Rash as a marker for the efficacy of Gemcitabine plus Erlotinib based in pancreatic cancer

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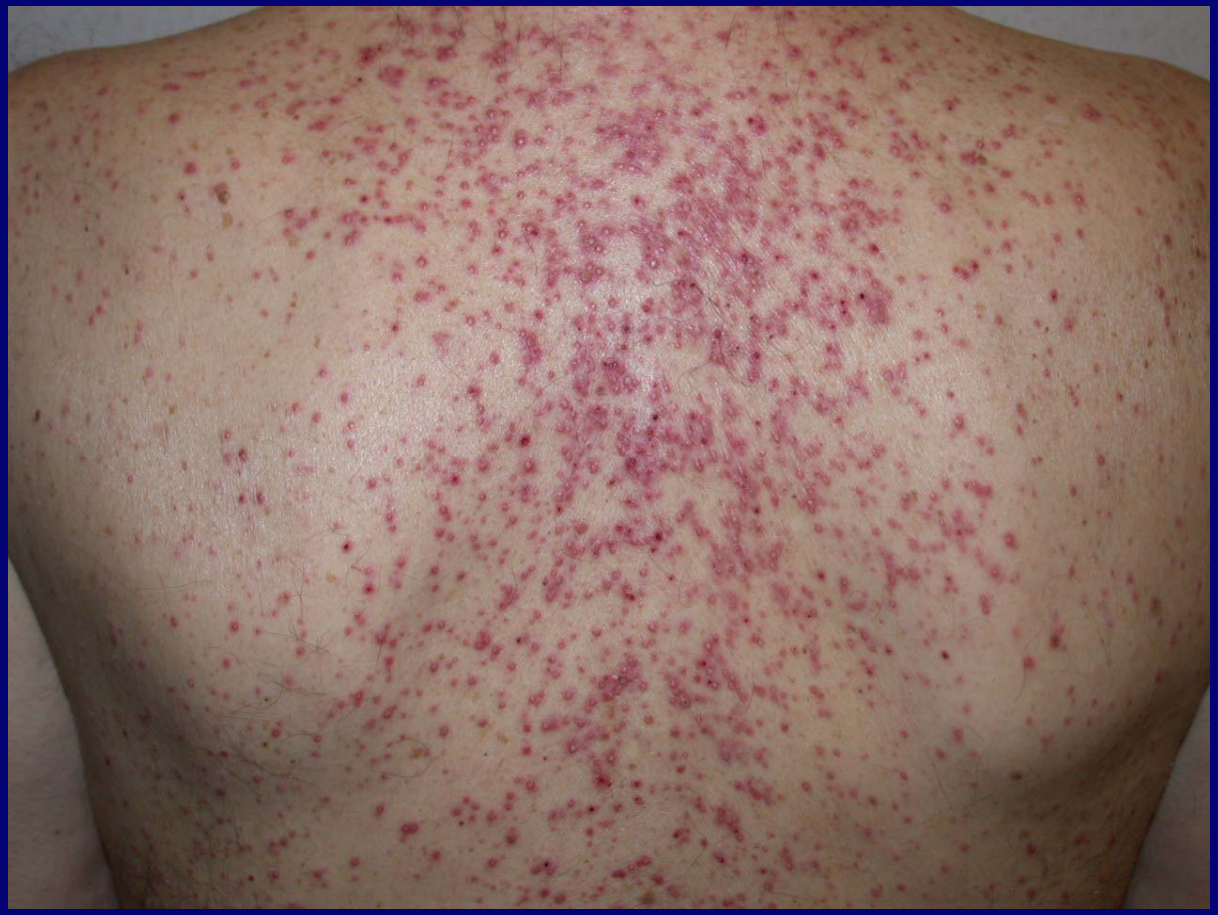
Treating advanced pancreatic cancer

- Pancreatic cancer is often diagnosed at advanced stage, with few effective treatment options available
- Erlotinib plus gemcitabine was first regimen to show significant survival benefit vs gemcitabine alone[1]
- Commitment to investigating rash as predictor of higher efficacy with this regimen

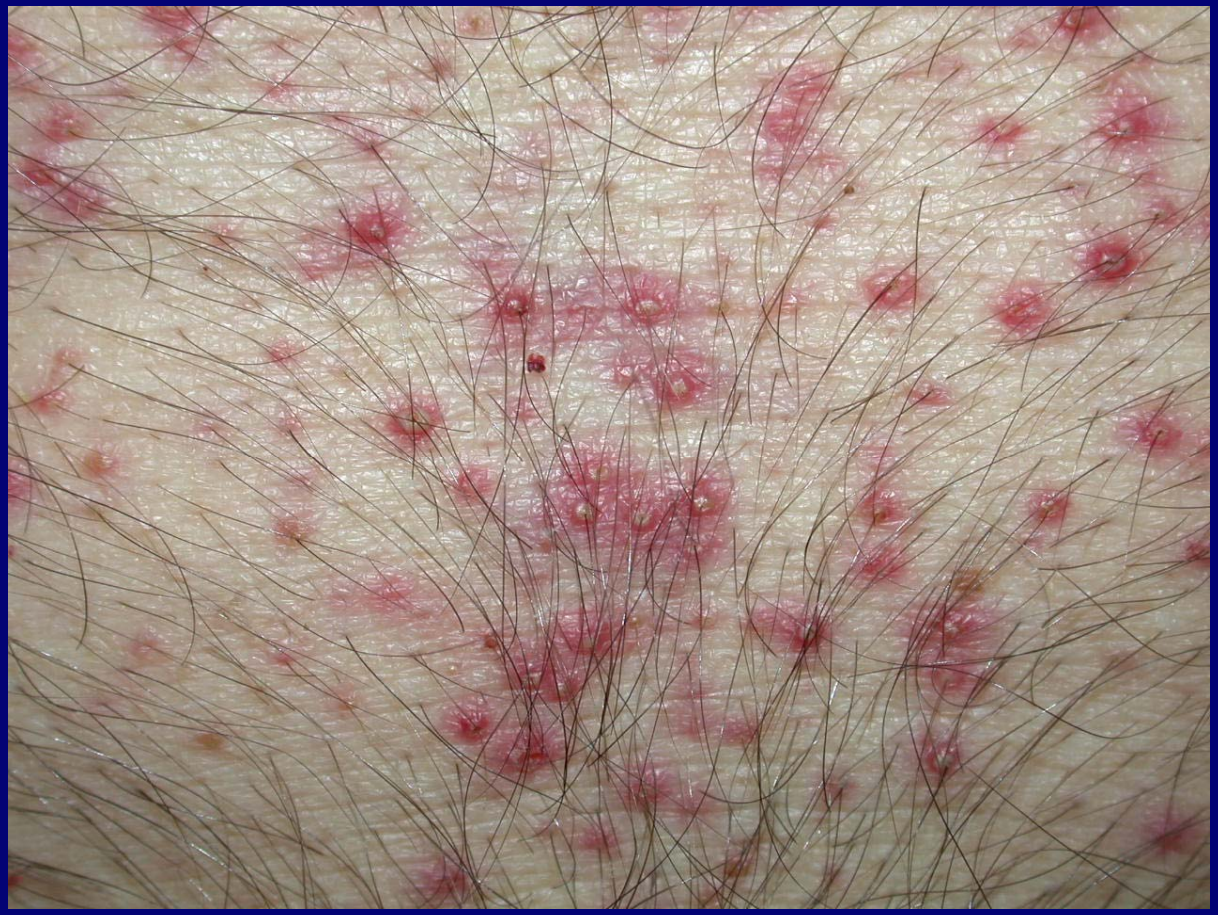
[1]Moore et al, JCO 2007

EGFR inhibitor-induced rash



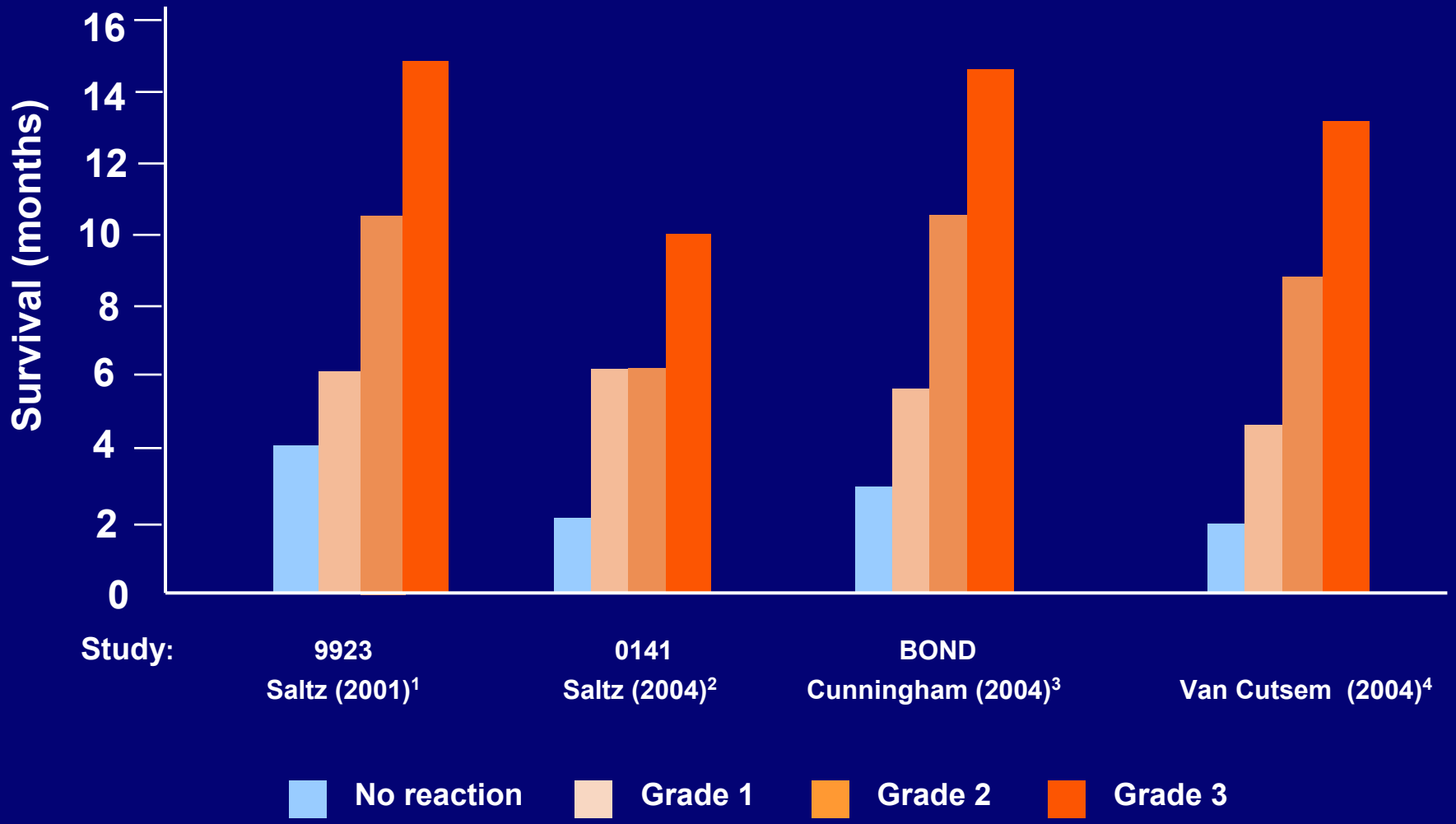
Pictures provided by S Segaert and E Van Cutsem (Leuven, Belgium).

EGFR inhibitor-induced rash



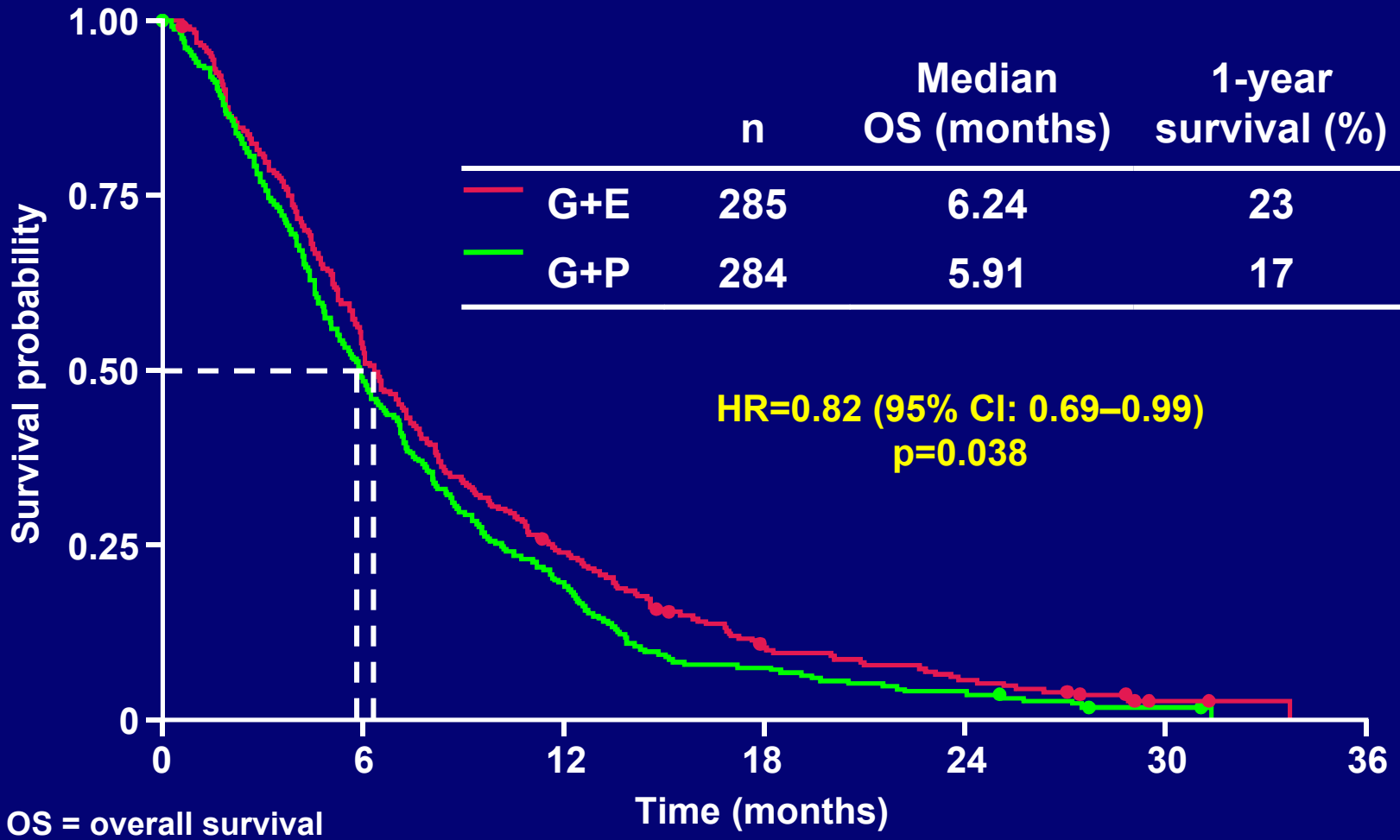
Pictures provided by S Segaert and E Van Cutsem (Leuven, Belgium).

Correlation of rash and survival after treatment with cetuximab in colon cancer



1. Saltz et al. *Proc ASCO* 2001. 2. Saltz et al. *J Clin Oncol* 2004.
3. Cunningham D*N Engl J Med* 2004. 4. Van Cutsem et al. EORTC/NCI Geneva 2004.

PA.3: significant improvement in OS with addition of erlotinib to gemcitabine



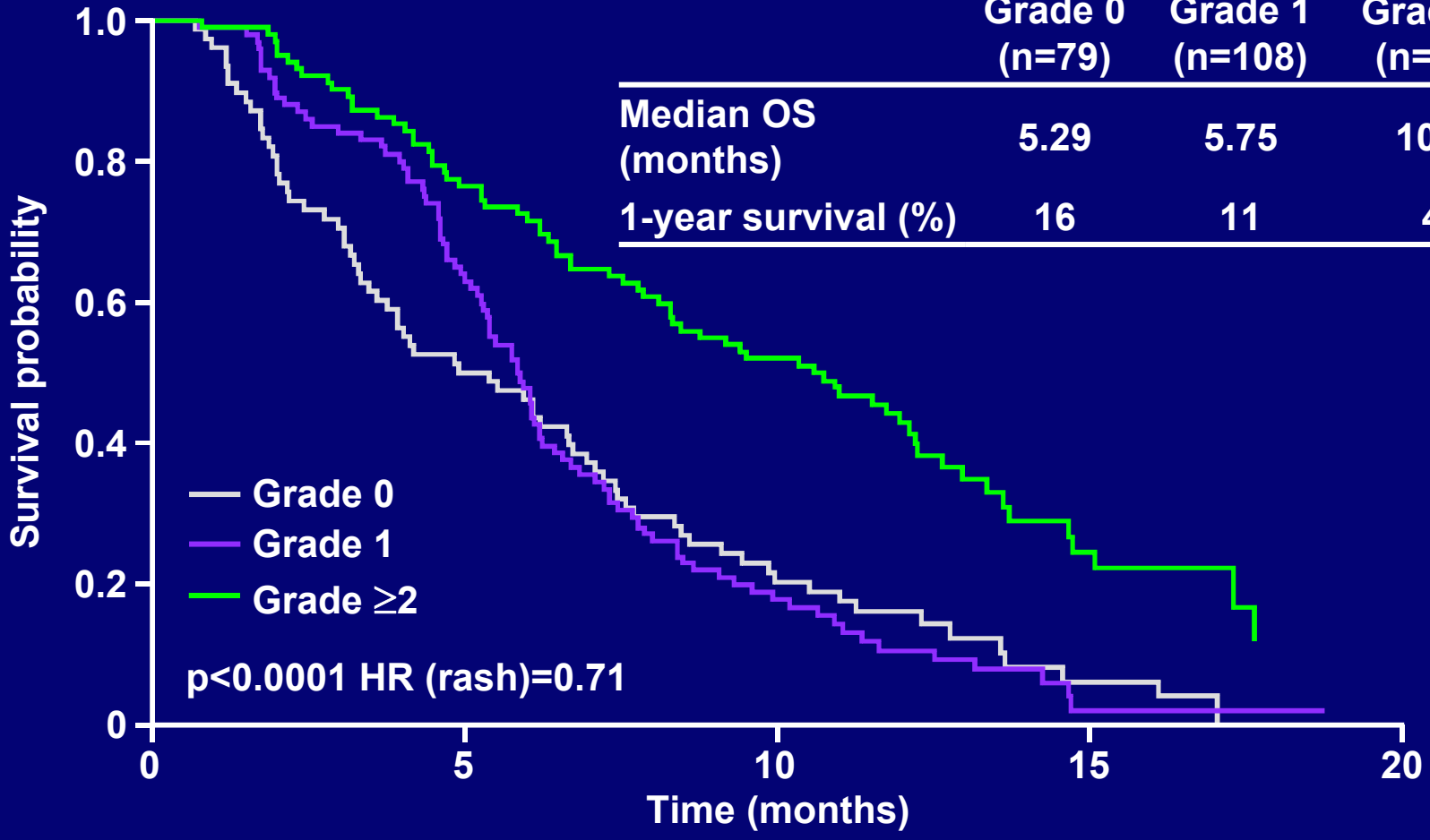
	n	Median OS (months)	1-year survival (%)
G+E	285	6.24	23
G+P	284	5.91	17

HR=0.82 (95% CI: 0.69–0.99)
p=0.038

OS = overall survival
G = gemcitabine; E = erlotinib; P = placebo

Moore M, et al. J Clin Oncol 2007;25:1960–6

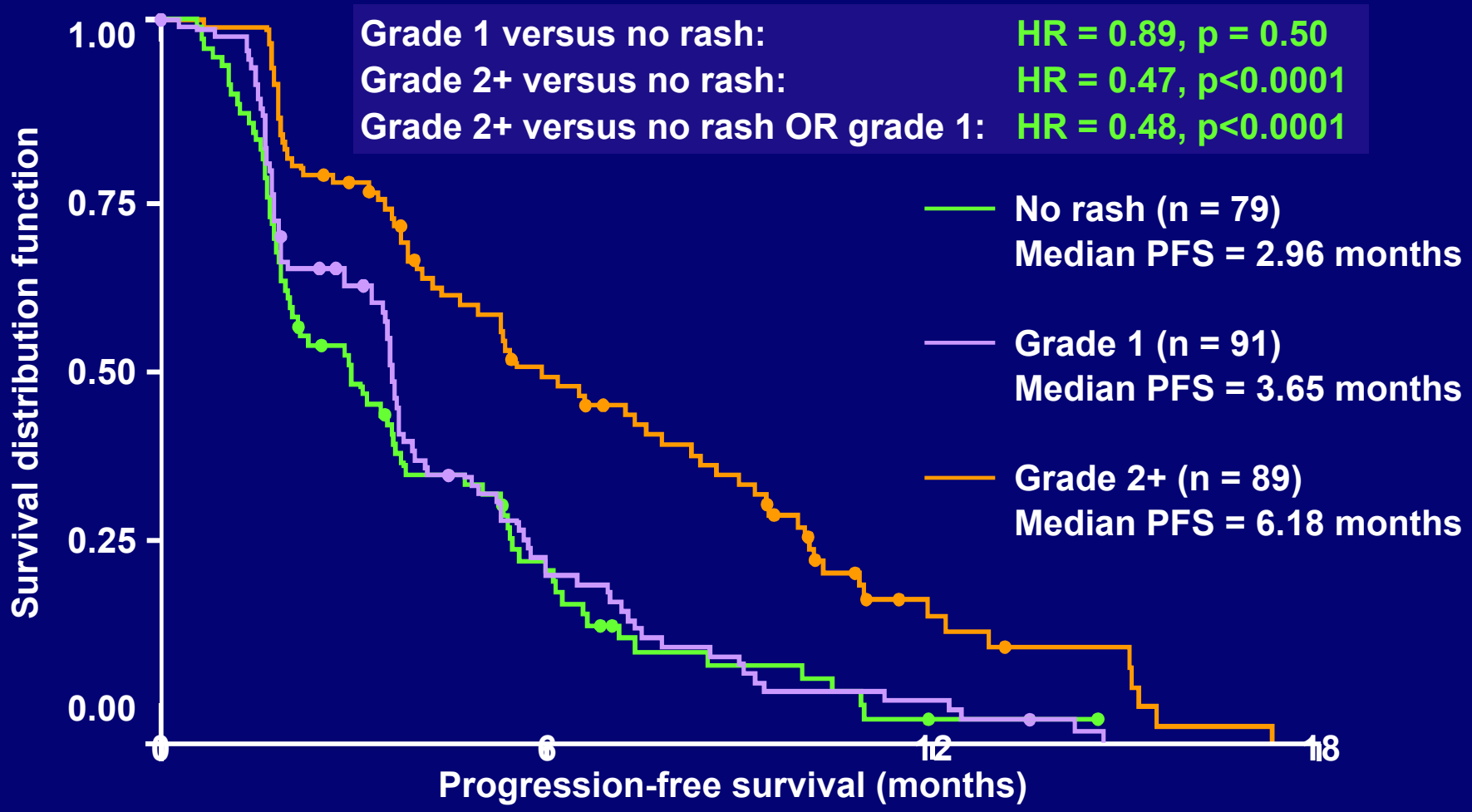
PA.3: OS relative to grade of rash



	Grade 0 (n=79)	Grade 1 (n=108)	Grade ≥2 (n=103)
Median OS (months)	5.29	5.75	10.51
1-year survival (%)	16	11	43

Moore M, et al. J Clin Oncol 2007;25:1960–6; Roche, data on file

Progression-free survival (PFS) on erlotinib according to grade of rash



Tumor Response by Occurrence of Rash

	% patients			
	Rash		No rash	
	Tarceva + gemcitabine n = 168	Placebo + gemcitabine n = 68	Tarceva + gemcitabine n = 74	Placebo + gemcitabine n = 171
CR + PR	10.7	10.3	5.4	6.4
SD	54.8	48.5	40.5	39.8
CR + PR + SD	65.5	58.8	45.9	46.2

Survival (OS) according to grade of rash in placebo arm…..

Univariate p-value (interaction) = 0.009
Multivariate p-value (interaction) = 0.082

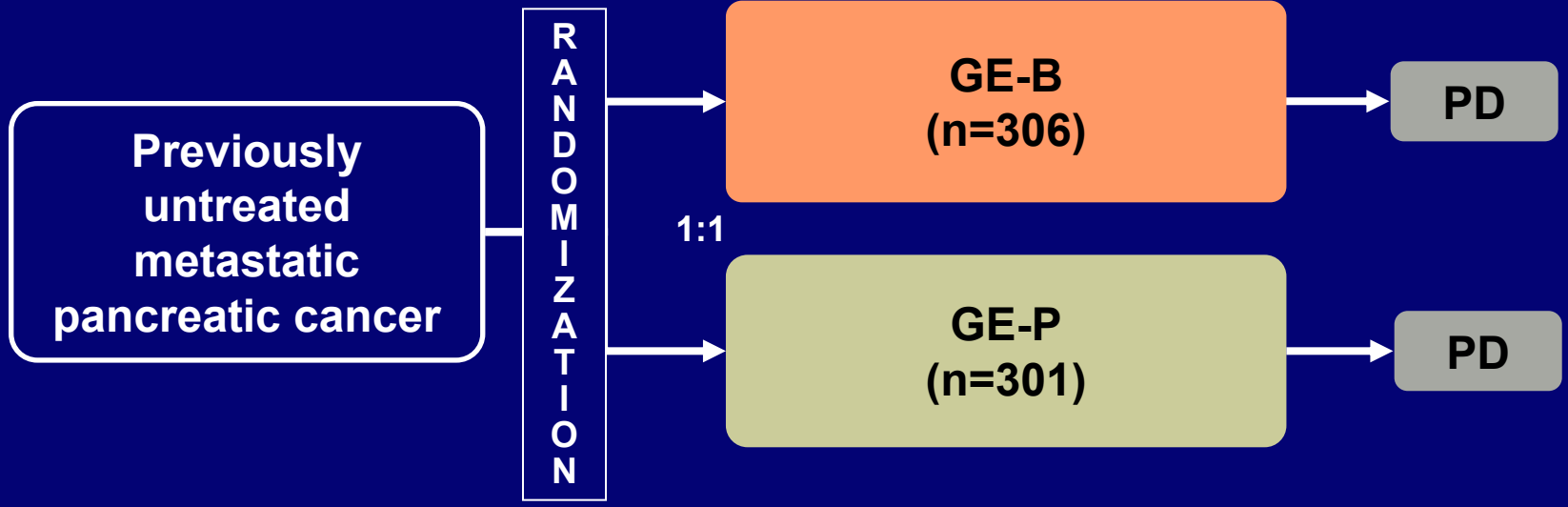
Median survival (months)		
None	Grade 1	Grade 2+
5.91	6.29	7.05

Low frequency of dose modifications and high dose intensity in the trial

	Gemcitabine + erlotinib N= 259		Gemcitabine + placebo N= 256	
	n	%	n	%
Dose reductions				
Rash	6	2	0	0
Diarrhoea	4	2	1	< 1
Dose interruptions				
Rash	11	3	3	1
Diarrhoea	4	2	1	< 1

- Diarrhoea and rash are manageable pharmacological side-effects
- Delivered dose intensity of erlotinib 99%

AViTA: study design



G: 1,000mg/m^2 on days 1, 8, 15, 22, 29, 36, 43 for first 8 weeks, days 1, 8, 15 in subsequent 4-week cycles; E 100mg/day; B 5mg/kg q2w

- Stratified according to country, KPS (<80% vs ≥80%), albumin level (<2.9g/dL vs ≥2.9g/dL)

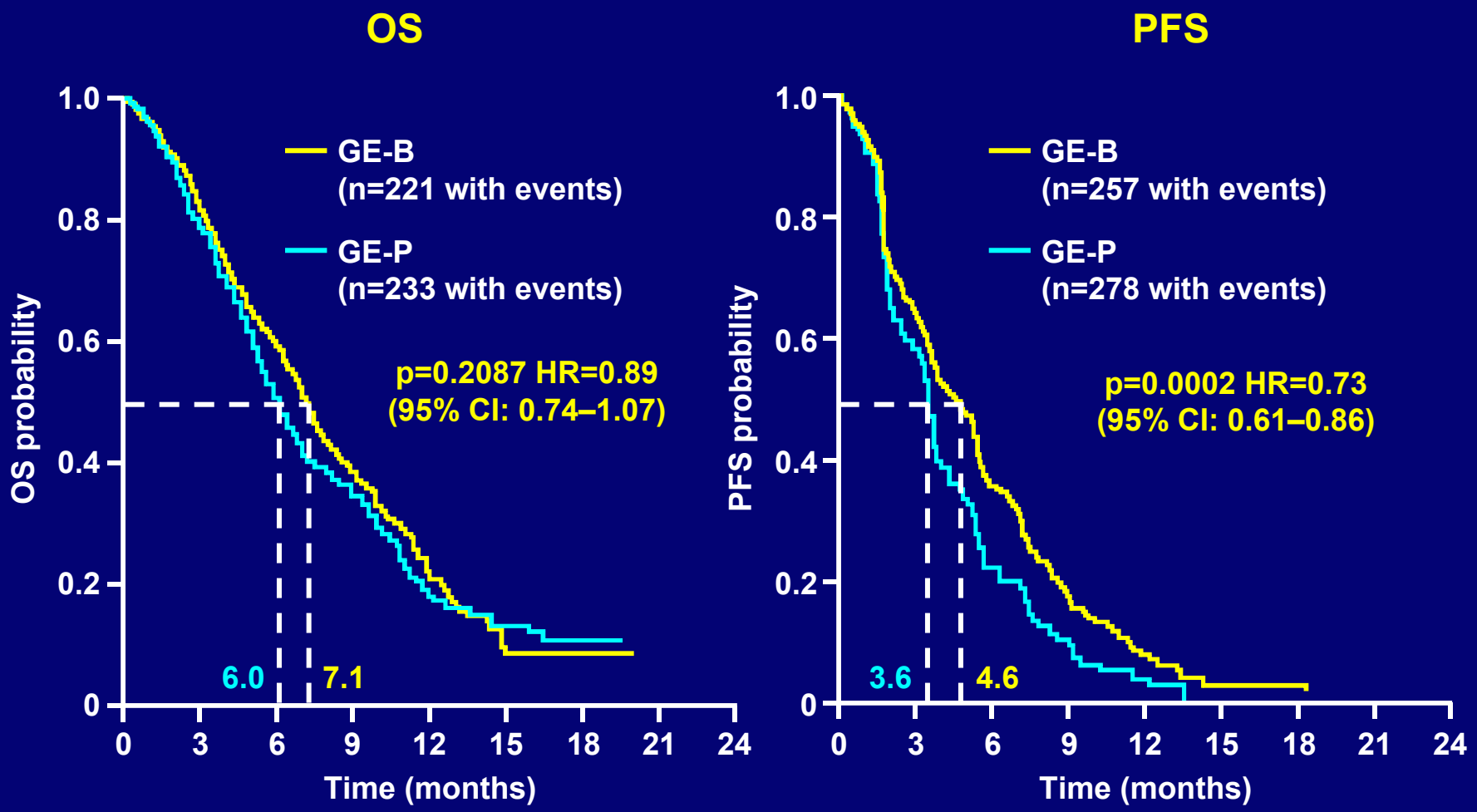
B = bevacizumab
KPS = Karnofsky performance status
PD = progressive disease

Vervenne W, Van Cutsem E, et al. J Clin Oncol 2008;26(Suppl.):214s (Abs. 4507)

AViTA objectives and inclusion/ exclusion criteria

- Primary endpoint:
  - OS
- Secondary endpoints:
  - Progression-free survival (PFS), response rate, and safety (adverse events [AEs] graded by NCI-CTC v3.0)
- Exploratory analysis
  - OS, PFS, and disease control rate according to occurrence and grade of rash
- Inclusion criteria
  - histologically confirmed, metastatic pancreatic adenocarcinoma; no prior therapy for metastatic disease; >6 months since adjuvant therapy; no prior gemcitabine or anti-vascular endothelial growth factor (VEGF) therapy; KPS ≥60; adequate hematologic, hepatic, and renal function
- Exclusion criteria
  - invasion of major blood vessels; surgery in last 28 days; bleeding disorders; significant cardiovascular disease

OS and PFS in AViTA



Vervenne W, Van Cutsem E, et al. J Clin Oncol 2008;26(Suppl.):214s (Abs. 4507)

Incidence of AEs in both treatment arms

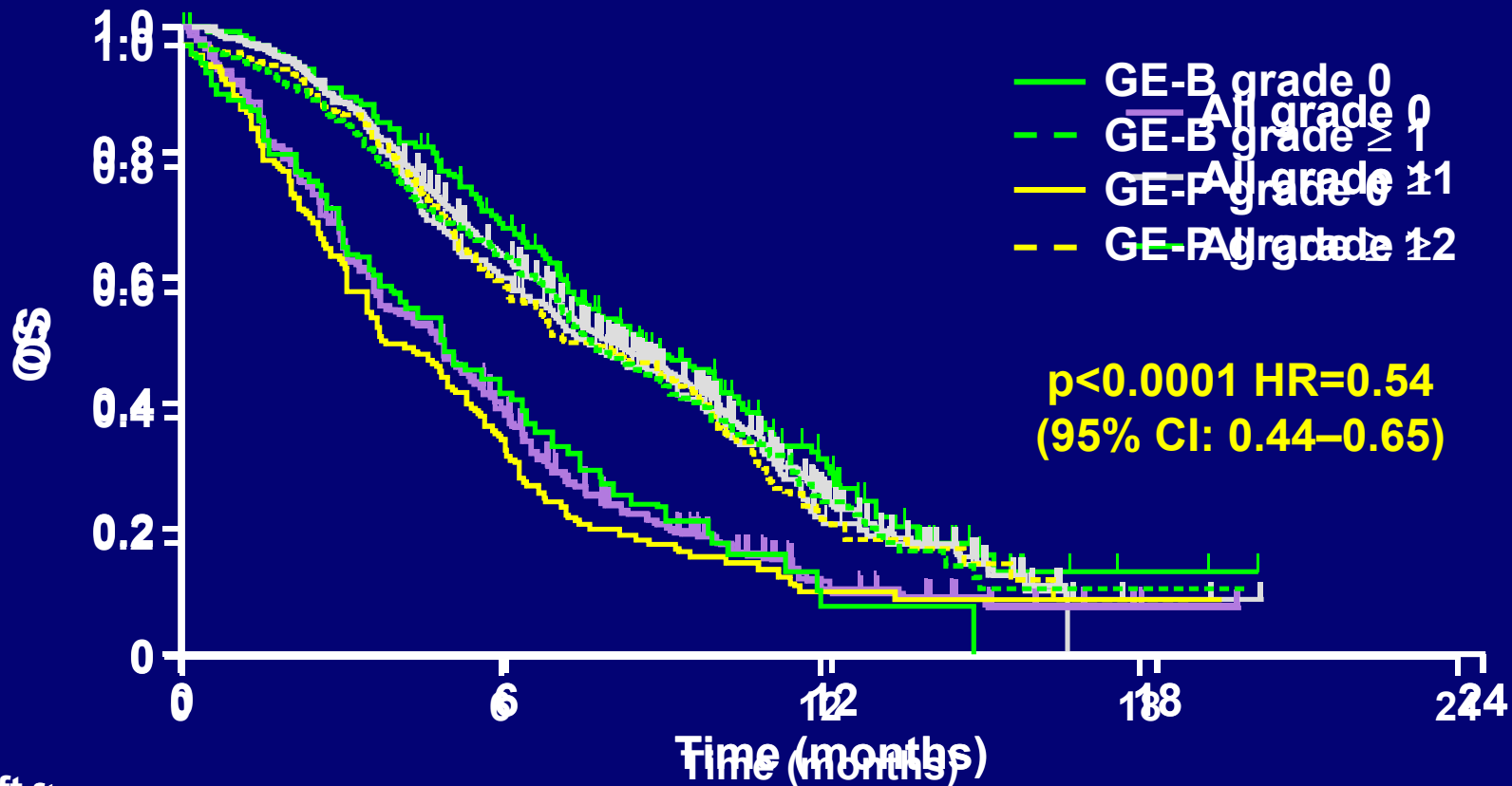
[a]One patient in the placebo arm had a grade 5 event

	GE-P (n=287)		GE-B (n=296)	
AE, %[a]	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Anemia	33	9	27	7
Thrombocytopenia	26	7	30	8
Neutropenia	26	17	29	21
Non-hematologic				
Diarrhea[a]	51	6	49	4
Nausea	51	3	46	4
Rash	44	3	49	8
Vomiting	42	4	37	5
Pyrexia	37	2	34	3
Fatigue	34	7	33	5
Constipation	23	<1	27	1
Anorexia	24	2	21	2
Epistaxis	11	0	29	<1
Peripheral edema	17	1	17	<1
Abdominal pain	15	1	16	3
Asthenia	15	6	14	5
Hypertension	9	1	19	3

Baseline characteristics by grade of rash

	Skin rash					
	NCI-CTC grade 0		NCI-CTC grade 1		NCI-CTC grade ≥ 2	
	GE-P (n=123)	GE-B (n=91)	GE-P (n=101)	GE-B (n=215)	GE-P (n=77)	GE-B (n=105)
Gender, male/female, %	64/36	46/54	55/45	57/43	69/31	66/34
<65 years / ≥65 years, %	59/41	56/44	68/32	61/39	68/32	61/39
Smoking status						
Current/Former/Never, %	**30/27/42**	**30/25/44**	**18/37/45**	**14/37/49**	**10/39/51**	**8/38/54**
Pack years, median (range)	30.0 (3–162)	30.0 (3–120)	20.0 (0–105)	25.0 (0–100)	20.0 (0–80)	20.0 (1–135)
Laboratory parameters, %						
Albumin, < or ≥ 2.9g/dL	7/93	8/92	2/98	5/95	4/96	3/97
LDH, ≤ or > ULN	67/33	68/32	72/28	68/32	67/33	63/37
Alkaline phosphatase, ≤ or >484U/L	85/15	88/12	91/9	89/11	86/14	89/11
CRP, ≤ or >1.4mg/dL	**36/64**	**34/66**	**55/45**	**62/38**	**61/39**	**49/51**
CA19, ≤ or >1350kU/L	41/59	47/53	60/40	49/51	70/30	51/49
Neutrophils, ≤ or >ULN	75/25	78/22	87/13	80/20	86/14	78/22

OS relative to rash



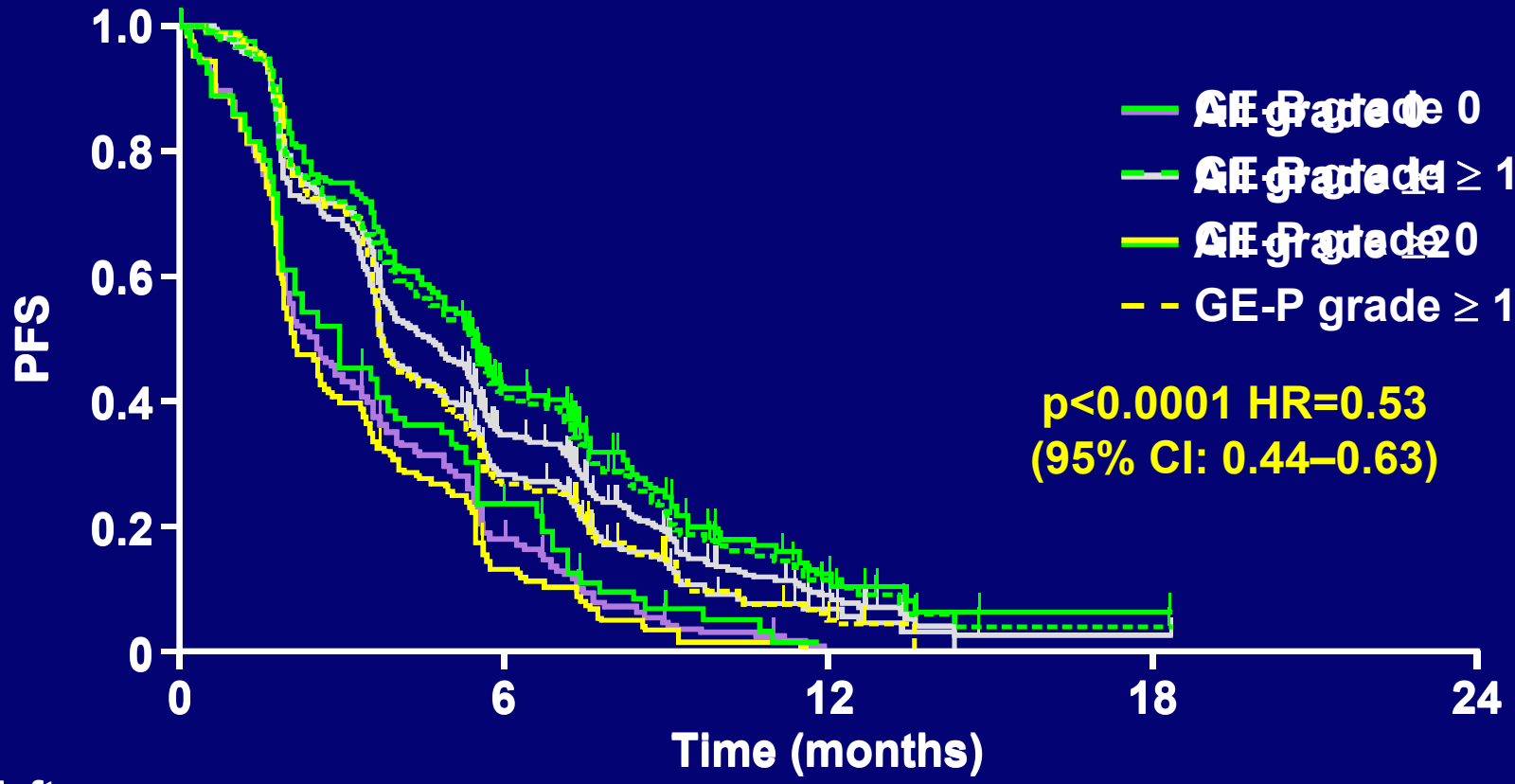
No. left					
GE-B gr 0	214	78	12	1	0
All gr 0	214	78	12	1	0
GE-B gr ≥1	215	127	25	1	0
All gr ≥1	293	220	28	2	0
GE-P gr 0	133	41	9	1	0
All gr ≥2	182	119	26	2	0
GE-P gr ≥1	178	103	21	1	0

OS according to severity of rash

	OS (months [95% CI])			
	No rash	Grade 1 rash	Grade ≥2 rash	Any rash
GE-P arm	4.3 (3.4–5.4)	7.1(6.1–9.6) HR=0.56 (95% CI: 0.41–0.76) p=0.0001	8.3 (6.0–10.7) HR=0.50 (95% CI: 0.36–0.70) p<0.0001	8.1 (6.6–9.6) HR=0.53 (95% CI: 0.41–0.68) p<0.0001
GE-B arm	5.0 (3.9–6.4)	7.4 (5.8–9.1) HR=0.60 (95% CI: 0.44–0.83) p=0.0017	8.4 (7.2–10.2) HR=0.49 (95% CI: 0.35–0.69) p<0.0001	7.9 (7.1–9.1) HR=0.54 (95% CI: 0.41–0.72) p<0.0001
All patients	4.8 (3.7–5.4)	7.4 (6.4–9.1) HR=0.59 (95% CI: 0.47–0.73) p<0.0001	8.4 (7.2–9.9) HR=0.50 (95% CI: 0.39–0.63) p<0.0001	8.0 (7.1–9.1) HR=0.54 (95% CI: 0.44–0.65) p<0.0001

N.B. All hazard ratios (HRs) are for rash versus no rash

PFS relative to rash



No. left					
GE-P gr 0	214	26	0	0	0
GE-P gr ≥1	295	52	6	0	0
GE-P gr ≥2	123	12	0	0	0
GE-P gr ≥1	178	45	5	0	0

PFS according to severity of rash

	PFS (months (95% CI])			
	No rash	Grade 1 rash	Grade ≥2 rash	Any rash
GE-P arm	2.1 (1.9–2.8)	3.7 (3.6–4.2) HR=0.67 (95% CI: 0.51–0.88) p=0.0033	4.1 (3.6–5.5) HR=0.47 (95% CI: 0.34–0.64) p<0.0001	3.8 (3.7–4.7) HR=0.56 (95% CI: 0.44–0.71) p<0.0001
GE-B arm	3.0 (2.1–3.9)	4.0 (3.4–5.4) HR=0.61 (95% CI: 0.45–0.83) p=0.0011	5.8 (5.4–7.3) HR=0.45 (95% CI: 0.33–0.62) p<0.0001	5.4 (4.5–5.8) HR=0.52 (95% CI: 0.40–0.68) p<0.0001
All patients	2.5 (2.0–3.0)	3.8 (3.6–4.4) HR=0.62 (95% CI: 0.51–0.76) p<0.0001	5.5 (4.7–6.0) HR=0.44 (95% CI: 0.35–0.55) p<0.0001	4.6 (3.9–5.3) HR=0.53 (95% CI: 0.44–0.63) p<0.0001

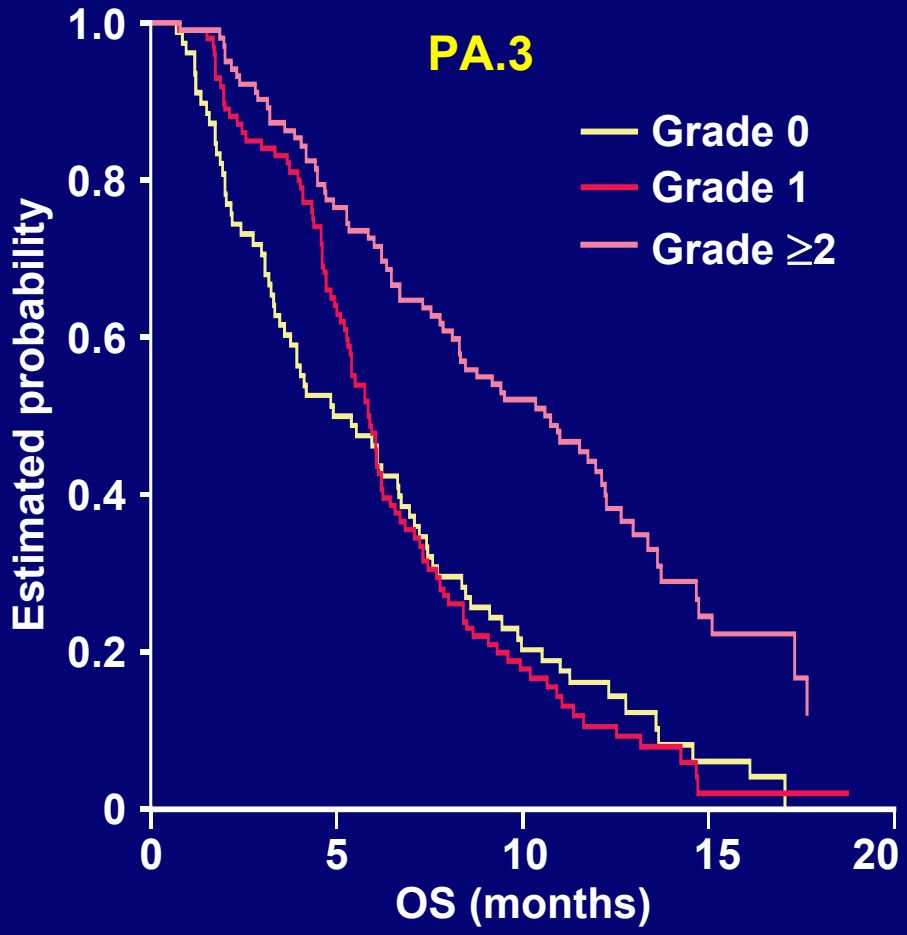
N.B. All HRs are for rash versus no rash

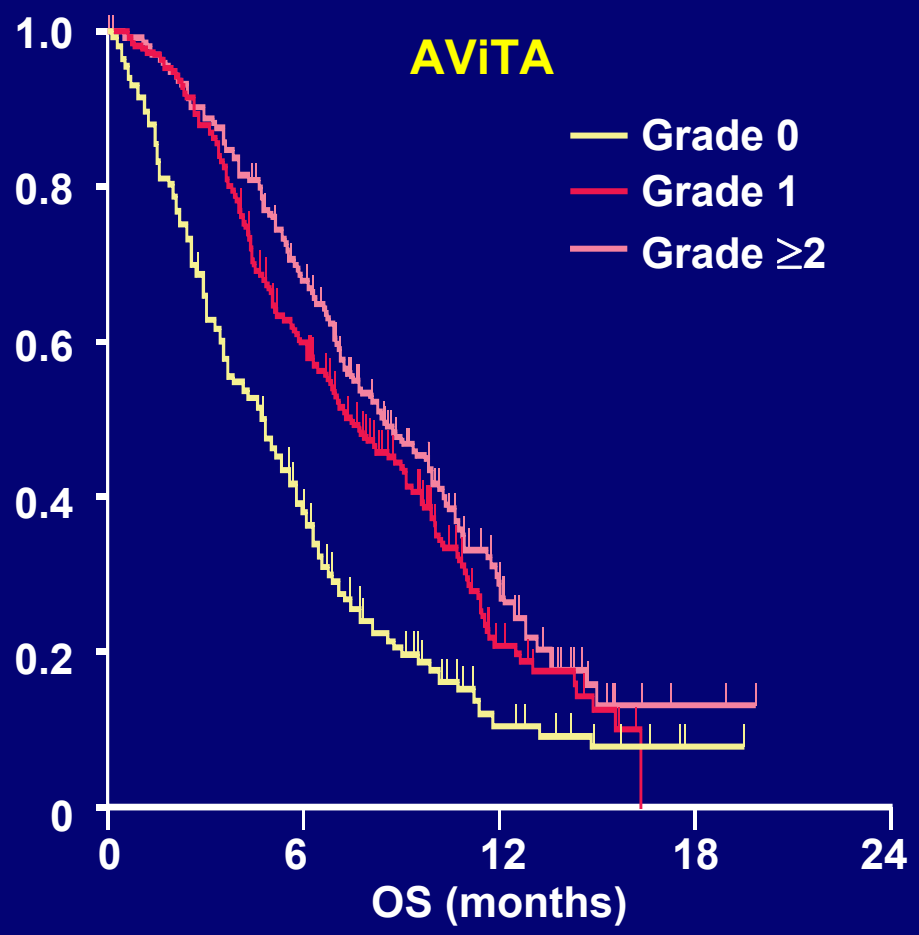
Conclusions

- Rash was associated with improved outcomes for erlotinib-based therapy in AViTA, confirming the results seen in PA.3
  - this was a retrospective exploratory analysis not corrected for multiple testing
- This association was consistent across treatment arms and endpoints
  - benefit was seen for all grades of rash, not just severe rash
- Some baseline characteristics appear to be associated with an increased incidence of rash and improved efficacy; this warrants further prospective investigation

Next steps ??

Both phase III trials showed improved OS in patients with skin rash





Moore et al, JCO 2007; Verslype et al, ASCO 2009

Grade of rash in AViTA varied according to baseline smoking status and CRP levels

- Clinical and laboratory baseline values were examined with respect to rash (grade 0 vs grade 1 vs grade ≥2)
  - smoking status and CRP were only parameters to vary with grade of rash

	No rash		Grade 1 rash		Grade ≥ 2 rash	
Baseline characteristics (%)	GE-P (n=123)	GE-B (n=91)	GE-P (n=101)	GE-B (n=215)	GE-P (n=77)	GE-B (n=105)
Current smoker	30	30	18	14	10	8
Former smoker	27	25	37	37	39	38
Never smoker	42	44	45	49	51	54
CRP ≤1.4mg/dL	36	34	55	62	61	49
CRP >1.4mg/dL	64	66	45	38	39	51

GE-P = gemcitabine + erlotinib + placebo
GE-B = gemcitabine + erlotinib + bevacizumab

Verslype et al, ASCO 2009

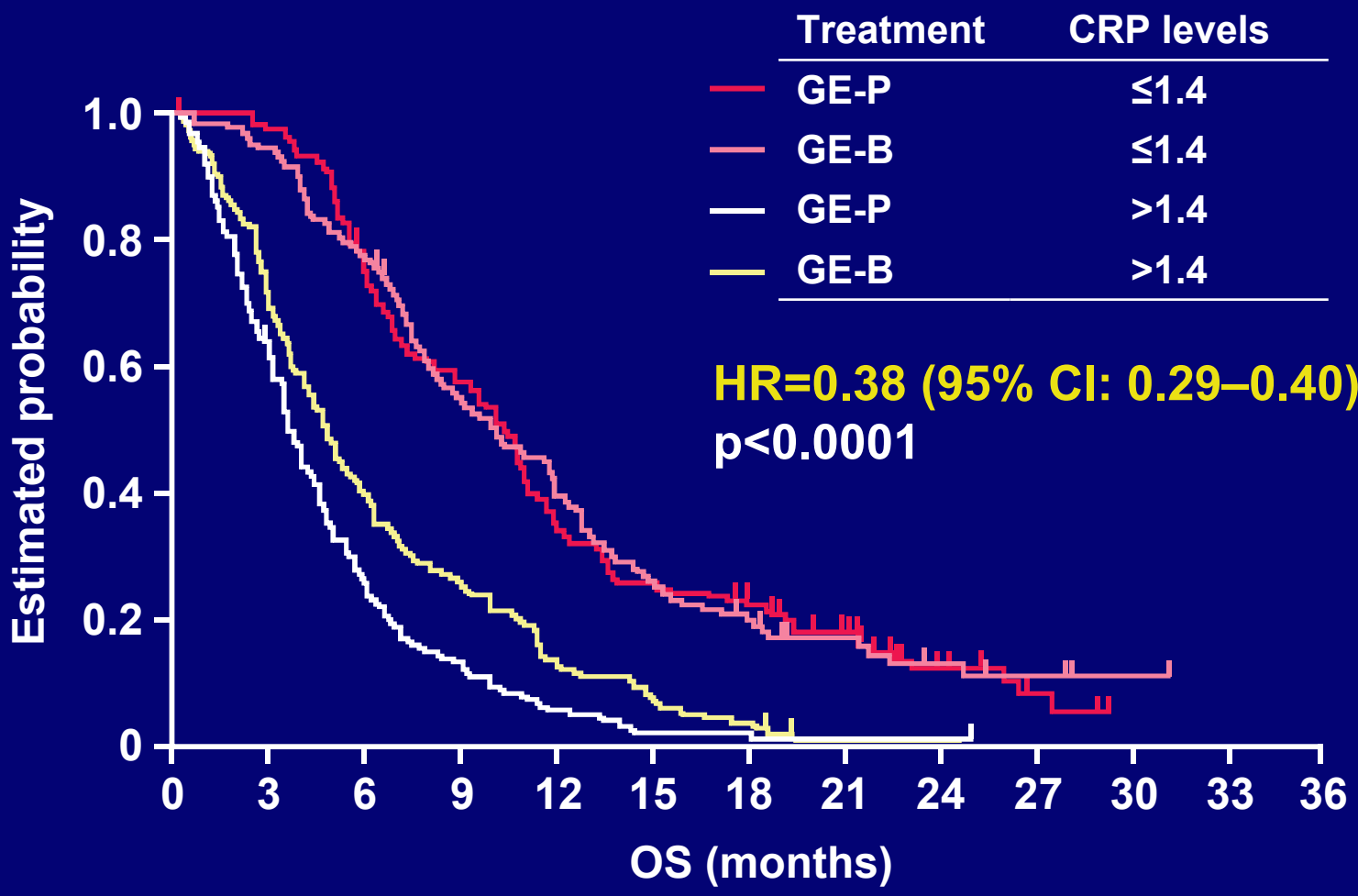
Multivariate analysis identified a significant relationship between rash and both CRP levels and smoking in AViTA

Variable	p	Odds ratio
CRP below *median (< 1.4)	0.0001‡	2.28
Not current smoker (former/never)	<0.0001‡	3.56
Other baseline characteristics	NS	

*analysis for continuous CRP levels was also significant (p=0.0039)
‡negative for interaction

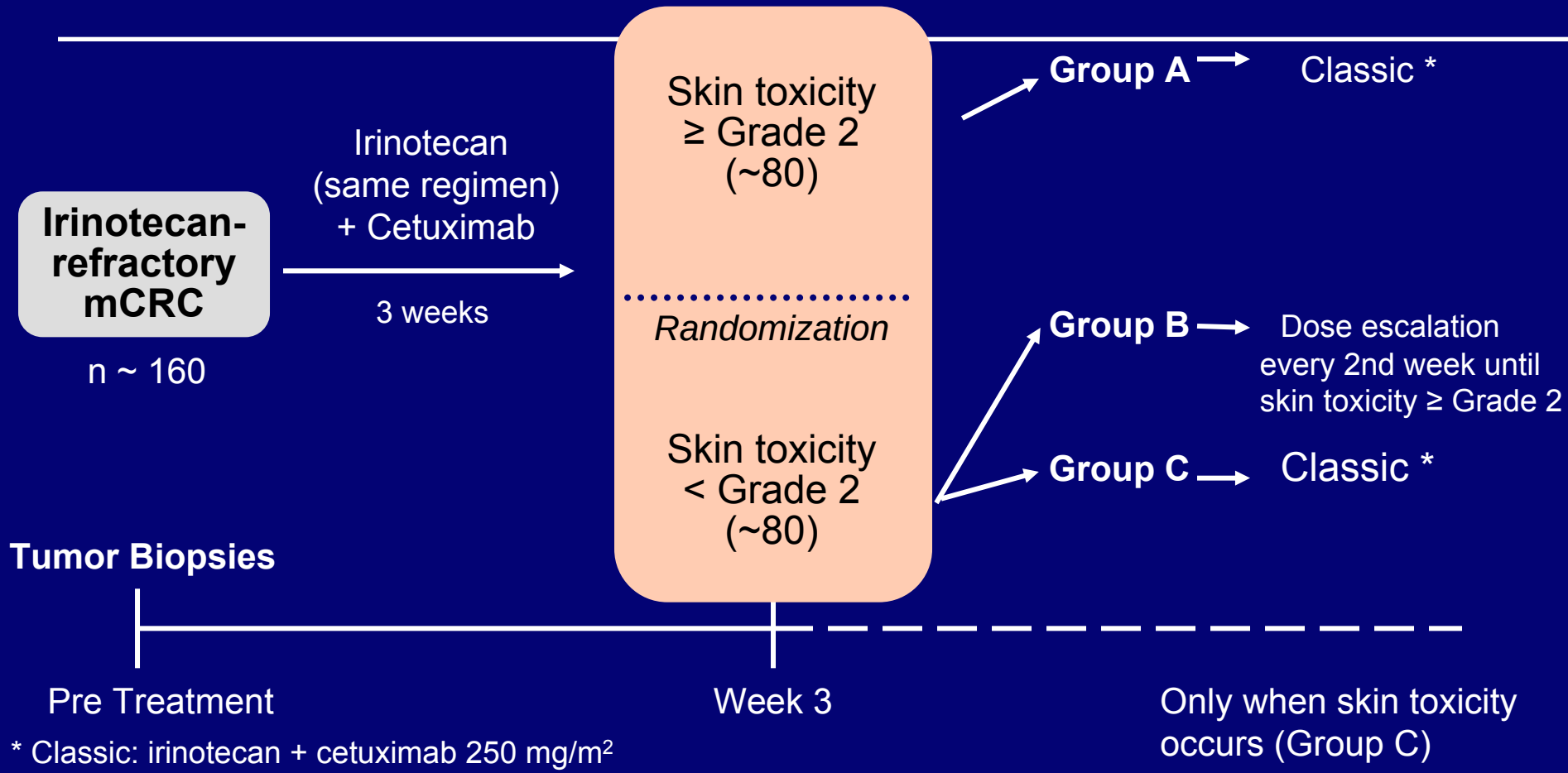
Verslype et al, ASCO 2009

Improved OS was seen in patients with baseline CRP levels of ≤1.4mg/dL



Verslype et al, ASCO 2009

Dose escalation until rash : Everest study

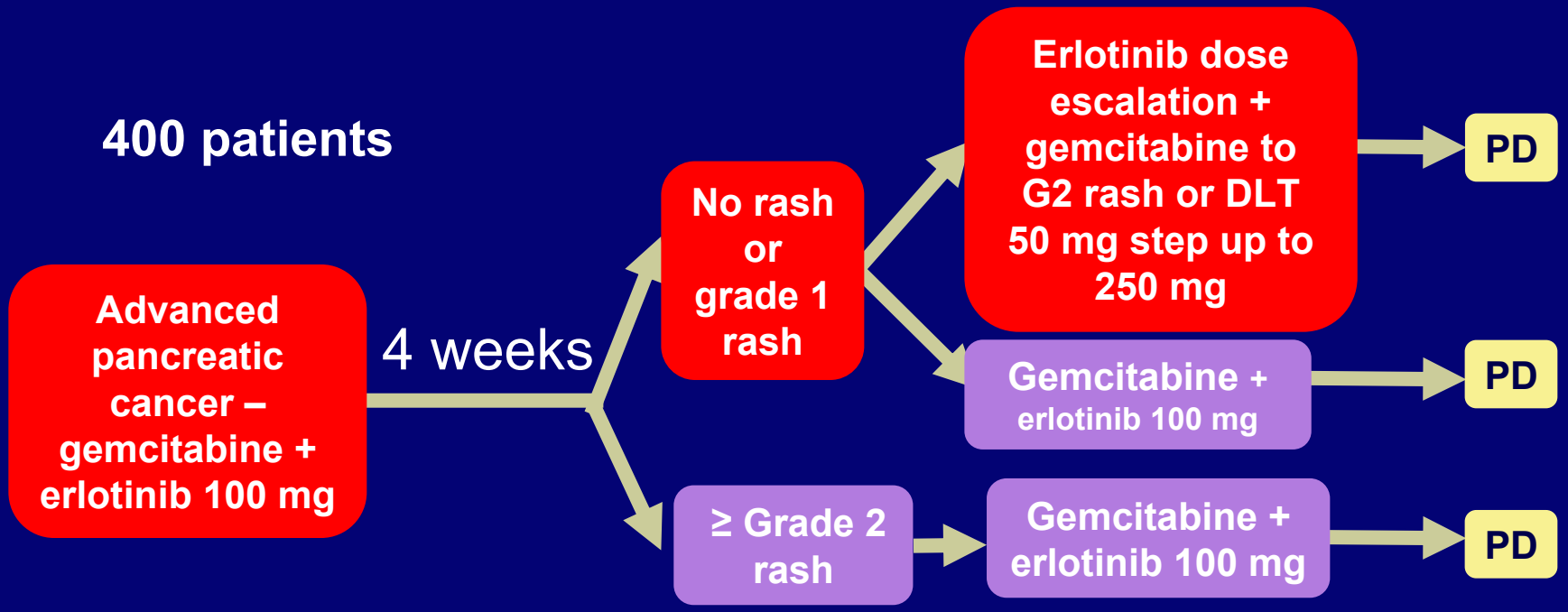


* Classic: irinotecan + cetuximab 250 mg/m^2

Primary endpoint: difference in expression of EGFR and other downstream signaling pathway markers in skin biopsies

Secondary endpoints: Pharmacodynamic and Pharmacogenomic markers, PK, safety, RR and TTP

RACHEL trial, rash driven study



- Primary endpoint: OS
- **Mandatory tissue collection**
- Secondary endpoints: PFS, disease control, safety, correlation of EGFR-related biomarkers with outcome (EGFR, EGF, TGFα, K-ras, pAKT, pMAPK)

Conclusion

- The benefit of erlotinib in pancreatic cancer has been shown in the context of two randomised phase III trials
  - patients who developed rash had greater benefit
- Multivariate logistic regression identified a significant correlation between CRP levels/smoking status and rash
- Further biomarker analysis of AViTA ongoing
- Currents study will investigate hypothesis of increased erlotinib metabolism in current smokers
- RACHEL trial is evaluating increased doses of erlotinib (rash driven study)
- CRP dynamics and value of baseline levels to predict rash will be investigated in ongoing RACHEL and MARK studies