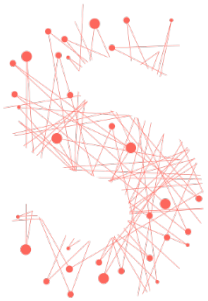
Biomarkers in oncology drug development

Andrew Stone

Stone Biostatistics Ltd

EFSPI Biomarkers and Subgroups June 2016



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E: andrew@stonebiostatistics.com
T: +44 (0) 7919 211836
W: stonebiostatistics.com – available from Aug 16

Statistical QI

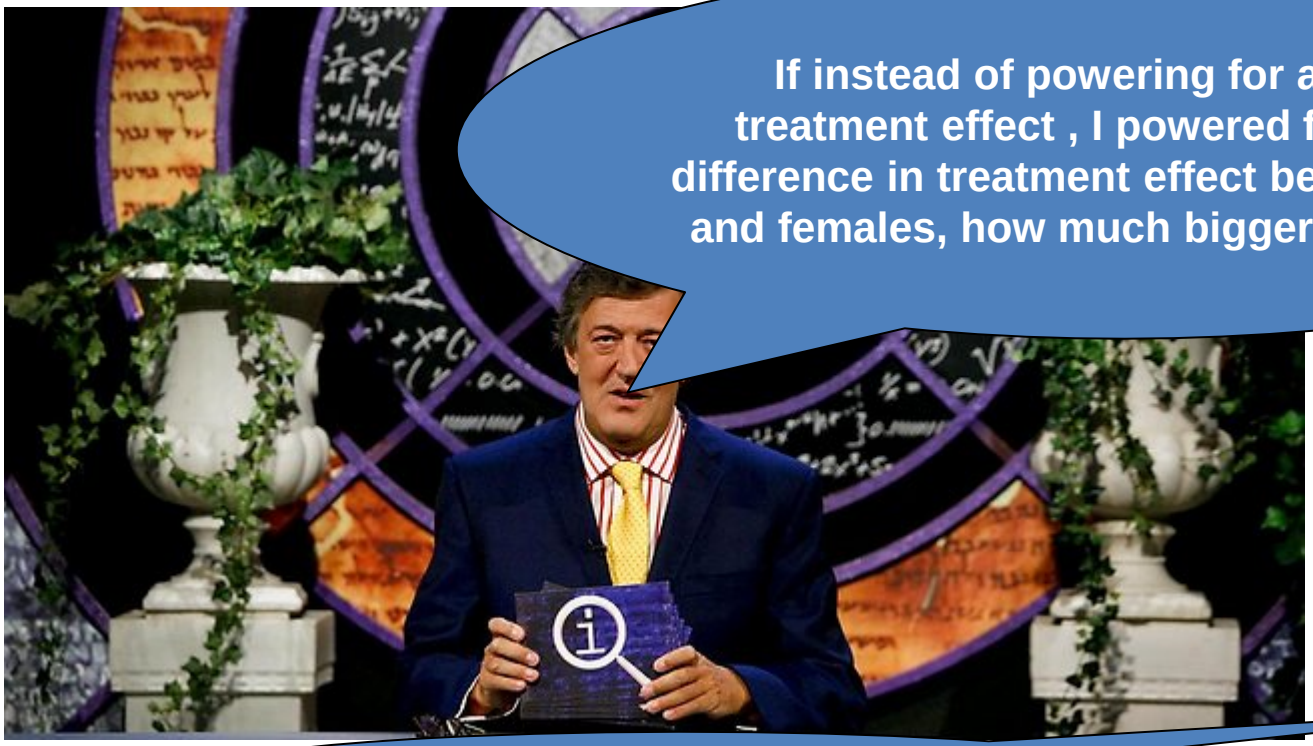
How many groups do I need to divide my dataset into before being odds-on of showing an effect reversal?

Only 6

If the treatment effect is identical per group and equal to the hypothesised treatment effect H1. Oh, and assuming equal n per group & trial has 80% power

Senn, Statistical Issues in drug development

Statistical QI



If instead of powering for a 10 unit treatment effect , I powered for 10 unit difference in treatment effect between males and females, how much bigger is the trial?

4

Assuming 50% were male

Byar, SIM, 1985, 255-63

Subgroups – what we can be certain of!

We have a serious false+ve problem

We also have a serious false-ve problem

$$\psi(x) \to \psi(x) + \varepsilon\varphi(x) \quad \{\text{A VARIATION } \varphi(x) \text{ IS ADDED}$$

$$\frac{\partial}{\partial\varepsilon}(\Delta x)^2(\Delta\mu)^2 = (\Delta\mu)^2\frac{\partial}{\partial\varepsilon}(\Delta x)^2 + (\Delta x)^2\frac{\partial}{\partial\varepsilon}(\Delta\mu)^2 = 0$$

$$(\Delta x)^2\left[\left(\frac{h}{4\pi}\right)^2\left(\frac{1}{\Delta x}\right)^4\frac{\partial}{\partial\varepsilon}(\Delta x)^2 + \frac{\partial}{\partial\varepsilon}(\Delta\mu)^2\right] = 0 \quad \{\text{UNCERTAINTIES } \Delta\mu \text{ REPLACED BY } \langle\ldots\rangle$$

$$\frac{\partial}{\partial\varepsilon}\left[-\left(\frac{h}{4\pi}\right)^2\left(\frac{1}{\Delta x}\right)^2 + (\Delta\mu)^2\right] = 0 \quad \{(\Delta x)^2 > 0, \text{ OTHERWISE } (\Delta\mu)^2 \to \infty \text{ AS } \varepsilon \to 0$$

$$\frac{\partial}{\partial\varepsilon}\left[-\left(\frac{h}{4\pi}\right)^2 \cdot 4\int\left(\frac{d\psi(x)}{dx}\right)^2 dx + 2m\int(E - V(x))\,\psi^2(x)\,dx\right] = 0 \quad \{\text{USING (5) \& (6)}$$

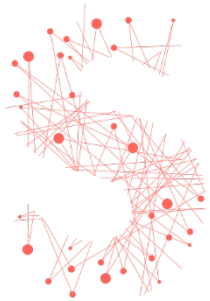
$$-\left(\frac{h}{2\pi}\right)^2\int\frac{d\psi(x)}{dx}\cdot\frac{d\varphi(x)}{dx}\,dx + 2m\int(E - V(x))\,\psi(x)\,\varphi(x)\,dx = 0 \quad \{\frac{\partial}{\partial\varepsilon}\mathcal{L} = 0 \ (7)$$

$$\int\left[\left(\frac{h}{2\pi}\right)^2\frac{d^2\psi(x)}{dx^2} + 2m(E - V(x))\psi(x)\right]\varphi(x)\,dx = 0 \quad \{\text{INTEGRATION BY PARTS; } \varphi(x) = 0 \text{ AT BORDERS}$$

$$\boxed{\frac{d^2\psi(x)}{dx^2} + 2m\left(\frac{2\pi}{h}\right)^2(E - V(x))\,\psi(x) = 0} \quad \{(7) = 0 \text{ FOR ALL VARIATIONS } \varphi(x)$$

SCHRÖDINGER'S WAVE EQUATION

But why would all patients have the same benefit and risk ??



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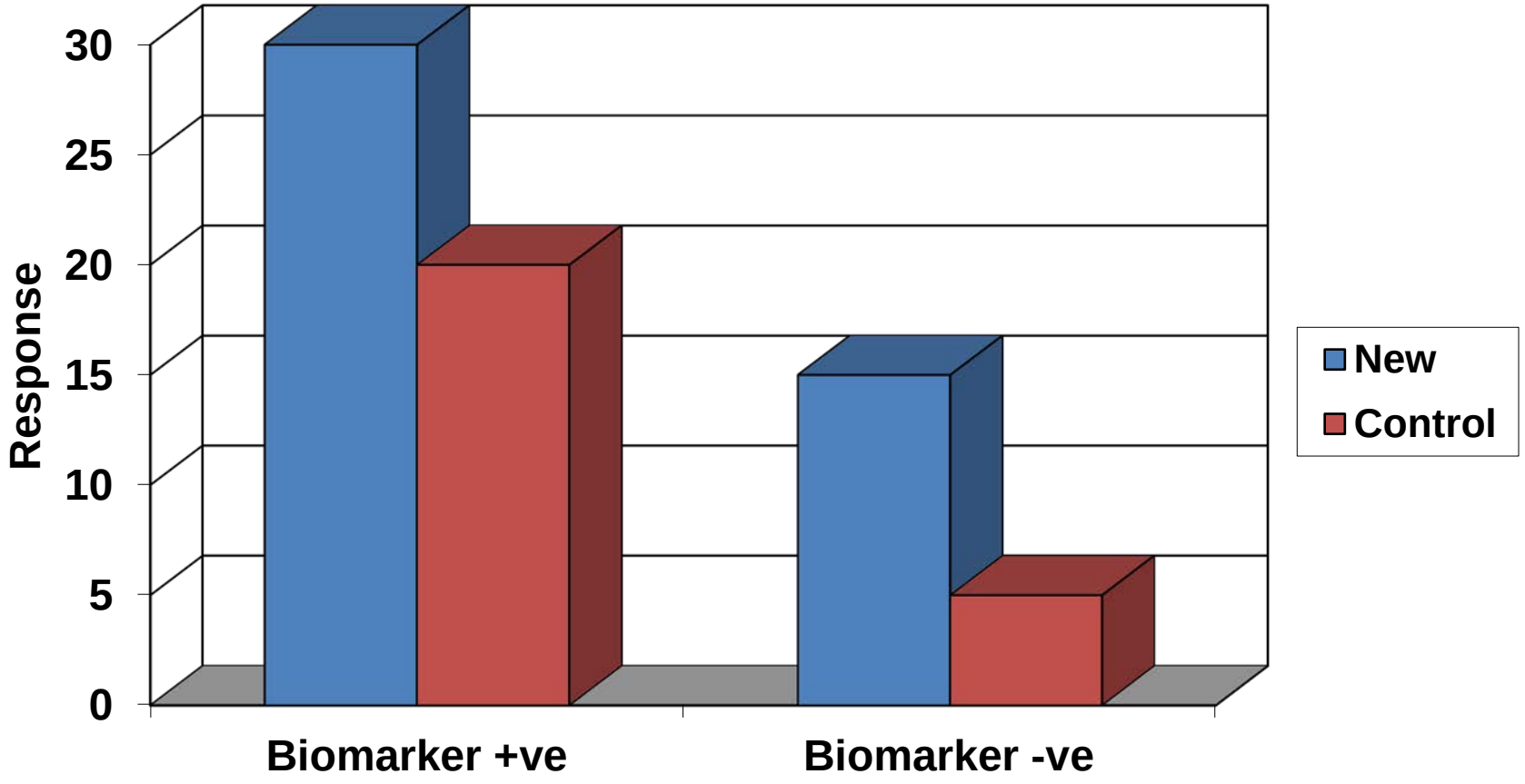
How best to learn

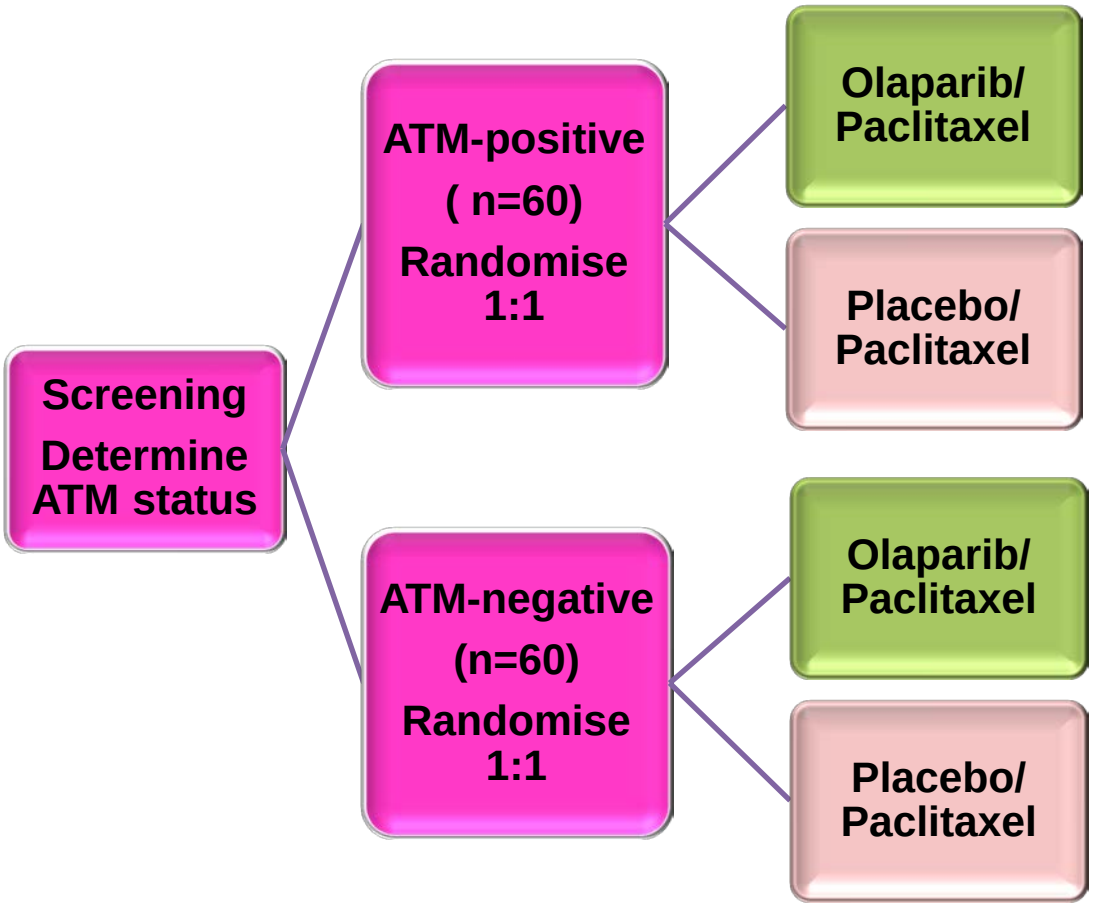
A common oversight

Importance of trial design - predictive vs. prognostic



Prognostic Biomarker identified

A good design - olaparib 2nd line gastric cancer



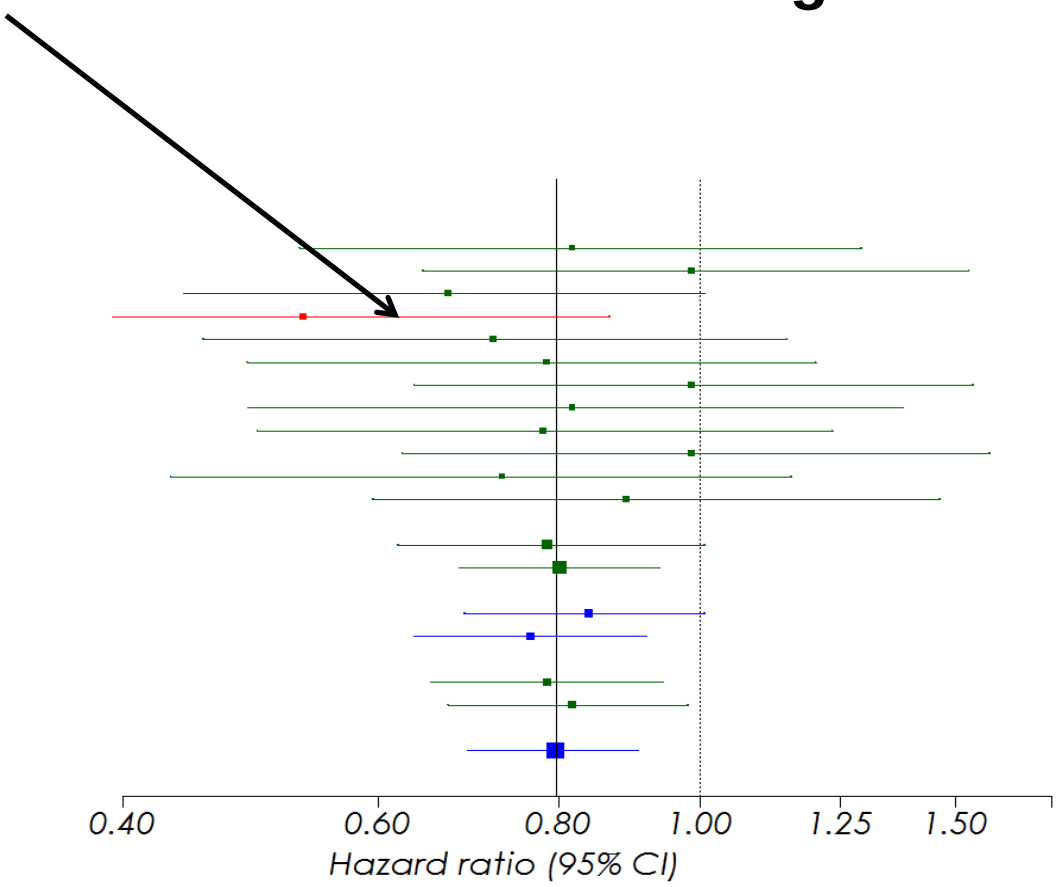
Recruitment to ATM positive arm was closed once 60 ATM positive patients had been randomised.

J Clin Oncol 31, 2013 (suppl; abstr 4013)

Interpreting the unexpected in Phase II

Is this real??

Taurus star sign!



Creating a structured approach to interpretation

Incorporating strength of prior evidence

• Pre-specify how likely there is to be a treatment-by-subgroup interaction of given size

• Use a bayesian approach to quantify likely over-estimation of effect*

• Extends following basic result for normal data
  – Prior ~ $N(\mu,\tau^2)$, Likelihood ~ $N(\delta,\sigma^2)$ - in this case $\mu = 0$ and τ^2 is pre-specified.
  – *Posterior*
    • mean = $(\sigma^2/\{\sigma^2+\tau^2\}).\mu + (\tau^2/\{\tau^2+\sigma^2\}).\delta$
    • Variance = $\tau^2\sigma^2/\{\sigma^2+\tau^2\}$

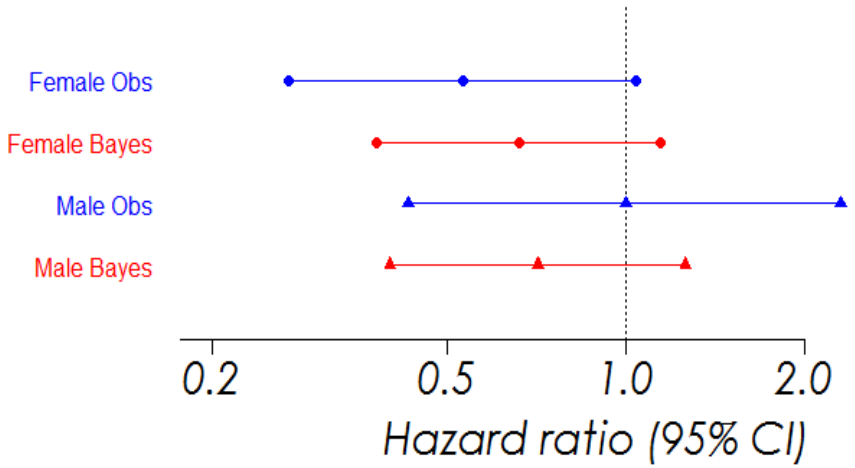
*Simon, SIM 2002 2909-16.
Related non-bayesian approach by Senn in Chapter 9 Statistical Issues in Drug Development

An example – strength of belief reflected in results

Pre-specify chance of interaction

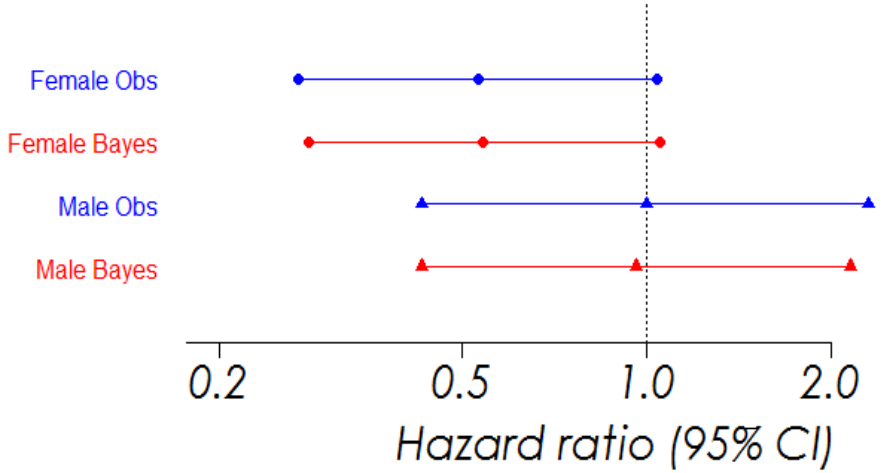
2.5% probability of interaction*

Female bayes = 0.67Female + 0.33male



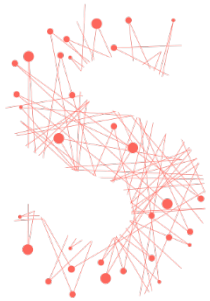
60% probability of interaction*

Female bayes = 0.96Female + 0.04male



* Probability HRfem/HRmale =0.67

- Do not interpret literally but use to give a guide of likely effect shrinkage
  - Based on conversation had prior to unblinding



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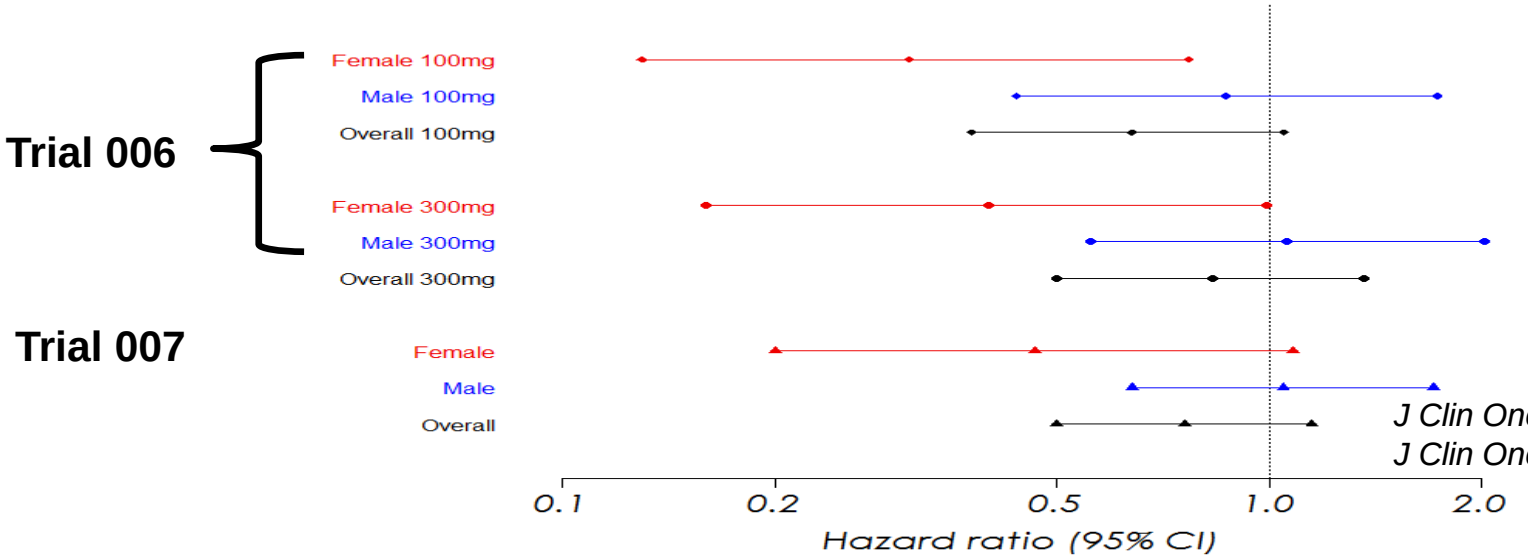
Confirming benefit

Normally uncertainty left

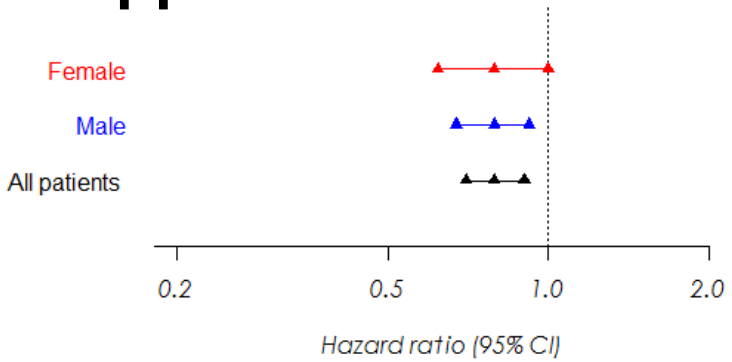
Best to spread bets – vandetanib NSCLC

Gender-by-trt interaction replicated in PII
No clear scientific rationale



J Clin Oncol 25:4270-4277. 2007
J Clin Oncol 26:5407-5415. 2008

PIII interaction disappears but α reserved for overall test

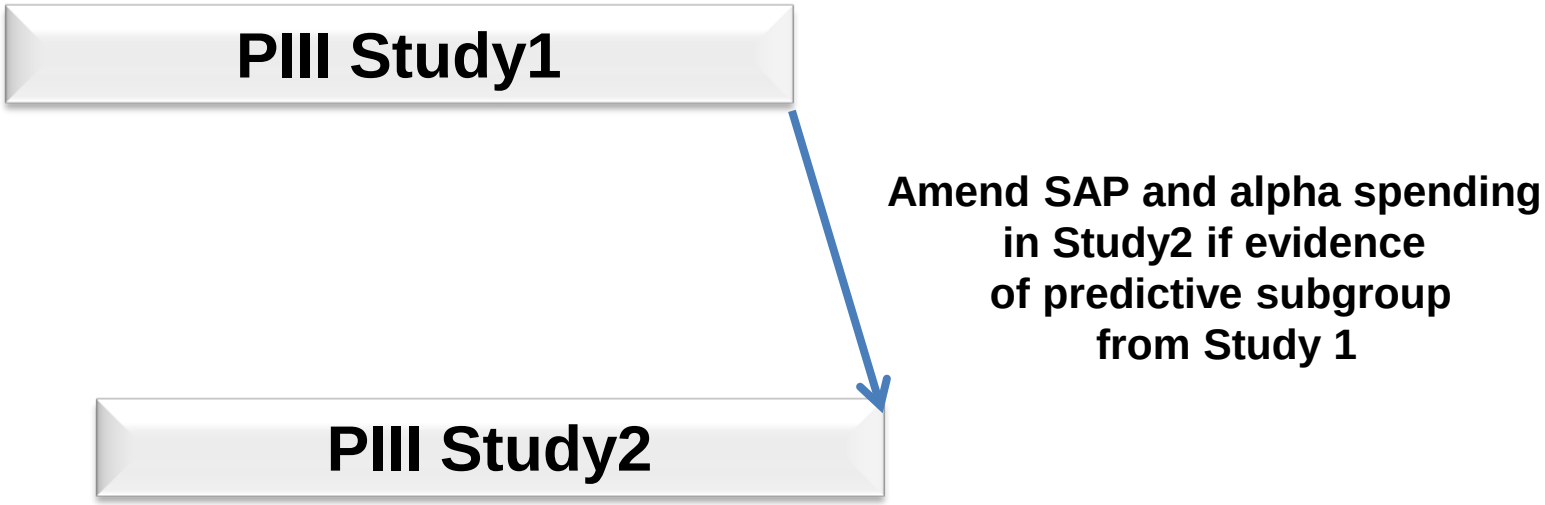


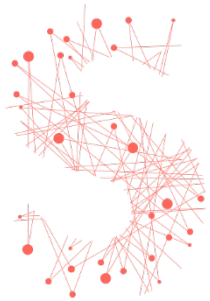
Lancet Oncol 11:619-626 2010

One pivotal trial to define subgroup population for the other

Hypothesised from prior PII data

20xx				20xx				20xx			
1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q





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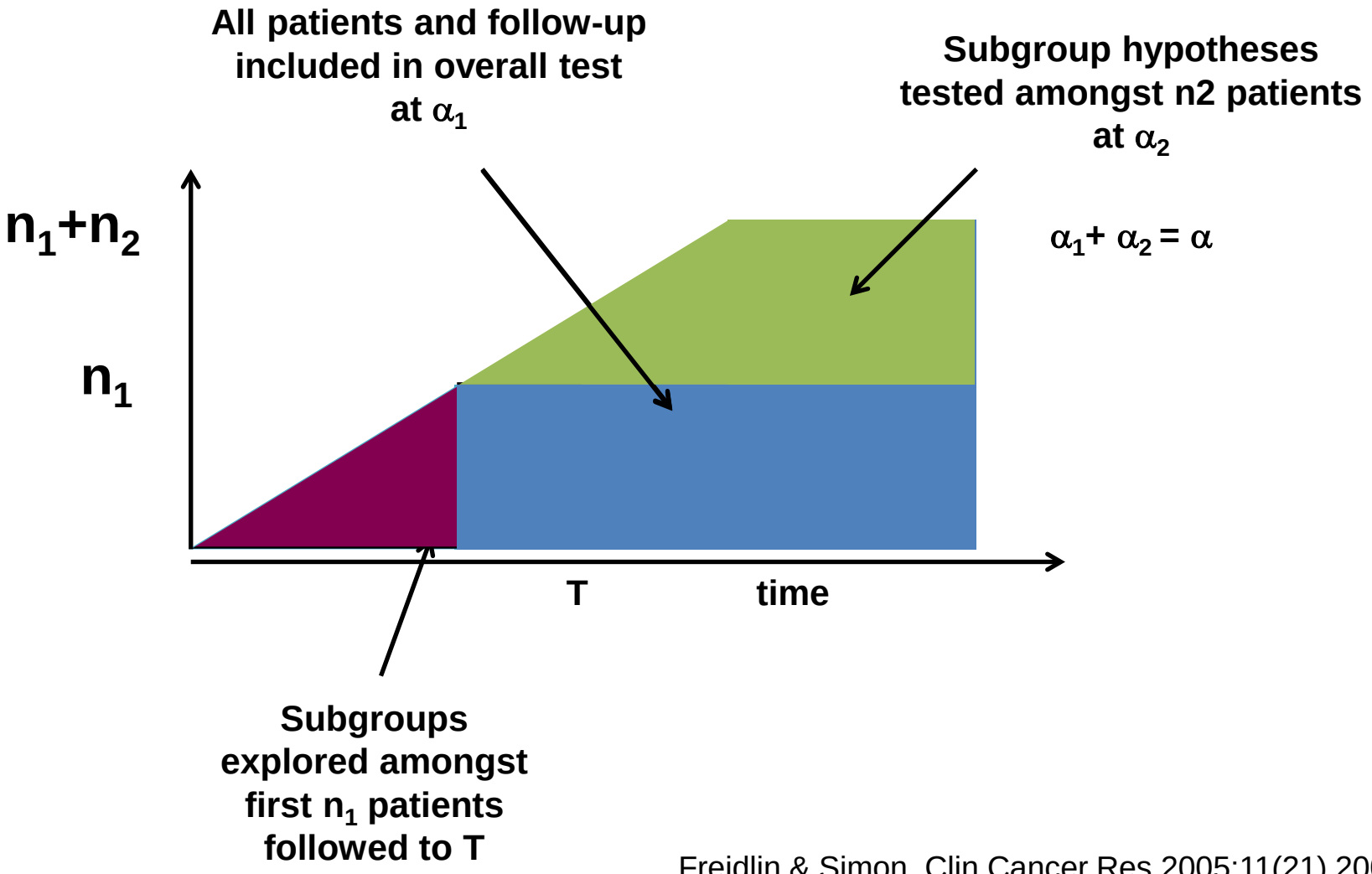
Learn and confirm?

Adaptive signature design

Learn and confirm within the same design



Freidlin & Simon, Clin Cancer Res 2005;11(21) 2005

Adaptive sub-population design

Pre-defined hypothesis available

Flexibly define Stage 2 popn = overall, subgroup or both - or stop for futility

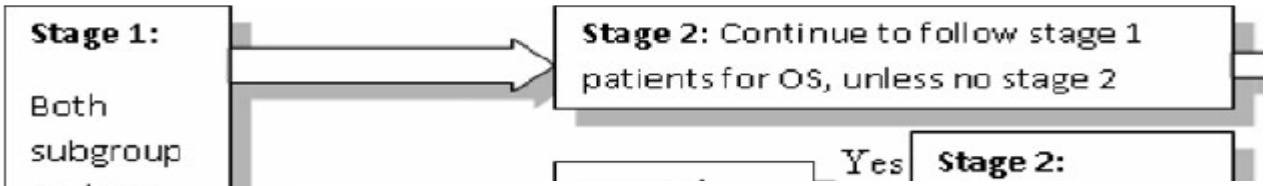


Table I. The weights and *p*-values to be used in combination tests.

Co-primary case – when considering both H_0^F and H_0^S

Testing H_0^F: $w_1\,\Phi^{-1}(1-p_1^F)+w_2\,\Phi^{-1}(1-p_2^F)$

Testing H_0^S: $w_1\,\Phi^{-1}(1-p_1^S)+w_2\,\Phi^{-1}(1-p_2^S)$

Testing H_0^{FS}: $w_1\,\Phi^{-1}(1-p_1^{FS})+w_2\,\Phi^{-1}(1-p_2^{FS})$

F only case – when considering H_0^F only

Testing H_0^F: $w_1\,\Phi^{-1}(1-p_1^F)+w_2\,\Phi^{-1}(1-p_2^F)$

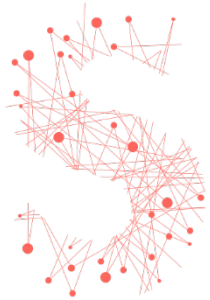
Testing H_0^{FS}: $w_1\,\Phi^{-1}(1-p_1^{FS})+w_2\,\Phi^{-1}(1-p_2^F)$

S only case – when considering H_0^S only

Testing H_0^S: $w_1\,\Phi^{-1}(1-p_1^S)+w_2\,\Phi^{-1}(1-p_2^S)$

Testing H_0^{FS}: $w_1\,\Phi^{-1}(1-p_1^{FS})+w_2\,\Phi^{-1}(1-p_2^S)$

Jenkins M, Stone A, Jennison C. *Pharm. Statistics 2011 4 347-356*



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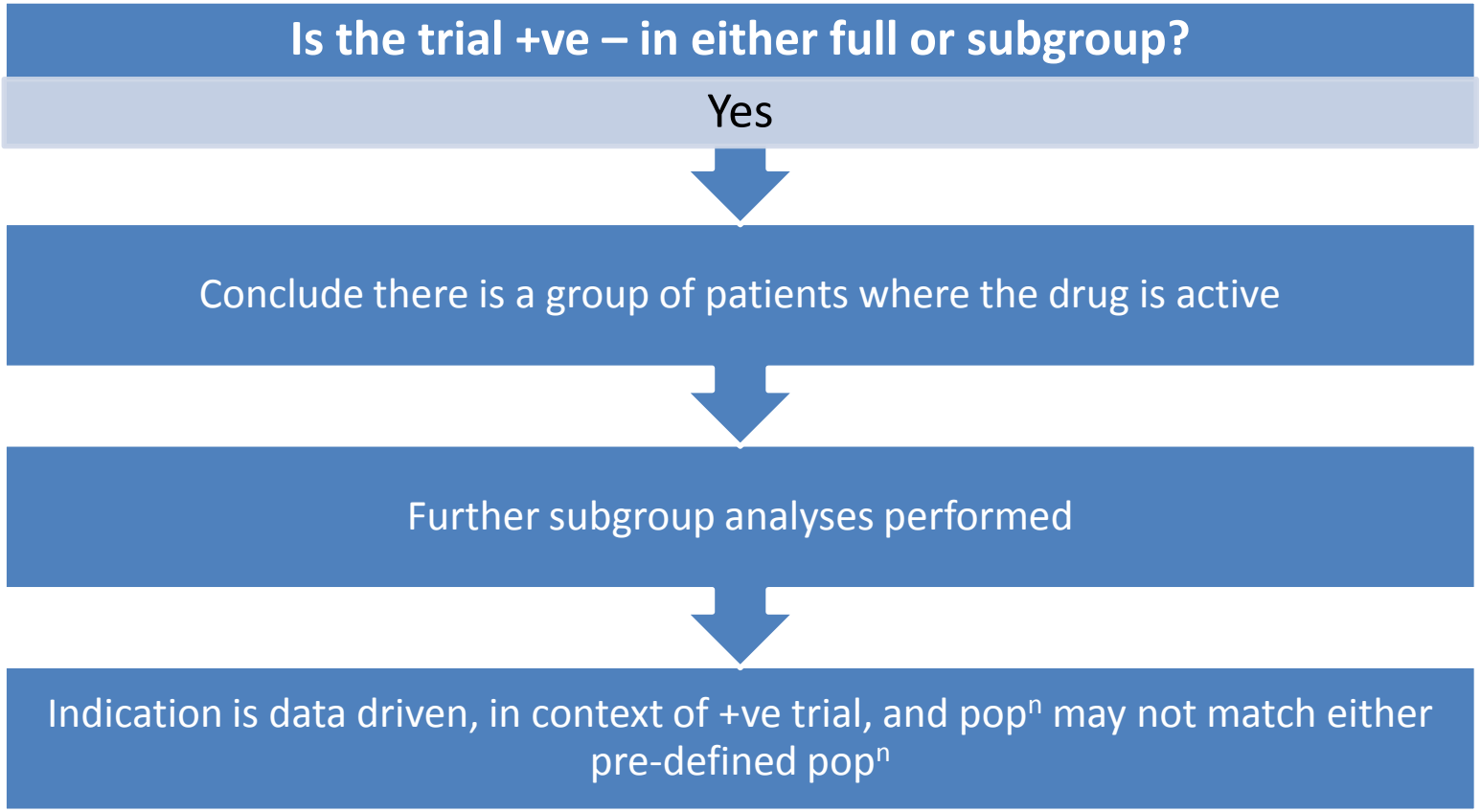
Re-learning

The licensing decision

What happens in the licensing decision



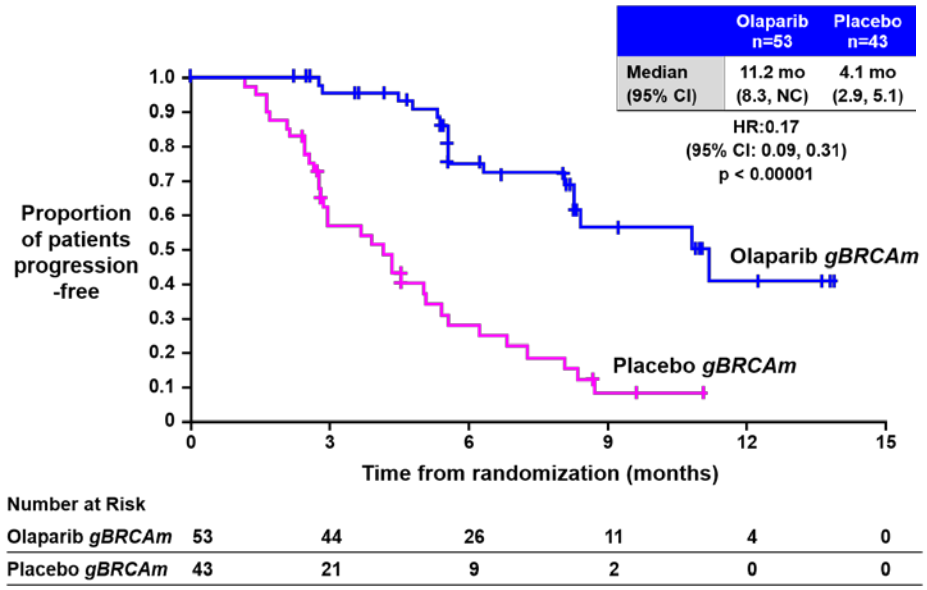
Therefore do not need to be absolutely perfect in definition of subgroup in PII or use to-be-marketed diagnostic (samples stored)

Need to do well enough to increase the chance of +ve trial and data will determine indication

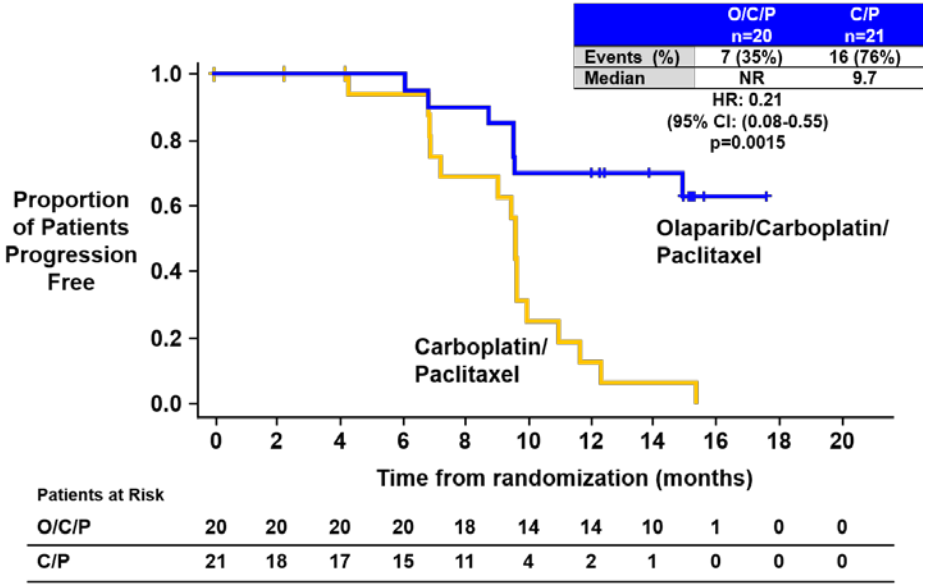
Science, replication and pre-specification

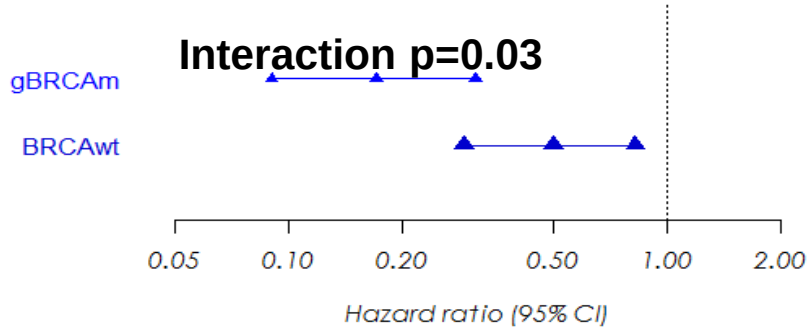
Olaparib BRCA+ve ovarian cancer

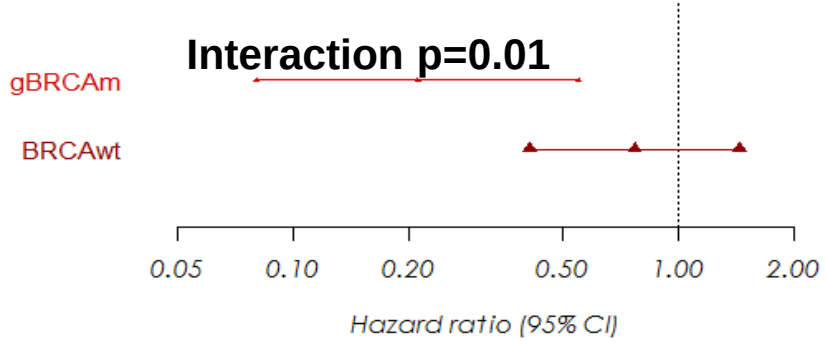
Study 19



Study 41







The Lancet Oncology , Volume 15 , Issue 8 , 852 – 861, 2014
The Lancet Oncology , Volume 16 , Issue 1 , 87 – 97, 2015
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM402209.pdf

Gefitinib case study

Biomarker emerges during clinical development.

Eventual approval in locally-advanced or metastatic NSCLC patients with activating mutations of EGFR-TK

Phase II efficacy in all-comers NSCLC

Efficacy parameter (95% CI)	IDEAL 1 (RoW) 250 mg n=103	IDEAL 1 (RoW) 500 mg n=105	IDEAL 2 (US) 250 mg n=102	IDEAL 2 (US) 500 mg n=114
ORR (%)	18.4 (11.5-27.3)	19.0 (12.1-27.9)	11.8 (6.2-19.7)	8.8 (4.3-15.5)
Disease control rate (%)	54.4 (44.3-64.2)	51.4 (41.5-61.3)	42.2 (32.4 –52.3)	36.0 (27.2-45.5)
PFS (months)	2.7 (2.0-2.8)	2.8 (1.9-3.8)	1.9 (1.8-2.8)	2.0 (1.6-2.2)
Median OS (months)	7.6 (5.3-10.1)	8.0 (6.7-9.9)	6.5 (4.8-8.0)	5.9 (4.6-7.2)
1-year survival (%)	35 (25-44)	29 (20-38)	29 (19-38)	24 (14-34)

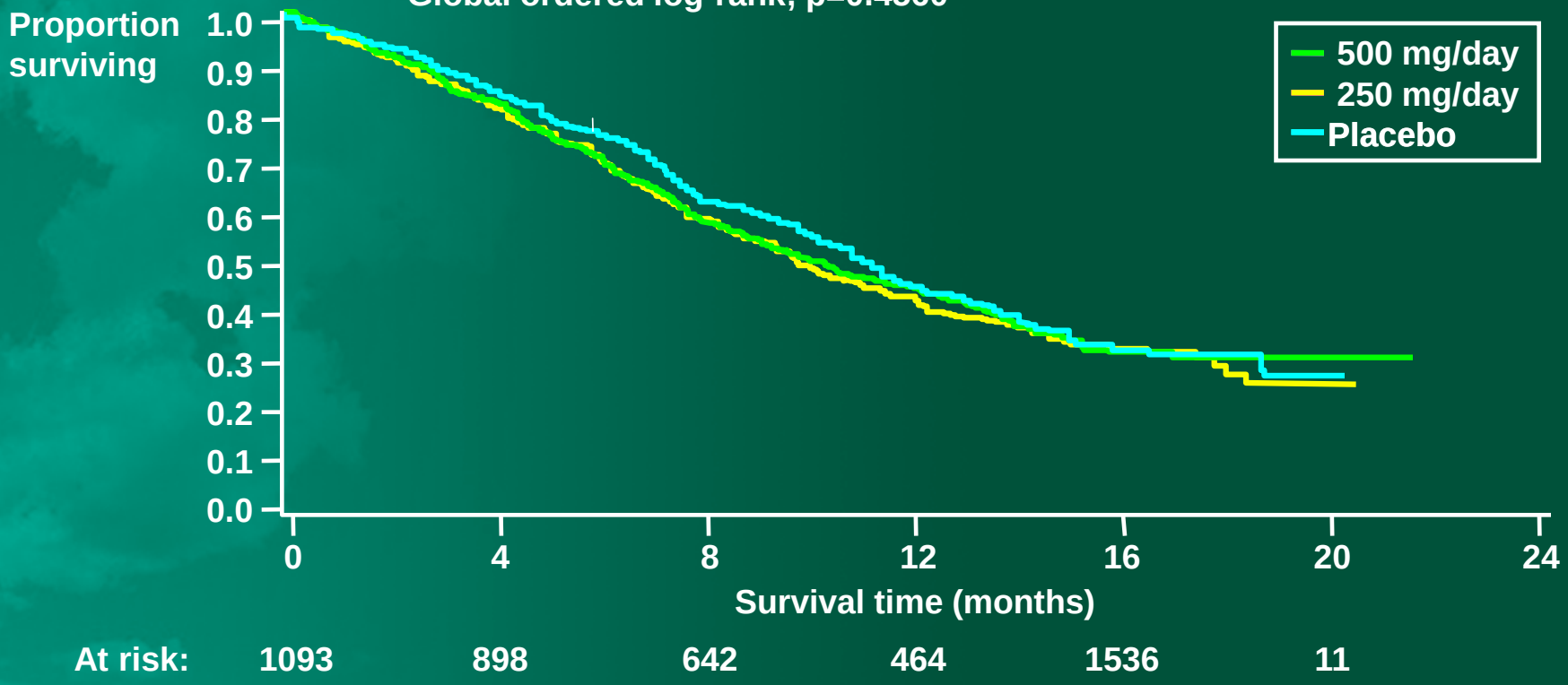
CI, confidence interval; RoW, rest of world;
PFS, progression-free survival; ORR, objective response rate
OS, overall survival

Fukuoka M et al. *J Clin Oncol* 2003; 21: 2237-2246.
Kris MG et al. *JAMA* 2003; 290: 2149-2158.

All comers, chemo combination: PIII no survival benefit

	500 mg	250 mg	Placebo
Median survival (months)	9.9	9.9	10.9
1-year survival rate	0.43	0.41	0.44

Global ordered log-rank; p=0.4560



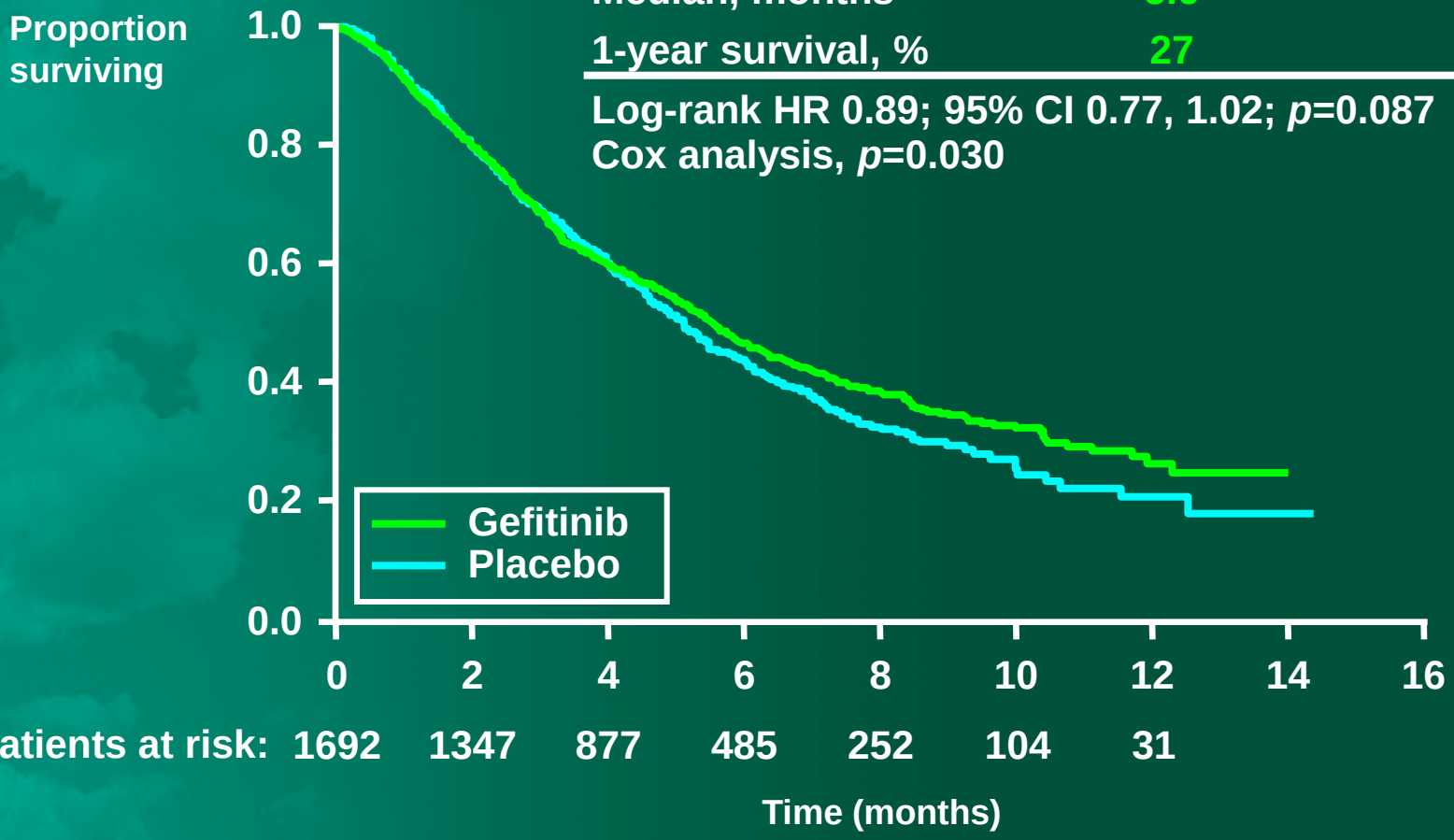
J Clin Oncol 2004; 22: 777-784
Similar result shown in 2nd PIII *J Clin Oncol* 2004; 22: 785-794

All comers, monotherapy (ISEL): primary analysis of survival data p>0.05

Median follow-up: 7 months (range 3-15); 58% deaths

	Gefitinib	Placebo
Median, months	5.6	5.1
1-year survival, %	27	21

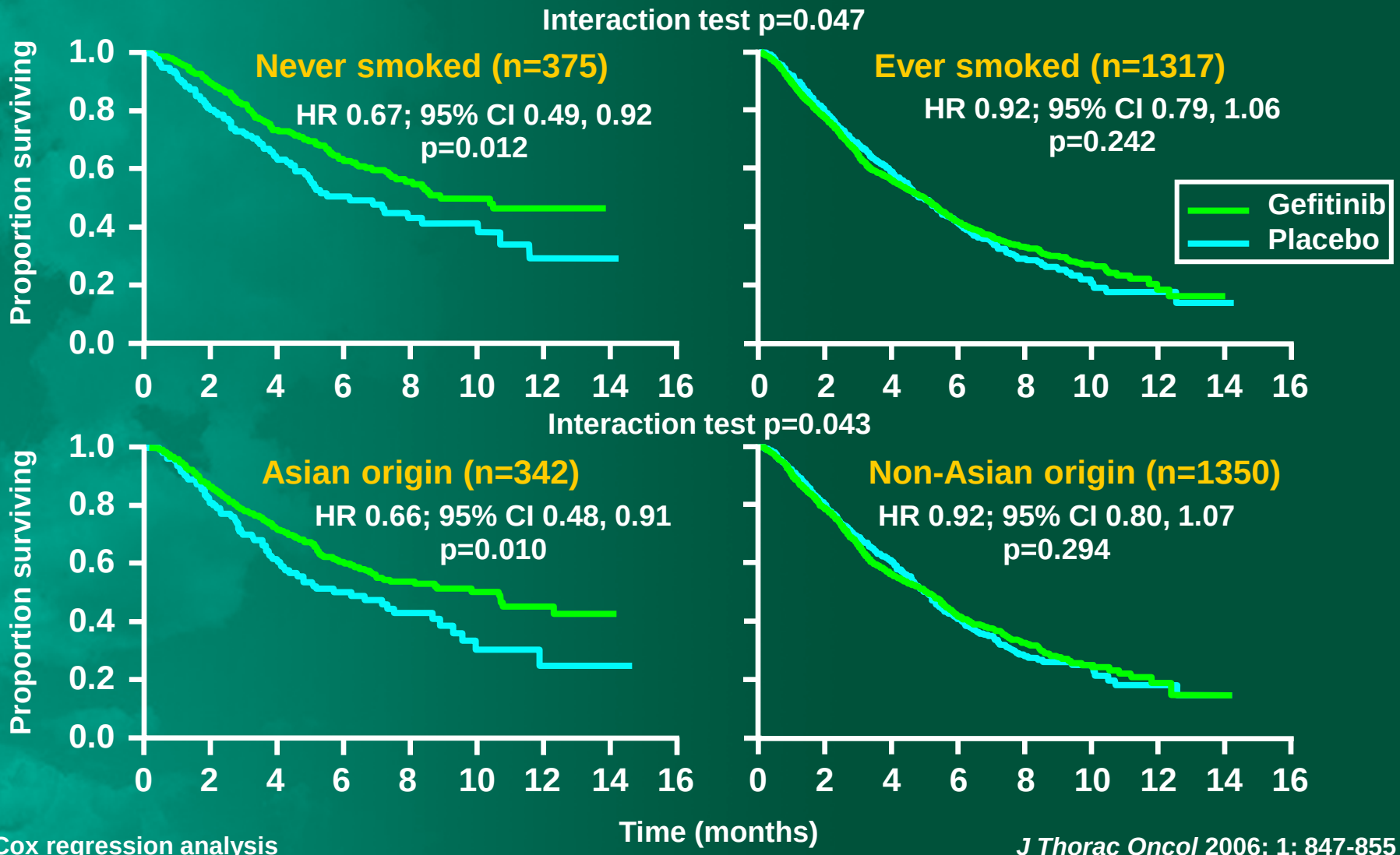
Log-rank HR 0.89; 95% CI 0.77, 1.02; *p*=0.087
Cox analysis, *p*=0.030



HR, hazard ratio

Lancet 2005; 366: 1527-1537

Intriguing findings emerged for certain patient characteristics



Cox regression analysis

J Thorac Oncol 2006; 1: 847-855

2004: the identification of EGFR mutations in lung cancers

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

Science 2004

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

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

N Engl J Med 2004

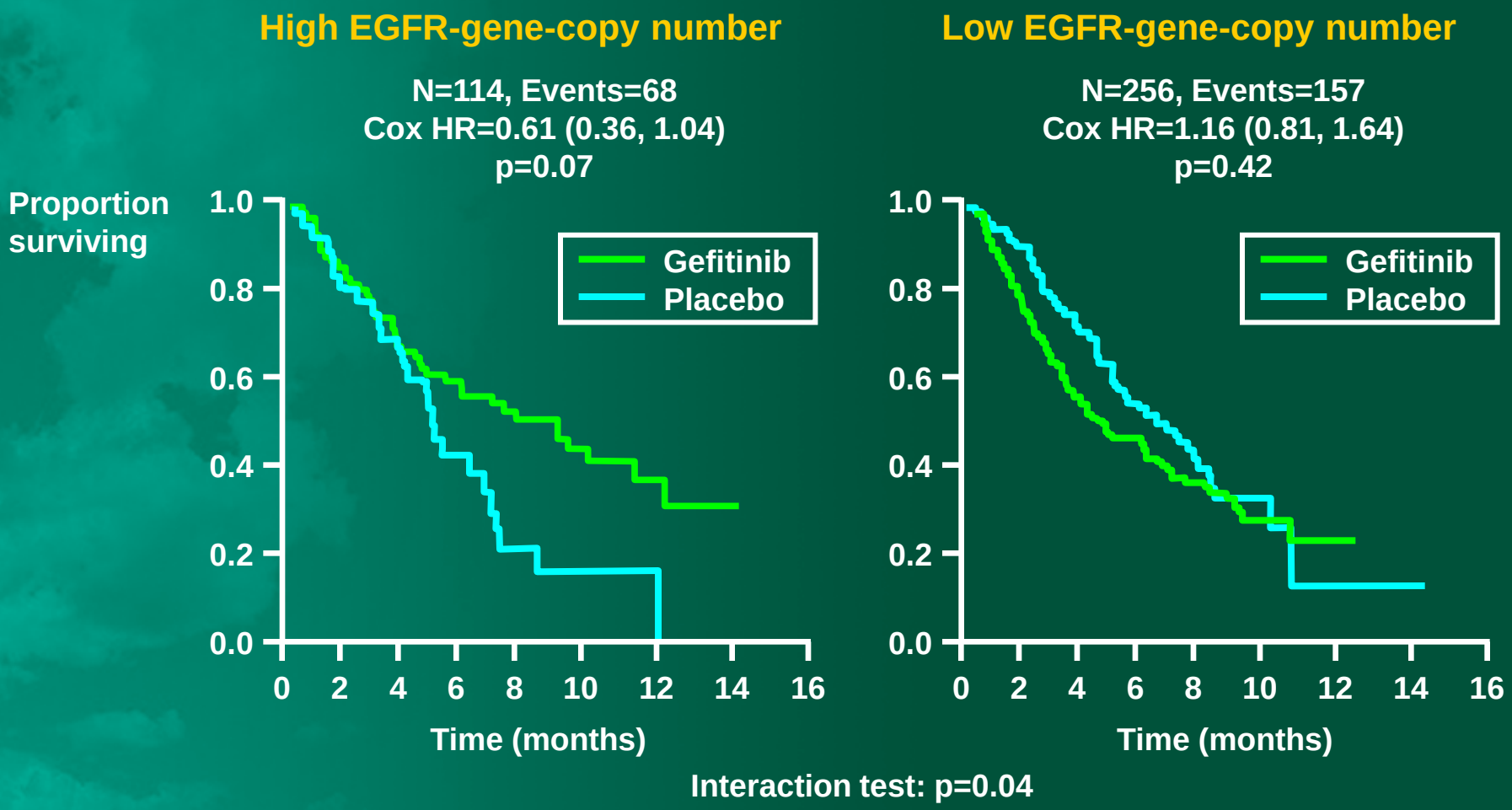
Gene-copy number as a predictor for gefitinib sensitivity

Journal of the National Cancer Institute, Vol. 97, No. 9, May 4, 2005

Epidermal Growth Factor Receptor Gene and Protein and Gefitinib Sensitivity in Non–Small-Cell Lung Cancer

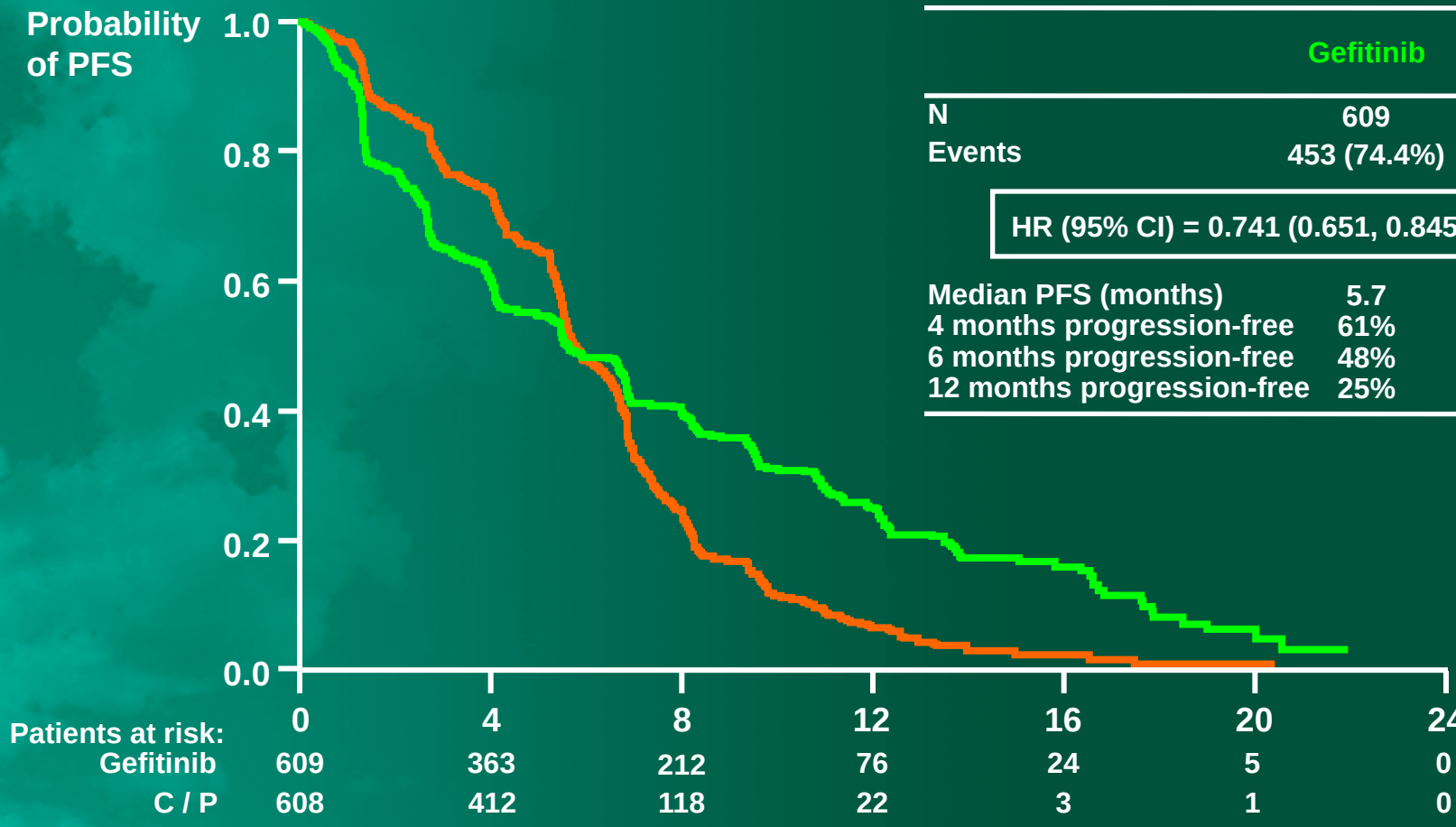
Federico Cappuzzo, Fred R. Hirsch, Elisa Rossi, Stefania Bartolini, Giovanni L. Ceresoli, Lynne Bemis, Jerry Haney, Samir Witta, Kathleen Danenberg, Irene Domenichini, Vienna Ludovini, Elisabetta Magrini, Vanesa Gregorc, Claudio Doglioni, Angelo Sidoni, Maurizio Tonato, Wilbur A. Franklin, Lucio Crino, Paul A. Bunn, Jr., Marileila Varella-Garcia

Subsequent analysis by gene-copy number



J Clin Oncol 2006; 24: 5034-5042.

Monotherapy selected population (Asian, never/light-ex smoker, adeno): IPASS study, PFS in ITT population

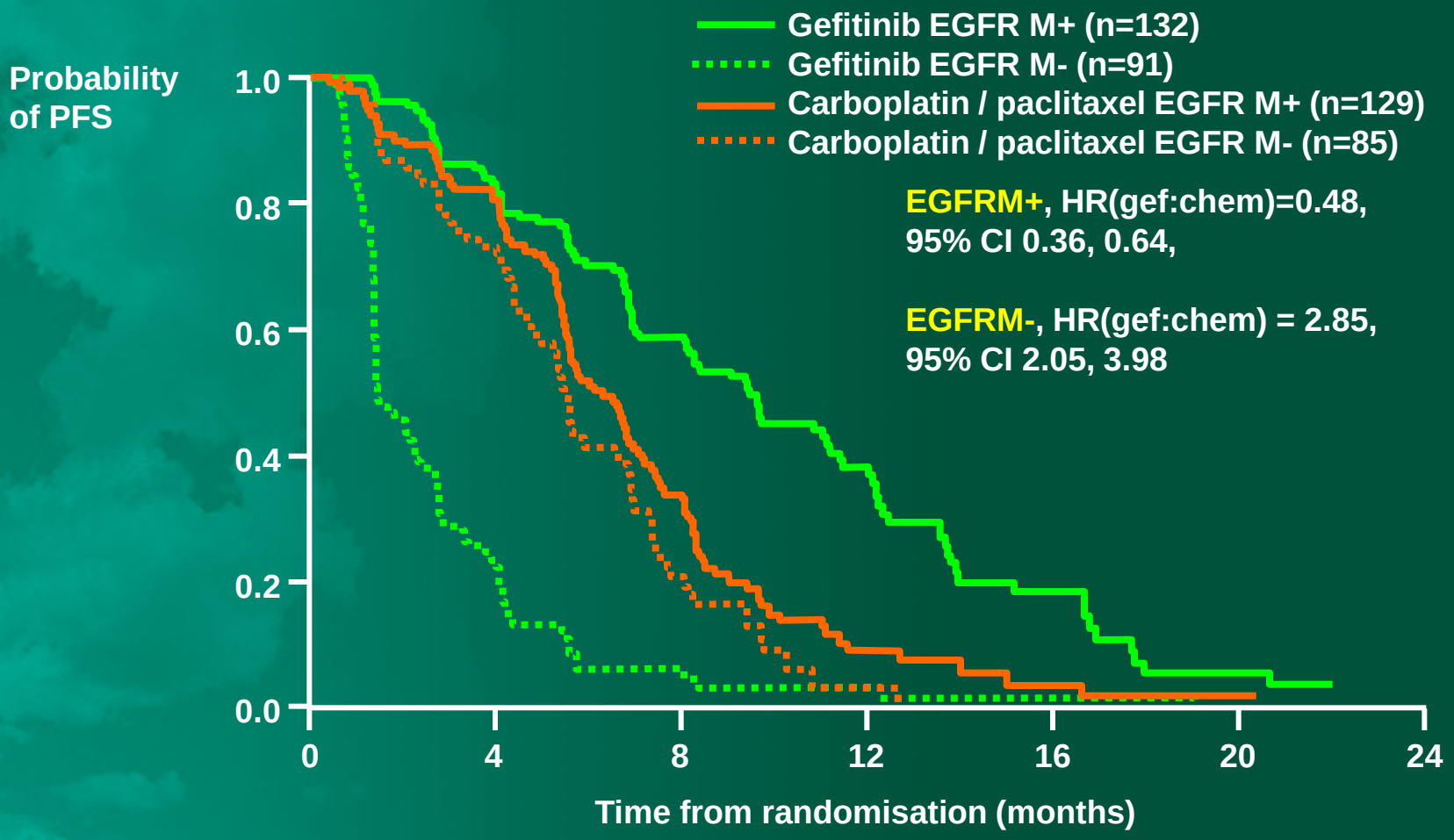


	Gefitinib	Carboplatin / paclitaxel
N	609	608
Events	453 (74.4%)	497 (81.7%)
HR (95% CI) = 0.741 (0.651, 0.845) p<0.001		
Median PFS (months)	5.7	5.8
4 months progression-free	61%	74%
6 months progression-free	48%	48%
12 months progression-free	25%	7%

Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib
C / P, carboplatin / paclitaxel

N Engl J Med 2009; 361: 947-957

IPASS: PFS by EGFR mutation status – pre-planned 2^0 analysis



Primary Cox analysis with covariates
HR <1 implies a lower risk of progression
M+, mutation positive; M-, mutation negative

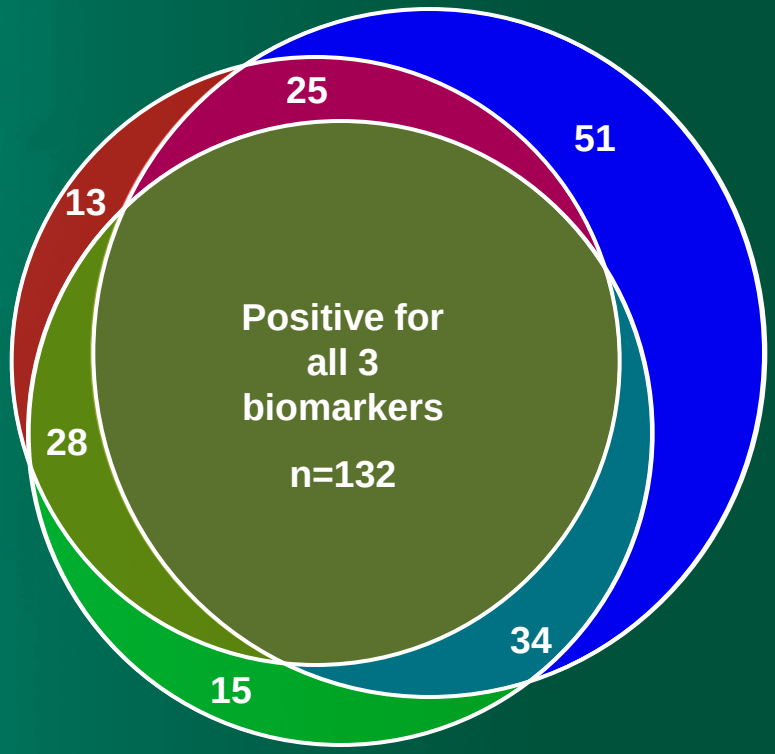
N Engl J Med 2009; 361: 947-957

Potential biomarkers – hugely correlated which one drives efficacy?

Further analyses, e.g. In gene copy number +ve but EGFR M-ve, showed that efficacy driven by EGFRM status

High EGFR-gene-copy number

n=198



EGFR protein expression positive

n=242

EGFR mutation-positive

n=209

Negative for all 3 biomarkers n=31

N=329 with known biomarker status for all 3 biomarkers

Mok et al WCLC 2009

Replication across studies for EGFR M+ – pivotal to licensing decision

	Response Rate	PFS: HR (95% CI)
IPASS n=261	71% v 47%	0.48 (0.36, 0.64)
INTEREST n=44	42% v 21%	0.16 (0.05, 0.49)
ISEL n=26	37% v 0%	NC too few events

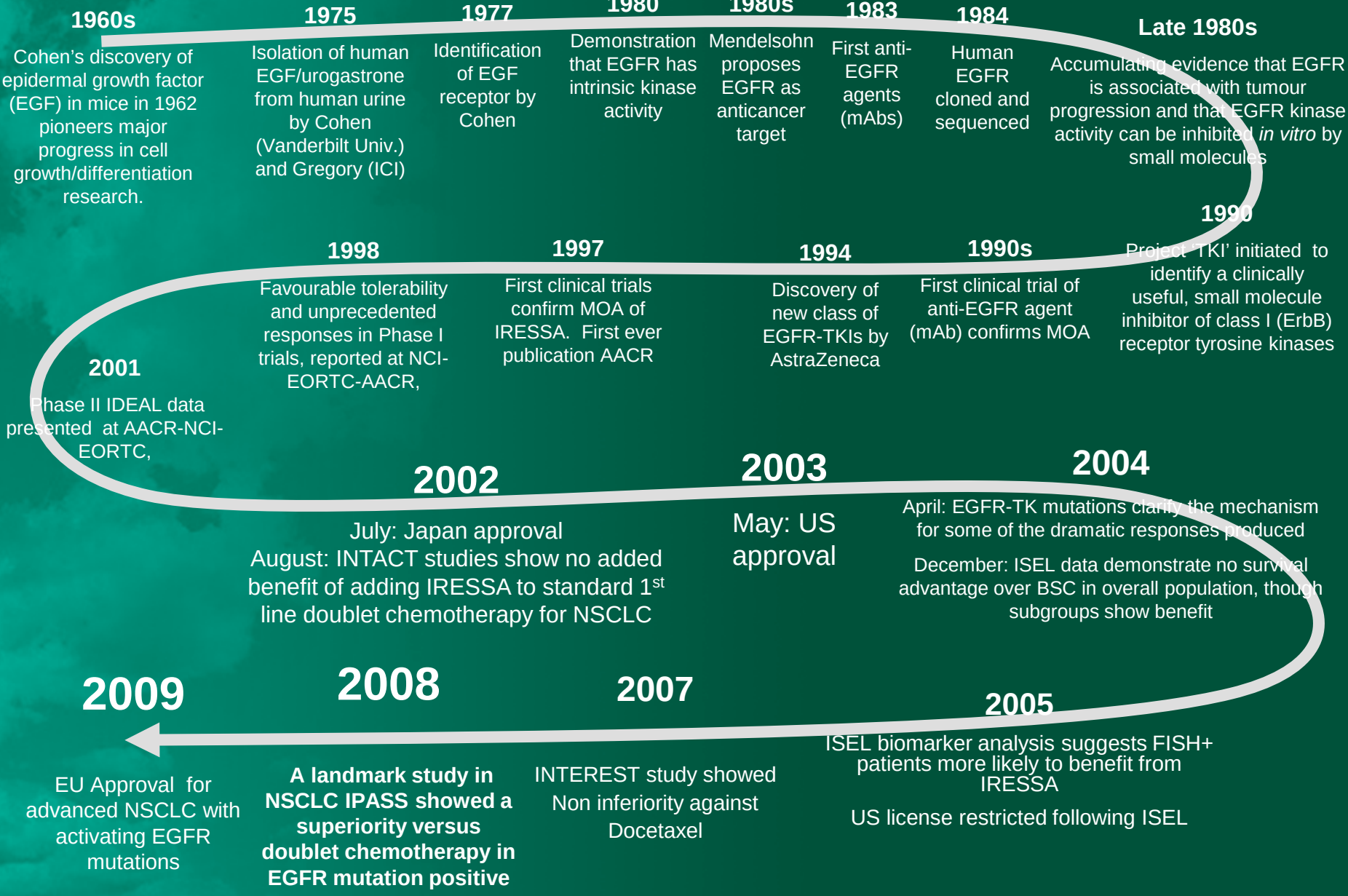
N refer to patients with evaluable sample

Eur Respir Rev 2010; 19: 117, 186–196

Conclusions

- Statistician has a key role to play
  - Technical
  - Influence
- Continued area of active research
- So we can better serve patients

EGFR and gefitinib milestones



1960s

Cohen's discovery of epidermal growth factor (EGF) in mice in 1962 pioneers major progress in cell growth/differentiation research.

1975

Isolation of human EGF/urogastrone from human urine by Cohen (Vanderbilt Univ.) and Gregory (ICI)

1977

Identification of EGF receptor by Cohen

1980

Demonstration that EGFR has intrinsic kinase activity

1980s

Mendelsohn proposes EGFR as anticancer target

1983

First anti-EGFR agents (mAbs)

1984

Human EGFR cloned and sequenced

Late 1980s

Accumulating evidence that EGFR is associated with tumour progression and that EGFR kinase activity can be inhibited *in vitro* by small molecules

1990

Project 'TKI' initiated to identify a clinically useful, small molecule inhibitor of class I (ErbB) receptor tyrosine kinases

1990s

First clinical trial of anti-EGFR agent (mAb) confirms MOA

1994

Discovery of new class of EGFR-TKIs by AstraZeneca

1997

First clinical trials confirm MOA of IRESSA. First ever publication AACR

1998

Favourable tolerability and unprecedented responses in Phase I trials, reported at NCI-EORTC-AACR,

2001

Phase II IDEAL data presented at AACR-NCI-EORTC,

2002

July: Japan approval

August: INTACT studies show no added benefit of adding IRESSA to standard 1st line doublet chemotherapy for NSCLC

2003

May: US approval

2004

April: EGFR-TK mutations clarify the mechanism for some of the dramatic responses produced

December: ISEL data demonstrate no survival advantage over BSC in overall population, though subgroups show benefit

2005

ISEL biomarker analysis suggests FISH+ patients more likely to benefit from IRESSA

US license restricted following ISEL

2007

INTEREST study showed Non inferiority against Docetaxel

2008

A landmark study in NSCLC IPASS showed a superiority versus doublet chemotherapy in EGFR mutation positive

2009

EU Approval for advanced NSCLC with activating EGFR mutations