

'Learning' Trial Designs

Intended to answer the following questions:

Does the intervention get to the where it needs to be?

At a sufficient concentration?

In a biologically active form?

Does it engage the target of interest?

Does it influence downstream biology or pharmacology?

At what dose?

With what toxicity?

Early Trial Design Issues

- Dosage Identification
 - Tolerability
 - Target Engagement
- Identification of Failure
 - Non-superiority
- Population Identification
 - Post-hoc
 - Adaptive

Identifying Populations

- All diseases have inherent variability that may predict response to treatment
- Identifying patient factors that may predict response, can better target therapies
- Such 'biomarkers' may not have a known role in disease pathogenesis
- Cancer examples include EGFR mutations in NSCLC and the current I-SPY2 trial

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Activating Mutations in the Epidermal Growth Factor
Receptor Underlying Responsiveness of Non–Small-Cell
Lung Cancer to Gefitinib

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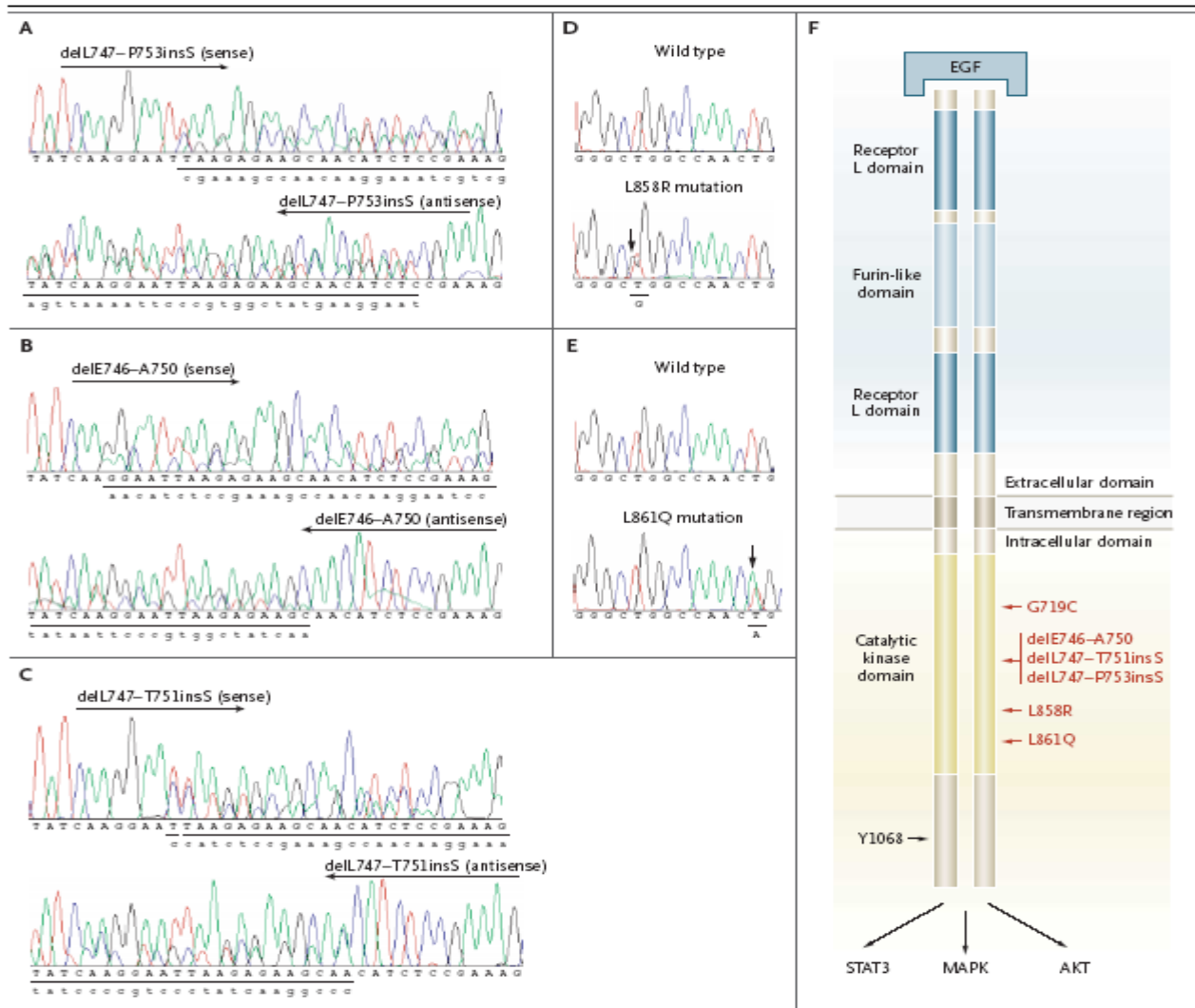
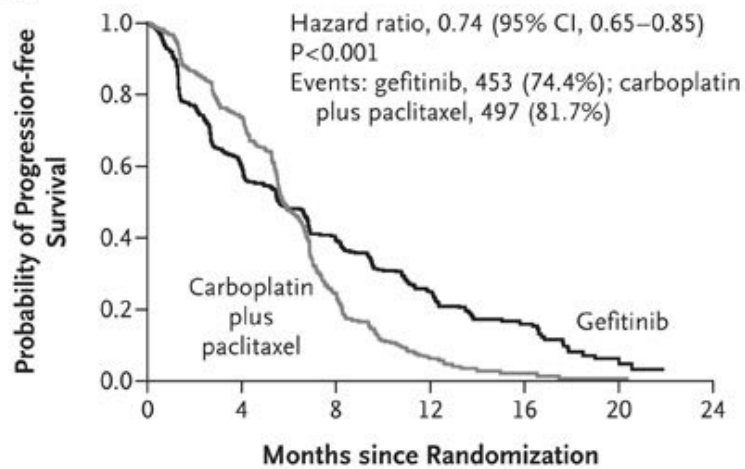


Figure 2. Mutations in the EGFR Gene in Gefitinib-Responsive Tumors.

Panels A, B, and C show the nucleotide sequence of the EGFR gene in tumor specimens with heterozygous in-frame deletions within the tyrosine kinase domain (double peaks). Tracings in both sense and antisense directions are shown to demonstrate the two breakpoints of the deletion; the wild-type nucleotide sequence is shown in capital letters, and the mutant sequence is in lowercase letters. The 5' breakpoint of the delL747–T751insS mutation is preceded by a T-to-C substitution that does not alter the encoded amino acid. Panels D and E show heterozygous missense mutations (arrows) resulting in amino acid substitutions within the tyrosine kinase domain. The double peaks represent two nucleotides at the site of heterozygous mutations. For comparison, the corresponding wild-type sequence is also shown. Panel F shows dimerized EGFR molecules bound by the EGF ligand. The extracellular domain (containing two receptor ligand [L] domains and a furin-like domain), the transmembrane region, and the cytoplasmic domain (containing the catalytic kinase domain) are highlighted. The position of tyrosine¹⁰⁶⁸ (Y1068), a site of autophosphorylation used as a marker of receptor activation, is indicated, along with downstream effectors activated by EGFR autophosphorylation—STAT3, MAP kinase (MAPK), and AKT. The locations of tumor-associated mutations, all within the tyrosine kinase domain, are shown in red.

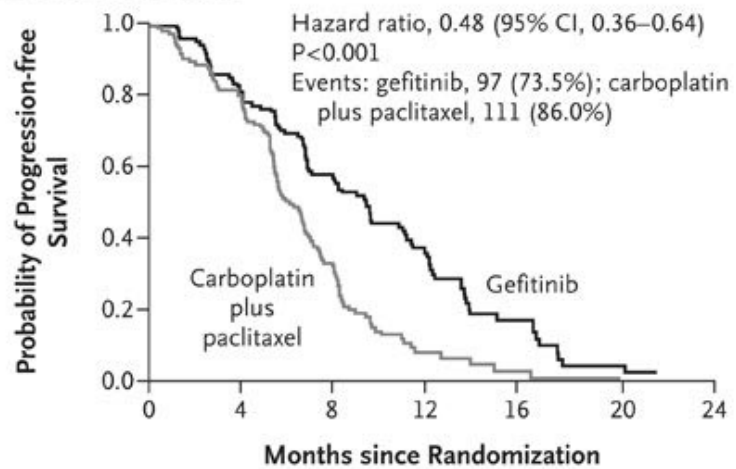
A Overall



No. at Risk

Gefitinib	609	363	212	76	24	5	0
Carboplatin plus paclitaxel	608	412	118	22	3	1	0

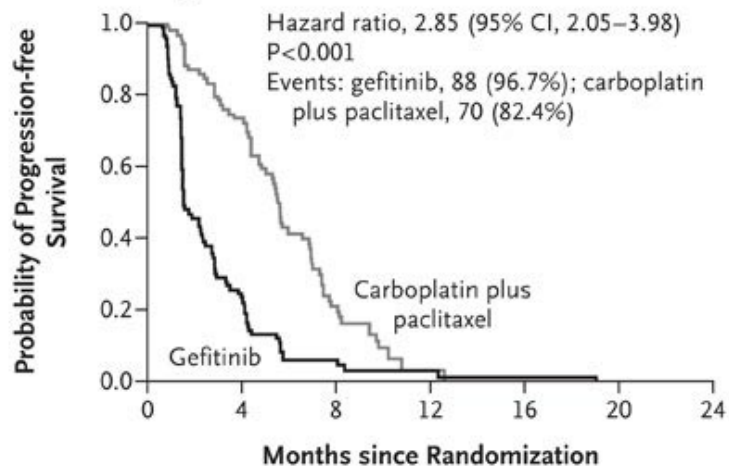
B EGFR-Mutation-Positive



No. at Risk

Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

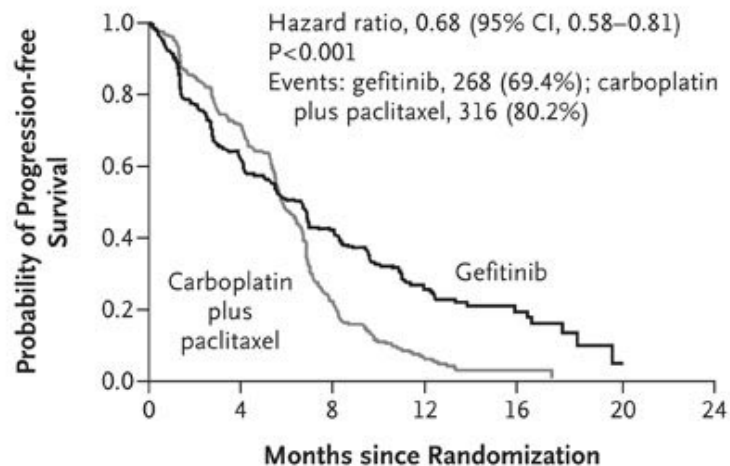
C EGFR-Mutation-Negative



No. at Risk

Gefitinib	91	21	4	2	1	0	0
Carboplatin plus paclitaxel	85	58	14	1	0	0	0

D Unknown EGFR Mutation Status



No. at Risk

Gefitinib	386	234	137	43	12	2	0
Carboplatin plus paclitaxel	394	251	67	14	1	0	0



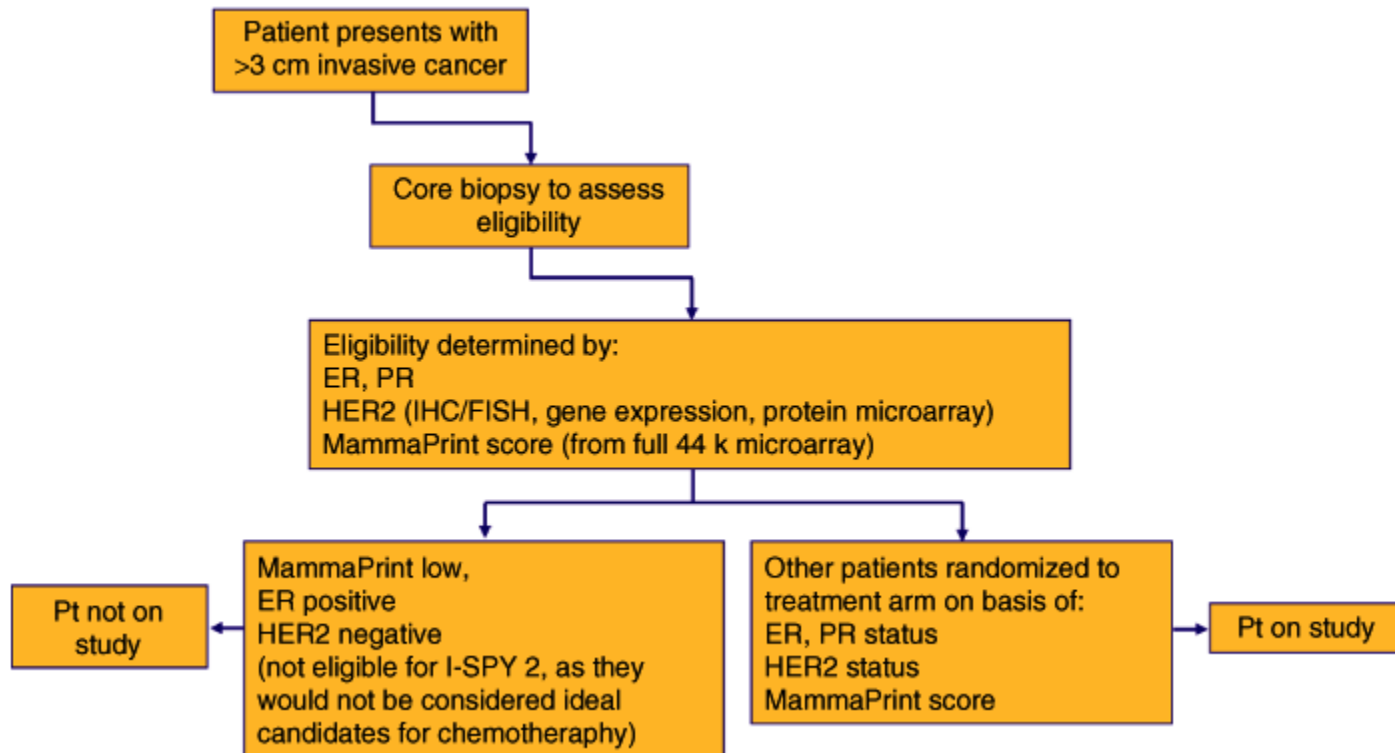
Breast Cancer Example

- I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy
- AD Barker, CC Sigman, GJ Kelloff, NM Hylton, DA Berry and L Esserman
- Clinical Pharmacology & Therapeutics, Vol 86 No 1, July 2009

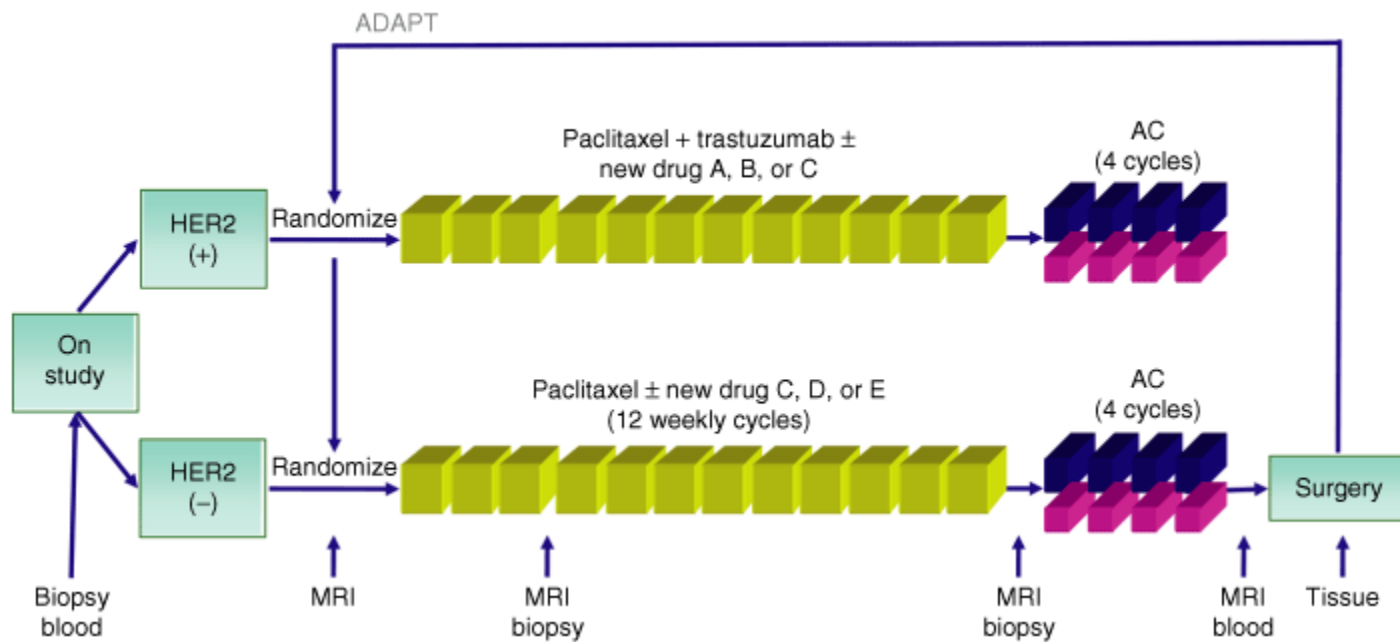
Breast Cancer

- I-SPY2 Adaptive Design Process
- Funded by FNIH: NCI, FDA, industry, academia, philanthropy
- Coordinated with FDA's CDER, CBER, CDRH from get-go
- Drugs from many companies
- Data sharing

Eligibility



Design



Breast Cancer

PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

1 cube = 10 patients

Traditional clinical trial

Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.

New trial design

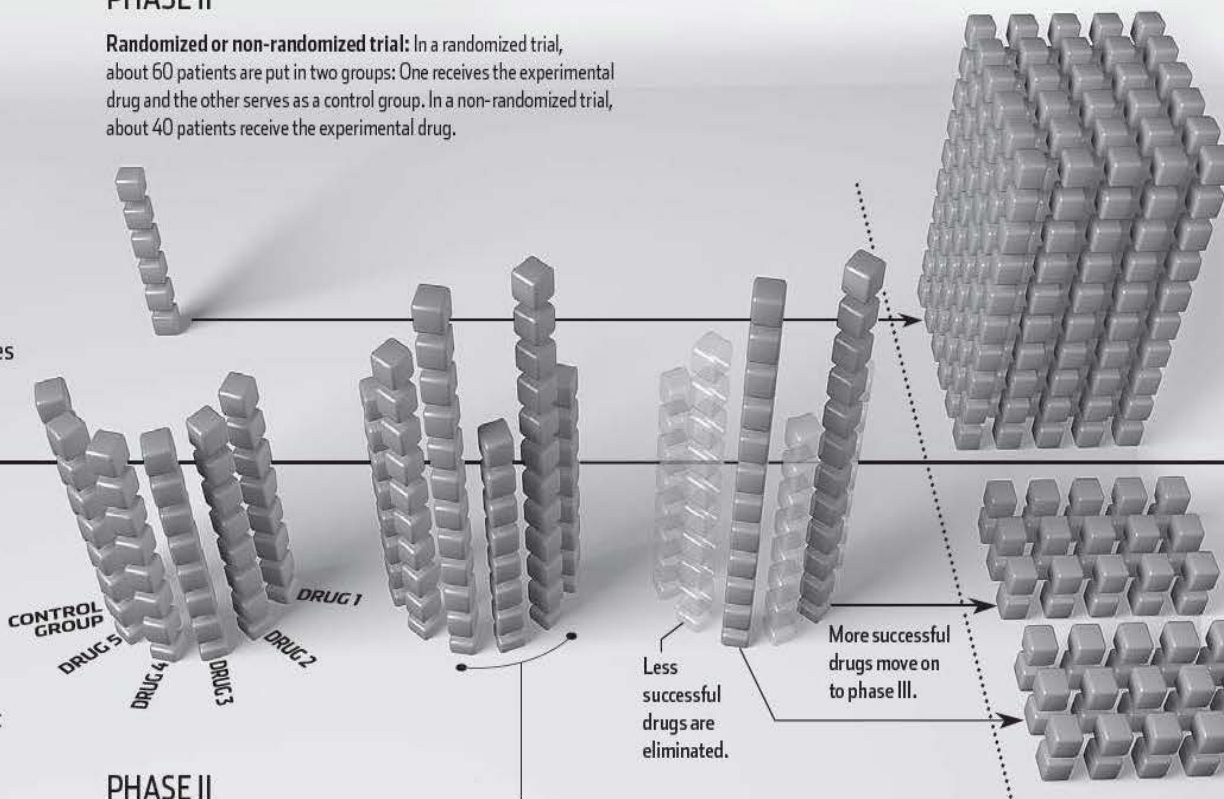
Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.

Note: In all clinical trials, phase I consists of testing on human subjects to determine toxicity levels.

Graphic by Maryanne Murray/WSJ

PHASE II

Randomized or non-randomized trial: In a randomized trial, about 60 patients are put in two groups: One receives the experimental drug and the other serves as a control group. In a non-randomized trial, about 40 patients receive the experimental drug.



PHASE II

Patients are placed in groups based on genetic profiles and are randomly assigned to either standard therapy or one of five different drugs plus standard care.

Early results increase chances that patients entering the trial later will be assigned to a drug showing benefit against tumors with their genetic profile.

It will take up to 120 patients for each drug to determine which ones graduate to phase III studies.

PHASE III

If a drug graduates to phase III, it typically takes 3,000 patients and about three years to determine if it is safe and effective enough for approval.



HISTORIC SUCCESS RATE

30 TO 40%

PHASE III

Researchers expect that drugs graduating from I-Spy 2 to phase III can be tested with 300 patients selected according to genetic profiles found to respond to the drug in phase II. It is hoped that this will shorten the time to approval.



PROBABILITY OF SUCCESS

85%

Source: Donald Berry, M.D. Anderson Cancer Center

I-SPY 2 Effects

- 40% savings on control arms
- Match drugs & combos with biomarker signatures
- Graduate drug/biomarker pairs to smaller ($n < 300$), more focused, more successful Phase 3
- Descendants of I-SPY 2 in melanoma, colorectal cancer, Alzheimer's, acute heart failure