Lung Cancer Consortia and EGFR Targeted Therapies

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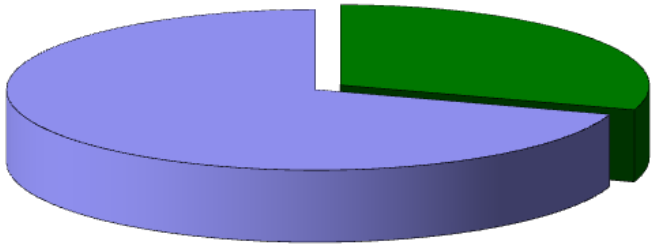
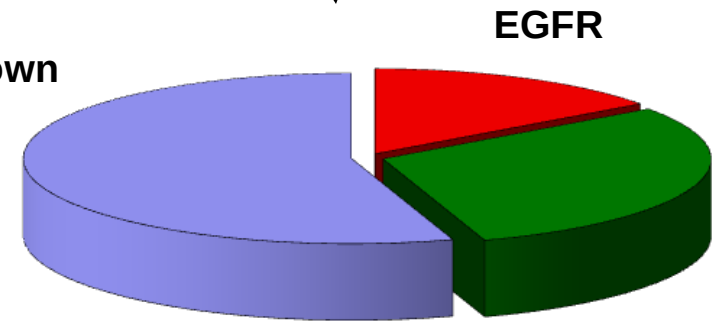
Abstracts for Discussion

- Lung Cancer Consortium
  - Peters et al.
- Erlotinib vs. Erlotinib/Chemo
  - Aerts et al.
- Chemo vs. Chemo/Erlotinib
  - Mok et al.

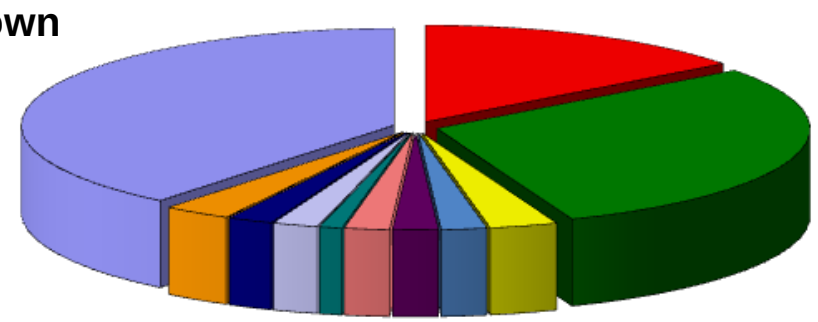
Lung Adenocarcinoma



1980s - 2003



2004



2012

BRAF

ERBB2

MEK 1

PIK3CA

MET amplification

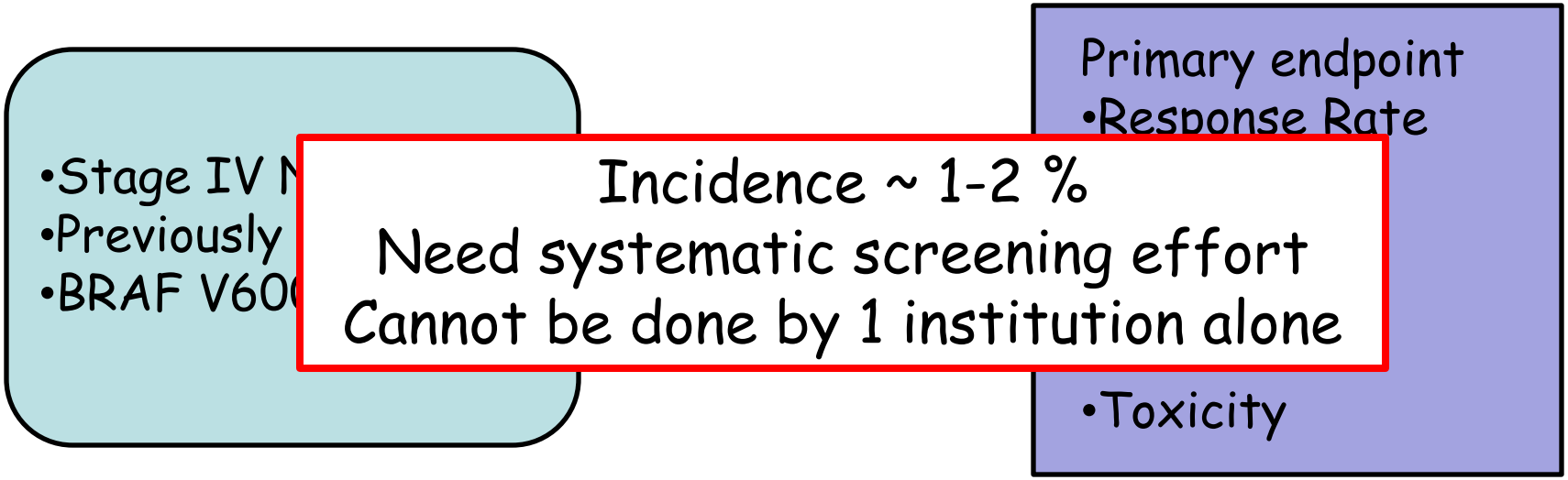
ALK

ROS

RET

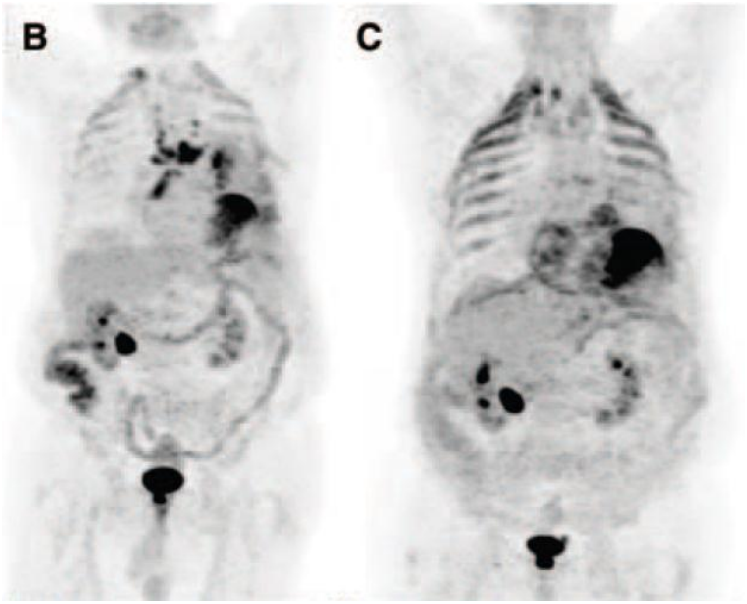
Fusion Oncogenes

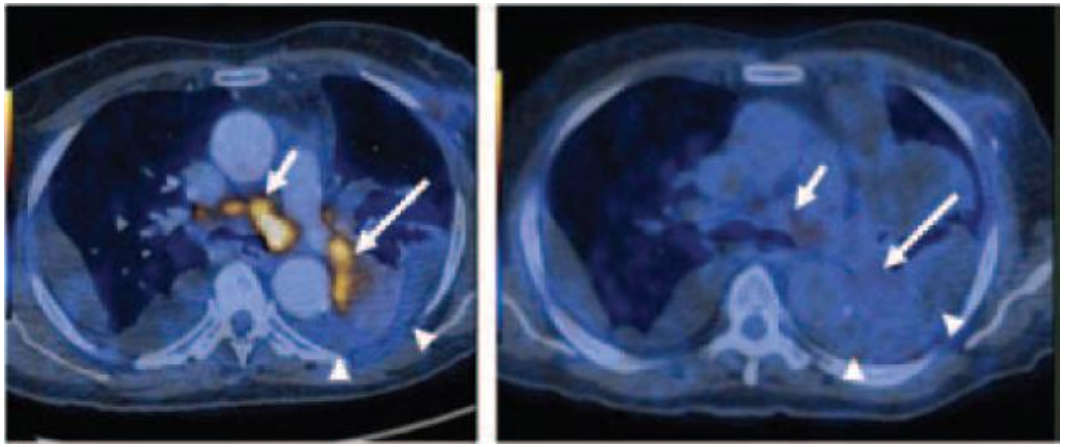
Phase II trial of GSK2118436



- Sample size: 40 patients
- Mutation testing can be done in any CLIA lab
- Correlative biomarkers: serum DNA for BRAF V600E

Vemurafenib in BRAF V600E mutant NSCLC

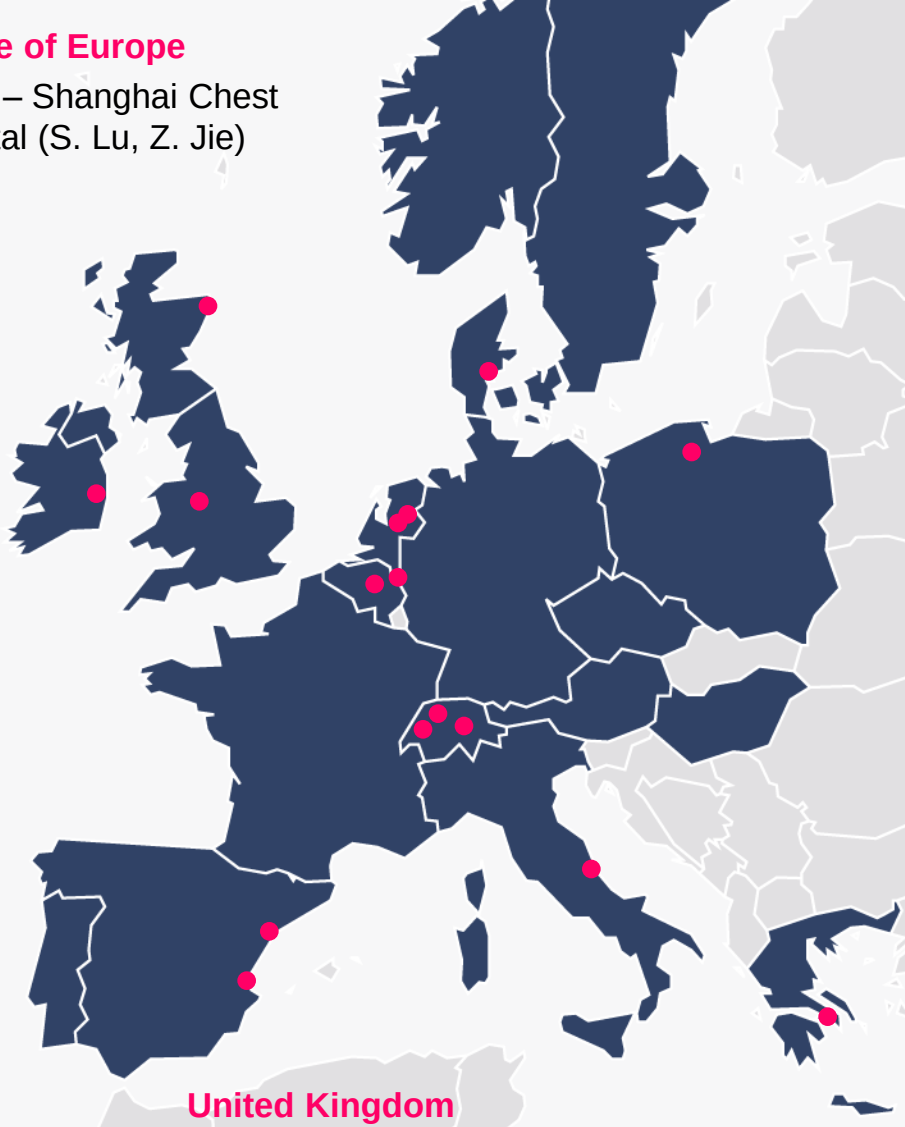




Gautschi, et al. JTO 2012

Why establish consortia ?

- Study large population of NSCLC patients
- Study the impact of a rare biomarker within the population
  - Accelerate translational research
- Centralized means of enrolling rare subsets of patients into clinical trials



Outside of Europe

- China – Shanghai Chest Hospital (S. Lu, Z. Jie)

Belgium

- Leuven:
  J. Vansteenkiste,
  E. Verbeken, C. Dooms

Denmark

- Aarhus:
  P. Meldgaard, H. Hager

Greece

- Frontier Science Hellas:
  U. Dafni

Ireland

- Dublin:
  K. O'Byrne, S. Finn,
  S. Gray

Italy

- Chieti:
  A. Marchetti, S. Malatesta

Poland

- Gdansk:
  R. Dziadziuszko,
  W. Biernat, A. Sejda,
  A. Wrona

United Kingdom

- Aberdeen:
  K.M. Kerr, N. Price,
  M. Nicolson
- Manchester:
  F. Blackhall, D. Nonaka,
  R. Peck

Spain

- Barcelona:
  E. Felip, J. Hernandez-Losa, M. T. Salcedo, M. Canela
- Badalona:
  R. Rosell, M. Taron
- Valencia:
  C. Camps, M. Martorell,
  E. Jantus-Lewintre

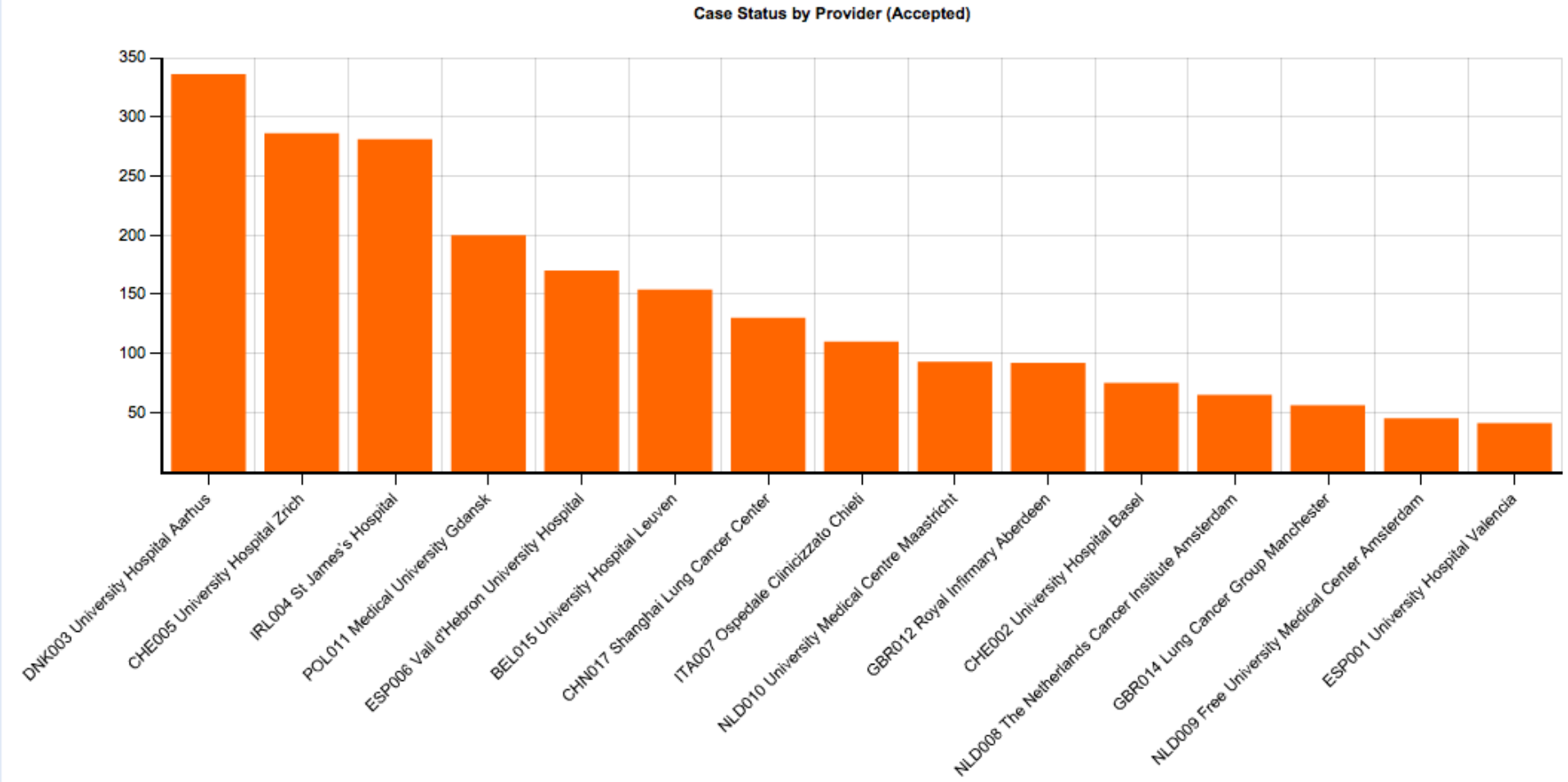
Switzerland

- ETOP Coordinating Center:
  A. Hiltbrunner, S. Peters,
  R. Kammler, R. King,
  R. Stahel
- Basel:
  L. Bubendorf, S. Savic
- Zurich:
  W. Weder, A. Soltermann

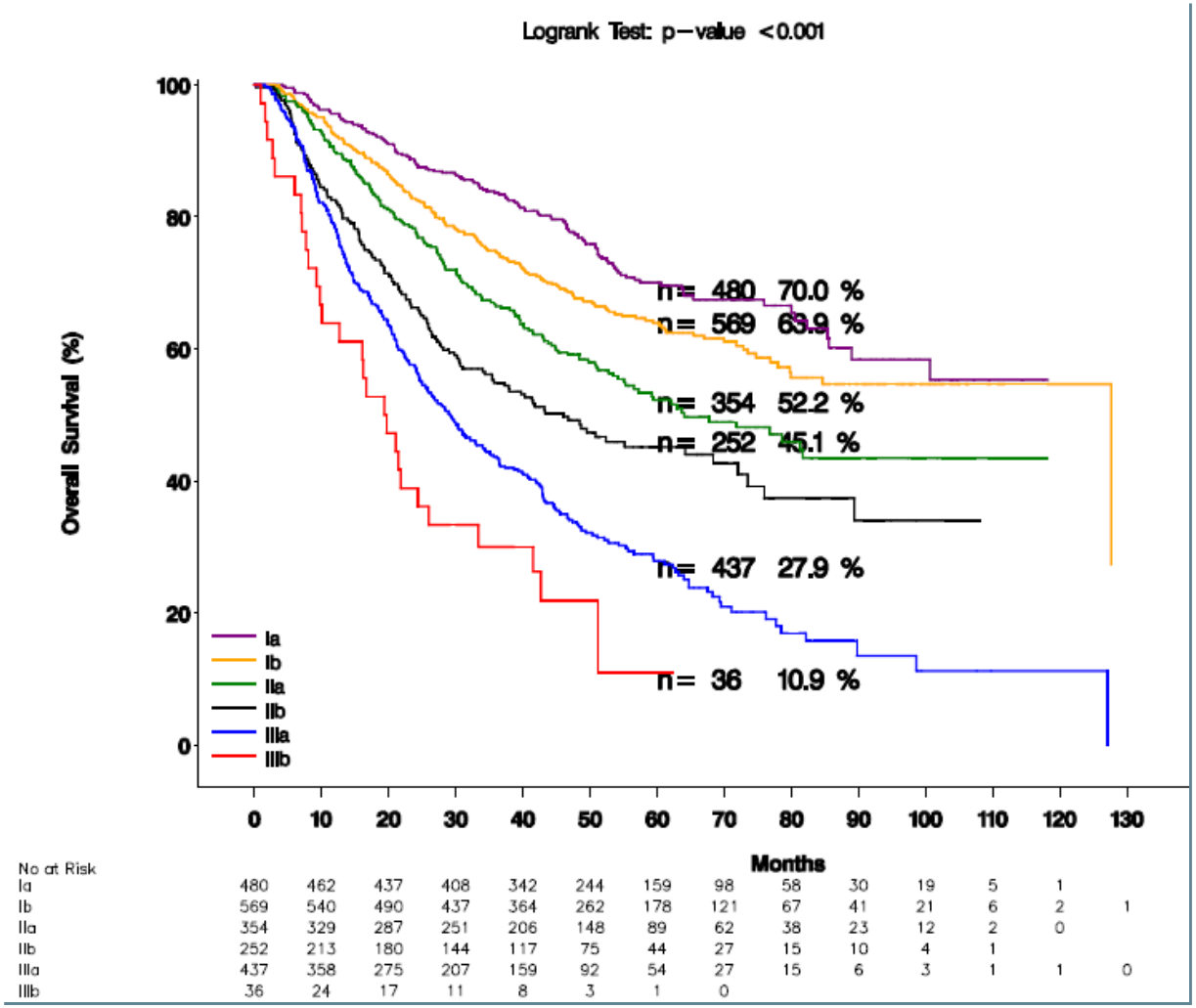
The Netherlands

- Amsterdam VU (E. Thunnissen, E. Smit
- Amsterdam NKI:
  P. Baas, J. de Jong
- Maastricht:
  A.-M. Dingemans,
  E-J.M. Speel

Cases by provider (n=2130)



Kaplan-Meier plot for overall survival by Stage



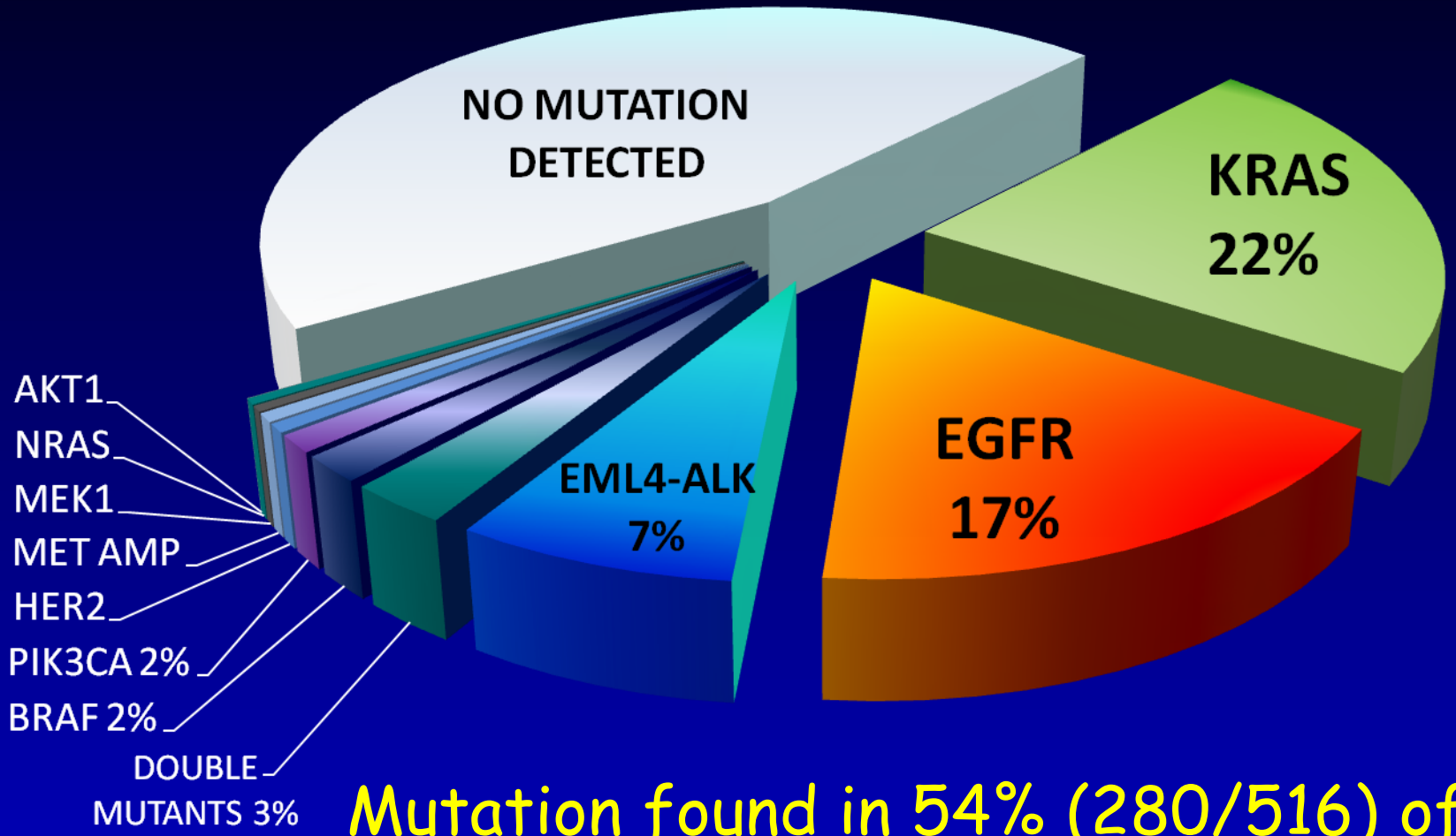
Note: Number of patients and 5-year OS by Stage, depicted in the figure

Questions for Lungscape

- Why focus only on stages I-IIIA ?
- How many patients were screened and not eligible ?
  - "Adequate quantity and quality of formalin-fixed paraffin embedded tissue"
- How will genotyping (or any biomarker) be done ?
  - Locally vs. centrally
- What are the plans for clinical trials ?

The Lung Cancer Mutation Consortium

Lung Cancer Mutation Consortium Incidence of Mutations Detected



Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)

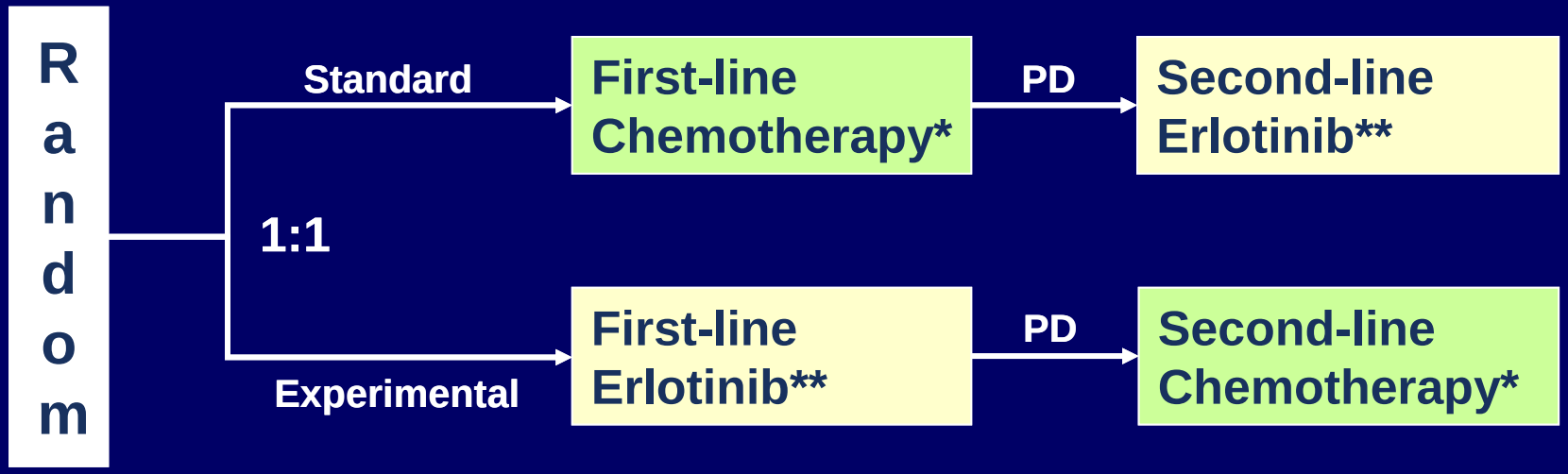
Johnson et al. IASCLC 2011

EGFR TKI as Standard First-Line Therapy for Patients with *EGFR* Mutation

Study	Drug	N (*EGFR* mut)	RR (TKI vs. chemotherapy)	Median PFS (mos)
IPASS	Gefitinib	261	**71.2%** vs 47.3%	9.8
First-SIGNAL	Gefitinib	42	**84.6%** vs 37.5%	8.4
WJTOG 3405	Gefitinib	198	**62.1%** vs 32.2%	9.2
NEJGSG002	Gefitinib	177	**73.7%** vs 30.7%	10.3
EURTAC	Erlotinib	86	**58.0%** vs 15.0%	9.7
OPTIMAL	Erlotinib	82	**83.0%** vs 36.0%	13.1
Lux Lung 3	Afatinib	230	**56.1%** vs 22.6%	11.1

Mok TS, et al. *N Engl J Med* 2009;361:947–957; Lee JS, et al. Presentation at WCLC 2009 (PRS.4);Mitsudomi T, et al. *Lancet Oncol* 2010;11:121–128;Maemondo M, et al. *N Engl J Med* 2010;362:2380–2388; Rossell et al. Lancet Oncol 2012; Zhou et al. Lancet Oncology 2011; Yang et al. ASCO 2012

TORCH - Study design



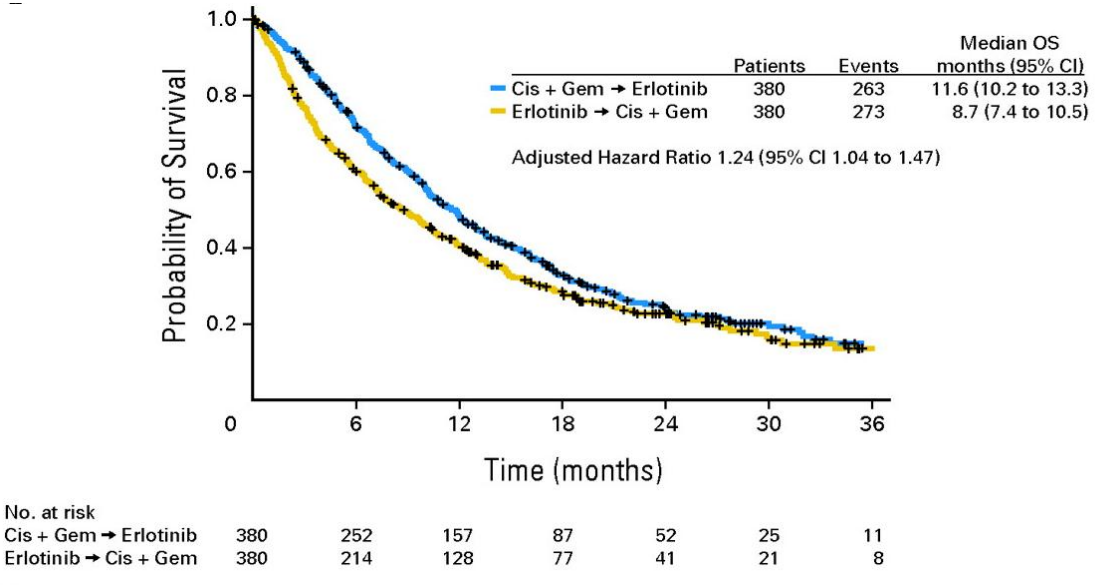
Strata:
- histology
- smoking status
- gender
- country (Italy, Canada)
- age
- ethnicity

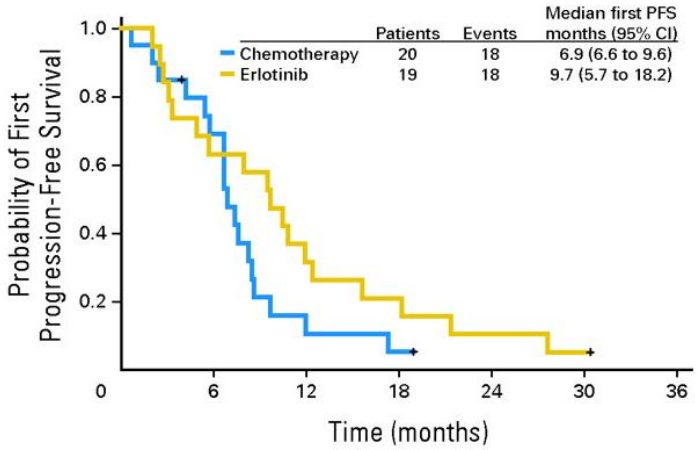
***Chemotherapy:**
- Cisplatin, 80 mg/m^2, day 1
- Gemcitabine, 1200 mg/m^2, day 1 and 8 every 3 weeks, for 6 cycles

****Erlotinib:**
150 mg/day p.o. until progression

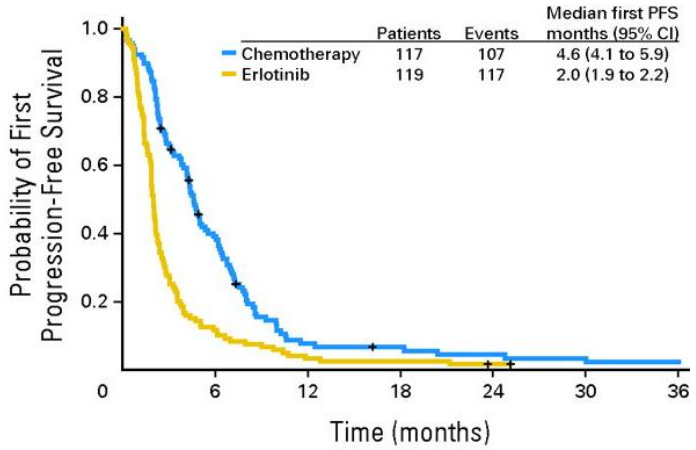
Gridelli C et al. JCO 2012;30:3002-3011

Chemotherapy first is more effective than erlotinib in unselected NSCLC patients





EGFR Mutant

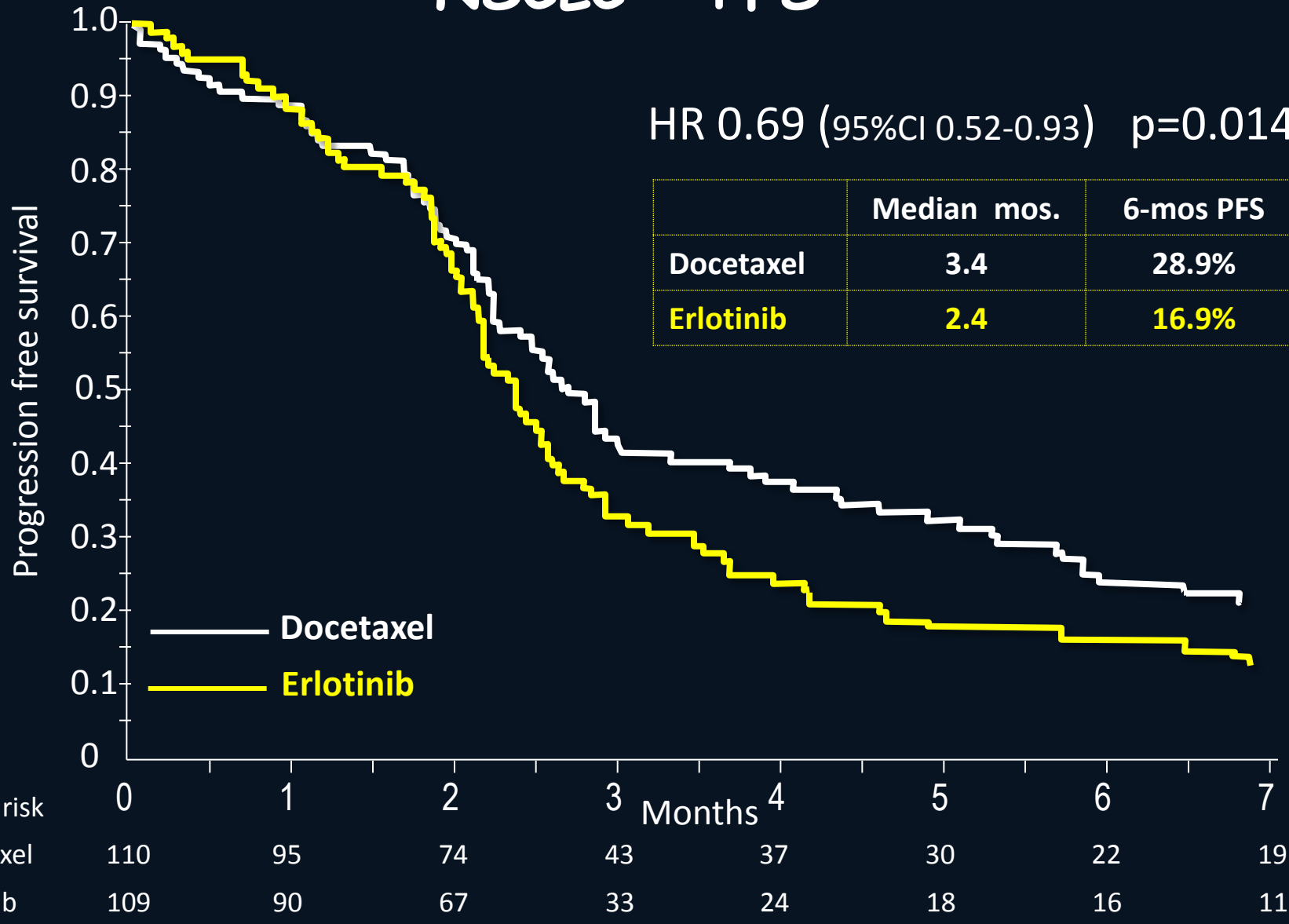


EGFR Wild Type

Gridelli C et al. JCO 2012;30:3002-3011

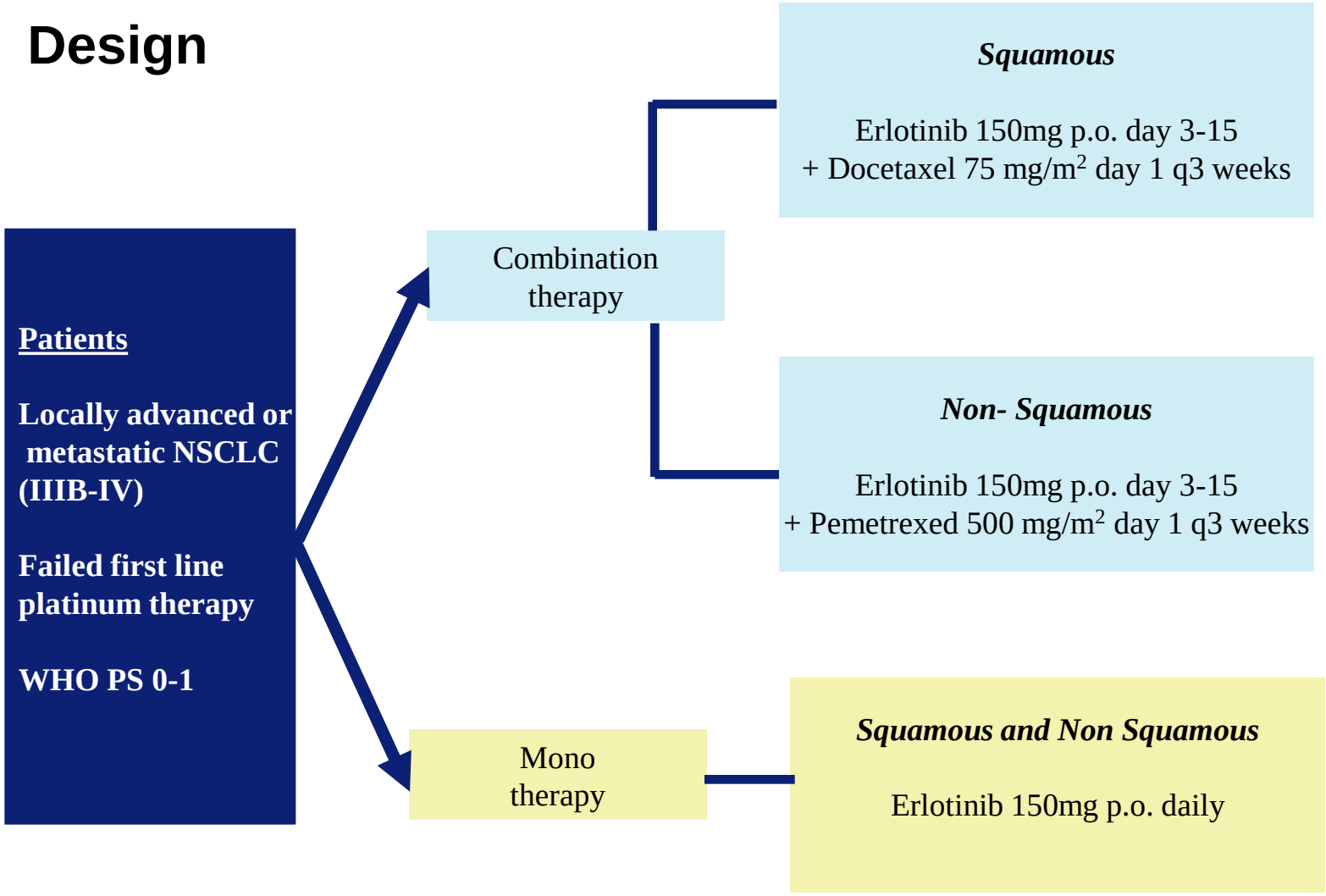
EGFR mutation rate: 14%

Docetaxel vs. Erlotinib in EGFR Wild Type NSCLC - PFS



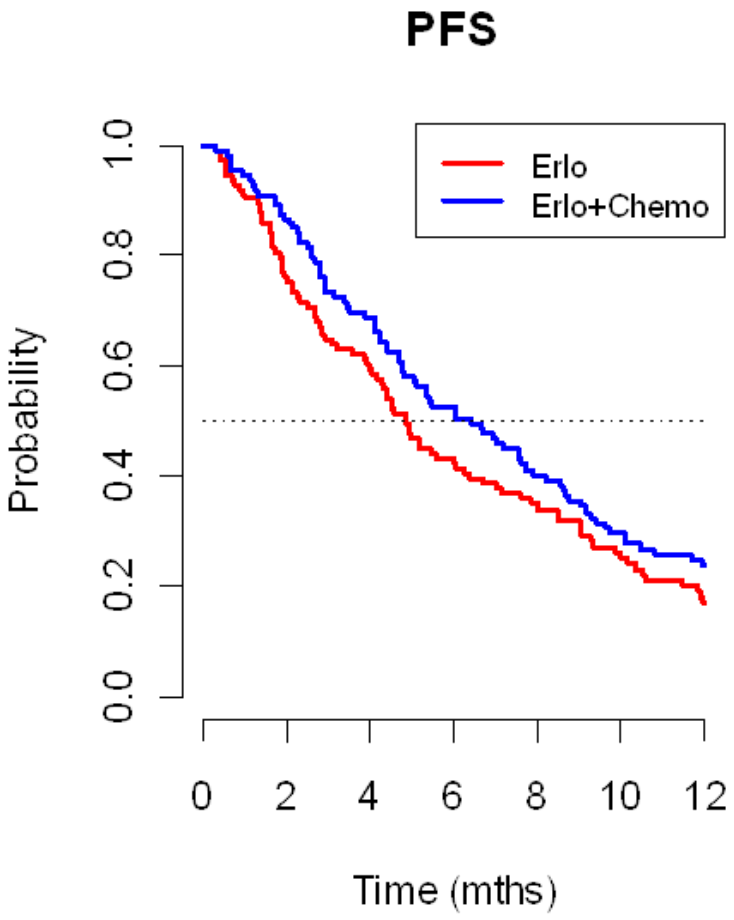
Garassino et al. ASCO 2012

Design

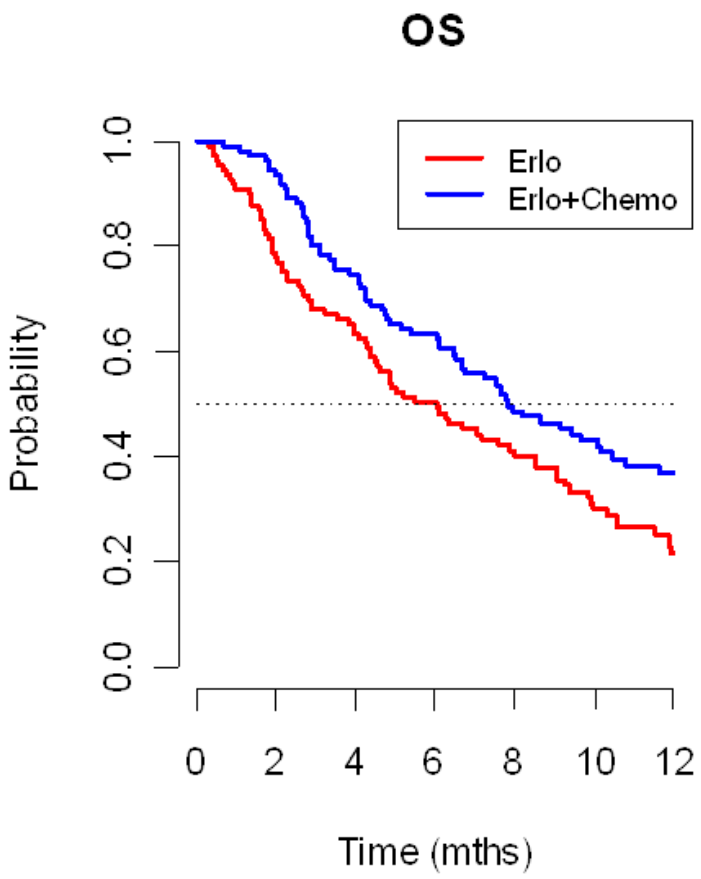


Chemotherapy planned 4 cycles
Erlotinib until disease progression

The NVALT-10 study PFS and OS



Adjusted for stratification factors:
p=0.09, HR=0.78 (0.59-1.04)



Adjusted for stratification factors:
p=0.02, HR=0.67 (0.50 - 0.93)

Questions for NVALT-10 (and future studies)

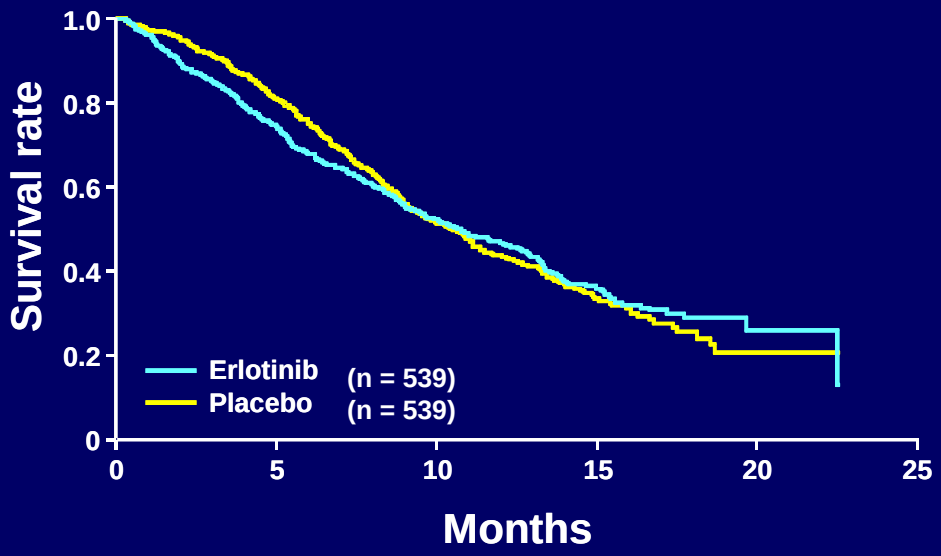
- Are the effects due to chemo being more effective than erlotinib in mostly EGFR WT population ?

- Should we perform future trials (even in second line setting) where erlotinib is the control arm in an EGFR WT population ?

- There is no "EGFT WT" cancer –
  - KRAS, BRAF, ERBB2, ALK, ROS, RET etc.

Chemotherapy With Erlotinib or Placebo TRIBUTE Trial

Intent-to-Treat

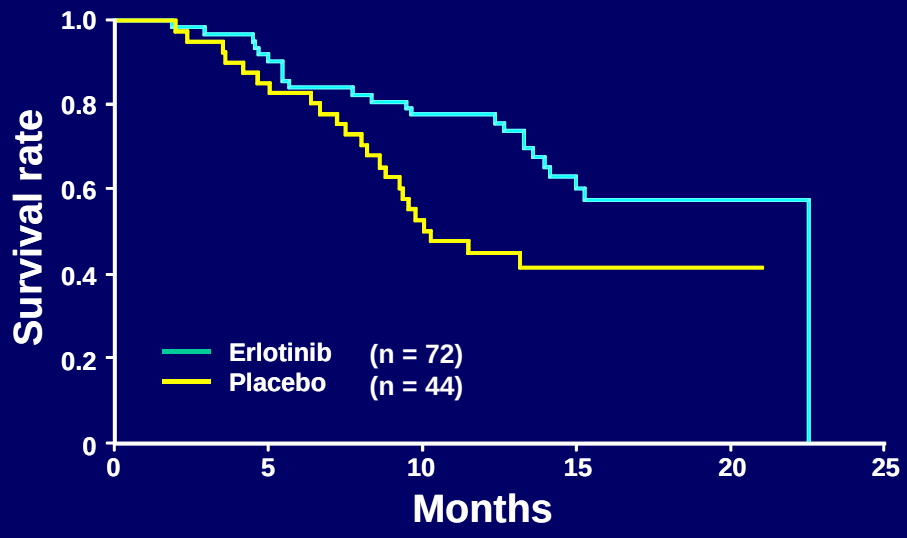


Median survival 10.6 vs. 10.5 mos

TTP 5.1 vs. 4.9 months

RR: 22% vs. 19 %

Never Smokers



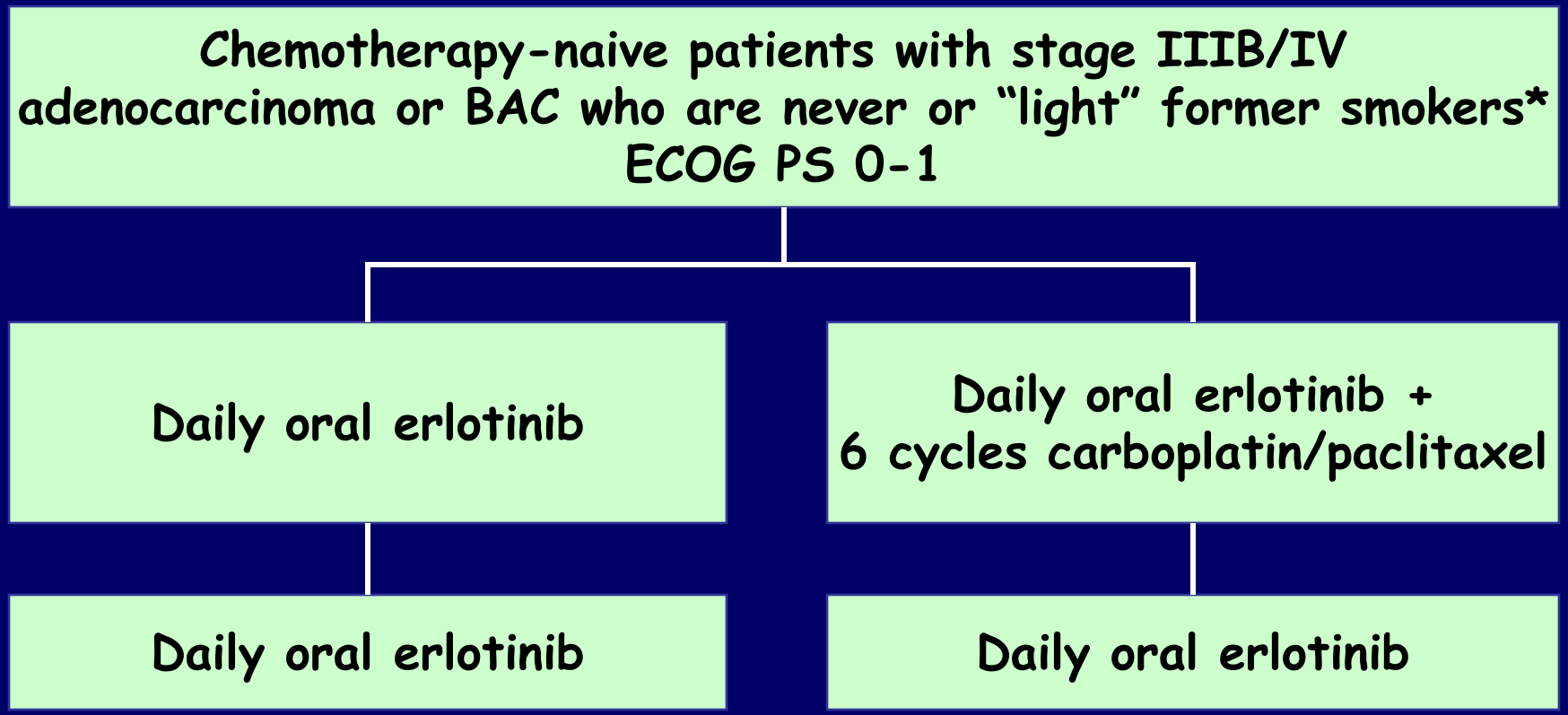
Median survival 22.5 vs. 10.1 mos

TTP 6.0 vs. 4.3 months

RR: 30% vs. 11 %

Herbst RS, et al. *J Clin Oncol.* 2005;23:5892-5899.

CALGB 30406 Randomized Phase II Study: Trial Design

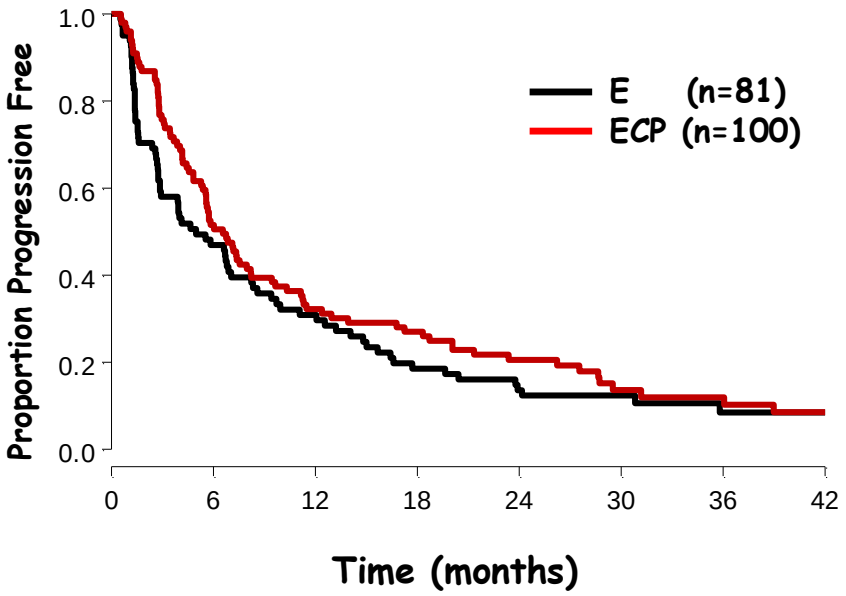


Response evaluation every 2 cycles (6 weeks). Therapy could continue until disease progression or toxicity

* never smoker: ≤ 100 cigarettes/lifetime; "light" former smoker: quit ≥ 1 year ago and ≤ 10 pack years

CALGB 30406 - Progression Free and Overall Survivals in all patients

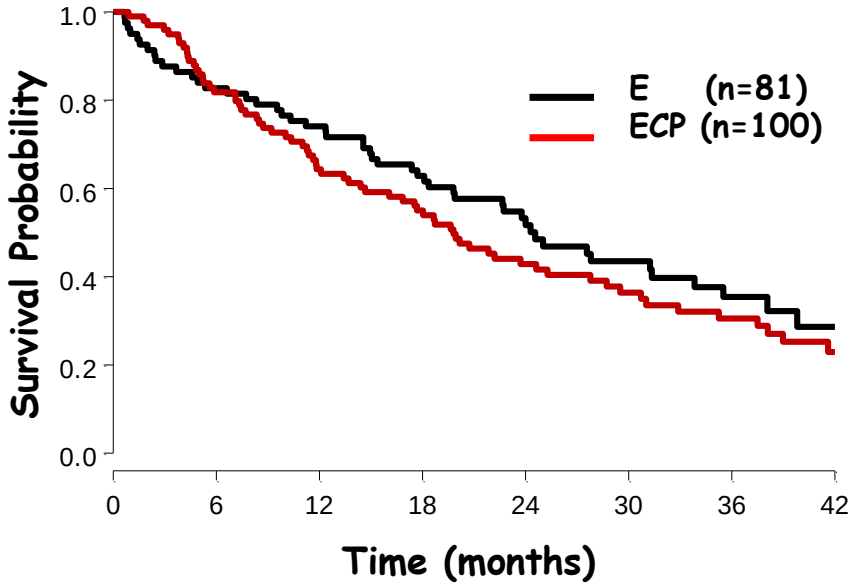
Progression Free Survival



Erlotinib : 5.0 (2.9-7.0)

Erlotinib/CP: 6.6 (5.4-8.2)

Overall Survival



Erlotinib : 24.6 (18.4 -33.8)

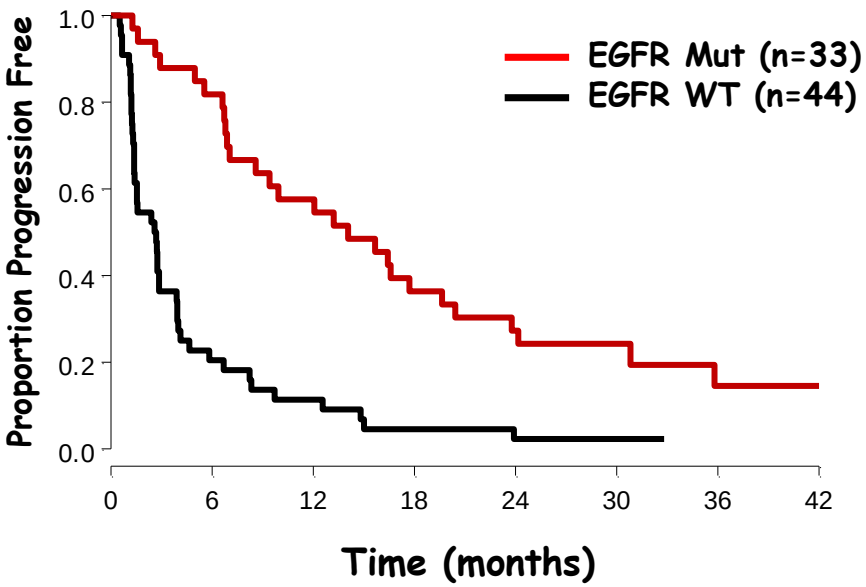
Erlotinib/CP: 19.8 (14.4 - 27.8)

Response Rate Erlotinib: 35% Erlotinib/CP: 46%

Jänne et al. JCO 2012

Erlotinib – PFS and OS by EGFR mutation

Progression Free Survival

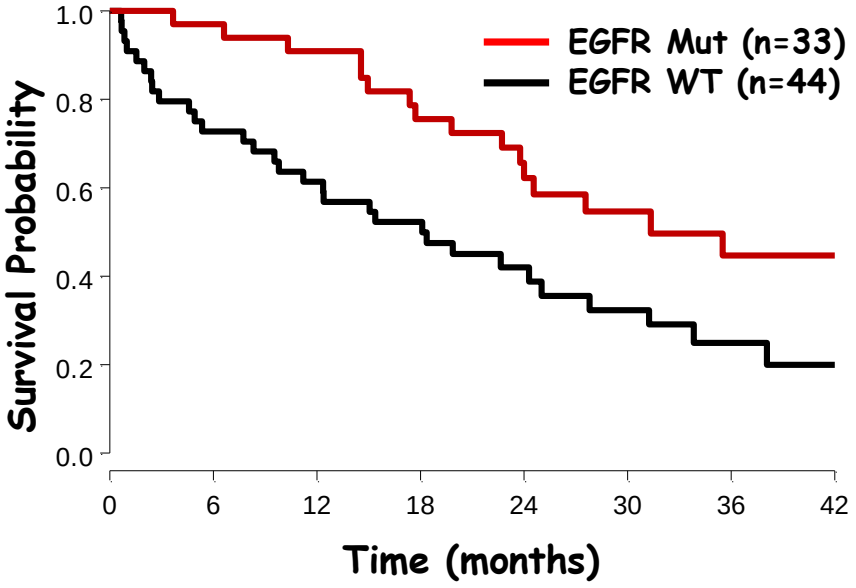


EGFR mutant : 14.1 (7.0 – 19.6)

EGFR WT: 2.6 (1.4 – 3.9)

P < 0.0001

Overall Survival



EGFR mutant : 31.3 (23.8–NA)

EGFR WT: 18.1 (9.5 -27.8)

P = 0.0198

Response Rate

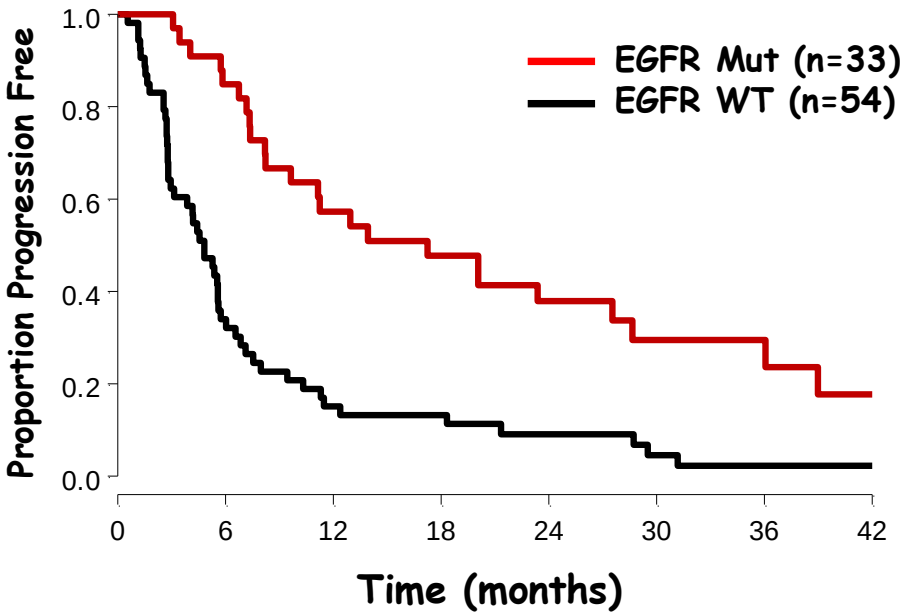
EGFR mutant: 70% EGFR WT: 9%

P < 0.0001

Jänne et al. JCO 2012

Erlotinib/CP – PFS and OS by EGFR mutation

Progression Free Survival

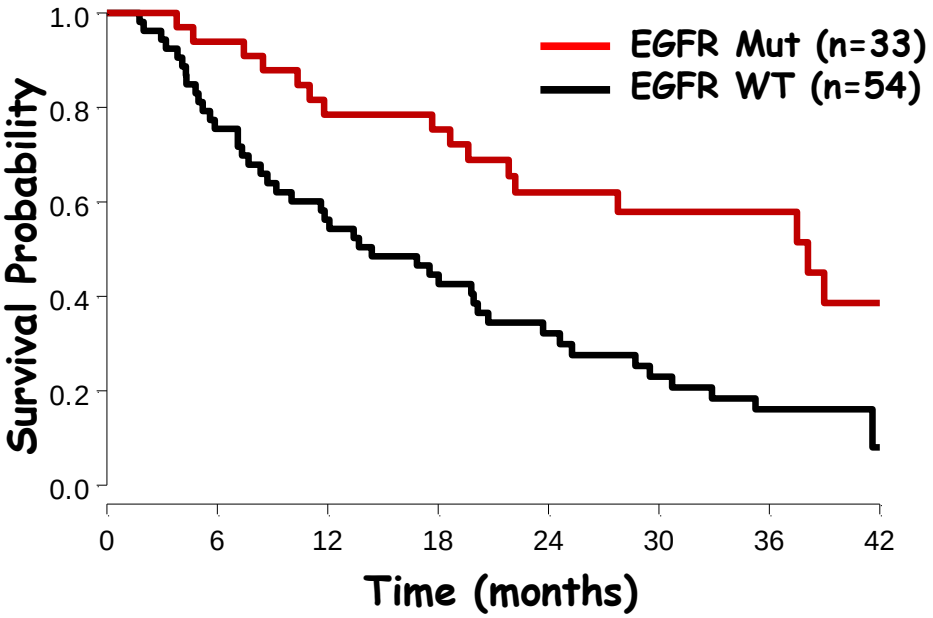


EGFR mutant : 17.2 (8.2 – 28.7)

EGFR WT: 4.8 (2.8 – 5.6)

P < 0.0001

Overall Survival



EGFR mutant : 38.1 (19.6 –NA)

EGFR WT: 14.4 (8.7-20.2)

P = 0.0011

Response Rate

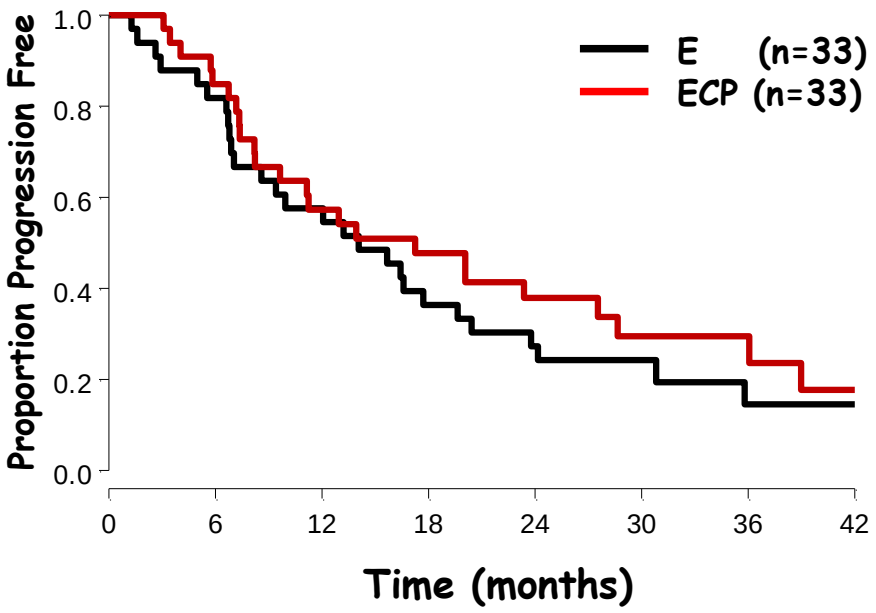
EGFR mutant: 73% EGFR WT: 30%

P < 0.0001

Jänne et al. JCO 2012

Erlotinib vs. Erlotinib/CP in EGFR Mutants

Progression Free Survival

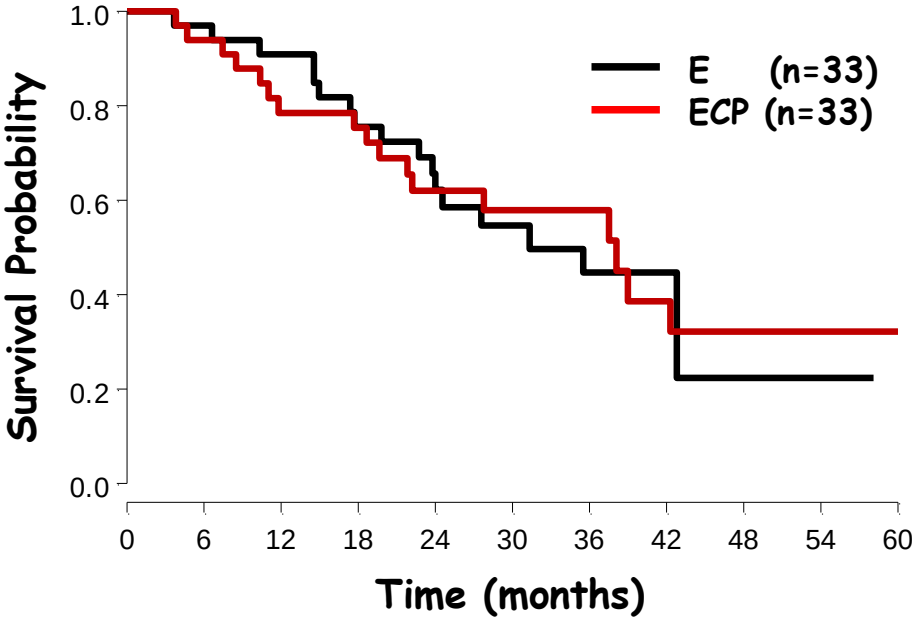


Erlotinib: 14.1 (7.0 – 19.6)

Erlotinib/CP: 17.2 (8.2 – 27.8)

P = 0.3490

Overall Survival

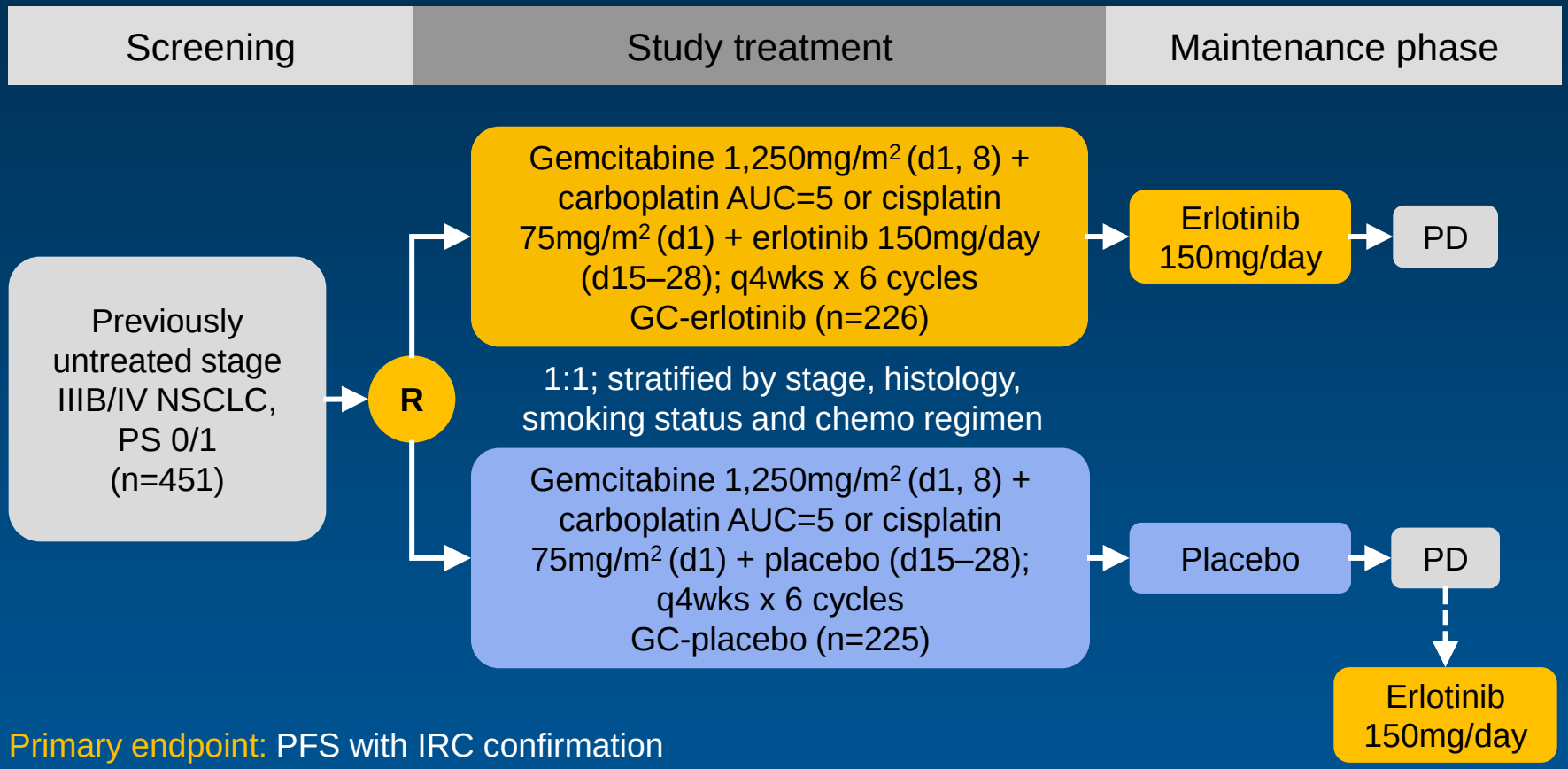


Erlotinib: 31.3 (23.8–NA

Erlotinib/CP: 38.1 (19.6 –NA)

P = 0.9227

FASTACT-2 (MO22201; CTONG0902) study design

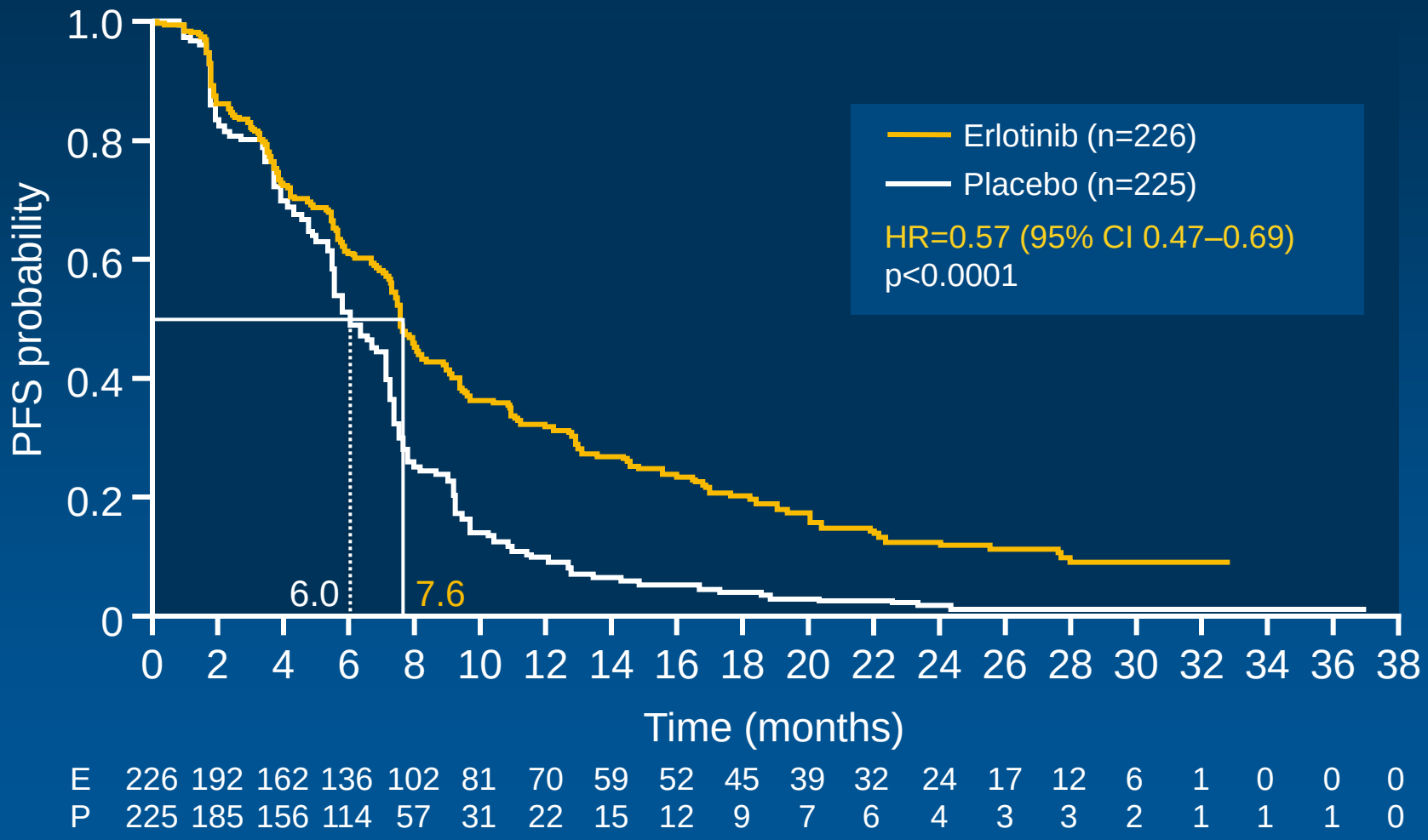


Primary endpoint: PFS with IRC confirmation

Secondary endpoints: subgroup analyses, OS in all patients and subgroups, ORR, duration of response, TTP, NPR at 16 weeks, safety, QoL

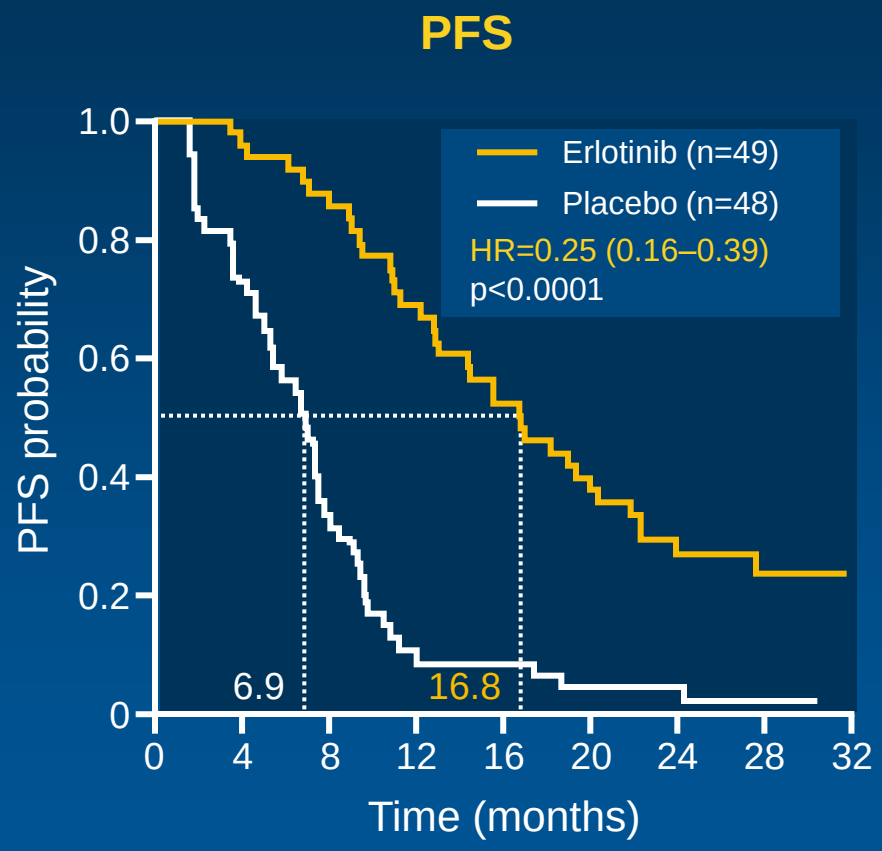
NSCLC = non-small cell lung cancer; PS = performance status; PD = disease progression; AUC = area under the curve; q4wks = every 4 weeks; IRC = independent review committee; OS = overall survival; ORR = objective response rate; TTP = time to progression; NPR = non-progression rate; QoL = quality of life

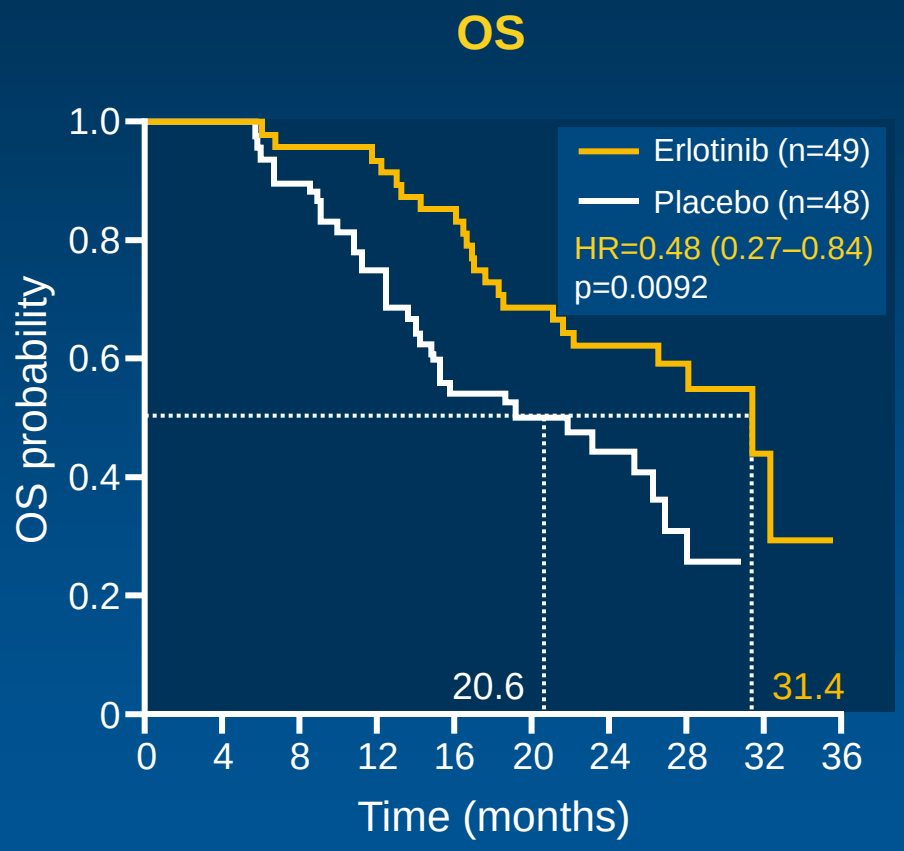
Updated primary endpoint: PFS in ITT population (22 Jun 2012)



CI = confidence intervals

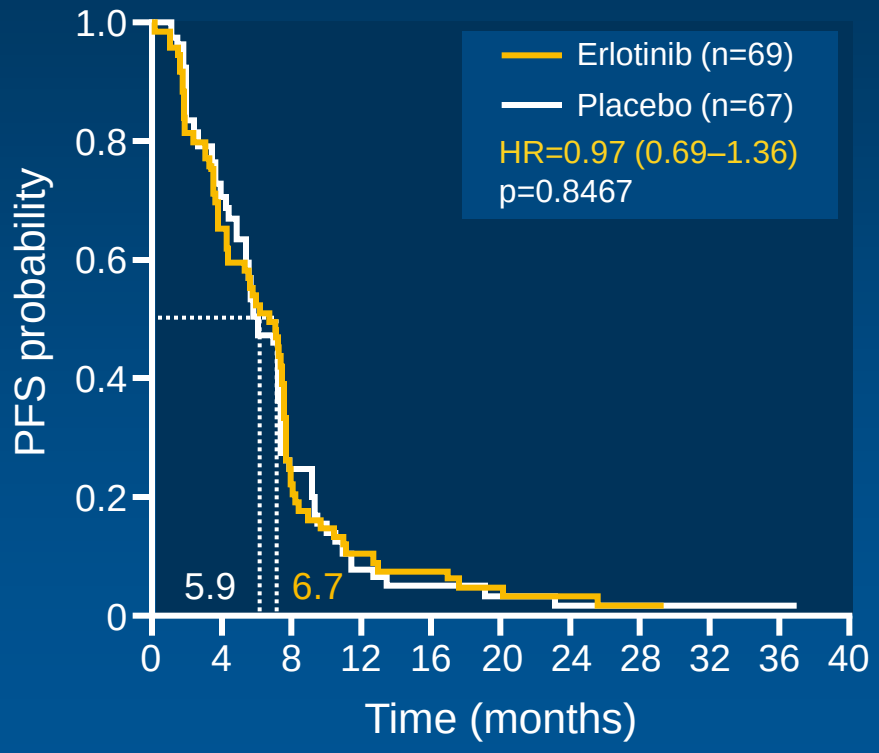
PFS and OS in *EGFR* Mut+ subgroup (22 Jun 2012)





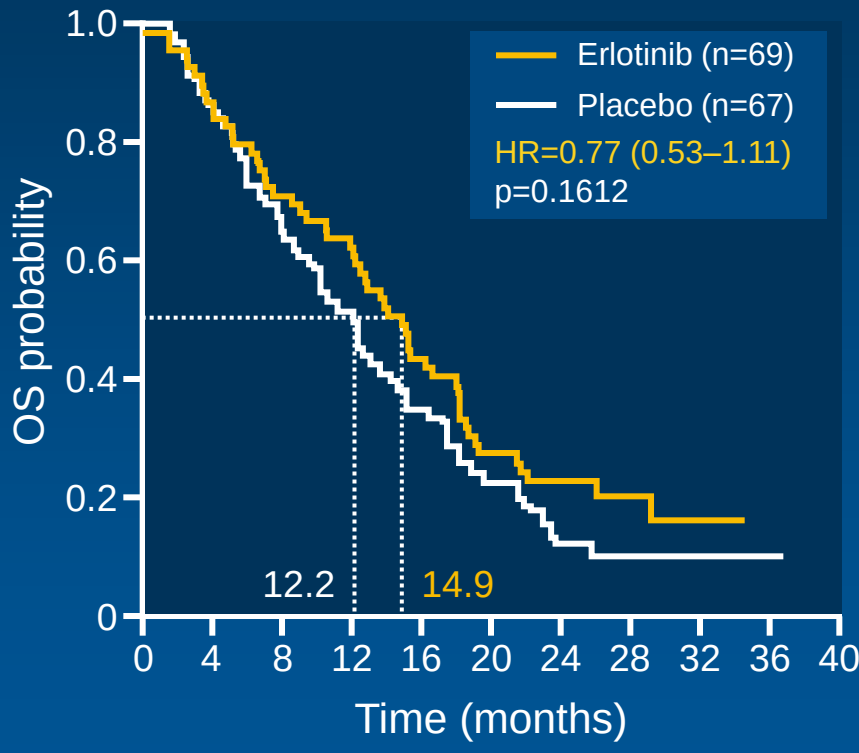
PFS and OS in *EGFR* WT subgroup (22 Jun 2012)

PFS



E	69	45	15	7	5	3	2	1	0	0	0
P	67	46	16	5	3	2	1	1	1	1	0

OS



E	69	60	49	43	30	19	12	6	4	0	0
P	67	57	43	34	23	15	7	3	2	1	0

Questions for FAST-ACT II

- Are the results due to the effects of erlotinib in an EGFR mutation enriched (40%; 97/241) patient population ?
- Would erlotinib alone achieve the same results but with less toxicity ?
- Should we pursue additional trials of chemo/EGFR TKI in EGFR mutant NSCLC ?