Is there a role for targeted agents in stage I-III NSCLC?

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Disclosure slide

- Involved in investigator-initiated clinical trials supported by Roche and Eli Lilly
- No other potential conflicts of interest

Current status

- Targeted agents are promising for selected patients with resectable NSCLC stage I-III.
- If possible, patients should be enrolled in clinical trials.

What we want

Use *cancer-specific* drugs that

- are highly active, well tolerated, and have no negative impact on surgery, radiation and chemotherapy,
- enhance cure rate (eradicate cancer), or at least delay tumor recurrence (control cancer).

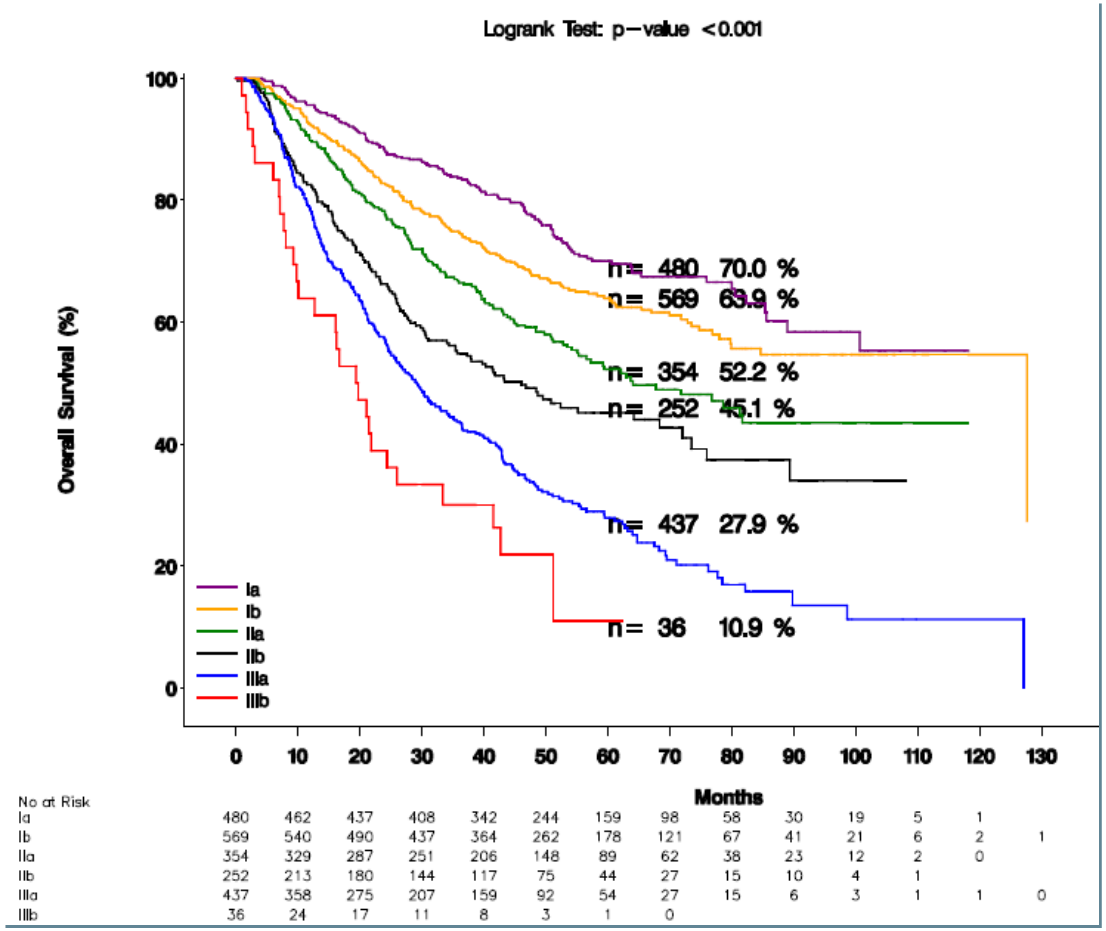
What we do *not* want

Add drugs which

- preclude curative standard therapy,
- increase (long-term) toxicity,
- produce secondary (lung) cancers,
- lead to early drug resistance.

The Problem: Prognosis

5-Year Survival Rates and Numbers of Cases

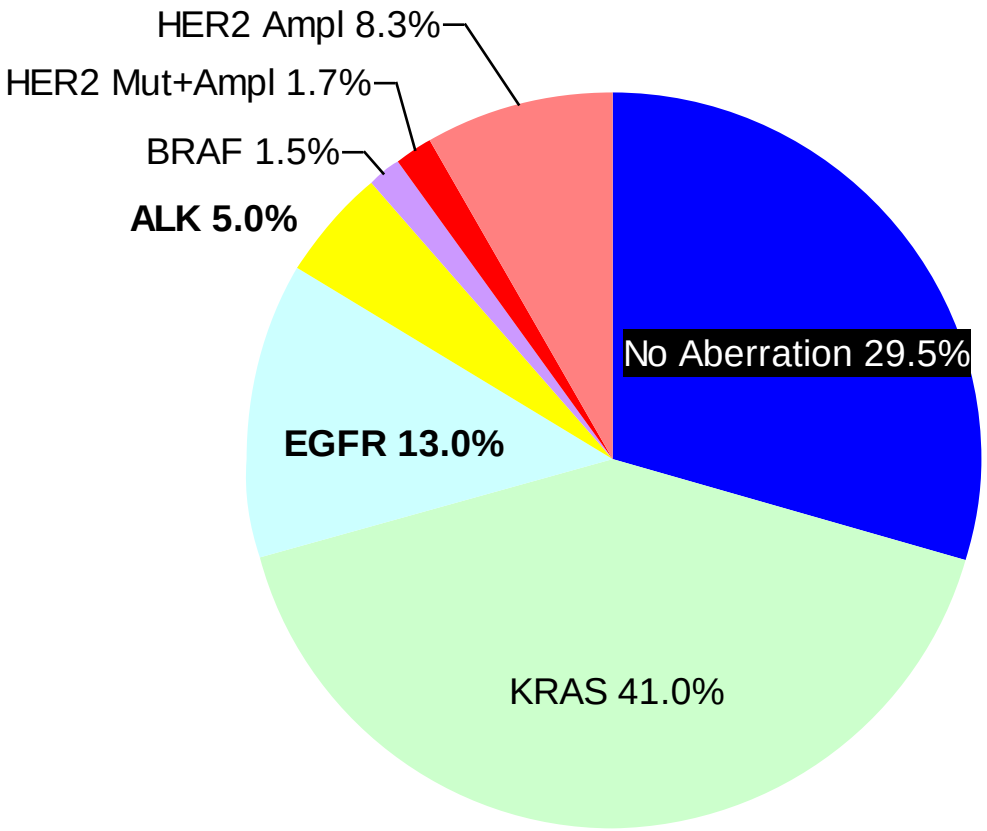


Courtesy of Solange Peters

etop
Information | Research

The Promise: Mutations

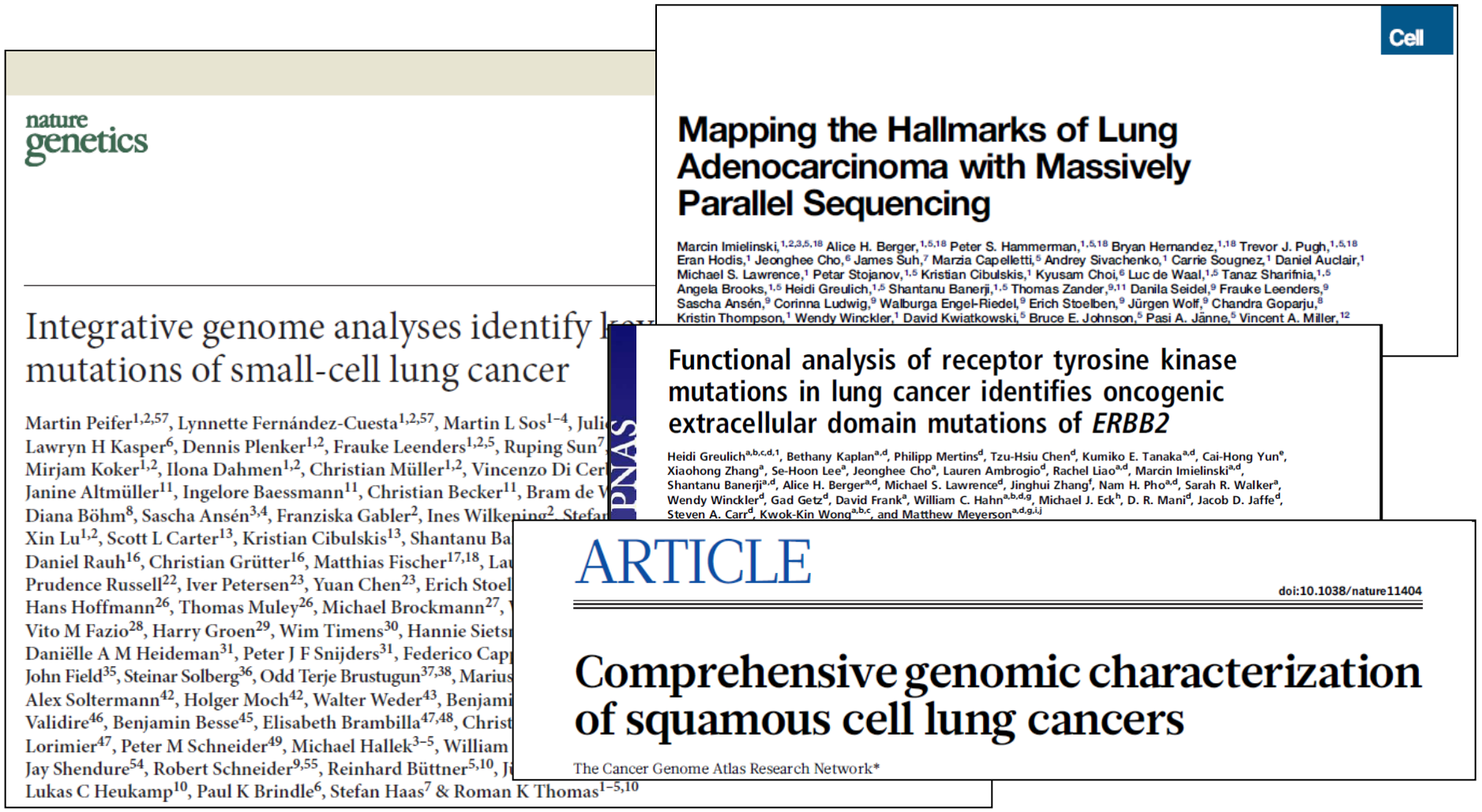
Clinical testing March 2011-June 2012 (N=105)



Courtesy of Joachim Diebold

luzerner kantonsspital
LUZERN SURSEE WOLHUSEN

September 2012 :
Lung Cancer Genome Unraveled



nature genetics

Integrative genome analyses identify k
mutations of small-cell lung cancer

Martin Peifer[1,2,57], Lynnette Fernández-Cuesta[1,2,57], Martin L Sos[1–4], Juli
Lawryn H Kasper[6], Dennis Plenker[1,2], Frauke Leenders[1,2,5], Ruping Sun[7]
Mirjam Koker[1,2], Ilona Dahmen[1,2], Christian Müller[1,2], Vincenzo Di Cer
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Diana Böhm[8], Sascha Ansén[3,4], Franziska Gabler[2], Ines Wilkeping[2], Stefa
Xin Lu[1,2], Scott L Carter[13], Kristian Cibulskis[13], Shantanu Ba
Daniel Rauh[16], Christian Grütter[16], Matthias Fischer[17,18], La
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Hans Hoffmann[26], Thomas Muley[26], Michael Brockmann[27],
Vito M Fazio[28], Harry Groen[29], Wim Timens[30], Hannie Sietsr
Daniëlle A M Heideman[31], Peter J F Snijders[31], Federico Capp
John Field[35], Steinar Solberg[36], Odd Terje Brustugun[37,38], Marius
Alex Soltermann[42], Holger Moch[42], Walter Weder[43], Benjami
Validire[46], Benjamin Besse[45], Elisabeth Brambilla[47,48], Christ
Lorimier[47], Peter M Schneider[49], Michael Hallek[3–5], William
Jay Shendure[54], Robert Schneider[9,55], Reinhard Büttner[5,10], Ji
Lukas C Heukamp[10], Paul K Brindle[6], Stefan Haas[7] & Roman K Thomas[1–5,10]

Cell

Mapping the Hallmarks of Lung Adenocarcinoma with Massively Parallel Sequencing

Marcin Imielinski,[1,2,3,5,18] Alice H. Berger,[1,5,18] Peter S. Hammerman,[1,5,18] Bryan Hernandez,[1,18] Trevor J. Pugh,[1,5,18] Eran Hodis,[1] Jeonghee Cho,[6] James Suh,[7] Marzia Capelletti,[5] Andrey Sivachenko,[1] Carrie Sougnez,[1] Daniel Auclair,[1] Michael S. Lawrence,[1] Petar Stojanov,[1,5] Kristian Cibulskis,[1] Kyusam Choi,[6] Luc de Waal,[1,5] Tanaz Sharifnia,[1,5] Angela Brooks,[1,5] Heidi Greulich,[1,5] Shantanu Banerji,[1,5] Thomas Zander,[9,11] Danila Seidel,[9] Frauke Leenders,[9] Sascha Ansén,[9] Corinna Ludwig,[9] Walburga Engel-Riedel,[9] Erich Stoelben,[9] Jürgen Wolf,[9] Chandra Goparju,[8] Kristin Thompson,[1] Wendy Winckler,[1] David Kwiatkowski,[5] Bruce E. Johnson,[5] Pasi A. Jänne,[5] Vincent A. Miller,[12]

PNAS

Functional analysis of receptor tyrosine kinase mutations in lung cancer identifies oncogenic extracellular domain mutations of *ERBB2*

Heidi Greulich[a,b,c,d,1], Bethany Kaplan[a,d], Philipp Mertins[d], Tzu-Hsiu Chen[d], Kumiko E. Tanaka[a,d], Cai-Hong Yun[e], Xiaohong Zhang[a], Se-Hoon Lee[a], Jeonghee Cho[a], Lauren Ambrogio[d], Rachel Liao[a,d], Marcin Imielinski[a,d], Shantanu Banerji[a,d], Alice H. Berger[a,d], Michael S. Lawrence[d], Jinghui Zhang[f], Nam H. Pho[a,d], Sarah R. Walker[a], Wendy Winckler[d], Gad Getz[d], David Frank[a], William C. Hahn[a,b,d,g], Michael J. Eck[h], D. R. Mani[d], Jacob D. Jaffe[d], Steven A. Carr[d], Kwok-Kin Wong[a,b,c], and Matthew Meyerson[a,d,g,i,j]

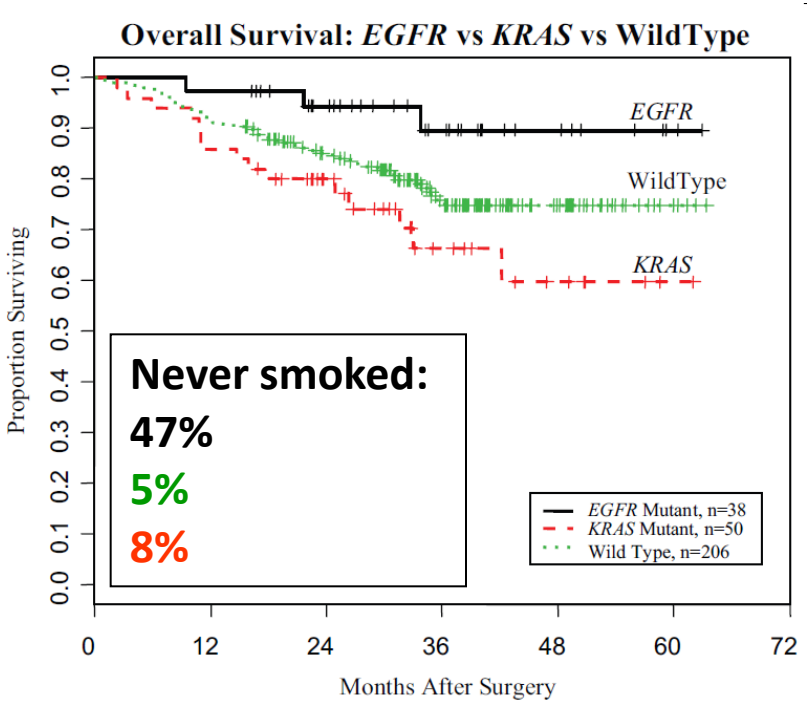
ARTICLE

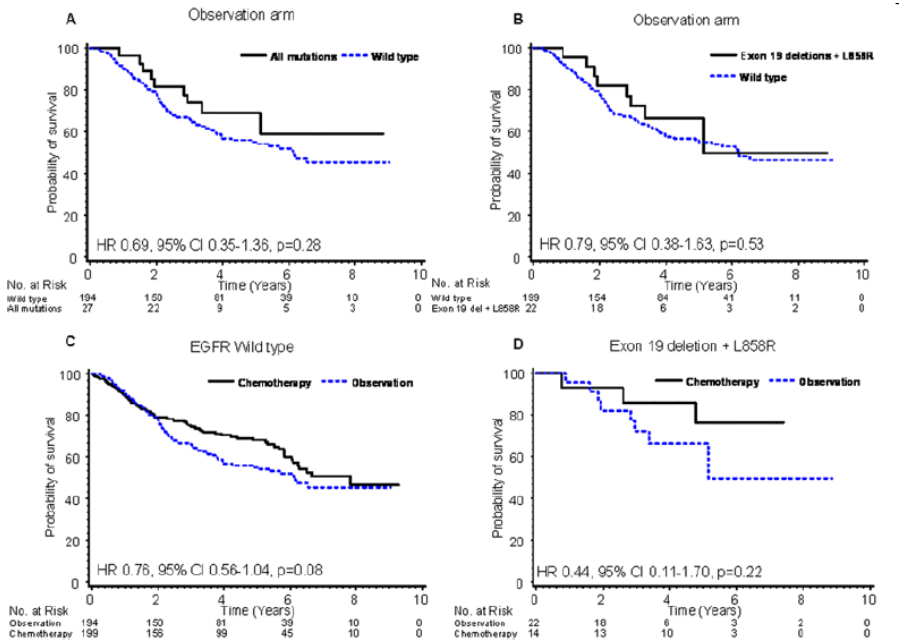
doi:10.1038/nature11404

Comprehensive genomic characterization of squamous cell lung cancers

The Cancer Genome Atlas Research Network*

Mutations: Do they affect prognosis and adjuvant chemotherapy ?

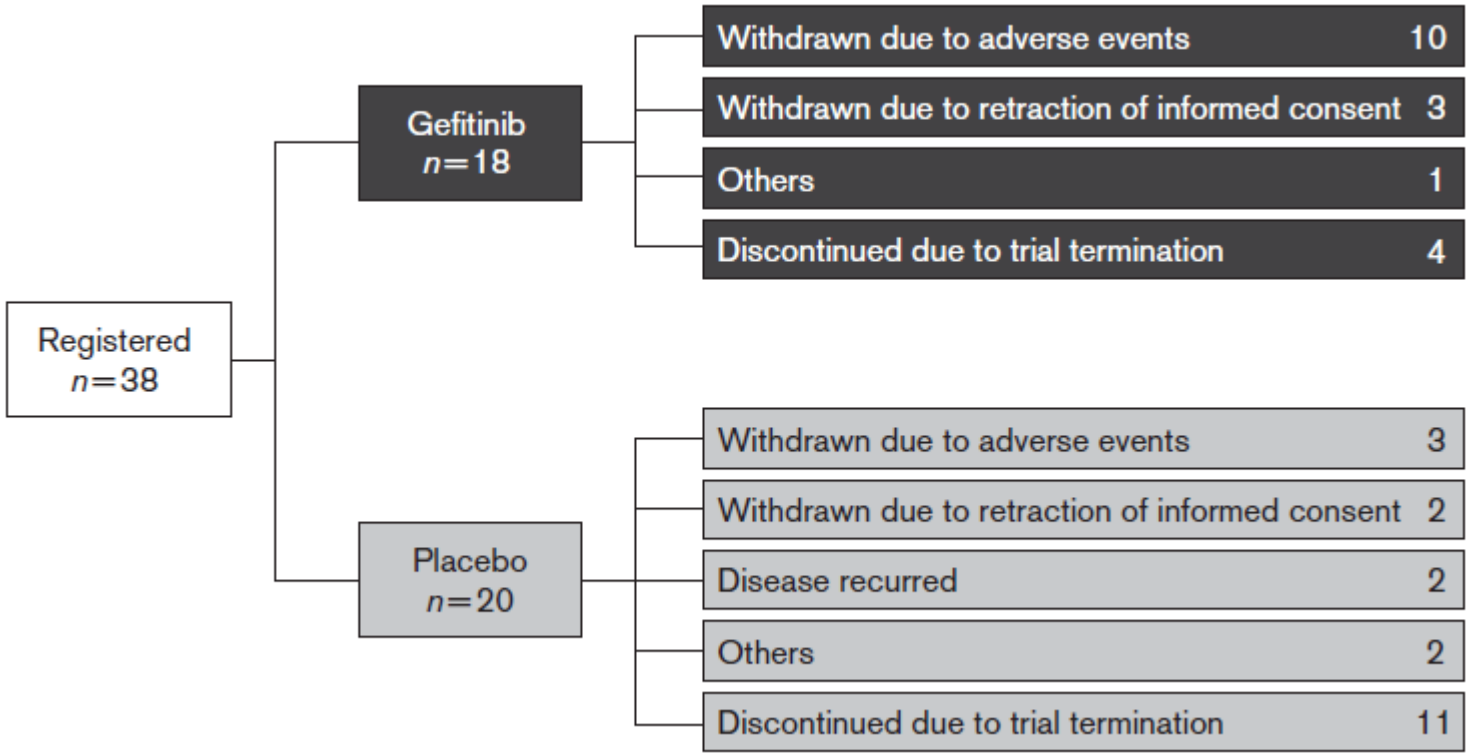




Marks, JTO 2008
Tsao, JTO 2011 (NCIC BR10)

Phase III adjuvant gefitinib (Japan)

Concern about ILD in advanced NSCLC: early closure

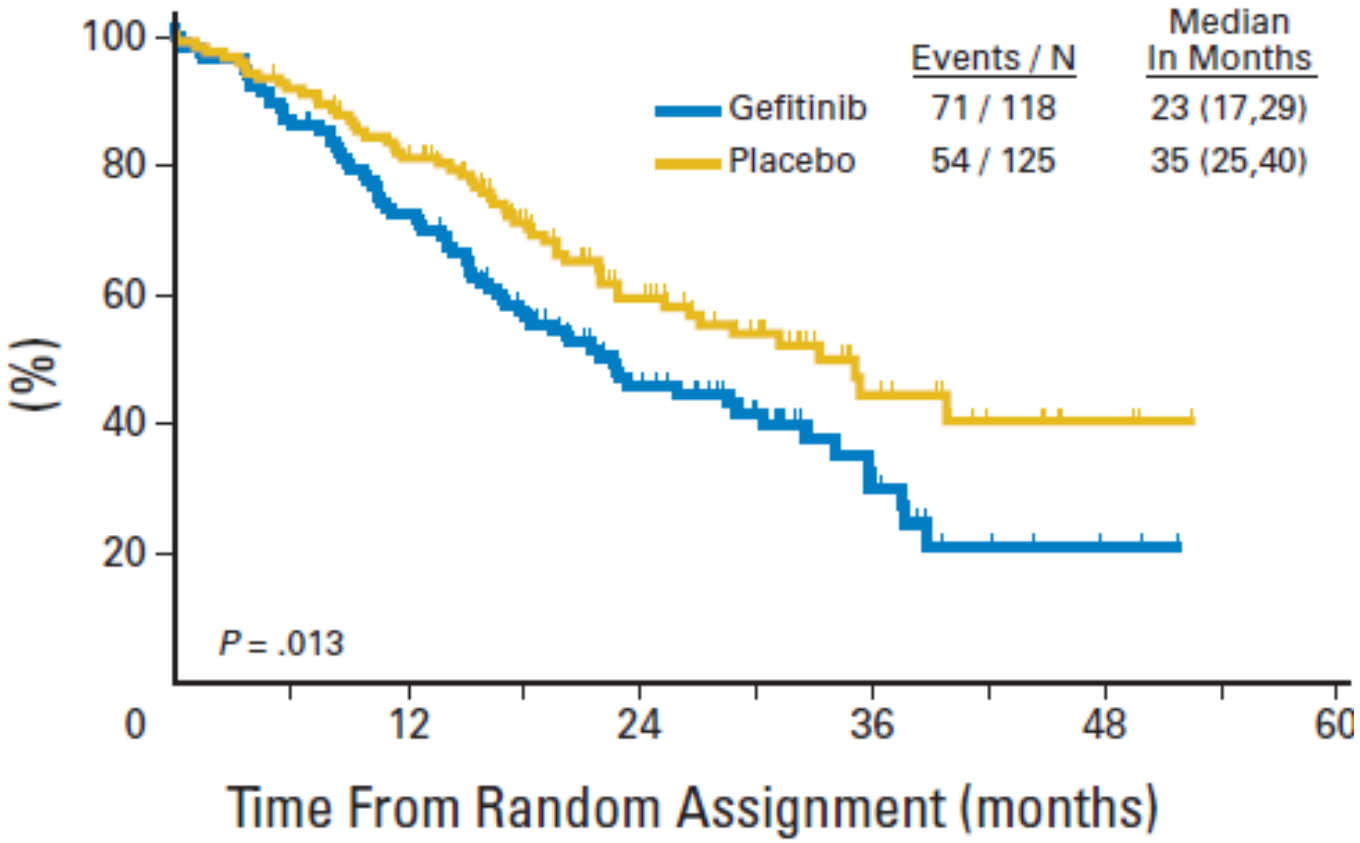


1 ILD

2 ILDs

Tsuboi, Anti-Cancer Drugs 2005

S0023: Maintainance gefitinib or placebo after CRT in stage III



Kelly JCO 2008

BR.19 - Schema

Pts with completely resected stage IB,II, and IIIA NSCLC

Stratified by
- stage
- histology
- post-op RT
- sex
- adjuvant chemotherapy*

Randomized 1:1

Gefitinib
250 mg po
daily x 2 yrs

Placebo
0 mg po
daily x 2 yrs

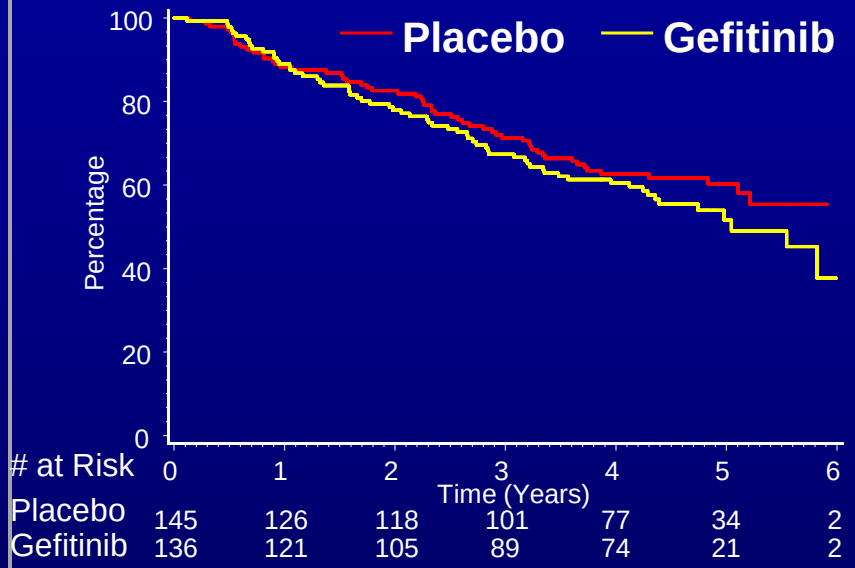
*Protocol amended January 2003 to allow adjuvant chemotherapy which became a stratification factor

NCIC CTG
NCIC GEC

Courtesy of G. Goss

Overall Survival by *EGFR* Mutation Status and Treatment

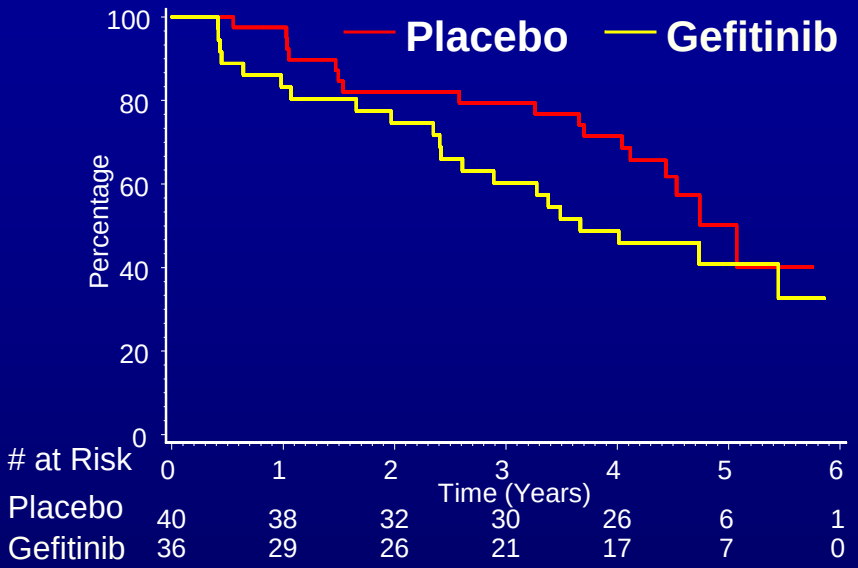
Wild type



HR (95% C.I.)
Gefitinib/Placebo: 1.21 (0.84, 1.73)
Log Rank: p=0.301

Median (95% C.I.)
-Placebo: Not reached (5.1, inf.)
-Gefitinib: 5.0 (4.3, inf.)

Sensitizing mutation



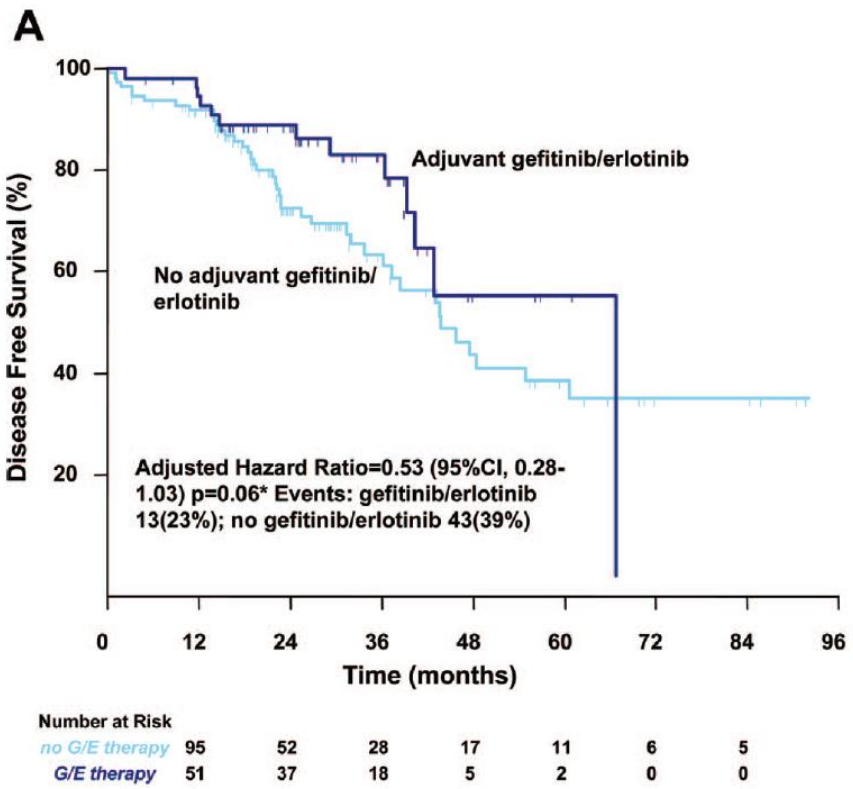
HR (95% C.I.)
Gefitinib/Placebo: 1.58 (0.83, 3.00)
Log Rank: p=0.160

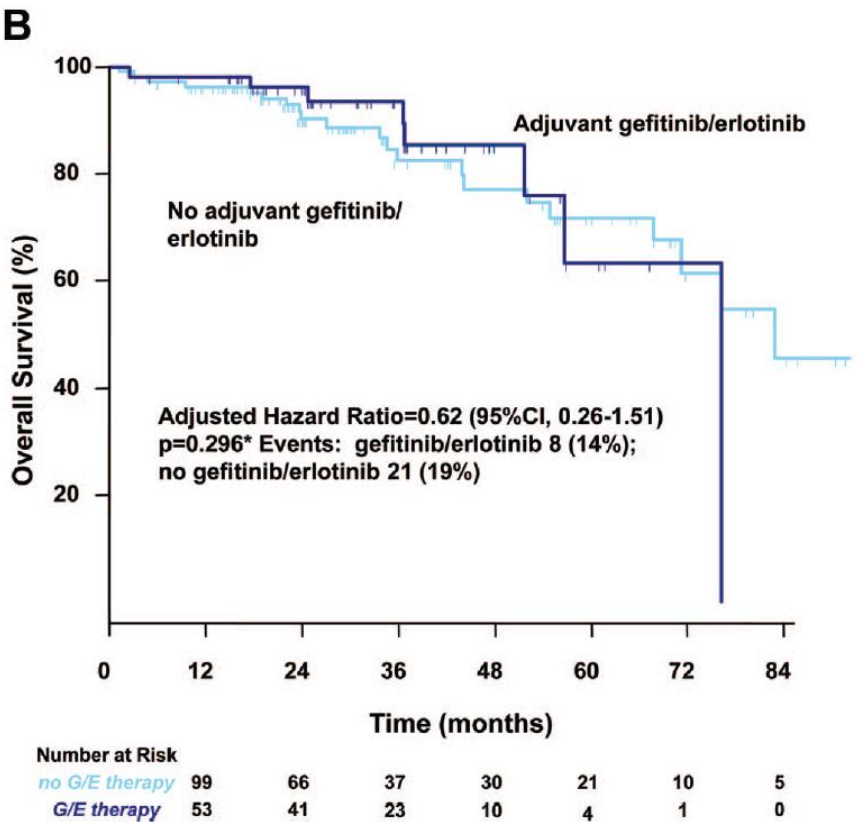
Median (95% C.I.)
- Placebo: 5.1 (4.4, inf.)
- Gefitinib: 3.7 (2.6, inf.)

NCIC CTG
NCIC GEC

Courtesy of G. Goss

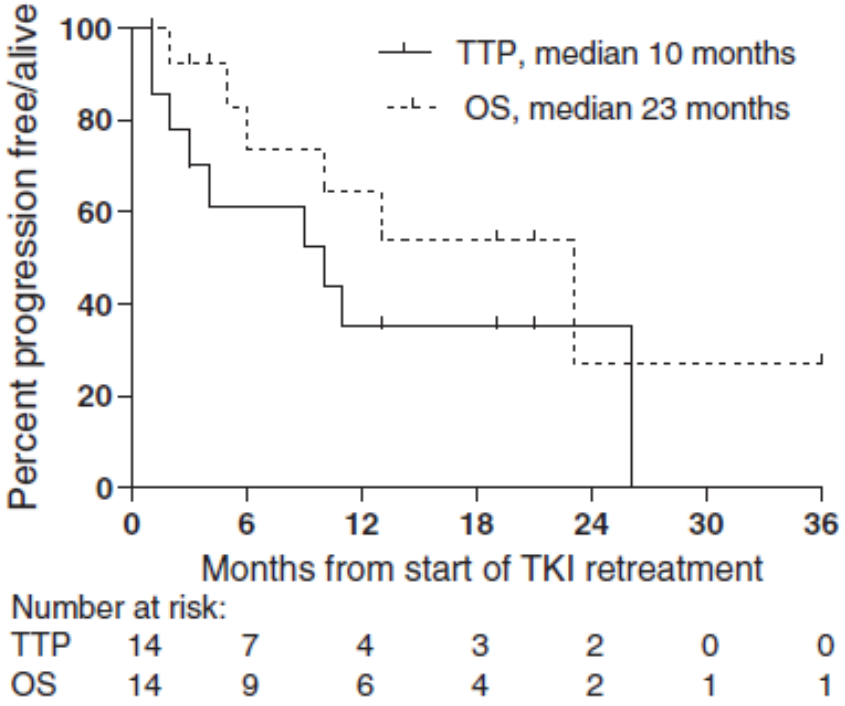
MSKCC-Cohort





Janjigian, JTO 2011

MSKCC: recurrences

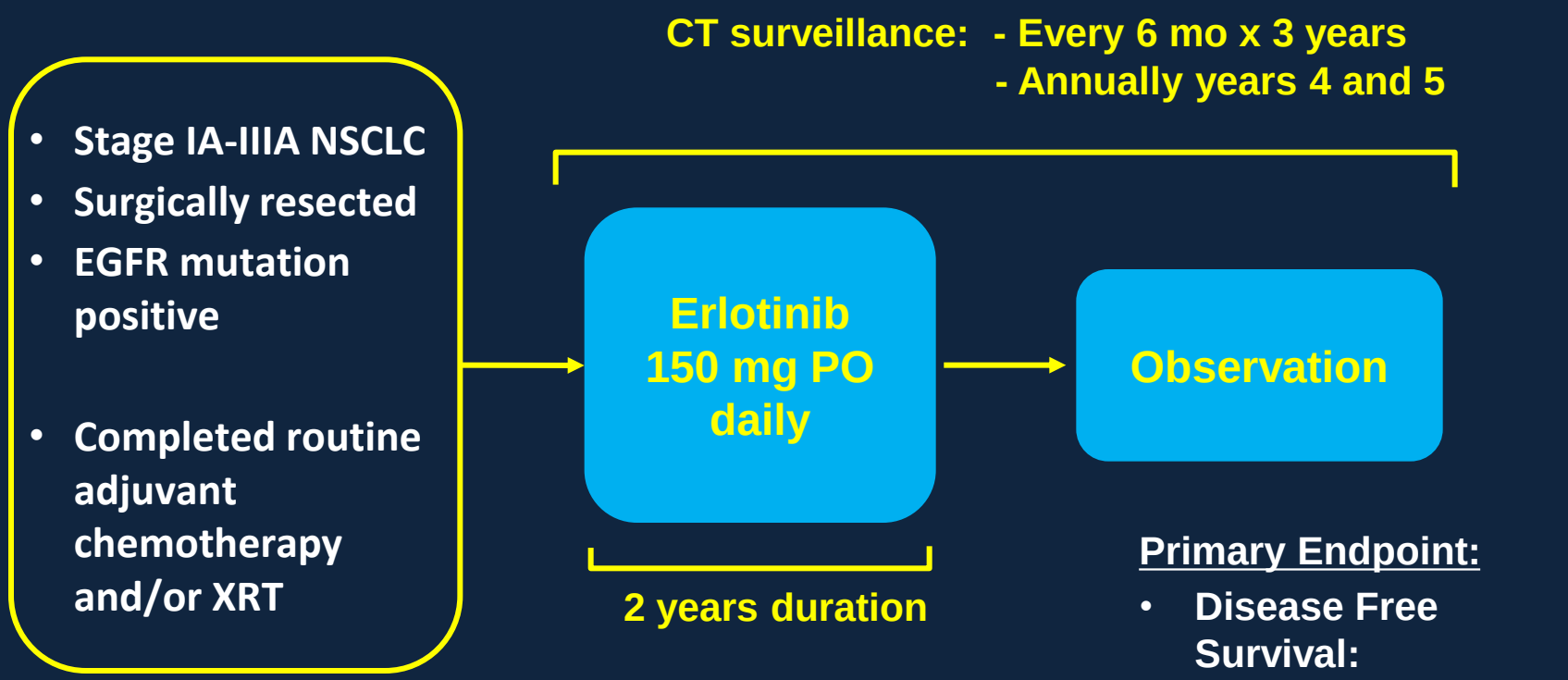


- 22/65 evaluable
- 15 on TKI, 7 after TKI
- 14 retreated with TKI
- ORR=73%

Oxnard, Clin Cancer Res 2011

SELECT: Study Design

- Single arm Phase II study
- Adjuvant erlotinib following surgery and "standard" therapy



Primary Endpoint:

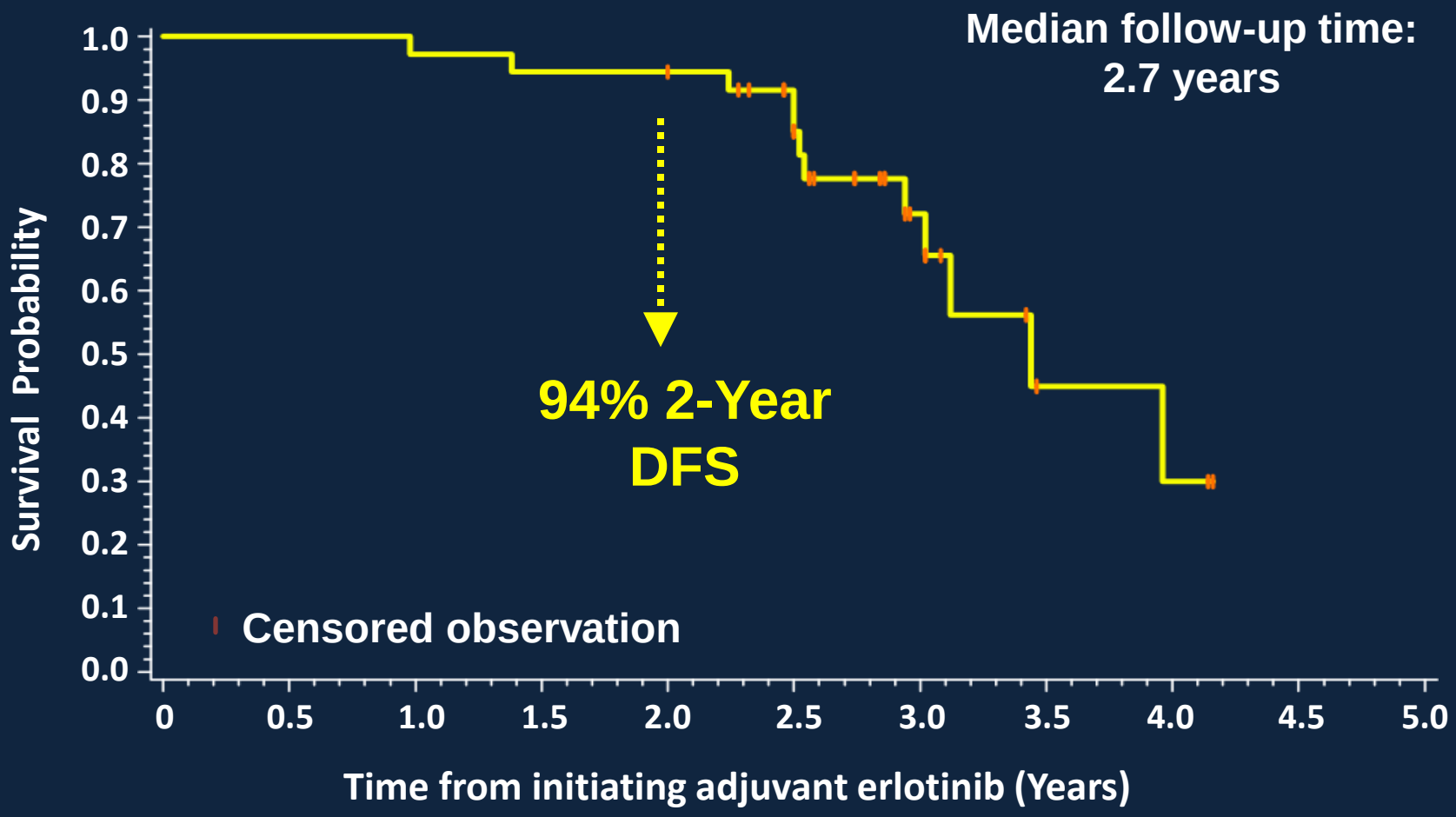
- Disease Free Survival:
  Goal: 2-year >86%

Secondary Endpoints:

- Safety and Tolerability
- Overall Survival

Courtesy of L. Sequist

SELECT: Disease Free Survival



Patients at Risk	36	35	34	34	33	19	7	3	1	0

Courtesy of L. Sequist

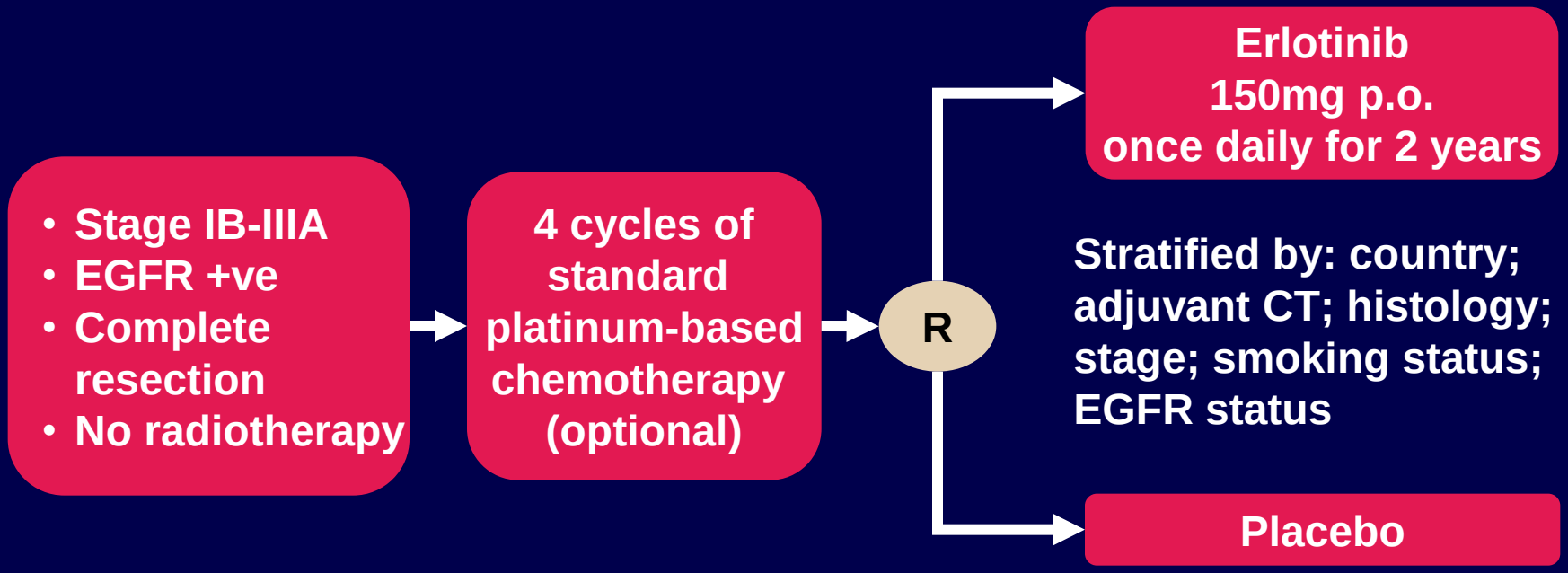
SELECT: Treatments After Progression

Initial stage	Adjuvant duration (mo)	Disease free interval (mo)	Site(s) of progression	Initial mutation	Repeat biopsy	Subsequent therapy	Response to erlotinib	Survival Post-Progression (mo)
IB	24	17	Lung nodules	Ex 19	Ex19	Erlotinib	Yes - PR	12+
IIB	24	3	Multiple brain, lung nodules	L858R	-	Erlotinib	Yes	26+
IB	24	23	Multiple brain + bone	L858R	-	Erlotinib	Yes - PR	4+
IIIA	11	24	Solitary lung	Ex 19	Ex19	Lung resection	-	6+
IIIA	23	13	Solitary bone	Ex 19	Ex19	Bone XRT -> Erlotinib	NMD	7+
IIA	23	14	Solitary brain	L858R	L858R+ T790M	Brain resection -> XRT	-	7+
IB	24	6	Solitary lung	L858R	L858R+ PIK3CA+ β-cat	Lung resection	-	12+
IIB	0.8	11	Lung nodules	Ex 19	-	Erlotinib	Yes	13 (Died)
IB	24	7	Solitary CNS	L858R	L858R	Brain resection -> Erlotinib	NMD	5+
IB	24	6	2 brain + Hilar node	L858R	L858R	Brain XRT -> erlotinib	Yes – CR	4+
IIIA	11	19	Lung, liver, adrenal, bone	L861Q	L861Q	Bone XRT -> Erlotinib	Yes	7+
IIB	16	0	Lung, brain	Ex 19	-	Brain XRT	-	2 (Died)

PR = partial response CR = complete response
PD = progressive disease NMD = no measurable disease

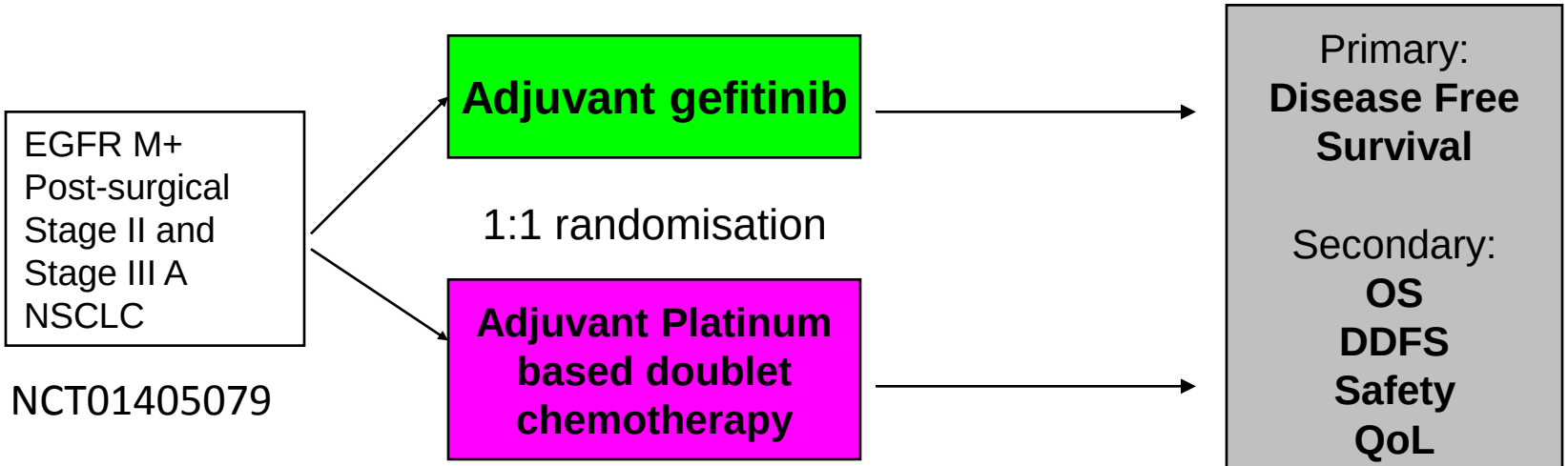
Courtesy of L. Sequist

RADIANT



- Primary endpoint = disease-free survival (all patients, IHC+ve and/or FISH+ve)
- Status: Closed
  - planned n=945 / actual accrual n=1252

CTONG1104: A national, multi center, randomized, open-label, phase III trial of gefitinib versus combination of vinorelbine plus platinum as adjuvant treatment in pathological stage II-IIIA(N1-N2) NSCLC with EGFR activating mutation (**ADJUVANT**)



FPI: Sep.15, 2011

- Sample size was estimated to be 220 when HR of DFS, the primary endpoint, was estimated to be 0.6, the enrollment period was to be 2 years, the period of follow-up after the final enrollment was to be 5 years, statistically significant level (α) was to be 0.05, and the statistical power was to be 80%. The estimated total events is 122 from 208 analysed patients

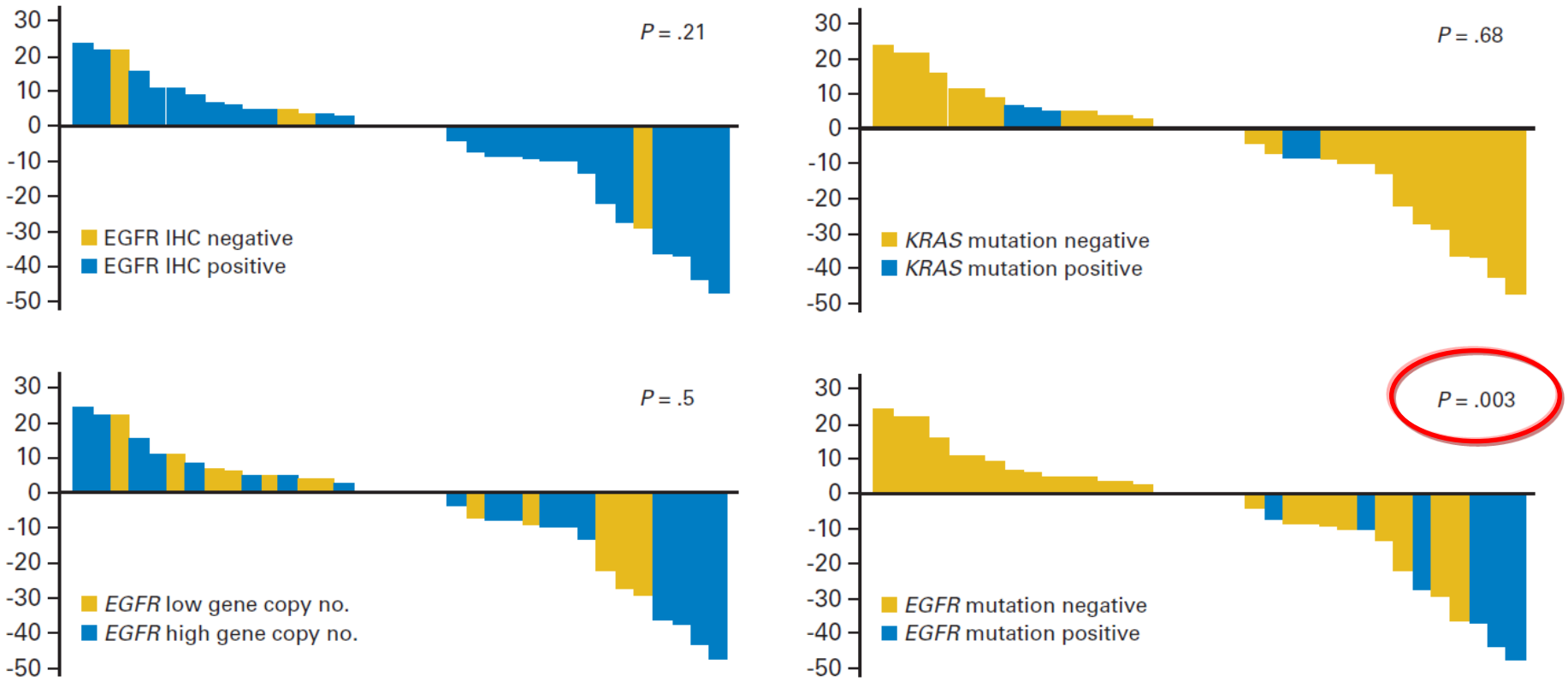
Courtesy of T. Wu

Window of opportunity trials

- Short course -> rapid results
- Preoperative -> tissue
- Confined sample size -> budget

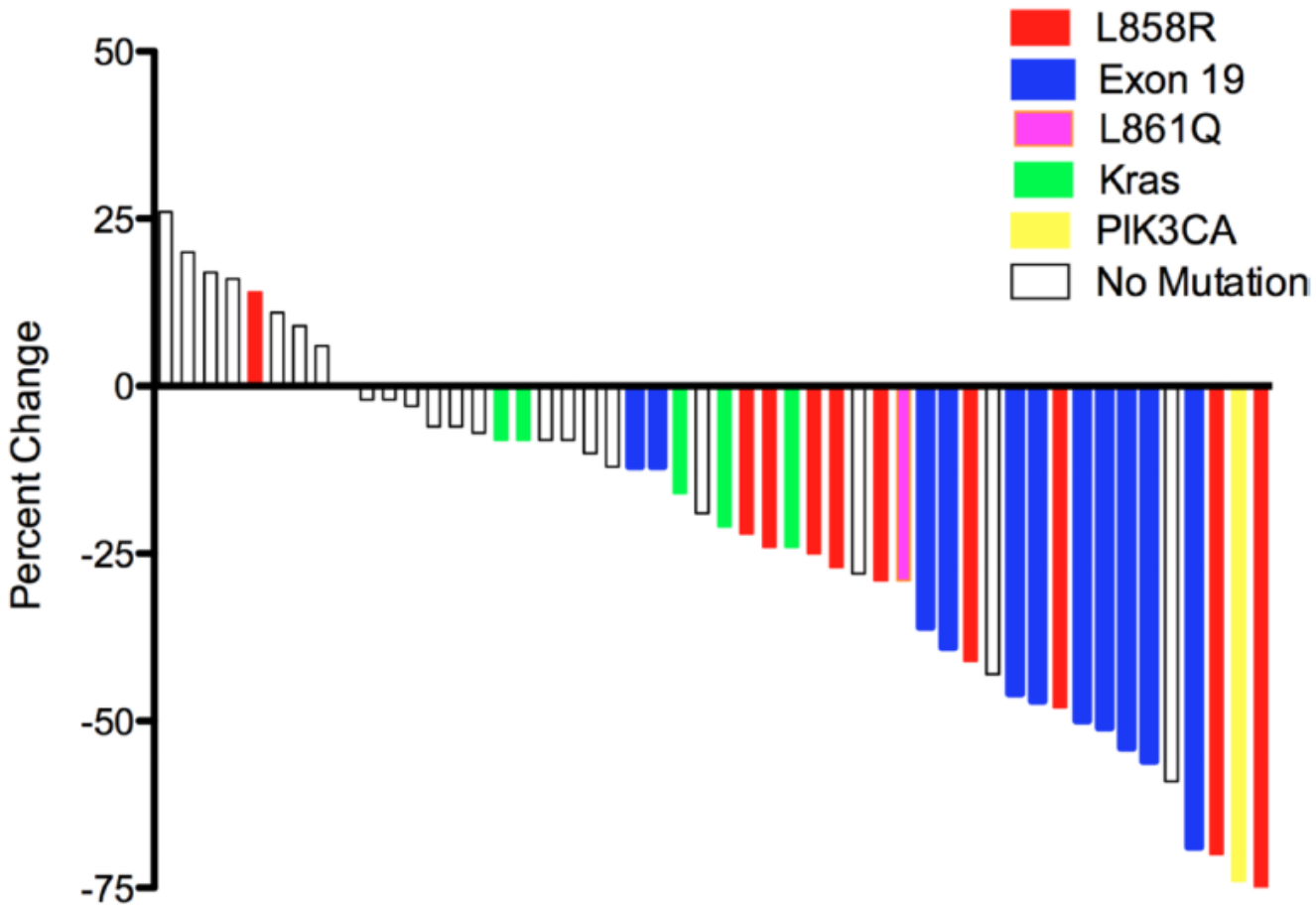
- Suitable to confirm predictive markers.
- Not suitable to define standard-of-care.

Preoperative gefitinib (Toronto)



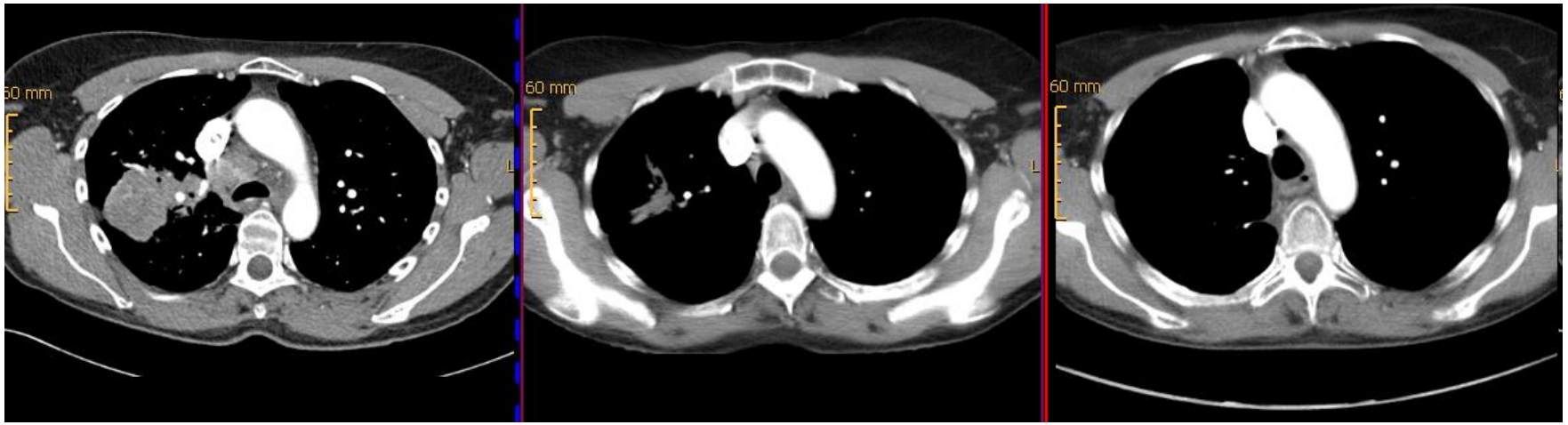
Lara-Guerra JCO 2009

Preoperative gefitinib (MSKCC)



Rizvi Clin Cancer Res 2011

Case presentation: induction therapy for stage IIIB with EGFR L858R

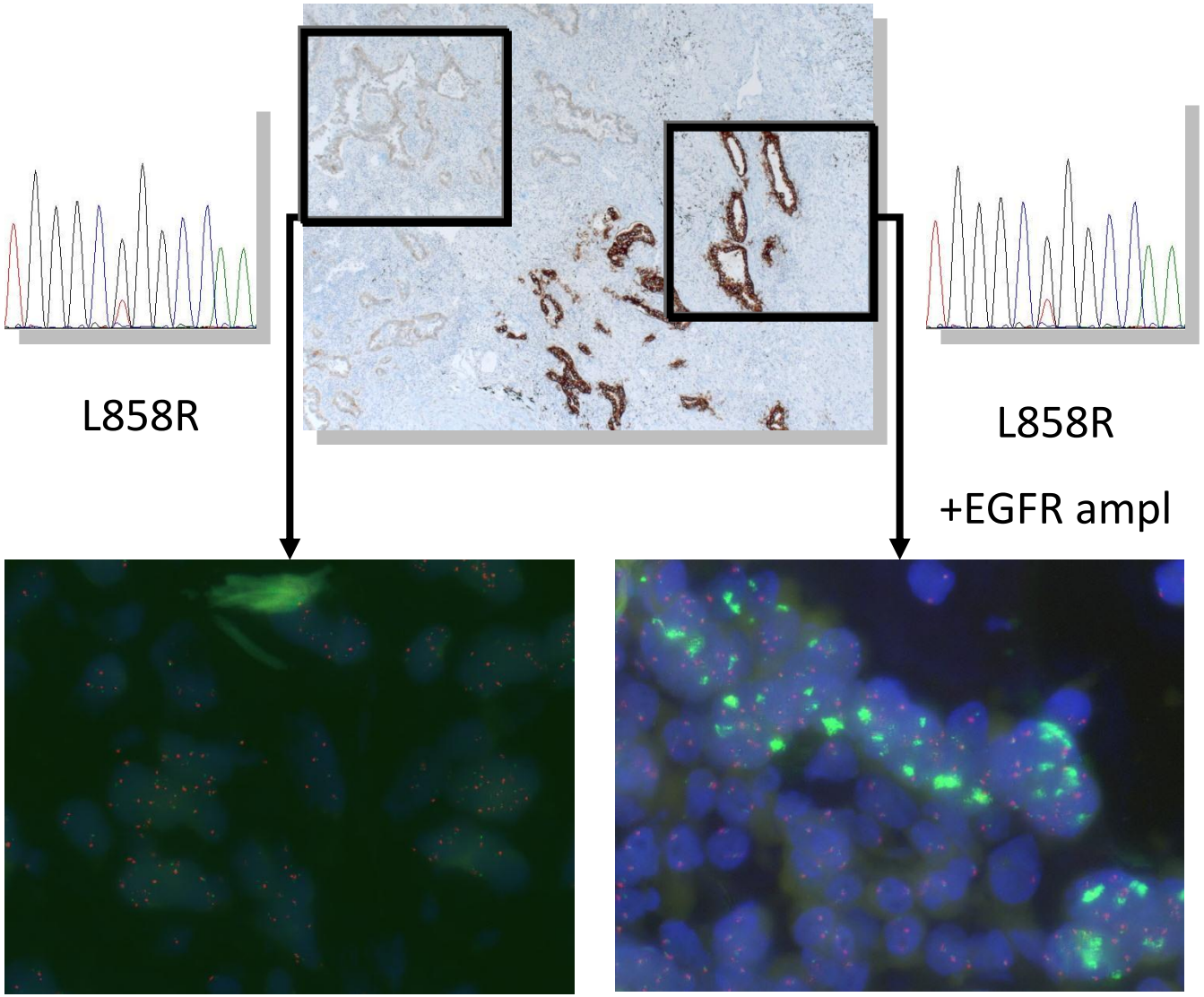


Baseline

After 3 months of EGFR-TKI

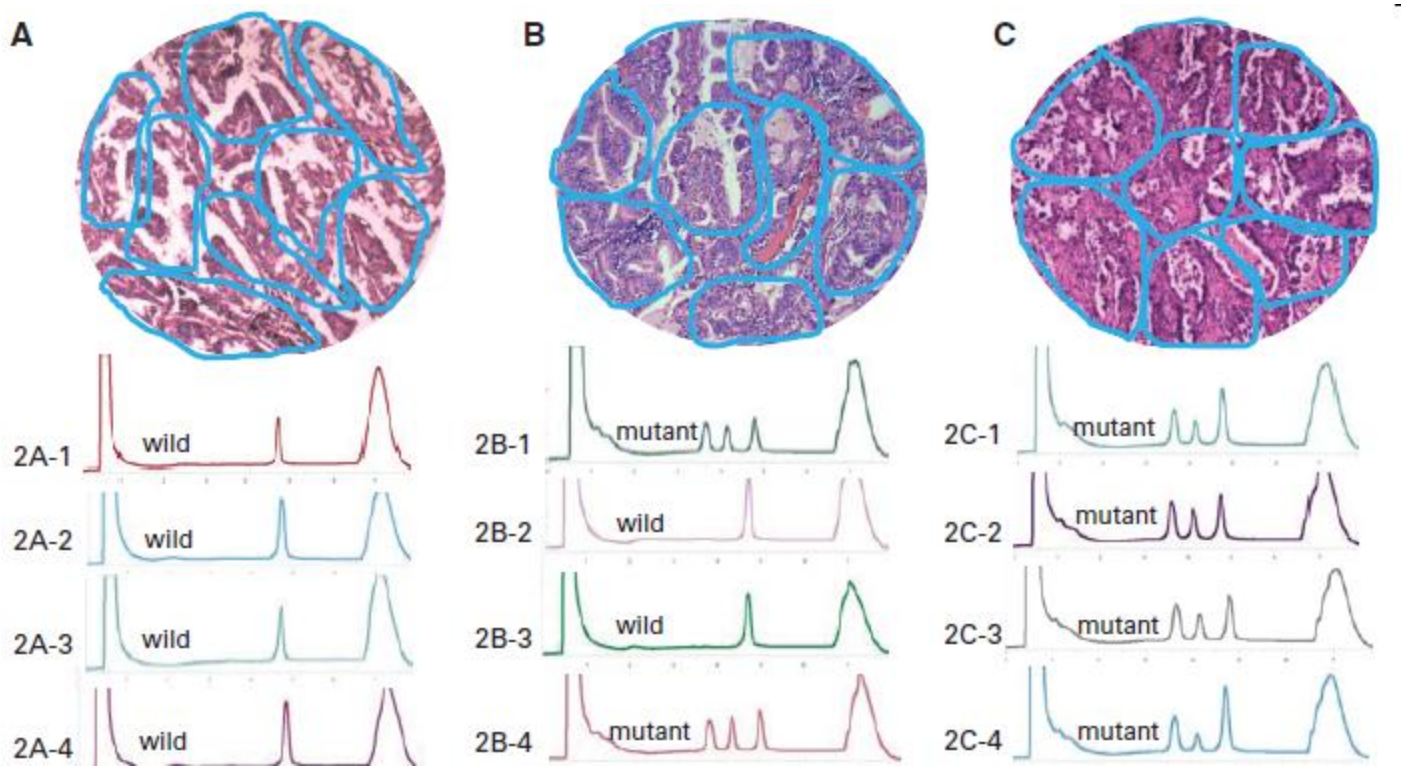
After surgery and chemoradiation

EGFR IHC on resected tumor



Courtesy of J. Diebold

Intratumor heterogeneity and change over time



Bai, JCO 2012

Perspectives

- Genomic characterization is feasible, let us focus on cancer-specific targets.
- Adjuvant TKI-therapy is promising, but promises must be fulfilled.
- New trial designs are important, but they are no substitute for phase III trials.

Acknowledgment

- S. Peters for ETOP-LUNGSCAPE data
- J. Diebold for IHC and FISH images
- G. Goss, L. Sequist and T. Wu for slides
- T. Mok and S. Aebi for discussion