Biomarkers of Response to EGFR-TKIs EORTC-NCI-ASCO Meeting on Molecular Markers in Cancer

November 17, 2007

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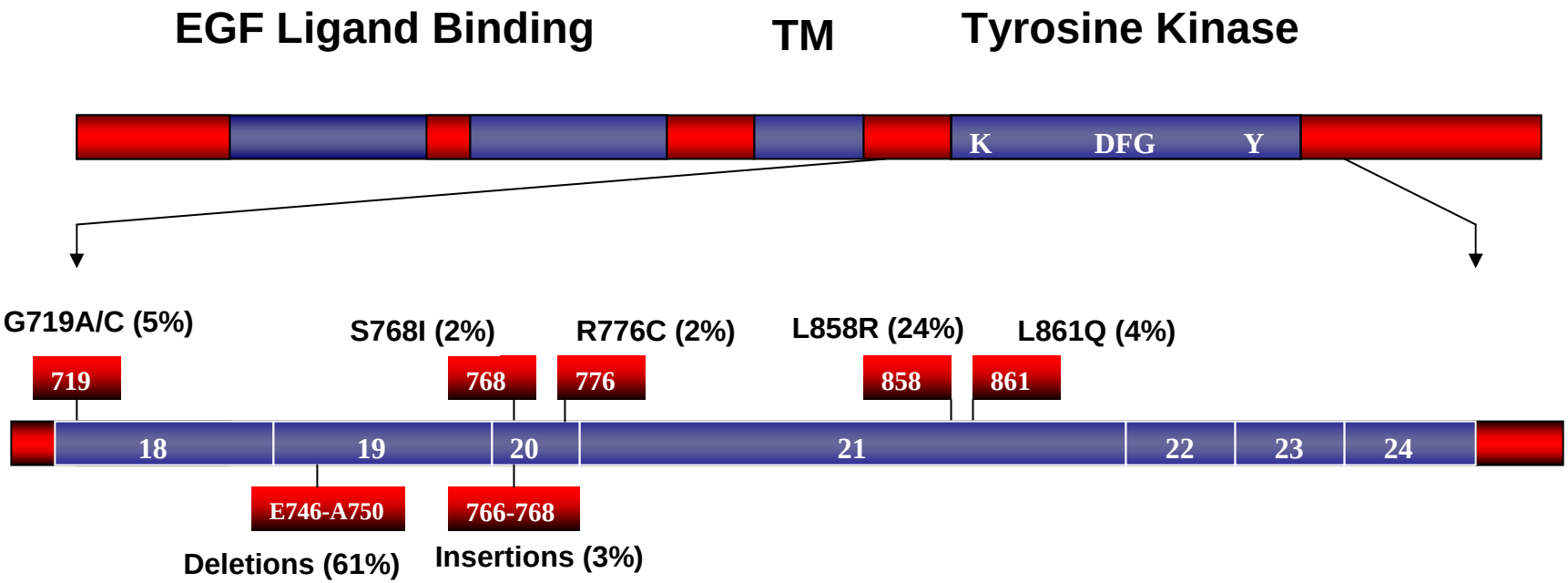
Biomarkers of Response to EGFR-TKIs

- **Biomarkers for Response to EGFR-TKIs**
- **Application of Biomarkers of Response to EGFR-TKIs in Retrospective Studies**
- **Application of Biomarkers of Response to EGFR-TKIs in Prospective Studies**

Mutations in EGFR are in exons 18-21 of the TK domain



Epidermal Growth Factor Receptor Assessed by FISH

1) Disomy (2 copies in >90% of cells)
2) Low trisomy (2 copies in 40% of cells, 3 copies in 10%–40% of the cells, 4 copies in <10% of cells)
3) High trisomy (2 copies in 40% of cells, 3 copies in 40% of cells, 4 copies in <10% of cells)

Cappuzzo et al JNCI 97:643, 2005

Epidermal Growth Factor Receptor Assessed by FISH

4) Low polysomy (4 copies in 10%–40% of cells)
5) High polysomy (4 copies in 40% of cells); and
6) Gene amplification (defined by presence of tight EGFR gene clusters and a ratio of EGFR gene to chromosome of 2 or 15 copies of EGFR per cell in 10% of analyzed cells

Cappuzzo et al JNCI 97:643, 2005

Epidermal Growth Factor Receptor Assessed by IHC

- **Dako kits (DakoCytomation)**
- **Positivity was defined as more than 10 percent of cells with membranous staining at any intensity for EGFR**

Shepherd et al. NEJM 353:123, 2005

Epidermal Growth Factor Receptor Assessed by IHC

0 = no appreciable staining in the tumor cells

1 = barely detectable staining in the cytoplasm and/or nucleus compared with the stromal elements

2 = readily appreciable brown staining distinctly marking the tumor cell cytoplasm and/or nucleus

3 = dark brown staining in tumor cells obscuring the cytoplasm and/or nucleus

4 = very strong staining of nucleus and/or cytoplasm.

The total score was calculated by multiplying the intensity score and the fraction score producing a total range of 0–400.

Cappuzzo et al JNCI 97:643, 2005

Application of Biomarkers of Response to EGFR-TKIs in Retrospective Studies

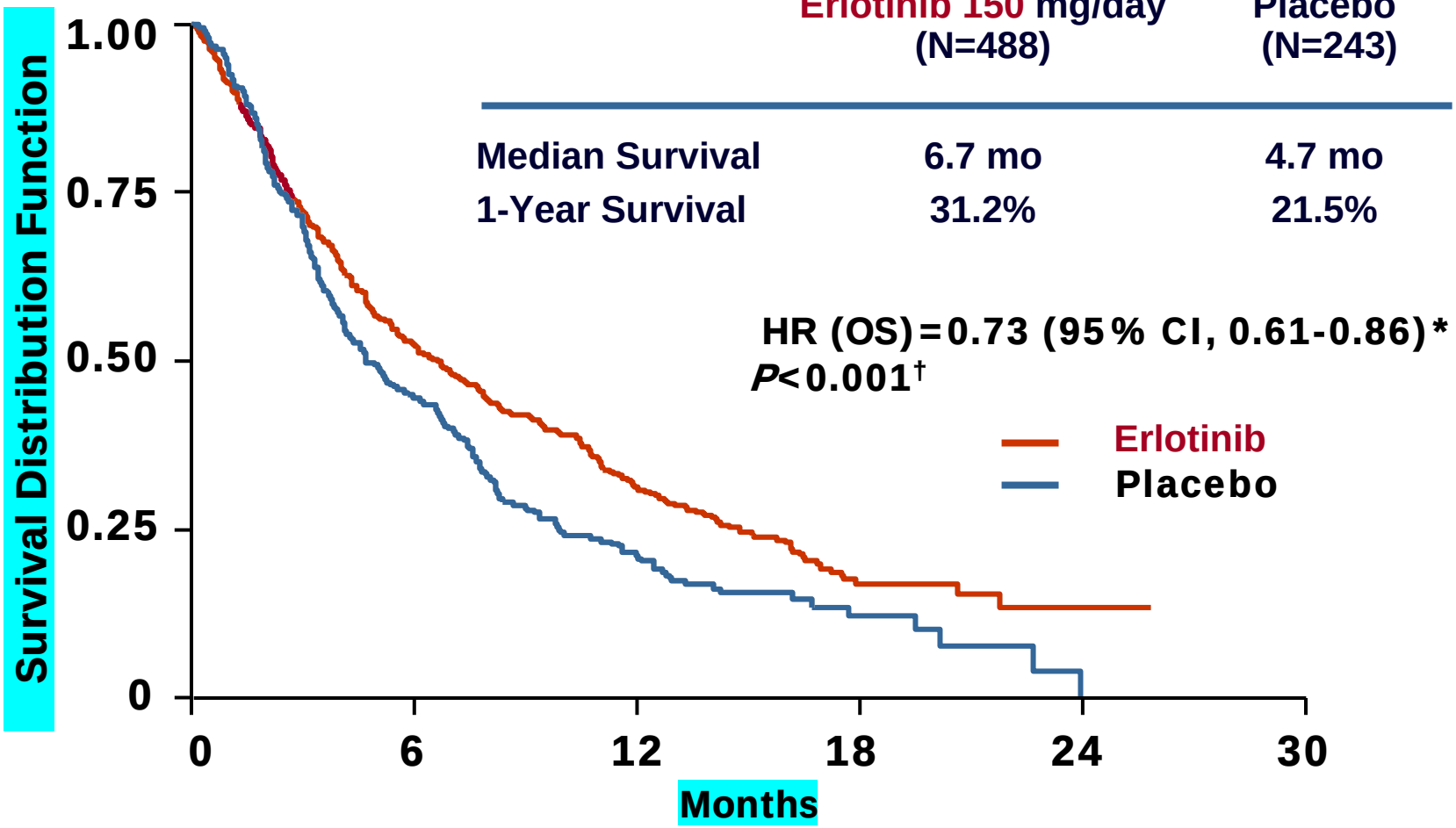
- **Hypothesis Generating Single Arm Treatment Studies did not Discern if Markers were Prognostic or Predictive**
- **Randomized Studies with Placebo Control Needed to Determine if Predictive for Outcome**
- **Two Large Randomized Studies of Gefitinib and Erlotinib versus Placebo**

Application of Biomarkers of Response to EGFR-TKIs in Retrospective Studies

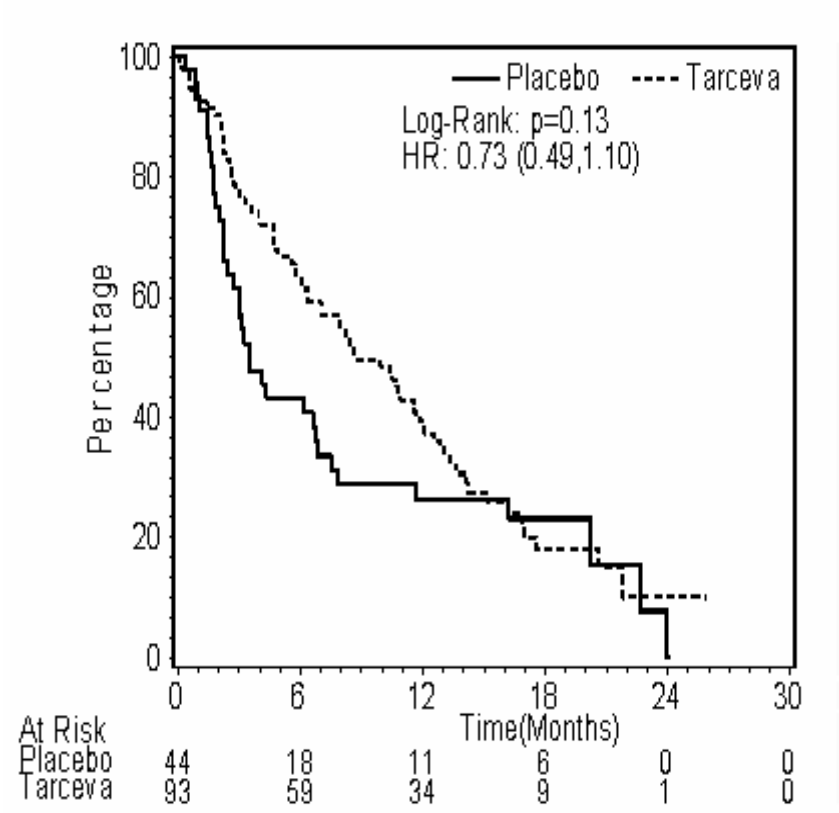
- **Erlotinib versus Placebo for Patients with Previously Treated NSCLC**
- **Gefitinib versus Placebo for Patients with Previously Treated NSCLC**

Phase III Trial of Erlotinib versus Placebo in Pts Treated with 1 or 2 Regimens of CT

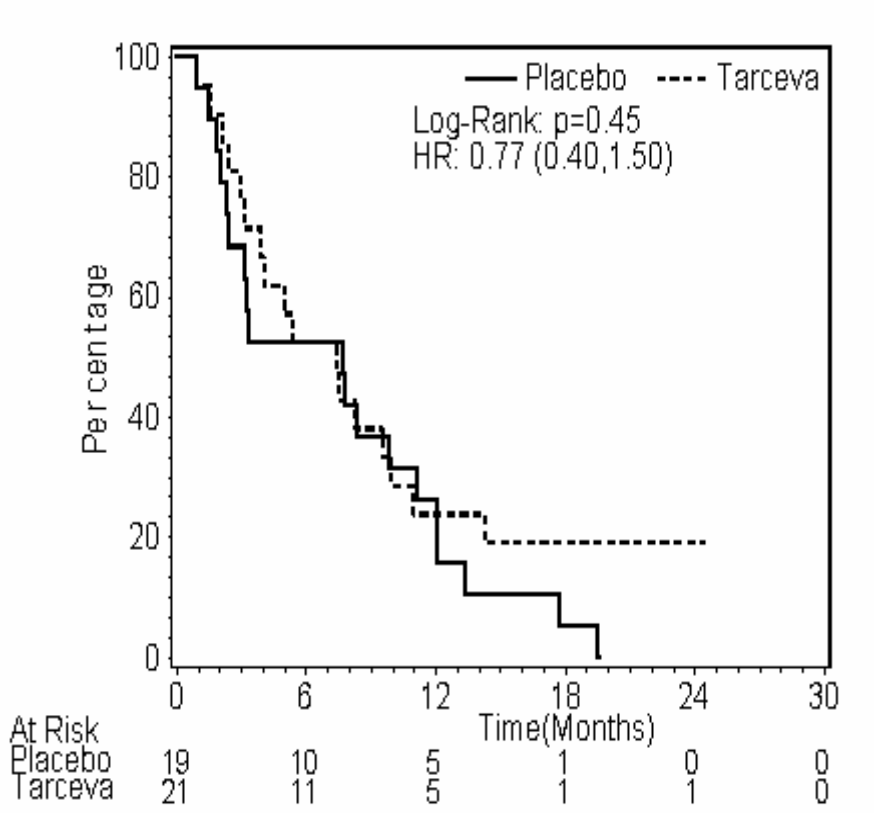
Shepherd et al NEJM 353:123, 2005



Mut Analyses in Trial of Erlotinib versus Placebo in Pts with Previously Treated NSCLC



No Mutation

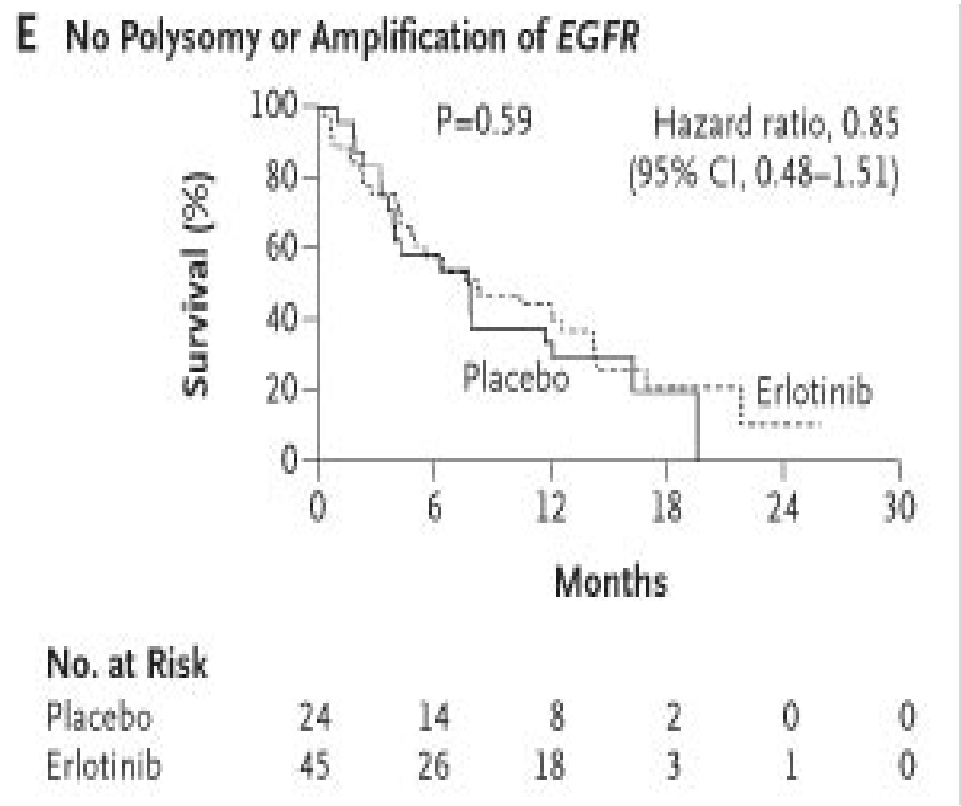


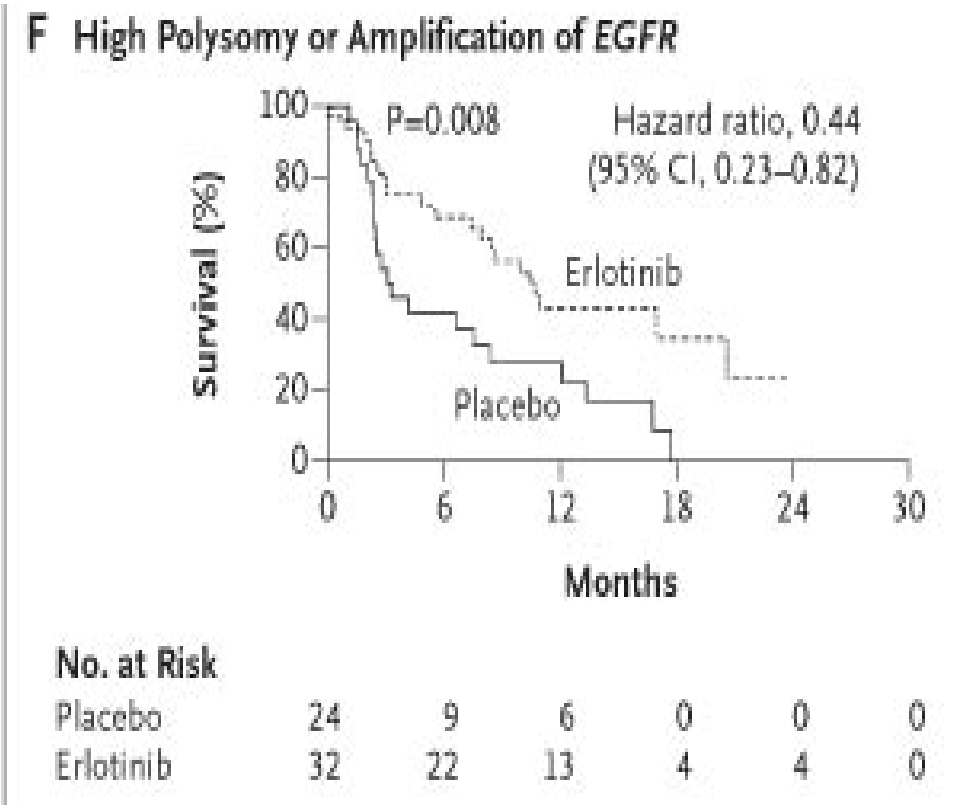
Mutation

- **N=177**

Tsao, M. et al. N Engl J Med 2005;353:133-144

FISH Analyses in Trial of Erlotinib versus Placebo in Pts with Previously Treated NSCLC

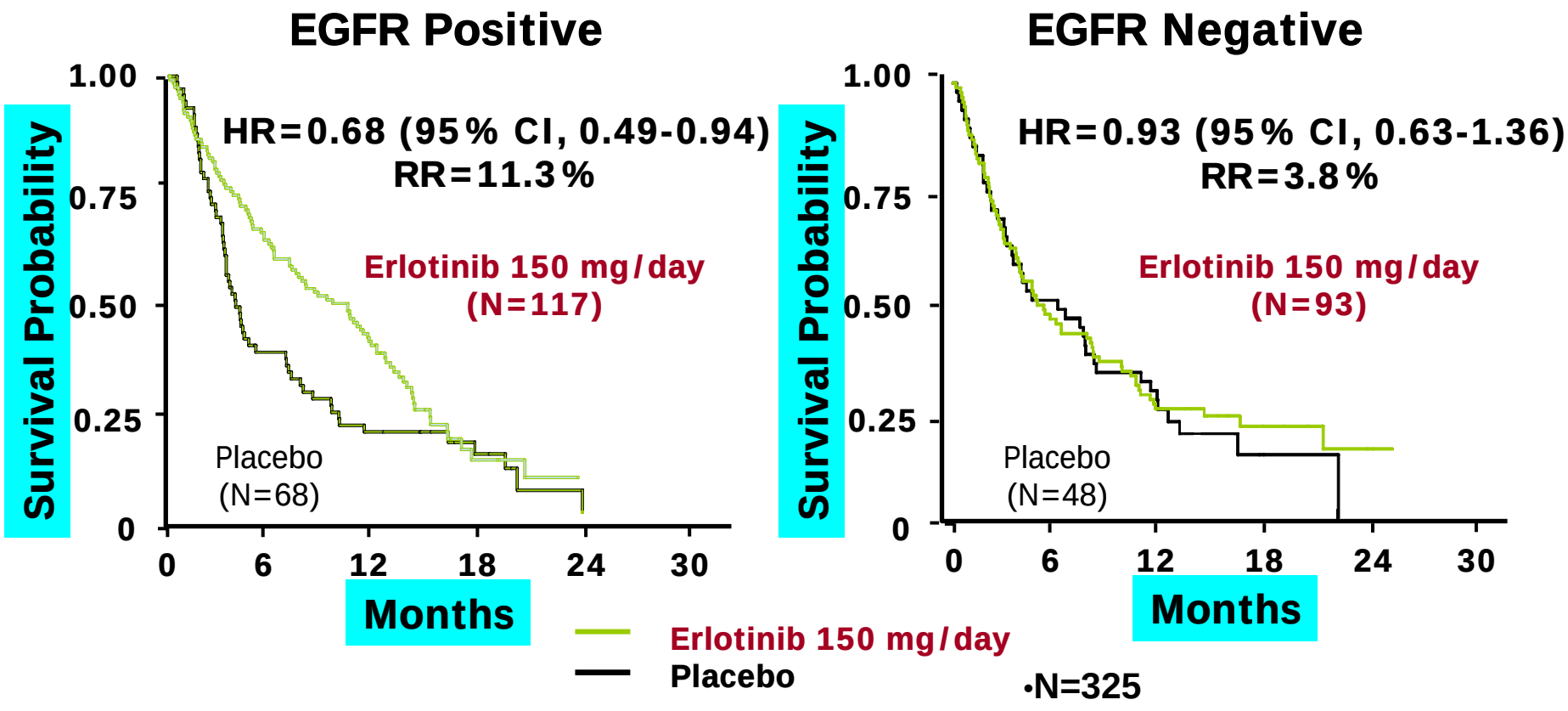




Tsao, M. et al. N Engl J Med 2005;353:133-144

- N=125

IHC Analyses in Trial of Erlotinib versus Placebo in Pts with Previously Treated NSCLC

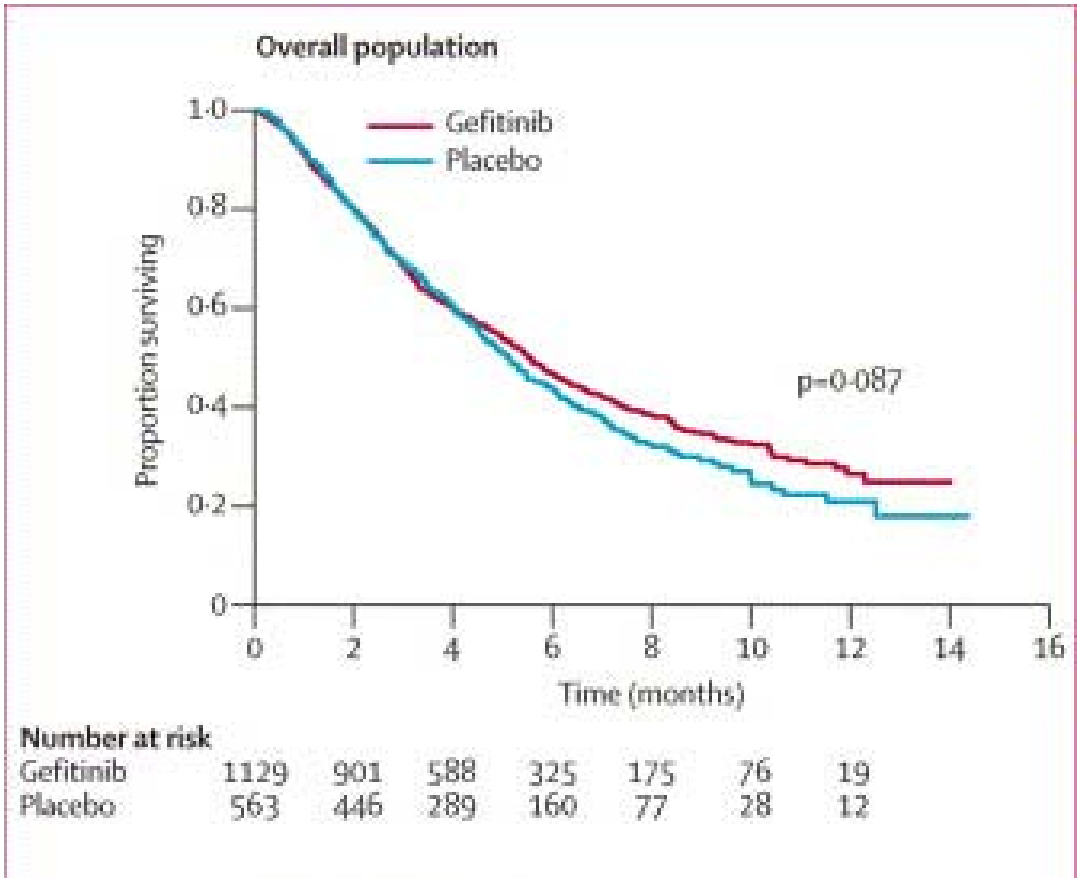


EGFR Gene Copy Number, EGFR Protein Expression, and EGFR Mutation Status Correlation With Clinical Benefit

				Survival	
	N (%)	Response	*P* Value	HR	*P* Value
FISH+	56 (45%)	20.0%	**0.03**	**0.44**	0.10
FISH-	69 (55%)	2.4%		**0.86**	
IHC+	184 (57%)	11.3%	0.10	**0.68**	0.25
IHC-	141 (43%)	3.8%		**0.93**	
EGFR Mut+	40 (23%)	15.8%	0.37	**0.77**	0.97
EGFR Mut-	137 (77%)	7.4%		**0.73**	

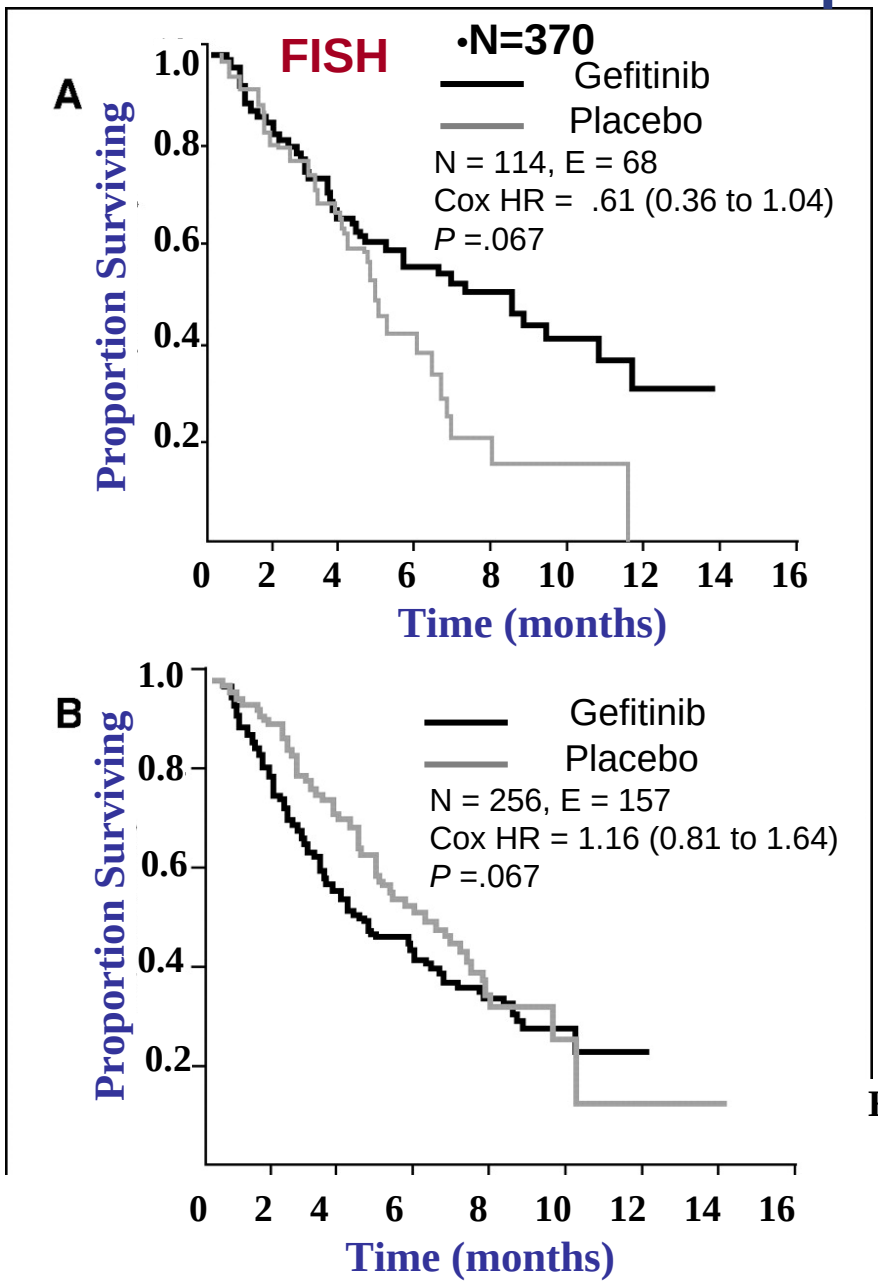
- **Tsao et al. NEM 353:133, 2005**

Phase III Trial of Gefitinib versus Placebo in Pts Treated with 1 or 2 Regimens of CT

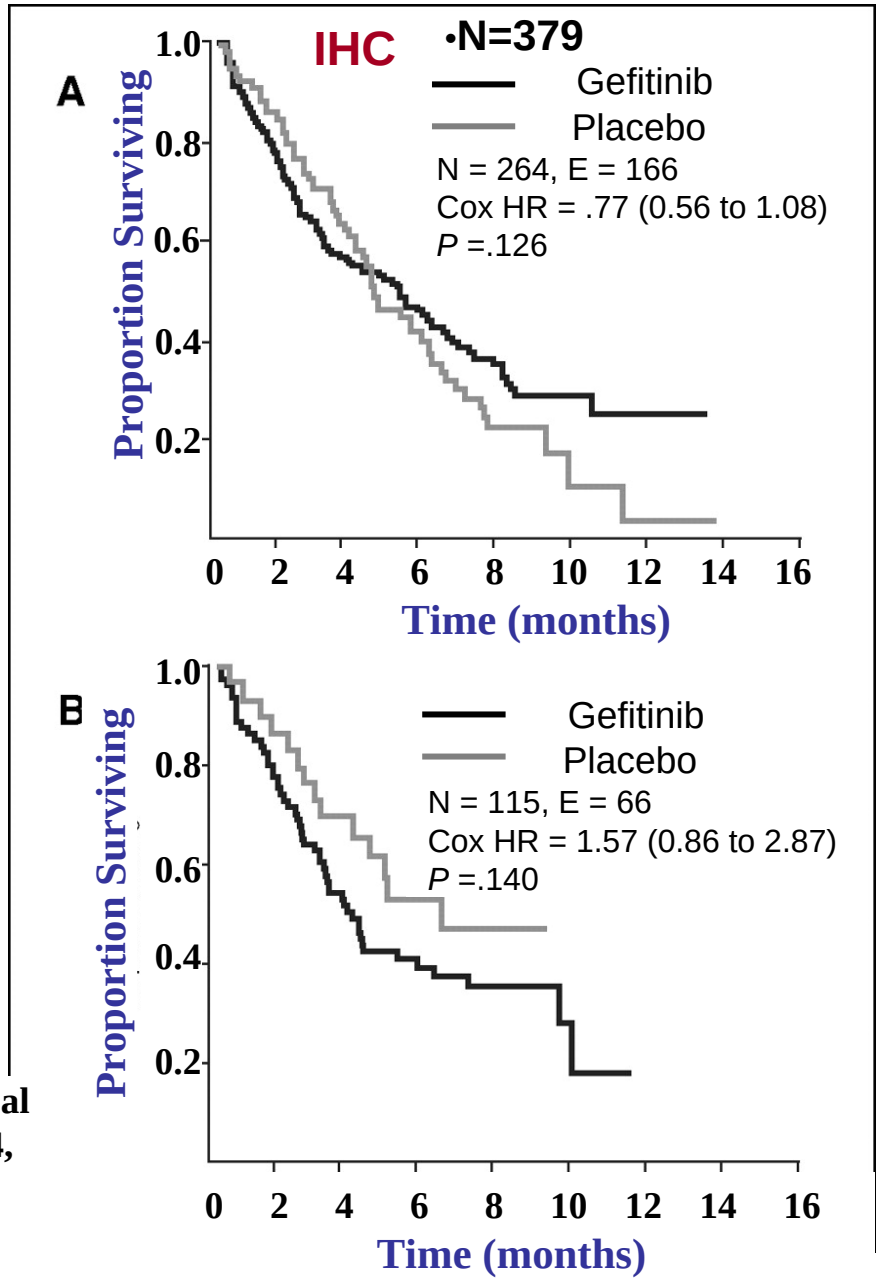


Thatcher et al Lancet 366:1527, 2005

Application of Biomarkers of Response to EGFR-TKIs in Retrospective Studies



Hirsch et al
JCO : 24, 2006



Application of Biomarkers of Response to EGFR-TKIs in Retrospective Studies

- **Studied Tumor Samples from Fewer than 25% of the Patients**
- **Tumor Samples Not Taken Before Start of Treatment with EGFR-TKI**
- **Treatment with Erlotinib with Favored in All Patient Subgroups**
- **Need Biomarker Predictive of Response to EGFR-TKI versus Chemotherapy**

Application of Biomarkers of Response to EGFR-TKIs in Prospective Studies

- **Gefitinib versus Docetaxel for Patients with Previously Treated NSCLC**

- **Gefitinib versus Vinorelbine for Patients with Previously Untreated Elderly NSCLC**

Application of Biomarkers of Response to EGFR-TKIs in Prospective Studies

- **Studied Tumor Samples from Fewer than <25% to >75 of the Patients**
- **Tumor Samples in INVITE Taken at Start of Treatment with EGFR-TKI**
- **No Evidence that FISH can Identify subset Benefit from Treatment with Gefitinib compared to Chemotherapy**
- **No Biomarker Predictive of Response to EGFR-TKI versus Chemotherapy**

Phase II Trial of Gefitinib in Patients with Previously Untreated NSCLC with Activating Mutations of *EGFR*

- **Stage IIIB/IV**
- **Need at Least 1 to Get Screened (Asian, Women, Adenocarcinoma, and Non-Smoker)**
- **Mutation of *EGFR* Detected by our Laboratories**

Gefitinib

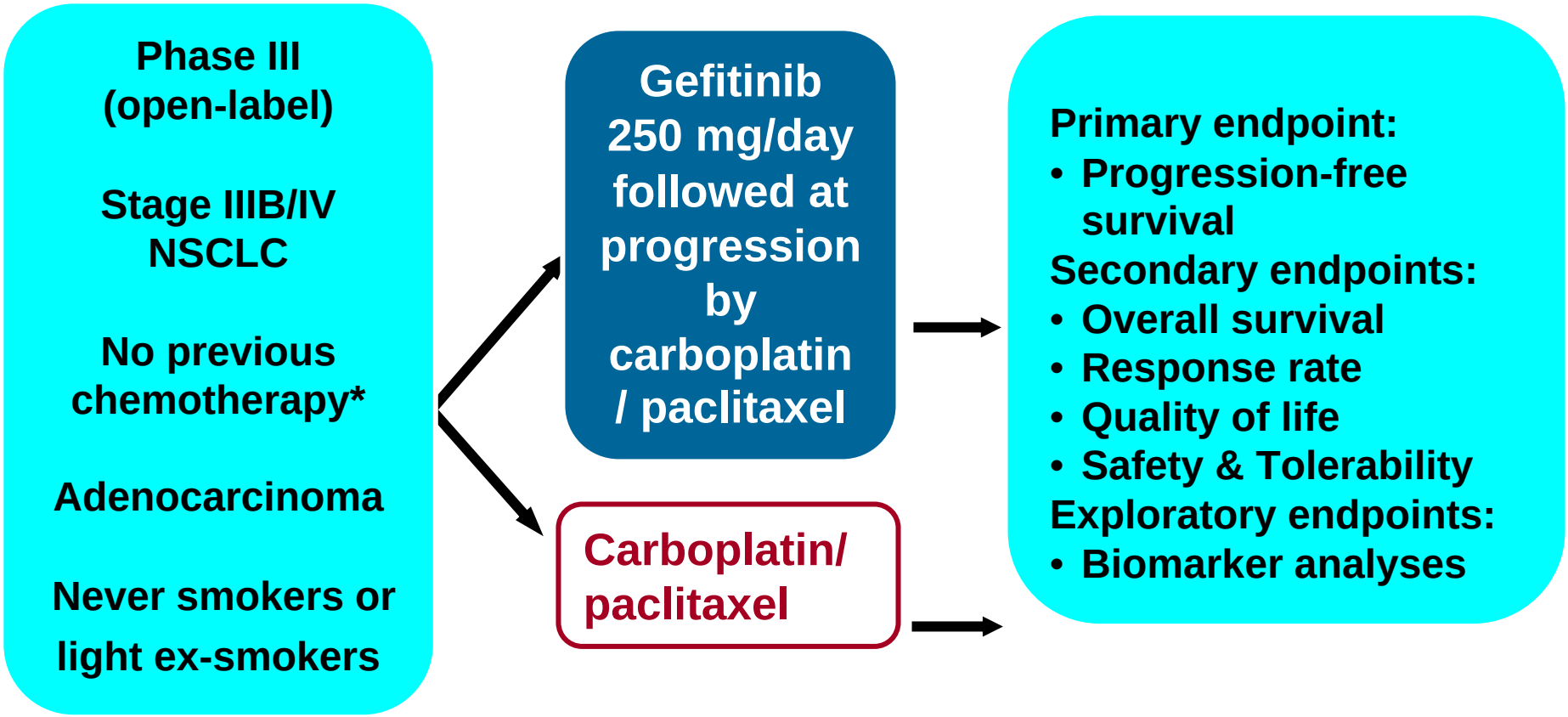
→

250 mg daily

Continuous

Continue until disease progression or development of toxicity

IPASS Trial Design

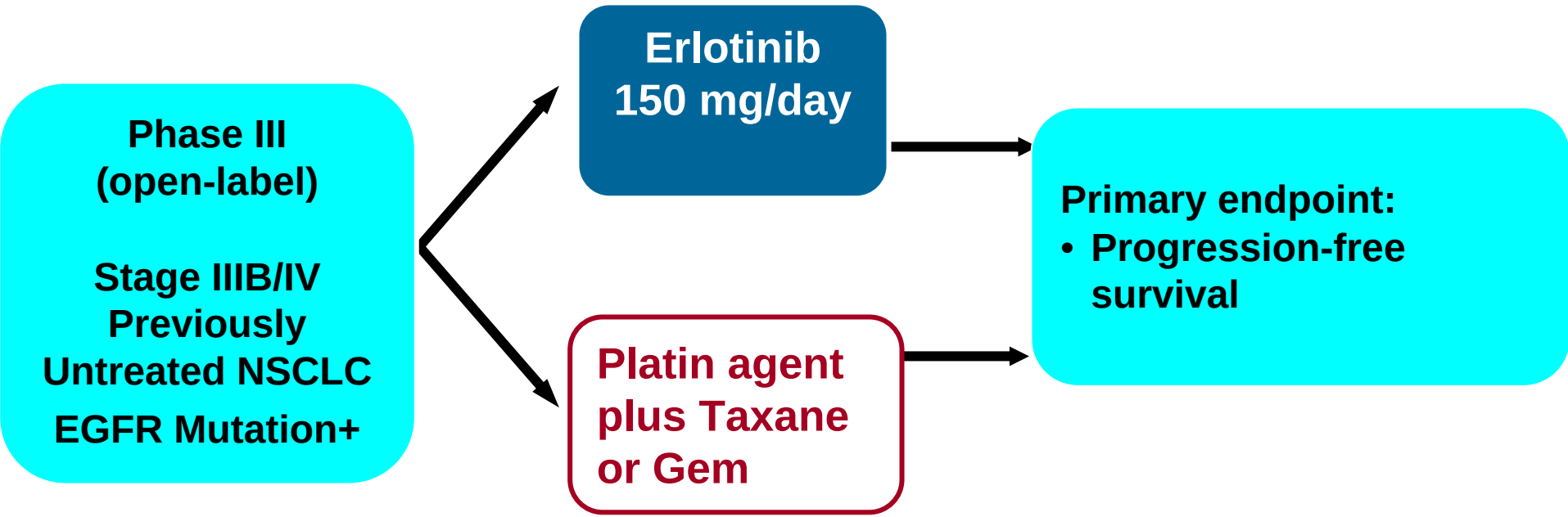


1:1 randomization

All centres in East and Southeast Asia

*** Excluding post-operative non-platinum based adjuvant chemotherapy**

Spanish Trial Design



1:1 randomization

Spanish Trial to Randomize 146 Patients

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