eLung: A Multicenter, Randomized Phase IIb Trial of "Standard" Platinum Doublets plus Cetuximab (CET) as First-line Treatment of Recurrent or Advanced Non-Small Cell Lung Cancer (NSCLC)

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Disclosure

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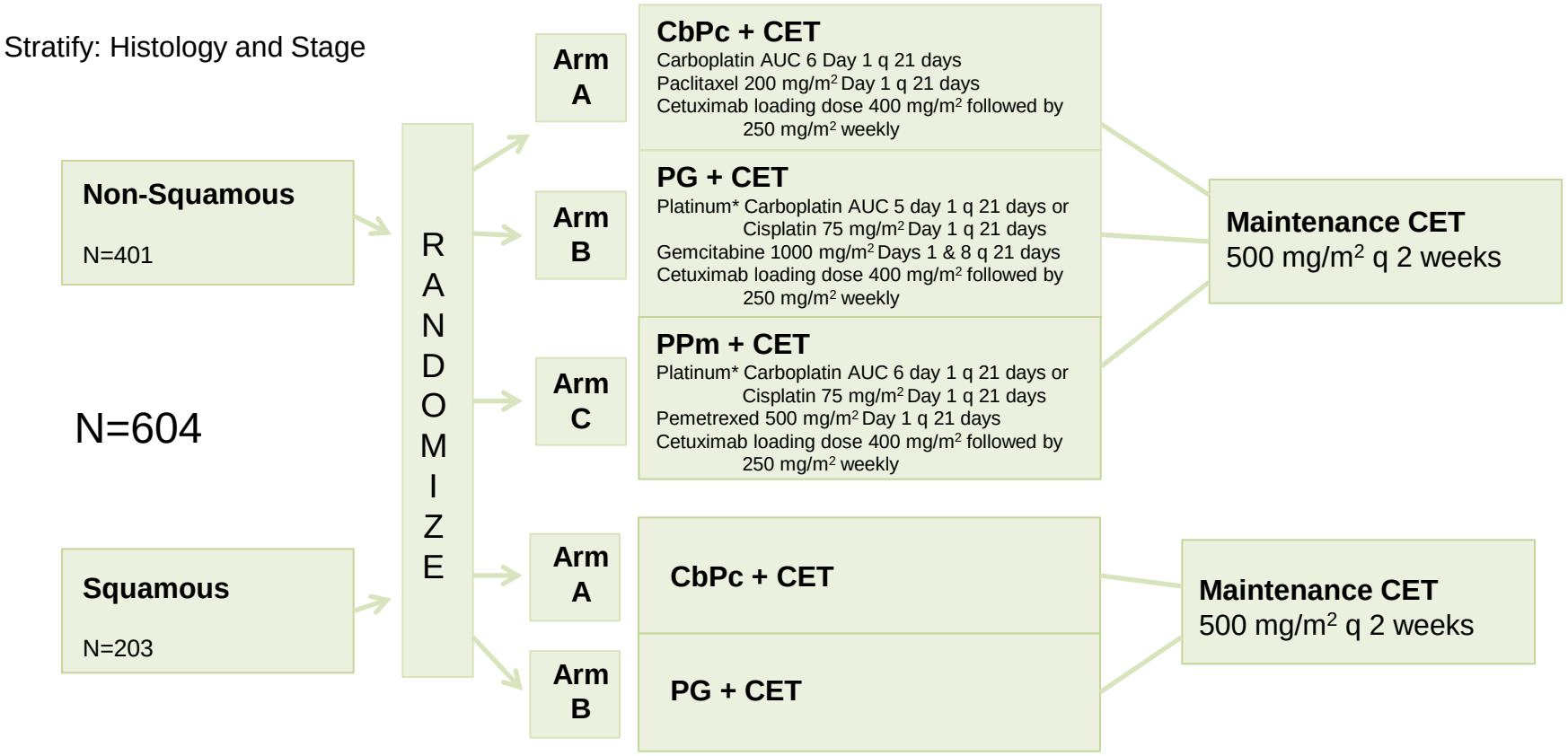
Background

- Platinum doublet therapy plus CET improves overall survival in NSCLC: Phase III FLEX trial (Pirker, Lancet 2009)
  - Median OS 11.3 mo vs. 10.1 mo
  - HR 0.871, p=0.044
- Meta-analysis of 4 randomized phase II and III studies testing addition of CET (Pujol, ESMO 2009)
  - Platinum regimens: vinorelbine/cis, carbo/doc, carbo/pac, cis/gem, carbo/gem
  - OS, HR=0.87, p<0.010
  - Median OS 10.3 mo vs. 9.4 mo
  - 1 year OS rate 44.8% vs. 40.0%, p=0.013

eLung Trial: Objectives

- Determine best platinum doublet with cetuximab: evaluating efficacy and toxicity
- Evaluate pemetrexed/platinum doublet in non-squamous with cetuximab
- Evaluate biomarkers in tumor and blood to determine subgroups with improved survival

eLung Study Design



Chemo + CET=4 to 6 cycles
*Physician and patient choice of cisplatin or carboplatin

Open-label, multicenter
Enrollment period:12/08-5/11

eLung Endpoints

Primary

- Overall Survival (OS)

Secondary

- Safety
- 1-year survival
- OS by histology

Exploratory

- Compliance, PFS, ORR
- OS by number of cycles received
- Survival by biomarker status

Statistical Considerations

- KM to compare median OS with historical control, by arm (α = .05, 1-tailed)
  - Null hypothesis rejected if OS > upper bound of control value
  - Arms A & B: control median OS 9 mo, UB 10.2 mo
  - Arm C: control median OS 10 mo, UB 11.8 mo
- Chi-square and ANOVA to compare arms on descriptive statistics (α = .05, 2-tailed)
- Cox regression for OS
  - Compare arms B & C with A
  - Demographics, clinical, prior treatment

Eligibility Criteria

- Key Inclusion Criteria
  - Histologically or cytologically confirmed stage IIIb, stage IV, or recurrent NSCLC
  - Measurable or evaluable disease per modified RECIST
  - Male or female ≥ 18 yrs of age
  - ECOG 0-1
- Key Exclusion Criteria
  - Prior chemotherapy for advanced NSCLC
  - Prior chemotherapy for earlier stage disease (neoadjuvant, post-operative adjuvant chemo and chemo given to patients who were not candidates for surgery) allowed if completed at least 12 months before study entry
  - Previous exposure to EGFR-targeted therapy
  - Bone as only site of disease
  - Carcinoid, atypical carcinoid, or small cell histology
  - Peripheral neuropathy ≥ grade 2

Demographics

	CbPc + CET	PG + CET	PPm + CET
Total No	235	236	130
Age (Years), Mean ± SD	65.3 ± 8.9	64.9 ± 9.5	65.6 ± 9.4
Gender, n (%)			
Male	138 (58.7)	146 (61.9)	66 (50.8)
Female	97 (41.3)	90 (38.1)	64 (49.2)
Race, n (%)			
White	193 (82.1)	189 (80.1)	108 (83.1)
Black/African American	24 (10.2)	26 (11.0)	10 (7.7)
Asian	3 (1.3)	1 (0.4)	1 (0.8)
Hispanic/Latino	1 (0.4)	5 (2.1)	0 (0)
American Indian	0 (0)	1 (0.4)	1 (0.8)
Not Available/Missing	14 (6.0)	14 (5.9)	10 (7.7)
Histology, n (%)			
Squamous	101 (43.0)	101 (42.8)	0 (0)
Non-Squamous			
Adenocarcinoma	112 (47.7)	110 (46.6)	109 (83.8)
Large Cell	6 (2.6)	6 (2.5)	4 (3.1)
Poorly Differentiated/ Not Specified	16 (6.8)	19 (8.1)	17 (3.1)

CbPc = carboplatin + paclitaxel; PG = platinum + gemcitabine; PPm = platinum + pemetrexed; CET = cetuximab

Disease Characteristics

	CbPc + CET	PG + CET	PPm + CET
Stage, n (%)			
IIIb	12 (5.1)	17 (7.2)	8 (6.2)
IV	223 (94.9)	219 (92.8)	122 (93.8)
ECOG Status, n (%)			
0	89 (38.0)	90 (38.3)	46 (35.4)
1	145 (62.0)	145 (61.7)	84 (64.6)
Number of Organs Involved, n (%)			
1	10 (4.3)	11 (4.7)	8 (6.2)
2	121 (51.5)	125 (53.0)	67 (51.5)
≥ 3	104 (44.3)	100 (42.4)	55 (42.3)
Sites of Metastases, n (%)			
Adrenal	35 (14.9)	27 (11.4)	16 (12.3)
Bone	69 (29.4)	73 (30.9)	40 (30.8)
Brain	26 (11.1)	40 (16.9)	15 (11.5)
Lymph Node	103 (43.8)	105 (44.5)	66 (50.8)
Liver	38 (16.2)	40 (16.9)	19 (14.6)
Prior Therapy, n (%)			
Surgery	21 (52.5)	16 (47.1)	9 (45.0)
Chemotherapy	10 (25.0)	7 (20.6)	4 (20.0)
Radiation	25 (62.5)	22 (64.7)	14 (70.0)

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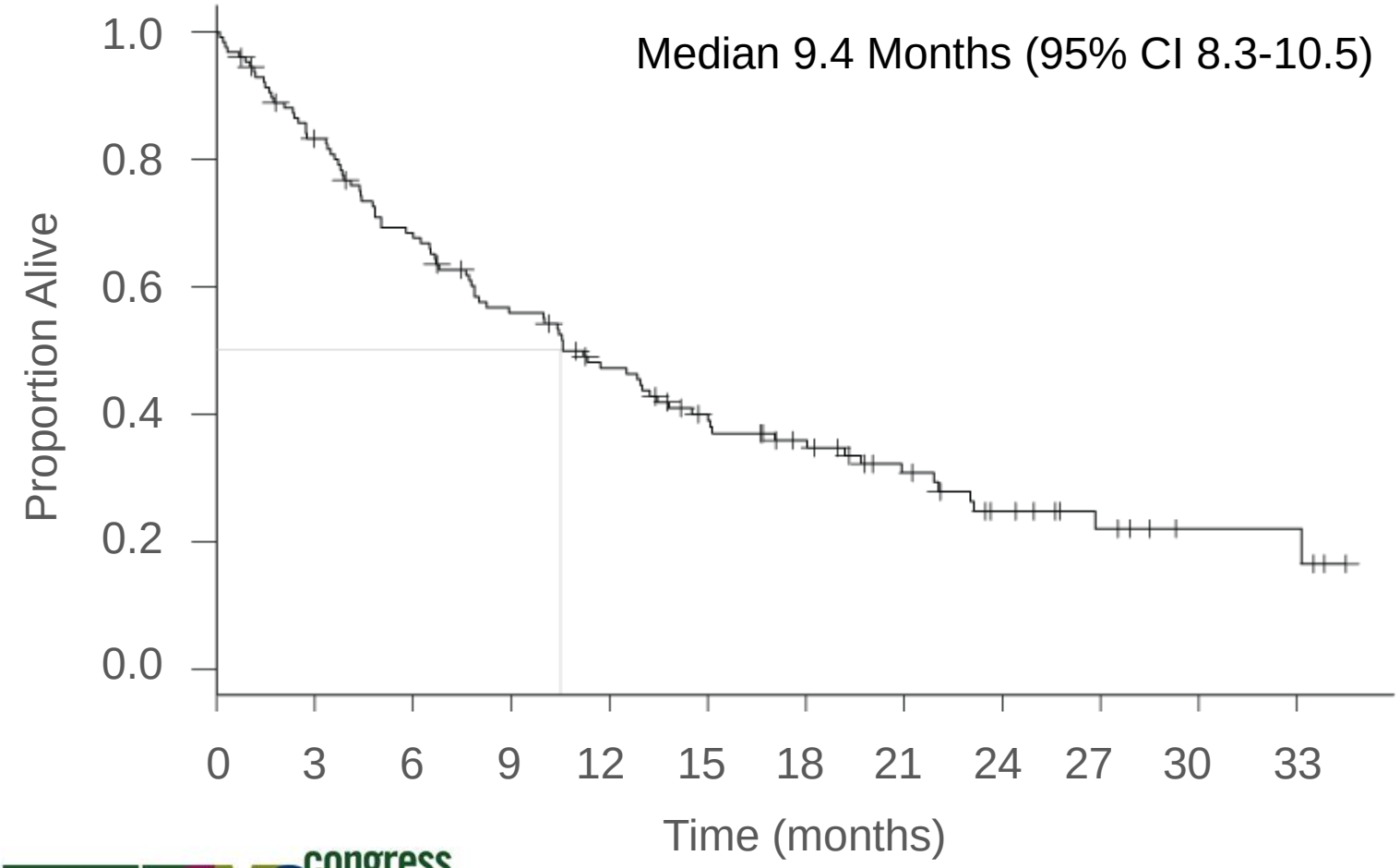
Reasons for Treatment Discontinuation

	CbPc + CET n (%)	PG + CET n (%)	PPm + CET n (%)
Progressive Disease or Recurrence	139 (60.2)	145 (62.5)	79 (62.7)
Withdrew Consent	11 (4.8)	7 (3.0)	10 (7.9)
Lost to Follow-up	1 (0.4)	2 (0.9)	0 (0)
Adverse Event	55 (23.8)	52 (22.4)	24 (19.0)
Death	0 (0)	1 (0.4)	0 (0)
Other	25 (10.8)	25 (10.8)	13 (10.3)

CbPc = carboplatin + paclitaxel; PG = platinum + gemcitabine; PPm = platinum + pemetrexed; CET = cetuximab

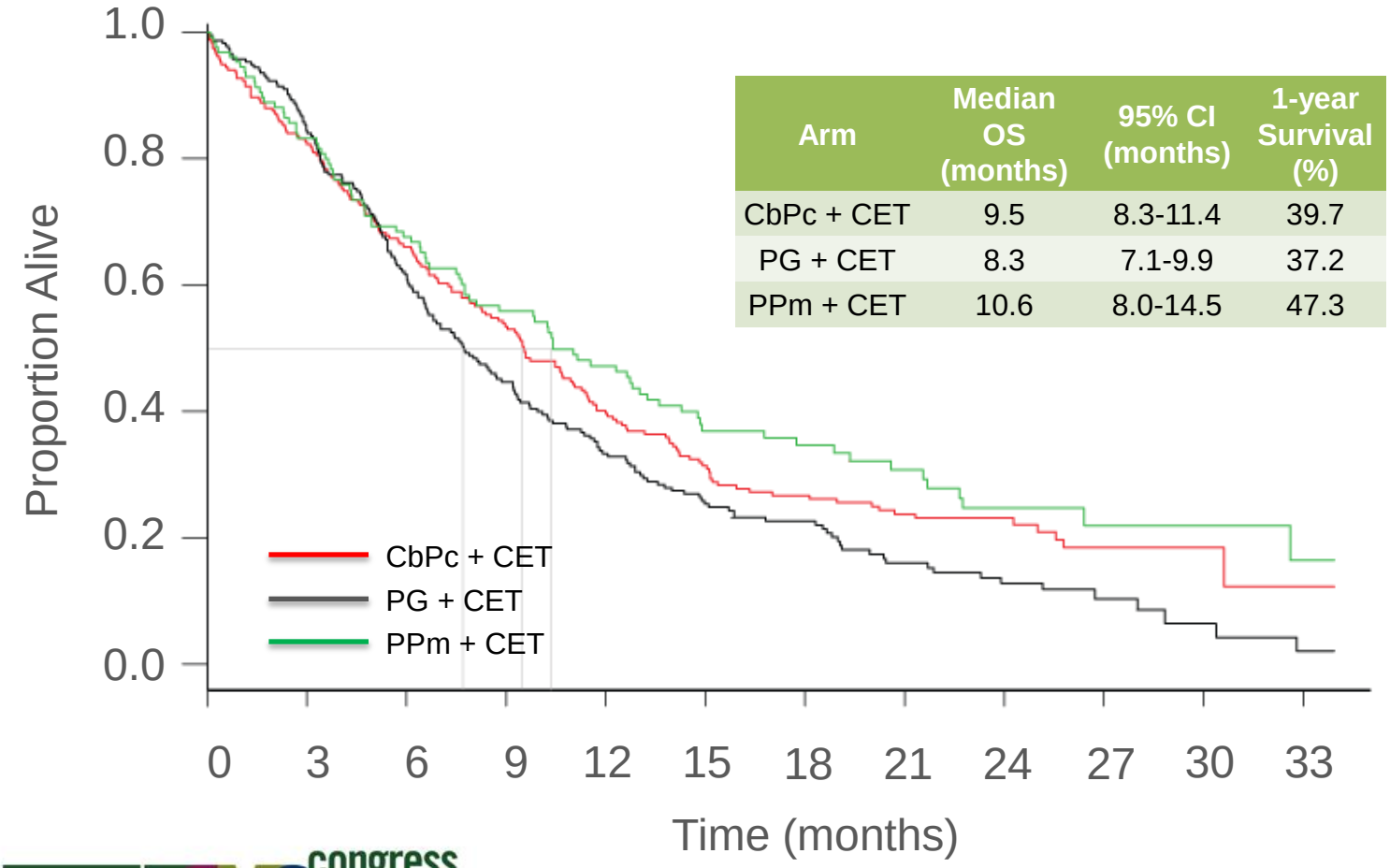
Overall Survival All Arms

ITT Analysis



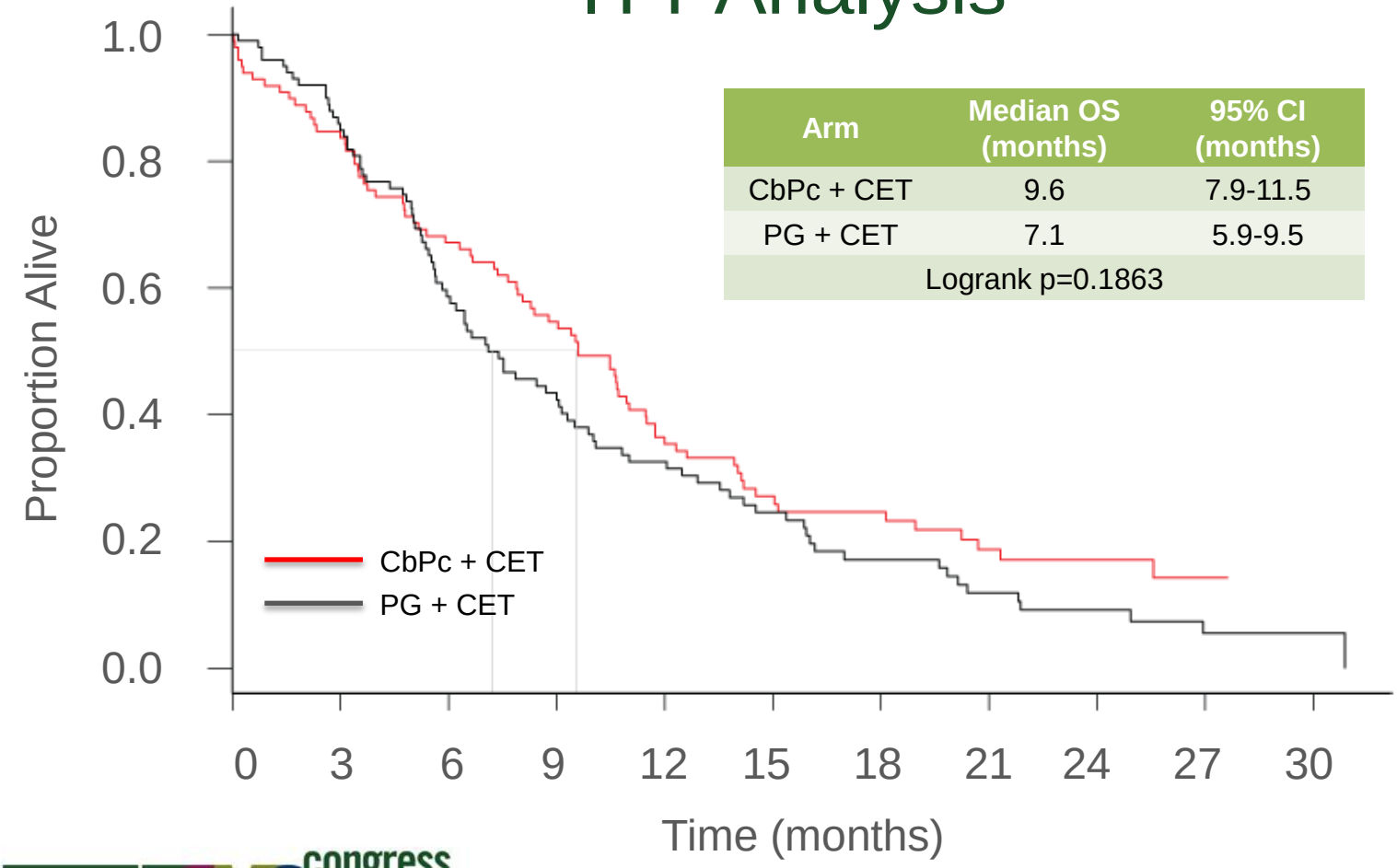
Overall Survival by Arm

ITT Analysis



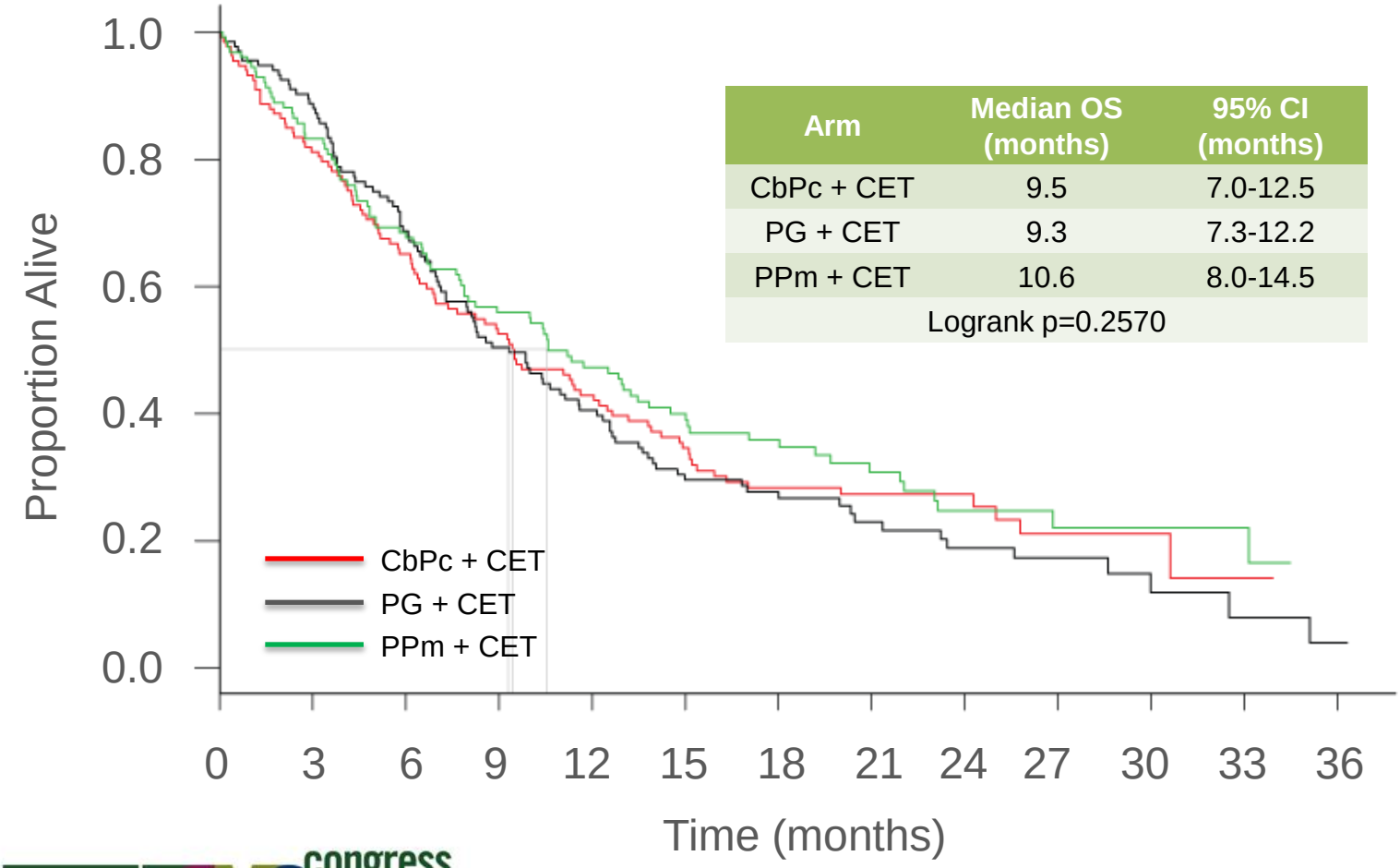
Arm	Median OS (months)	95% CI (months)	1-year Survival (%)
CbPc + CET	9.5	8.3-11.4	39.7
PG + CET	8.3	7.1-9.9	37.2
PPm + CET	10.6	8.0-14.5	47.3

Overall Survival by Arm
Squamous Histology
ITT Analysis



Arm	Median OS (months)	95% CI (months)
CbPc + CET	9.6	7.9-11.5
PG + CET	7.1	5.9-9.5
Logrank p=0.1863		

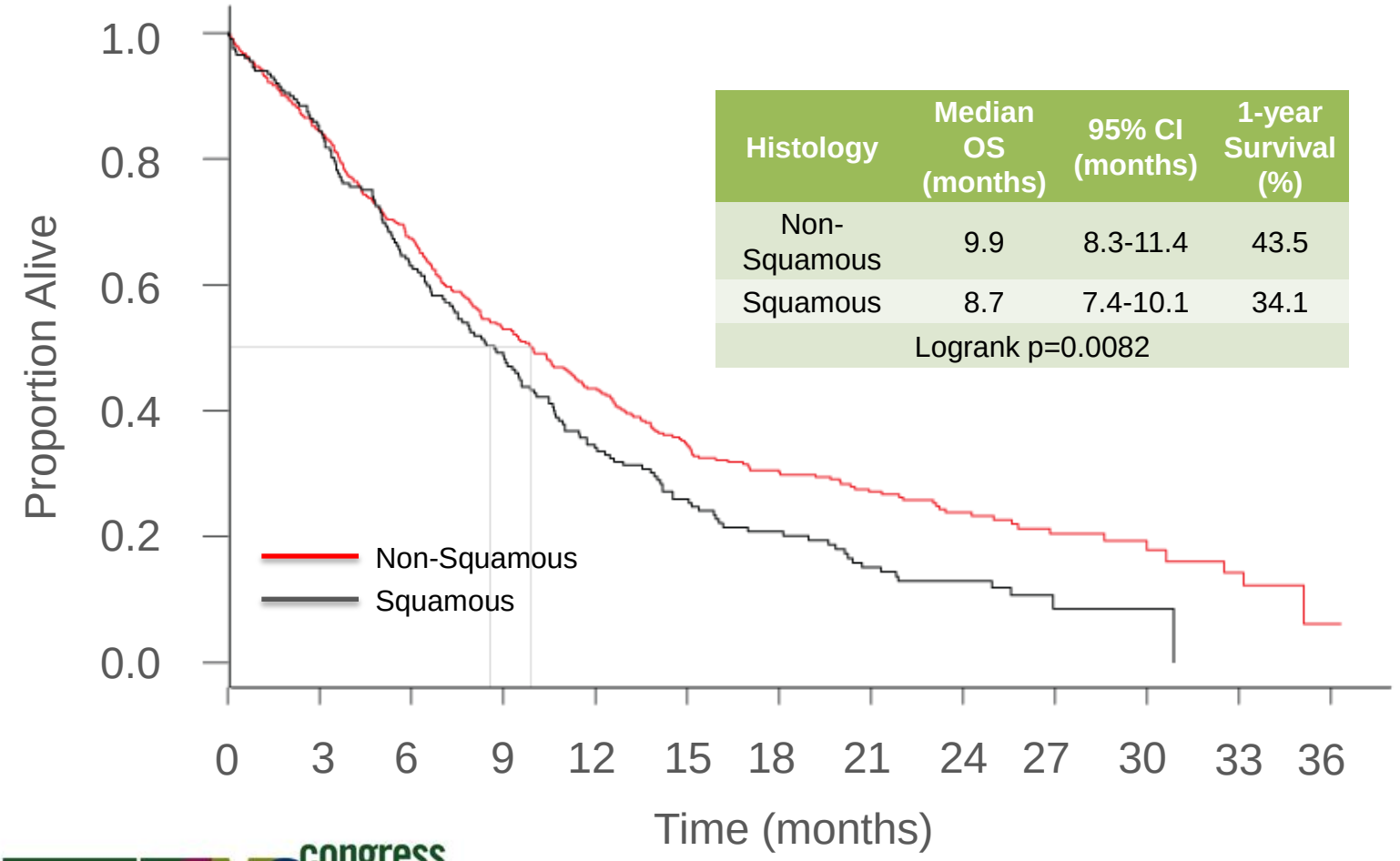
Overall Survival by Arm
Non-Squamous Histology
ITT Analysis



Arm	Median OS (months)	95% CI (months)
CbPc + CET	9.5	7.0-12.5
PG + CET	9.3	7.3-12.2
PPm + CET	10.6	8.0-14.5
Logrank p=0.2570		

Overall Survival by Histology

ITT Analysis



Histology	Median OS (months)	95% CI (months)	1-year Survival (%)
Non-Squamous	9.9	8.3-11.4	43.5
Squamous	8.7	7.4-10.1	34.1
Logrank p=0.0082			

1-Year Survival

All Randomized, ITT	
Arm (N)	**1-year Survival % (95% CI)**
CbPc + CET (233)	39.7 (33.7 – 46.6)
PG + CET (236)	37.2 (31.3 – 44.2)
PPm + CET (130)	47.3 (39.1 – 57.1)

By Histology, ITT		
Arm (N)	**1-year Survival % (95% CI)**	
	NSQ	SQ
CbPc + CET (233)	42.9 (35.1-52.4)	35.4 (27.0-46.5)
PG + CET (236)	40.6 (32.8-50.1)	32.6 (24.3-44.0)
PPm + CET (130)	47.3 (39.1-57.1)	N/A

CbPc = carboplatin + paclitaxel; PG = platinum + gemcitabine; PPm = platinum + pemetrexed; CET = cetuximab

Cox Multivariate Analysis

Factors	Hazard Ratio	95% CI	P
Age (Years)	1.0023	0.9921, 1.0127	0.6584
Male Gender	1.2960	1.0688, 1.5714	**0.0084**
Race - Black	1.0550	0.7674, 1.4505	0.7414
Race - Other	0.8576	0.6019, 1.2218	0.3949
PG (Arm B)	1.1067	0.8989, 1.3627	0.3393
PPm (Arm C)	0.8577	0.6478, 1.1358	0.2841
Squamous Histology	1.1562	0.9329, 1.4329	0.1851
Stage IV	1.9508	1.2613, 3.0172	**0.0027**
ECOG Status 1	1.3465	1.1045, 1.6415	**0.0032**
Prior Radiation	1.2691	0.8988, 1.7919	0.1758
Prior Chemo	0.7624	0.4272, 1.3606	0.3585
Metastases Sites > 2	1.1913	0.9027, 1.5722	0.2161

PG = platinum + gemcitabine; PPm = platinum + pemetrexed

Drug Exposure

	CbPc + CET	PG + CET	PPm + CET
Cycles Completed Mean ± SD Median (IQR)	 3.9 ± 1.8 4.0 (2.0, 6.0)	 3.9 ± 1.9 4.0 (2.0, 6.0)	 4.2 ± 1.8 4.0 (2.0, 6.0)
Patients Completing ≥ 4 Cycles	146 (64.9)	142 (62.3)	79 (65.8)
Patients Receiving Treatment Until Progression	37 (16.4)	36 (15.8)	17 (14.2)

CbPc = carboplatin + paclitaxel; PG = platinum + gemcitabine; PPm = platinum + pemetrexed; CET = cetuximab

CTC Grade 3/4/5 Hematologic
AEs ≥ 5%

AE	CbPc + CET n (%)	PG + CET n (%)	PPm + CET n (%)
Anemia	12 (5.1)	41 (17.4)	10 (7.7)
Lymphopenia	8 (3.4)	6 (2.5)	9 (6.9)
Neutropenia	65 (27.7)	65 (27.5)	24 (18.5)
Thrombocytopenia	22 (9.4)	95 (40.3)	28 (21.5)

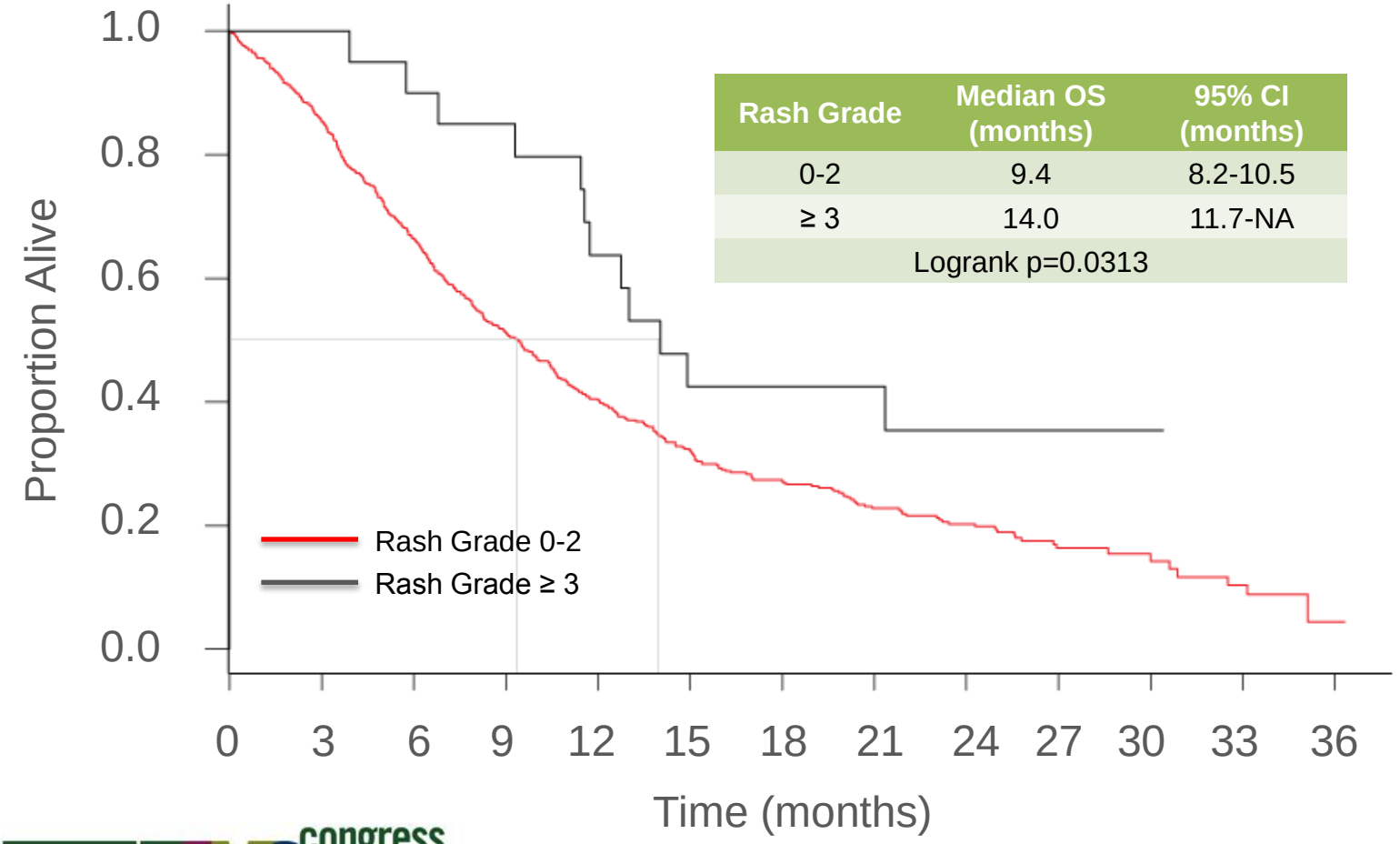
CbPc = carboplatin + paclitaxel; PG = platinum + gemcitabine; PPm = platinum + pemetrexed; CET = cetuximab

CTC Grade 3/4/5 Non-Hematologic AEs ≥ 5% by Arm

AE	CbPc + CET n (%)	PG + CET n (%)	PPm + CET n (%)
Back Pain	2 (0.9)	3 (1.3)	6 (4.6)
Decreased Appetite	9 (3.8)	6 (2.5)	6 (4.6)
Dehydration	12 (5.1)	9 (3.8)	8 (6.2)
Diarrhea	9 (3.8)	5 (2.1)	6 (4.6)
Dyspnea	13 (5.5)	19 (8.1)	9 (6.9)
Fatigue	23 (9.8)	24 (10.2)	11 (8.5)
Hypokalemia	11 (4.7)	9 (3.8)	8 (6.2)
Hypomagnesemia	16 (6.8)	9 (3.8)	4 (3.1)
Hyponatremia	7 (3.0)	4 (1.7)	6 (4.6)
Nausea	3 (1.3)	6 (2.5)	6 (4.6)
Pneumonia	12 (5.1)	9 (3.8)	5 (3.8)
Pulmonary Embolism	13 (5.5)	13 (5.5)	4 (3.1)
Rash	18 (7.7)	18 (7.6)	9 (6.9)

CbPc = carboplatin + paclitaxel; PG = platinum + gemcitabine; PPm = platinum + pemetrexed; CET = cetuximab

Overall Survival by Rash
Per Protocol Sample



Rash Grade	Median OS (months)	95% CI (months)
0-2	9.4	8.2-10.5
≥ 3	14.0	11.7-NA
Logrank p=0.0313		

Discussion

- Results appear comparable to OS seen in prior North American chemo + cetuximab trials
- No arm met formal statistical goal of surpassing upper limit of historical median OS
- Biomarker analysis, including EGFR H-score, underway

Conclusions

- No new safety signals for standard platinum doublets + cetuximab identified
- No significant differences in outcome by chemotherapy regimen
  - Numerically better OS in NSQ histology for platinum + pemetrexed + cetuximab
- NSQ patients receiving chemotherapy + cetuximab have improved survival compared to SQ patients

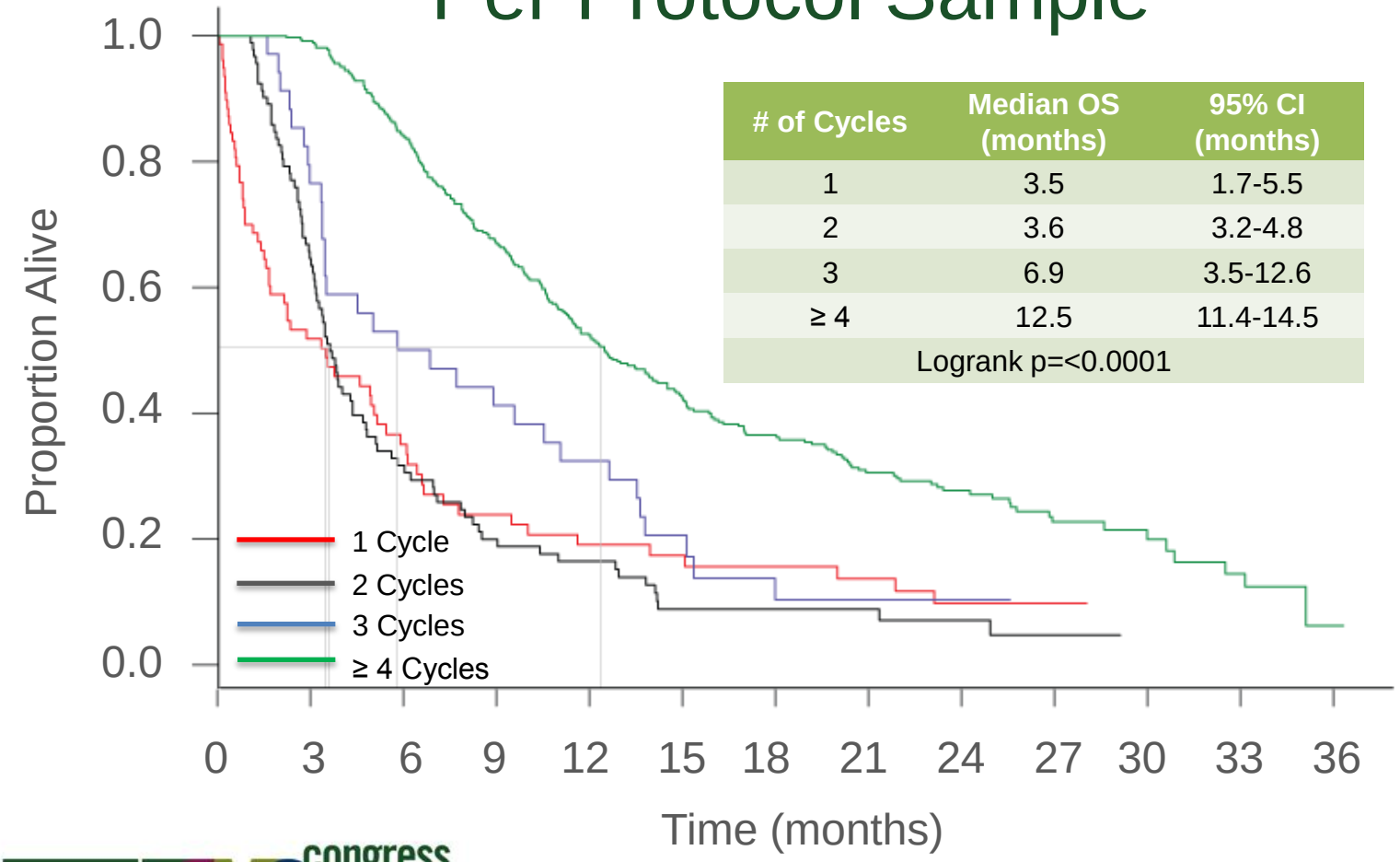
Acknowledgements

- All the patients and their families who participated in this trial
- The investigators and study coordinators from 91 sites who enrolled patients on the eLung study

Back-up Slides

Overall Survival by Number of Treatment Cycles Received

Per Protocol Sample



# of Cycles	Median OS (months)	95% CI (months)
1	3.5	1.7-5.5
2	3.6	3.2-4.8
3	6.9	3.5-12.6
≥ 4	12.5	11.4-14.5
Logrank p=<0.0001		

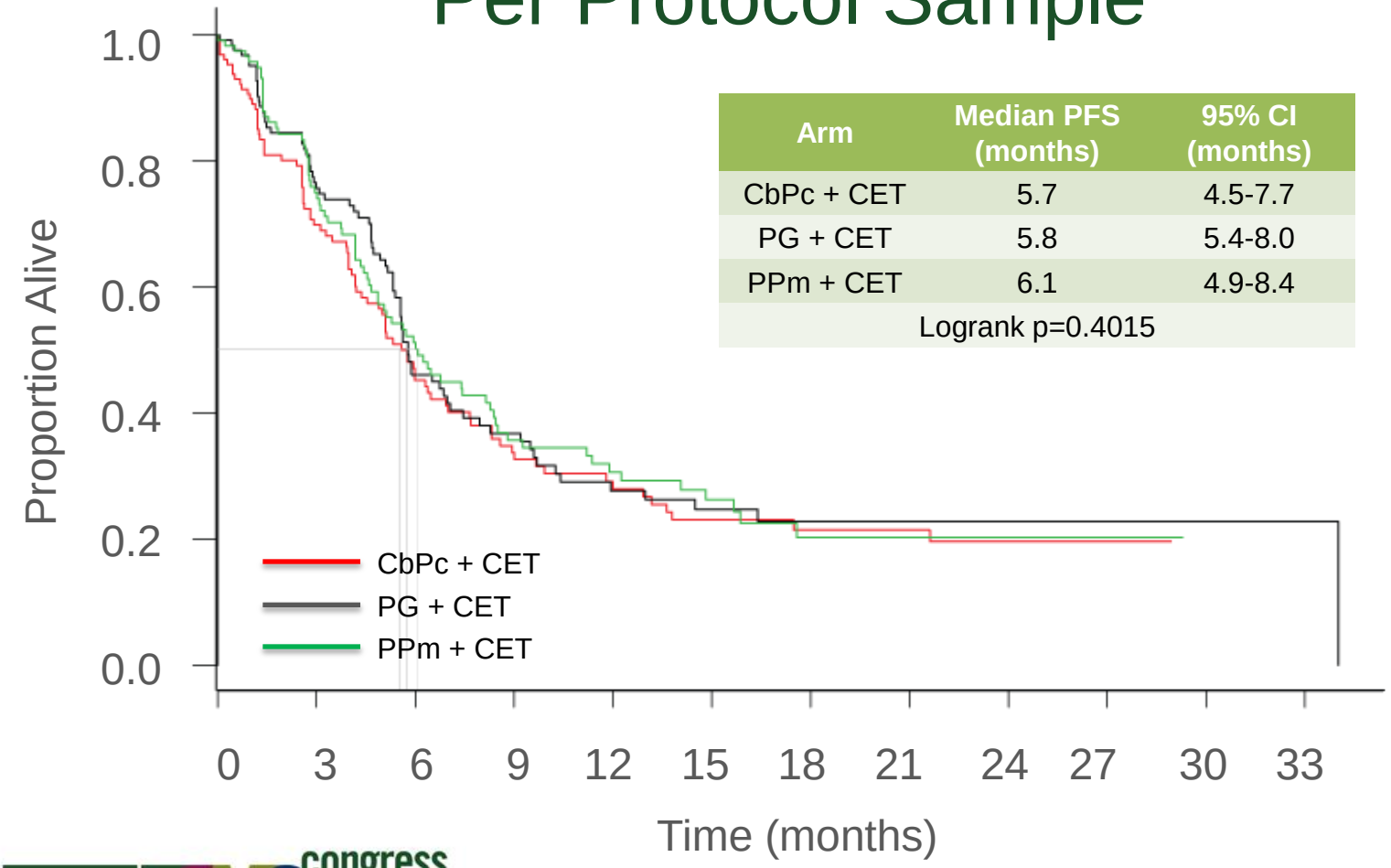
Overall Response Rate

	CbPc + CET	PG + CET	PPm + CET
ORR, n (%)	73 (35.3)	62 (29.5)	23 (21.5)

CbPc = carboplatin + paclitaxel; PG = platinum + gemcitabine; PPm = platinum + pemetrexed; CET = cetuximab

Progression Free Survival Non-Squamous

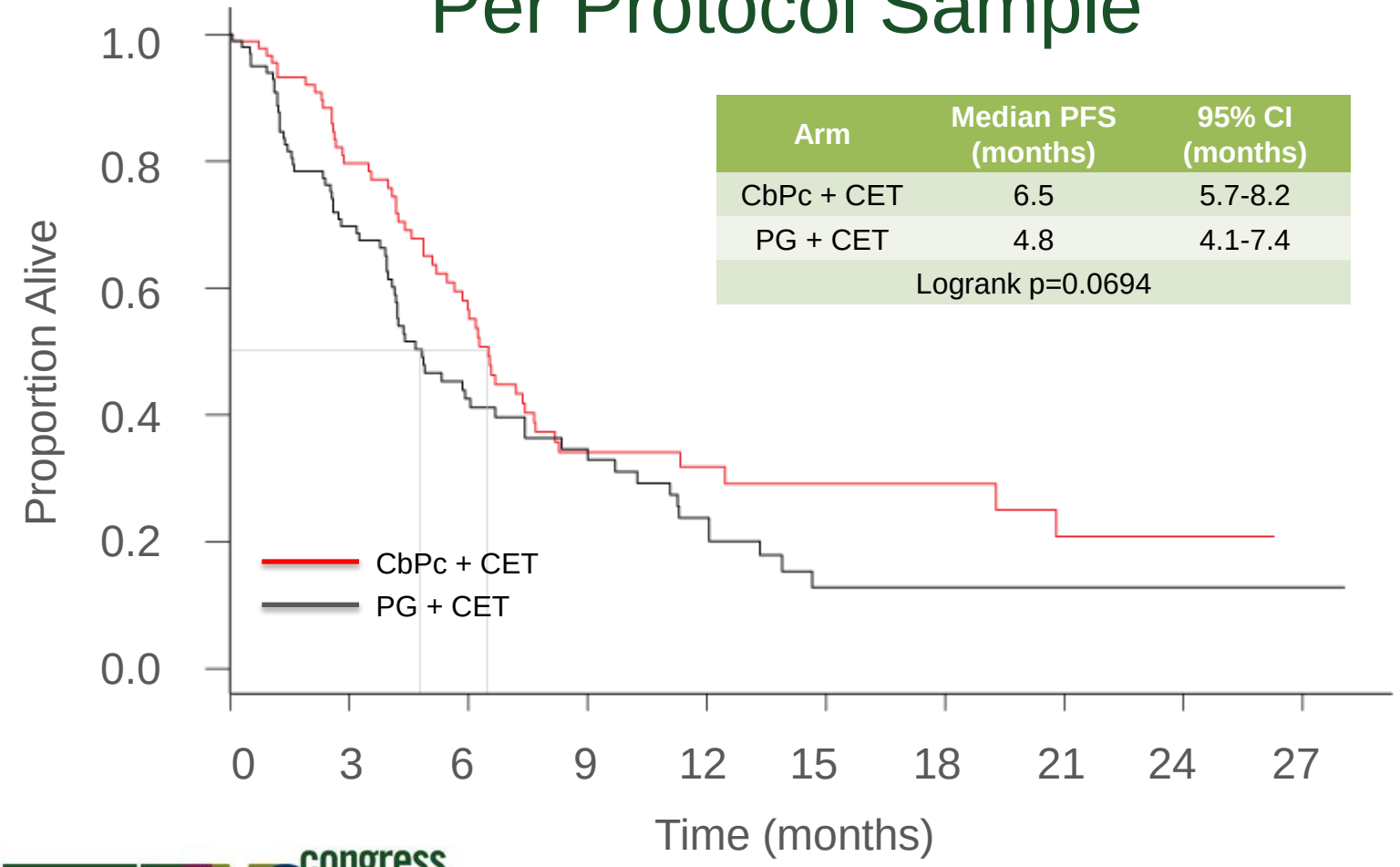
Per Protocol Sample



Arm	Median PFS (months)	95% CI (months)
CbPc + CET	5.7	4.5-7.7
PG + CET	5.8	5.4-8.0
PPm + CET	6.1	4.9-8.4
Logrank p=0.4015		

Progression Free Survival Squamous

Per Protocol Sample



Arm	Median PFS (months)	95% CI (months)
CbPc + CET	6.5	5.7-8.2
PG + CET	4.8	4.1-7.4
Logrank p=0.0694		