STUDI CLINICI: METODOLOGIA

"A good foundation"

PRIMA SESSIONE

# Criteri di selezione dei pazienti

- Criteri restrittivi *vs.* inclusivi
- Conseguenze su trasferibilità e precisione delle evidenze


**Emilio Bria**

**Oncologia Medica, Dipart. di Medicina, Università di Verona, Az. Osp. Univ. Int., Verona**

emilio.bria@univr.it


*Negrar (VR), 22 Gennaio 2016*

# Disclosures

- Advisory Boards/Honoraria/Speakers' fee/Consultant for:
  - MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis
- Research Support / Grants from:
  - A.I.R.C. (Associazione Italiana Ricerca sul Cancro)
  - I.A.S.L.C. (International Association for the Study of Lung Cancer)
  - Fondazione *Cariverona*

FONDAZIONE *Cariverona*

AIRC

IASLC
International Association for the Study of Lung Cancer

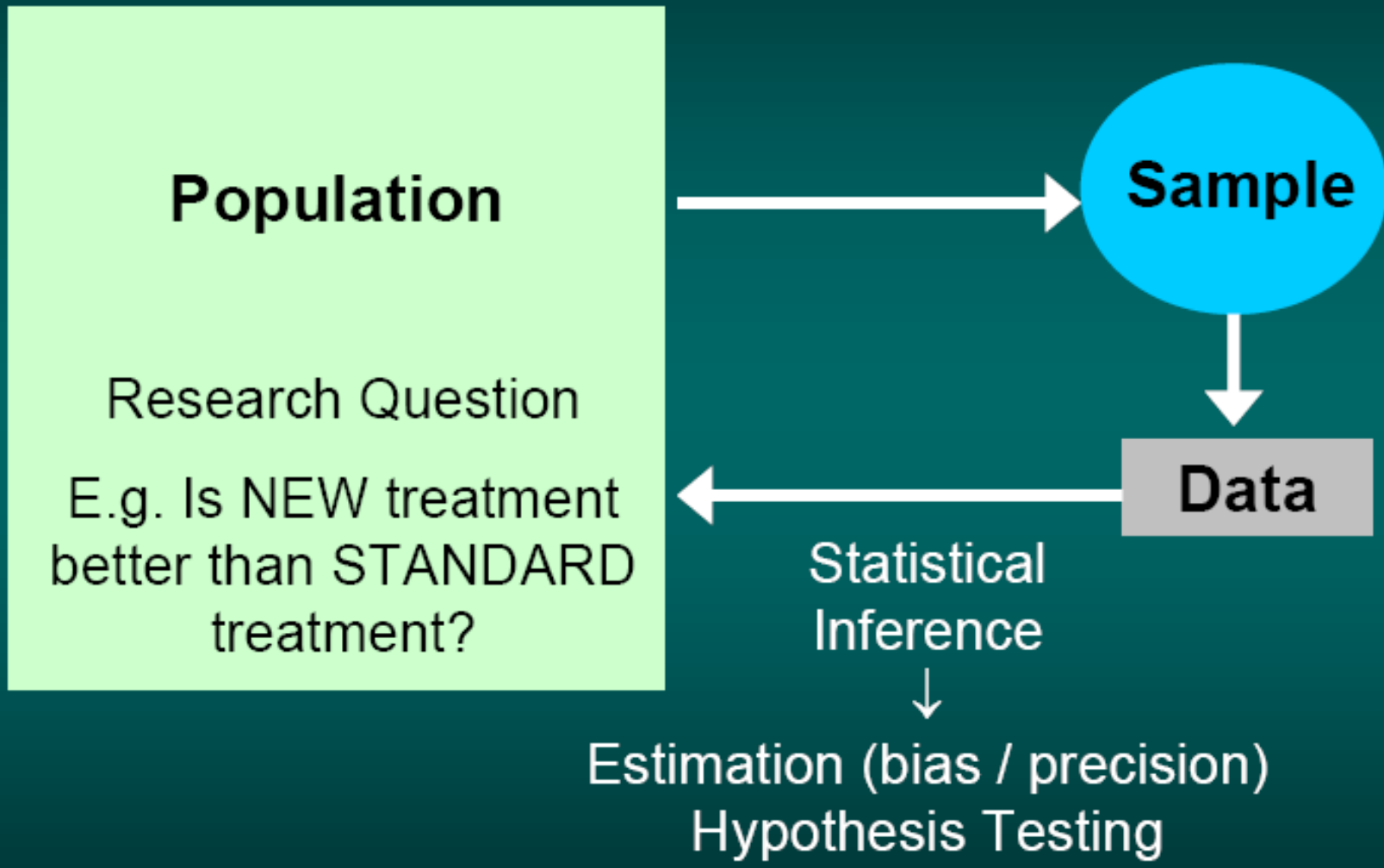
# '*Main*' Disclosure….

- I am a Physician, not a Statistician, so this is just my view, aimed to put things in perspectives for:
  - Insights for '*basic*' understanding
  - Critically review the available evidences
  - Increase '*doubts*' when data are presented or relased

# Additional Disclosures….

- Shared materials, opinions and thoughts with:

# Why Do We Need Statistics?




**Aim of statistical analysis: search for the truth**

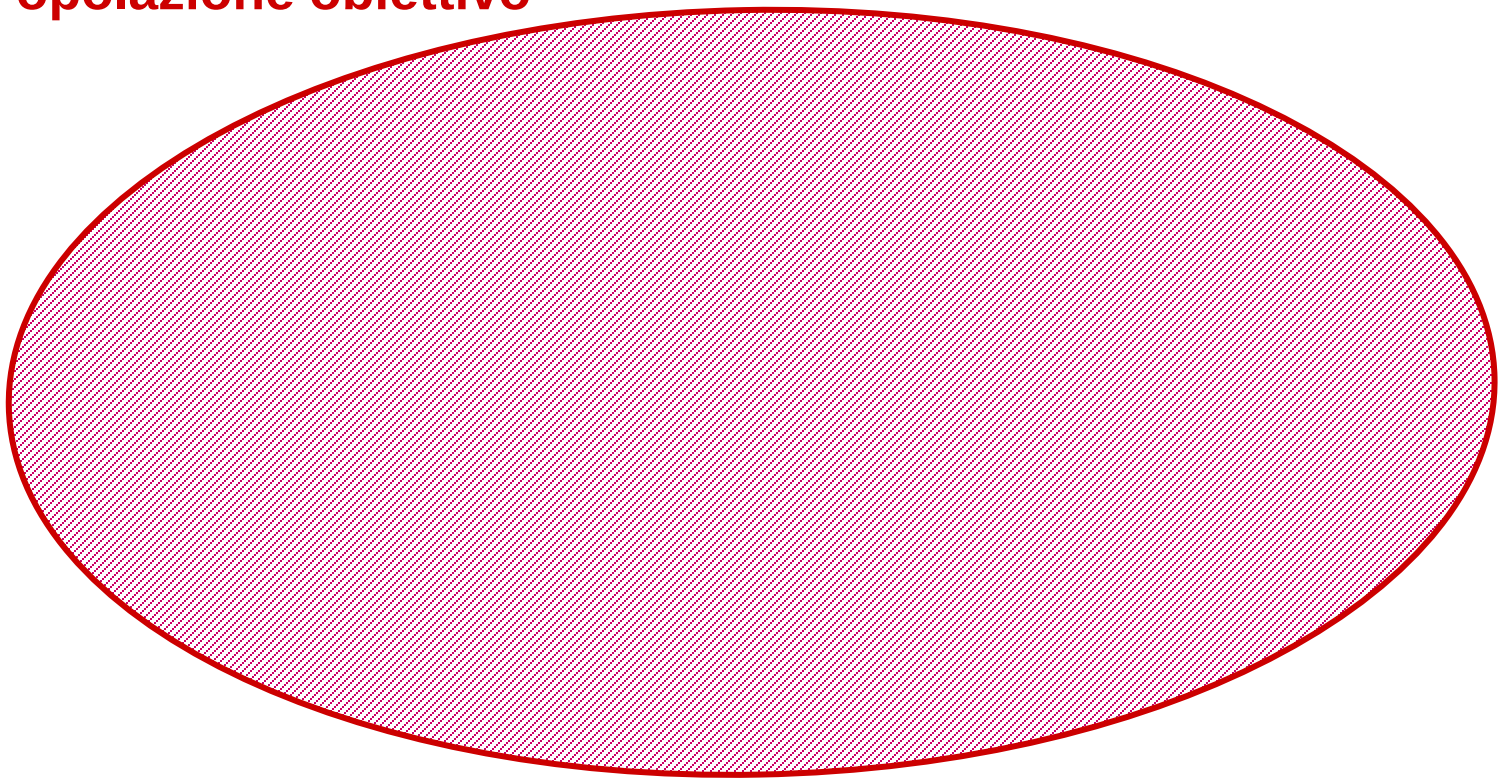
# Hypothesis Testing

| Assumption | Evidence | Is there sufficient evidence against the original assumption? | Judgement |
|---|---|---|---|
|  Innocent |  |  |  |
| **Research Question**<br>**New superior**<br>No difference (NH) | **Data from Sample** | **P-value = p(data given NH true)** | **Data consistent or inconsistent with NH** |

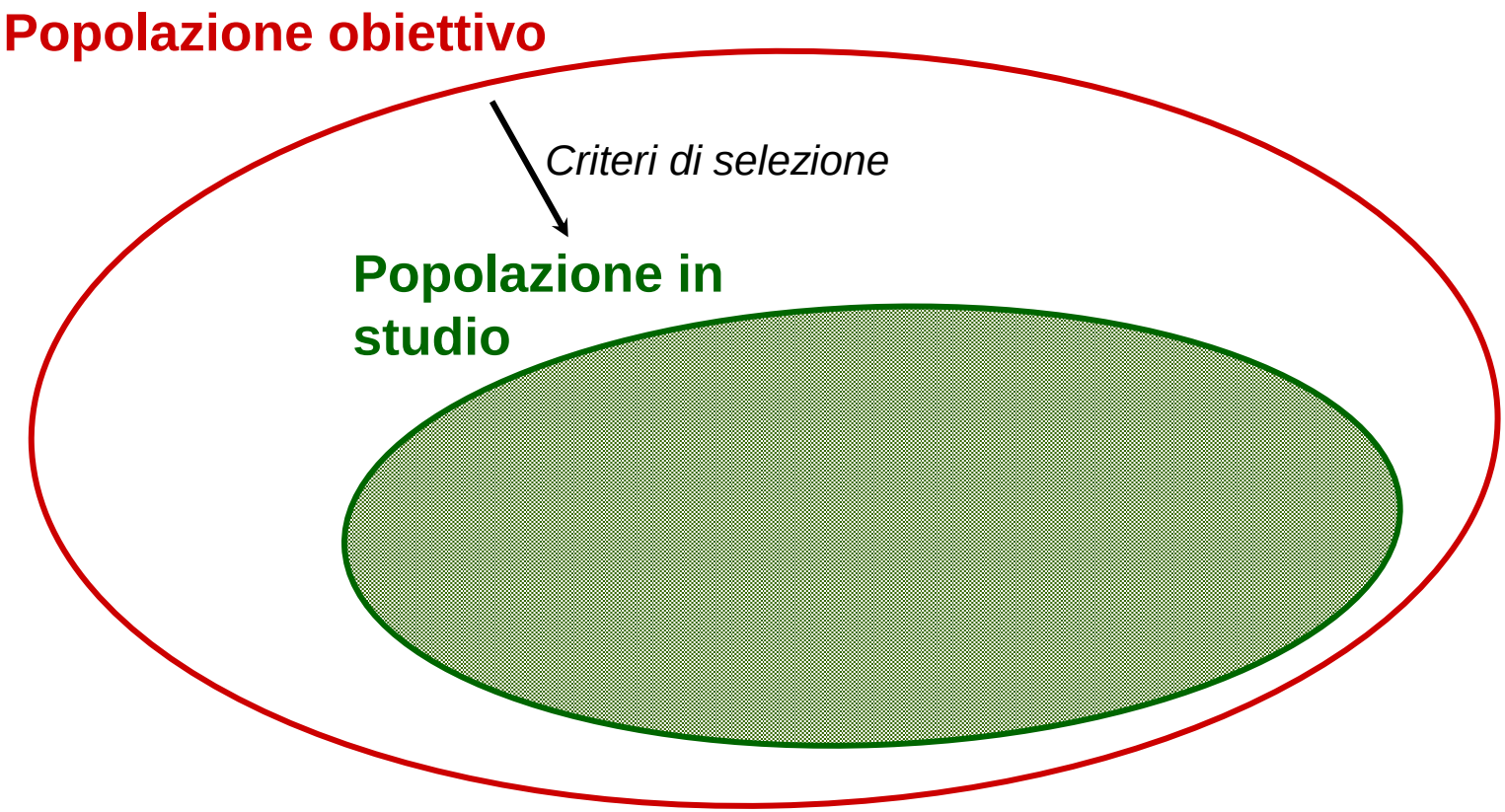
***Courtesy of Billingham C, 2008***

# La popolazione obiettivo

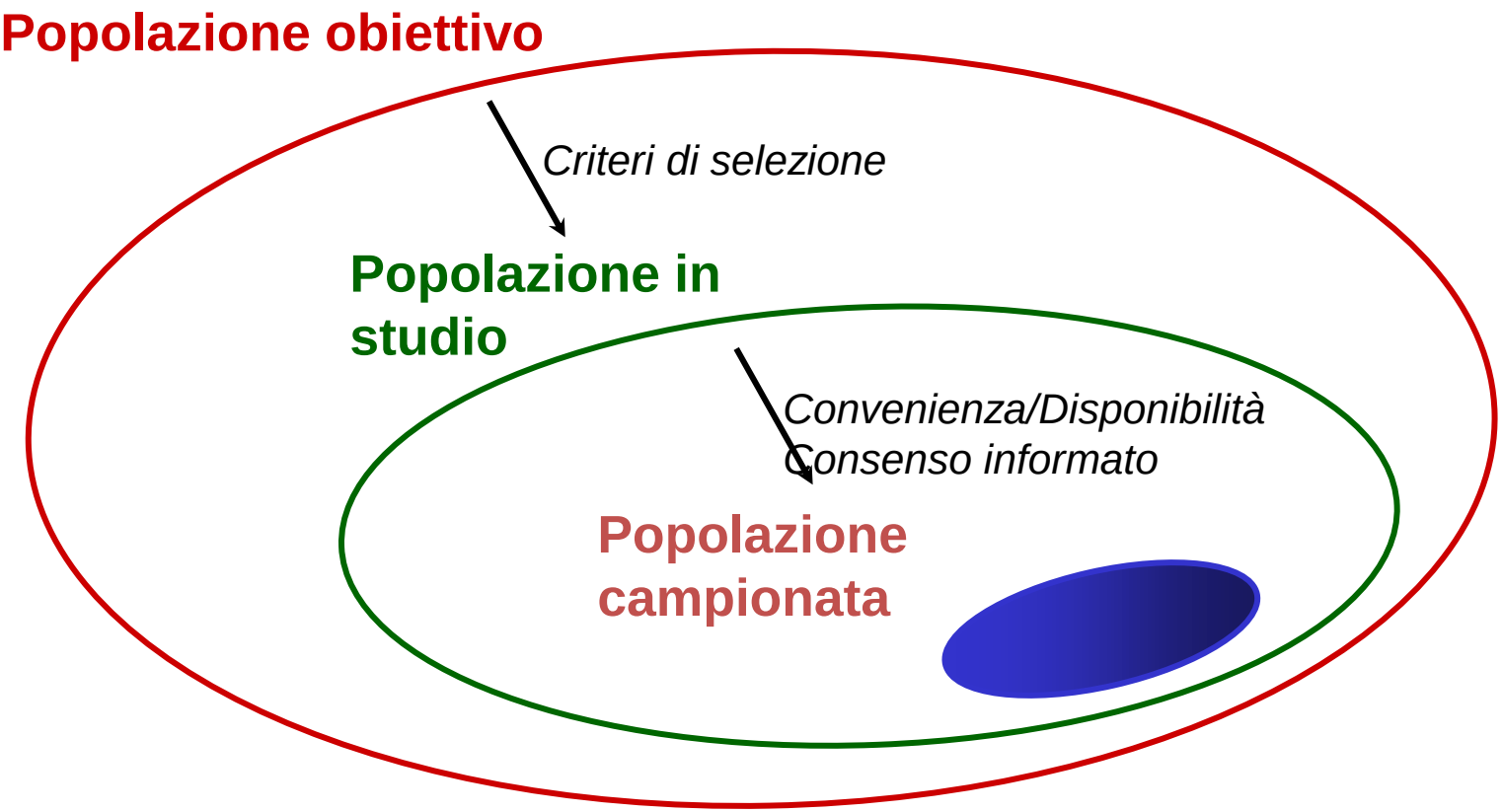
**Popolazione obiettivo**



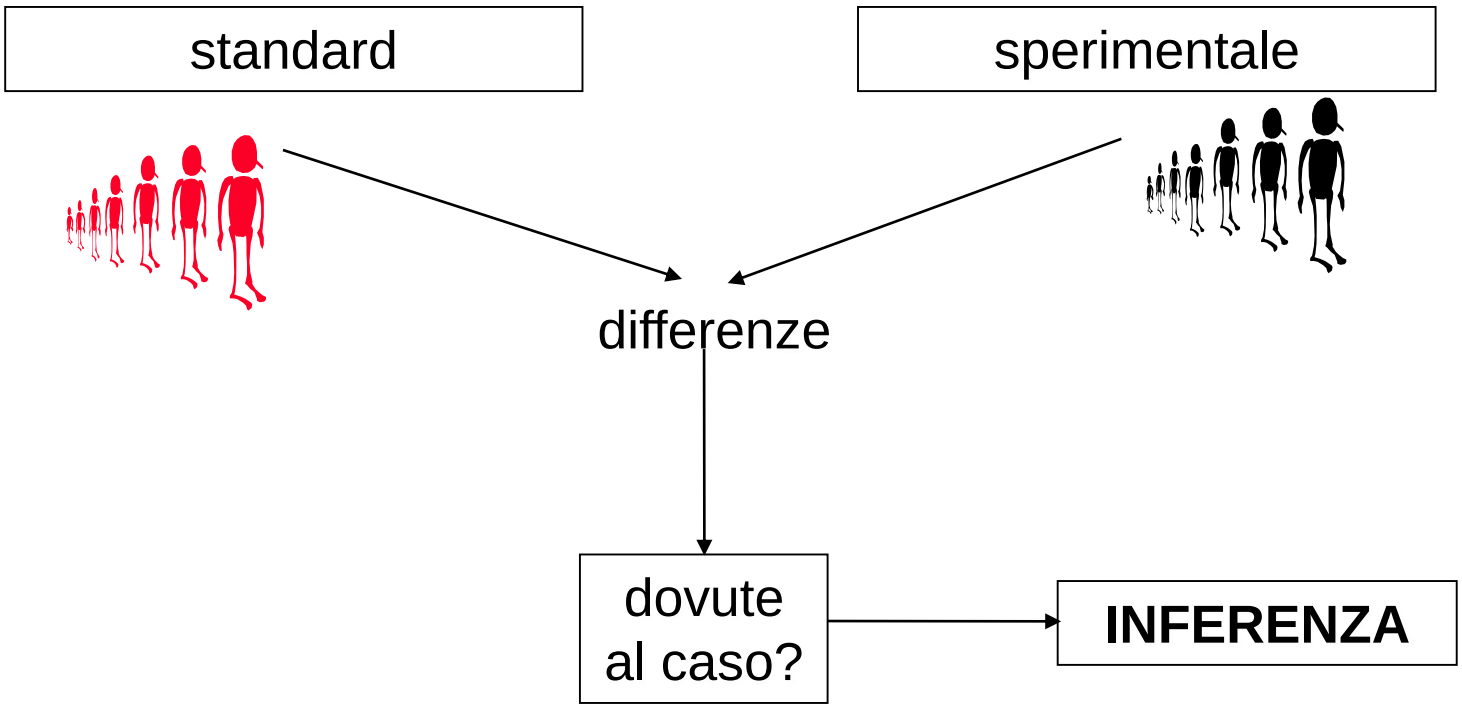
# La popolazione oggetto di studio



# La popolazione campionata



# Inferenza

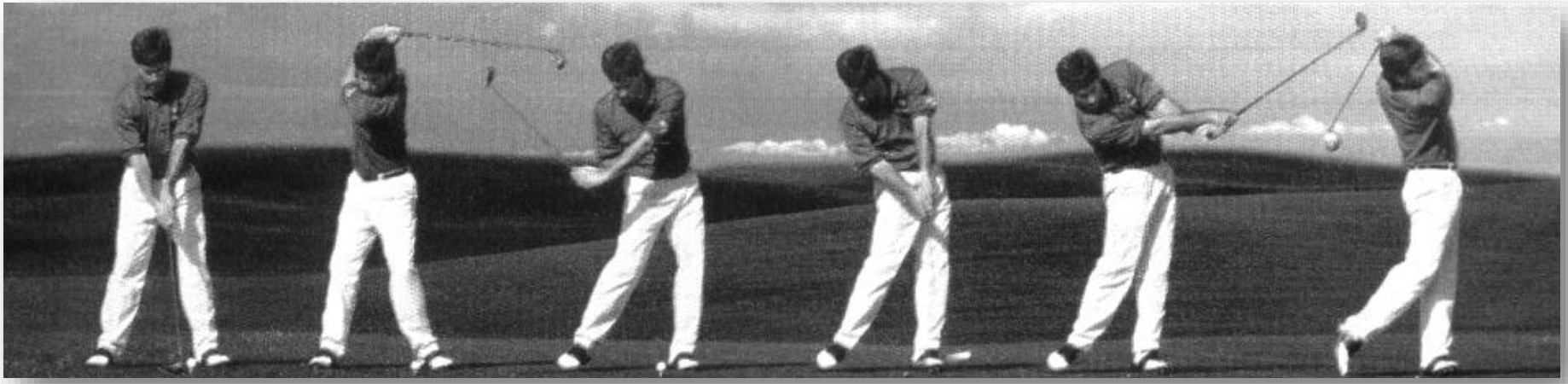

standard
sperimentale
differenze
dovute
al caso?
INFERENZA

# Le fasi di studio

| Fase | Obiettivi | Soggetti | Centrato su |
|---|---|---|---|
| I | Farmacocinetica<br>Tossicità | Volontari sani<br>Malati avanzati | Farmaco |
| II | Attività terapeutica<br>Tollerabilità a breve termine | Malati | Malattia |
| III | **Efficacia terapeutica** | **Malati** | **Malato** |

# Traditional Drug Development according to Phases and Aims

Phase 1 → Phase 2 → Phase 3 → Phase 4



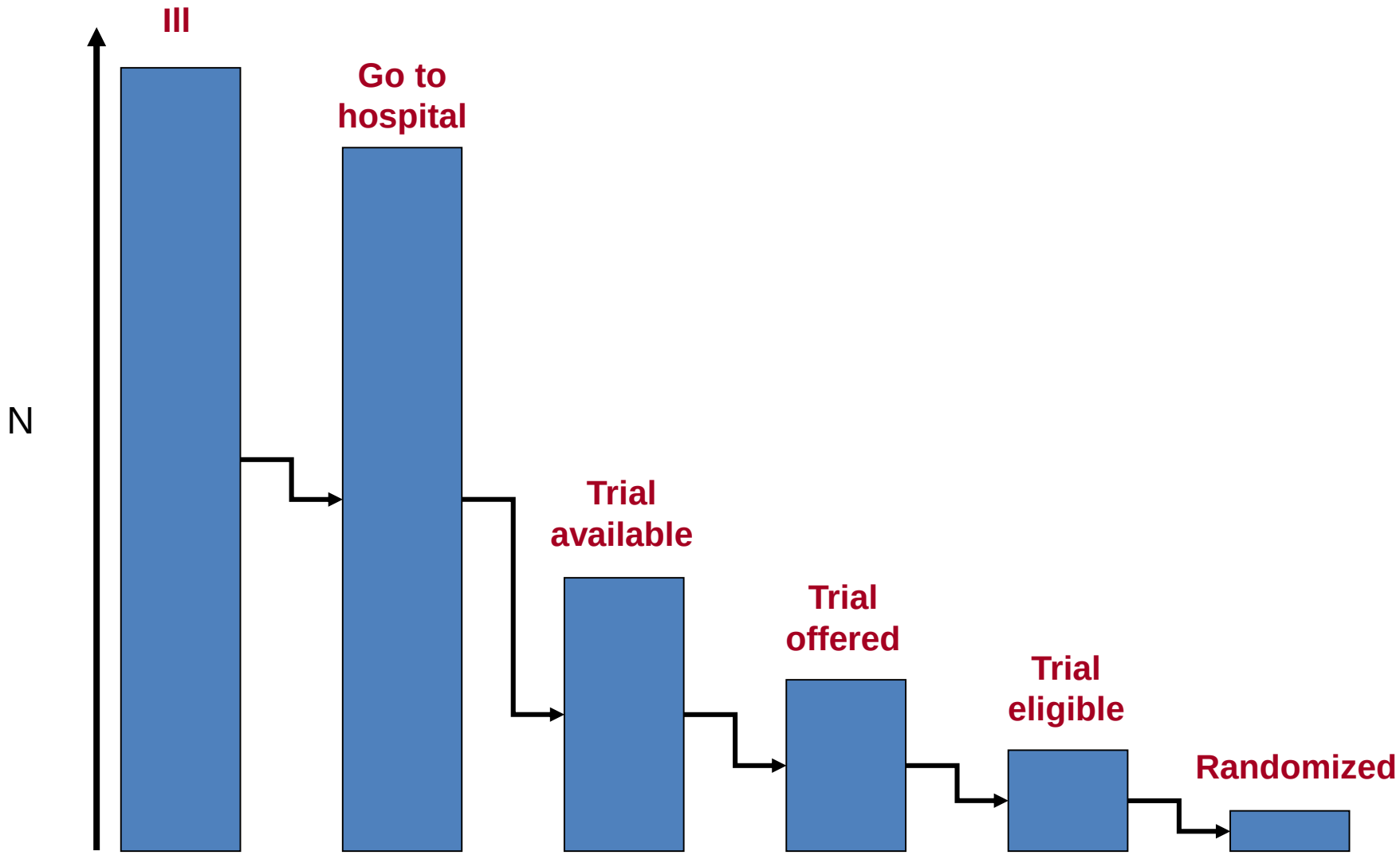
| Phase 1 | Phase 2 | Phase 3 | Phase 4 |
|---|---|---|---|
| MTD | Safety<br>Activity | Efficacy | Effectiveness<br>Other |

# Internal vs external validity

- ***Internal validity:*** Can the observed differences between groups be attributed to the intervention?

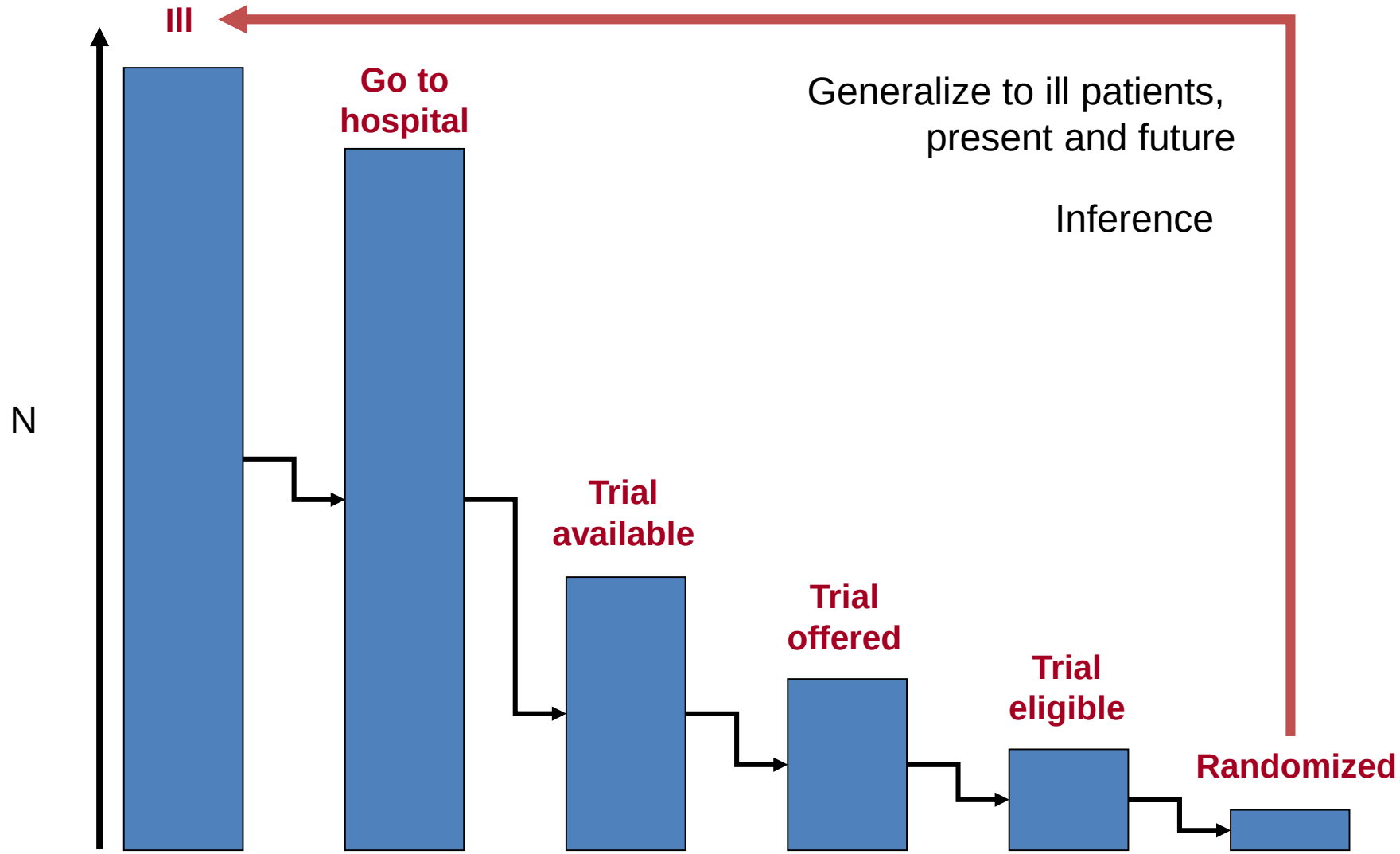
- ***External validity:*** Are the patients enrolled in the study representative of patients/subjects in general?

# Il problema del *selection bias…*



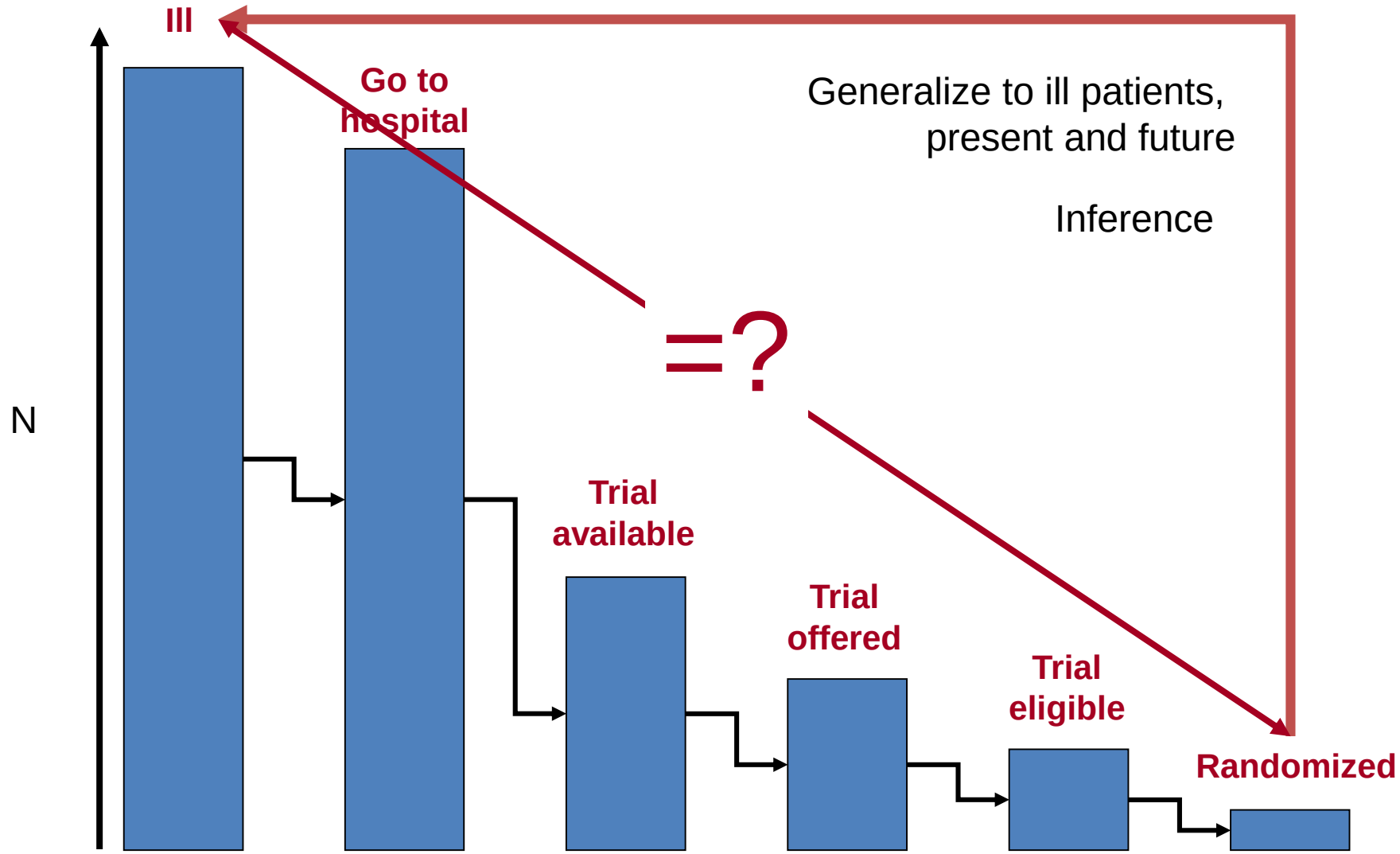

Courtesy of Francesco Perrone

# Il problema del *selection bias…*



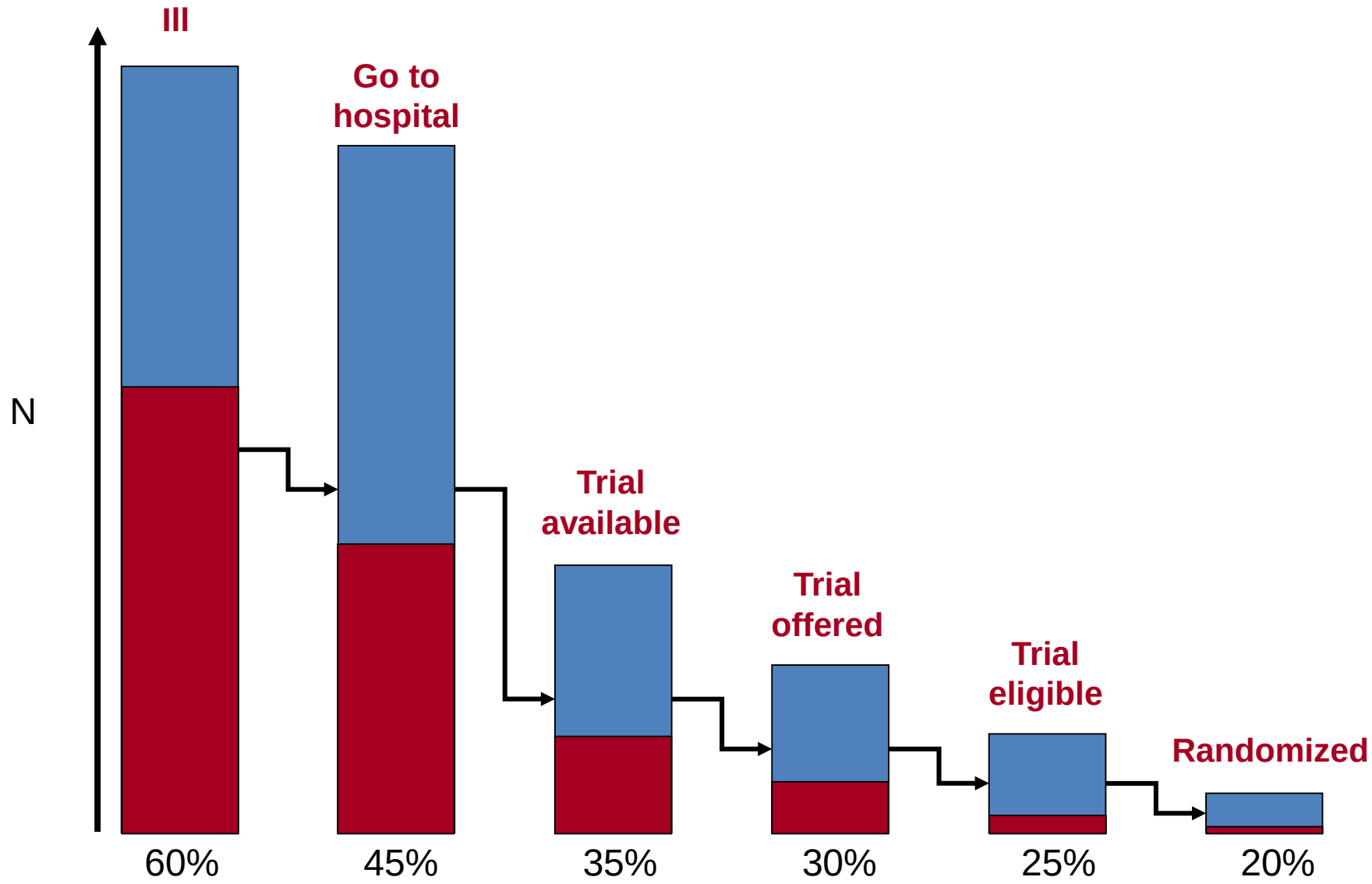

Courtesy of Francesco Perrone

# Il problema del *selection bias…*



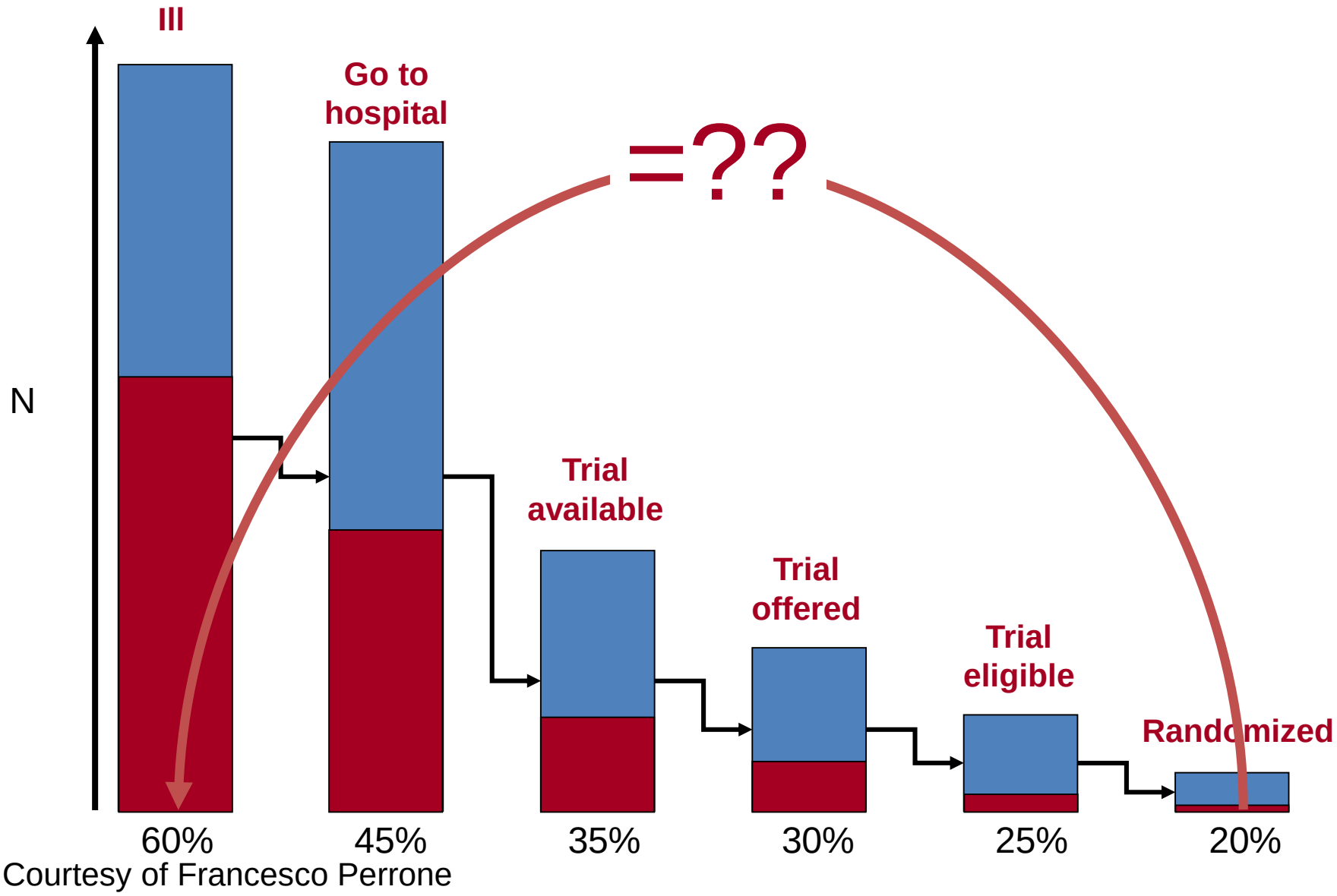

Courtesy of Francesco Perrone

# Il sottogruppo di pazienti anziani...



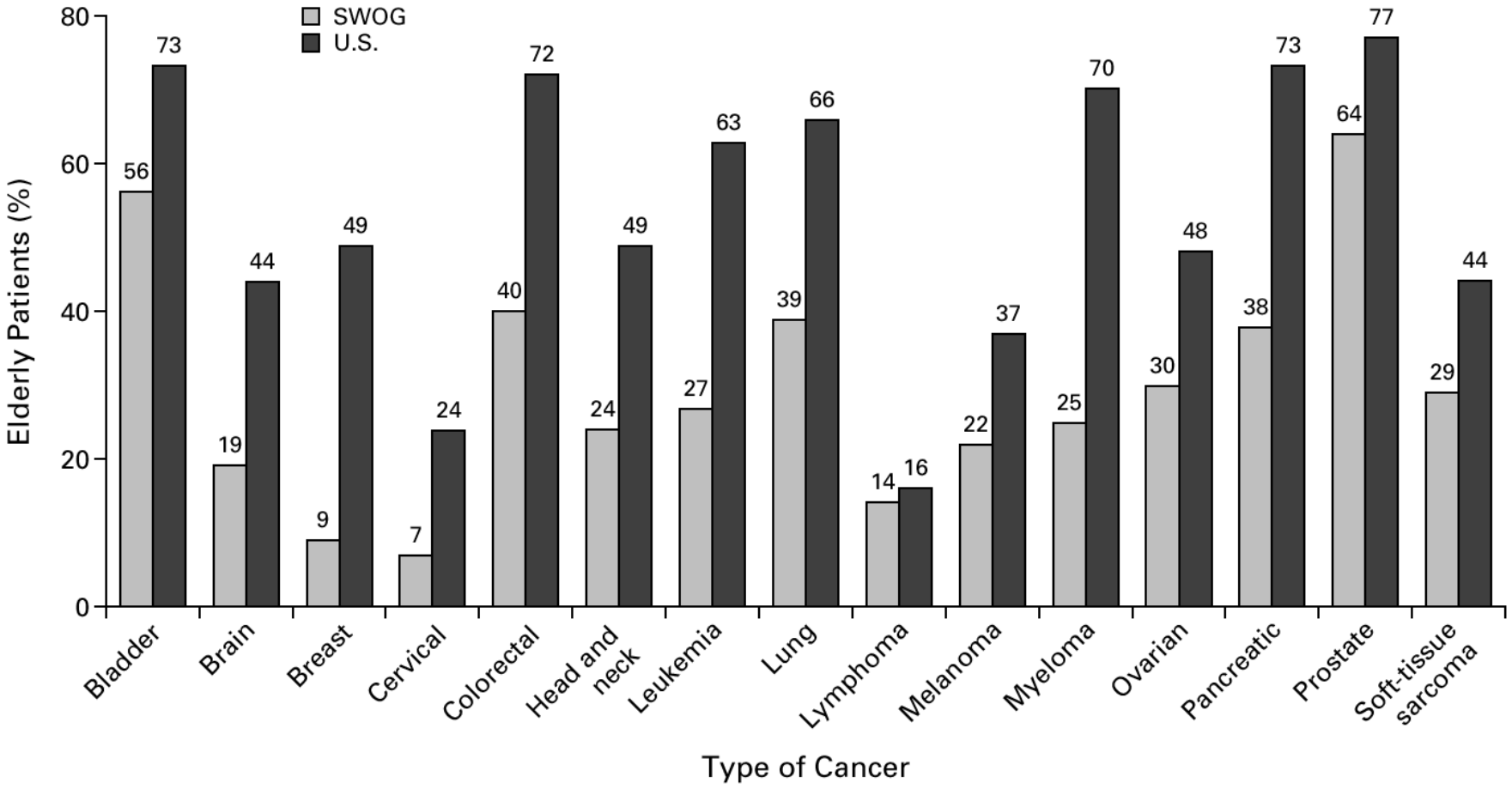

Courtesy of Francesco Perrone

# Il sottogruppo di pazienti anziani...




Courtesy of Francesco Perrone

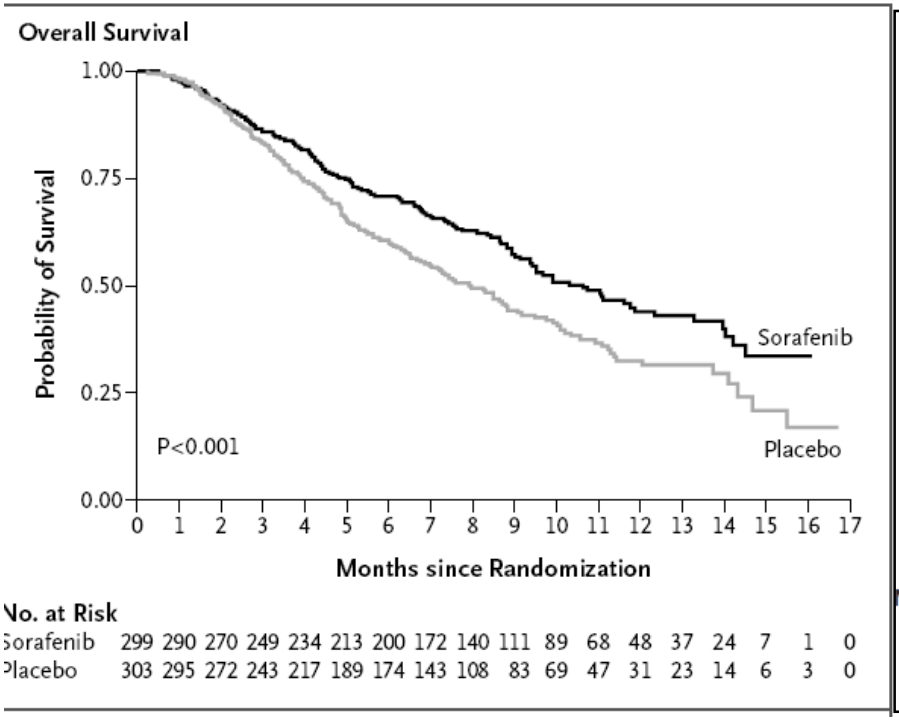
# "*underrepresentation*" dei pazienti anziani nei *trials*



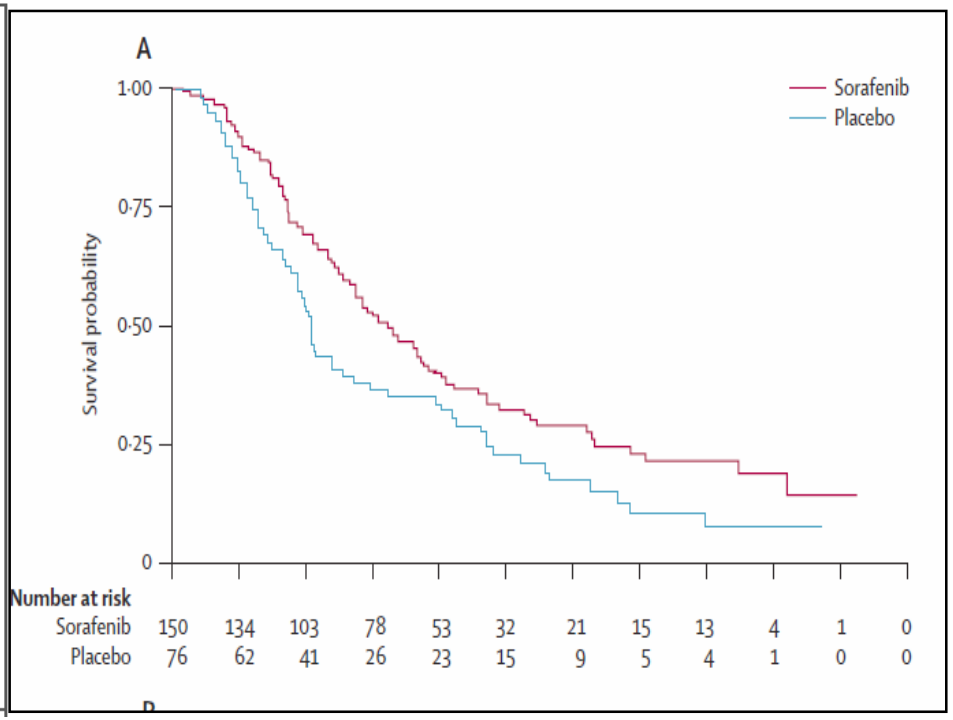

Hutchins LF et al, *N Engl J Med* 341:2061; 1999

# Bias di selezione negli studi randomizzati: l'esempio del sorafenib nell'epatocarcinoma

## SHARP




## Asia-Pacific




| | SHARP | Asia - Pacific |
|---|---|---|
| Median, sorafenib | 10.7 months | 6.5 months |
| Median, placebo | 7.9 months | 4.2 months |
| Hazard Ratio (95% CI) | 0.69 (0.55 – 0.87) | 0.68 (0.50 – 0.93) |

Llovet et al. N Engl J Med 2008; 359:378-390
Cheng AL *et al.* Lancet Oncol 2009; 10: 25-34

**TABLE 1. Characteristics and main results of two randomized phase III trials with sorafenib in advanced HCC**

| | SHARP [123] | ASIA-PACIFIC [124] |
|---|---|---|
| **Countries** | Europe, North America, Central and South America, Israel, Australia | East Asia (China, Taiwan, Korea) |
| Total number of patients | 602 | 226 |
| Number of patients assigned to sorafenib | 299 | 150 |
| Number of patients assigned to placebo | 303 | 76 |
| **Characteristics of patients** | | |
| Median age (range) | 67 (21–89) | 51 (23–86) |
| Etiology | | |
| HCV+ | 28% | 8% |
| HBV+ | 18% | 73% |
| Alcohol-related | 26% | NA |
| Unknown / Other | 27% | NA |
| Child-Turcotte-Pugh | | |
| A | 97% | 97% |
| B | 3% | 3% |
| Performance Status | | |
| 0 | 54% | 26% |
| 1 | 38% | 69% |
| 2 | 8% | 5% |
| BCLC stage | | |
| B (intermediate) | 17% | 4% |
| C (advanced) | 82% | 96% |
| Extrahepatic disease | 51% | 69% |
| Macroscopic vascular invasion | 38% | 35% |

Daniele B, Di Maio M. Hot Topics Oncol. 2009;5:19-29.

NEWS & VIEWS

| “Methodological purism” | “Clinical pragmatism” |
| --- | --- |
| • Physicians strictly consider the external validity of trial results, denying sorafenib to Child B patients | • Physicians consider the absence of therapeutic alternatives and offer sorafenib to Child B patients |
| • Treatment of Child B patients remains unmet need | • Caution in monitoring adverse effects |
| • No therapeutic chance is offered to these patients | |

Di Maio M, et al. Nature Rev Clin Oncol. 2009;6:505-6.

# Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

N Engl J Med 2012;366:109-19.

| Characteristic | Placebo plus Trastuzumab plus Docetaxel (N=406) | Pertuzumab plus Trastuzumab plus Docetaxel (N=402) |
|---|---|---|
| Prior adjuvant or neoadjuvant chemotherapy — no. (%) | | |
| No | 214 (52.7) | 218 (54.2) |
| Yes§ | 192 (47.3) | 184 (45.8) |
| Anthracycline | 164 (40.4) | 150 (37.3) |
| Hormone | 97 (23.9) | 106 (26.4) |
| Taxane | 94 (23.2) | 91 (22.6) |
| Trastuzumab | 41 (10.1) | 47 (11.7) |

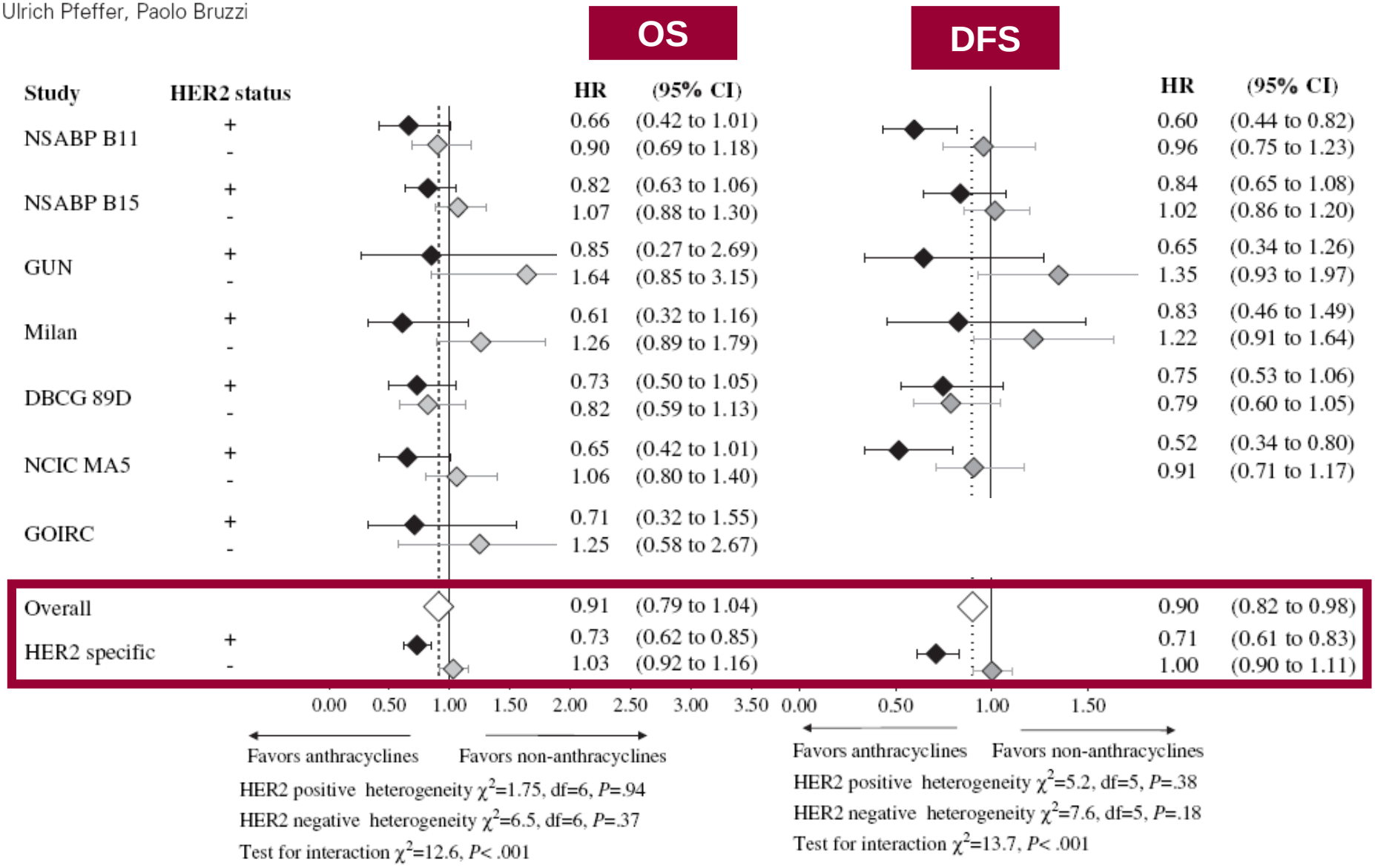
**Non rappresentativo della pratica clinica corrente**

# *HER2* Status and Efficacy of Adjuvant Anthracyclines in Early Breast Cancer: A Pooled Analysis of Randomized Trials

**TAXANE-HERC free Pts!**

J Natl Cancer Inst 2008;100:14–20

Alessandra Gennari, Maria Pia Sormani, Paolo Pronzato, Matteo Puntoni, Mariantonietta Colozza, Ulrich Pfeffer, Paolo Bruzzi




HER2 positive heterogeneity $\chi^2$=1.75, df=6, $P$=.94

HER2 negative heterogeneity $\chi^2$=6.5, df=6, $P$=.37

Test for interaction $\chi^2$=12.6, $P$< .001

HER2 positive heterogeneity $\chi^2$=5.2, df=5, $P$=.38

HER2 negative heterogeneity $\chi^2$=7.6, df=5, $P$=.18

Test for interaction $\chi^2$=13.7, $P$< .001

# Is that useful for the next relevant patient?

- Yes, but how many HER-2 positive, node-positive patients, in your daily clinical practice do not receive:
  - Taxanes?
    - Good point, maybe 15-20%?
  - Trastuzumab?
    - Cardiac comorbidity rules that out, but even anthracyclines are contraindicated as well!
- How much this sample resembles your practice?

# Criteri restrittivi *vs.* inclusivi

| | Registrative trials | Post-registrative trials |
|---|---|---|
| **Approach** | "Explanatory" | "Pragmatic" |
| **Comparison** | New drug *vs.* comparator "acceptable" for regulatory agencies | Comparison between sequences - strategies |
| **Inclusion criteria** | **Restrictive** | **Large, more similar to clinical practice** |
| **Endpoint** | PFS, RR | Overall survival |
| **Results [if positive]** | More Precise, Less Reliable | Less Precise, More Reliable |

***Courtesy of Bruzzi P, Pappagallo G & Di Maio M***

# Fattori legati allo studio

- Razionale dello studio irrilevante
- Protocolli troppo complessi o mal disegnati
- **Criteri di eleggibilità troppo restrittivi**
- Presenza di un braccio di controllo senza trattamento attivo
- Grandi differenze tra i bracci
  - es. chirurgia *verso* radioterapia
- Tossicità della terapia sperimentale

***Ellis PM, Ann Oncol 11:939; 2000***

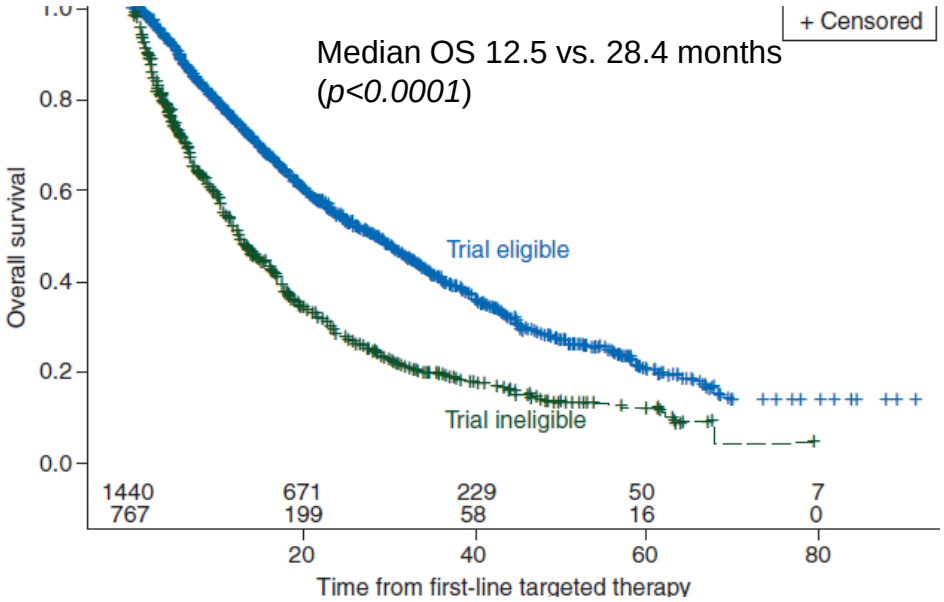
# Targeted Therapy Performance in the '*Real World*'

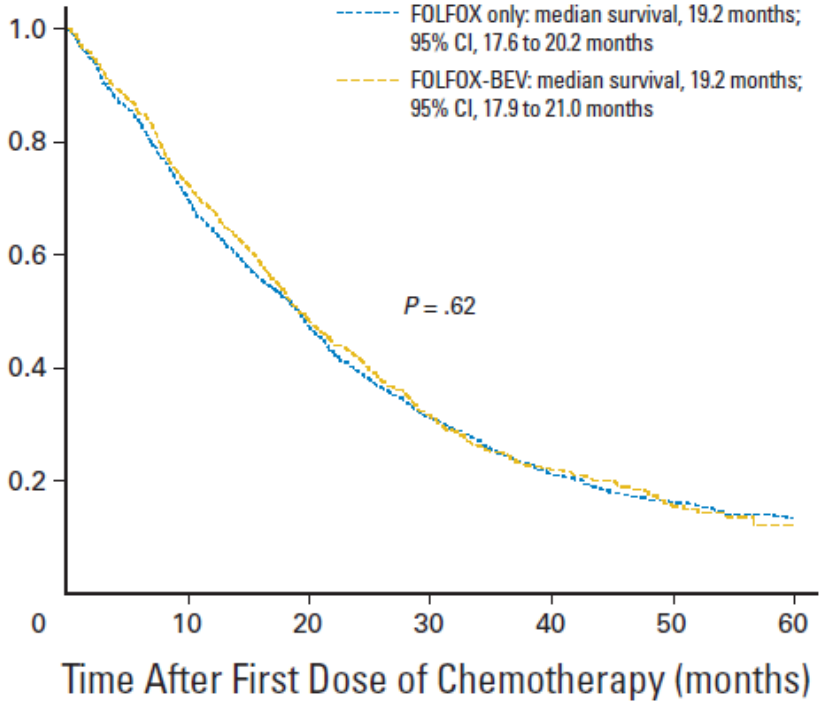
**Outcomes of patients with metastatic renal cell carcinoma that do not meet eligibility criteria for clinical trials**

Effectiveness of Bevacizumab With First-Line Combination Chemotherapy for Medicare Patients With Stage IV Colorectal Cancer

**Trials' *Ineligible* Pts vs. *Eligible* (all receiving targeted agents)**

**Addition of Bevacizumab to FOLFOX, '*Registry*' Context**

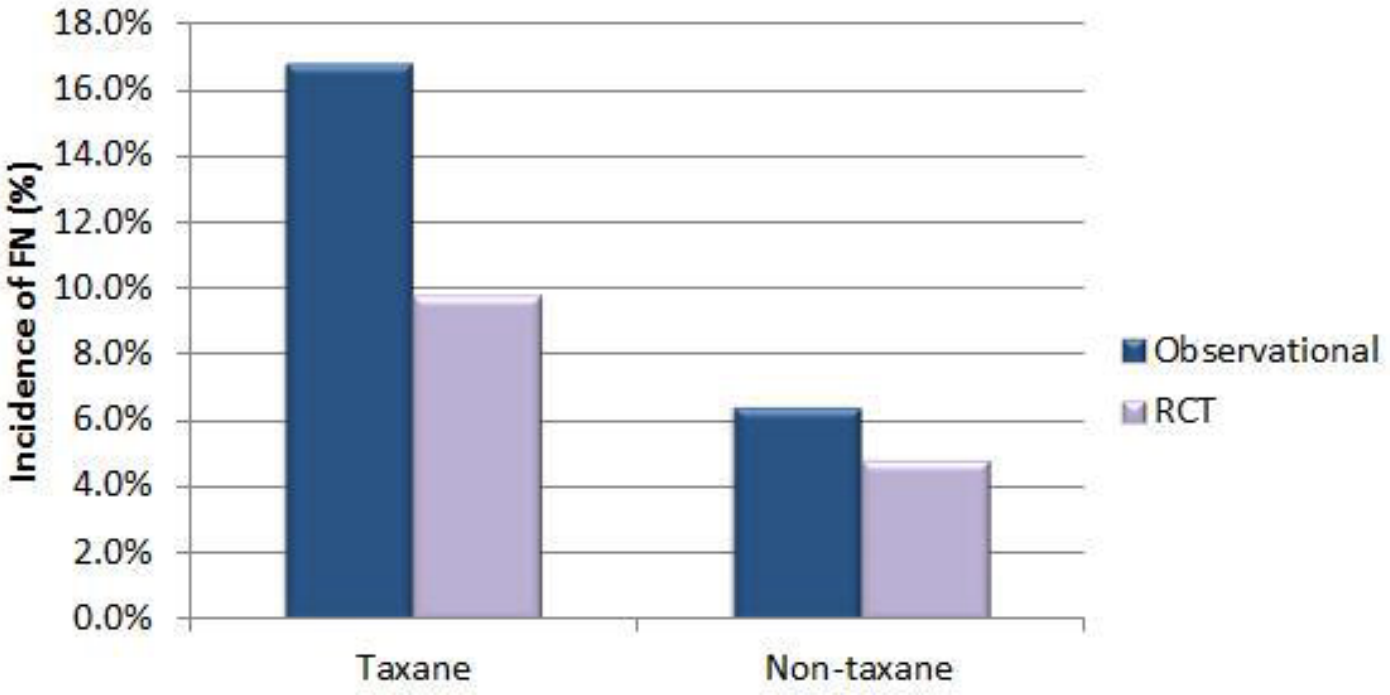


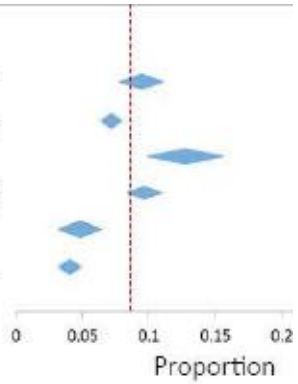

*Deng DY et al, Ann Oncol 2014*

*Meyerhardt T et al, JCO 2012*

# Febrile Neutropenia:
# Observational *vs.* RCTs




| Type of Study | Study | Random Effects Estimate (95% C.I.) | Ev/Trt |
|---|---|---|---|
| All Studies | Obs. (I^2=93%, *P*<0.001) | 0.094 (0.077, 0.111) | 930/7812 |
| | RCT (I^2=96%, *P*<0.001) | 0.072 (0.064, 0.080) | 3334/42257 |
| Taxane Subgroup | Taxane Obs. (I^2=90%, *P*<0.001) | 0.128 (0.098, 0.157) | 695/4148 |
| | Taxane RCT (I^2=97%, *P*<0.001) | 0.097 (0.084, 0.110) | 2579/26506 |
| Non-taxane Subgroup | Non-taxane Obs. (I^2=92%, *P*<0.001) | 0.046 (0.030, 0.063) | 235/3664 |
| | Non-taxane RCT (I^2=92%, *P*<0.001) | 0.041 (0.033, 0.049) | 755/15751 |



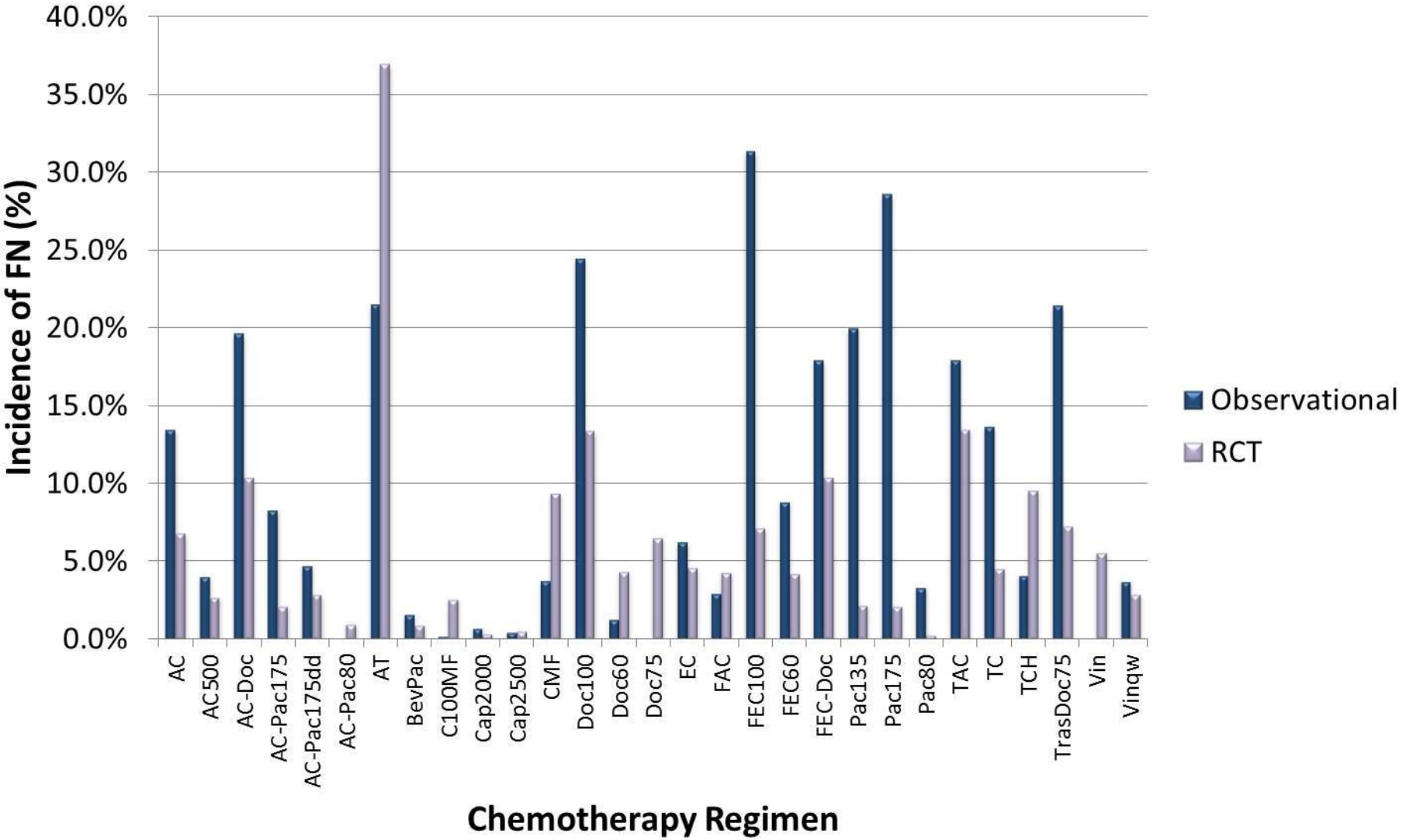

***Truong J et al, Ann Oncol [in press]***

# Febrile Neutropenia:
# Observational *vs.* RCTs

| Characteristic | Observational Design | | RCT Design | |
|---|---|---|---|---|
| | Cohorts (*n*=65) | Patients (*n*=7,812) | Cohorts (*n*=110) | Patients (*n*=42,257) |
| Method of data collection | | | | |
| Prospective | 17 | 1,015 | - | - |
| Retrospective | 48 | 6,797 | - | - |
| Mean age (range) | 53.7 ± 6.08 (43-73) | - | 52.1 ± 3.78 (45-69) | - |
| Total number of patients evaluable for FN | - | 7,812 | - | 42,257 |
| Median number of patients/cohort | - | 62 | - | 222 |
| Taxane-based regimen | | | | |
| Yes | 45 | 4,148 | 65 | 26,506 |
| No | 20 | 3,664 | 45 | 15,751 |
| Chemotherapy Intent | | | | |
| Palliative | 21 | 1,942 | 33 | 6,173 |
| Adjuvant | 34 | 4,255 | 47 | 27,189 |
| Neo-adjuvant | 2 | 370 | 19 | 4,186 |
| Adjuvant and Neo-adjuvant | 4 | 1,005 | 2 | 2,697 |
| Any | 3 | 218 | 9 | 2,012 |
| N/A | 1 | 22 | - | - |

***Truong J et al, Ann Oncol [in press]***

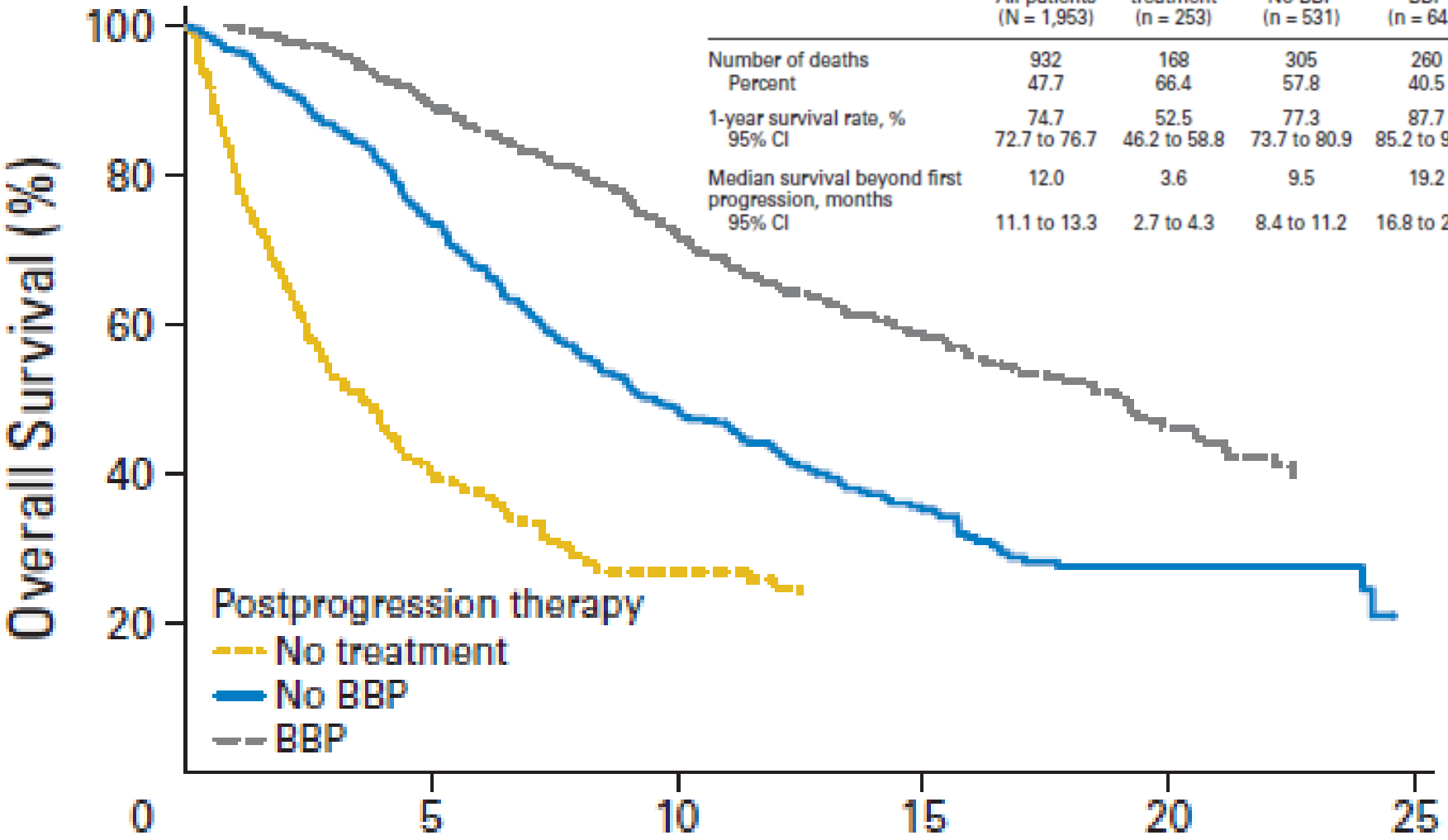
# Febrile Neutropenia:
# Observational *vs.* RCTs




***Truong J et al, Ann Oncol [in press]***

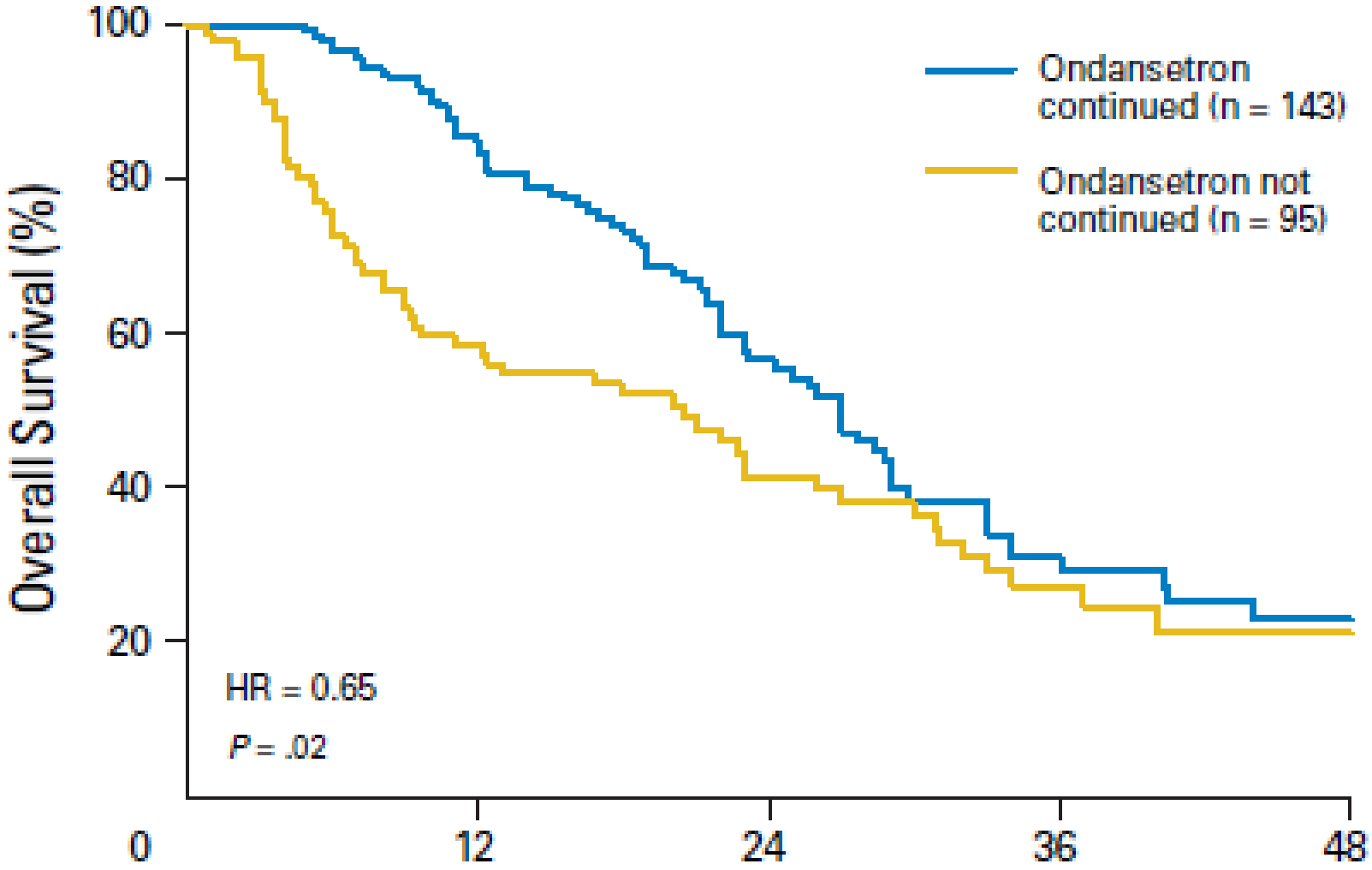
# Bevacizumab Beyond First Progression Is Associated With Prolonged Overall Survival in Metastatic Colorectal Cancer: Results From a Large Observational Cohort Study (BRiTE)

| | All patients (N = 1,953) | No post-progression treatment (n = 253) | No BBP (n = 531) | BBP (n = 642) |
|---|---|---|---|---|
| Number of deaths | 932 | 168 | 305 | 260 |
| Percent | 47.7 | 66.4 | 57.8 | 40.5 |
| 1-year survival rate, % | 74.7 | 52.5 | 77.3 | 87.7 |
| 95% CI | 72.7 to 76.7 | 46.2 to 58.8 | 73.7 to 80.9 | 85.2 to 90.3 |
| Median survival beyond first progression, months | 12.0 | 3.6 | 9.5 | 19.2 |
| 95% CI | 11.1 to 13.3 | 2.7 to 4.3 | 8.4 to 11.2 | 16.8 to 20.7 |




***Grothey A, JCO 2008***

# Hidden Biases in an Observational Study of Bevacizumab Beyond Progression

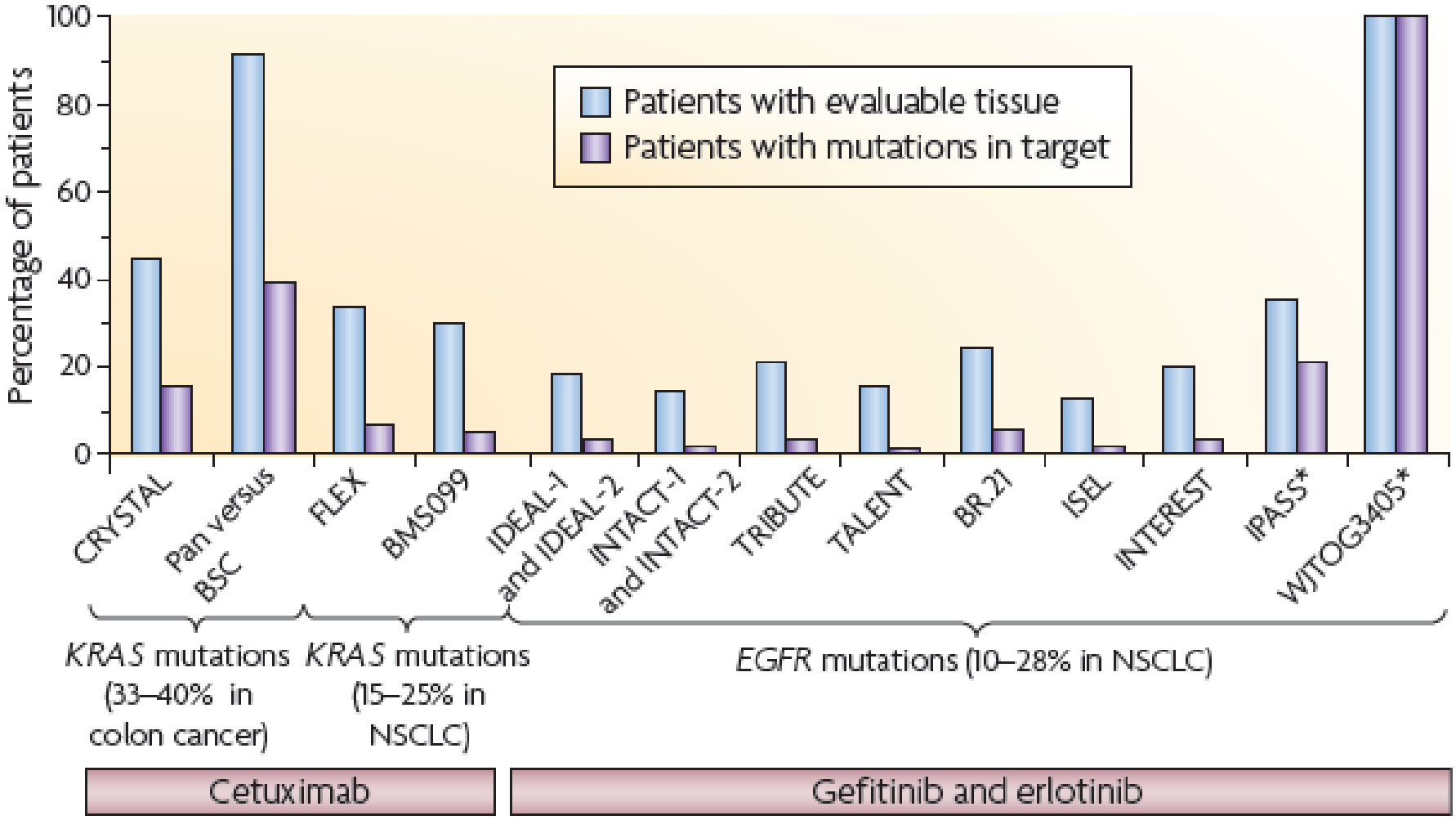



***Kopetz S, JCO 2009***

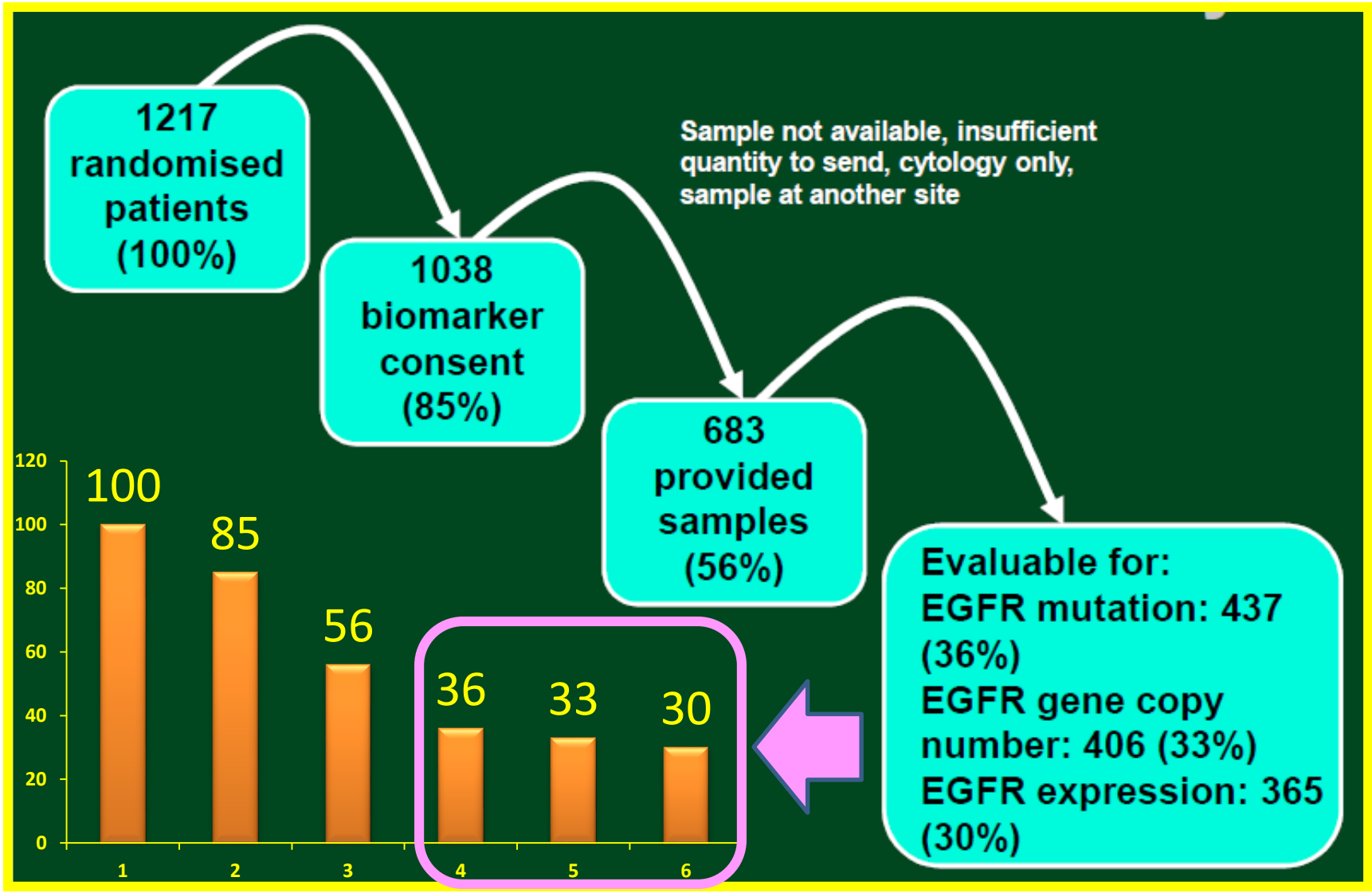
# Rational, biologically based treatment of *EGFR*-mutant non-small-cell lung cancer

*William Pao* and Juliann Chmielecki‡*

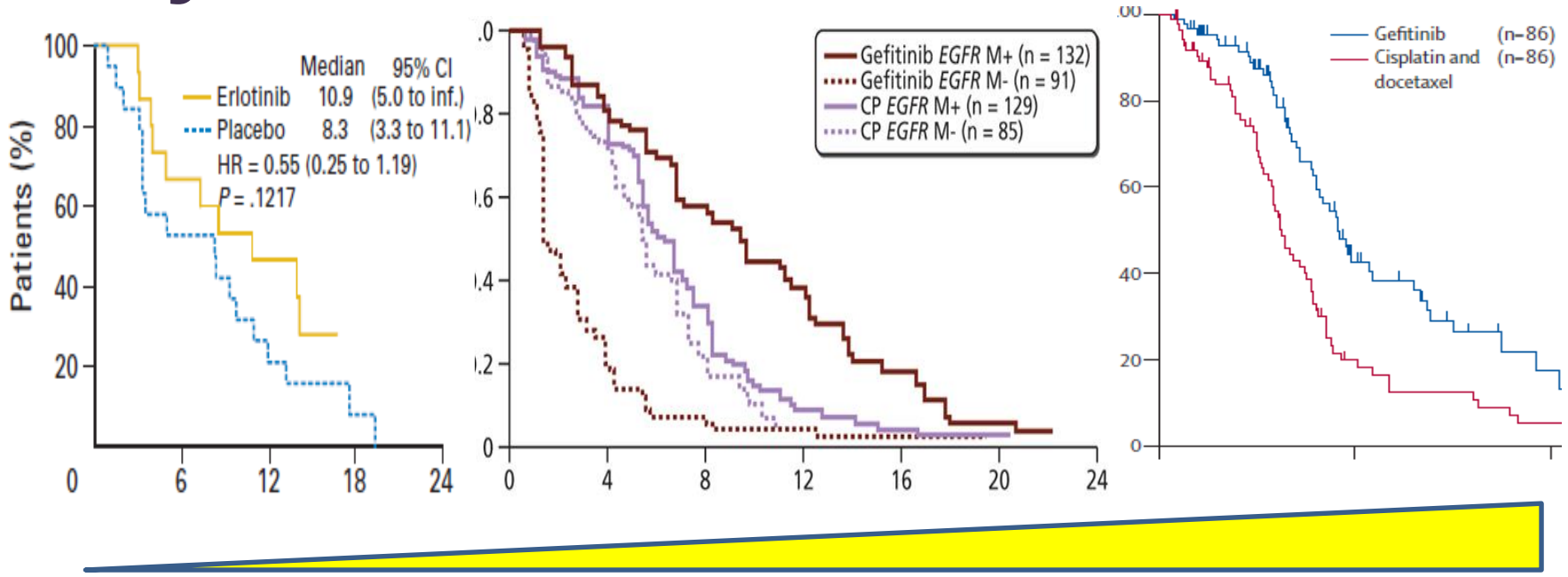
## Tissue accrual across multiple trials.



# Attrition rates in biomarker analysis: the IPASS study



# Attrition rates in biomarker analysis: BR.21, IPASS & WTOJ45

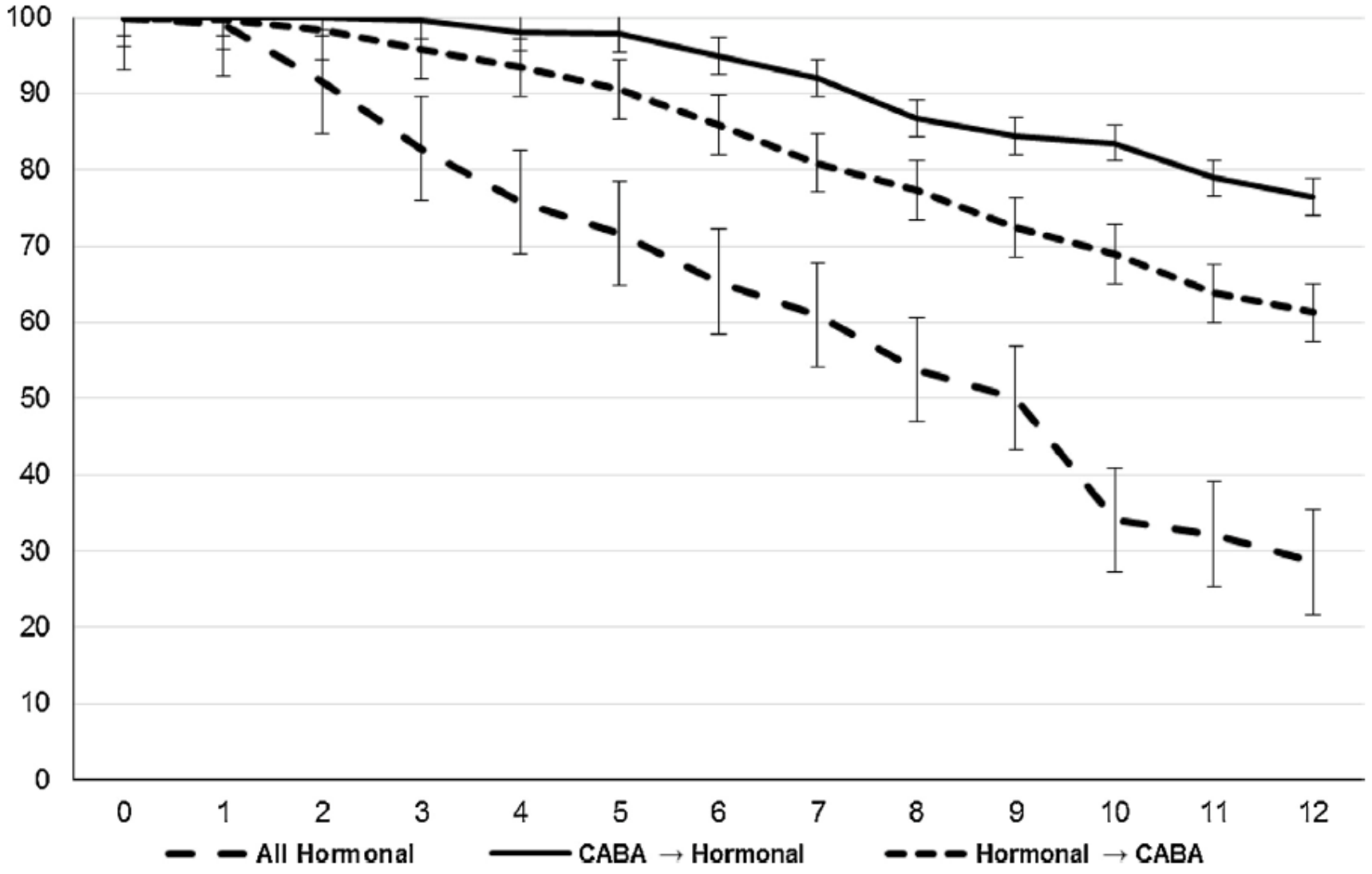



| Pts Analyzed | 20% | 36% | 100% |
|---|---|---|---|
| EGFR+ | 3% | 20% | 100% |

HIGH → LOW

VOLUME 26 · NUMBER 26 · SEPTEMBER 10 2008
JOURNAL OF CLINICAL ONCOLOGY
N Engl J Med 2009;361.
www.thelancet.com/oncology

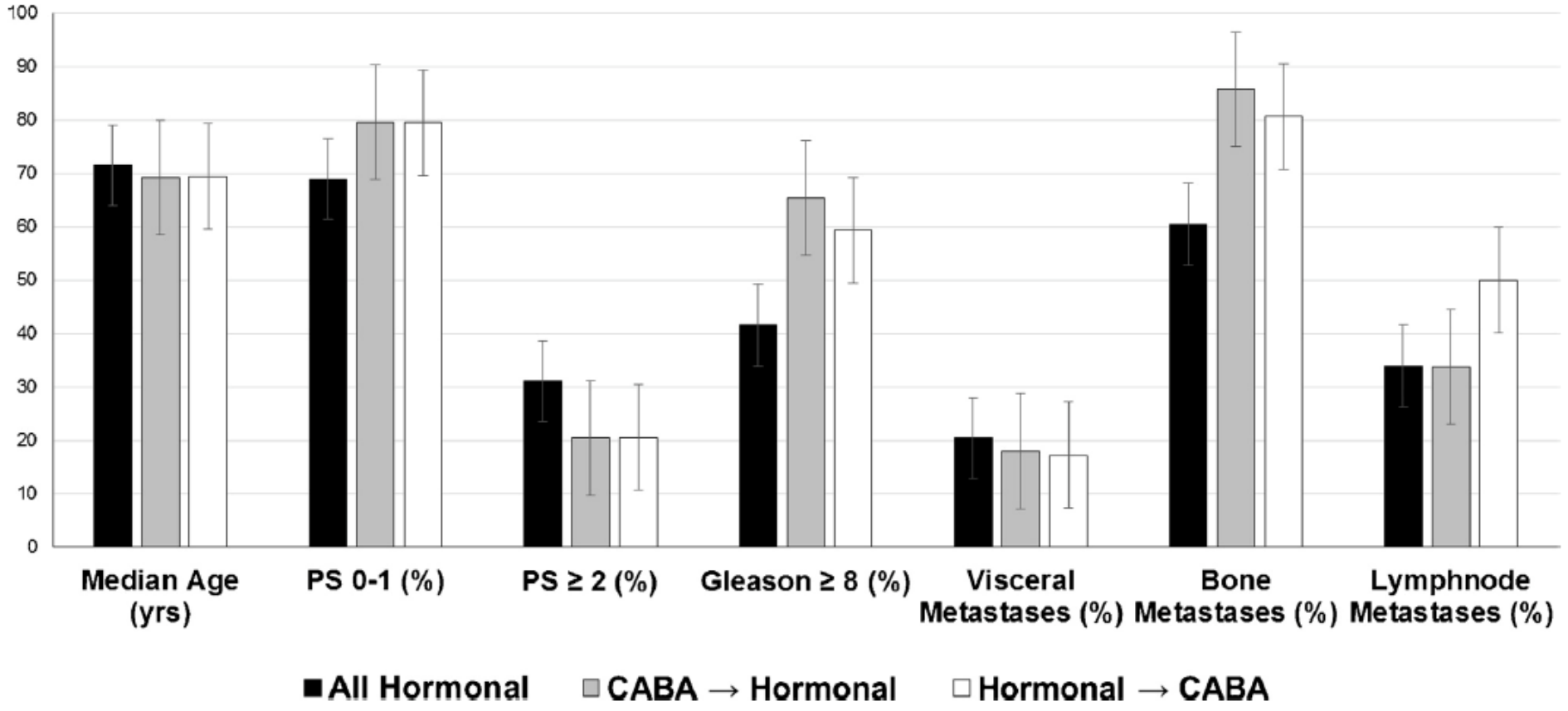
# Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer




***Maines F et al, CROH 2015***

# Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer

## Known prognostic factors according to groups




*Maines F et al, CROH 2015*

# Analysis of Observational Studies in the Presence of Treatment Selection Bias

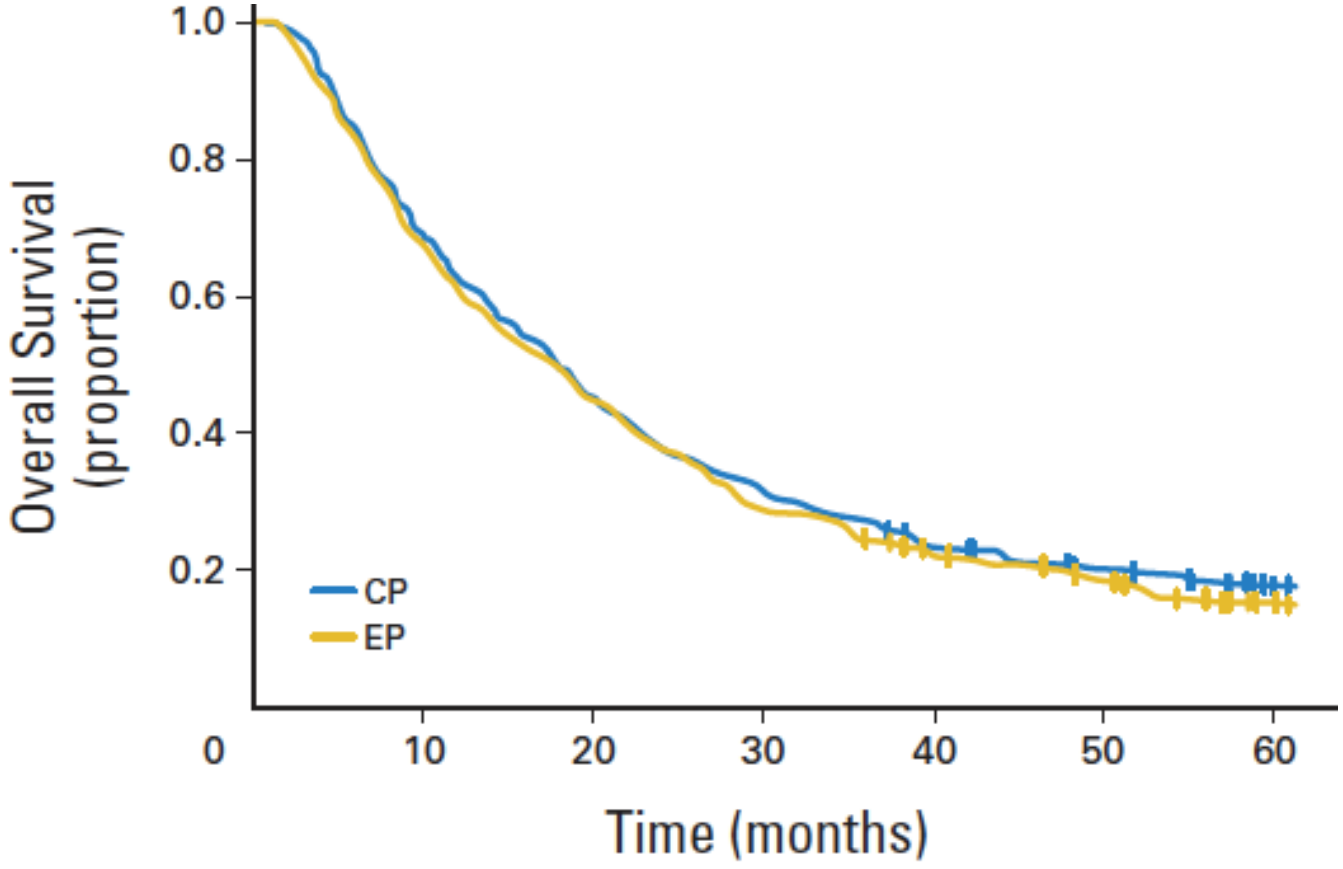

| | |
|---|---|
| Thérèse A. Stukel, PhD | David A. Alter, MD, PhD |
| Elliott S. Fisher, MD, MPH | Daniel J. Gottlieb, MS |
| David E. Wennberg, MD, MPH | Marian J. Vermeulen, MHSc |


*JAMA. 2007;297:278-285*

**Propensity Score Risk Adjustment.** The propensity score is the probability of receiving treatment for a patient with specific prognostic factors.[17-19] It is a scalar summary of all observed confounders. Within propensity score strata, covariates in treated and control groups are similarly distributed, so that stratifying on propensity score strata removes more than 90% of the overt bias due to the covariates used to estimate the score.

**Instrumental Variable Analysis.** Instrumental variable analysis is an econometric method used to remove the effects of hidden bias in observational studies. Rather than compare patients with respect to the actual treatment received since this might be biased, instrumental variable analysis compares groups of patients that differ in likelihood of receiving the treatment.

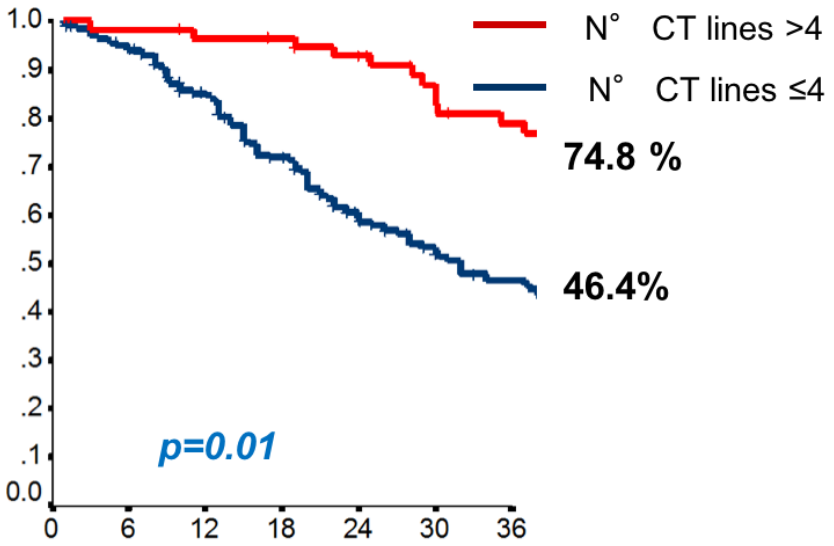
# Cisplatin and Etoposide Versus Carboplatin and Paclitaxel With Concurrent Radiotherapy for Stage III Non–Small-Cell Lung Cancer: An Analysis of Veterans Health Administration Data

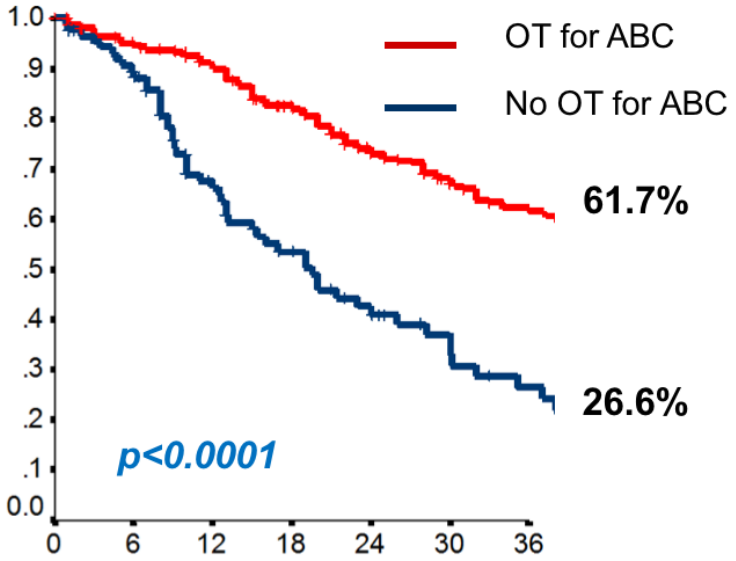


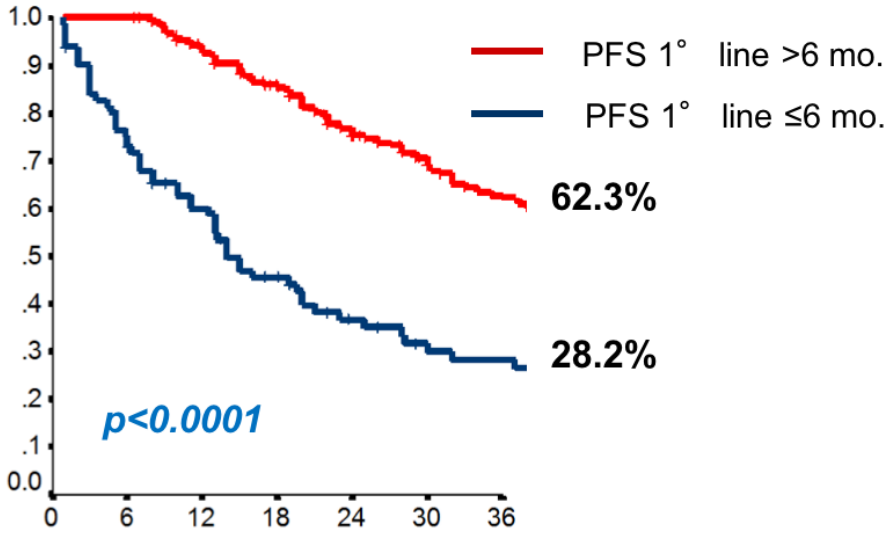

| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| CP | 381 | 262 | 172 | 119 | 87 | 69 | 49 |
| EP | 381 | 257 | 172 | 111 | 81 | 65 | 42 |

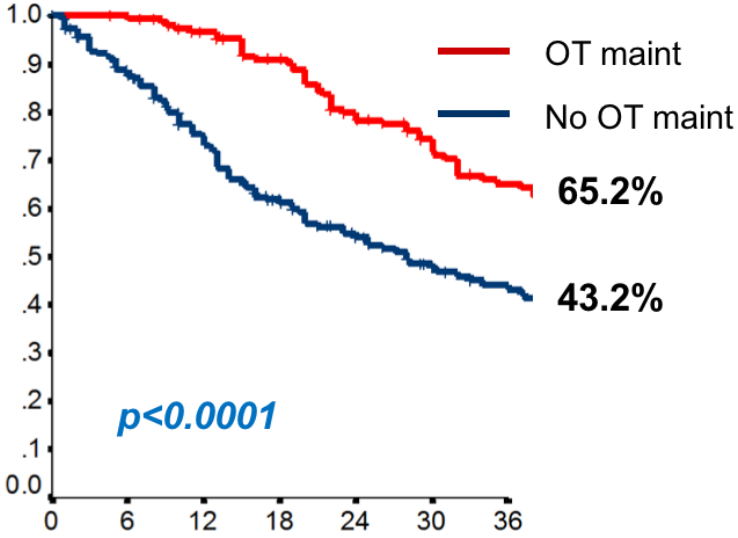
***Santana-Davila et al, JCO 2015***

# Results – OS [Treatment Variables]



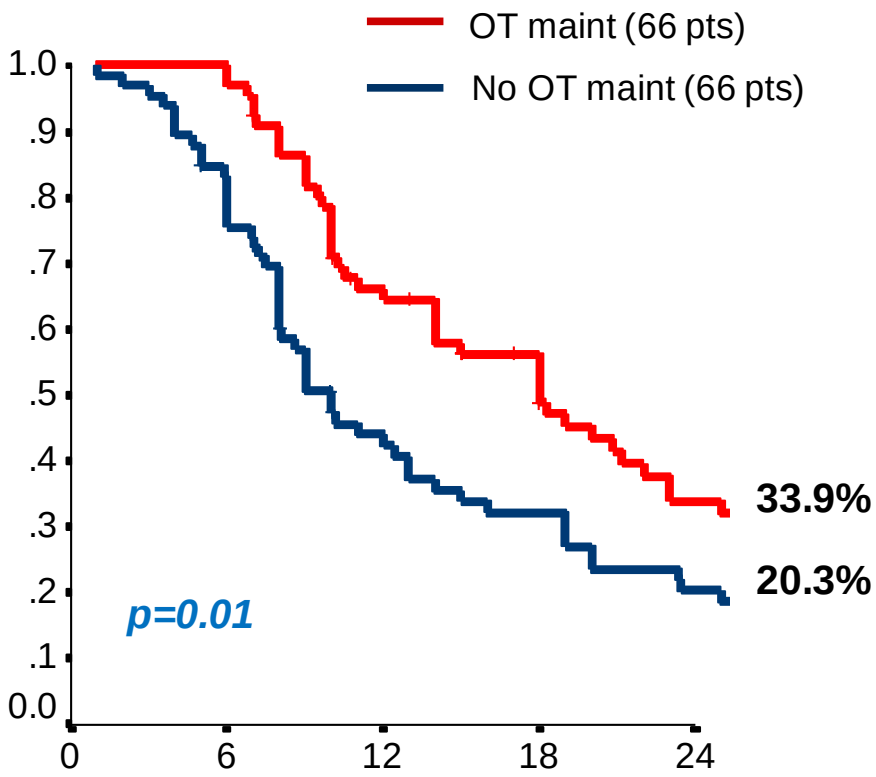




*Carbognin L et al, AIOM 2015*

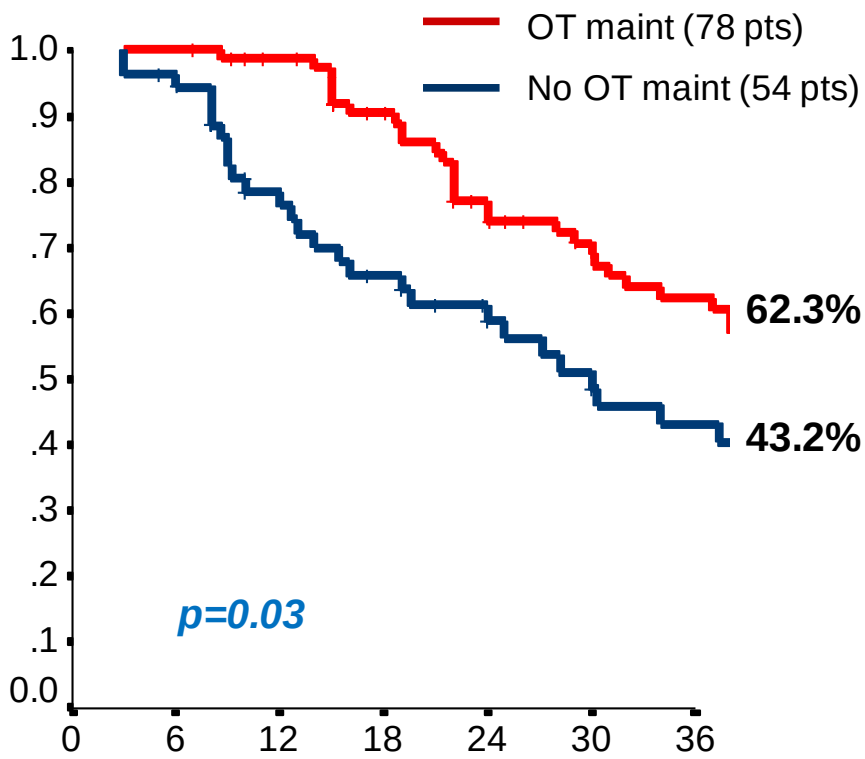
# Results - PFS & OS (Hormonal Maintenance)

## [Pts non progressive after First Line Chemotherapy]

## Exploratory Analysis




**PFS**




**OS**

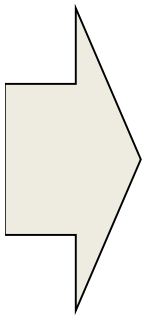
Curves adjusted for Propensity Score

*Carbognin L et al, AIOM 2015*

# A novel clinical prognostic score incorporating the number of resected lymph-nodes to predict recurrence and survival in non-small-cell lung cancer

- **Internal Model Validation:**
  - In order to address the multivariate model overfit and to validate the results, a cross validation technique which evaluates the replication stability of the final Cox multivariate model in predicting all outcomes was investigated.
    - A re-sampling procedure considering those variables independent at the multivariate analysis for at least one outcome was adopted.
    - This technique generates a number of simulation datasets (at least 100, each approximately 80% of the original size), by randomly selecting patients from the original sample, in order to establish the consistency of the model across less powered patient' samples.
    - The cross validation allows to test the accuracy of the found multivariate model.

| Variables | Top Model Mean HR | Standard Error | Replication Rate (%) |
|---|---|---|---|
| *Stage* | 2.79 | *0.04* | 100 |
| *N-status* | 1.61 | *0.02* | 39 |
| *age* | 1.66 | *0.01* | 94 |
| *#RNs* | 1.77 | *0.01* | 100 |
| *Sex* | 1.44 | *0.01* | 37 |
| *Grading* | 1.47 | *0.01* | 65 |
| *Histology* | 1.19 | *0.01* | 6 |



Risk factors

HRFs:
- Stage
- N-status
- Age
- #RNs

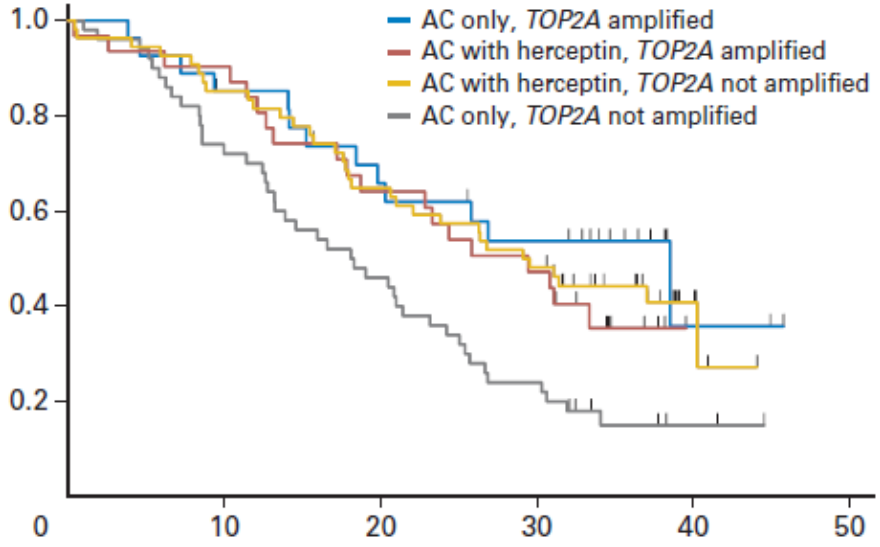
IRFs:
- Sex
- Grading
- Histology

***Bria E, Lung Cancer 2009***

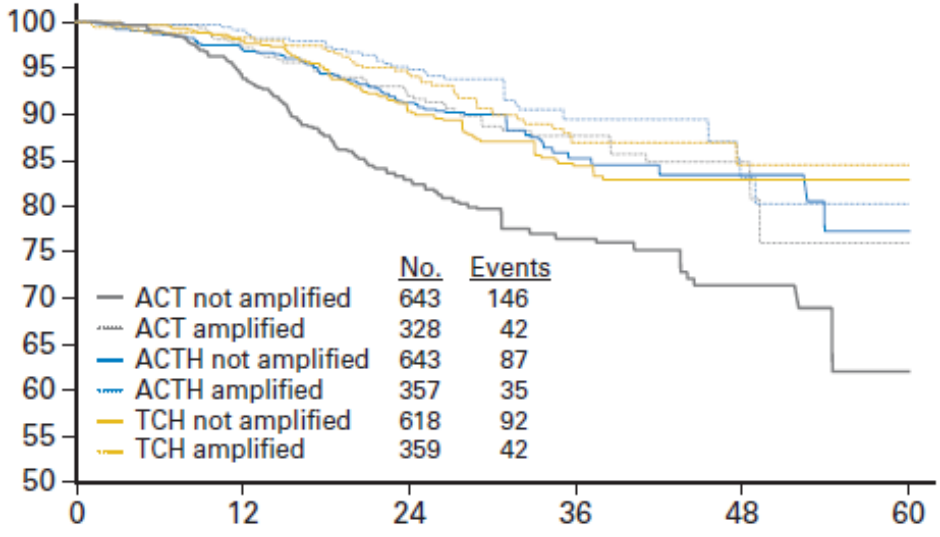
# Alteration of Topoisomerase II–Alpha Gene in Human Breast Cancer: Association With Responsiveness to Anthracycline-Based Chemotherapy

*Michael F. Press, Guido Sauter, Marc Buyse, Leslie Bernstein, Roberta Guzman, Angela Santiago, Ivonne E. Villalobos, Wolfgang Eiermann, Tadeusz Pienkowski, Miguel Martin, Nicholas Robert, John Crown, Valerie Bee, Henry Taupin, Kerry J. Flom, Isabelle Tabah-Fisch, Giovanni Pauletti, Mary-Ann Lindsay, Alessandro Riva, and Dennis J. Slamon*

**Training**




**Validation**




**Conclusion**

In a study involving nearly 5,000 breast malignancies, both test set and validation set demonstrate that *TOP2A* coamplification, not *HER2* amplification, is the clinically useful predictive marker of an incremental response to anthracycline-based chemotherapy. Absence of *HER2/TOP2A* coamplification may indicate a more restricted efficacy advantage for breast cancers than previously thought.

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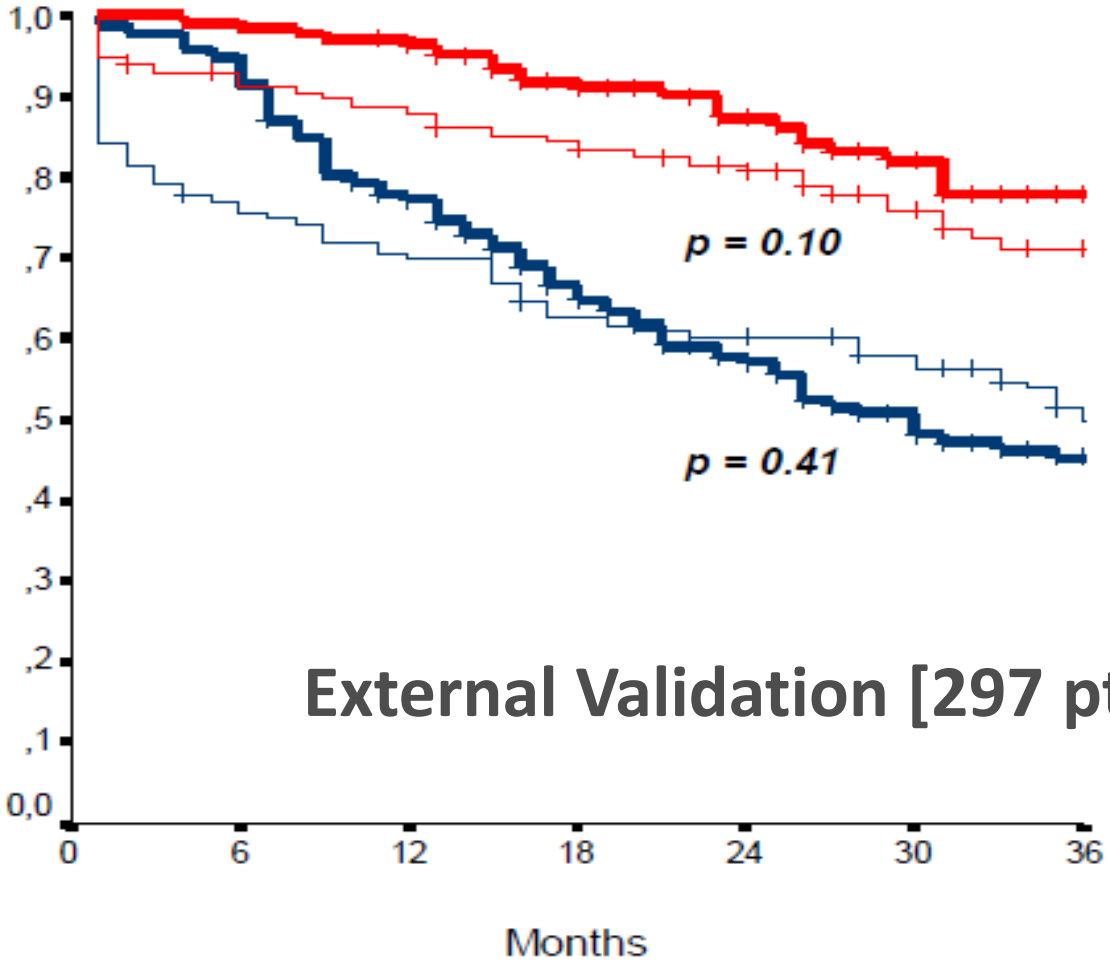
JOURNAL OF CLINICAL ONCOLOGY

A novel clinical prognostic score incorporating the number of resected lymph-nodes to predict recurrence and survival in non-small-cell lung cancer

**Figure 3b.** Overall survival (OS) at 3 years according to High- and Medium- risk-classes.




**Medium:** 78.0%
**Medium [VS]:** 71.3%

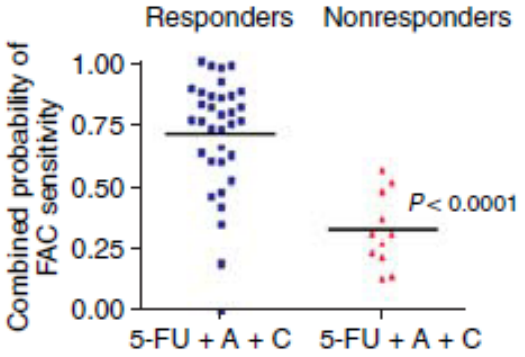
**High [VS]:** 49.8%
**High:** 45.2%

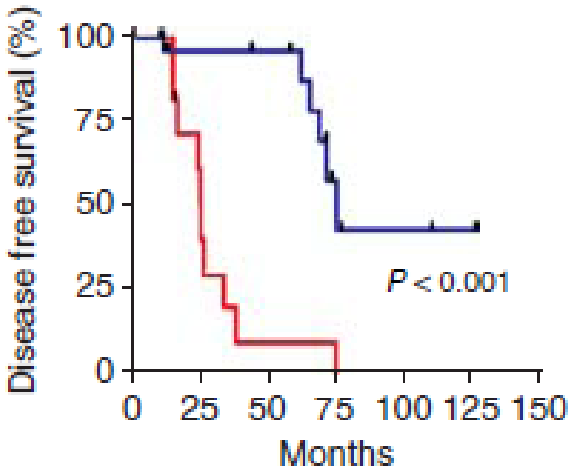
**External Validation [297 pts]**

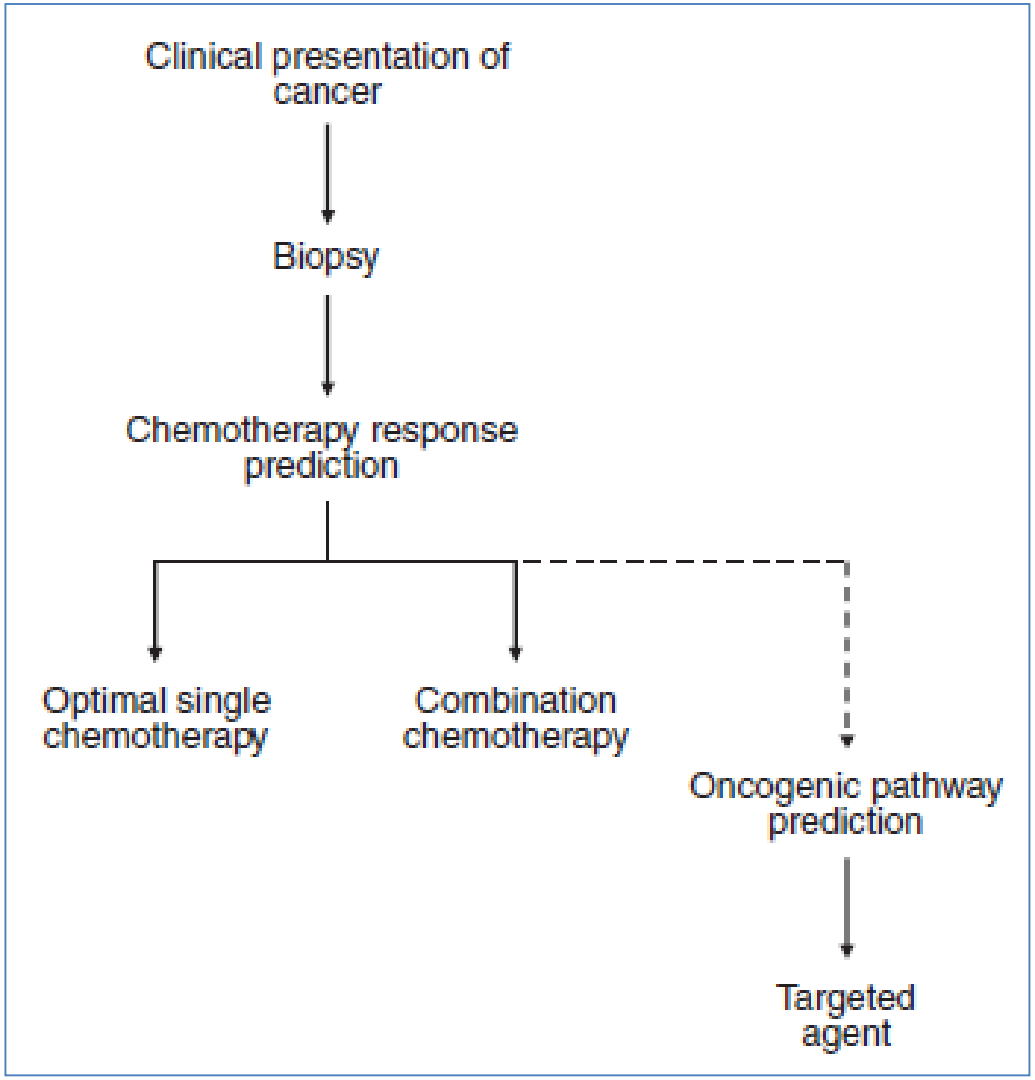
***Bria E, Lung Cancer 2009***

# Genomic signatures to guide the use of chemotherapeutics

Anil Potti[1,2], Holly K Dressman[1,3], Andrea Bild[1,3], Richard F Riedel[1,2], Gina Chan[4], Robyn Sayer[4], Janiel Cragun[4], Hope Cottrill[4], Michael J Kelley[2], Rebecca Petersen[5], David Harpole[5], Jeffrey Marks[5], Andrew Berchuck[1,6], Geoffrey S Ginsburg[1,2], Phillip Febbo[1–3], Johnathan Lancaster[4] & Joseph R Nevins[1–3]



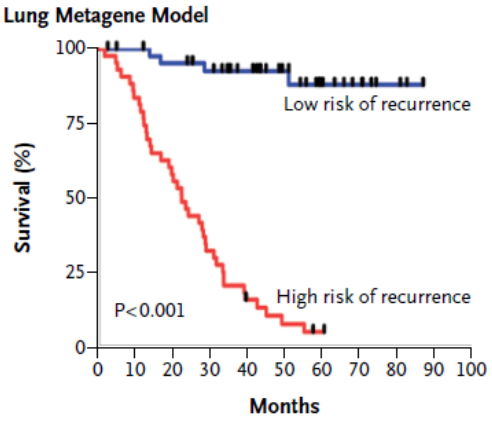



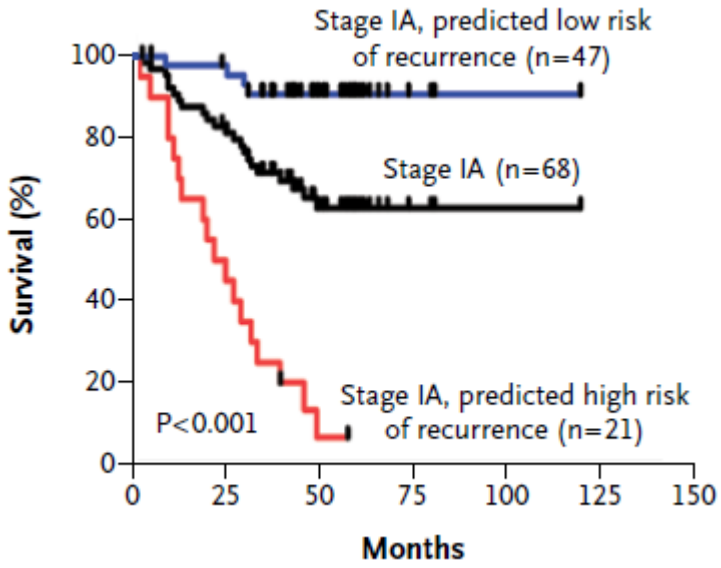



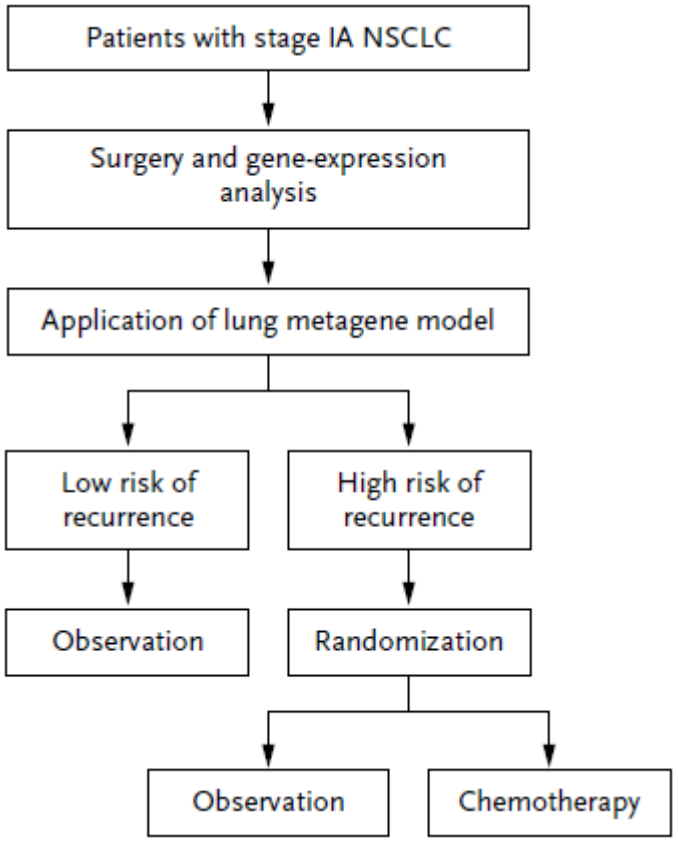

nature medicine

# A Genomic Strategy to Refine Prognosis in Early-Stage Non–Small-Cell Lung Cancer

Anil Potti, M.D., Sayan Mukherjee, Ph.D., Rebecca Petersen, M.D., Holly K. Dressman, Ph.D., Andrea Bild, Ph.D., Jason Koontz, M.D., Robert Kratzke, M.D., Mark A. Watson, M.D., Ph.D., Michael Kelley, M.D., Geoffrey S. Ginsburg, M.D., Ph.D., Mike West, Ph.D., David H. Harpole, Jr., M.D., and Joseph R. Nevins, Ph.D.

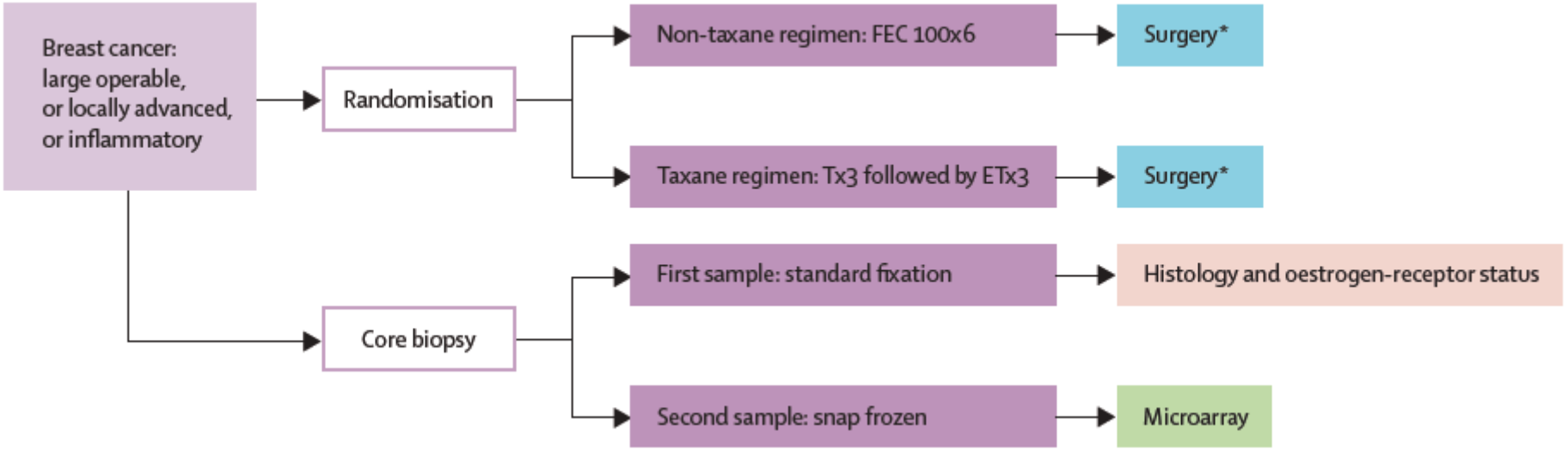


# Validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: a substudy of the EORTC 10994/BIG 00-01 clinical trial

*Hervé Bonnefoi, Anil Potti, Mauro Delorenzi, Louis Mauriac, Mario Campone, Michèle Tubiana-Hulin, Thierry Petit, Philippe Rouanet, Jacek Jassem, Emmanuel Blot, Véronique Becette, Pierre Farmer, Sylvie André, Chaitanya R Acharya, Sayan Mukherjee, David Cameron, Jonas Bergh, Joseph R Nevins, Richard D Iggo*




| | FEC group | | TET group | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| Size T3 *vs* T1 and T2 | 0·77 (0·25–2·33) | 0·62 | 0·26 (0·06–0·96) | 0·03 |
| Grade 1 and 2 *vs* 3 | 0·39 (0·11–1·35) | 0·11 | 0·67 (0·16–2·54) | 0·56 |
| Nodal status 1 and 2 *vs* 0 | 0·87 (0·29–2·64) | 0·81 | 0·57 (0·17–1·87) | 0·42 |
| *ERBB2* status A *vs* N* | 1·76 (0·44–7·33) | 0·37 | 0·95 (0·28–3·21) | 1·00 |
| Age older *vs* younger† | 1·63 (0·55–4·95) | 0·46 | 1·41 (0·45–4·49) | 0·60 |
| FEC signature‡ | 8·65 (2·55–33·84) | 0·0001 | 2·10 (0·67–6·87) | 0·20 |
| TET signature‡ | 2·72 (0·90–8·61) | 0·08 | 14·76 (3·78–70·24) | <0·0001 |

Lancet Oncol 2007; 8: 1071–78

Expression of concern—validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: a substudy of the EORTC 10994/BIG 00-01 clinical trial

**RETRACTION**

Retraction: Genomic signatures to guide the use of chemotherapeutics

**Retraction: A Genomic Strategy to Refine Prognosis in Early-Stage Non–Small-Cell Lung Cancer. N Engl J Med 2006;355:570-80.**

**Retraction—validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: a substudy of the EORTC 10994/BIG 00-01 clinical trial**

**TO THE EDITOR:** We would like to retract our article, "A Genomic Strategy to Refine Prognosis in Early-Stage Non–Small-Cell Lung Cancer,"[1] which was published in the *Journal* on August 10, 2006. Using a sample set from a study by the American College of Surgeons Oncology Group (ACOSOG) and a collection of samples from a study by the Cancer and Leukemia Group B (CALGB), we have tried and failed to reproduce results supporting the validation of the lung metagene model described in the article. We deeply regret the effect of this action on the work of other investigators.

# Varmus's Second Act

*"There's an imbalance between the money available, the work that needs to be done, and the number of people who would need to be supported to make the world feel like a more comfortable place."*

***Varmus H, Science 2013***