

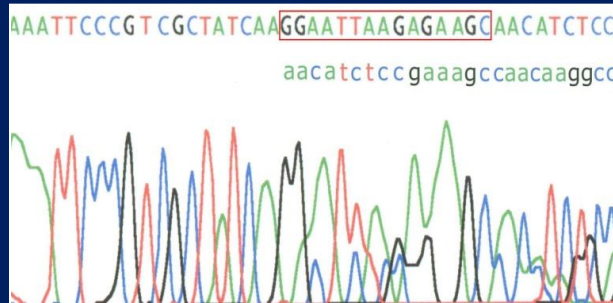


EGFR assessment in prospective clinical trials

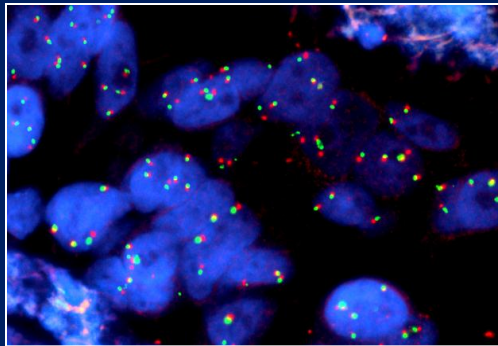
Rafal Dziadziuszko

Medical University of Gdańsk, Poland

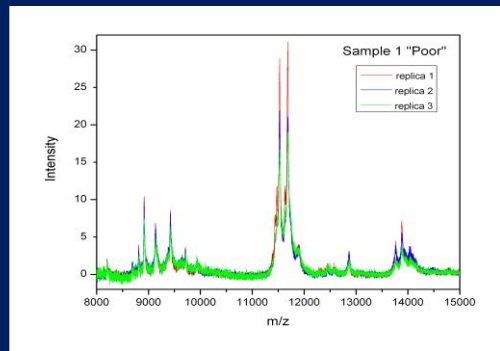
Prospectively assessed EGFR abnormalities in NSCLC



Activating EGFR mutations



High EGFR gene copy number



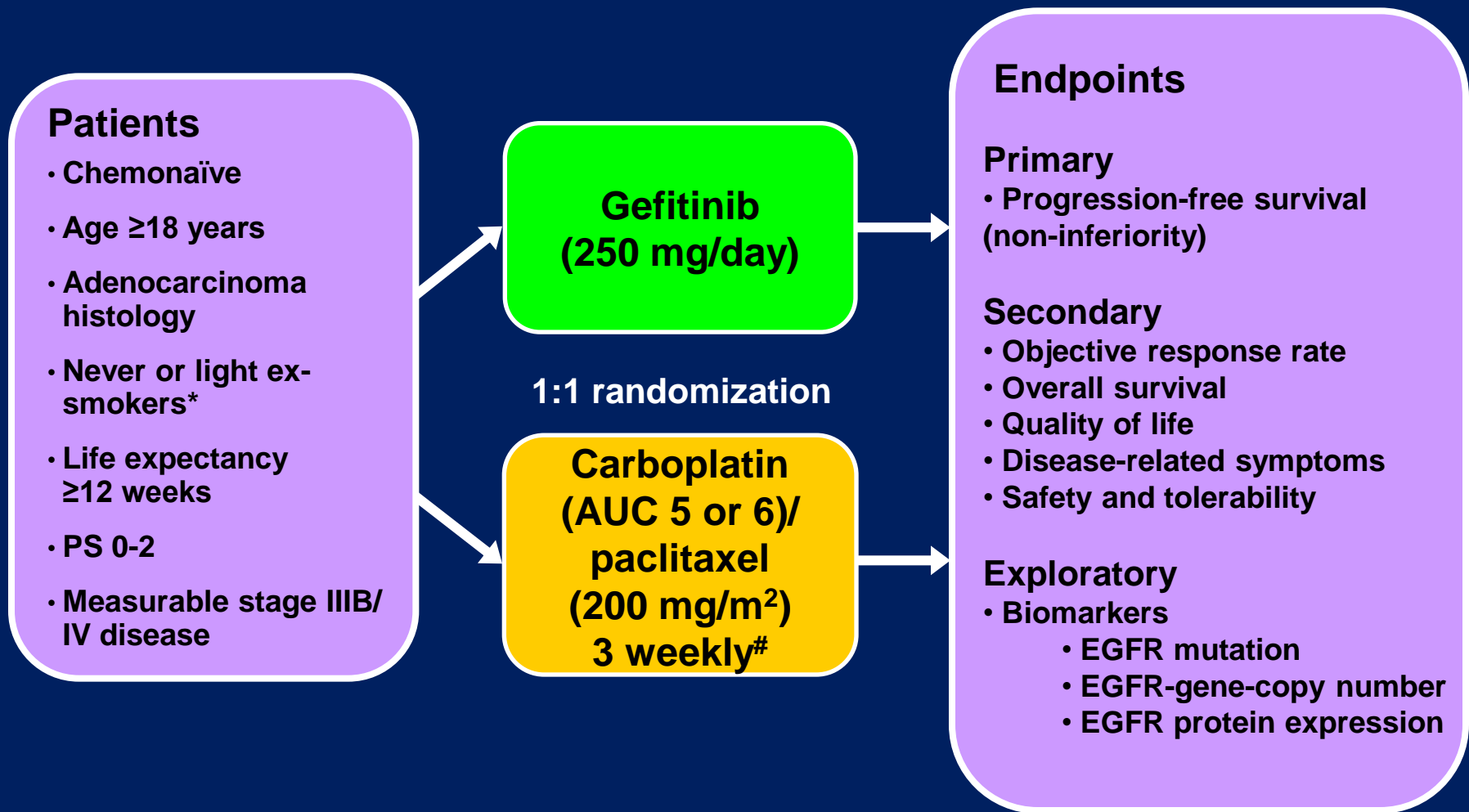
Serum proteomics

Prospectively assessed EGFR abnormalities in NSCLC



Activating EGFR mutations

IPASS Phase III trial



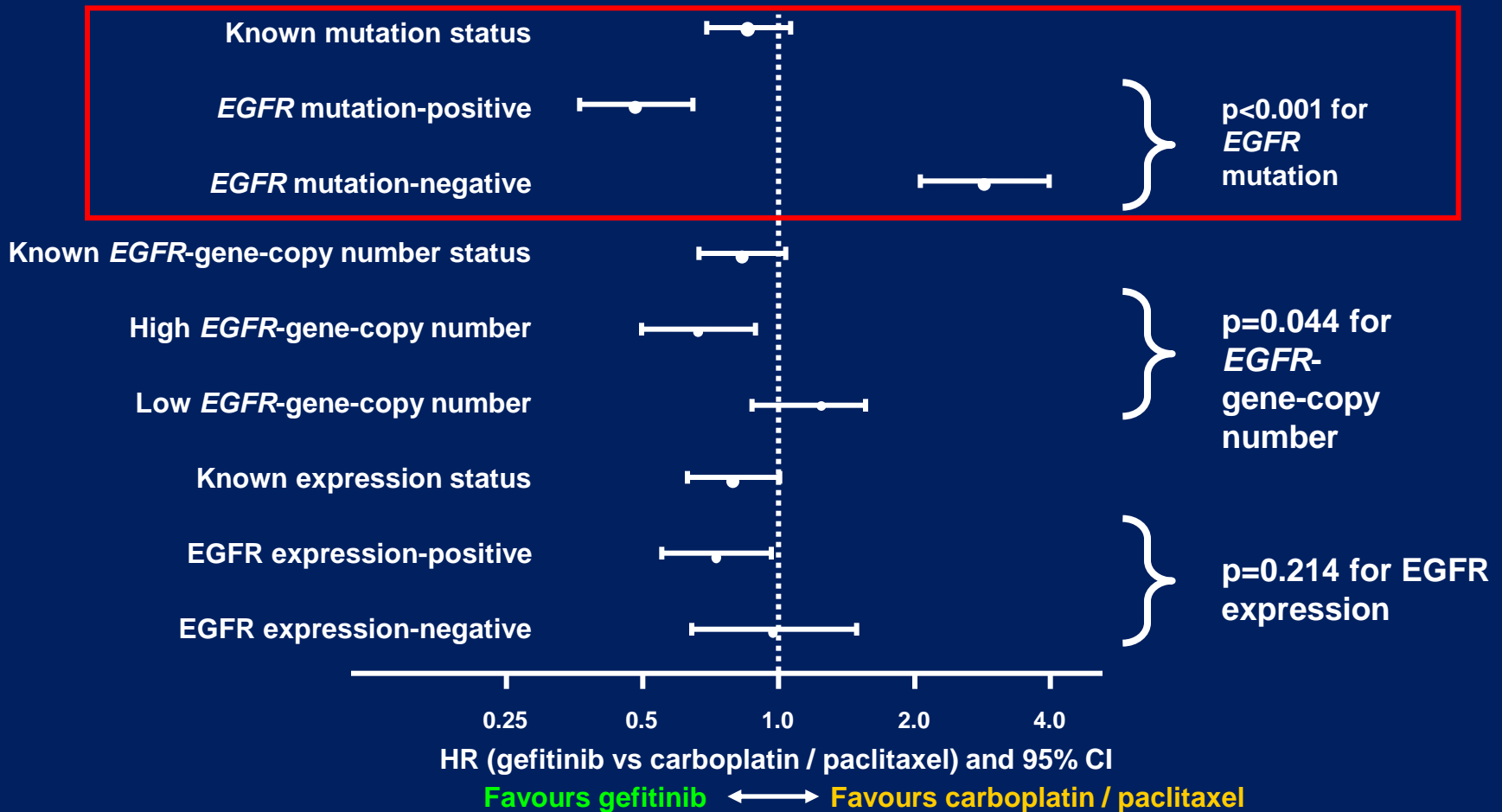
*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥ 15 years ago and smoked ≤ 10 pack years

[#]Limited to a maximum of 6 cycles

Carboplatin/paclitaxel was offered to gefitinib patients upon progression

IPASS: progression-free survival by biomarkers

Treatment-by-subgroup interaction test p-value



Intent-to-treat population

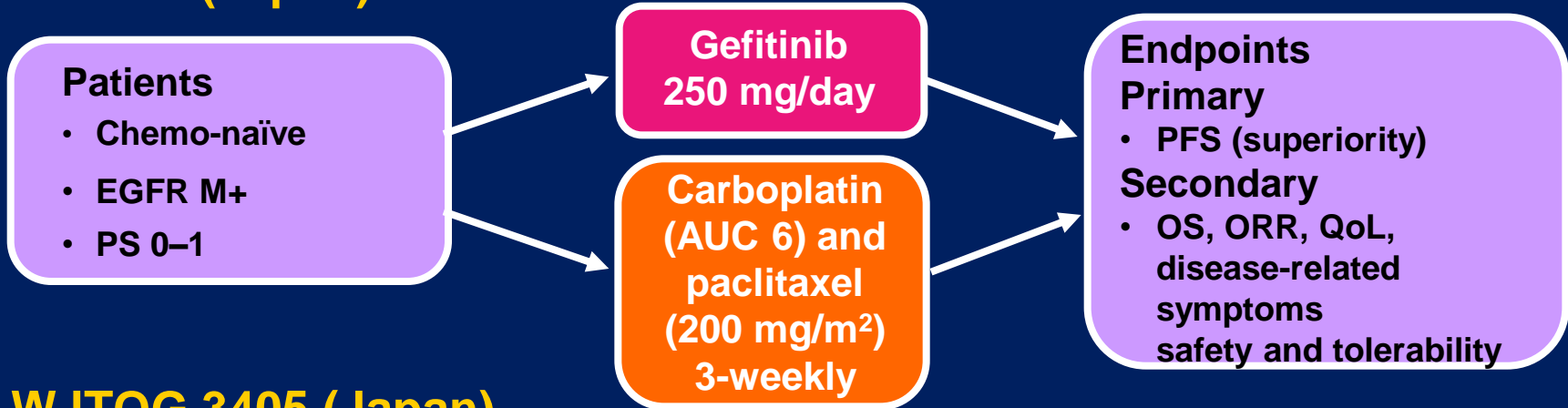
Mok et al. N Engl J Med 2009;
Fukuoka et al. ASCO 2009

Prospective first-line studies comparing EGFR inhibitor and chemotherapy in patients with tumors having activating EGFR mutation

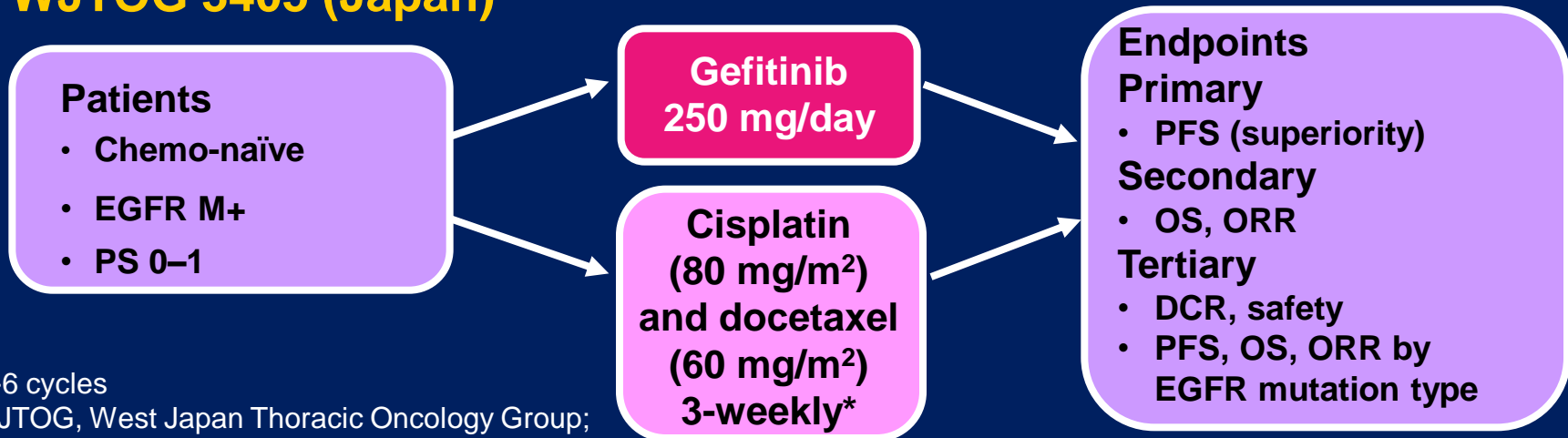
| Group | Drug | EGFR mutation | Primary endpoint | N | Trial status |
|---------------------------|-----------|--------------------------|------------------|-----|--------------|
| NEJ 002 | Gefitinib | X19, L858R, G719X, L861Q | PFS | 320 | Reported |
| WJOG 3405 | Gefitinib | X19, L858R | PFS | 200 | Reported |
| Spanish Lung Cancer Group | Erlotinib | X19, L858R | PFS | 170 | Ongoing |
| China | Erlotinib | EGFR mutation | PFS | 150 | Ongoing |

Recently reported Phase III studies of gefitinib as first-line treatment for EGFR M+ NSCLC

NEJ002 (Japan)



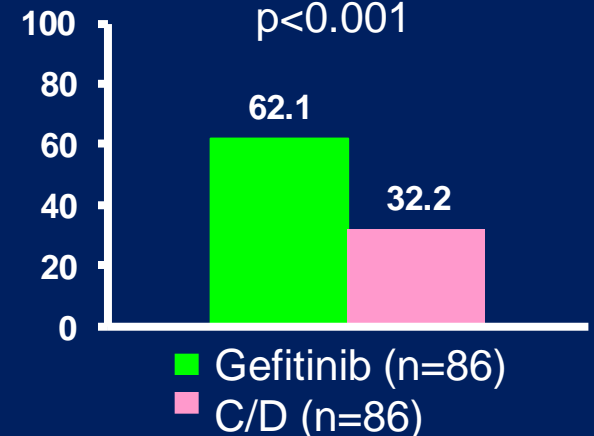
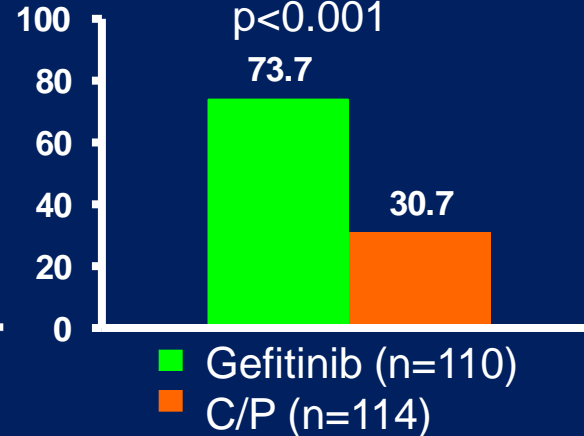
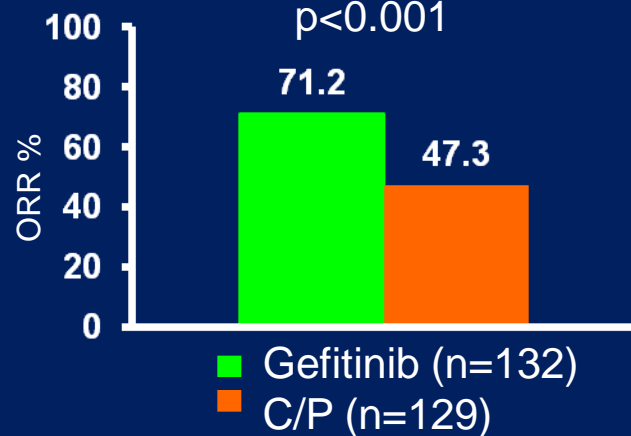
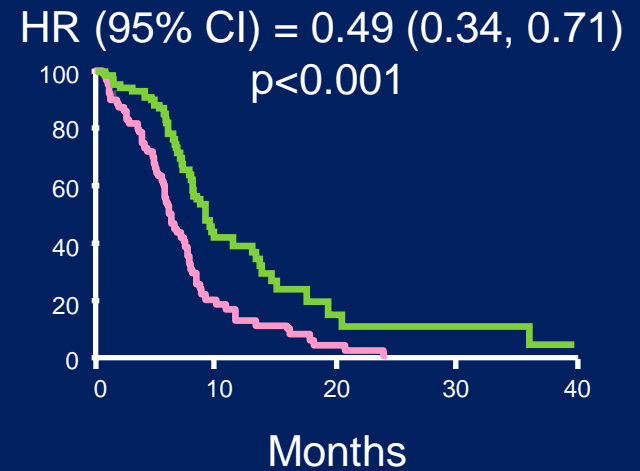
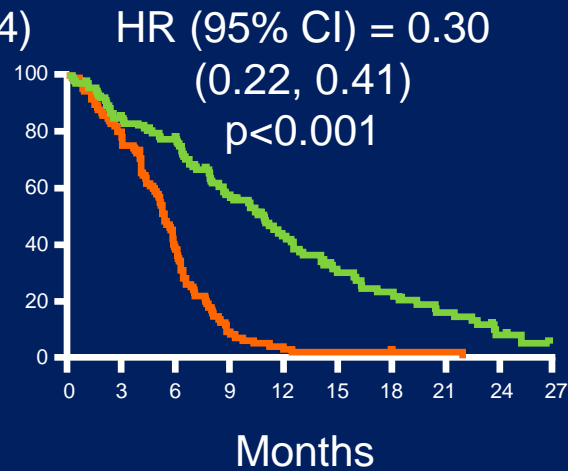
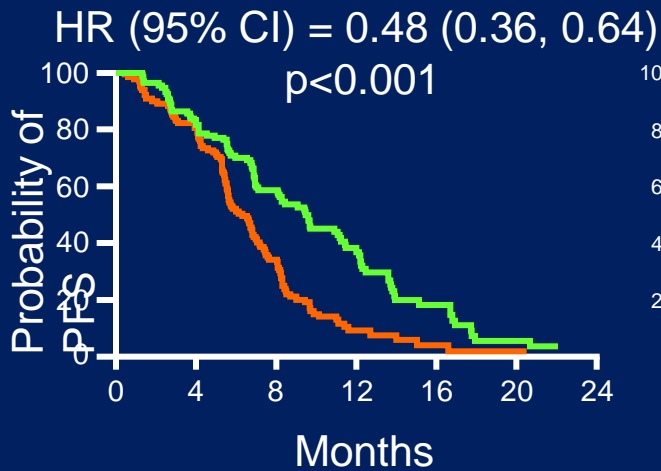
WJTOG 3405 (Japan)



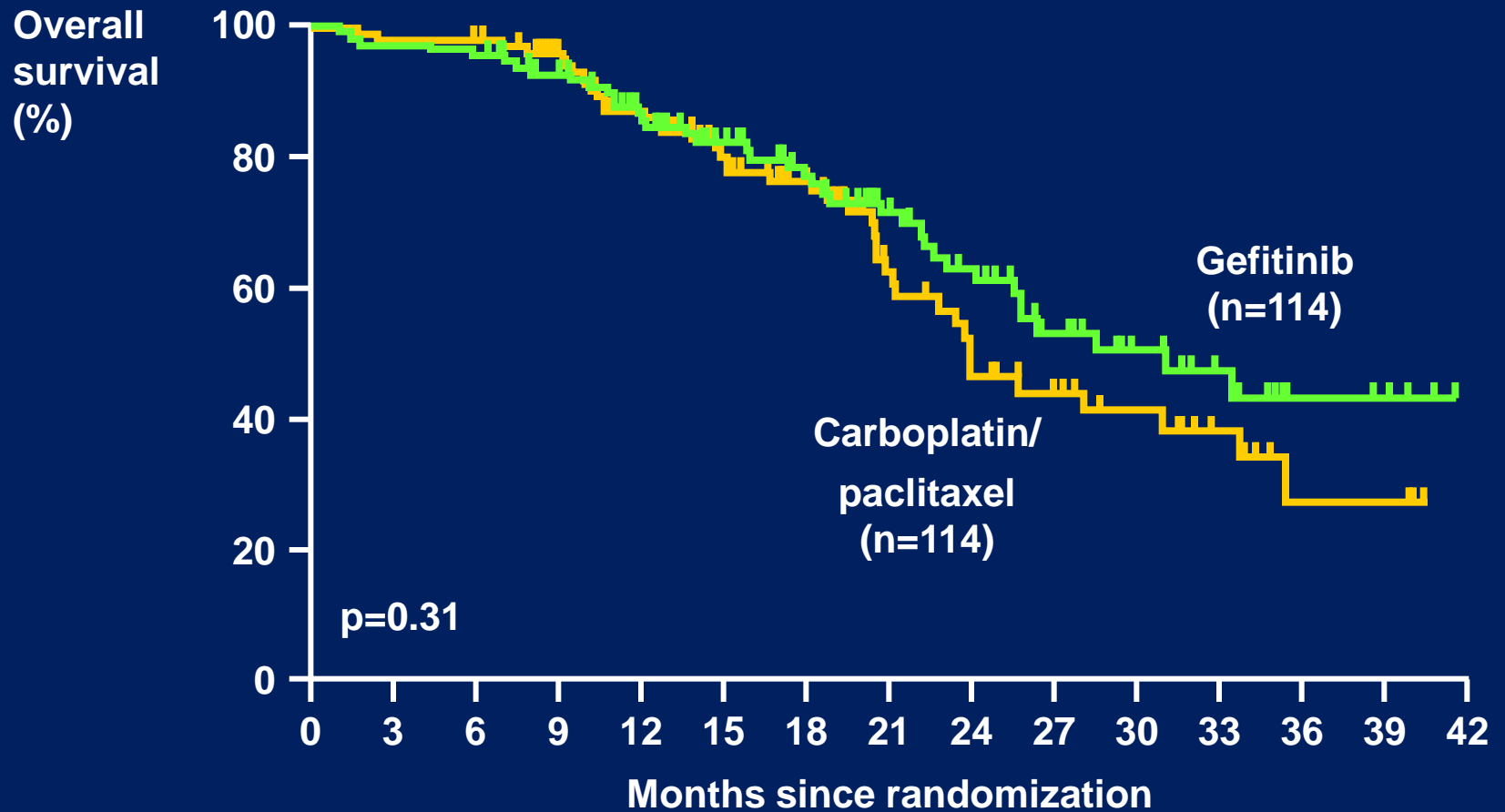
*3-6 cycles

WJTOG, West Japan Thoracic Oncology Group;
DCR, disease control rate

PFS and ORR with first-line gefitinib versus doublet chemotherapy in EGFR M+ Asian patients across 3 Phase III studies



NEJ002: Overall survival



Neratinib (HKI-272) Phase II

- Advanced NSCLC
- Measurable lesions
- ≤3 lines of chemotherapy
- No prior EGFR TKI
- ECOG PS 0 or 1

N=91

Failure on EGFR TKI >12 weeks
AND EGFR MUT+

N=48

Failure on EGFR TKI >12
AND EGFR WT

N=28

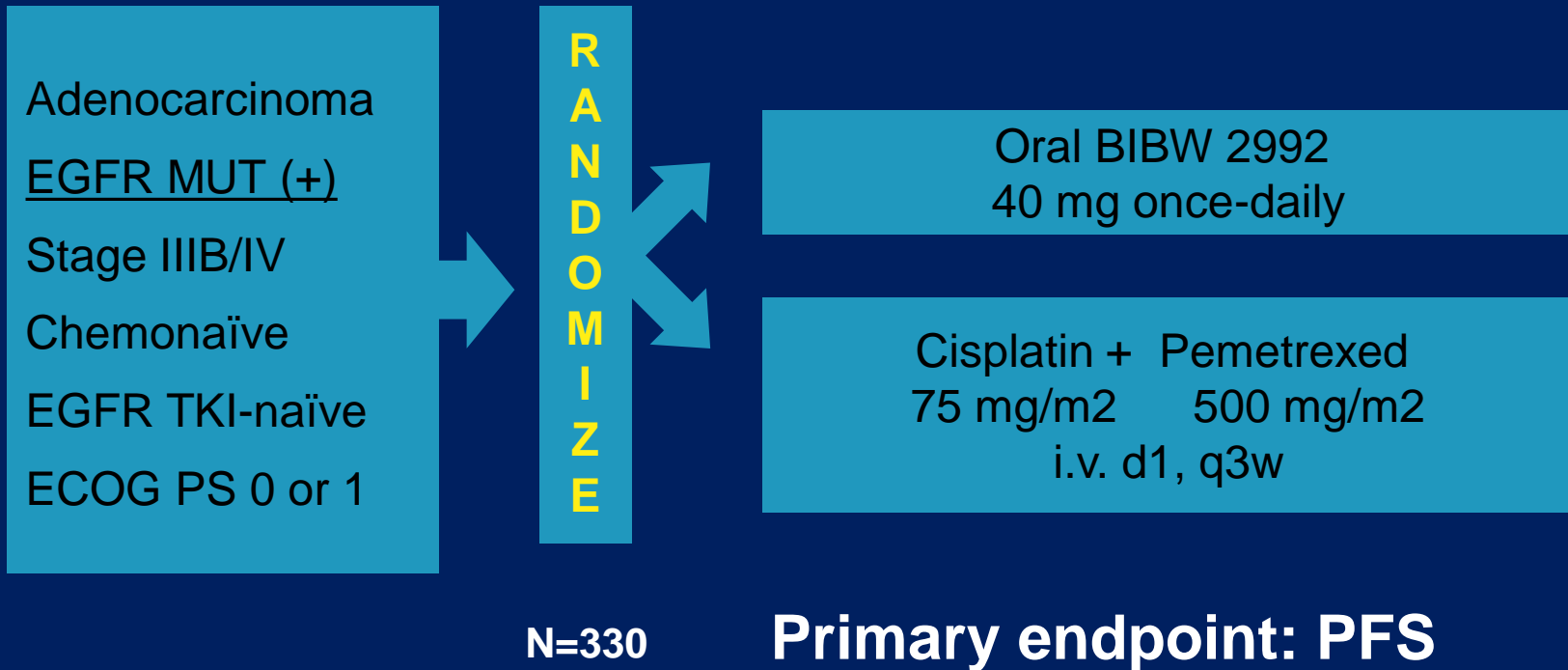
EGFR TKI naïve

Neratinib
320mg
(240mg)
Once daily

Primary endpoint: response rate

LUX LUNG3 Phase III

Afatinib (BIBW2992) vs. chemotherapy



TASTE Phase II

adjuvant postsurgical feasibility study

- Stage II-III A
- Adequate surgical resection
- Non-squamous histology

EGFR MUTATION STATUS
AND ERCC1 EXPRESSION

R
A
N
D
O
M
I
Z
E

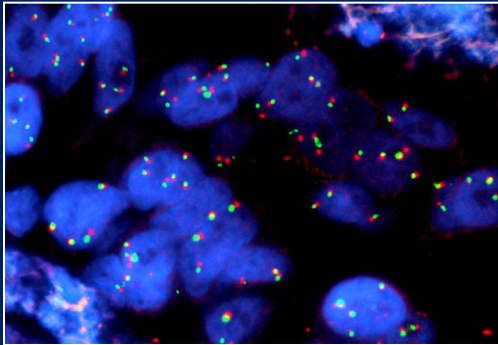
N=108

STANDARD CHEMOTHERAPY

Customized treatment based on biomarkers
ERLOTINIB if EGFR MUTATION+
PEMETREXED/DDP if ERCC1-
NO TREATMENT if ERCC1+

Primary endpoint: Feasibility
Secondary endpoint: DFS

Prospectively assessed EGFR abnormalities in NSCLC



High EGFR gene copy number

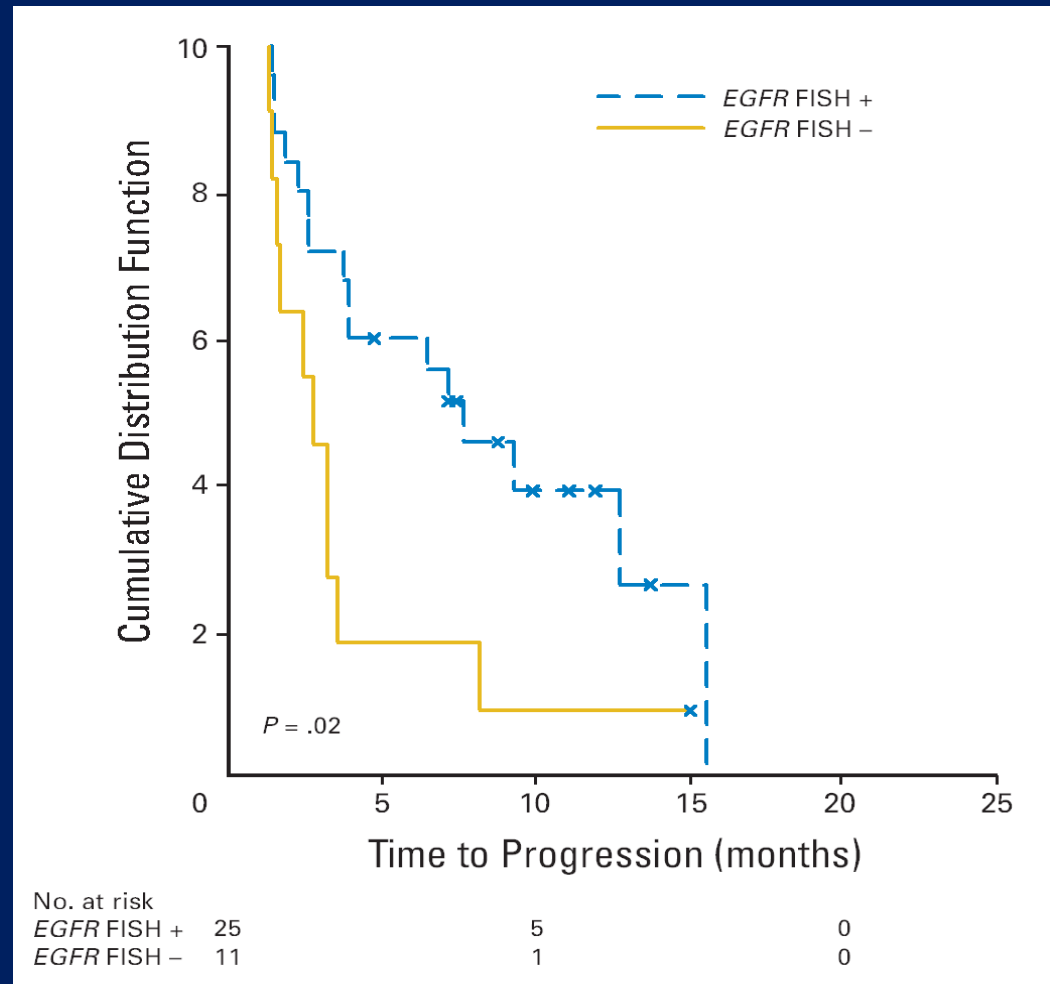
Prospective single arm first-line phase II studies in patients with advanced tumors having high EGFR gene copy number by FISH

| Study | Drug | Prospective tests | Primary endpoint | N | Trial status |
|---|-----------|----------------------|------------------|-----|-----------------|
| ONCOBELL | Gefitinib | EGFR FISH, p-Akt IHC | RR | 42 | Reported |
| OSI-774-203 | Erlotinib | EGFR FISH, EGFR IHC | PFS | 143 | Reported (ASCO) |
| Central and East European Oncology Group FLIKER trial | Erlotinib | EGFR FISH | PFS | 72 | Ongoing |

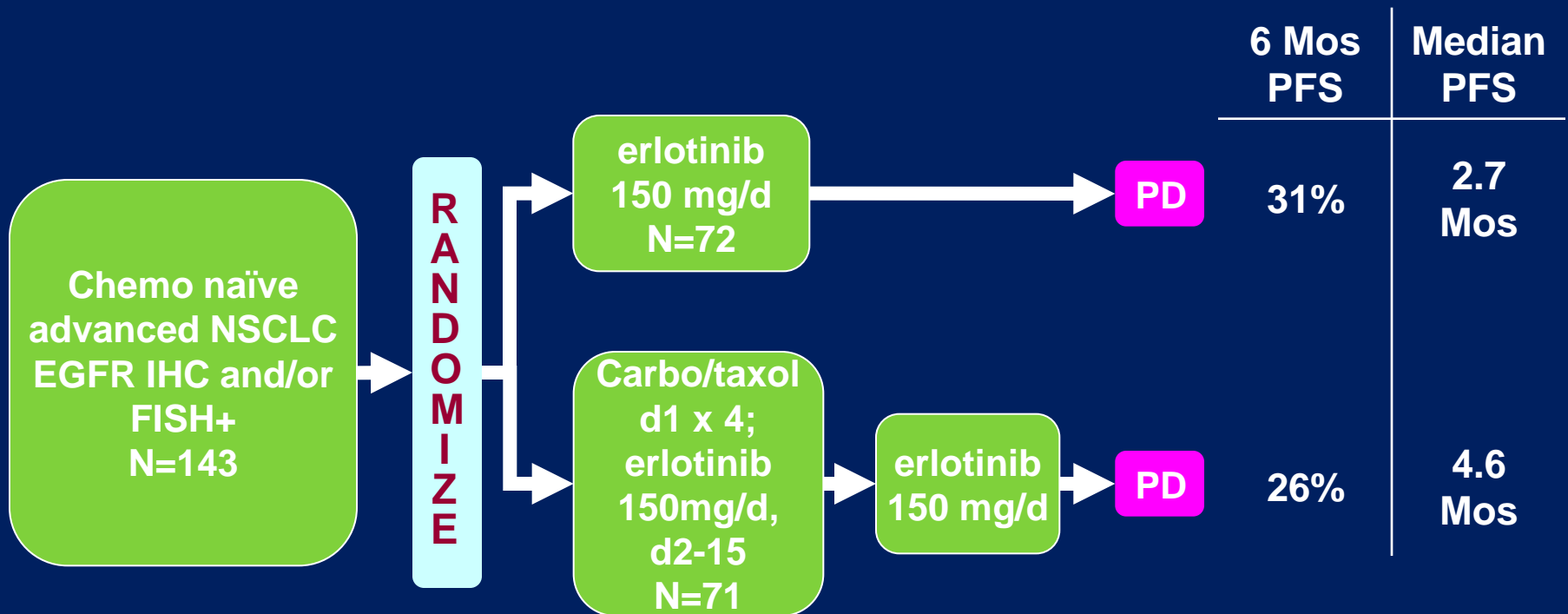
The ONCOBELL trial

Eligibility:

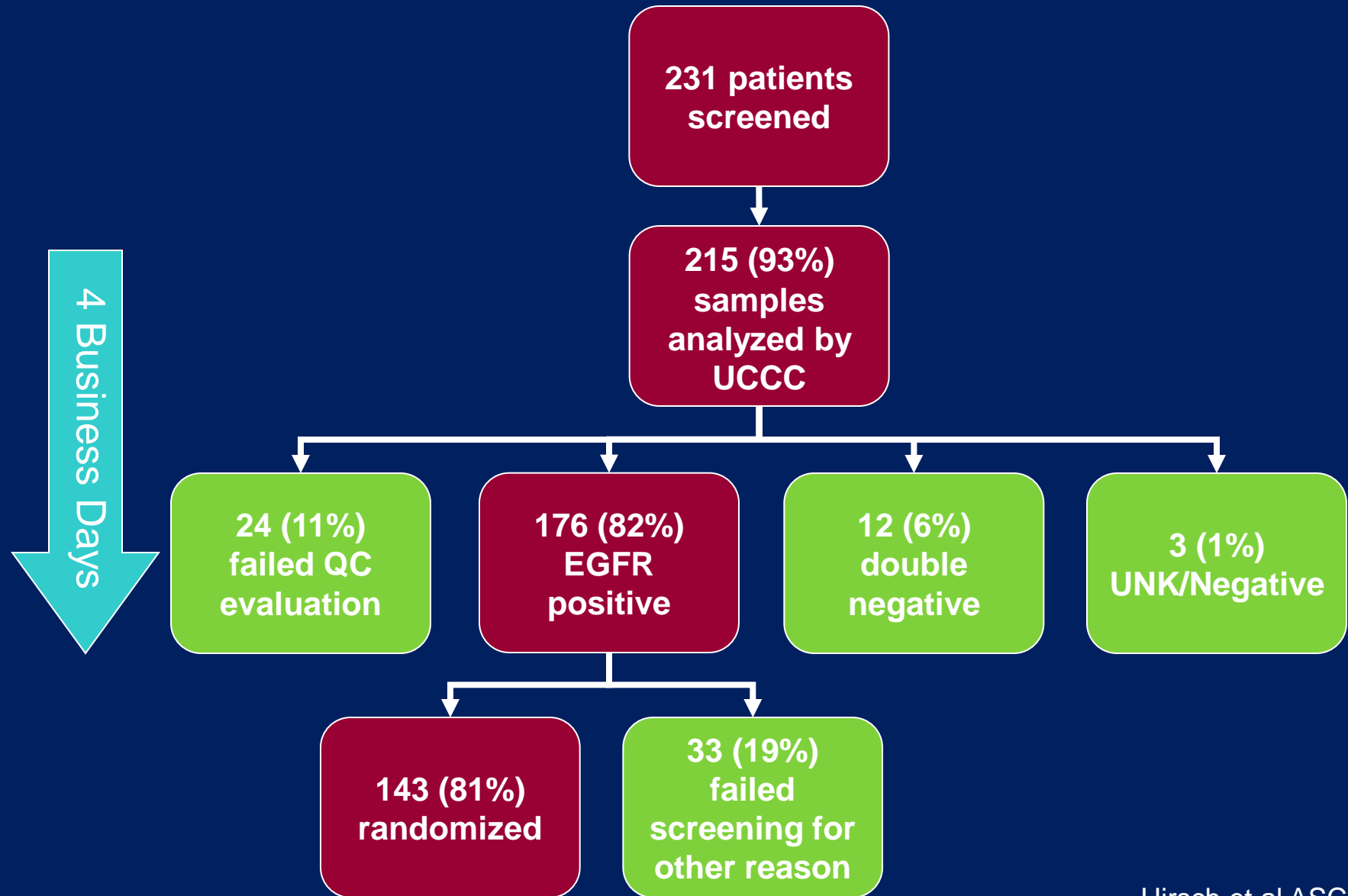
- Never-smokers
 - EGFR FISH +
or p-AKT +
- Smokers
 - EGFR FISH +
and p-AKT +



The OSI-774-203 trial

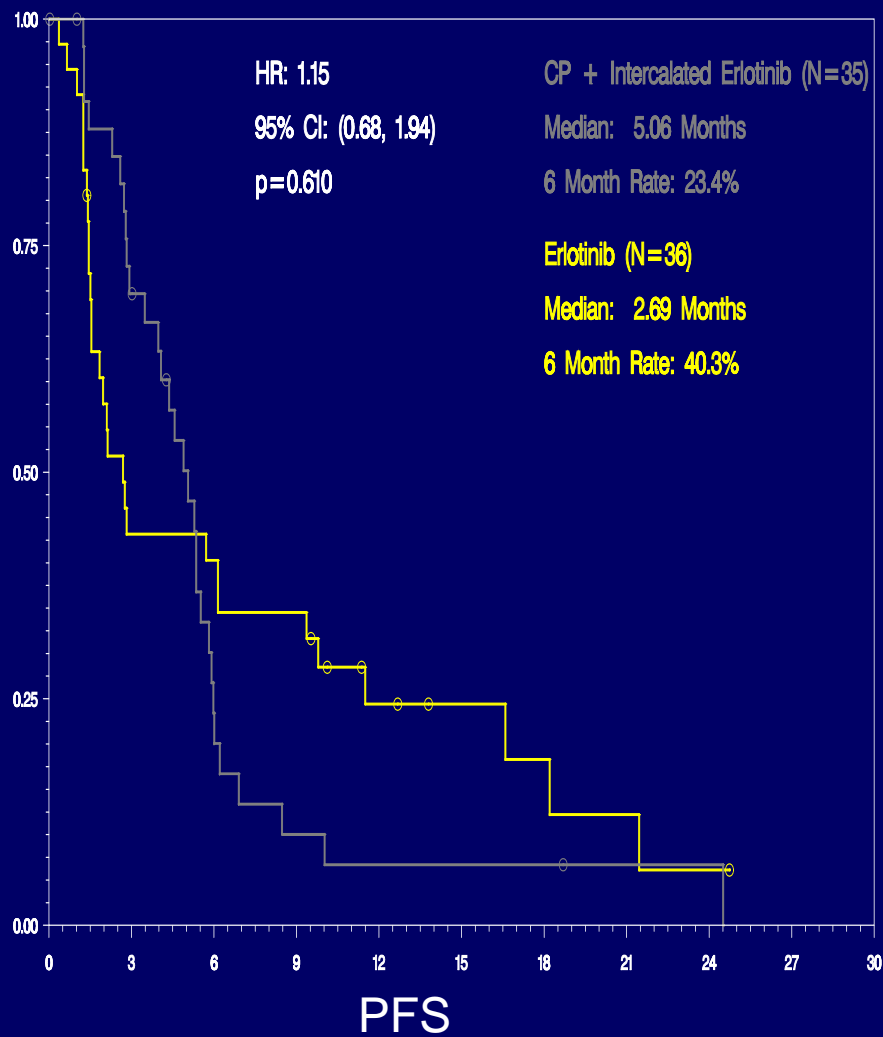


The OSI-774-2003 trial

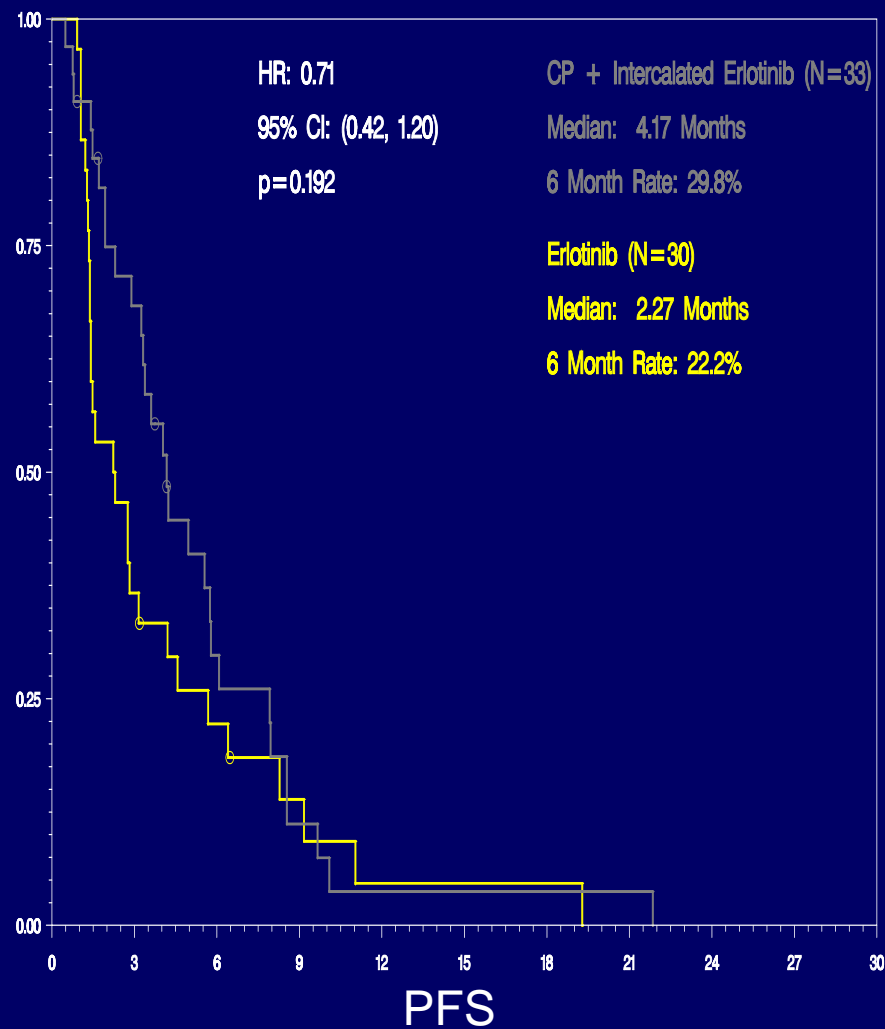


The OSI-774-2003 trial

EGFR FISH (+)

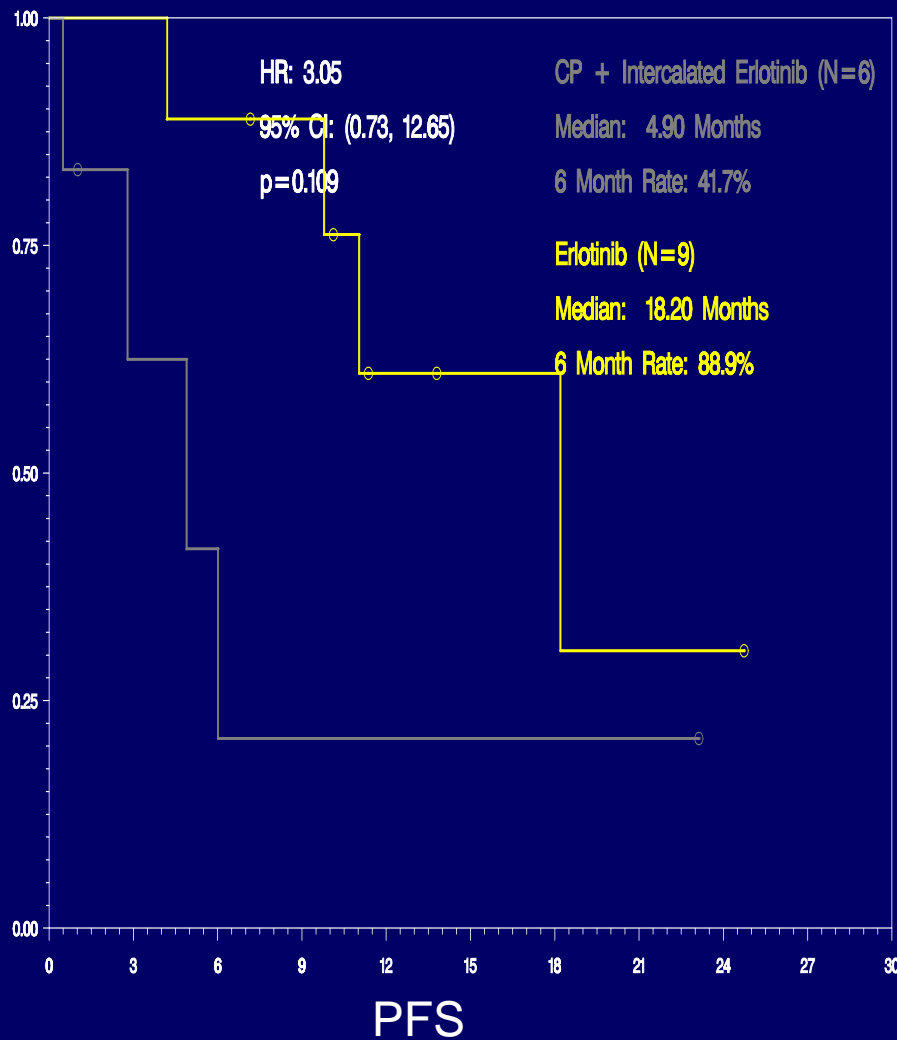


EGFR FISH (-)

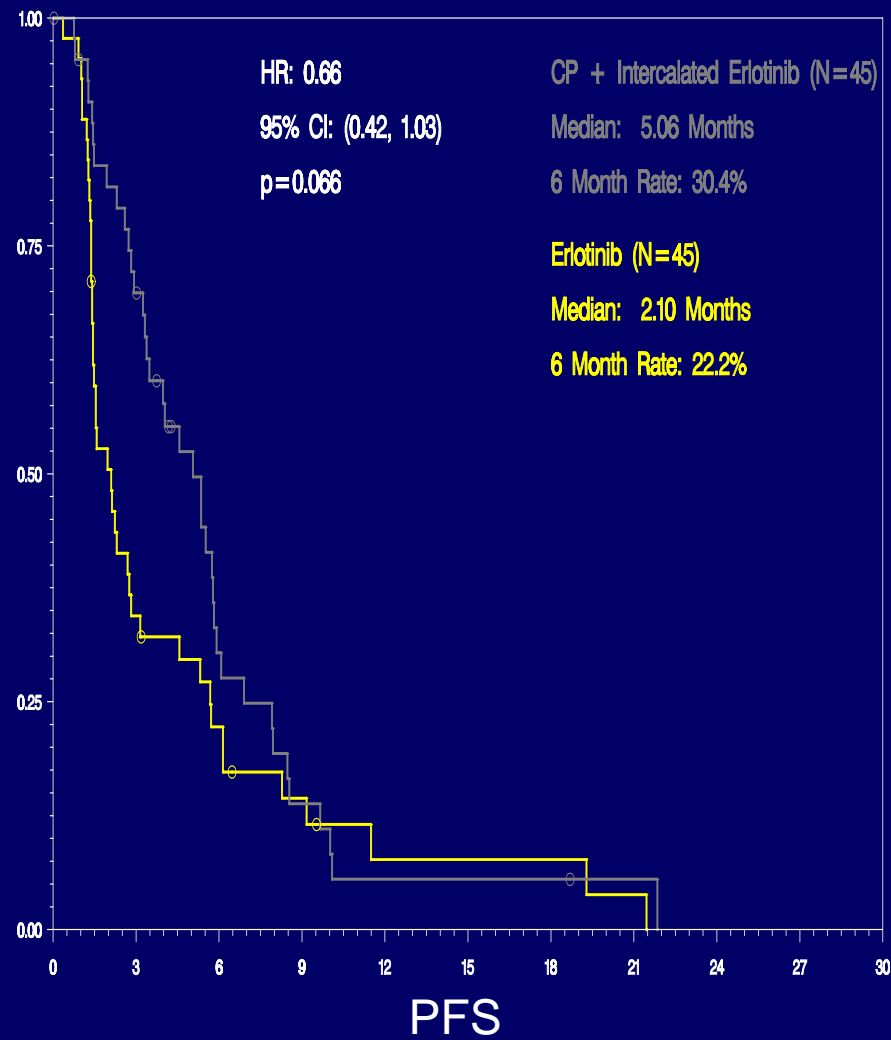


The OSI-774-203 trial

EGFR MUTATION (+)

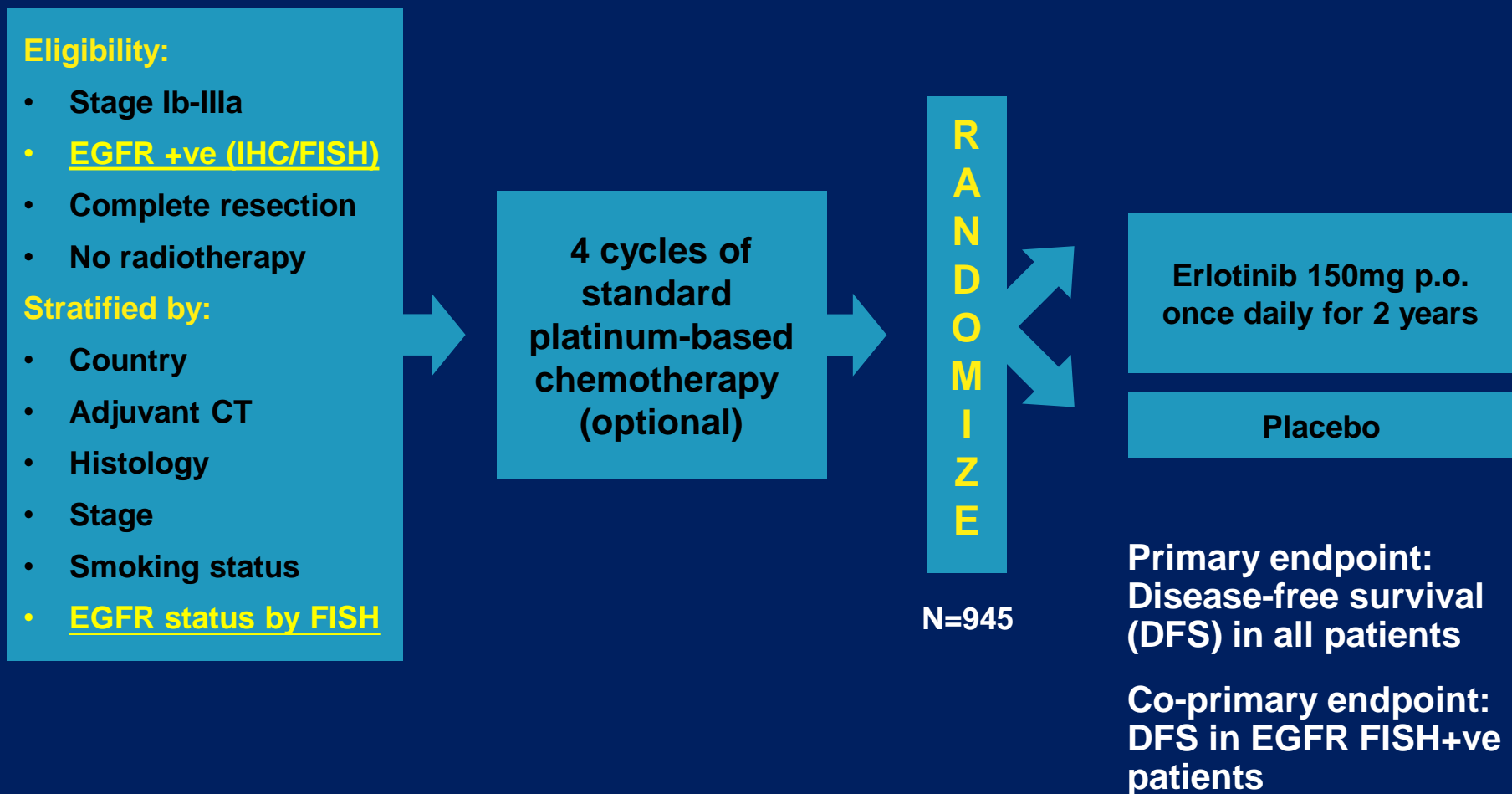


EGFR WT

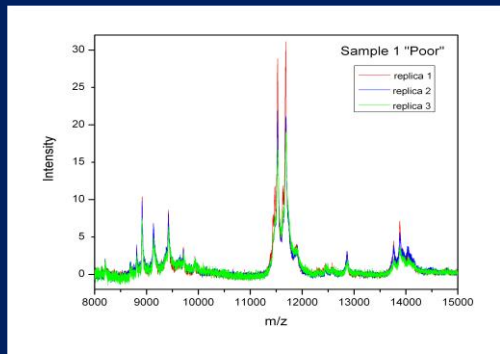


RADIANT Phase III trial

adjuvant postsurgical treatment

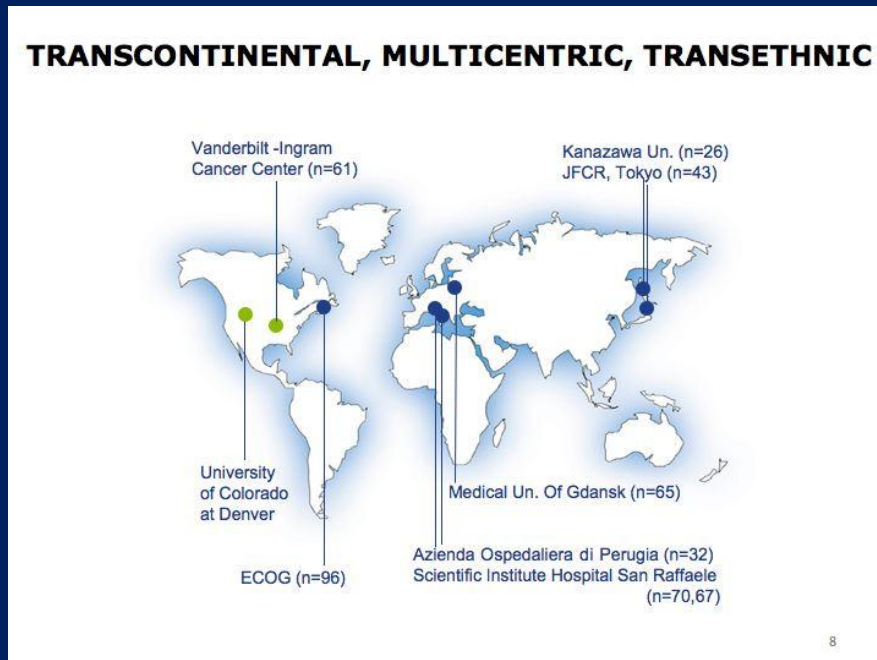


Prospectively assessed EGFR abnormalities in NSCLC



Serum proteomics

Serum proteomic profiling in NSCLC - background

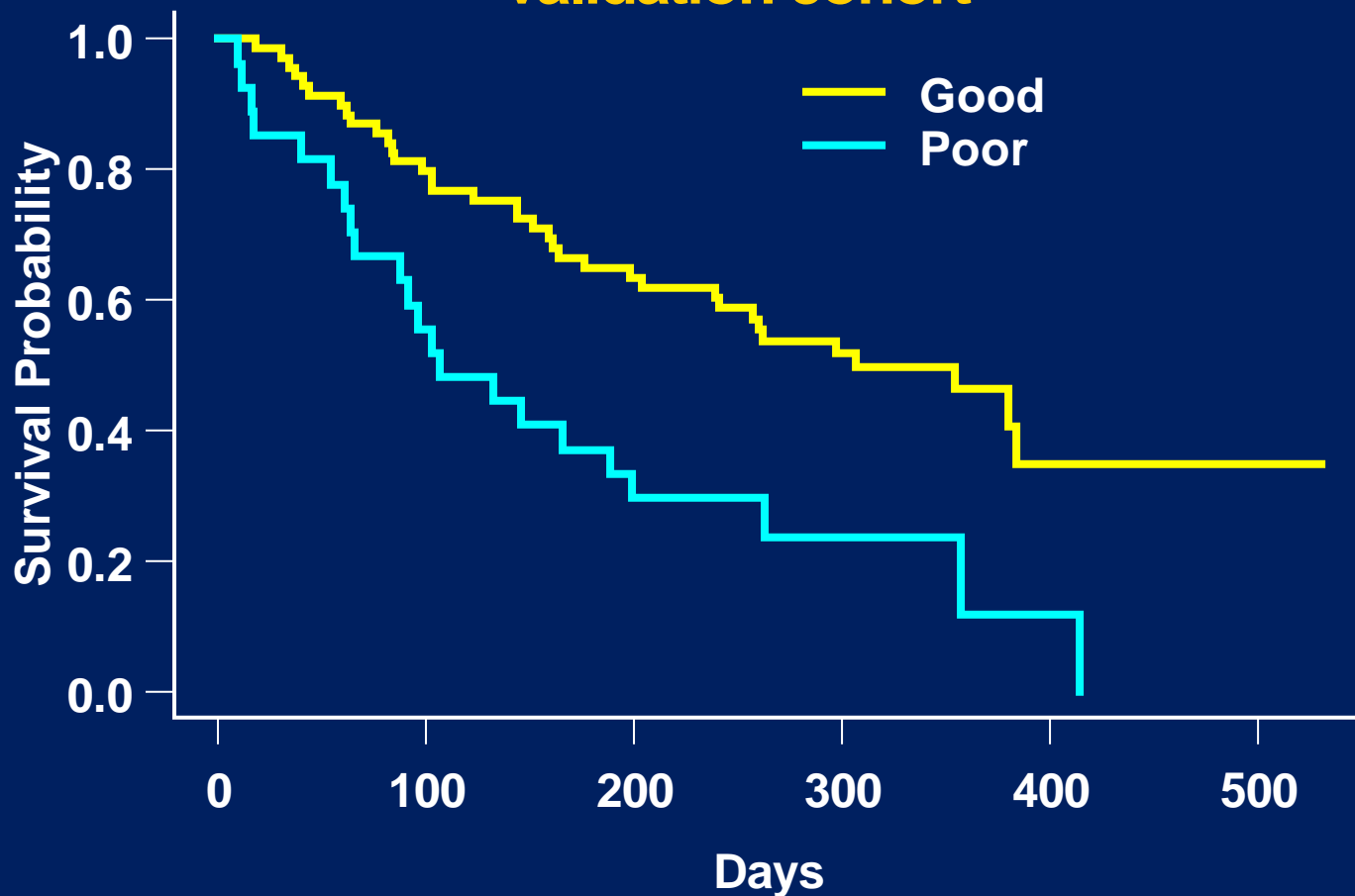


VeriStrat proteomic profile:

based on 8 m/z features of pretreatment sera analyzed by **MALDI MS** in patients with NSCLC

E3503 - overall survival by MALDI-MS risk classification (n=96)

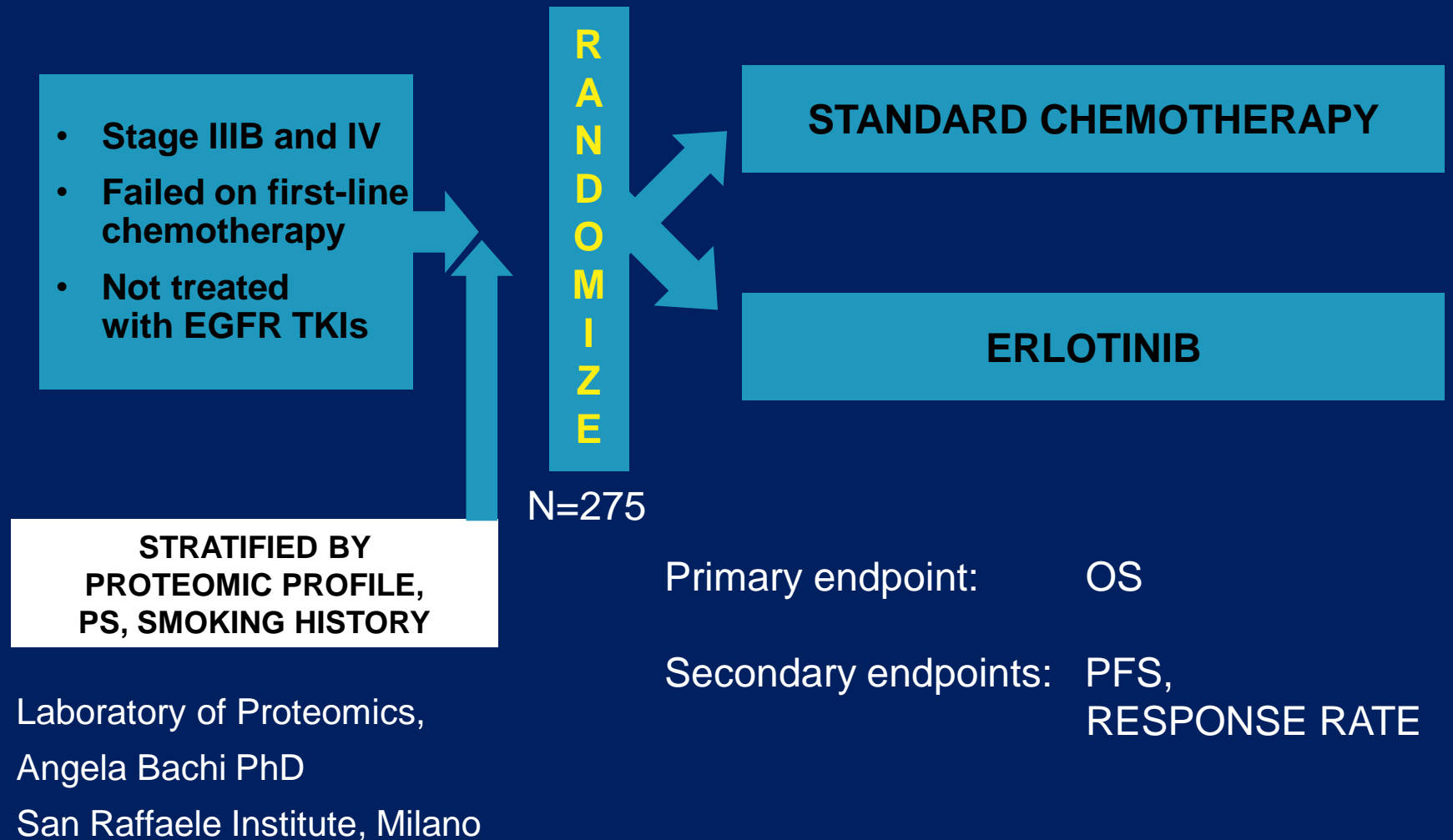
validation cohort



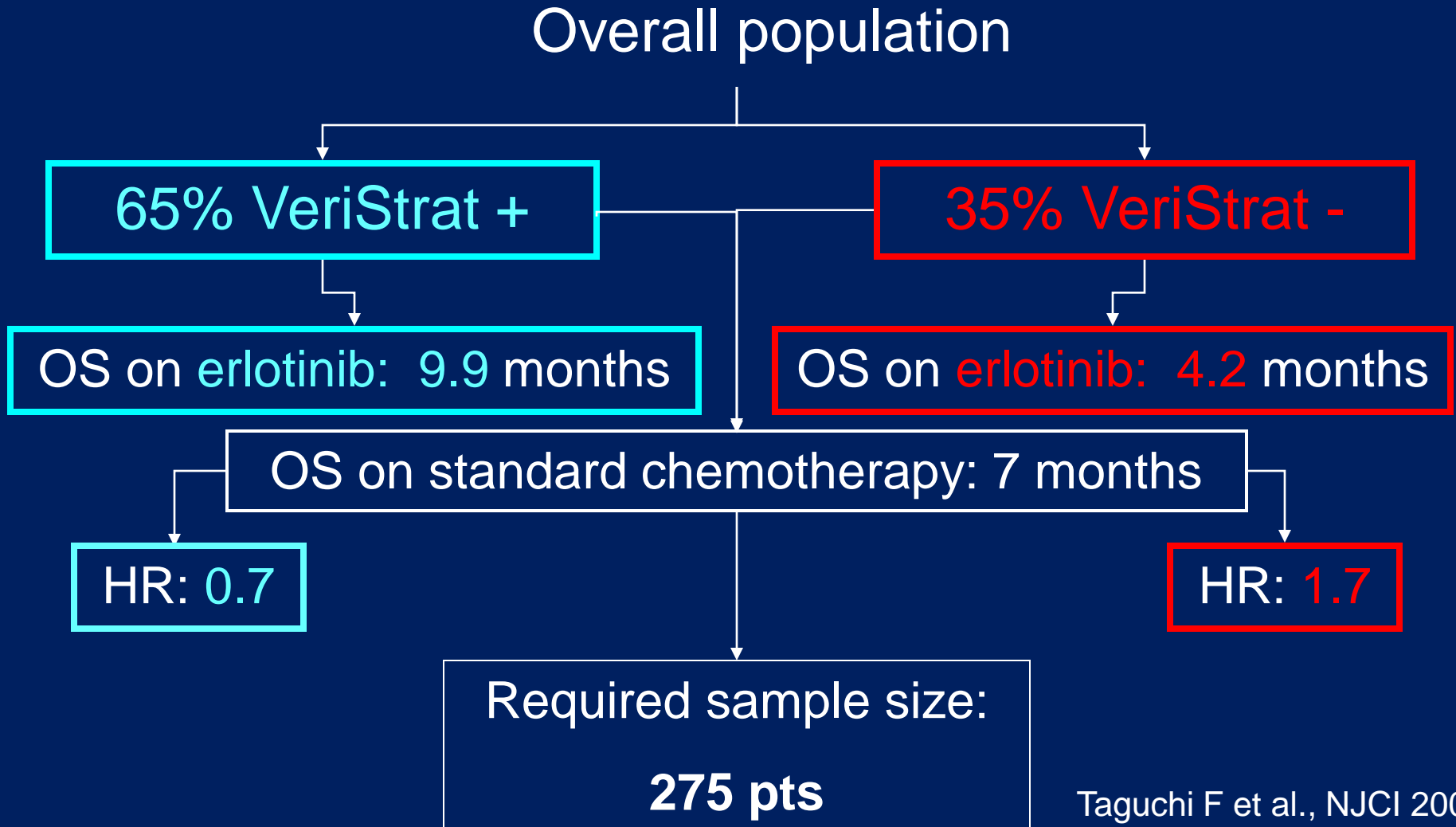
median survival of 306 days (Good) vs. 107 days (poor)

HR = 0.41 [0.17,0.63] p = 0.0007

PROSE Phase III study



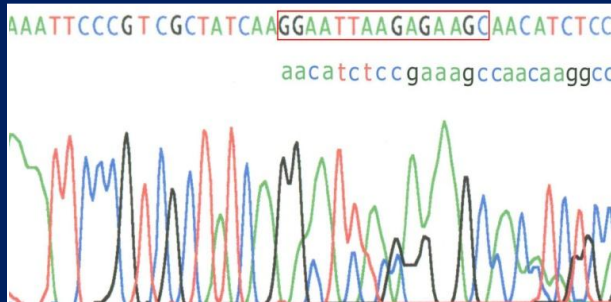
PROSE statistical design



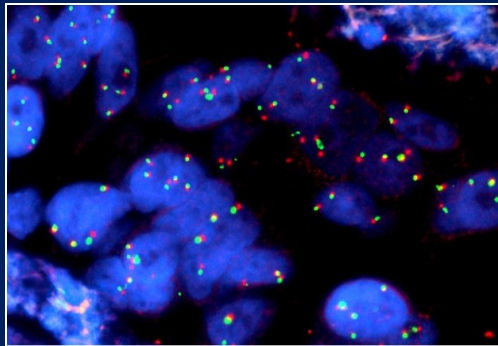
Taguchi F et al., NCI 2007

Spreafico et al., in press

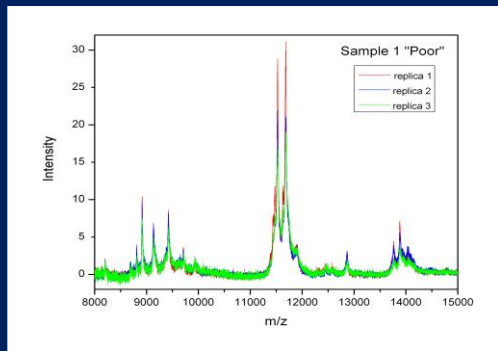
Summary



Activating EGFR mutations
Established



High EGFR gene copy number
Not for the first line tx



Serum proteomics
Work in progress

Conclusions

- **Progress in individualization of lung cancer treatment is achieved through well designed clinical trials with prospective biomarker assessment**
- **EGFR targeted therapy trials serve as example for new molecule developments in oncology**