



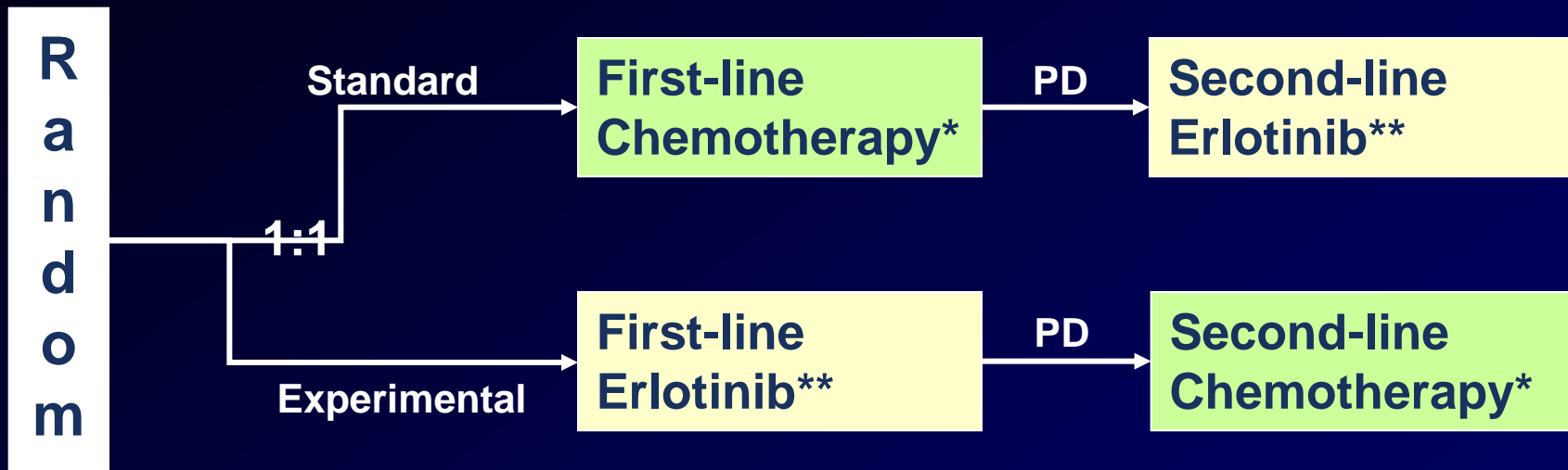
TREATMENT DURATION AND SEQUENCING OF EGFR-TKIs

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EGFR-TKIs efficacy in unselected NSCLC

Reference	#	Line	Drug	RR (%)	PFS (months)	OS (months)
Akerley	40	I	Erlotinib	15	1.9	11.5
Hesketh	81	I	Erlotinib	8	2.1	5
Jackman	80	I	Erlotinib	10	3.5	10.9
Giaccone	53	I	Erlotinib	22.7	2.7	12.8
Govindan	198	I	Gefitinib	6.3	NR	6
Niho	42	I	Gefitinib	30	NR	13.9
West	136	I/II	Gefitinib	17	NR	13
Janne	200	I/II+	Gefitinib	4.1	NR	4.5
Kubota	62	II/III	Erlotinib	28.3	2.5	14.7
Perng	299	II/III	Erlotinib	29	5.6	NR
Perez-Soler	57	II/III	Erlotinib	12.3	2.1	8.4
Fukuoka	210	II/III	Gefitinib	18.4	2.7	7.6
Cappuzzo	106	II/III	Gefitinib	14	3.4	9.4
Kris	216	III	Gefitinib	12	NR	7
Simon	183	I/II/III+	Gefitinib	3.8	3.6	8.8
Chen	36	II/III/IV	Gefitinib	33.3	4.7	9.5
Felip	83	II/III/IV	Erlotinib	10	1.4	3.9

Do we need a selection for first-line therapy? TORCH study



Strata:

- histology
- smoking status
- gender
- country (Italy, Canada)
- age
- ethnicity

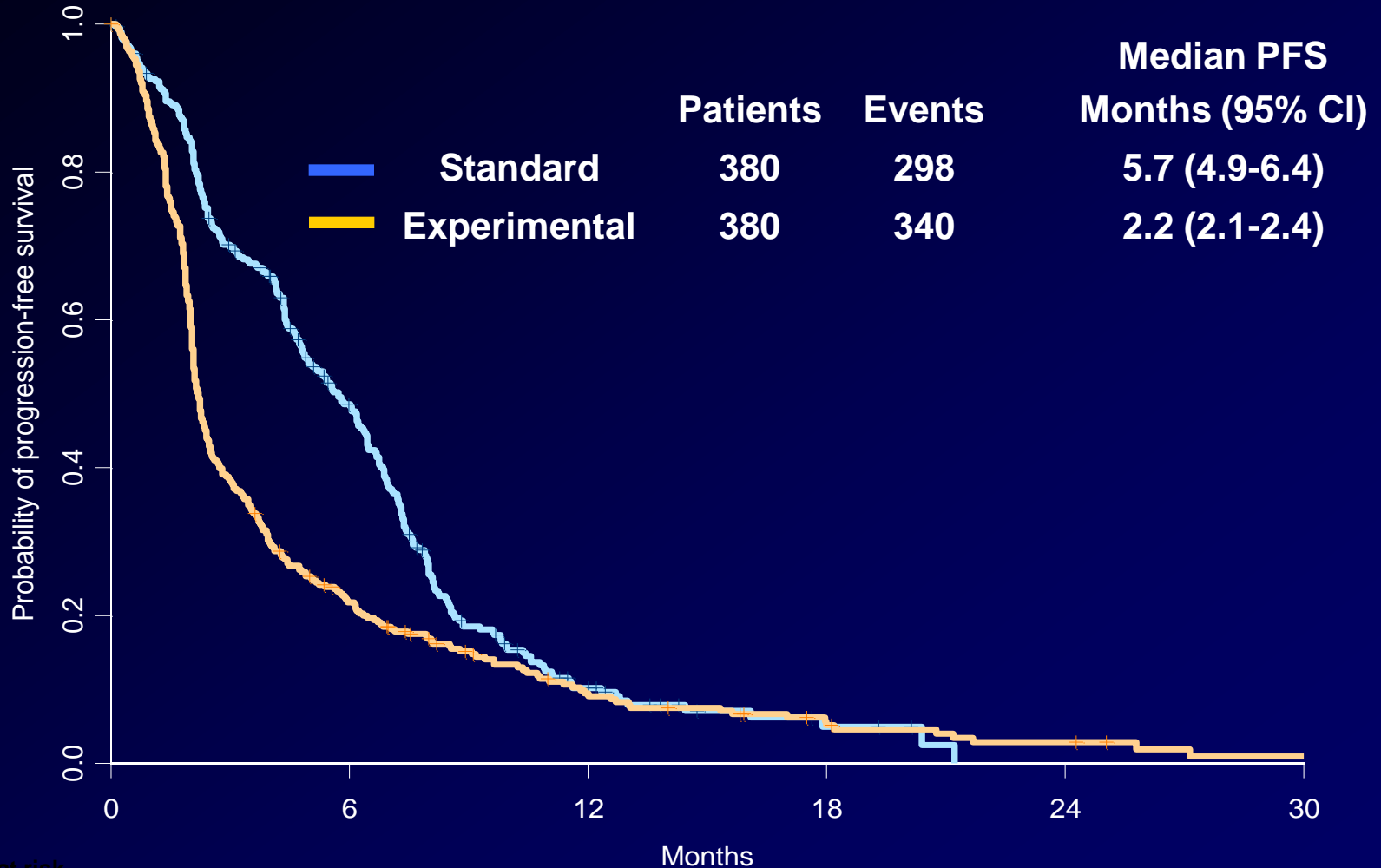
*Chemotherapy:

- Cisplatin, 80 mg/m², day 1
- Gemcitabine, 1200 mg/m², day 1 and 8 every 3 weeks, for 6 cycles

**Erlotinib:

150 mg/day p.o. until progression

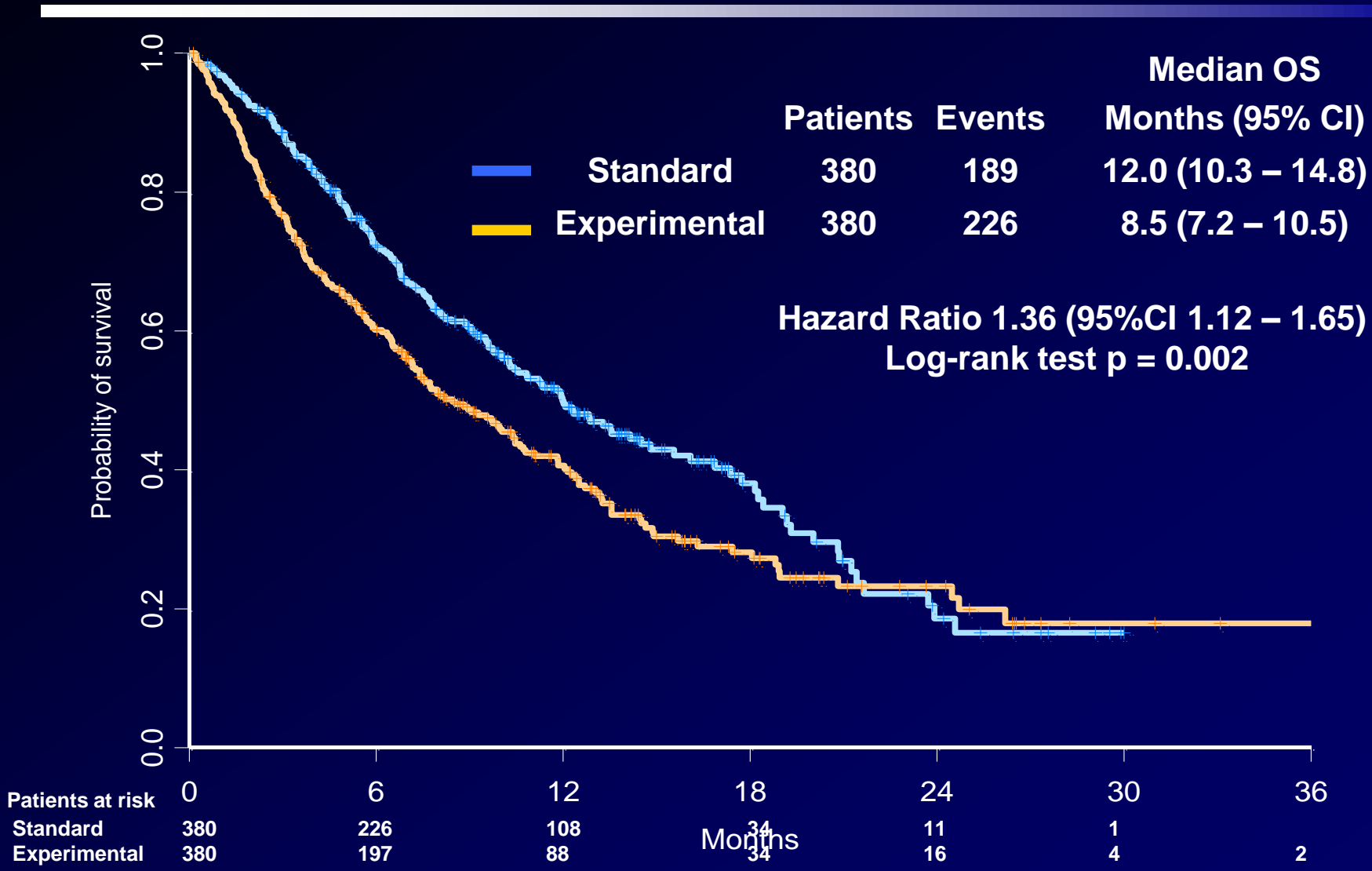
Progression-free survival



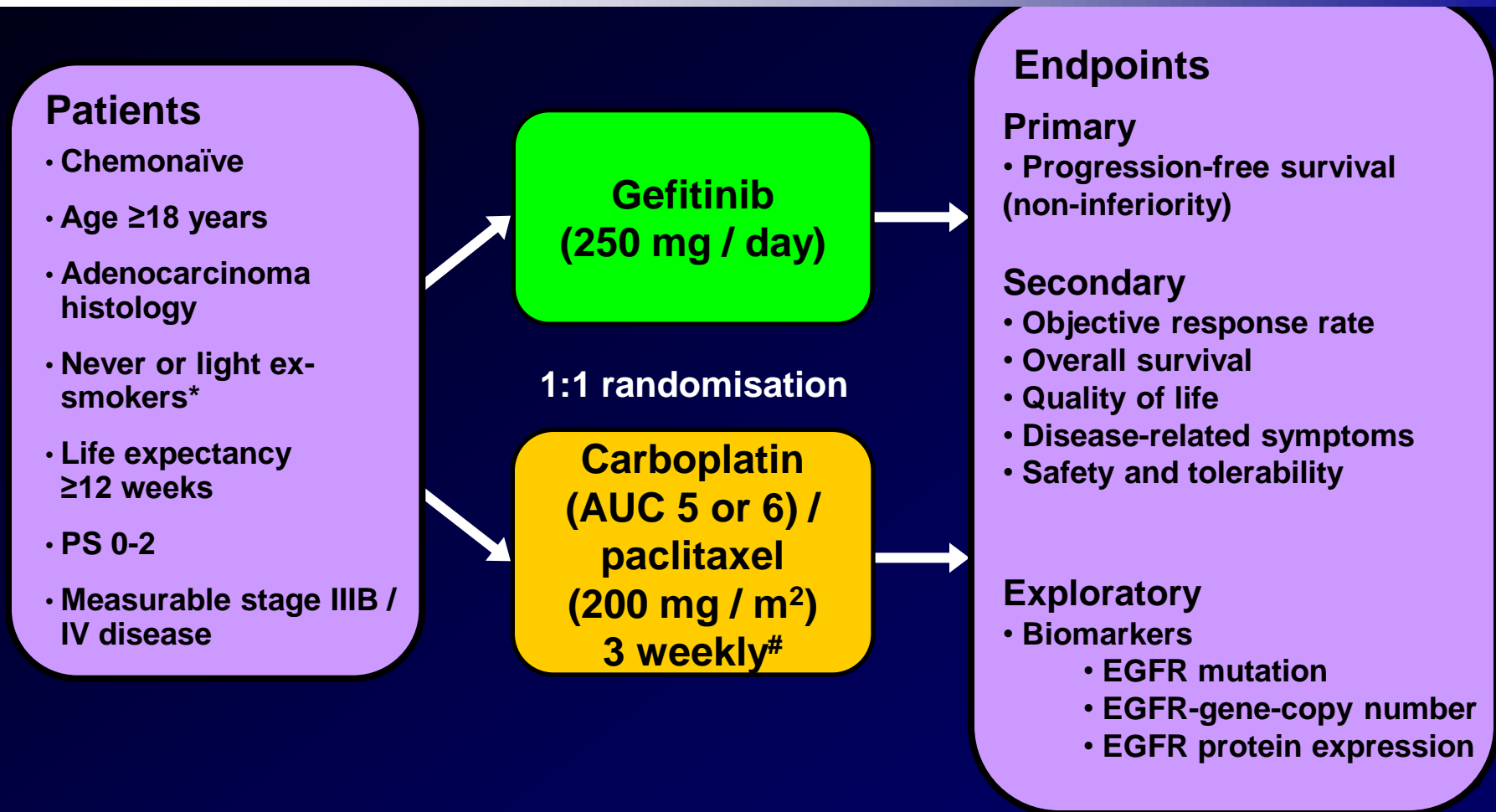
Patients at risk

	0	6	12	18	24	30
Standard	380	151	23	5	-	-
Experimental	380	74	24	12	6	2

Overall survival



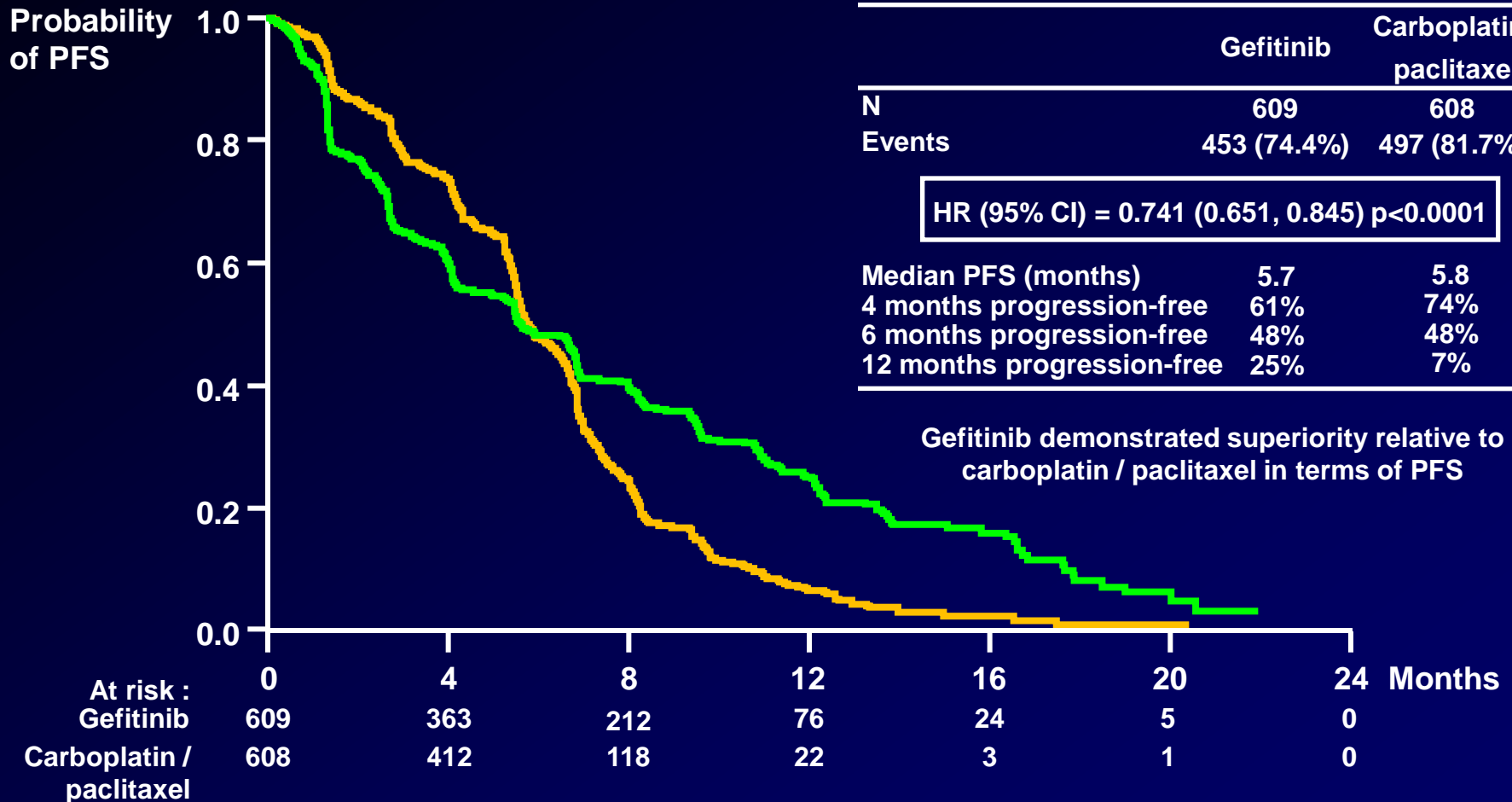
Do we need a selection for first-line therapy? The IPASS Trial



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

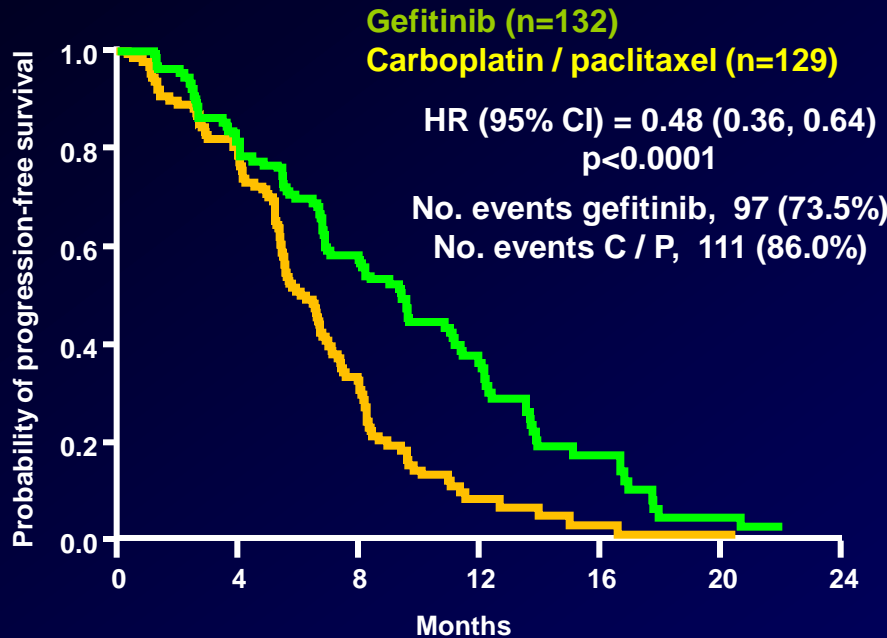
Progression-free Survival in ITT Population



Primary Cox analysis with covariates
 HR <1 implies a lower risk of progression on gefitinib

Progression-free Survival in EGFR Mutation Positive and Negative Patients: Two Important Findings

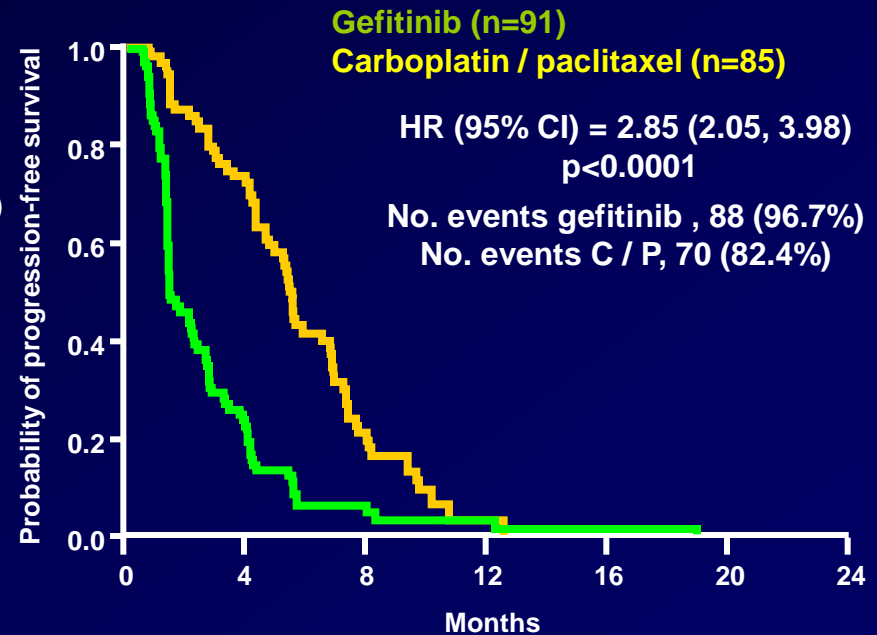
EGFR mutation positive



At risk :

Gefitinib	132	108	71	31	11	3	0
C / P	129	103	37	7	2	1	0

EGFR mutation negative



Gefitinib	91	21	4	2	1	0	0
C / P	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p < 0.0001

ITT population

Cox analysis with covariates

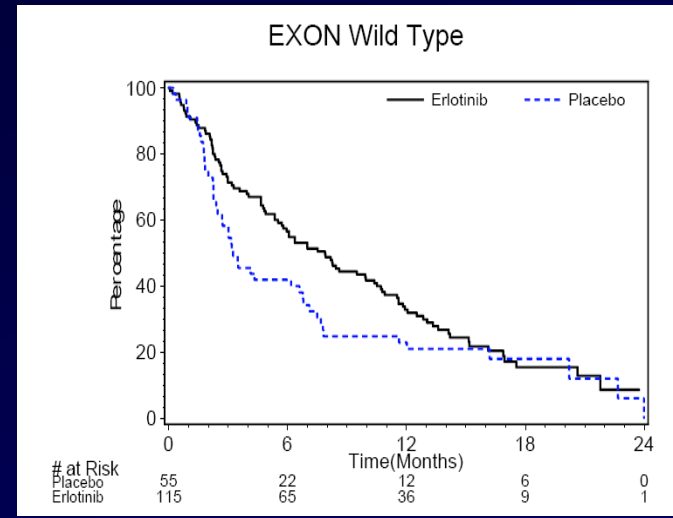
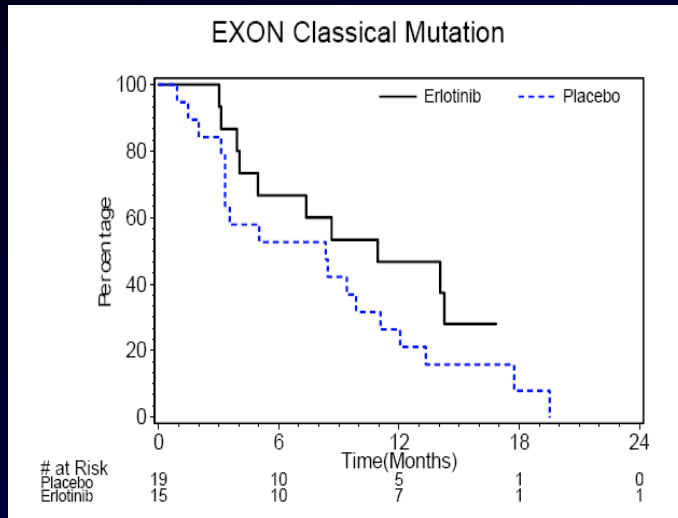
When should we use EGFR-TKIs after front-line chemotherapy

Three different clinical possibilities:

- EGFR mutation status defined only once front-line chemotherapy was initiated
- Maintenance setting
- Second-line

EGFR mutation test is not crucial for EGFR-TKI selection in pretreated NSCLC

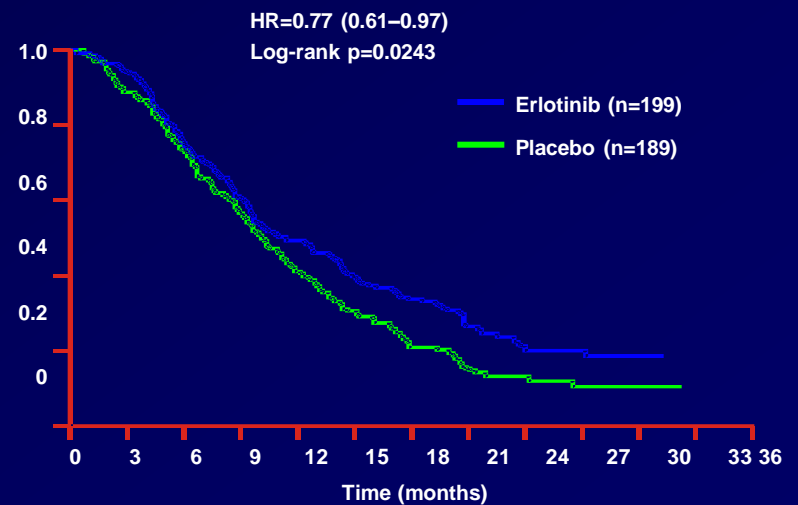
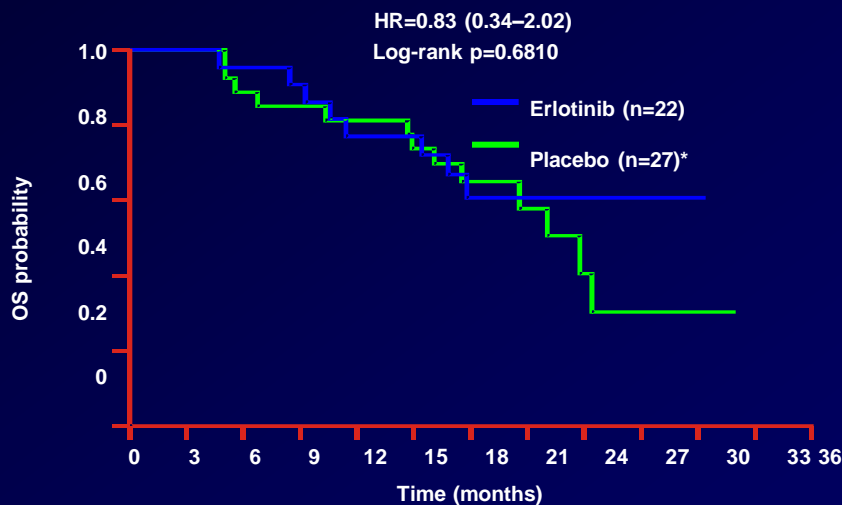
BR 21



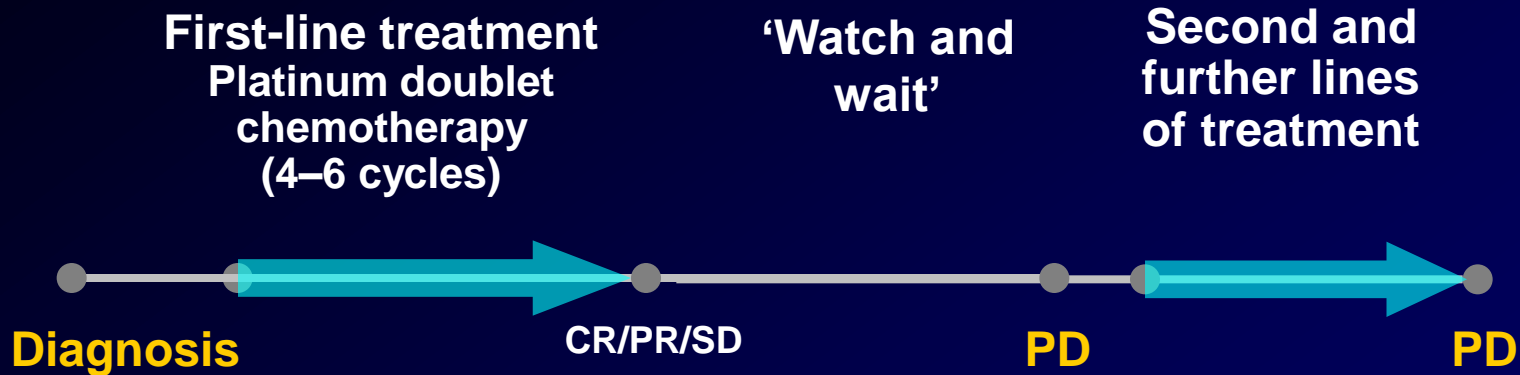
EGFR mutation+

EGFR wild-type

SATURN

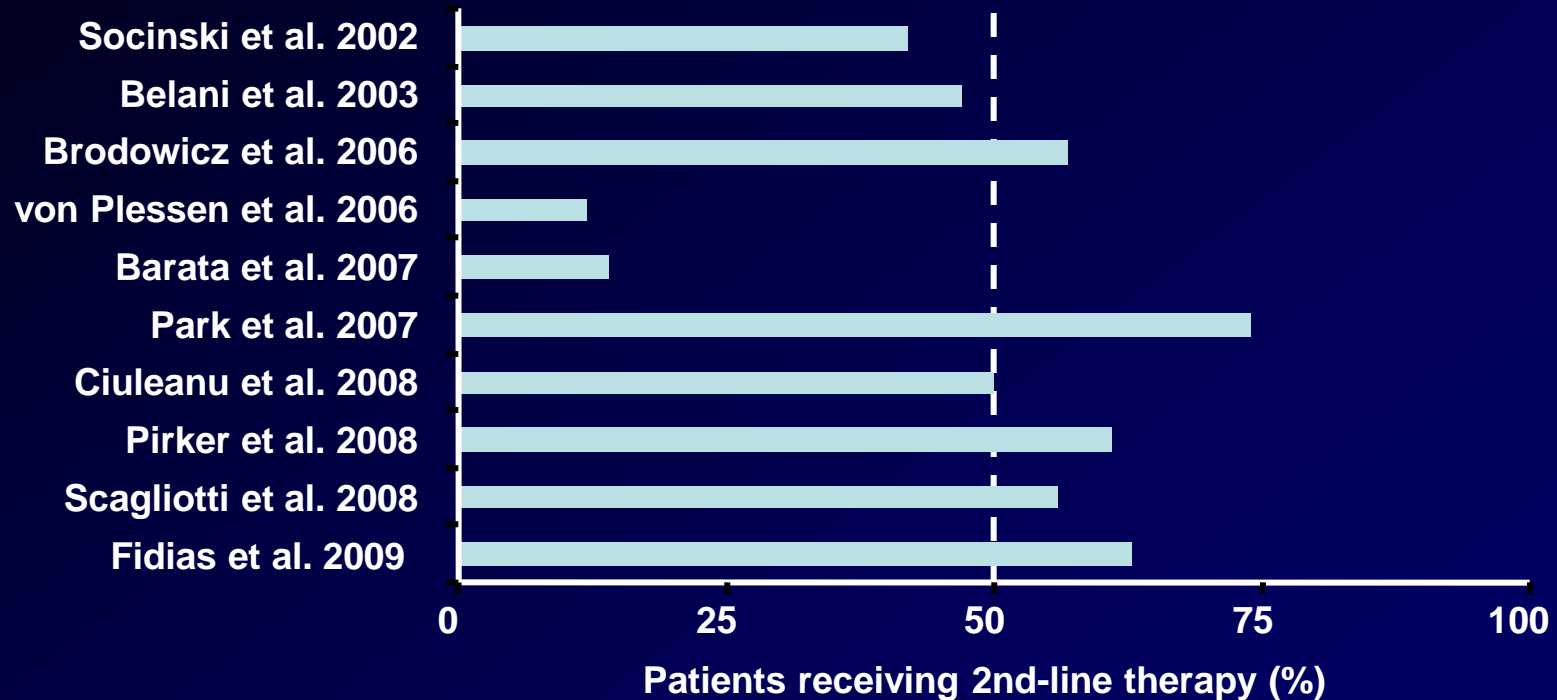


Should we use EGFR-TKIs in the maintenance setting?



- As a result of cumulative toxicity, patients receive a limited number of cycles of chemotherapy
- According to ASCO guidelines¹, those with stable disease or better will be observed, with regular follow up to check for disease progression – ‘watch and wait’ approach

Patients may not be eligible for further therapy upon progression after first-line chemotherapy

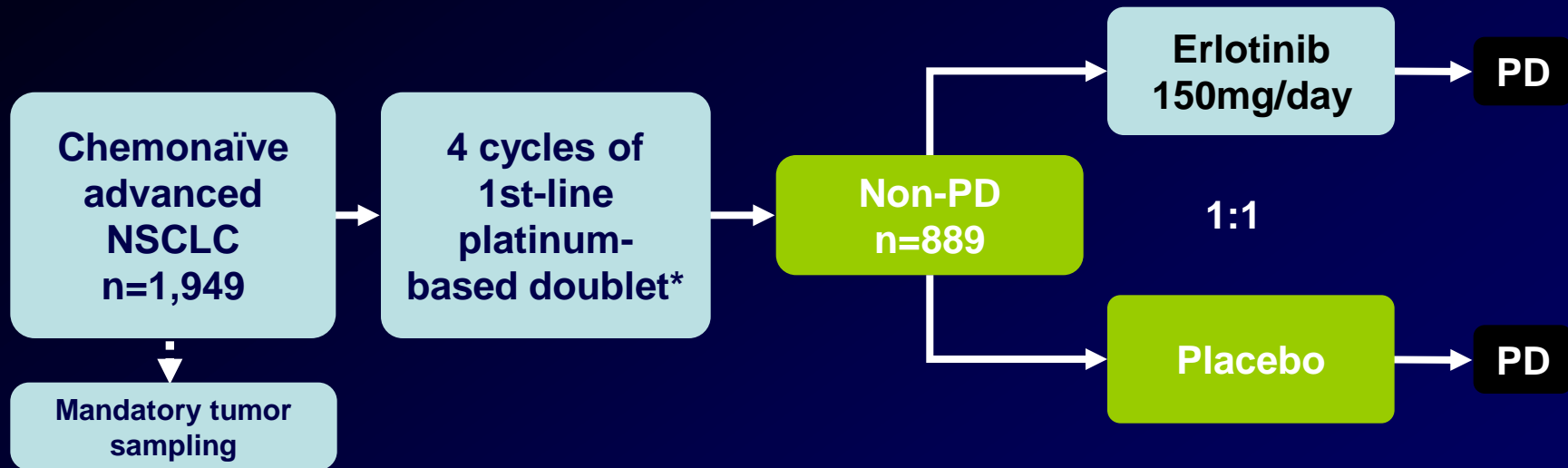


In recent studies, approximately 50% of patients did not receive second-line therapy

Recent studies evaluating the role of maintenance therapy in NSCLC

- **Studies with cytotoxic agents used in first-line combinations:**
 - Gemcitabine
- **Studies with cytotoxic agents not used in first-line combinations:**
 - Docetaxel
 - Pemetrexed
- **Studies with targeted agents used in first-line combinations:**
 - Bevacizumab
 - Cetuximab
- **Studies with targeted agents not used in first-line combinations:**
 - Erlotinib
 - Gefitinib

SATURN study design



Stratification factors:

- EGFR IHC (positive vs negative vs indeterminate)
- Stage (IIIB vs IV)
- ECOG PS (0 vs 1)
- CT regimen (cis/gem vs carbo/doc vs others)
- Smoking history (current vs former vs never)
- Region

Co-primary endpoints:

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

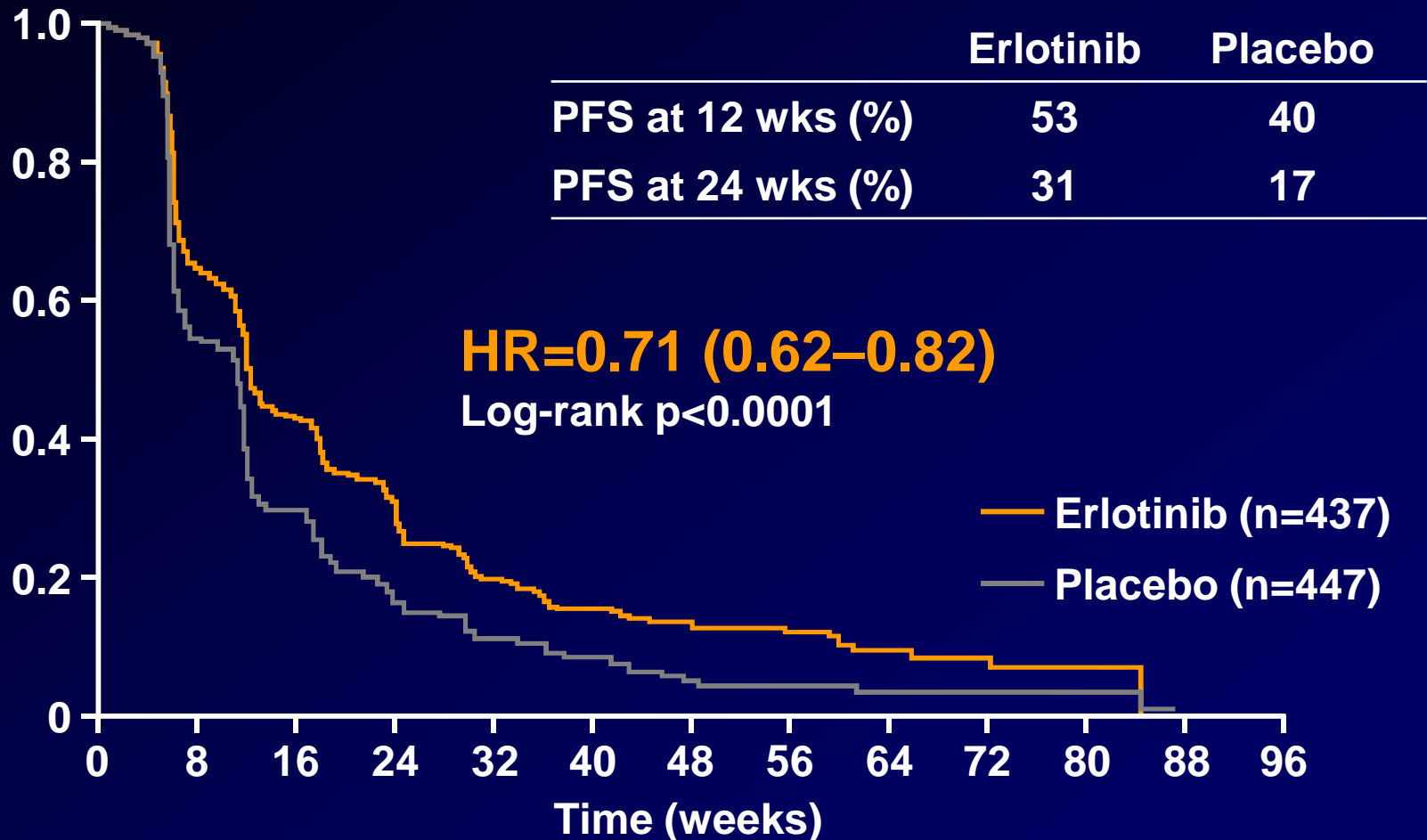
Secondary endpoints:

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

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

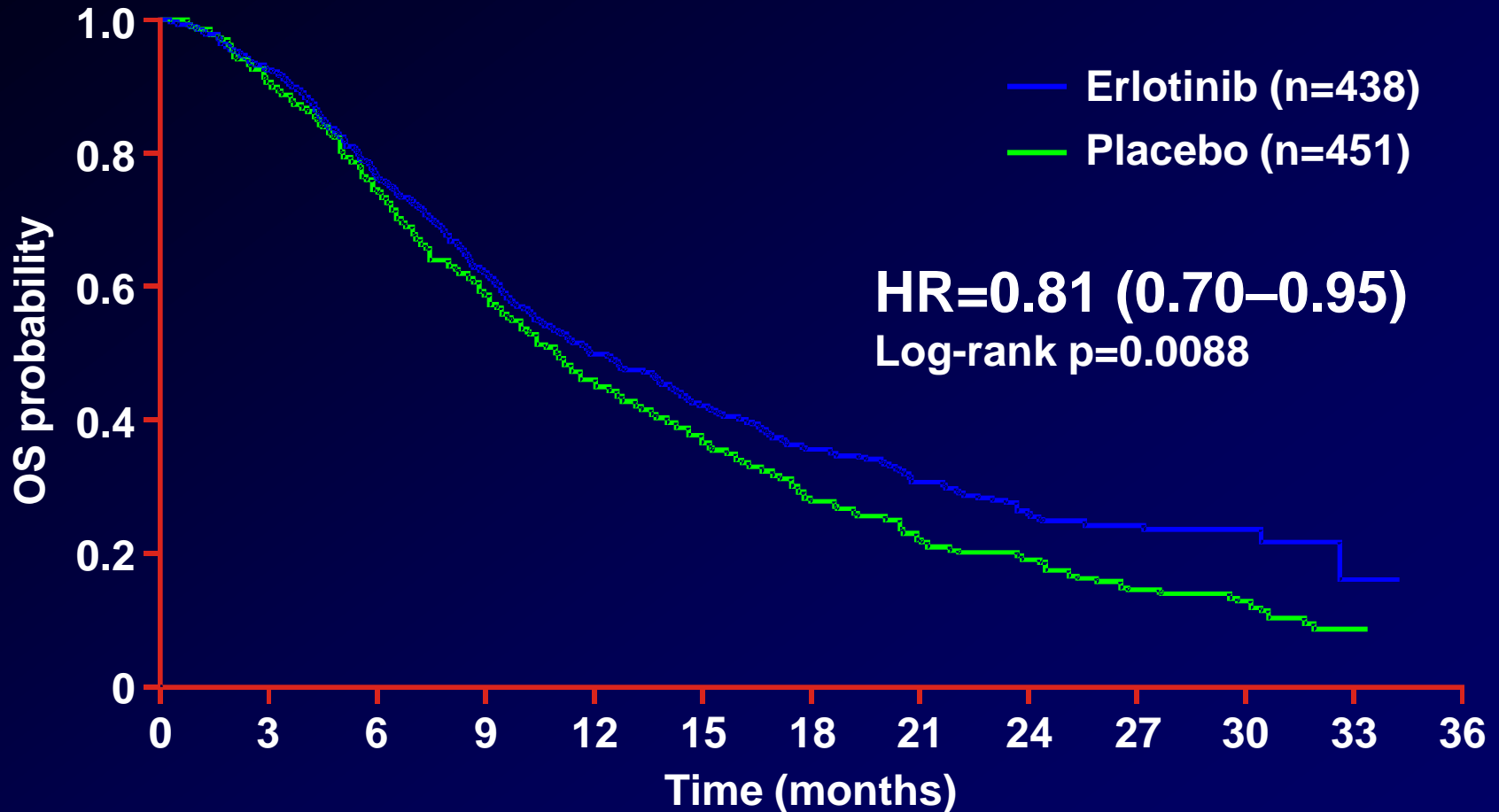
PFS*: all patients (ITT)

PFS probability



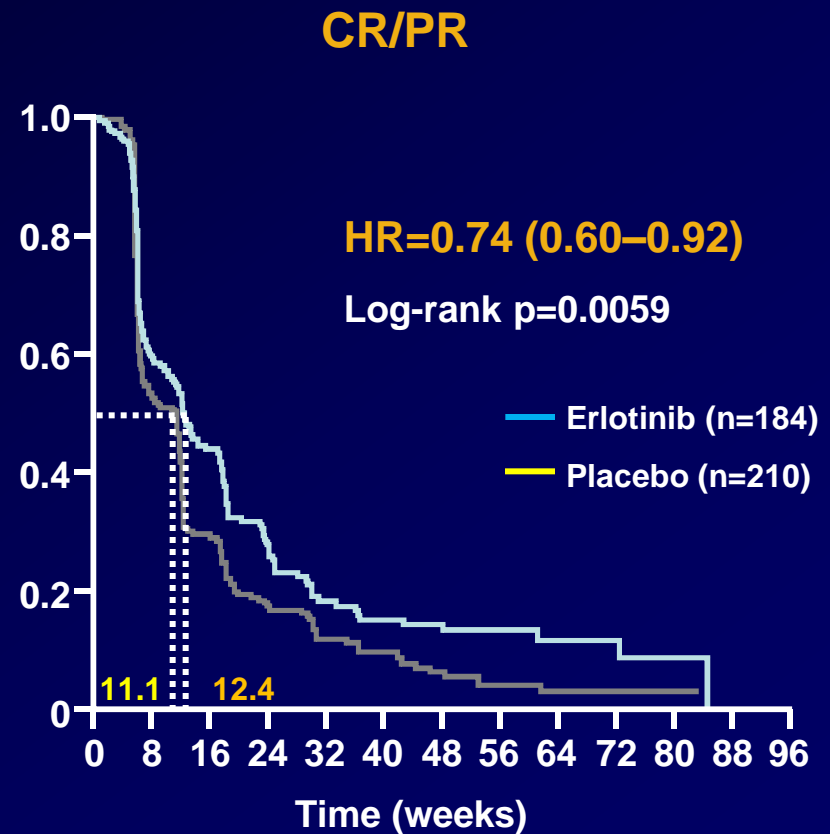
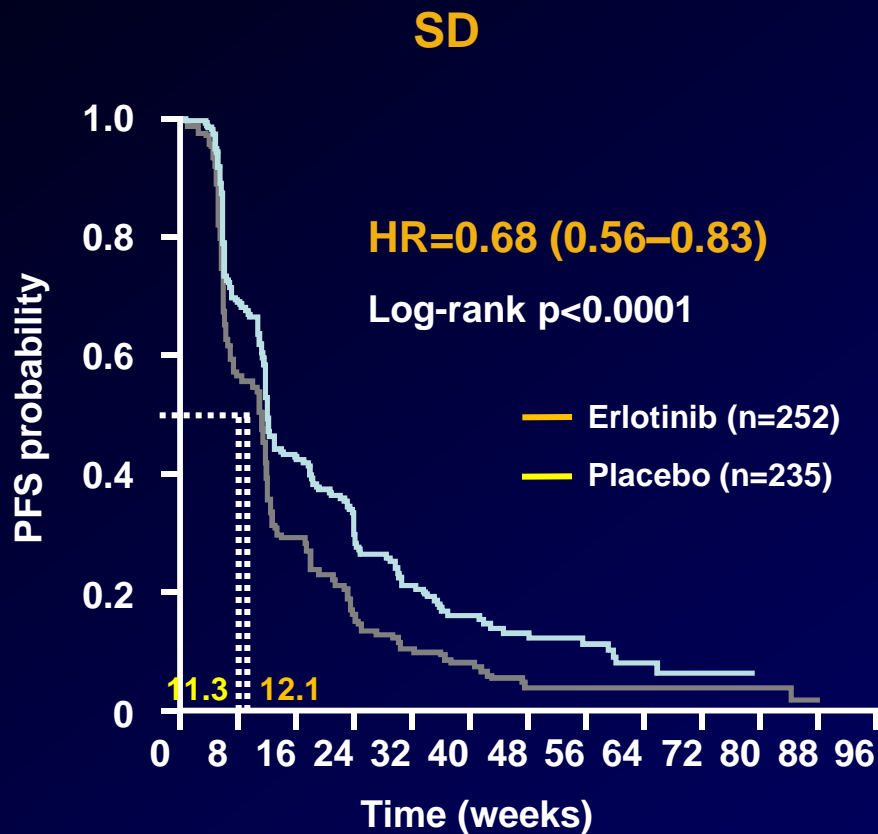
*PFS is measured from time of randomization into the maintenance phase; assessments were every 6 weeks

SATURN: OS in all patients (ITT)

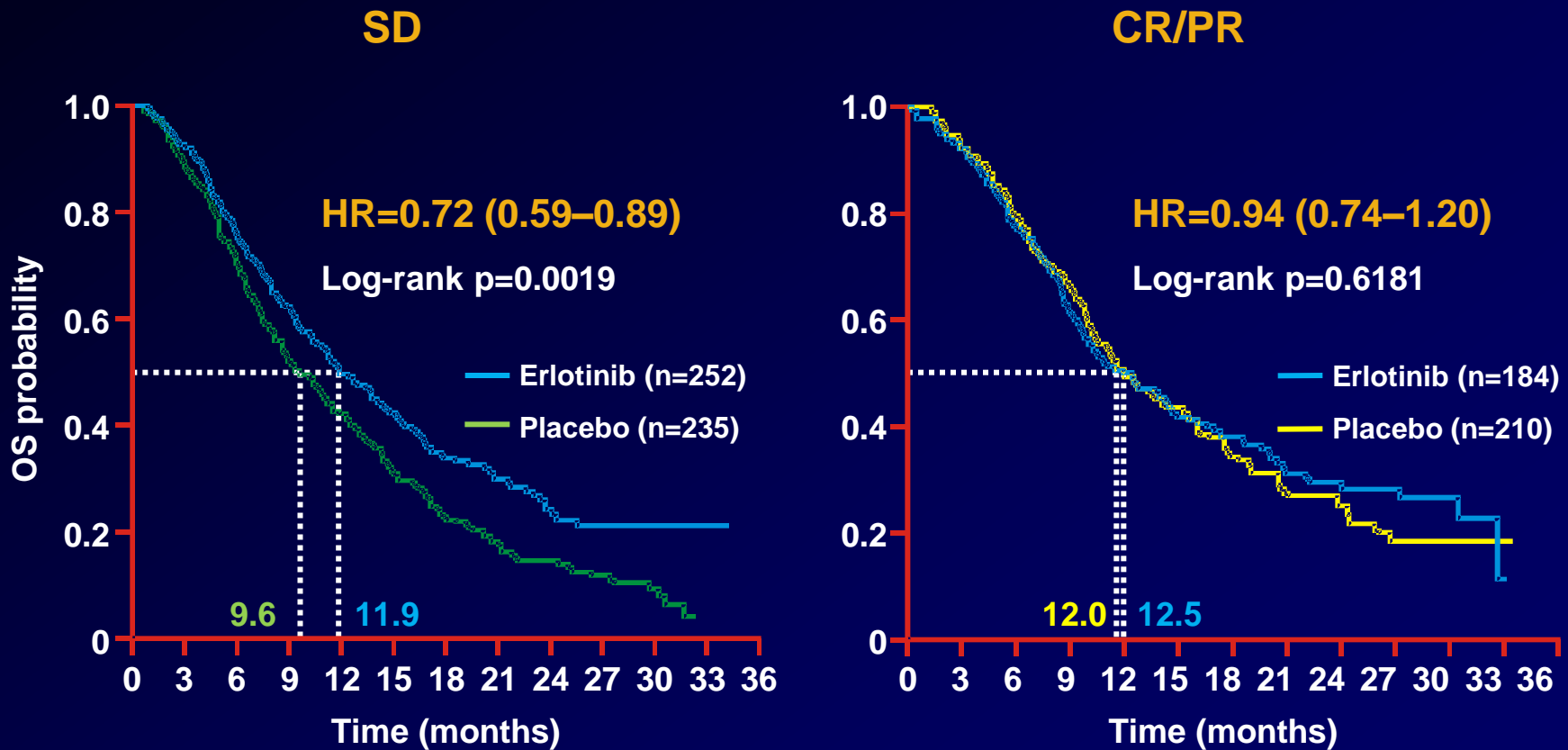


*OS is measured from time of randomisation into the maintenance phase;
ITT = intent-to-treat population

PFS according to response to first-line chemotherapy

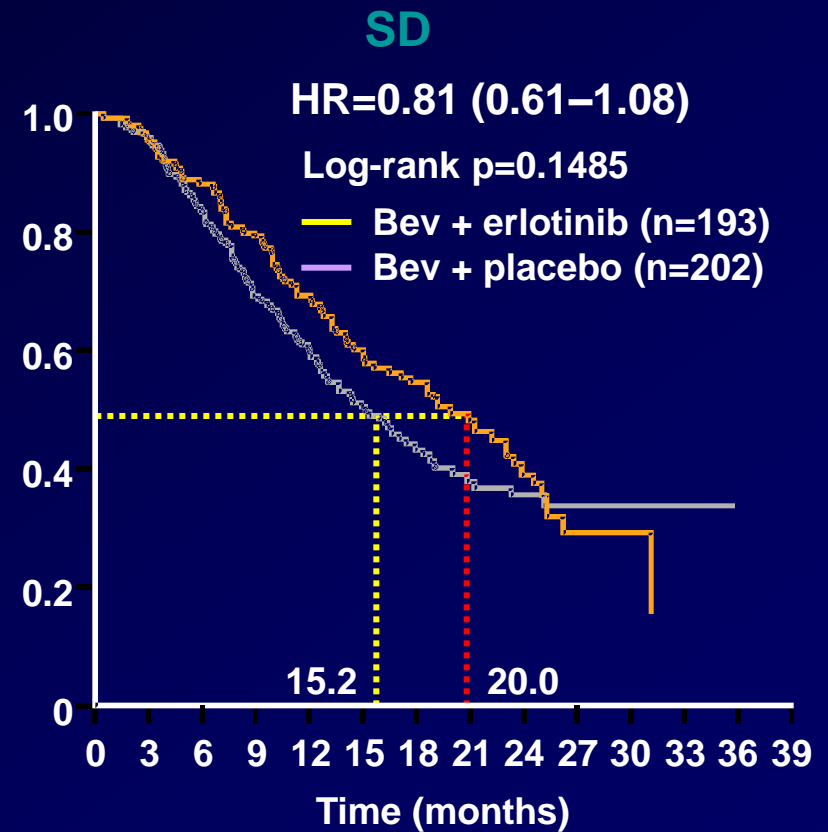
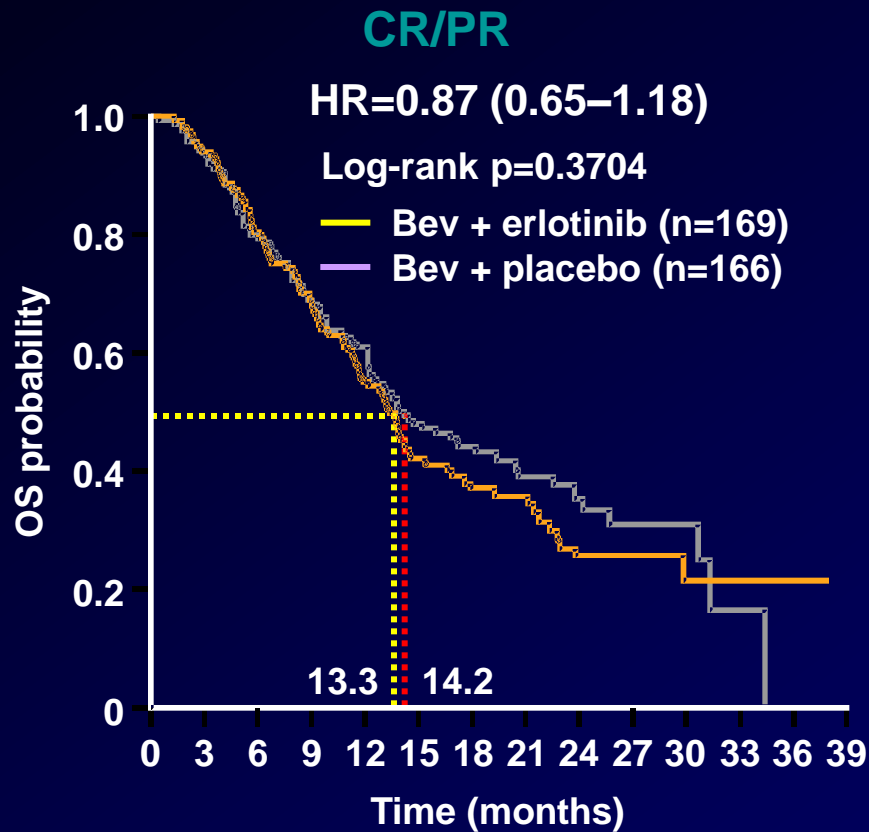


OS according to response to first-line chemotherapy*



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

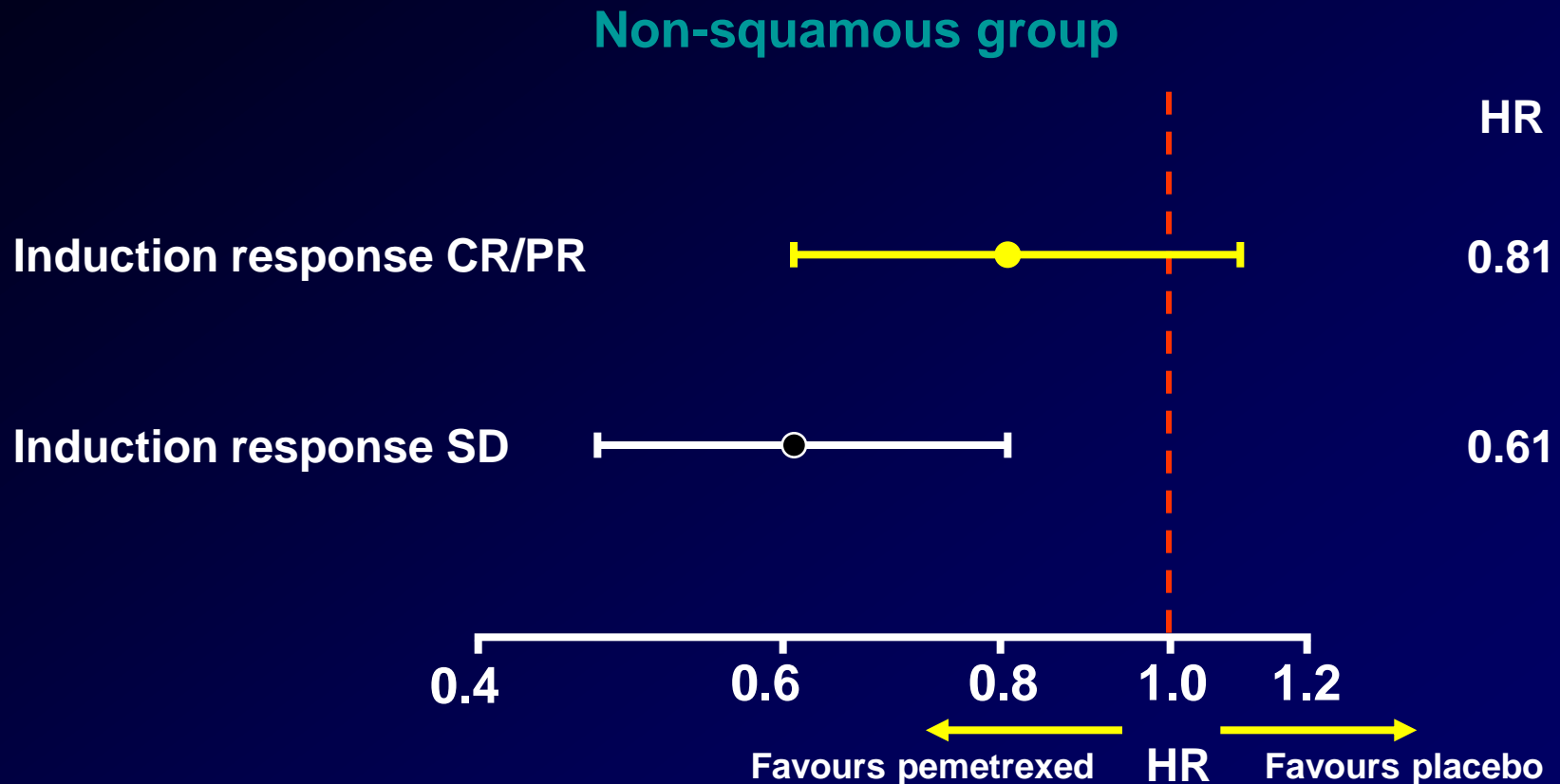
ATLAS: OS according to response to first-line chemotherapy + bevacizumab



(19 June 2009 cut-off; 57% OS events)

F. Hoffmann-La Roche, data on file

JMEN: OS according to response to first-line chemotherapy



Maintenance therapy paradigm

First-line platinum-based chemotherapy x 4-6 cycles

No Progression-PS 0-1

Refuse of any therapy

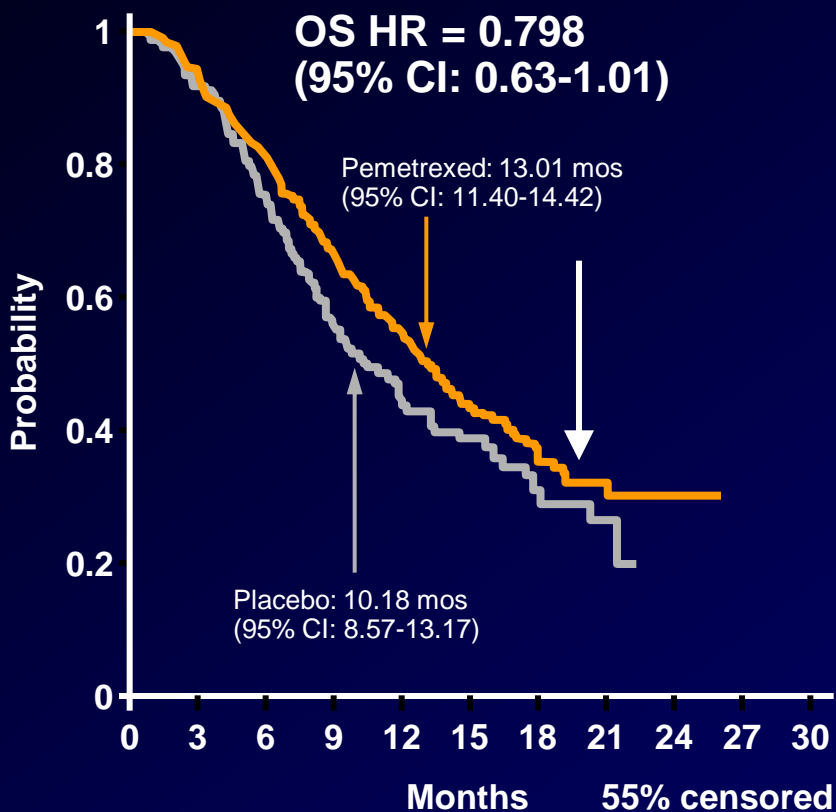
**Prevent PS
deterioration: strict
FU (q 4-6 weeks)**

In favor of therapy

Maintenance therapy

Maintenance Chemotherapy – OS: Curves Separate Early and Come Together by 20 Months

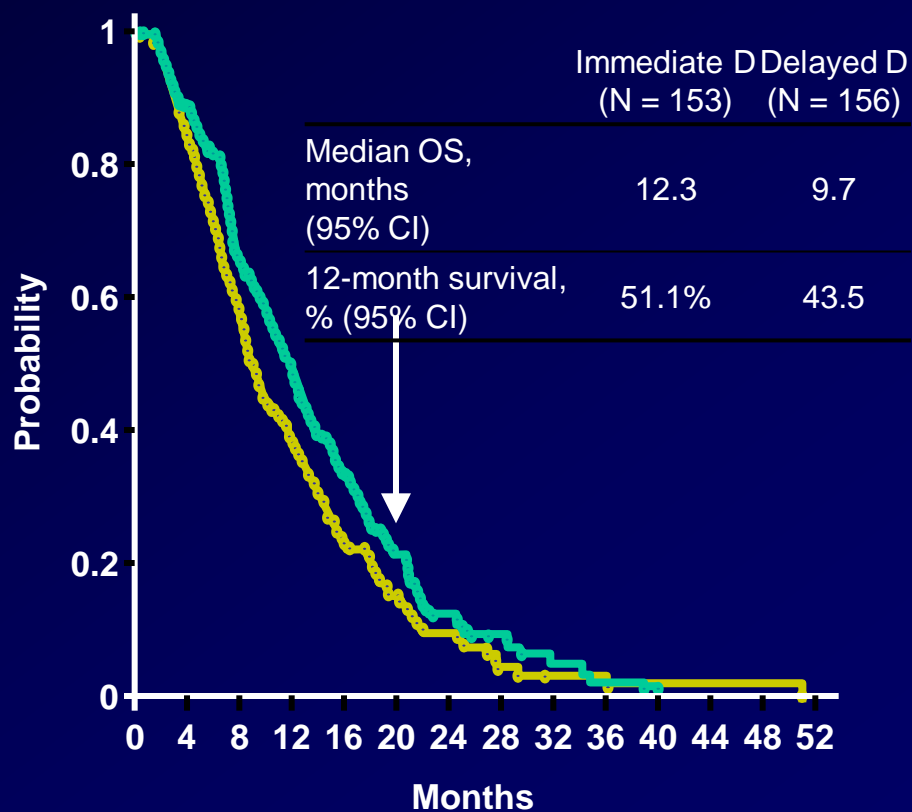
Pemetrexed vs. Placebo



— Pemetrexed
— Placebo

Ciuleanu T et al. *The Lancet* 2009;374(9699):1432-1440.

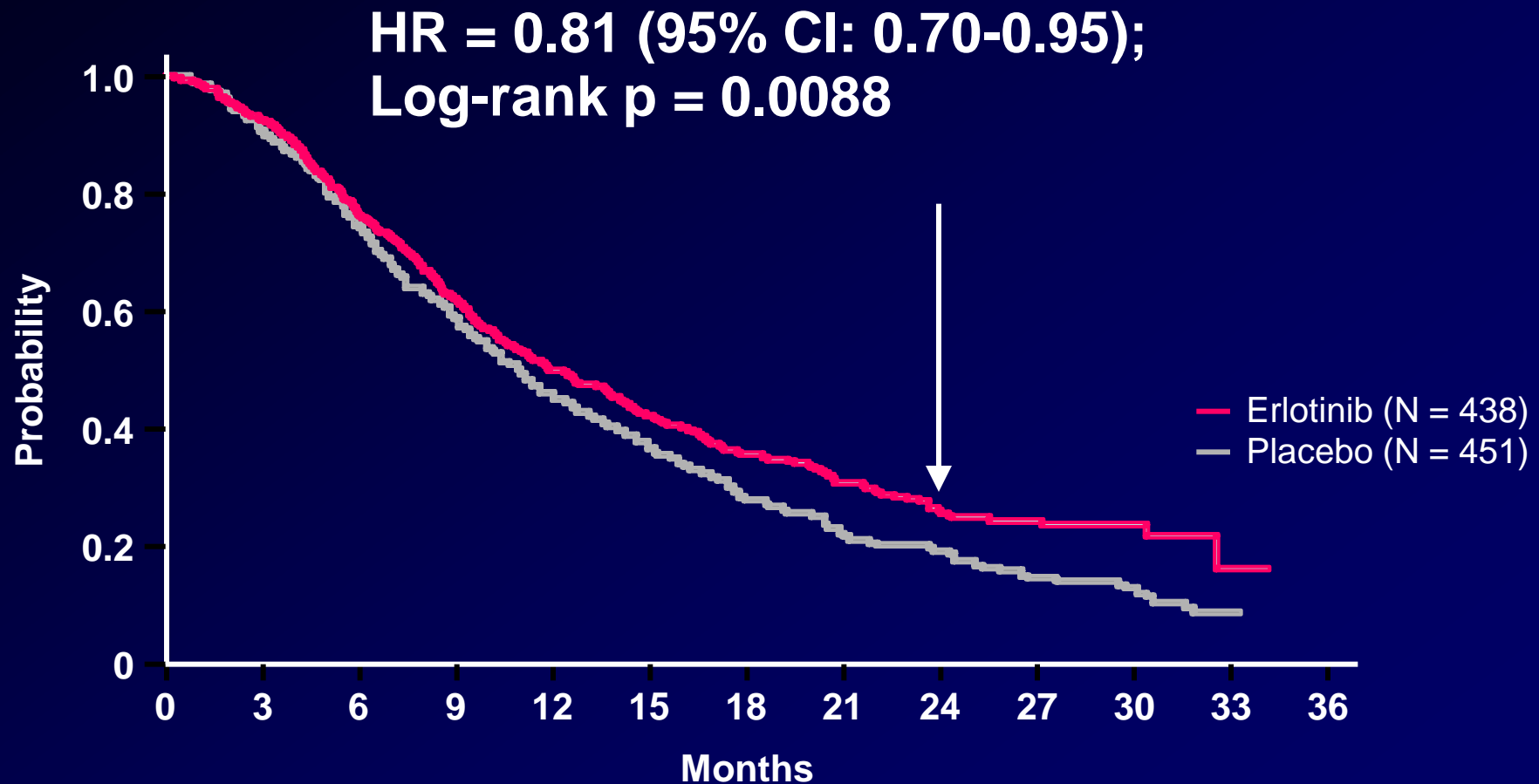
Docetaxel vs. Placebo



— Immediate Docetaxel
— Delayed Docetaxel

Fidas PM, et al. *J Clin Oncol.* 2009;27(4):591-598.

Maintenance Erlotinib – SATURN OS: Curves Separate Late and Stay Separated for Many Months



Conclusions

- **In untreated NSCLC, EGFR-TKIs represent the optimal choice only in presence of activating EGFR mutations**
- **In pretreated NSCLC a substantial survival benefit is detectable in the EGFR wild-type population**
- **Maintenance EGFR-TKI therapy is an option that should be discussed with the patient**
- **EGFR-TKI therapy should be continued until disease progression, unacceptable toxicity or patient refusal**