Right Medicines, Right Patients

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Pfizer Inc

A Doctor's Decision

What is the right therapeutic plan for the patient who is sitting before me?

- **What are the options for my patient with the unique combination of phenotype and genotype presentation?**
- **What are the benefits and risks of each option?**
- **Are the available data applicable to my patient?**

Source: Briggs Morrison (2011).

Factors Affecting Benefit-Risk

Intrinsic

- **Genetics**
  - **Drug Metabolism**
  - **Immune response**
  - **Disease genetics (eg – tumor)**
- Age
- Race
- Organ function
- Body Mass

Extrinsic

- Exogenous consumables
  - Food
  - Con meds
  - Tobacco
  - Alcohol
  - Compliance
- Medical Practice
- Cultural Practices
- Disease Definition

Source: Briggs Morrison (2011)

Personalised Medicines

The right treatment at the right dose for the right person at the right time for the right outcome

Expectations raised for:

Safer, 'More Effective' Drugs: No more 'one-size-fits-all' drugs. New drugs will be safe and effective for specific populations

Faster Developments at Less Cost and Less Risk: Speedier clinical trials based on high 'responder' populations, higher R&D success rates and lower overall development costs.

Cost-Effective Healthcare: Reduced costs, due to avoidance of futile treatments in large populations who do not benefit, reimbursement challenges reduced

Source: Kevin Carroll (2011).

But It Is Not That Simple

- How sure are we that the defined subgroup will benefit to a greater extent, or the remaining subgroup will not benefit at all?
- If a subgroup is biologically defined, is the profile of the subgroup reproducible?
- Do we have a reliable test with acceptable specificity and sensitivity to identity the subgroup? A poor test can seriously impact the value of a pre-specified subgroup approach.
- Often, the real danger is we think we know the answer before we have the data; or the data we rely on are flawed.

Source: Kevin Carroll (2011).

Duke University Scandal

- Duke researchers used micro-arrays to identify biomarkers that were correlated with response in easily available data from cell lines. These markers were then examined in patient samples to predict the best chemotherapy.
- The researchers published results in *Nature Medicine* in Nov 2006 and claimed success. Trials were initiated based on the research findings.
- Findings could not be reproduced by other researchers. Persistent search for the cause found problems with the data and the software (computer algorithms) used.
- Eventually, the leading Duke researcher resigned and admitted to problems with the data. Several publications were retracted and trials were stopped.

Source: Darrel Ince (2011). Significance, 8(3), Sept.

Implications

- **Duke University and the Institute of Medicine (IOM) in the US commenced a general inquiry into the level of evidence that should be required before "omics" based signatures are used to guide treatment in clinical trials.**
- **Duke University management recommended to IOM that**

  "Sustained statistical collaboration is critical to assure proper management of these complex datasets for translation to clinical utility… The fundamental methods of managing data and validating statistical algorithms are not something basic scientists are generally familiar with, thus statisticians need to take an active role in participating in basic science research, both in terms of teaching research methods and in improving the design of studies…"

Source: Darrel Ince (2011). Significance, 8(3), Sept.

The Paths to TCT*s Are Often Rugged

Gefitinib (IRESSA): The EGFR Story

- **Based on Kevin Carroll's presentation at the European Medicines Agency Workshop on Subgroup Analysis, 18 Nov 2011, (slides 9 – 17) (**http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/10/event_detail_000536.jsp&mid=WC0b01ac058004d5c3&murl=menus/news_and_events/news_and_events.jsp)

***TCT: Targeted Cancer Therapy**

IRESSA Background

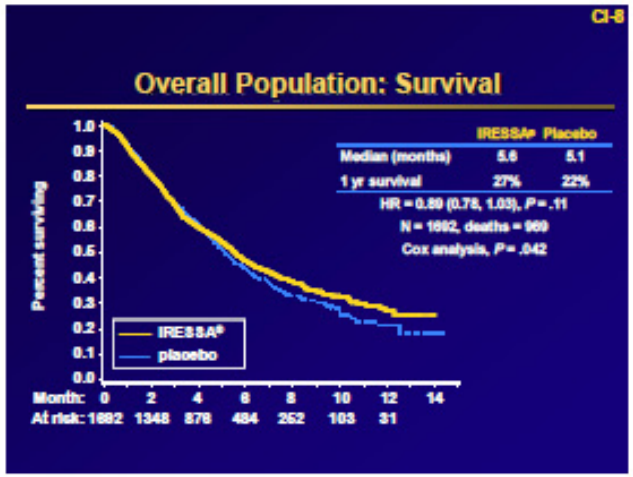
- IRESSA is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). It targets and blocks the EGFR-TK pathways implicated in cancer cell proliferation and survival.
- It is the first EGFR-TKI to gain market approval for NSCLC in some parts of the world including Japan (2002). It received conditional approval in US in May 2003.
- The initial approvals were based on data from two phase 2 trials which showed a positive effect in previously treated NSCLC. About 50% of patients in these studies experienced tumor shrinkage or disease stabilization.

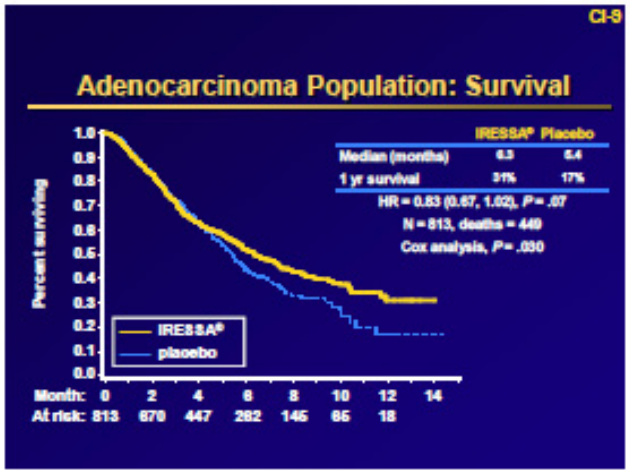
The ISEL Study

- ISEL: IRESSA Survival Evaluation in Lung Cancer
- ISEL is a phase 3 global trial, comparing IRESSA to placebo in patients with advanced NSCLC who failed one or more lines of chemotherapy.
- The primary endpoint was overall survival. The study was designed to observe 900 deaths.
- Overall and adenocarcinoma populations were co-primary, Hochberg procedure to control type I error rate.
- Several subgroup analyses were pre-planned, subgroups identified by clinical and biologic factors (e.g. gender, smoking status and race).

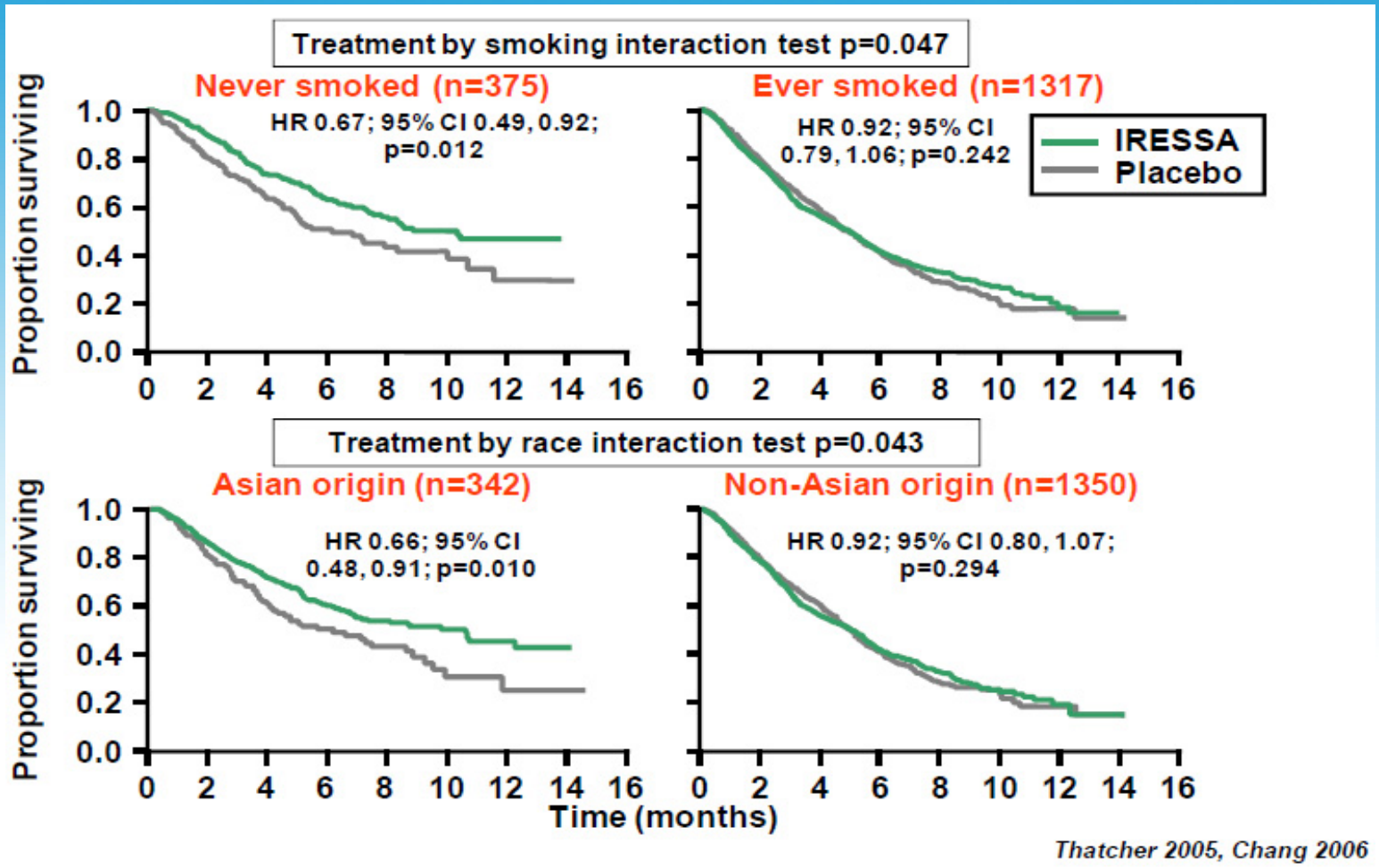
Findings from The ISEL Study

- **Results were available in December 2004. P-values for comparing IRESSA with placebo in the overall and the adenocarcinoma population using the "stratified logrank test" are 0.11 and 0.07. Neither achieved statistical significance under the Hochberg procedure. The corresponding P-values under the Cox's regression model are 0.042 and 0.030, both significant under Hochberg.**





Subgroups by Smoking Status and Race

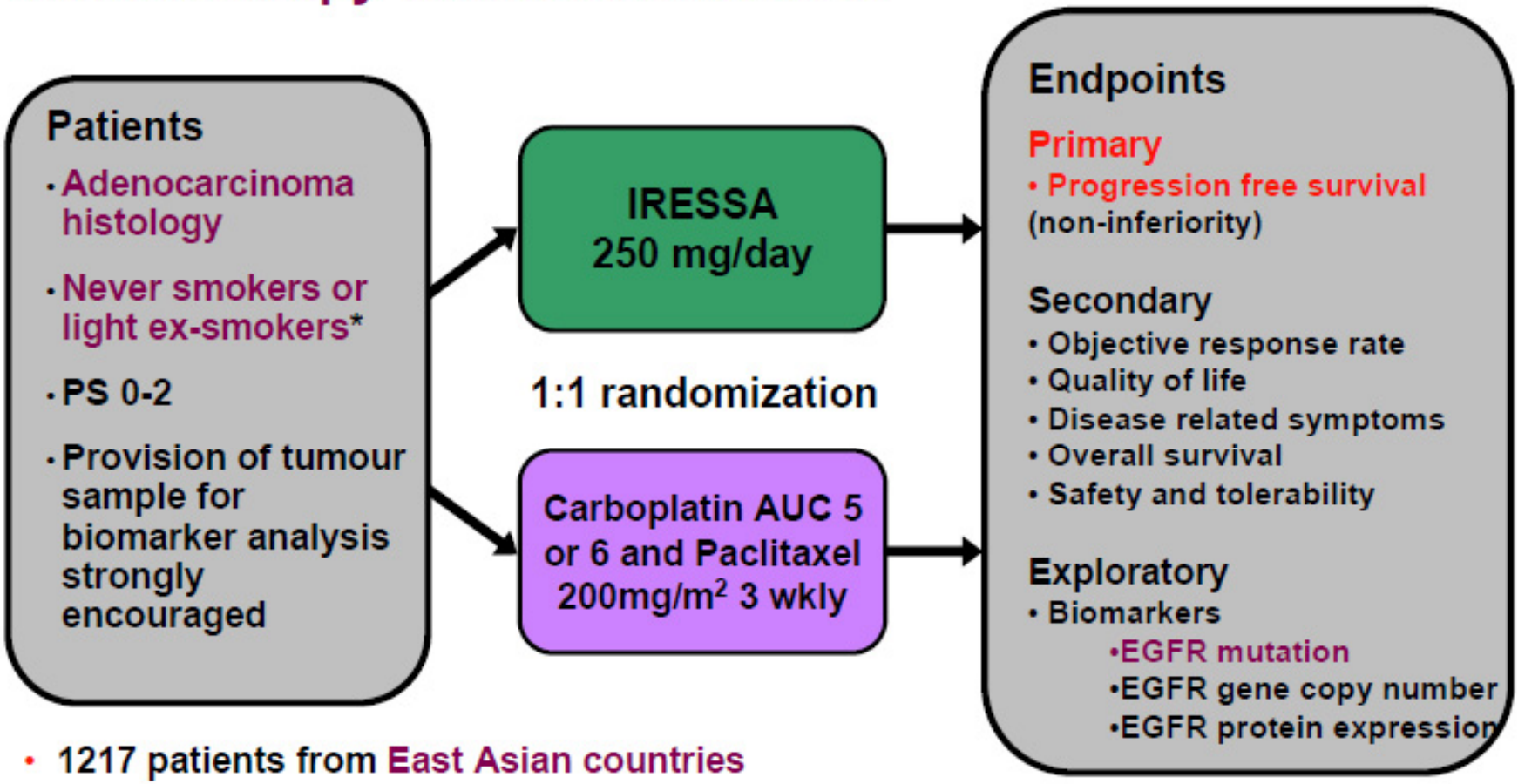


Thatcher 2005, Chang 2006

Impact of the ISEL Study

- The sponsor voluntarily withdrew the European submission after ISEL results were available.
- A number of countries in the West (US, Switzerland and Canada) limited the use of IRESSA to those already experiencing benefit from the drug. In the US, refill prescriptions were done through the IRESSA Access Program starting on 15 September 2005.
- Results in the Asian populations and the fact that Asian populations have a relatively high incidence of somatic mutations in the region of the EGFR gene led to the initiation of a Pan-Asia Study IPASS in March 2006 for 1st line therapy.

IPASS: Phase III study of IRESSA versus doublet chemotherapy in first line NSCLC



- 1217 patients from East Asian countries

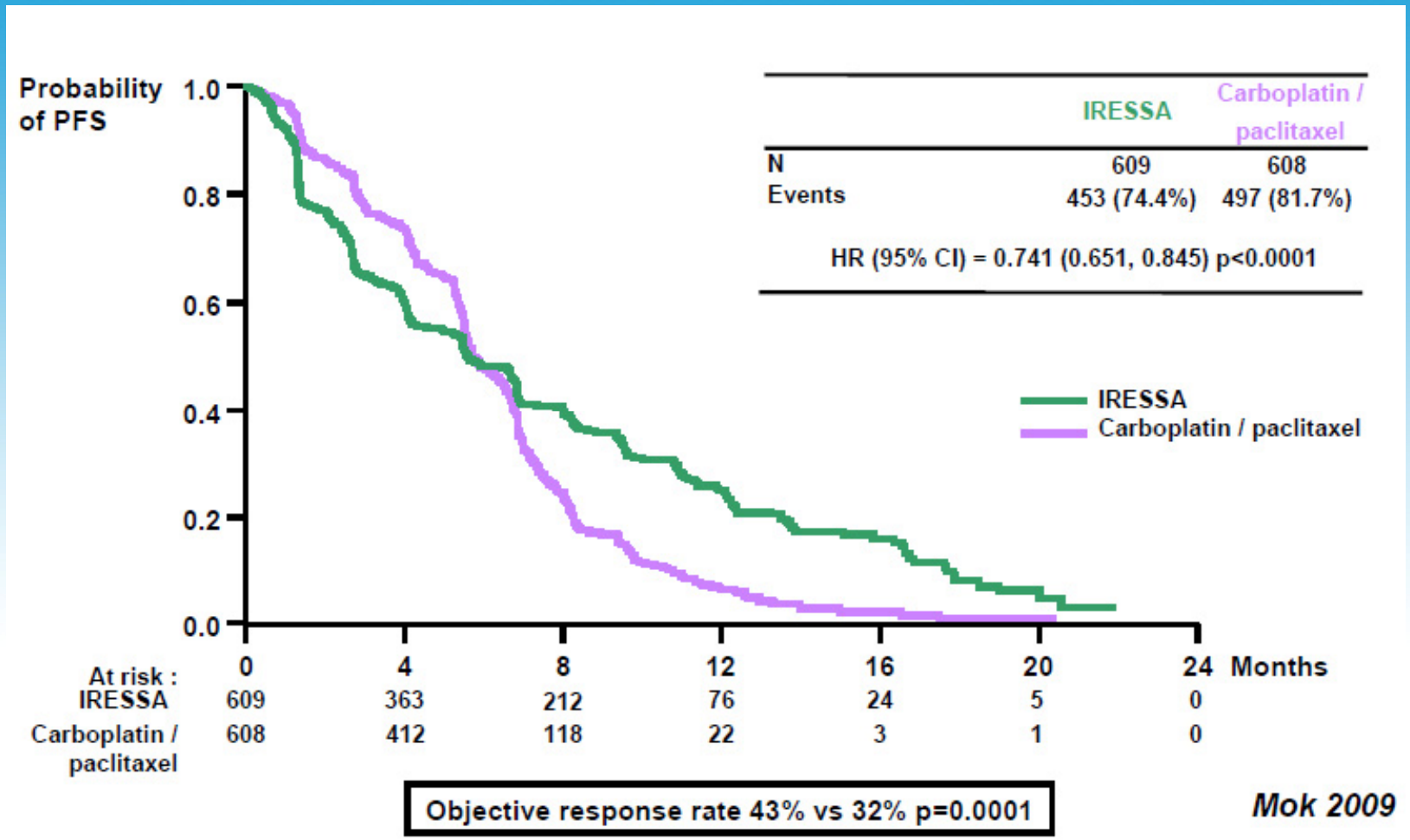
*Never smokers:<100 cigarettes in lifetime; light ex-smokers: stopped ≥15 years ago and smoked ≤ 10 pack yrs

Carboplatin/paclitaxel was offered to IRESSA patients upon progression

PS, performance status; EGFR, epidermal growth factor receptor

Mok 2009

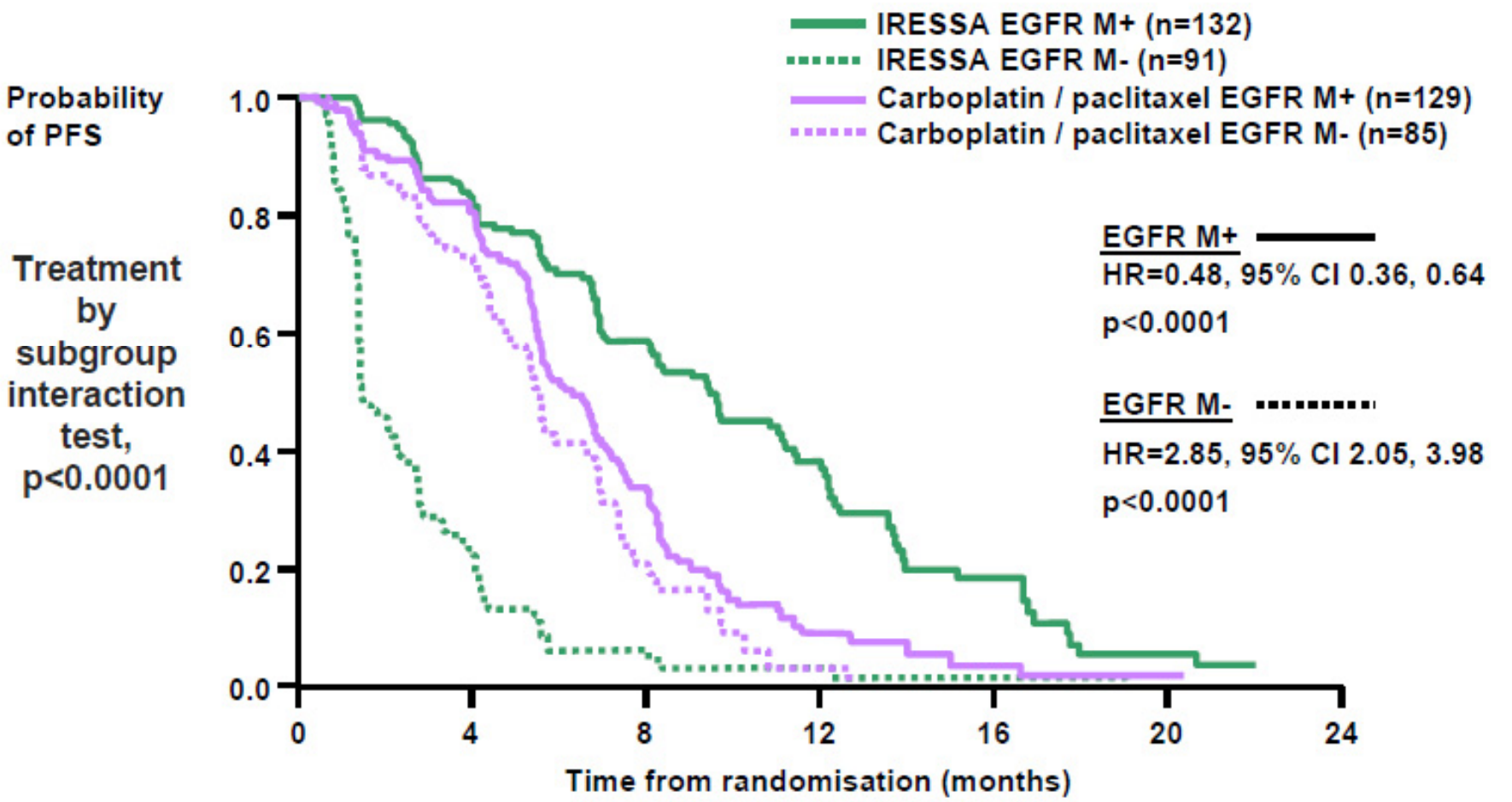
IRESSA Demonstrated a Positive Effect



Objective response rate 43% vs 32% p=0.0001

Mok 2009

IPASS: EGFR mutation is a strong predictor for differential PFS benefit between IRESSA and doublet chemotherapy



Mok 2009

M+, mutation positive; M-, mutation negative

Outcome

- European regulators approved IRESSA for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK in July 2009 for all lines of therapy.
- There has been no change in the US label since 2005.

Observations

- None of the phase 3 studies selected patients based on their EGFR mutation status at enrollment.
- Subgroups defined by EGFR mutation status were pre-specified in IPASS. The plan was to evaluate them in an exploratory analysis.
- Continuous research and accumulating knowledge led the sponsor to identify probably the strongest predictor (so far) for IRESSA's effect on progression free survival, i.e. EGFR mutation status.
- Identifying the EGFR mutation+ group greatly improved the benefit-risk profile of IRESSA.

Targeted Cancer Drugs in the News, June 2011

THE WALL STREET JOURNAL.

MONDAY, JUNE 6, 2011 - VOL. CCLVII NO. 130 ★★★★ $2.00

DJIA 12151.26 ▼290.32 -2.3% NASDAQ 2732.78 ▼2.3% NIKKEI 9492.21 ▼0.3% STOXX 600 273.67 ▼1.9% 10-YR TREASURY ▲ 22/32, yield 2.997% OIL $100.22 ▼$0.37 EURO $1.4634 YEN 80.24

What's News—

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nan plans to accuse

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World-Wide

■ **Yemen's youth opposition celebrated Saleh's departure.** The president left for surgery in Saudi Arabia after he was wounded in a rocket attack, handing power to his vice president. Protesters saw an end to Saleh's 33-year rule and rival tribes maneuvered for power. But Saleh supporters insisted he planned to return. A1, A14

Major Shift in War on Cancer

Drug Studies Focus on Genes of Individual Patients; Testing Obstacles Loom

By Ron Winslow

CHICAGO—New research is signaling a major shift in how cancer drugs are developed and patients are treated—offering the promise of personalized therapies that reach patients faster and are more effective than other medicines.

At the heart of the change: an emerging ability for researchers to use genetic information to match drugs to the biological drivers of tumors in individuals.

Studies released at the annual meeting of the American Society of Clinical Oncology here are helping to support previous findings that personalized medicine—introduced more than a decade ago—is closer to being realized as a weapon to fight cancer.

"A pattern is developing at an accelerated pace where we are able to match genetic information about a tumor to a new agent and get results," says John Mendelsohn, president of Houston's MD Anderson Cancer Center.

Despite the progress, researchers stress, most personalized treatments don't necessarily offer a cure. Currently about 800 cancer drugs are in development, many of them designed to target specific mutations. It may take changes in regulatory policy and the development of new diagnostic tests in order for successful therapies to come onto the market. Another issue is cost. The targeted drugs already available run into the tens of thousands a year.

One study led by doctors at

Please turn to the next page

Xalkori Approved in US, 26 Aug 2011

- US FDA granted accelerated approval to crizotinib (250 mg orally, twice daily) for the treatment of locally advanced or metastatic NSCLC that is ALK+.
- On the same day, FDA approved the Vysis ALK Break-Apart Fish Probe Kit as a diagnostic test for ALK.
- The approval was based on objective response rate (ORR) in two multi-center single-arm trials (sample size of 136 and 119 each) in patients with locally advanced or metastatic ALK+ NSCLC.
- ORR is 50% with a median response duration of 42 weeks in one study (A8081005, primary) and 61% with a 48 weeks duration in another (A8081001, supportive).

Crizotinib in ALK-Positive Advanced NSCLC

Protocol	Setting	ALK+ Patient Selection	Trial Design	Primary Endpoints
A8081001	All Lines Solid Tumors ALK-Positive NSCLC	LDT*	Single-Arm, Open-Label	Safety, PK, ORR
A8081005	≥2nd-Line	IUO**	Single-Arm, Open-Label	ORR, Safety
A8081007 (confirmatory Phase 3)	2nd-Line	IUO**	Crizotinib vs. Pemetrexed or Docetaxel, Open-Label	Progression free survival (PFS)
A8081014 (confirmatory Phase 3)	1st-Line	IUO**	Crizotinib vs. Pem/Carbo or Pem/Cis, Open-Label	Progression free survival (PFS)

* Laboratory Developed Test – multiple used but most samples confirmed by one (MGH)
** Investigational Use Only, Abbott's test

Xalkori: A Poster Child for TCT Development

- Clinical testing began with A8081001 in 2006.
- Discovery of the EML4-ALK fusion gene was published in *Nature*, Aug 2 2007.
- A8081001 had multiple amendments.
  - Part 1 was to determine MTD.
  - In April 2007, study was amended to include a cohort of molecularly targeted patients. In October 2007, study was amended to add EML4 as an option. Part 2 included only molecularly targeted patients (NSCLC ALK+ and others).
- Observed clinical responses in ALK+ NSCLC in 2008.
- The first phase 3 trial was initiated in 2010.

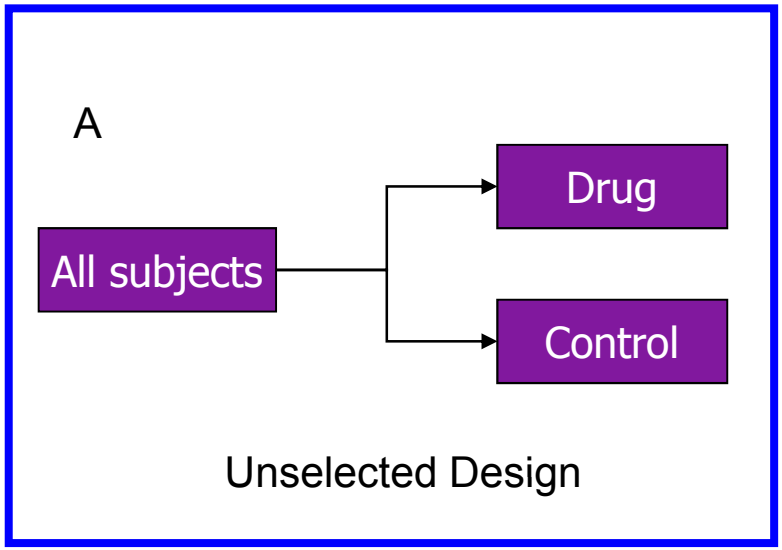
Returning to the IRESSA Story

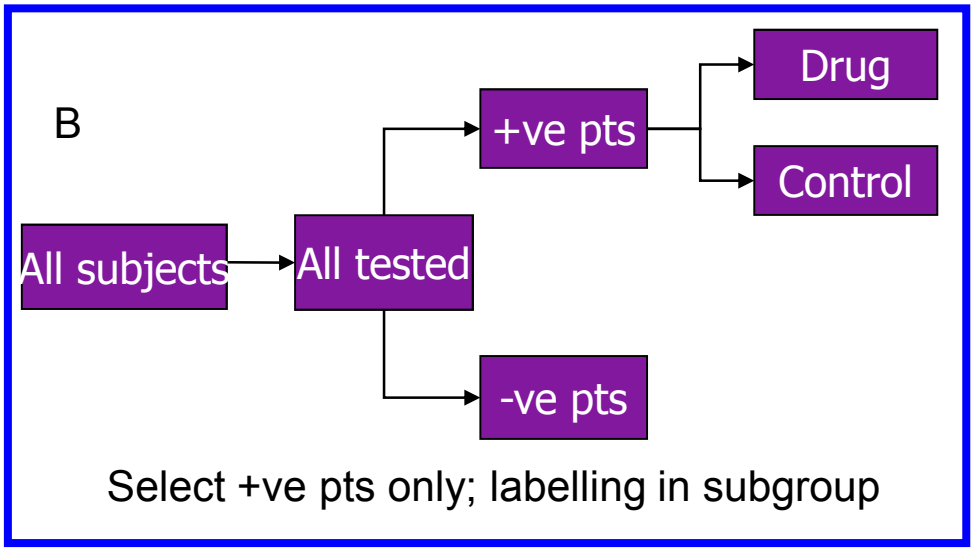
- In the final analysis of IPASS, overall survival (a secondary endpoint) was similar between patients who received IRESSA and who received the comparator.
- With highly effective targeted cancer therapies, our ability to demonstrate an overall survival benefit may be in doubt because of the strong need to let patients cross over upon disease progression (Shaw et al, www.thelancet.com/oncology, online Sept 19 2011).
- How will the above change the current paradigm regarding endpoint selection and study design?

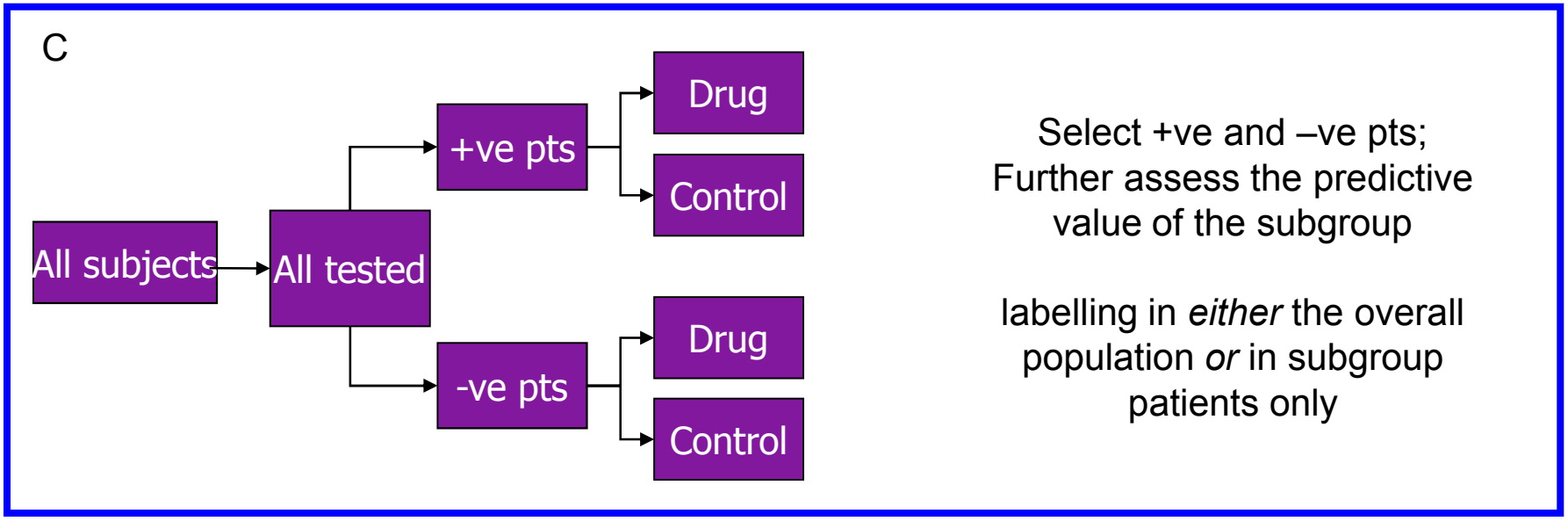
Revisit the Subgroup Question

- In general, do we enroll all comers? Or do we have enough confidence or preliminary info in a biomarker to limit enrollment to a biomarker-defined subgroup?
- IRESSA program pre-specified several subgroups for exploratory analyses. When are we ready to make a subgroup analysis confirmatory and willing to control Type I error over the subgroup analysis?
- How much faith do we have in the diagnostic test for the biomarker? Is the test a laboratory developed test, a test for investigational use only or is it commercially available? What do we have to do to develop a treatment and the companion diagnostic simultaneously?

Best Choice for Phase 3 (Kevin Carroll, 2011)?







Some Adaptations for All-comers Design

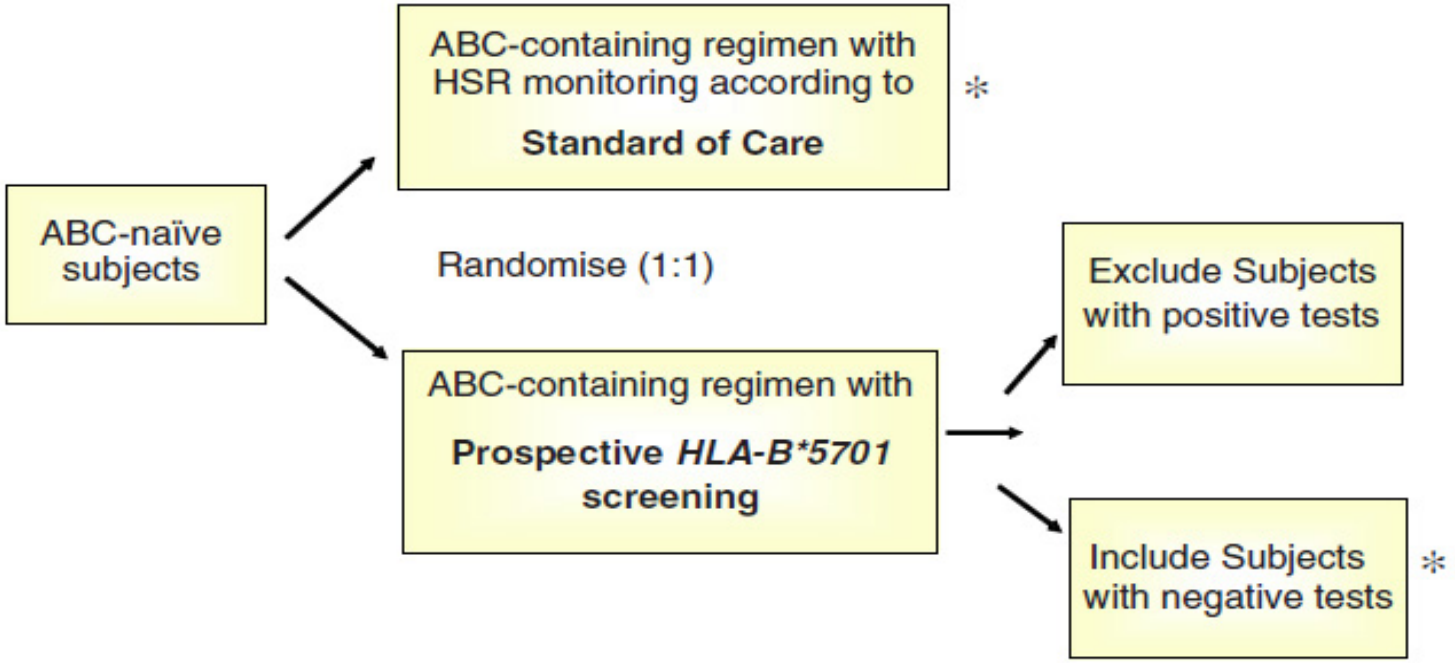
- **Adaptive Selection Design**
  - Enroll all comers to start with; select a subgroup based on an interim analysis and limit future enrollment to the subgroup.
- **Adaptive Signature Design**
  - Enroll all comers; use 0.04 to test for all patients or use the first half to search for the subgroup most likely to benefit and test this subgroup using the second half at the 0.01 level (Freidlin and Simon, 2005).
- **Biomarker Adaptive Threshold Design**
  - Assay is ready for use except for the cutoff (Jiang, 2007).

PREDICT-1 : Background

- First adequately powered, double-blind prospective trial using pharmacogenetic screening to reduce drug adverse event. Recruitment April – Sept 2006.
- Background
  - Abacavir (ABC) is a nucleoside-analogue reverse-transcriptase inhibitor antiretroviral drug.
  - ABC is associated with hypersensitivity reaction (ABC HSR) in about 5% - 8% patients.
  - Retrospective studies suggest a strong association between ABC HSR and the presence of the major histocompatibility complex HLA-B*5701 in chromosome 6.

Source: Hughes et al. (2008). Pharm Stat, 7:121-129.

Design of PREDICT-1



*Clinically suspected HSR confirmed using patch testing
(blinded analysis by independent dermatologist)

Figure 1. Illustration of basic study design.

Source: Hughes et al. (2008). Pharm Stat, 7:121-129.

Results from PREDICT-1

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*	P Value
	no. of patients/total no. (%)			
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	P<0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	P<0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	P<0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	P<0.001

*: P-values, odds ratios, and 95% confidence intervals were obtained from fitting logistic regression models with several covariates.

Source: Mallal et al. (2008). NEJM, 358:568-579.

Concordance Study

- A laboratory-developed test (LDT) is used in the trials. An Investigational Use Only (IUO) test is being developed for commercial use and supporting drug approval. What are the regulatory expectations of IUO to win approval?
- PPA = Positive % Agreement; NPA: Negative % Agreement

		IUO	
		+	-
LDT	+	*a*	*b*
	-	*c*	*d*

$$PPA = \frac{a}{a + b}$$

$$NPA = \frac{d}{c + d}$$

Implicit Regulatory Expectations

- **FDA guidance (2007)* recommends reporting a two-sided 95% CI for PPA and NPA, respectively.**
- **In one case, it was hinted that the lower limit of a one-sided 95% CI for PPA (NPA) should be > 95%.**
- **Questions**
  - What is the scientific rationale for the expectations? Could we relax the rule a bit if the treatment effect in the marker+ and marker- subgroups by LDT differ *substantially*? When the target prevalence is low, should we have different criteria for PPA and NPA?
  - An area for research.

Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests.

At the Xalkori Launch, 25 Oct 2011

Patient testimonials

- **"I was one of the first to go on the crizotinib trial back in 2008… I took this chance and I had a phenomenal experience. I am fortunate enough to be one of the first travelers on this boat into this new world."**
- **"We are on the precipice of something amazing. I think we're going to be seeing more and more therapies emerging in the near future, which bring us all a great deal of hope…"**

Personalized Medicines,

Targeted Therapies,

Beacons of Hope for Patients.

Acknowledgment

- **Kevin Carroll**