RANDOMISED PHASE III STUDY OF ERLOTINIB VERSUS OBSERVATION IN PATIENTS WITH NO EVIDENCE OF DISEASE PROGRESSION AFTER FIRST LINE, PLATINUM-BASED CHEMOTHERAPY FOR HIGH-RISK STAGE I AND STAGE II-IV OVARIAN EPITHELIAL, PRIMARY PERITONEAL, OR FALLOPIAN TUBE CANCER

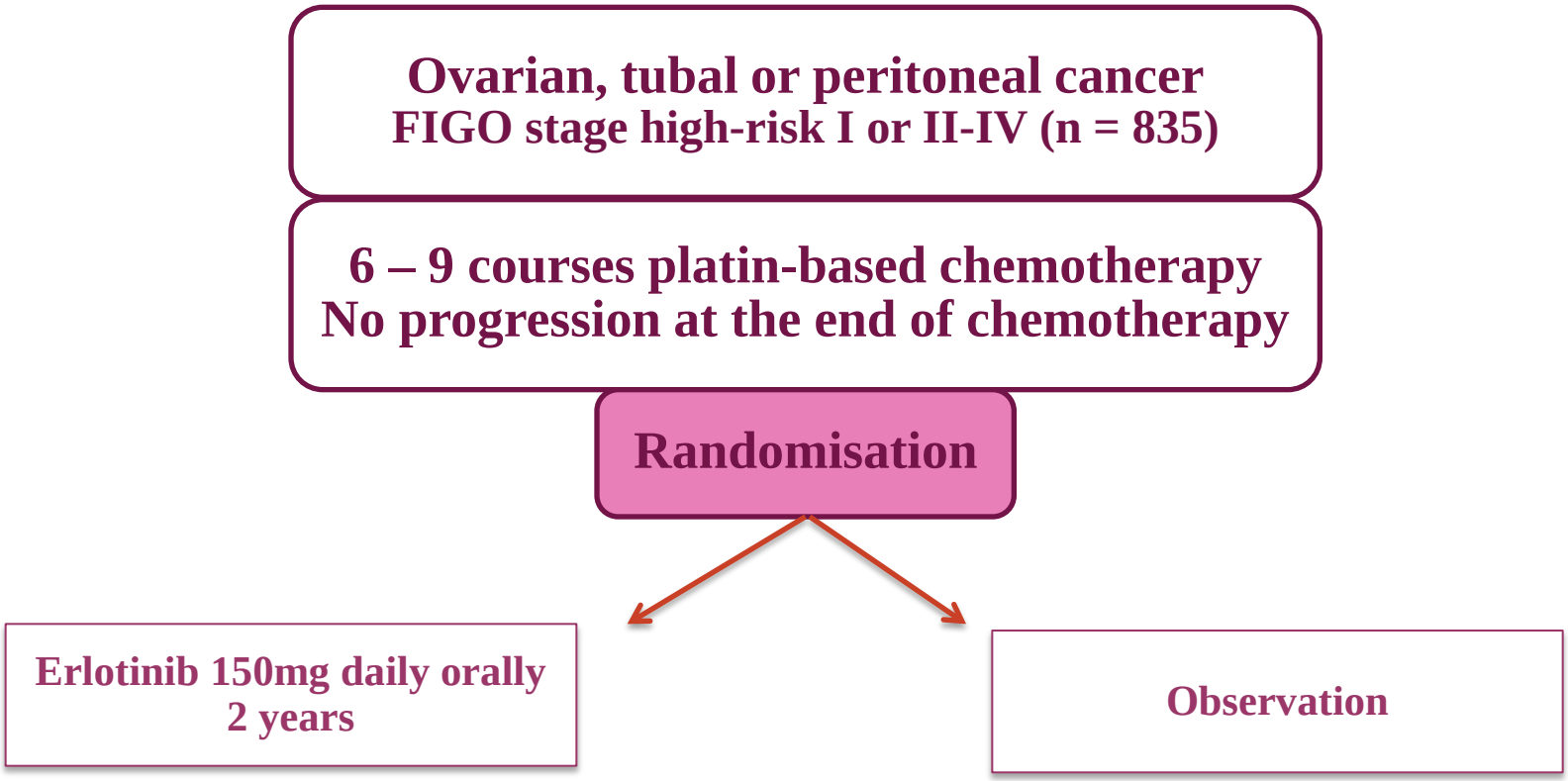
Presented at the 2012 ASCO Annual Meeting. Presented data is the property of the author.

ASCO Annual '12 Meeting

Rationale: ErbB targeted therapy in refractory/resistant ovarian cancer

		n	ErbB+	DRUG	ORR	SD
Bookman	2003	837	95	Herceptin	7%*	39%
Schilder	2005	27	27	Gefitininb	3%	15%
Gordon	2005	34	34	Erlotinib	6%	44%
Campos	2005	105	82+	CI-1003	0%	34%/26%
Friberg	2006	13	NK	Erlot + Bev	15%	54%
Seiden	2007	75	37	Matuzumab	0%	8%
Schilder	2007	25	26	Catuximab	0%	8%
Gordon	2007	117	28	Pertuzumab	4%	7%

Randomised trial on Erlotinib vs observation in first-line ovarian cancer



Primary Endpoint: Progession-free survival

Secondary endpoints: Overall Survival, Quality of Life, Complications

Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Eligibility

- Histologically confirmed ovarian epithelial, primary peritoneal, and fallopian tube cancer:
  - High-risk FIGO stage I (grade 3, or aneuploid grade 1 or 2, or clear cell), or
  - Stages II-IV.
- CR, PR or SD at end of first-line therapy.
- No more than 6 weeks since the end of first line chemotherapy.
- 6-9 cycles of Carboplatin AUC 5-6/3weeks or Cisplatin dose > 60 mg/m²/3 weeks alone or in combination with other agents.

Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Statistical observations

- Stratification factors:
  - FIGO stage (I-II versus III-IV),
  - Institution,
  - Age (65 years and < vs. > 65 years),
  - Clinical response to first-line therapy (NED/CR vs. PR vs. SD, as defined by RECIST),
  - First-line therapy (platinum alone vs. platinum-based doublet vs. platinum-based triplet)
- Progression according to RECIST or GCIG criteria including CA125 whatever occurred first (interim analysis showed that CA125 was a reliable marker during erlotinib treatment).

Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Sample size and objectives

- Estimated median PFS of 15 months (from end of the first line CT) in the control group
- Increase of 25% in median PFS from 15 to 18.75 months (hazard ratio=0.8)
- With 80% power, two-sided test, 0.05 alpha level, **632 events** (deaths and/or progressions) were required.
- Assuming accrual of 370 patients, **830 patients** needed to obtain 632 events.
- Estimated accrual time was 30 months with another 24 months of follow up.

Randomised trial on Erlotinib vs observation in first-line ovarian cancer:
Study conduct

- Between 17/10/2005 and 19/02/2008, a total of 835 patients were randomized by 125 institutions in 10 countries.
- On November 2011 the IDMC agreed to perform the final analysis despite the number of events needed was not reached due to very slow occurrence of events at the end of follow-up (625 of the 632 events needed are reported).
- Median follow-up was 51 months (4.3 years).
- Only 4 patients did not fulfill all eligibility criteria.
- Safety population excludes these 4 ineligible patients + 7 who did not receive the allocated treatment (5 in erlotinib and 2 in observation arm).

Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Baseline characteristics (1)

	Erlotinib	Observation
Age (y, median)	59	59
Performance status (%)		
0	67	67
1	33	33
Primary (%)		
Ovary	93	89
Fallopian tube	2	4
Peritoneum	6	7
FIGO (%)		
I	8	6
II	7	8
III	65	70
IV	21	16

Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Baseline characteristics (2)

	Erlotinib	Observation
Histological type (%)		
Serous	66	58
Response first-line CT (%)		
CR	71	73
PR	25	24
SD	4	3
First-line chemo (%)		
Carbo-paclitaxel	96	96
Carbo mono	1	3
Cisplatinum	3	1
Median CA125 at randomization (KU/L)	12	11

Randomised trial on Erlotinib vs observation in first-line ovarian cancer:
Baseline characteristics (3)

	Erlotinib	Observation
Surgery (%)		
PDS	69	75
IDS	33	28
R0 (%)		
PDS	48	48
IDS	66	60

Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Treatment modifications

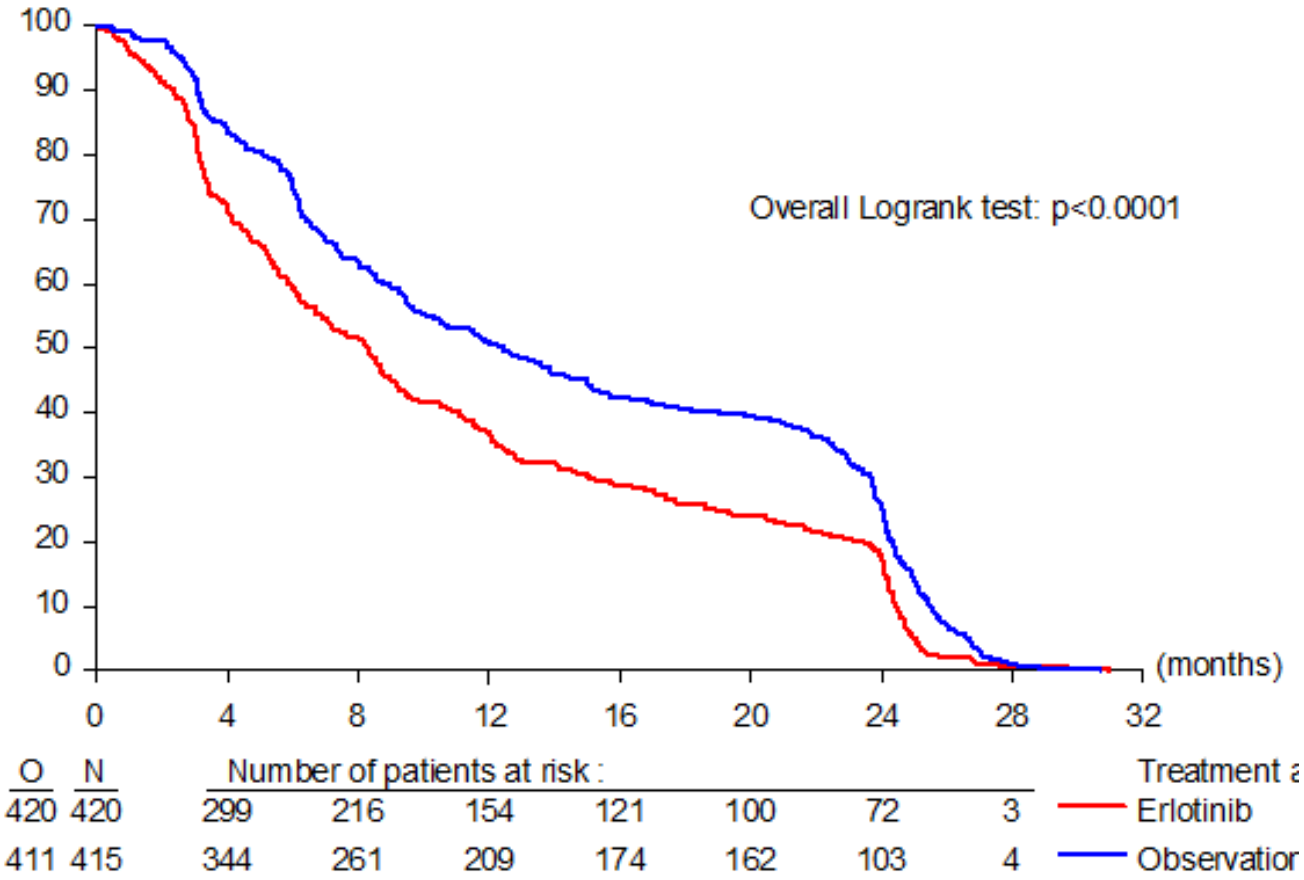
	Erlotinib	Observation
Reasons for stopping treatment (%)		
Normal completion	19	33
PD	51	64
Unacceptable AE	25	0
Refusal	3	1
Other	1	2
Treatment deviations (%)	11	0
Undertreatment	7	
Overtreatment	3	
Both	1	

Randomised trial on Erlotinib vs observation in first-line ovarian cancer:

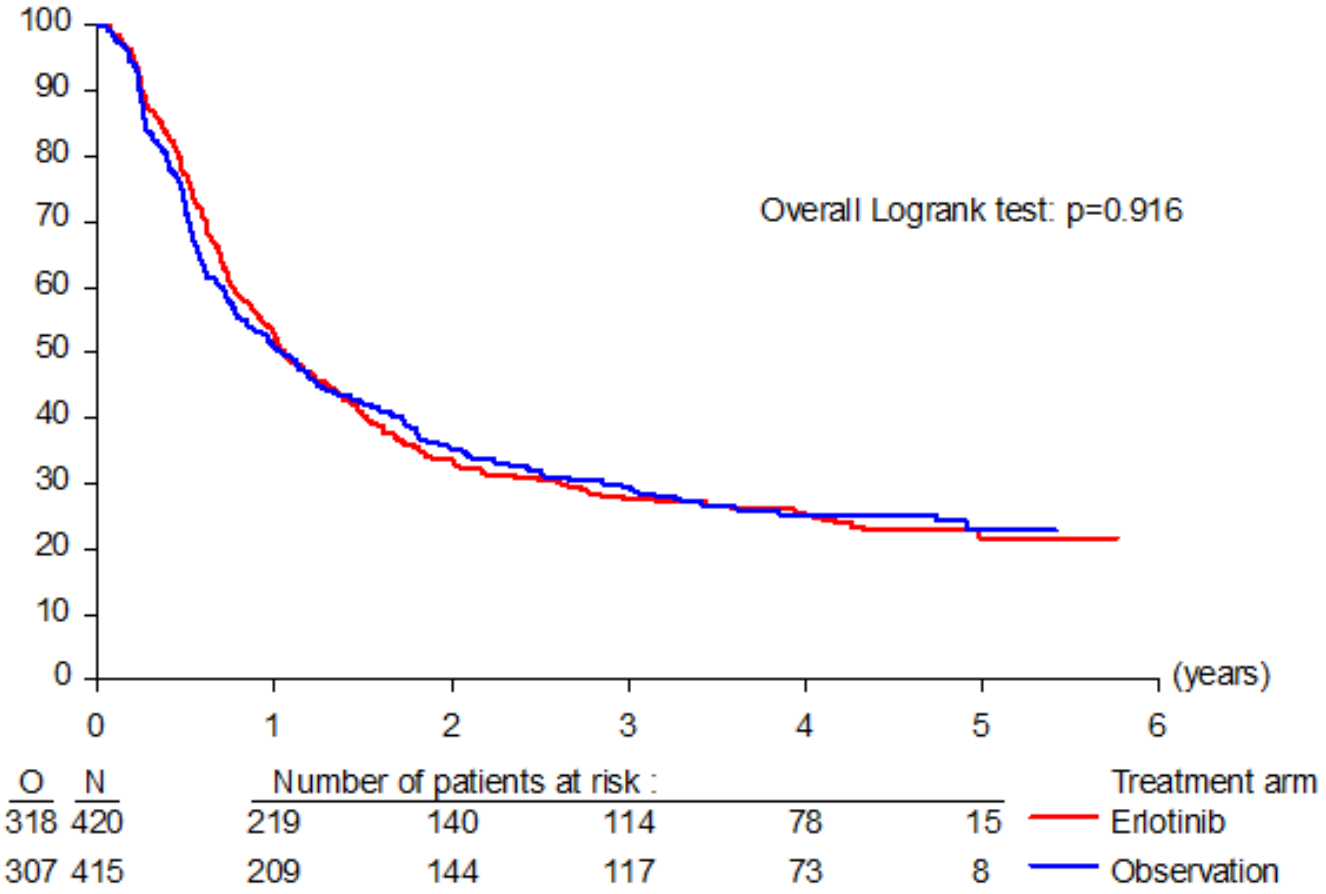
Toxicity

	Erlotinib	Observation
Diarrhea (%)		
G1	34	9
G2	21	2
G3	5	1
G4	0	0
Missing	1	15
Rash (%)		
G1	29	1
G2	37	1
G3	12	0
G4	1	0
Missing	1	15

Randomised trial on Erlotinib vs observation in first-line ovarian cancer:
Treatment duration



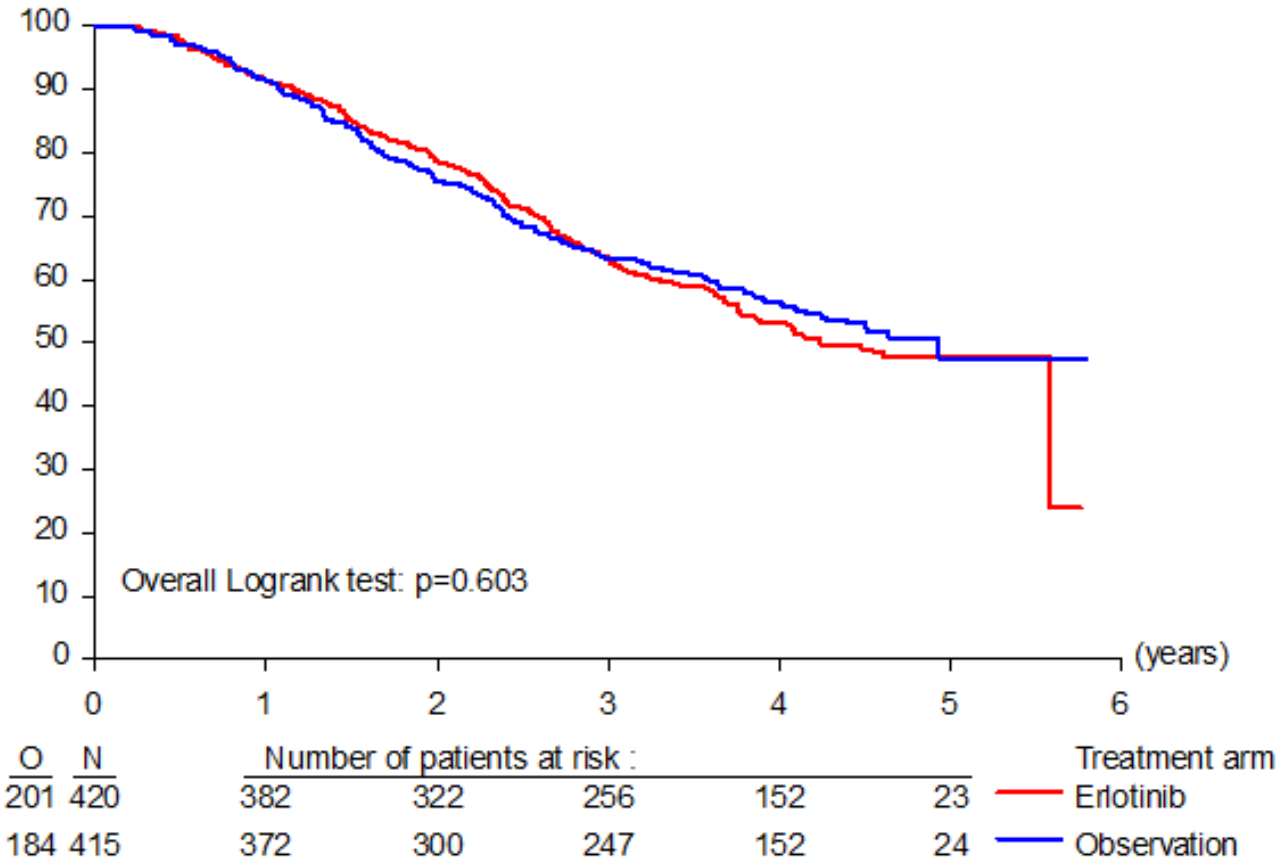
Randomised trial on Erlotinib vs observation in first-line ovarian cancer:
Progression-free survival



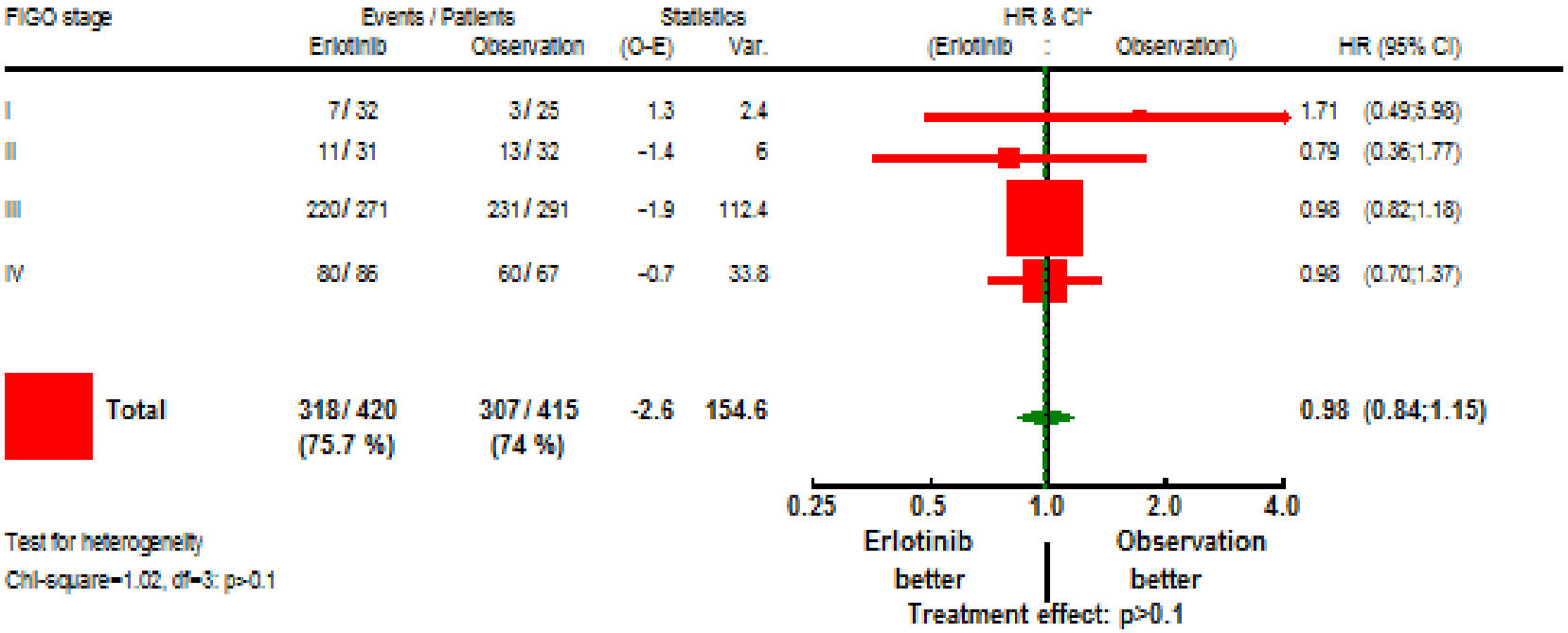
Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Progression based on:

	Erlotinib	Observation
Progression based on (%)		
CA125	8	11
RECIST	33	31
CA125+RECIST simultaneously	7	6
RECIST -> CA125	14	15
CA125 -> RECIST	37	37

Randomised trial on Erlotinib vs observation in first-line ovarian cancer:
Overall Survival



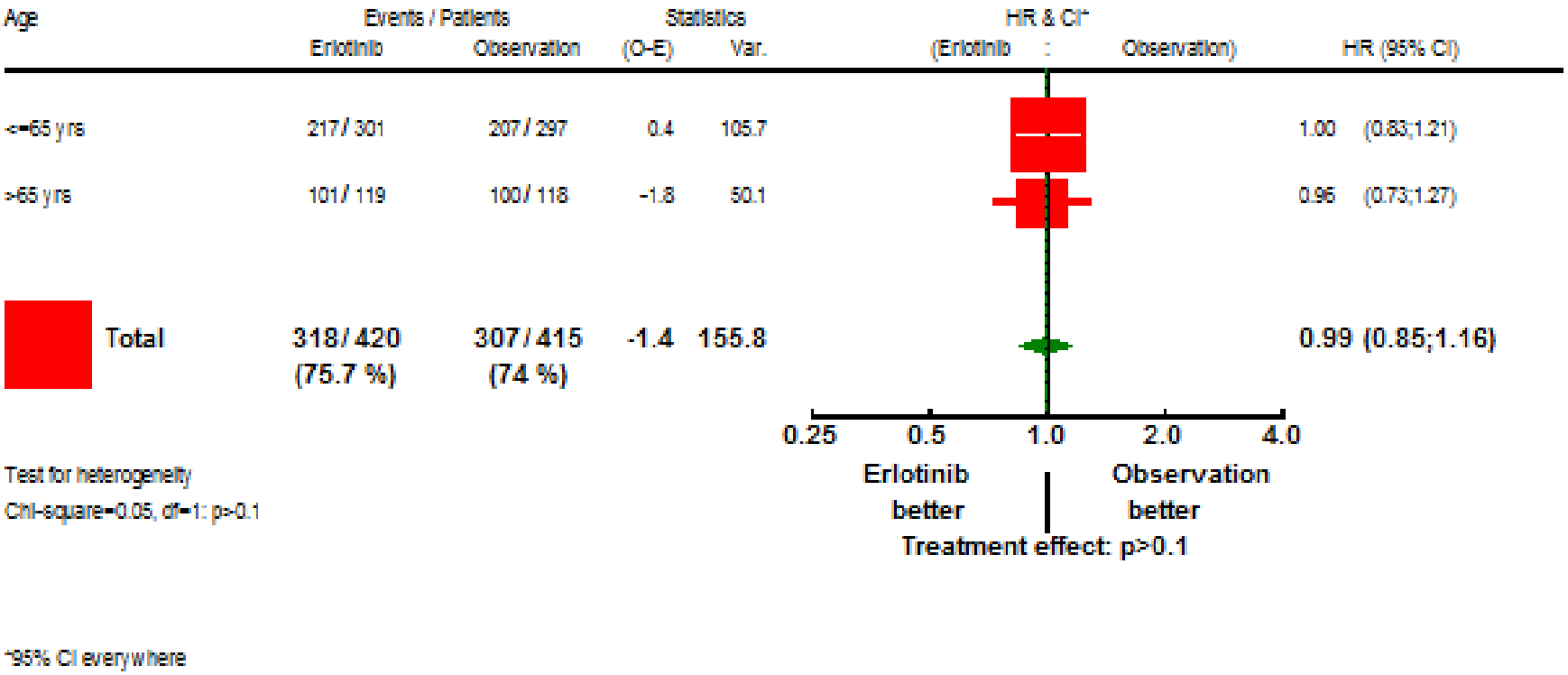
Randomised trial on Erlotinib vs observation in first-line ovarian cancer:
Are there any risk groups?
FIGO stage and PFS



Randomised trial on Erlotinib vs observation in first-line ovarian cancer:

Are there any risk groups?

Age and PFS

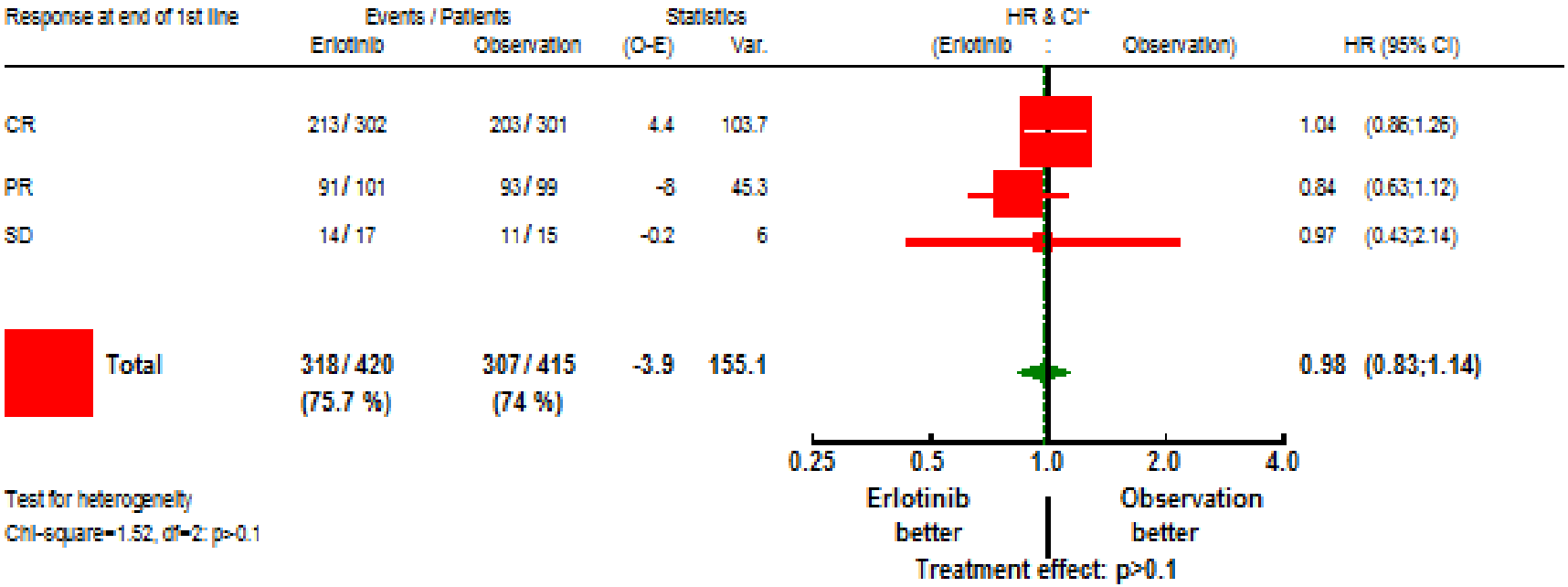


*95% CI everywhere

Randomised trial on Erlotinib vs observation in first-line ovarian cancer:

Are there any risk groups?

Response at end of first-line CT and PFS



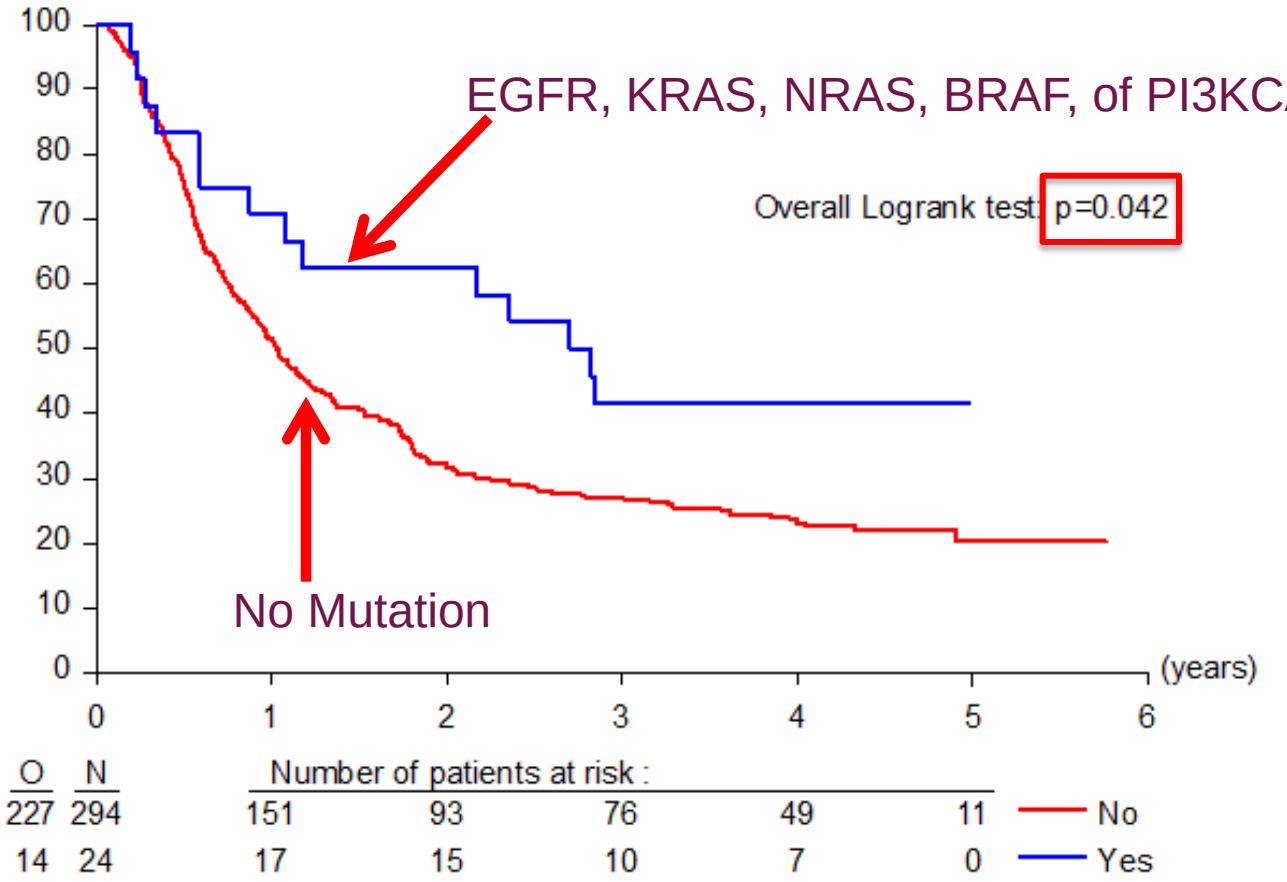
Other analyses

- Quality of life analysis: planned
- Mutation analyses, Immunohistochemistry, and FISH analysis of EGFR.
- Relation to the development of rash

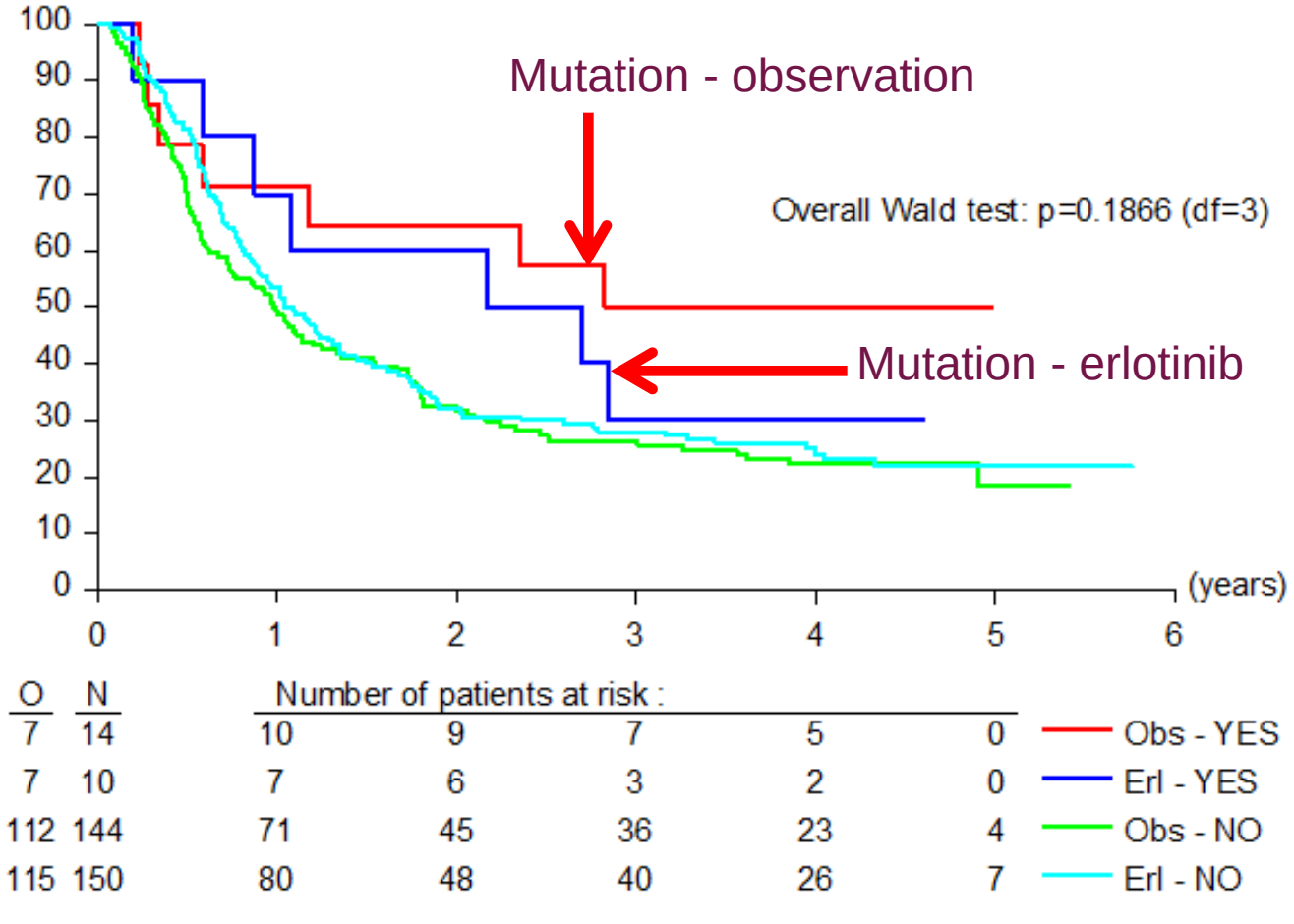
EGFR related Mutations (n = 318)

	Erlotinib (n=160)	Observation (n= 158)
EGFR (%)	1 (0.6)	2 (1.2)
KRAS (%)	5 (3.1)	4 (2.5)
NRAS (%)	1 (0.6)	1 (0.6)
BRAF (%)	-	2 (1.3)
PI3KCA (%)	6 (3.7)	6 (3.8)

EGFR related Mutation analysis (n = 318) and Progression-free survival



EGFR related Mutation analysis (n = 318) and Progression-free survival

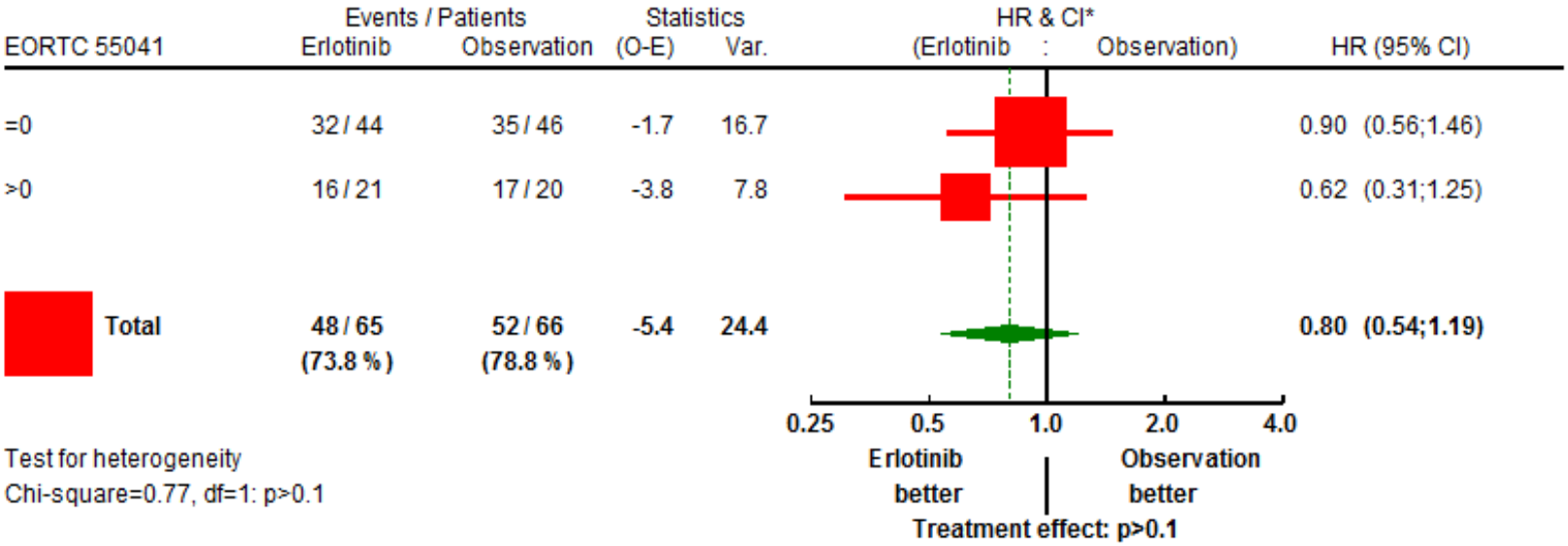


EGFR Immunohistochemistry and FISH (n = 133)

- EGFR Immunohistochemistry:
  - Positive membranous staining : 40/133 (30%)
- EGFR Fish Lung score positive:
  - 23/110 (21%)

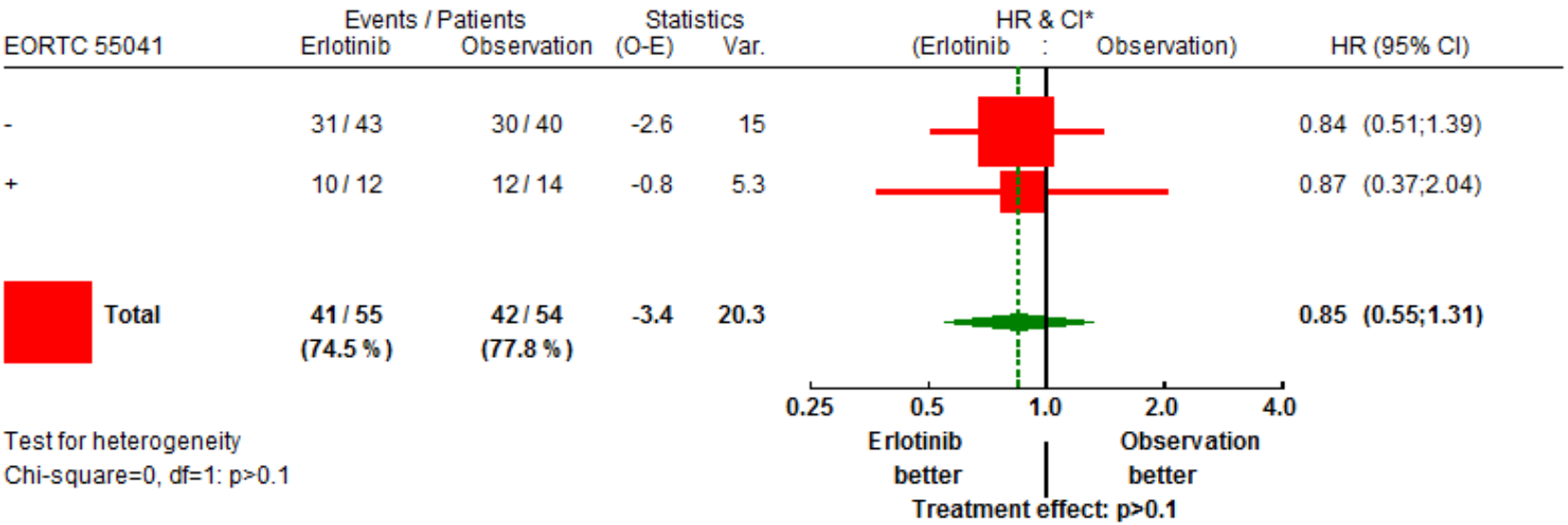
The EGFR lung score was regarded as positive if more than 3 copies were present per cell (Cappuzzo et al., JNCI 2005).

EGFR IHC and PFS



*95% CI everywhere

EGFR FISH lung score and PFS



*95% CI everywhere

Erlotinib related rash and PFS Landmark analysis

- There was no significant relationship between PFS and the development of rash during erlotinib treatment.

Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Conclusions

1. Maintenance erlotinib after first line chemotherapy in patients with ovarian, peritoneal or fallopian tube cancer did not increase PFS nor OS.
2. 25% of the patients stopped the treatment due to side effects (mainly rash).
3. Currently there was no subgroup identified that might benefit from erlotinib maintenance therapy after first-line chemotherapy for ovarian cancer.

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