THE PLACE OF EGFR *TKI* IN ADVANCED NSCLC

Nick Thatcher,
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1st TOPIC
BRAIN METASTASES (BM)

A) Is there a place for EGFR-TKI in the treatment of BM ?

B) Should we treat 1st with RT (to break BBB) or just with RT?

C) What to do if only progression in the brain but not elsewhere?

D) is it safe to give RT and tki together?

2ND TOPIC

A) If Mut +ve is 1st line CT or TKI best ?

Mitsudomi et al Lancet Oncology 2011

B) Any difference between the tkis ?

Hata et al Lung Cancer 2011

Maintenance or wait and then 2nd line?

Is there a role for TKI in EGFR wt?

Garassino et al J Clin Oncol 2011

C) Which pathways are responsible for TKI resistance ?

What to do if PD during TKI continue or stop?

Oxnard et al Clin Cancer Res 2011

3rd TOPIC
EGFR TESTING

A) IHC testing only in non-squamous only?

B) Mutation testing in non-squamous only?

1st TOPIC
BRAIN METASTASES (BM)

A) Is there a place for EGFR-TKI in the treatment of BM ?

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Recommendation 3: patients with symptomatic brain metastases may be considered for treatment with an EGFR TKI.
Strength of recommendation: B
Level of evidence: V

Felip et al 1st ESMO consensus Ann Oncol 2011

BRAIN METASTASES (BM)

- BBB does not prevent metastatic cells entering brain

If BM < 0,25 mm – BBB is intact

If BM > 0,25 mm – BBB becomes leaky *Fidler, Lancet Oncol 2002*

Incidence about 30% but increasing –better imaging and longer survival with systemic treatment . DCR ≥90 days with TKI - 26% CNS failure rate vs 4% if no DCR

EGFR mut +ve may predispose to BM ; Mut +ve 64% vs 31% in patients with and without BM *Lee Cancer 2010 ;Lee et al ASCO 2011 Abs 18065*

Med Surv 4-11 weeks untreated or 4-6 months treated

Mehta et al JNeuro Onco 2011; Jamal-Hanjani Clin. Cancer Res. 2011

- **Oligometastatic BM** surgery or SRS+WBRT ↑local control ? ↑ OS vs. WBRT alone *ESMO Clinical practice guidelines D`Addario et al Ann Oncol 2010 Jamal-Hanjani Clin. Cancer Res. 2011*

EGFR TKI CNS PENETRATION

TABLE 3. Cerebrospinal Fluid Concentrations of Erlotinib and OSI-420 on Day 8, Tumor Response, and Change of PS

	Erlotinib		OSI-420			
Case	$C_{CSF}0$ (ng/ml)	$C_{CSF}0$: $C_{plasma}0$ (%)	$C_{CSF}0$ (ng/ml)	$C_{CSF}0$: $C_{plasma}0$ (%)	Tumor Response	Change of PS
1	42	4.7	4.7	8.1	Partial response	3 → 2
2	87	5.0	22.3	9.3	Stable disease	4 → 3
3	67	3.2	11.1	1.5	Partial response	3 → 2
4	18	7.7	5	4.4	Stable disease	3 → 3
Mean ± SD	54 ± 30	5.1 ± 1.9	10.8 ± 8.2	5.8 ± 3.6		

CSF, cerebrospinal fluid; $C_{CSF}0$, CSF concentration just before administration of erlotinib; $C_{plasma}0$, CSF concentration just before administration of erlotinib; PS, performance status.

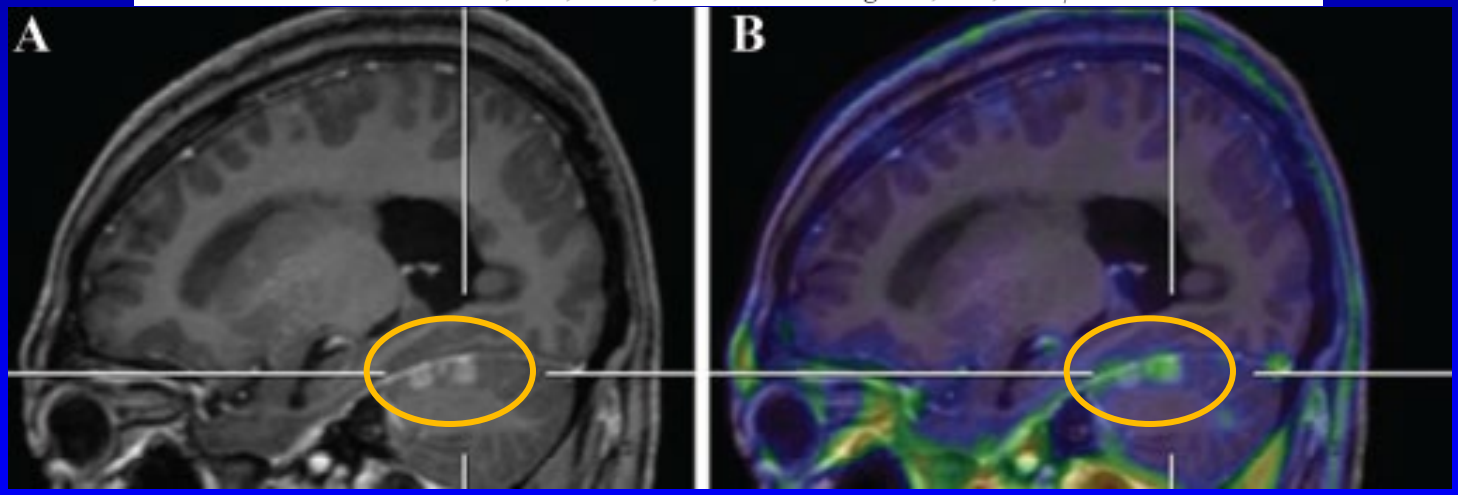
- At standard dosing (150mg/daily), erlotinib levels in CSF high enough to inhibit WT disease
  - erlotinib penetration rate to CSF was approximately 5% and erlotinib concentration exceeded the IC_{50} of erlotinib in intact tumour cells with WT *EGFR* gene (20 nmol/l; 7.9 ng/ml)[1]
- In contrast, the gefitinib penetration rate to CSF was reported to be less than 1%, and gefitinib CSF concentration did not exceed the IC_{50} of gefitinib when 250 mg gefitinib was administered daily[2,3]

1. Togashi, et al. JTO 2010; 2. Fukuhara, et al. Tohoku J Exp Med 2008
3. Wu, et al. Lung Cancer 2007

EGFR TKI CNS PENETRATION

Erlotinib Accumulation in Brain Metastases from Non-small Cell Lung Cancer: Visualization by Positron Emission Tomography in a Patient Harboring a Mutation in the Epidermal Growth Factor Receptor

Britta Weber, MD,† Michael Winterdahl, MMSc,‡ Ashfaque Memon, MD, PhD,* Boe S. Sorensen, PhD,* Susanne Keiding, MD, DMSc,‡ Leif Sorensen, MD,§ Ebba Nexo, MD, DMSc,* and Peter Meldgaard, MD, PhD†*



- Erlotinib accumulates in *EGFR* mut+ CNS met lesions, but absent from normal brain tissue

Weber et al. J Thor Oncol 2011

BRAIN METASTASES TKIS RCTS

- SAKK 70/03 phase II WBRT 30 Gy + gefitinib or temozolamide trial closed; MS Gef 6.3 months Tmz 4.9 months

Pesce et al Eur J Cancer 2012

- TACTIC (WBRT +/- erlotinib). Closed endpoint not reached (after 2 months, ≥ 20 patients are alive and neurological progression-free on the Tarceva arm)

- But 1st line Mut +ve trials included patients with controlled brain metastases

Zhou et al Lancet Oncol 2011
Rosell et al. ASCO 2011abstr 7503

ACTIVITY of EGFR TKI in BM

Jamal-Hanjani Clin. Cancer Res. 2011

Study	Treat	Selection	Pat No.	RR%	Survival months
Ceresoli	G	Europe	41	27	PFS 3
Wu	G	EA Adeno	40	32	PFS 9
Porta	E	M +ve	17	82	PFS 11.7 OS 12.9
Kim	G/E	M +ve	23	70	PFS 6.6 OS 19.8
Wu	G	M +ve	110	89	
Wu	E	M +ve or Adeno	48	56 intra + extracranial	PFS +ve 2 3.2 wt 8.2
Kim	G/E	EA Non Smoker	23	74	PFS 7.1 OS 18.8

IS ERLOTINIB EFFECTIVE FOR BM?

- Erlotinib has shown to be effective in case reports, case series and phase II trial .Higher RR in BM in Mut +ve, but also effective in wt EGFR

Erlotinib can be effective for BM even after gefitinib failure (penetration rate in CSF higher) *Togashi, J Thor Oncol 2010,5*

Jamal-Hanjani Clin. Cancer Res. 2011

- T790M mutation is associated with multiple metastatic sites but not always with BM . Isolated CNS failure may not have acquired resistance T790 , may respond to reinduction of erlotinib

Jackman et al J Clin Oncol 2006;2010; Balak et al Clin Cancer Res 2006 ; Ruppert et al, Eur Resp J 2009

- Patients with BM without pre-treatment T790M outcome similar to other Mut+ve lung cancers with extra cranial metastases

Moran et al. J Clin Oncol ASCO 2011 abstr 7590

WHAT IF PROGRESSION OF BM?

Sensitivity may remain but need ↑ dose or switch to erlotinib

- TKI dose escalation: erlotinib 300mg alt die

CNS response despite prior gefitinib ,CT,WBRTand 150mg erlotinib *Hata et al J Thor Oncol 2011*

- EGFR mut +ve: erlotinib pulsed weekly 1500 mg despite previous 150 mg dose 9 patients: CNS RR 67% MS 12 months *Grommes et al Neuro Oncol 2011*

- Patients with PD in BM but not extra cranially may not have acquired resistance. Continuing erlotinib after PD in BM post RT; RR 41% DCR 76% MS 403 days *Shukuya et al Lung Cancer 2011*

- Or switch after gefitinib failure to erlotinib 125 patients OR 9% MS11.8 months ; 62 pts BM RR 34%(without RT) *Hata et al Lung Cancer 2011*

SUMMARY

- TKI is valid option for BM especially if mut+ve but surgery or SRS for oligometastic disease

Jamal-Hanjani Clin. Cancer Res. 2011 ;Ceresoli et al Curr Cancer Drug Targets 2012

- Concurrent Erlotinib +WBRT safe *Lind et al IJROBT 2009*

- TKI may potentiate effectiveness of WBRT

Gow et al Clin Cancer Res 2008

- TACTIC trial WBRT +Erlotinib vs WBRT result awaited

BRAIN METASTASES

- Is there a place for EGFR-TKI in the treatment of BM ?

  Yes

- Should we treat 1st with RT (to break BBB) or just with TKI ?

  Symptomatic EGFR wt RT +/- tki

  Mut +ve TKI +/- RT

- What to do if only progressive in the brain but not elsewhere?

  Continue TKI (switch to erlotinib, ↑dose) and brain RT

- Is it safe to give RT and tki together? Yes

2ND TOPIC

A) If Mut +ve is 1st line CT or TKI best ?

Mitsudomi et al Lancet Oncology 2011

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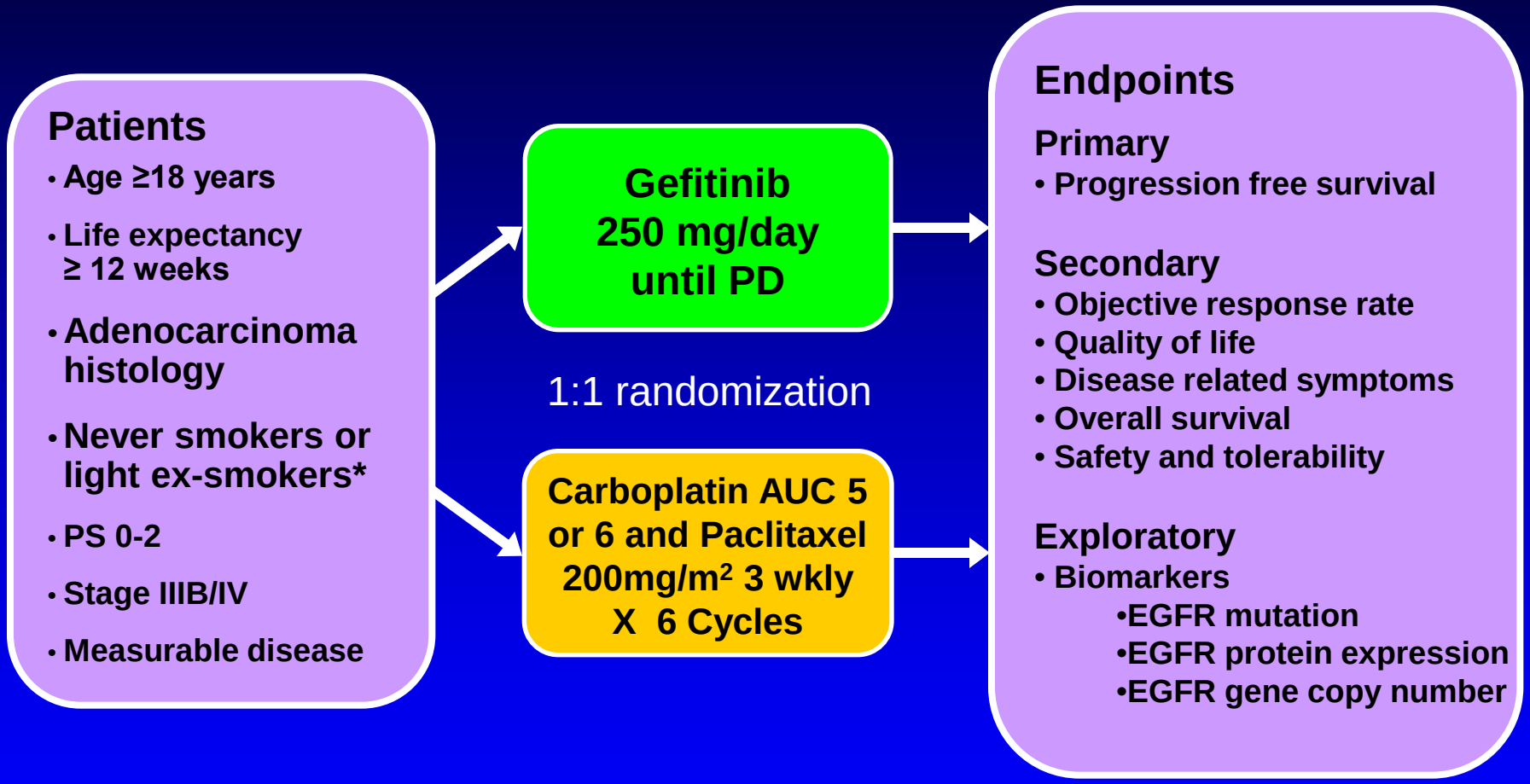
Oxnard et al Clin Cancer Res 2011

IPASS STUDY DESIGN

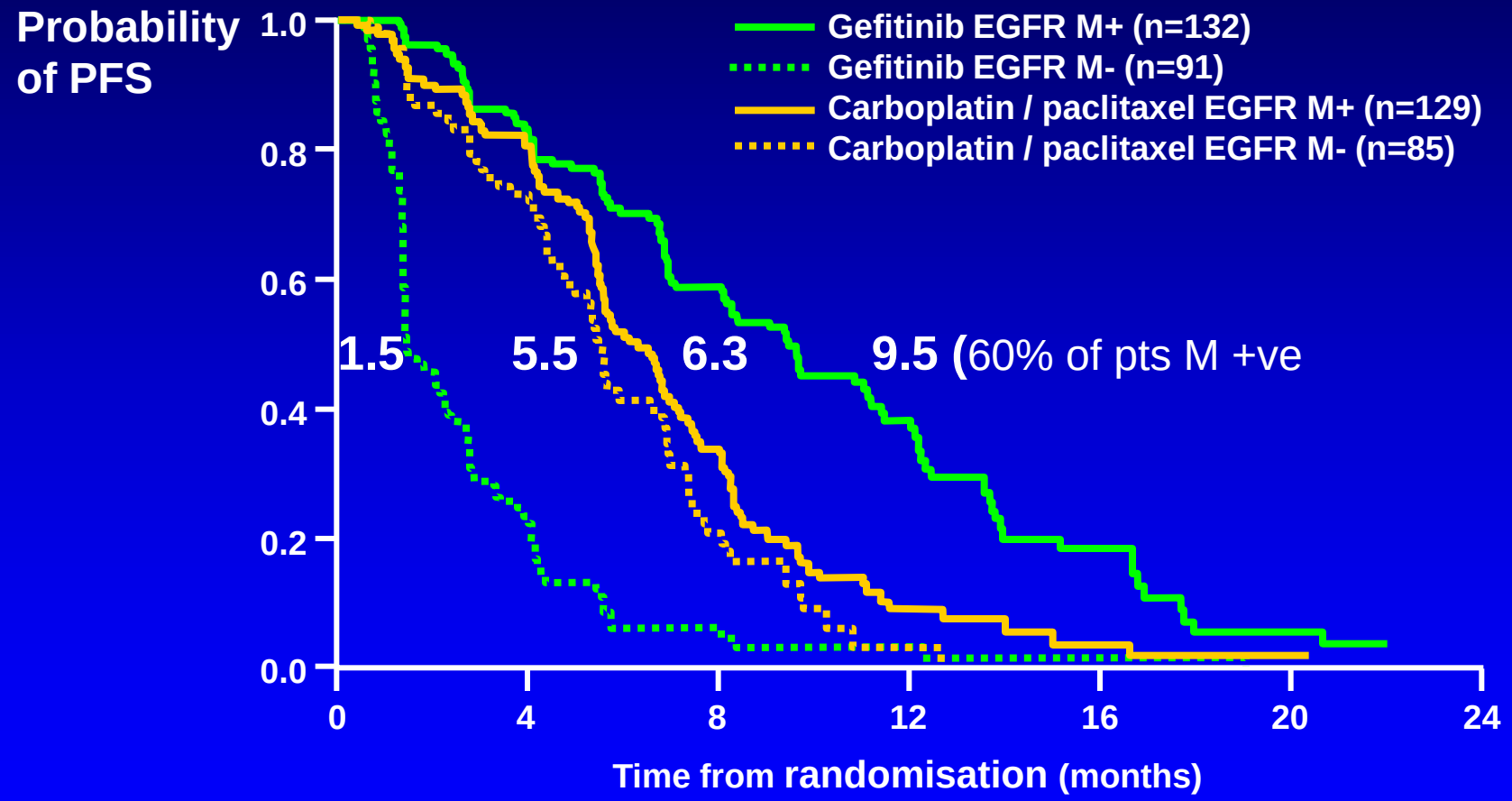


*Never smokers:<100 cigarettes in lifetime; light ex-smokers: stopped ³ 15 years ago and smoked £10 pack yrs

Carboplatin/paclitaxel was offered to gefitinib patients upon progression

Mok et al N Eng J Med 2009

COMPARISON OF PFS BY MUTATION STATUS (60% of selected patients Mut +ve)



PFS treatment by *EGFR* mutation status interaction test: $P < .0001$

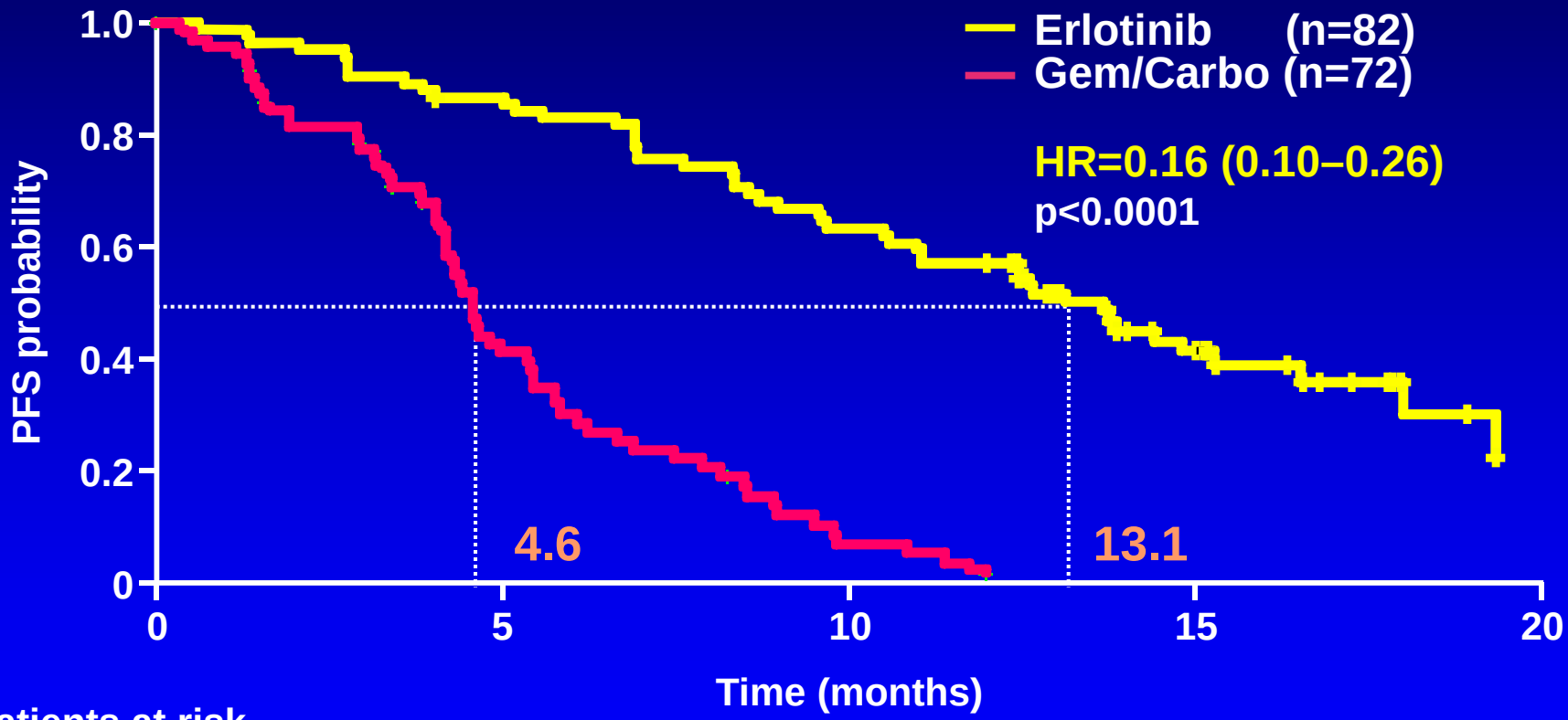
Exon 19 deletion advantages > L858R mutation

Mok et al N Eng J Med 2009

Fukuoka et al ASCO 2009 abst 8006

Mok et al WCLC 2009 abst B9.5

OPTIMAL PFS: updated analysis



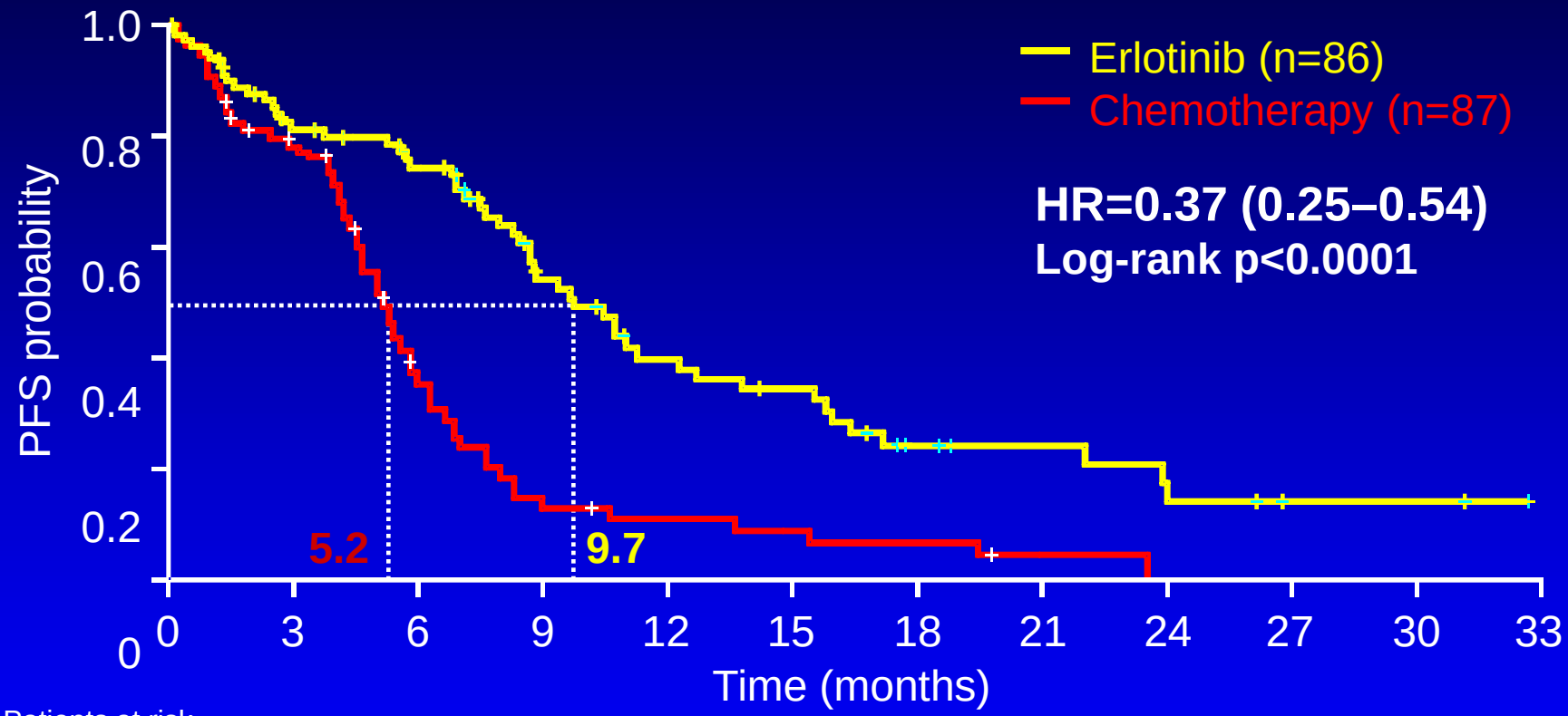
Patients at risk					
Erl	82	70	51	20	2
GCb	72	26	4	0	0

*Sanger DNA sequencing

Zhou, et al. Lancet Oncol 2011

PFS in ITT POPULATION

(UPDATED ANALYSIS 26 Jan 2011)



Patients at risk

Erlotinib	86	63	54	32	21	17	9	7	4	2	2	0
Chemo	87	49	20	8	5	4	3	1	0	0	0	0

Rosell et al. ASCO 2011abstr 7503

1st line EGFR tki in POOR PS PATIENTS

Parameter	Lilenbaum erlotinib	Hesketh erlotinib	**Inoue gefitinib**
Pat No.	52	81	**30**
PS	2	2	**2-4**
EGFR mut +ve %	0	na	**100**
OR%	4	8	**66**
OS mos	6.6	5	**17.8**

Langer J Clin Oncol 2009
Inoue et al J Clin Oncol 2009

FIRST LAW OF ONCOLOGY

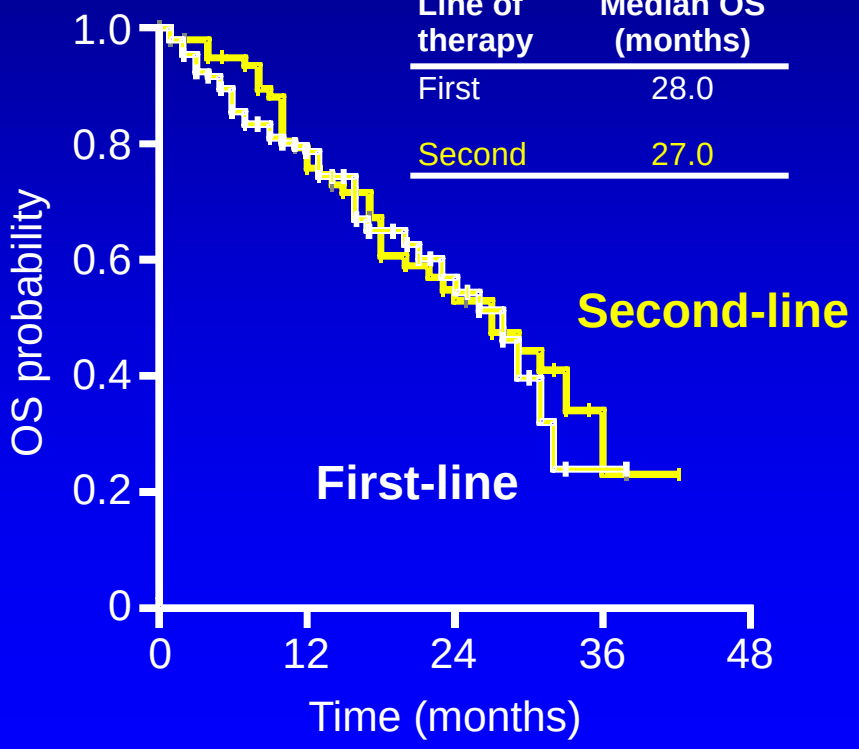
Tumour must shrink faster than the patient

TIME TO USE EGFR TKIs IN *EGFR* MUT+ NSCLC

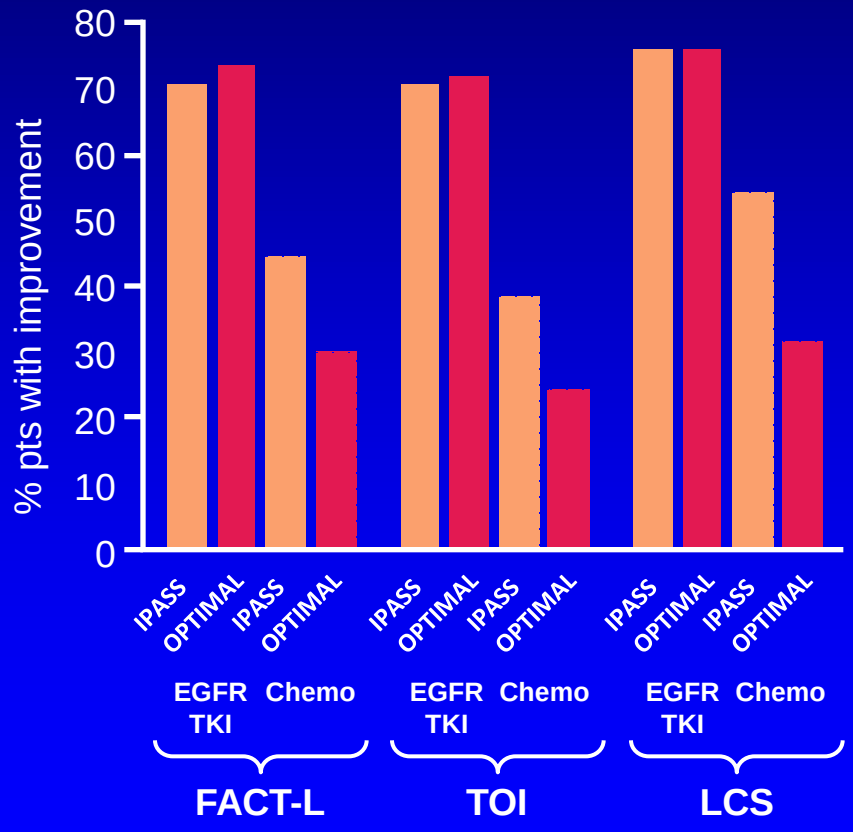
No difference in OS according to line of treatment

BUT…

First-line EGFR TKI provides QoL benefit over chemotherapy



Line of therapy	Median OS (months)
First	28.0
Second	27.0



Rosell, et al. NEJM 2009; Mok, et al. NEJM 2009; Zhou, et al. ASCO 2011

SUMMARY: EGFR TKIS IN *EGFR* MUT+ NSCLC

- **Significant benefits with first-line EGFR TKIs** vs chemotherapy in *EGFR* M +ve

  significantly longer PFS ;more favourable toxicity profile

  convenient oral preparation ; QoL benefits

First-line erlotinib has shown superiority over chemotherapy in both Caucasian and Asian patients with *EGFR* Mut+ NSCLC,

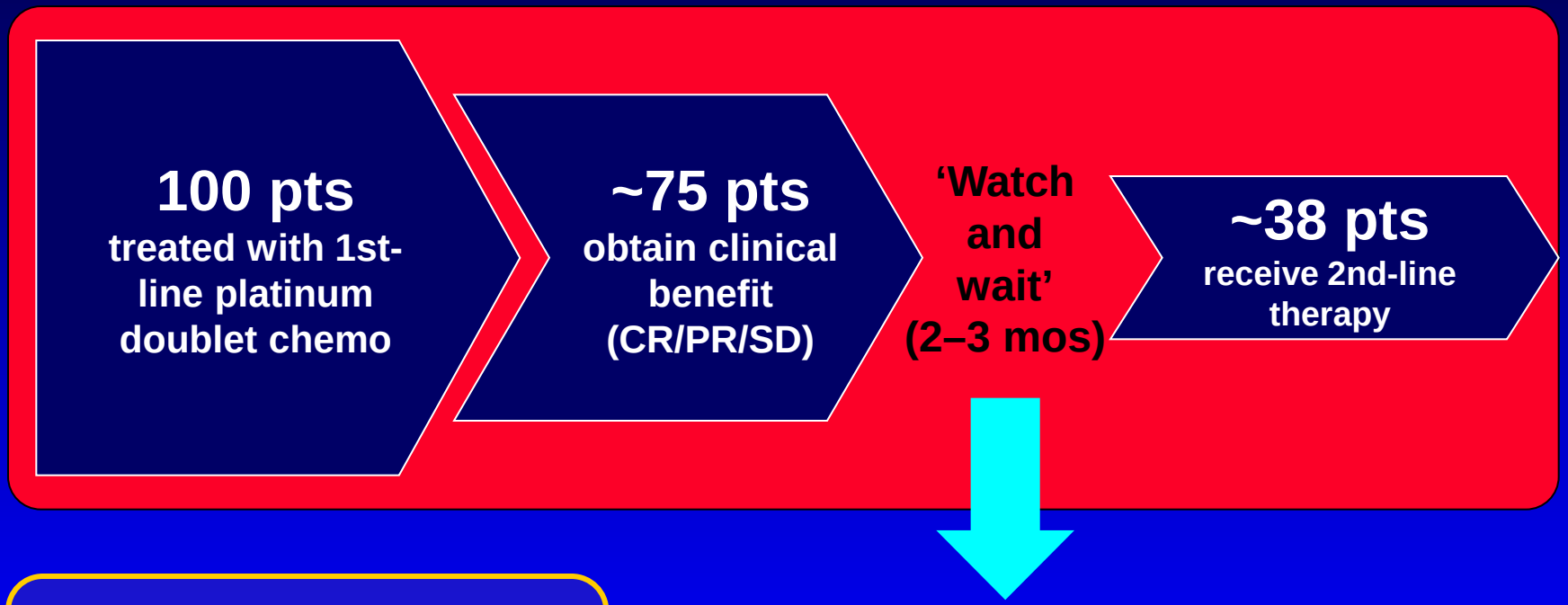
EGFR mutation testing should be performed to guide first-line treatment decisions

Recommendation 12

– An EGFR TKI is the preferred first-line treatment in patients whose tumor harbors an activating EGFR mutation

First ESMO Consensus Felip et al Ann Oncol 2011

LIMITATIONS OF THE HISTORICAL 'WATCH AND WAIT' APPROACH



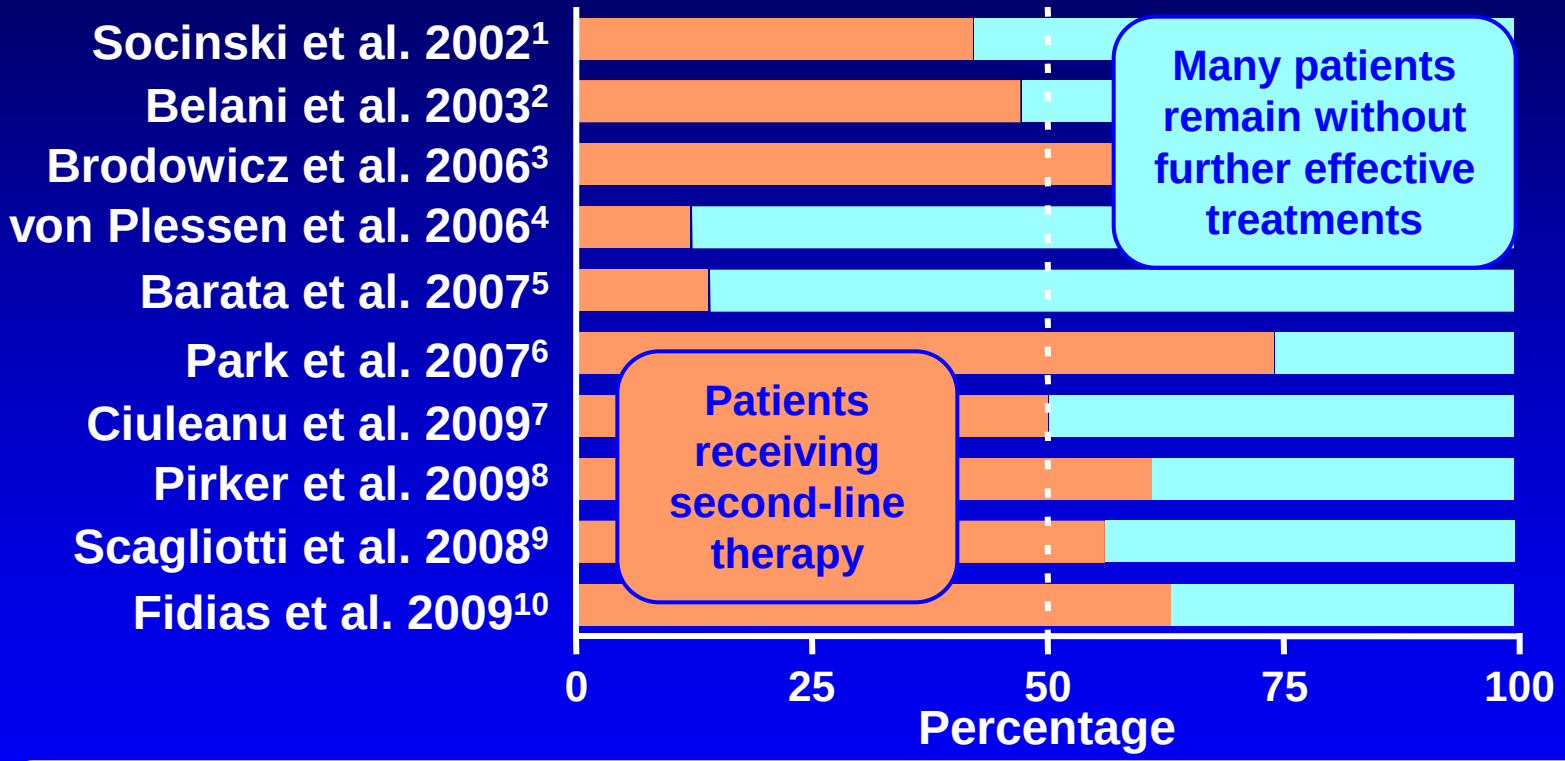
"The treatment paradigm that successfully delivers multiple lines of effective therapy… will be the paradigm that is most likely to improve survival."

Stinchcombe and Socinski, 2009

Many patients receive no further therapy due to rapid deterioration in symptoms and performance status

Stinchcombe and Socinski J Thoracic Oncol 2009

ONLY ~50% OF PATIENTS RECEIVE SECOND-LINE THERAPY



1ST LINE therapy could delay disease progression and provide active treatment for **MORE** patients

[1]J Clin Oncol 2002; [2]J Clin Oncol 2003; [3]Lung Cancer 2006; [4]Br J Cancer 2006; [5]J Thoracic Oncol 2007; Abs. P2-235; [6]J Clin Oncol 2007;[7] Lancet 2009; [8] Lancet 2009; [9]J Clin Oncol 2008; [10]J Clin Oncol 2009

JMEN: MAINTENANCE ALIMTA® (PEMETREXED) AFTER PRIOR PLATINUM IN STAGE IIIB/IV NSCLC

- Stage IIIB/IV NSCLC
- PS 0-1
- 4 prior cycles of gemcitabine, taxane + cisplatin or carboplatin, **with CR, PR, or SD**

2:1 Randomization 28-42 days after cycle 4

Pemetrexed 500 mg/m^2 (d1,q21d) + BSC (N=441)*

Placebo (d1, q21d) + BSC (N=222)*

- Primary endpoint from randomisation
  PFS in all patients
- Secondary endpoints
  OS ; OR ; safety; time to symptom progression; quality of life (PRO)

*B_{12}, folate, dexamethasone given in both arms

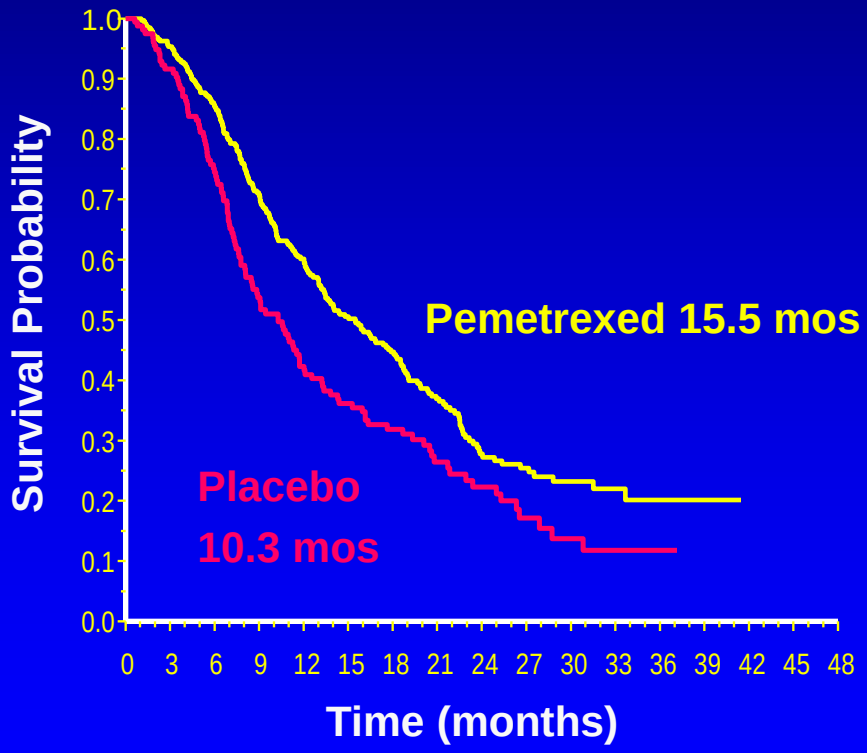
Ciuleanu et al Lancet 2009

OVERALL SURVIVAL BY HISTOLOGY

Non-squamous (n=481)

HR=0.70 (95% CI: 0.56-0.88)

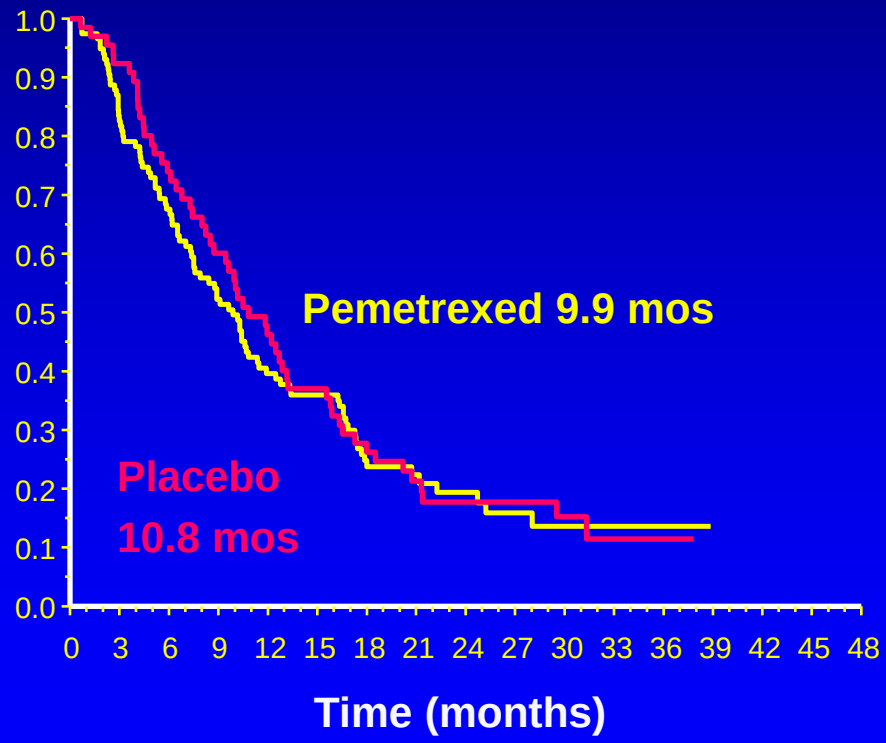
P =0.002



Squamous (n=182)

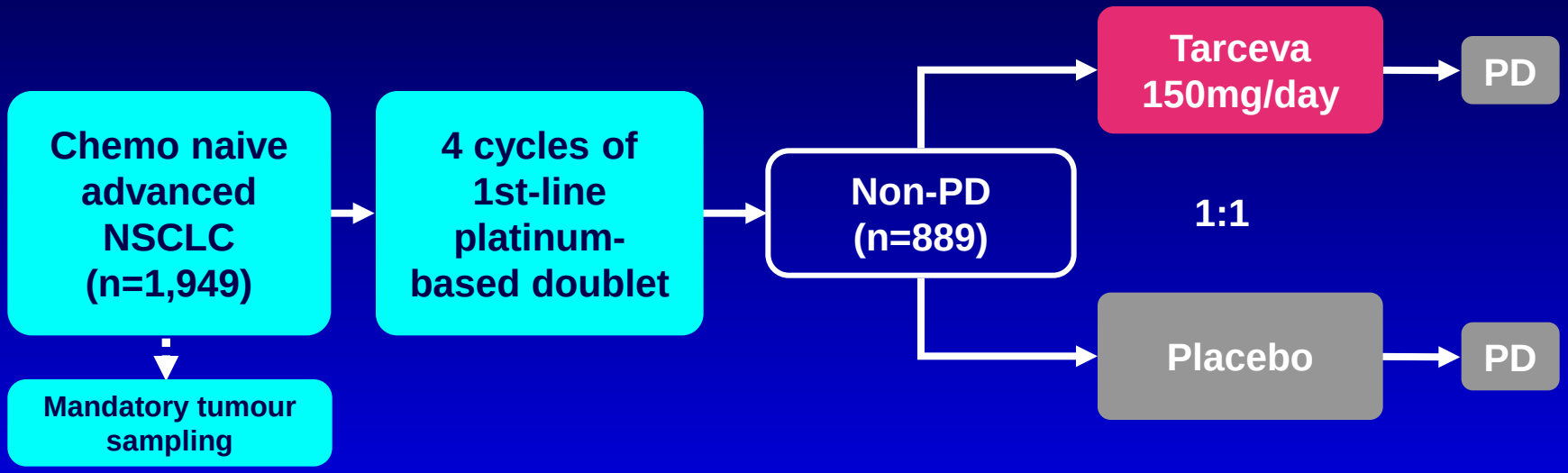
HR=1.07 (95% CI: 0.77–1.50)

P =0.678



Ciuleanu et al Lancet 2009

SATURN: MAINTENANCE TARCEVA (ERLOTINIB) AND BIOMARKERS



Co-primary endpoints from randomisation

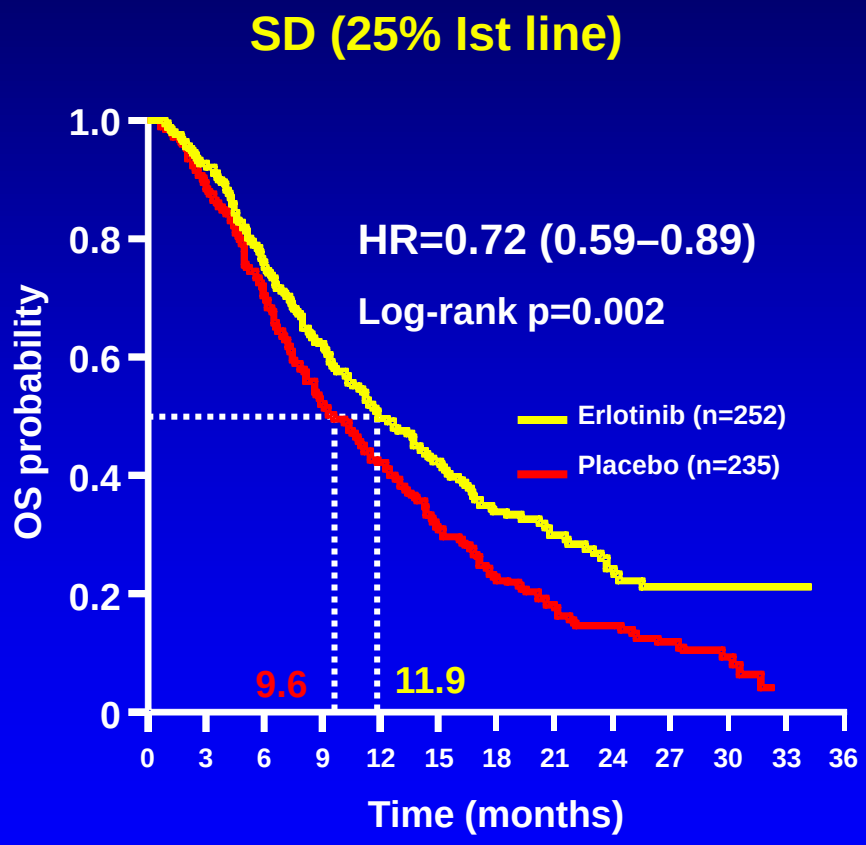
- PFS in all patients
- PFS in patients with EGFR IHC+ ve

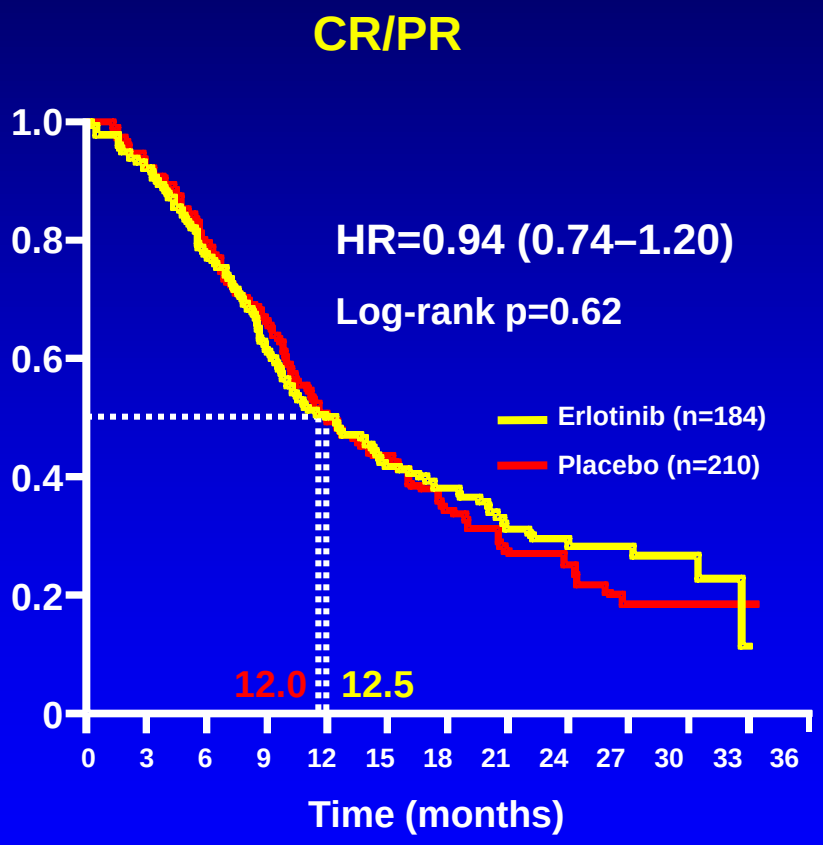
Secondary endpoints

- OS in all patients and those with EGFR IHC+ tumours, OS and PFS in EGFR IHC– tumours; biomarker analyses; safety; time to symptom progression; quality of life (QoL)

Cappuzzo et al Lancet Oncol 2010

OS ACCORDING TO RESPONSE TO FIRST-LINE CHEMOTHERAPY*

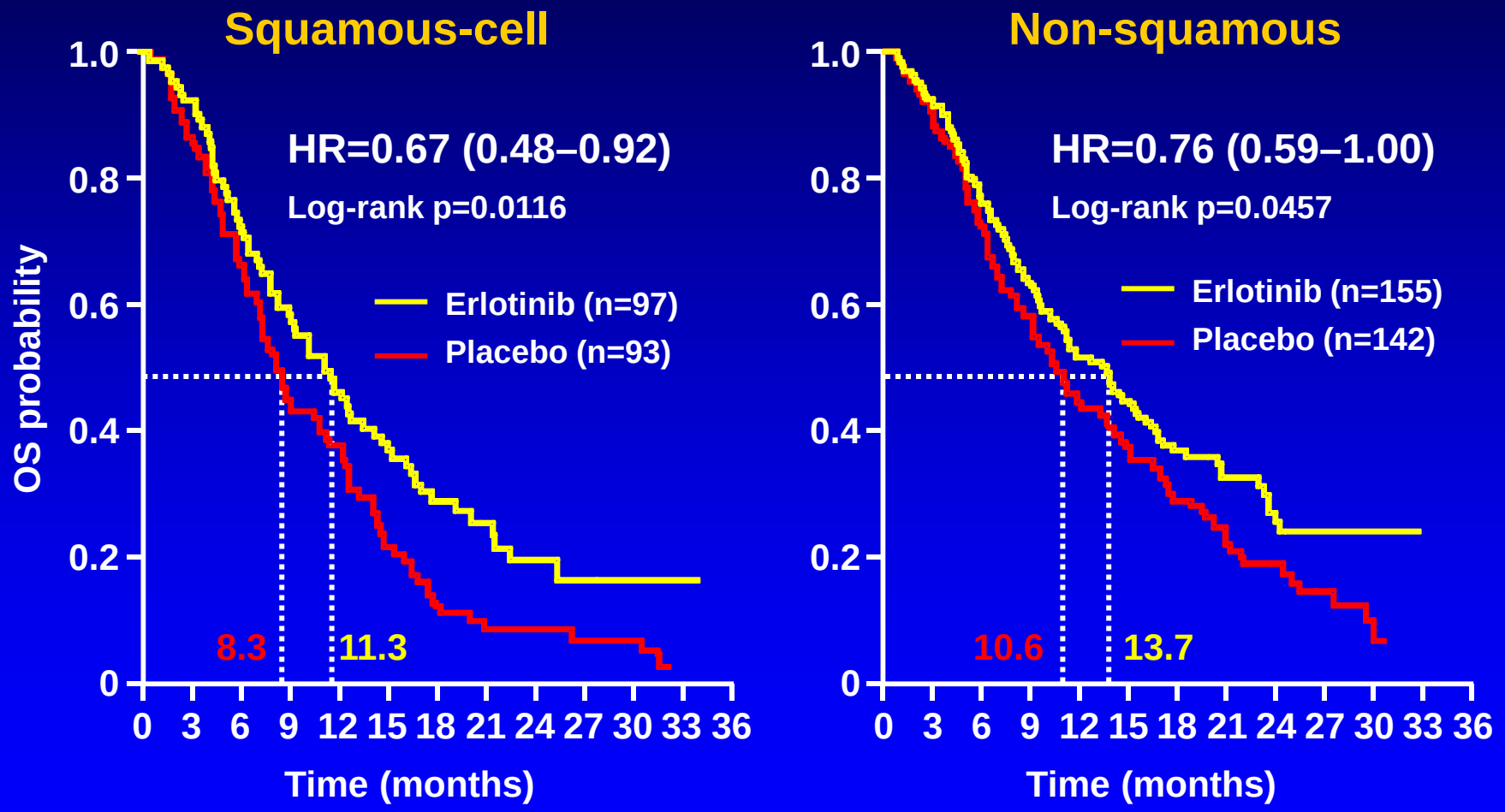




*OS is measured from time of randomisation into the maintenance phase

Cappuzzo et al Lancet Oncol 2010

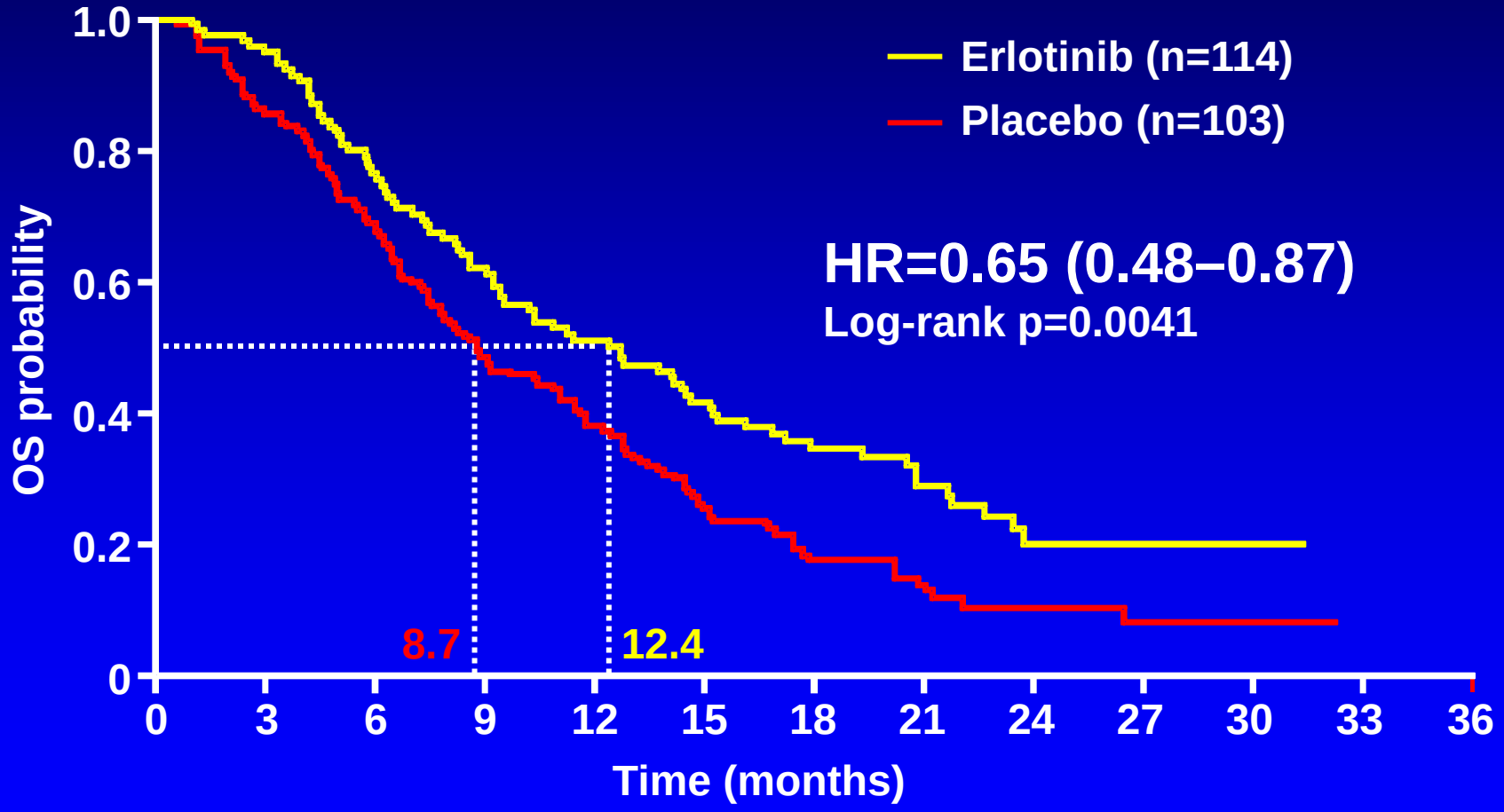
OS IN PATIENTS WITH SD ON FIRST-LINE CHEMOTHERAPY ACCORDING TO HISTOLOGY



Measured from time of randomisation into the maintenance phase

Coudert et al, ELCC 2010 abst 2040

OS in *EGFR* WILD-TYPE GROUP with SD on FIRST-LINE CHEMOTHERAPY



Measured from time of randomisation into the maintenance phase

Coudert et al, ELCC 2010 abst 2040

MAINTENANCE THERAPY
ESMO, ASCO GUIDELINES

Recommendation 9

- 'Switch maintenance' treatment with erlotinib or pemetrexed following completion of first-line chemotherapy is an option. Decision factors for the use of 'switch maintenance' include histology, type and response to first-line chemotherapy, residual toxicity, patient's symptoms and preference. Any patient whose tumor harbors an EGFR activating mutation should receive an EGFR TKI as maintenance, if not yet received as first line

For those with **stable disease or response after four cycles, immediate treatment with an alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients , or erlotinib in unselected patients may be considered.**

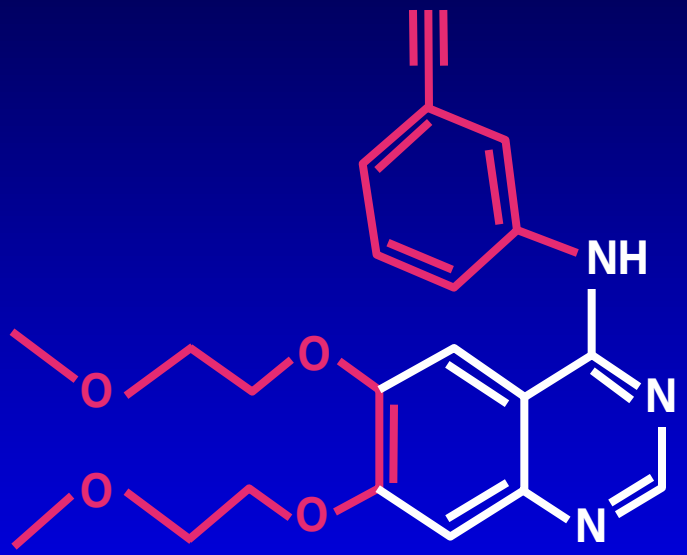
Focused Update of Recommendation A6 J Clin Oncol 2011

IS THERE A DIFFERENCE BETWEEN TKIs ?

USE OF TKI IN *EGFR* WILD TYPE NSCLC

ERLOTINIB AND GEFITINIB:

SIMILAR STRUCTURES, DIFFERENT ACTIVITY



Erlotinib

IC_{50}=0.002μM

Gefitinib

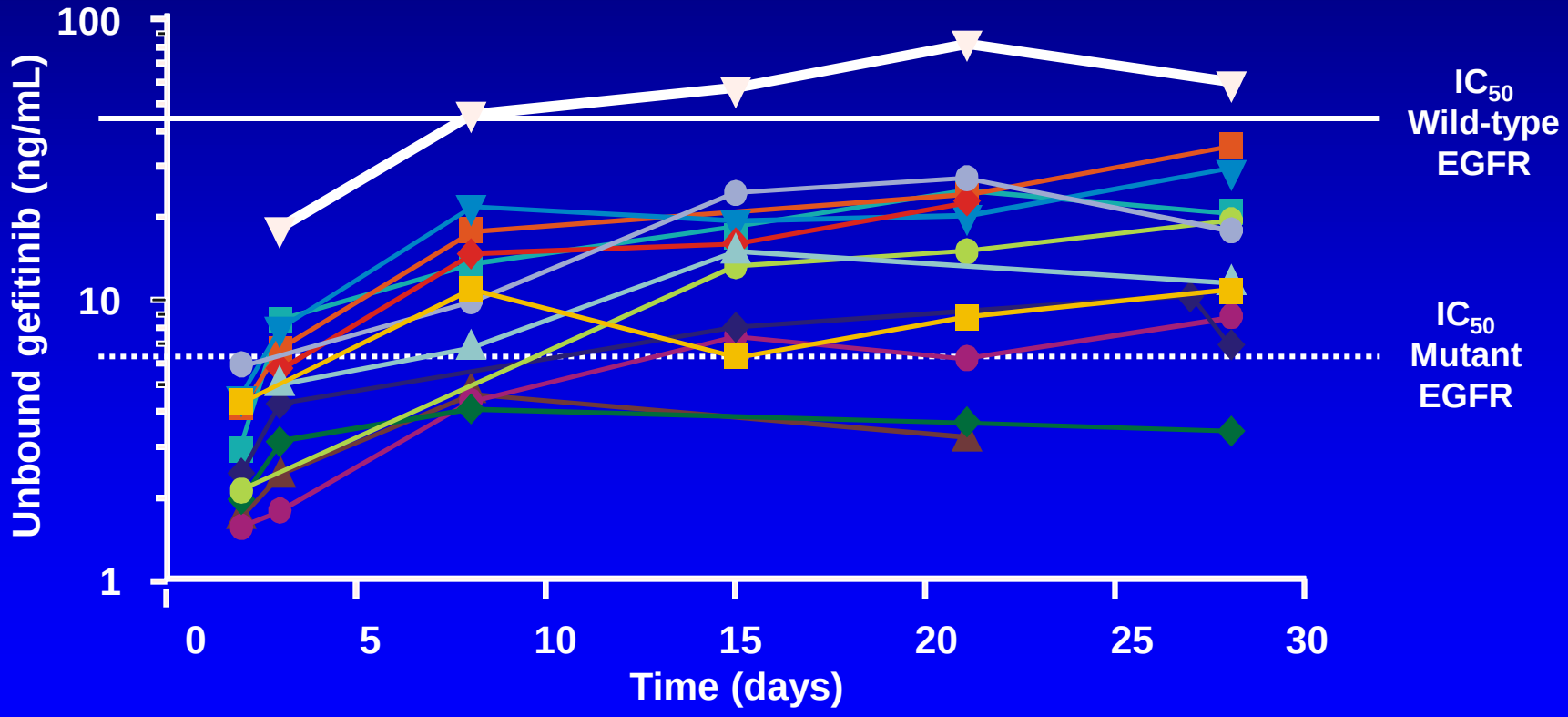
IC_{50}=0.02μM

- Structural differences may affect :plasma, tumour and normal tissue distribution, metabolism ,in-vitro activity, clinical efficacy and toxicity

- Switch after gefitinib failure to erlotinib 125 patients OR 9% DCR 44% MS11.8 months ; 62 pts BM RR 34%(without RT) *Hata et al Lung Cancer 2011*

EXPOSURE TO GEFITINIB MAY BE INSUFFICIENT TO INHIBIT WILD-TYPE EGFR

Plasma concentrations versus time in 13 cancer patients, following gefitinib 250mg/day



Li J et al. J Natl Cancer Inst 2006

ERLOTINIB IN 2ND LINE OR MAINTENANCE IS EFFECTIVE IN *EGFR* wt DISEASE

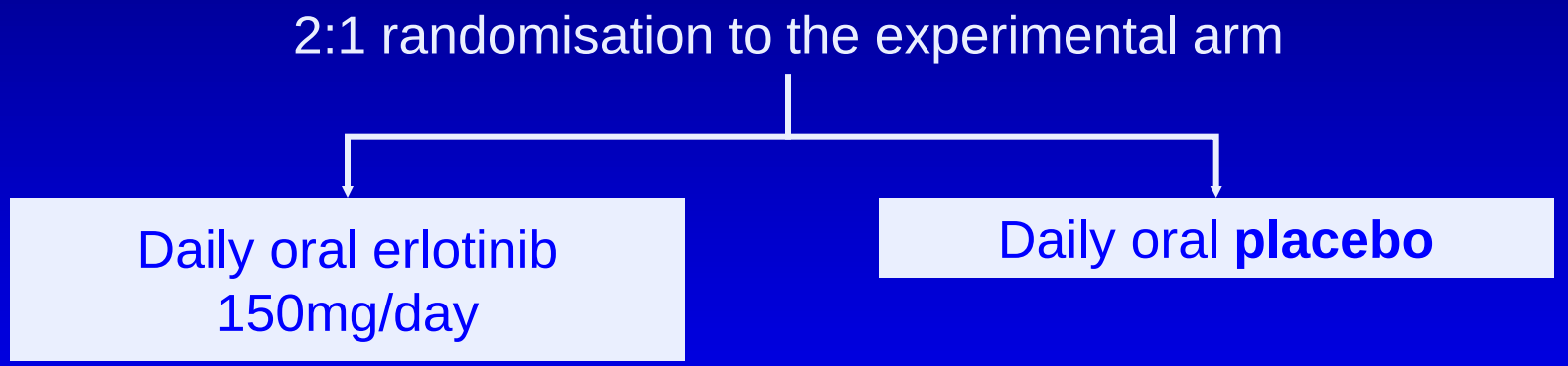
Study	Patients with *EGFR* WT disease	HR (95% CI) Erlotinib vs placebo		Testing method(s)
BR.21[1–2]	Erlotinib (n=115) Placebo (n=55)	PFS	HR=0.57 p=0.001	EGFR Scorpions IM kits; direct gene sequencing and fragment analysis
		OS	HR=0.74 p=0.0924	
SATURN ITT population[4]	Erlotinib (n=199) Placebo (n=189)	PFS	HR=0.78 p=0.0185	Sanger DNA sequencing
		OS	HR=0.77 p=0.0243	
SATURN SD population[3]	Erlotinib (n=114) Placebo (n=103)	PFS	HR=0.72 p=0.0231	
		OS	HR=0.65 p=0.0041	

[1]Zhu, et al. JCO 2008; [2]Tsao, et al. NEJM 2005; [3]Coudert, et al. Ann Oncol 2011; [4]Brugger, et al. JCO 2011

BR.21: ERLOTINIB PHASE III STUDY IN ADVANCED, REFRACTORY NSCLC

Patients with stage IIIB/IV, refractory NSCLC; PS0–3;
failed one or two prior regimens

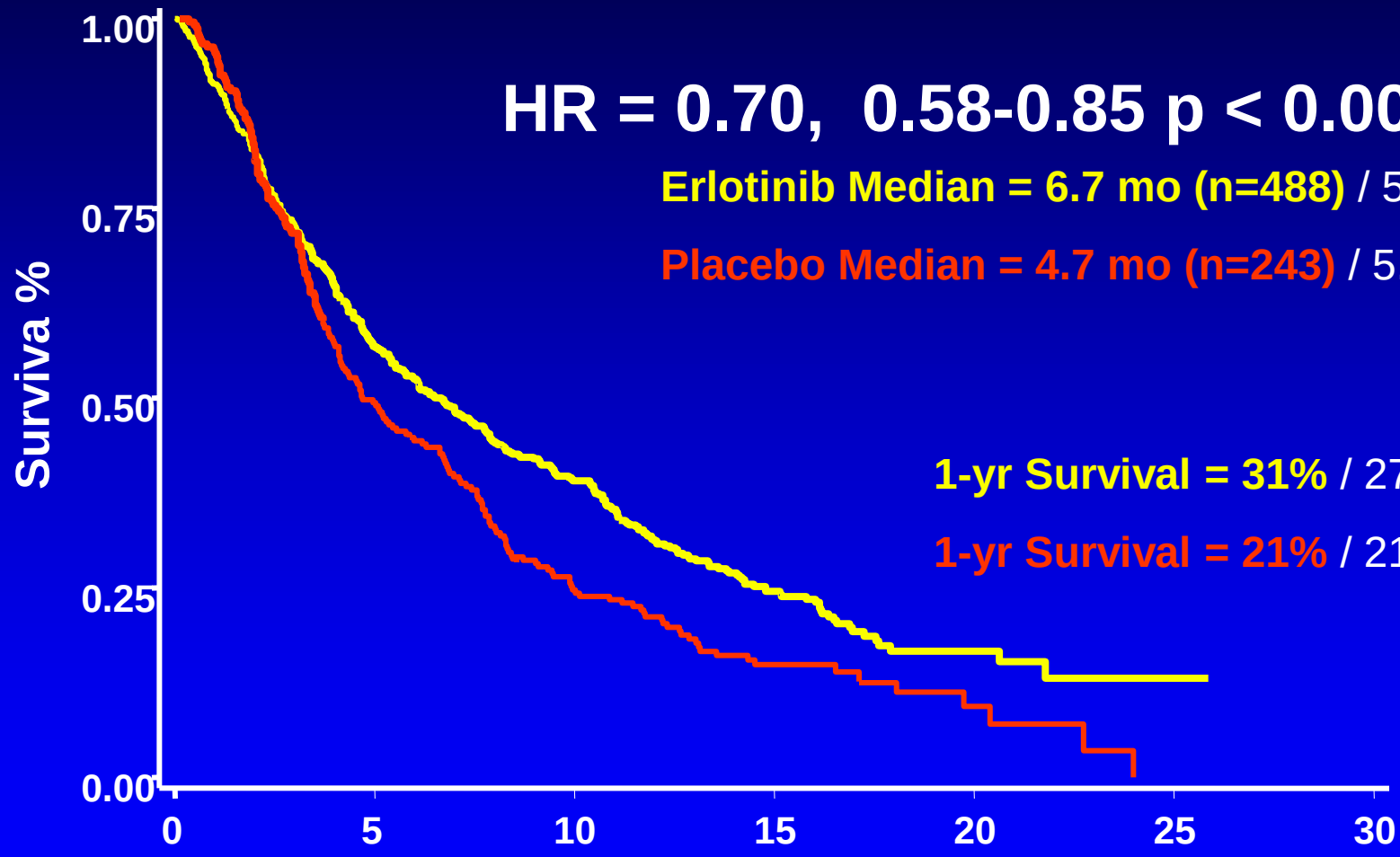
EGFR +ve not required



- n=731 patients
- Primary objective: overall survival
- Secondary objectives: response rate, stable-disease rate, duration of response, time to disease progression, and QoL
- 90% power to detect a 33% survival benefit

Shepherd et al N Eng J Med 2005

OVERALL SURVIVAL
ALL PATIENTS



HR = 0.70, 0.58-0.85 p < 0.001

Erlotinib Median = 6.7 mo (n=488) / 5.6

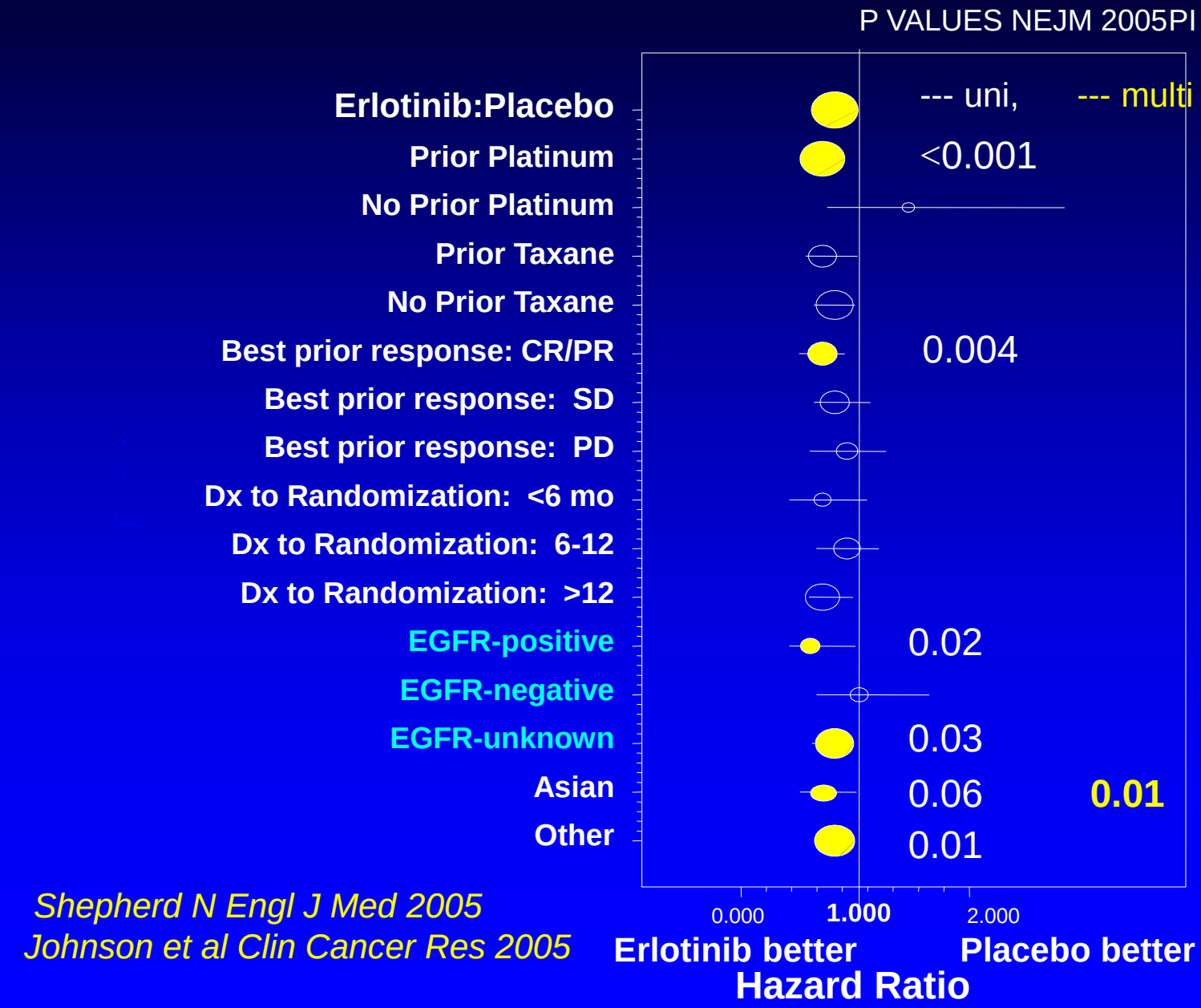
Placebo Median = 4.7 mo (n=243) / 5.1

1-yr Survival = 31% / 27%

1-yr Survival = 21% / 21%

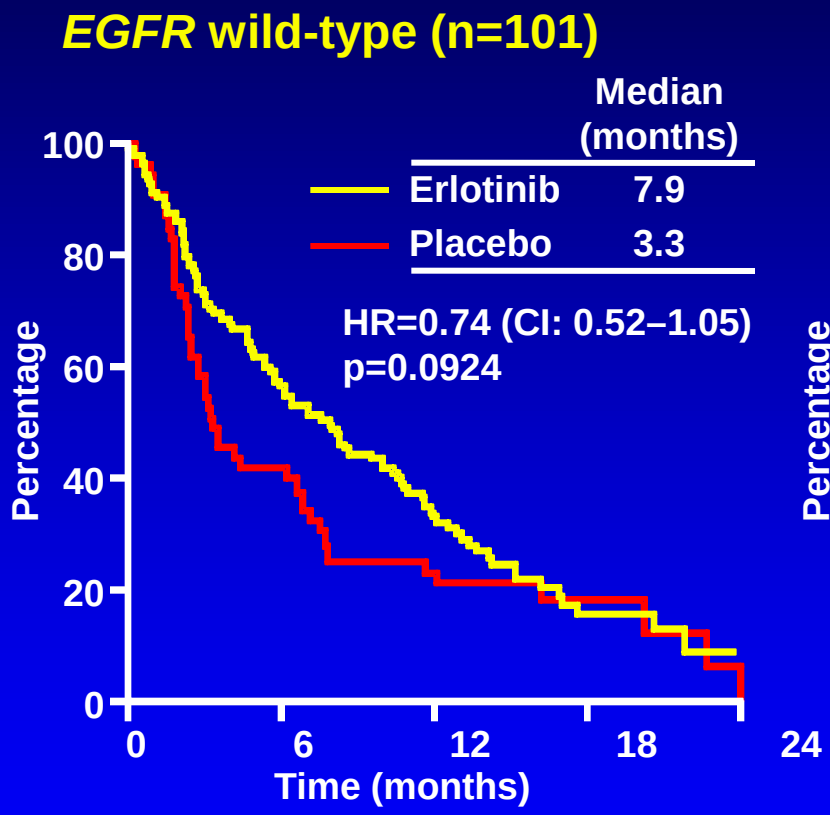
Shepherd et al N Eng J Med 2005
Thatcher et al Lancet 2005
Blackhall et al Lancet Onc 2006

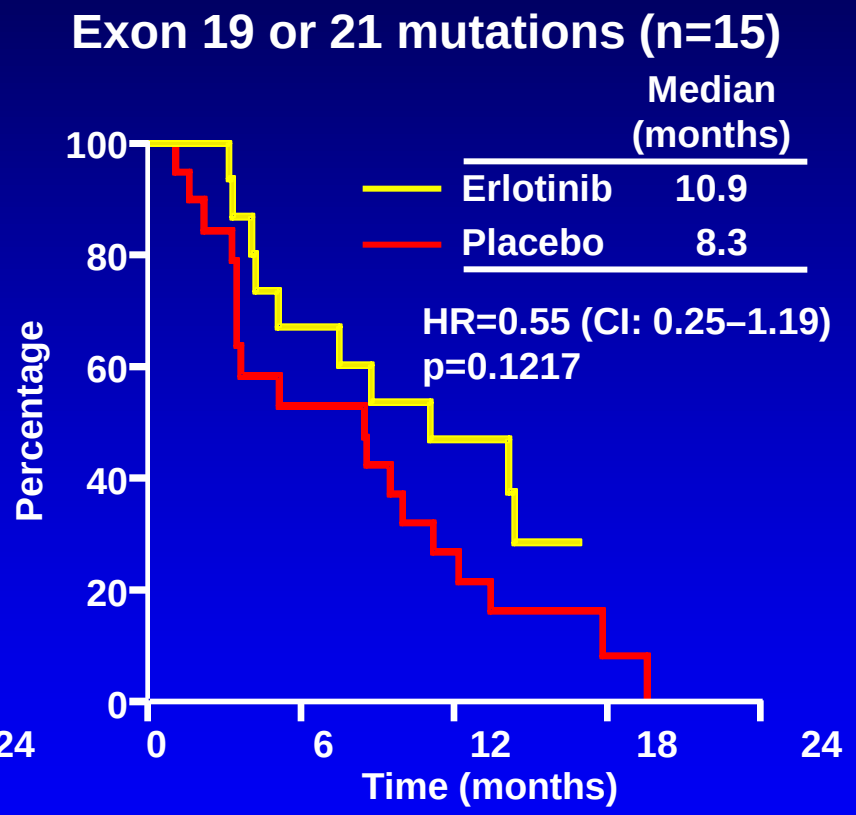
HAZARD RATIO FOR DEATH BY SUBSETS



Shepherd N Engl J Med 2005
Johnson et al Clin Cancer Res 2005

BR.21 RETRO ANALYSIS: SURVIVAL ACCORDING TO *EGFR* MUTATION STATUS

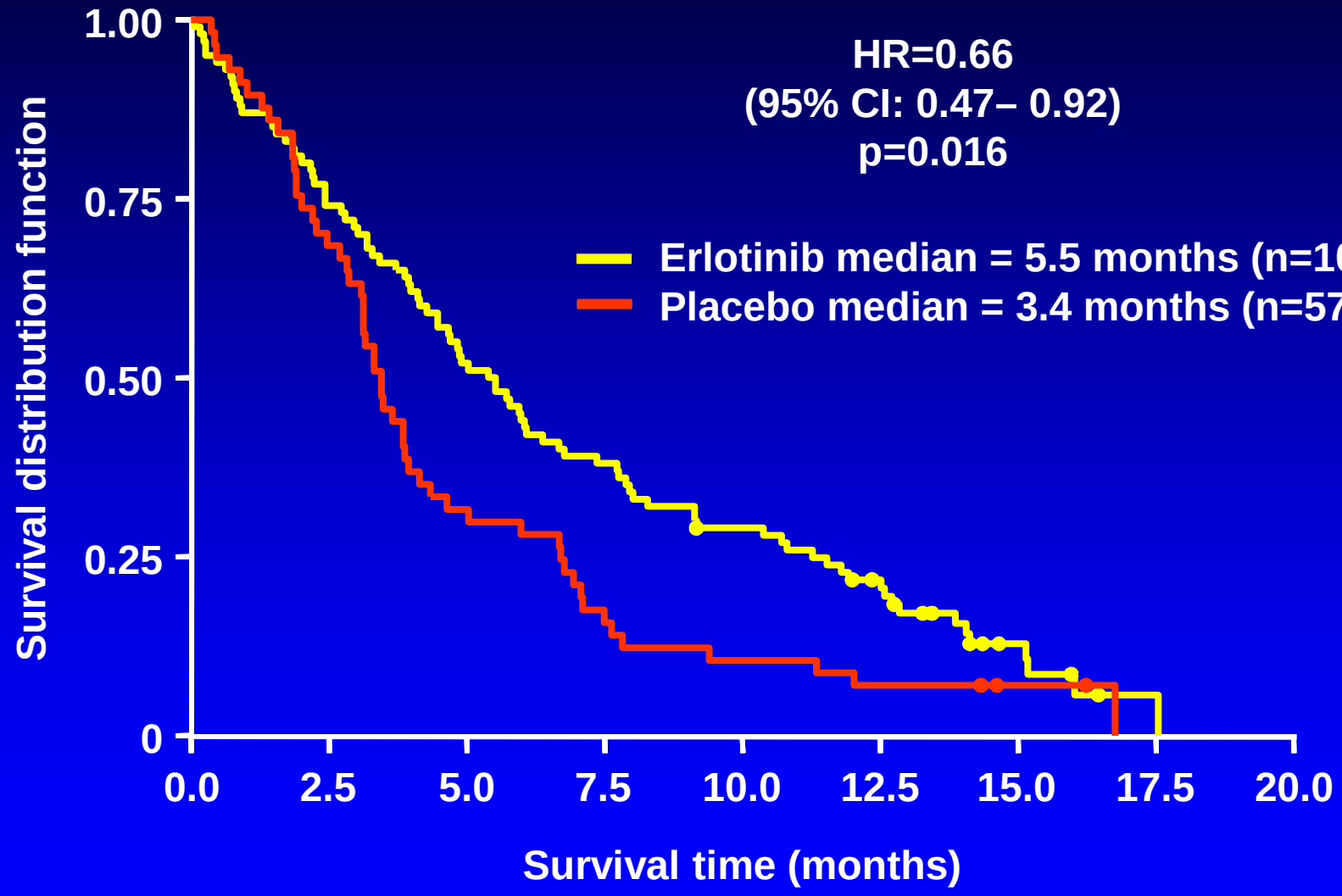




Interaction p=0.47 (not significant)

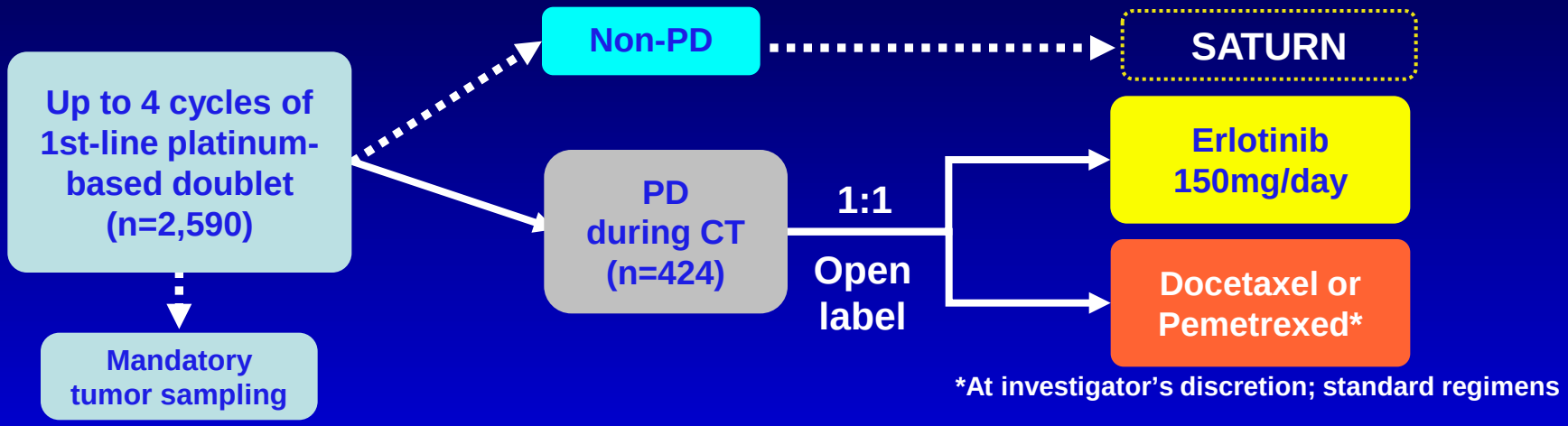
Zhu et al J Clin Oncol 2008

IS THERE A CLINICAL BENEFIT WITH TARCEVA FOR MALE SMOKERS WITH SQUAMOUS-CELL CARCINOMA?



Clark et al Clin Lung Cancer 2006

TITAN STUDY DESIGN



Primary endpoint

- Overall survival (OS)

Secondary endpoints

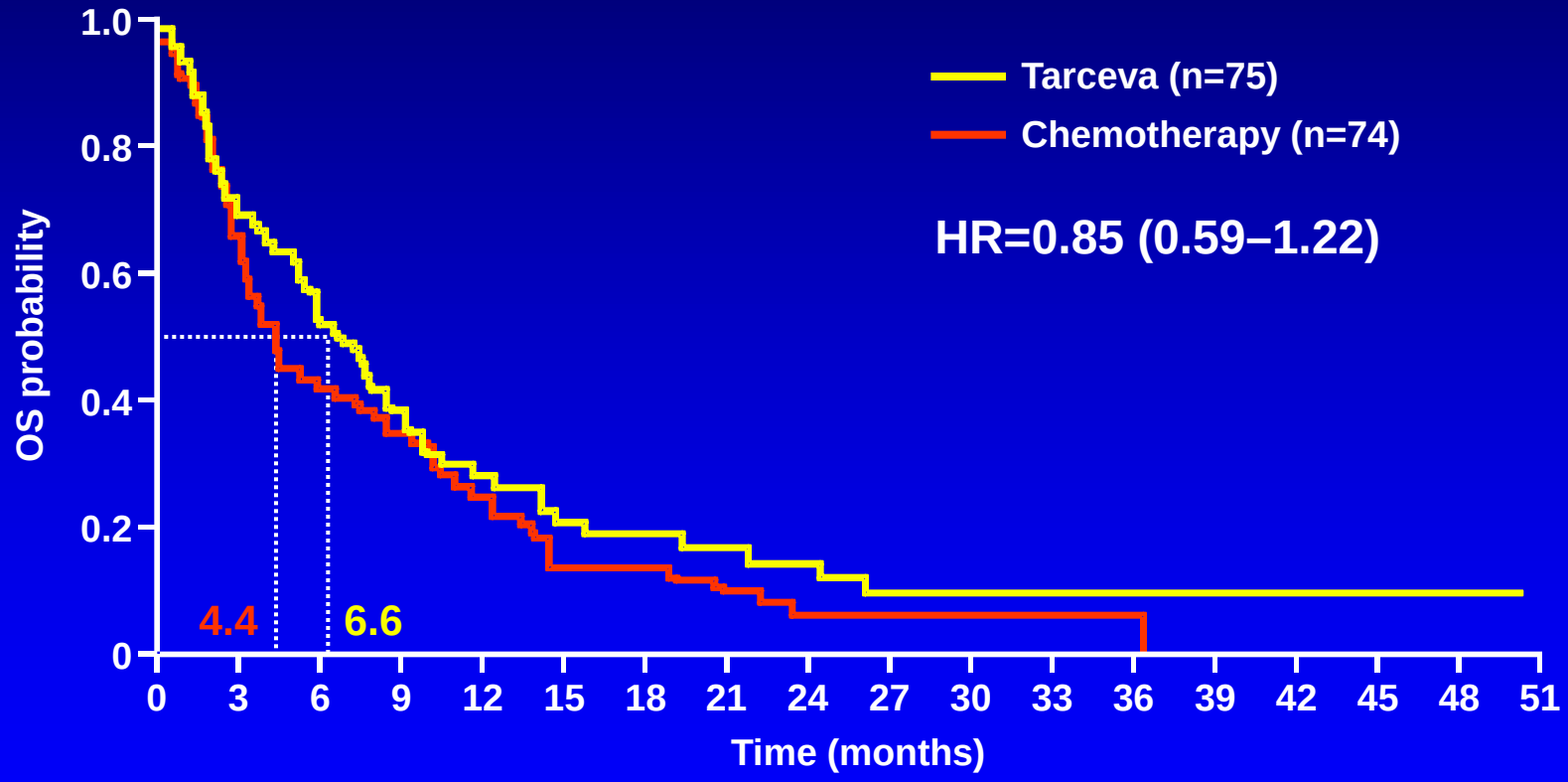
- PFS, RR, QoL (FACT-L), correlation of biomarkers with clinical outcome

Stratification factors

- Stage of disease at start of chemotherapy (IIIB vs IV)
- ECOG PS (0 or 1 vs 2)
- Smoking history (current vs former vs never)
- Region

Ciuleanu et al IASLC Chicago 2010 abstr 6 /LBOA5

TITAN:OS with erlotinib vs chemotherapy in *EGFR* wild type NSCLC



Ciuleanu et al IASCLC Chicago 2010 abstr 6 /LBOA5

2ND TOPIC

A) If Mut +ve is 1st line CT or TKI best ? TKI best but if CT first make sure to give TKI afterwards

B) Any difference between the tkis ? Yes

Maintenance or wait and then 2nd line? Maintenance in some

Is there a role for TKI in EGFR wt? Yes ,erlotinib in maintenance and 2nd line (Saturn; BR21: Titan)

C) Which pathways are responsible for TKI resistance ?

What to do if PD during TKI continue or stop?

Oxnard et al Clin Cancer Res 2011

ASPECTS of RESISTANCE to EGFR TKIs

COMBINATION OF TARGETED AGENTS

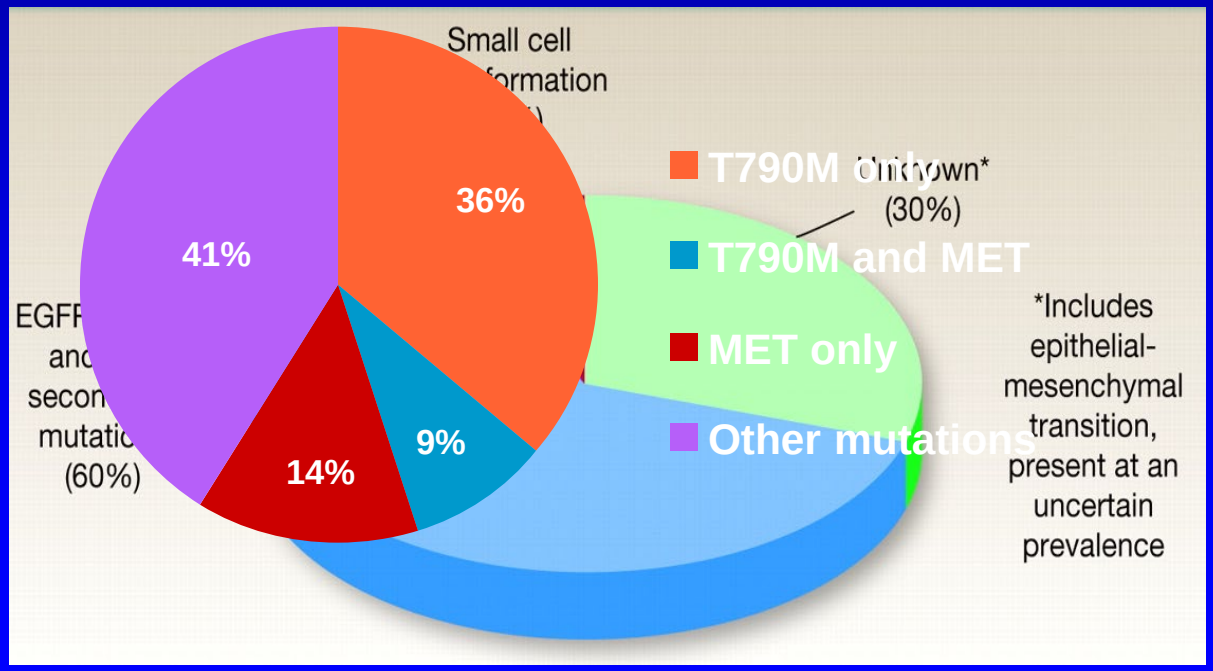
Primary Resistance

- De novo T790M mutation
- PIK3CA mutation
- PTEN loss
- IGF1R
- Others

Acquired Resistance

- T790M mutation
- c-MET amplification
- EMT
- Others

Kobayashi et al, NEJM 2005
Inukai M et al Cncer Res 2006;;
Engeglman JCI 2006
Bean et al. Proc Natl Acad Sci. 2007;
Engelman et al. Science 2007
Frederick et al Mol Cancer Ther 2007
Sos et al Cancer Res 2009
Gong et al, PLoS ONE 2009

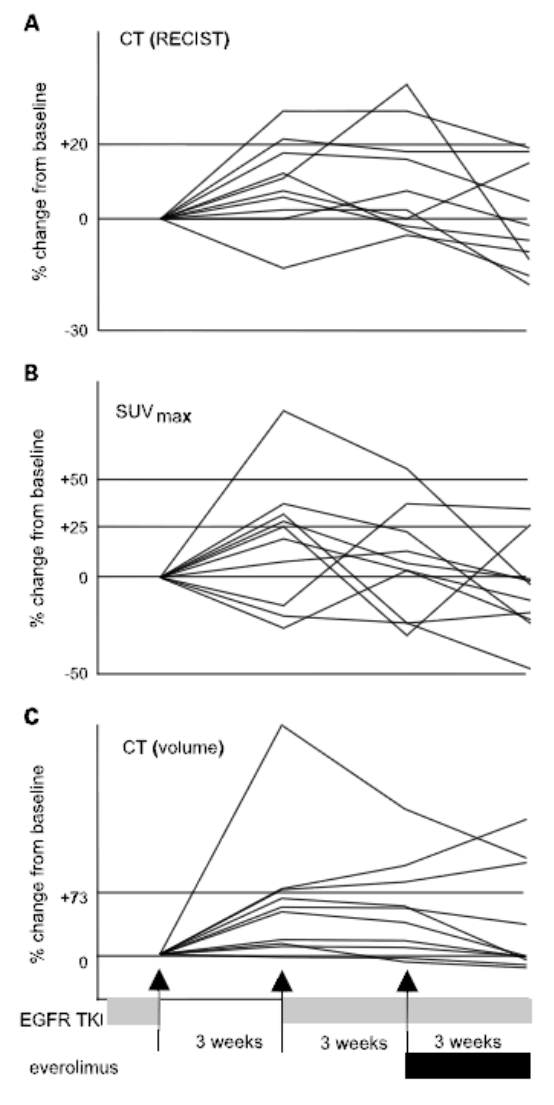


Oxnard et al Clin Cancer Res 2011

WHAT CAN WE DO AFTER TKI FAILURE ?

- Switch to chemotherapy or add CT to TKI
- Continue EGFR-TKI
- Switch to another EGFR-TKI
  gefitinib to erlotinib
  Irreversible EGFR-TKI?
- Is it better to treat resistance or try to prevent it from emerging ?

RE-CHALLENGE OF EGFR TKI IN RESISTANCE TO EGFR TKI ?



10 patients, resistance to EGFR TKIs

Stop EGFR TKIs for 3 weeks, then restart

EGFR TKIs, 3 weeks later add everolimus

After stop : 18% SUVmax and 9% tumor size

Symptomatic progression

Restart EGFR TKI: 4% decreased SUV max

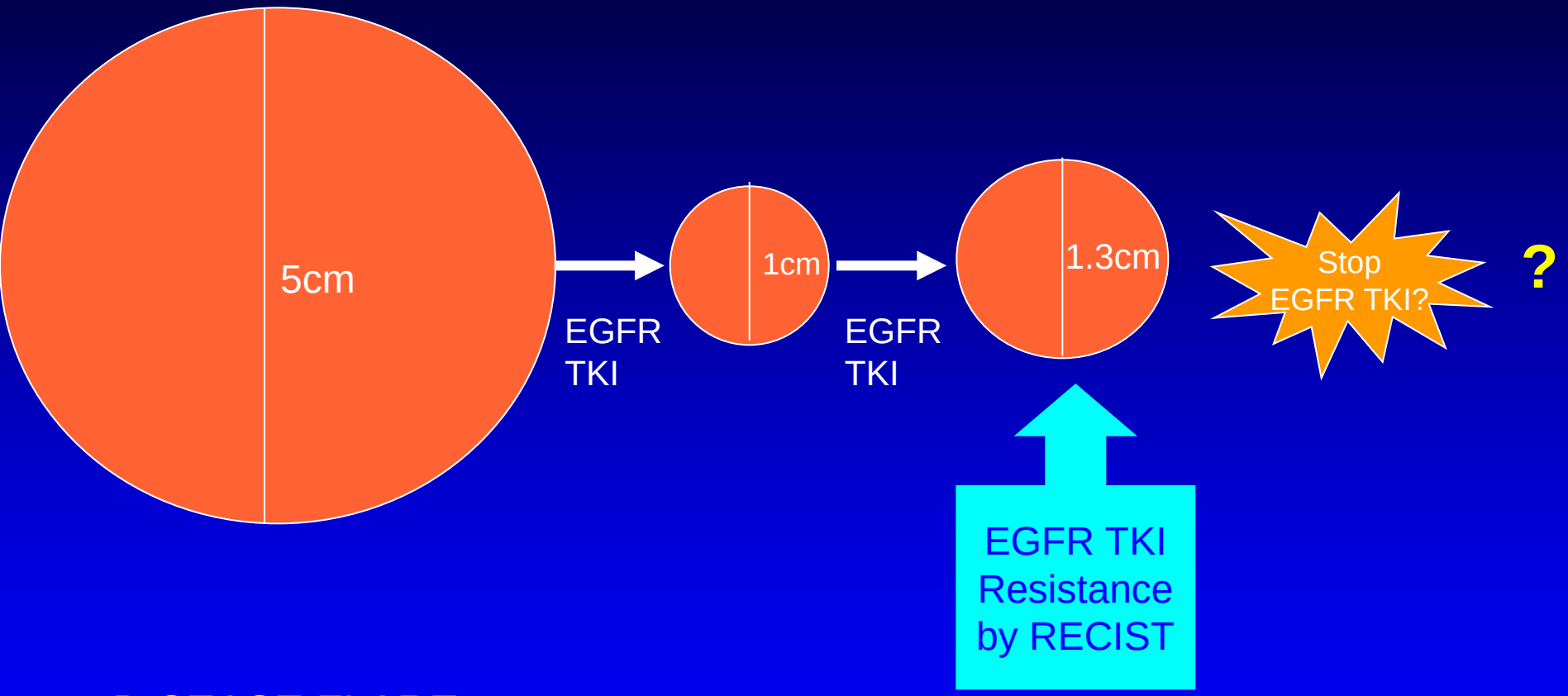
1% decreased in tumor

Symptom improvement

Suggesting that some tumor cells remain sensitive to EGFR TKIs

Riely et al Clin Cancer Res 2007

RECIST Criteria



DISEASE FLARE

61 patients with acquired resistance (RECIST PD after benefit)

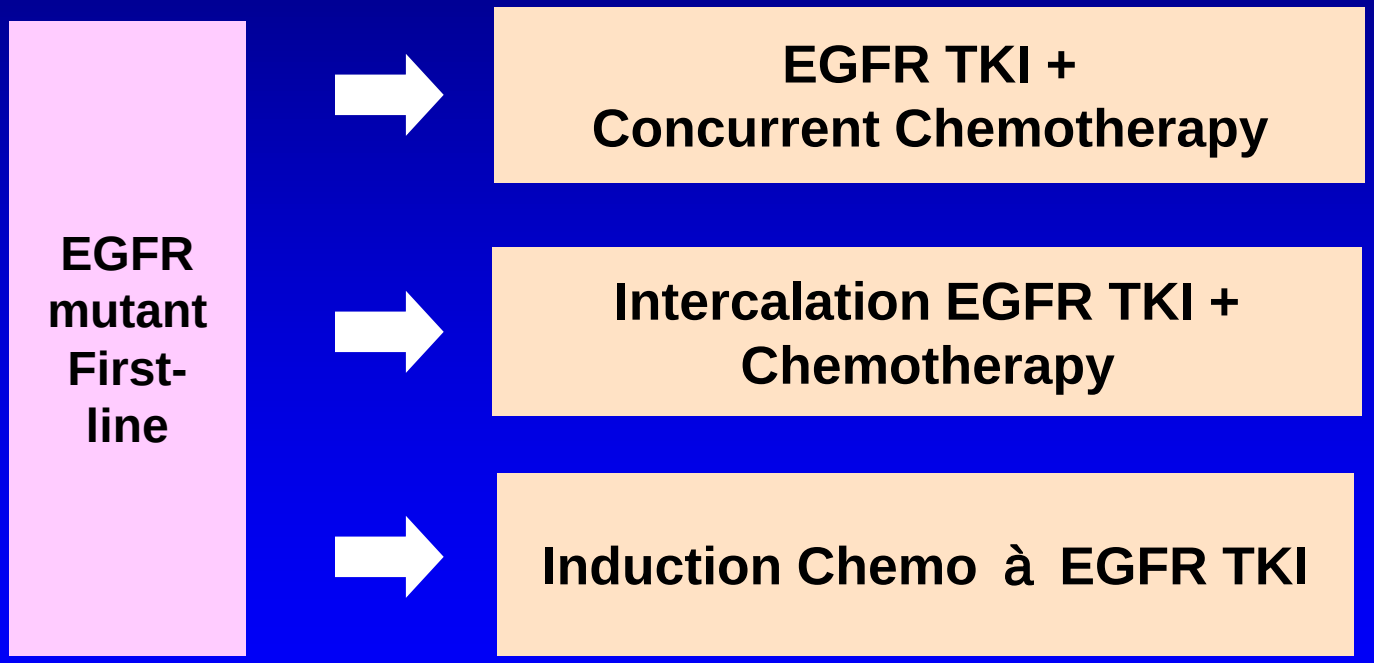
23% disease flare (hospitalization/death due to PD during wash out)

Shorter TTP, pleural/CNS mets. Not mut stus including T790M

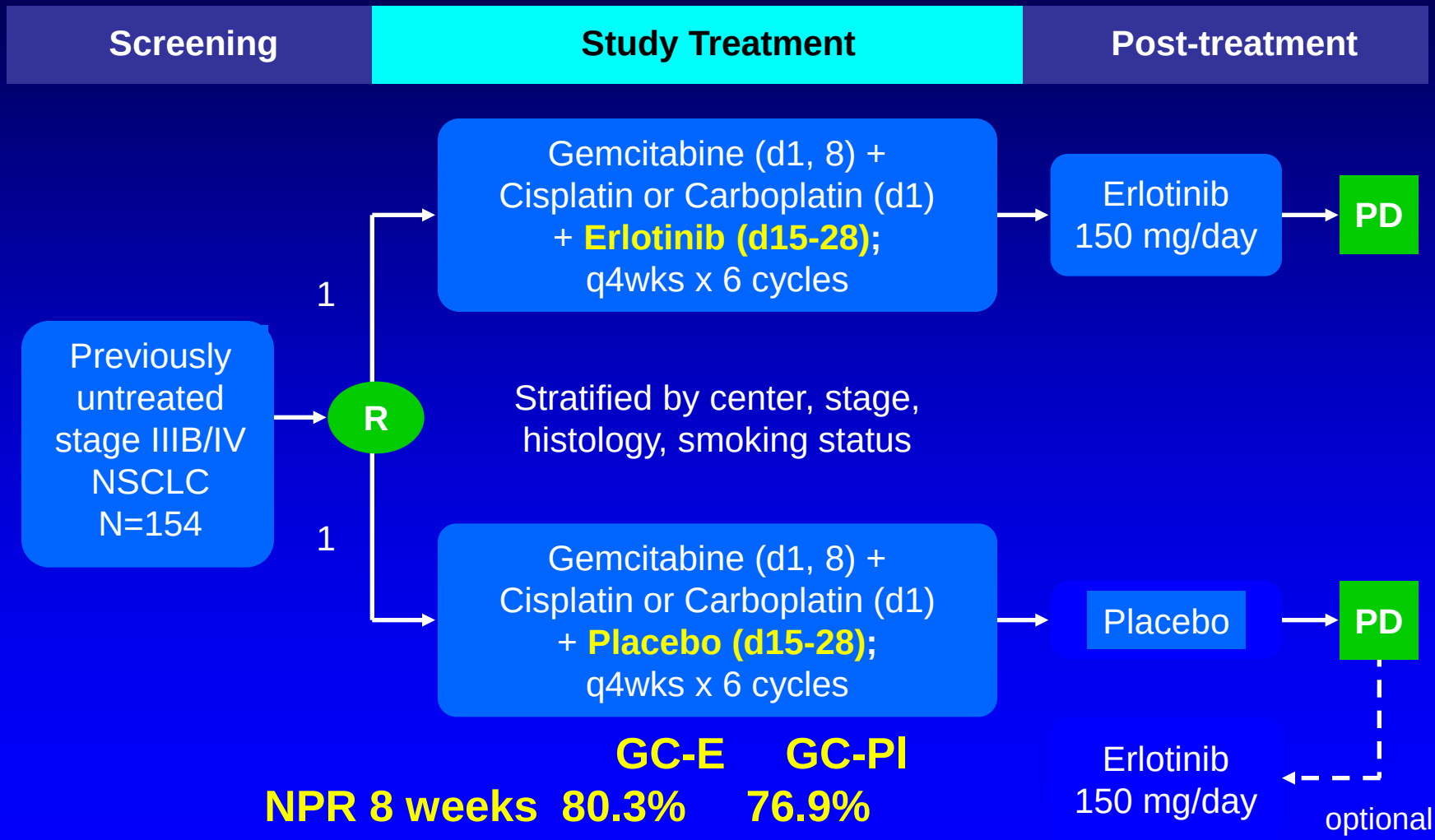
Chaft et al Clin Cancer Res 2011

ADD CHEMOTHERAPY TO *TKI*

Incorporation of chemotherapy



FIRST-LINE ASIAN SEQUENTIAL TARCEVA PLUS CHEMOTHERAPY TRIAL (FASTACT)



	GC-E	GC-Pl
NPR 8 weeks	80.3%	76.9%
PFS weeks	29.4	23.4

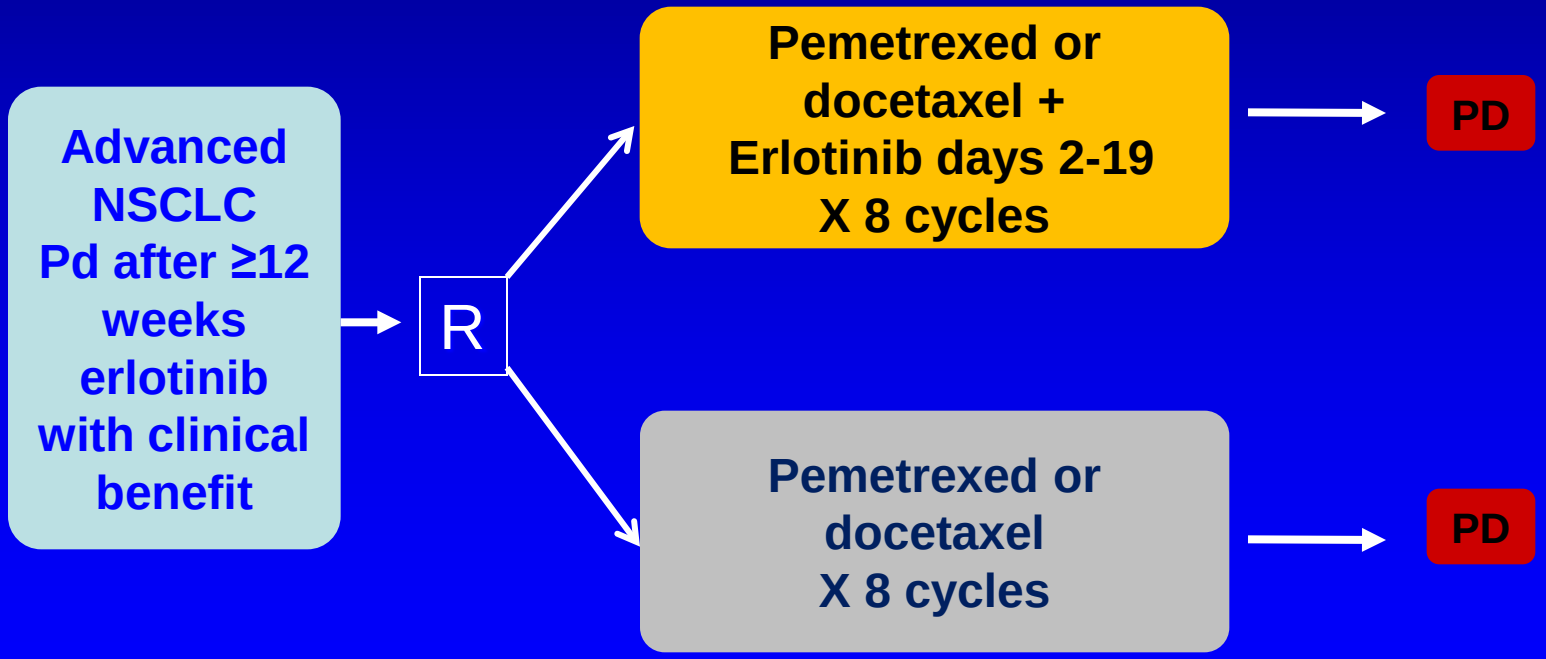
p=0.0002

Mok et al J Clin Oncol 2009

TRIAL DESIGN : Continuation of EGFR TKIs

On relapse only some clones carry resistance mutations,
Others remain dormant while the EGFR pathway remains inhibited
Tumour rebound/ flare when EGFR *tki* stopped on progression

Randomised Phase II
Primary endpoint increase PFS by 50% (3to 4.5 months)
23/78 patients enrolled

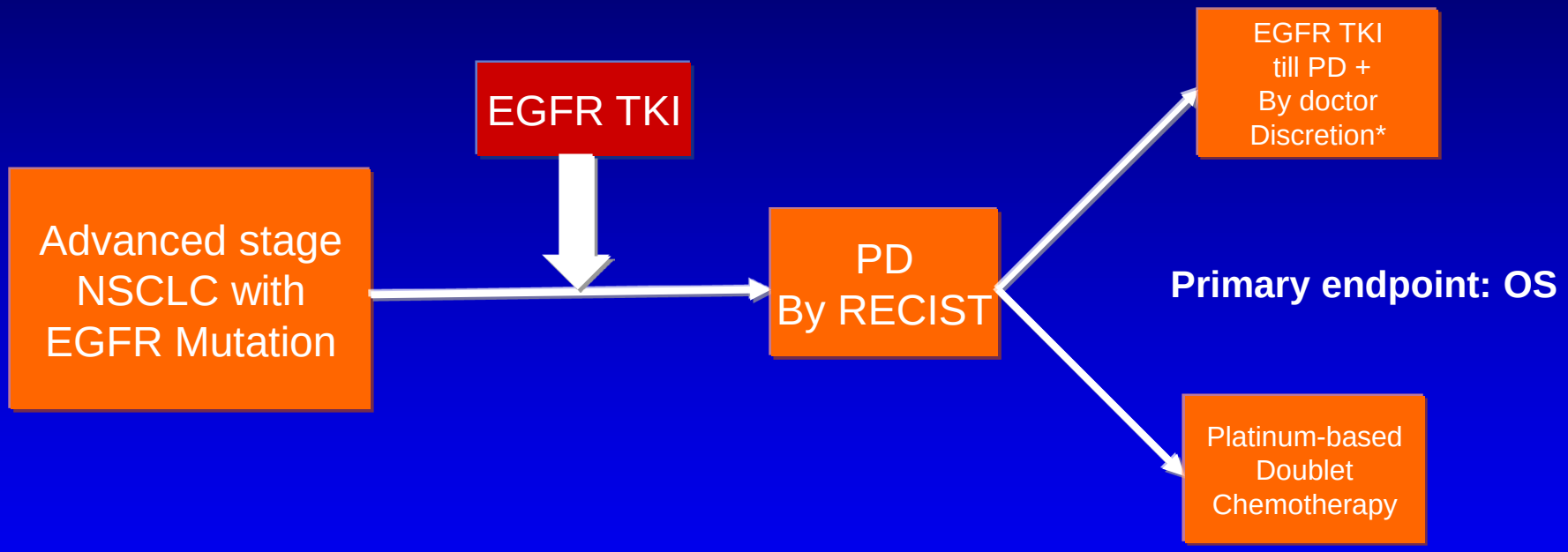


Halmos et al ASCO 2011abst TPS211

TREATMENT-BEYOND-PROGRESSION

ASPIRATION

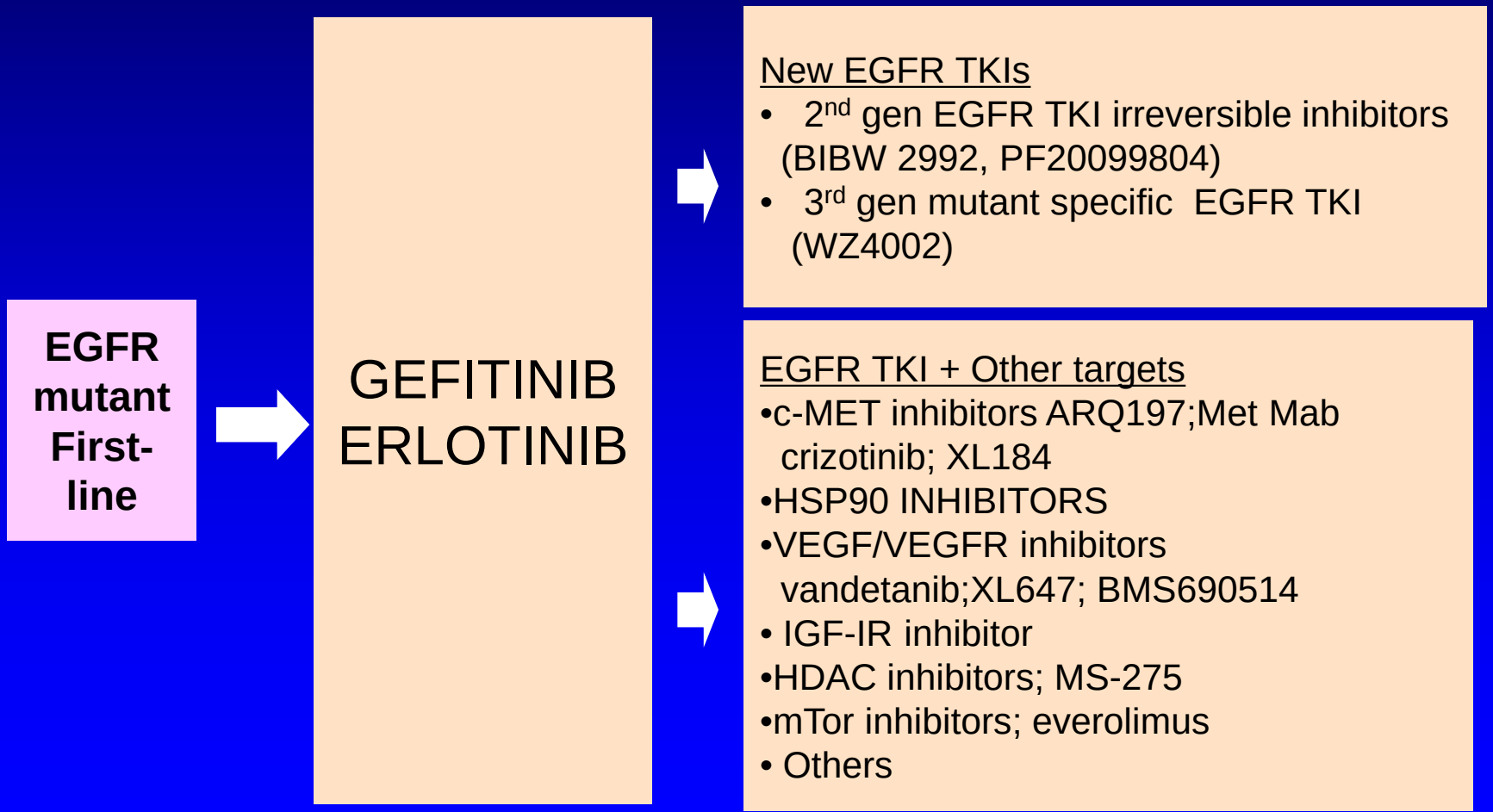
(ASIA PACIFIC TRIAL OF TARCEVA AS FIRST LINE IN EGFR MUTATION+ NSCLC)



*Doctor Discretion: Symptomatic progression, multiple progression
Threat to major organ…etc

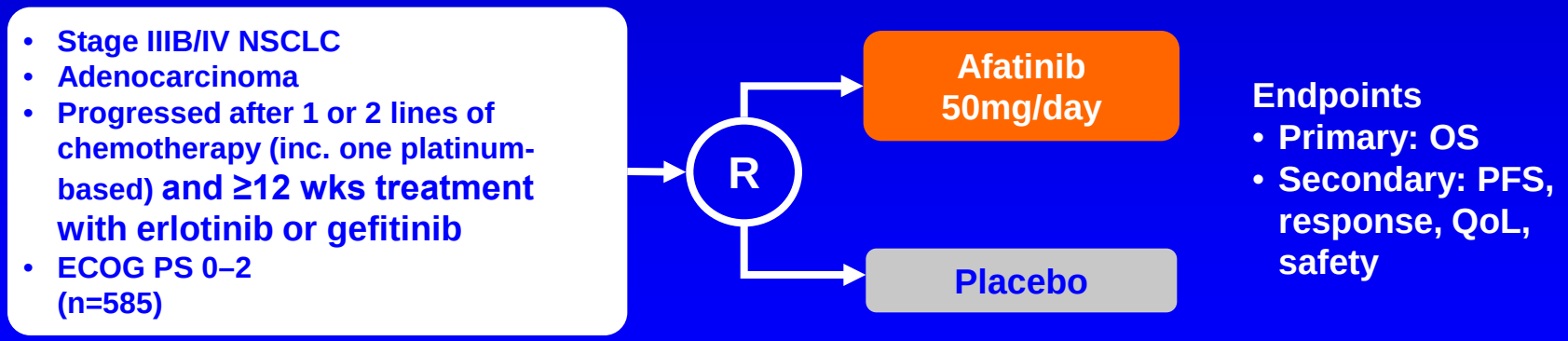
DELAY OR PREVENT THE APPEARANCE OF RESISTANCE TO EGFR TKIS

New EGFR TKIs or combination with new targets



BIBW 2992
LUX-LUNG 1: RATIONALE

- Patients sensitive to gefitinib (G) or erlotinib (E) eventually progress
  - T790M mutation most common cause of resistance
  - Detected in ~50% of such patients
- Afatinib (BIBW 2992)
  - Irreversible EGFR and HER2 inhibitor
  - Preclinical activity against NSCLC with T790M mutations



Miller et al ESMO 2010 abst LBA1

2ND TOPIC

A) If Mut +ve is 1st line CT or TKI best ?

TKI best but if CT first make sure to give TKI afterwards

B) Is there a role for TKI in EGFR wt ? Yes in maintenance and 2nd line (Saturn;BR21; Titan)

Any difference between the tkis ? Yes Erlotinib efficacy after gefitinib failure *Hata et al Lung Cancer 2011*

C) What to do if PD during TKI continue or stop? Stop and switch to 1st line CT (but emerging data)

Which pathways are responsible for TKI resistance ? T790M, c-MET and others

Is it better to treat resistance or try to prevent it from emerging ?

3rd TOPIC
EGFR TESTING

A) IHC testing only in non-squamous only? No

B) Mutation testing in non-squamous only? Yes

NSCLC pathology and molecular testing

Recommendation 1

–EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR TKIs

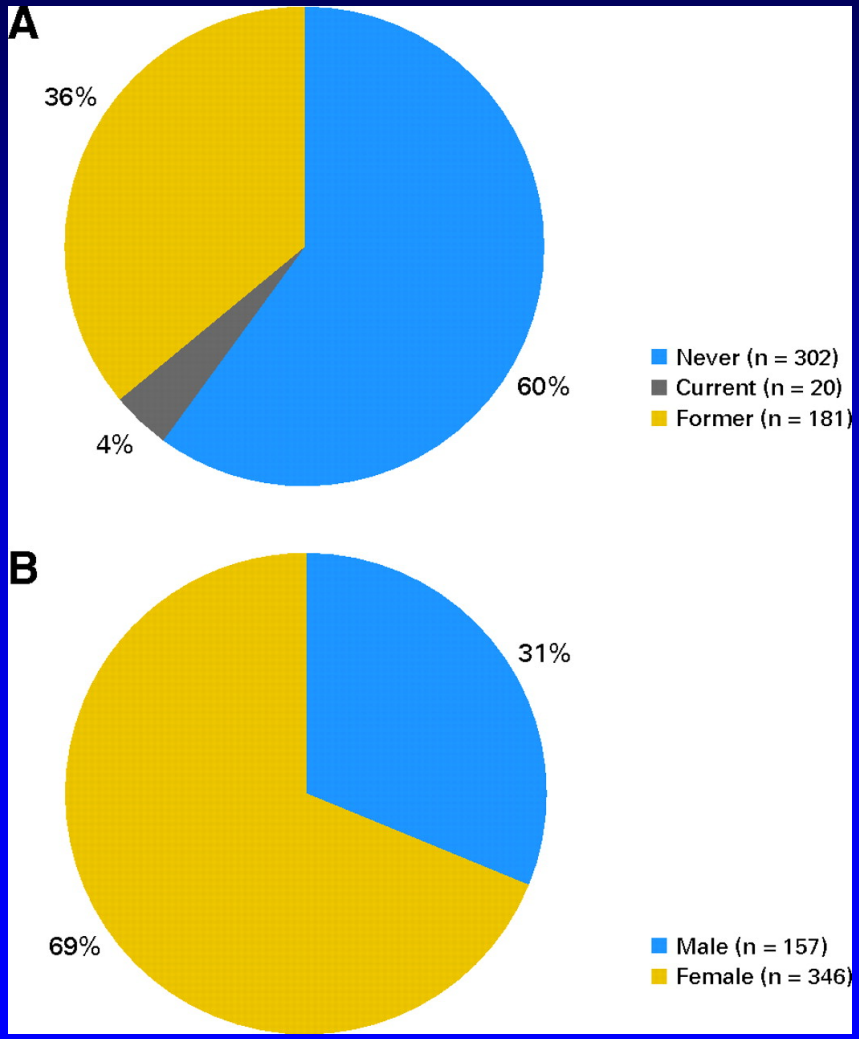
–Never/former light smokers (<15 packs per year) or patients withnonsquamous histology should be tested for EGFR mutation status regardless of PS

–Patients harboring sensitizing EGFR mutations should be treated with EGFR TKIs regardless of the genotype of the sensitizing mutation (del 19 versus L858R in exon 21)

–IHC and FISH for EGFR are not recommended for routine clinical use

–The concomitant presence of T790M resistance mutation shouldnot preclude the use of EGFR TKIs in the first-line setting

ADENOCARCINOMA
EGFR MUTATION BY (A) SMOKING STATUS AND (B) SEX.



40% smokers

D'Angelo et al. JCO 2011

EGFR MUTATION TEST: NONSQUAMOUS ONLY

- US: There were no *EGFR* mutations in 454 squamous carcinomas *Marchetti et al J Clin Oncol 2005*

- Japan: Squamous Ca *EGFR* mutations rate was 3/87 3.4% (possibly adeno squamous) *Miyamae et al Oncology Reports 20111/230*

  Phase III gefitinib vs CT 5/228 2.2% *Maemondo et al N Eng J Med 2010*

- The NCCN recommends erlotinib in the United States as first-line therapy for patients who have an ***EGFR*** mutation and who have advanced, recurrent, or metastatic nonsquamous cell NSCLC.

- Similar to NICE UK and Royal College pathologists report

PLACE OF TKIS IN ADVANCED NSCLC

NSCLC stage IIIB & IV

	EGFR mutated (exon 19 or 21)	EGFR wild type & EGFR mutation status unknown	
		Non-squamous	Squamous
1 L	• TKI # or • (Platinum-based doublet)	Platinum- pemetrexed doublet (+/- bevacizumab)	Platinum-based doublet
M	TKI # (after chemotherapy)	• Erlotinib# (if stable disease) • Bevacizumab • Pemetrexed	Erlotinib # (if stable disease)
2 L	• Docetaxel or • Pemetrexed* or • TKI	• Erlotinib **or • Docetaxel or • Pemetrexed	• Erlotinib** or • Docetaxel

*only in non-squamous NSCLC ** IHC + needed for reimbursement # EGFR mut + test