EGFR and derived treatment strategies

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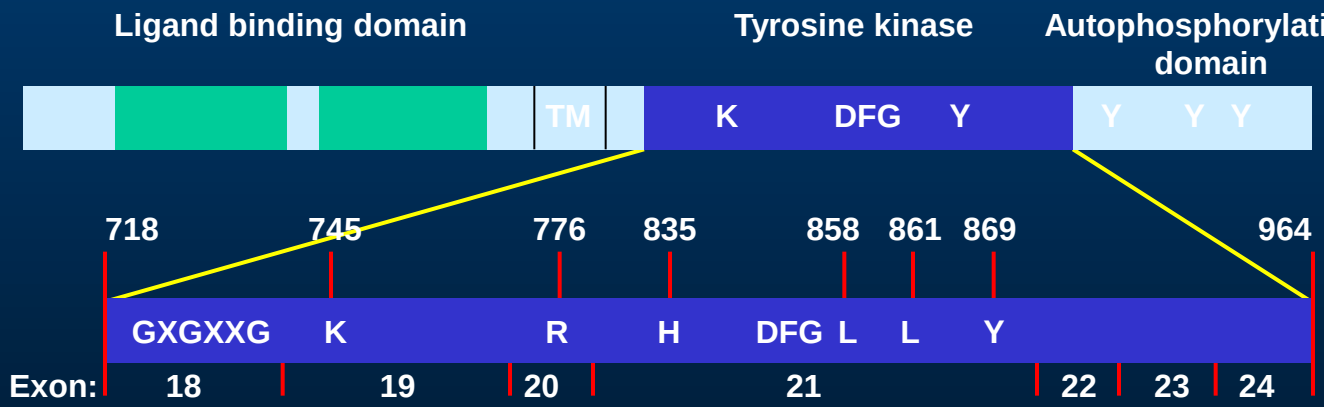
Disclosure statement

- Advisory role for Pfizer, Roche, AstraZeneca, Boehringer-Ingelheim

Presentation outline

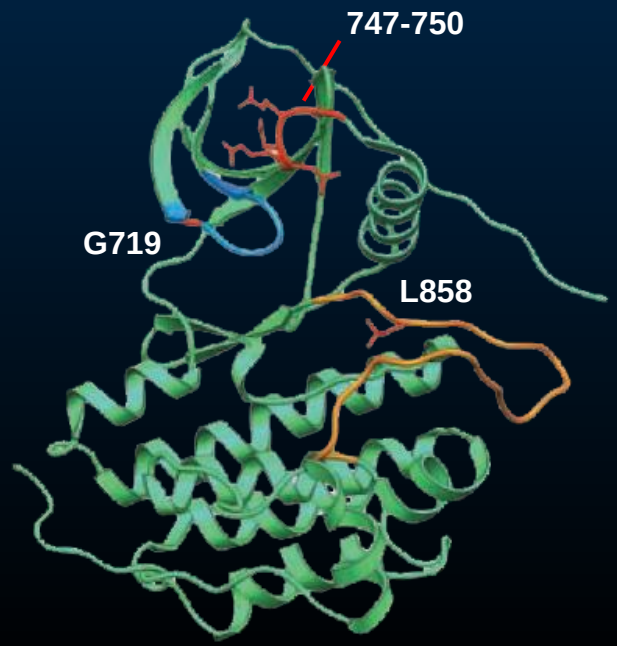
- **EGFR inhibitors in EGFR M+ NSCLC**
- **EGFR inhibitors in EGFR WT NSCLC**

EGFR gene mutations: 2004



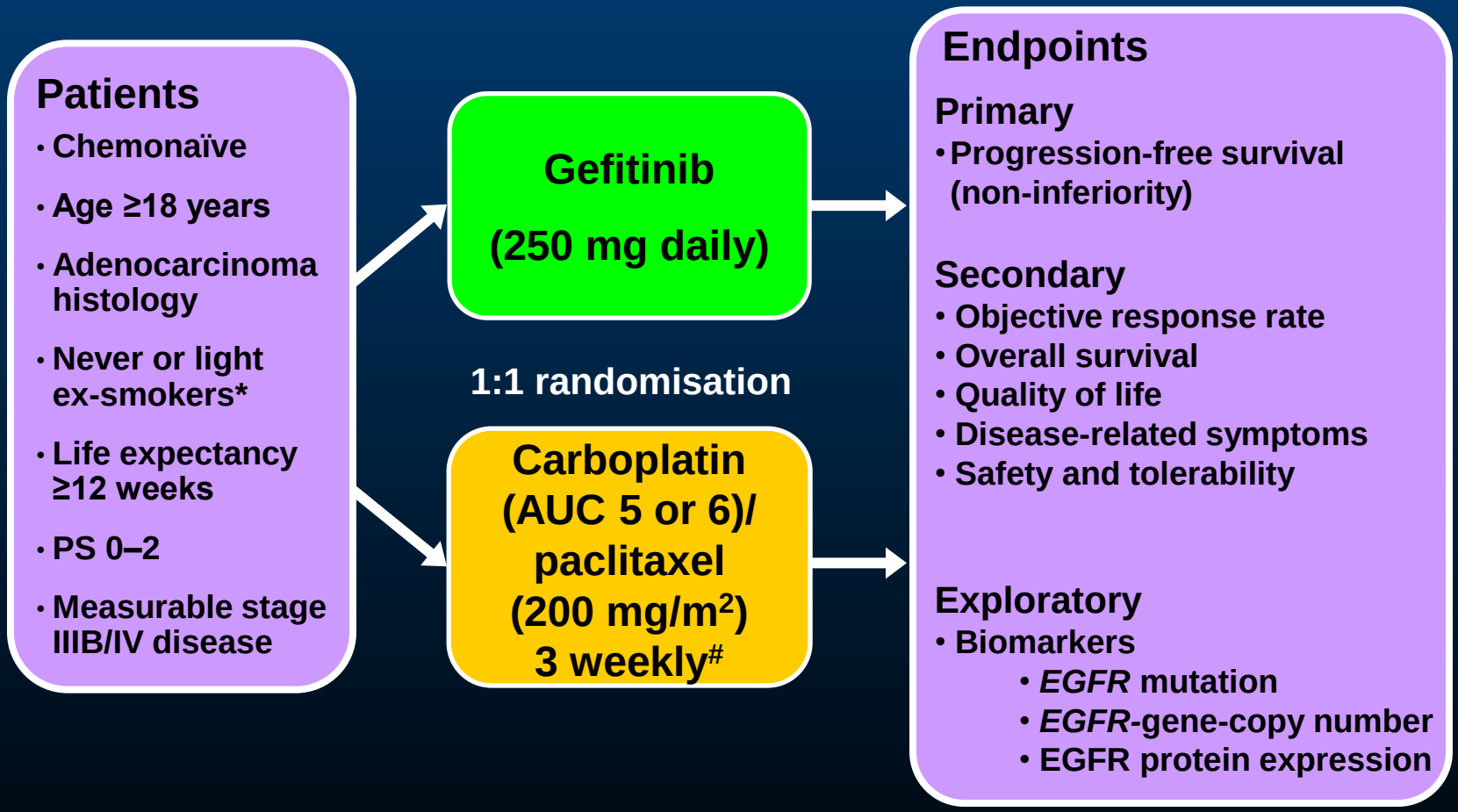
Point mutations

Deletions



Pao W et al., PNAS 2004;101(36):13306-11; Paez J et al., Science 2004;304 (5676): 1497-1500

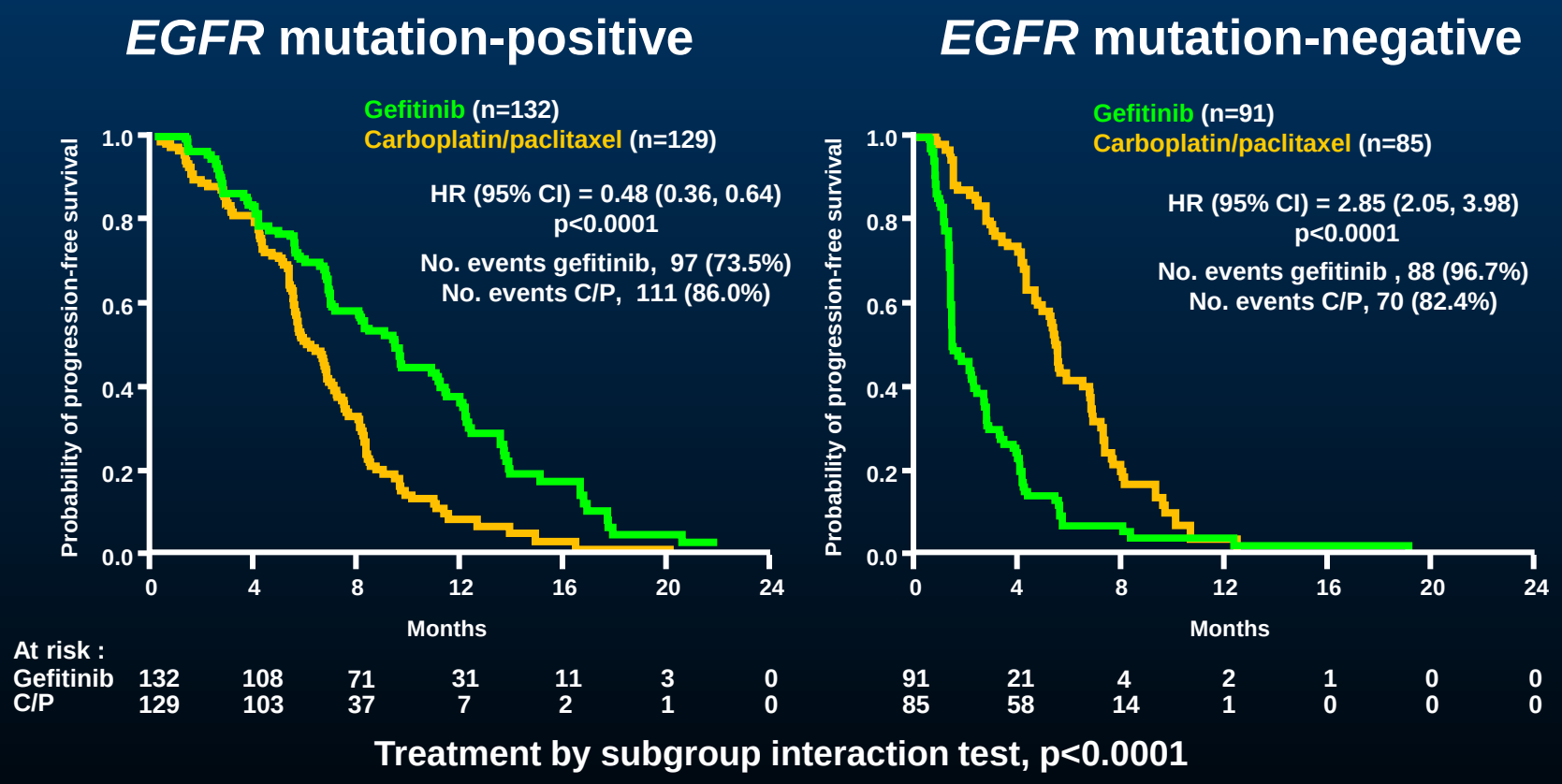
IPASS trial design



* 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 at progression
PS, performance status; EGFR, epidermal growth factor receptor

Mok T et al., N Engl J Med 2009;361(10):947–957

Progression-free survival in *EGFR* mutation-positive and -negative patients

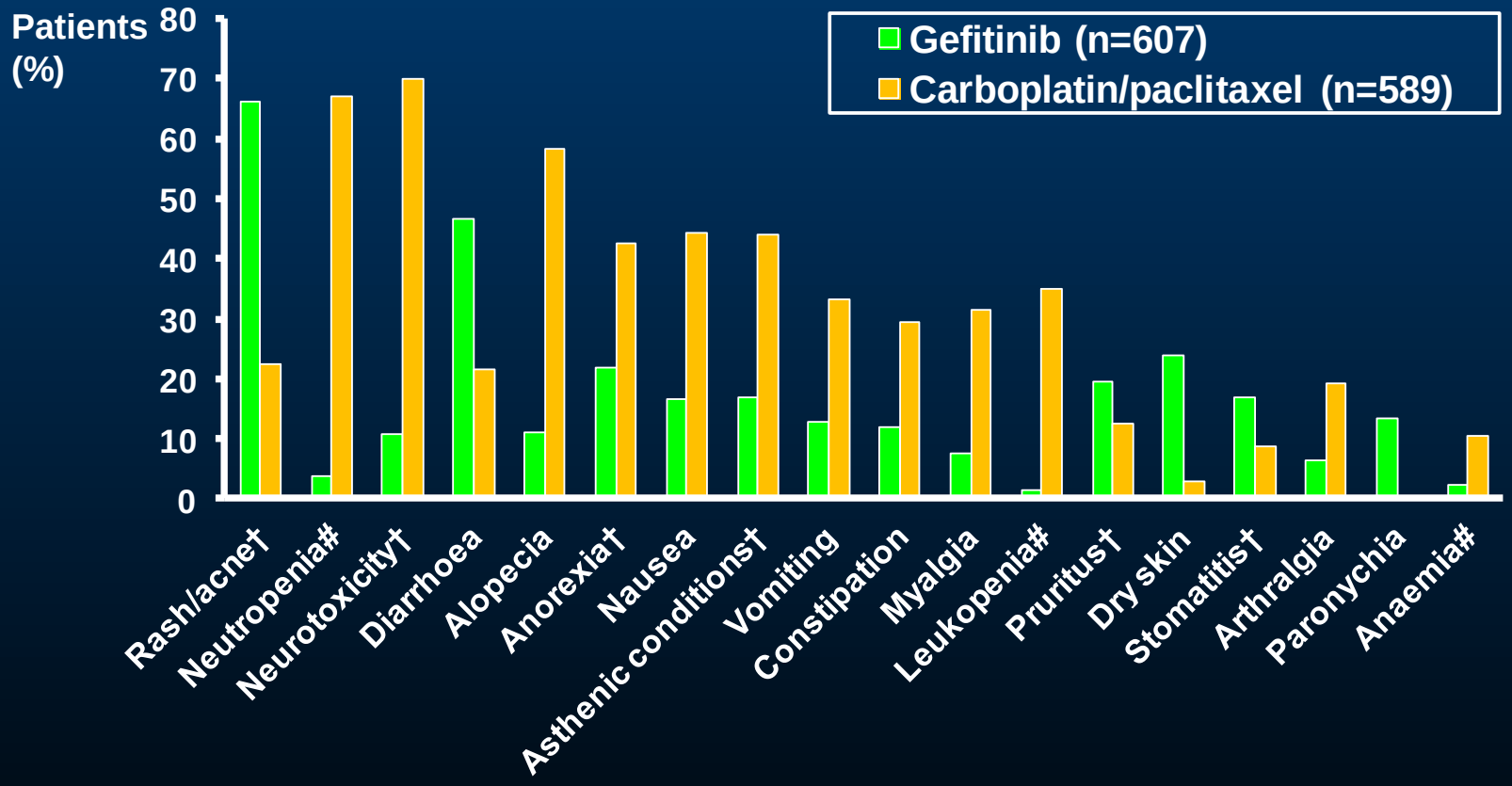


Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

Mok T et al., N Engl J Med 2009;361(10):947–957

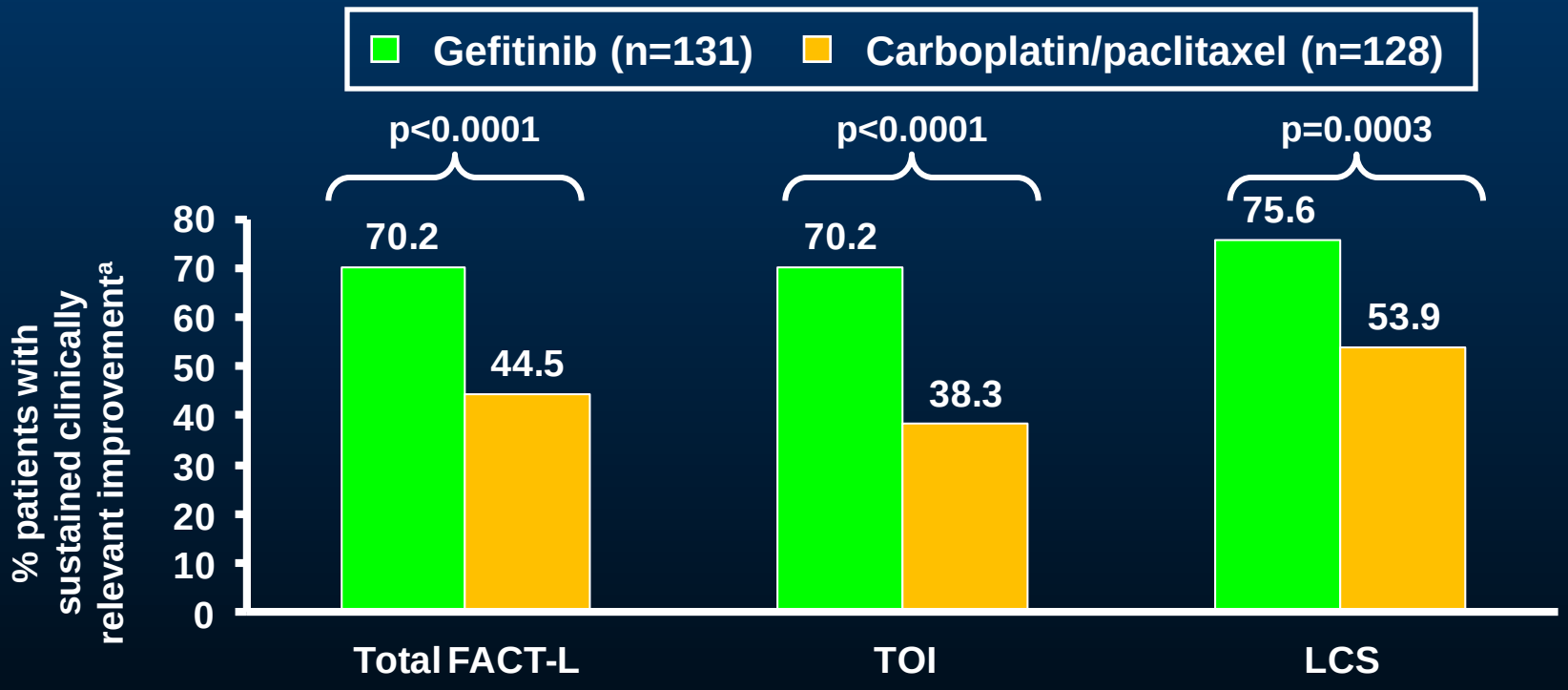
IPASS: most common AEs*



*≥10% on either treatment
#Absolute neutrophil count, white blood cell count, or haemoglobin worsened from baseline to CTC grade 3 / 4; gefitinib n=599, carboplatin/paclitaxel n=577
†Grouped term (sum of several preferred terms)

Mok T et al., N Engl J Med 2009;361(10):947–957

IPASS: post hoc QoL and symptom improvement rates for *EGFR* M+ patients



Evaluable for QoL population; logistic regression model with covariates
[a]6-point improvement (FACT-L and TOI); 2-point improvement (LCS), maintained ≥21 days

Mok T et al., N Engl J Med 2009;361(10):947–957

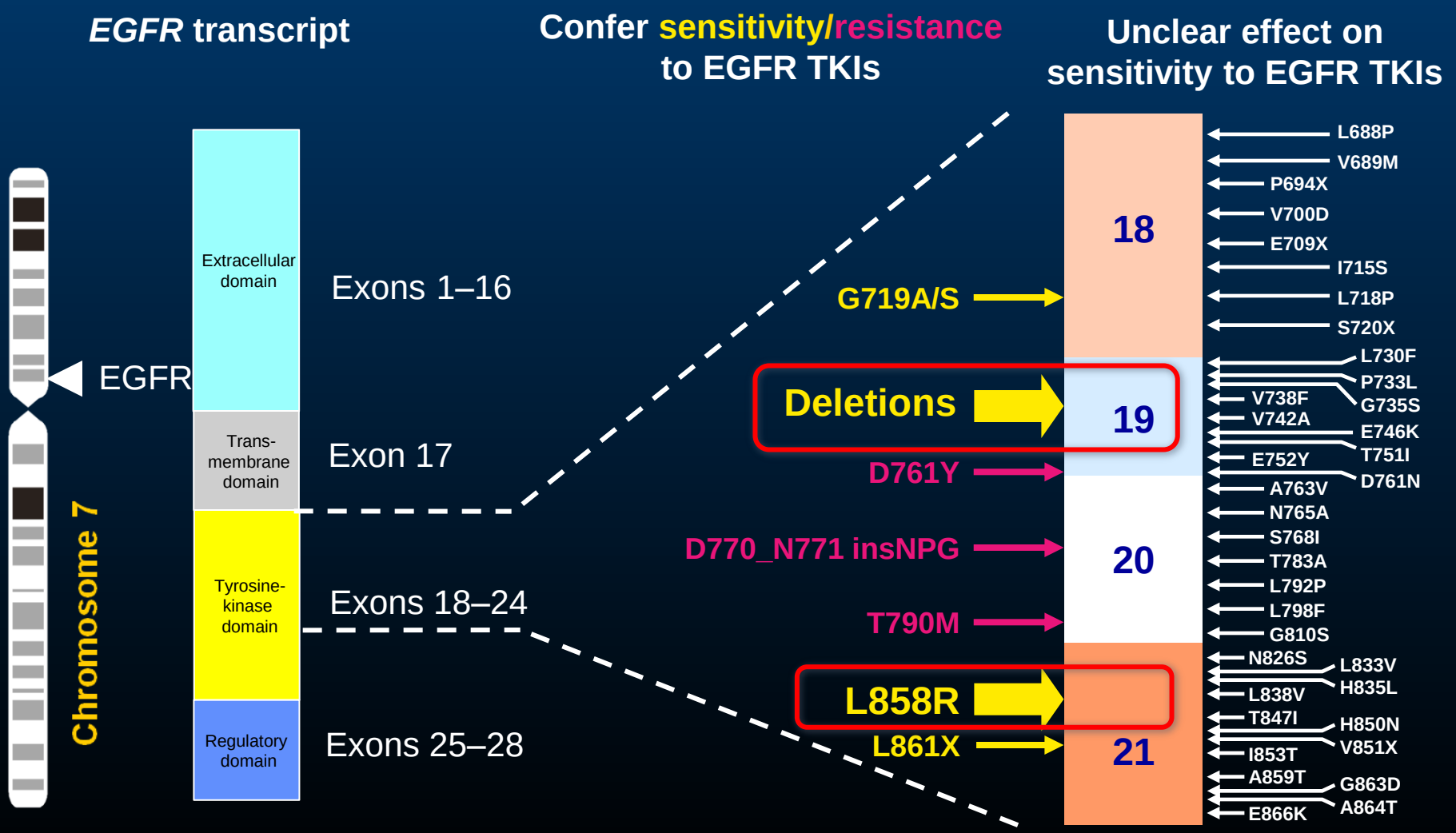
Randomised phase III studies with first-line EGFR inhibitors in *EGFR* M+ NSCLC

	EGFR TKI	Comparator	N (Total)	*EGFR* mutation -positive	Response rate (%)	Progression-free survival (months)	Overall survival (months)
IPASS[1,2]	Gefitinib	Carboplatin/ paclitaxel	1217	261	71 vs 47 p=0.0001	9.5 vs 6.3 HR 0.48 (0.36–0.64)	21.6 vs 21.9 HR 1.0 (0.76–1.33)
First-SIGNAL[3]	Gefitinib	Gemcitabine/ cisplatin	309	42	85 vs 38 p=0.002	8.0 vs 6.3 HR 0.54 (0.27–1.10)	27.2 vs 25.6 HR 1.04 (0.50–2.18)
NEJ002[4]	Gefitinib	Carboplatin/ paclitaxel	224	224	74 vs 31 p<0.001	10.8 vs 5.4 HR 0.30 (0.22–0.41)	30.5 vs 23.6
WJTOG-3405[5]	Gefitinib	Cisplatin/ docetaxel	172	172	62 vs 32 p<0.0001	9.2 vs 6.3 HR 0.5 (0.34–0.71)	30.9 vs NR HR 1.64 (0.75–3.6)
OPTIMAL[6]	Erlotinib	Gemcitabine/ carboplatin	154	154	83 vs 36 p<0.0001	13.1 vs 4.6 HR 0.16 (0.10–0.26)	Not mature
EURTAC[7]	Erlotinib	Chemotherapy	173	173	58 vs 15	9.7 vs 5.2 HR 0.37 (0.25–0.54)	19.3 vs 19.5 HR 1.04 (0.65–1.68)
LUX-LUNG 3[8]	Afatinib	Pemetrexed/ cisplatin	345	345	56 vs 23 p<0.0001	11.1 vs 6.9 HR 0.58 (0.43–0.78)	Not mature

NR = not reported

1. Mok T et al., N Engl J Med 2009;361(10):947–957; 2. Fukuoka M et al., J Clin Oncol 2011; 29(21):2866–2874; 3. Han J-Y et al., J Clin Oncol 2012; 30 (10):1122–128; 4. Maemondo M et al., N Engl J Med 2010;362(25):2380–2388; 5. Mitsudomi T et al., Lancet Oncol 2010;11(2):121–128; 6. Zhou C et al., Lancet Oncol 2011;12(8):735–742; 7. Rosell R et al., Lancet Oncol 2012;13(3):239–246; 8. Yang JC et al., J Clin Oncol 2012;30 (Suppl. 16):LBA 7500

Distribution of mutations in the TK domain of *EGFR* gene



Riely J et al., Clin Cancer Res 2006;12(24):7232-41

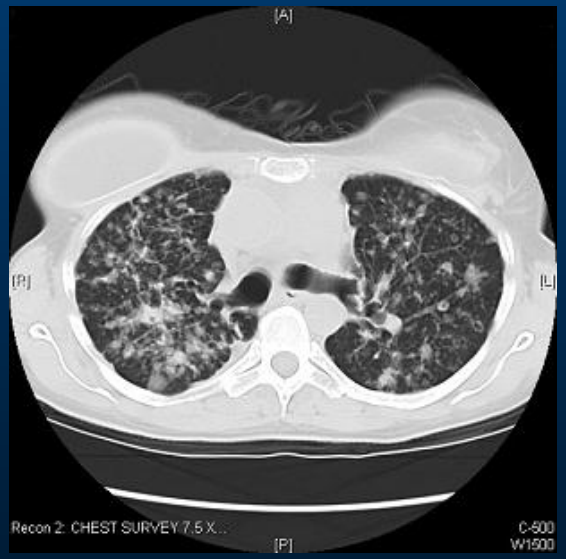
Rare *EGFR* mutations* in Caucasian NSCLC patients (n=10117)

- **Patients tested** — **10117**
- ***EGFR* M+** — **1047 (10%)**
  - **Rare *EGFR* M+** — **102 (10%)**
    - **- Exon 18** — **41**
    - **- Exon 20** — **49**
    - **- Complex** — **12**
- **Median PFS (gefitinib, erlotinib)** — **6 months**

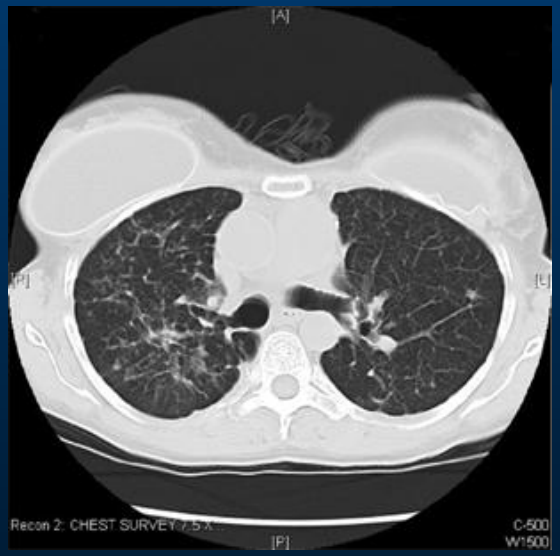
**Various standardised techniques*

Beau-Faller M et al., J Clin Oncol 2012;30 (Suppl 16):LBA 10507

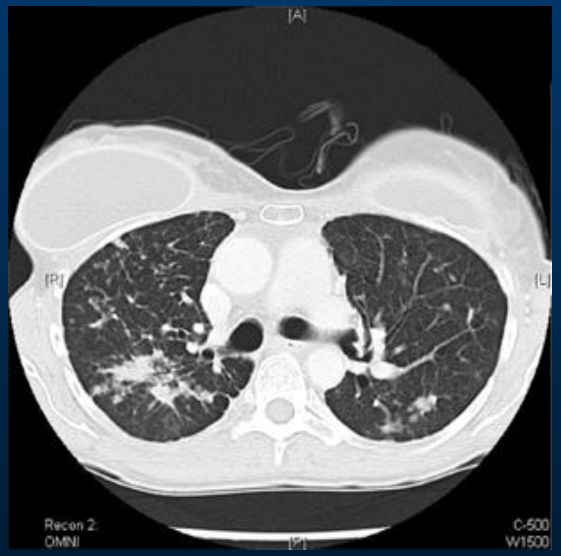
NSCLC M+: EGFR-TKI acquired resistance



Baseline



Tumor regression



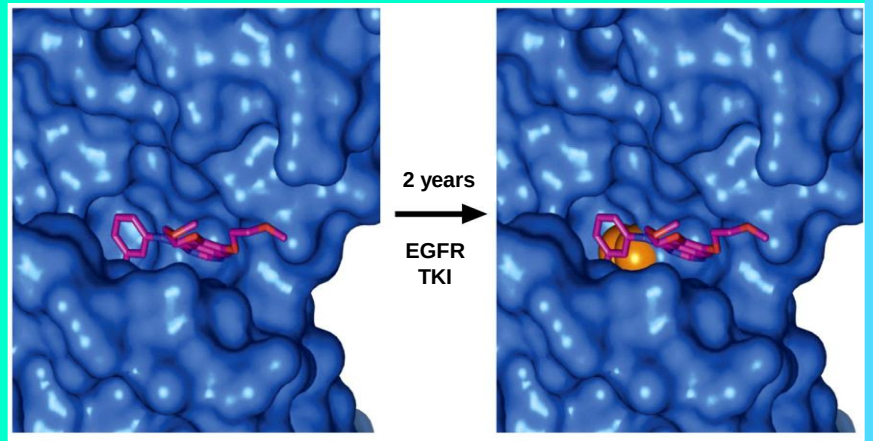
Progression
(median 9 months)

Disease Flare ~25% of patients: Hospitalization and/or death attributable to disease progression after discontinuation of gefitinib or erlotinib and before initiation of study drug

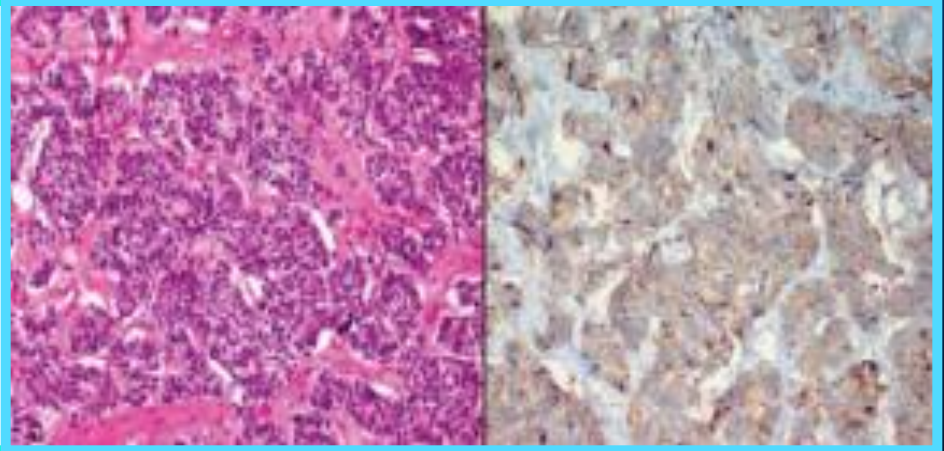
Slide courtesy Prof. F. Cappuzzo

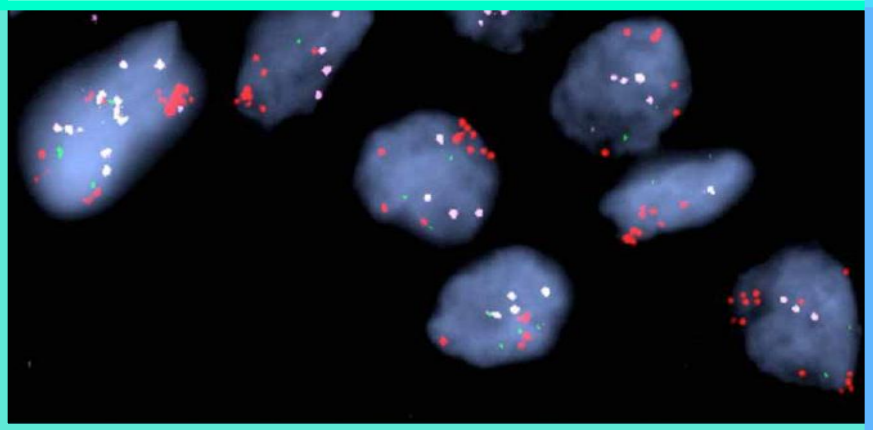
Acquired resistance mechanisms to EGFR TKIs

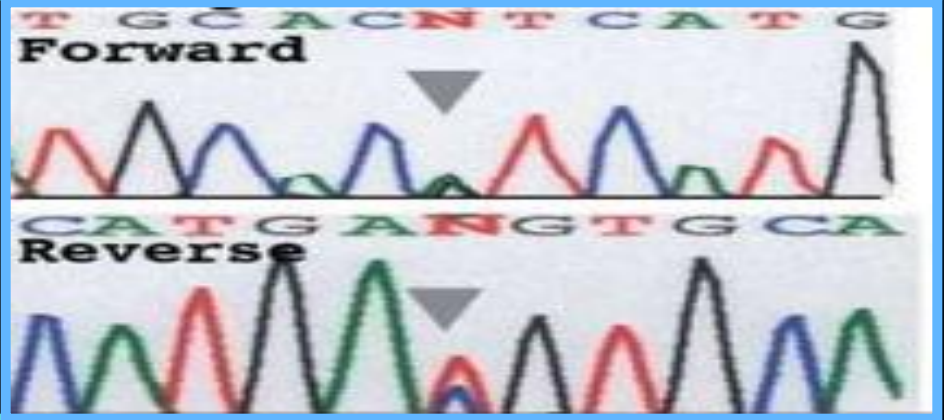
EGFR T790M



SCLC







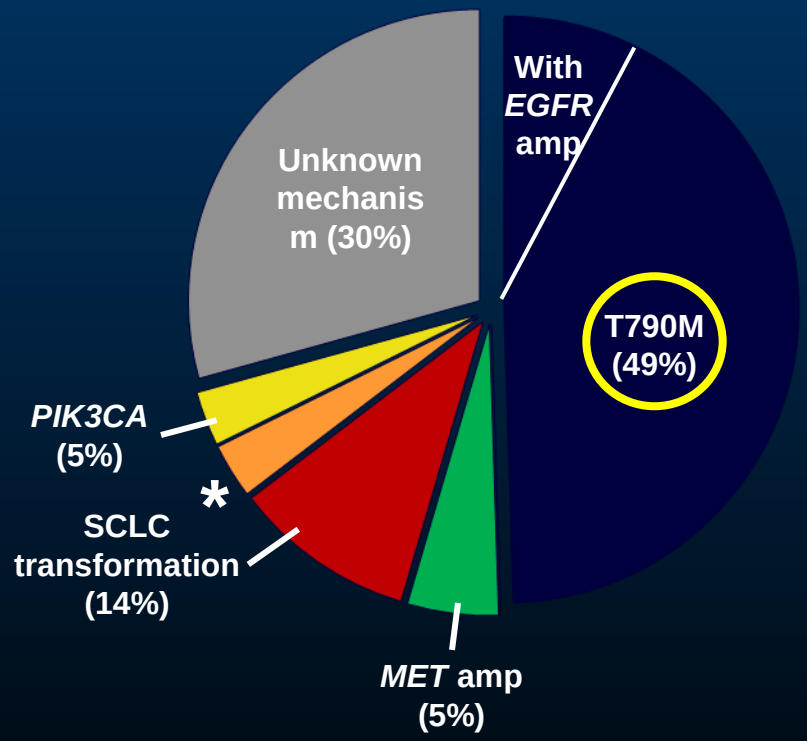
MET

PIK3CA

Kobayashi S et al., N Engl J Med 2005;352(8):786-92; Engelman JA et al., Science 2007;316(5827):1039-1043,

Sequist LV et al., Sci Transl Med 2011;3(75):75ra26

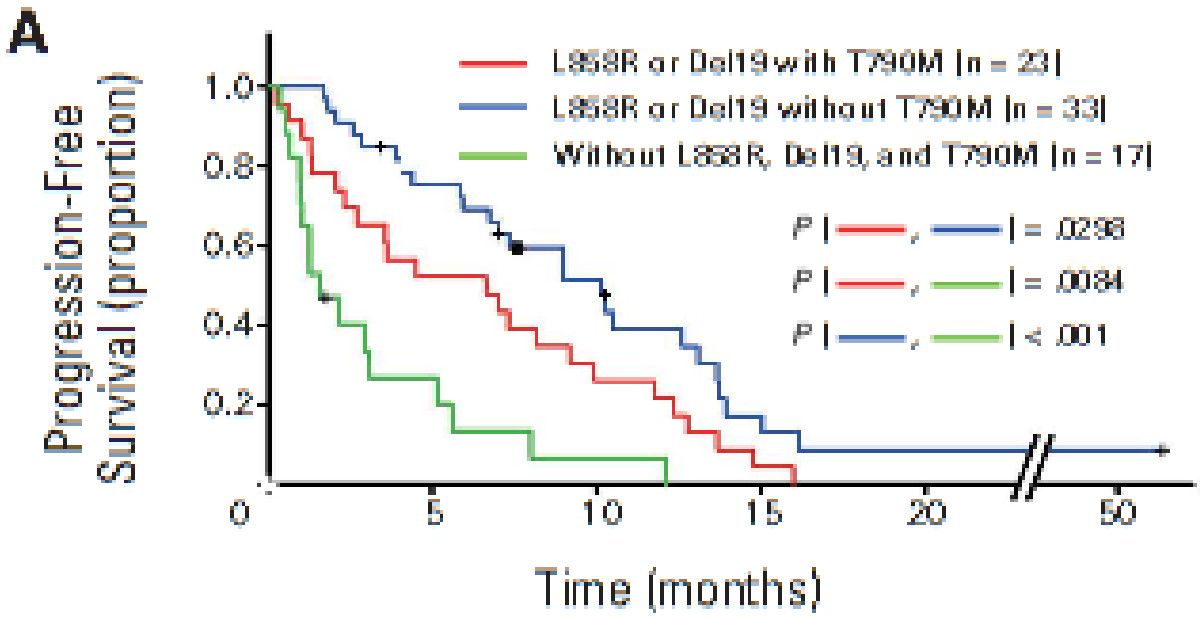
Acquired resistance mechanisms to EGFR TKIs, N=37



*1 pt with *PIK3CA* and SCLC transformation

Adapted from Sequist LV et al., Sci Transl Med 2011;3(75):75ra26

Prognostic significance of *T790M* mutation in pre-treatment biopsy

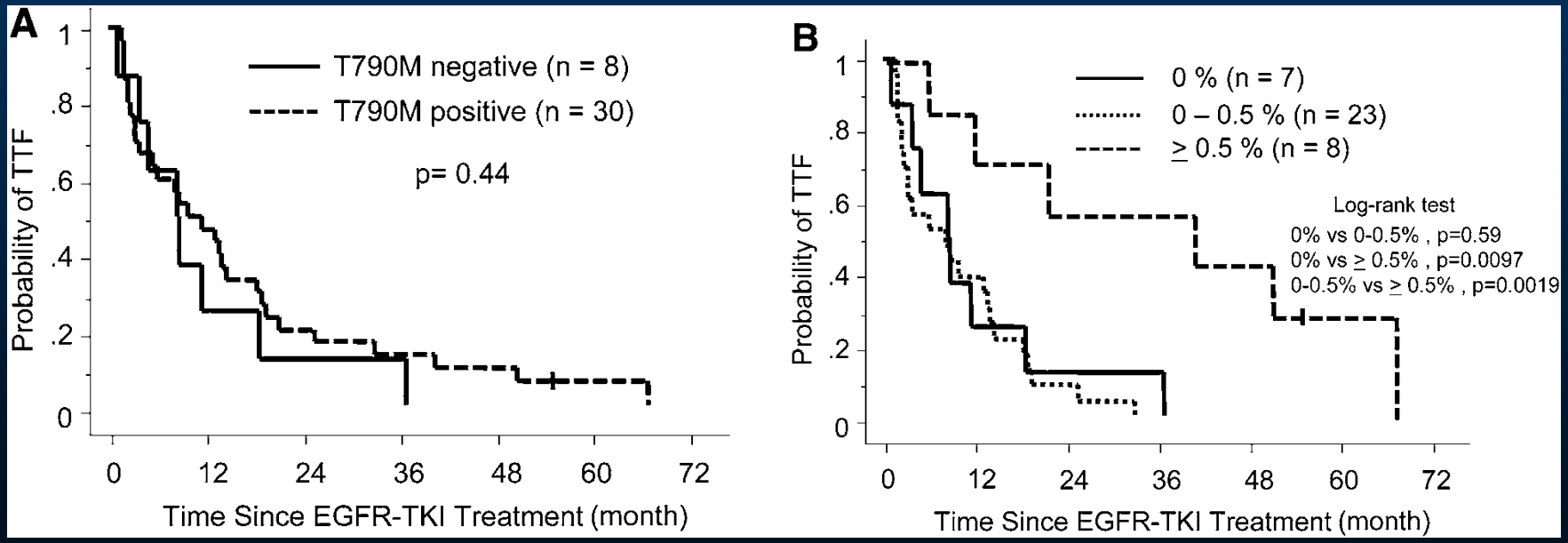


Cox Regression Model

Variable	Hazard Ratio	95% CI	*P*
L858R or Del19 without T790M	1.000		
L858R or Del19 with T790M	1.854	1.044 to 3.292	.035
Without L858R, Del19, and T790M	4.965	2.524 to 9.765	< .001

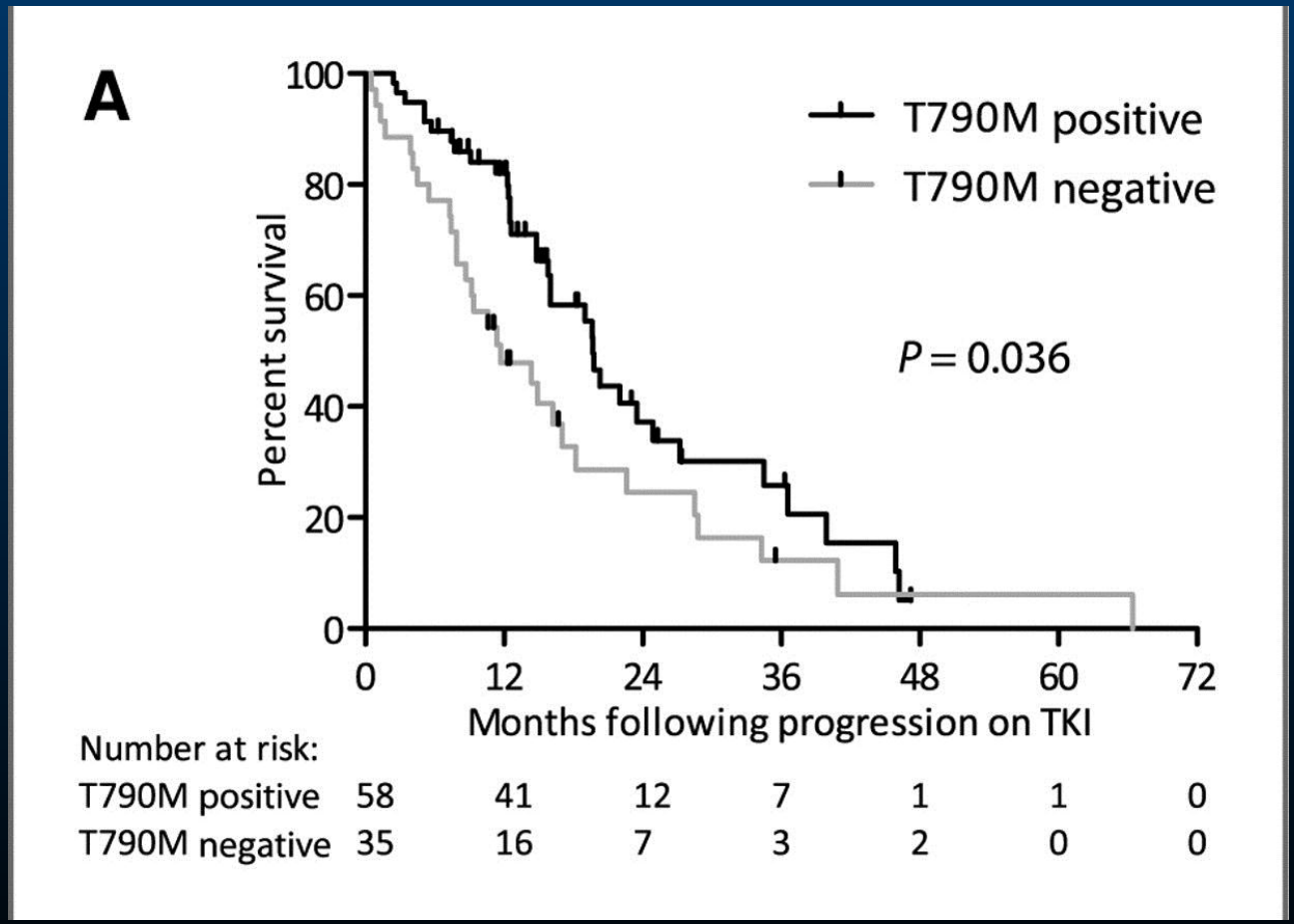
Su KY et al., JCO 2012

Prognostic significance of *T790M* mutation in pre-treatment biopsy



Fujita Y et al., JTO 2012

Prognostic significance of *T790M* mutation after progression was observed



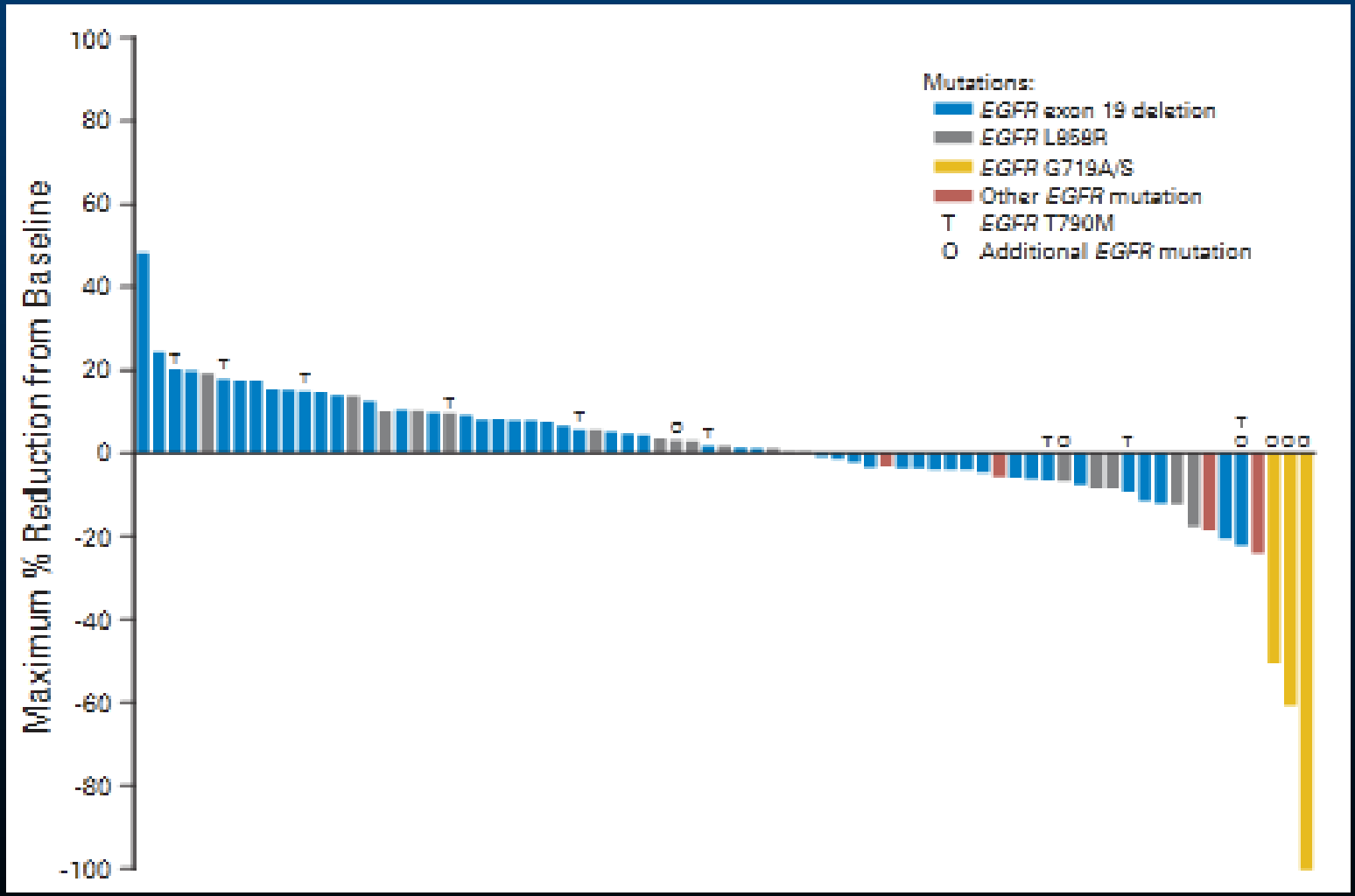
Oxnard et al., JTO 2011

Current treatment options for patients with *EGFR* M+ advanced NSCLC

- **Reversible EGFR inhibitors: gefitinib, erlotinib**
- **Irreversible EGFR inhibitors: afatinib*, dacomitinib*, neratinib***
- **Chemotherapy**
- **Local treatment (surgery, stereotactic RT - selected patients)**

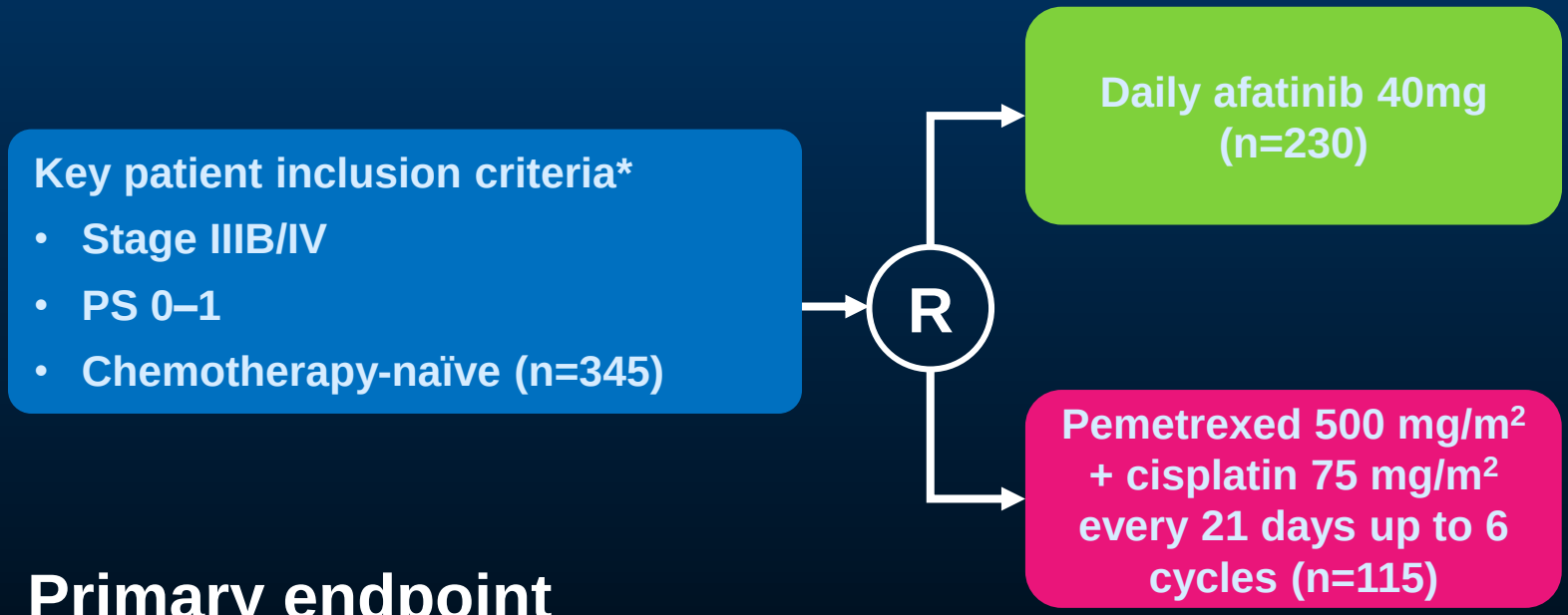
*Investigational

Neratinib (HKI272) in *EGFR* M+ patients



Sequist LV et al., JCO 2010

Afatinib in *EGFR* M+ patients
LUX-Lung 3 Trial



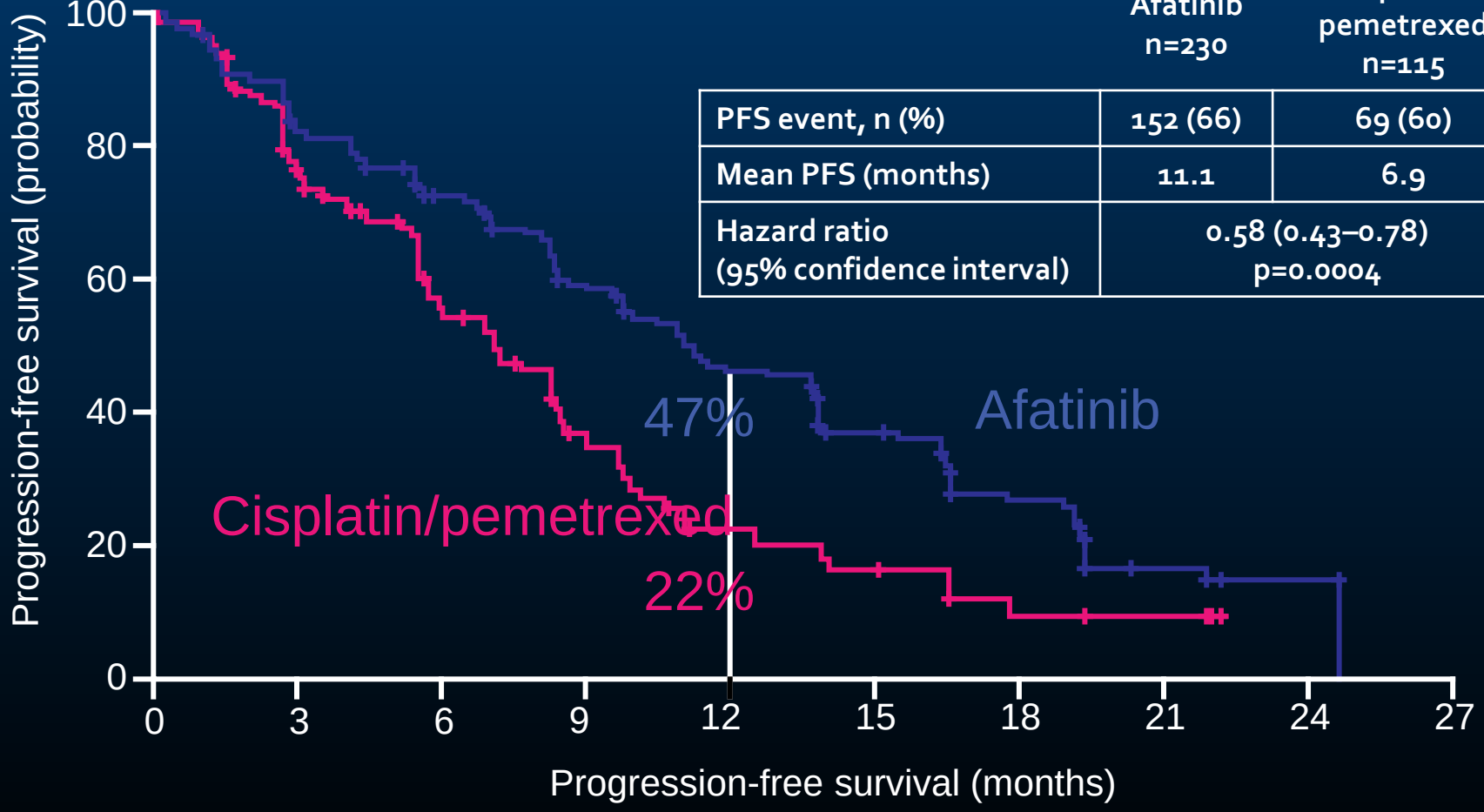
Primary endpoint

- PFS

*Central testing was performed for EGFR mutations (companion diagnostic TheraScreen EGFR RGQ PCR kit)

Yang et al. J Clin Oncol 30, 2012 (suppl; abstr LBA7500)

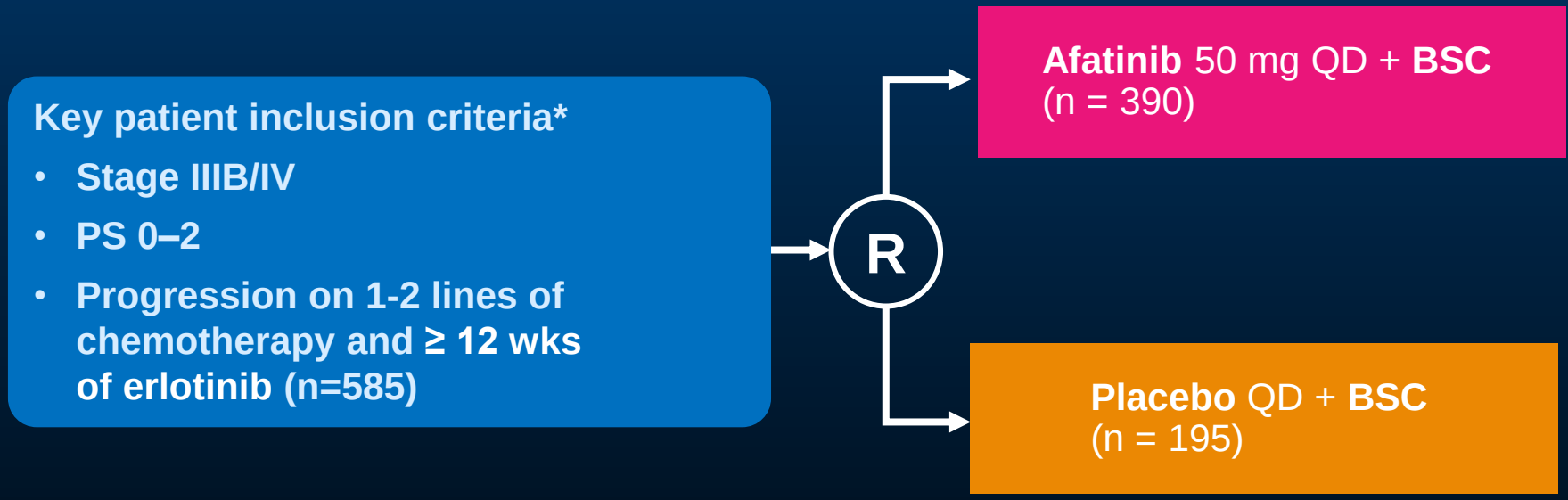
Afatinib in *EGFR* M+ patients
LUX-Lung 3 Trial



	Afatinib n=230	Cisplatin/ pemetrexed n=115
PFS event, n (%)	152 (66)	69 (60)
Mean PFS (months)	11.1	6.9
Hazard ratio (95% confidence interval)	0.58 (0.43–0.78) p=0.0004	

Yang et al. J Clin Oncol 30, 2012 (suppl; abstr LBA7500)

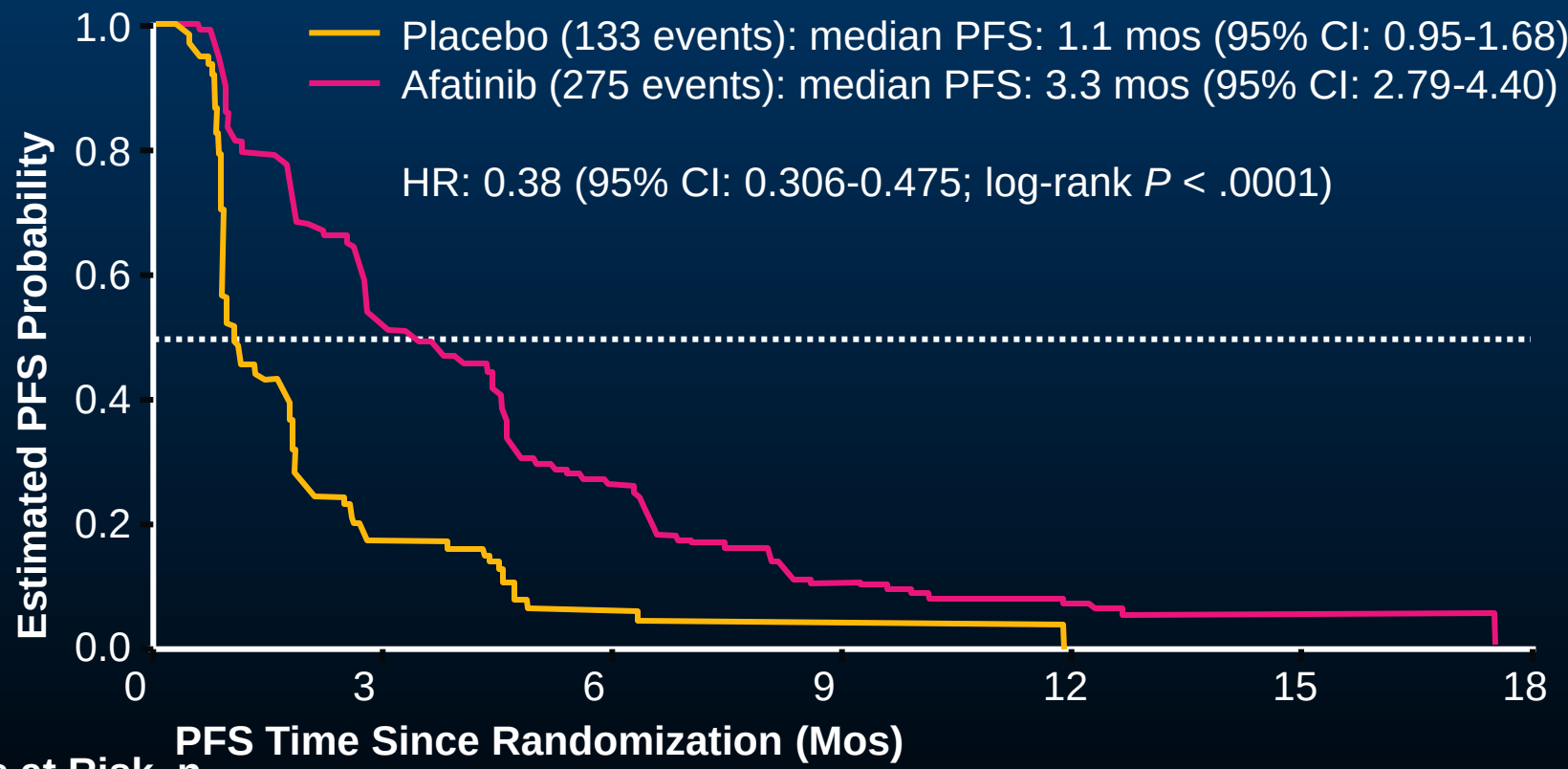
Afatinib in *EGFR* TKI pretreated NSCLC LUX-Lung 1 Trial



- **Primary endpoint: OS**
- **Secondary endpoints: PFS, response, QoL, safety**

Miller VA et al., Lancet Oncology 2012

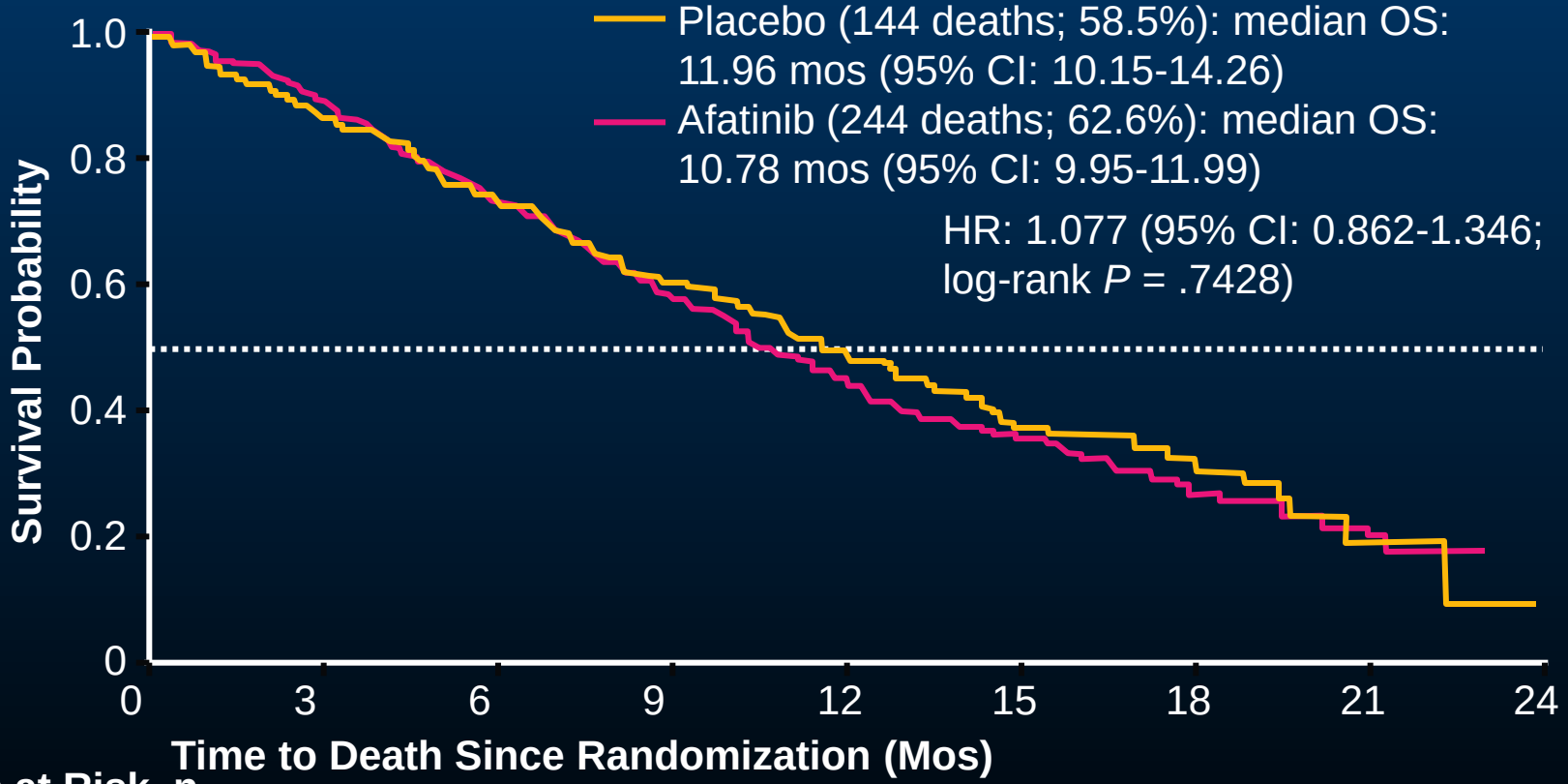
Afatinib in *EGFR* TKI pretreated NSCLC LUX-Lung 1 Trial



Pts at Risk, n						
Placebo	195	15	4	2		
Afatinib	390	152	65	16	9	3

Miller VA et al., Lancet Oncology 2012

Afatinib in *EGFR* TKI pretreated NSCLC LUX-Lung 1 Trial



Pts at Risk, n

Placebo	195	169	142	112	65	33	18	5
Afatinib	390	344	283	217	122	69	32	12

Miller VA et al., Lancet Oncology 2012

Afatinib + Cetuximab in acquired EGFR TKI resistance: preclinical data

AFATINIB

C/L858R

4/4 CRs

C/T790M

2/2 PDs

C/L858+T790M

6/7 SDs
1/7 PD

Regales et al., J Clin Invest. 2009

Afatinib + Cetuximab in acquired EGFR TKI resistance: preclinical data

CETUXIMAB

C/L858R

5/5 CRs

C/T790M

2/2 SDs

C/L858+T790M

2/7 PRs
5/7 SDs

Regales et al., J Clin Invest. 2009

Afatinib + Cetuximab in acquired EGFR TKI resistance: preclinical data

CETUXIMAB + AFATINIB

C/T790M

3/3 CRs

C/L858+T790M

7/8 CRs
1/8 PR

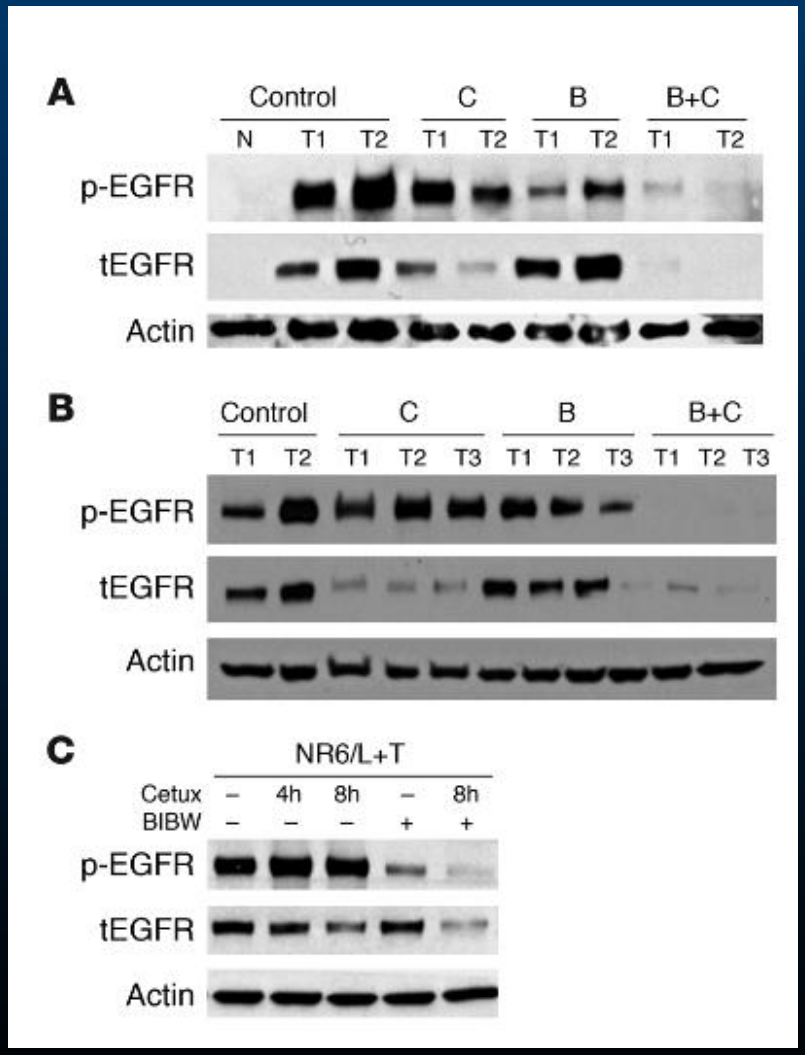
Regales et al., J Clin Invest. 2009

Afatinib + Cetuximab in acquired EGFR TKI resistance: preclinical data

C/L858R +T790M cells

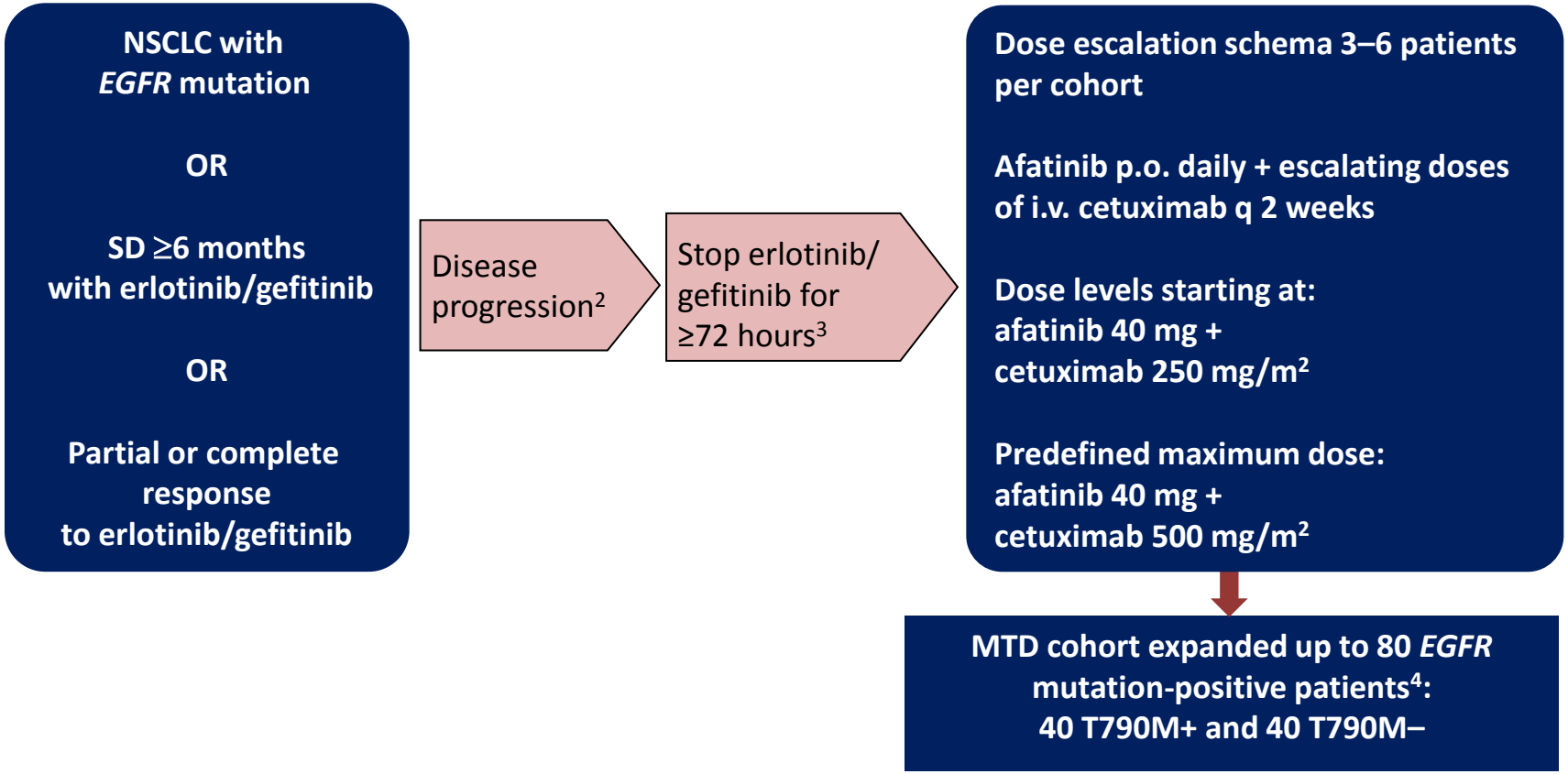
H1975 cells

NR6 fibroblasts transfected with EGFR L858R+T790M



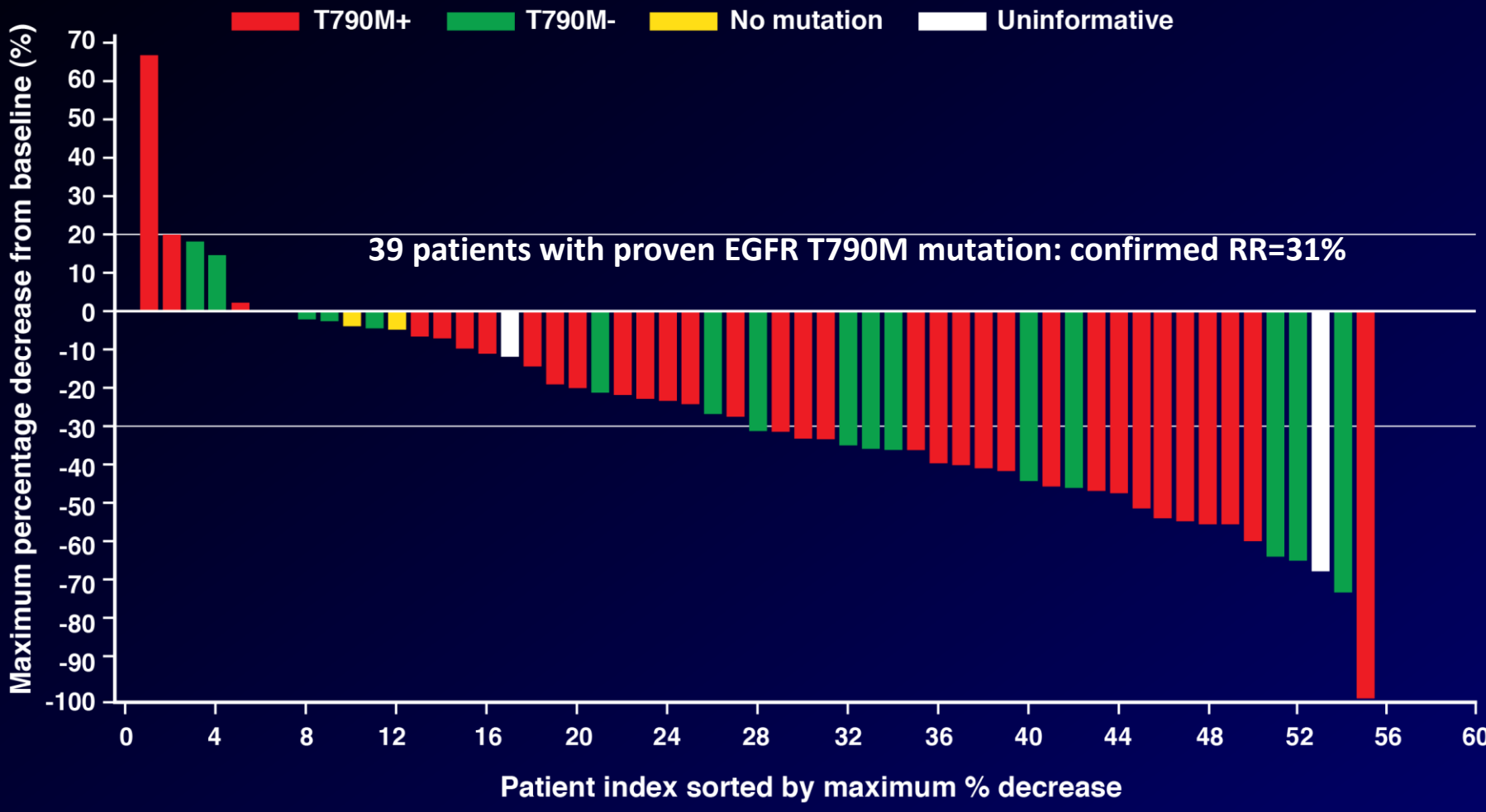
Regales et al., J Clin Invest. 2009

Afatinib + cetuximab for metastatic NSCLC with resistance to EGFR TKI: Study Design



Yanjigian et al., presented at ASCO 2011

Afatinib + cetuximab: Tumor Regression by T790M Mutation Status at Recommended Dose



Yanjigian et al., presented at ASCO 2011

Dacomitinib in *EGFR* M+ patients Phase II data, ASCO 2012

- **Study design**
  - **Open-label phase II study: Dacomitinib once daily continuously at 45 mg or 30 mg with the option to escalate to 45 mg**
  - **Primary endpoint: PFS rate at 4 months**
- **Results**
  - **47 pts had *EGFR* mutation in exons 19 (n=25) or 21 (n=21), 32 were female and 26 Asian**
  - **Preliminary PFS at 4M was 96% (95% CI: 84–99)**
  - **Preliminary PFS rate was 77% at 1 year and preliminary median PFS was 17 months**
  - **34/46 evaluable pts with *EGFR* exon 19 or 21 mutations had a PR (PR rate = 74%; 95% CI: 59–86)**

Kris et al. J Clin Oncol 30, 2012 (suppl; abstr 7530)

Irreversible pan-EGFR inhibitors
Conclusions

- Promising activity as monotherapy (except neratinib) and in combination with cetuximab
- No direct comparison data to reversible EGFR TKIs
- In vivo mechanisms of resistance should be studied

Local treatment strategies for advanced EGFR M+ NSCLC

- **Include SBRT, conventional RT or surgery in very selected patients**
- **Theoretically justified by relatively indolent course of the disease**
- **Retrospective data suggest favorable outcomes but no prospective data availabe**

Weickhardt A et al. ASCO 2012

Presentation outline

- EGFR inhibitors
  in EGFR M+ NSCLC

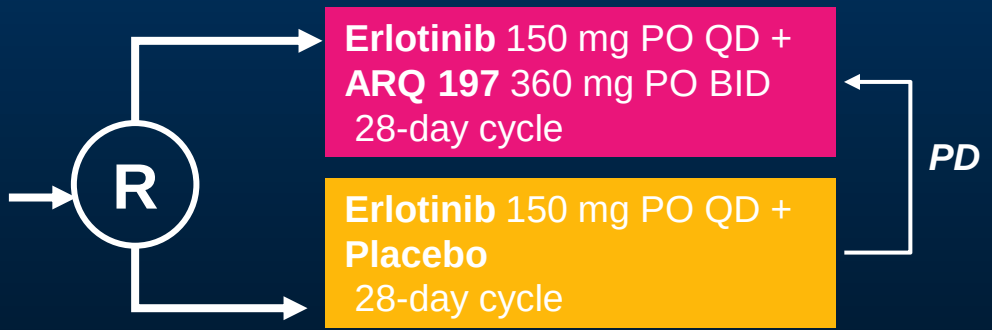
- EGFR inhibitors
  in EGFR WT NSCLC

Combined MET/EGFR inhibition: Tivantinib (ARQ-197) + Erlotinib

N=167

NSCLC

- Inoperable locally adv/metastatic disease
- ≥ 1 prior chemo (no prior EGFR TKI)



Endpoints

- Primary: PFS
- Secondary: ORR, OS
- Subset analyses
- Crossover: ORR

33 sites in 6 countries

Study accrual over 11 mos (10/08-9/09)

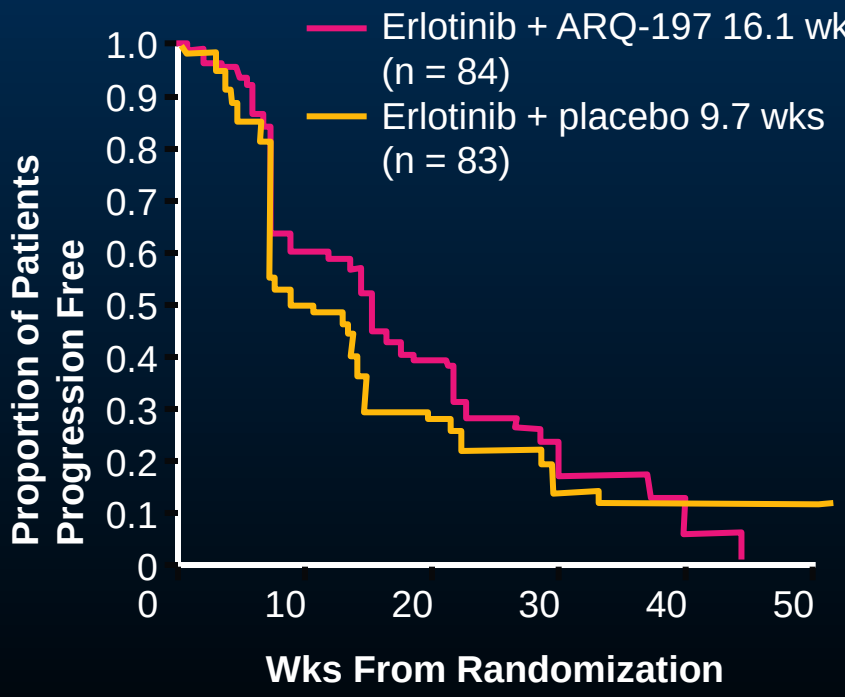
Stratified by prognostic factors including sex, age, smoking, histology, performance status, previous therapy and best response, and geography

Schiller JH, et al. ASCO 2010. Abstract LBA7502.

Combined MET/EGFR inhibition: Tivantinib (ARQ-197) + Erlotinib

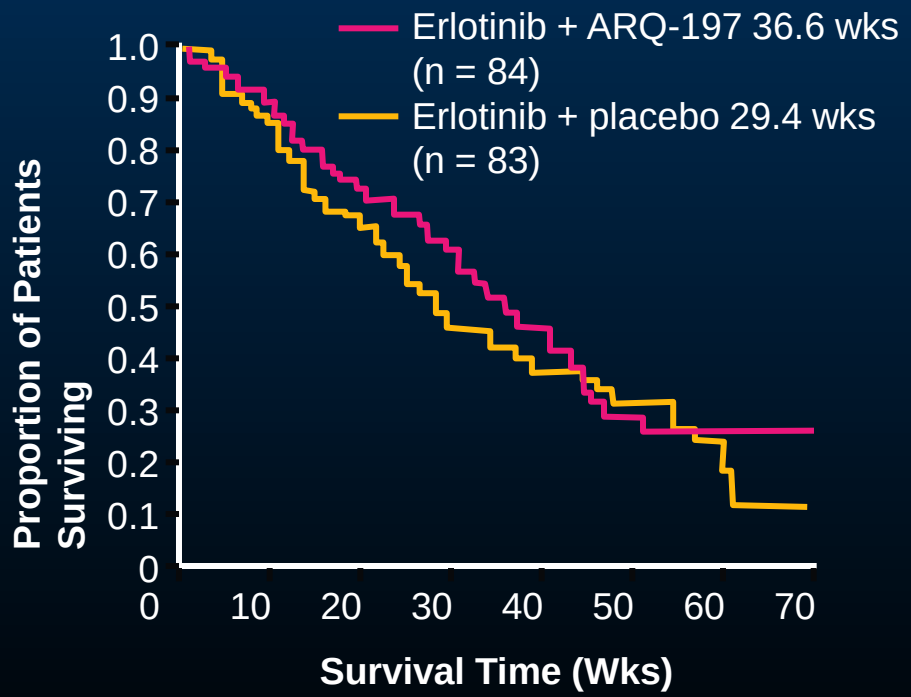
PFS (ITT Population)

HR: 0.81 (95% CI: 0.57-1.15; *P* = .24)
Adjusted HR: 0.68 (95% CI: 0.47-0.98; *P* < .05)



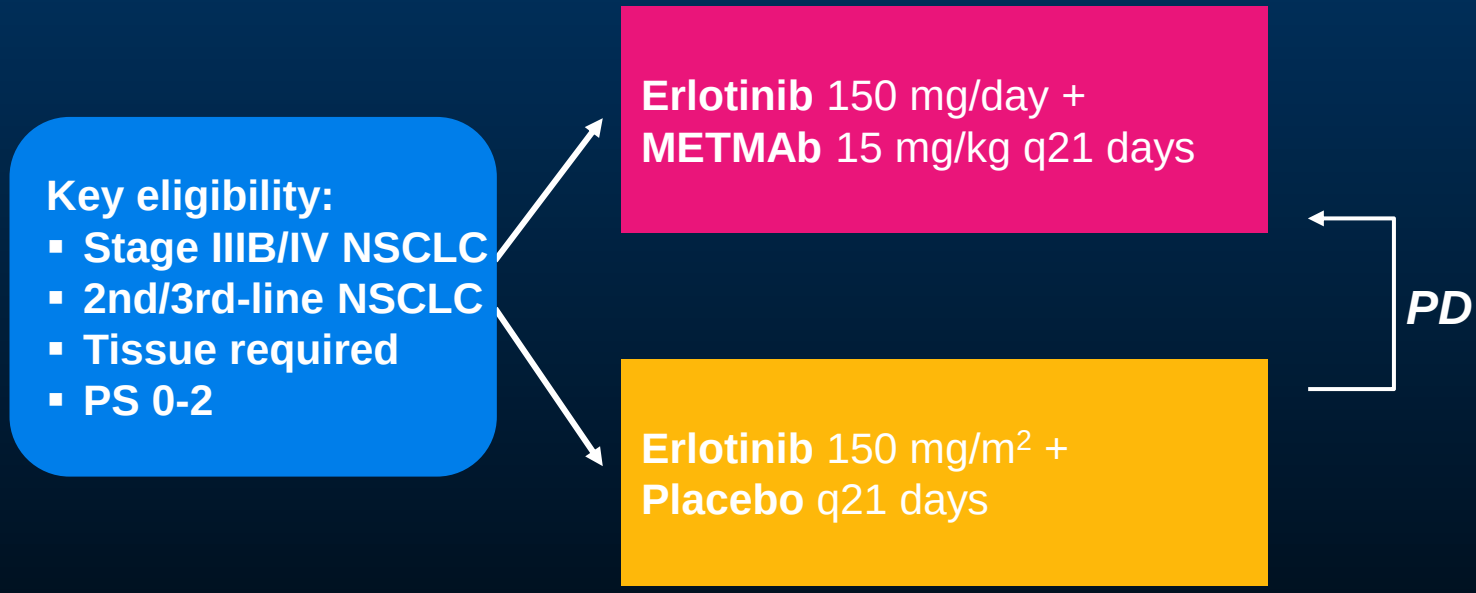
OS (ITT Population)

HR: 0.81 (95% CI: 0.57-1.15; *P* = .24)
Adjusted HR: 0.68 (95% CI: 0.47-0.98; *P* = .52*)



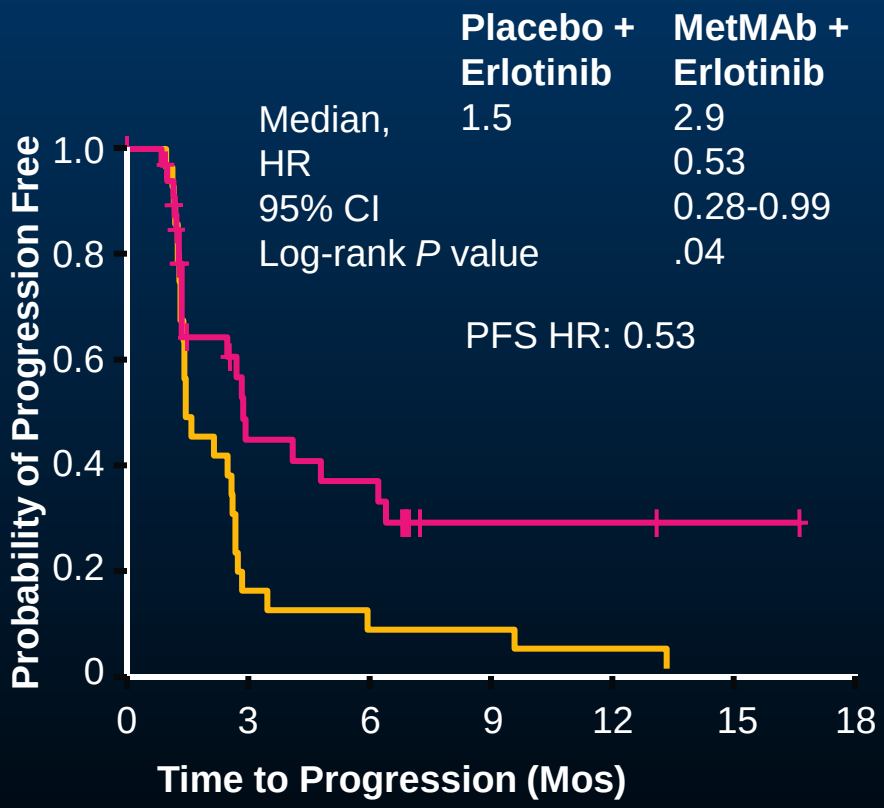
Schiller JH, et al. ASCO 2010. Abstract LBA7502.

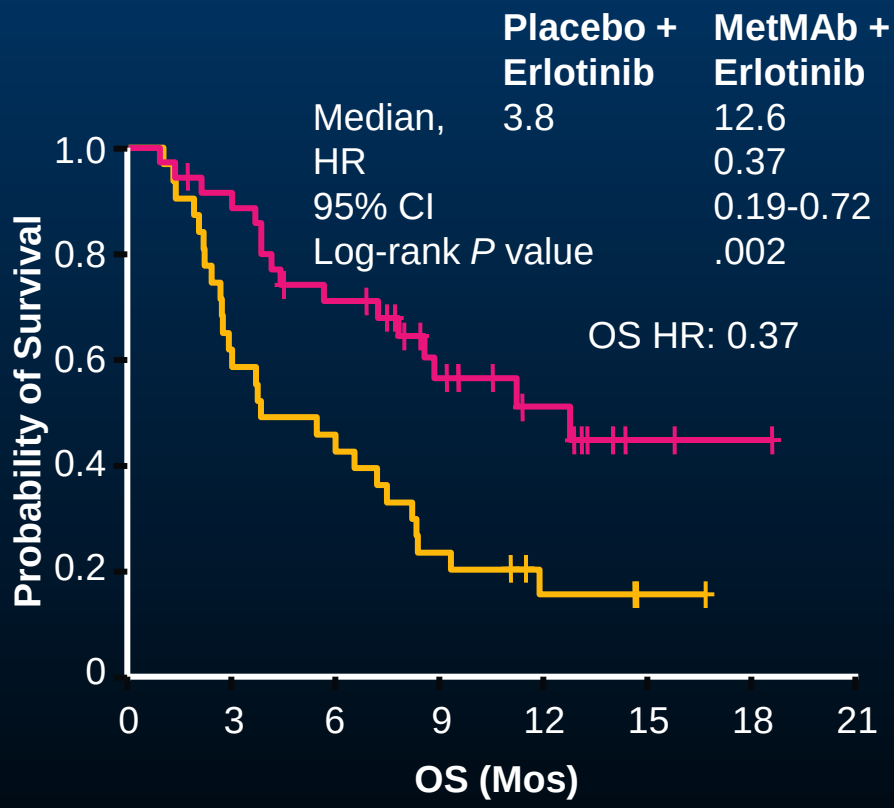
Combined MET/EGFR inhibition: METMAb + Erlotinib phase II Trial



Spigel DR, et al. ASCO 2011. Abstract 7505.

Combined MET/EGFR inhibition: METMAb + Erlotinib; MET IHC+ tumors





Spigel DR, et al. ASCO 2011. Abstract 7505.

Dacomitinib in pretreated NSCLC
phase III trials

- BR.26 (NCIC):
  A double-blind, placebo-controlled randomized trial
  - patients with advanced NSCLC with varying histologies and molecular subtypes, after at least one chemotherapy regimen and erlotinib or gefitinib

- ARCHER 1009: A randomized, double-blind, multicenter trial evaluating dacomitinib versus erlotinib
  - patients with advanced NSCLC following at least one prior chemotherapy

Future perspectives

- **EGFR M+ NSCLC is now recognized as biologically distinct entity with research efforts to overcome resistance mechanisms**

- **Several promising clinical trails with EGFR inhibitors are being conducted in patients with EGFR WT tumors**