

## Lecture 5: Adaptive Clinical Trial Designs

*Example: I-SPY 2 - An adaptive breast cancer trial of neoadjuvant chemotherapies*

### Goals:

1. To identify improved treatment regimens for patient subsets on the basis of *molecular characteristics (biomarker signatures)* of their disease.
2. To test, analytically validate, and qualify biomarkers as new drugs are tested.
3. To employ an adaptive trial design to enable efficient learning about each drug's biomarker signature.
4. To utilize organizational management principles and sophisticated bioinformatics in order to eliminate the current inefficiencies in clinical trials.

**Background:** Breast cancer is a number of heterogeneous diseases.

- Directing drugs to molecular pathways that characterize the disease in subsets of patients will improve treatment efficacy.
- The development and use of biomarkers for early measures of therapeutic response would facilitate
  - the efficient evaluation of new agents in focused early clinical trials and
  - enable the development of more informed, smaller phase III trials.

## Biomarker Signatures

In a sample of 2,676 men with prostate cancer, we built a model predicting time to recurrence following prostatectomy. Predictors included one blood-based covariate, *PSA* (categorized as  $< 6$ , 6-10, 10-20,  $\geq 20$  ng/mL) and five pathology-based biomarkers: Gleason sum (categorized in 4 levels), *pSM*, *pECE*, *pSVI*, and *pLN*.  $\Rightarrow$  256 possible biomarker signatures

- Only 72 of 256 possible signatures included at least 1 patient, with 5-year RFS rates of 5.8% – 83.9%
- Only 22 of 72 observed signatures included at least 20 patients
- Eight signatures accounted for 71.4% of the sample, with 5-year RFS rates of 5.8% – 25.7%

**Idea:** Paired relationship between biomarker signatures and outcomes (e.g., 5-year RFS rates).  
Paired relationship between biomarker signatures and therapies.  
 $\Rightarrow$  Give right therapy to person whose outcome needs improvement.

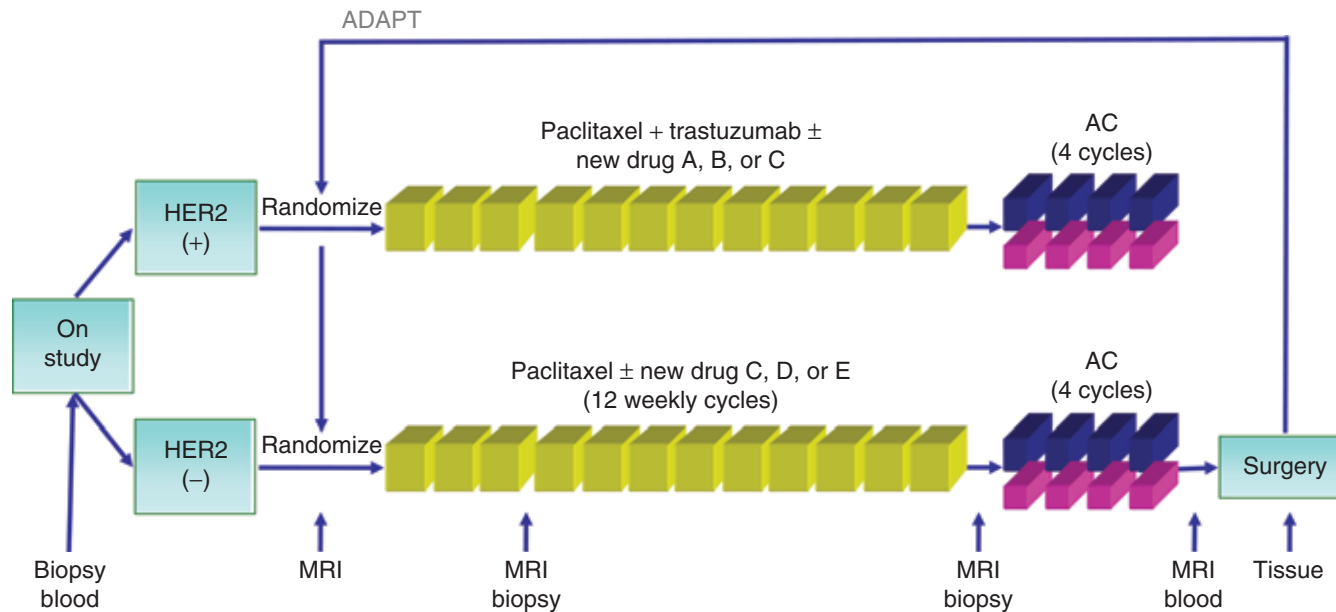
**Question:** Which biomarker signatures identify risk levels amenable to therapy?

Are only  $22 - 8 = 14$  biomarker signatures both in need of neoadjuvant or adjuvant therapy (5-year RFS rate  $> 25.7\%$ ; Aside: How to choose this threshold?) and sufficiently prevalent to study in a phase II trial?

**CON:** Barker et al, 2009, mention that “triple negative” breast cancer patients  $\{HER2-, ER-, PR-\}$  need therapies.

Can an individual covariate (e.g., *pLN*) identify a unique molecular pathway with an identifiable target?  
Should we also study patients with low-prevalence, high-risk predictors (e.g., *pLN*) without regard for complete biomarker signature?

How do biomarkers qualify for inclusion in such a model? How do they differ from those used by Barker et al, 2009?



**Methods:** I-SPY 2 will compare the efficacy of novel drugs in combination with standard chemotherapy ( $E+C$ ) with the efficacy of standard therapy alone ( $C$ ).

- Regimens that show a high Bayesian predictive probability of being more effective than standard therapy will graduate from the trial *with their corresponding biomarker signature(s)*.
- Regimens will be dropped if they show a low probability of improved efficacy with any biomarker signature.
- New drugs will enter as those that have undergone testing are graduated or dropped.

**Biomarkers:** “Fourteen signatures of possible interest based on the biology they represent and their expected high prevalence in the study population have been characterized for I-SPY 2.” Examples:

- $HER2+$  tumor
- $HER2-$  tumor,  $ER-$ ,  $PR-$

**Primary outcome:** Pathologic complete response (typical for phase II trials)

**Sample size:** “Each drug will be tested in a minimum of 20 patients and a maximum of 120 patients.”

Biomarker signature	<i>HER2</i> – Agent				Biomarker signature	<i>HER2</i> + Agent			
	<i>C</i> <sub>–</sub>	<i>E</i> <sub>1</sub>	<i>E</i> <sub>2</sub>	<i>E</i> <sub>3</sub>		<i>C</i> <sub>+</sub>	<i>E</i> <sub>3</sub>	<i>E</i> <sub>4</sub>	<i>E</i> <sub>5</sub>
1					1				
2					4				
3					5				
⋮					⋮				

**Adaptive Allocation:** Randomization probabilities will be determined using the accumulating results pertaining to all the drugs in the trial.

- Each drug’s Bayesian predictive probability (of being successful in a phase III confirmatory trial) will be calculated for each possible signature.
  - Drugs that do well within a specific molecular signature will be preferentially assigned within that signature.
  - Drugs will be dropped from the trial for reasons of futility when this probability drops sufficiently low for all signatures.
  - Drugs that have high Bayesian predictive probability of being more effective than standard therapy will graduate along with their corresponding biomarker signatures, allowing these agent-biomarker(s) combinations to be tested in smaller phase III trials.
- Depending on the patient accrual rate, new drugs can be added at any time during the trial as other drugs are either dropped or graduated.

## Summary

- Screening candidate agents: Process or Trial?
  - Many candidates evaluated in the same experiment, with results updated continuously.
  - $N$  will be large only when effectiveness and toxicity are not clear; enables resolution of uncertainty.
- Adaptive allocation: To treat patients in the trial as effectively as possible
  - Advantages: Promote consent; treat trial patients optimally; learn efficiently & fast.
- Seamless phase II-III trials: To learn efficiently and rapidly
  - “Phases” of drug development are arbitrary and not necessarily helpful; can insert pauses between phases.
  - Bayesian approach: No quantity is perfectly known; carries uncertainty into next experiment. Process should be continuous.
    - \* Algorithms guide trial conduct. At each interim analysis (weekly!!!), one of the possible paths is chosen:
      1. Continue study
      2. Stop for lack of efficacy: (i) predictive probabilities suggest futility or benefit, or (ii)  $N$  is reached.
      3. Shift to confirmatory study
    - \* Investigators needn't know if/when current number of agents has shifted from 6 to 2!

## References

Barker et al. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009; 86:97-100.

Berry. Bayesian clinical trials. Nature Reviews Drug Discovery. 2006; 5:27-36.

## Adaptive Trial Designs More Generally

The word adaptation has been used in many different and often in conflicting ways when applied to randomized trials. Brown et al categories:

- Adaptation in the context of an ongoing trial: planned modification of characteristics of the trial itself based on information from the data already accumulated.
  - Examples (Table 1): Early stopping; Adaptive allocation
- Adaptation across trials: use the results of completed trials to inform the next stage of scientific evaluation.
  - Examples (Table 2): To replicate this trial in some form; To follow up the same subjects to evaluate longer-term impact; To focus on a new research question that leads to a different research design; To end this line of research because questions are sufficiently answered or trials in this area are no longer ethical or fruitful.
  - Extraim analyses: If a trial is underpowered, start a new trial or extend the current trial?
    - \* Potential problem: This increases the type-I error rate, as in interim analyses.
    - \* Solution: Build in the possibility of continuing, with  $\alpha$ -adjustment, depending on the results.
    - \* Advantage: Increase in  $N$  (say, 20%) yields substantial increase in power (e.g., 80% to 95%) because this step will only be taken if results are promising.
    - \* Control: Include futility analyses as part of the design.

### Reference

Brown et al. Adaptive designs for randomized trials in public health. Annual review of public health. 2009; 30:1-25.