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25th World Congress of the Society of Arts and Sciences
Tabor, Czech Republic
June 28th 2010

Indirect and Direct Evidence in Oncology

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Tábor,
thank you for having us

Indirect and Direct Evidence in Oncology - Goals

- Contrast indirect evidence with direct evidence
- "Evidence Based Medicine " (EBM) elevated indirect evidence but is less useful in oncology in particular in the era of biologicals
- Show that the heterogeneity of cancer makes direct evidence very valuable for oncology
- Sources of cancer heterogeneity and its relevance for targeted therapy
- Modern "Biomarker" driven studies
- Future

The Court Room Vignette

- A convenience store owner in the Bronx was shot
- An 85 years old white lady was caught on security cameras and confessed when shown the images
- Her public defendant produced statistics showing that
  - 98 percent of crimes in the Bronx are committed by black males
  - 90 percent of the perpetrators are below the age of 35 and
  - 99.9 percent below the age of 75
- He argues that the old lady is innocent and should be exonerated

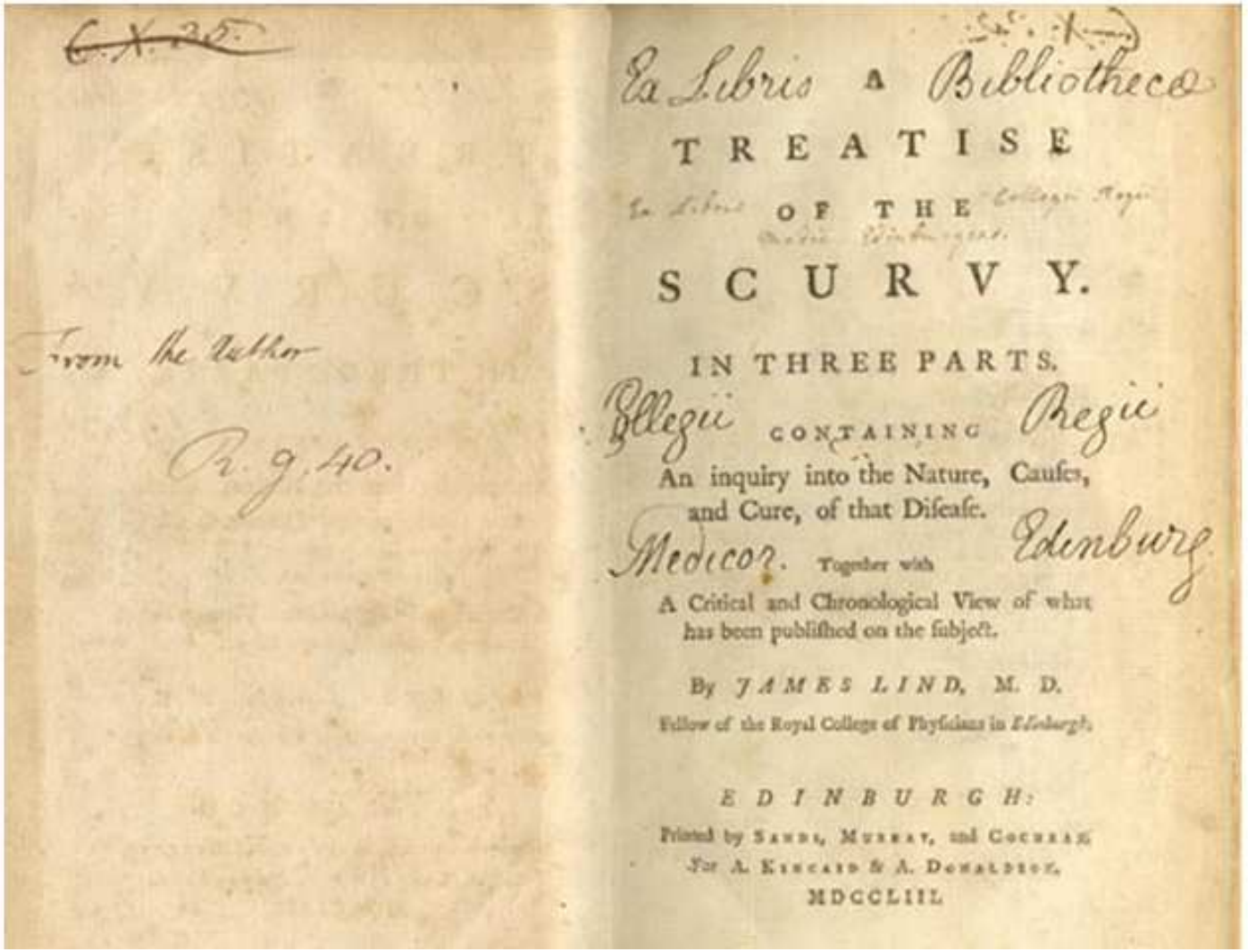
I vote for direct evidence and conviction

- You are the judge, do you trust the indirect evidence of perfect statistics or the direct evidence captured by a videocamera?

Medicine Before The Era of Evidence-Based-Medicine

- Keen observation
- Reliance on ancient authorities and often centuries old textbooks
- Practice driven by
  - Tradition
  - Scientific hypotheses – which were mostly wrong as a consequence of the complexicity of biological systems
- Therefore, most of the interventions unhelpful

The First Clinical Trial



C. X. 25.

From the Author

R. 9. 40.

Ex Libris A Bibliotheca

TREATISE

OF THE

SCURVY.

IN THREE PARTS.

Collegii CONTAINING Regii

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

Medicor. Together with Edinburg.

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.

The First Clinical Trial - Scurvy

- Captain James Lind studied citrus fruits in the diet to prevent scurvy on board of HMS Salisbury in 1747
- All scurvy patients were given the same general diet supplemented with various additional items and divided into 6 groups, 2 patients each
  - Cider
  - Elixir of vitriol
  - Vinegar
  - Seawater
  - Nutmeg
  - Oranges and lemons

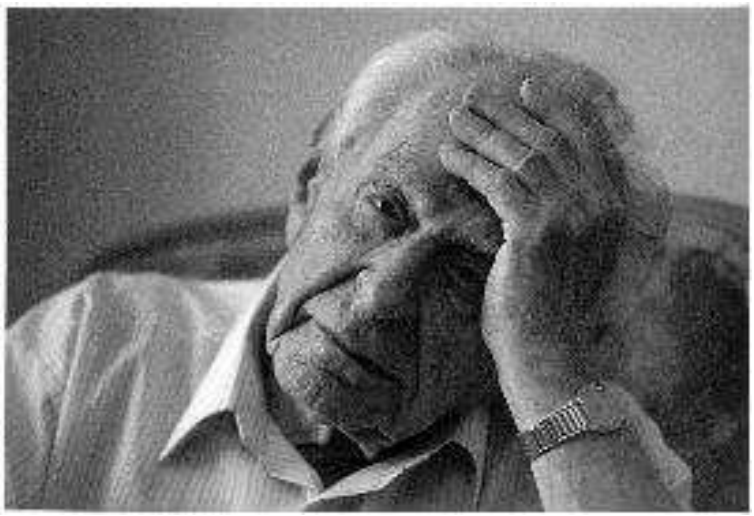
- In just six days, those patients taking citrus fruits were fit for duty
- Although the results were clear, Lind hesitated to recommend the use of oranges and lemons because they were too expensive. It was nearly 50 years before the Navy eventually made lemon juice a compulsory part of the seafarer's diet, and this was soon replaced by lime juice because it was cheaper

Sir Karl Popper (1902-1994)

Proposed that scientific theories are hypotheses from which statements testable by observation can be deduced.

If observations falsify these statements, the hypothesis is refuted.

If the hypothesis survives efforts to falsify it, it may be tentatively accepted, although no scientific theory can be conclusively established.



Picture of Karl Popper taken by MUDr. Milan Jíra in Prague in 1994

Statistical Inference -> Sir Ronnie Fisher

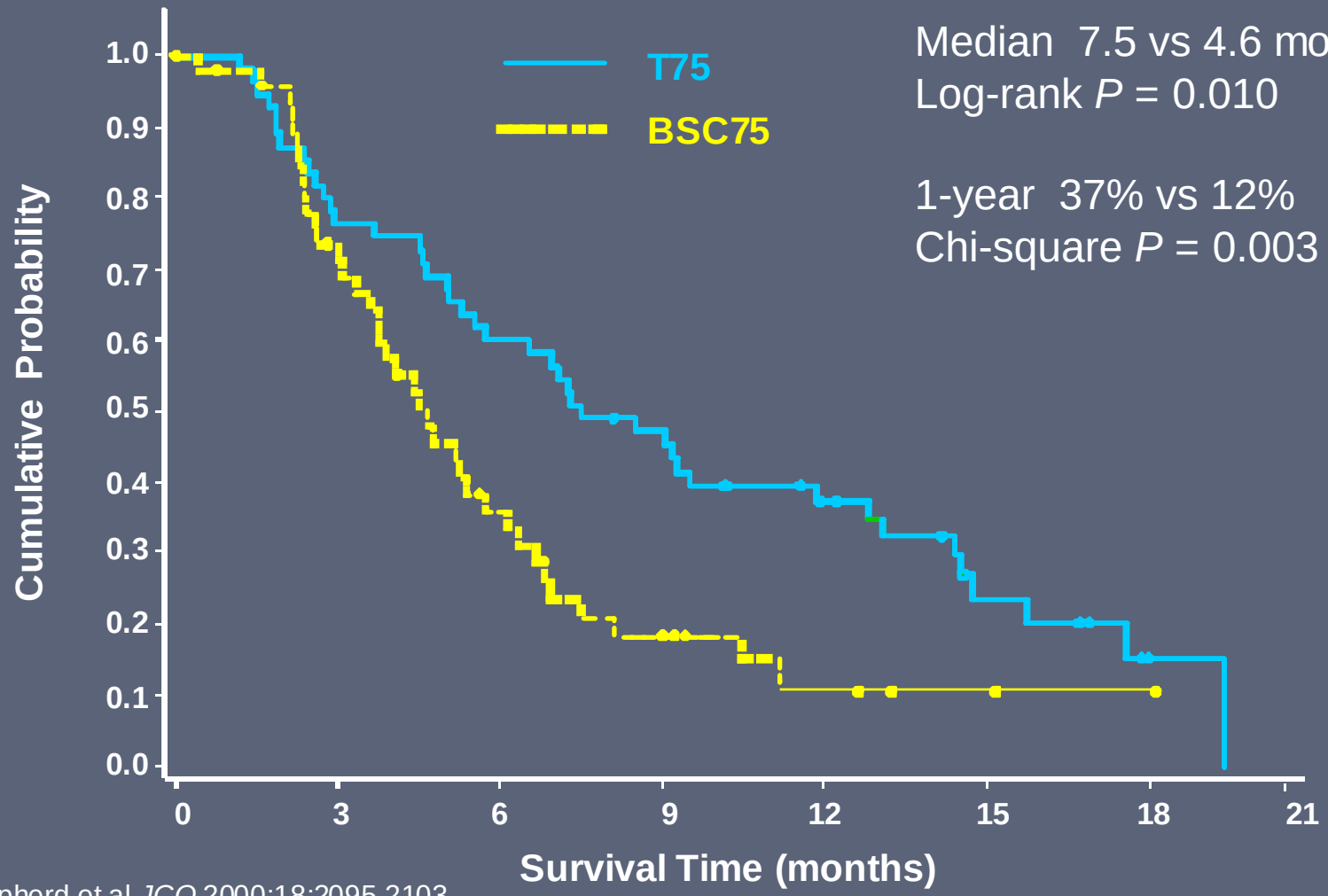
Evidence

- Indirect evidence
  - Collected from patients who carry the same diagnosis as the patient who is to be treated – traditional clinical trials

Evidence-Based-Medicine

- The practice of medicine has to be build on structured clinical observation and unbiased data collection – clinical trials
  - Meta-analysis of randomized clinical trials has the highest validity of evidence
  - Single randomized trial
  -
  -
  - Case history = direct observation
    - Has the lowest validity for generalization
    - The highest validity for individual patients

TAX 317B - Survival
Taxotere 75 mg/m2 vs BSC



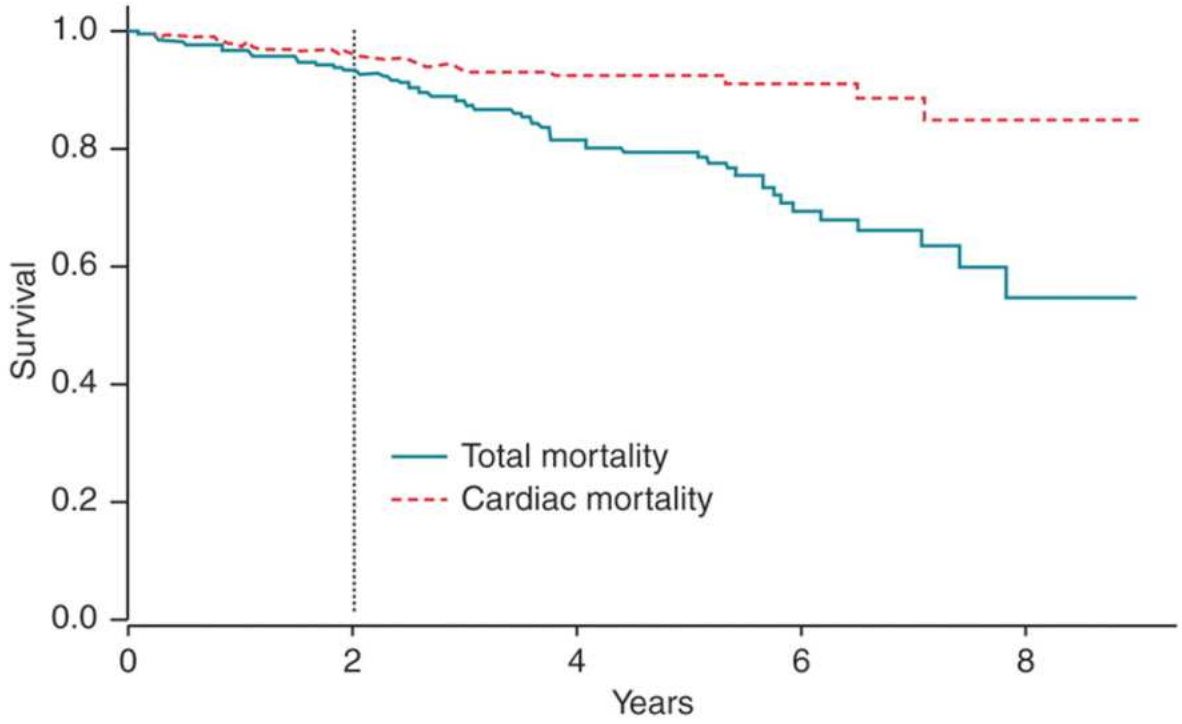
Median 7.5 vs 4.6 mos.
Log-rank *P* = 0.010

1-year 37% vs 12%
Chi-square *P* = 0.003

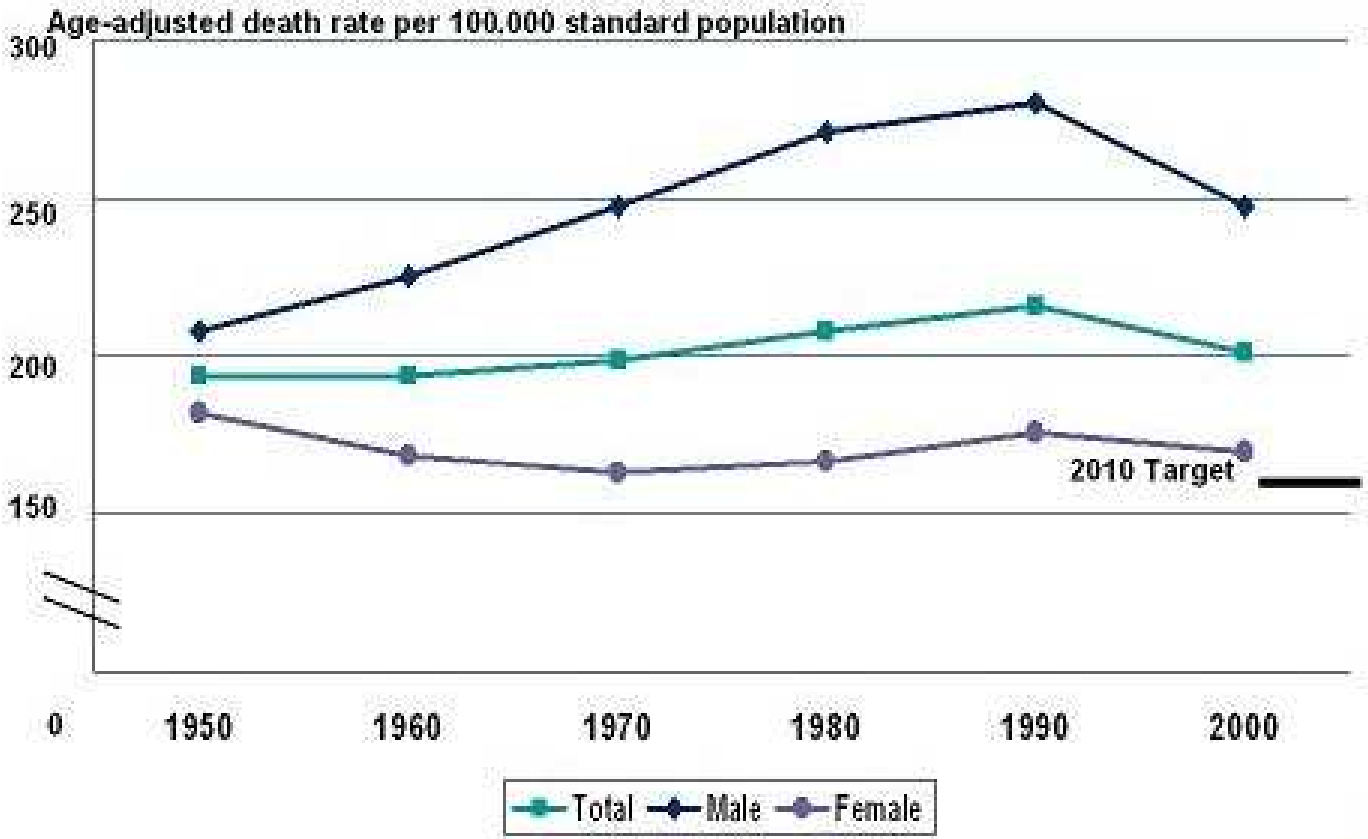
Shepherd et al *JCO* 2000;18:2095-2103

EBM Contributed Substantially To Recent Successes Of Medicine

- Advances in internal medicine
  - Cardiac mortality substantially decreased



Total Cancer Mortality: by sex, 1950-2000

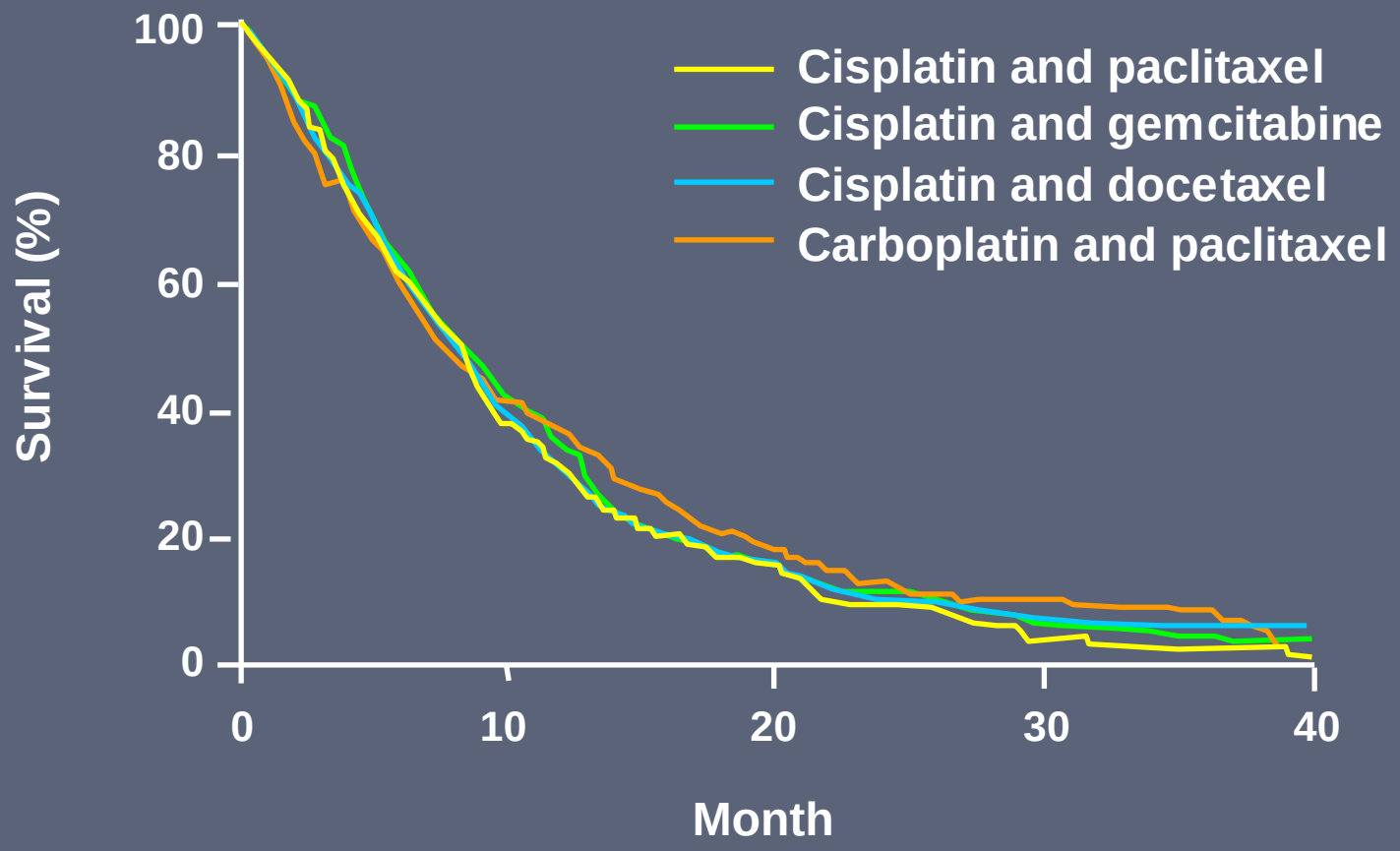


Note: Data are age adjusted to the 2000 standard population.
Source: National Vital Statistics System-Mortality (NVSS-M) , NCHS, CDC.

EBM Contributed Substantially To Recent Successes Of Medicine

- Advances in internal medicine
  - Cardiac mortality substantially decreased
- Some advances in surgery
- Advances in oncology recently hit a ceiling
  - E.g. Last 6 large trials in non-small cell lung cancer chemotherapy did not lead to improvement with exception of personal

ECOG 1594: Kaplan-Meier Estimates of Overall Survival



Schiller et al. *N Eng J Med*; 2002; 346:92-8

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- Crisis of evidence based medicine overreliance on indirect evidence and under-appreciation of direct evidence

Populations Studied

- The population of patients studied in clinical trials does not represent any patient population
- Highly selected, dedicated patients are enrolled
- Only a very small part of the patient population is being studied (2%), the rest of the information is wasted
- Even that small size might decrease in the future

Criticism Of Clinical Trials In Medicine

- This system based on clinical trials is largely accidental, carrying on the "frozen accidents" of former trials, which were often irrelevant
- The whole system of trials in a given disease might explore an accidental branch of possibilities that is far removed from relevant and optimal therapy.
- The questions asked through clinical trials form a self-serving historically developed system

Application of results

- Given the selection of the population the application of results gained is not straight forward
- Given the absence of other associated information in clinical trials, the "refinement" or individualization in specific patient situations encountered every day is difficult or impossible

Timing

- Due to slow accrual trials take to long
- Questions answered by a trial are at the time of publication often irrelevant
- There is no mechanism for coordination of trials which would provide answers in a logical manner

Simplicity

- The simplicity of the questions asked makes the results irrelevant in most patient situations, particularly if an individualized approach is tried
- Correlated information is not available
- Very small trials often impact on big patient populations so that patients are treated according to results obtained in a group that did not contain a single patient similar to the treated one

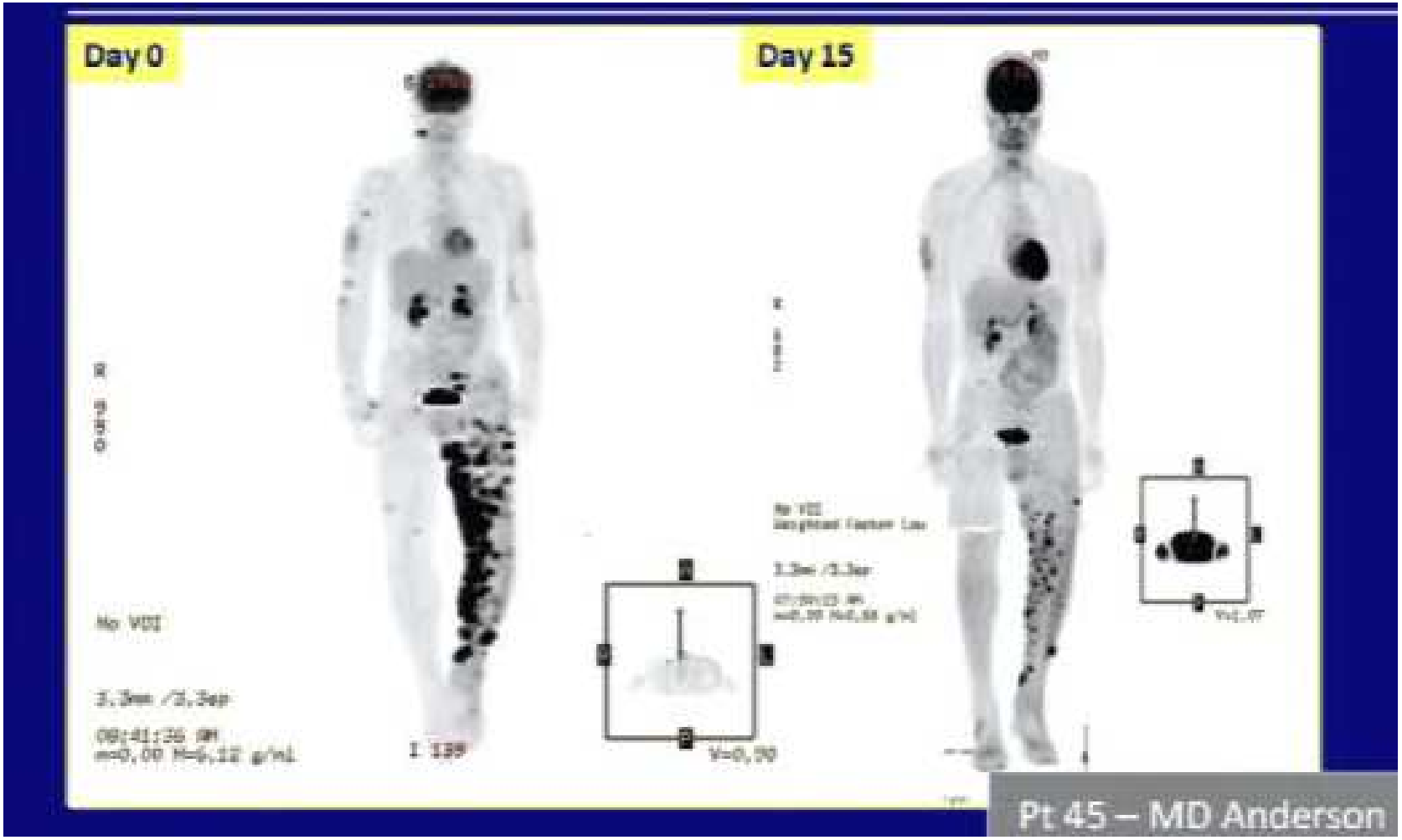
Indirect Information Inappropriately Favored

- Relative to any patient that has to be treated, information gained from trials is always indirect
- Using this indirect information to override direct information, if available, is a common mistake
- E.g. response to earlier chemotherapy might guide future chemotherapy better than information gained from a trial

Direct Evidence

- Indirect evidence
  - Collected from patients who carry the same diagnosis as the patient who is to be treated – traditional clinical trials
- Direct evidence
  - Collected from the patient
    - Detailed clinical history usually available including epidemiologic information (e.g. smoking history), pharmacogenomics
  - Collected from the patient's cancer
    - Pathology and molecular pathology unique to the patient
  - Response to previous and current therapy (feed-back information)

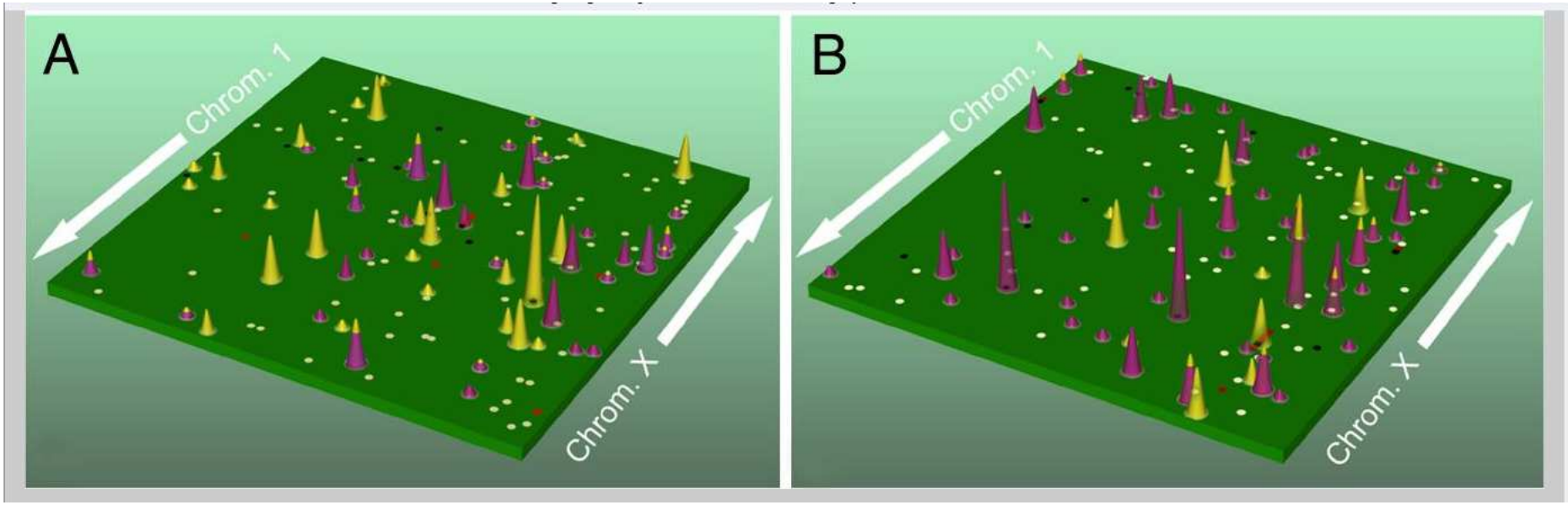
Feedback:
PET at Baseline and D15 After PLX4032



Why This Agent or Combination of Agents Active In This Disease?

- Specificities of biology of the disease
- Stage – spread
- Tumor volume doubling time
- Chemodistribution
- % hypoxic, necrotic
- % growth phase
- Metastatic potential and preferential sites
- Apoptotic "readiness" of the cancer population
- Immunogenic and Antigenic potential

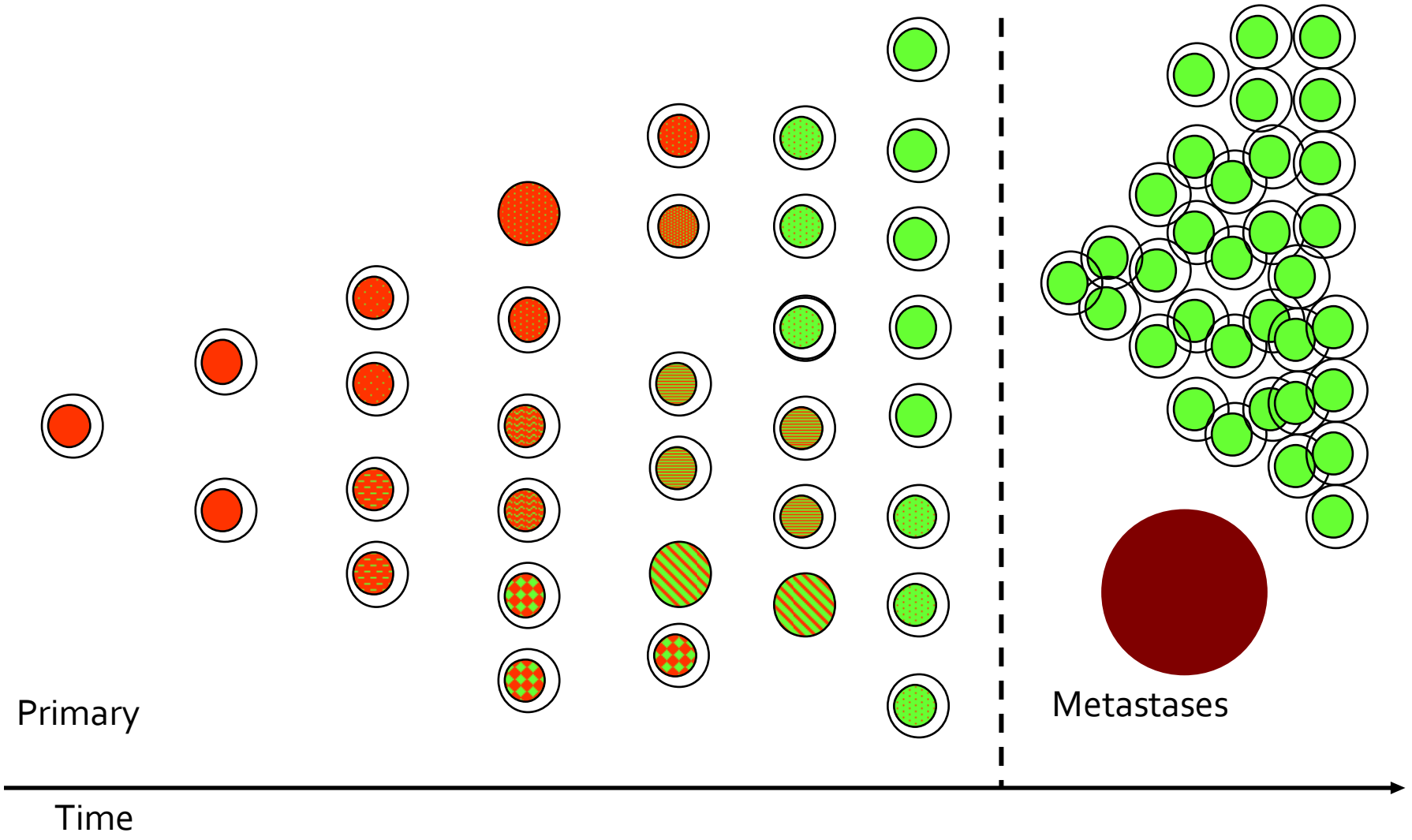
Significant Heterogeneity Of Cancers



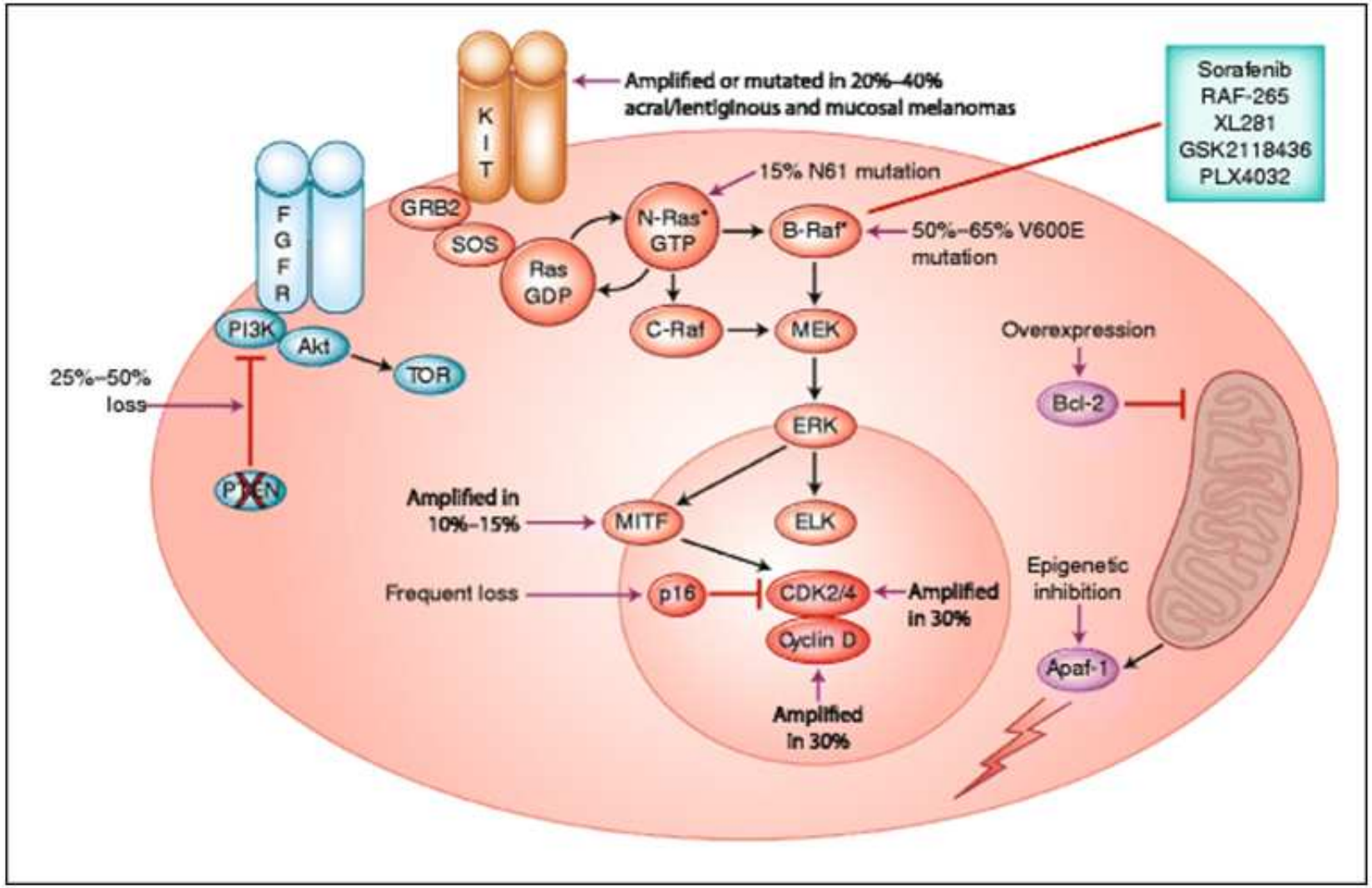
Genomic landscape of copy number and nucleotide alterations in two typical cancer samples. *A* indicates breast cancer alterations, whereas *B* indicates colorectal cancer alterations.

Leary, RJ.: Proc Natl Acad Sci U S A. 2008 Oct 21;105(42):16224-9

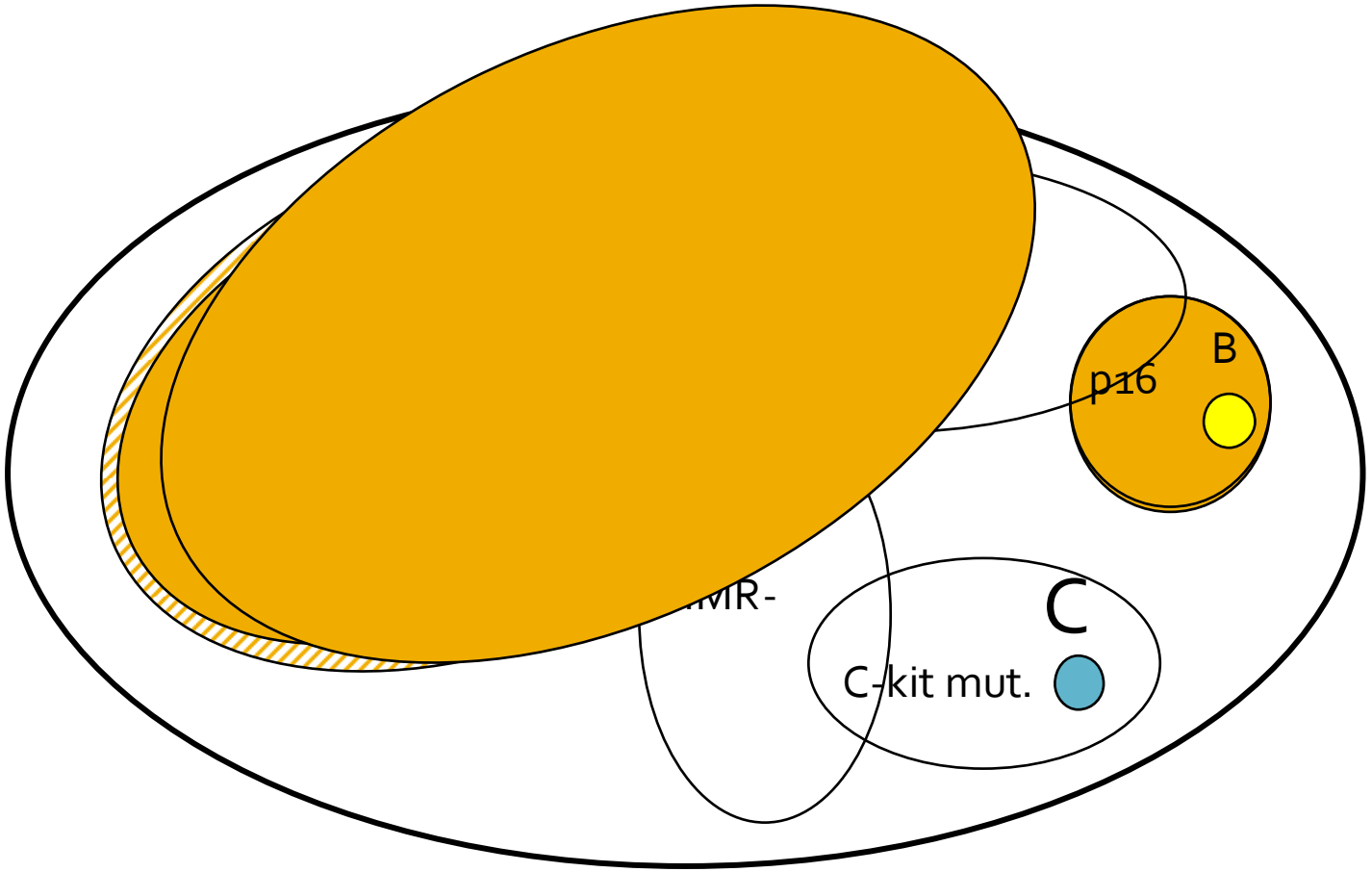
Chemosensitivity of Primary Contrasted with Metastases



Melanoma: MAPK Pathway Defects and Fixes



Clinical Trials Optimize Therapy For The Largest Subgroup



The First Clinical Trial Was in Fact Very Modern

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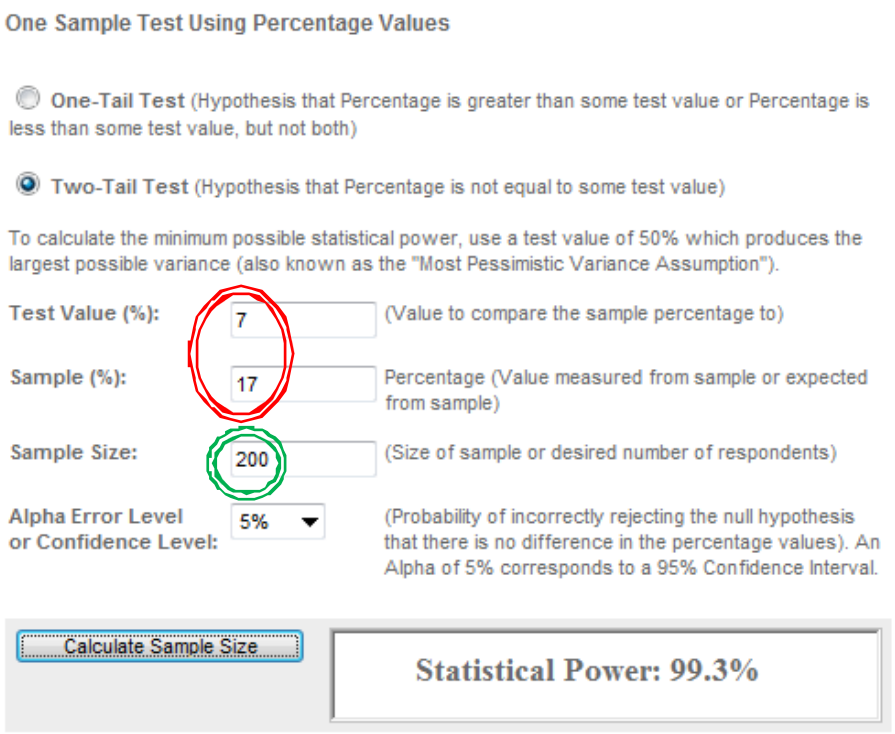
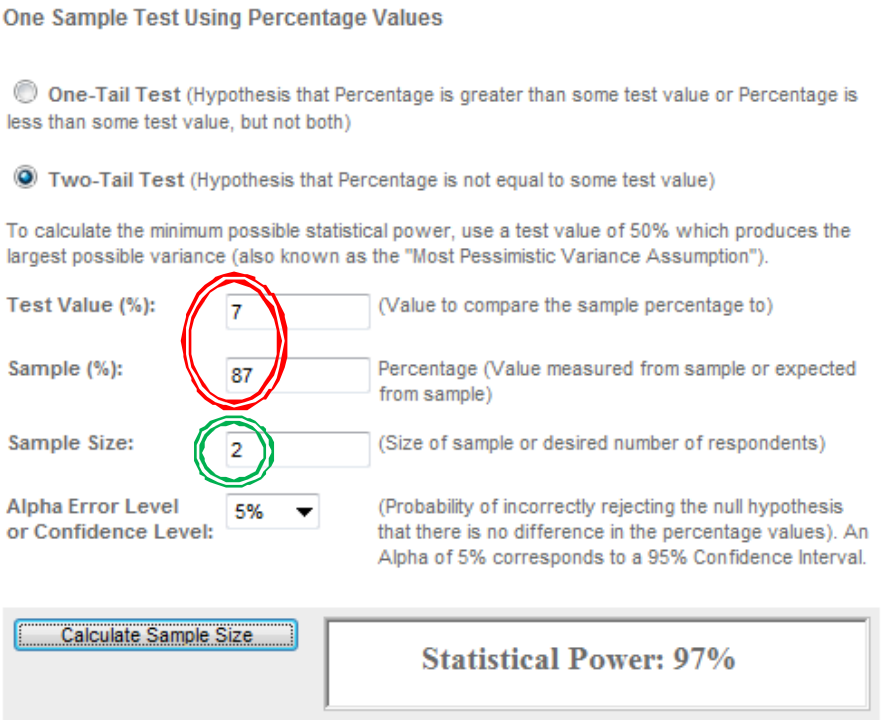
Power Calculations

Unselected population



Selected population



Cancer Therapy In a Historic Perspective

All diseases treated alike

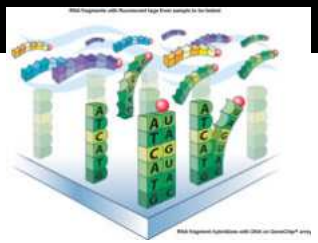
Neolitic

Breast cancer identified and treated with hot iron, but known to be incurable

Egypt
1600 BC

Hundreds of cancers recognized- surgery - radiation - chemo since WW2 - immuno

19th and 20th Century



Some tumors further **subcategorized**

Molecular **staging**

21st Century

metastasis recognized

Uniqueness of each patient's **cancer** recognized

Uniqueness of each **patient** recognized

Personalized Medicine

BR.21 Study By Shephard

Table 2.

Survival Results From the BR.21 Trial of Erlotinib vs Placebo*

End Points	Erlotinib (n = 488)	Placebo (n = 243)	p Value
Progression-free survival, mo	2.2	1.8	< 0.001
Overall survival, mo	6.7	4.7	< 0.001
1-yr survival, %	31	22	NA

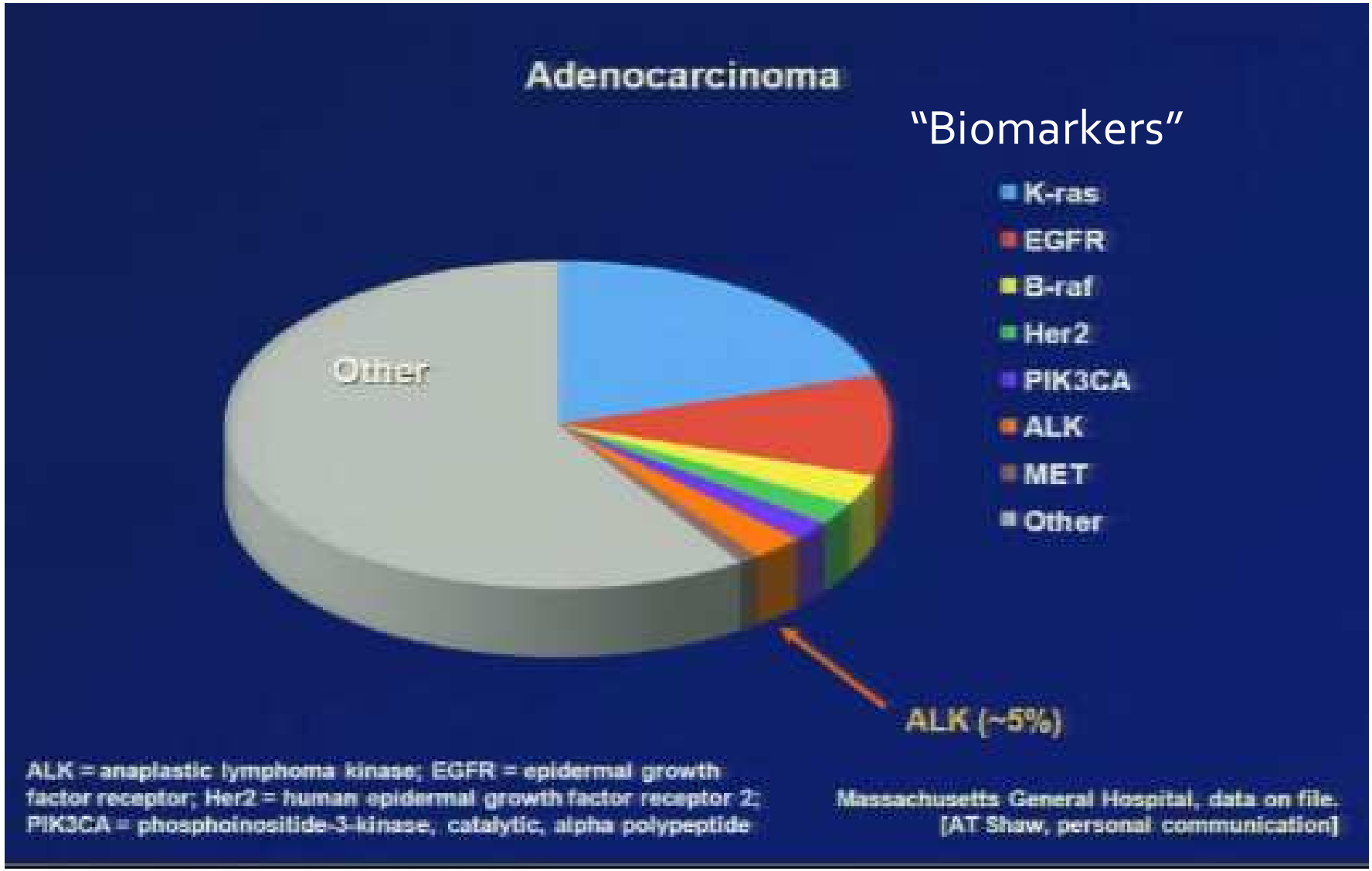
- * Data are from Shepherd et al.[28] NA = not applicable.

BR.21 Study By Shephard – Subset Analysis

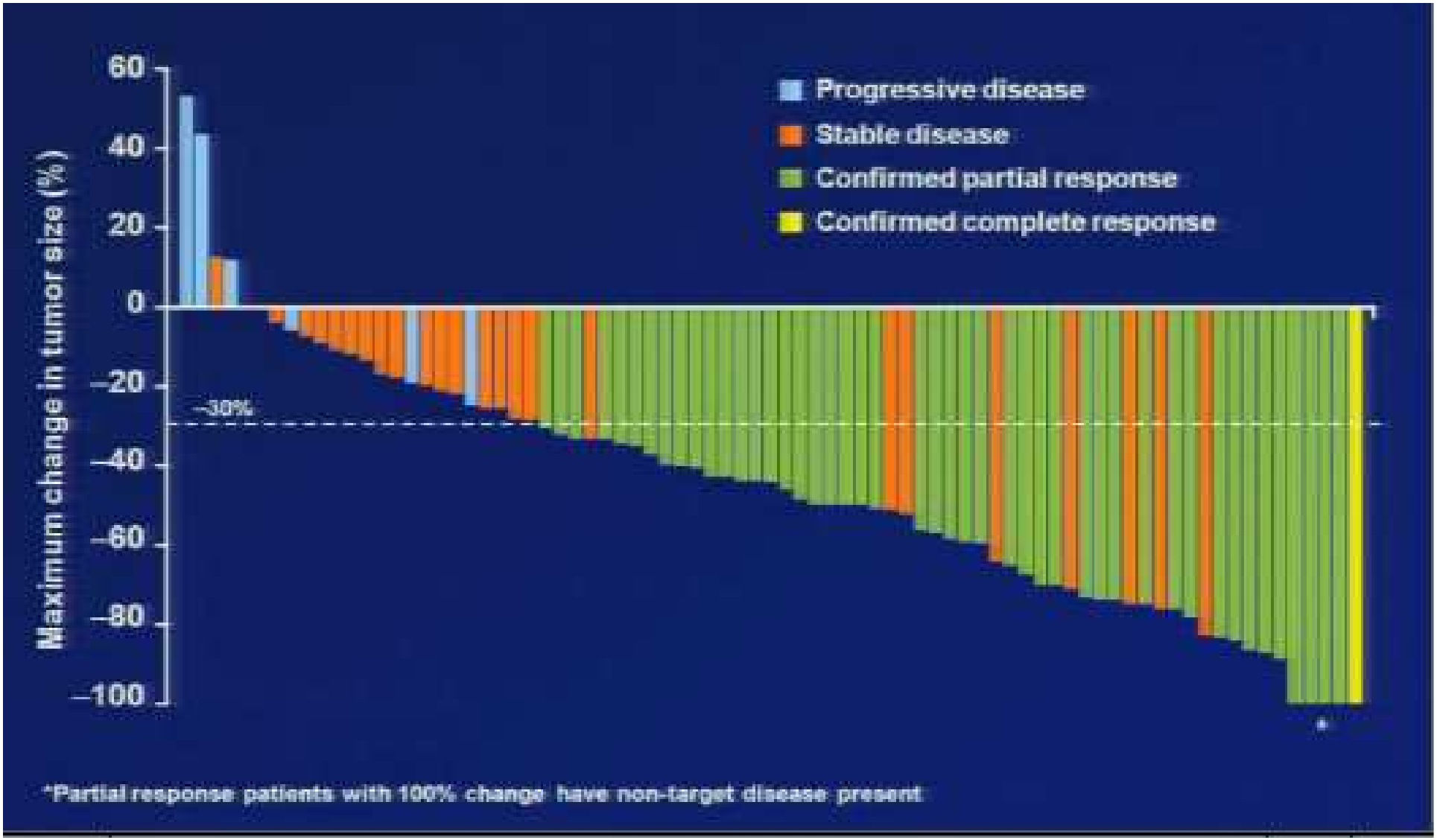
Test	Response Rate
EGFR expression [15,16]	
IHC-positive	11% to 21%
IHC-negative	4% to 5%
EGFR copy number [15-17]	
FISH-positive	20% to 36%
FISH-negative	2.5% to 11%
EGFR mutation [15,18-22]	
Mutation present	30% to 94%
Mutation absent	9% to 14%

Exon 19 deletion mutations

Potential Oncogenic "Driver Mutations" in Non-small Cell Lung Cancer



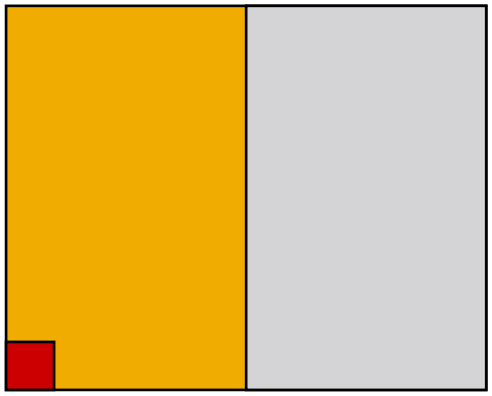
Tumor Response to Crizotinib for Patients with ALK-positive NSCLC



Clinical Trials in the Era of Personalization

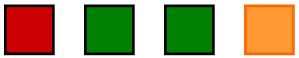
Subdivide, Analyze

Start with a group and divide



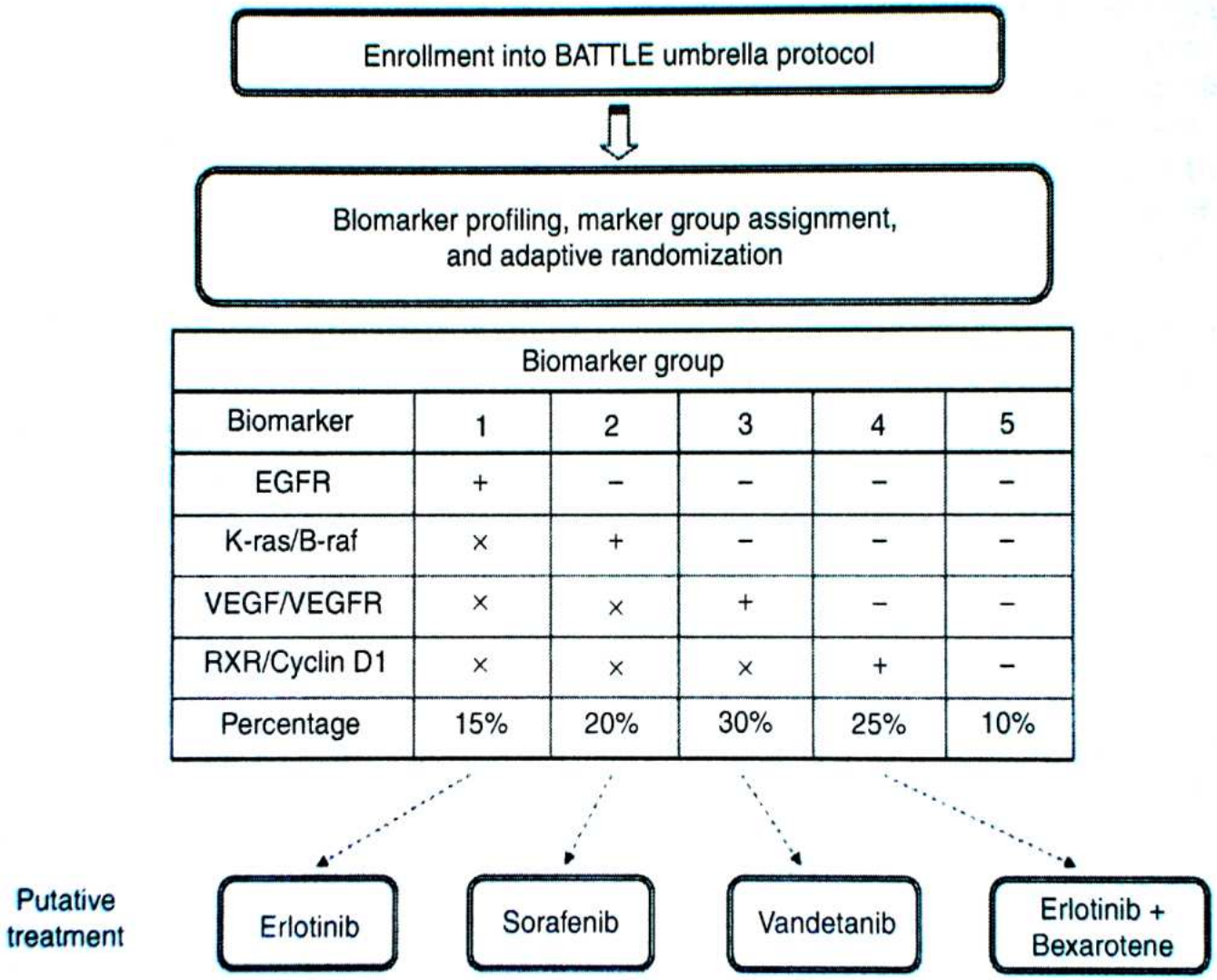
Synthesize

Test individuals then synthesize

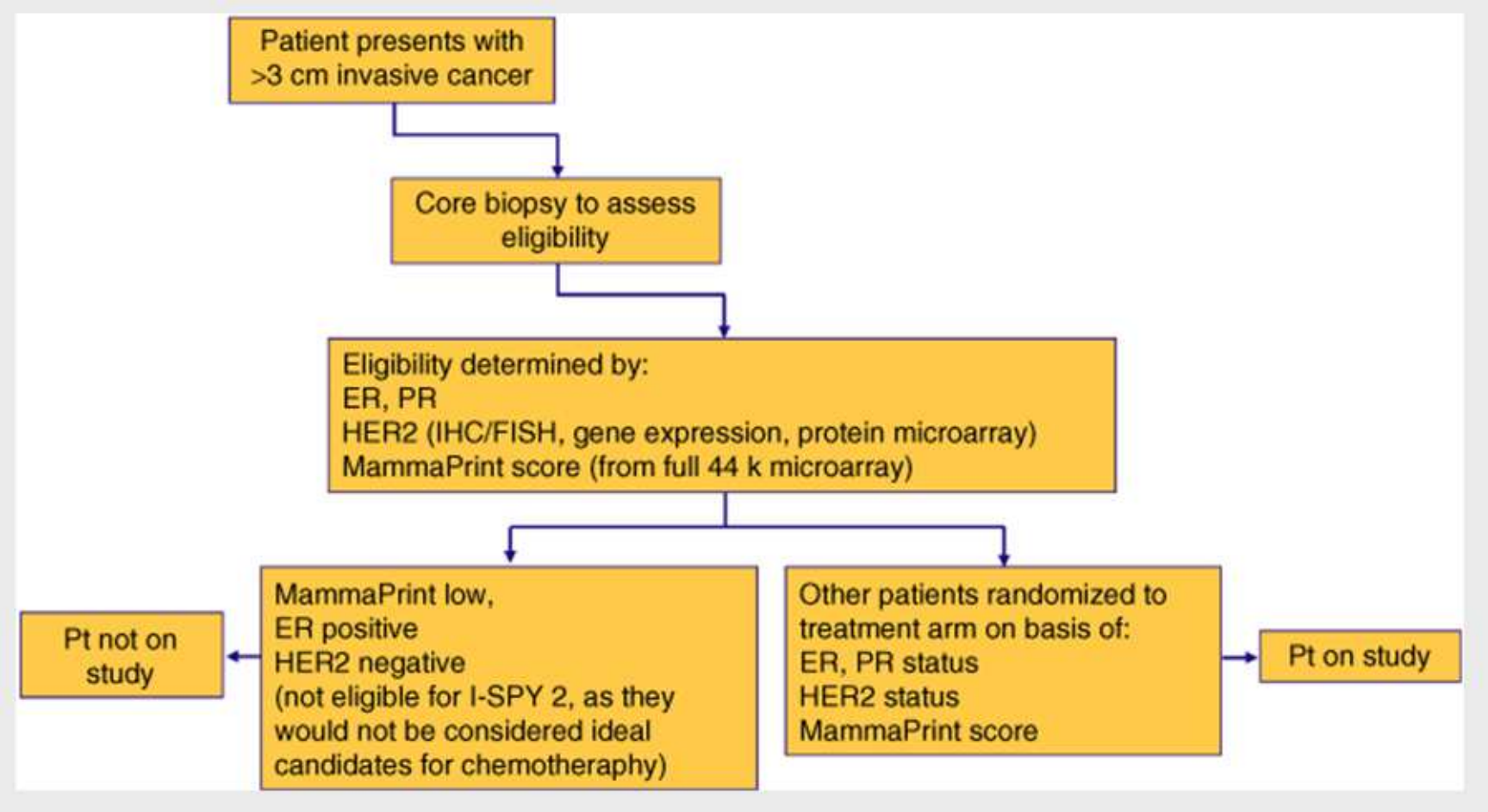


"Shotgun approach"

Bayesian Adaptive Design
Zhou, X.: Clinical Trials 2008;5:181-193



I-Spy 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy - Design



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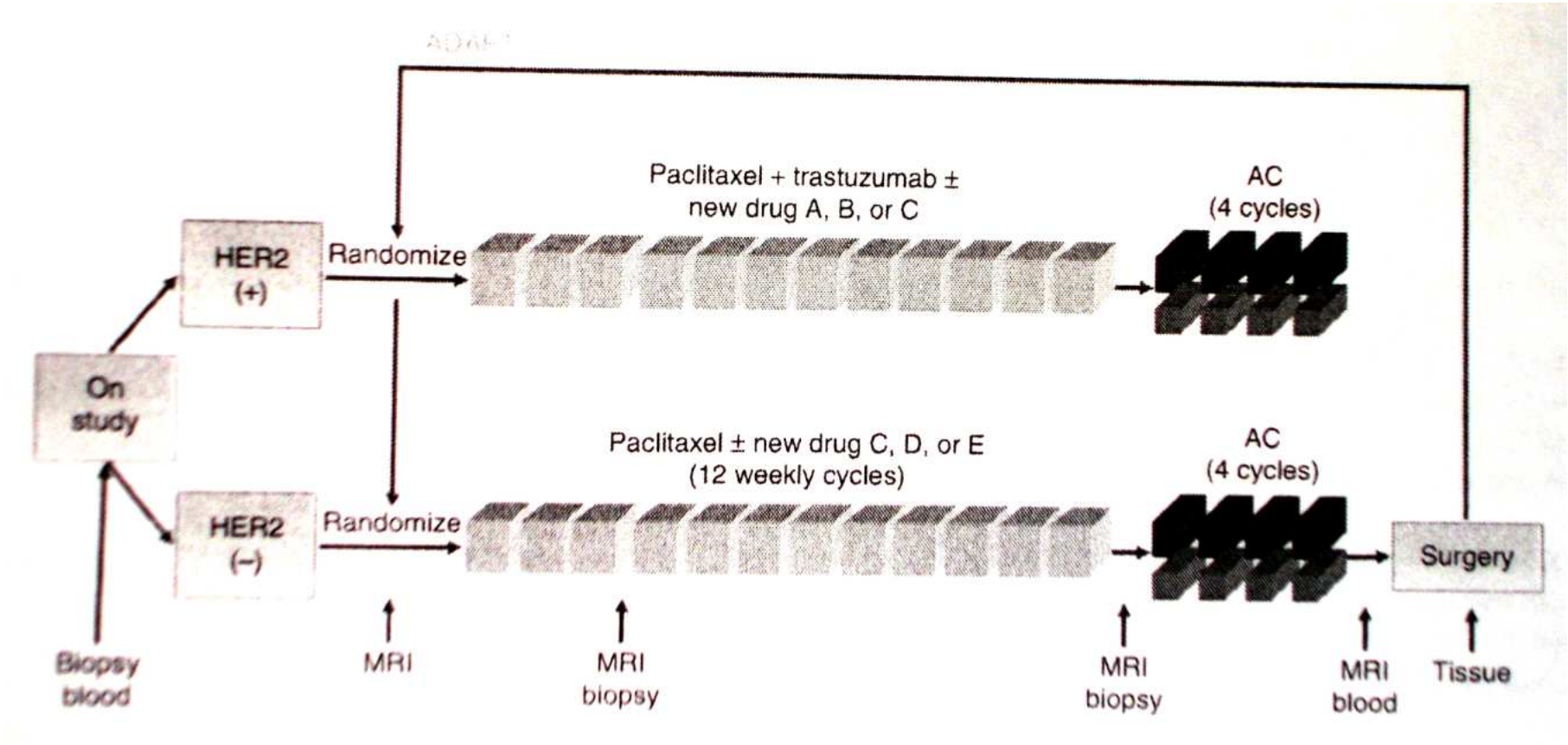

Baraker, AD: Clin. Pharm. Therap. 2009, 1-4

Summary

- Emphasis on indirect evidence though extremely expensive has moved oncology significantly forward but recently hit its limit
- The heterogenity of cancer makes indirect evidence often useless
- Biomarkers = driver mutations predict response
- Treatment based on the presence of driver mutations (direct evidence) is much better and can be tested on small numbers of patients
- These are being developed through novel Baysian adaptive clinical trials

Sometime Somewhere In The Future

- Ideal ??
  - Based on clinical history, imaging and molecular workup reconstruct oncogenic pathways, and from them understand etiology, timming, progression factors and predict sensitivity to therapy – then treat and cure
  - Towards this end
    - Identify driving mutations
    - Agents acting on these mutations
    - Agents working when the mutation mutatets
    - Develop "theranostic" systems working 100% of time and lead to cure