Biomarker analyses and overall survival from the randomized, placebo-controlled, phase III, FASTACT-2 study of intercalated erlotinib with first-line chemotherapy in advanced non-small-cell lung cancer (MO22201; CTONG0902)

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Conflict of interest disclosure

- Honoraria
  - AstraZeneca
  - Eli Lilly
  - Eisai
  - BeiGene
  - Pfizer
  - Boehringer Ingelheim
  - Hoffmann-La Roche
  - Merck Serono
  - Bristol-Myers Squibb
  - AVEO
  - Taiho
  - GlaxoSmithKline Biologicals
- Speaker
  - AstraZeneca
  - Eli Lilly
  - Boehringer Ingelheim
  - Hoffmann-La Roche
  - Merck Serono
- Research Funding
  - AstraZeneca

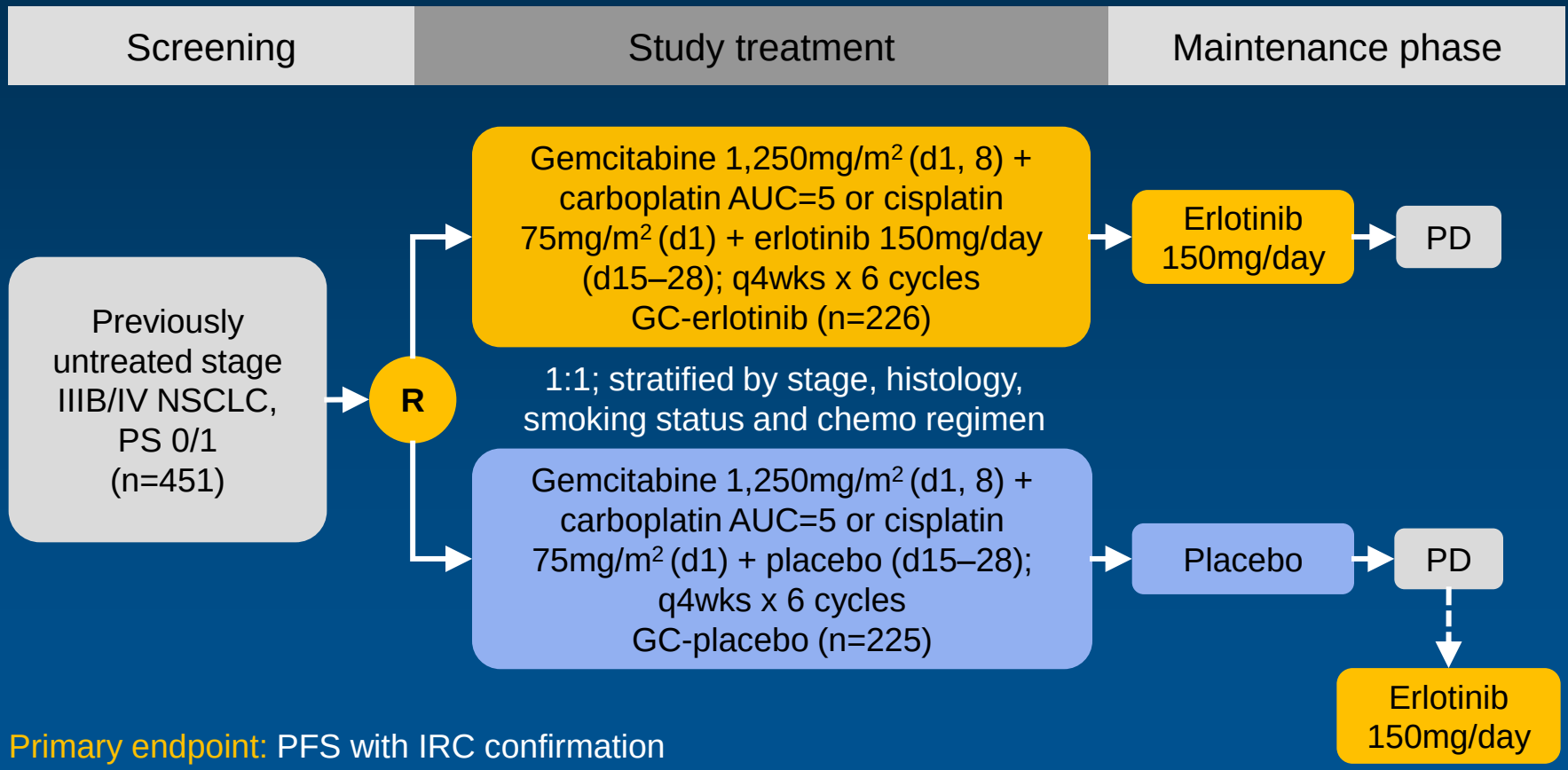
Background and Rationale

- Pharmacodynamic separation of chemotherapy followed by EGFR TKI may improve treatment outcomes[1]
- It remains unclear if sequential intercalated combination of chemotherapy and EGFR TKI may benefit patients with and without *EGFR* mutations[2]
- A randomised phase II study (FASTACT) demonstrated that intercalated administration of erlotinib and first-line platinum-based CT significantly prolongs PFS versus CT alone[3]
  - limited biomarker analysis data were available
- FASTACT-2 was a phase III, randomised, placebo-controlled, double-blind study designed to confirm the positive outcome of FASTACT and to explore the biomarker subgroup analysis

EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; PFS = progression-free survival; CT = chemotherapy; FASTACT = First-line Asian Sequential Tarceva And Chemotherapy Trial

[1]Gandara D. Clin Cancer Res 2005;11:5057–62
[2]Li T. Curr Drug Targets 2010;11:85–94
[3]Mok T. J Clin Oncol 2009;27:5080–7

FASTACT-2 (MO22201; CTONG0902) study design



Primary endpoint: PFS with IRC confirmation

Secondary endpoints: subgroup analyses, OS in all patients and subgroups, ORR, duration of response, TTP, NPR at 16 weeks, safety, QoL

NSCLC = non-small cell lung cancer; PS = performance status; PD = disease progression; AUC = area under the curve; q4wks = every 4 weeks; IRC = independent review committee; OS = overall survival; ORR = objective response rate; TTP = time to progression; NPR = non-progression rate; QoL = quality of life

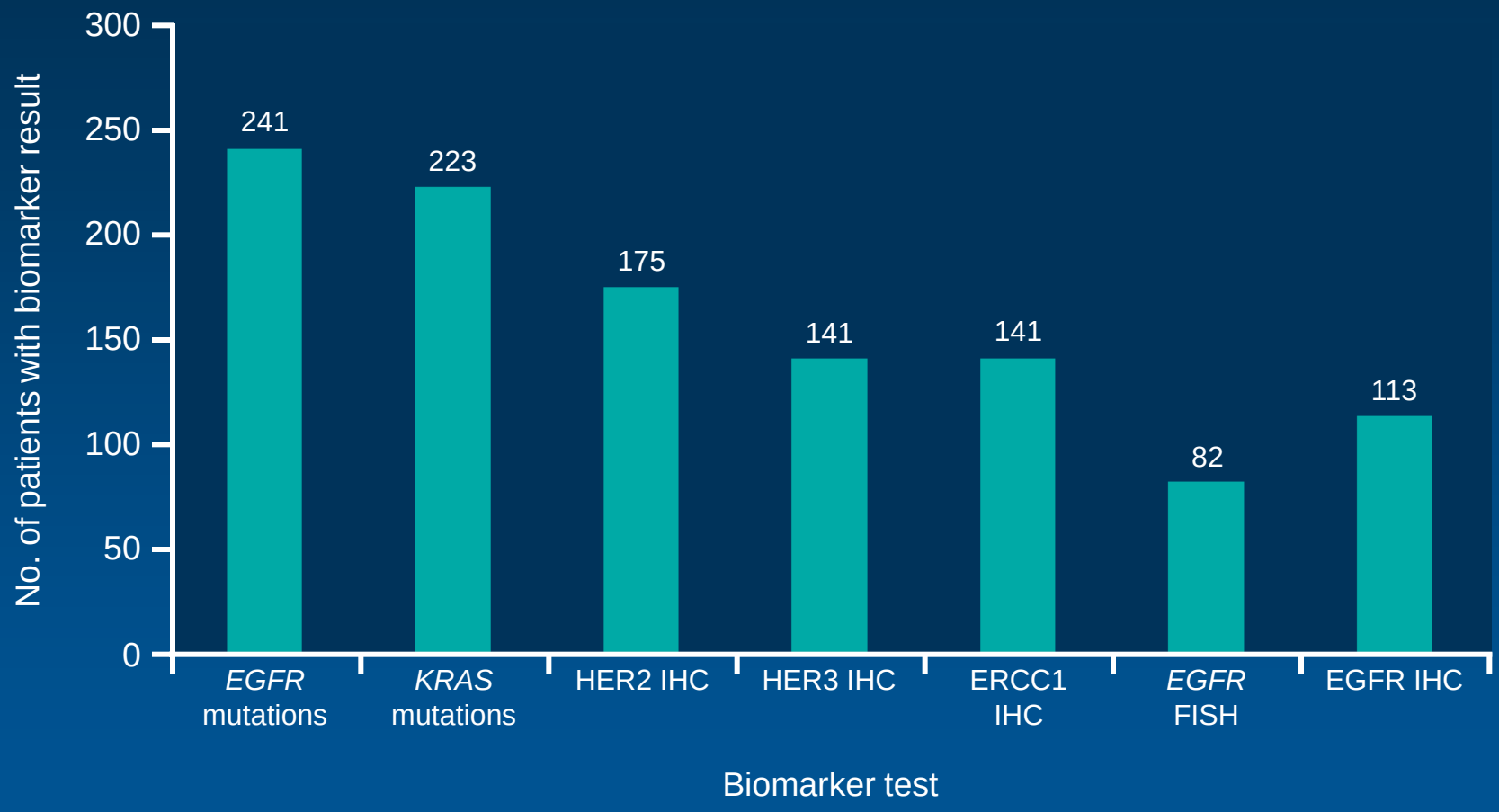
Biomarker analysis

397 (88%) patients consented to biomarker analysis → 301 (66.7%) samples were available for analysis → 283 (62.7%) samples were suitable for analysis

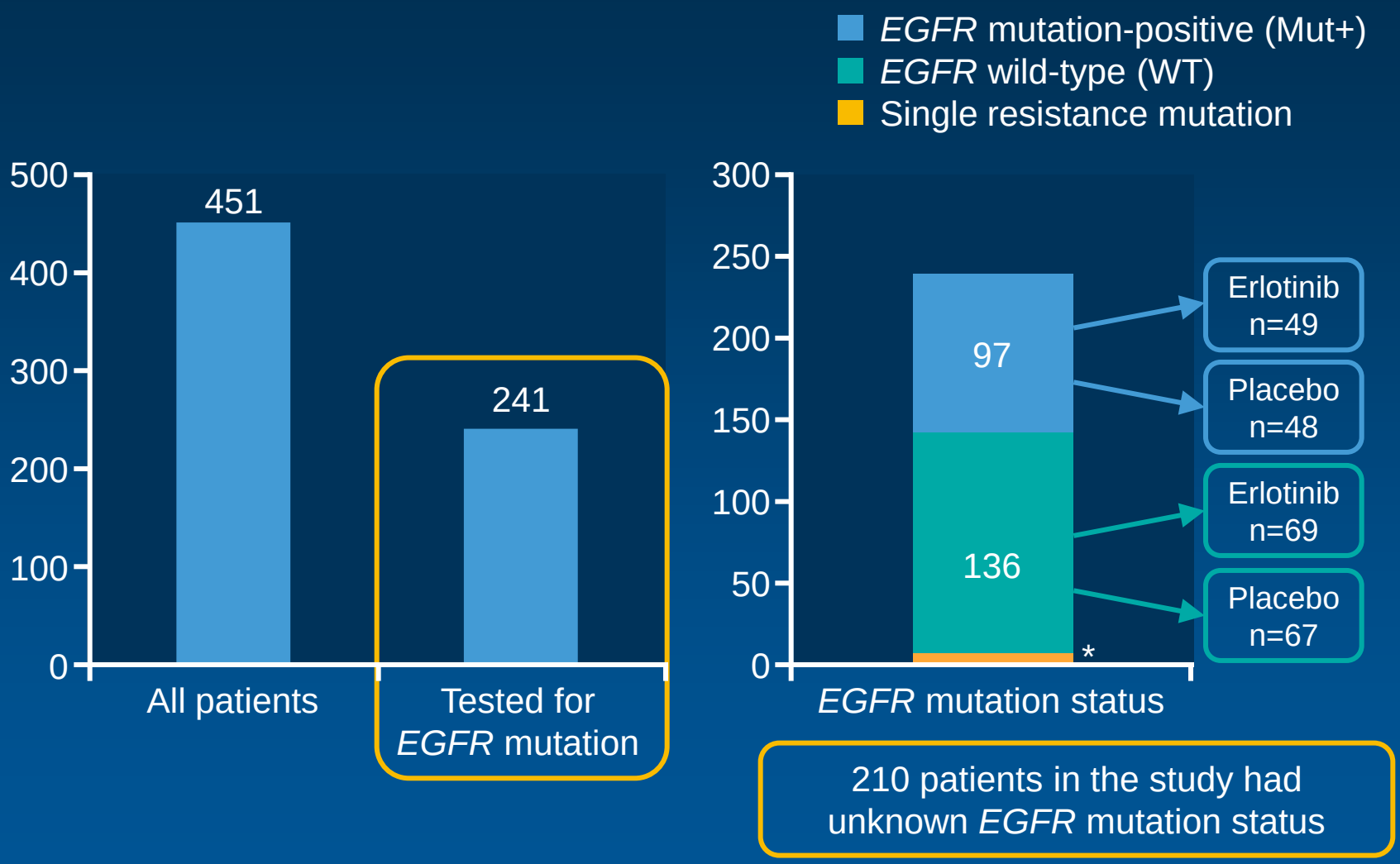
Biomarker test in order of prioritisation	Manufacturer	Test/antibody
EGFR mutation	RMS	cobas® 4800 platform
KRAS mutation	RMS	cobas® 4800 platform
HER2 IHC	Dako	HercepTest™ Rabbit
HER3 IHC	Labvision	Anti-human HER3 (clone DAK-H3-IC)
ERCC1 IHC	Labvision	Anti-human ERCC1 Ab-2 (clone 8F1)
EGFR FISH	Abbott	LSI® EGFR Dual Color Probe-Hyb set
EGFR IHC	Dako	Dako EGFR PharmDX monoclonal mouse antibody

IHC = immunohistochemistry; FISH = fluorescence in-situ hybridisation

Biomarker analyses: number of patients with results for each marker



EGFR mutation status in FASTACT-2



* n=8: one with T790M (received placebo); one with S768I (received placebo); six with exon 20 mutations (two received erlotinib, four received placebo)

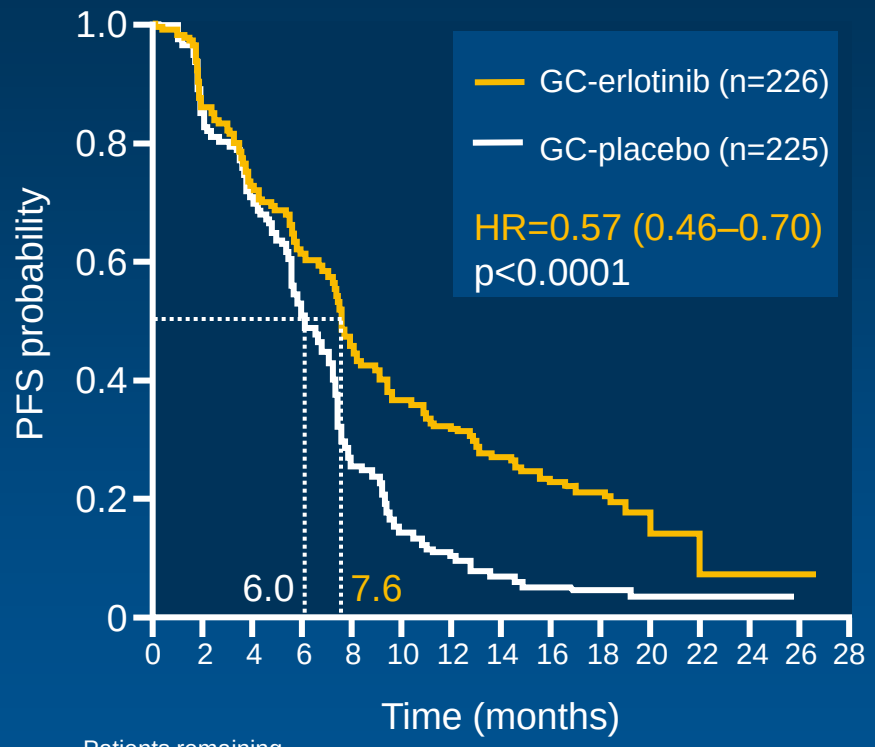
Summary of baseline characteristics for all patients and by *EGFR* status

	Total study population (n=451)		Known *EGFR* Mut+ status (n=97)		Known *EGFR* WT status (n=136)	
	GC-erlotinib (n=226)	GC-placebo (n=225)	GC-erlotinib (n=49)	GC-placebo (n=48)	GC-erlotinib (n=69)	GC-placebo (n=67)
Sex, %						
Male	58	62	43	48	59	76
Female	42	38	57	52	41	24
Disease stage, %						
IIIB	9	11	2	4	16	12
IV	91	89	98	96	84	88
ECOG PS, %						
0	26	26	27	26	30	25
1	74	74	73	74	70	75
Smoking status, %						
Current smoker	29	29	16	15	32	39
Former smoker	22	23	12	17	25	30
Never smoker	50	48	71	69	43	31
Histology, %						
Adenocarcinoma	77	75	92	92	70	67
Non-adenocarcinoma	23	25	8	8	30	33

% values rounded to the nearest whole number; ECOG PS = Eastern Cooperative Oncology Group performance status

PFS data from FASTACT-2 in ASCO 2012 (ITT population)[1]

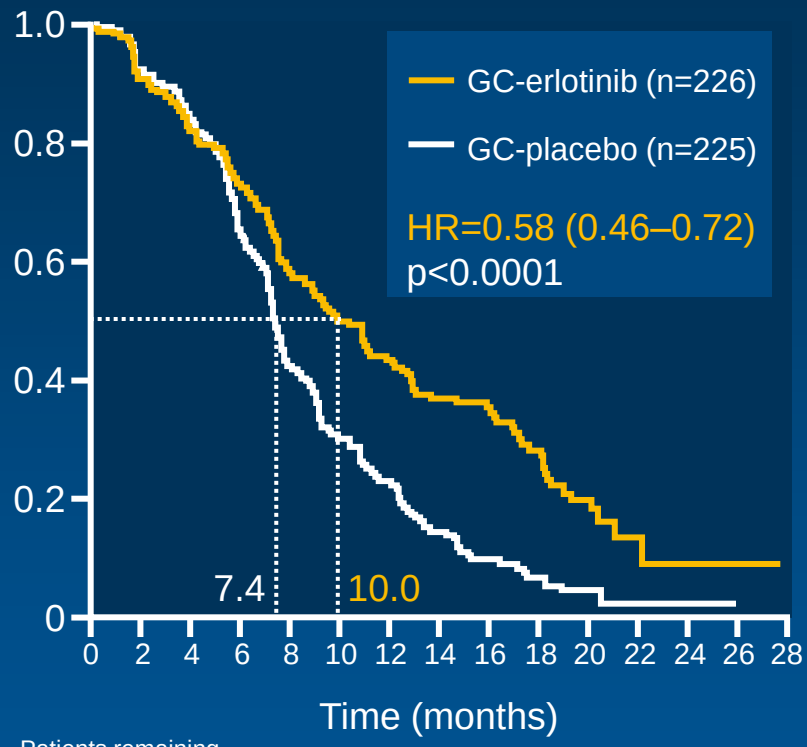
Original analysis (21 Oct 2011)



Patients remaining

E	226	192	162	136	102	81	65	46	33	23	5	2	1	1	0
P	225	185	156	114	57	31	21	13	7	4	2	1	1	0	0

IRC review (26 Mar 2012)



Patients remaining

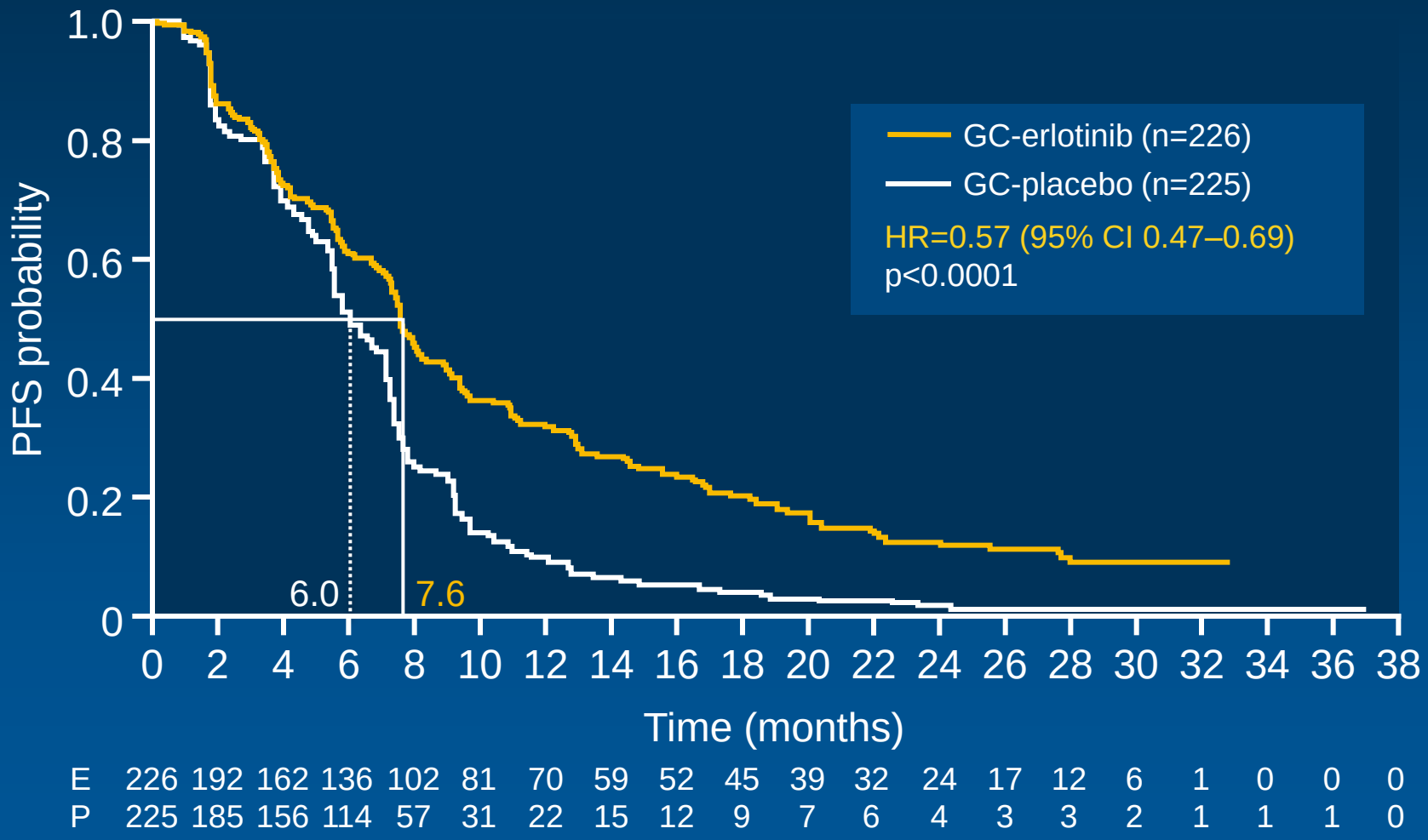
E	226	200	177	151	114	93	76	59	43	29	14	3	1	1	0
P	225	200	179	134	79	51	35	19	12	7	3	1	1	1	0

OS data were not yet mature

ITT = intention-to-treat; HR = hazard ratio

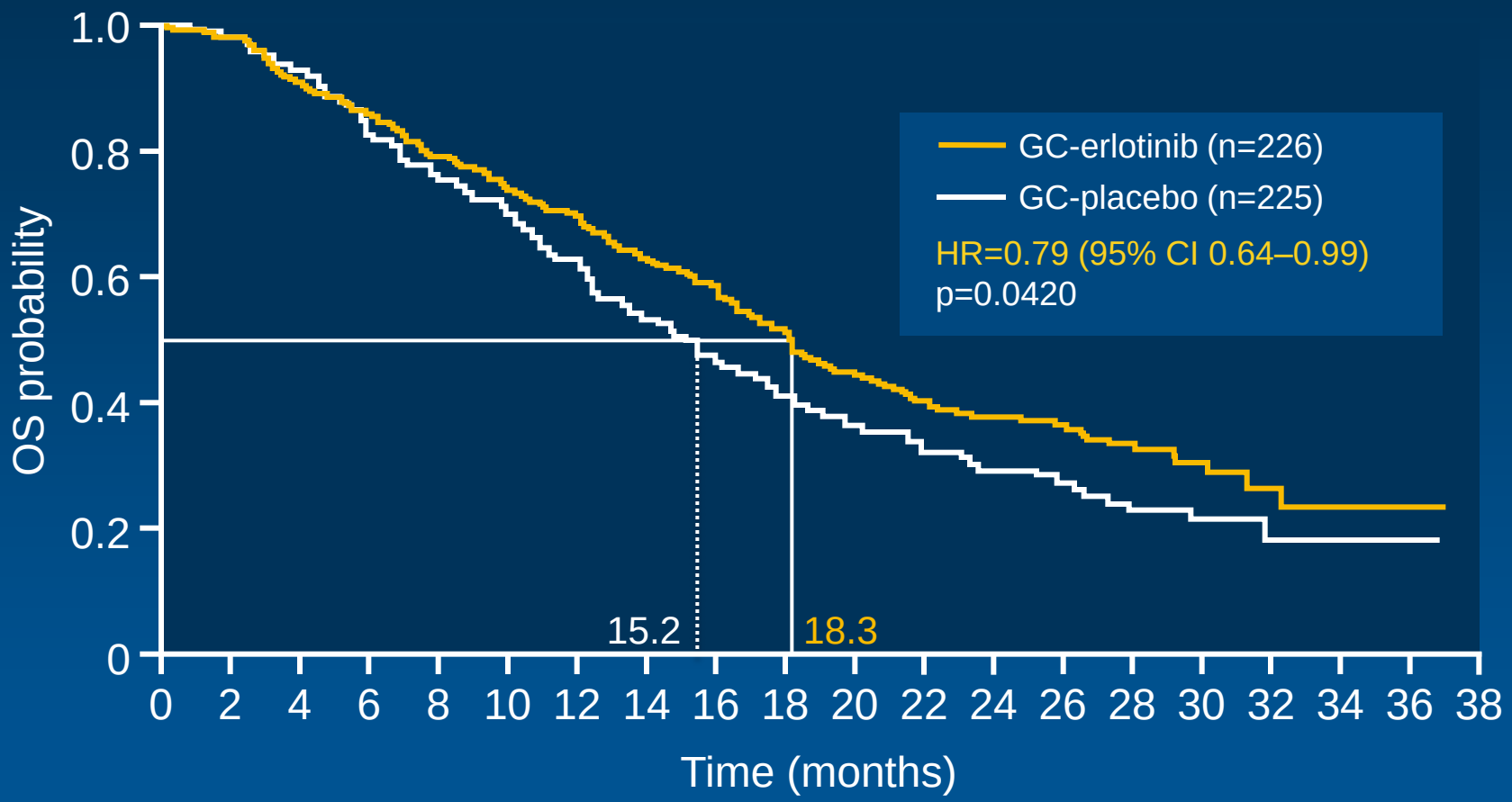
[1]Mok T, et al. J Clin Oncol 2012;30 (Suppl 30 Pt I):484s (Abst. 7519)

Updated primary endpoint: PFS in ITT population (22 Jun 2012)



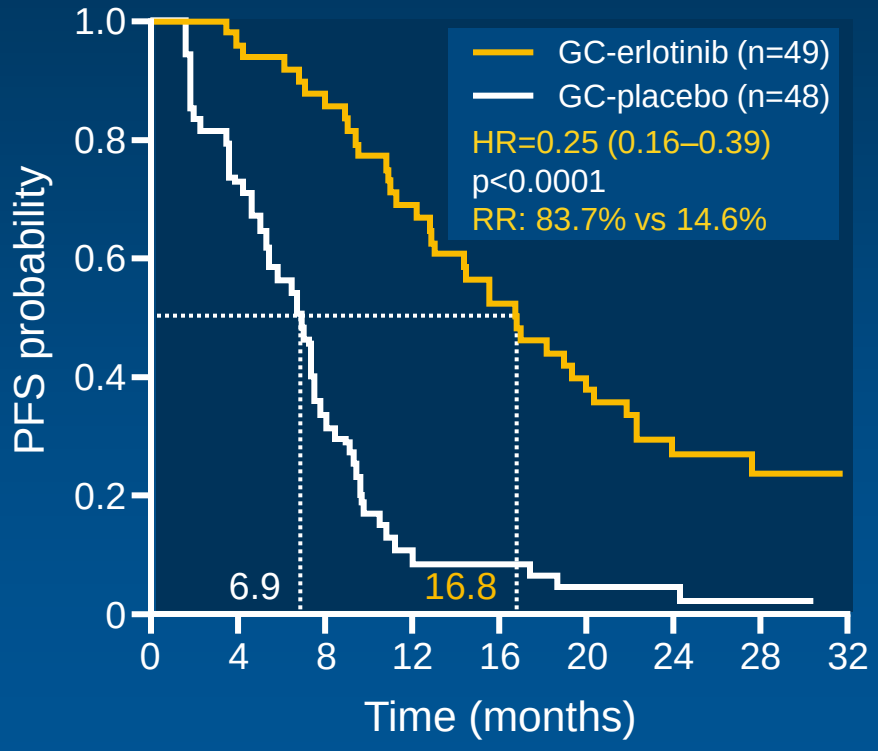
CI = confidence intervals

OS in ITT population (22 Jun 2012)



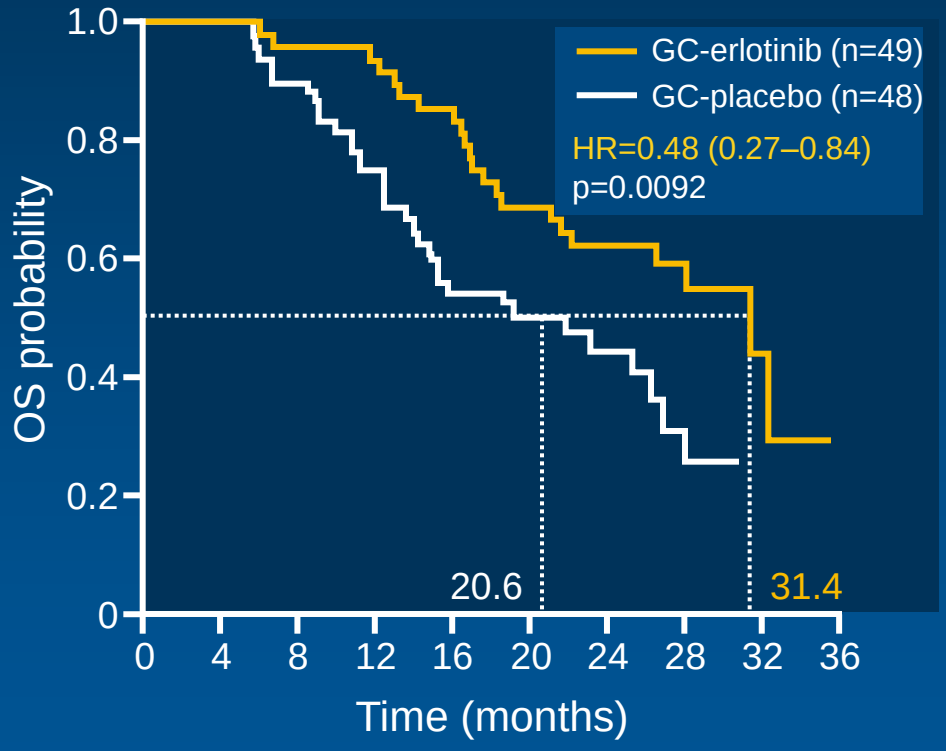
PFS and OS in *EGFR* Mut+ subgroup (22 Jun 2012)

PFS



E	49	46	42	33	25	19	11	6	0
P	48	35	16	5	4	2	2	1	0

OS



E	49	48	46	45	41	33	24	15	3	0
P	48	48	43	36	26	24	14	6	0	0

Erlotinib as post-study therapy

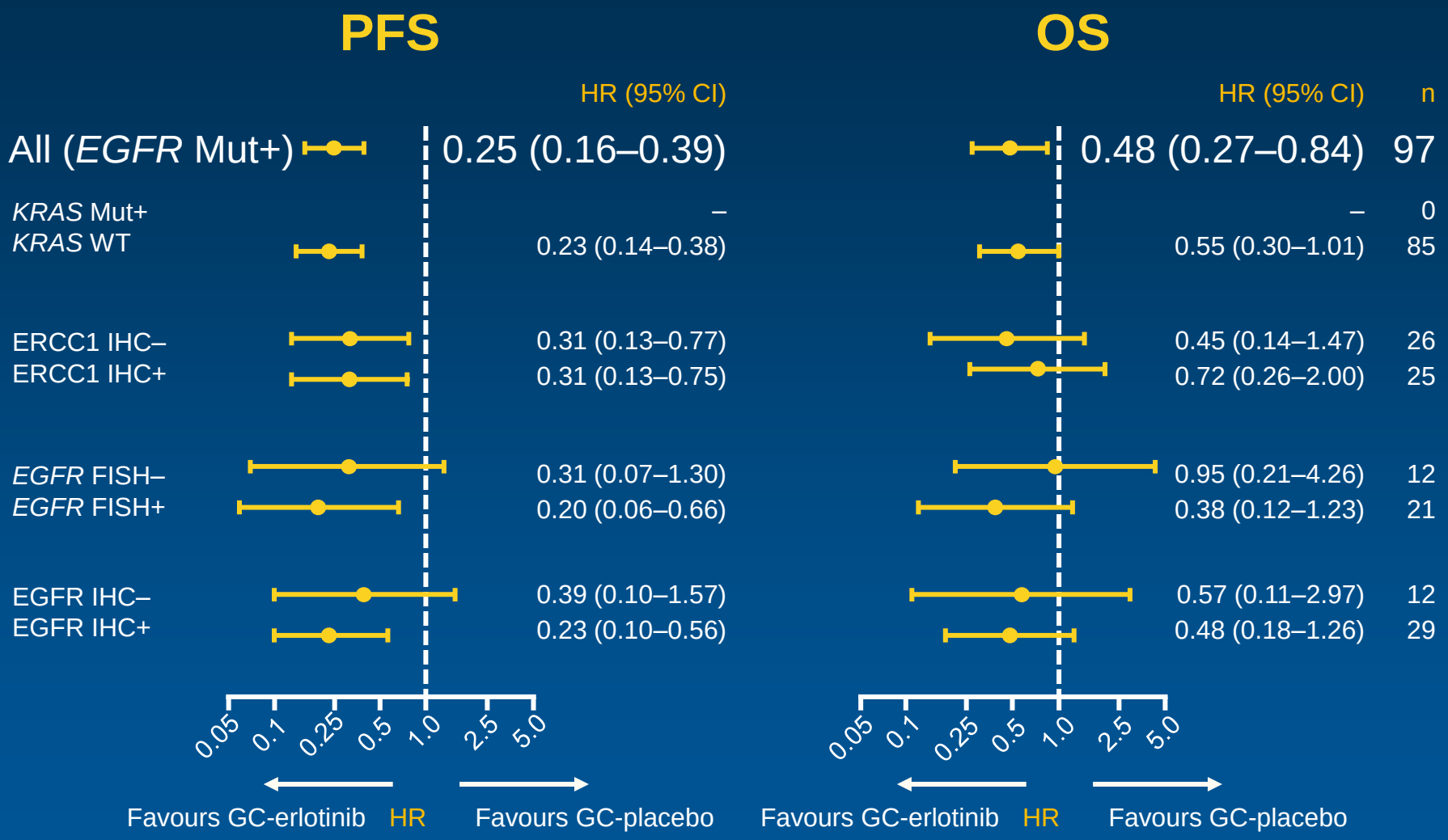
All patients	GC-erlotinib (n=226) %	GC-placebo (n=225) %
Any	48	82
2nd line: TKIs	4	79
2nd line: Erlotinib	<1	77
2nd line: Antimetabolites	20	1
2nd line: Taxanes	19	2
2nd line: Platinum compounds	10	0

Note: high crossover rate in GC-placebo arm was likely due to free availability of second-line erlotinib

EGFR Mut+	GC-erlotinib (n=49) %	GC-placebo (n=48) %
Any	47	85
2nd line: TKIs	6	85
2nd line: Erlotinib	2	83
2nd line: Antimetabolites	18	2
2nd line: Taxanes	18	0
2nd line: Platinum compounds	8	0

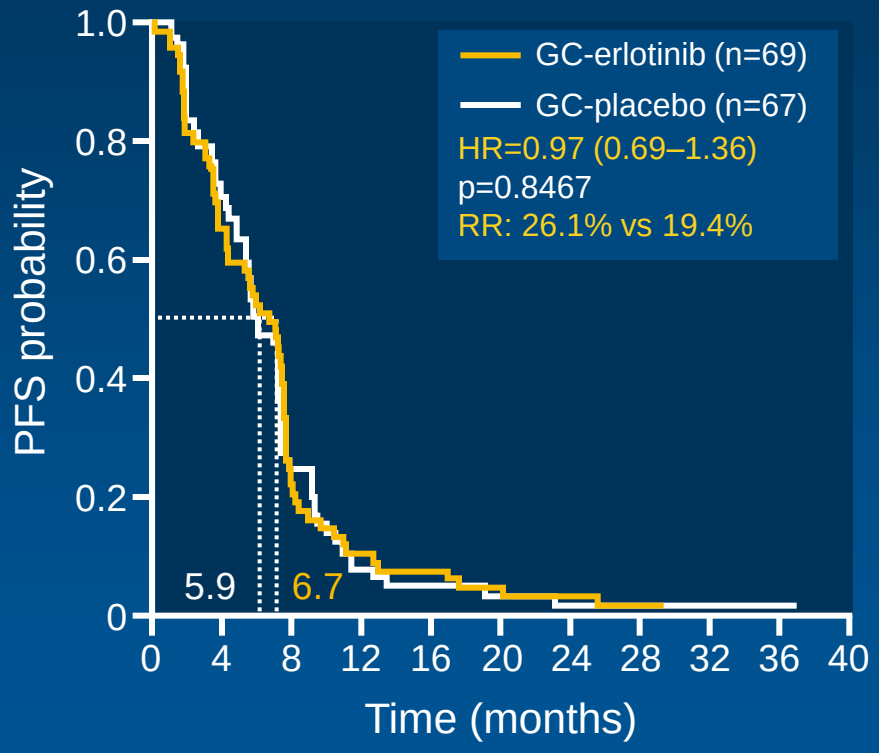
Percentages correspond to patients who received at least one treatment

PFS and OS by biomarker subgroups in *EGFR* Mut+ subgroup (22 Jun 2012)



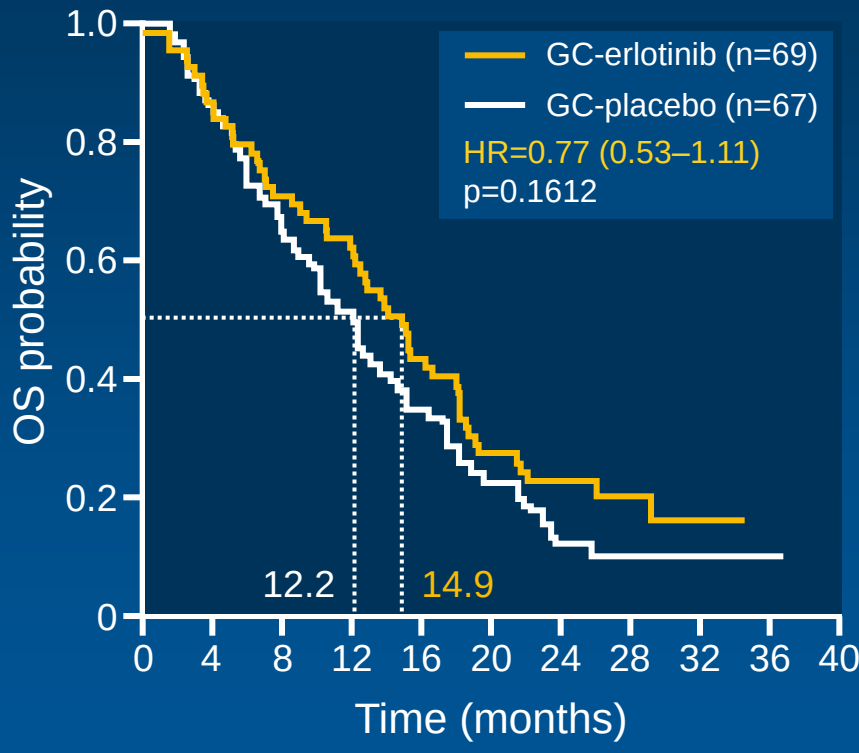
PFS and OS in *EGFR* WT subgroup (22 Jun 2012)

PFS



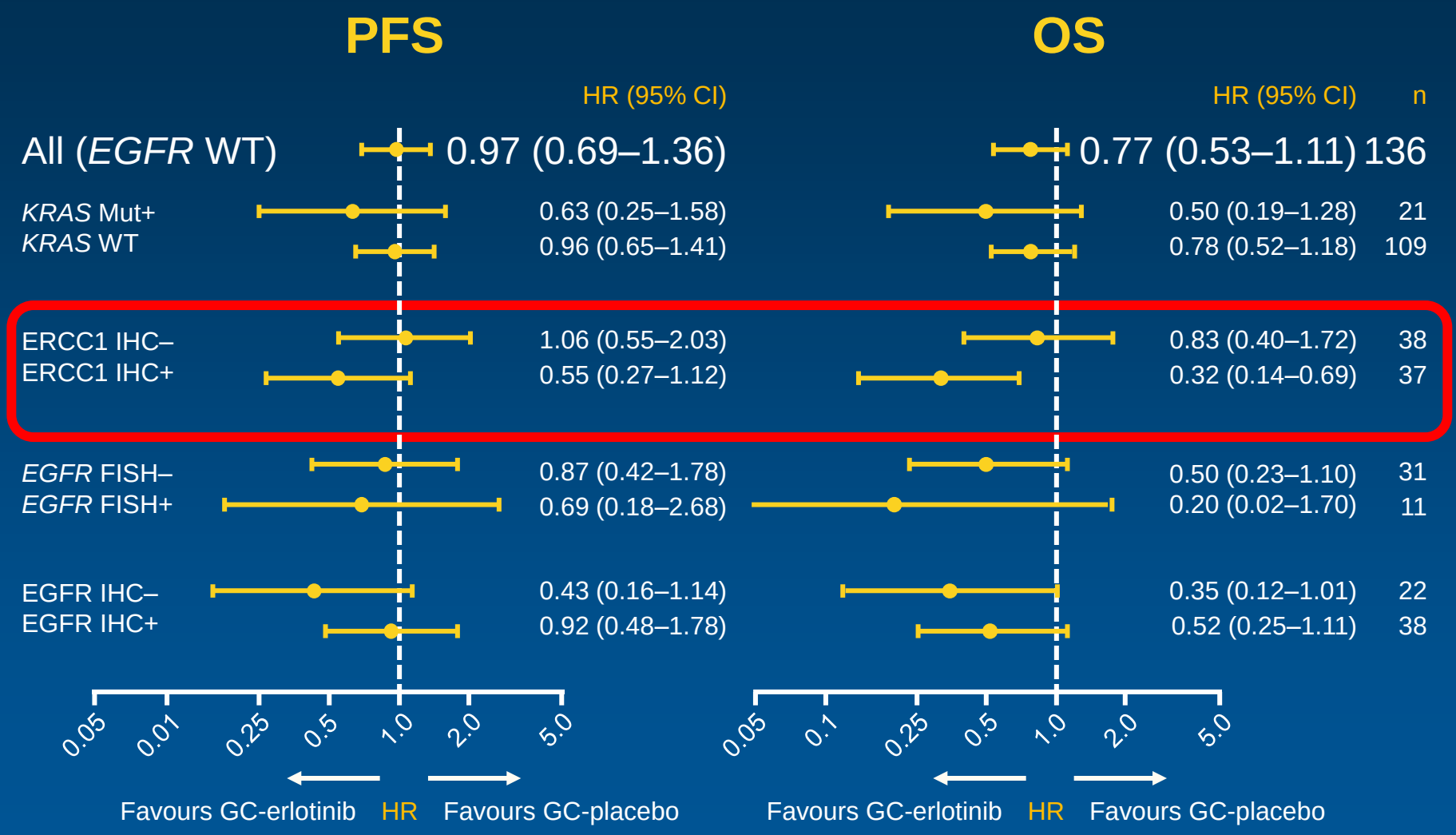
E	69	45	15	7	5	3	2	1	0	0	0
P	67	46	16	5	3	2	1	1	1	1	0

OS

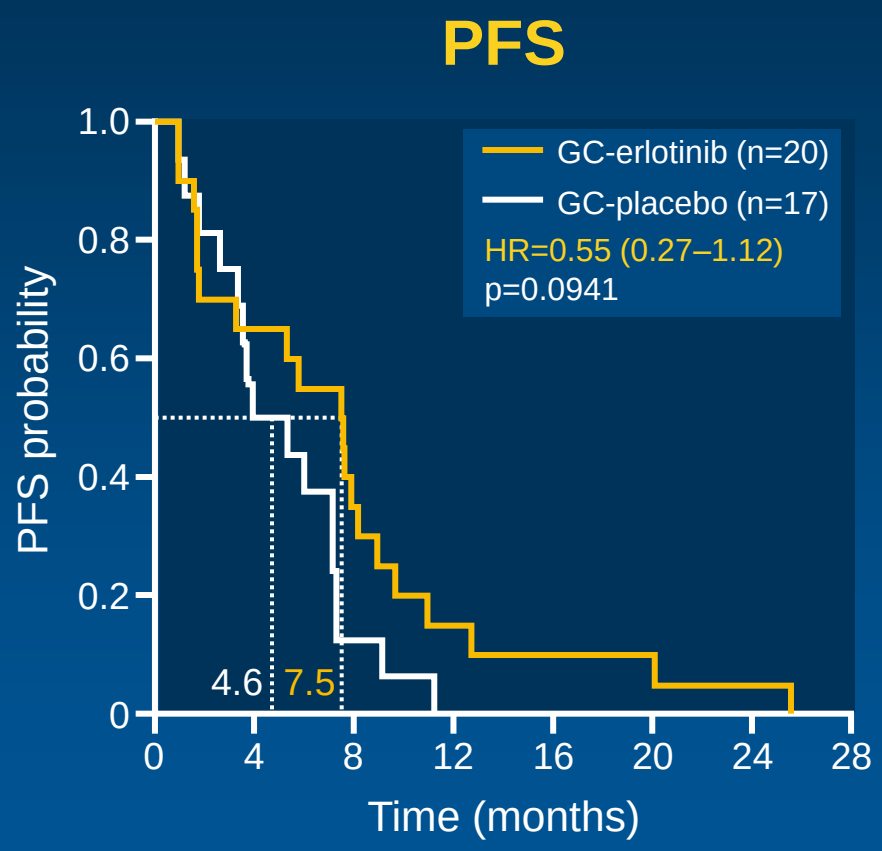


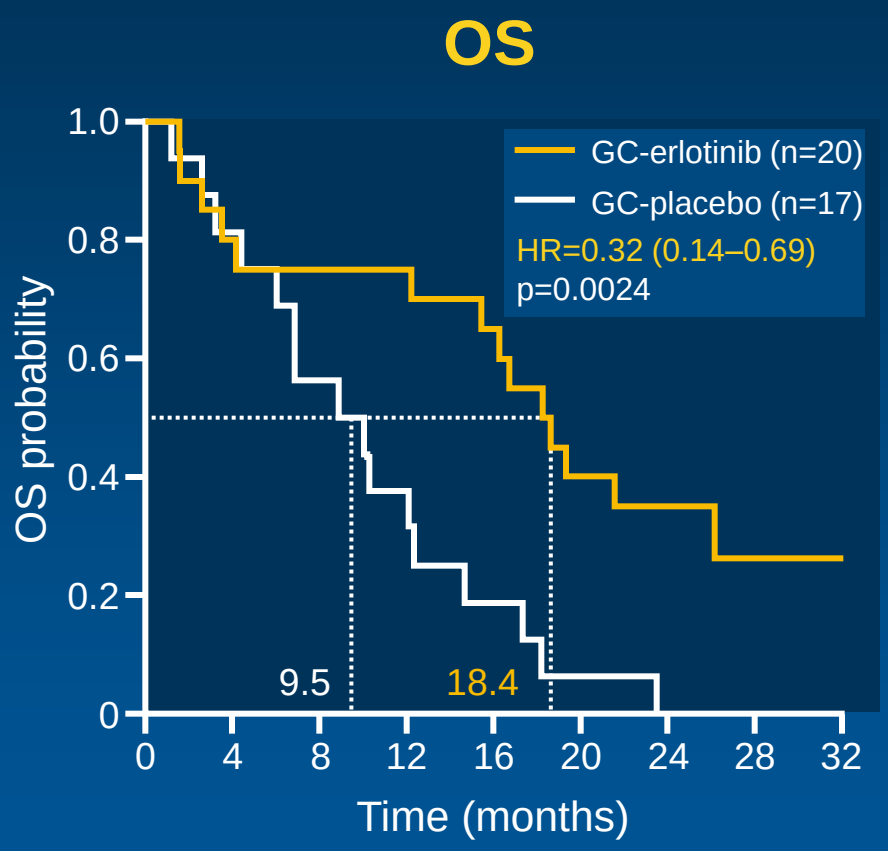
E	69	60	49	43	30	19	12	6	4	0	0
P	67	57	43	34	23	15	7	3	2	1	0

PFS and OS by biomarker subgroups in *EGFR* WT subgroup (22 Jun 2012)



PFS and OS in patients with *EGFR* WT and ERCC1 IHC+ status (22 Jun 2012)





Summary of safety data

	GC-erlotinib (n=226) n (%)	GC-placebo (n=222) n (%)
AEs of any cause, all grades	225 (100)	221 (100)
AEs of any cause, grade 5	12 (5)	7 (3)
Treatment-related AEs, all grades	220 (97)	214 (96)
Treatment-related AEs, grade ≥3	128 (57)	108 (49)
Any serious AEs	69 (31)	76 (34)
Treatment-related serious AEs	37 (16)	48 (22)
Dose modification/interruption due to AE	137 (61)	140 (63)
Dose modification/interruption due to treatment-related AE	128 (57)	125 (56)
Discontinuation due to AEs	16 (7)	13 (6)
Discontinuation due to treatment-related AE	5 (2)	11 (5)

AE = adverse event

Conclusions

- **Updated analysis of FASTACT-2 shows both PFS and OS are significantly prolonged with GC-erlotinib versus GC-placebo: HR=0.57; p<0.0001 and HR=0.79; p=0.042, respectively**
- **Patients with *EGFR* Mut+ disease benefited from the intercalated regimen of GC-erlotinib versus GC-placebo: PFS HR=0.25; p<0.0001 and OS HR=0.48; p=0.009**
  - the difference between arms was statistically significant for OS, noting that 85% of placebo patients had a second-line EGFR TKI
- **Patients with *EGFR* WT disease did not benefit more from GC-erlotinib versus GC-placebo**
  - however, *EGFR* WT group had no detrimental effect from the addition of erlotinib
  - ERCC1 is a potential biomarker for patients with *EGFR* WT NSCLC; further studies are required
- **The intercalated regimen was well tolerated**
- **Intercalated erlotinib and chemotherapy could be considered as a treatment option for patients with unknown *EGFR* mutation status**
  - those with *EGFR* mutations would gain additional benefit and those with *EGFR* WT disease would have the same benefit as with standard chemotherapy

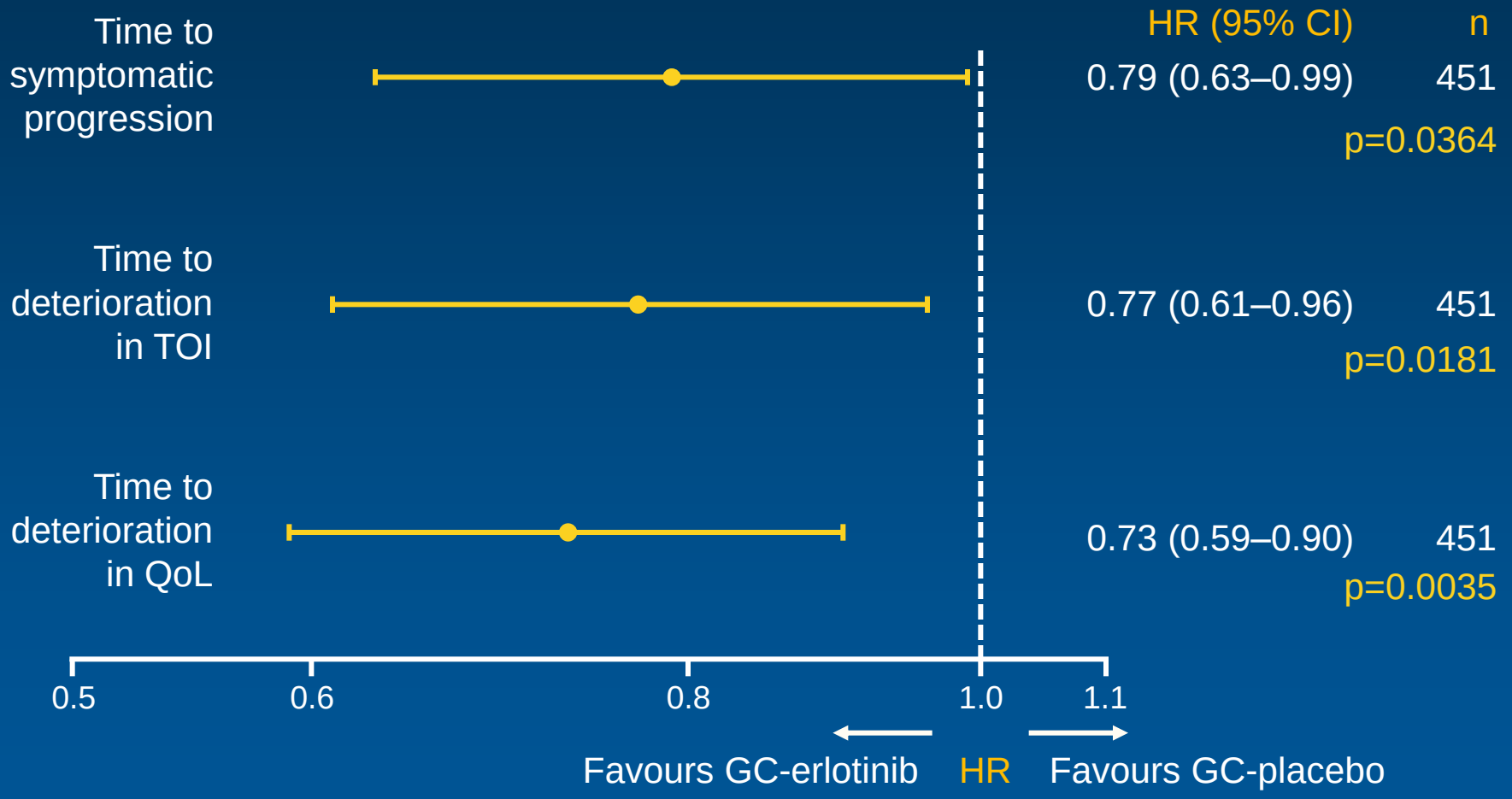
Acknowledgments

- The authors would like to thank all investigators, participating patients and their families

Backup slides

Back-up slide

QoL analyses



TOI = trial outcomes index