MADRID 2014 ESMO Congress
Joint ESMO-ASCO Symposium
The evolution of the clinical trial landscape
September 29, 2014

The evolution of clinical trials in oncology: Randomised controlled trials to real world studies

Gary H Lyman, MD, MPH, FRCP, FASCO
Co-Director, Hutchinson Institute for Cancer Outcomes Research
Fred Hutchinson Cancer Research Center and
Professor of Medicine, Public Health, and Pharmacy
University of Washington, Seattle, WA, USA

Disclosure slide

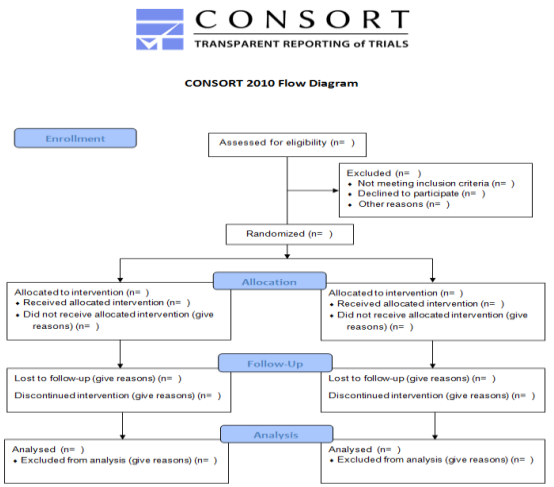
- No relevant conflicts to disclose

History of Clinical Trials

- Comparative experiments mentioned as far back as the Old Testament and the ancient Persians.
- First systematic clinical trial to prevent scurvy (1747)
- Principles of experimental design (RA Fisher 1920s)
- Randomized experiments first appeared in psychology, education and agriculture
- First published RCT (1948): MRC study of Streptomycin in TB
- Concepts of modern RCT further developed by Austin Bradford Hill and others

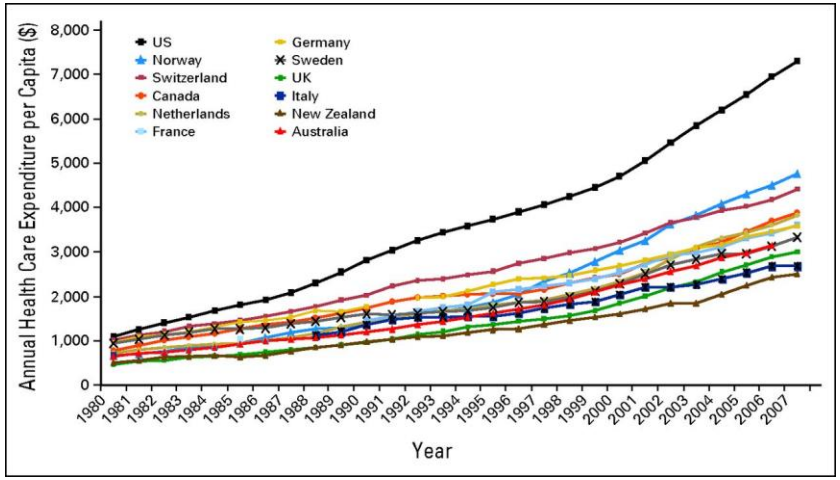
History of Clinical Trials

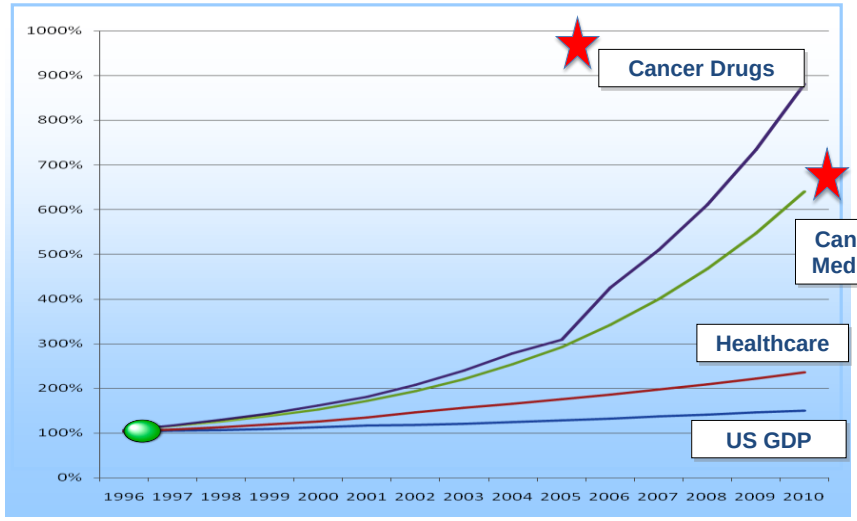
- As goals/limitations identified, many variations developed:
  - **By design:** parallel; cross over; cluster; factorial; single blind/double blind; placebo controlled
  - **By phase:** 0 – 4
  - **By hypothesis:** superiority; non-inferiority; equivalence
  - **By randomization:** simple; restricted; cluster; nested
  - **By blinding:** Open; single blind; double blind; triple blind
  - Other variants: LSTs; pragmatic trials; adaptive; enrichment etc.
- **CONSORT:** *Consolidated Standards of Reporting Trials:*
  - now broadly accepted



Challenges in Modern Healthcare

- Information explosion & rapid developments in IT
  - → information overload
  - → availability of 'big data'
- Rapid rise in cost of healthcare
  - Aging of Population
  - Emerging MDx/MPx tests & Targeted Therapies
  - Advanced Imaging
- Limited improvement in health outcome measures





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Comparative Effectiveness Research

- Rigorous evaluation of evidence directly comparing the benefits, harms and overall value of alternative interventions.
- Determine which interventions work for which patient in a real world setting.
- Core question of comparative effectiveness research:

"Which treatment works best, for whom, and under what circumstances"

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Official Journal of the American Society of Clinical Oncology

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Guest Editor: G.H. Lyman

Consultant Editor: M.N. Levine

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Lyman GH et al: *J Clin Oncol* 2012; 30: 4181-4184

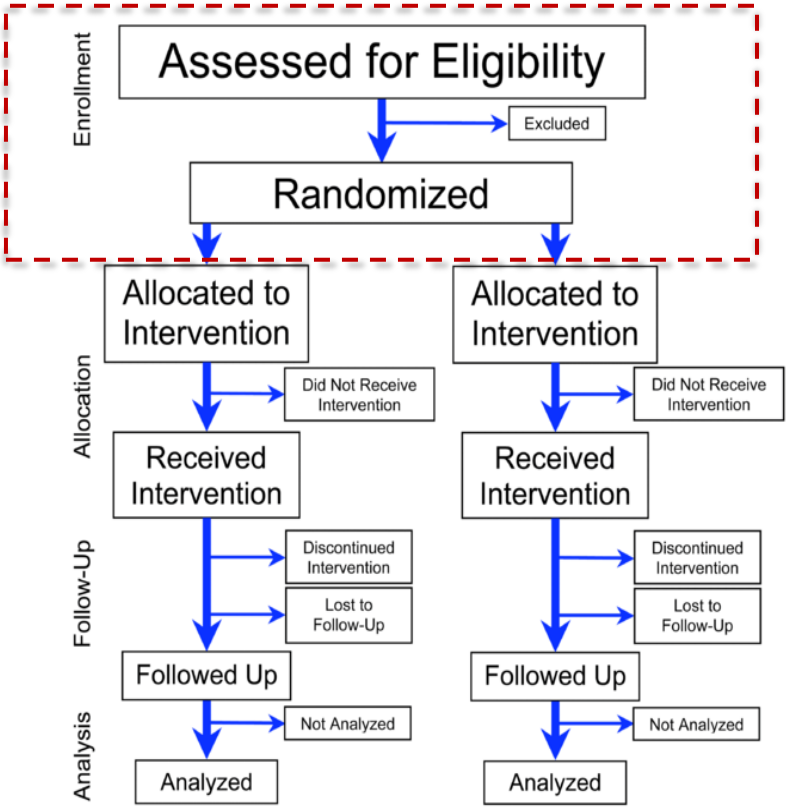
Comparative Effectiveness Research

Toolbox

- **Randomized controlled trials (RCTs)**
- **Systematic reviews and meta-analyses**
- **Observational studies**
  - Retrospective: Registries and administrative and claims data
  - Prospective: Cohort studies and rapid learning systems
- **Risk, prognosis and prediction studies**
  - Precision and genomic medicine
- **Clinical simulation studies**
  - Clinical decision models
  - Cost-effectiveness and cost utility analyses
  - Quality of life studies including PROs

Key Strengths of RCTs

- **Minimize selection bias:** balances known and unknown covariates on average across treatment groups.
- **Internal validity:** accurate measures of efficacy within selected population under ideal conditions.
- **Validity of statistical tests** are assured without additional assumptions due to independence of observations

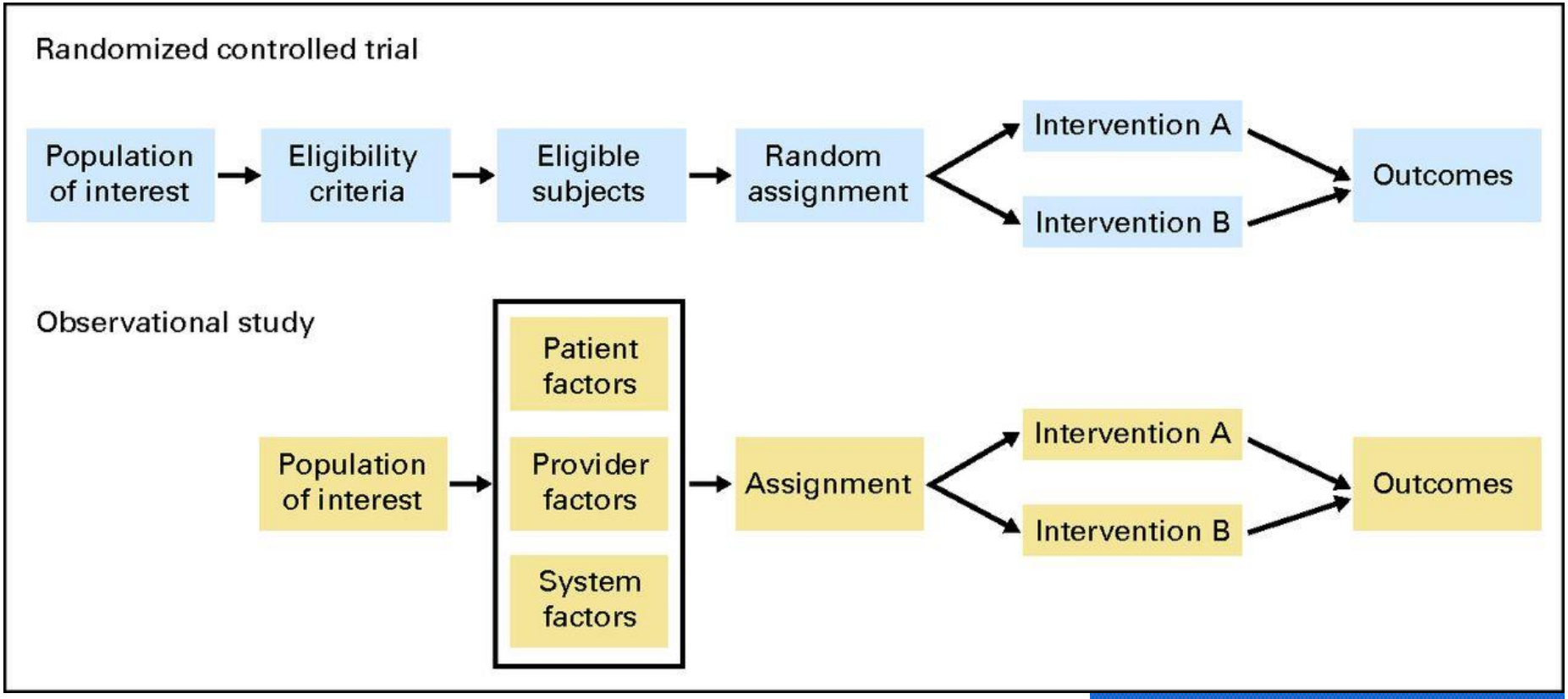


Key Limitations of RCTs

- **Limited external validity:**
  - ➢ poor generalizability due to narrow eligibility criteria
- **Limited info on vulnerable subgroups:** elderly; comorbidities
- **Feasibility and ethical issues**
- **Costly:** time and resources
- **Treatment imbalance by chance**
- **Limited attention to toxicities:**
  - ➢ especially rare/delayed effects
  - ➢ not powered for toxicity events

Kuderer N, Wolff A: JCO 2014 32: 1990-1993
Booth CM, Tannock IF: BJC 2014; 110: 551-555

Experimental & Observational Study Designs



Armstrong K JCO 2012;30:4208-4214

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RCTs or Observational Studies

Trait	RCTs	OSs
Bias	Low	High
Resources: Time, $	High	Low
Causal inference	High	Low
Transportability	Low/Medium	High
Reporting biases	Low/Medium	High
Real world: Interventions, outcomes, comparators	Low	High
Patient Centered	Low	High
Data quality	High	Low
Ethicality	Low	High
Sample Size	Low/medium	High

The Balancing Act

Strong internal validity

Balanced groups

Outcomes clearly defined

Defined treatment alternatives

Limited patient population

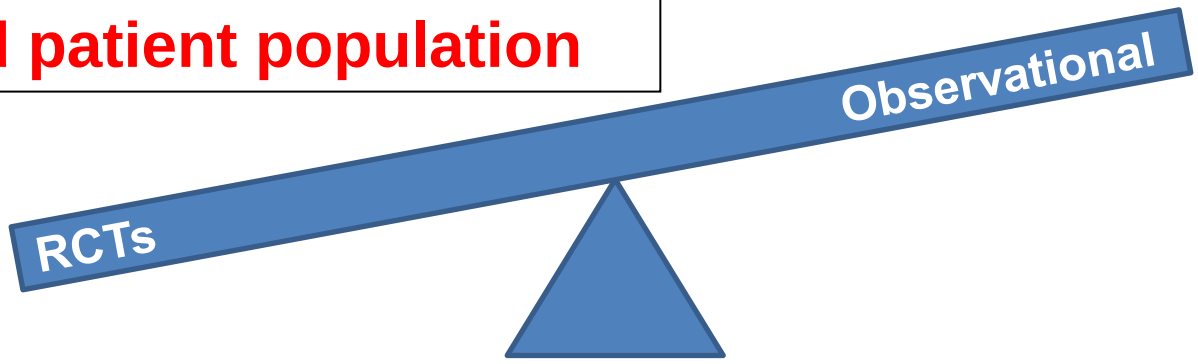
Longer follow-up

Strong external validity

Real world settings

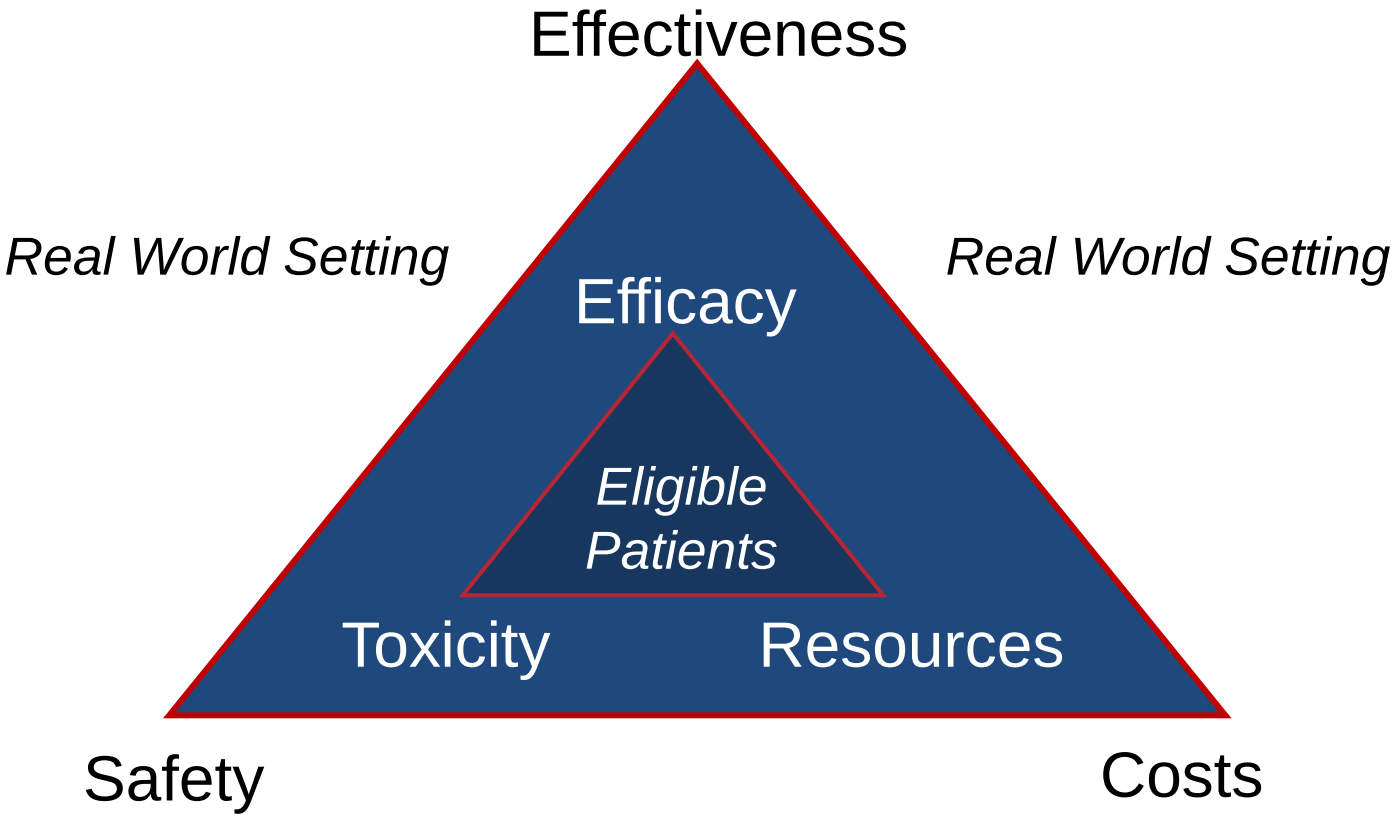
Large sample size

Confounded



Efficacy versus Effectiveness

Outcome Measures



Efficacy: *Can it work?*
Effectiveness: *Does it work; is it safe; is it better, is it worth it?*

Luce BR et al: The Milbank Quarterly 2010; 88: 256-276

Randomized Controlled Trials

The Changing Landscape

Secondary Analyses of RCTs

Targeted or Enrichment Designs

Adaptive RCTs

Cluster RCTs

Pragmatic RCTs

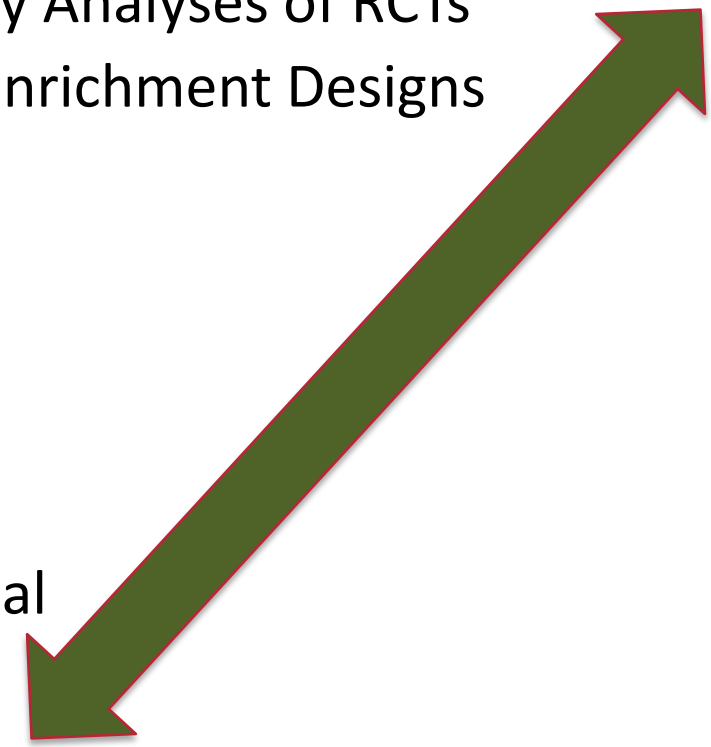
Large, Simple RCTs

Relax Eligibility Criteria

Classical Randomized Controlled Trial

Clinical Trial Registries

Meta-Analyses of RCTs (PRISMA)



Observational Studies

The Changing Landscape

Big Data and Rapid Learning Systems

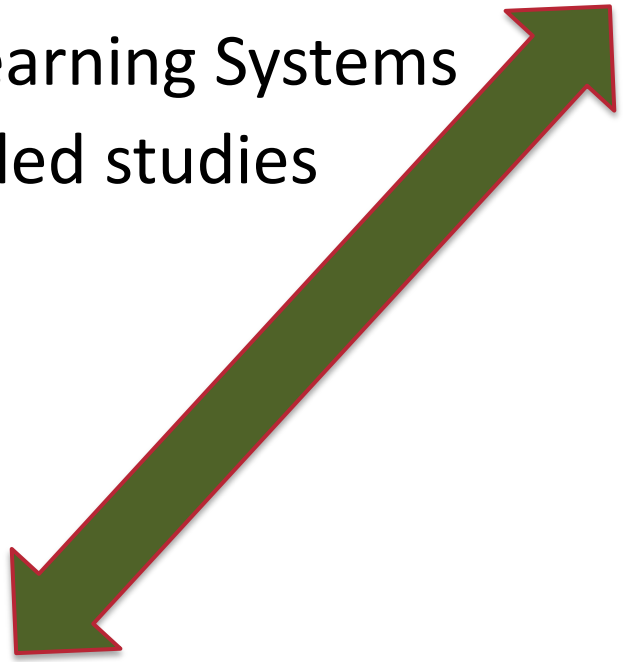
Non-randomized controlled studies

Cohort Studies

Population Studies

Cancer Registries

Administrative and Claims Databases

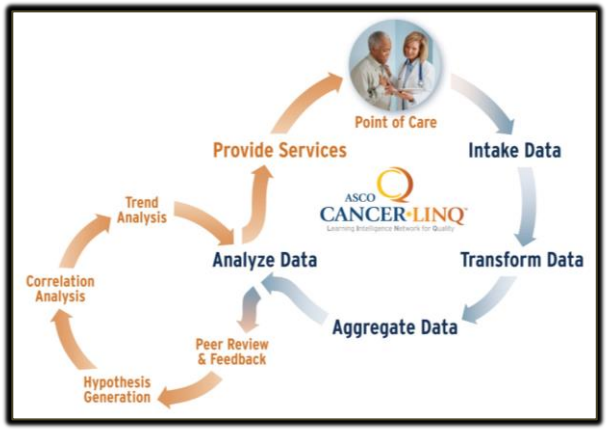


Big Data & Rapid Learning Healthcare

Opportunities and Challenges

- Potential Advantages
  - **Synchronized EHRs** adaptable to rapid pace of increasing evidence
  - Improve quality of **patient care**
  - Enhance **clinical research** including data mining
  - Potential for integration of CDS systems
- Challenges:
  - **Data limitations**: data is observational
    - Data quality (missing values)
    - Confounding of treatment selection and outcomes
  - **Analytic limitations**

ASCO CANCER·LINQ™
Learning Intelligence Network for Quality



Must avoid the temptation to assume that observational data gathered electronically in great quantities and processed rapidly are necessarily better or more reliable

Ginsburg G S, Kuderer N M JCO 2012;30:4233-4242

Methods to Improve Observational Studies

Statistical Adjustment

- Proper cohort selection
- Matching
- Regression-Based Risk Adjustment
- Propensity Score Analysis
  - Multivariable scoring collapses observed predictors into one value
  - Used in matching, stratification, regression & weighting
- Instrumental Variable Analysis
  - Instrument variables randomly associated with individual case
  - Correlated with treatment but not with outcomes
  - Attempts to control for unobservable differences in groups

Similar rigor in design, conduct, analysis, and reporting including statistical oversight as that applied in RCTs

Methods to Improve Observational Studies

Standardization of Methods and Reporting

- **STROBE:** Strengthening the Reporting of Observational Studies in Epidemiology Recommendations
- **GRACE:** Good Research for Comparative Effectiveness Principles
- **ENcEPP:** European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Methodological Standards
- **Editorial guidance:** major medical journals
- **Protocol & *a priori* statistical analysis plan:** similar to RCTs
  - Population, endpoints, objectives, hypothesis, adjustments, and statistical methods (missing data, subgroups, and methods for addressing potential confounding and interaction)

Lyman GH et al: J Clin Oncol 2012; 30: 4181-4184

Biomarker Studies

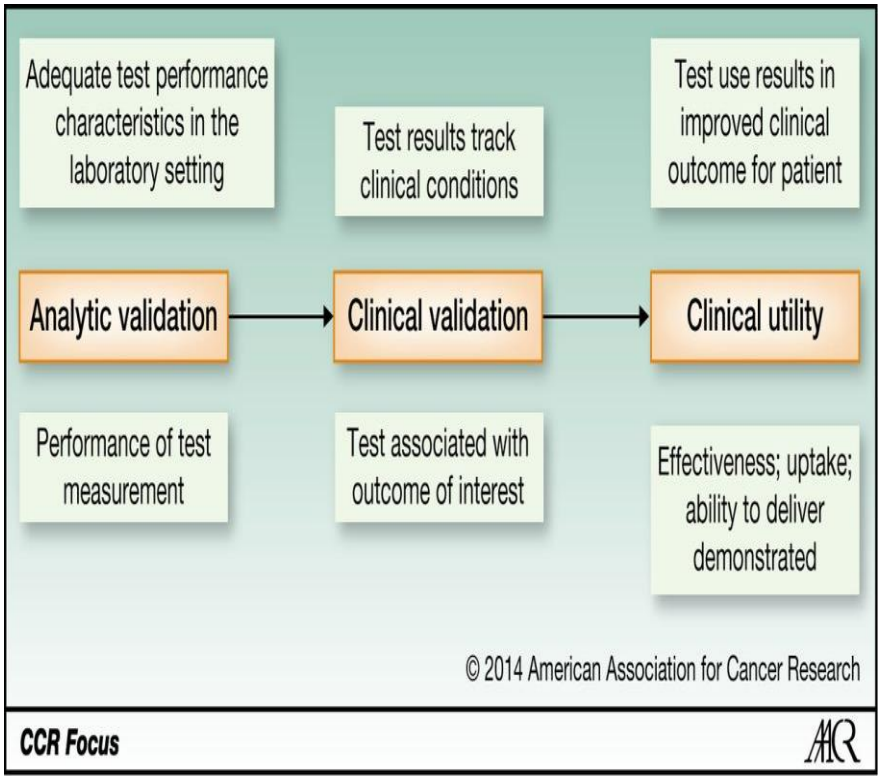
Levels of Evidence

Level	Definition
I	Prospective, Marker Primary Objective, Well-powered trial or meta-analysis
II	Prospective, Marker Secondary Objective
	MOST BIOMARKER STUDIES
III	Retrospective, Outcomes, Multivariate Analysis
IV	Retrospective, Outcomes, Univariate
V	Retrospective, Correlation with Other Markers No Outcomes

Hayes, et al; *JNCI* 88:1456, 1996

Predictive/prognostic molecular biomarkers
Clinical Utility

1. Greater methodologic rigor & standardization of reporting
2. Evaluate in cohorts independent of those utilized for development
3. Clinical utility further assessed in effectiveness studies compared to available clinical/laboratory measures

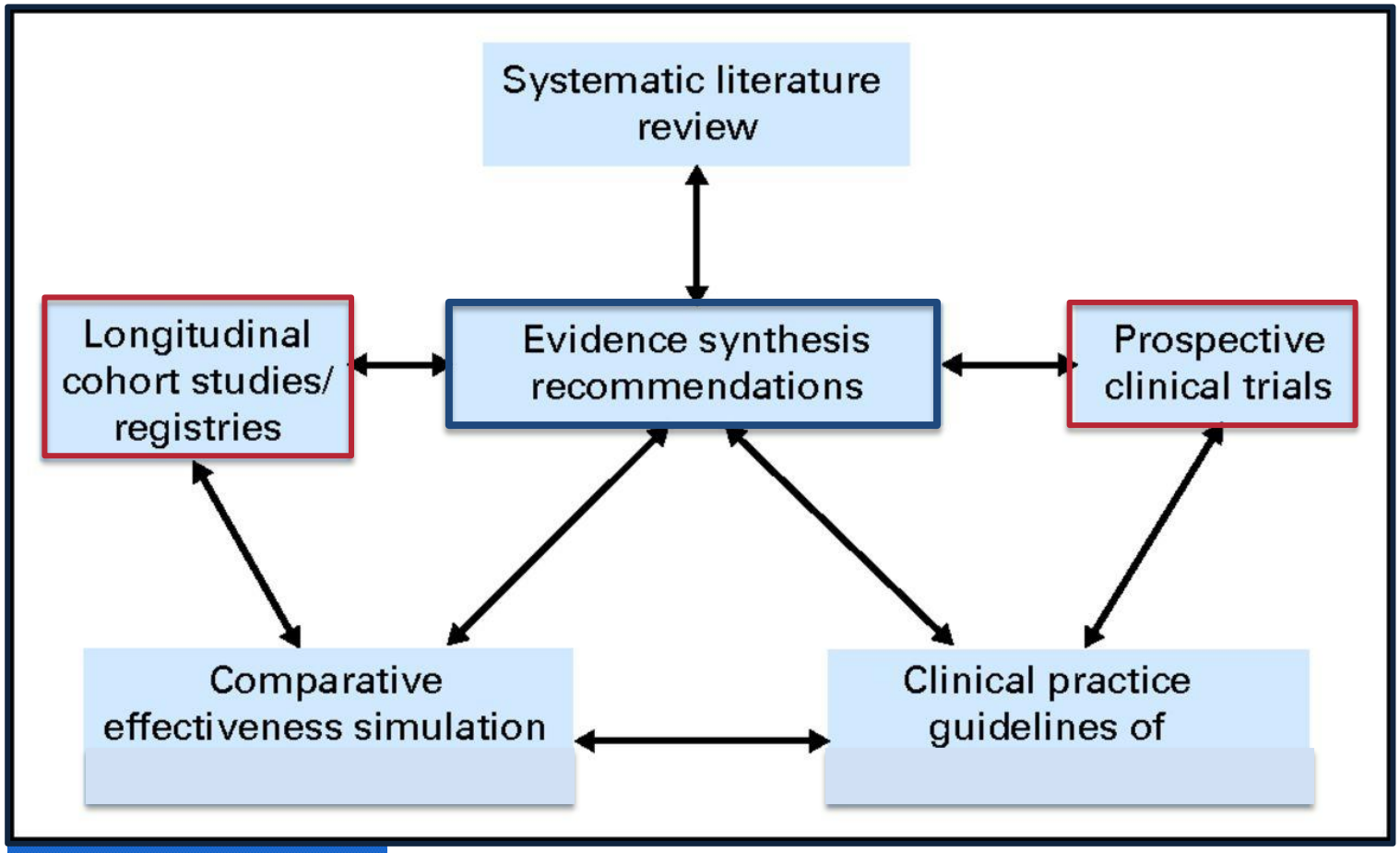


Parkinson D R et al. CCR 2014;20:1428-1444

http://www.cmtpnet.org/effectiveness-guidance-documents/molecular-diagnostics-egd/

Comparative Effectiveness Research

Evidence Sources



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Ginsburg GS , Kuderer NM JCO 2012;30:4233-4242

CONCLUSIONS

- **Challenges:** information explosion; new tests/agents rising costs
- **Changing Landscape:** New trial designs and methodologies for both RCTs and observational CER
- **RCTs:**
  - Remains gold standard for efficacy
  - Toxicity secondary and often underestimated
  - Need for novel, clinically relevant, pragmatic RCTs
  - Generalizability, duration and costs remains challenges
- **Observational Research:**
  - More generalizable & captures delayed/less common events
  - Data quality & confounding remain challenge for efficacy
  - Need for better methodologies and data sources:
- ***Optimal CER needs high quality, valid evidence from BOTH RCTs and observational studies***


Thank You

FRED HUTCHINSON
CANCER RESEARCH CENTER

UNIVERSITY OF WASHINGTON
LVX SIT
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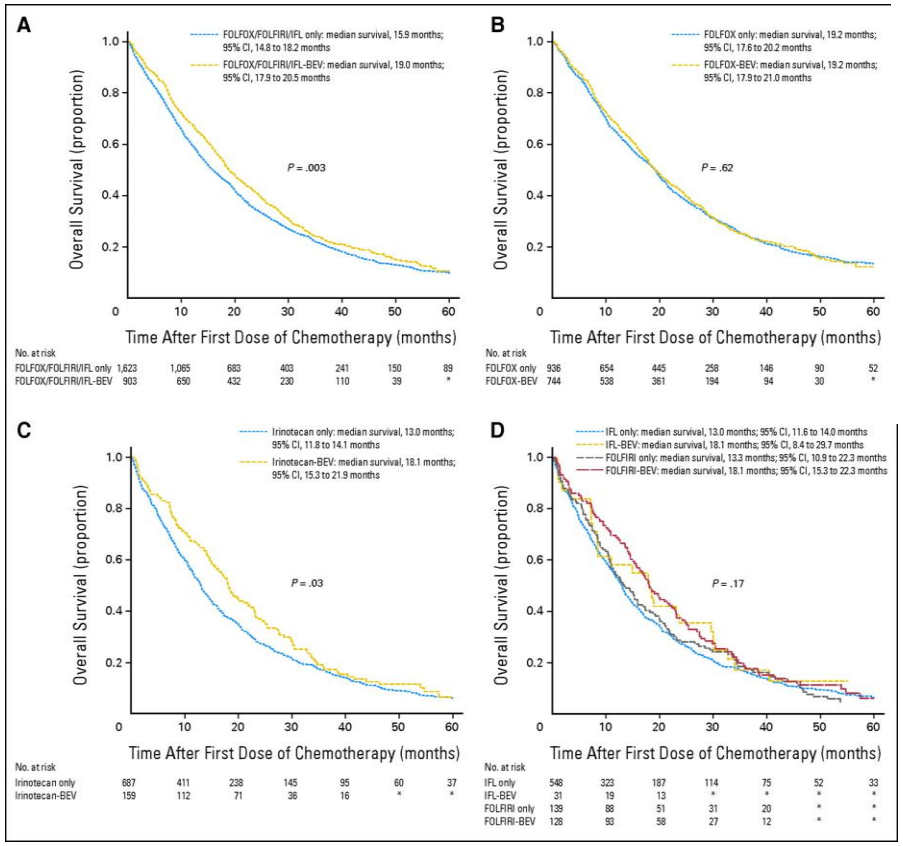
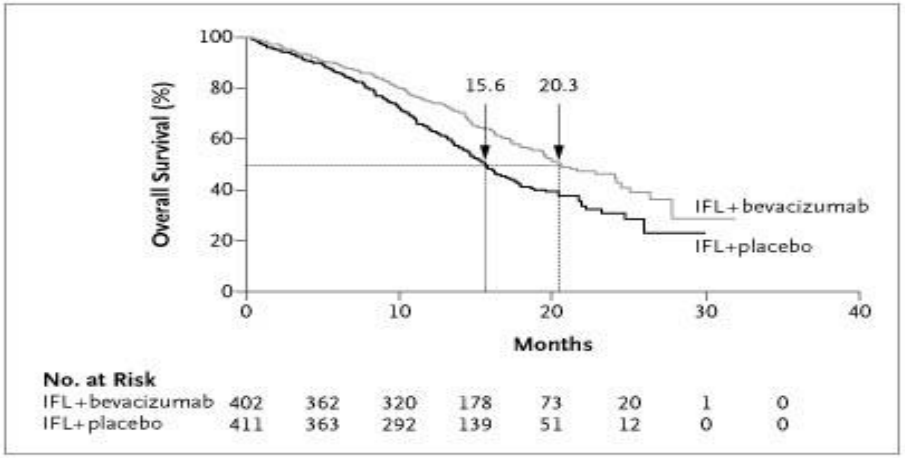
Efficacy Based on Observational Data

SEER-Medicare Data

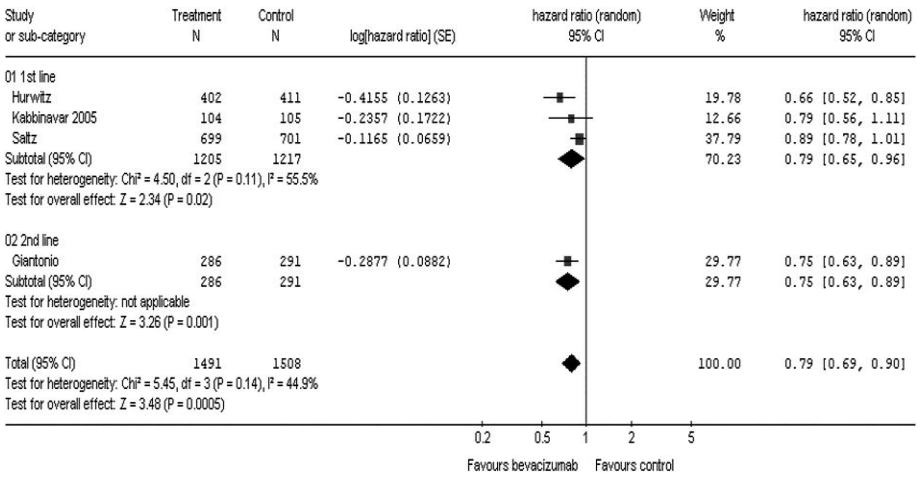


Meyerhardt J A et al. JCO 2012;30:608-615

Randomized Controlled Trials



Hurwitz, H. et al. NEJM 2004;350:2335-2342

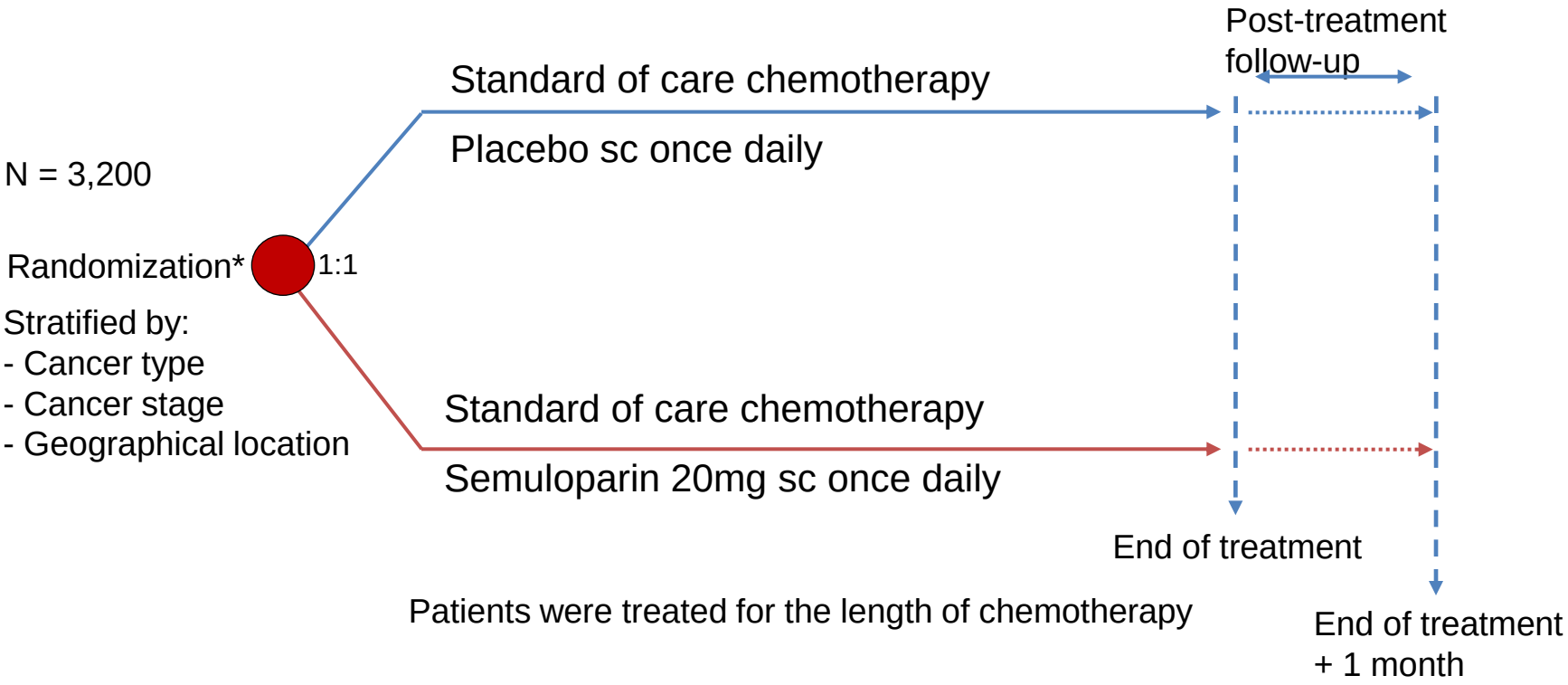


Welch S et al. Ann Oncol 2010;21:1152-1162

SAVE-ONCO Study

Study Design

Multinational, randomized, double-blind, parallel-group study



* metastatic or locally advanced solid tumor of lung, pancreas, stomach, colon/rectum, bladder or ovary initiating a chemotherapy regimen with a minimum treatment intent of 3 months

Agnelli et al: NEJM 2012; 366: 601-609

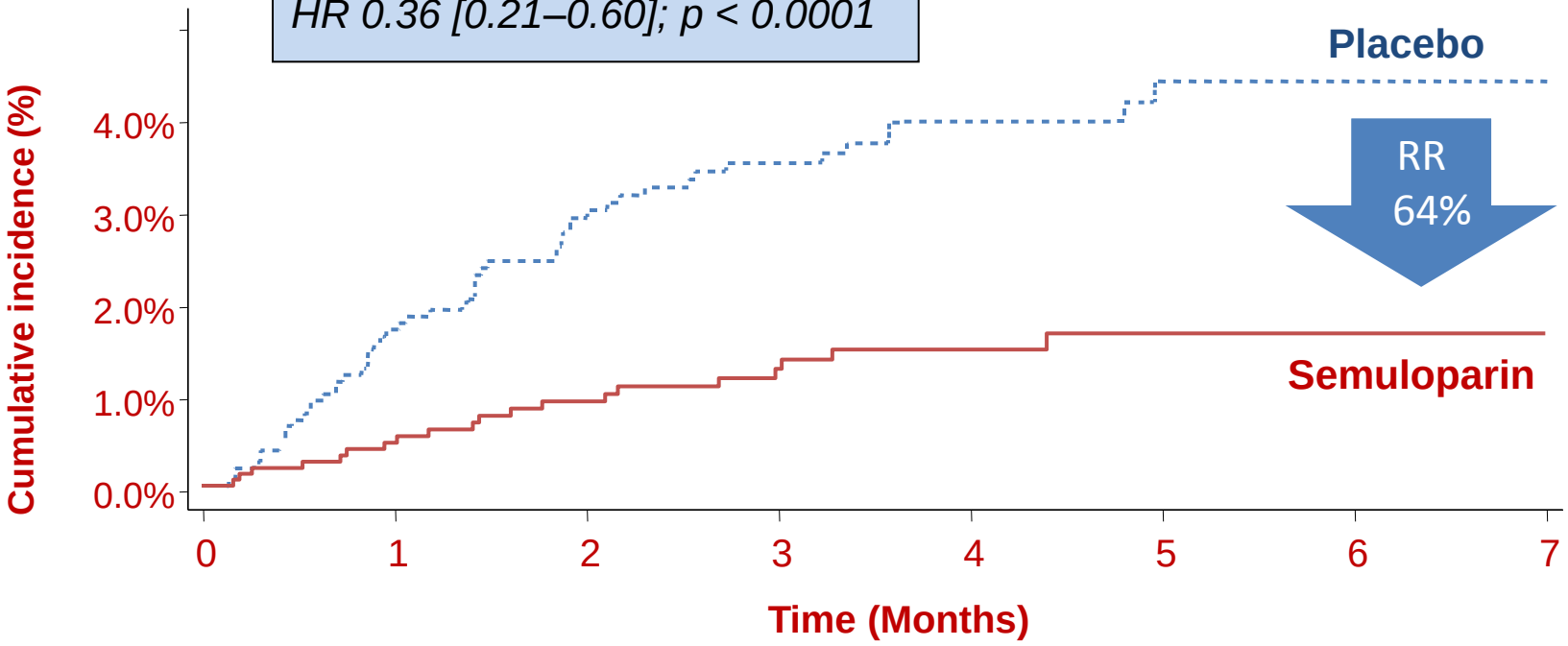
Primary efficacy endpoint

Composite of symptomatic DVT and any PE

Placebo 3.4% (55/1,604)

Semuloparin 1.2% (20/1,608)

HR 0.36 [0.21–0.60]; p < 0.0001



Placebo	1,604	1,375	1,212	985	689	403	201	92
Semuloparin	1,608	14,10	1,227	986	681	384	197	77

Agnelli et al: NEJM 2012; 366: 601-609

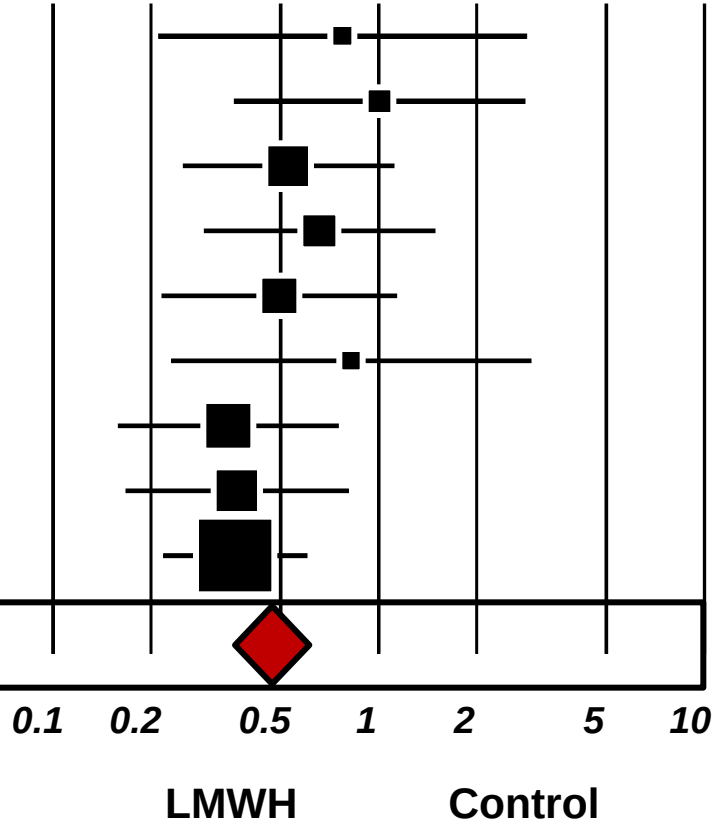
LMWH Prophylaxis in Cancer Patients

Venous Thromboembolism: Relative Risk

	Relative Risk	Lower limit	Upper limit	p-Value
FAMOUS	0.775	0.211	2.840	0.700
TOPIC-1	1.006	0.360	2.808	0.991
TOPIC-2	0.529	0.251	1.111	0.093
PRODIGE	0.659	0.292	1.489	0.316
PROTECHT	0.495	0.217	1.132	0.096
SIDERAS	0.824	0.231	2.938	0.765
CONKO004	0.345	0.159	0.752	0.007
FRAGEM	0.367	0.168	0.806	0.012
SAVEONCO	0.363	0.218	0.602	<.001
Combined	**0.471**	**0.362**	**0.613**	**<.001**

Statistics for each study

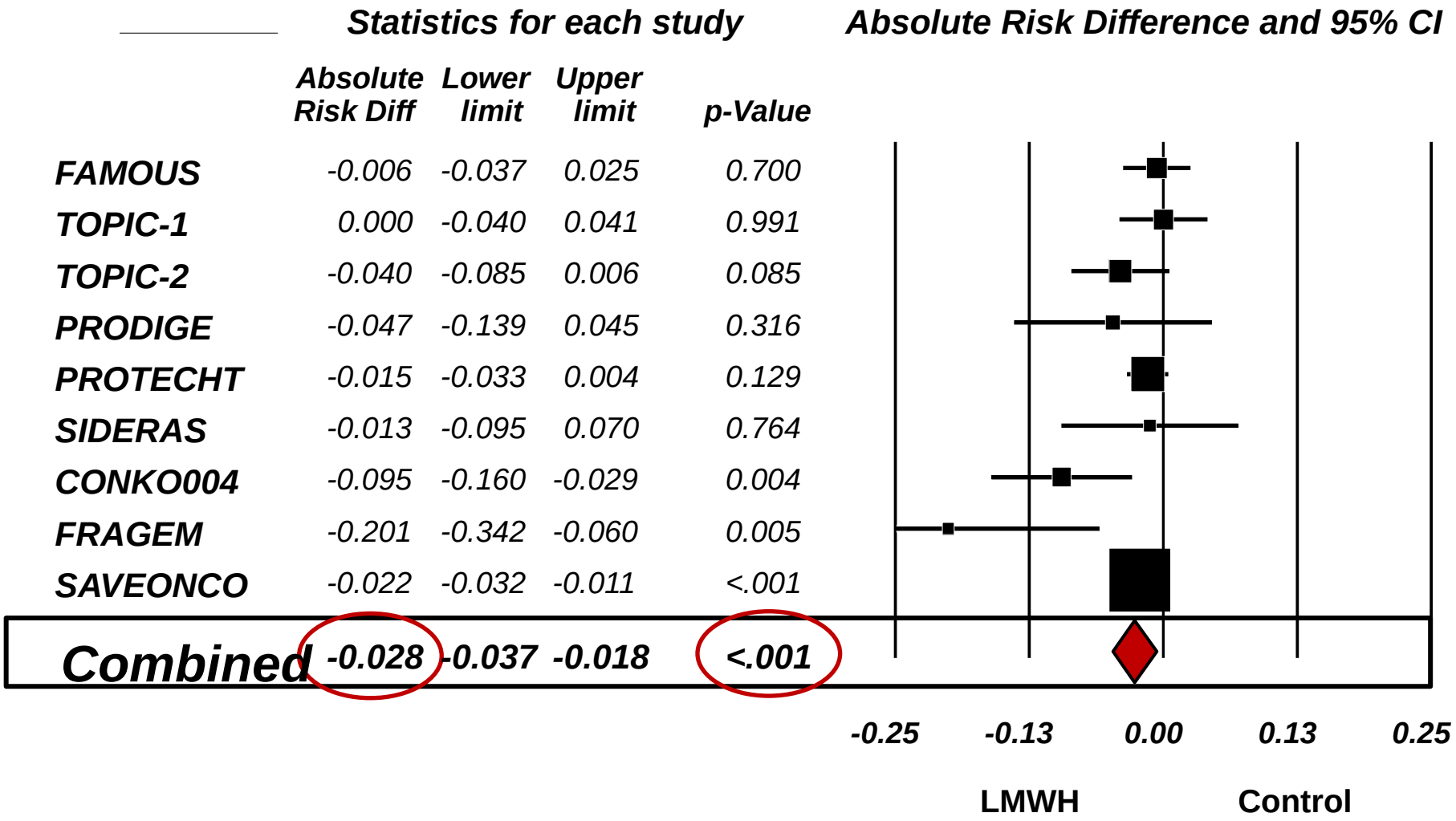
Relative Risk and 95% CI



Modified from Kuderer NM et al. *ASH* 2009

LMWH Prophylaxis in Cancer Patients

Venous Thromboembolism: Absolute Risk



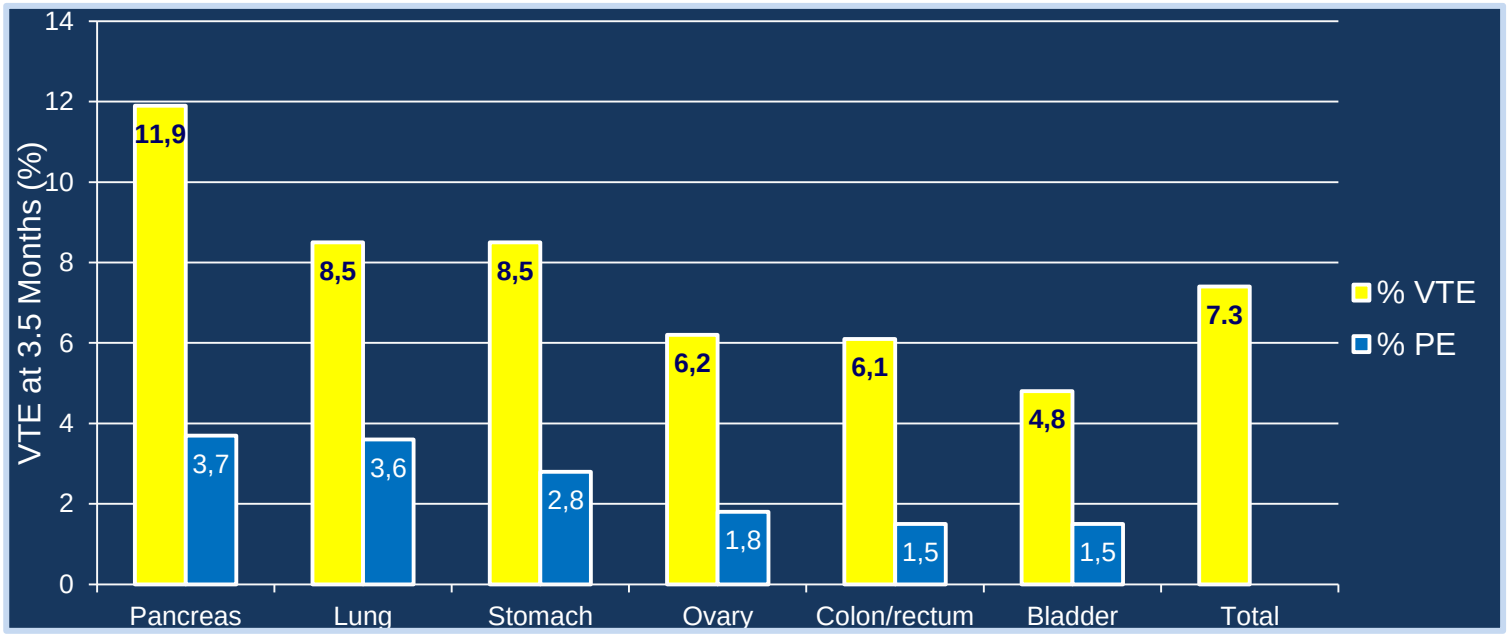
VTE and Site of Cancer

Population data from US Healthcare Database

US Impact database: national database of complete medical records on over 100 million individuals with managed care health plans.

30,552 patients with lung, pancreatic, stomach, colon/rectum, bladder or ovarian cancer initiating chemotherapy between January 1, 2005 and December 31, 2008.

Patients with ≥12 months of coverage prior to the index date and without prior VTE, major bleeding, or recent anticoagulant treatment were included.



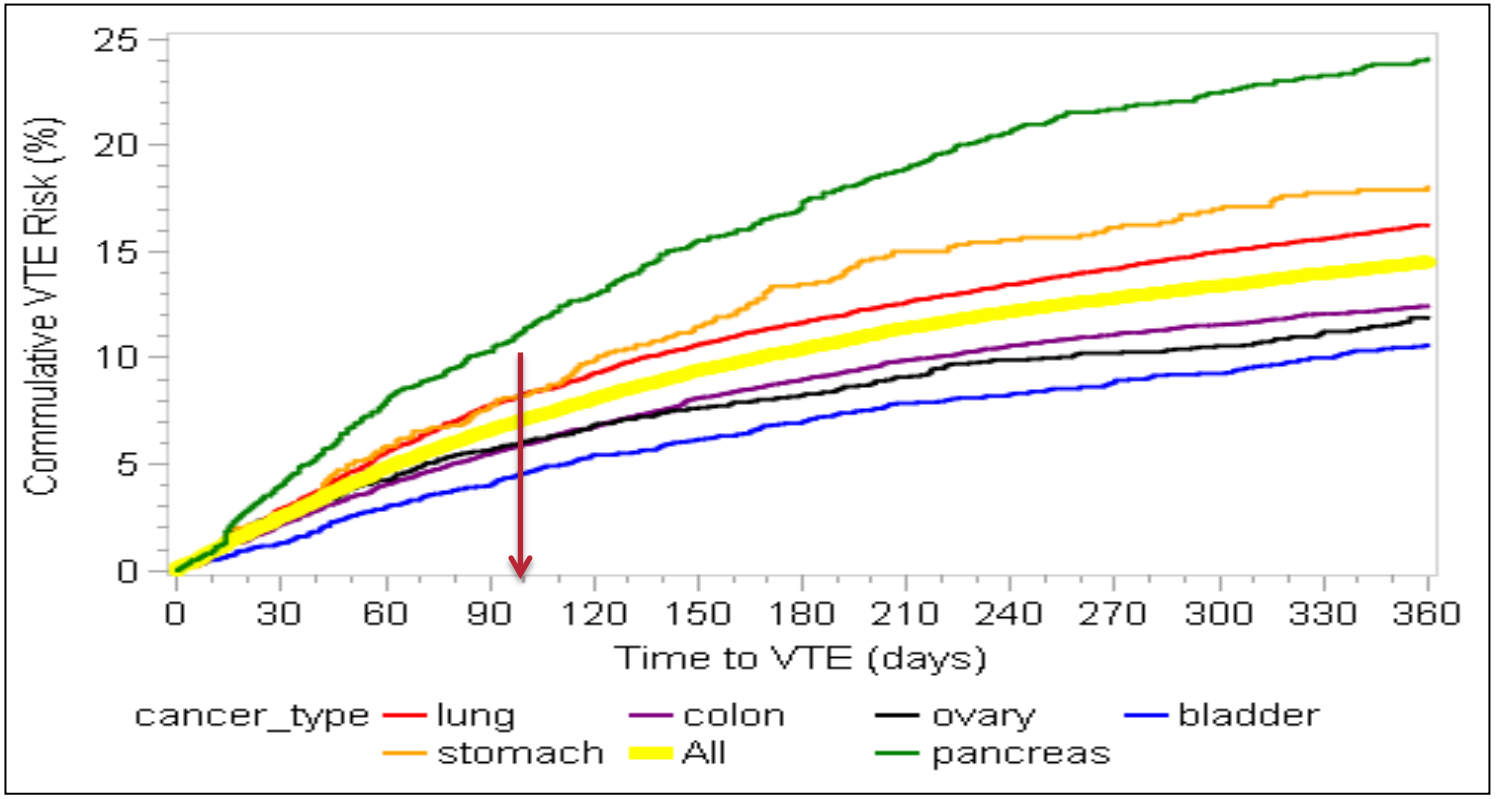
Lyman, GH et al: The Oncologist 2013; 18: 1321-1329

VTE and Site of Cancer

Risk of VTE in Cancer Patients Receiving Chemotherapy

US Impact database: complete medical records >100 million individuals

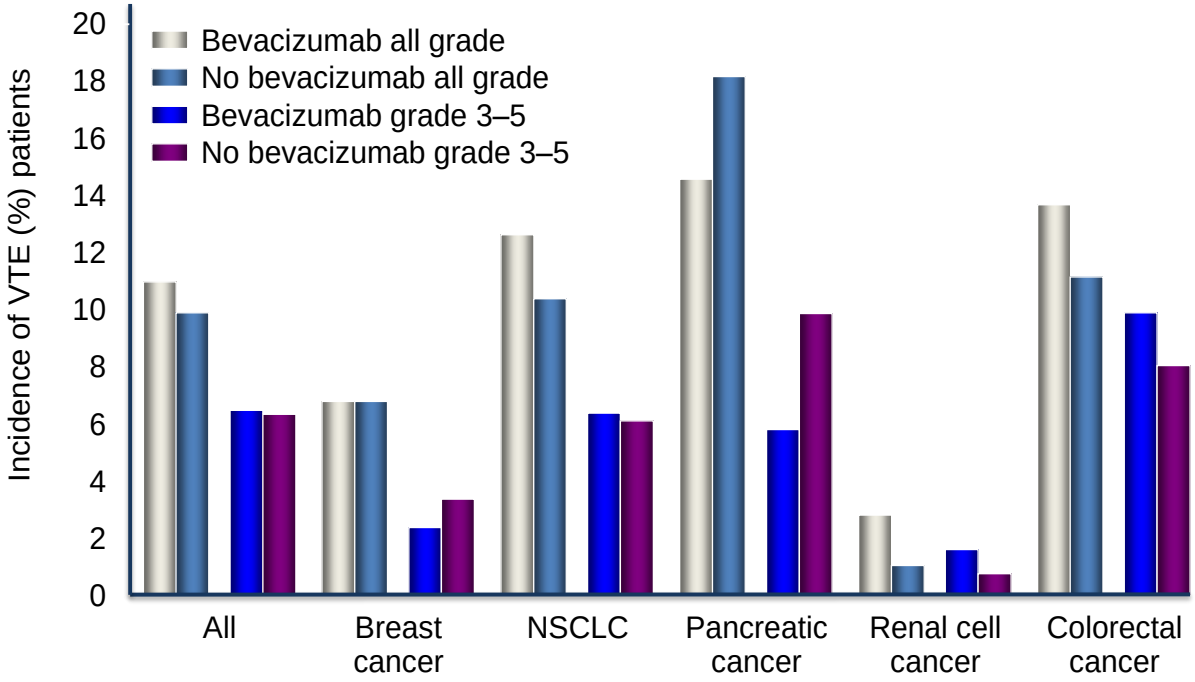
30,552 lung, pancreatic, stomach, colon/rectum, bladder or ovarian cancer pts initiating chemotherapy between January 2005 and December 2008

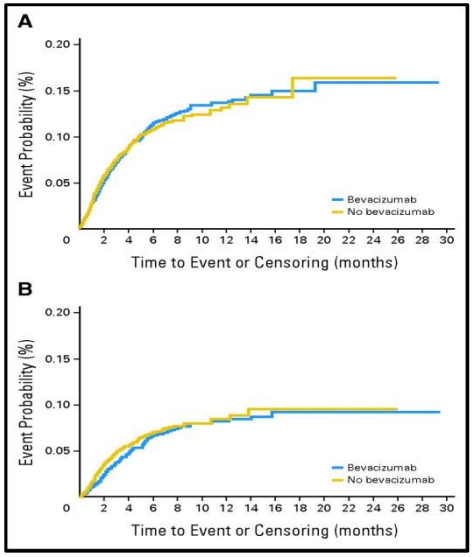


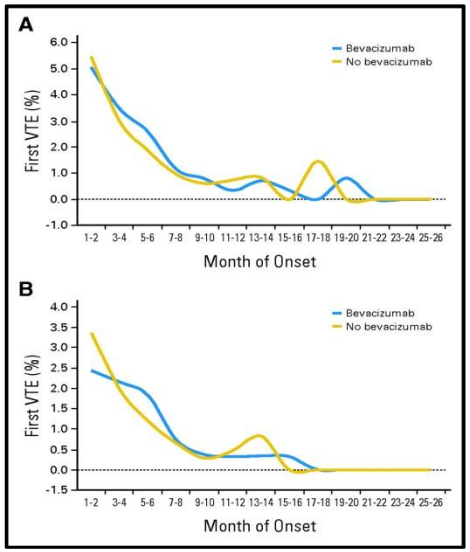
Lyman, GH et al: *The Oncologist* 2013; 18: 1321-1329

Risk of VTE Across RCTs

IPD Meta-Analysis of Data from 10 RCTs of Bevacizumab







Hurwitz HI, et al. J Clin Oncol. 2011;29:1757-64.

Lyman G H et al. J Clin Oncol 2011;29:3490-3491