L'Oncologo Sperimentatore nel Disegno e nella Conduzione dello Studio Clinico

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LA SETTIMANA DEL GOIRC

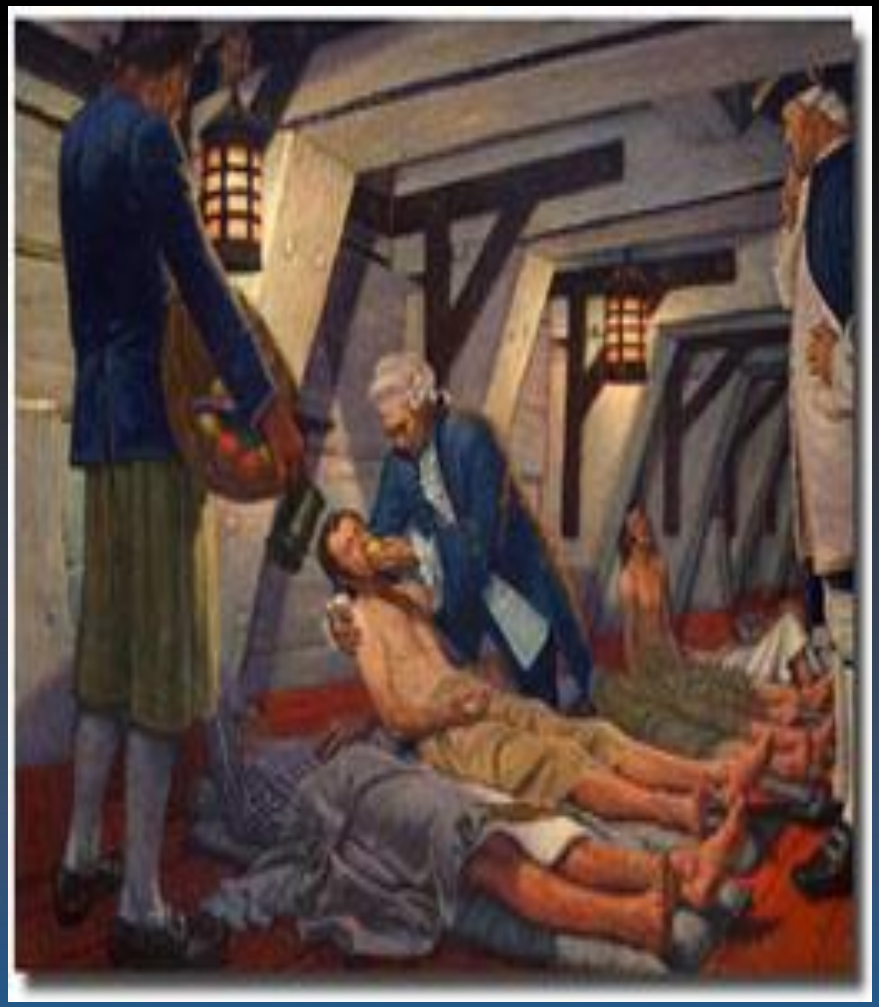
Negrar, 29 Aprile 2014

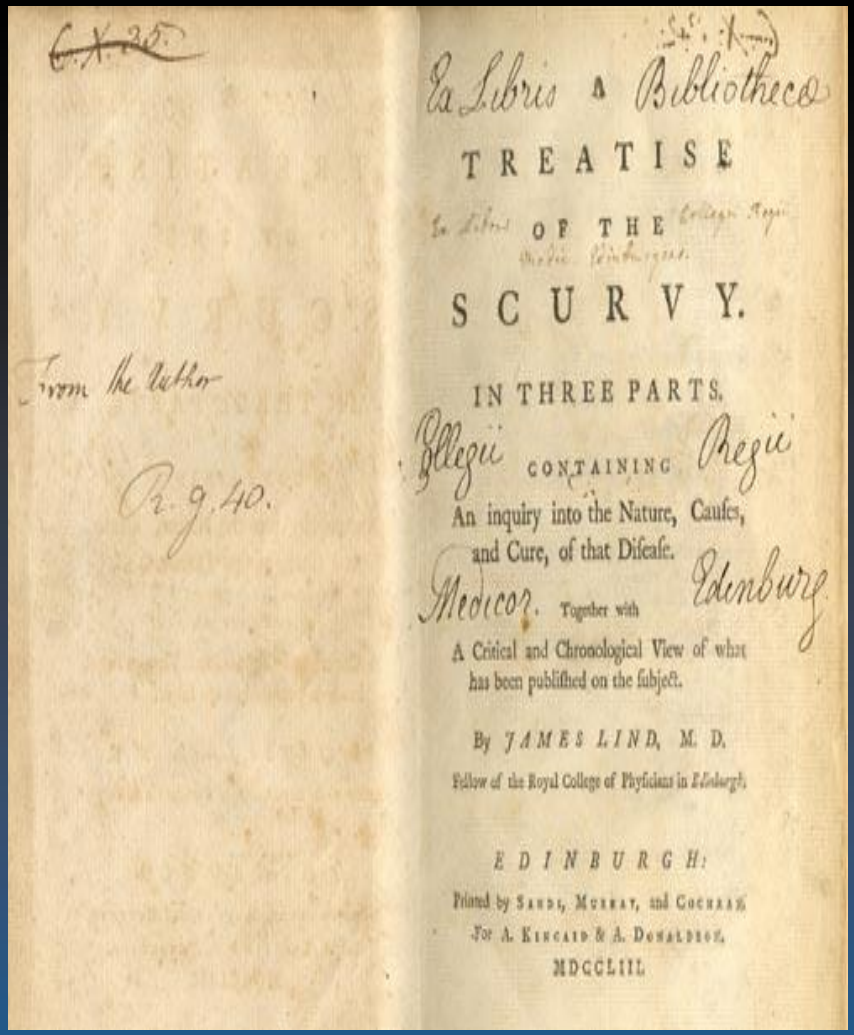
What is Research?

- Research is the endeavor to discover new facts, procedures, methods, and techniques by the scientific study of a course of critical investigation

Clinical Research

- Clinical research involves working with human subjects to answer questions relevant to their well-being





C. X. 25.

From the Author

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Ex Libris A Bibliotheca

TREATISE

Ex Libris OF THE

SCURVY.

IN THREE PARTS.

CONTAINING

An inquiry into the Nature, Cauſes, and Cure, of that Diſeaſe.

Together with

A Critical and Chronological View of what has been publiſhed on the ſubject.

By JAMES LIND, M. D.

Fellow of the Royal College of Phyſicians in Edinburgh.

EDINBURGH:

Printed by SANDS, MURRAY, and COCHRAN,

For A. KINCAID & A. DONALDSON.

MDCCLIII.

"A treatise of the scurvy" James Lind 1753

Good Research

- **CLEAR**
  - Essential for both the problem and the answer
- **ACCURATE**
  - Exactness and precision come from hard work and responsible effort
- **RELIABLE**
  - If repeated will the answer be the same?

Good Research

- **OBJECTIVE**
  - **The researcher exposes all possible prejudices at the onset of the study design and strives to overcome them**
  - **Will the research be untarnished by personal gain, biases, vested interests, etc?**

Researcher Qualities

- Knowledgeable
- Observant
- Logical
- Open-minded
- Honest
- Motivated
- Independent
- Flexible
- Careful

Researcher Qualities

- Curious
- Inquisitive
- Eager to learn
- Skeptical
- Perceptive
- Persistent
- Patient
- Original
- Creative

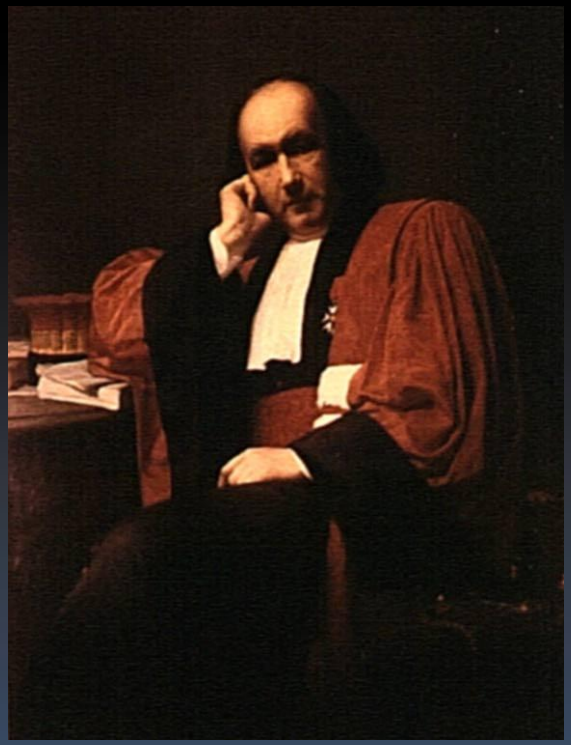
Stages in Creativity

- **SENSE**
  - Realize the need for a study
- **PREPARE**
  - Gather relevant information
- **INCUBATE**
  - Think through the problem
- **ILLUMINATE**
  - Imagine possible solutions
- **VERIFY**
  - Evaluate the solutions you have generated

Hypothesis

- **Thesis is the position that you believe represents truth**
- **Hypothesis is the foundation on top of which you build your thesis**

Claude Bernard (1813-1878)



The first requirement…in practicing experimental medicine, is to be an observing physician and to start from pure and simple observations of patients made as completely as possible.

"An Introduction to the Study of Experimental Medicine" **1865.**
He is considered as the "Father of Physiology".

A Good Hypothesis Should:

- Be testable
- Convey the nature of the relationship being tested
- State exactly what variables form this relationship
- Reflect all variables of interest
- Be formulated early on in the planning stage

Methods

- Define methods carefully
- Decrease variability
- Check reliability/reproducibility
- Are you testing what you think you are testing?

Data

- Data are the facts you measure
- They should be carefully recorded in an unbiased manner
- They should be measured in a manner that minimizes random variation
- They should be derived from the operational definitions you have developed

Data Interpretation

- Do not interpret/analyze data until after study is completed
- Do not 'unblind' subjects until the study is completed other than for safety reasons
- Do not interpret/analyze data until after data has been validated and the data set closed

Writing a Clinical Research Protocol

- Introduction/Abstract
- Objectives (including study schema)
- Background/Rationale
- Eligibility criteria
- Study design/methods (including drug/device info)
- Safety/adverse events
- Regulatory guidance
- Statistical section (including analysis and monitoring)
- Human subjects protection/informed consent

Study Population

- Age
- Gender
- Ethnicity/Race
- Disease characteristics
- Exclusions
- Number
- Stratification
- Randomization

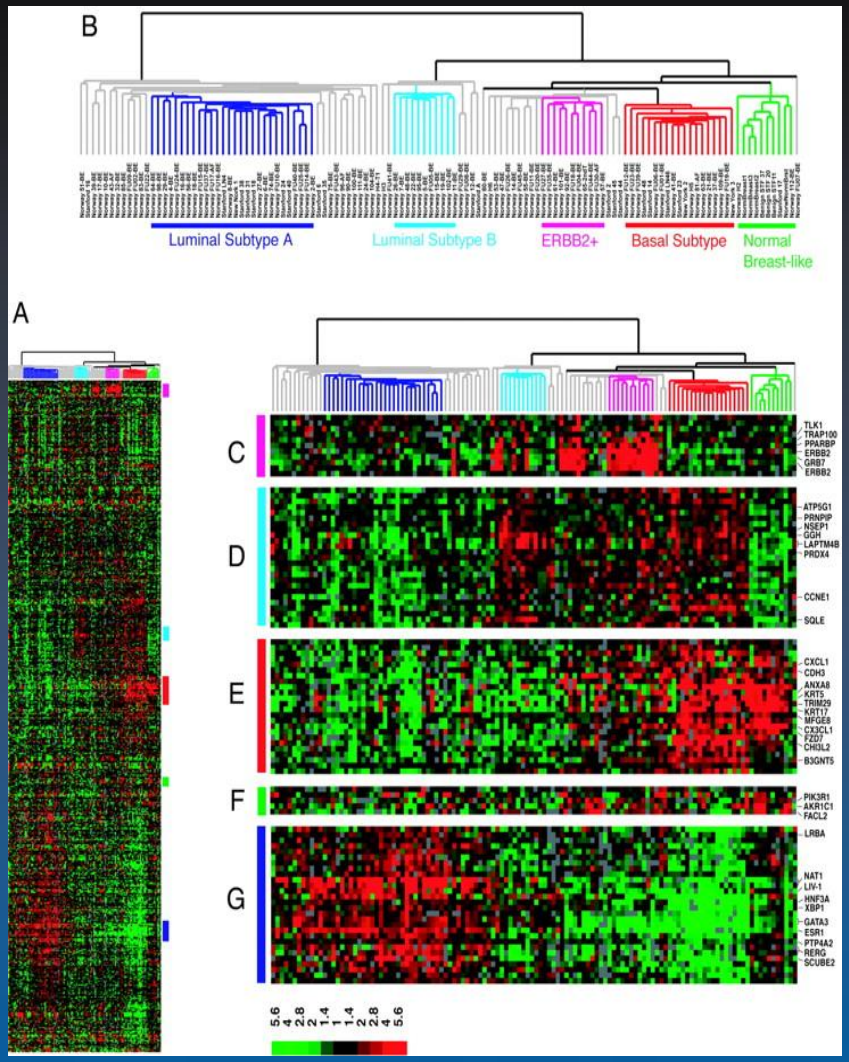
Writing Eligibility Criteria

STOP BEFORE YOU WRITE!

- **Eligibility criteria are the largest barrier to accrual to clinical trials.[1]**
- **Poorly written or poorly conceived criteria may undermine a trial's generalizability and scientific validity.[2]**

[1]Fuks A, J Clin Epidemiol, 1998
[2]George SL, J Clin Oncol, 1996

Breast Cancer Subtypes



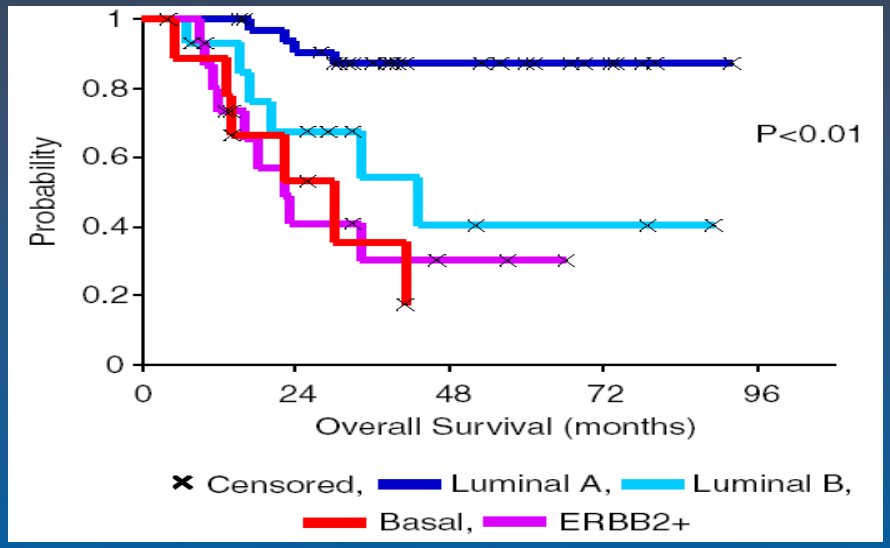
Luminal A

ER+ 65-75%

Luminal B

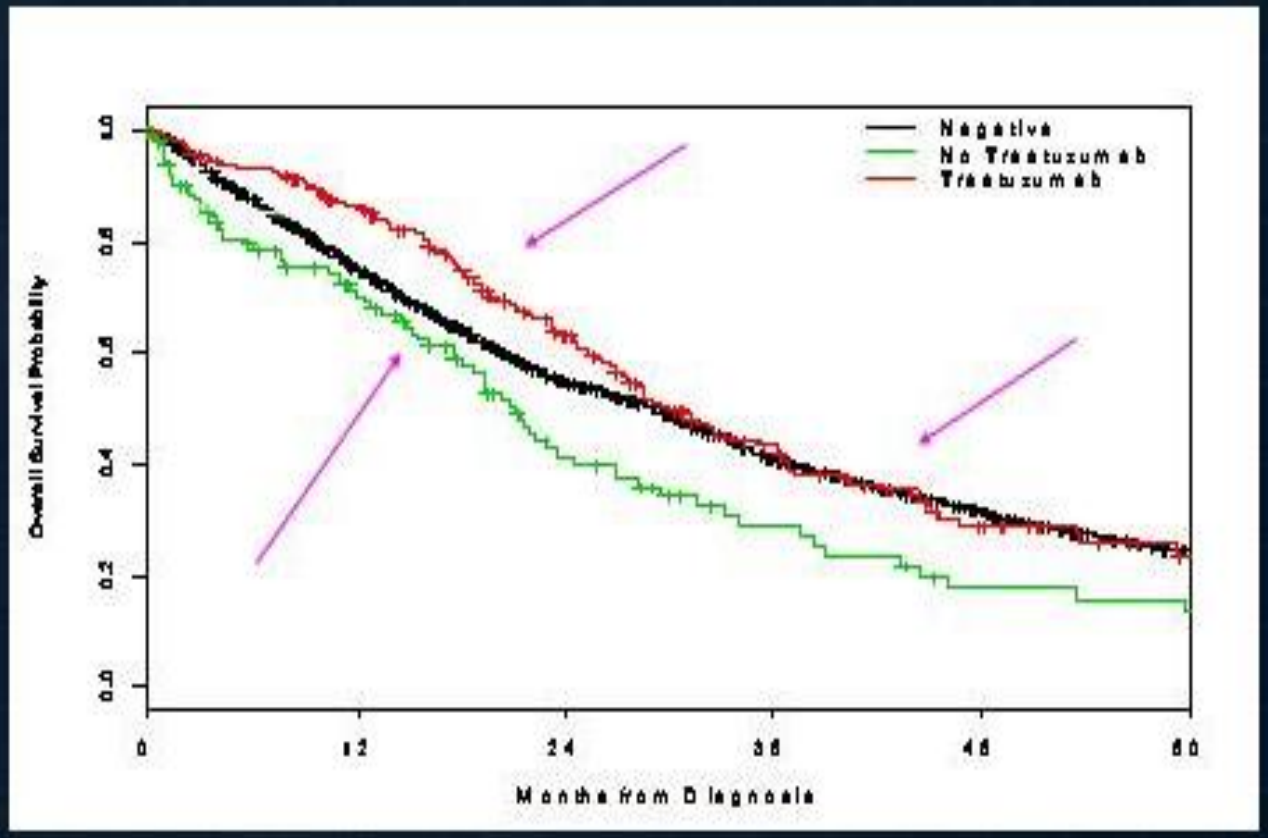
Basal-Like **ER- 15%**

HER2+ **ER- 15-20%**



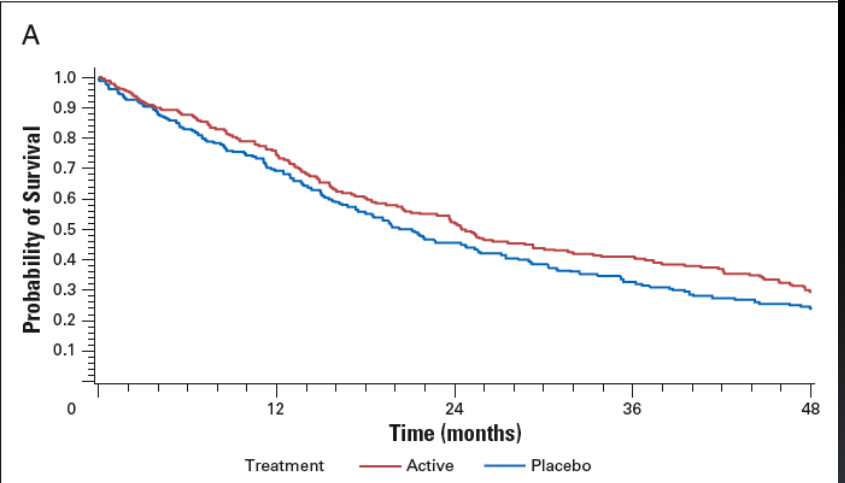
Solie et al. Eur J Cancer 2004

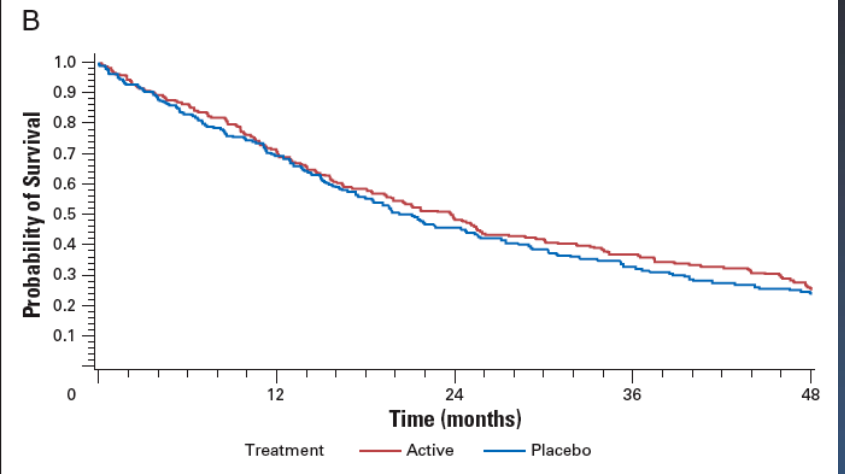
Overall Survival by Trastuzumab Treatment Groups

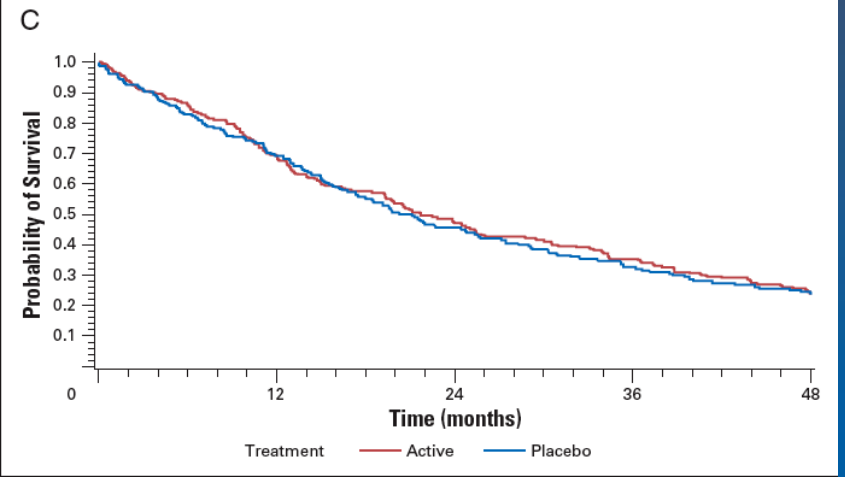


ASCO Annual '08 Meeting

2008 ASCO Merit Award Recipient







A Simulation of a Phase III Trial:

Two subgroups (A and B):

A is sensitive to targeted therapy and will have a 25% improvement in median survival from 22→27 mo.

B is insensitive to targeted therapy

Three scenarios:

A representing 100, 50, and 25% of the study population.

Types of Clinical Trials

- Randomized
- Non-Randomized
- Single-Center
- Multi-Center
- Phase I, II, III, IV Trials

ESMO congress Milan 2010

LBA11 Iniparib Study Design

Multi-center, open-label, randomized Phase II

- Metastatic TNBC - about 70% had prior chemotherapy for early BC
- Measurable disease -median number of metastatic sites = 3
- 0-2 prior chemotherapy regimens for metastatic disease - no prior chemo~60%
- No prior gemcitabine, carboplatin, cisplatin, PARP inhibitor
- Stable brain metastases allowed
- ECOG PS 0–1 - two thirds PS = 0

Randomization (1:1)

Gemcitabine	1000 mg/m^2, IV, d 1, 8
Carboplatin	AUC 2, IV, d 1, 8
21 day cycles	

N=62*

Iniparib	5.6 mg/kg, IV, d 1, 4, 8, 11
Gemcitabine	1000 mg/m^2, IV, d 1, 8
Carboplatin	AUC 2, IV, d 1, 8
21 day cycles	

N=61

RESTAGING: Every 2 Cycles (RECIST)

PRIMARY ENDPOINTS: CBR = CR + PR + SD ≥6mo, Safety
SECONDARY ENDPOINTS: DFS, ORR, Toxicity

* 30 patients randomized to gem/carbo crossed over to receive gem/carbo + Iniparib (BSI-201) at disease progression

Response Rate

	BSI-201 + Gem/Carbo (n = 42)	Gem/Carbo (n = 44)	P Value (HR [95% CI])
Tumor response,[1] n (%)			
▪ ORR	20 (48)	7 (16)	.002
▪ (			
Su			
▪ mPFS[1]	6.9 (n = 57)	3.3 (n = 59)	< .0001 (0.342 [0.200-0.584])
▪ mOS[2]	12.2 (n = 61)	7.7 (n = 62)	.005 (0.50 [0.30-0.82])

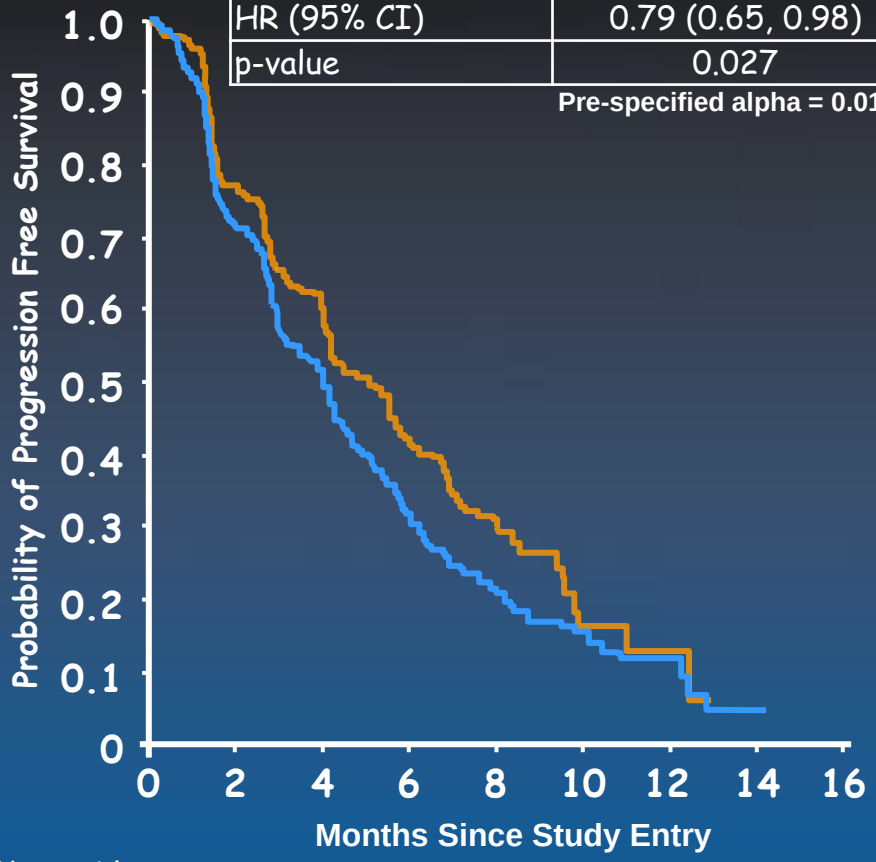
No Increase in Toxicity

O'Shaughnessy. ASCO 2009

Phase III study of Iniparib in Metastatic TNBC

PFS	GC (N=258)	GCI (N=261)
Median PFS, mos (95% CI)	4.1 (3.1, 4.6)	5.1 (4.2, 5.8)
HR (95% CI)	0.79 (0.65, 0.98)	
p-value	0.027	

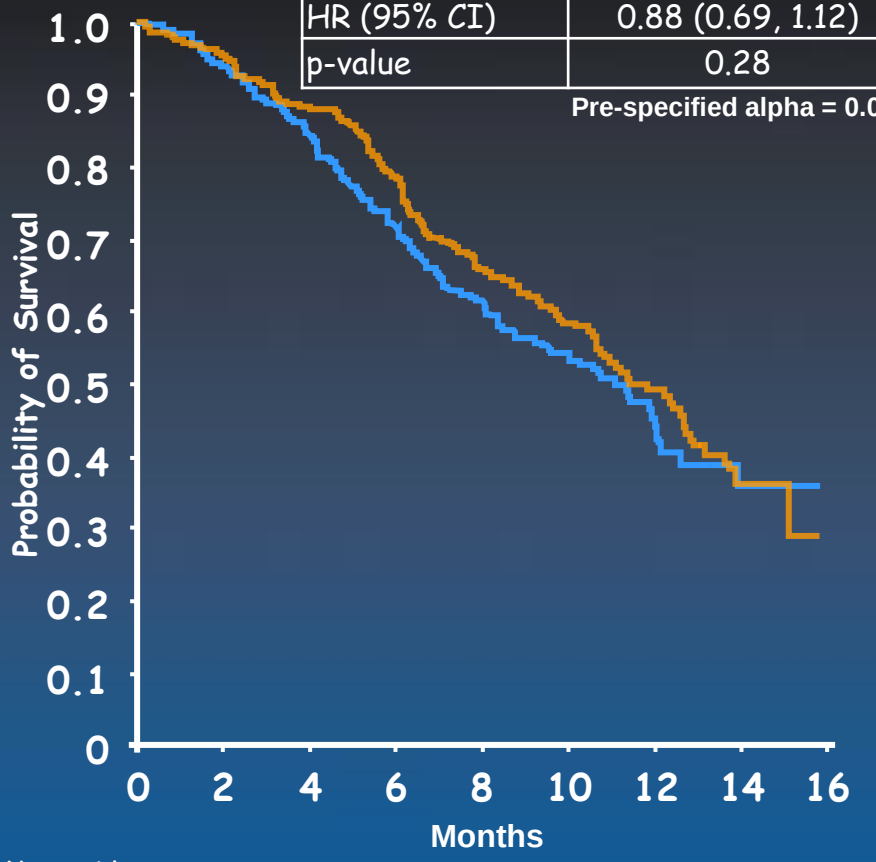
Pre-specified alpha = 0.01



No. at risk									
GC	258	171	116	63	38	18	6	1	0
GCI	261	187	138	83	53	11	2	0	0

OS	GC (N=258)	GCI (N=261)
Median OS, mos (95% CI)	11.1 (9.2, 12.1)	11.8 (10.6, 12.9)
HR (95% CI)	0.88 (0.69, 1.12)	
p-value	0.28	

Pre-specified alpha = 0.04



No. at risk									
GC	258	239	214	181	151	99	38	11	0
GCI	261	248	230	204	169	111	52	15	0

O' Shaughnessy. ASCO 2011

Which Endpoint to Choose?

- "Progression-free survival" (PFS): commonly used
  - PFS: time from treatment initiation to tumor progression or death from any cause, with censoring of patients who are lost to follow-up
- "Time to tumor progression" (TTP): used much less often
  - TTP: the only event of interest is disease progression
- Response rate (WHO, RECIST, modified RECIST, Choi…)
- Biomarker
  - Disease marker definitely tied to outcomes [e.g. viral load in HIV]
  - Tumor marker [e.g. PSA]
  - Imaging [e.g. PET SUV_{max}]
- Patient-reported outcomesto test impact of study intervention on "how a patient feels, functions or survives"

"Direct" Endpoints

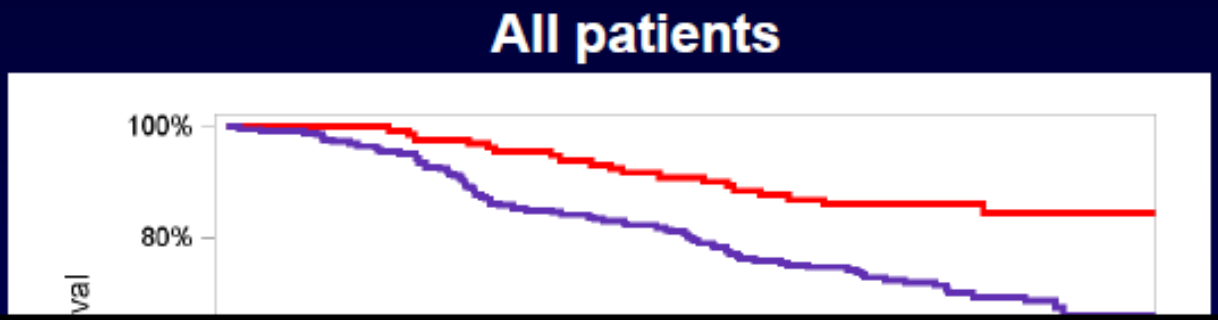
- Clinically meaningful endpoints that directly measure how a patient **feels**, **functions**, or **survives**
- Endpoints that in themselves represent or characterize the clinical outcome of interest
  - Objective: survival, disease exacerbation, clinical event (e.g. MI, stroke), etc.
  - Subjective: symptom score, "health related quality of life" (validated instrument), etc.
- Customarily, the basis for approval of new drugs

Note: The term "direct" is used here to distinguish from "surrogate" endpoints, but this term is not uniformly utilized. Others may refer to these as "true" or "clinically meaningful" endpoints

Surrogate Endpoints

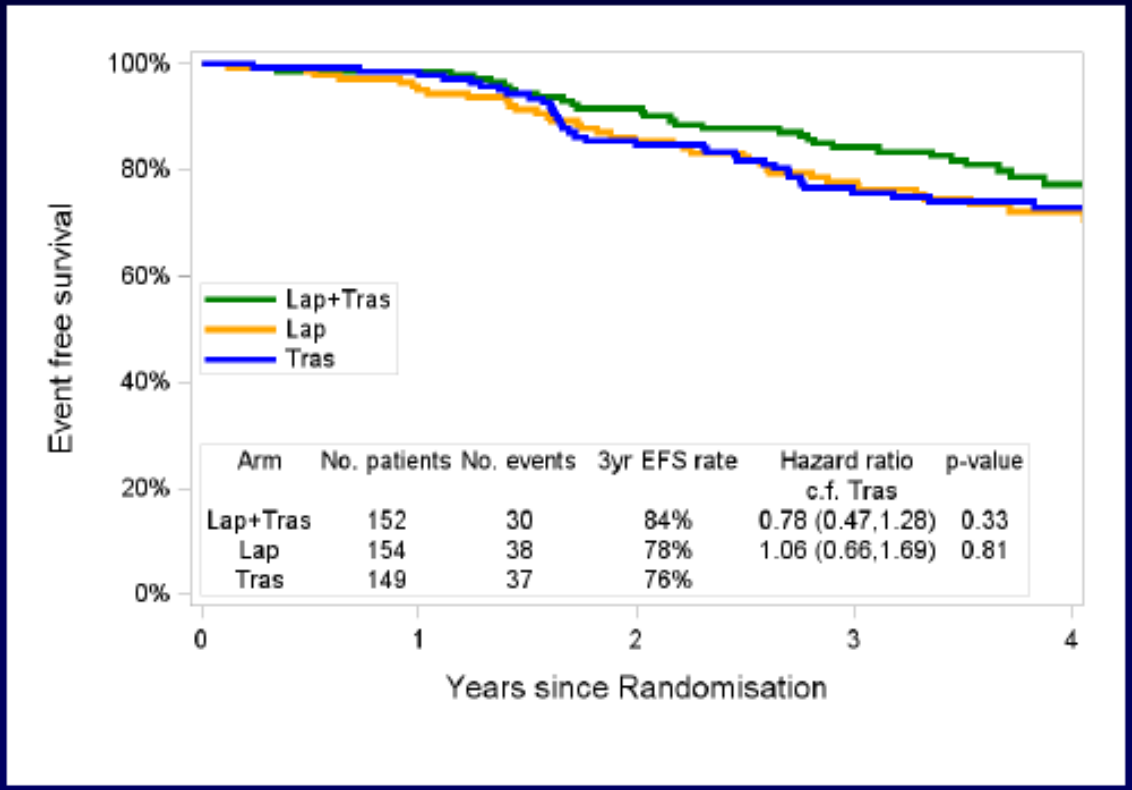
- A surrogate endpoint is a laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint.
- Ideally, the surrogate should exist within the therapeutic pathway between the drug and meaningful benefit
  - i.e. the drug results in the therapeutic benefit by virtue of its effect on the surrogate
- Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.

Landmark Analysis: EFS by pCR



Event-Free Survival Analysis

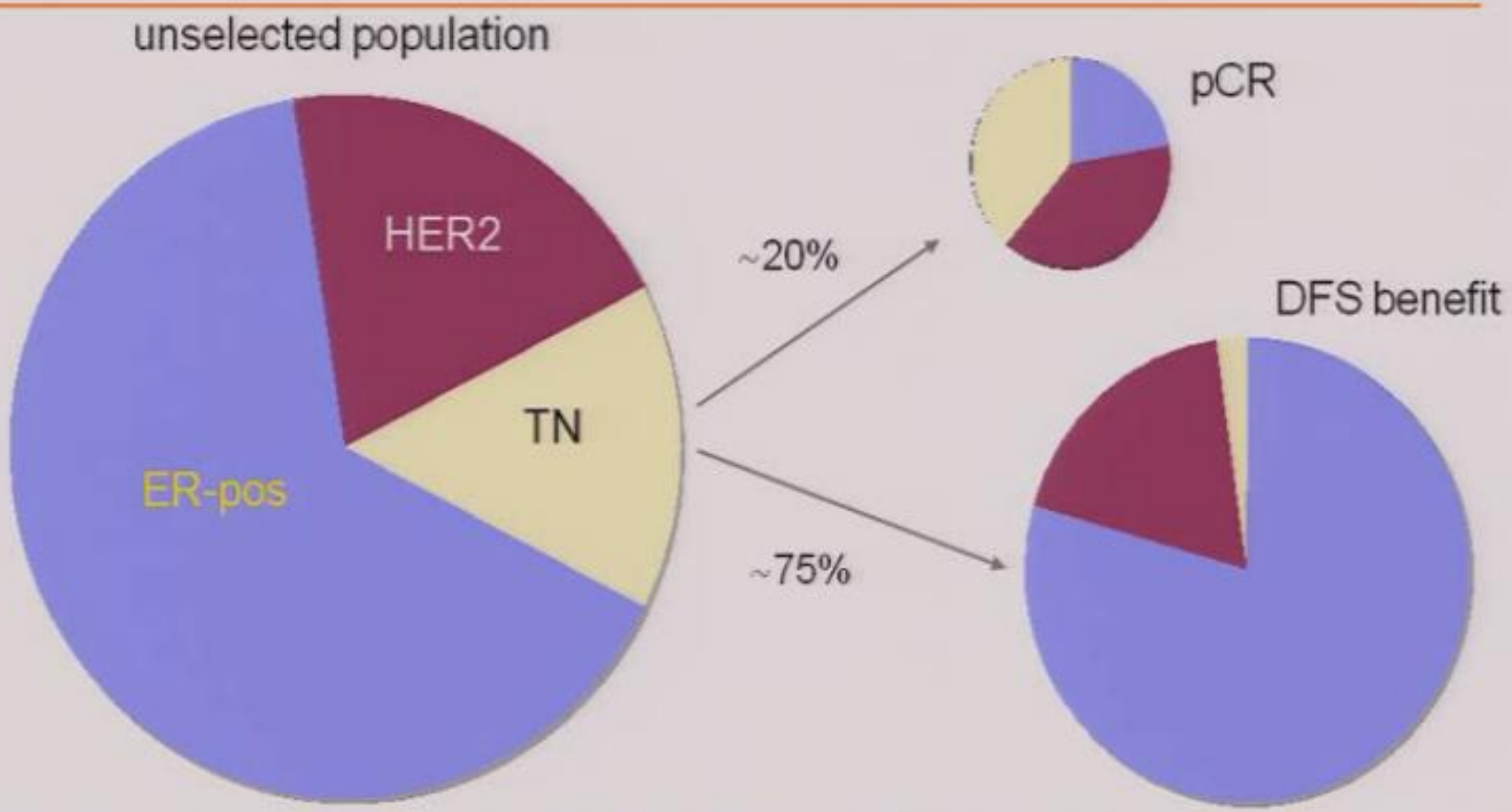
All patients



Arm	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	152	30	84%	0.78 (0.47,1.28)	0.33
Lap	154	38	78%	1.06 (0.66,1.69)	0.81
Tras	149	37	76%		

Piccart M, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-01.

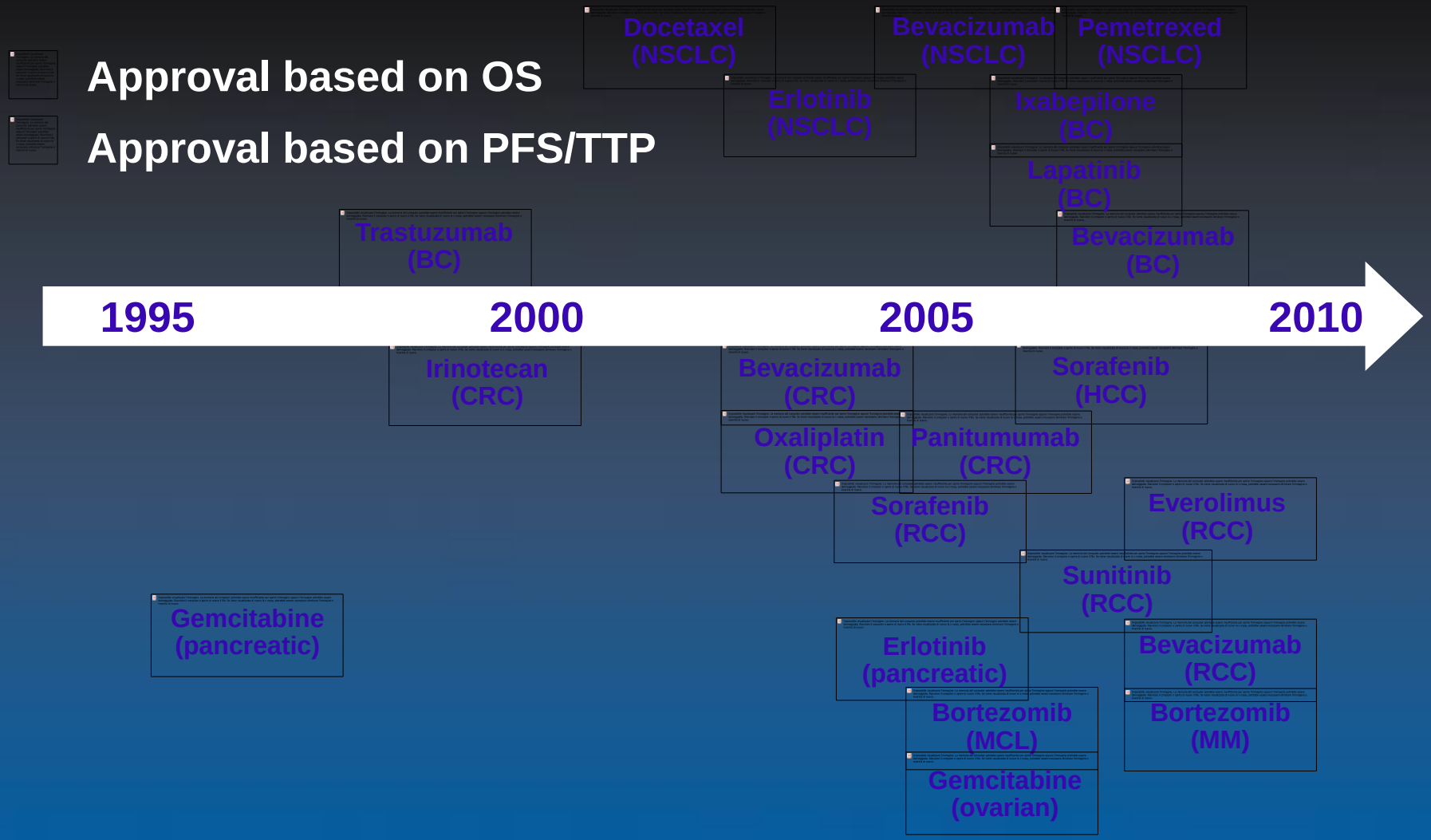
Neoadjuvant Trials and Tumor Heterogeneity



- **Likelihood of pCR and and DFS is different for different molecular subsets**
- **Predictors of pCR do not predict DFS in unselected cases**
- **A single predictive biomarker cannot fit all tumor types**

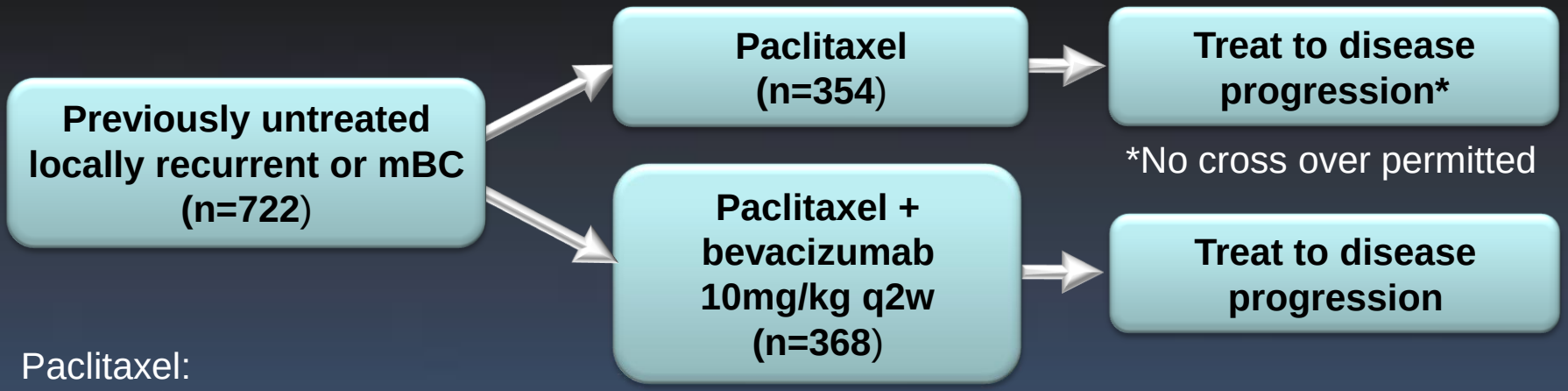
L. Gianni, ASCO 2011

Increasing Acceptance of PFS as a Basis for FDA Approval



www.cancer.gov/cancertopics/druginfo

Phase III trial of Bevacizumab + Paclitaxel in First-line mBC (E2100)

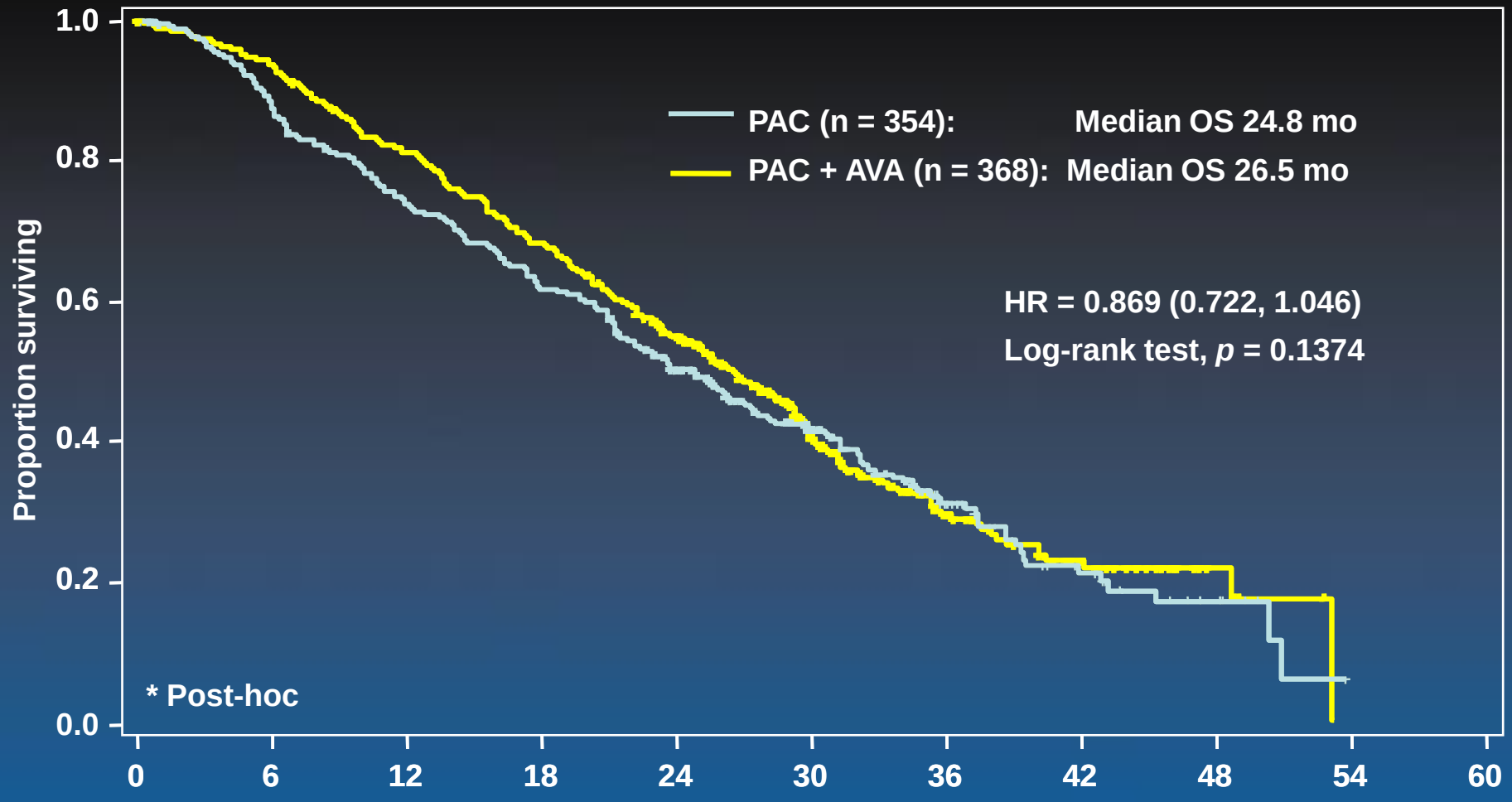


Paclitaxel:
90mg/m^2/w for 3 weeks
of a 4-week cycle

- Primary endpoint: Progression-free survival
  - other endpoints: Overall response rate, overall survival, quality of life

Miller, et al. NEJM 2007

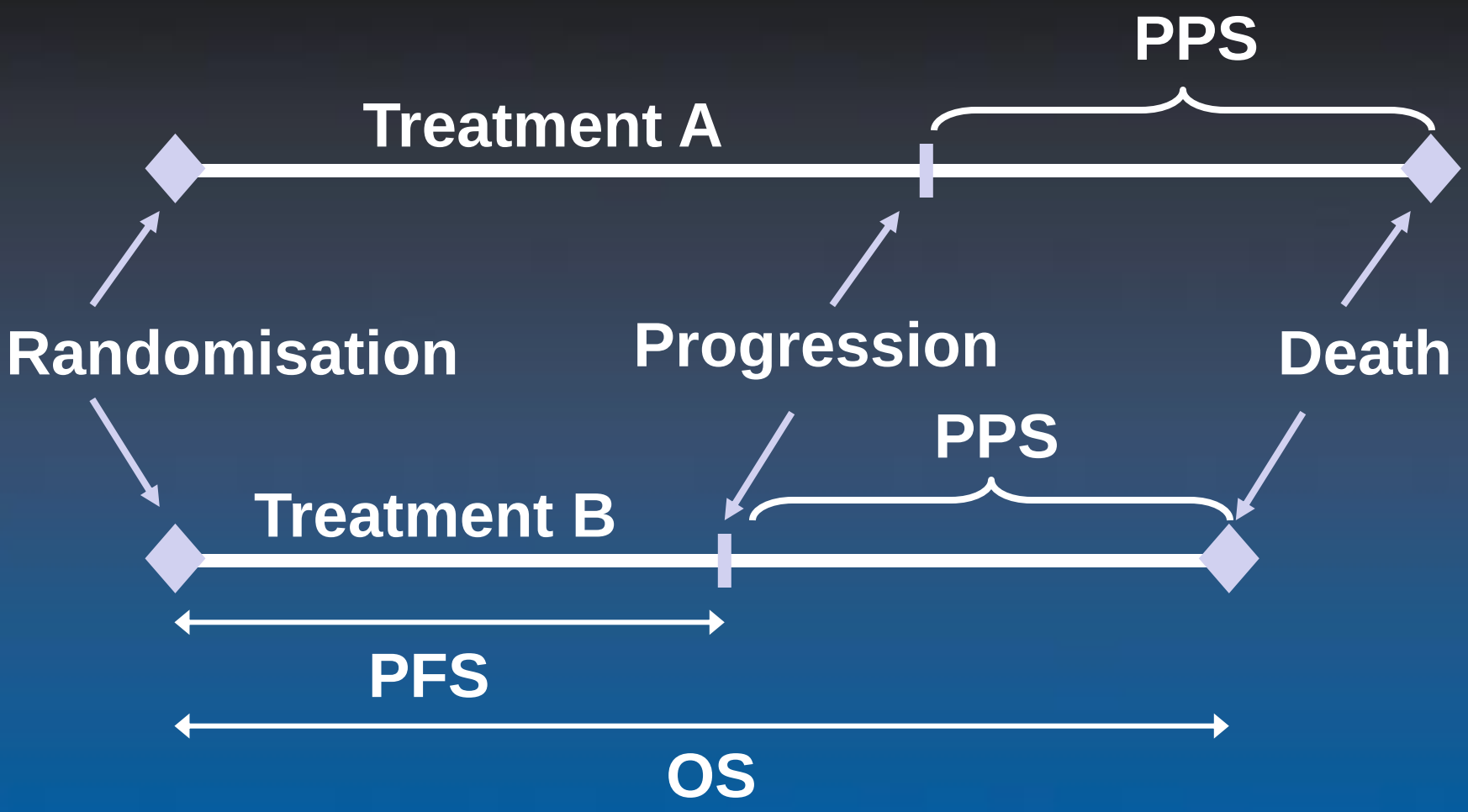
E2100—Overall Survival



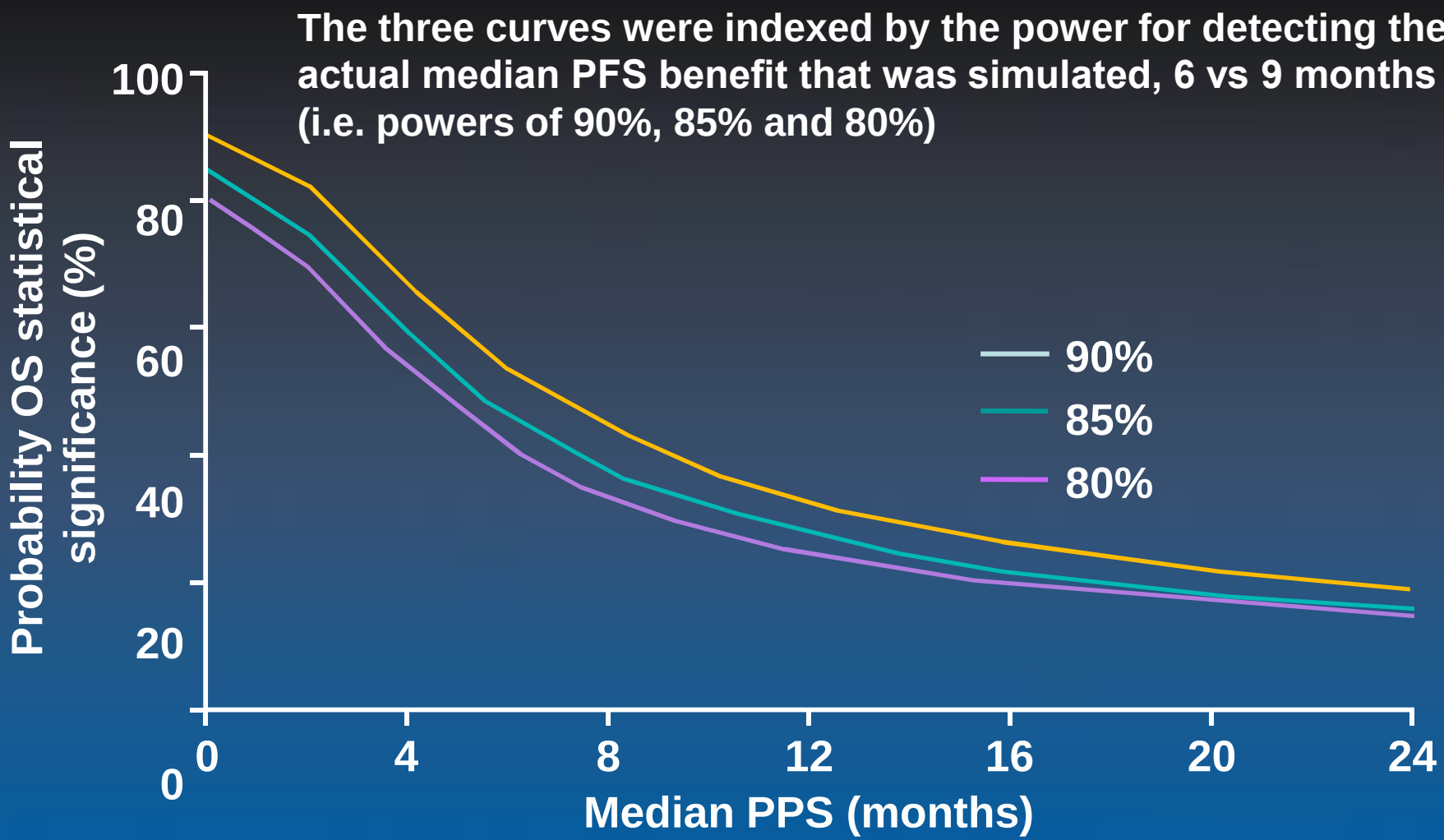
No. of patients at risk

PAC+AVA	368	344	297	249	193	104	48	23	5	0
PAC	354	307	258	215	165	103	48	19	8	0

Post-progression Survival

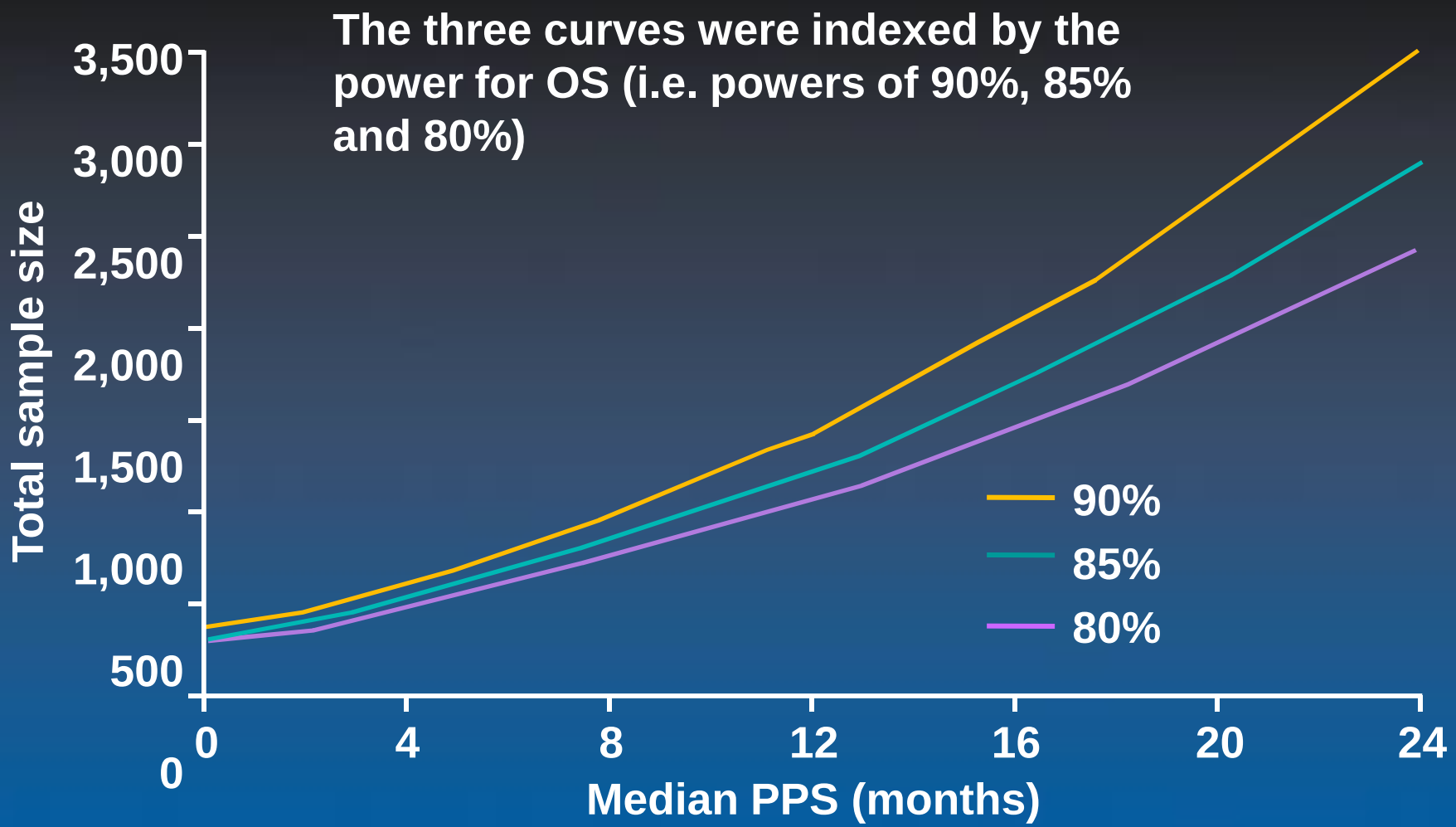


If PPS is >12 months, There is a <30% Chance a Trial Will Report a Significant OS



Broglio, Berry. Detecting an overall survival benefit that is derived from progression-free survival. JNCI 2009;101(23):1642–9, by permission of Oxford University Press

Long Median PPS May Influence Trial Designs



Broglio, Berry. Detecting an overall survival benefit that is derived from progression-free survival. JNCI 2009;101(23):1642–9, by permission of Oxford University Press

EMBRACE: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Vs. Eribulin

Global, open-label, randomised, phase III study

Patients (n=762)
- Locally recurrent or MBC
- 2–5 prior chemotherapies
  - ≥ 2 for advanced disease
  - Prior anthracycline and taxane
- Progression ≤ 6 months of last chemotherapy
- Neuropathy ≤ grade 2
- ECOG ≤ 2

Eribulin mesylate (n=508)
1.4 mg/m^2* IV over
2-5 minutes on Day 1,8 q21 days

RANDOMISATION 2:1

TPC (n=254):
- Any monotherapy (cytotoxic, hormonal, biological)**; or
- Palliative treatment; or
- Radiotherapy

Primary Endpoint:
- OS

Secondary Endpoints:
- PFS
- ORR
- Safety

Stratification:
- ✓ **Geographical region**
- ✓ **Prior capecitabine**
- ✓ **HER2 status**

*Equivalent to 1.23 mg/m^2 eribulin

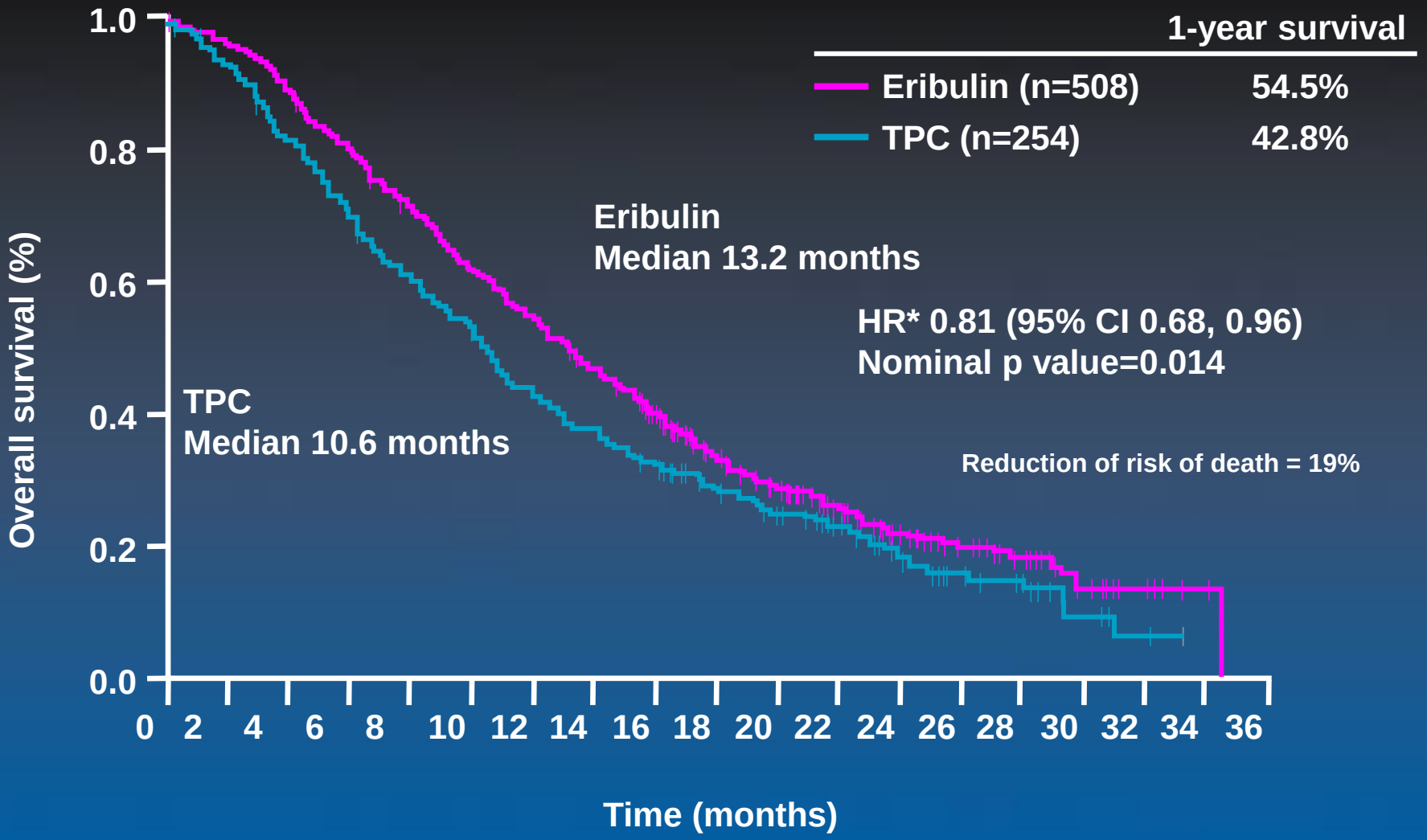
**Approved for treatment of cancer and administered according to local practice

Exploratory subgroups: Hormone receptor expression status (ER, PgR, HER2, triple-negative); number of organs involved; sites of disease

ECOG, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor type 2; ER, estrogen receptor; HER2/neu, human epidermal growth factor receptor 2; PgR, progesterone receptor

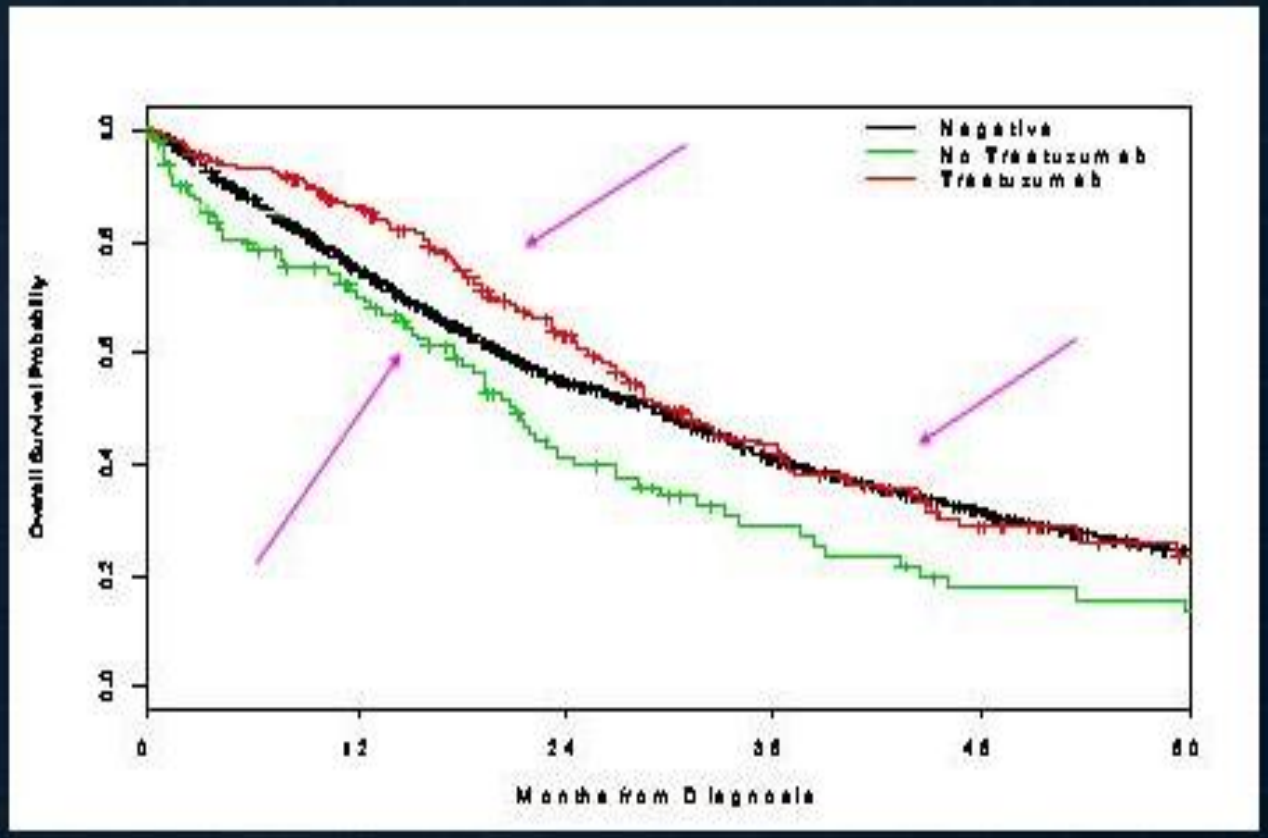
Cortes J, et al. Lancet. 2011

Overall Survival Primary Endpoint



Cortes J, et al. Lancet 2011

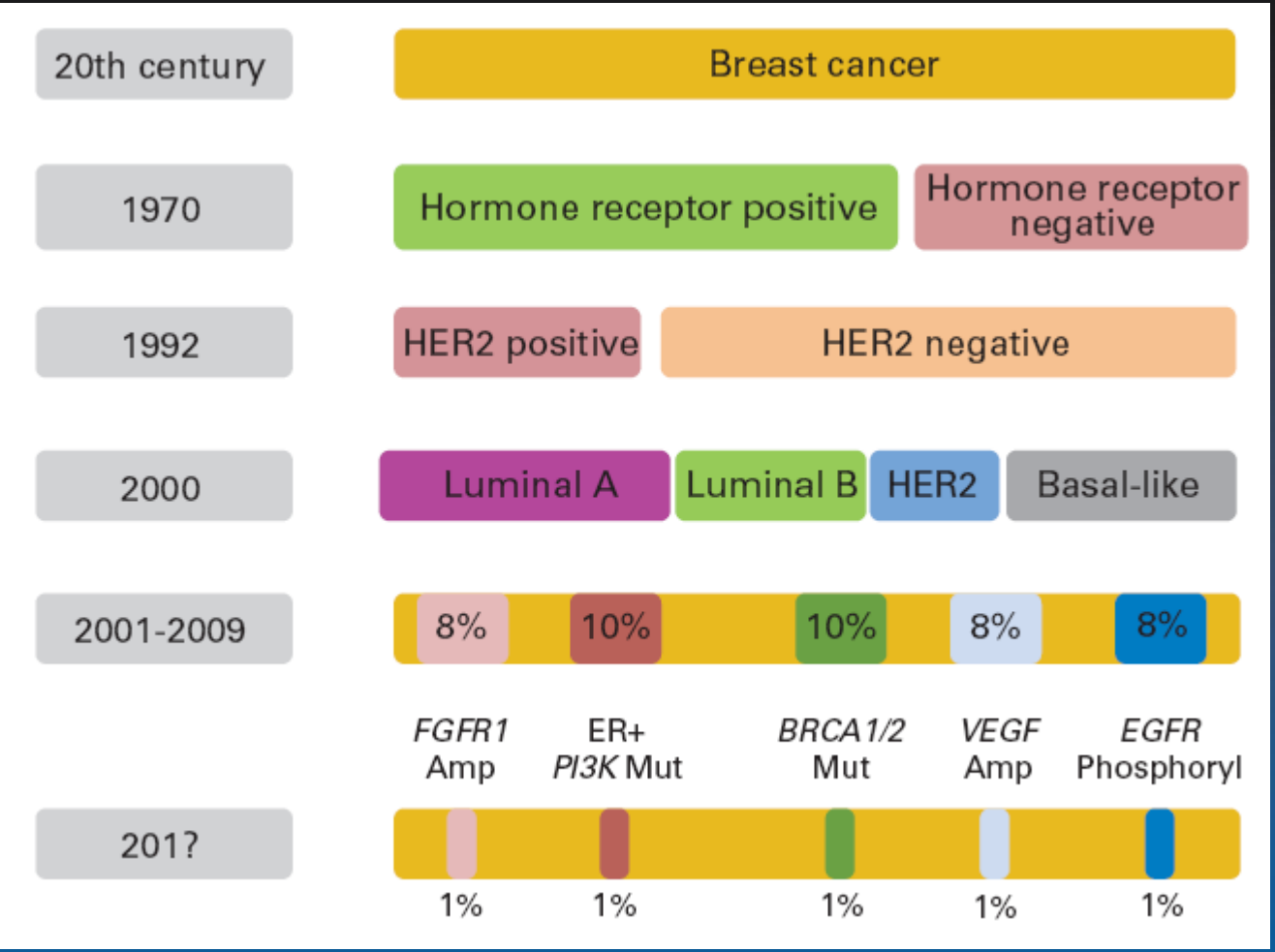
Overall Survival by Trastuzumab Treatment Groups



ASCO Annual '08 Meeting

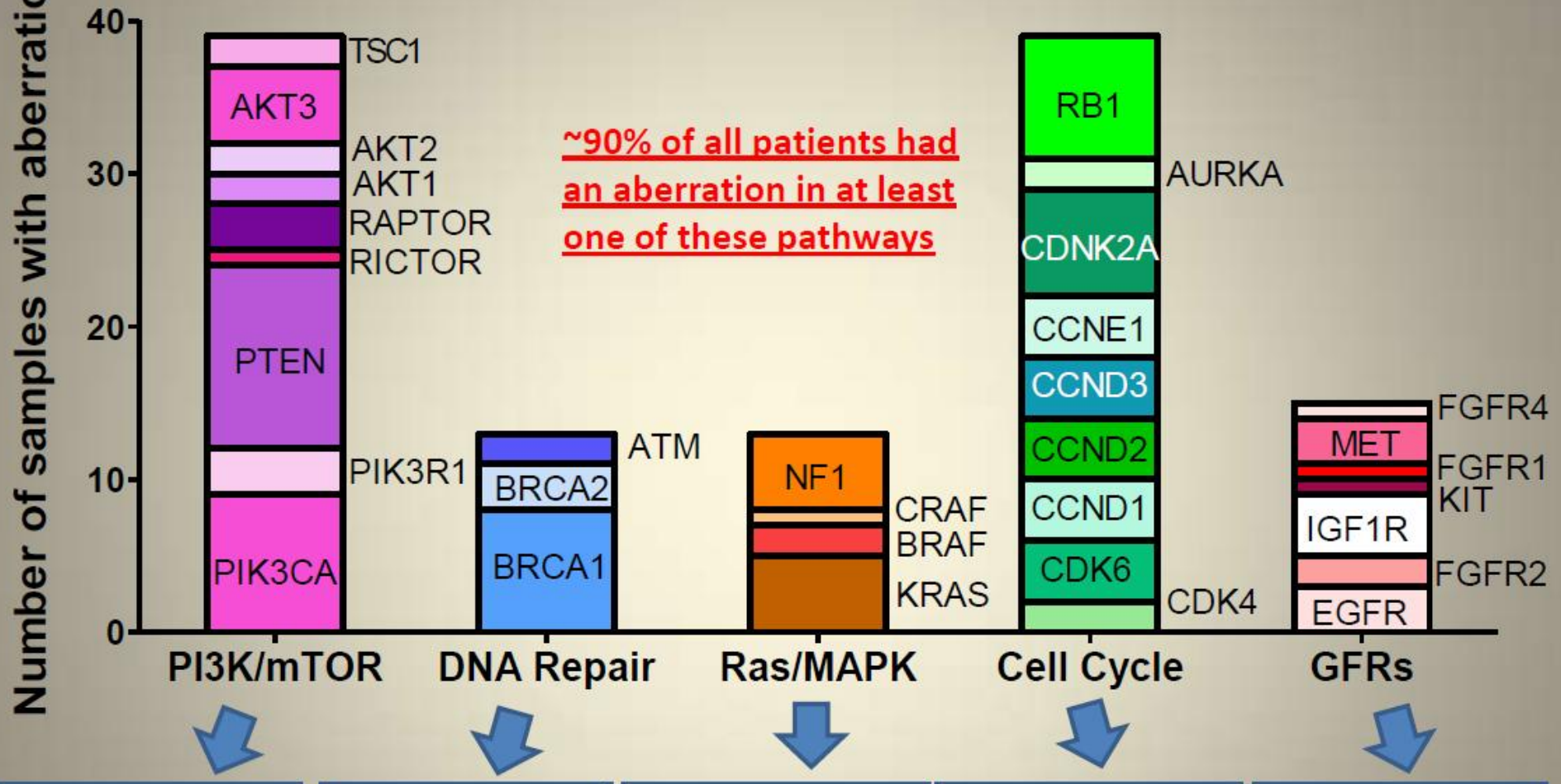
2008 ASCO Merit Award Recipient

Timelines of Biologic Breast Cancer Subclassification



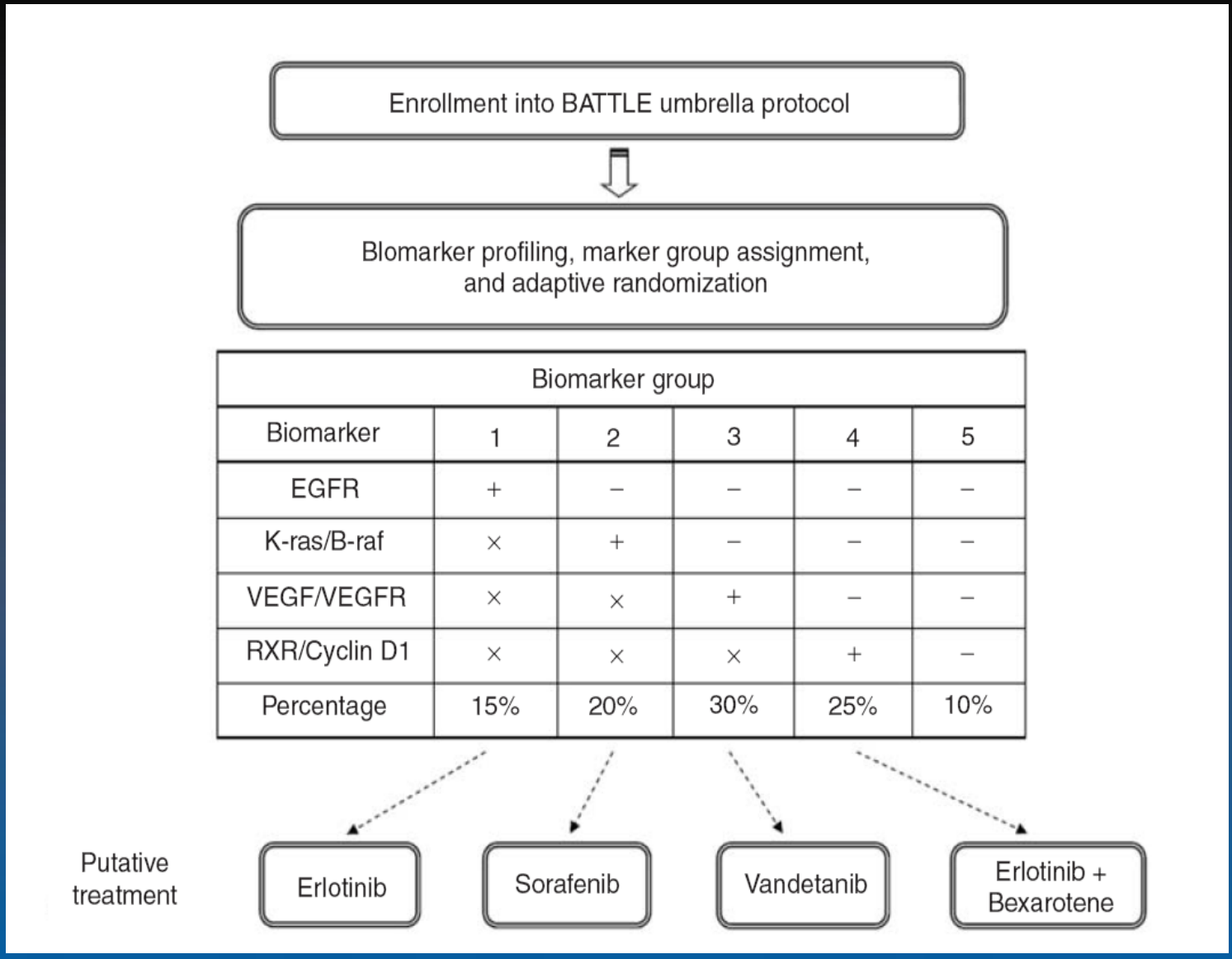
Harbeck N, et al. J Clin Oncol 2012

Clinically Targetable Pathways in Breast Cancer



PI3K/mTOR inhibitors	DNA-repair targeting agents	RAF/MEK inhibitors	Cell cycle/mitotic spindle inhibitors	Targeted RTK inhibitors

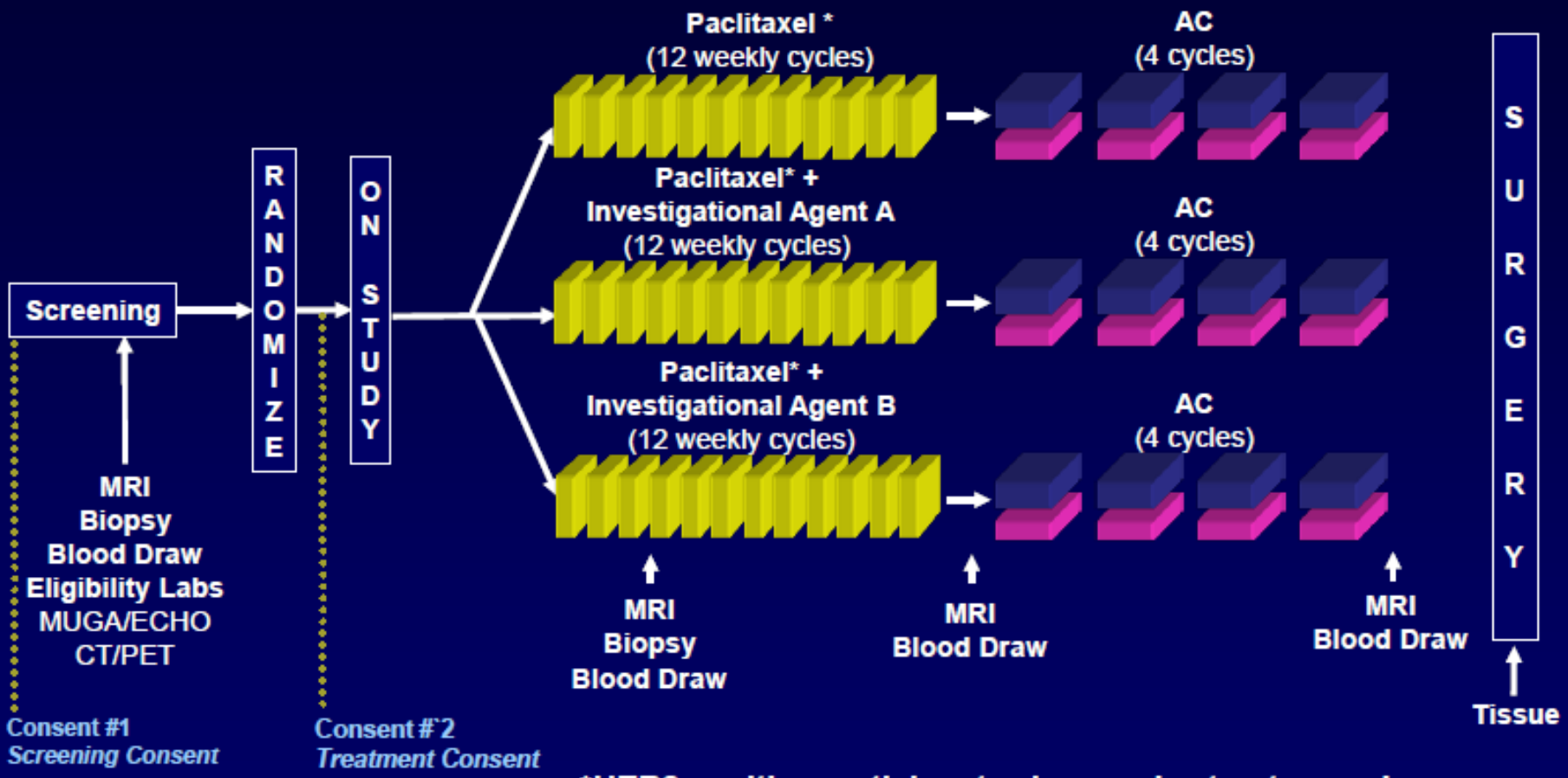
Adaptive Studies



Kim ES. et al. Cancer Discovery 2011

ISPY-2 Trial

Summary of Study Plan



*HER2 positive participants also receive trastuzumab.
An investigational agent may be used instead of trastuzumab.

Rugo HS, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract S5-02.

Cancer Therapy: Clinical

Clinical Cancer Research

The Cross-Validated Adaptive Signature Design

Boris Freidlin[1], Wenyu Jiang[2], and Richard Simon[1]

Abstract

Purpose: Many anticancer therapies benefit only a subset of treated patients and may be overlooked by the traditional broad eligibility approach to design phase III clinical trials. New biotechnologies such as microarrays can be used to identify the patients that are most likely to benefit from anticancer therapies. However, due to the high-dimensional nature of the genomic data, developing a reliable classifier by the time the definitive phase III trail is designed may not be feasible.

Experimental Design: Previously, Freidlin and Simon (*Clinical Cancer Research*, 2005) introduced the adaptive signature design that combines a prospective development of a sensitive patient classifier and a properly powered test for overall effect in a single pivotal trial. In this article, we propose a cross-validation extension of the adaptive signature design that optimizes the efficiency of both the classifier development and the validation components of the design.

Results: The new design is evaluated through simulations and is applied to data from a randomized breast cancer trial.

Conclusion: The cross-validation approach is shown to considerably improve the performance of the adaptive signature design. We also describe approaches to the estimation of the treatment effect for the identified sensitive subpopulation. *Clin Cancer Res; 16(2); 691–8. ©2010 AACR.*

Due to the molecular heterogeneity of most human cancers, only a subset of treated patients benefit from a given therapy. This is particularly relevant for the new generation of anticancer agents that target specific molecular pathways (1–3). Genomic (or proteinomic) technologies such as microarrays provide powerful tools for identifying a genetic signature (diagnostic test) for patients who are most likely to benefit from a targeted agent. Ideally, such diagnostic test should be developed and validated before commencing the definitive phase III trial (4). However, due to the complexity of signaling pathways and the large number of genes available for analysis, the development of a reliable diagnostic classifier using early nonrandomized phase II data is often not feasible. Conducting a phase III randomized clinical trial (RCT) requires considerable time and resources. Therefore, clinical trial designs that allow combining the definitive evaluation of a new agent with the development of the companion diagnostic test can considerably speed up the introduction of new cancer therapies.

Previously, the adaptive signature design (ASD) has been proposed for settings where a signature to identify sensitive patients is not available (5). The design combines the prospective development of a pharmacogenomic diagnostic test (signature) to select sensitive patients with a properly powered test for overall effect. It was shown that when the proportion of patients sensitive to the new drug is low, the ASD substantially reduces the chance of false rejection of effective new treatments. When the new treatment is broadly effective, the power of the adaptive design to detect the overall effect is similar to that of the traditional design.

The signature component of the ASD carries out signature development and validation on the mutually exclusive subgroups of patients (e.g., half of the study population is used to develop a signature and another half to validate it). Although the conceptual simplicity of this approach is appealing, it also limits its power as only half of the patients are used for signature development and half for validation. This is especially relevant in the present setting because (*a*) signature development in high dimensional data requires large sample sizes, and (*b*) when the fraction of sensitive patients is low, a large number of patients needs to be screened to identify the sufficient number of sensitive patients to achieve acceptable power.

In this article, we describe an extension of the ASD in which signature development and validation are embedded in a complete cross-validation procedure. This allows the use of virtually the entire study population in both signature development and validation steps. We develop a procedure that preserves the study-wise type I error while substantially increasing the statistical power for establishing a statistically significant treatment effect for an identified subset of patients who benefit from the experimental treatment. We also examine approaches to estimation of treatment effect for the identified sensitive subset.

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Adaptive Signature Design: An Adaptive Clinical Trial Design for Generating and Prospectively Testing A Gene Expression Signature for Sensitive Patients

Boris Freidlin and Richard Simon

Abstract

Purpose: A new generation of molecularly targeted agents is entering the definitive stage of clinical evaluation. Many of these drugs benefit only a subset of treated patients and may be overlooked by the traditional, broad-eligibility approach to randomized clinical trials. Thus, there is a need for development of novel statistical methodology for rapid evaluation of these agents.

Experimental Design: We propose a new adaptive design for randomized clinical trials of targeted agents in settings where an assay or signature that identifies sensitive patients is not available at the outset of the study. The design combines prospective development of a gene expression – based classifier to select sensitive patients with a properly powered test for overall effect.

Results: Performance of the adaptive design, relative to the more traditional design, is evaluated in a simulation study. It is shown that when the proportion of patients sensitive to the new drug is low, the adaptive design substantially reduces the chance of false rejection of effective new treatments. When the new treatment is broadly effective, the adaptive design has power to detect the overall effect similar to the traditional design. Formulas are provided to determine the situations in which the new design is advantageous.

Conclusion: Development of a gene expression – based classifier to identify the subset of sensitive patients can be prospectively incorporated into a randomized phase III design without compromising the ability to detect an overall effect.

Developments in tumor biology have resulted in shift toward molecularly targeted drugs (1 – 3). Most human tumor types are heterogeneous with regard to molecular pathogenesis, genomic signatures, and phenotypic properties. As a result, only a subset of the patients with a given cancer is likely to benefit from a targeted agent (4). This complicates all stages of clinical development, especially randomized phase III trials (5, 6). In some cases, predictive assays that can accurately identify patients who are likely to benefit from the new therapy have been developed. Then, targeted randomized designs that restrict eligibility to patients with sensitive tumors should be used (7). However, reliable assays to select sensitive patients are often not available (8, 9). Consequently, traditional randomized clinical trails with broad eligibility criteria are routinely used to evaluate such agents. This is generally inefficient and may lead to missing effective agents.

Genomic technologies, such as microarrays and single nucleotide polymorphism genotyping, are powerful tools that hold a great potential for identifying patients who are likely to benefit from a targeted agent (10, 11). However, due to the large number of genes available for analysis, interpretation of these data is complicated. Separation of reliable evidence from the random patterns inherent in high-dimensional data requires specialized statistical methodology that is prospectively incorporated in the trial design. Practical implementation of such designs has been lagging. In particular, analysis of microarray data from phase III randomized studies is usually considered secondary to the primary overall comparison of all eligible patients. Many analyses are not explicitly written into protocols and done retrospectively, mainly as "hypothesis-generating" tools.

We propose a new adaptive design for randomized clinical trials of molecularly targeted agents in settings where an assay or signature that identifies sensitive patients is not available. Our approach includes three components: (*a*) a statistically valid identification, based on the first stage of the trial, of the subset of patients who are most likely to benefit from the new agent; (*b*) a properly powered test of overall treatment effect at the end of the trial using all randomized patients; and (*c*) a test of treatment effect for the subset identified in the first stage, but using only patients randomized in the remainder of the trial. The components are prospectively incorporated into a single phase III randomized clinical trial with the overall false-positive error rate controlled at a prespecified level.

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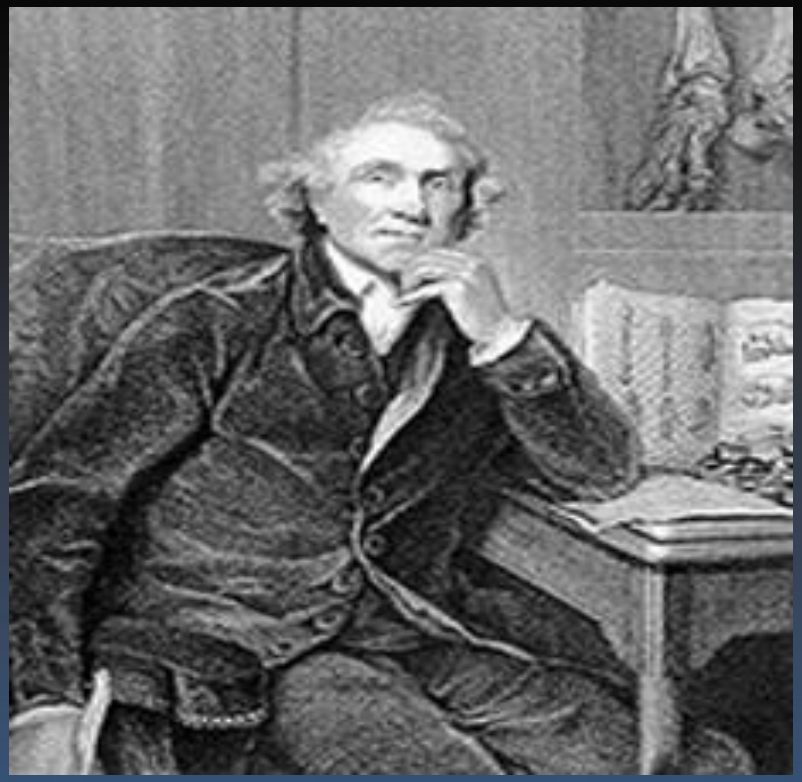

But why think, why not try the experiment?

John Hunter, 1775


Grazie

Back-up

Getting Started

- Learn your subject
- Read, Read, Read
- Start general and then focus
- Begin with the problem