EGFR-targeted antibodies: clinical and molecular sensitivity predictors

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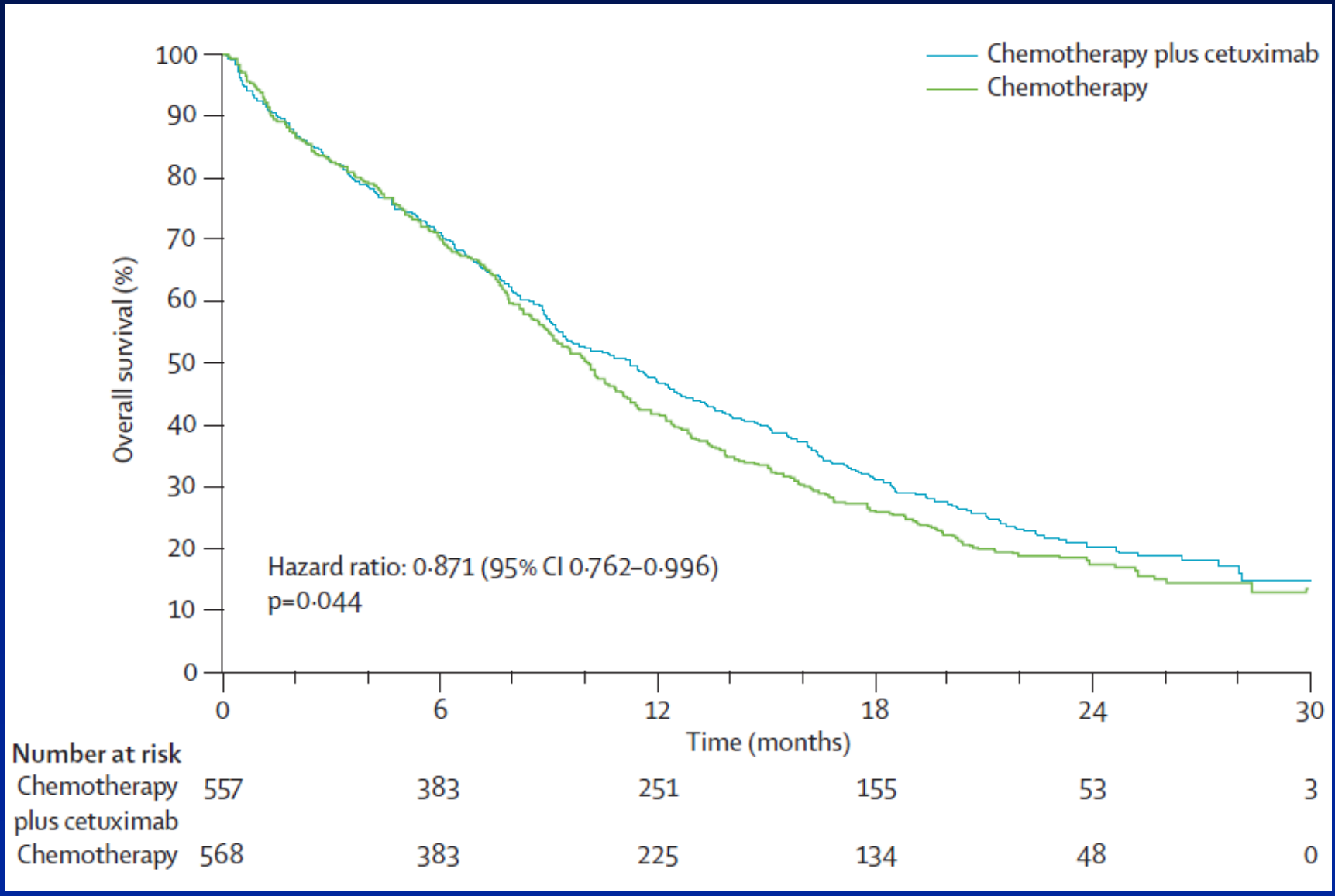
Conflict of Interest

- Honoraria for Advisory Board/Consulting
  - Merck KGaA
  - Roche
  - Eli Lilly
  - AstraZeneca
- Speaker‘s fee
  - Merck KGaA
  - Roche
  - Eli Lilly
  - Pierre Fabre
  - AstraZeneca
  - Sanofi-Aventis

1st-line chemotherapy plus Cetuximab in advanced NSCLC

- Single-arm phase II studies
- Randomized phase II trials
- Phase III studies
  - FLEX
    Pirker R et al. J Clin Oncol 2008, 18 S (abstract 3)
    Pirker R et al. Lancet 2009, 373, 1525
  - BMS 099
    Lynch T et al. J Thorac Oncol 2007, 2 (Suppl. 4), S340
- Meta-analysis
  Thatcher N et al. WCLC 2009

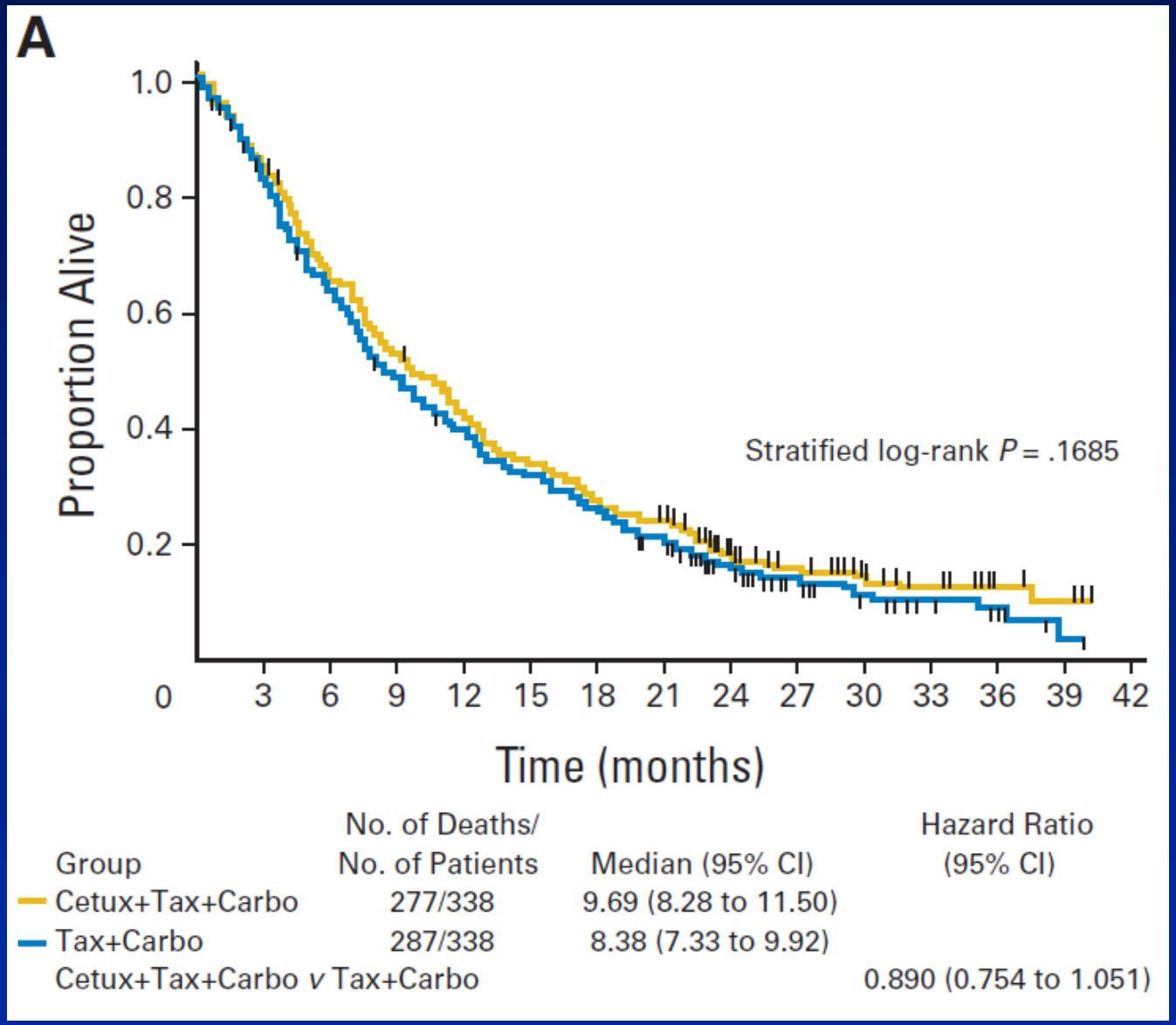
FLEX: Overall Survival



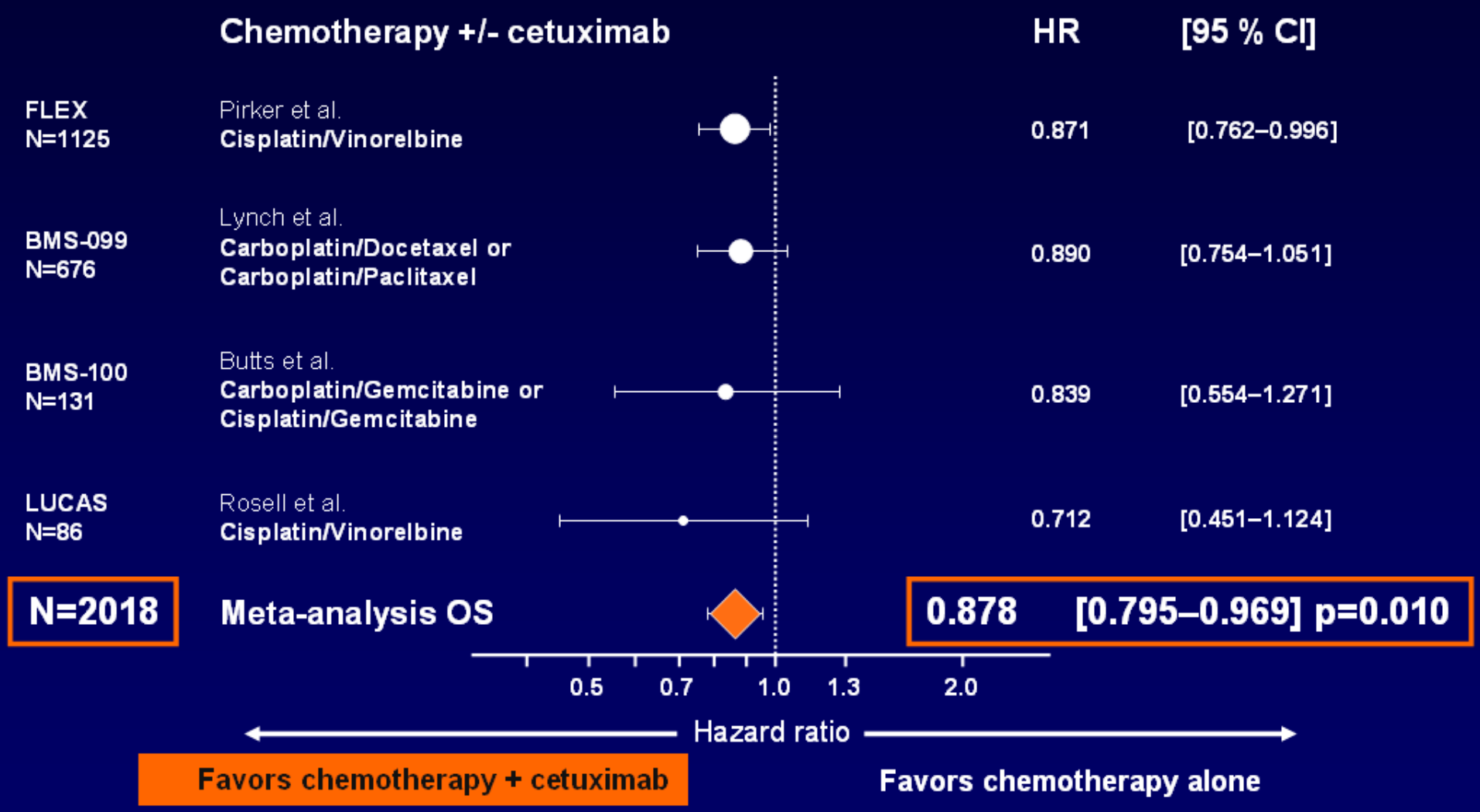
Pirker R et al. Lancet 2009, 373, 1525

OS

Lynch TL et al. JCO 2010, 28



Meta-analysis of Overall Survival

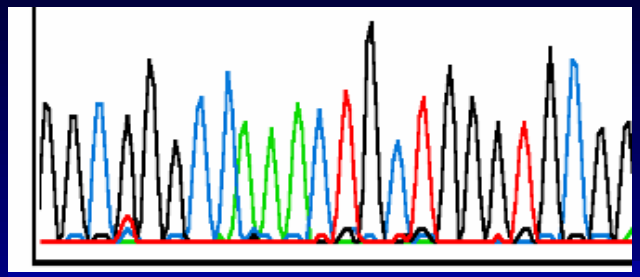


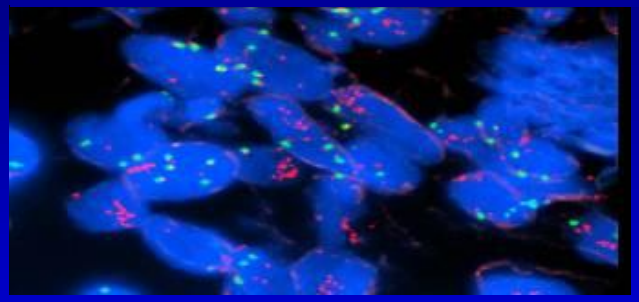
Thatcher et al, WCLC 2009, oral presentation (Abstract A3.7)

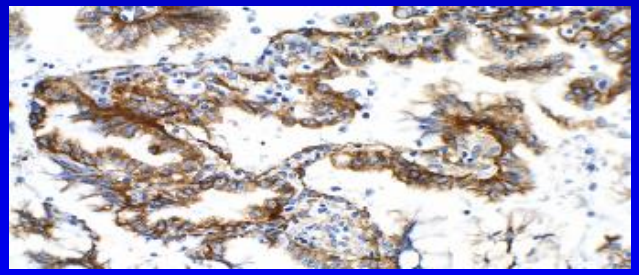
Cetuximab
Predictive markers

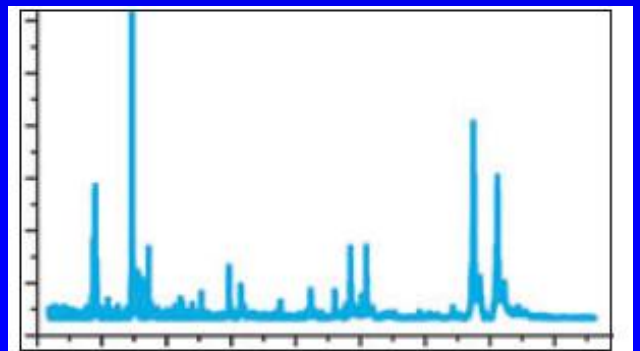
- Molecular markers
  - EGFR status
  - KRAS mutations
  - E-cadherin expression
  - HER-2, PI3 kinase mutations
  - Epithelial membrane protein 1 overexpression
  - others
- Immunological markers
- Clinical parameters

Assessment of EGFR Status





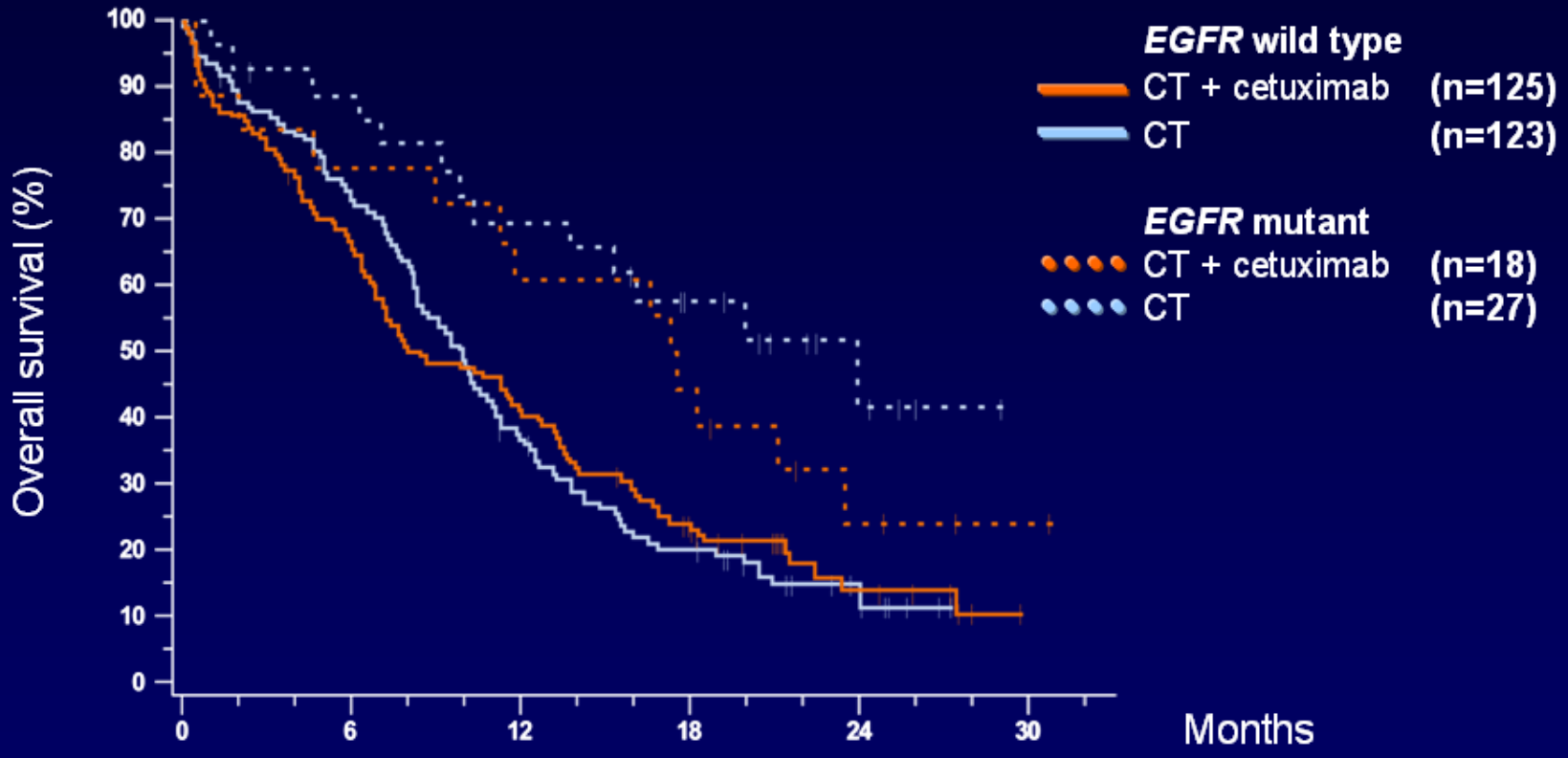




- EGFR mutation status by gene sequencing
- EGFR gene copy number by fluorescence in situ hybridization (FISH)
- EGFR protein expression by immunohistochemistry:
  - 85% positive in FLEX
- Serum Proteomics by MALDI MS

Modified from Courtesy D Gandara

EGFR mutation analysis: OS

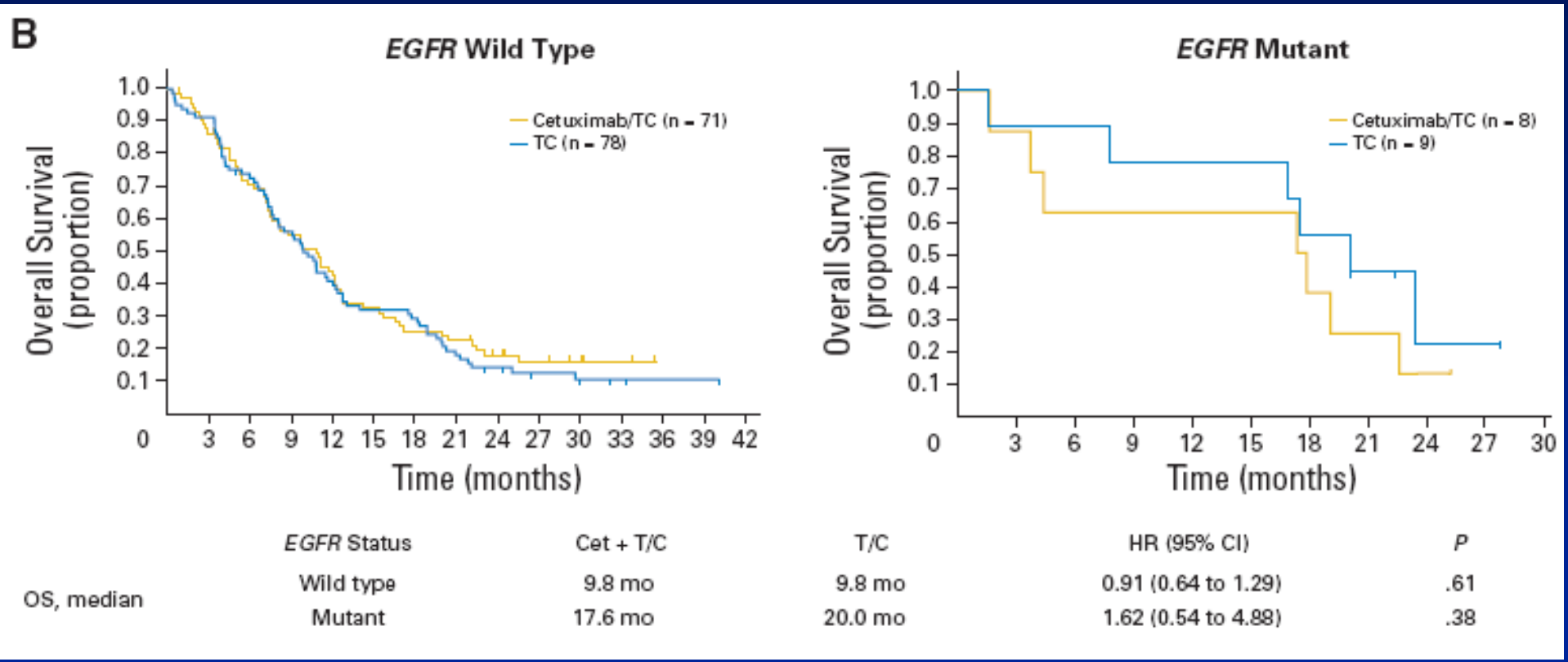


CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival

Gatzemeier et al, WCLC 2009, oral presentation (Abstract B2.3)

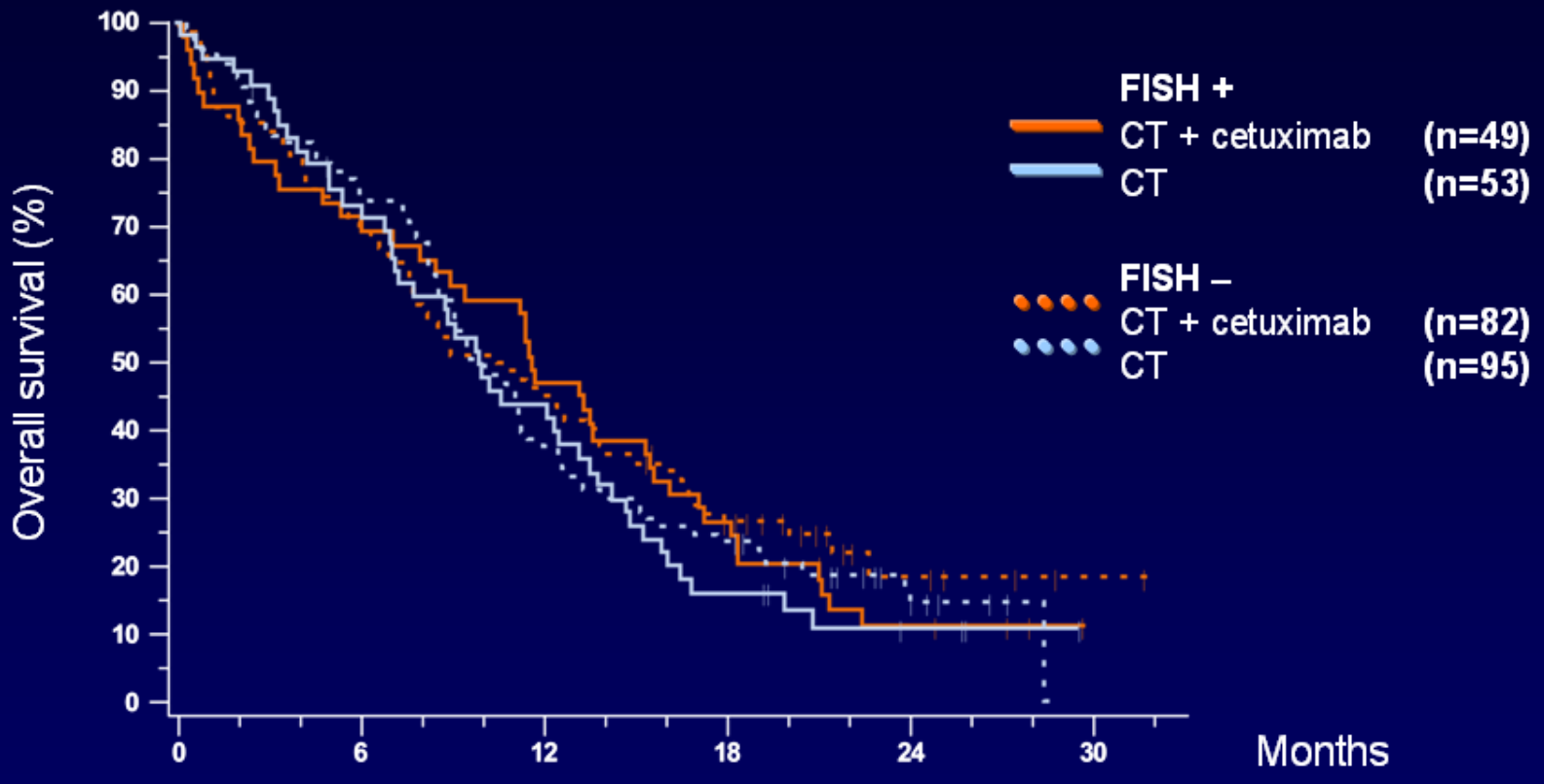
Biomarkers: BMS 099

Khambata-Ford S et al. JCO 2010, 28



	EGFR Status	Cet + T/C	T/C	HR (95% CI)	P
OS, median	Wild type	9.8 mo	9.8 mo	0.91 (0.64 to 1.29)	.61
	Mutant	17.6 mo	20.0 mo	1.62 (0.54 to 4.88)	.38

EGFR FISH analysis: OS

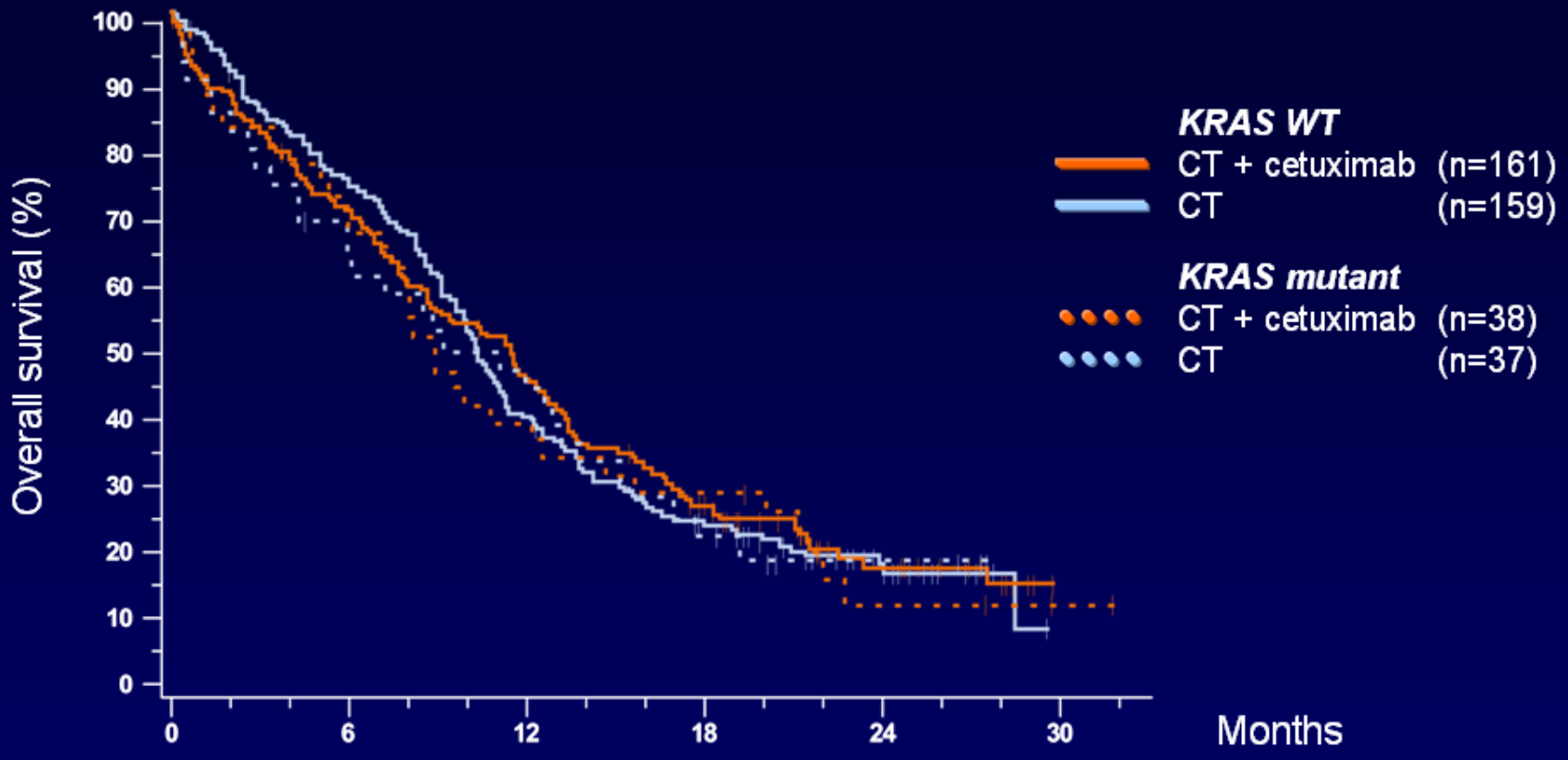


	FISH status	CT + cetuximab	CT	HR (95% CI)	p-value
Median OS	FISH -	10.6 mo	10.0 mo	0.91 (0.65–1.26)	0.56
	FISH +	11.6 mo	9.9 mo	0.85 (0.56–1.29)	0.44

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival

O'Byrne KJ, et al. J Clin Oncol 2009; 27(15s):suppl; abstr 8007

KRAS mutation analysis: OS



	KRAS status	CT + cetuximab	CT	HR (95% CI)	p-value
Median OS	Wild type	11.4 mo	10.3 mo	0.96 (0.75–1.23)	0.75
	Mutant	8.9 mo	11.1 mo	1.00 (0.60–1.66)	1.00

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Biomarkers: BMS 099

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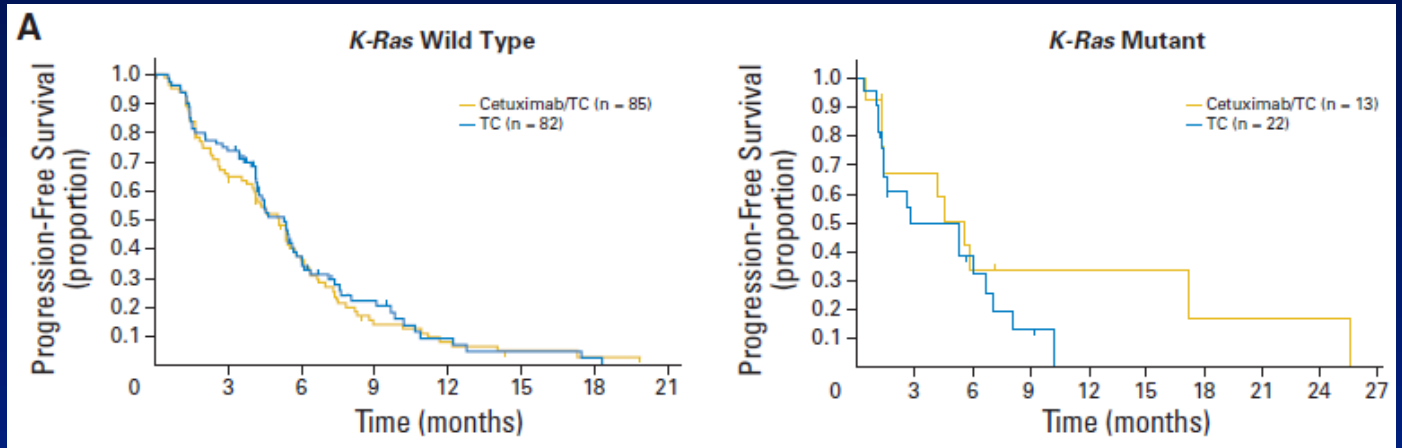
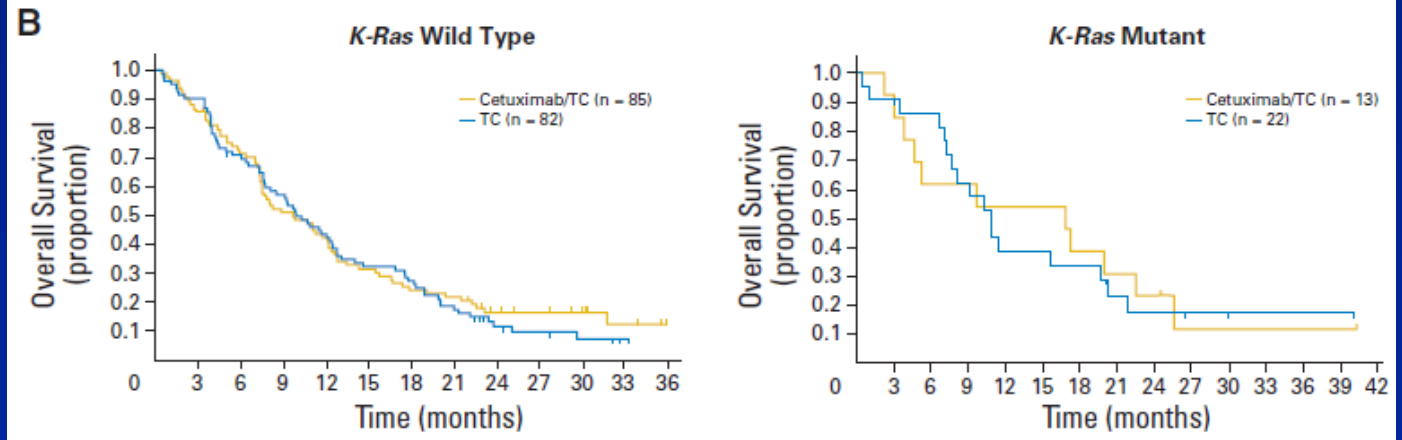


	K-Ras Status	Cet + T/C	T/C	HR (95% CI)	*P*
PFS, median	Wild type	5.1 mo	5.3 mo	1.07 (0.77 to 1.50)	.69
	Mutant	5.6 mo	2.8 mo	0.64 (0.27 to 1.50)	.30



	K-Ras Status	Cet + T/C	T/C	HR (95% CI)	*P*
OS, median	Wild type	9.7 mo	9.9 mo	0.93 (0.67 to 1.30)	.68
	Mutant	16.8 mo	10.8 mo	0.97 (0.45 to 2.07)	.93

Cetuximab trials (FLEX, BMS 099)
Predictive factors

- No predictive role of
  - EGFR mutation status
  - EGFR copy numbers (FISH)
  - K-ras mutation status
- Number of samples do not allow to exclude small differences
- Assays reliable enough ?
- Results raise several issues on predictive factors in advanced NSCLC

Predictive factors in NSCLC
Issues

- Heterogeneous disease (molecularly & clinically)
- Complex molecular mechanisms/pathways
- Clinical heterogeneity
  - Many organs as metastatic sites
  - Brain metastasis
  - Co-morbidity
  - Performance status
- Are tumor specimens representative of a complex disease ?
- Assays: reliable, fast, available for routine practice
- Molecular imaging in the future
  - Sensitivity might be too low borderline cases

1st-cycle rash: CT + cetuximab incidence and grade

Rash		No rash
Any grade (1-3)	**vs**	**Grade 0**
n=290 (56%)		**n=228 (44%)**

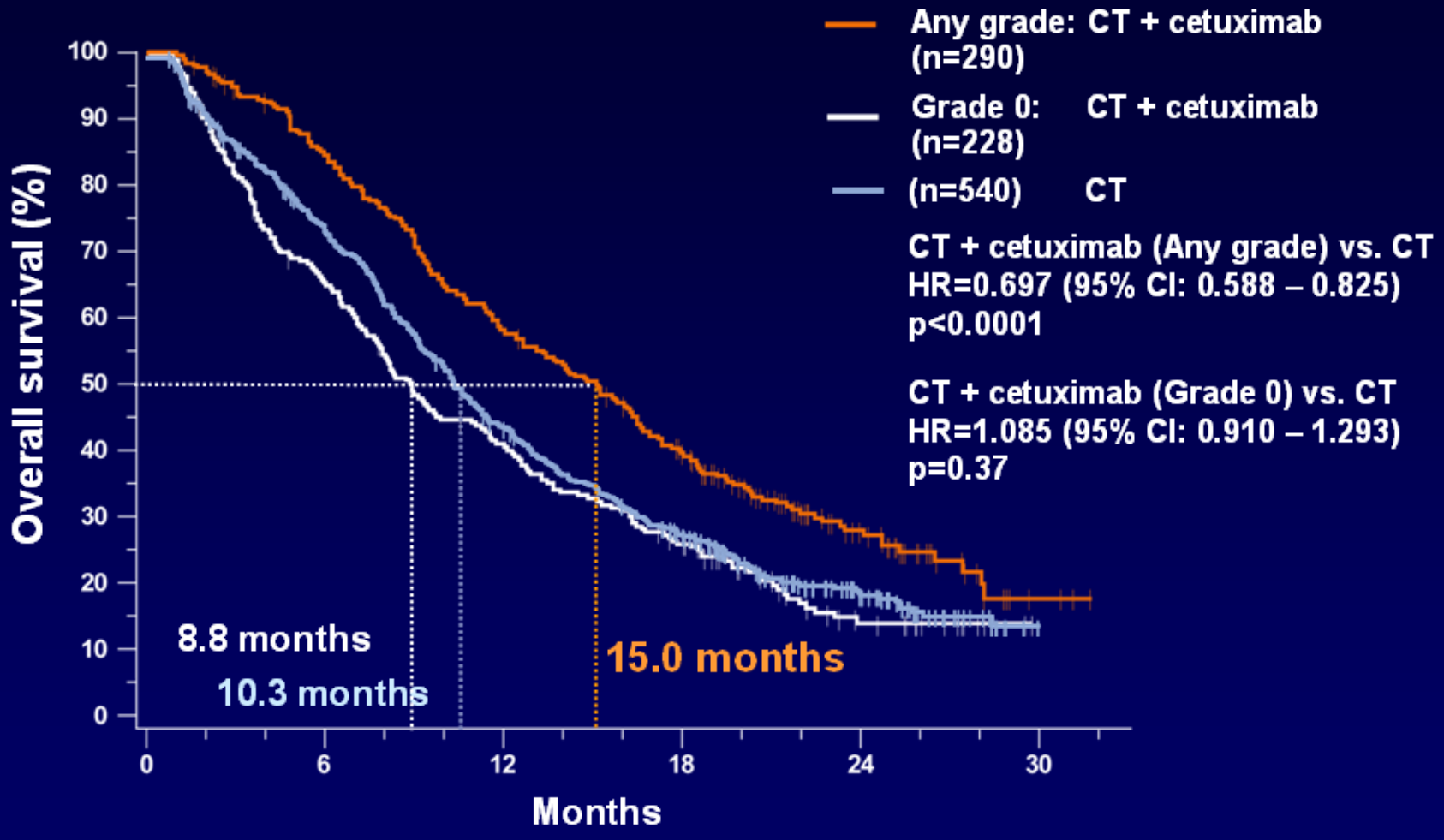
518/557 patients were included in analysis

1st-cycle rash	No. of patients (%)	
Grade 0	**228**	**(44%)**
Grade 1	**170**	**(33%)**
Grade 2	**92**	**(18%)**
Grade 3	**28**	**(5%)**
Grade 4	**0**	**–**

CT, chemotherapy

Gatzemeier et al. JTO 2008;3(Suppl. 4):S265 (Abstract 8)

1st-cycle rash and OS



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Summary

- Cetuximab added to first-line chemotherapy increases survival of patients with advanced NSCLC
- EGFR-activating mutations, EGFR copy numbers and KRAS mutation status do not predict benefit
- First-cycle rash associated with better prognosis