Correlative Studies in Phase III Trials: Design elements of biomarker studies

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NCIC CTG NEW INVESTIGATOR CLINICAL TRIALS COURSE

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Learning Objectives

Session: Correlative Studies in Phase III Trials

Title: Design elements of biomarker studies

Objectives:

- To define biomarker and the types of biomarkers
- To understand the issues in designing appropriate biomarker studies
- To understand the roles of biomarkers in phase I, II and III studies
- To understand different biomarker trial designs

What is a Biomarker?

"Biomarker" covers 3 aspects – characteristic of interest, the method measurement and context

- **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**

  Biomarkers Definitions working Group National Institutes of Health 2000

- **Assay: A method for determining the presence or quantity of a component**
- **Test: A procedure that makes use of an assay for a particular purpose**

Good biomarkers ≠ Good Assays ≠ Tests

Why do biomarker studies?

- To understand cancer biology
- To improve treatments
- To change medical practice

The most important biomarkers yield results that will influence treatment recommendations

Not all biomarkers are prospectively validated in trials.

Biomarker Examples

A "Biological measure" – may be tissue, plasma, urine, imaging

Type of setting	Examples of Biomarkers
RISK of developing cancer in normal individuals	▪ BRCA carrier ▪ Hepatitis B infection
EARLY DETECTION	▪ Mammogram
PROGNSOSIS	▪ Lymph node status ▪ HER2 + in breast
PREDICTIVE treatment benefit or harm	▪ ER/PR in breast cancer ▪ HER2+ in breast cancer
MONITOR disease	▪ PSA in prostate
SURROGATE ENDPOINT for efficacy	▪ Objective response ▪ ?PET scan ▪?CTC in prostate/other

Why are successful biomarker studies uncommon?

- Biological heterogeneity
  - Cellular, tumour, patient
- Assay variability
  - Within assay, between assays
- Specimen variability
- Effect size
- Context e.g. primary versus metastatic, prior treatment

A lot of "noise" that blur marker and outcome correlation

Trial Designs and Biomarkers

Trial Phase	Purpose	Biomarkers	Modifications
0	Define dose Select agents	Target modulation PK	Normal Volunteers Pre-surgical
I Metastatic	Safe dose/shedule	Target Modulation PK Toxicity Activity	Expanded cohorts to evaluate target , toxicity or screen activity
II Metastatic	Activity	Predictive markers Monitoring	Randomized
III Metastatic	Efficacy/Clinical benefit	Predictive markers Monitoring	Subset analyses
III Adjuvant	Efficacy/Clinical benefit	Predictive Prognostic/Risk	Subset analyses

Type of marker changes depending on phase of trial

Phase 1 Trials: Considerations

- Primary goal: To identify an appropriate dose/schedule for further evaluation
- Design principles:
  - Maximize safety
  - Minimize patients treated at biologically inactive doses
  - Optimize efficiency
- Study population:
  - Patients for whom no standard therapy

Phase 1 Trials: Considerations

- Primary goal: To identify an appropriate dose/schedule for further evaluation

Small patient numbers

- Design principles:
  - Maximize safety
  - Minimize patients treated at biologically inactive doses
  - Optimize efficiency

Heterogenous Refractory Tumours

- Study population:
  - Patients for whom no standard therapy

Expect target modulation but not anti-tumour activity

Pharmacodynamics (PD)

- Study the effect of drug on the body (normal tissue) or tumour
- Most drugs are designed to inhibit activity of target molecules
- Potential markers are chosen based on known biochemical and signaling pathways of the targets
- Pathways are better known for some targets than others

Issue: what to measure, how, in what, when, what does change mean?

Biomarker(s) for Treatment Selection

- **Predictive** biomarkers
  - **differential effects of treatment are seen** based on the marker test result

- Prognostic markers may be used for treatment selection:
  - The marker defines such a GOOD prognosis group that NO treatment is offered (or reverse)

Ideally, trials should be designed to distinguish predictive versus prognostic effects

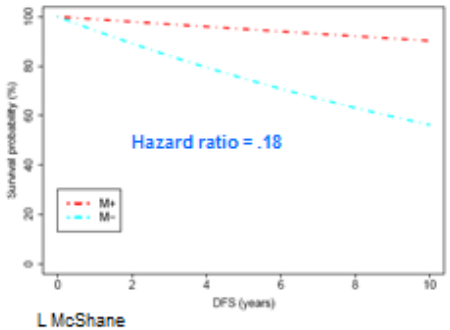
Prognostic versus Predictive Markers

Prognostic Marker

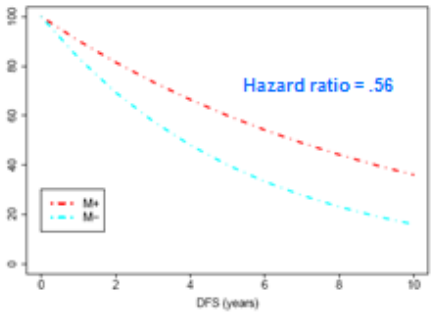
Measurement associated with clinical outcome in absence of therapy or with standard therapy that all patients are likely to receive.

- Examples: Oncotype DX, uPA/PAI-1 by ELISA in breast cancer
- Correlation with outcome not necessarily sufficient to impact clinical decisions, may suggest targets for therapy

Good prognosis don't need adjuv. Rx



Useful prognostic information?

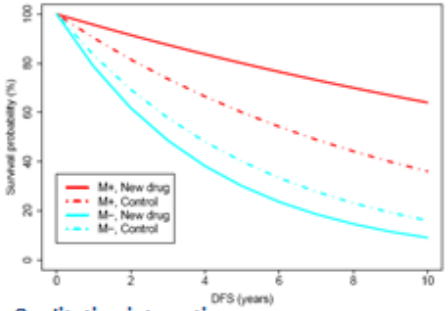


L McShane

Predictive Marker

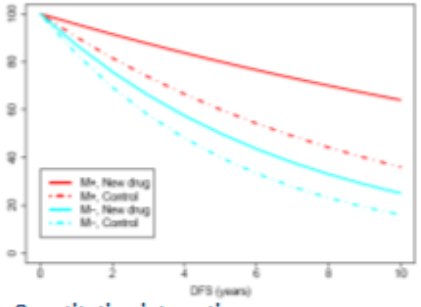
Measurement associated with response or lack of response to a particular therapy.

- Examples: ER/PgR for endocrine Rx benefit in breast cancer
- Statistical wisdom: Test for treatment by marker interaction



Qualitative interaction

- New drug better for M+ (h.r. = 0.44)
- Control drug better for M— (h.r. = 1.31)
- Interaction = 0.44/1.31 = 0.33



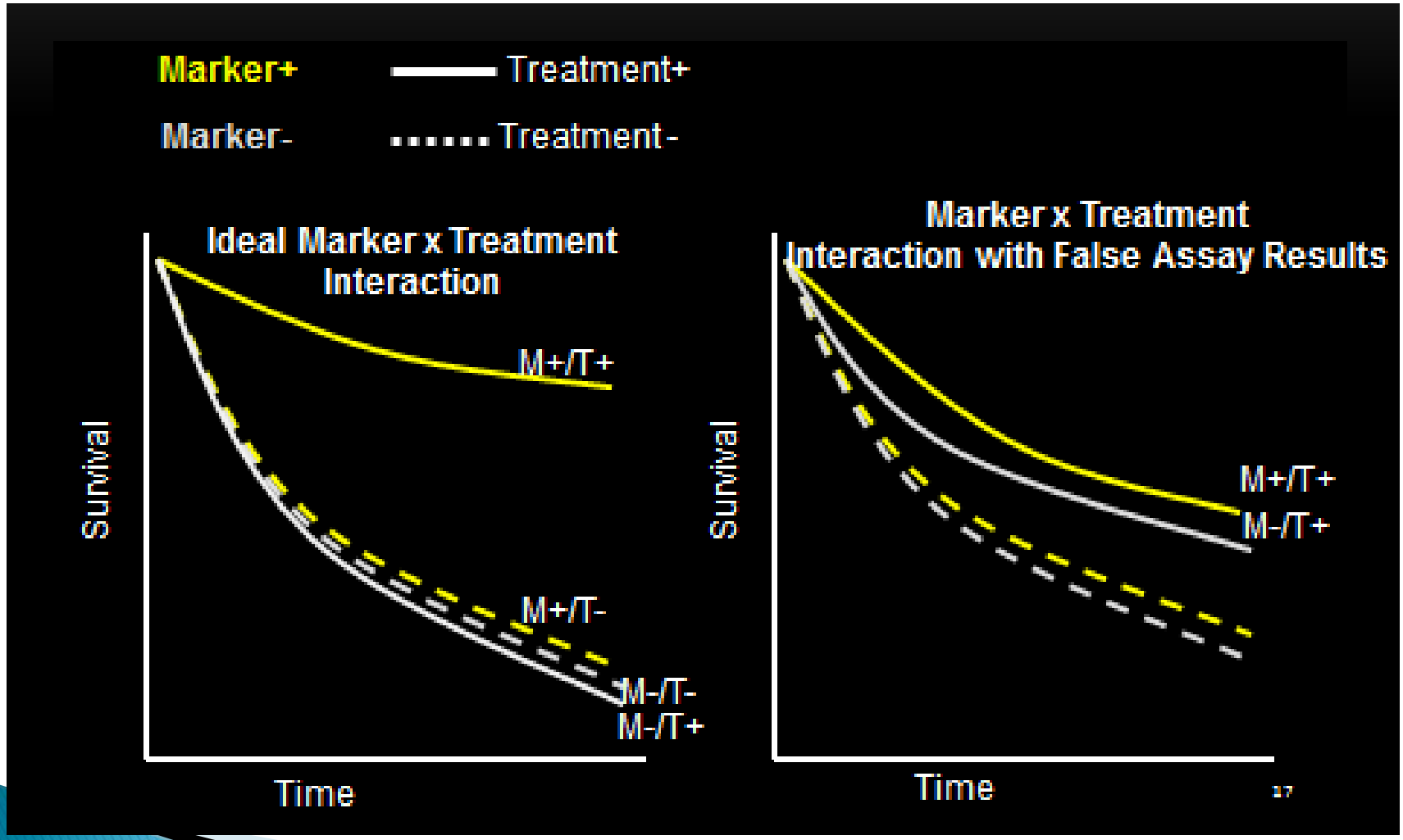
Quantitative interaction

- New drug better for M+ (h.r. = 0.44)
- New drug better for M— (h.r. = 0.76)
- Interaction = 0.44/0.76 = 0.58

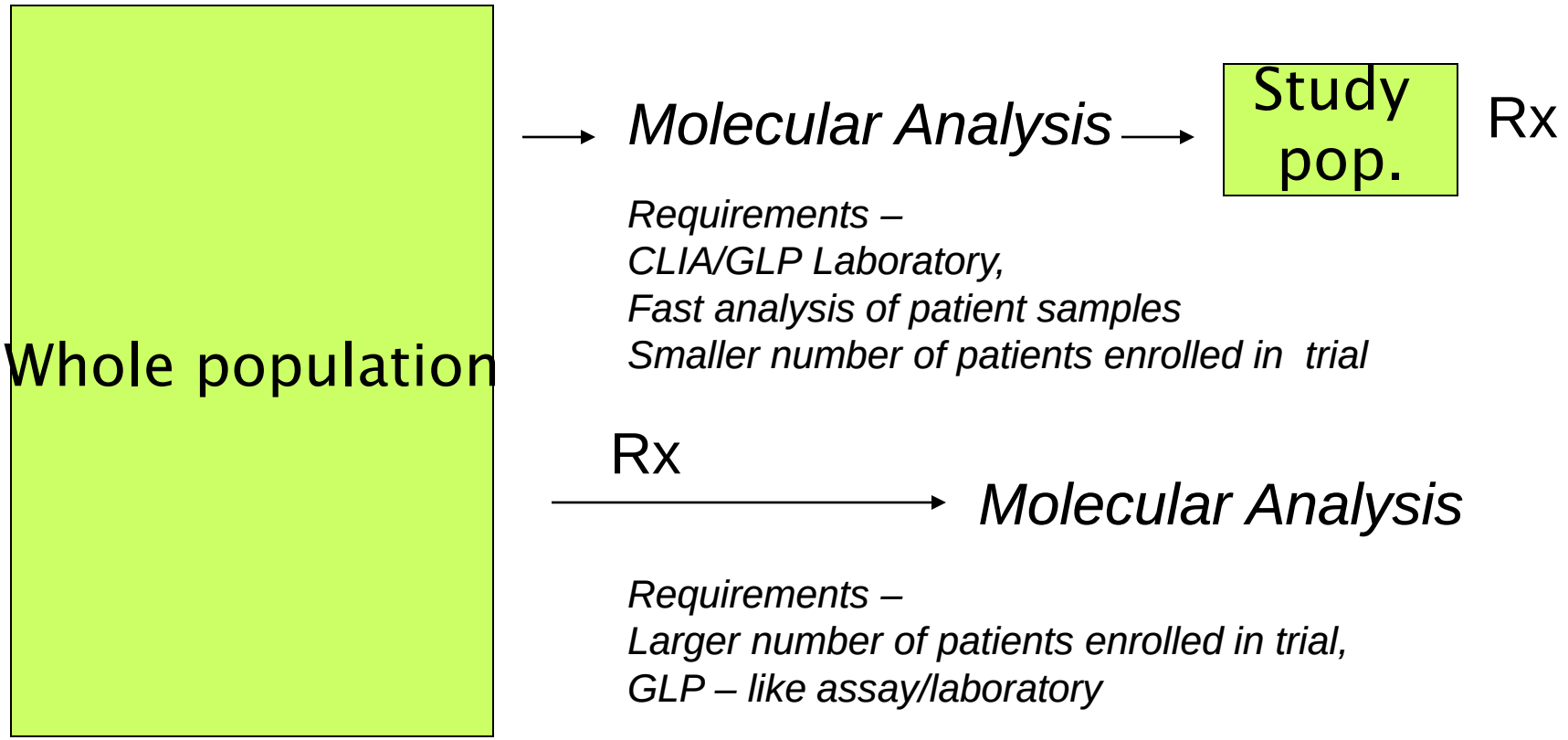
Biomarkers in Phase II/III: PREDICTION

- Drug/treatment activity
- Differential treatment effects within patient marker subsets
- Prevalence of Marker+ and/or Marker- groups
- Trial design distinguish predictive and prognostic effects
- Reliable assay (and lab) to assess the biomarker
- Sufficient samples (number, quality)
- Feasible (scientific, operational, economic)

Phase 3 (or 2) Trial –Effect of Assay False Positive and Negatives is to Make things look the same



Types of Trials – Stratified Medicine



Is there a strong hypothesis and compelling rationale?
Is there a validated assay?
NOTE: The population size screened does not change

Suppose we have a new targeted therapy designed to be effective in patients with Marker A.

What types of clinical trials should we design?

Biomarker Clinical Trial Designs

- Target Selection or Enrichment Designs
- Unselected or All-comers designs
  - Marker by treatment interaction designs (biomarker stratified design)
  - Adaptive analysis designs
  - Sequential testing strategy designs
  - Biomarker-strategy designs
- Hybrid designs

Target Selection/Enrichment Designs

If we are sure that the therapy will not work in Marker-negative patients

AND

We have an assay that can reliably assess the Marker

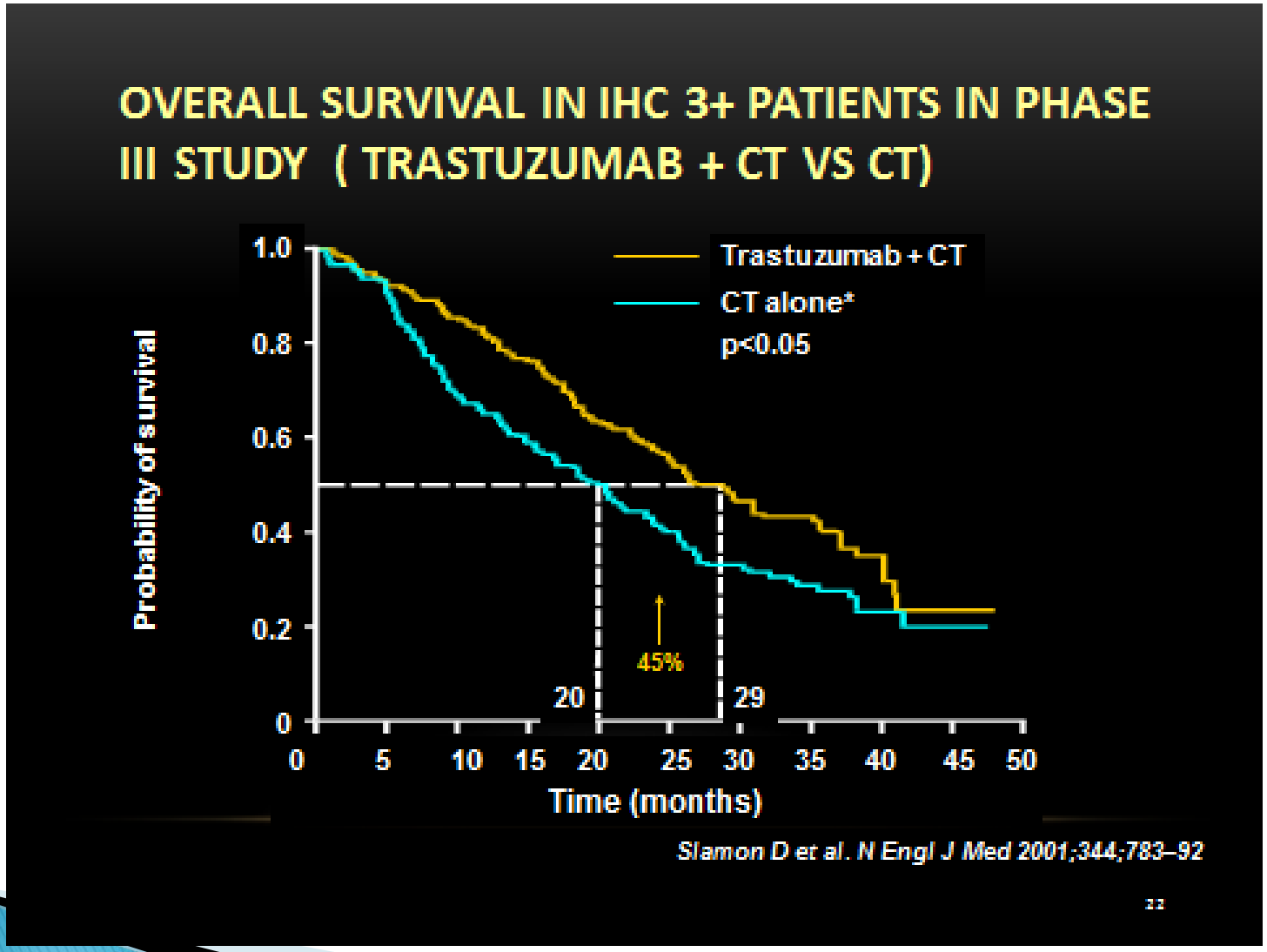
THEN

We might design and conduct clinical trials for Marker-positive patients or in subsets of patients with high likelihood of being Marker-positive

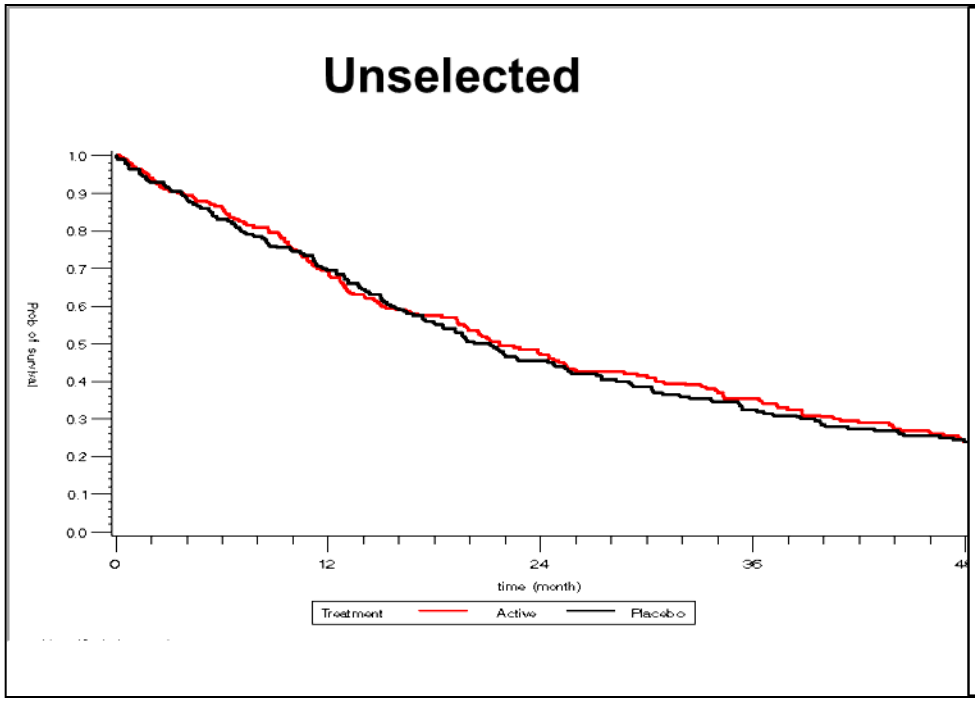
HER2 and Anti-HER2 Breast Cancer Therapy

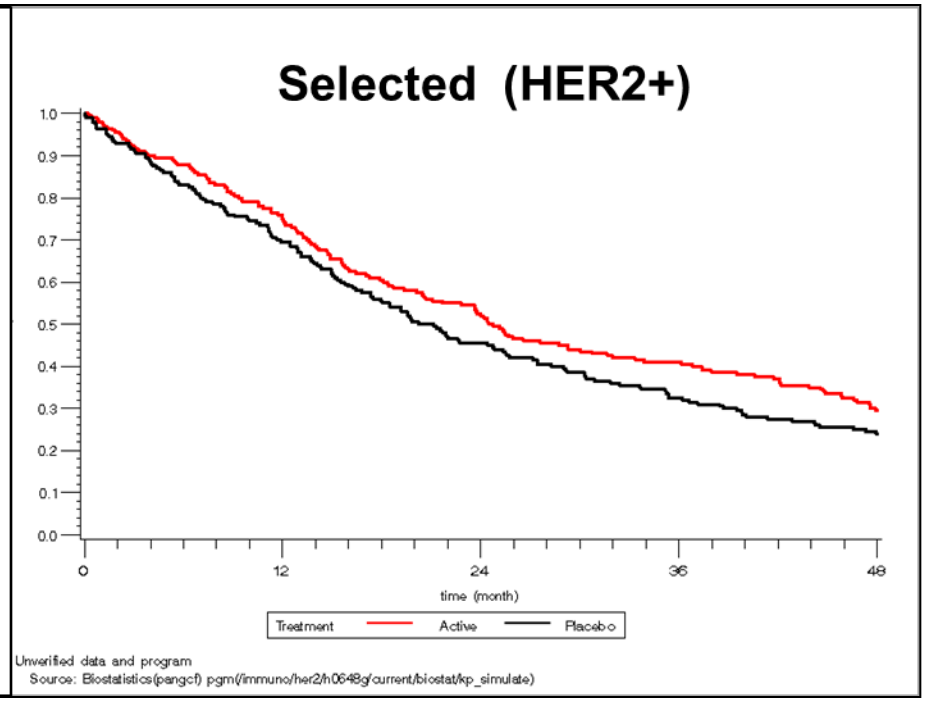
- Background
  - 1980s: HER2 over-expression poor prognostic factor in BC
  - 1992: Phase I clinical trials with humanized MOAb begin: only patients with HER2 overexpression enrolled (2-3+ IHC)
  - Improved survival in trial of chemo +/- trastuzumab in metastatic disease; cardiotoxicity noted (Slamon, NEJM 2001)
  - 1998: FDA approval for trastuzumab approved for combination chemo in metastatic disease along with test to measure HER2
  - 2005/6: Adjuvant trials show improved DFS. FDA approval

Enrichment Design



TRASTUZUMAB: The Power of Patient Selection





	Unselected	Selected
Target prevalence	25%	100%
Expected survival benefit	1.25m (5.7%)	5m (22.7%)
Sample size	11,000	1,250
Study duration	349m	52m

Bajamonde, Genentech

Concordance of the HercepTest® to the Clinical Trial Assay

HercepTest®	Clinical Trial Assay +	Clinical Trial Assay –	Clinical Trial Assay Total
+	216	59	275
–	58	215	273
Total	274	274	548

Concordance = **79%** (76%-82%) 95% Confidence interval

Consider how a positive biomarker trial result would lead to clinical uptake

Need to consider technology and knowledge translation (e.g. a test and how to use it)

Summary: Enrichment Design

- Strong scientific rational
- Small % of BC patients are HER2+
- Expensive agent
- Need for test to define that population
- Biomarker was *presumed* to be predictive.
- Test is not perfect and outcome is not certain (often indicate who not to treat rather than who will benefit)
- Questions: activity in marker negatives, sensitivity, specificity of the test.

Unselected "All Comers" Trial Designs

If we are not sure that the Marker will define groups of patients that will benefit/not benefit from treatment

OR

There isn't a validated assay that can reliably assess the status of the Marker

THEN

We might design and conduct clinical trials in unselected patients and try to identify predictive markers and robust assays.

Retrospective and Prospective Analysis Designs

Retrospective Analyses Designs

- Hypothesis generation studies
  - Retrospective analyses based on convenience samples
- Prospective/retrospective designs

Prospective Designs

- Marker by treatment interaction designs (biomarker stratified design)
- Adaptive analysis designs
- Biomarker-strategy designs
- Sequential testing strategy designs

Hybrid designs

Prospective/Retrospective Design

- Well-conducted randomized controlled trial
- Prospectively stated hypothesis, analysis techniques, and patient population
- Predefined and standardized assay and scoring system
- Upfront sample size and power calculation
- Samples collected during trial and available on a large majority of patients to avoid selection bias
- Biomarker status is evaluated after the analysis of clinical outcomes

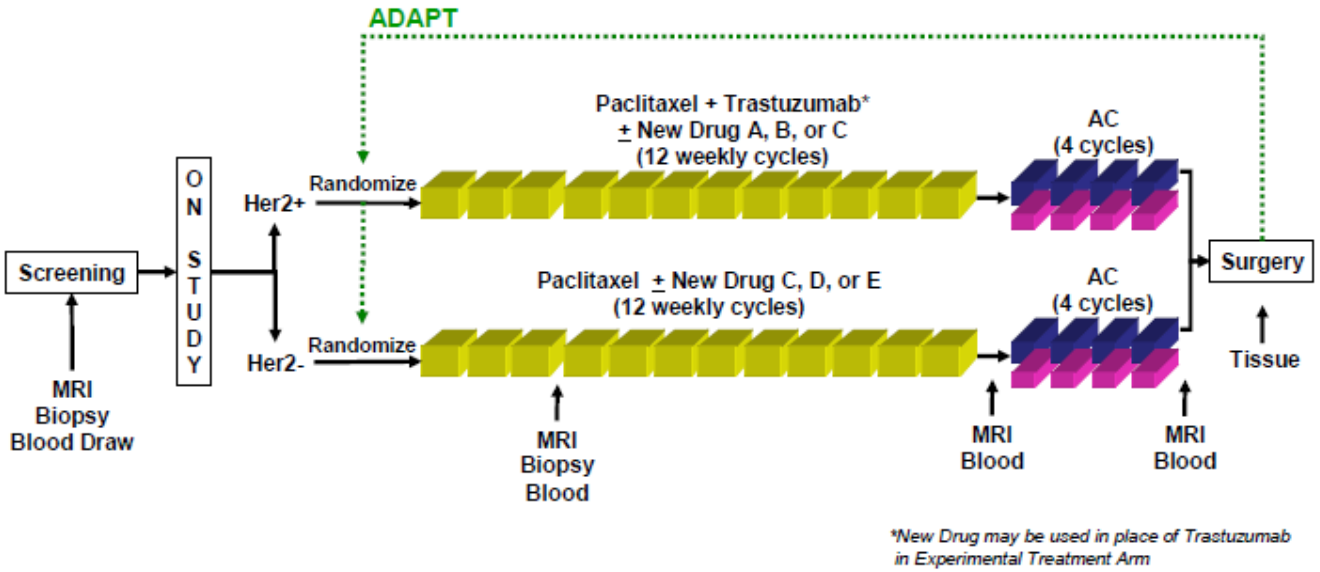
Prospective

- Results are confirmed by independent RCT(s)

Retrospective

Phase 2 – I-SPY-2

Breast Cancer Patients, candidates for neoadjuvant therapy



Accrual: Anticipate 800 patients over 3–4 years

Enroll: ~20 patients per month

Participating Sites: 15–20 across US and Canada

4-5 investigational drugs identified for initial testing

Suppose we want to find out if using a biomarker to select treatment is better?

Marker-based Strategy Design

If we think that one therapy will work in Marker-negative and another therapy will work in the Marker-positive patients

AND

We have a validated assay that can reliably assess the Marker status

THEN

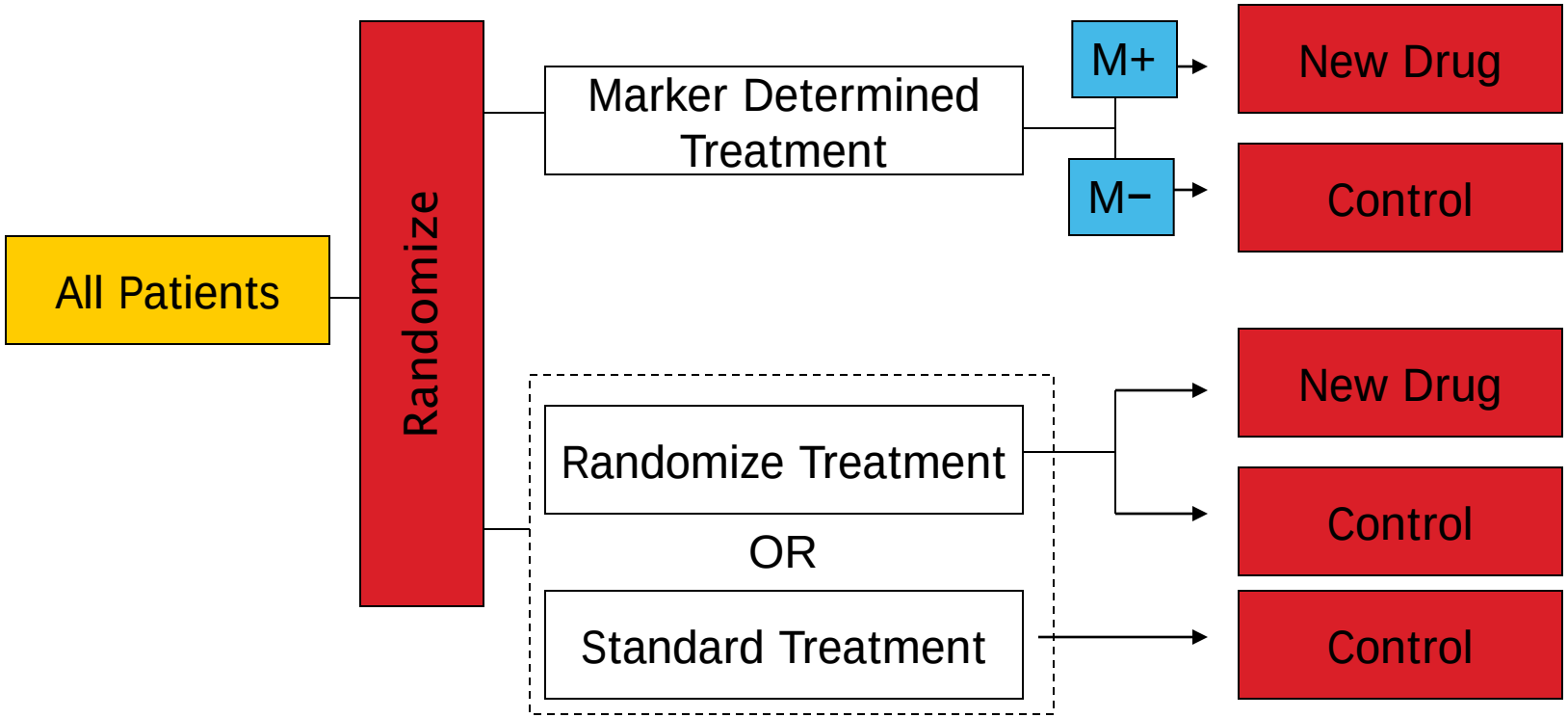
We might design and conduct clinical trial to test whether using the biomarker to select treatment for patients is better than not using the marker to select treatment

Marker-based Strategy Design

Marker-Guided Randomized Design

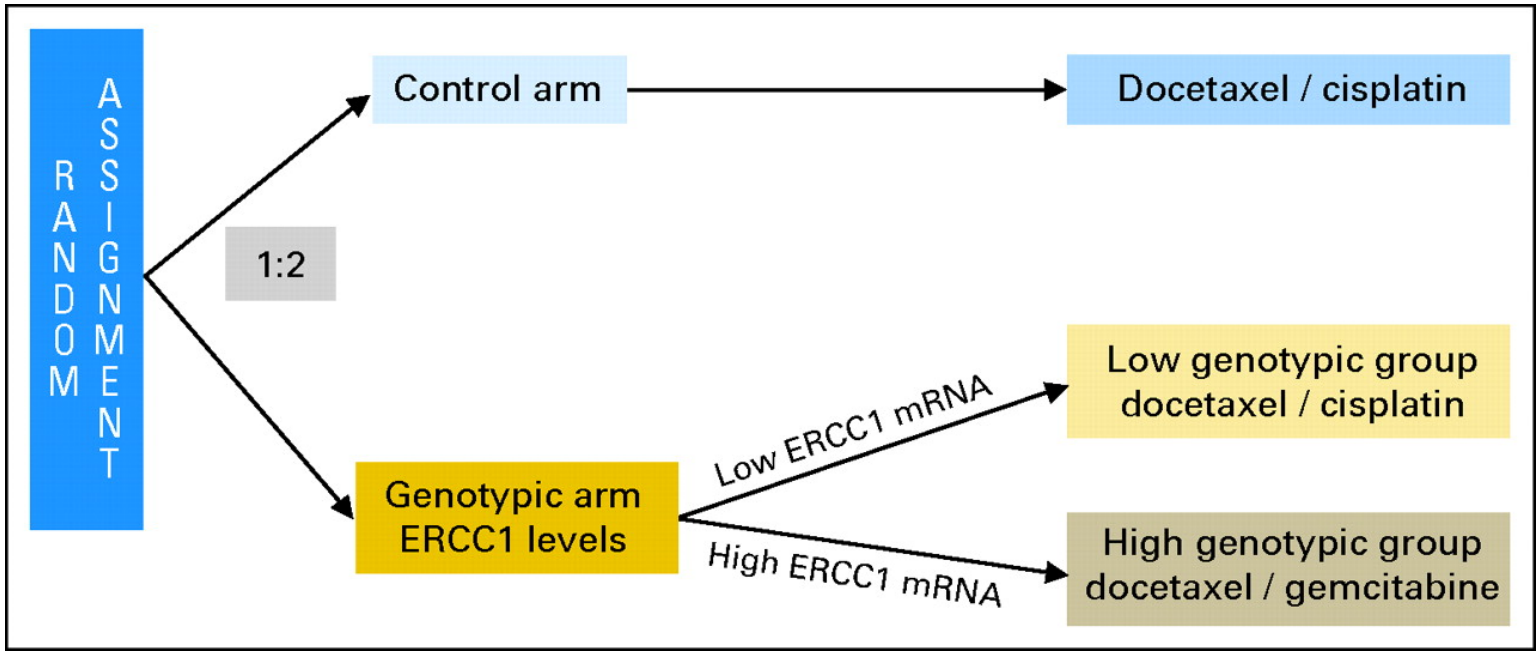
Randomize To Use Of Marker Versus No Marker Evaluation

Control patients may receive standard or be randomized



- **Provides measure of patient willingness to follow marker-assigned therapy**
- **Marker guided treatment may be attractive to patients or clinicians**
- **Inefficient compared to completely randomized or randomized block design**

Example: ERCC1: Customizing Cisplatin Based on Quantitative Excision Repair Cross-Complementing 1 mRNA Expression



- 444 chemotherapy-naïve patients with stage IIIB/IV NSCLC enrolled,
- 78 (17.6%) went off study before receiving chemotherapy, due insufficient tumor for ERCC1 mRNA assessment.
- 346 patients assessable for response: Objective response was 39.3% in the control arm and 50.7% in the genotypic arm (P = .02).

Cobo M et al. J Clin Oncol; 25:2747-2754 2007

Predictive Markers Trials: Considerations – Summary

- Is the drug/treatment active?
- Do we have a marker/markers?
- What are the treatment effects within patient subsets?
  - Are there enough patients to assess treatment effects in Marker+ and/or Marker– groups?
- Does the trial design distinguish predictive and prognostic effects?
- Is there a reliable assay to assess the biomarker?
- Good laboratory/ies that can reliability conduct the testing
- What are the sample requirements?
- Is it feasible?

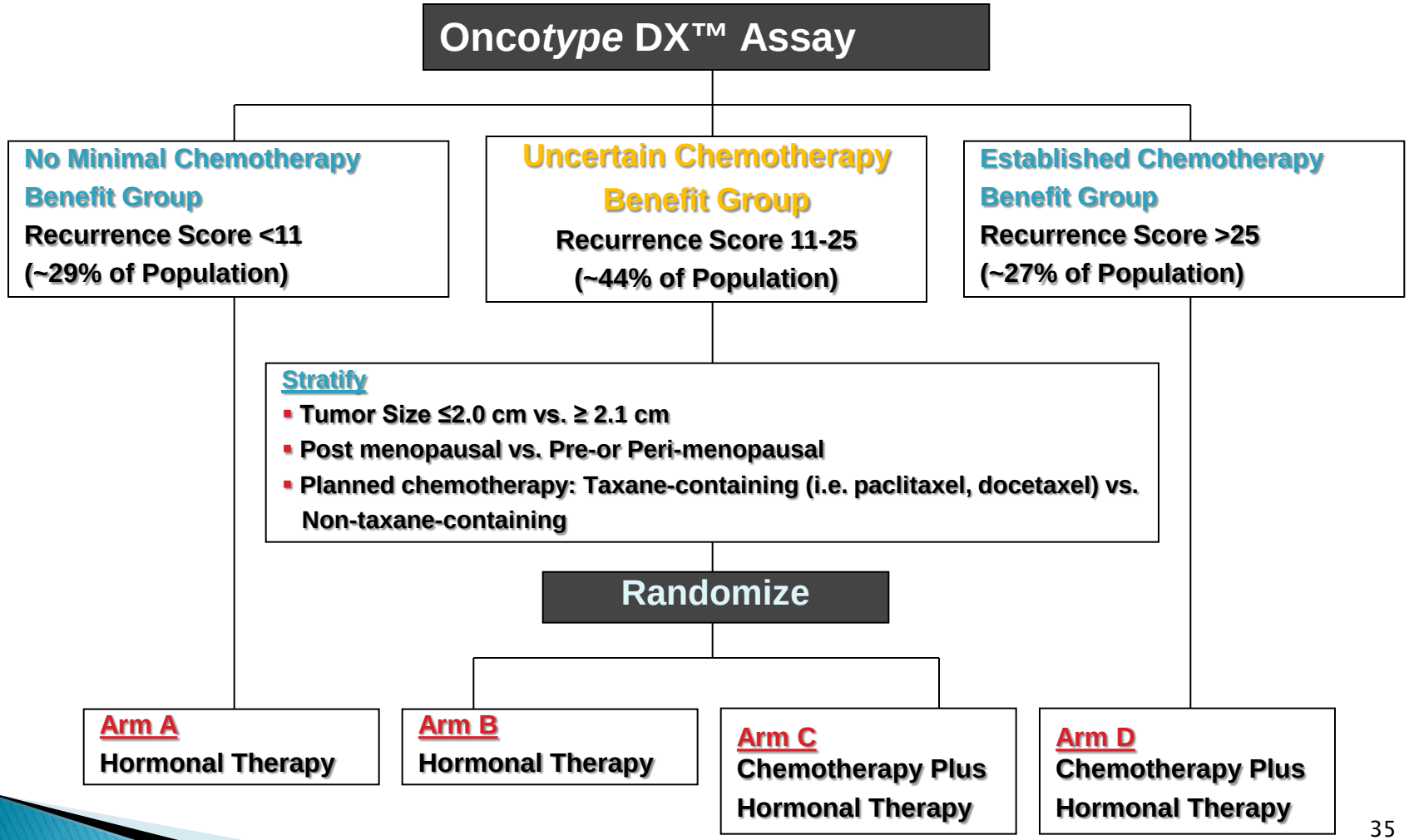
Hybrid Designs: Identifying Recurrence Risk in Breast Cancer

- Many newly diagnosed breast cancers have low risk of recurrence
- 90% receive chemotherapy
- Question: Can we identify those with excellent prognosis without chemo (define good risk group) that is NOT identified by current prognostic markers

Molecular Signatures:

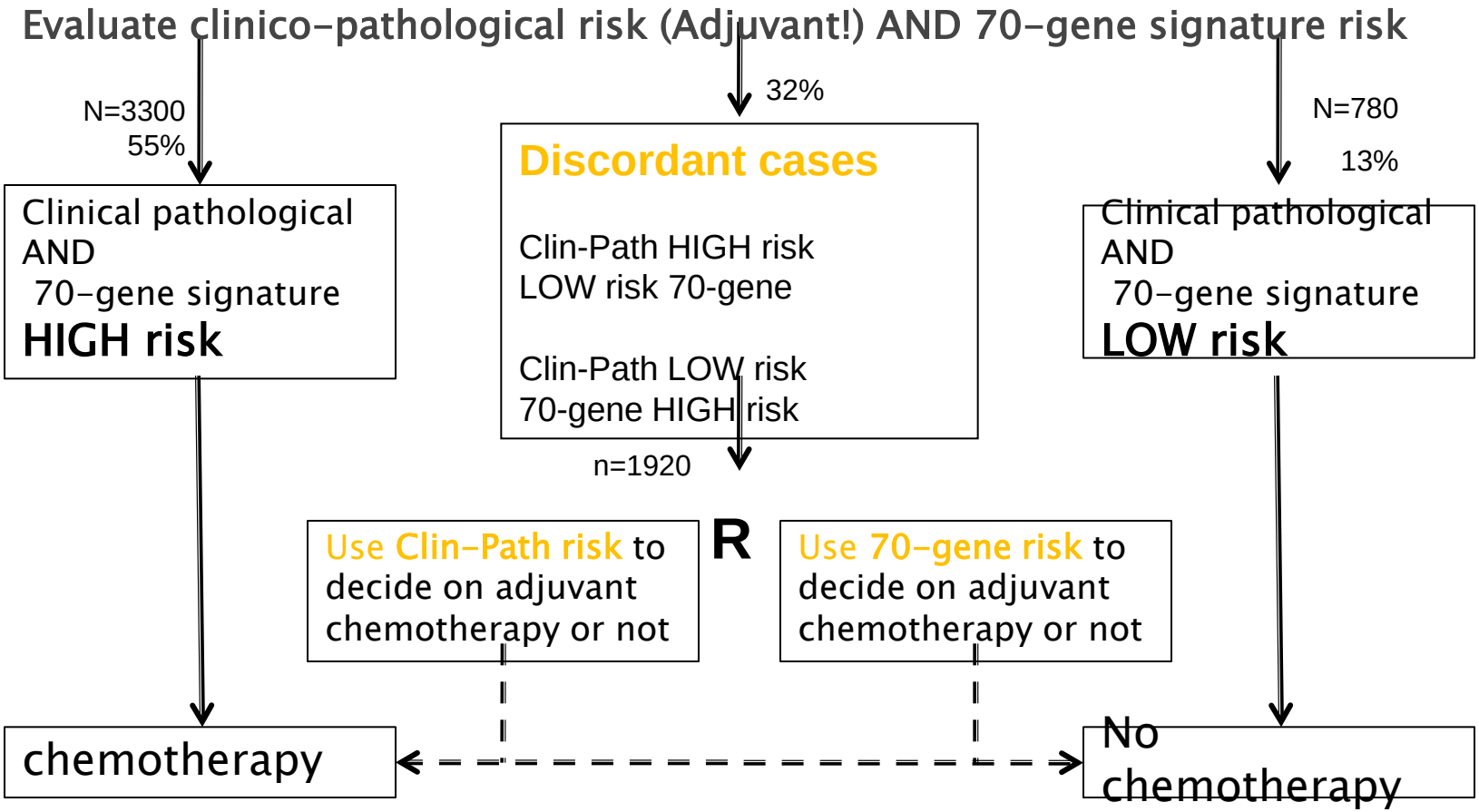
- Oncotype DX Recurrence Score:
  - Calculates recurrence risk by quantitative RT-PCR analysis of 21 genes (can use paraffin fixed tissue)
  - Score identifies **high risk vs. low risk ER+ pts**
  - Growing use in adjuvant decision making (although no RCT to prove utility)
    - ASCO and NCCN Guidelines (2007)
    - Adjuvant RCT ongoing
- 70 gene MammaPrint test
  - Undergoing large adjuvant trial in Europe (MINDACT) (uses fresh frozen tissue)

TAILORx - Study Design: Trial will address how to use the test



MINDACT Design

(Microarray in Node-Negative Disease May Avoid Chemotherapy Trial)



All hormone responsive patients receive endocrine therapy

Summary: Unprecedented Opportunity

- Rapid advances in understanding of cancer biology
- Rapid advances in technology
- An increasing arsenal of active agents available commercially or under clinical development
- Many opportunities for biomarker evaluation

8 Considerations for Biomarkers in Clinical Trials

- What is the question?
- Biomarker(s) – What we want to measure
- Assay – How we measure it
- Specimen – What we measure it in
- Study/Trial Design – Why, when, how we study it
- Study Execution – Can we get the study done
- Study Outcome – What it tells us
- Likely Impact – Whether we use it