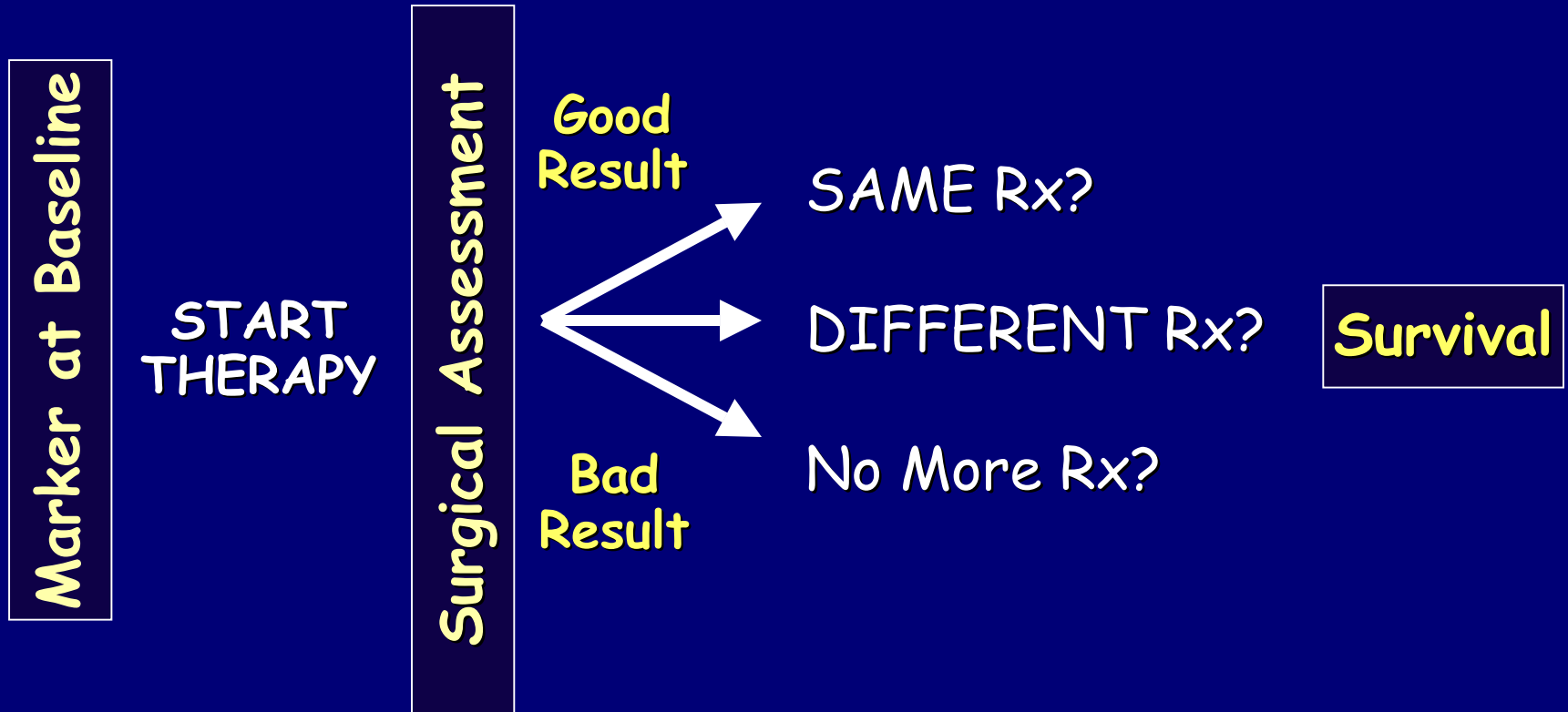
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- .Assumes that you have a good marker*
- .Assumes that you have a good 2<sup>nd</sup> therapy!*

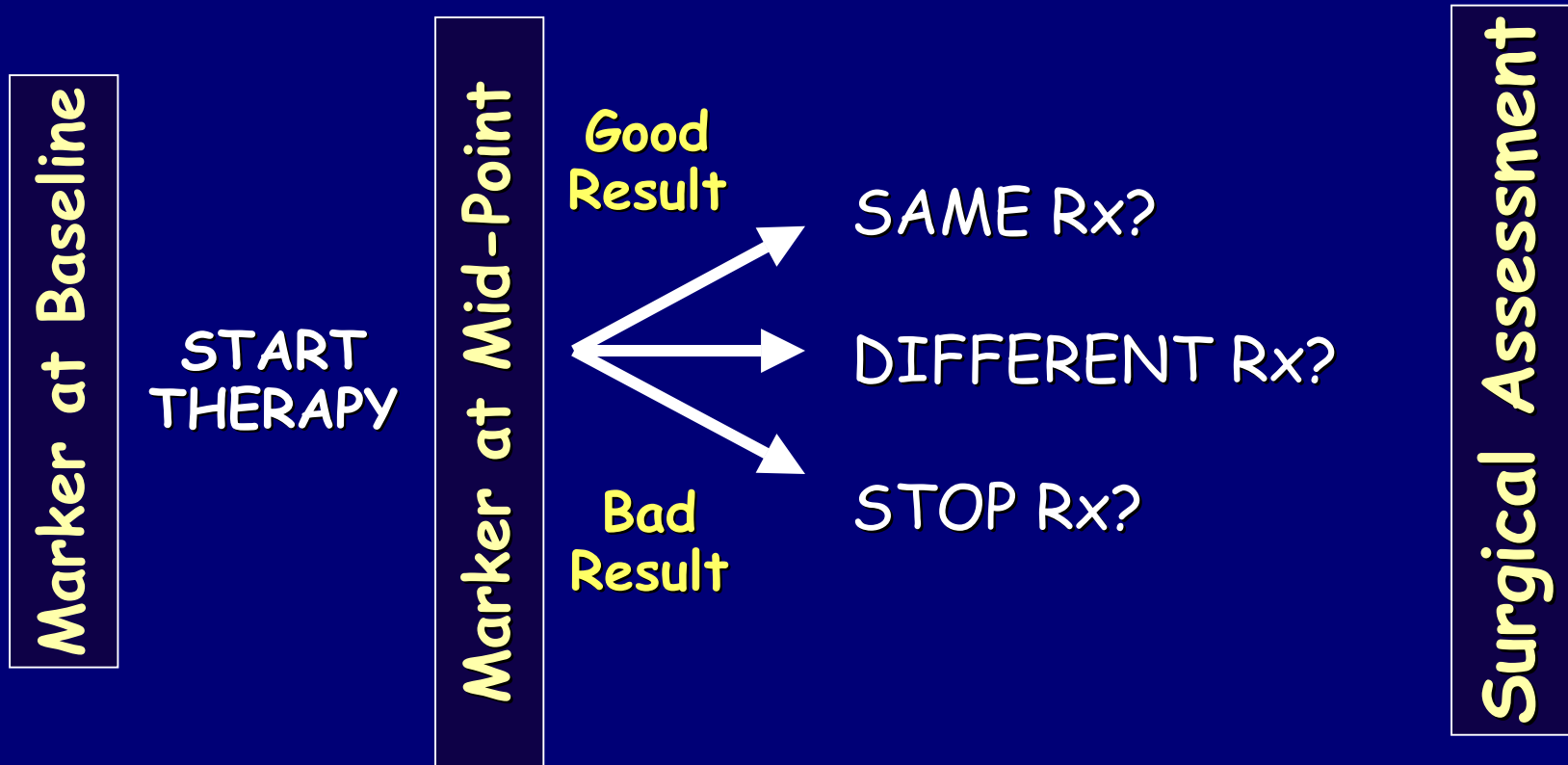
# For Post-Operative Decisions ...

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# For Preoperative Decisions ...

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*.Is the prognostic utility of pCR different if achieved after therapy  $x$ ,  $2x$ , or  $x+y$  therapy?*

# Take Home Messages

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- Surrogate markers are affected by:
  - Population (tumor subtypes)
  - Intervention (therapy of interest)
  - Timing of assessment (depends on therapy and on tumor subtype)
  - Endpoint (survival is the gold standard)



# Take Home Messages

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- Surrogate markers are affected by:
  - Population (tumor subtypes)
  - Intervention (therapy of interest)
  - Timing of assessment (depends on therapy and on tumor subtype)
  - Endpoint (survival is the gold standard)
- Predictive markers at baseline are more critical than intermediate surrogate markers ... at least right now

Is pCR a Useful Surrogate Marker?

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Unequivocally  
Yes!

*But, it depends ...*

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Thank you!

*I think ...*