PROGNOSTIC AND PREDICTIVE BIOMARKERS IN NSCLC

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Prognostic versus predictive

- Prognostic: In presence of the biomarker patient outcome independent of the treatment
- Predictive: In presence of the biomarker patient outcome is different according to the treatment

Predictive Factors for EGFR-TKI Sensitivity

	Predictive for Response	Predictive for Survival
Clinical	•Gender •Histology •Smoking history •Ethnicity	•Smoking history •Response to prior therapy •PS •Histology •Previous Platinum •Skin rash •Ethnicity
Biological	•EGFR Gene mutation •EGFR high copy number •HER2 high copy number •Akt activation	•EGFR gene mutation •EGFR high copy number

	Predictive for Resistance
Primary Resistance	• K-Ras Mutation • EGFR exon 20 insertion • HER2 exon 20 mutation
Acquired Resistance	• EGFR T790M-D761Y • MET Amplification

EGFR mutations in prospective studies: the strongest predictor for response

Reference	#	Selection criterion	Line	Drug	RR (%)	PFS (months)	OS (months)
Asahina	16	EGFR mutation	I	Gefitinib	75	8.9	Not reached
Inoue	30	EGFR mutation	I	Gefitinib	66	6.5	17.8
Inoue	16	EGFR mutation	I	Gefitinib	75	9.7	Not reported
Kimura	13	EGFR mutation	I	Gefitinib	53.8	3.2	10.1
Rosell	217	EGFR mutation	I/II	Erlotinib	70.6	14	27
Rosell	12	EGFR mutation	I	Erlotinib	90	13	>28.0
Sequist	34	EGFR mutation	I	Gefitinib	55	9.2	17.5
Yang	55	EGFR mutation	I	Gefitinib	69	8	24
Sugio	20	EGFR mutation	I/II	Gefitinib	63.2	7.1	20
Sunaga	21	EGFR mutation	I/II	Gefitinib	76	12.9	Not reached
Sutani	38	EGFR mutation	I/II	Gefitinib	78	9.4	15.4
Yoshida	27	EGFR mutation	I/II	Gefitinib	90.5	7.7	Not reached
Han	17	EGFR mutation	I/II+	Gefitinib	64.7	21.7	30.5
Tamura	28	EGFR mutation	I/II/III	Gefitinib	75	11.5	Not reached

EGFR-TKIs versus chemotherapy in first-line: Phase III trials in "clinically selected" patients

IPASS

- Chemonaive
- Age> 18
- Adenocarcinoma
- Never/light smokers
- ECOG PS:0-2
- Stage IIIB-IV

R 1 → Gefitinib (250 mg / day)

R 1 → Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m^2) 3 weekly#

FIRST SIGNAL

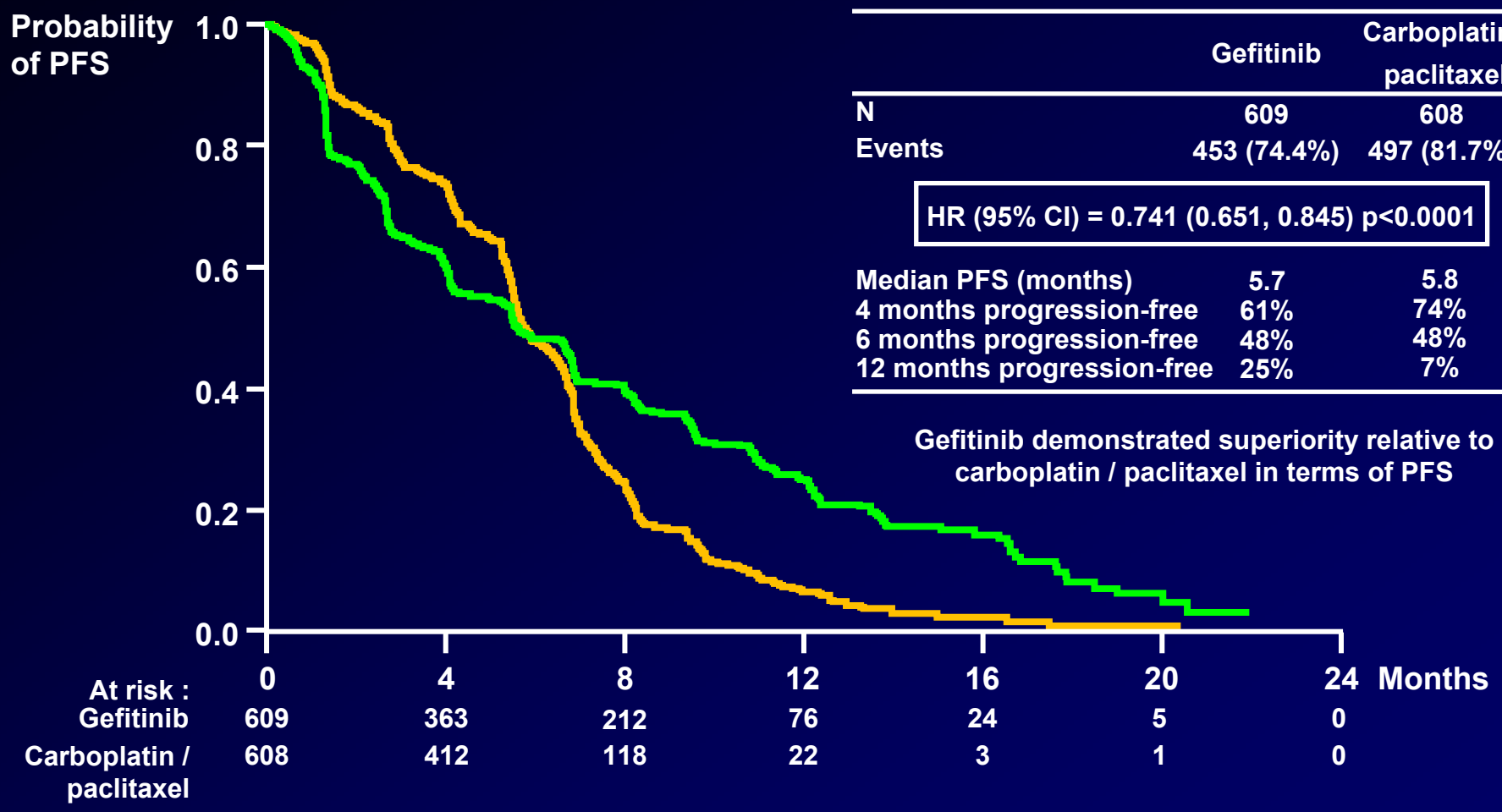
- Chemonaive
- Age 18-75 years
- Adenocarcinoma
- Never smokers
- ECOG PS:0-2
- Stage IIIB-IV

R 1 → Gefitinib (250 mg / day)

R 1 → Gemcitabine 1250 mg/mq 1,8
Cisplatin 80 mg/mq 1
Q 21 days, up to 9 cycles

Primary end-point: PFS

IPASS:PFS in ITT population



	Gefitinib	Carboplatin / paclitaxel
N	609	608
Events	453 (74.4%)	497 (81.7%)

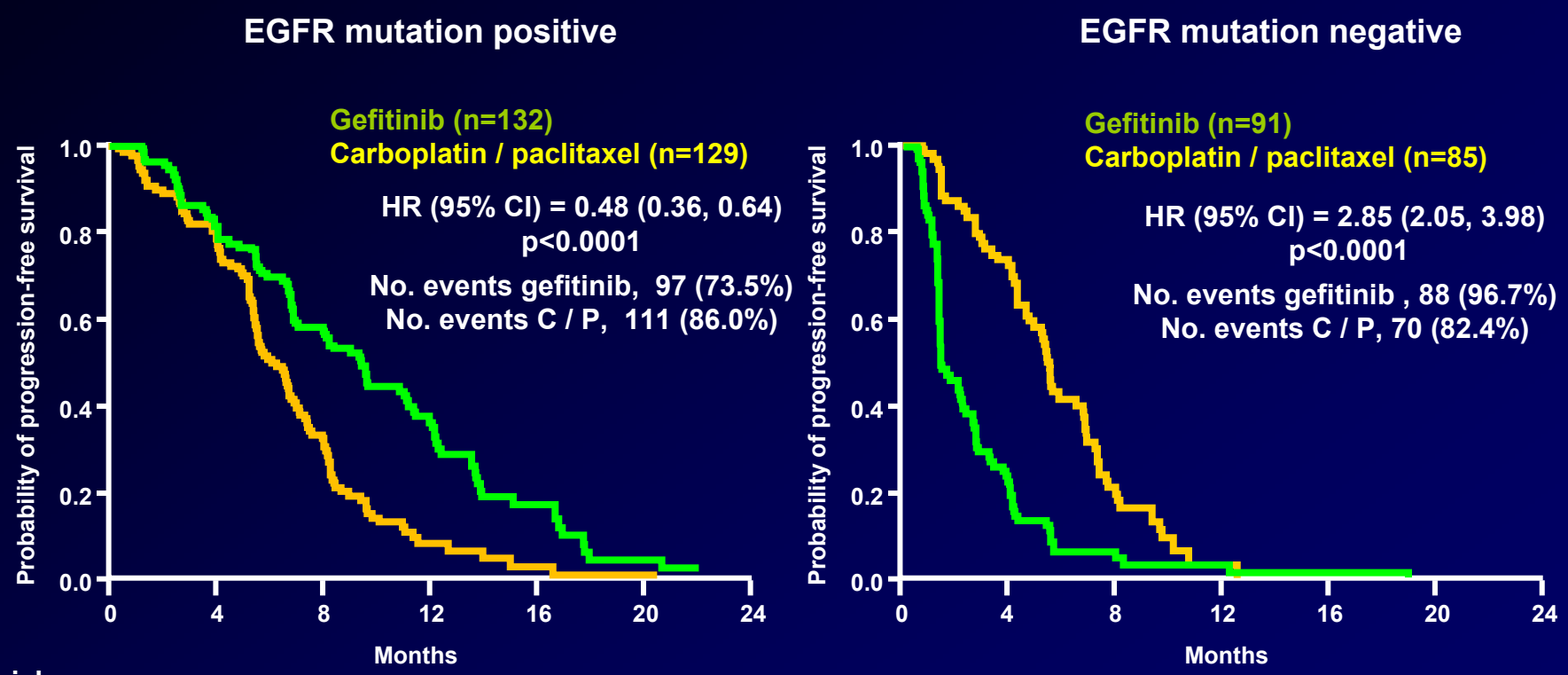
HR (95% CI) = 0.741 (0.651, 0.845) p<0.0001

Median PFS (months)	5.7	5.8
4 months progression-free	61%	74%
6 months progression-free	48%	48%
12 months progression-free	25%	7%

Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

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



At risk :

Gefitinib	132	108	71	31	11	3	0	91	21	4	2	1	0	0
C / P	129	103	37	7	2	1	0	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

EGFR-TKIs versus chemotherapy in first-line: Phase III trials in "biologically selected" patients

NEJ002

- Chemonaive
- Age 20-75 years
- EGFR mutation+
- ECOG PS:0-1
- Stage IIIB-IV

R (1 : 1)

- Gefitinib (250 mg / day)
- Carboplatin/ paclitaxel q 3 weeks

WJTOG3405

- Chemonaive
- Age >20 years
- EGFR Mutation+
- ECOG PS:0-1
- Stage IIIB-IV

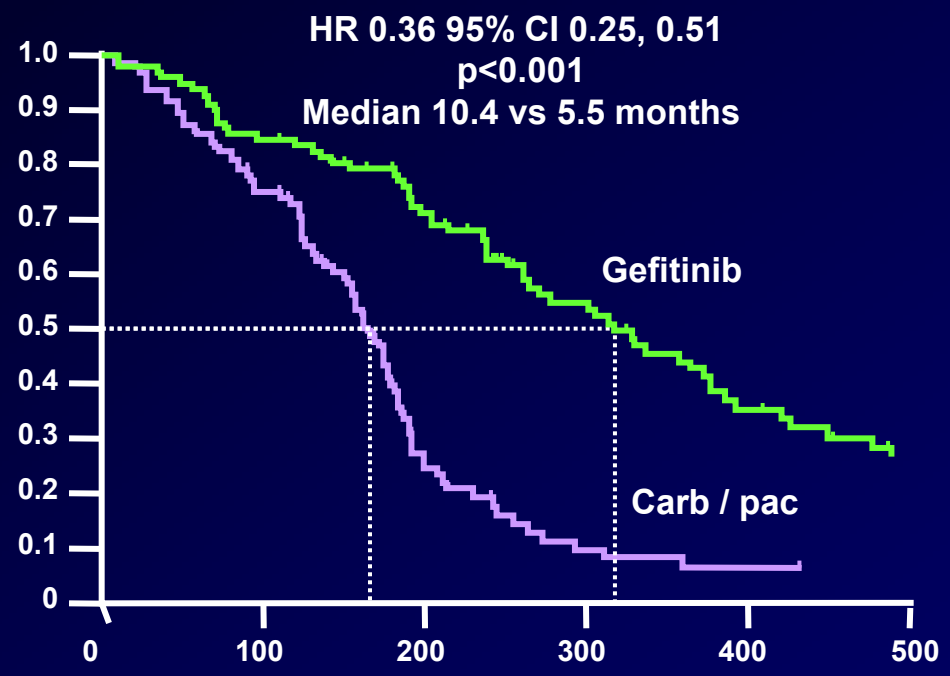
R (1 : 1)

- Gefitinib (250 mg / day)
- docetaxel 60 mg/mq
  Cisplatin 80 mg/mq
  Q 21 days, up to 6 cycles

Primary end-point: PFS

Gefitinib more effective than chemotherapy in EGFR Mutation+ NSCLC

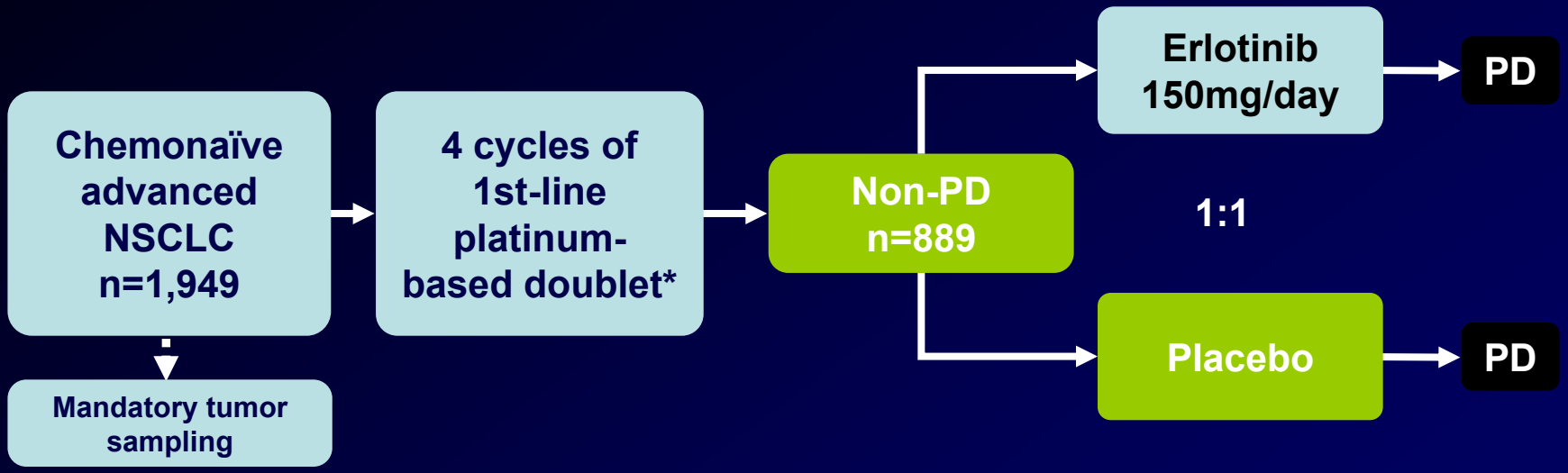
NEJ002: PFS



WJTOG3405

	Gef	CT	p	HR
RR (%)	56.3	25.3		
PFS (months)	9.2	6.3	<0.001	0.48

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:

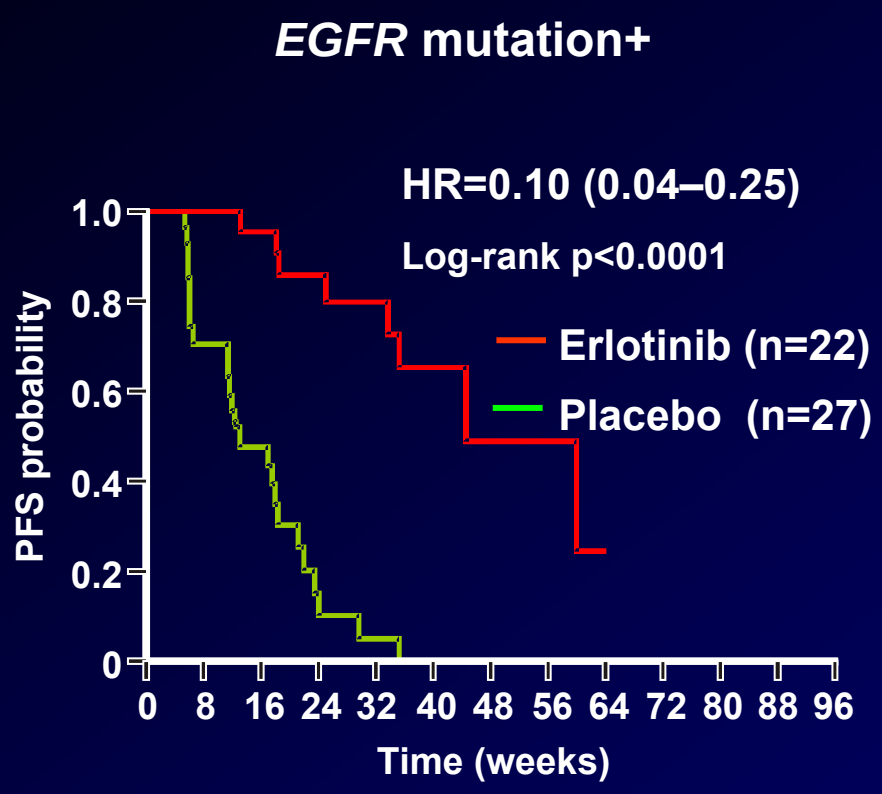
- PFS in all patients
- PFS in patients with EGFR IHC+ tumors

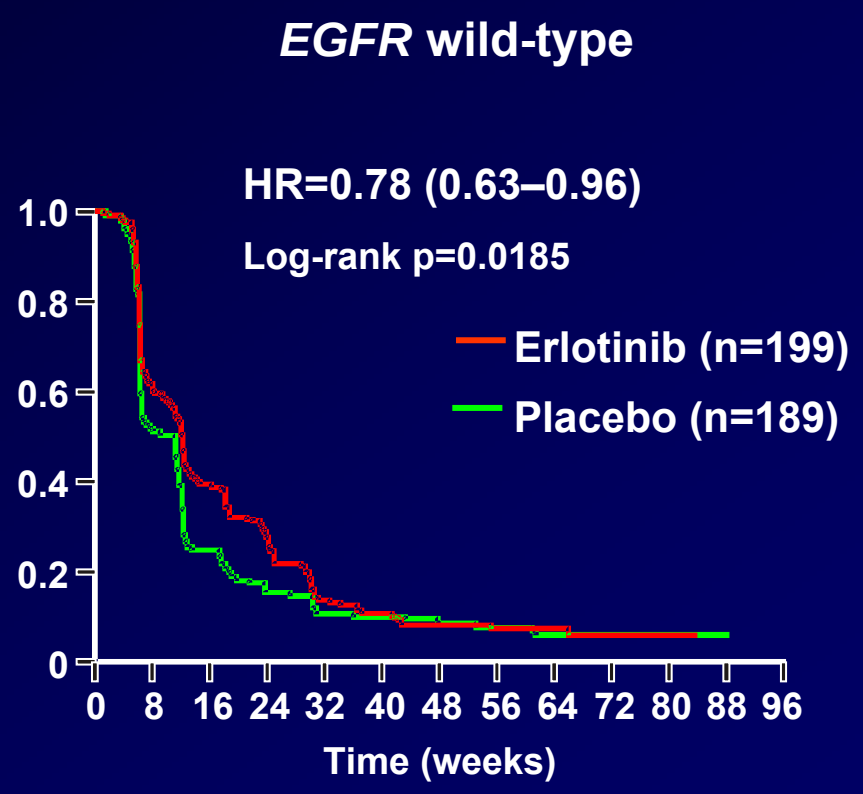
Secondary endpoints:

- 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

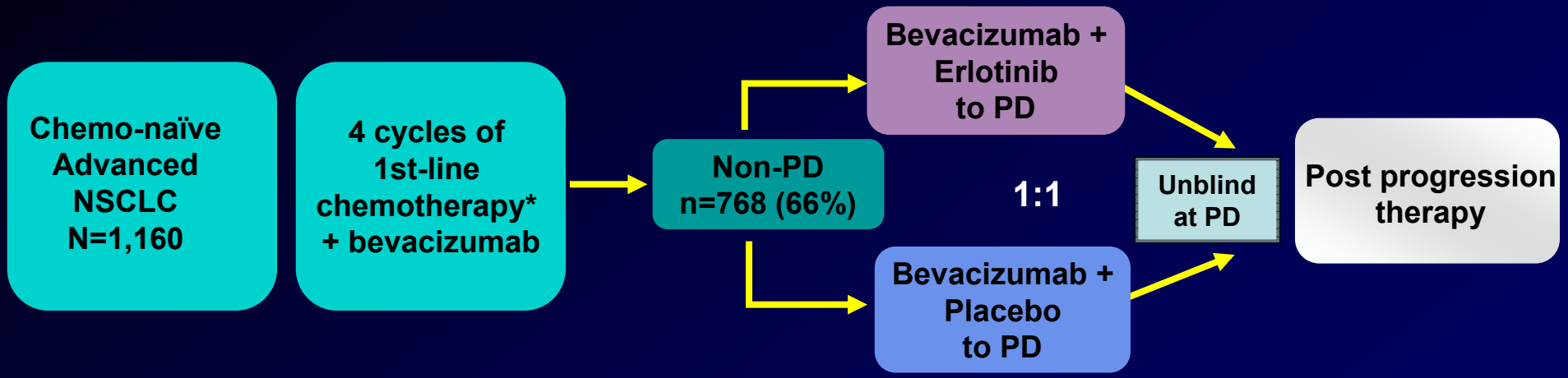
Largest PFS benefit with erlotinib in patients with *EGFR* mutated tumours





Interaction p<0.001

ATLAS Study Design



Eligibility

- Stage III/IV NSCLC
- ECOG performance status 0-1

Stratification factors

- Gender
- Smoking history (never vs former/current)
- ECOG performance status (0 v ≥1)
- Chemotherapy regimen

Primary endpoint

- PFS in all randomized pts

Secondary endpoints

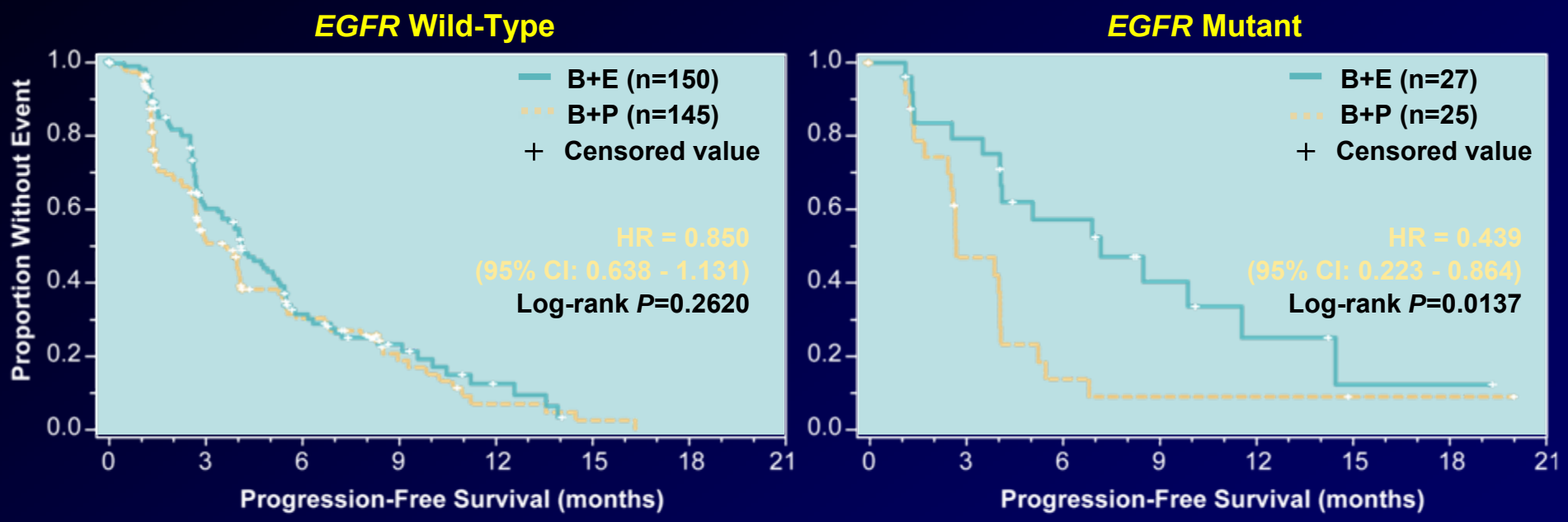
- Overall survival
- Safety

Exploratory endpoints

- Biomarker analyses (IHC, FISH, EGFR & K-Ras mutation)

Carbo/paclitaxel; cis/vinorelbine; carbo or cis/gemcitabine; carbo or cis/docetaxel.

PFS K-M Curves by *EGFR* Mutation Status

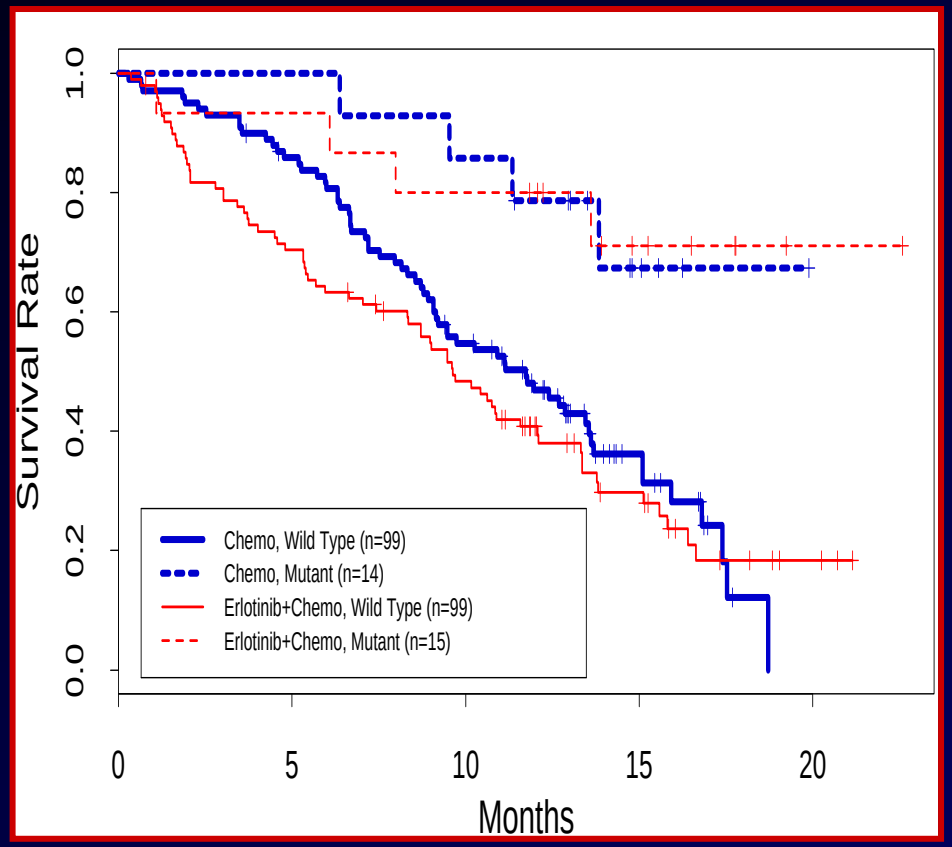


No.of patients at Risk

B+E:	150	66	25	12	4	0	0	0	27	19	12	6	3	1	1	0
B+P:	145	58	27	11	3	1	0	0	25	10	3	2	2	1	1	0

IS EGFR MUTATION TESTING THE BEST PREDICTOR FOR PATIENT SURVIVAL?

EGFR Mutations: A Positive Prognostic Factor?



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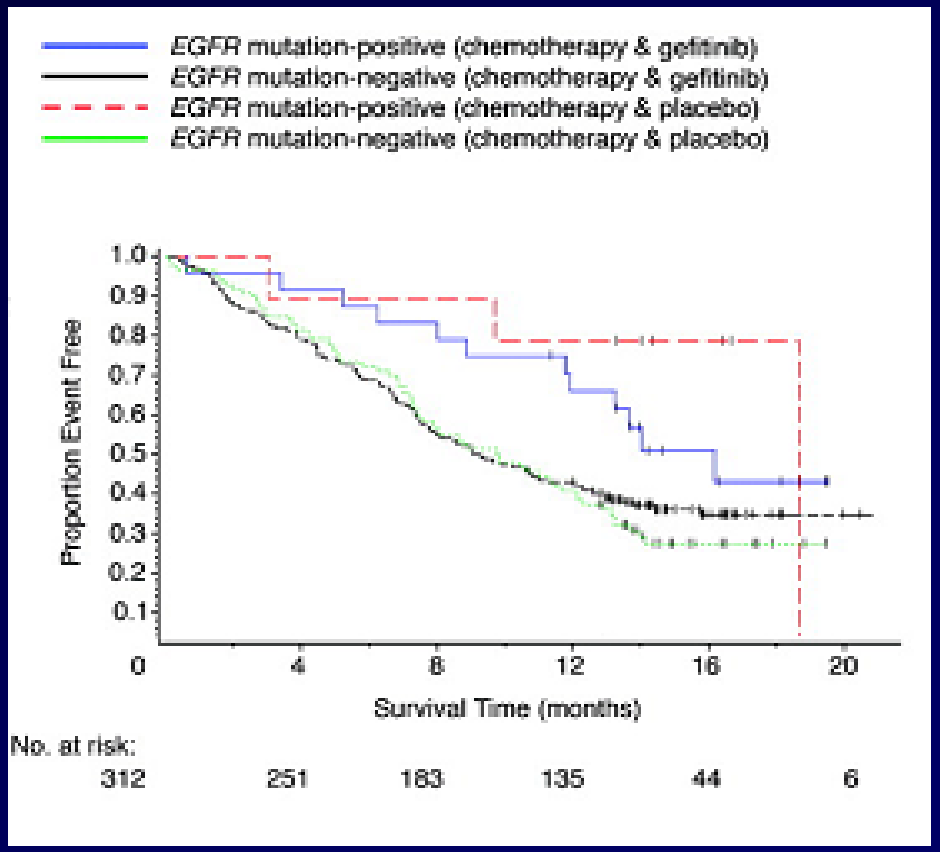
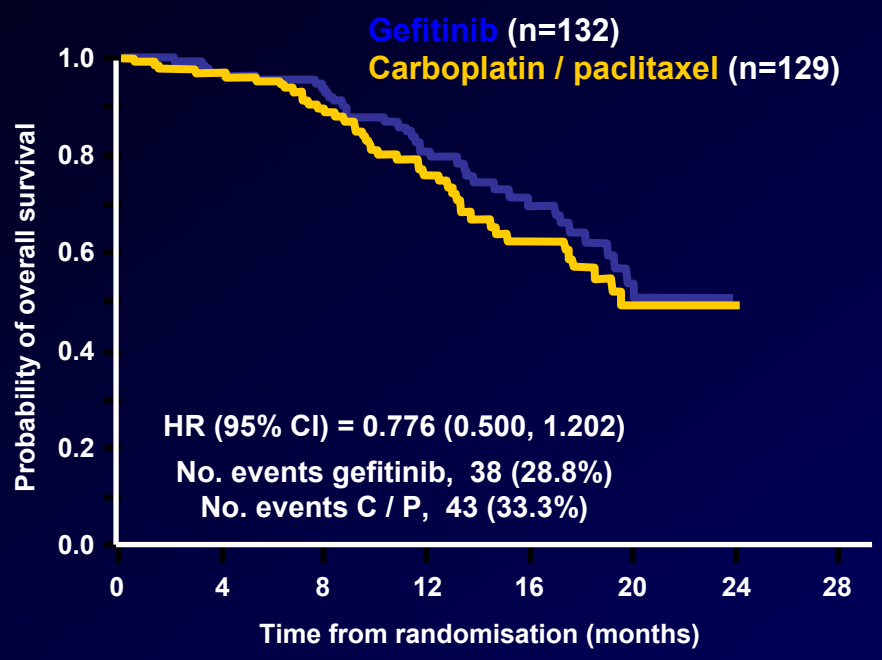


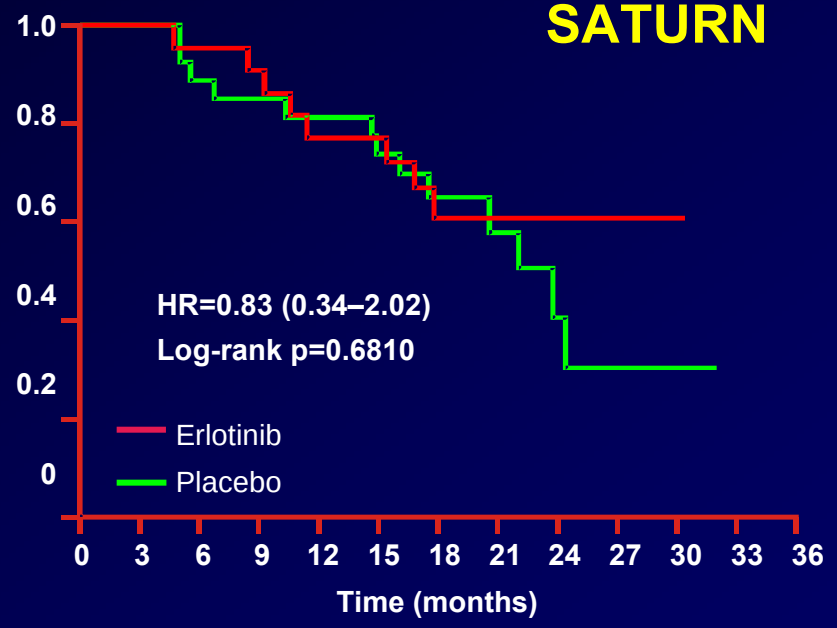
INTACT 1&2

No trial demonstrated survival benefit for EGFR mutated patients treated with TKIs

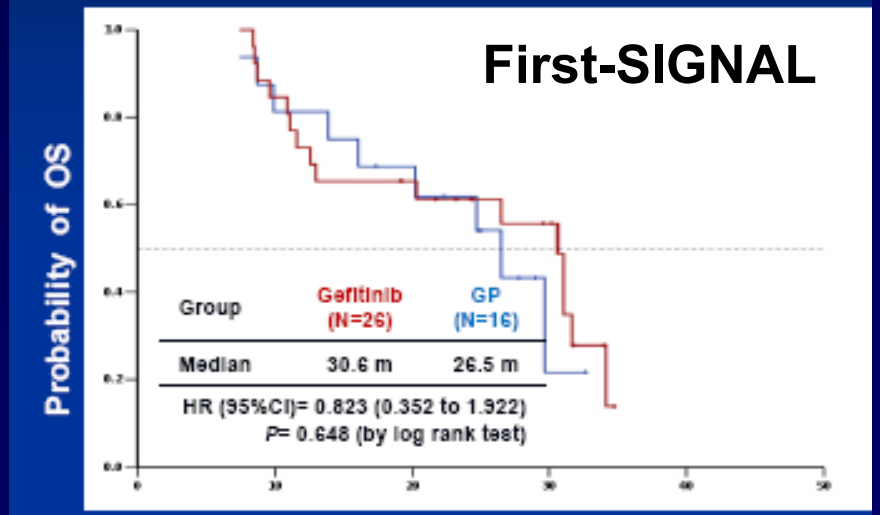
IPASS



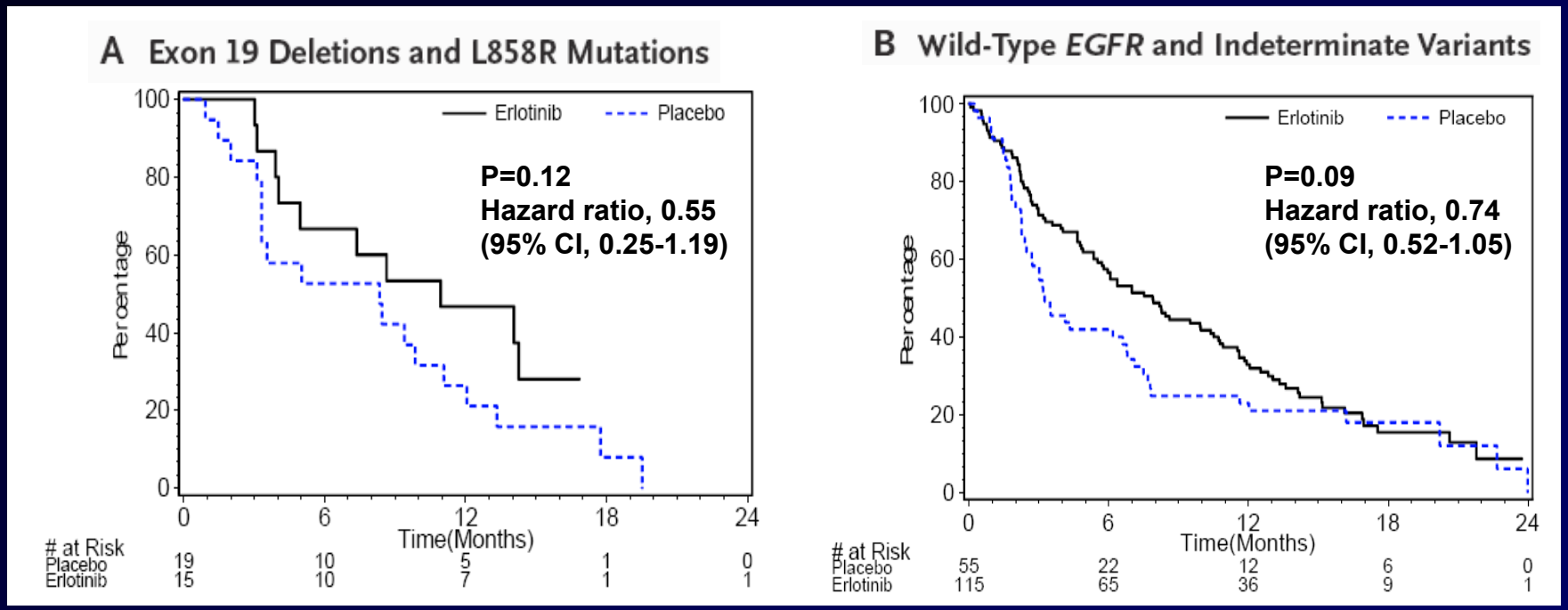
SATURN



First-SIGNAL



BR21: Survival According to Updated *EGFR* Mutation Status



Interaction P value = 0.47

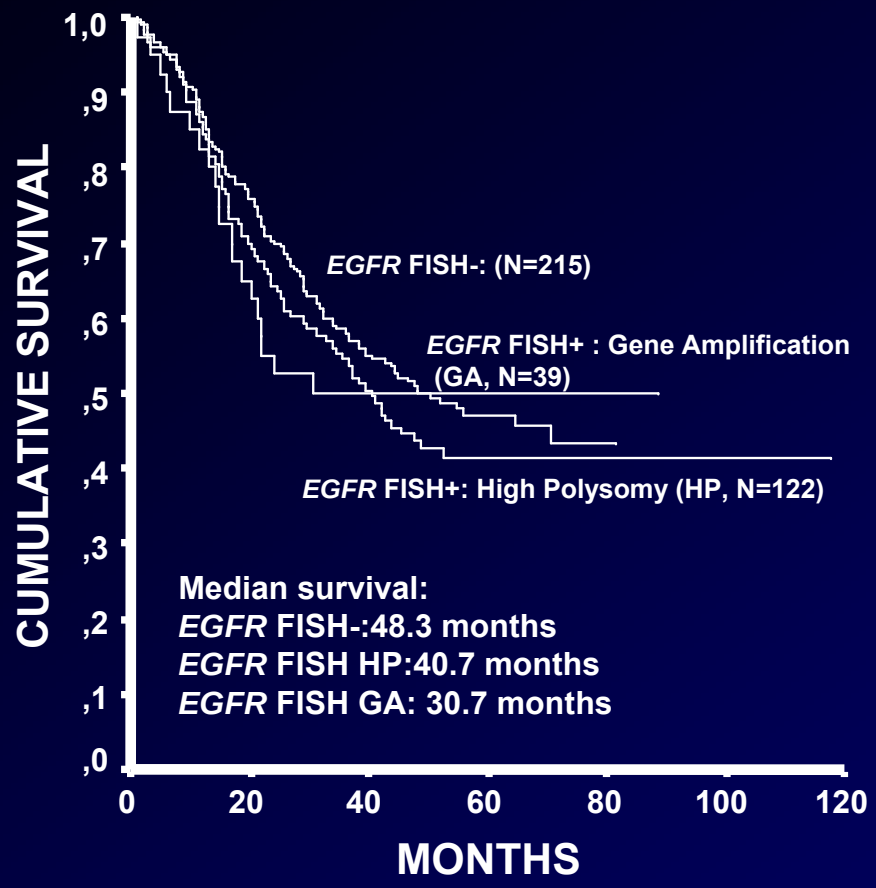
Shepherd et al, ASCO 2007

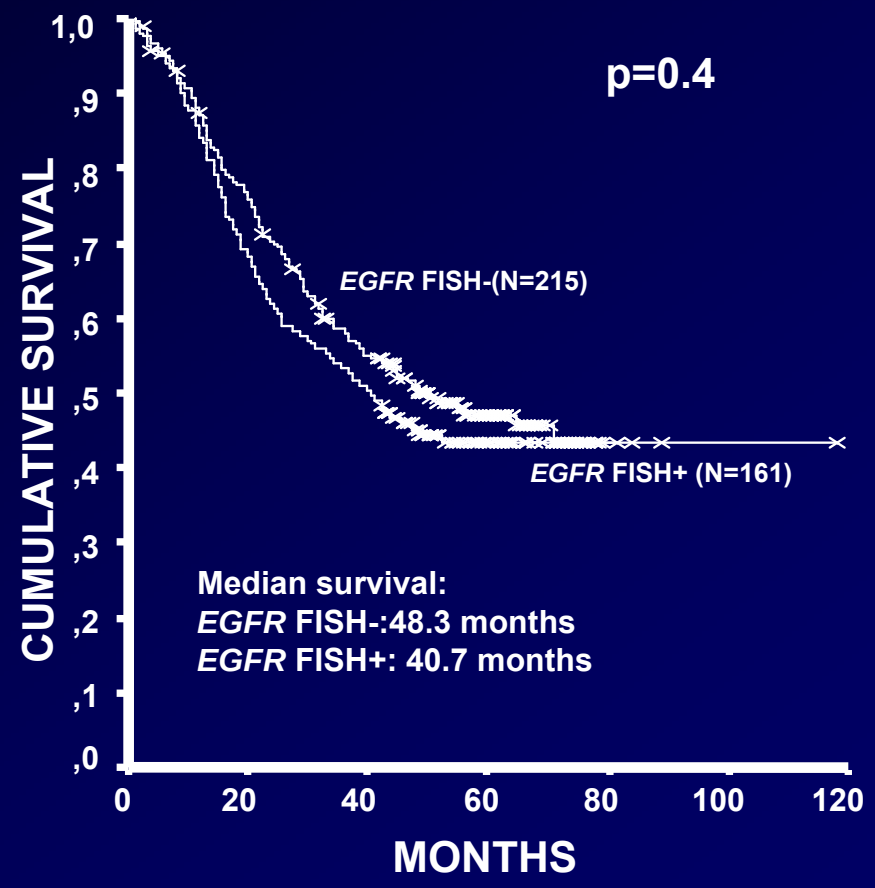
EGFR Gene Gain: A Prognostic Factor?

Reference	Method	Total Number	Survival (months)		P value
			EGFR+	EGFR-	
Hirsch	FISH	183	15.0	22.0	0.13
Jeon	FISH	262	44	NR	0.12
Suzuki	FISH	71	NA	NA	0.9

NR: Not Reached; NA: Not available

EGFR Gene Copy Number and Survival in the NSCLC Cohort



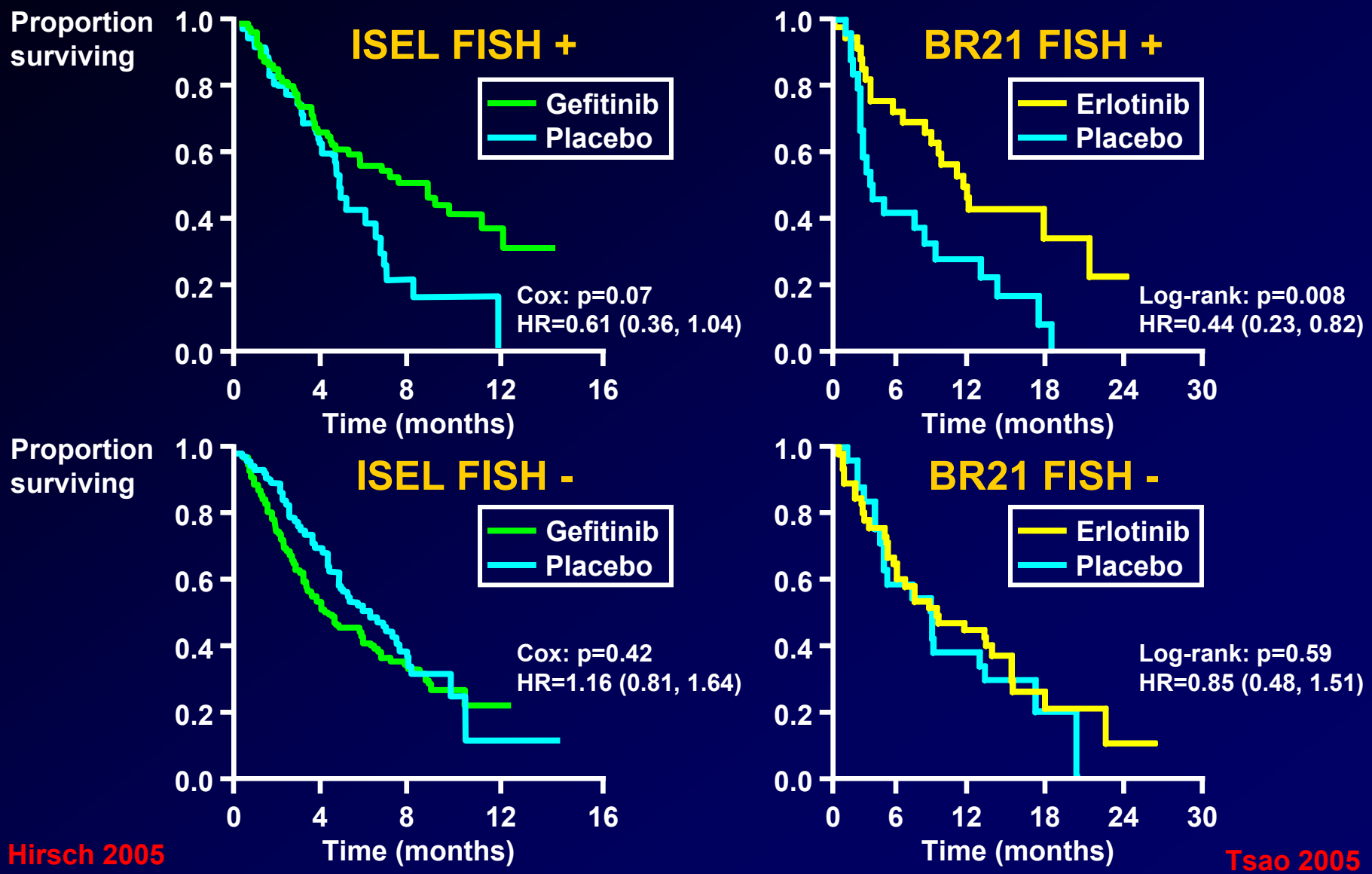


At risk	376	191	4
Negative	215	111	1
HP	122	61	2
GA	39	19	1

At risk	376	191	4
FISH+	161	80	3
FISH-	215	111	1

Cappuzzo et al. JCO 2009

FISH Predicts Benefit of EGFR-TKIs

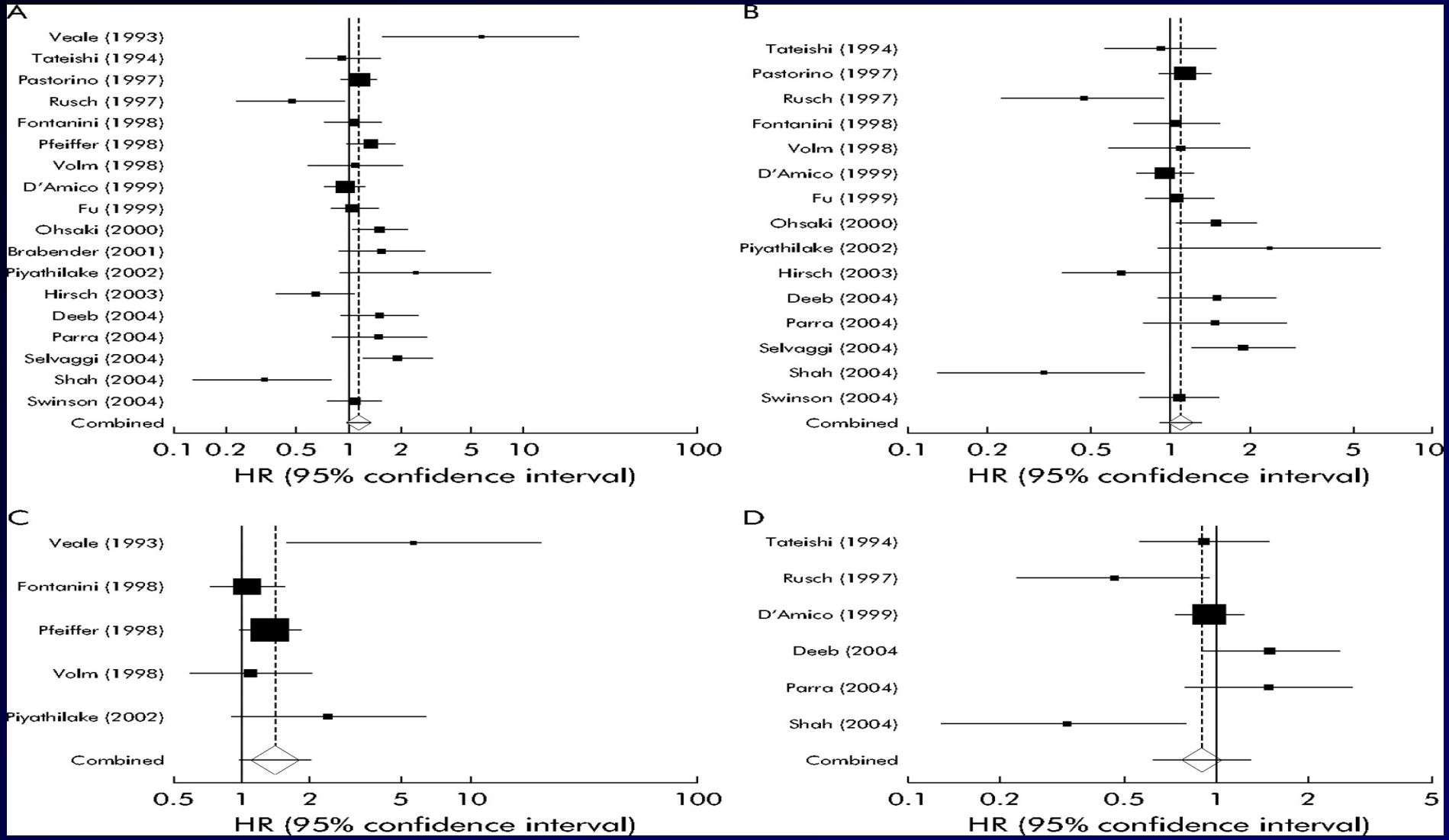


Hirsch 2005

Tsao 2005

EGFR EXPRESSION: THE WEAKEST PREDICTOR

EGFR IHC: No Prognostic Effect in Resected NSCLC in Large Meta-Analysis



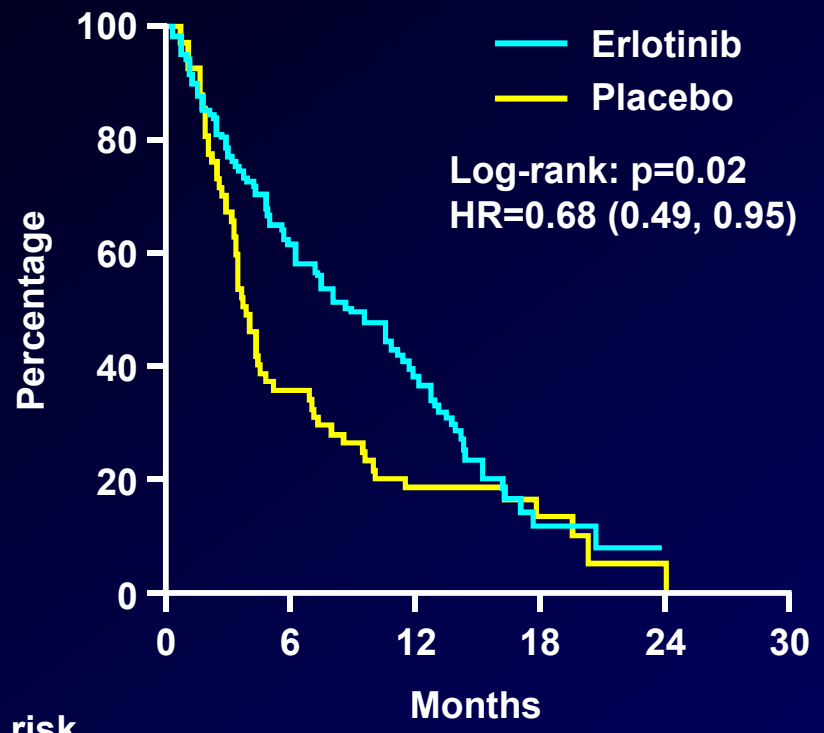
Nakamura et al., Thorax 2005

RESPONSE ACCORDING TO EGFR IHC - ISEL, IDEAL & BR.21

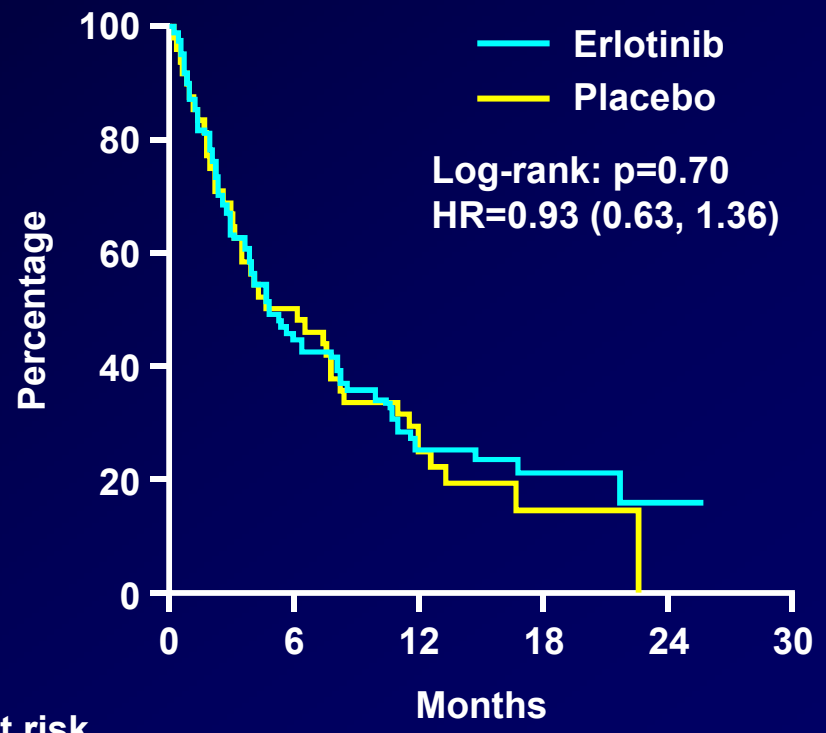
EGFR Status	ISEL	IDEAL	BR.21	TOTAL
	ORR (%)	ORR (%)	ORR (%)	ORR (%)
EGFR +ve	N=158 13 (8.2%)	N=84 13 (13.4%)	N=106 12 (11.3%)	N=348 38 (10.9%)
EGFR -ve	N=69 1 (1.5%)	N=17 1 (5.6%)	N=80 3 (3.8%)	N=166 5 (3.0%)

*P=0.003

BR.21 Survival According to EGFR Protein Expression



At risk						
Erlotinib	117	71	43	5	5	0
Placebo	67	23	12	5	0	0

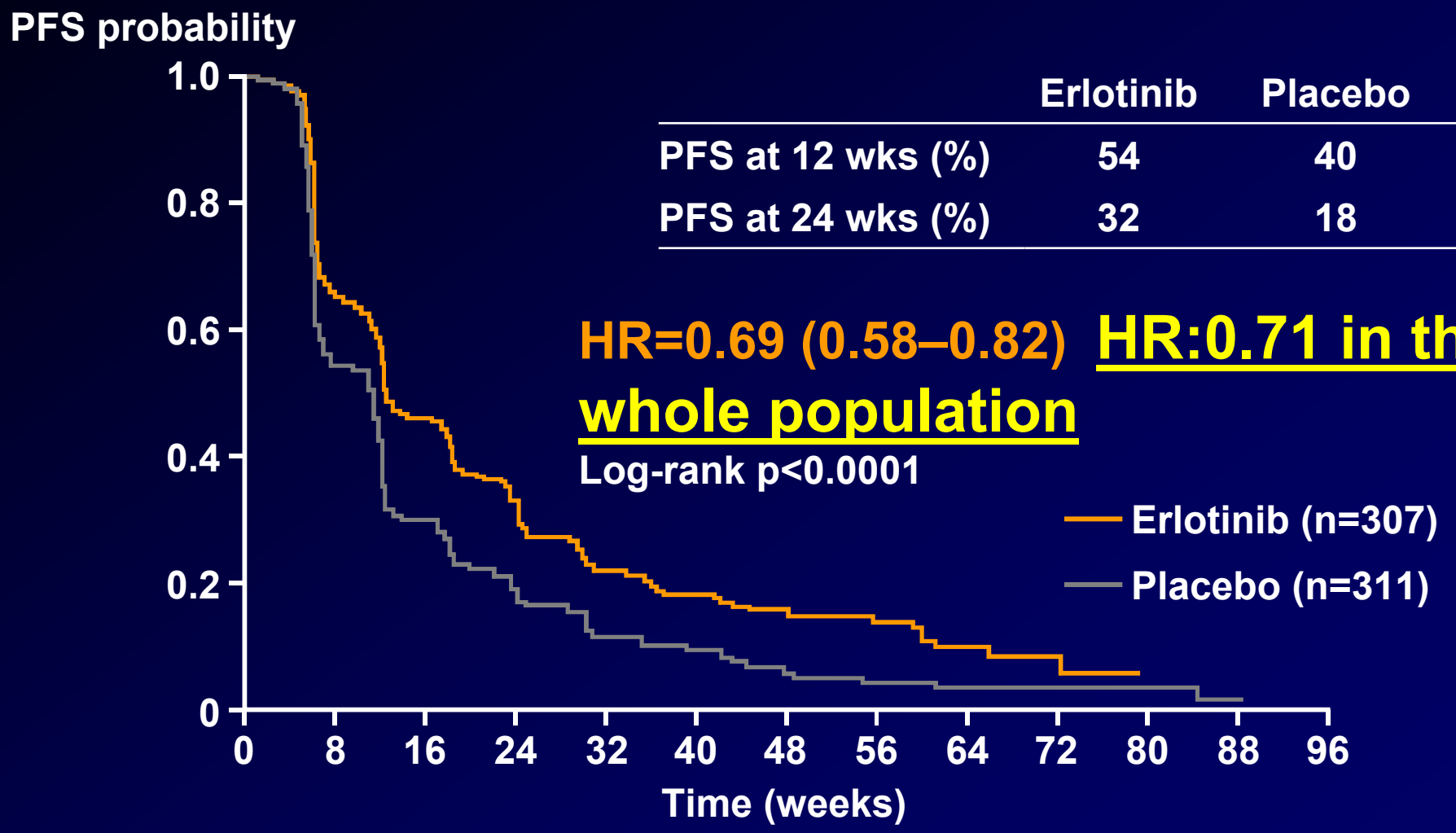


At risk						
Erlotinib	93	42	22	8	3	0
Placebo	48	24	14	3	0	0

p value for interaction = 0.25

Shepherd et al. N Engl J Med, 2005

SATURN: PFS in EGFR IHC+ tumors



	Erlotinib	Placebo
PFS at 12 wks (%)	54	40
PFS at 24 wks (%)	32	18

HR:0.71 in the whole population

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

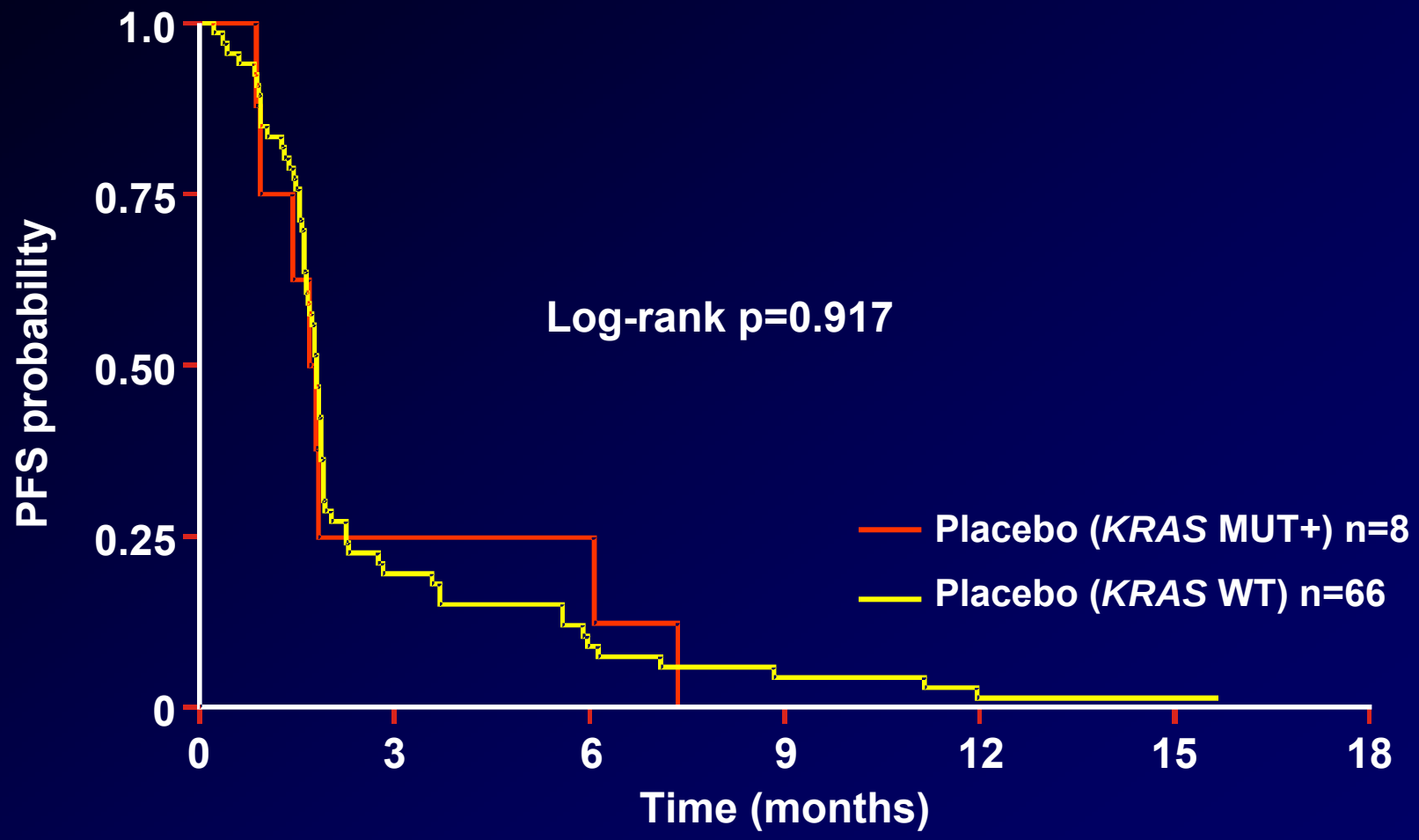
OTHER BIOMARKERS: KRAS AND MET

KRAS Mutations and Survival: Prognostic or Predictive?

- Over 50 studies published
- Different methods for detection (IHC versus PCR)
- Conflicting results

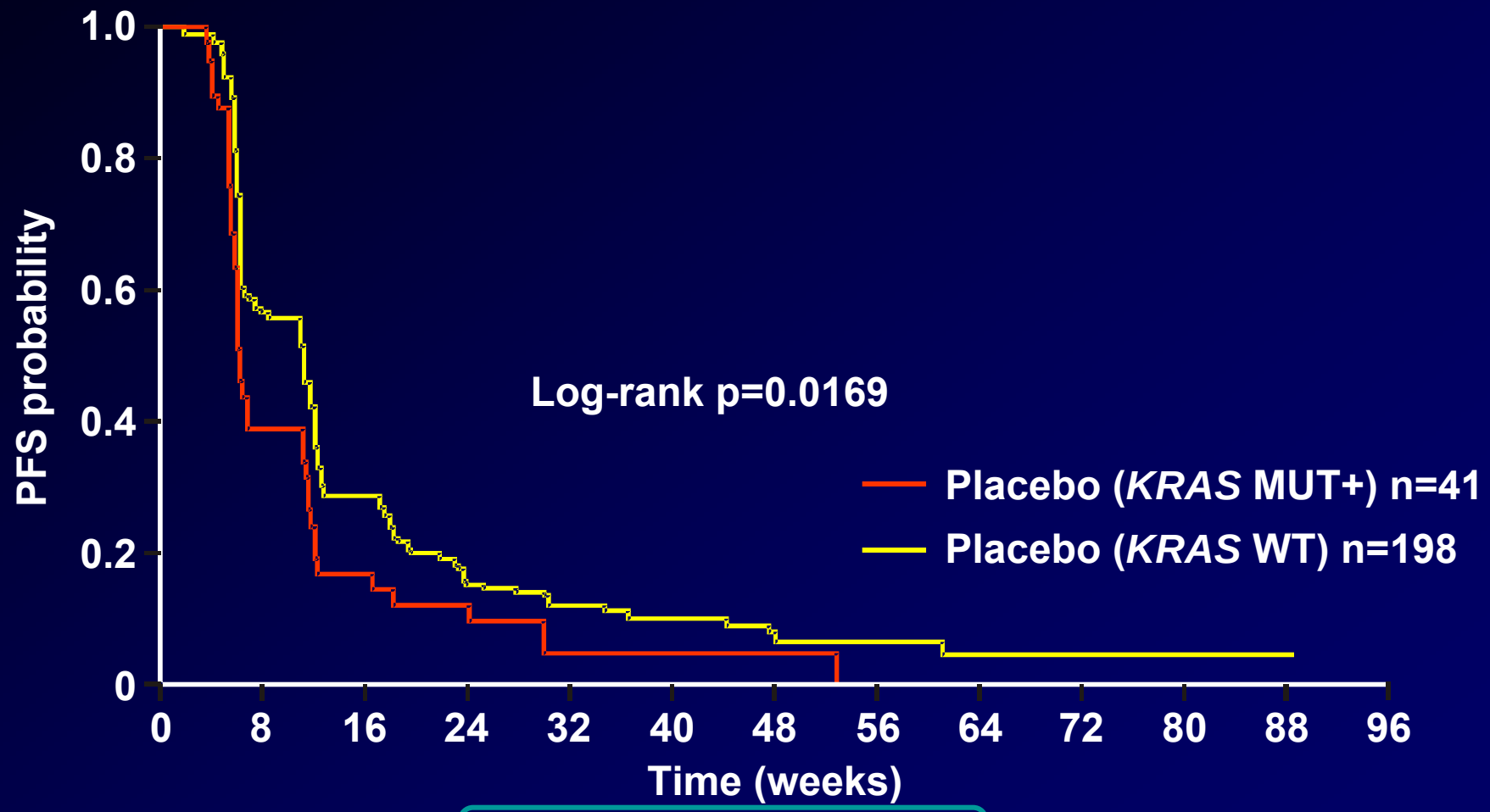
Reference	N	% Mutated	p value
Tsao	450	26.0	0.3
Schiller	197	24.0	0.4
Graziano	260	16.4	0.3
Siegfried	181	31.5	0.6
Fukuyama	159	6.9	<0.05
Huang	144	8.3	0.03
Miyake	187	8.0	0.03

BR.21: prognostic analysis for *KRAS* mutation (PFS) in placebo arm



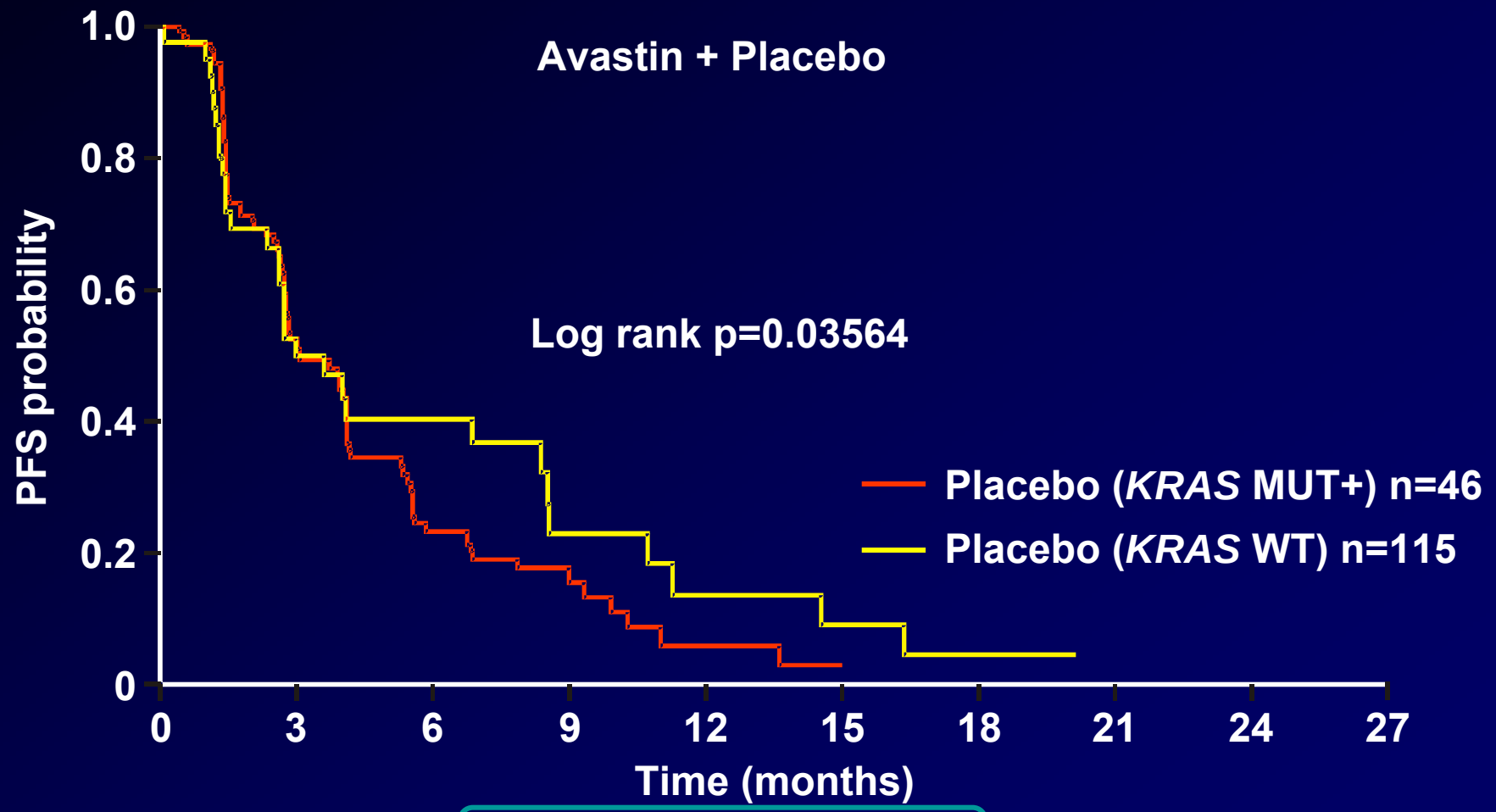
Conclusion: not prognostic

SATURN: prognostic analysis for *KRAS* mutation (PFS) in placebo arm



Conclusion: prognostic

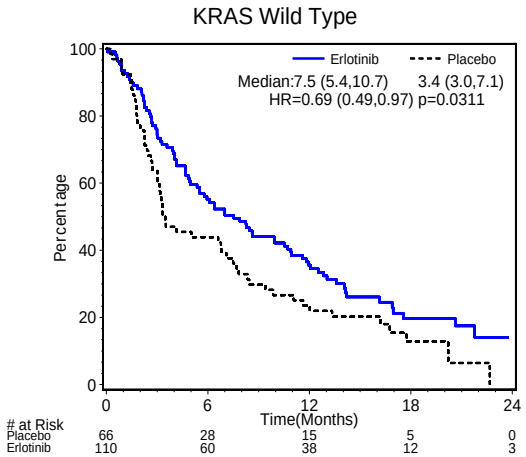
ATLAS: prognostic analysis for *KRAS* mutation (PFS) in placebo arm

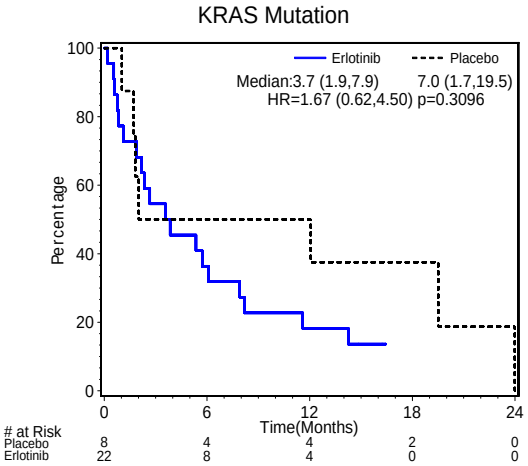


Conclusion: prognostic

KRAS Mutations: predictive for worst survival?

BR21





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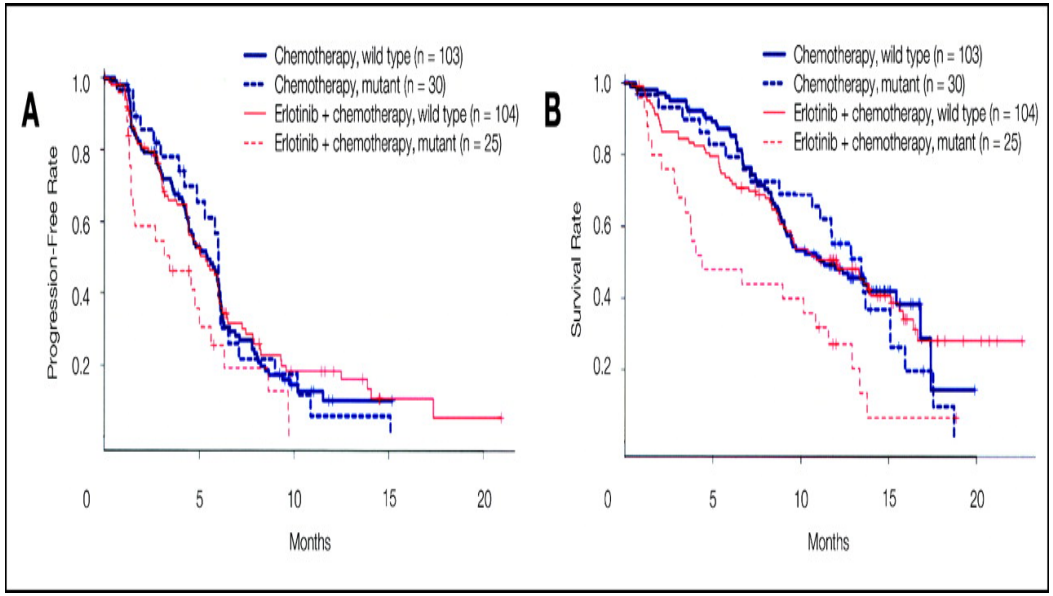
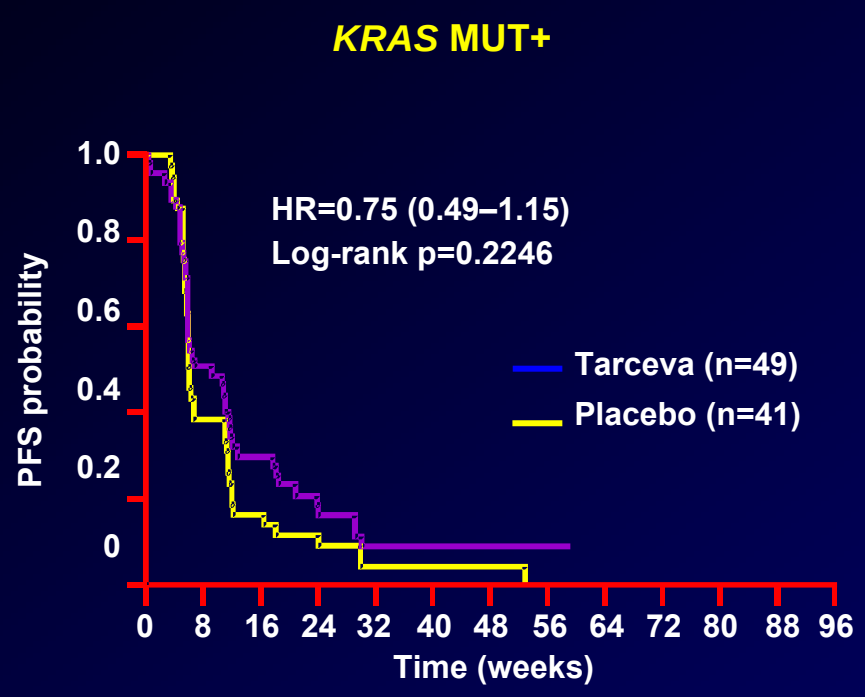
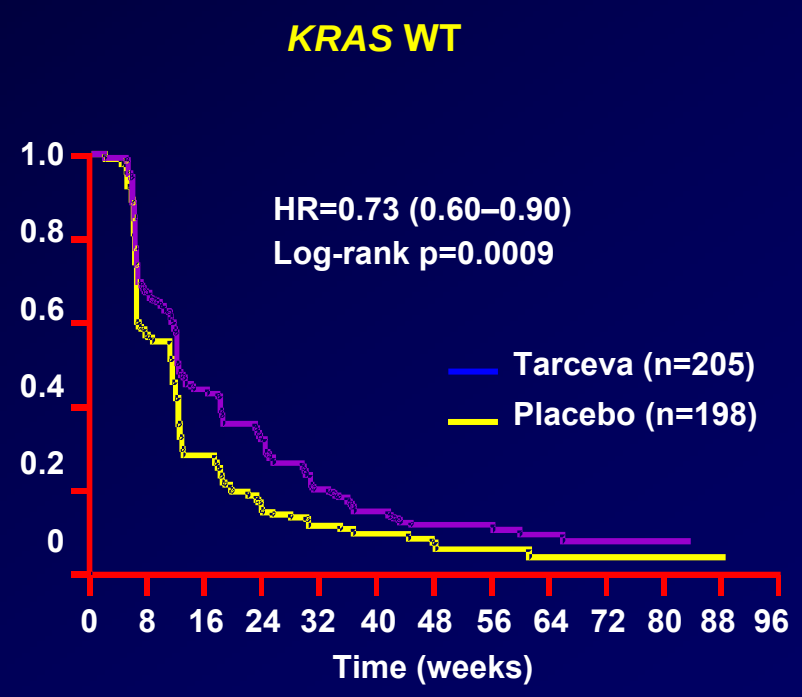


- **Few data in low patient number**
- **~50% of KRAS mutated are EGFR FISH+**

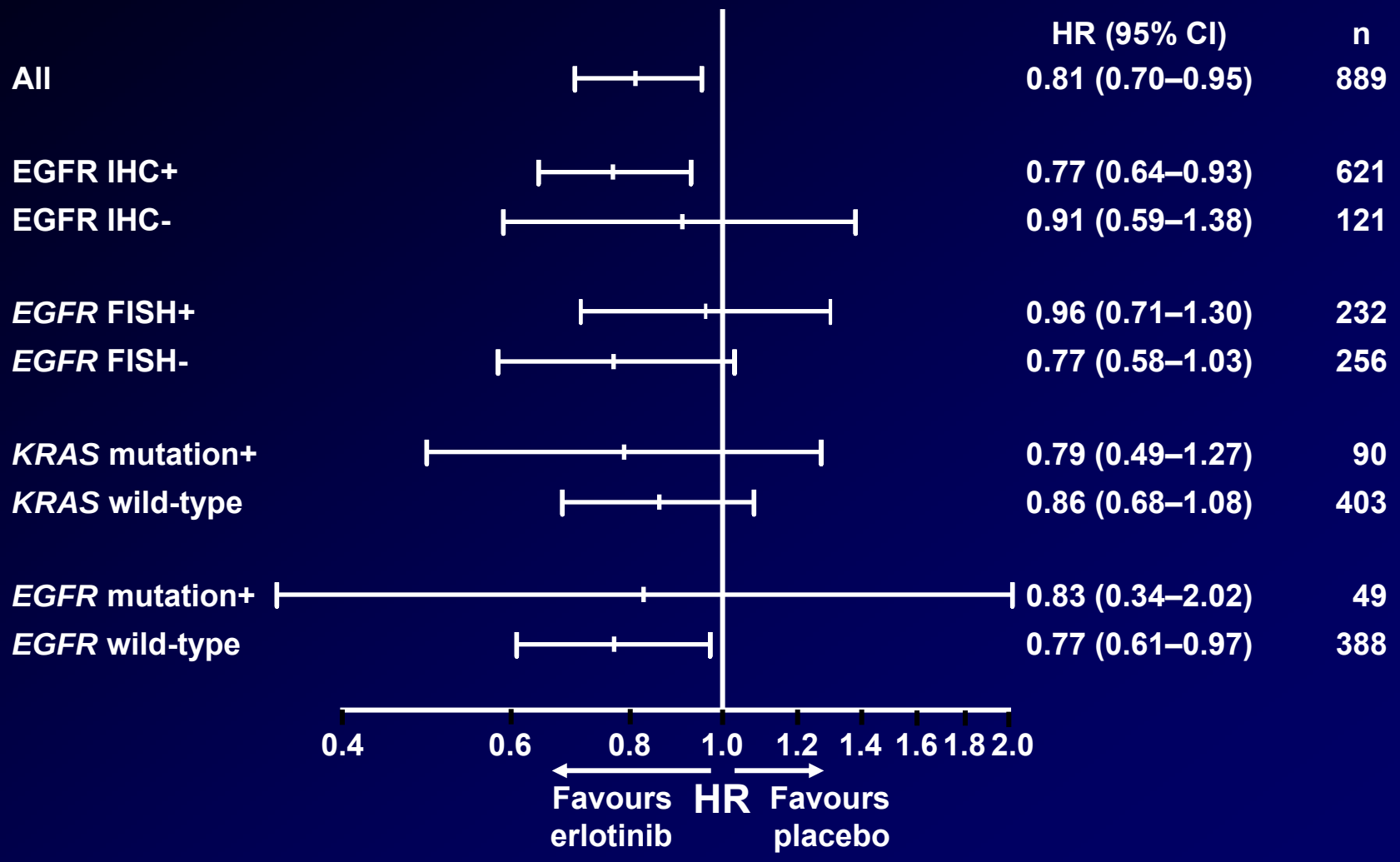
SATURN: PFS according to KRAS status





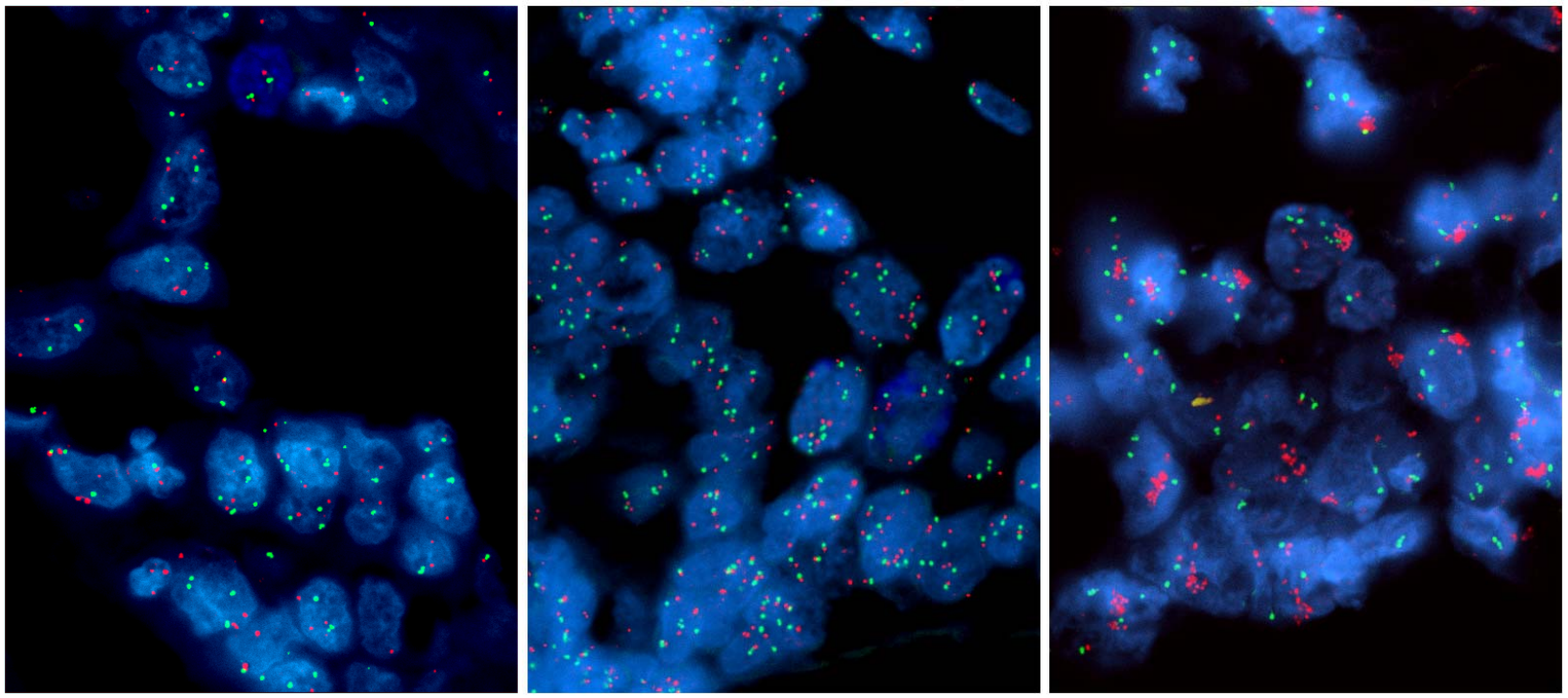
Interaction p=0.95

OS in SATURN: biomarker subgroup analyses



MET FISH Results

Total evaluated: 435

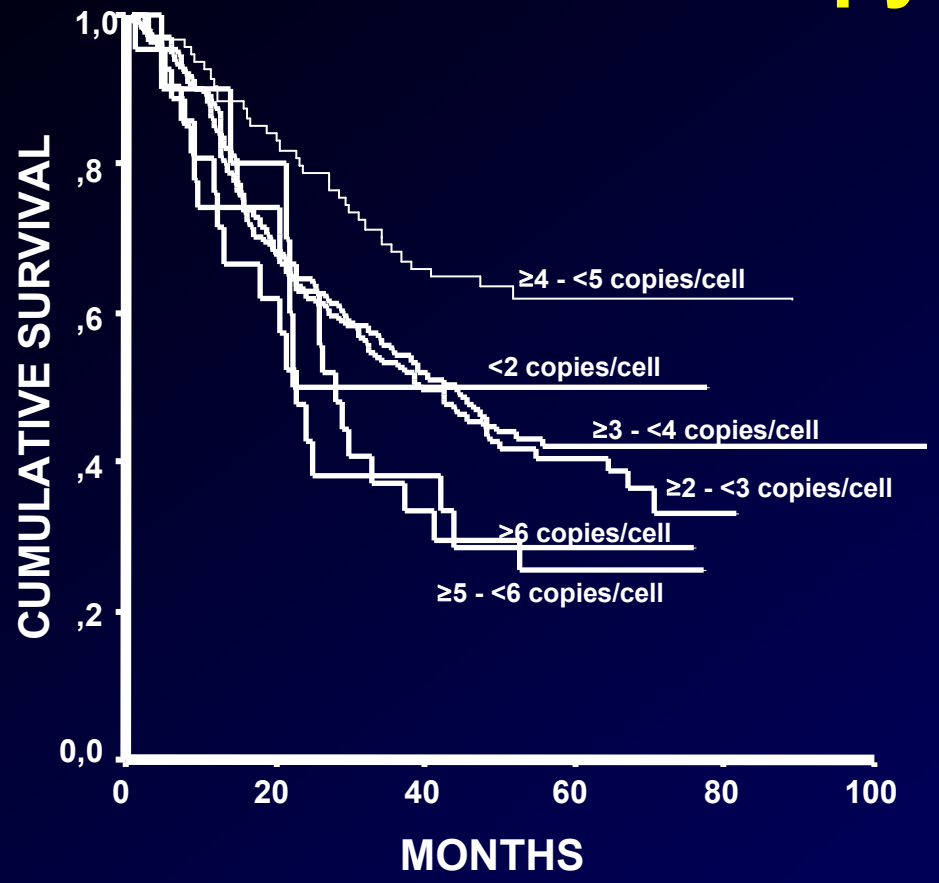


Low copy number:
383 (88.9%)

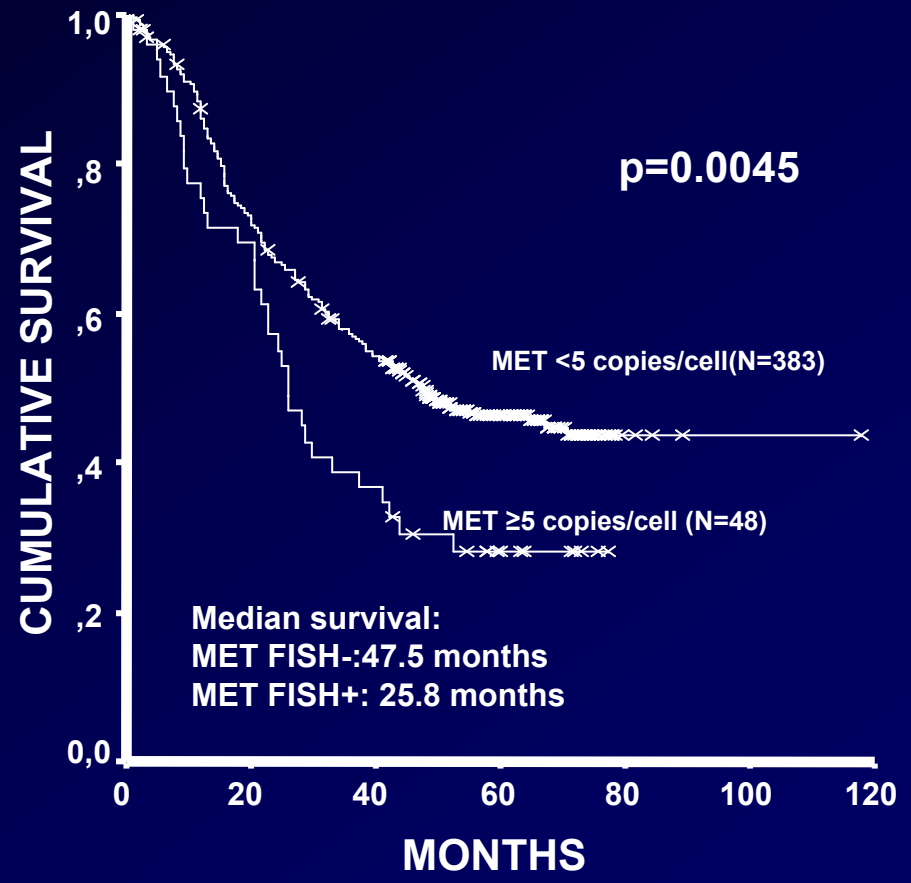
High polysomy:
30 (7.0%)

Gene amplification:
18 (4.1%)

Survival of Resected NSCLC According to *MET* Copy Number



At risk	431	216	4
<2	10	5	0
≥2 - <3	129	65	1
≥3 - <4	149	69	1
≥4 - <5	95	61	2
≥5 - <6	28	9	0
≥6	20	7	0



At risk	431	216	4
MET+	48	16	0
MET-	383	200	4

Cappuzzo et al., JCO 2009

Conclusions

- EGFR expression is the weakest predictor with no prognostic role
- At the gene level EGFR testing identifies patients with the highest benefit in response (mutation) or survival (FISH)
- KRAS testing is not recommended in clinical practice for patient selection
- MET gene copy number is a negative prognostic factor