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**Department of Radiation Oncology**  
**University of Alabama at Birmingham**  
**Birmingham, AL**



**Welcome**



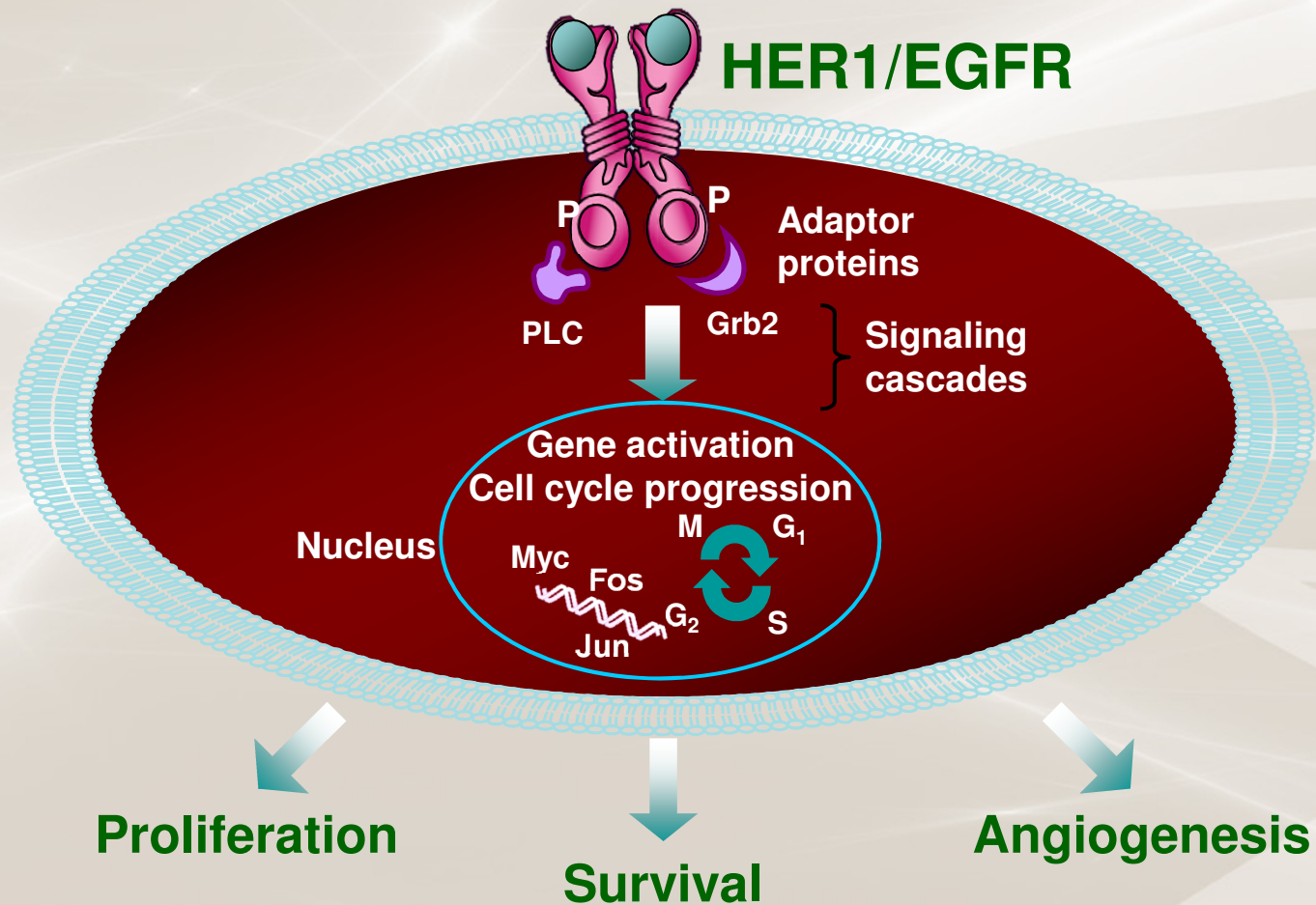
# Locoregionally Advanced Head and Neck Cancer



## Search for New Agents



# HER1/EGFR Signaling: Survival, Proliferation, Angiogenesis



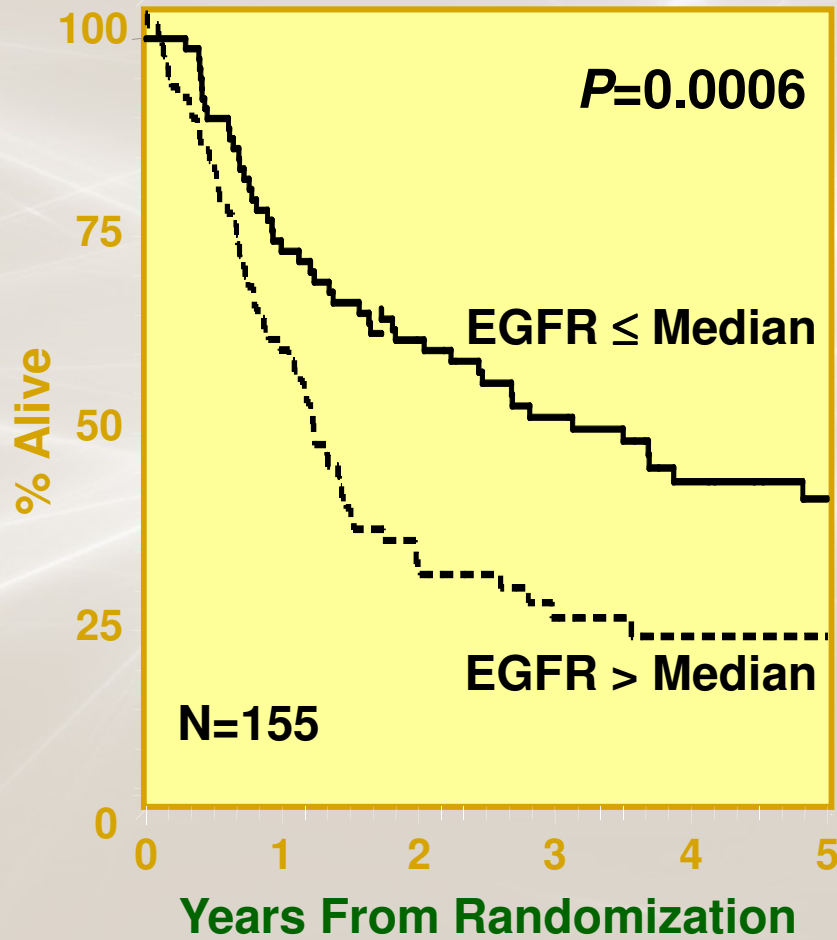
Harari and Huang. *Clin Cancer Res.* 2000;6:323; Herbst. *Int J Radiat Oncol Biol Phys.* 2004;59(suppl):21.



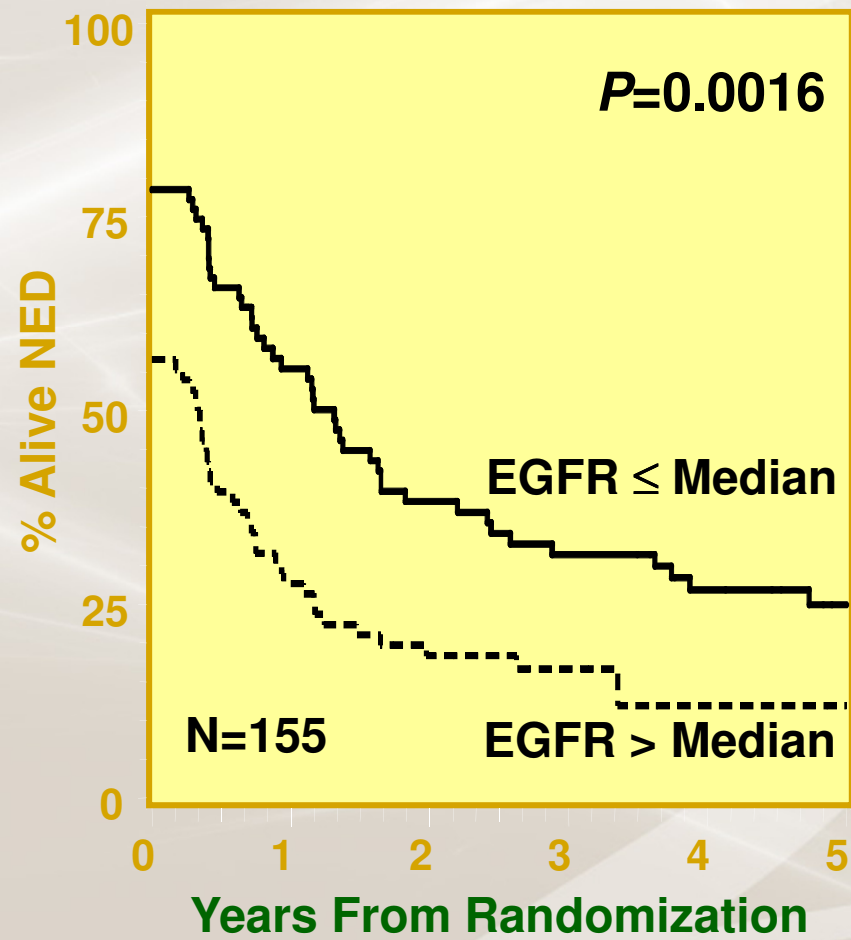
# EGFR Expression vs. Survival

## Locoregionally Advanced Head and Neck Cancer

### Overall Survival



### Disease-Free Survival

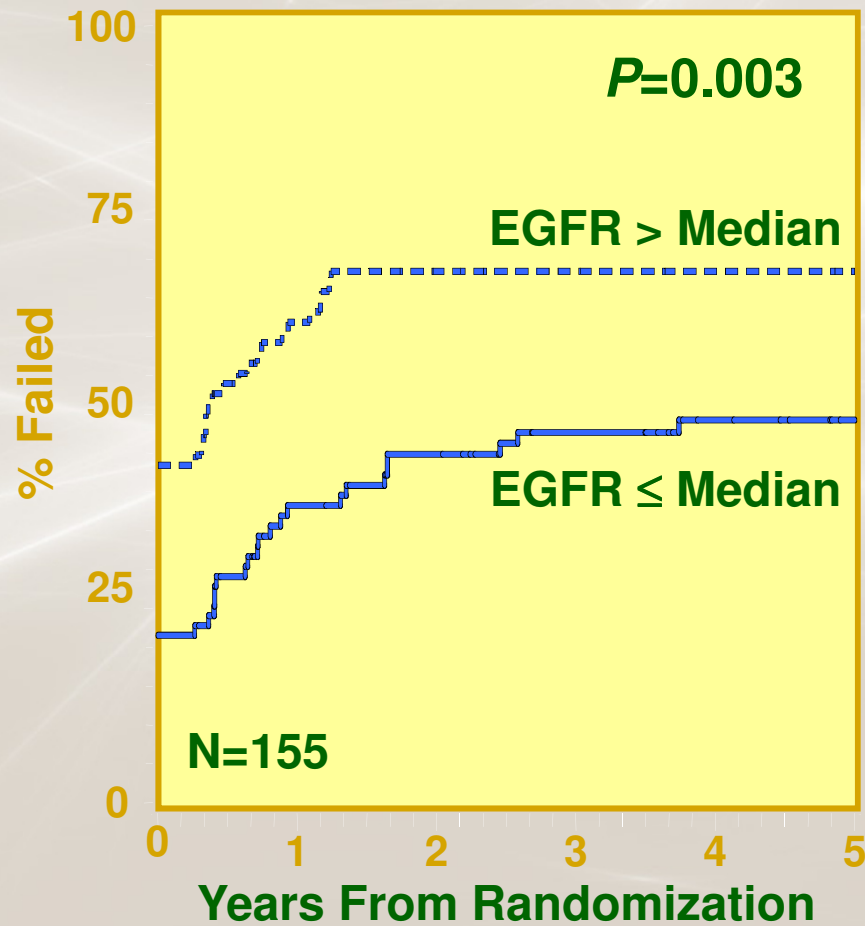


Ang et al. Cancer Res. 2002;62:7350

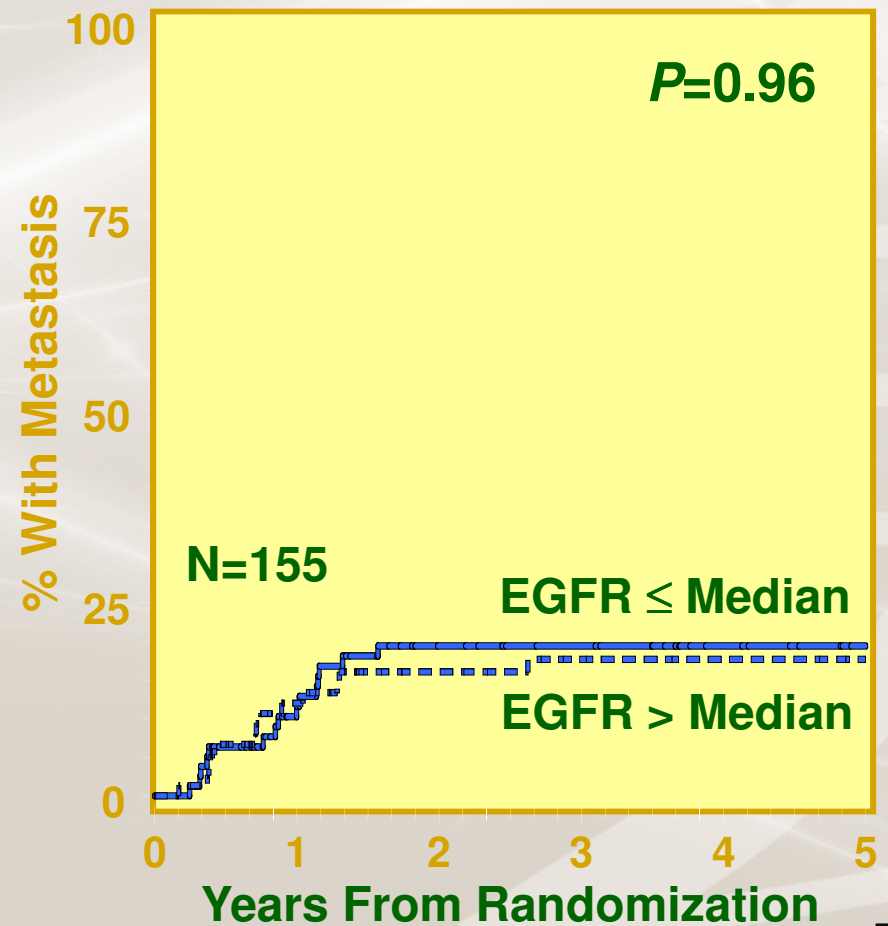


# EGFR Expression vs. Pattern of Failure

## Local-Regional Relapse



## Distant Metastasis

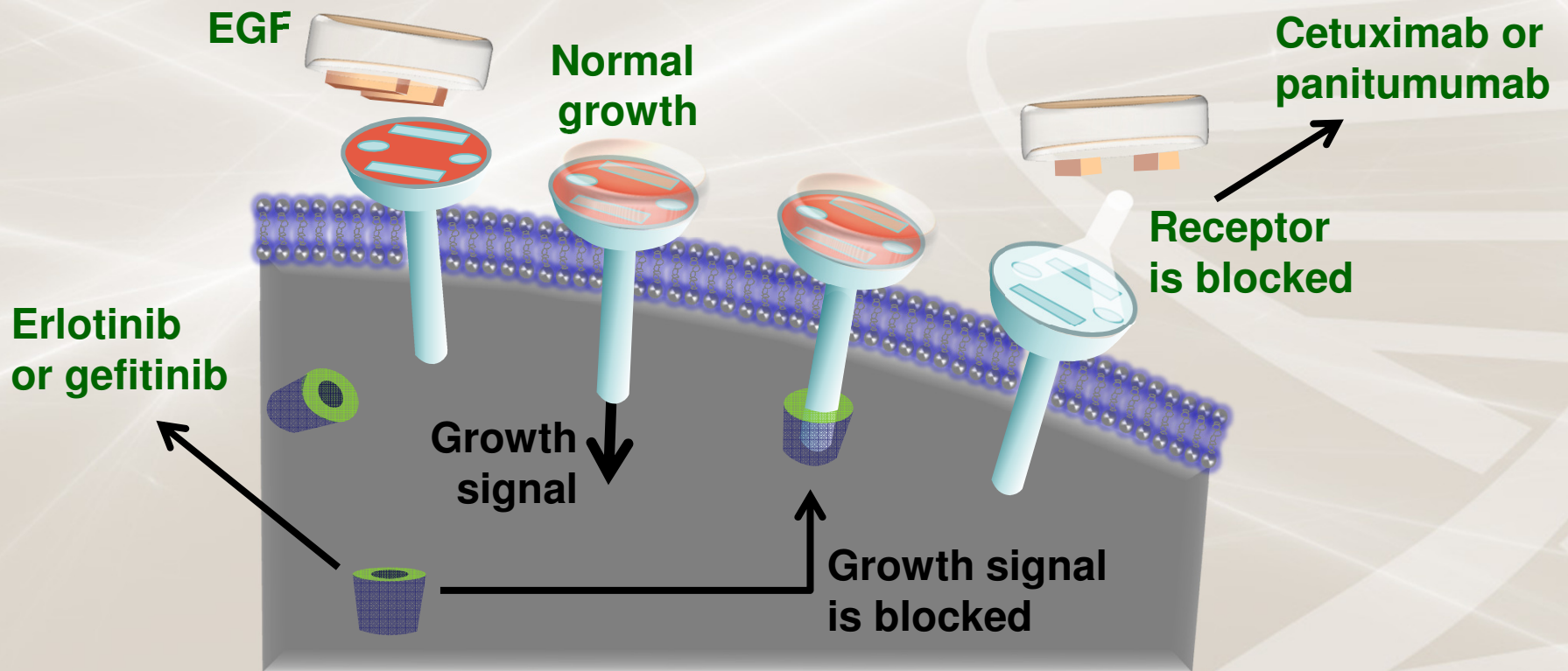


Ang et al. *Cancer Res.* 2002;62:7350



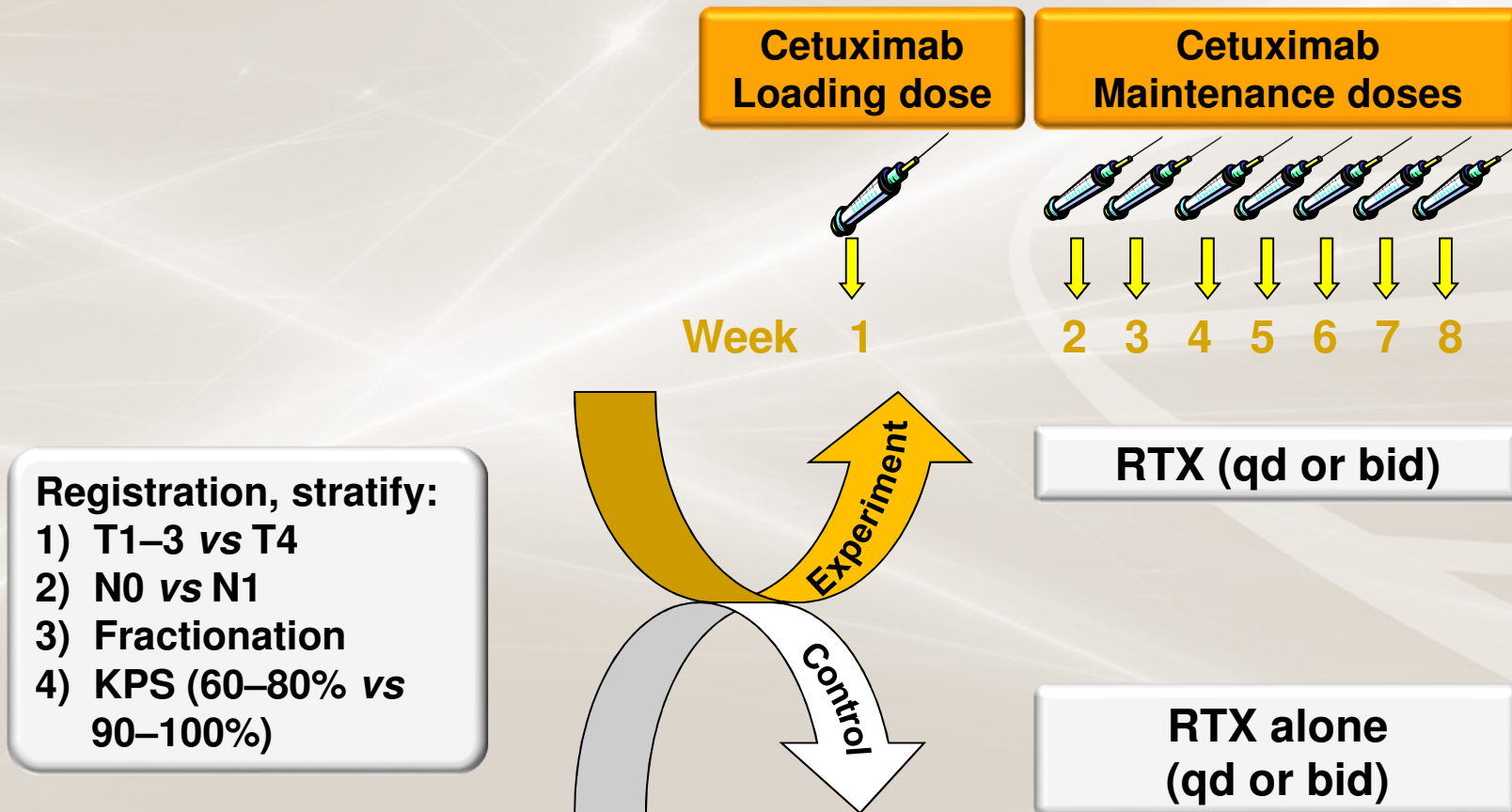
# Blockade of EGFR

Gefitinib and erlotinib block the internal growth signal, while cetuximab or panitumumab block the external part of the receptors





# Radiotherapy ± cetuximab phase III trial in head and neck cancer: Study design

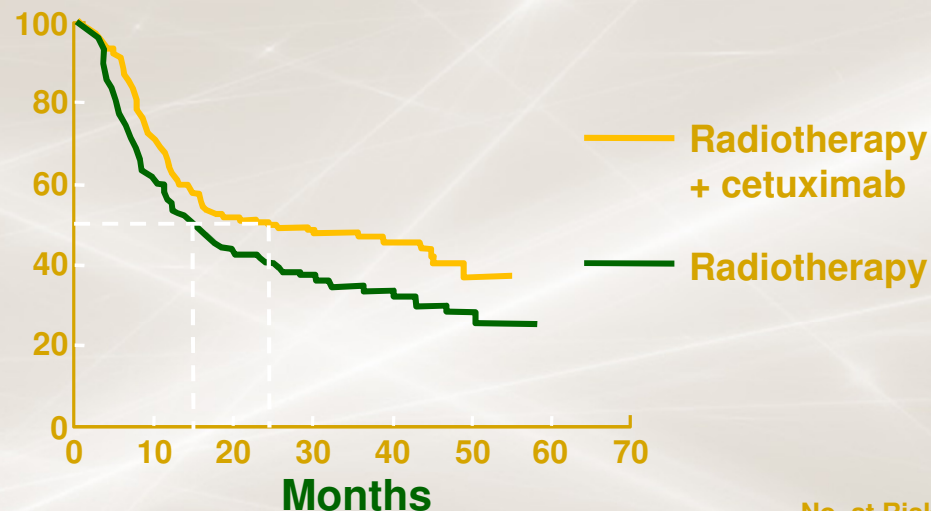




# Radiotherapy ± cetuximab phase III trial in head and neck cancer: Antitumor efficacy

## 54 months median follow-up

**Locoregional control (%)**

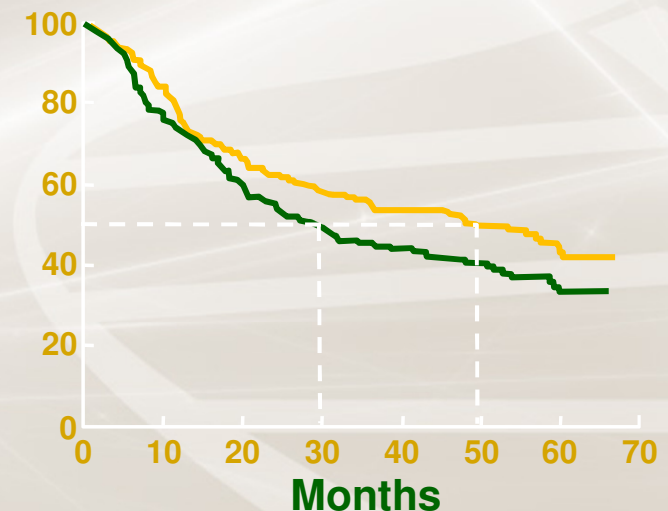


No. at Risk	0	10	20	30	40	50	60	70
RT	213	122	80	51	30	10		
RT + Cet	211	143	101	66	35	9		

**p=0.005**

Locoregional C.	RT	RT+C
3 year (%)	34	47
Median	14.9 m	24.4 m
Hazard ratio	0.68 (0.52–0.89)	

**Overall survival (%)**



No. at Risk	0	10	20	30	40	50	60	70
RT	213	162	122	97	73	47	22	
RT + Cet	211	177	136	116	98	61	24	

**p=0.03**

Overall survival	RT	RT+C
3 year (%)	45	55
Median	29.3 m	49.0 m
Hazard ratio	0.74 (0.57–0.97)	

**Bonner *et al*, N Engl J Med 2006; 354: 567–78**

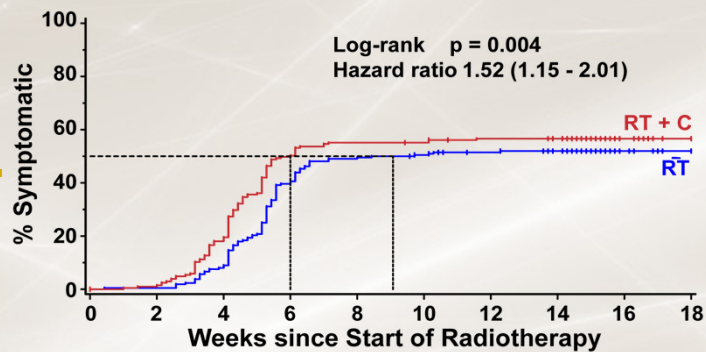




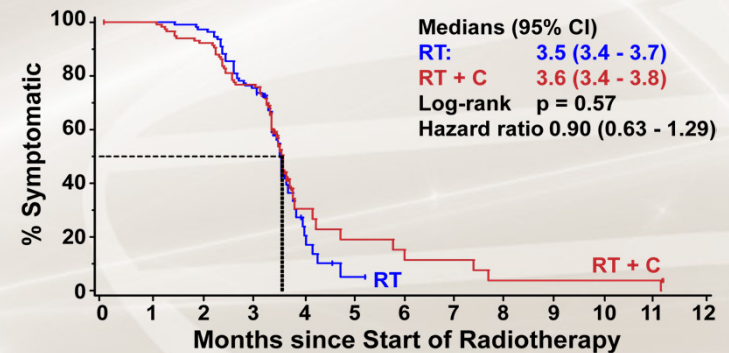
# Cetuximab Does Not Alter Radiation-Induced Mucositis or Dysphagia

## Mucositis

### Mucositis Onset 3/4

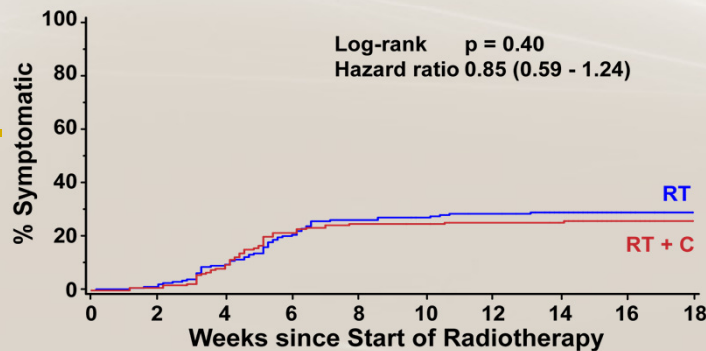


### Mucositis Resolution

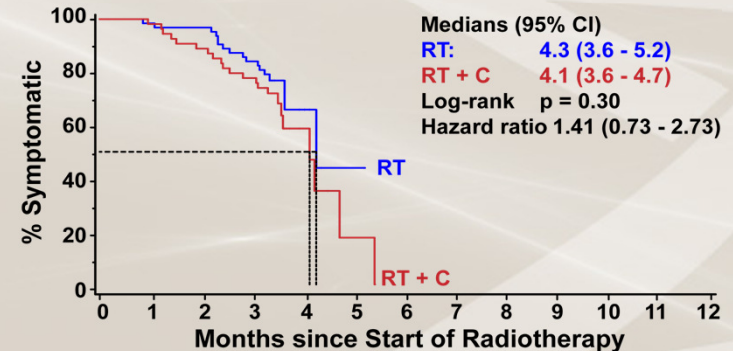


## Dysphagia

### Dysphagia Onset 3/4



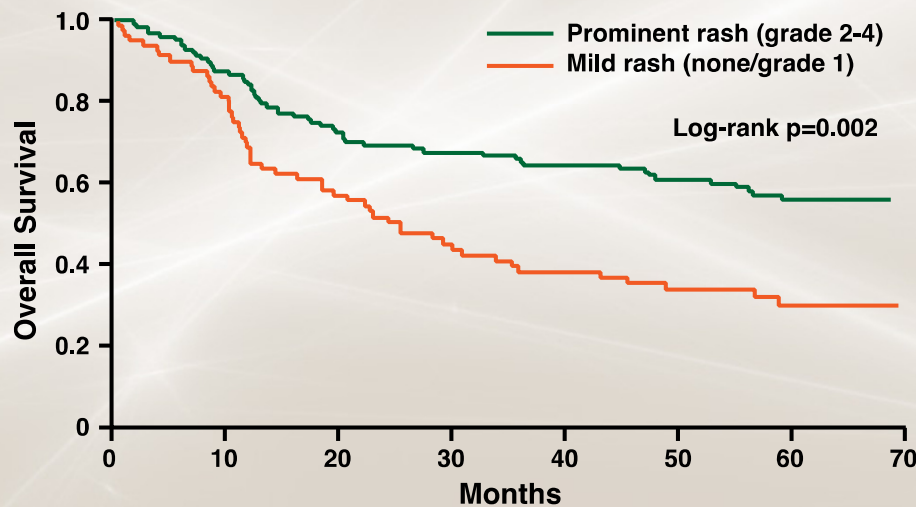
### Dysphagia Resolution





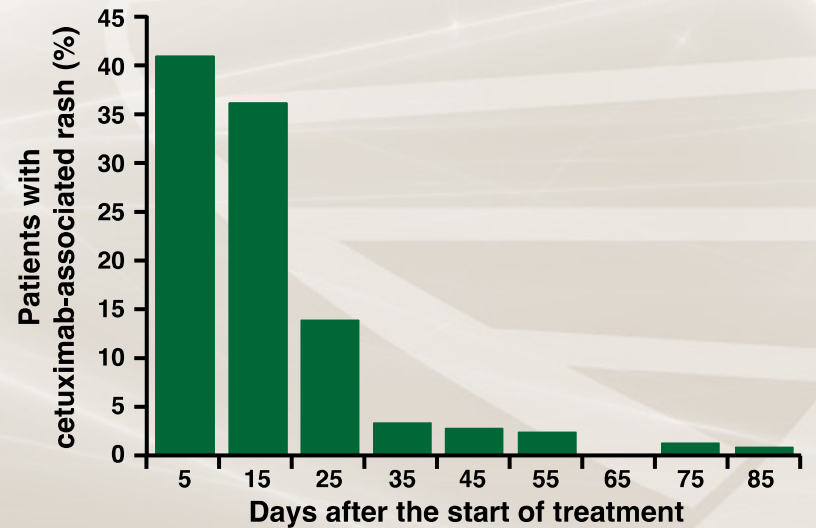
# Cetuximab-Induced Acneiform Rash \*

## Survival Base on Severity of the Rash



Number at risk	0	10	20	30	40	50	60	70
Prominent rash	127	111	92	84	78	68	39	--
Mild rash	81	65	43	33	27	22	10	--

## Time of Onset of the Rash

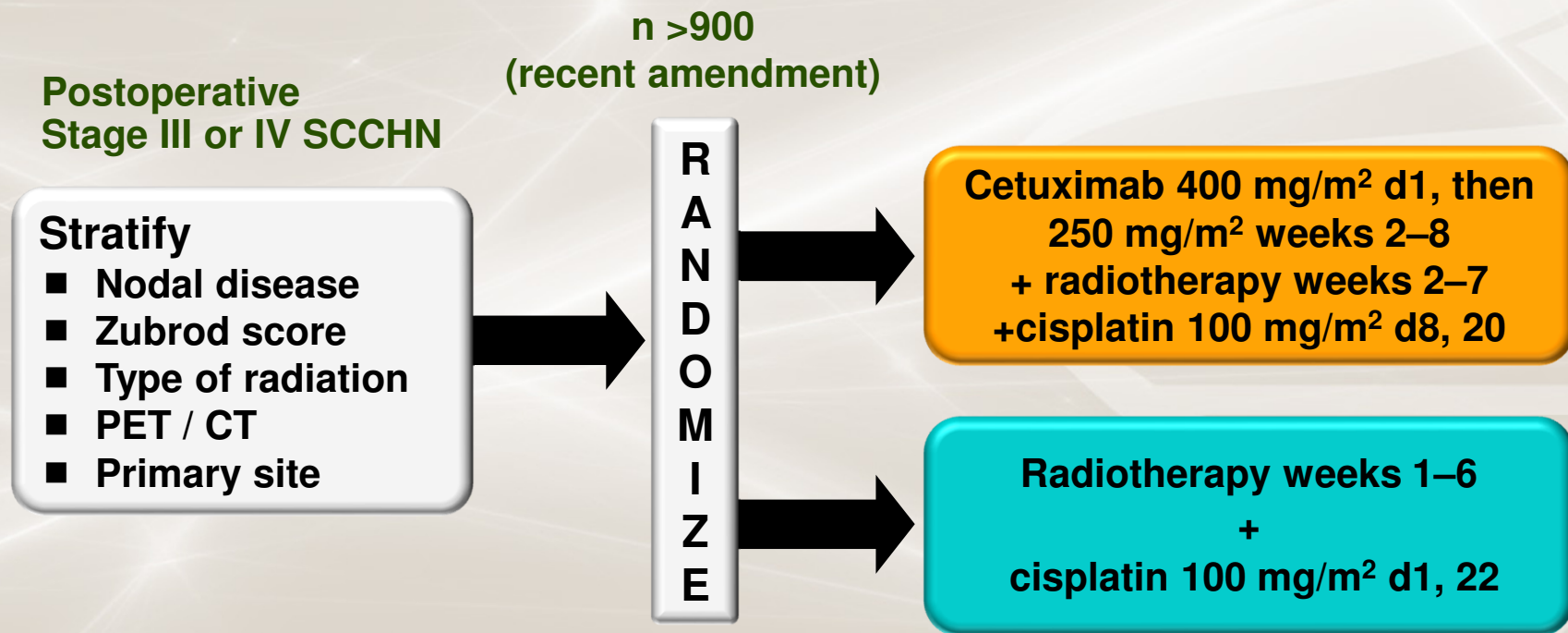


**CAN THE RASH BE USED TO DIRECT FURTHER THERAPY?**

\* Bonner JA, et al. Lancet Oncol; 11:21-28, 2010



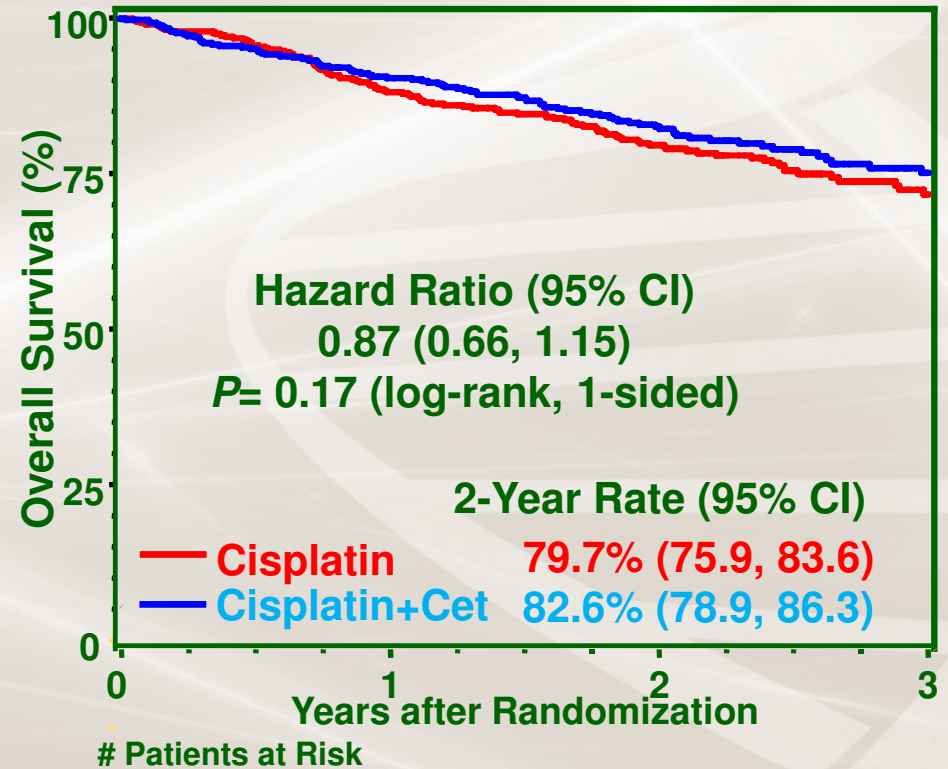
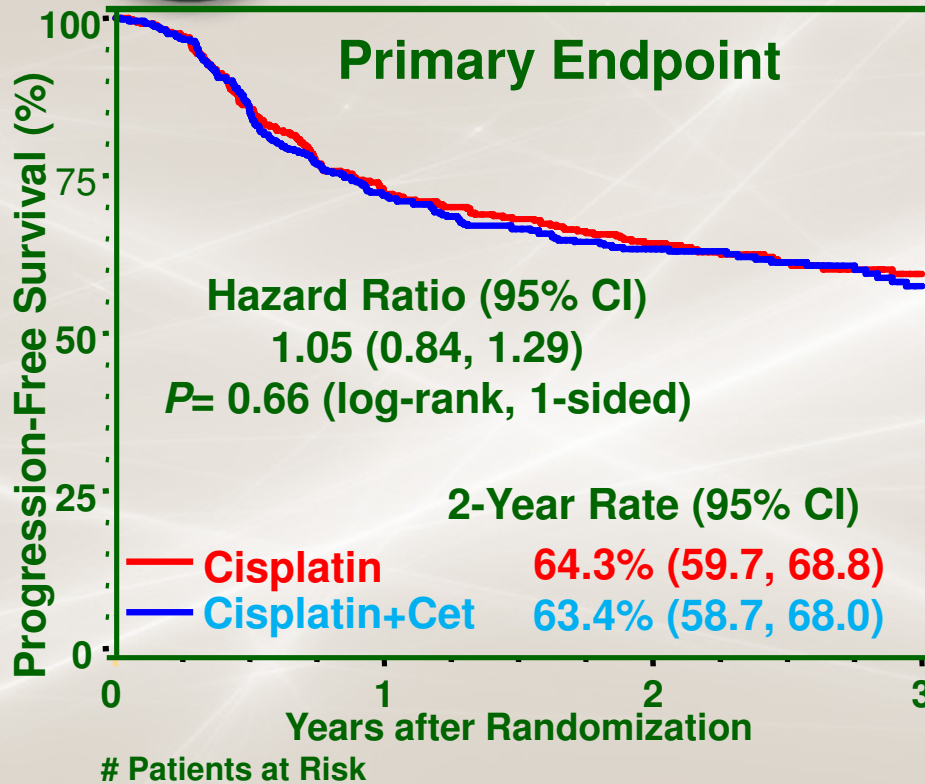
## RTOG 0522: Phase III Trial of Cisplatin Chemoradiation ± Cetuximab in Advanced SCCHN



Following chemoradiotherapy, patients with poor response were selected to proceed to surgery



## RTOG 0522: Progression-Free Survival & Overall Survival

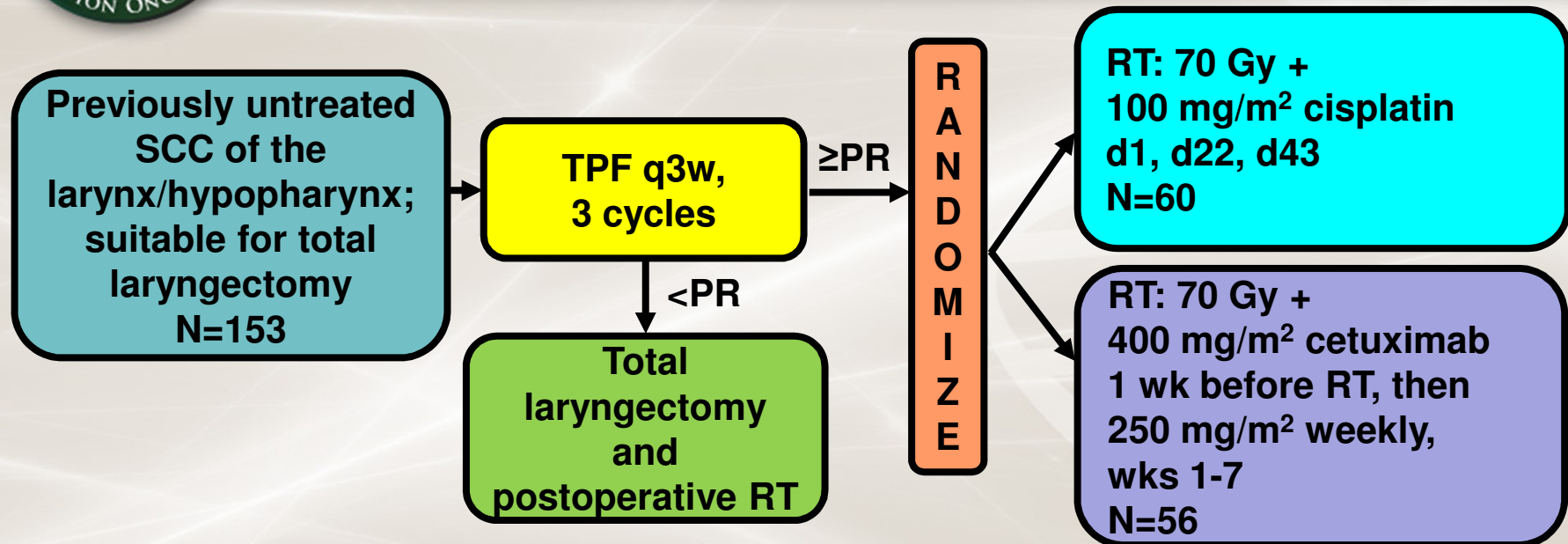


### Questions:

1. Would maintenance cetuximab help (included in Phase II)?
2. Would a taxane/cetuximab induction regimen help?



## Phase II TREMPLIN Study: Sequential CRT with Cetuximab for Larynx Preservation



T=75 mg/m<sup>2</sup> docetaxel on d1; P=75 mg/m<sup>2</sup> cisplatin on d1;  
F=750 mg/m<sup>2</sup> 5-FU on d1-5

- Primary endpoint: larynx preservation 3 mos post treatment
- Secondary endpoints: larynx function preservation and survival 18 mos post treatment, treatment tolerance, and salvage surgery



# TREMPLIN Results

Primary Endpoint (3 Mos Post Therapy)	Cisplatin (n=60)	Cetuximab (n=56)	P Value
Larynx preservation (larynx in place without tumor)	95%	93%	0.63
Secondary Endpoints (18 Mos Post Therapy)	Cisplatin (n=60)	Cetuximab (n=56)	P Value
Larynx function preservation (larynx in place without tumor, tracheotomy, or feeding tube)	87%	82%	0.68
OS	92%	89%	0.44

**Late toxicity and treatment-compromising acute toxicity are more common in the cisplatin arm**



# TREMP LIN Compliance & Safety

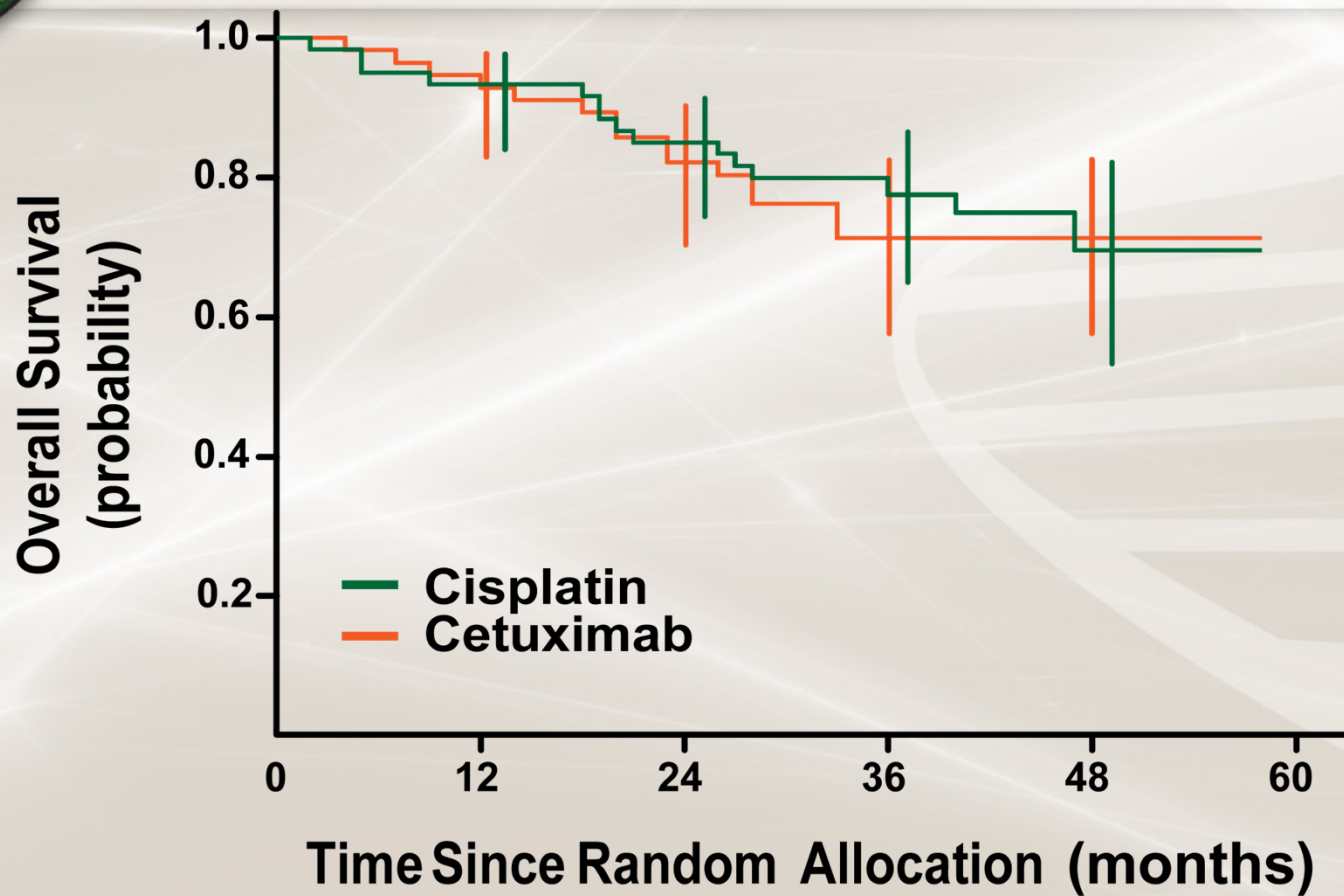
	Cisplatin/RT (n=58)	Cetuximab/RT (n=56)	
Acute Toxicities	Mucositis (Grade 3)	25 (43%)	24 (43%)
	Mucositis (Grade 4)	2 (3%)	1 (2%)
	In-field skin toxicity (Grade 3)	14 (24%)	29 (52%)
	In-field skin toxicity (Grade 4)	1 (2%)	3 (5%)
	Renal	9 (15%)	0
	Hematologic	8 (14%)	0
	Poor performance	7 (12%)	1 (1.7%)
	Infusion-related	0	3(5%)
	Protocol modified due to acute toxicity	33 (57%)	19 (34%)
Late Toxicities	Residual renal dysfunction at last evaluation (all Gr 1)	13 (22.4%)	0
	Mucosal (grade 3/4)	2 (3.5%)	1 (1.8%)
	Xerostomia (grade 3/4)	6 (10.3%)	5 (8.9%)
	Subcutaneous fibrosis (grade 3/4)	4 (7.0%)	1 (2.0%)
	Neuropathy (grade 3/4)	2 (3.4%)	0
	Laryngoesophageal (grade 3/4)	5 (8.6)	5 (9.0%)

- Lower incidence of select acute and late toxicities in cetuximab/RT arm
- Compliance: 87.5% of patients on cetuximab received  $\geq 4$  planned cycles of CRT versus 0.0% patients in the cisplatin arm

Lefevbre JL, *et al.* J Clin Oncol. 2013;31(7):853-859.



# TREMPLIN Study



Cisplatin	60	56 (0.93)	51 (0.84)	32 (0.78)	13 (0.70)
Cetuximab	56	52 (0.93)	45 (0.82)	25 (0.71)	11 (0.71)

Lefebvre JL, et al. *J Clin Oncol*. 2013, Jan 22.



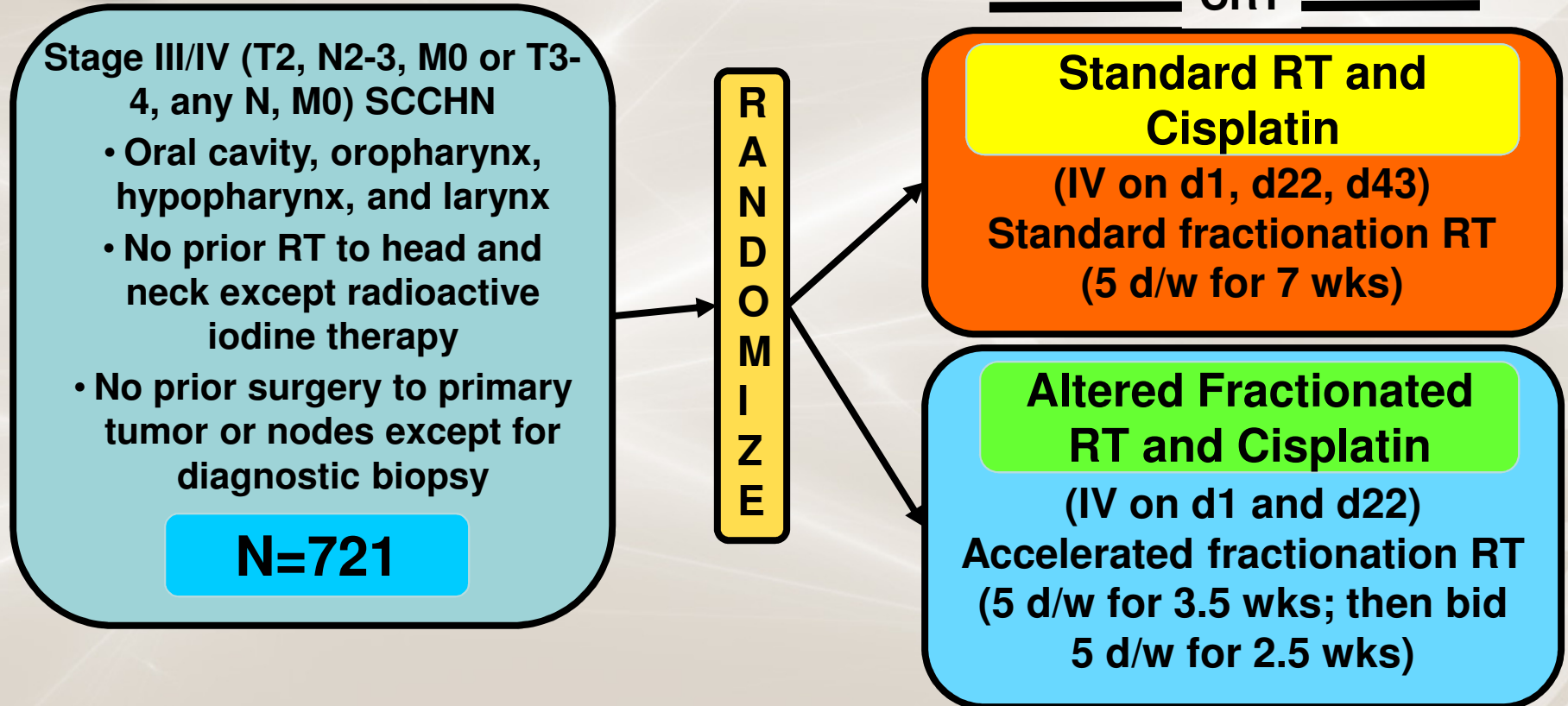


# **The Significance of HPV in Head and Neck Cancer**



## RTOG 0129 Phase III Trial: Concomitant CRT with Standard vs. Accelerated Fractionation RT in Advanced SCCHN

**CRT**

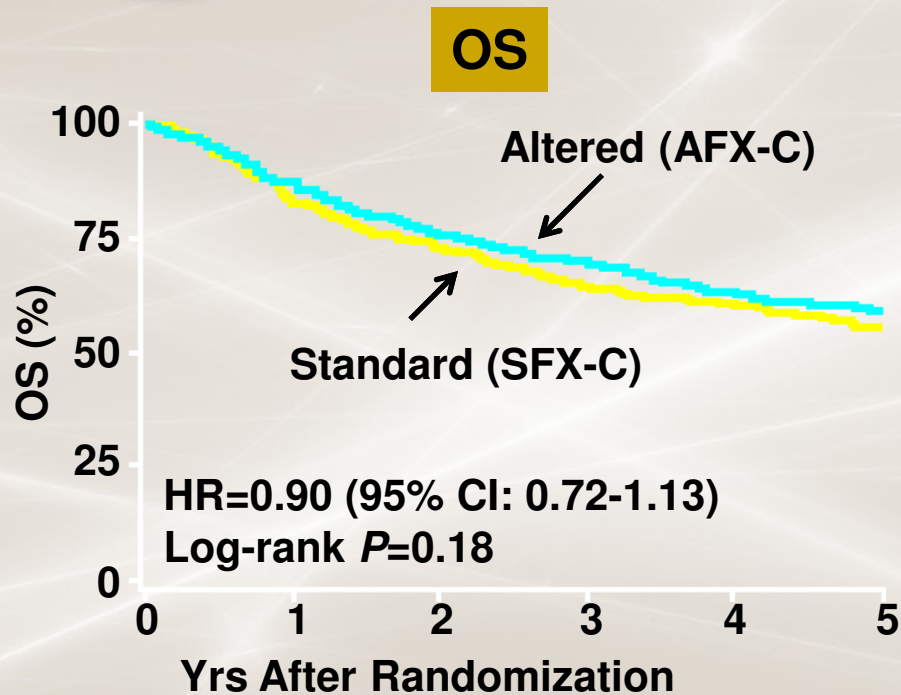


- Based on RTOG 99-14 trial demonstrating feasibility of accelerated fractionation RT plus cisplatin

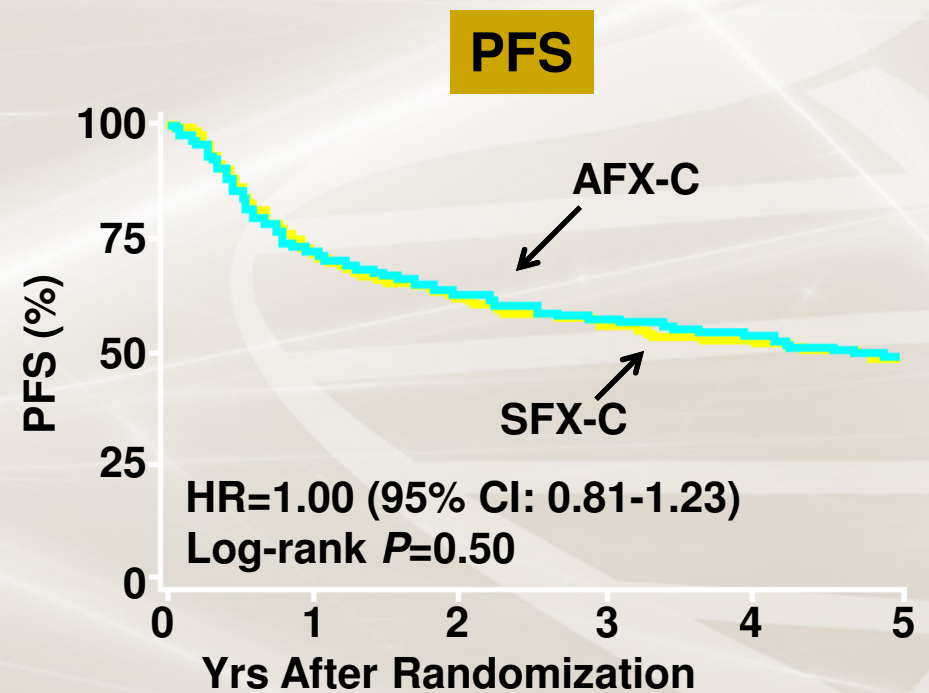
AFX-C=accelerated fractionation-cisplatin; SFX=standard fractionation.



# RTOG 0129 Results: OS and PFS



	3-Yr Estimate (95% CI)
SFX	64.3% (59.3-69.2)
AFX-C	70.3% (65.6-75.1)



	3-Yr Estimate (95% CI)
SFX	55.8% (50.6-60.9)
AFX-C	57.0% (51.8-62.1)

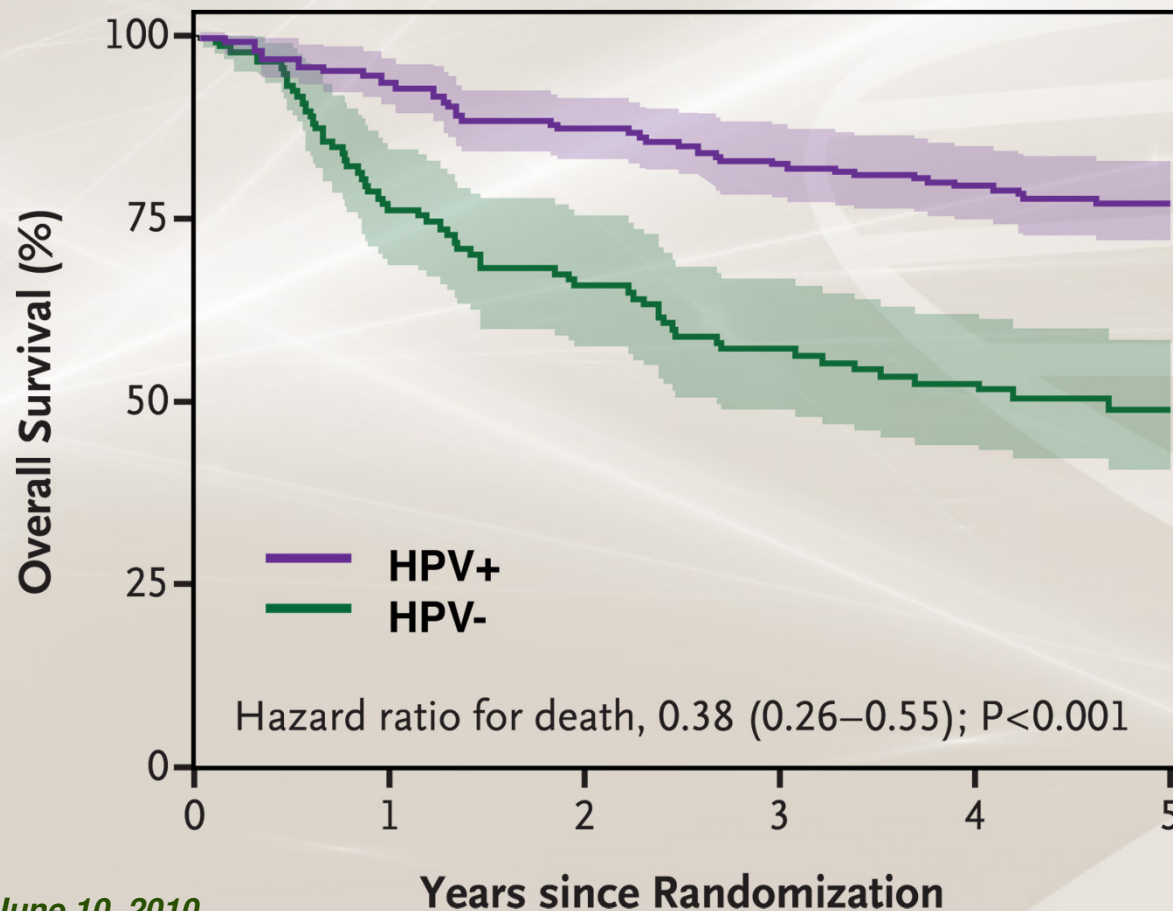
- No difference in survival between the 2 arms

Ang. *NEJM*; 363(1):24, 2010.



## Locoregionally Advanced Oropharyngeal Cancer Treated with Definitive Radiotherapy (Conventional or Accelerated) and Cisplatin: Significance of HPV

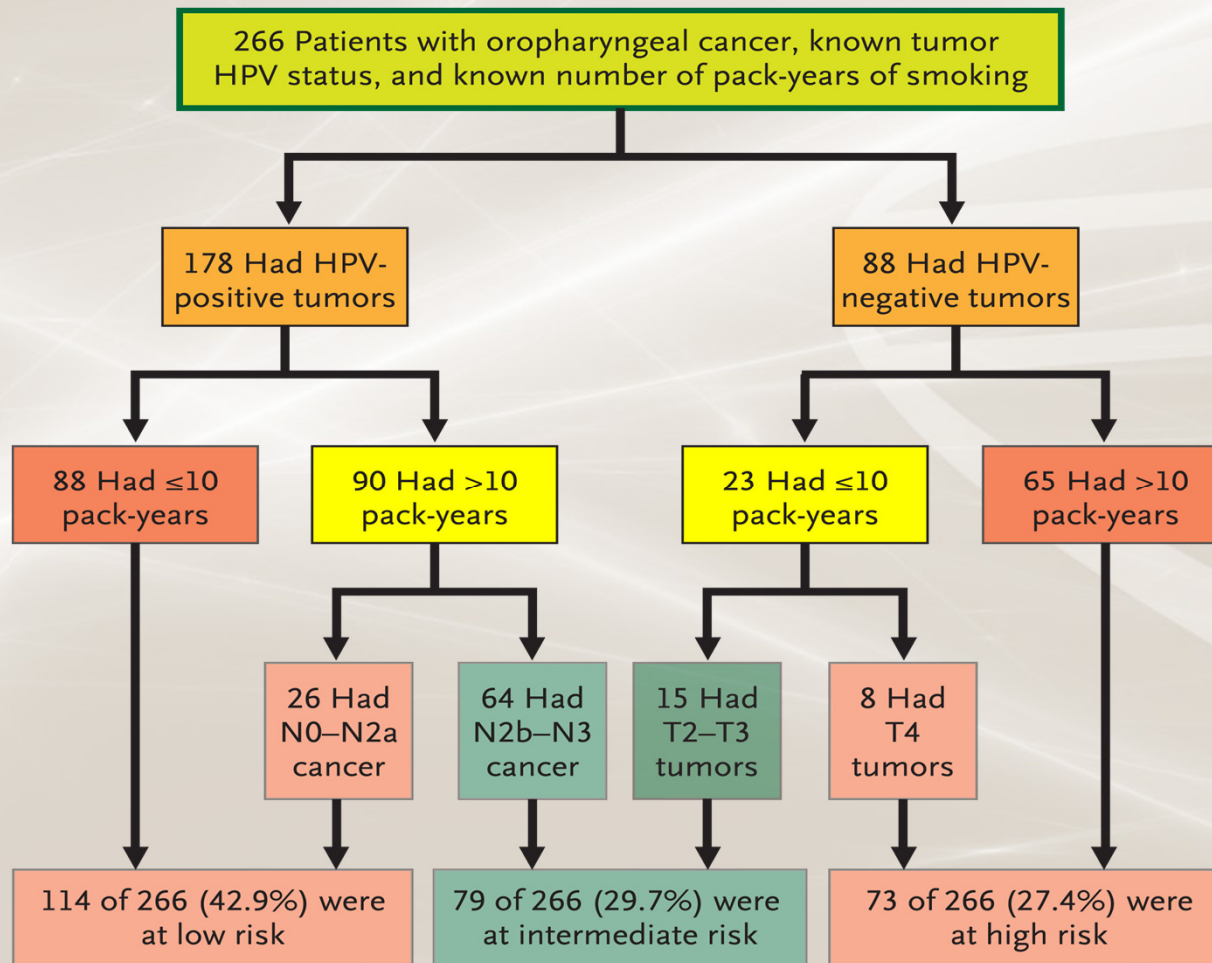
RTOG 0129



Ang KK, NEJM, June 10, 2010

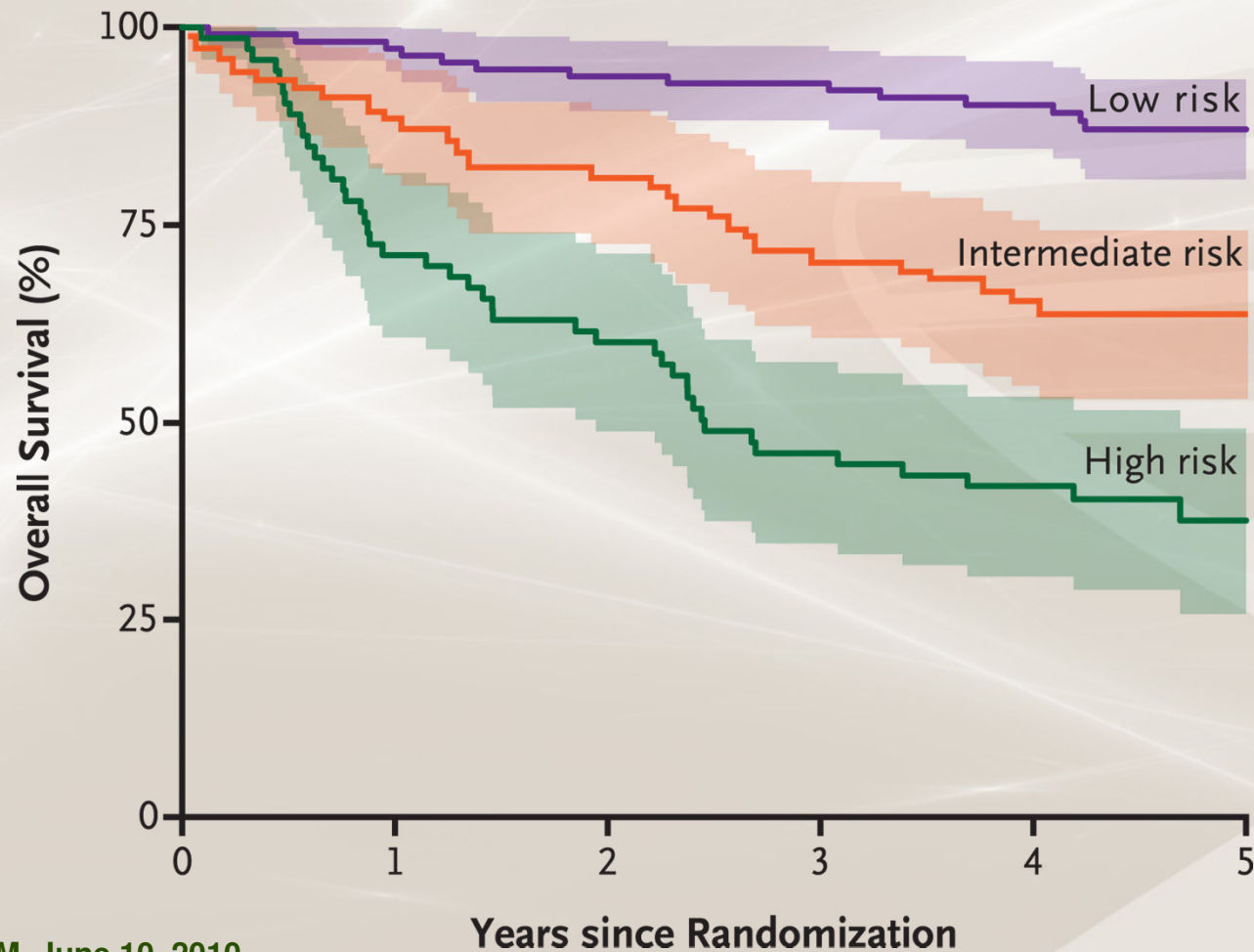


# Recursive-Partitioning Analysis to Identify Prognostic Factors (Key Factors: HPV, Smoking, N Stage)





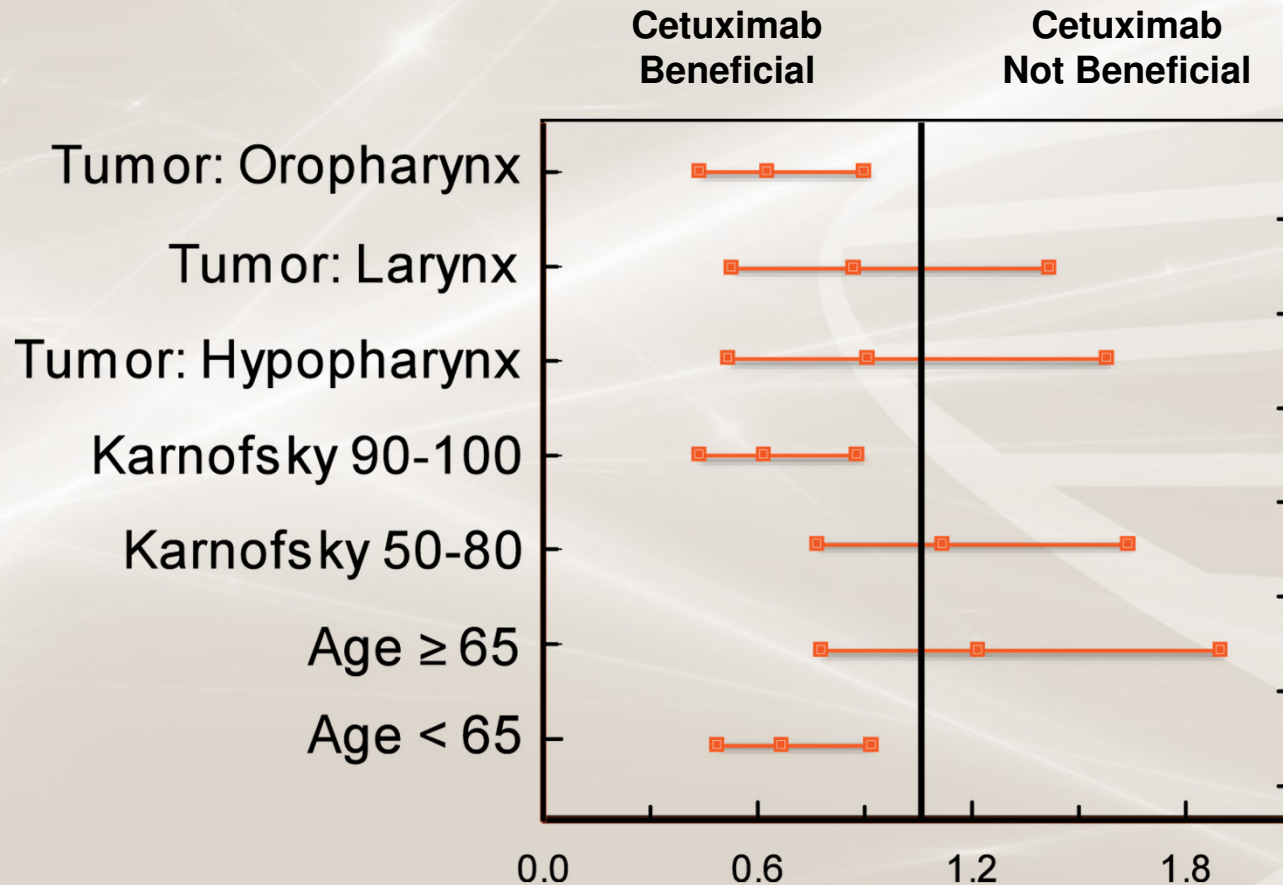
## Survival for the Three Risk Groups Determined by Recursive Partitioning



Ang KK, NEJM, June 10, 2010



# Radiation vs. Cetuximab and Radiation: Forest Plot Implications for HPV





# Human Papillomavirus (HPV)

**Association of human papillomavirus (HPV)/p16 status with efficacy and safety in patients with oropharyngeal cancer (OPC) in the phase 3 radiotherapy (RT)/cetuximab registration trial**

**J. A. Bonner<sup>1</sup>, P.M. Harari<sup>2</sup>, J. Giralt<sup>3</sup>, D. Bell<sup>4</sup>, D. Raben<sup>5</sup>,  
J. Liu<sup>6</sup>, J. Schulten<sup>7</sup>, K. Ang<sup>4</sup>, D. I. Rosenthal<sup>4</sup>**

<sup>1</sup>University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL, USA; <sup>2</sup>University of Wisconsin, Madison, WI, USA; <sup>3</sup>Hospital Vall d'Hebron, Barcelona, Spain; <sup>4</sup>The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>5</sup>University of Colorado School of Medicine, Aurora, CO, USA; <sup>6</sup>Merck Serono, Beijing, China; <sup>7</sup>Merck KGaA, Darmstadt, Germany





# Methods

- **p16 IHC status is a useful surrogate marker of HPV status in oropharyngeal squamous cell carcinoma<sup>1</sup>**
- **We used immunohistochemical detection of p16INK4A (p16) to determine HPV status (CINtec® Histology Kit)**
  - **p16 positivity was defined as strong and diffuse nuclear staining in >70% of tumor cells**

<sup>1</sup> Gillison ML *et al.* J Clin Oncol 2012;30:2102-11



# Statistical analyses

- Rates for LRC, PFS, and OS by treatment arm and p16-positive status were estimated by the Kaplan–Meier method
- A Cox proportional hazards model, with treatment arm and p16 status as explanatory variables, was used to estimate HRs (95%CI) and to examine the interaction of treatment and p16 status
  - Proportional hazards assumptions were examined by means of log-log survival plots and Schoenfeld residuals
- Of the 424 patients, 311 were p16 evaluable and 182 oropharyngeal patients were p16 evaluable

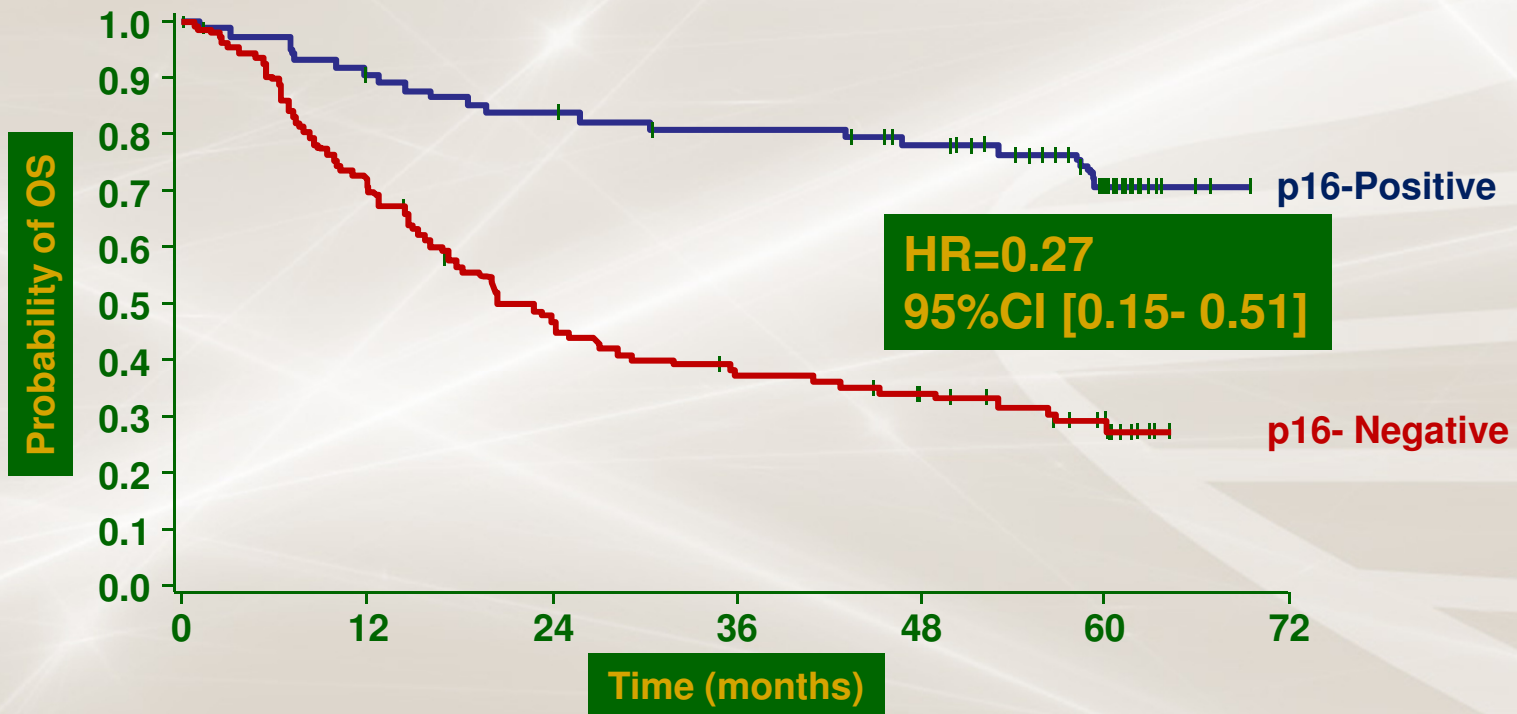


## Characteristics of the p16 evaluable OPC population were well balanced between the groups

Parameter		OPC	OPC	OPC		OPC	
		all	p16 evaluable	p16-positive		p16-negative	
		n=253 (%)	n=182 (%)	RT + cet n=41 (%)	RT n=34 (%)	RT + cet n=43 (%)	RT n=64 (%)
Sex	Male	81	79	83	82	77	77
Age	<65 years	77	75	81	74	81	67
Site of primary tumor	Oropharynx	100	100	100	100	100	100
Karnofsky score	>80	73	76	90	82	65	70
Nodal stage	N0	11	13	7	9	14	17
Tumor stage	T1-3	72	71	83	88	51	69
EGFR expression: % positive cells	≤50%	46	59	71	62	51	55
	>50%	32	40	27	38	49	44
	Unknown	22	1	2	0	0	2
Radiation fractionation	Concomitant boost	58	65	78	71	56	59
	Once-daily	23	21	2	9	35	30
	Twice-daily	17	13	17	21	9	9
Region	United States	64	64	95	91	47	41



# p16 status is a strong prognostic factor in locally advanced OPC: OS (n = 182)



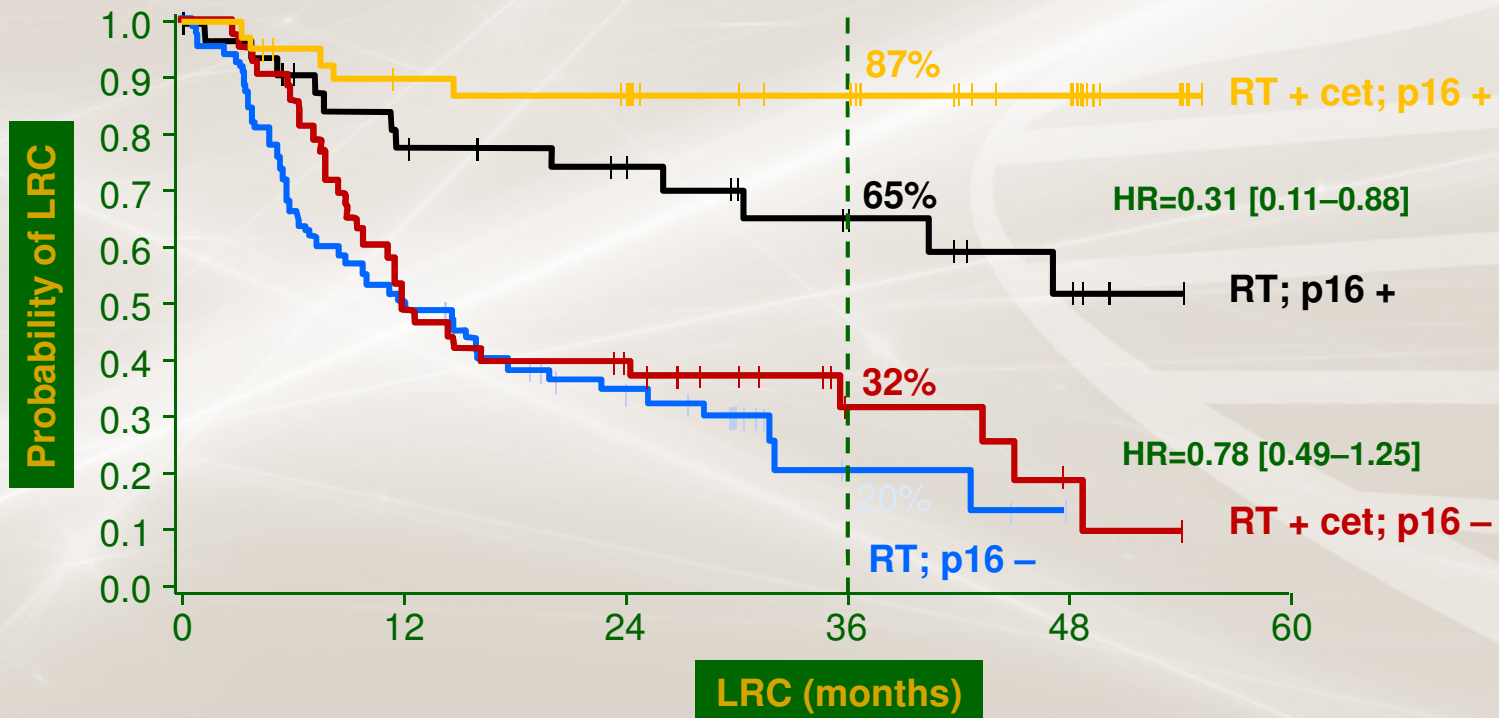
No. of patients at risk (n=182)

P16 –Negative	107	76	49	37	31	19	0
P16- Positive	75	67	61	57	52	27	0



# LRC in OPC subpopulation according to p16 status and treatment effect of RT + cetuximab vs. RT alone

**LRC interaction test p=NS**



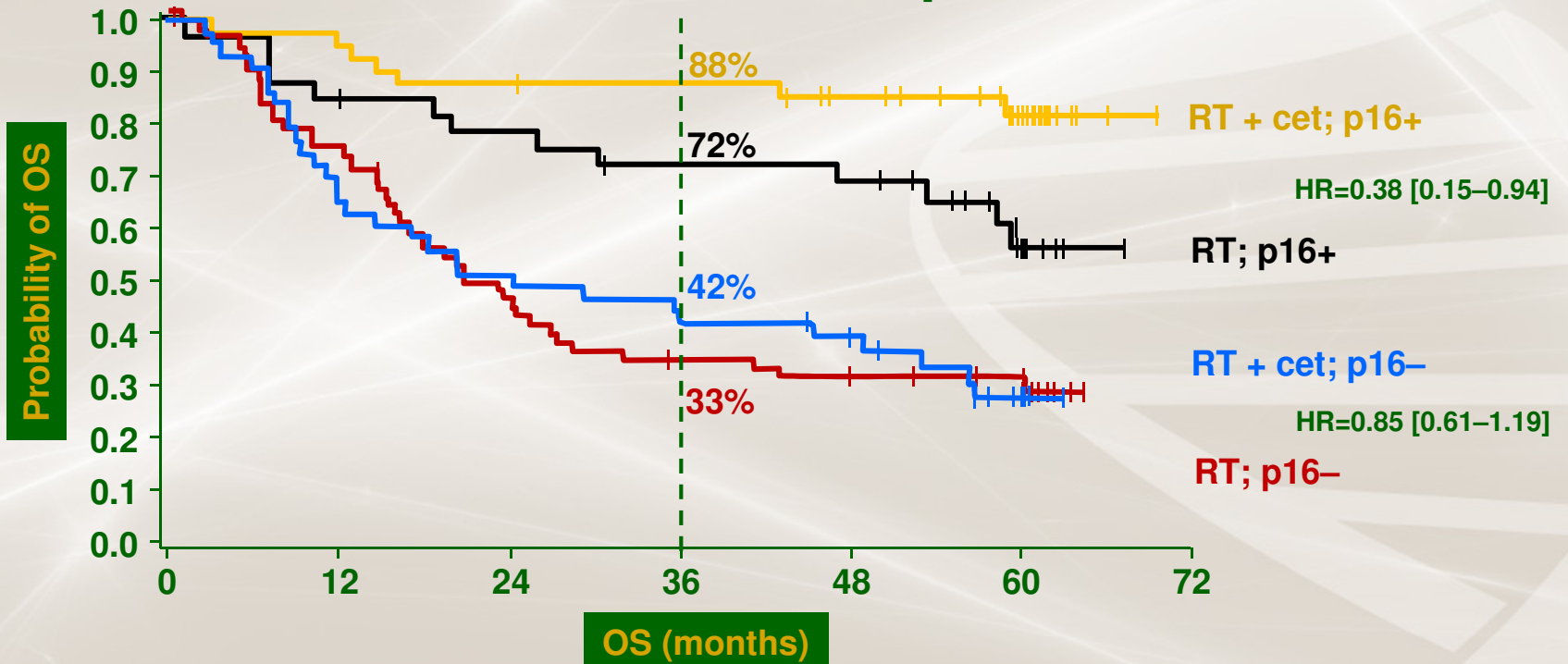
No. at risk OPC p16 evaluable (n=182)

RT p16 negative	64	31	17	3	0	0
RT p16 positive	34	24	20	12	6	0
RT + cet p16 negative	43	21	16	6	2	0
RT + cet p16 positive	41	33	30	21	12	0



# OS in OPC subpopulation according to p16 status and treatment effect of RT + cetuximab vs. RT alone

OS interaction test p=NS



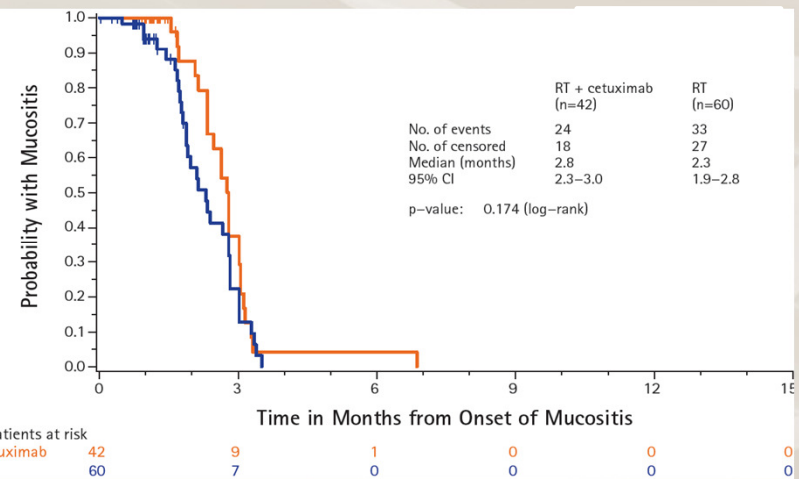
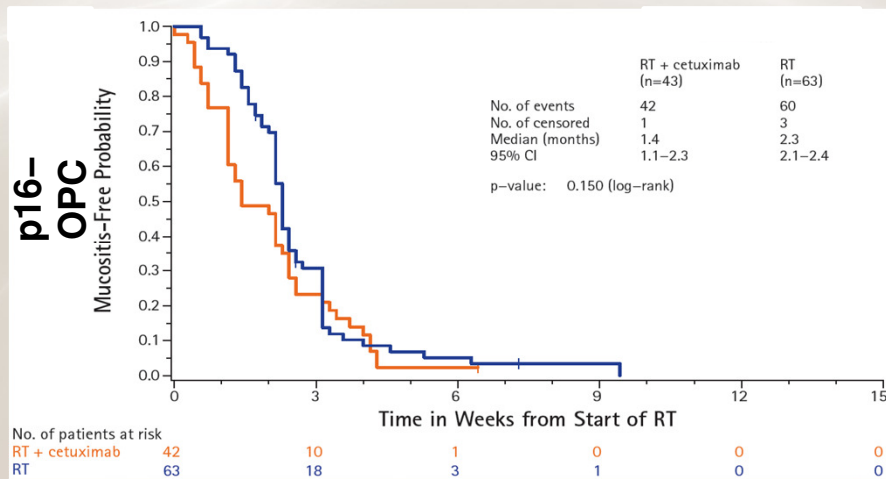
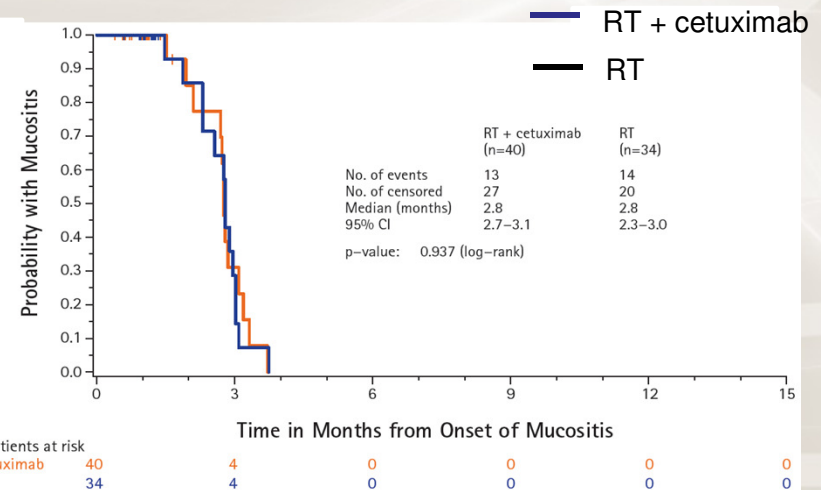
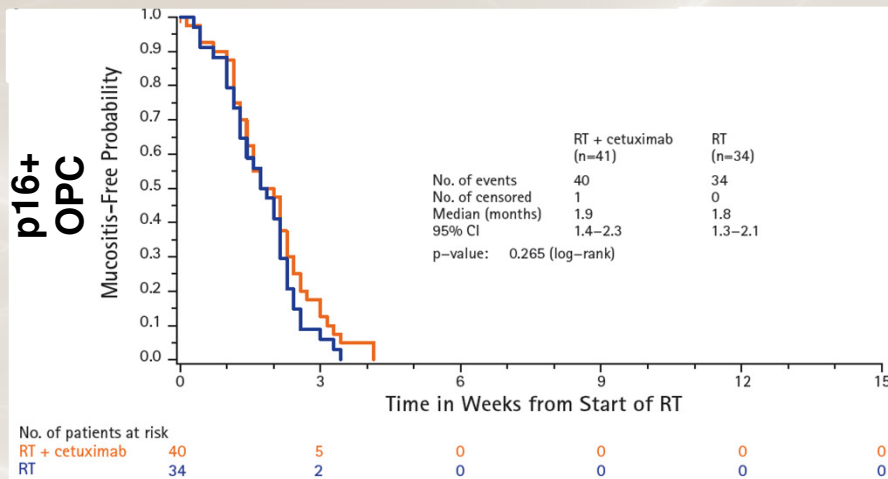
No. at risk OPC p16 evaluable (n=182)							
RT p16 negative	64	47	27	19	16	13	0
RT p16 positive	34	28	25	22	21	10	0
RT + cet p16 negative	43	29	22	18	15	6	0
RT + cet p16 positive	41	39	36	35	31	17	0



# Adding cetuximab to RT did not alter the time to onset or duration of mucositis in patients with p16+ or p16- OPC<sup>a</sup>

Time to Onset

Duration

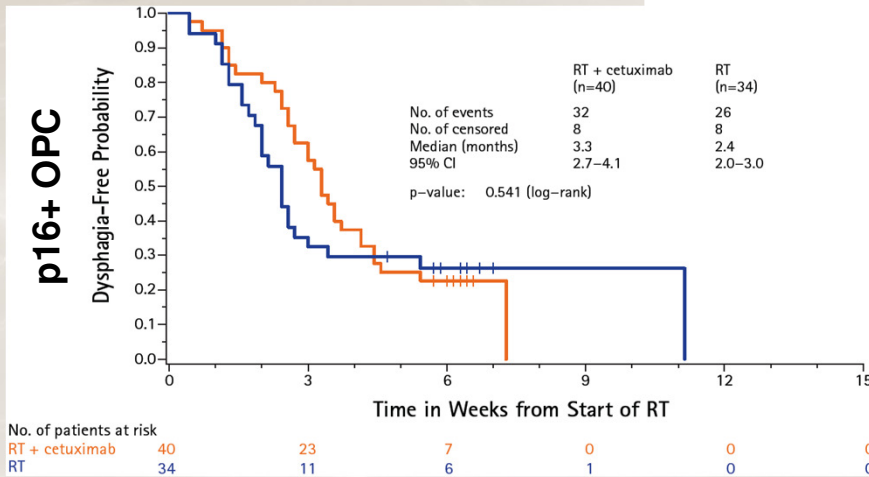


<sup>a</sup> All grades of mucositis were considered  
ESTRO / ICHNO, Nice, February 2015

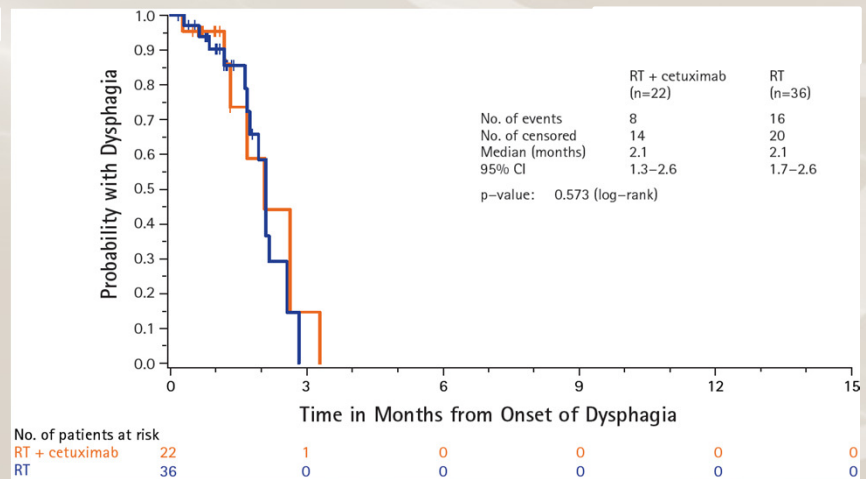
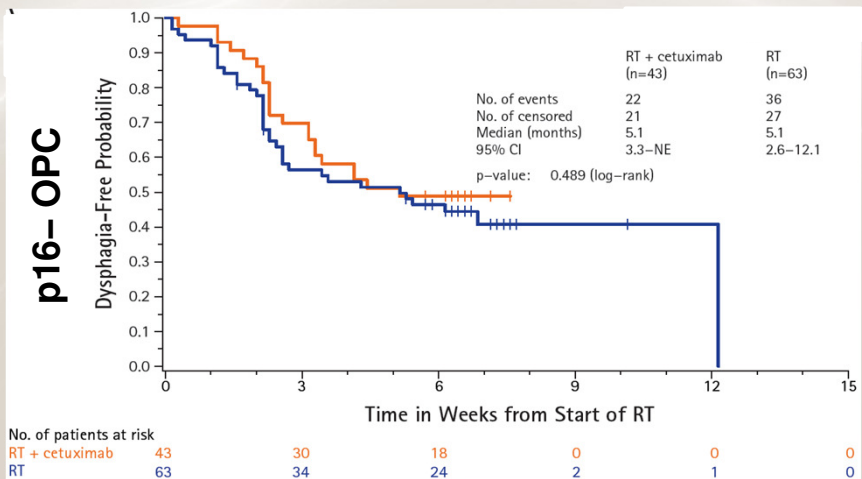
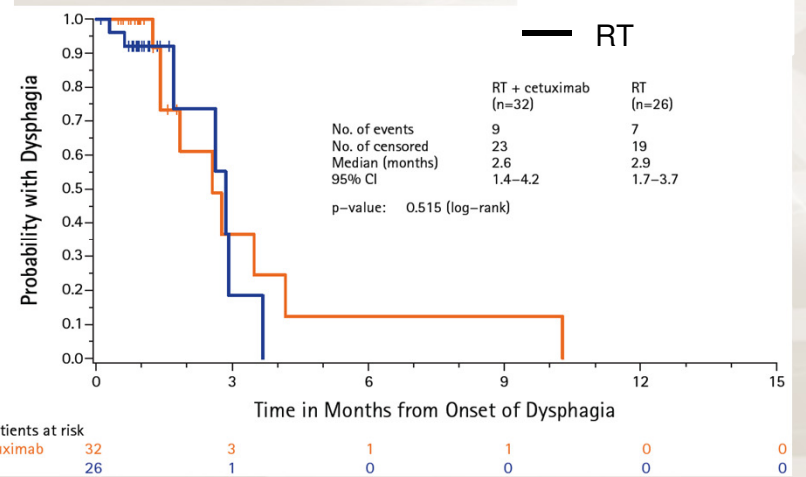


# Adding cetuximab to RT did not alter the time to onset or duration of dysphagia in patients with p16+ or p16- OPC<sup>a</sup>

**Time to Onset**



**Duration**



<sup>a</sup> All grades of dysphagia were considered  
ESTRO / ICHNO, Nice, February 2015

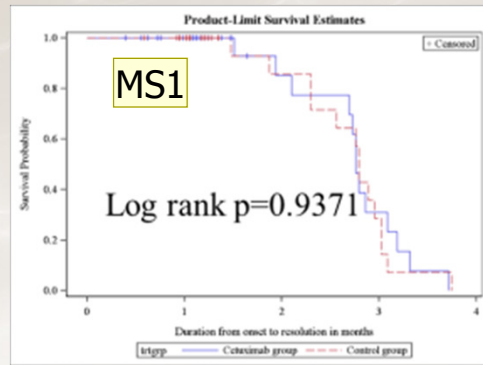




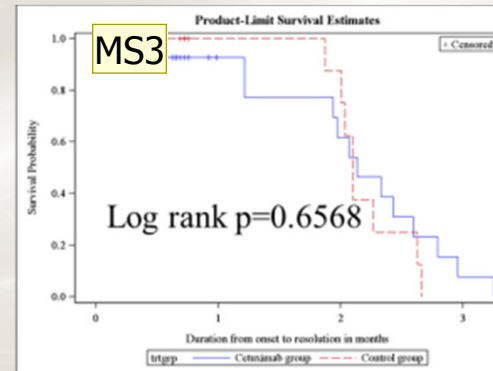
# The association of the addition of cetuximab to RT with grade 3/4 mucositis in patients with p16+ and p16- OPC

p16+ OPC

Time to Onset

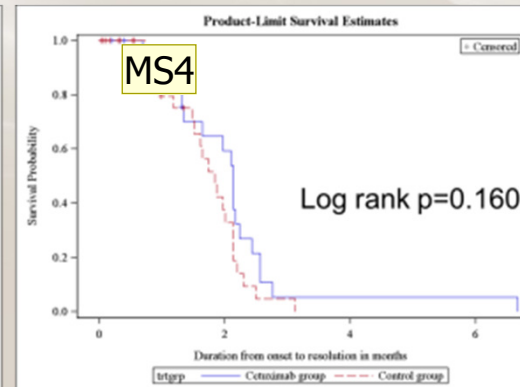
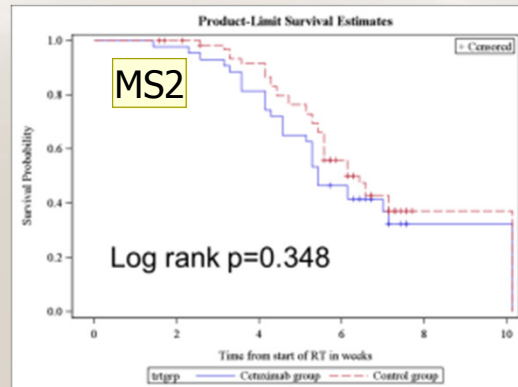


Duration



**BLUE =  
Cetuximab  
and RT**

p16- OPC



**RED =  
RT Alone**

## Slide 33

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**MS1** Note to authors: in this figure, the axes' titles will read as follows:

X-axis: Time in weeks from start of RT; Y-axis: mucositis -free probability

Meghan Sullivan, 8/14/2014

**MS2** Note to authors: in this figure, the axes' titles will read as follows:

X-axis: Time in weeks from start of RT; Y-axis: mucositis -free probability

Meghan Sullivan, 8/14/2014

**MS3** Note to authors: in this figure, the axes' titles will read as follows:

X-axis: Time in months from onset of mucositis; Y-axis: Probability with mucositis

Meghan Sullivan, 8/14/2014

**MS4** Note to authors: in this figure, the axes' titles will read as follows:

X-axis: Time in months from onset of mucositis; Y-axis: Probability with mucositis

Meghan Sullivan, 8/14/2014

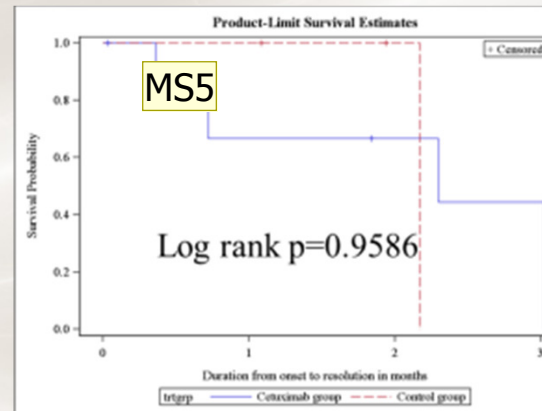
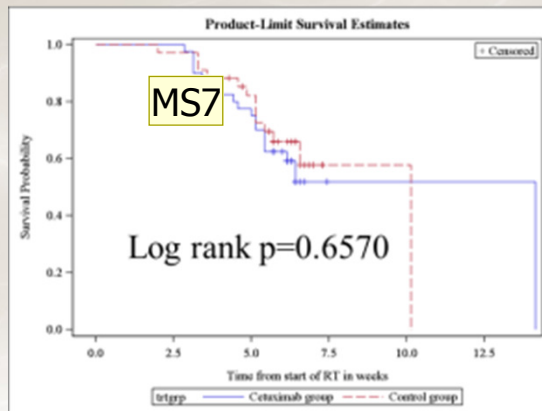


# The association of the addition of cetuximab to RT with grade 3/4 dysphagia in patients with p16+ and p16- OPC

Time to Onset

Duration

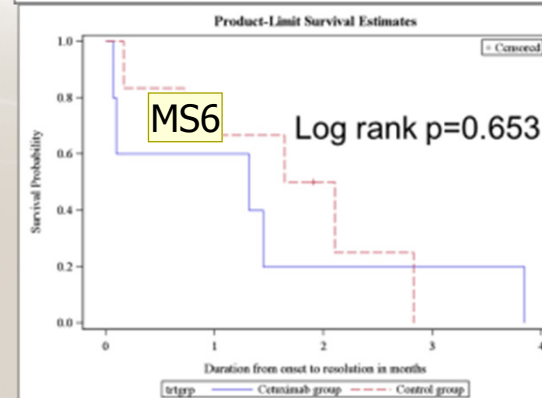
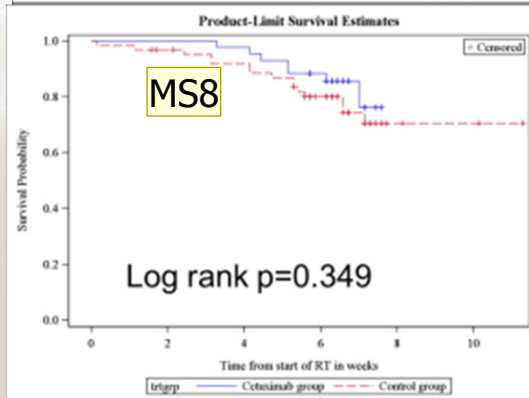
p16+ OPC



**BLUE =  
Cetuximab  
and RT**

**RED =  
RT Alone**

p16- OPC



## Slide 34

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**MS5** Note to authors: in this figure, the axes' titles will read as follows:

X-axis: Time in months from onset of dysphagia; Y-axis: Probability with dysphagia

Meghan Sullivan, 8/14/2014

**MS6** Note to authors: in this figure, the axes' titles will read as follows:

X-axis: Time in months from onset of dysphagia; Y-axis: Probability with dysphagia

Meghan Sullivan, 8/14/2014

**MS7** Note to authors: in this figure, the axes' titles will read as follows:

X-axis: Time in weeks from start of RT; Y-axis: dysphagia -free probability

Meghan Sullivan, 8/14/2014

**MS8** Note to authors: in this figure, the axes' titles will read as follows:

X-axis: Time in weeks from start of RT; Y-axis: dysphagia -free probability

Meghan Sullivan, 8/14/2014

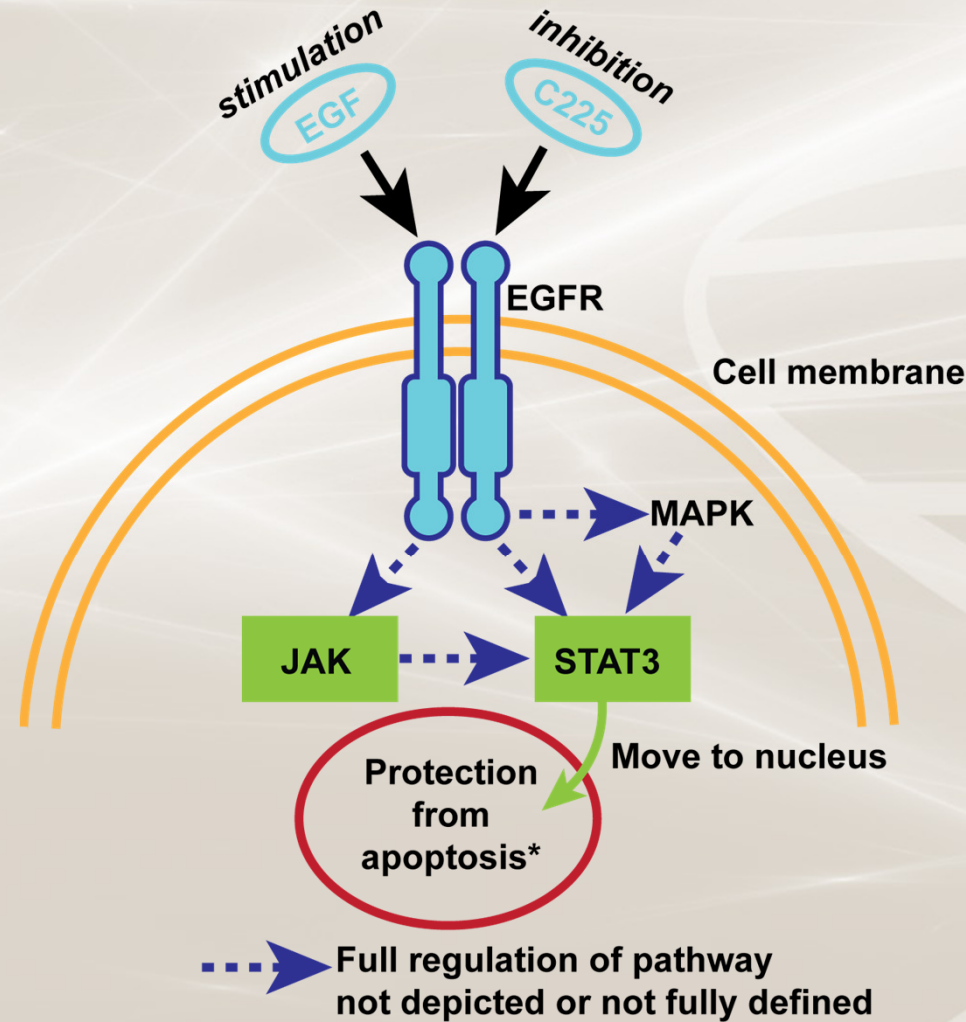


# Be aware of the whole iceberg





# Other Potential Clinical Targets Downstream of EGFR, STAT-3

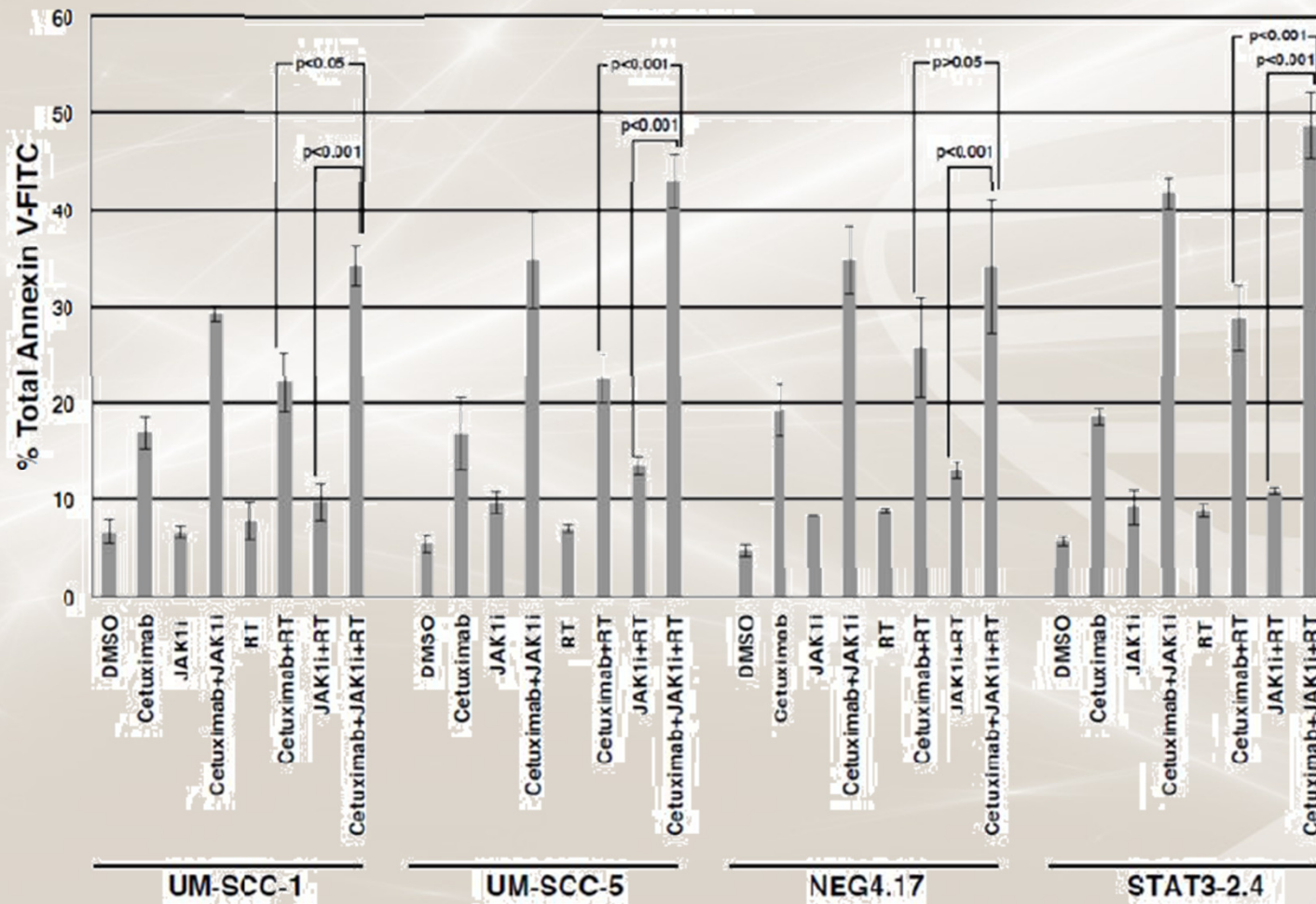


\* Facilitate proliferation



# Apoptosis

## RT + Cetuximab + JAK1 Inhibitor





# Conclusions

- OS and LRC results for RT + cetuximab vs RT in both p16+/HPV+ and p16+/HPV- OPC resemble results of a prior p16 subgroup analysis, which suggested that both patients with p16+ and patients with p16- OPC benefited when cetuximab was added to RT<sup>1</sup>
- Regardless of HPV status, patients with p16+ OPC have a favorable prognosis
- The addition of cetuximab to RT did not alter the time to onset or duration of resolution of mucositis or dysphagia in patients with OPC, irrespective of p16 status
- The present findings should be regarded as hypothesis generating and provide an impetus for future studies with larger sample sizes



# Thank You!

