ESMO 2010 Lung Cancer Update

Sunil Verma MD, MSEd, FRCPC

Director of Post Graduate Medical Education Program

Medical Oncologist

Sunnybrook Odette Cancer Centre

Assistant Professor, University of Toronto

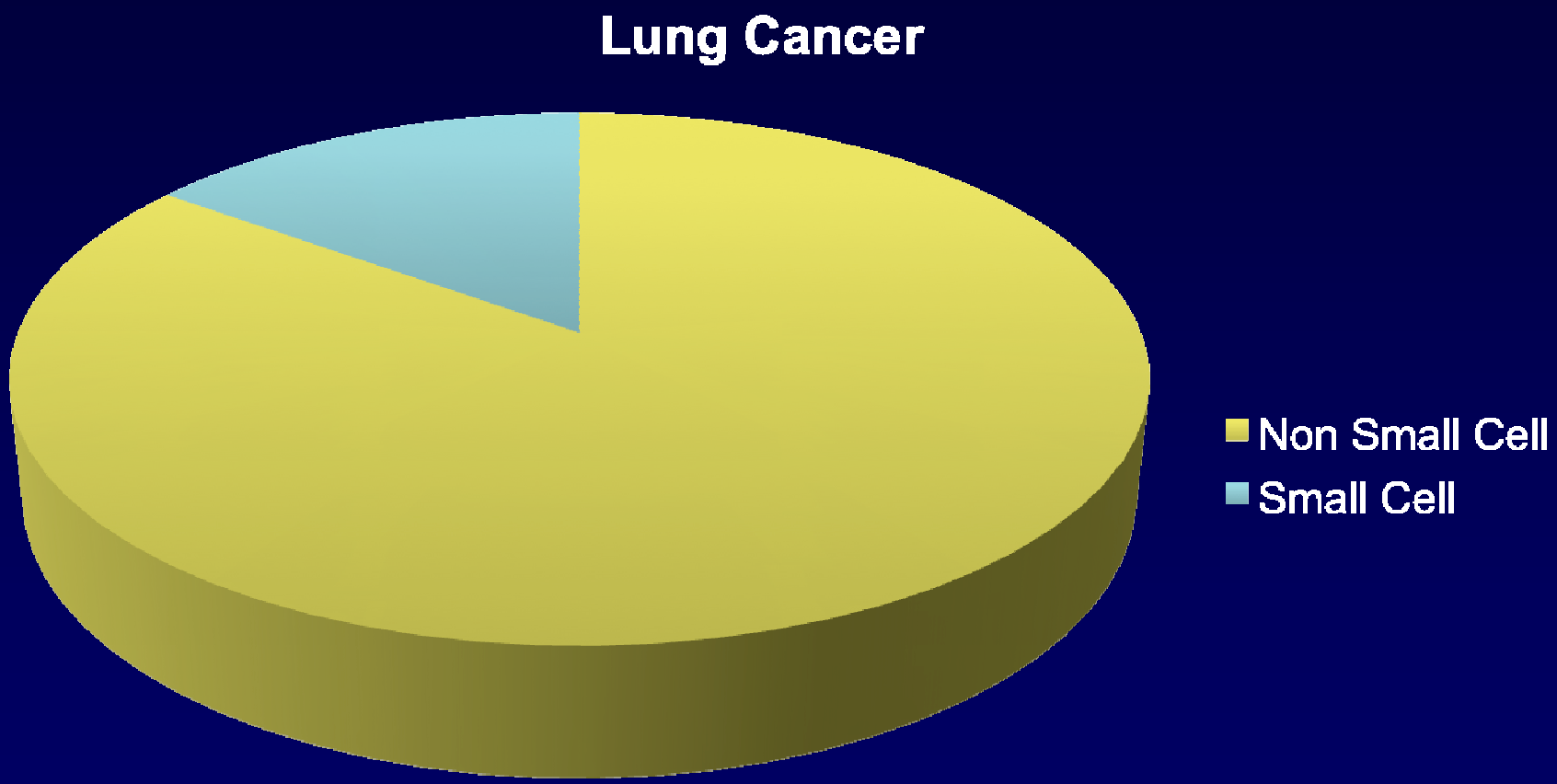
Thank you for downloading this update. Please feel free to use it for educational purposes.

We request that you acknowledge OncologyEducation.ca and Dr. Sunil Verma when using these slides.

Objectives

- To review the key trial results that are helping us personalize the management of NSCLC
- To provide key lung cancer updates from ASCO 2010 and ESMO 2010
- To discuss current controversies in the management of lung cancer

Lung Cancer – what it looked like in 2000?



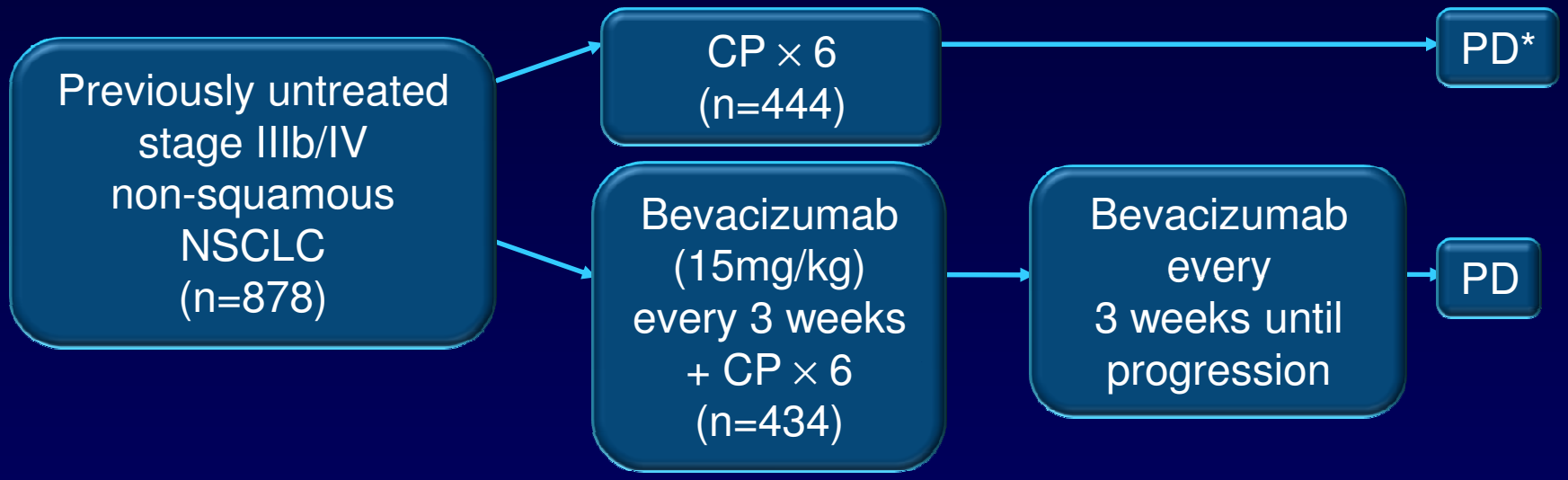
Outline

- Anti-Angiogenics in first line setting
- EGFR Targeted Therapies
  - Update from the IPASS Trial
  - OPTIMAL Study – Erlotinib in the first line setting
  - New Generation of EGFR TKI – first line and beyond
  - Combining Anti-Angiogenics to EGFR TKI
- The role of Maintenance
  - Who Benefits the most?

Outline

- **Anti-Angiogenics in first line setting**
- EGFR Targeted Therapies
  - Update from the IPASS Trial
  - OPTIMAL Study – Erlotinib in the first line setting
  - New Generation of EGFR TKI – first line and beyond
  - Combining Anti-Angiogenics to EGFR TKI
- The role of Maintenance
  - Who Benefits the most?

Phase III trial of Bevacizumab Plus CP in NSCLC (E4599): Trial design

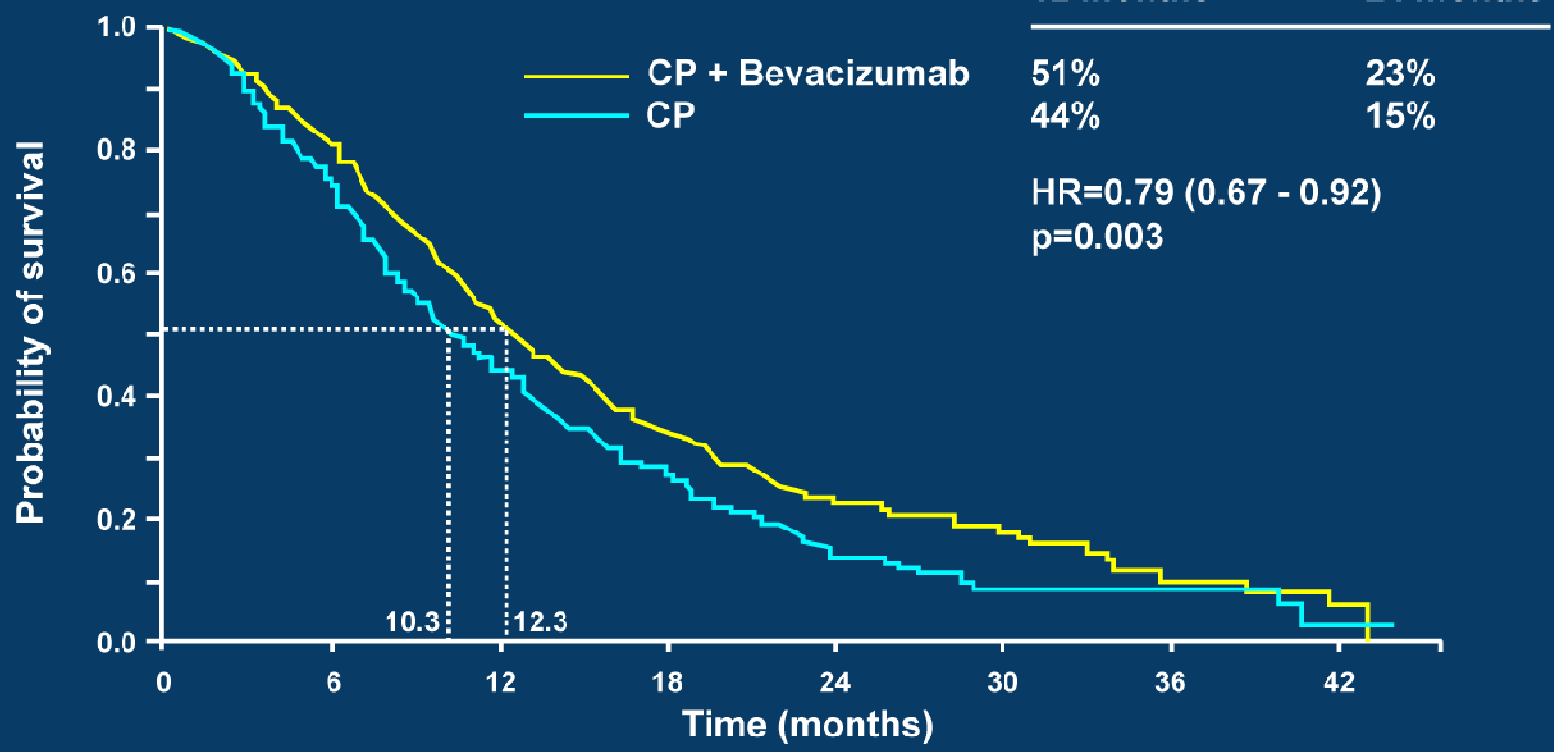


- Primary endpoint: overall survival
- Bevacizumab 15mg/kg i.v. administered every 3 weeks
- Carboplatin i.v. to AUC 6mg/mL and paclitaxel 200mg/m^2 i.v. every 3 weeks

*No cross over permitted
PD = progression of disease; i.v. = intravenous; AUC = area under the curve

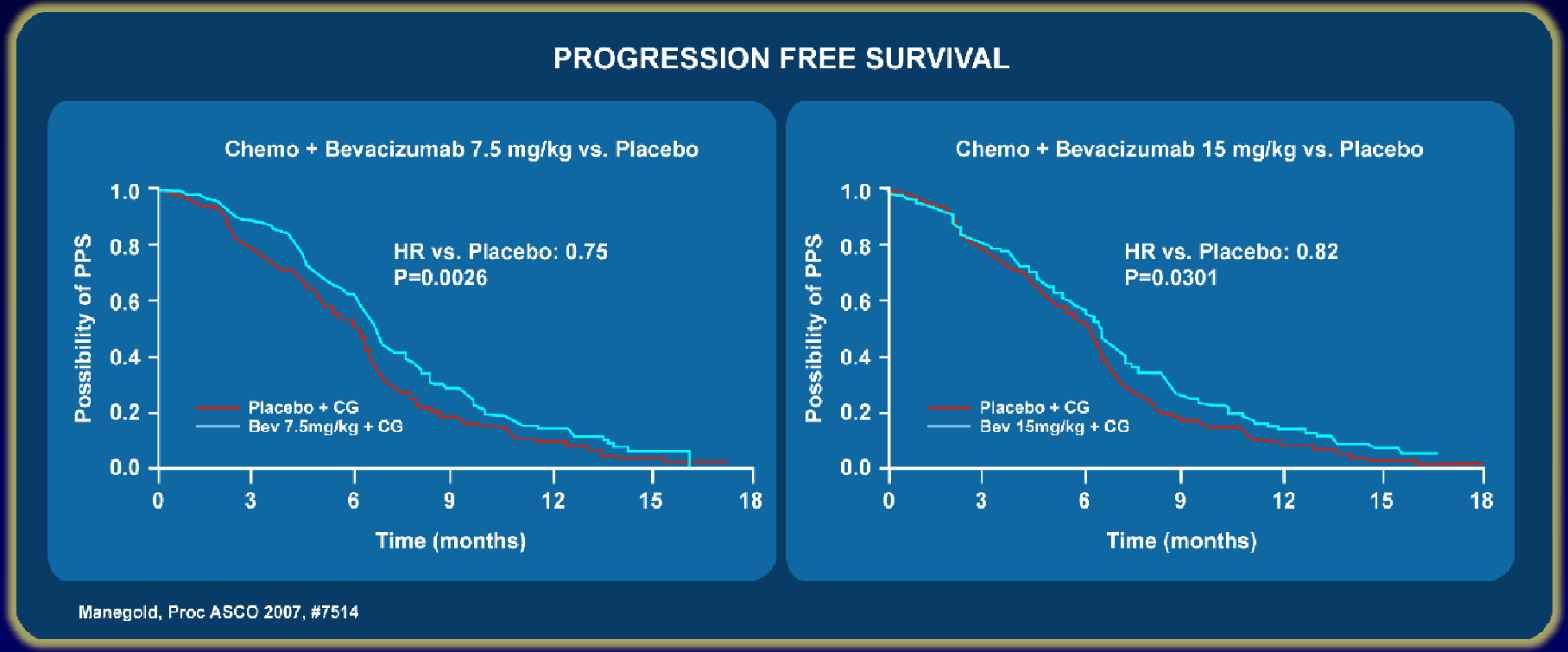
Adapted from Sandler A, et al. *N Engl J Med* 2006;355:2542–50.

Phase III Trial of Bevacizumab in NSCLC (E4599): Overall survival



Adapted from Sandler A, et al. *N Engl J Med* 2006;355:2542–50.

AVAIL:
cis/gem +/- bevacizumab



ESMO update:	7.5mg	15mg	placebo
Median survival	13.4m	13.6m	13.1m

Currently Gemzar+Cis combined with Bevacizumab is not indicated in the Gemzar label

Adapted from Manegold C, et al. Presented at the 2007 ASCO Annual Meeting. Chicago, Illinois. June 2007.
Adapted from Manegold C, et al. Presented at the 33rd ESMO Congress, Stockholm, Sweden. September 2008.

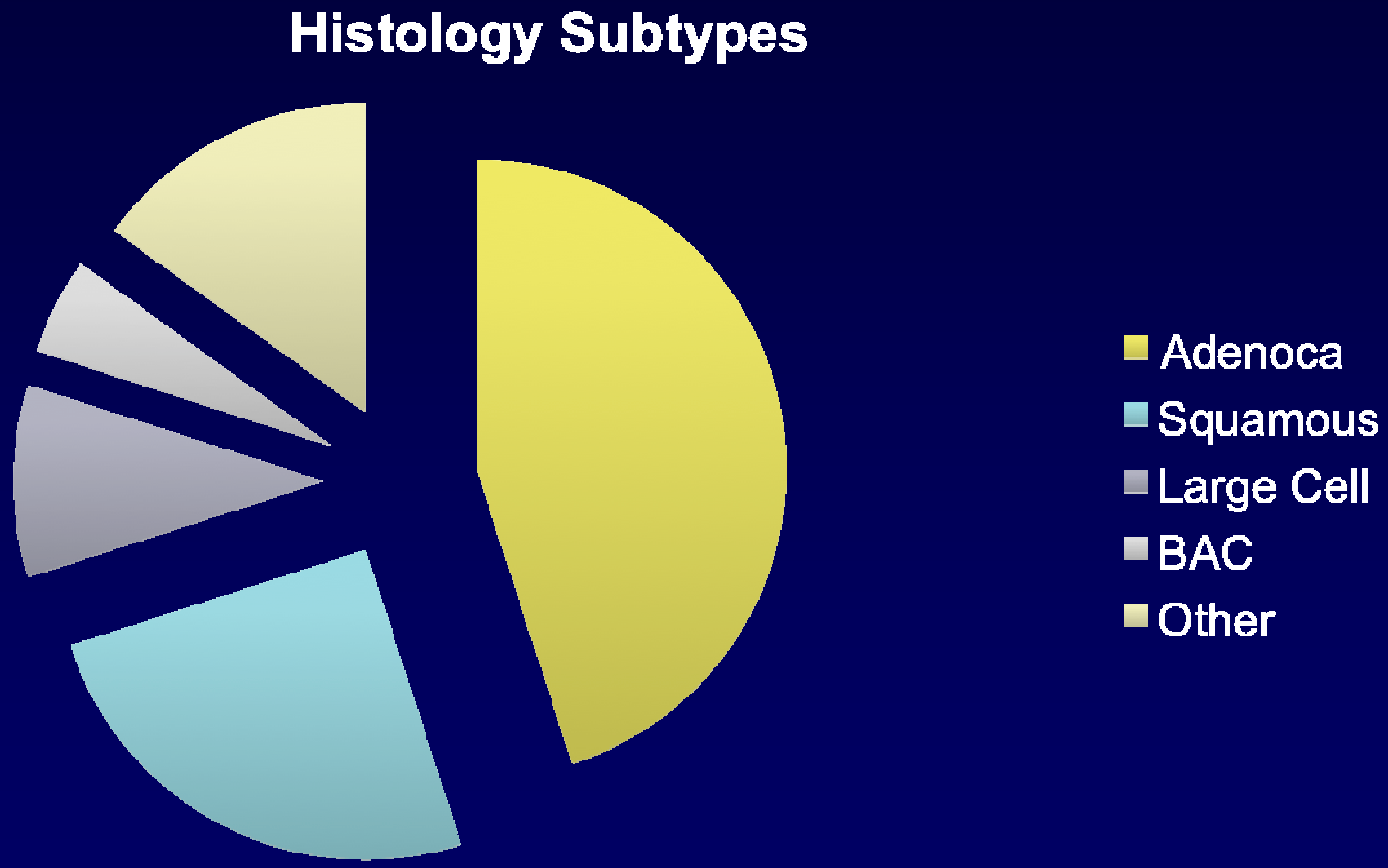
New Anti-Angiogenics – First Line

- **NExUS:**
  - Gemcitabine+ Cisplatin +/- Sorafenib
  - Randomized Phase III, double-blind, placebo controlled
  - Study population: Non-Squamous NSCLC
- **Key results**
  - Slight improvement in PFS 5.5 m to 6.0m
  - No difference in OS
  - There is potentially negative effect on patients with squamous cell histology (ESCAPE trial)

Study Comments

- Anti-Angiogenics are clearly effective in NSCLC.
- However, we need to identify appropriate biomarkers to help identify those who benefit the most
- Monoclonal Ab may be better suited to be used with chemotherapy than TKI-chemo partners due to a more selective and targeted MOA

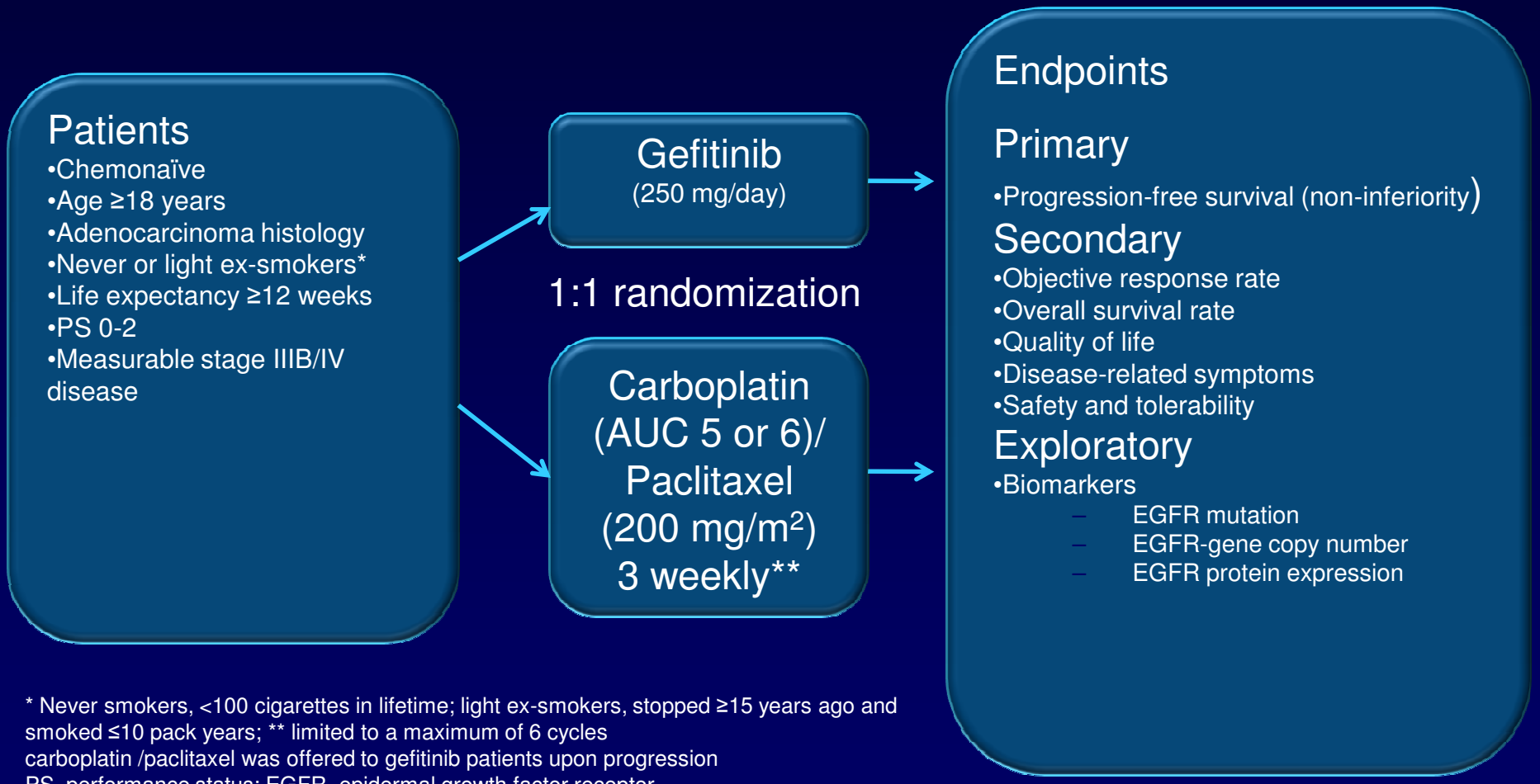
Lung Cancer – 2010 – Histology is important!



Outline

- Anti-Angiogenics in first line setting
- EGFR Targeted Therapies
  - Update from the IPASS Trial
  - OPTIMAL Study – Erlotinib in the first line setting
  - New Generation of EGFR TKI – first line and beyond
  - Combining Anti-Angiogenics to EGFR TKI
- The role of Maintenance
  - Who Benefits the most?

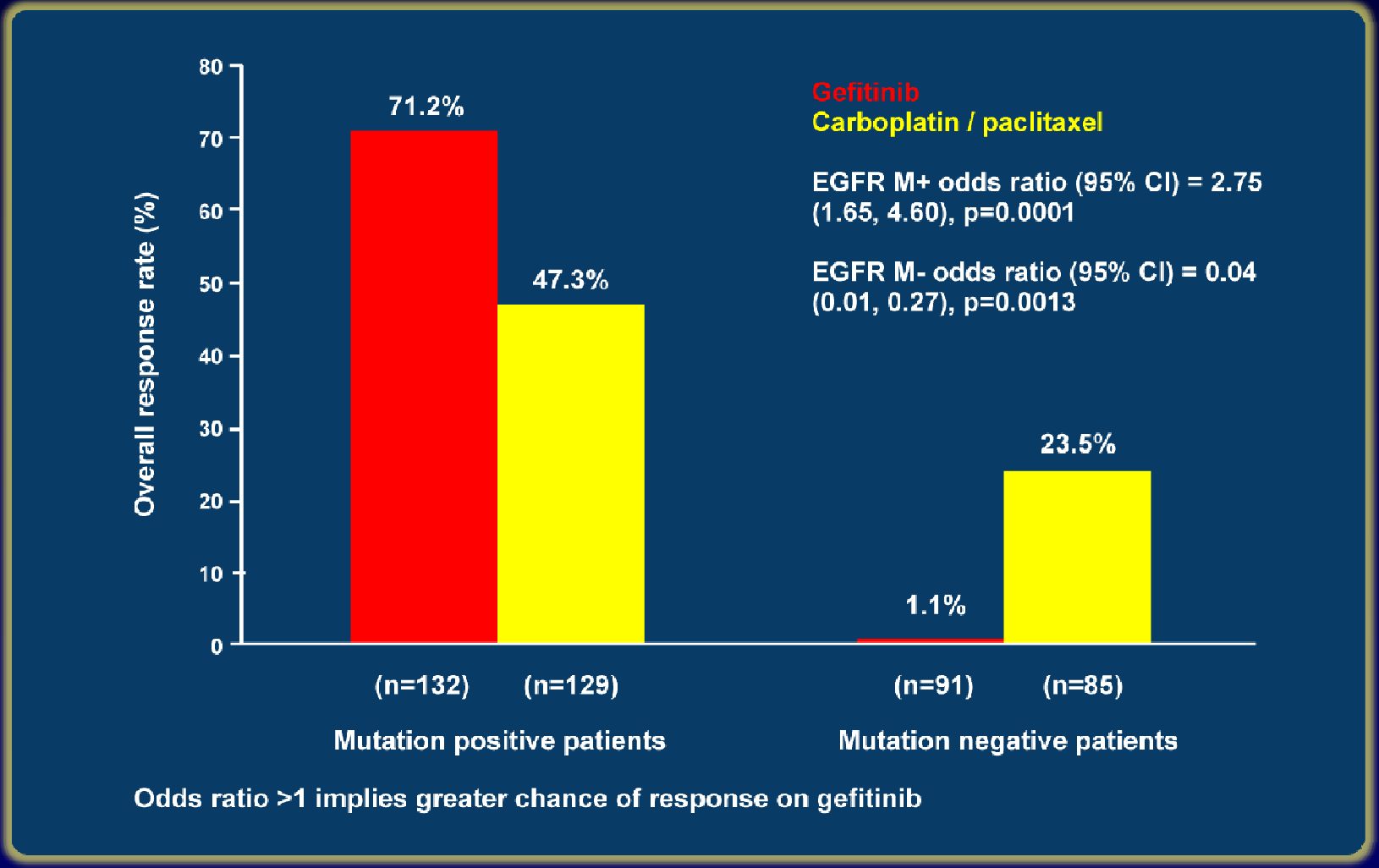
A Phase III, Open-Label, First-Line Study of Gefitinib vs. Carboplatin/Paclitaxel in Clinically Selected Patients with Advanced Non-Small Cell Lung Cancer (IPASS)



* Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; ** limited to a maximum of 6 cycles
carboplatin /paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

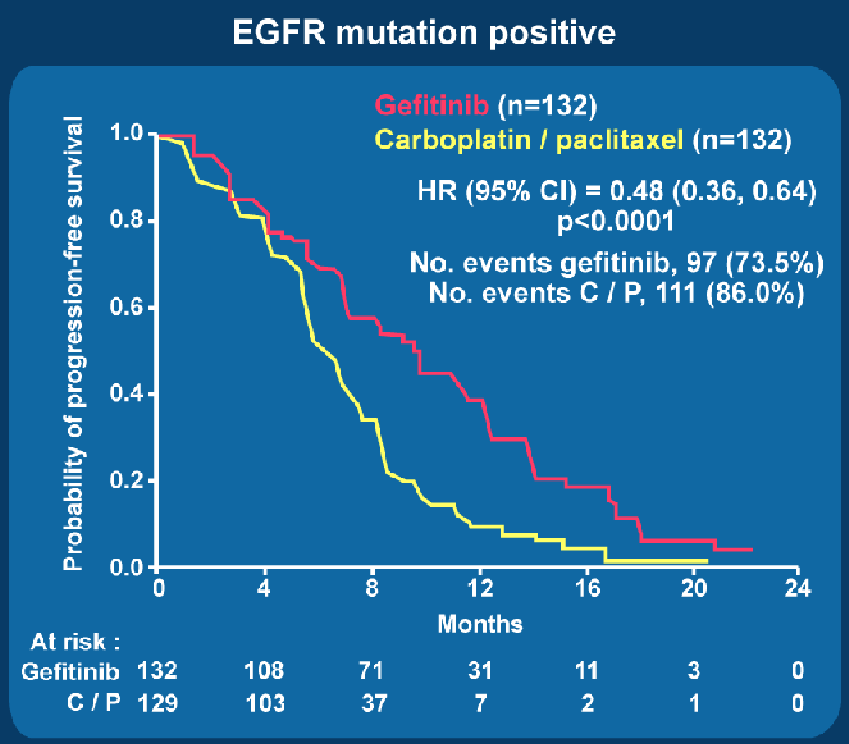
Adapted from Mok T, et al. *Discov Med* 2009;8:227-31.

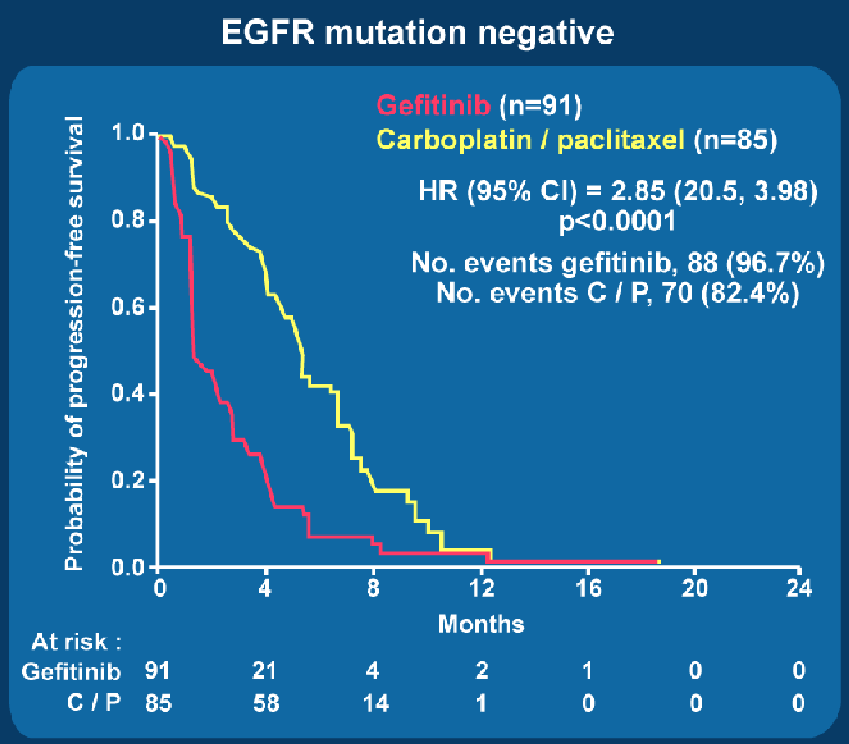
Objective Response Rate in EGFR Mutation Positive and Negative Patients



Adapted from Mok T, et al. *Discov Med* 2009;8:227-31.

Progression-free Survival in EGFR Mutation Positive and Negative Patients





Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

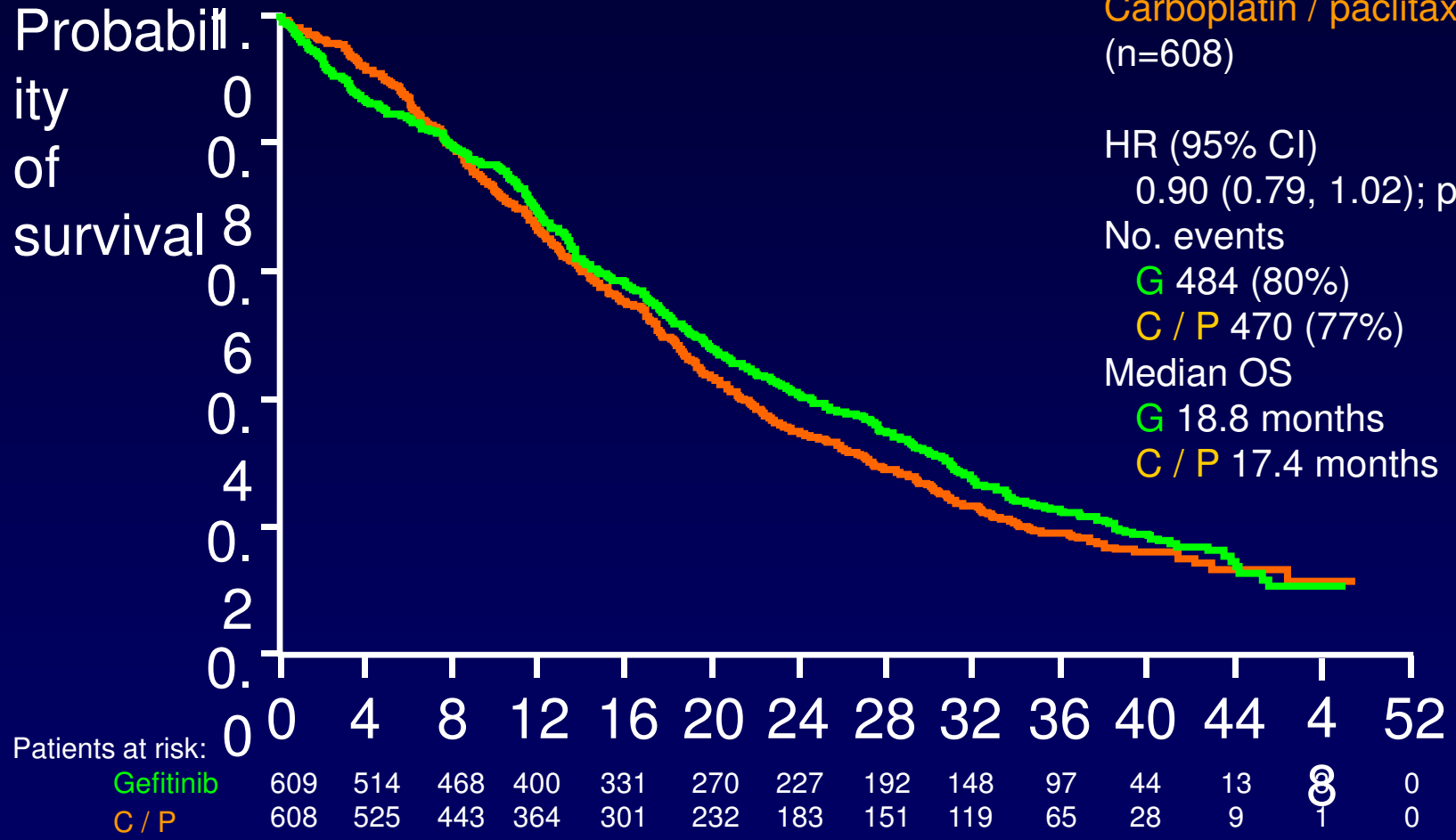
Adapted from Mok T, et al. *Discov Med* 2009;8:227-31.

Final overall survival results from a Phase III, randomised, open-label, first-line study of gefitinib vs carboplatin / paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS)

Chih-Hsin Yang,[1] Masahiro Fukuoka,[2] Tony S. Mok,[3] Yi-Long Wu,[4] Sumitra Thongprasert,[5] Nagahiro Saijo,[2] Da-Tong Chu,[6] Haiyi Jiang,[7] Emma L. Duffield,[8] Yukito Ichinose[9]

[1]National Taiwan University Hospital and College of Medicine, Taipei, Taiwan; [2]Kinki University School of Medicine, Osaka, Japan; [3]State Key Laboratory in Oncology in South China, Sir YK Pao Center for Cancer, Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, China; [4]Guangdong General Hospital, Guangzhou, China; [5]Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai, Thailand; [6]Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [7]AstraZeneca, Osaka, Japan; [8]AstraZeneca, Macclesfield, UK; [9]National Kyushu Cancer Center, Fukuoka, Japan

IPASS: 2010 updated OS analysis (ITT)



Gefitinib (n=609)
Carboplatin / paclitaxel (n=608)

HR (95% CI)
0.90 (0.79, 1.02); p=0.109
No. events
G 484 (80%)
C / P 470 (77%)
Median OS
G 18.8 months
C / P 17.4 months

Primary Cox analysis with covariates
A hazard ratio <1 implies a lower risk of death on gefitinib
No formal adjustment made for multiple testing

Yang CH et al. ESMO 2010

IPASS: 2010 summary of subsequent systemic therapy (ITT)

	Gefitinib (n=609)*	C / P (n=608)
No further systemic treatment	31%	38%
Chemotherapy	65%	41%
Platinum based**	60%	9%
C / P**	49%	1%
EGFR TKI**	20%	52%
Gefitinib#	5%	41%
Erlotinib#	12%	14%
Other#	5%	6%

*% exclude 20 patients in the gefitinib arm with ongoing randomised treatment
**Patients may have also received other chemotherapy and / or EGFR TKI during the study. Excludes single platinum based chemotherapy
#Categories are not mutually exclusive
Radiotherapy, surgery, medical procedures and other treatments excluded

Yang CH et al. ESMO 2010

Study Comments

- IPASS study is one of the most pivotal trials in lung cancer
- EGFR TKI therapies are beneficial for patients even when given in second/third line setting
- The question may not be the destination but the journey i.e. which is the best sequence of therapy?

Efficacy results from the randomised phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin (CBDCA) plus gemcitabine (GEM), in Chinese advanced non-small-cell lung cancer (NSCLC) patients (pts) with *EGFR* activating mutations

Caicun Zhou,[1] Yi-long Wu,[2] Gongyan Chen,[3] Jifeng Feng,[4] Xiaoqing Liu,[5] Changli Wang,[6] Shucai Zhang,[7] Jie Wang,[8] Songwen Zhou,[1] Shengxiang Ren,[1] on behalf of the OPTIMAL investigators

[1]Shanghai Pulmonary Hospital, Tongji University, Shanghai; [2]Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou; [3]The Cancer Hospital of Harbin Medical University, Harbin; [4]Jiangsu Province Cancer Hospital, Nanjing; [5]307 Hospital of the Academy of Military Medical Sciences, Cancer Center, Beijing; [6]Tianjin Cancer Hospital, Tianjin; [7]Beijing Chest Hospital, Beijing; [8]Peking University School of Oncology, Beijing Cancer Hospital, Beijing; China

OPTIMAL study design

- Chemonaïve
- Stage IIIB/IV NSCLC
- *EGFR* Act Mut+ (exon 19 deletion or exon 21 L858R mutation)
- ECOG PS 0–2
- (n=165)

R

1:1

Erlotinib 150mg/day

Gemcitabine (1,000 mg/m^2 d1,8) Carboplatin (AUC5 d1) q3w, up to 4 cycles

Primary endpoint

- Progression-free survival (PFS)

Secondary endpoints

- Overall survival (OS), objective response rate (ORR), time to disease progression, duration of response, safety, HRQoL (FACT-L, LCSS), exploratory biomarker analyses

Stratification factors

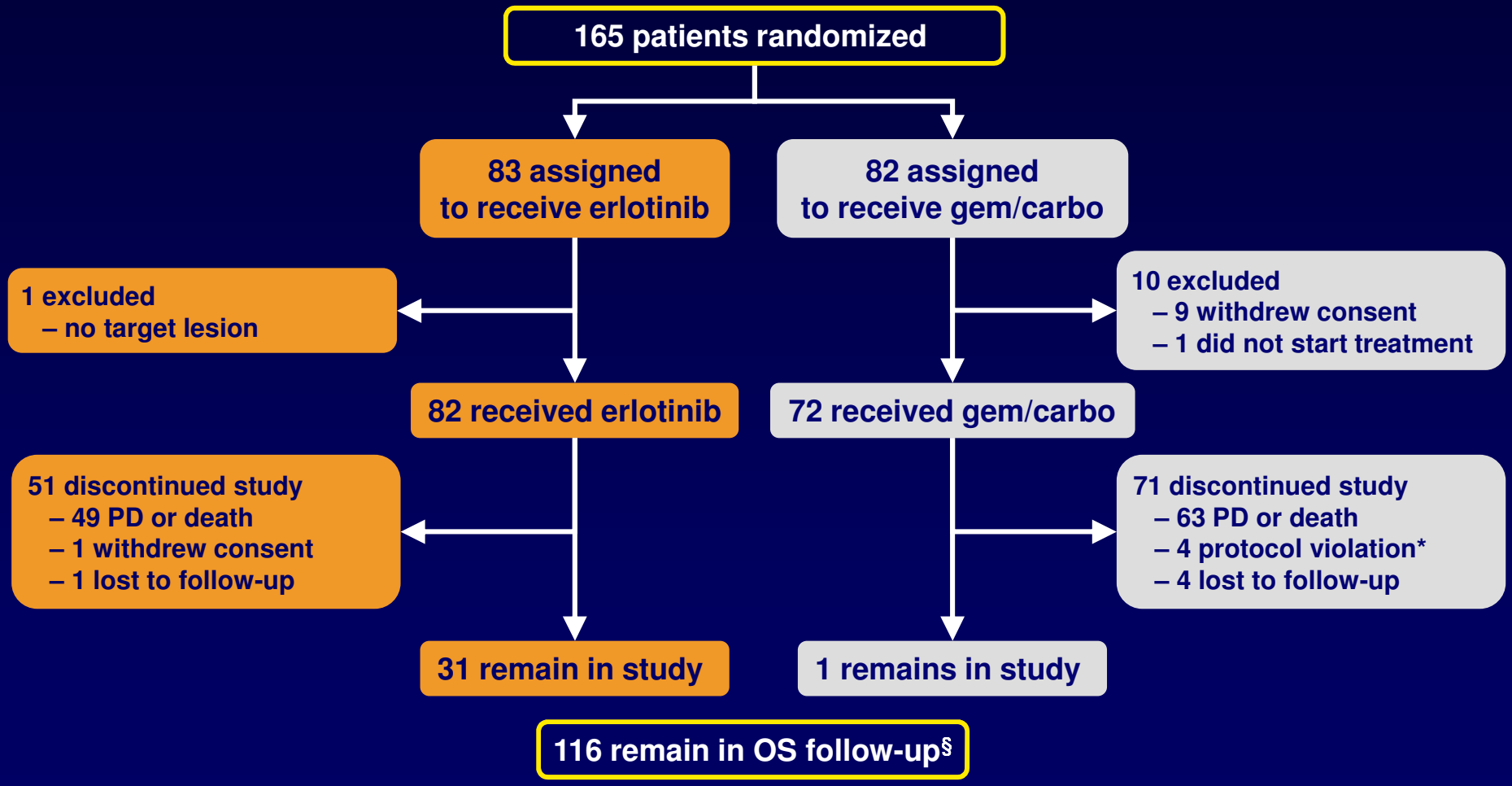
- Mutation type
- Histology
- Smoking status

Efficacy assessment

- Every 6 weeks

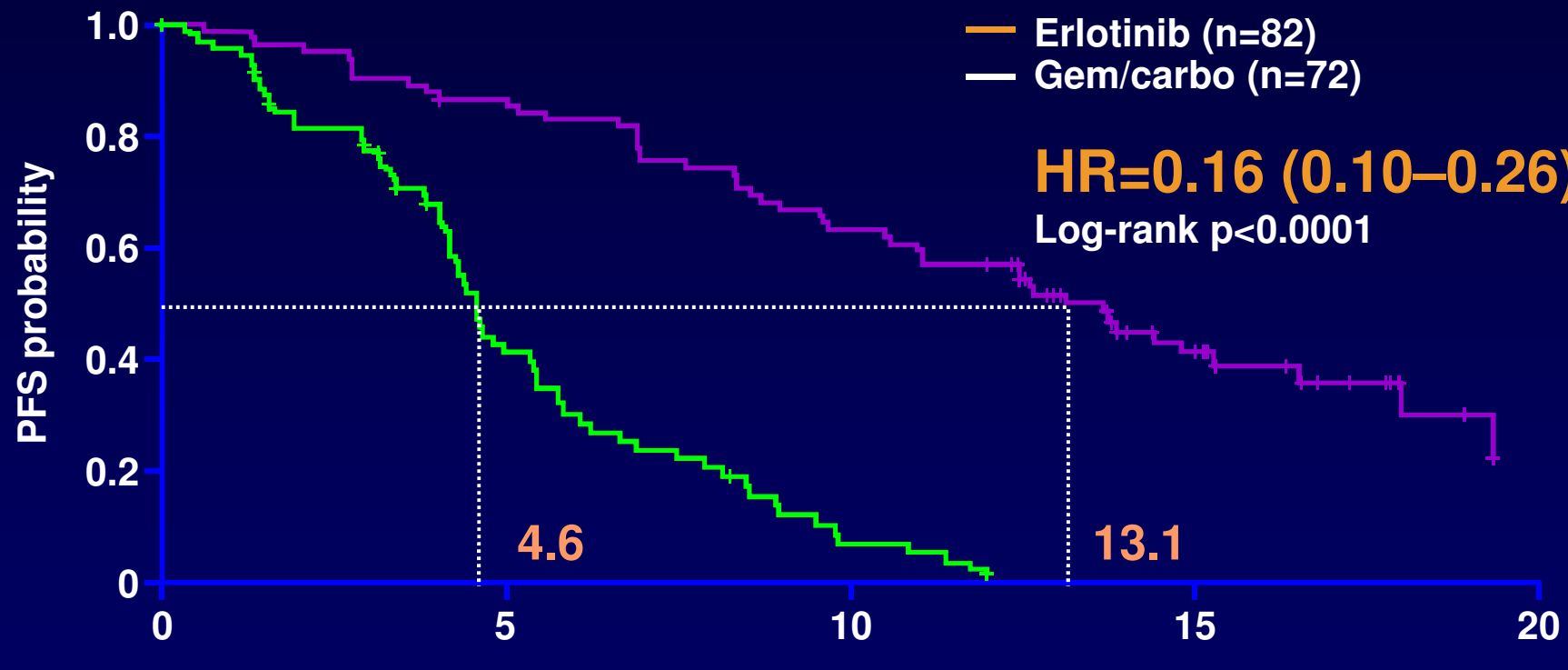
Act Mut+ = activating mutations; ECOG = Eastern Cooperative Oncology Group; PS = performance status
HRQoL = health-related quality of life; FACT-L = Functional Assessment of Cancer Therapy-Lung; LCSS = lung cancer symptom scale

Study profile (16 August 2010)



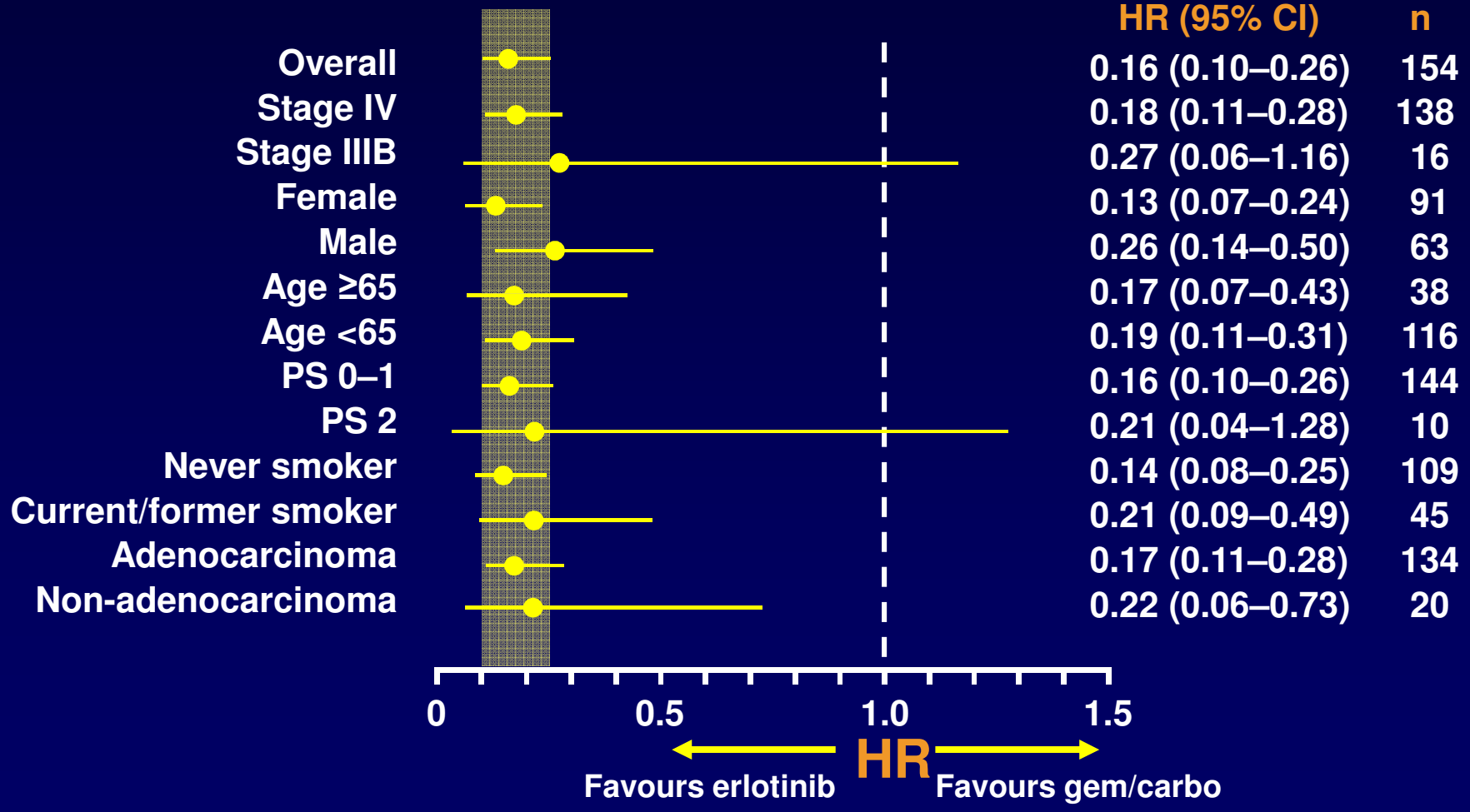
*Received erlotinib (3) or gefitinib (1) after chemotherapy, but before PD
§112 events had occurred by 16 August 2010; PD = progressive disease

OPTIMAL PFS: updated analysis (ITT)



Patients at risk					
Erlotinib	82	70	51	20	2
Gem/carbo	72	26	4	0	0

Subgroup analysis of PFS



Best tumour response*

	Erlotinib [n=82] n (%)	Gem/carbo [n=72] n (%)	
CR	2 (2)	0 (0)	
PR	66 (81)	26 (36)	
ORR	*68 (83)*	*26 (36)*	p<0.0001
SD	11 (13)	33 (46)	
DCR	*79 (96)*	*59 (82)*	p=0.002
PD	3 (4)	12 (17)	

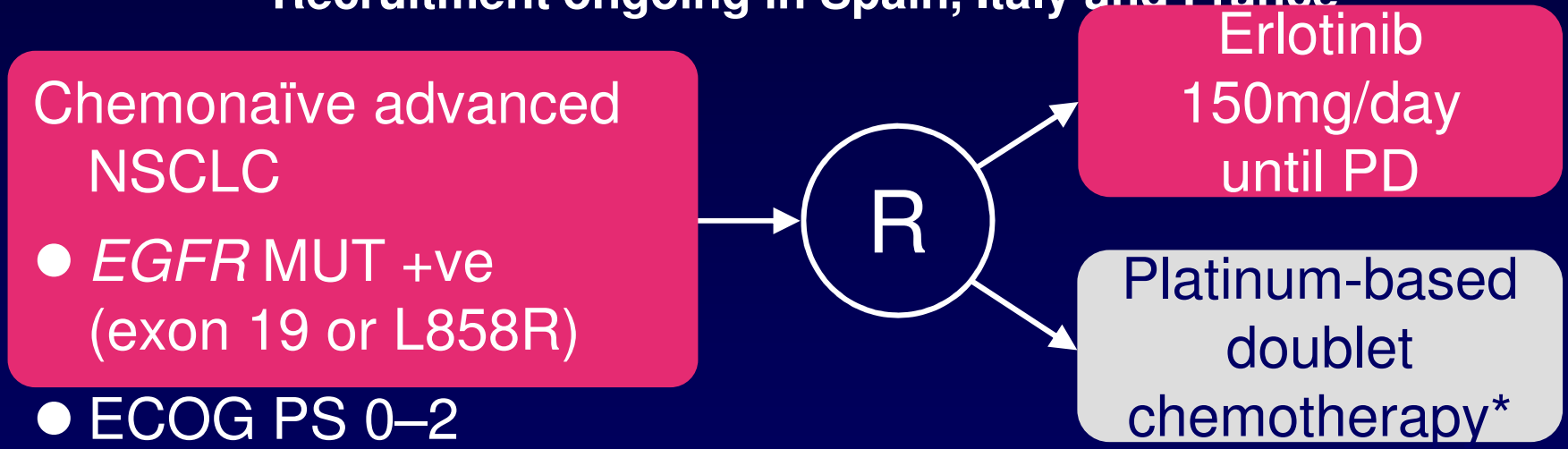
*in evaluable patients; CR = complete response; PR = partial response; SD = stable disease; DCR = disease control rate (CR + PR + SD)

Study Comments

- This is the first trial studying efficacy of Erlotinib in the first line setting for EGFR mutation positive patients
- The results are very impressive and ask the question on how this agent compares with Gefitinib – trials ongoing
- The ongoing EurTac trial will be an important trial to help confirm the efficacy in the caucasian patient population

Ongoing trial of first-line erlotinib vs chemotherapy in *EGFR* MUT +ve NSCLC: EURTAC

- **Phase III study initiated by the SLCG**
- **Recruitment ongoing in Spain, Italy and France**



- Primary endpoint: PFS (n=178)
- Secondary endpoints: ORR, 1-year survival, OS, safety, QoL, localisation of PD

*All cycles every 21 days, up to 4 cycles; ORR = objective response rate

LBA18

Efficacy and Safety of PF-00299804 as First-Line Treatment of Patients with Advanced NSCLC Selected for Activating Mutation of Epidermal Growth Factor Receptor (EGFR)

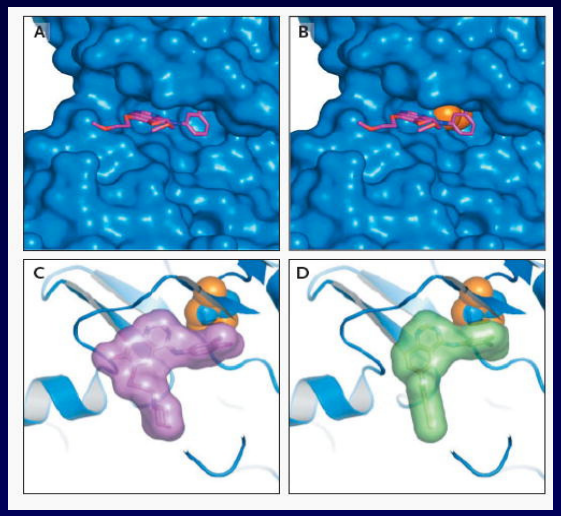
T Mok,[1] DR Spigel,[2] K Park,[3] MA Socinski,[4] S Tung,[5] DW Kim,[6] SI Ou,[7] H Zhang,[8] JP O'Connell,[9] P Jänne[10]

[1]The Chinese University of Hong Kong, Shatin, Hong Kong; [2]SCRI-Sarah Cannon Research Institute, Nashville, TN, USA; [3]Samsung Medical Center, Seoul, Republic of Korea; [4]University of North Carolina, Chapel Hill, NC, USA; [5]Tuen Mun Hospital, Tuen Mun, Hong Kong; [6]Seoul National University, Seoul, Republic of Korea; [7]School of Medicine, University of California at Irvine, Irvine, CA, USA; [8]Pfizer (China) Research & Development Co. Ltd, Shanghai, China; [9]Pfizer Oncology, New London, CT, USA [10]Dana-Farber Cancer Institute, Boston, MA, USA

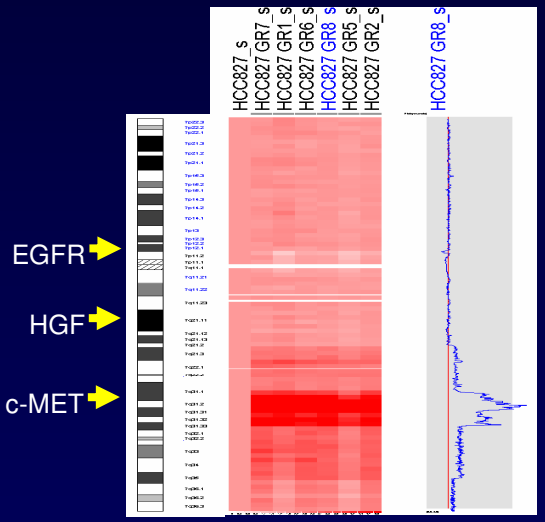
Presented at the 35th Congress of the European Society for Medical Oncology (ESMO), Milan, Italy, October 8–12, 2010

Known Mechanisms of EGFR TKI Resistance

Exon 20 *T790M* Mutation



c-MET Amplification



Study	N	*T790M* n/N (%)	*Met* amplification n/N (%)	Both n/N (%)	Neither n/N (%)
Engelman et al.	18	10/18 (56)	4/18 (22)	2/18 (11)	6/18 (33)
Bean et al.	43	20/43 (47)	9/43 (21)	4/43 (9)	18/43 (42)

Left-hand figure from Kobayashi S, et al. *N Engl J Med* 2005;352:786–792

Right-hand figure from Engelman JA, et al. *Science* 2007;316:1039–1043. Reprinted with permission from AAAS
Bean J, et al. *Proc Natl Acad Sci U S A* 2007;104:20932–20937

Trial Design and Dosing Regimen

Patients clinically selected

Never-* or former light† smoker; Asian or *KRAS* WT non-Asian

OR

Known *EGFR* mutation

Additional inclusion criteria:

- Adenocarcinoma histology
- Chemotherapy naïve
- ECOG PS 0/1

PF299
45 mg QD
(amended to 30 mg)

Endpoints

Primary
- PFS rate at 4 months

Secondary:
- PFS
- OS
- ORR
- Safety

Exploratory:
- Serial tissue- and blood-based biomarkers (*T790M*)

Data cut-off: July 28, 2010

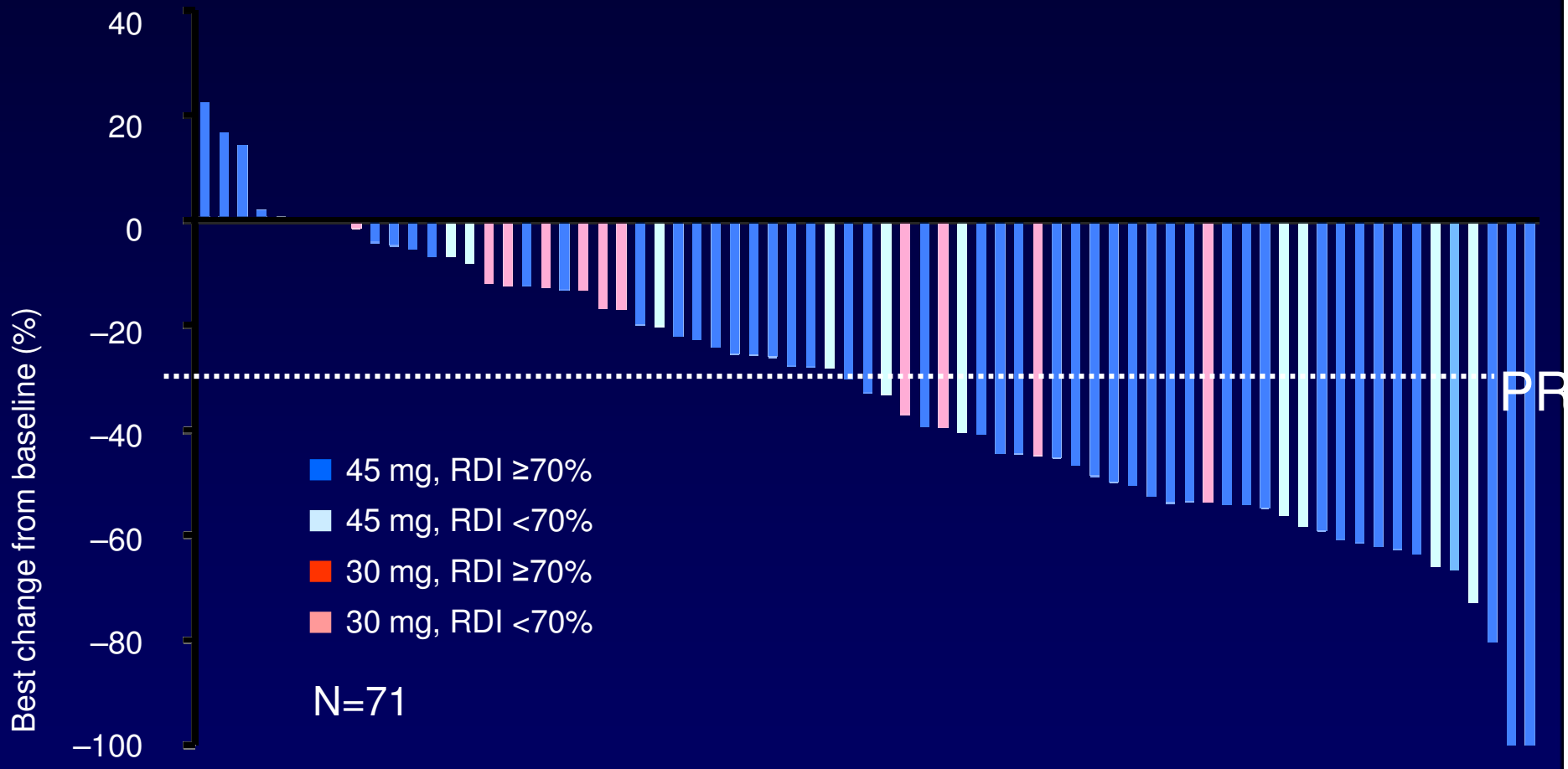
Study Conduct

- 30 patients from 17 US centers and 44 patients from 8 Asian centers
- Study start March 2009: 45 mg QD starting dose, completed May 2010
- Toxicity data reviewed July 2010

Protocol amendment:

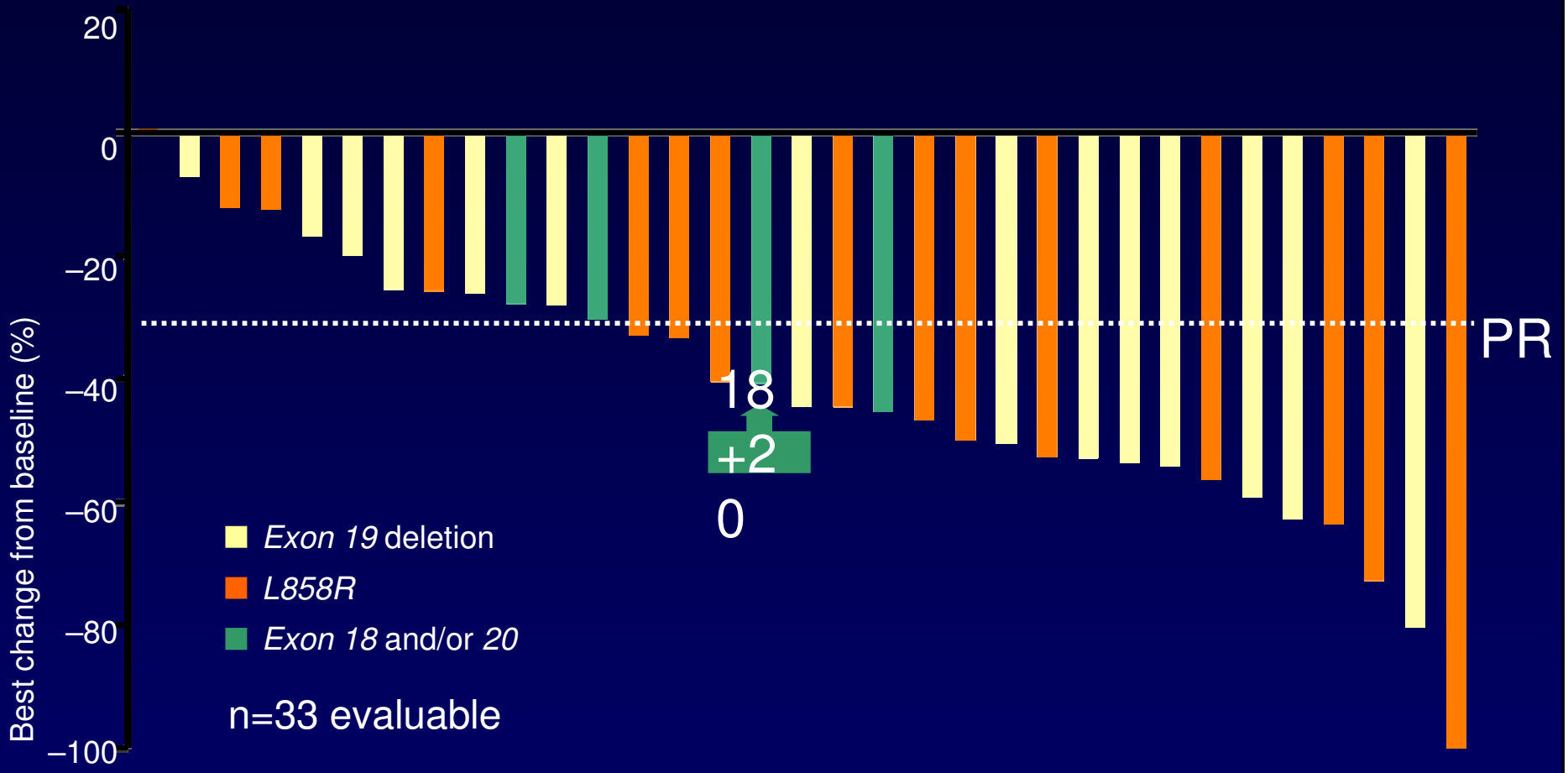
- Starting dose changed to 30 mg QD with dose escalation to 45 mg QD after 8 weeks of treatment in absence of grade >1 toxicity for ε1 month
- Enrollment at starting dose of 30 mg QD ongoing
- Median duration of follow-up:
  - 45-mg starting dose, 5.6 months
  - 30-mg starting dose, 1.9 months

Best Tumor Change in Target Lesions: Overall Population



- **Relative dose intensity (RDI) based on 45-mg starting dose**
- **Among patients who achieved >30% decrease from baseline, 3 starting on 45 mg and 1 starting on 30 mg were not confirmed**

Best Tumor Change in Target Lesions: Patients with *EGFR* Mutation



- **1 patient appeared to have an increase in tumor size (0.6%)**
- **All patients with typical *EGFR* mutations had some degree of tumor shrinkage**
- **Responses for 2 patients who achieved >30% tumor decrease were not confirmed due to early drop out**

Best Objective Response

Response, %	All patients (N=71)	*Exon 19* deletion or *L858R* (n=27)	*EGFR* mutation* (n=33†)
Complete response	1	0	0
Partial response	41	59	55
Stable disease	44	37	39
Progressive disease	8	0	0
Indeterminate	6	4	6
Objective response rate (95% CI)	42 (31, 55)	59 (39, 78)	55 (36, 72)
Disease control rate‡ (95% CI)	86 (76, 93)	96 (81, 100)	94 (80, 99)

*Includes 4 patients with mutations in exon 18, exon 20, or exon 18 + 20

†Evaluable patients

‡Complete response + partial response + stable disease

Conclusions: Efficacy

- PF299 shows encouraging preliminary efficacy for first-line treatment of clinically or molecularly selected patients with NSCLC
- Tumor shrinkage was observed in all patients with typical *EGFR*-activating mutations in exons 19 or 21 (disease control rate 96%)
- In addition to activity against tumors with classic activating mutations, PF299 also showed preliminary indications of activity against tumors with other *EGFR* mutations, including exon 20, and against *EGFR* wild-type tumors
- PFS data are not mature

Study Comments

- Promising drug that shows high activity level in EGFR mutation positive patients
- Givne toxicity profile, need to better identify those who are most likely to benefit c/w standard EGFR TKI therapy
- Ongoing NCIC BR 26 trial is investigating this agent in those who have progressed on standard treatment

Phase IIb/III trial of afatinib (BIBW 2992) + best supportive care (BSC) vs. placebo + BSC in patients failing 1–2 lines of chemotherapy and erlotinib/gefitinib (LUX-Lung 1)

V. A. Miller[1], V. Hirsh[2], J. Cadranel[3], Y.-M. Chen[4], K. Park[5],
S.-W. Kim[6], Z. Caicun[7], M. Oberdick[8], M. Shahidi[9], C.-H. Yang[10]

[1] Memorial Sloan-Kettering Cancer Center, New York, USA, [2] McGill University Health Center, Montreal, Canada, [3] Hôpital Tenon, Paris, France [4] Veterans General Hospital, Taipei City, Taiwan [5] Samsung Medical Center, Seoul, Korea, [6] Asan Medical Center, Seoul, Korea [7] Shanghai Pulmonary Hospital, Tongii University, Shanghai, China, [8] Boehringer Ingelheim Pharmaceuticals, Ridgefield, USA, [9] Boehringer Ingelheim Limited, Bracknell, UK, [10] National Taiwan University Hospital, Taipei, Taiwan

Afatinib: Background

- Orally bioavailable, small molecule tyrosine kinase inhibitor (TKI)
- Designed to irreversibly bind to the ATP binding pocket of EGFR and HER2
- Highly specific for EGFR and HER2
  - EGFR IC_{50}: 0.50 nM
  - HER2 IC_{50}: 14 nM

LUX-Lung 1: Rationale

- Presence of EGFR-activating mutation in NSCLC confers exquisite sensitivity to EGFR TKIs
- Patients sensitive to gefitinib (G) or erlotinib (E) eventually progress
  - T790M mutation is the most common cause of resistance
    - Detected in ~50% of such patients
- Afatinib is an irreversible EGFR and HER2 inhibitor with preclinical activity against H1975 (L858R/T790M) (EC_{50}: 99 nM)
- No approved therapy available for locally advanced or metastatic NSCLC in patients who have failed chemotherapy and progressed after treatment with EGFR TKI

LUX-Lung 1: Trial design

Patients with:

- Adenocarcinoma of the lung
- Stage IIIB/IV
- Progressed after one or two lines of chemotherapy (incl. one platinum-based regimen) and ≥12 weeks of treatment with erlotinib or gefitinib
- ECOG 0–2

N=585

Randomization 2:1
(Double Blind)

Oral afatinib 50 mg once daily
plus BSC

Oral placebo once daily
plus BSC

Primary endpoint: Overall survival (OS)

Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

- Radiographic assessments at 4, 8, 12 wks and every 8 wks thereafter
- Exploratory biomarkers:
  - Archival tissue testing for EGFR mutations (optional; central lab)
  - Serum EGFR mutational analysis (all patients)

Statistical design and study conduct

- Statistical design
  - Primary analysis for overall survival
    - 359 events were needed for a 90% power to detect a HR of at least 0.70 (e.g., an increase in median survival from 4.7 to 6.7 months) at one-sided 0.025 significance level
- Study conduct
  - 697 patients screened/585 patients randomized from May 2008 to Sept 2009
  - 84 sites in 15 countries located in North America, Europe and Asia
  - 358 events (61%) reached in July 2010

Disease control rate and objective responses

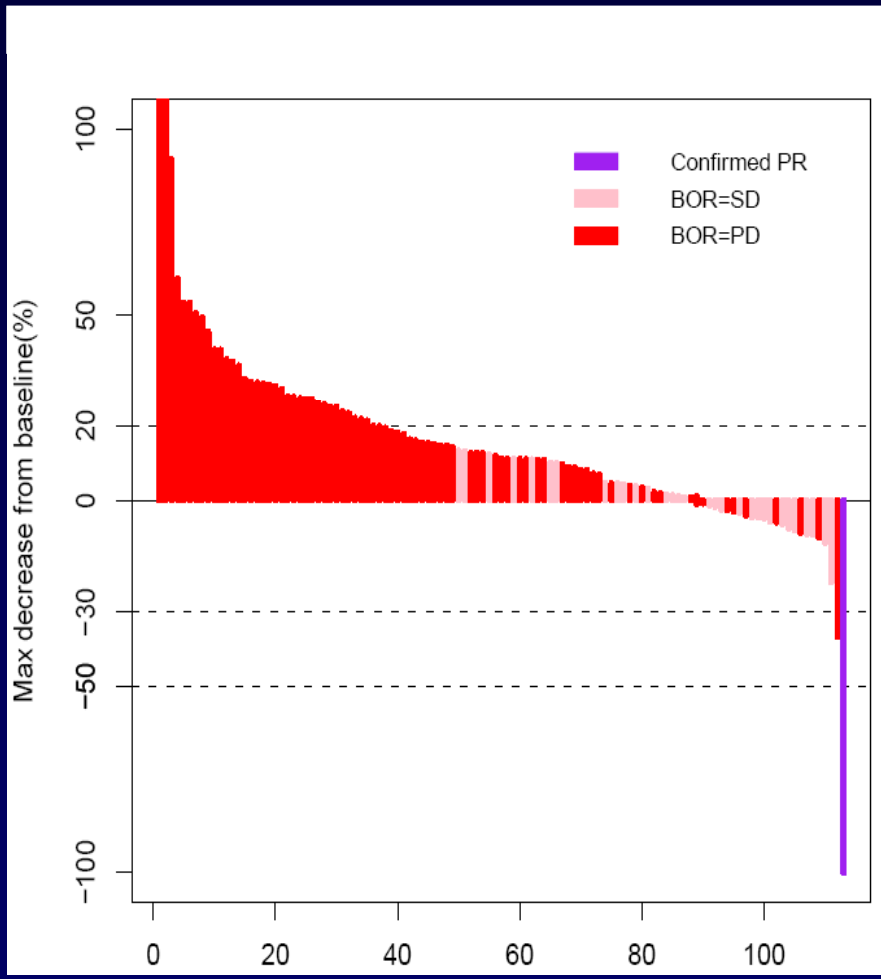
	Independent Review	
	Afatinib (%)	**Placebo (%)**
PR, (regardless of confirmation)	13*	0.5
PR, (confirmed)	7*	0.5
SD ≥ 8 wks	51	18
DCR (PR+SD) ≥ 8 wks	58**	19

Median duration of confirmed response: 24 weeks

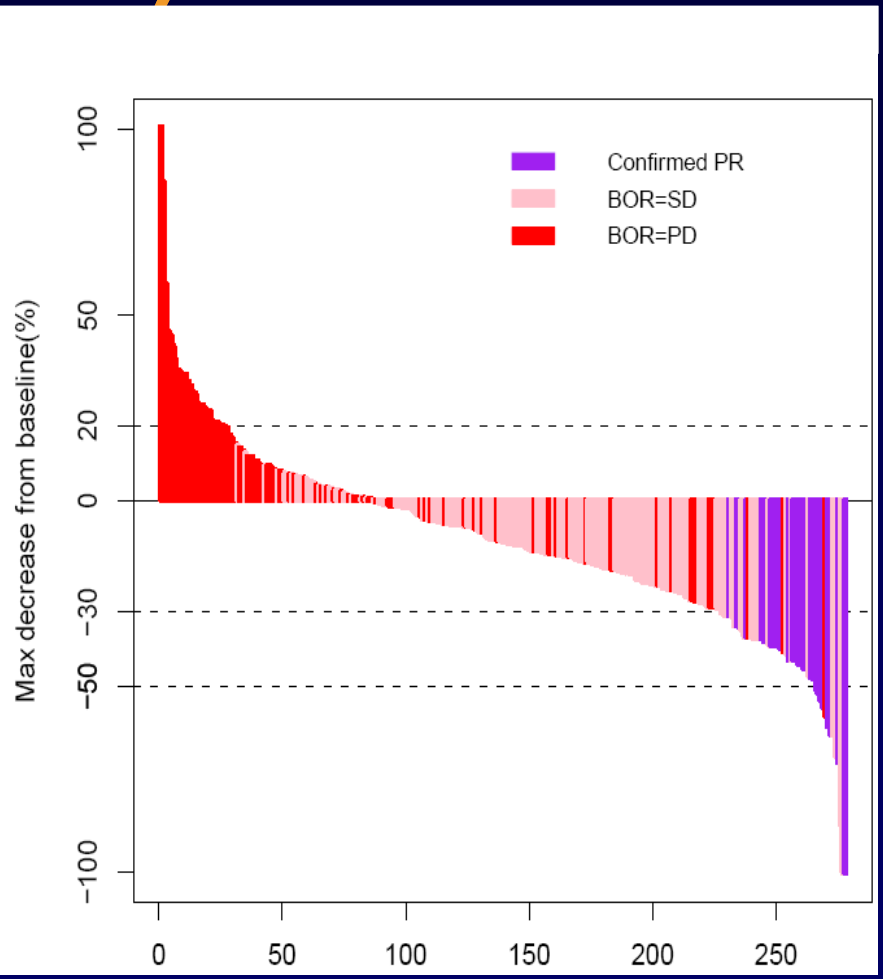
* P < 0.01 compared to placebo
** P < 0.0001 compard to placebo

Maximum decrease in tumor size from baseline (independent review)

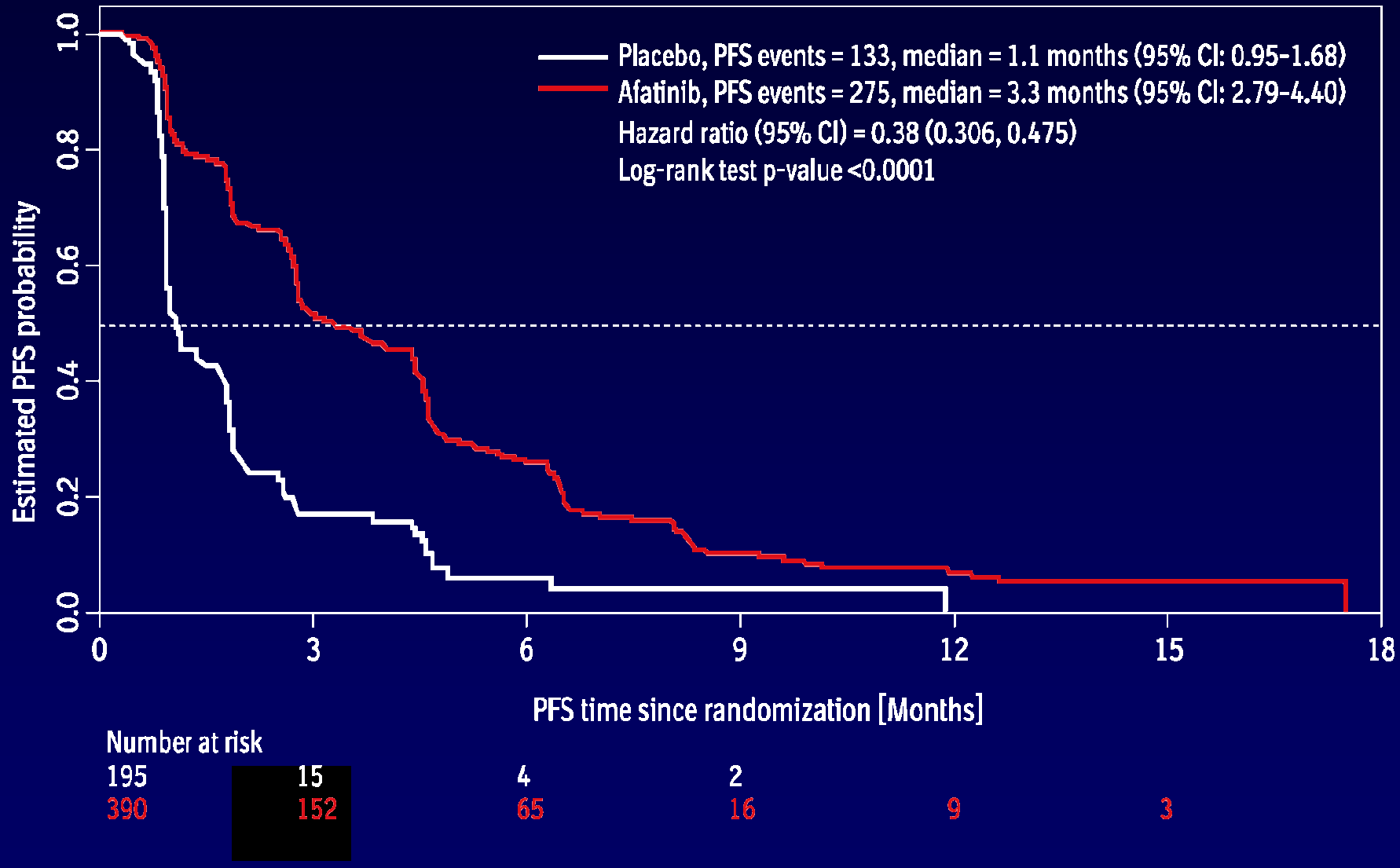
Placebo



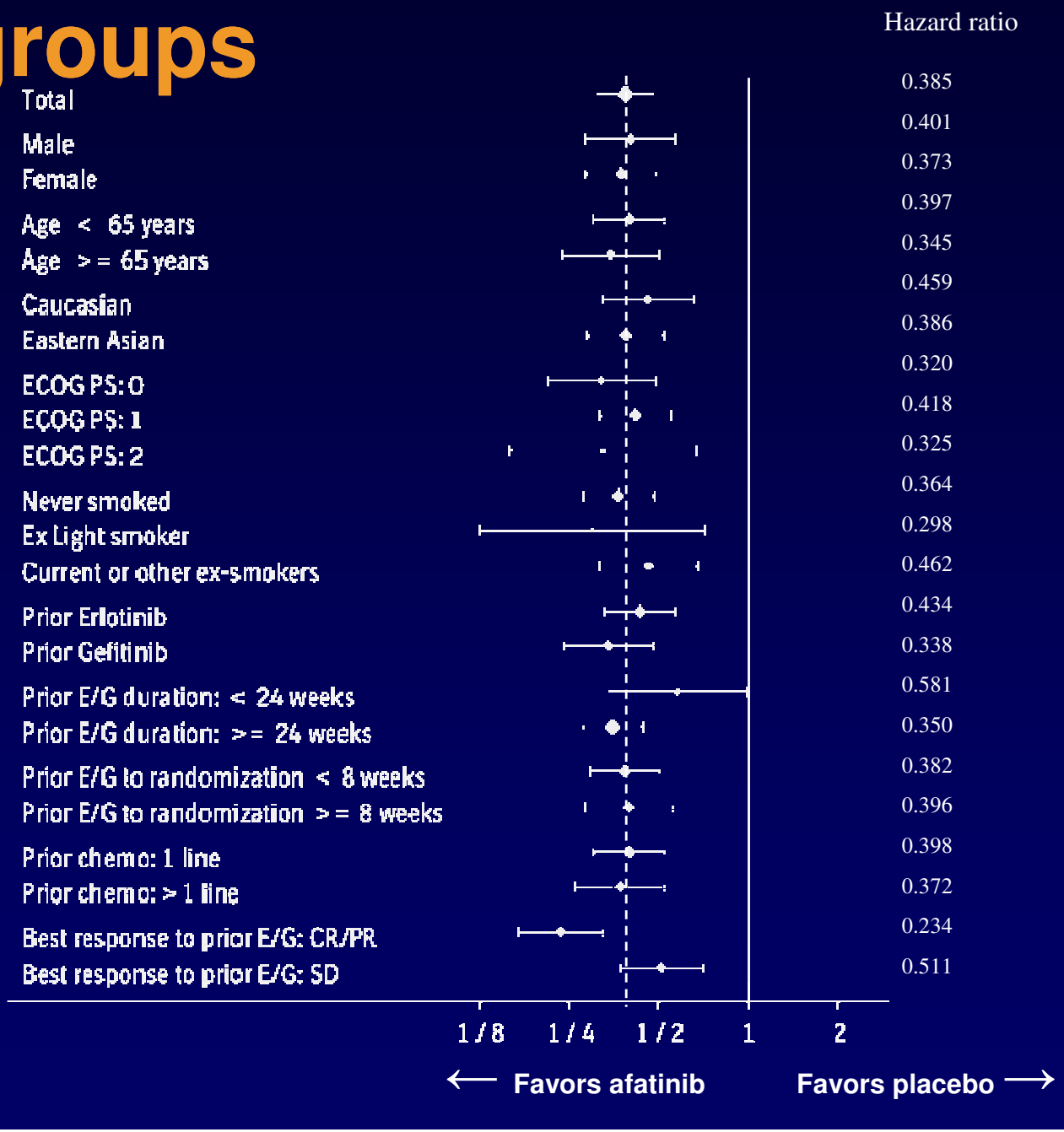
Afatinib



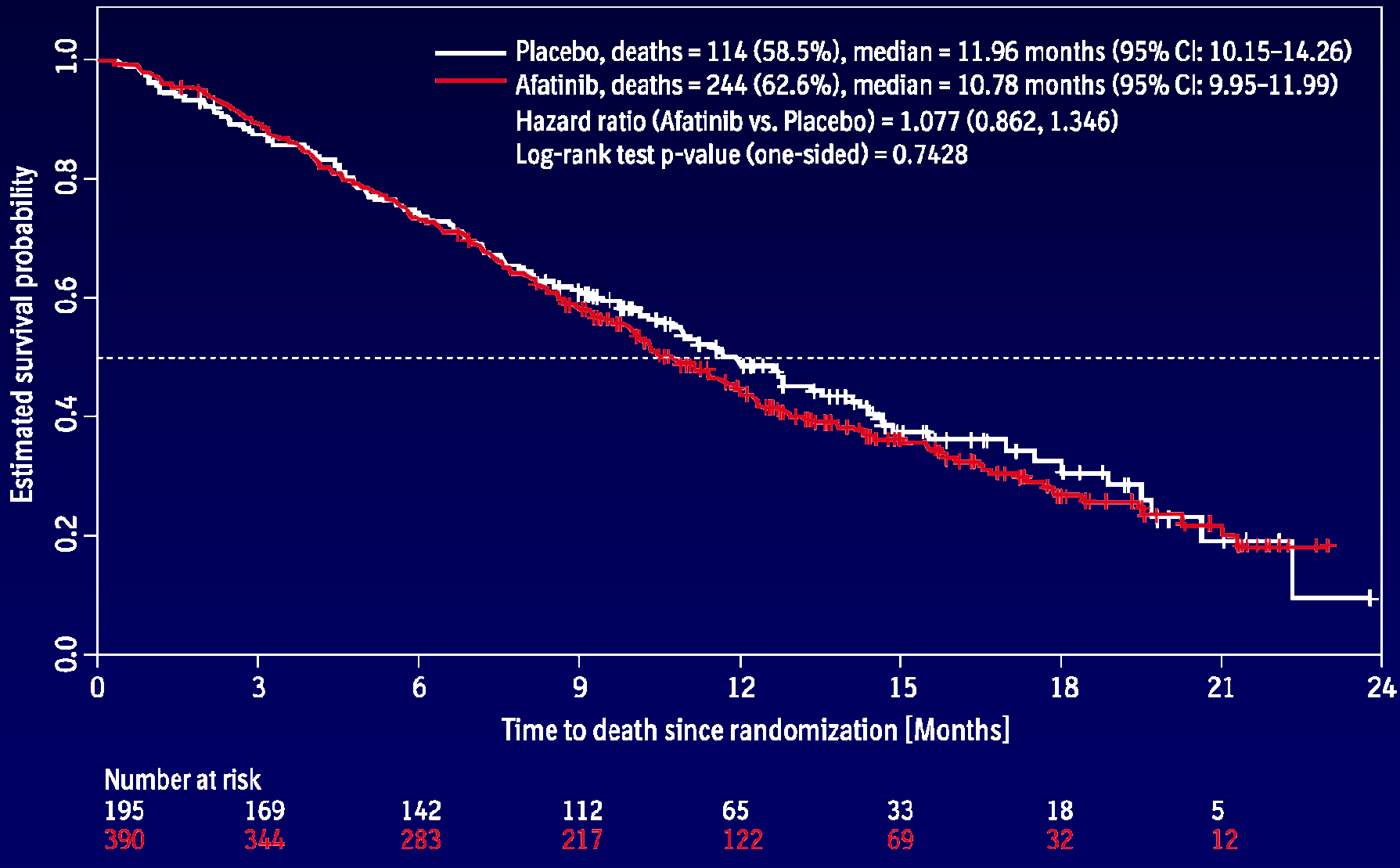
PFS by independent review



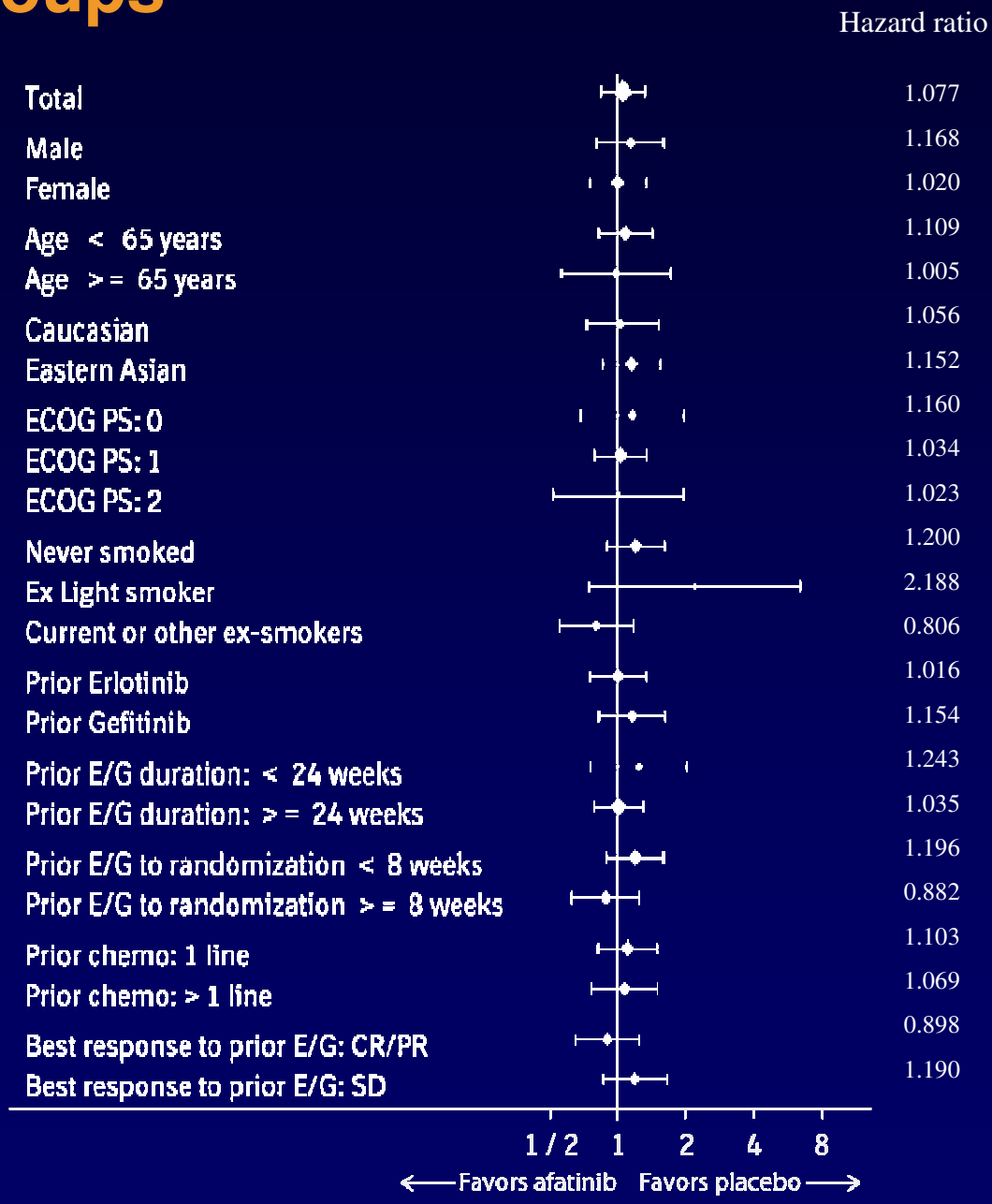
PFS by subgroups



Primary analysis: Overall survival



OS by subgroups



Summary of anticancer therapy after treatment discontinuation

Anticancer therapy	Afatinib (%)	Placebo (%)
Any	68	79
Chemotherapy	61	70
Pemetrexed	36	47
Docetaxel	21	26
Vinorelbine	15	19
Other	26	26
EGFR TKI	12	24
Anti-angiogenesis	4	6
Radiotherapy	9	14

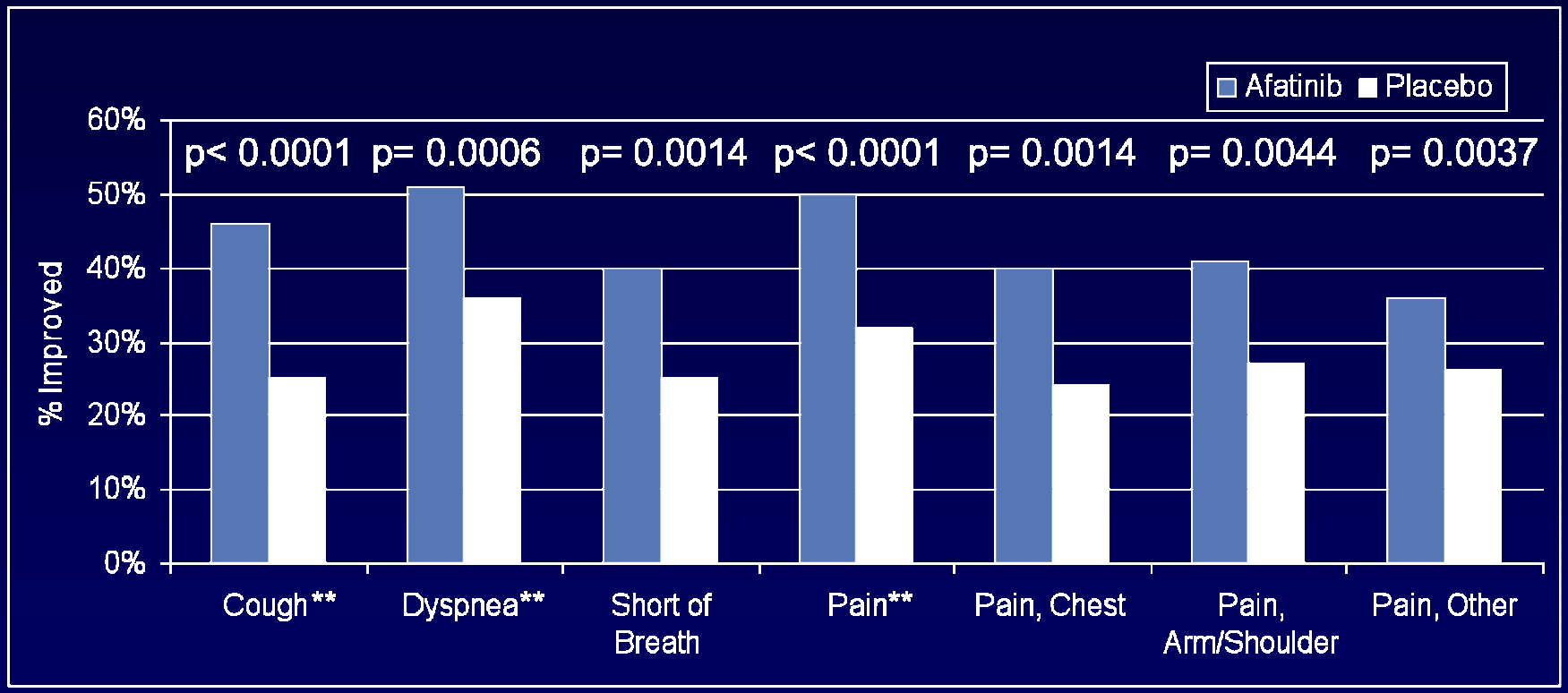
Most common AEs: >10% difference between treatments

AE*	Afatinib all Grades (%)	Placebo, all Grades (%)	Afatinib, Grade 3 (%)	Placebo, Grade 3 (%)
Diarrhea	87	9	17	0
Rash/acne**	79	16	14	0
Stomatitis**	62	5	3	0
Nail effect**	39	1	5	0
Decreased appetite	31	11	4	1
Epistaxis	19	1	0	0
Pruritis	18	6	0	0

* AE: Adverse Event
** Group of MedDRA Preferred Terms

Patient reported outcomes

Percent of patients with improvement in cough, dyspnea and pain*



*All scores were estimated from the EORTC QLQ-LC13 except for "Short of Breath" and "Pain" which used EORTC QLQ-C30; improved means that EORTC symptom scores were ≥10 points lower than baseline at any time during the study

**EORTC cough, dyspnea and pain endpoints as pre-specified in the trial protocol

Conclusions

- In this study population, the addition of afatinib to BSC did not improve overall survival
- Afatinib significantly improved progression free survival (HR = 0.38)
  - 2 month absolute increase in median PFS
  - Robust effect across all subgroups and by both independent and investigator assessments
- Significantly higher ORR and DCR on afatinib
- Clinically relevant improvement in three pre-specified lung cancer related symptoms in the afatinib arm
- Safety profile of afatinib as expected
  - Most common AEs: Diarrhea and rash managed effectively by dose interruption/reduction

Study Comments

- Why is there no improved OS despite a statistically and clinically significant increase in PFS?
  - Significant PPS – survival in control arm of 12.0 months
  - Subsequent lines of therapy
    - About 2/3 of patients went on to get other line of treatment
      - 47% of patients in the control arm went on to receive Pemetrexed treatment

Study Comments

- Study Population
  - 45% of patients had more than >48 weeks of treatment on TKI
  - more than half the patients started within 8 weeks of discontinuing
  - about half the patients had received prior CR or PR
- Highly EGFR TKI sensitive patient population – is this the right populaiton to study this drug?
- What about the EGFR TKI non-responding patients?

Study Comments

- Is this an active drug?
  - Yes - improved PFS and symptom control
- Is there a place for this drug in our current treatment protocol?
  - Yes - generally don't have any standard therapy for those progressing on a TKI in the second/third line setting

Next Steps

- How do the second generation of TKIs compare to our current standard?
- When is the best time to introduce these agents?
- Which is the best population to study these agents?
- How best to address the increase in toxicity (esp. diarrhea)?

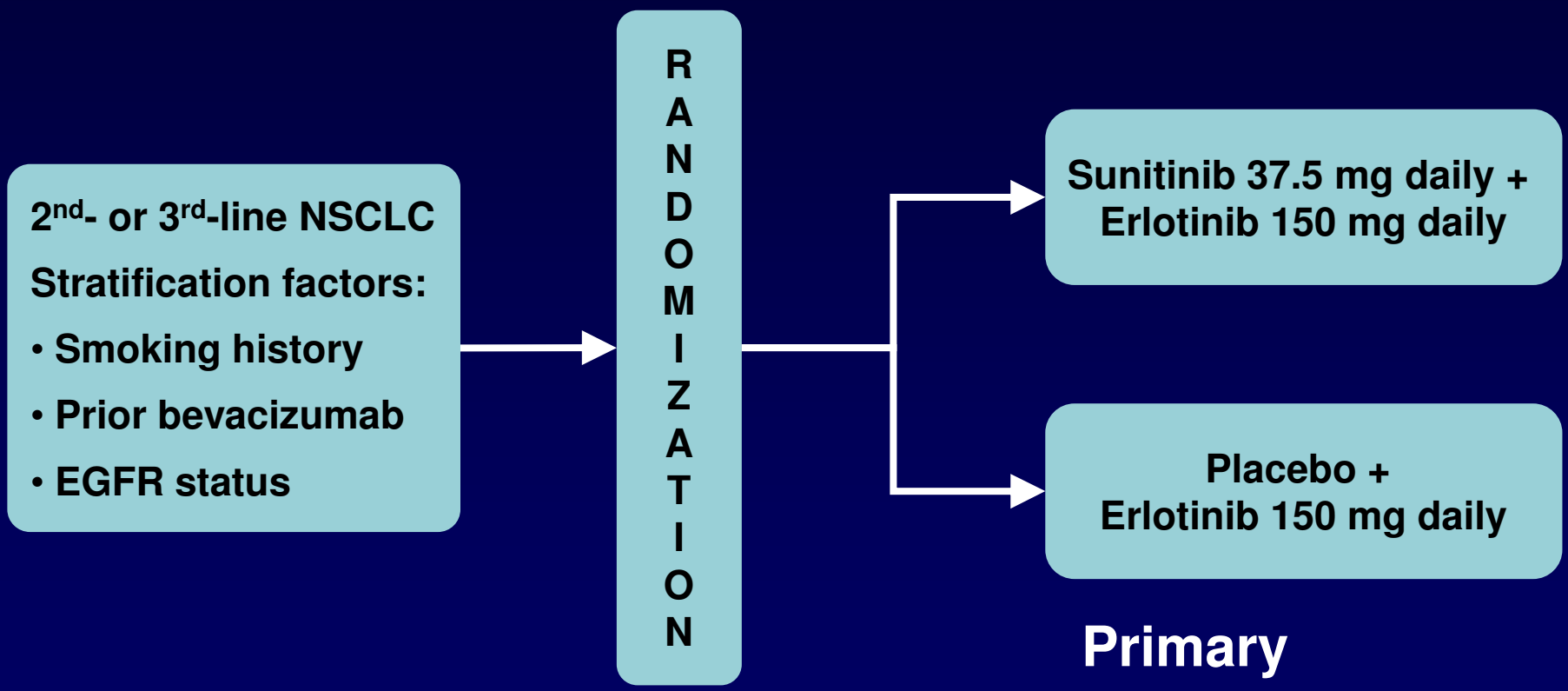
Abstract No. LBA6

Sunitinib in Combination with Erlotinib for the Treatment of Advanced/ Metastatic Non-Small Cell Lung Cancer (NSCLC): A Phase III Study

GV Scagliotti,[1] M Krzakowski,[2] A Szczesna,[3] J Strausz,[4] A Makhson,[5] M Reck,[6] L Tye,[7] P Selaru,[7] RC Chao,[7] R Govindan[8]

[1]University of Turin, Department of Clinical and Biological Sciences, Orbassano (Turin), Italy [2]The Maria Sklodowska-Curie Memorial Cancer Center Institute of Oncology, Warsaw, Poland [3]Regional Lung Diseases Hospital, Otwock, Poland; [4]Koranyi National Institute for Pulmonology Budapest, Hungary; [5]Moscow City Clinical Hospital of Oncology, Moscow, Russian Federation [6]Hospital Grosshansdorf, Department of Thoracic Oncology, Grosshansdorf, Germany; [7]Pfizer Oncology, Clinical Development, La Jolla, CA, USA; [8]Washington University School of Medicine, St Louis, MO, USA

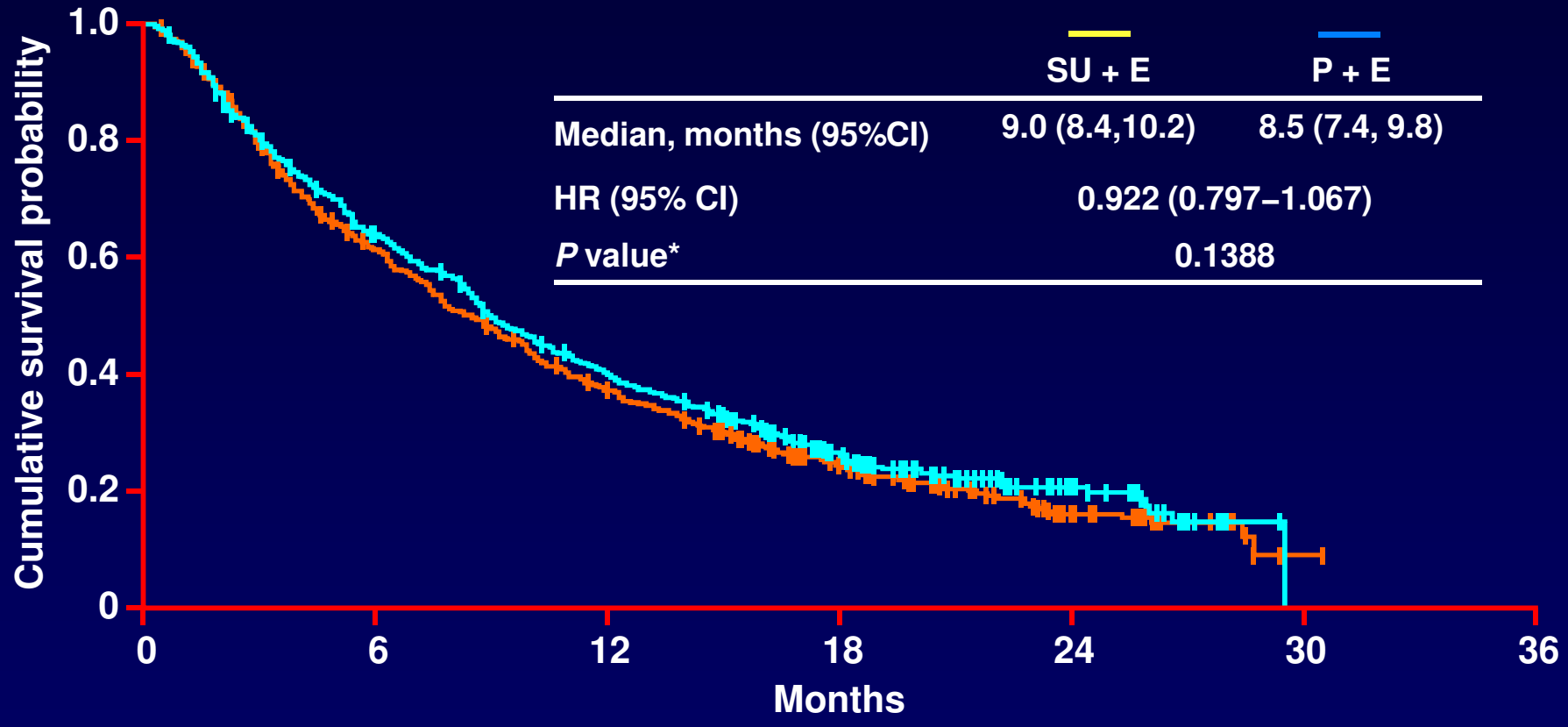
Study Design



Primary Endpoint: OS

NCT00457392

Overall Survival



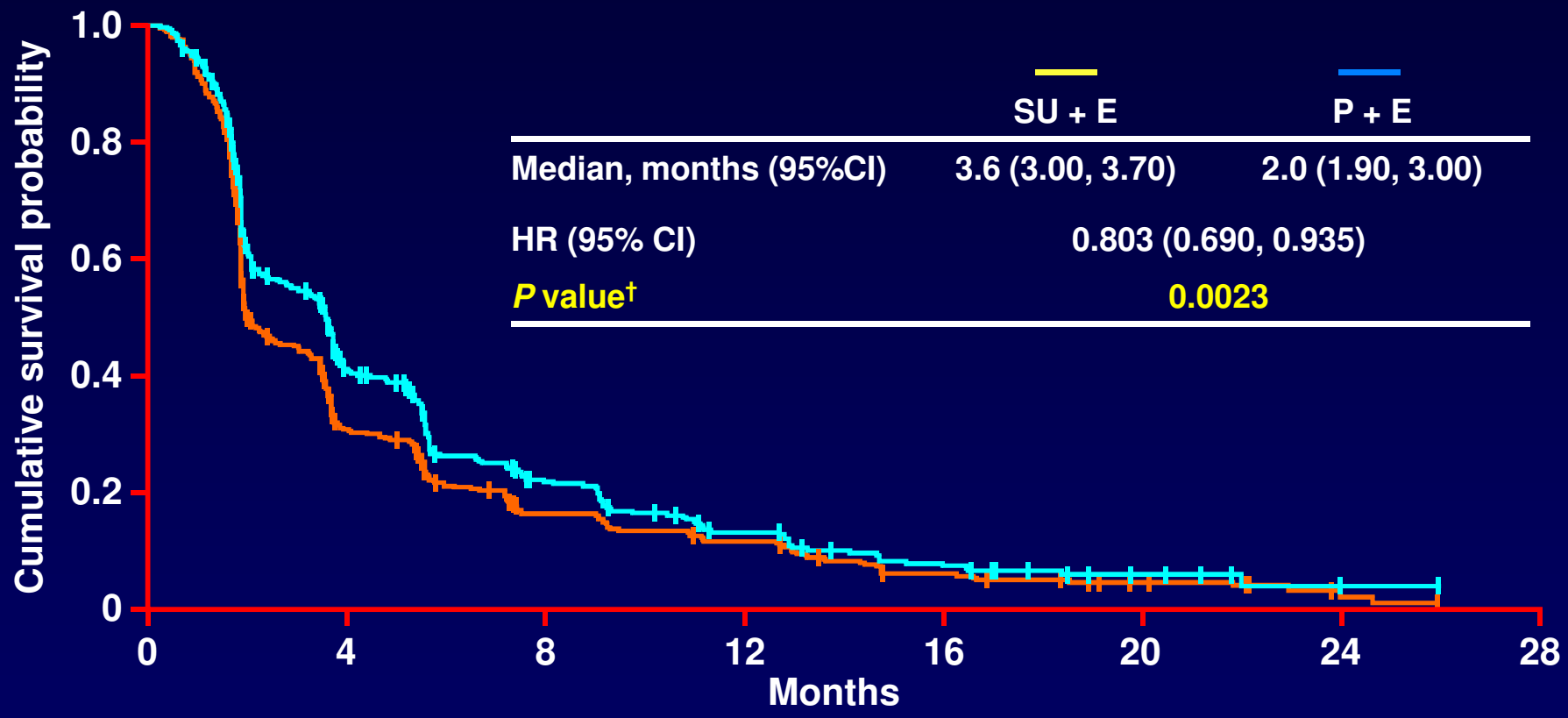
	SU + E	P + E
Median, months (95%CI)	9.0 (8.4,10.2)	8.5 (7.4, 9.8)
HR (95% CI)	0.922 (0.797–1.067)	
P value*	0.1388	

Number at risk

SU + E	480	298	183	88	28	0
P + E	480	284	170	89	29	1

*1-sided (stratified log-rank)
SU = sunitinib; E = erlotinib; P = placebo

Progression-free Survival*



	SU + E	P + E
Median, months (95%CI)	3.6 (3.00, 3.70)	2.0 (1.90, 3.00)
HR (95% CI)	0.803 (0.690, 0.935)	
P value†	0.0023	

Number at risk							
SU + E	480	140	66	35	18	7	2
P + E	480	121	56	39	18	9	3

*Investigator assessment
†1-sided (stratified log-rank)
SU = sunitinib; E = erlotinib; P = placebo

Objective Response Rate

	Sunitinib + Erlotinib (n=480)	Placebo + Erlotinib (n=480)
Objective response rate, % (95% CI)*	10.6 (8.01, 13.73)	6.9 (4.78, 9.52)
Two-sided *P*-value	0.0471	
Best response, %		
Complete response	1.0	0
Partial response	9.6	6.9
Stable disease	32.3	28.1
Disease progression	32.5	47.9
Not evaluable†	24.5	17.2
Median (range) duration of response, weeks‡	39.6 (31.3, 48.9)	32.3 (24.2, 48.0)

*Complete response + partial response
†Includes not evaluable, not assessed and indeterminate
‡Calculated for patients with complete response or partial response

Post-study Systemic Therapies*

Follow-up systemic therapies	N (%) Sunitinib + Erlotinib n=480	N (%) Placebo + Erlotinib n=480
Any	188 (39.2)	203 (42.3)
Pemetrexed	81 (16.9)	80 (16.7)
Docetaxel	71 (14.8)	82 (17.1)
Gemcitabine	48 (10.0)	43 (9.0)
Vinorelbine	47 (9.8)	36 (7.5)
Carboplatin	36 (7.5)	37 (7.7)
Cisplatin	19 (4.0)	24 (5.0)
Erlotinib	25 (5.2)	13 (2.7)
Paclitaxel	21 (4.4)	15 (3.1)

*Therapies for the primary diagnosis

Conclusions

- In patients with recurrent NSCLC, triple target inhibition of EGFR, VEGFR, and PDGFR with sunitinib plus erlotinib did not significantly prolong OS compared with placebo plus erlotinib
- Treatment with sunitinib plus erlotinib was associated with significantly longer PFS and greater ORR
  - Additional exploratory analyses are under consideration
- Treatment-related AEs, including rash and diarrhea, and dosing modifications were more frequent in the sunitinib plus erlotinib arm
- Similar results have been observed with combined VEGF and EGFR inhibition using bevacizumab and erlotinib in pretreated NSCLC[1]

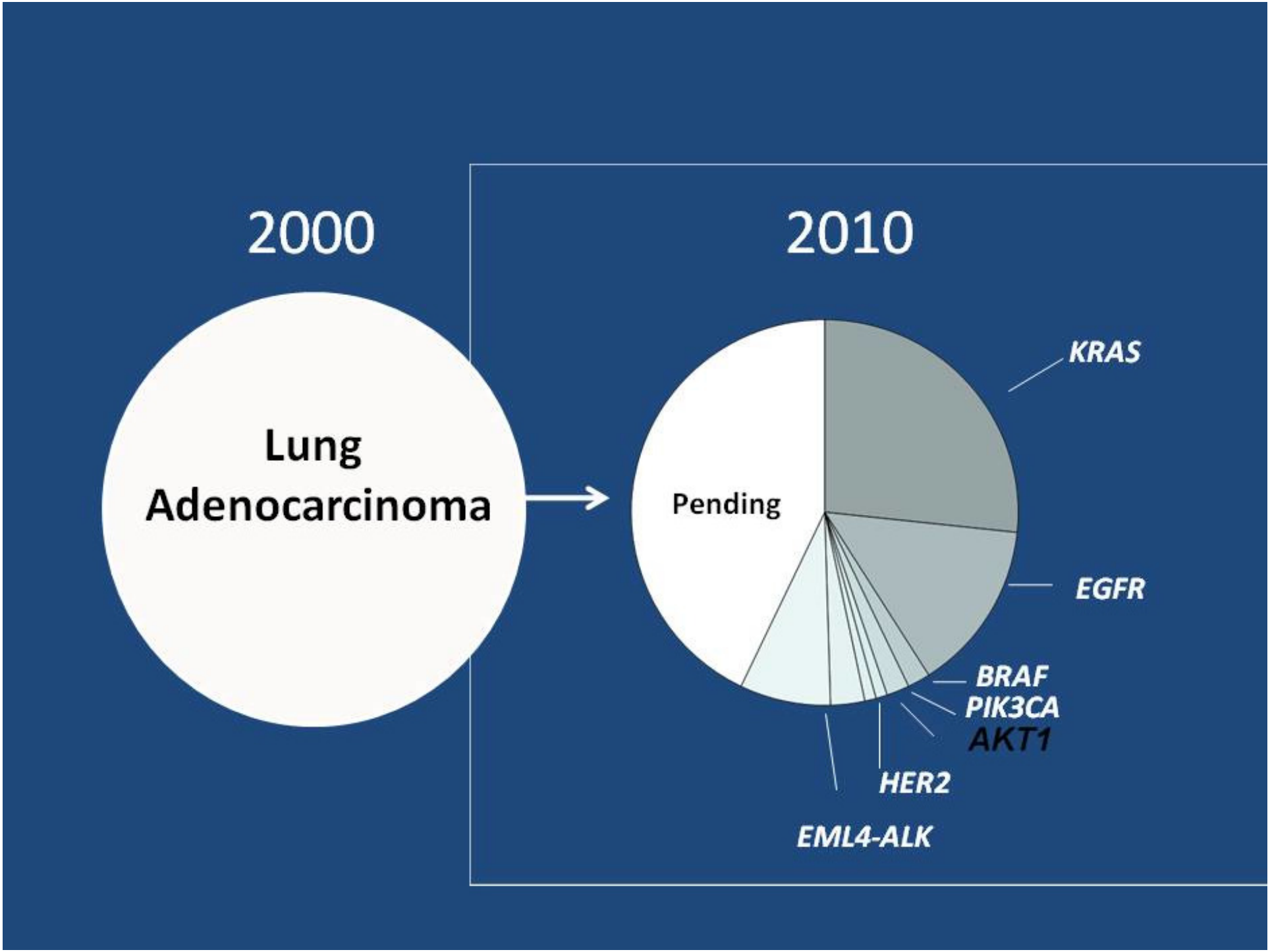
[1]Hainsworth et al. J Thoracic Oncol 2008;3(Suppl 4):S302

Study comments

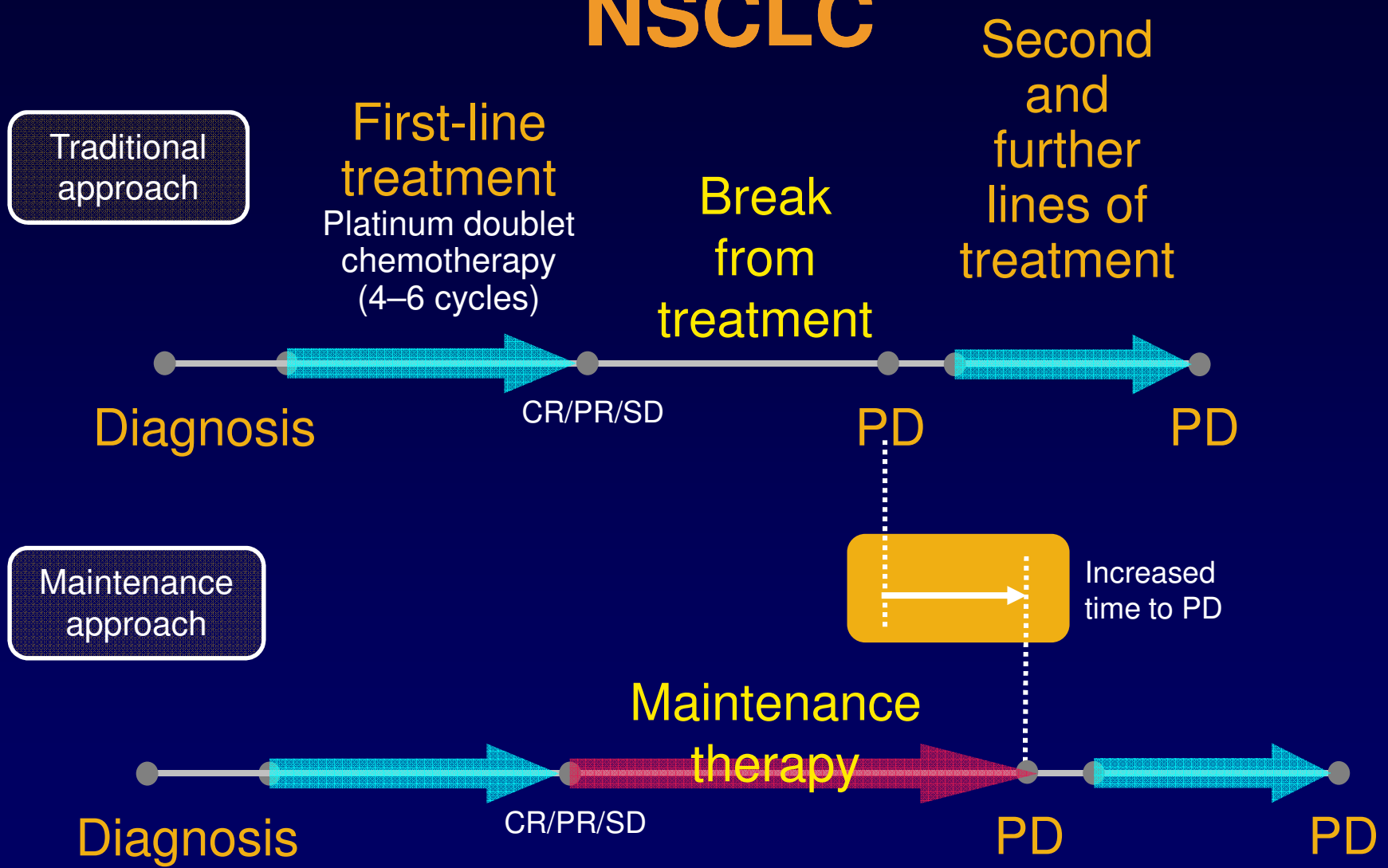
- EGFR inhibitors can be combined with anti-angiogenics
- We need to come up with better biological markers before routinely including these agents in combination with standard treatments
  - Costs and toxicities are too prohibitive as of now

EGFR Conclusion

- We shouldn't be using EGFR TKIs in the first line setting in an unselected group of patients
- EGFR TKI testing should be offered to patients with non-squamous histology
- EGFR mutation positive patients derive a significant benefit from TKIs and should be offered this therapy in the first line setting
- Newer EGFR TKIs have promising activity beyond standard lines of treatment


2000
2010
Lung
Adenocarcinoma
Pending
KRAS
EGFR
BRAF
PIK3CA
AKT1
HER2
EML4-ALK

Maintenance therapy in advanced NSCLC



CR = complete response; PR = partial response; SD = stable disease

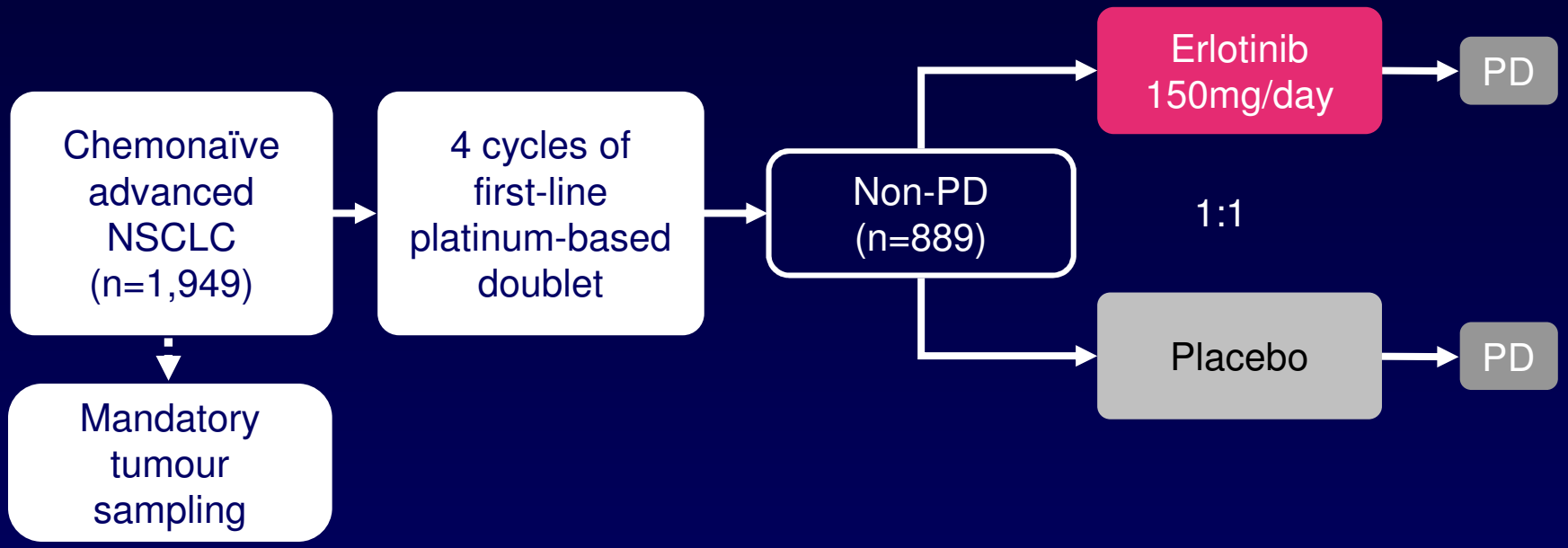
Do we need maintenance therapy? Results of recent phase III studies

Reference	n	Therapy	Primary end-point	PFS (HR)	OS (HR)
Fidias[1]	309	Docetaxel	OS	NR	NR
Ciuleanu[2]	663	Pemetrexed	PFS	0.60	0.79
Belani[3]	255	Gemcitabine	OS	1.09	0.97
Cappuzzo[4]	889	Erlotinib	PFS	0.71	0.81
Miller[5]	768	Erlotinib + bevacizumab	PFS	0.72	0.92
Pérol[6]	464	Erlotinib Gemcitabine	PFS	0.82 0.55	0.91 0.86
Takeda[7]	604	Gefitinib	OS	0.68	0.86

NR = not reported

1. Fidias, et al. JCO 2009; 2. Ciuleanu, et al. Lancet 2009; 3. Belani, et al. ASCO 2010
4. Cappuzzo, et al. Lancet Oncol 2010; 5. Miller, et al. ASCO 2009
6. Pérol, et al. ASCO 2010; 7. Takeda, et al. JCO 2010

SATURN: study of maintenance erlotinib and biomarkers



Co-primary endpoints

- PFS in all patients
- PFS in patients with EGFR IHC+ tumours

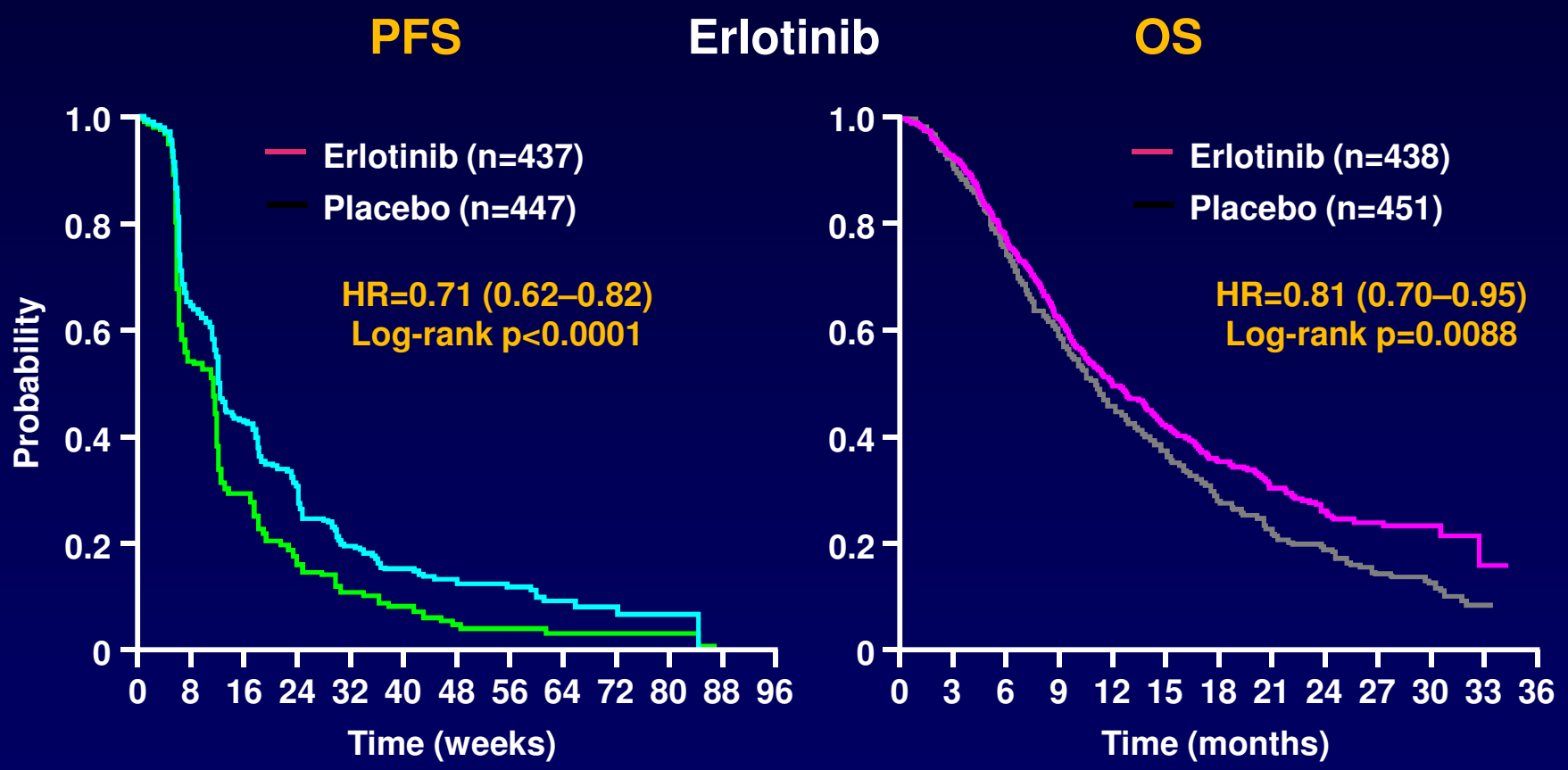
Secondary endpoints

- OS in all patients and those with EGFR IHC+ tumours; OS and PFS in EGFR IHC– tumours; biomarker analyses; safety; time to symptom progression; QoL

*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel carboplatin/paclitaxel

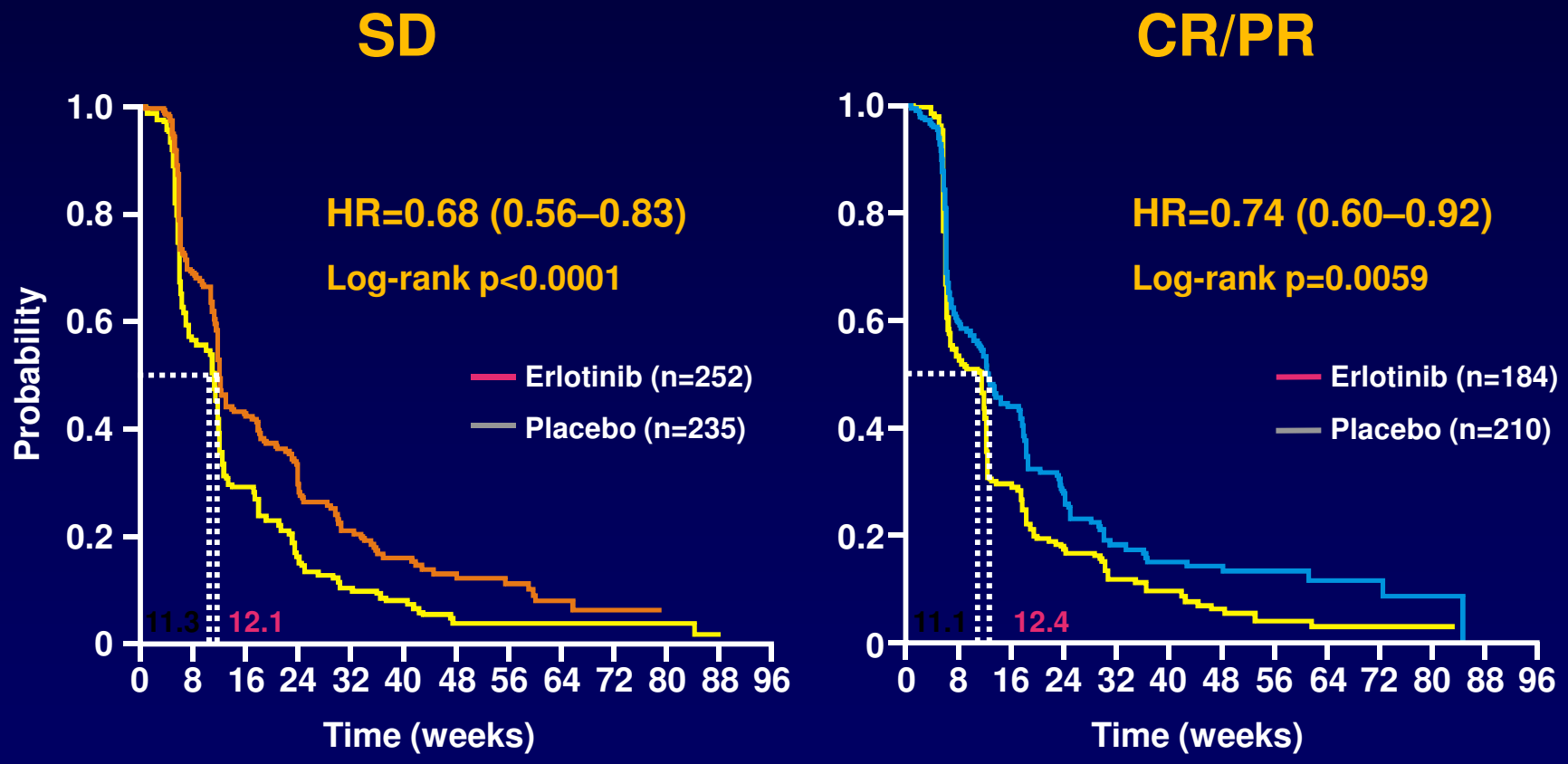
Cappuzzo, et al. Lancet 2010

Maintenance treatment with an EGFR TKI



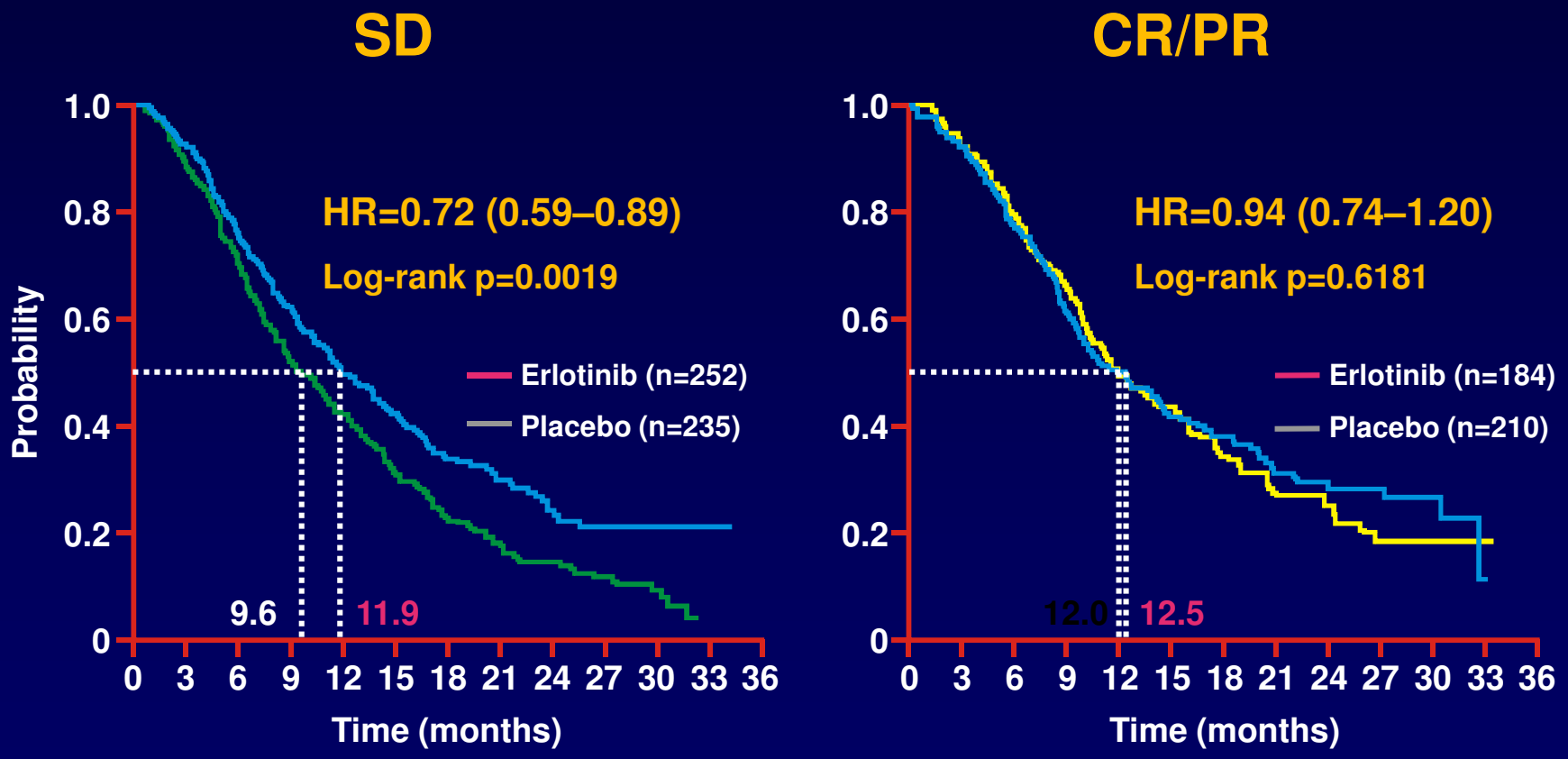
Cappuzzo, et al. Lancet Oncology 2010

SATURN: PFS with erlotinib according to response to first-line chemotherapy



Coudert, et al. ELCC 2010

SATURN: OS with erlotinib according to response to first-line chemotherapy



OS is measured from time of randomisation onto the maintenance phase

Coudert, et al. ELCC 2010

Road to Personalized Care

- We now increasingly need to take a personalized approach to our management of NSCLC
  - Tumor – histology based
  - Mutational analysis – EGFR, ALK
  - Patient related factors – Age
  - Comprehensive approach – Multidisciplinary
  - The decision to maintain or not to maintain
- The era of using targeted drugs for ‘untargeted’ population needs to end

Discussion