

# *Head and Neck Cancer:*

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# Predictive Biomarkers: HPV

- **Abstract 6003: Survival Outcomes By HPV Status In Oropharyngeal Cancer In RTOG 0129, Gillison, et al**
- **Abstract 6004: Prognostic Significance Of HPV And P16 Status In Patients With Oropharyngeal Cancer Treated On A Large International Phase III Trial, Rischin, et al**
- **Abstract 6001: The Implication of Tobacco Usage in the Development of Distant Metastases & Tumor Recurrence in Patients with HPV (+) Squamous Cell Cancers of the Oropharynx : F Worden et al**

# Predictive Biomarkers: Other

- **Abstract 6000: Mass spectrometry profile as a predictor of overall survival benefit after treatment with epidermal growth factor receptor inhibitors in head and neck squamous cell carcinoma**
- **Abstract 6005: Biomarker Potential Of *EGFR* Gene Copy Number In The Phase III EXTREME Study: Platinum-based CT  $\pm$  Cetuximab In R/M SCCHN, Licitra, et al**

**Abstract 6003**

**Survival Outcomes By HPV Status In  
Oropharyngeal Cancer In RTOG 0129**

**Gillison, et al**

# Results Of Laboratory Analysis

- 433 (60%) Of 721 Had Oropharynx Primary
- 323 (75%) Of 433 Had HPV Determination
- 206 (64%) Of 323 Were HPV-positive
- 198 (96%) Of 206 Were HPV16-positive

	<b>P16-positive</b>	<b>P16-negative</b>
<b>HPV-positive</b>	<b>192 (96%)</b>	<b>7 (4%)</b>
<b>HPV-negative</b>	<b>22 (19%)</b>	<b>94 (81%)</b>

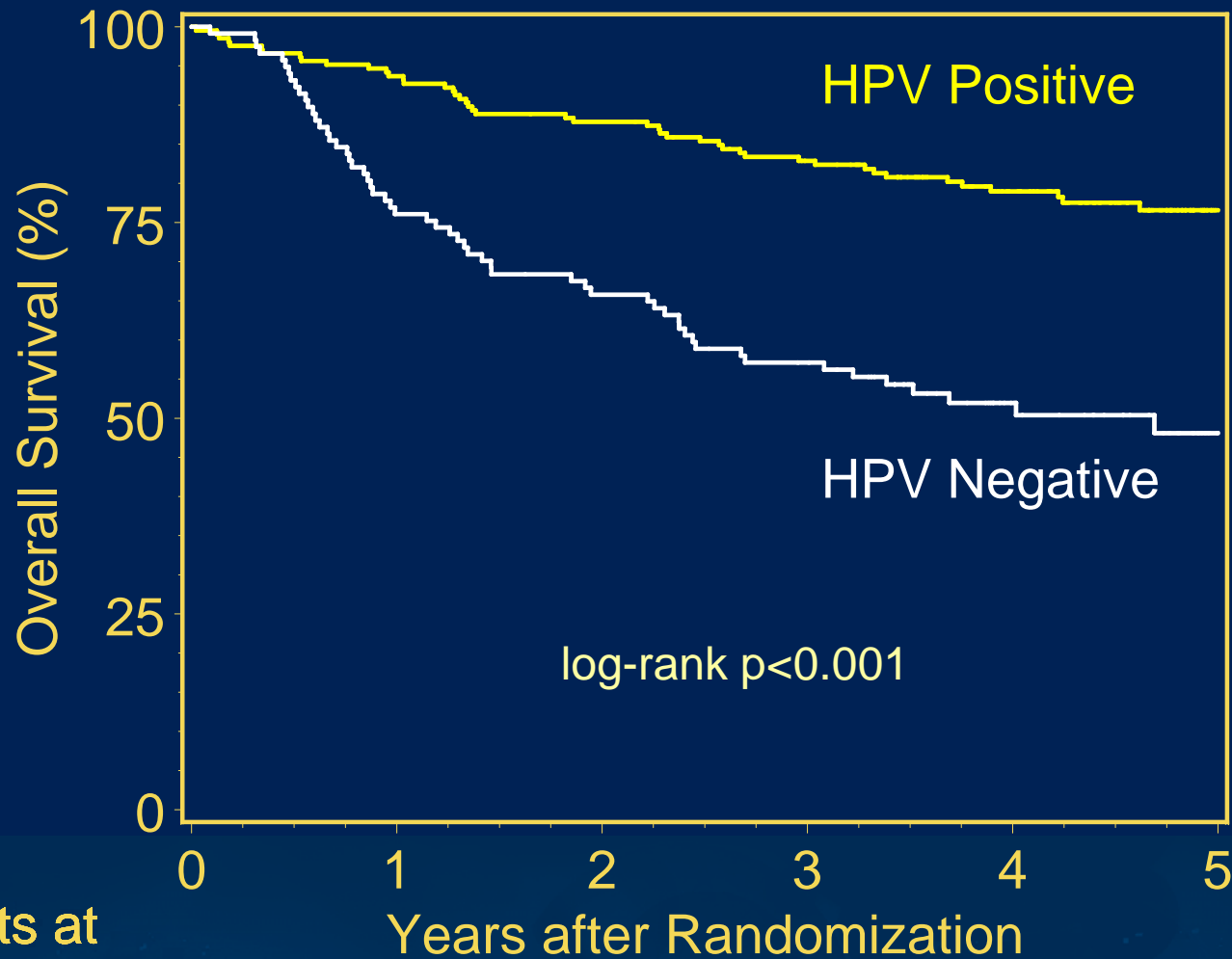
Kappa = 0.80: 95%CI 0.73-0.87

# Two-year Outcomes

Variable	HPV-Positive (%)	HPV-Negative (%)	P-value
Overall Survival	87.9	65.8	<0.001
<i>Progression-free Survival</i>	<i>71.8</i>	<i>50.4</i>	<i>&lt;0.001</i>
Local-regional Failure	13.6	24.8	0.004
Distant Metastases	9.7	12.9	0.26
Second Primary Tumor	3.9	11.1	0.01
Aerodigestive SPT	2.9	7.7	0.04

Gillison, et al

# Overall Survival by HPV Status



Patients at Risk

HPV Pos.	206	193	180	162	119	30
HPV Neg.	117	89	76	64	34	9

5-year Difference 29%; 95% CI:12-45

Gillison, et al

# Patient Characteristics By HPV Status

Variable	HPV-Positive	HPV-Negative	P-value
Treatment, SFX (%)	51.5	50.4	0.86
Age, Years (Median)	53.5	57.0	0.02
Race, White (%)	92.2	75.2	<0.001
Zubrod PS, 0 (%)	68.4	56.4	0.03
AJCC Stage, IV (%)	87.9	83.8	0.30
T Stage, 2-3 (%)	75.2	60.7	0.008
N Stage, N0-2a (%)	30.1	38.5	0.14
Pack-years, < 20 (%)	51.0	22.2	<0.001

Gillison, et al

# Tumor HPV, Smoking Status, and OS

	<b>Hazard Ratio</b>	<b>95% CI</b>
HPV-positive, <20 pack-years	1.00	-
HPV-positive, ≥ 20 pack-years	1.91	1.20 - 3.05
HPV-negative, < 20 pack-years	2.25	1.44 - 3.50
HPV-negative, ≥ 20 pack-years	4.30	2.40 - 7.71

Adjusted for age, race, T stage, N stage, and treatment assignment

**Gillison, et al**

## **Abstract 6004**

**Prognostic Significance Of HPV And P16 Status In  
Patients With Oropharyngeal Cancer Treated On A  
Large International Phase III Trial**

**Rischin, et al**

# Results of Laboratory Analysis

## Head Start Trial

Total Entered Into the Study	853
Total Oropharynx	465
Total Slides Available	228
Total Minimal Compliance (60-70 cGy)	208
HPV Tested	195
<i>Positive</i>	54 (28%)
P16 Tested	186
<i>Positive</i>	107(58%)

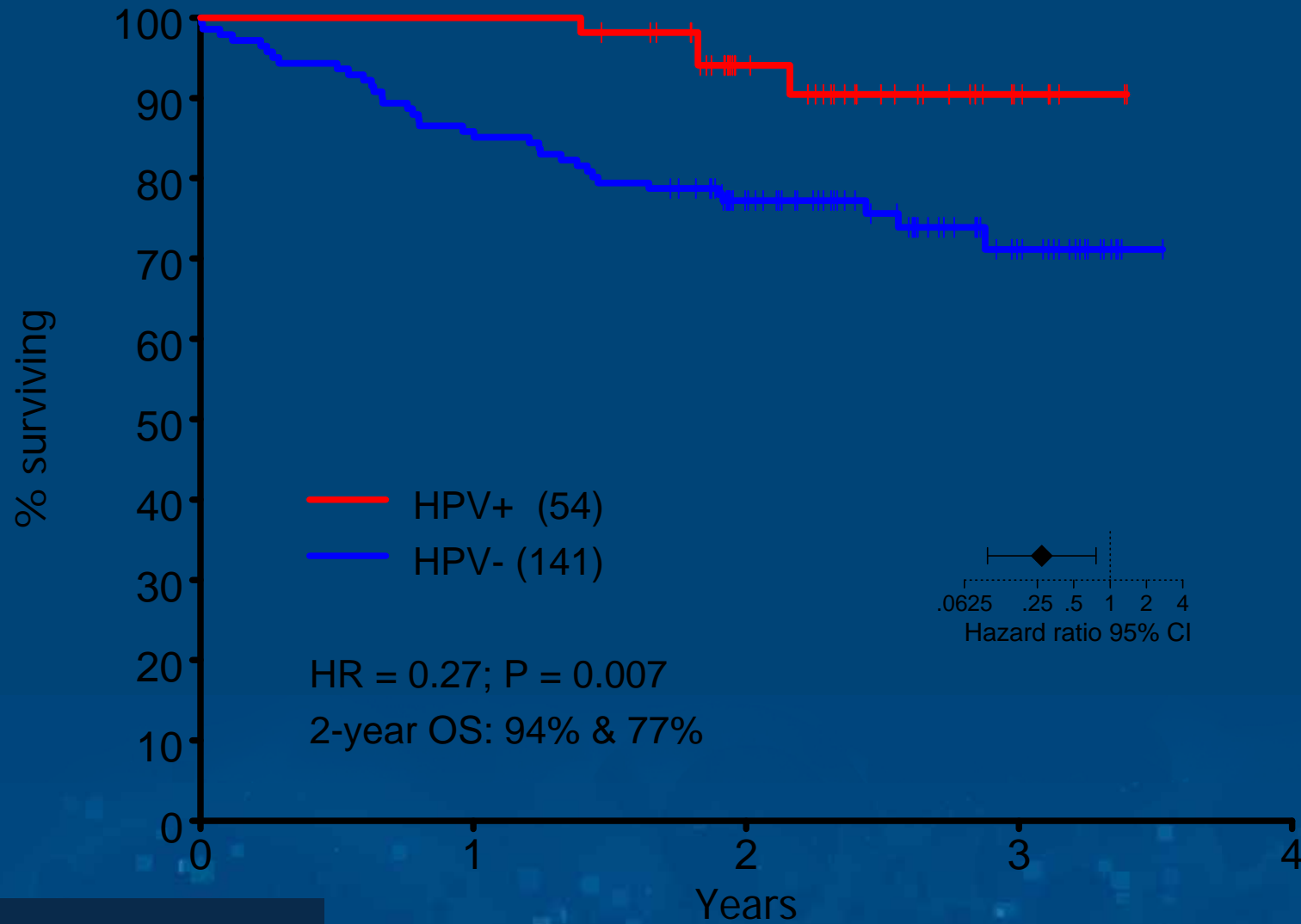
# Patient Characteristics

	<b>HPV -</b>	<b>HPV+</b>	<b>P16 -</b>	<b>P16 +</b>
<b>Male</b>	83%	91%	81%	87%
<b>Median Age</b>	56	55	58	54
<b>T Stage 3-4</b>	75%	74%	84%	63%*
<b>N Stage 2-3</b>	73%	87%*	65%	86%*
<b>ECOG PS 0</b>	65%	76%	57%	79%*
<b>Current Smoker</b>	37%	15%*	45%	15%*

\* P < 0.05

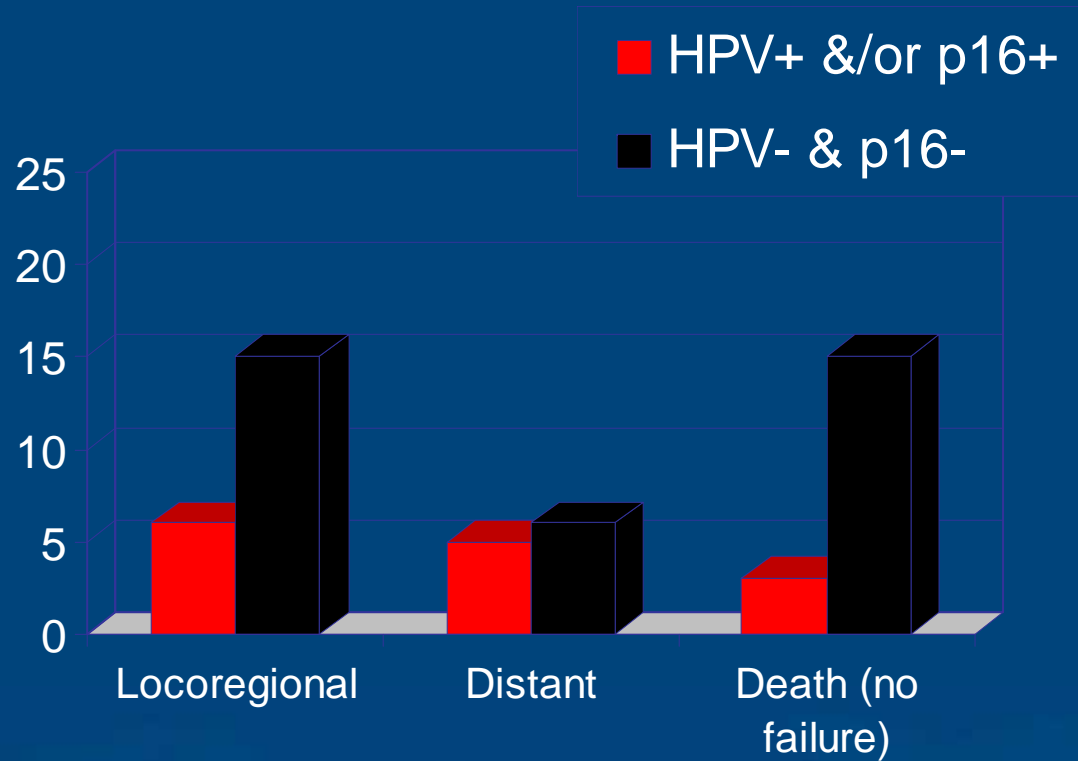
**Rischin, et al**

# Overall Survival – HPV+ / HPV-



# Site of First Failure

percentage  
of patients

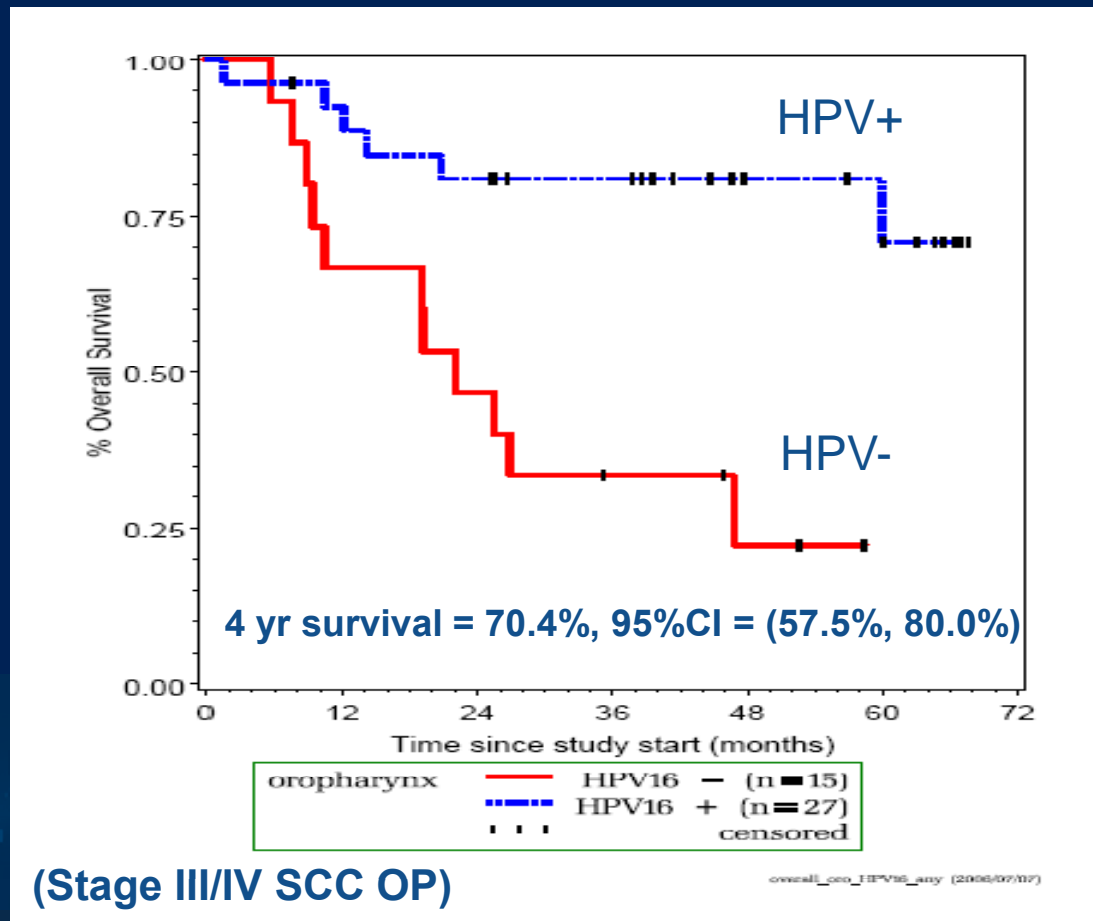


**Abstract 6001**

**The Implication of Tobacco Usage in the  
Development of Distant Metastases & Tumor  
Recurrence in Patients with HPV (+) Squamous  
Cell Cancers of the Oropharynx**

**F Worden et al**

# Univ of Michigan Protocol 9921 Overall Survival by HPV-16 Status



p=0.006

# Questions Outstanding

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- Why do some patients with HPV (+) tumors ultimately die from disseminated disease?
- Do smokers with HPV (+) tumors have the same favorable prognosis as non-smokers?
- Can treatment for HPV (+) tumors be tailored based on smoking status?

# Objectives

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- To evaluate the association of HPV status with long-term outcomes in oropharynx cancer patients.
- To evaluate the effect of tobacco use on long-term outcomes in HPV positive (+) oropharynx cancer patients.

# Methods

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- Retrospective Review: 124 patients with stage III/IV SCC of the oropharynx, treated on 2 sequential phase II, chemoradiotherapy protocols.
- Adequate tumor DNA for HPV analysis.
- All were candidates for surgical resection.

# Tobacco Usage

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- History of tobacco use: cigarettes, cigars, pipes, and chewing tobacco
- Determined via two methods:
  1. Chart review
  2. Self-reporting at the time of study enrollment
- Discrepancies: cross-referenced with the treating physicians

# Definitions of Tobacco Usage

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- Never: never used chewing tobacco, cigars, or pipes, with the equivalent of  $< 100$  cigarettes in a life time.
- Current: present, including those who quit  $< 1$  year prior to diagnosis.
- Former: quit  $\geq 1$  year prior to diagnosis.

# Patient Characteristics

	Number	Percentage
Total Study Group	124	
Male	103	83%
Female	21	17%
Median Age	57 years	
HPV (+)	102	82%
HPV (-)	22	18%
HPV (+) Never Tobacco	33	27%
HPV (+) Any Tobacco	69	56%
HPV (-) Never Tobacco	0	0%
HPV (-) Any Tobacco	22	18%
Base of Tongue	62	50%
Tonsil	57	46%
Other Oropharynx	5	4%
Stage III	17	14%
Stage IVA	92	74%
Stage IVB	15	12%

# Patient Characteristics

Tobacco Use	Total	HPV+ (n=102)	HPV- (n=22)
Never	33	33 (32%)	0 (0)
Former	52	46 (45%)	6 (28%)
Current	39	23 (23%)	16 (72%)

# Results

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- Objective (1): HPV Incidence and its effect on recurrence, OS, and DSS
- Objective (2): The effect of tobacco on long-term outcomes among HPV + patients

# HPV Incidence by Cohort

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UMCC 9921

UMCC 0221

HPV (-)	14 (34%)	8 (10%)
HPV (+)	27 (66%)	75 (90%)

# Patterns of Recurrent Disease by HPV Status and Use of Tobacco

	HPV+	HPV-
<b>Never-Tobacco User</b>	<b>2/33 (6%)</b>	<b>0/0</b>
Loco-Regional	0	0
Distant Metastases	1	0
Second Primary	1	0
<b>Current</b>	<b>8/23 (35%)</b>	<b>8/16 (50%)</b>
Loco-Regional	0	2
Distant Metastases	6	4
Second Primary	2	2
<b>Former</b>	<b>9/46 (20%)</b>	<b>3/6 (50%)</b>
Loco-Regional	3	1
Distant Metastases	4	1
Second Primary	2	1

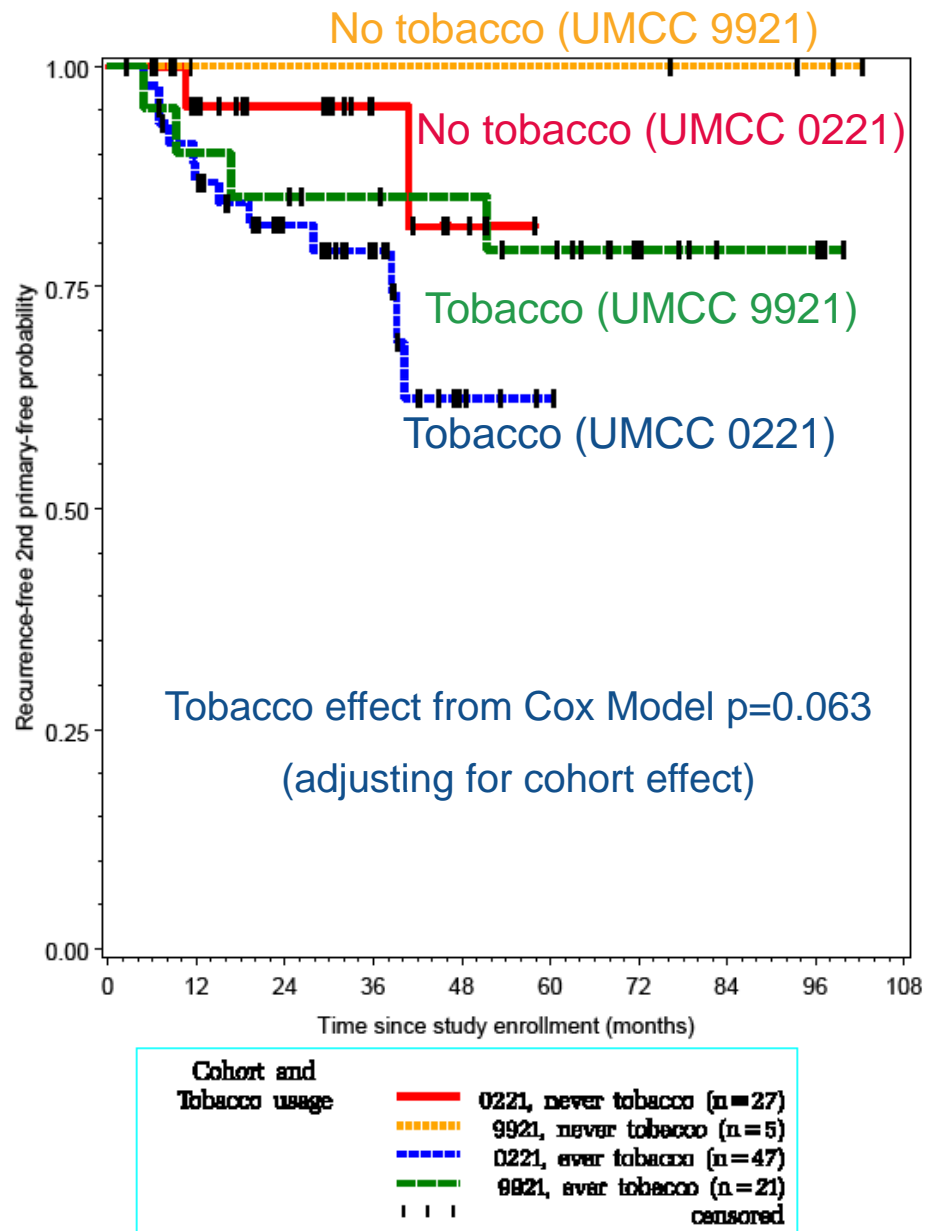
# Risk of Recurrence\*

## HPV (+) Patients

Tobacco Status	Hazard Ratio	(95% CI)	p value
Current vs Never	5.2	(1.1-24.4)	0.038
Former vs Never	2.9	(0.6-13.6)	0.18
Current vs Former	1.8	(0.7-4.8)	0.24

\*  $p = 0.063$  for overall effect of tobacco using Cox proportional hazards model adjusting for cohort effect.

# Time to Recurrence in HPV (+) Patients by Tobacco Usage



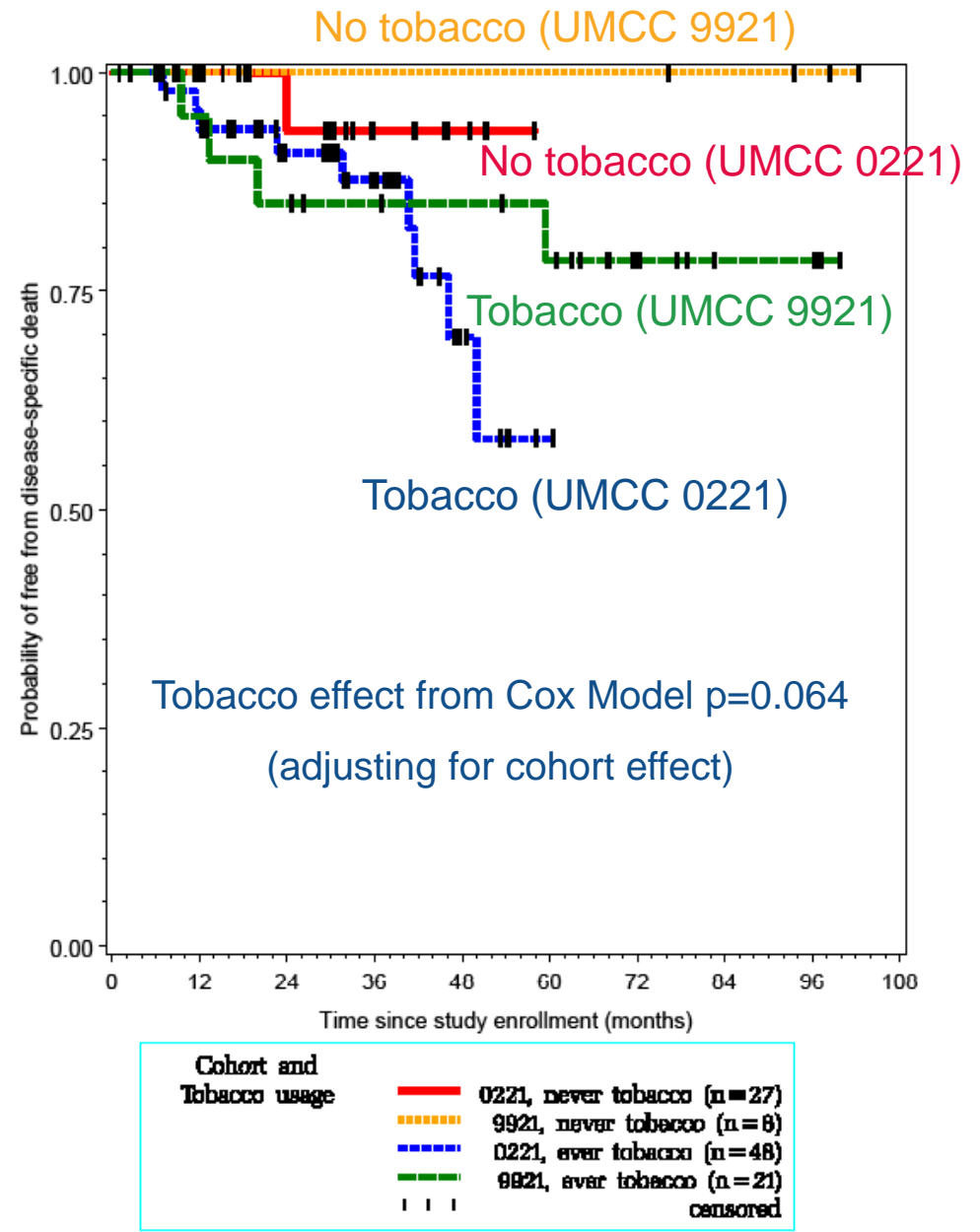
# Disease Specific Survival\*

## HPV (+) Patients

Tobacco Status	Hazard Ratio	(95% CI)	p value
Current vs Never	7.2	(0.88-58.4)	0.07
Former vs Never	3.6	(0.43-30.1)	0.24
Current vs Former	1.99	(0.66-6.03)	0.22

\*  $p = 0.064$  for overall effect of tobacco using Cox proportional hazards model adjusting for cohort effect.

# Disease Specific Survival by Cohort and Tobacco Usage



# Conclusions

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- HPV (+) tumors have more favorable OS and DSS compared to HPV (-) tumors.
- HPV (+) tumors have lower risk of disease recurrence.
- Patients who are HPV (+) and are current tobacco users have a higher risk of disease recurrence compared to HPV (+) never-tobacco users.

# HPV and Prognosis

## Gillison et al

- Tumor HPV Status Is A Strong And Independent Predictor Of OS And PFS.
- Rates For Local-regional and Not Distant Recurrence Were Lower in HPV+ Patients
- P16 Is Highly Correlated With Tumor HPV Status And Is Valid Surrogate.
- Tobacco Use Appears To Modify The Biological Behavior Of HPV+ Tumors
- Tumor HPV Status Or P16 Must Be A Stratification Factor In Clinical Trials That Include Oropharynx Patients.

## Rischin et al

- HPV Positive Oropharyngeal Cancer is Associated With Improved Prognosis
- p16 Identifies A Larger Group With An Improved Prognosis
- Future Head And Neck Cancer Trials Require Stratification By HPV Or P16 Status
- Information About HPV Status And Radiation Quality Important For Interpretation Of Trials Of Chemoradiation In Head And Neck Cancer

# HPV and Prognosis: Conclusions

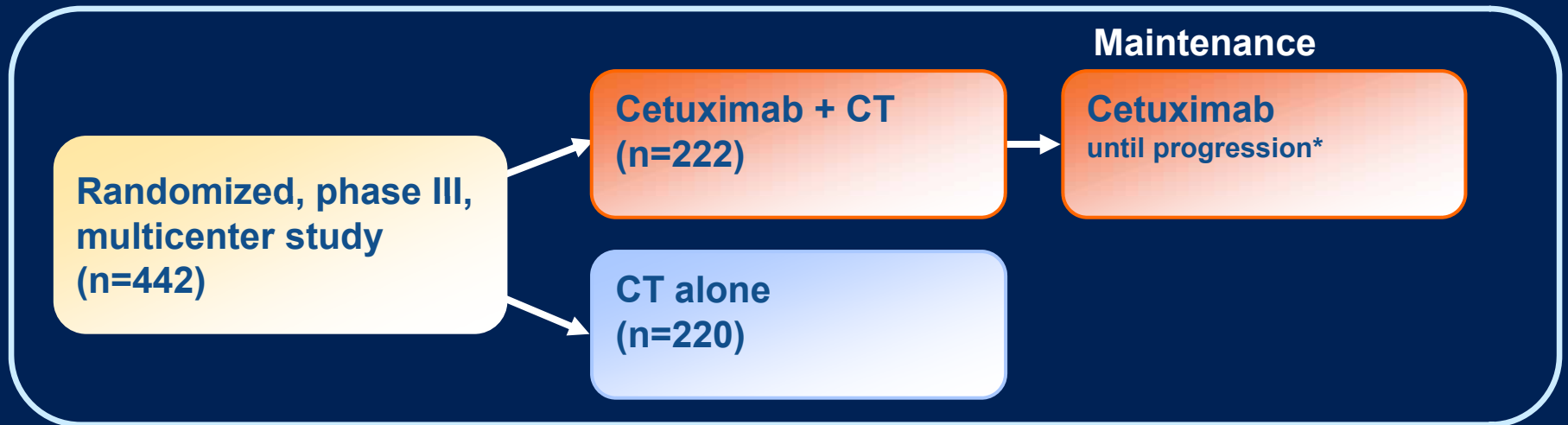
- **HPV Related HNC Is A Unique Disease**
  - Better Prognosis Based On LRC
  - Different Biology
- **The Demographic Profile Of HPV+ HNC Supports A Better Outcome**
  - PS, Age, Smoking, Ethnicity
  - Reduced Second Primary, Death From “Non-Cancer Causes”
  - Better Compliance
- **Survival Statistics Are Early**
  - Distant Metastases Are Likely to Occur Late
  - PFS More Directly Predicts Cancer Mortality In Oropharynx, This is a Young Population, Hence Longer Follow Up is Needed to Better Understand Outcomes

## Abstract 6005

**Biomarker Potential Of *EGFR* Gene Copy  
Number In The Phase III EXTREME  
Study: Platinum-based CT  $\pm$  Cetuximab In  
R/M SCCHN**

**Licitra, et al**

# EXTREME study design



**Licitra**

Vermorken JB, et al. NEJM 2008;359:1116-1127

# Overview of EGFR Signals

- Tumors from 312 of the 442 patients (71%) in the ITT population were evaluable by FISH
- Treatment arms were similar in terms of:
  - *EGFR* signals
  - Clinical outcomes

	Cell count/patient, median (range)		
	Cetuximab + CT (n=158)	CT alone (n=154)	All patients (n=312)
<b>CEP7</b>	2.3 (1.1–6.2)	2.4 (1.2–5.8)	2.3 (1.1–6.2)
<b><i>EGFR</i></b>	2.6 (1.1–26.8)	2.8 (1.0–43.2)	2.7 (1.0–43.2)
<b><i>EGFR</i>:CEP7</b>	1.0 (0.6–10.7)	1.1 (0.5–20.8)	1.1 (0.5–20.8)

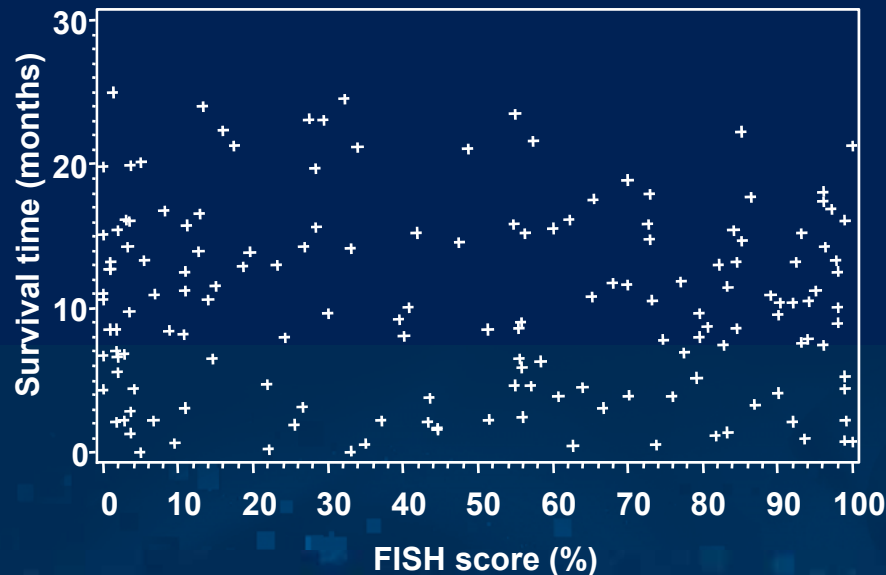
CEP7, centromere-specific probe for chromosome 7; CT, chemotherapy;  
FISH, fluorescence in situ hybridization

# No Association Between Overall Survival And FISH Score

- In either treatment arm
- For any model

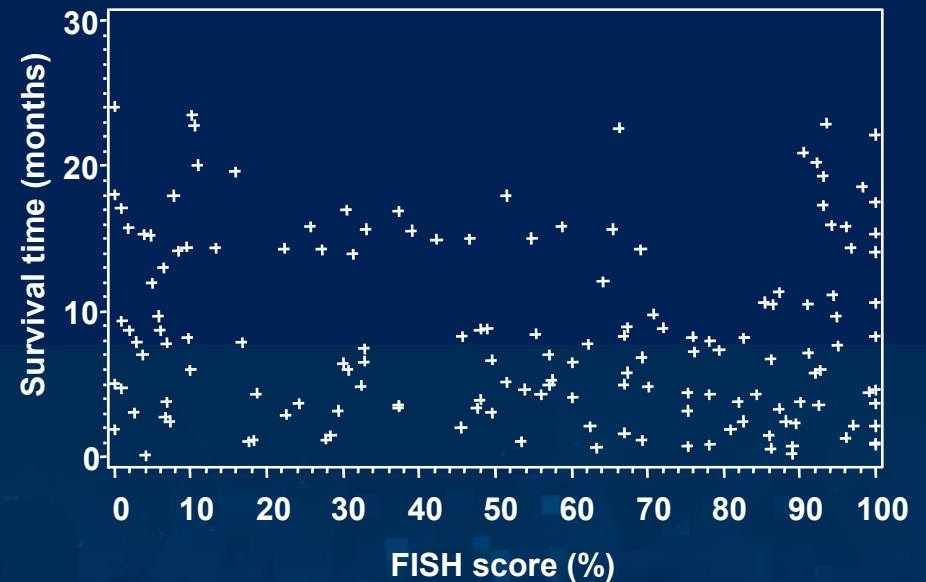
OS time versus FISH score per patient in Model B

Cetuximab + CT (n=158)



OS time versus FISH score per patient in Model B

CT alone (n=154)



CT, chemotherapy; FISH, fluorescence in situ hybridization;  
OS, overall survival

# Conclusions

## Cetuximab Benefit in HNC

- Not Associated with Increased EGFr Copy Number
- Not associated with Known EGFr Mutations
- Not Associated with Mutations in Known Signaling Pathways
- Is Associated with Rash

## **Abstract 6000**

**Mass spectrometry profile as a predictor of overall survival benefit after treatment with epidermal growth factor receptor inhibitors in head and neck squamous cell carcinoma**

**Chung et al**

# Introduction

- Epidermal growth factor receptor (EGFR) pathway is deregulated in head and neck squamous cell carcinoma (HNSCC)
  - Overexpression of EGFR by immuno-staining
  - Increased *EGFR* gene copy number by fluorescence in situ hybridization
- EGFR inhibitors have shown to provide clinical benefits in HNSCC patients although response rates to monotherapy are low (4-13%)  
=> It is important to identify biomarkers of clinical benefit

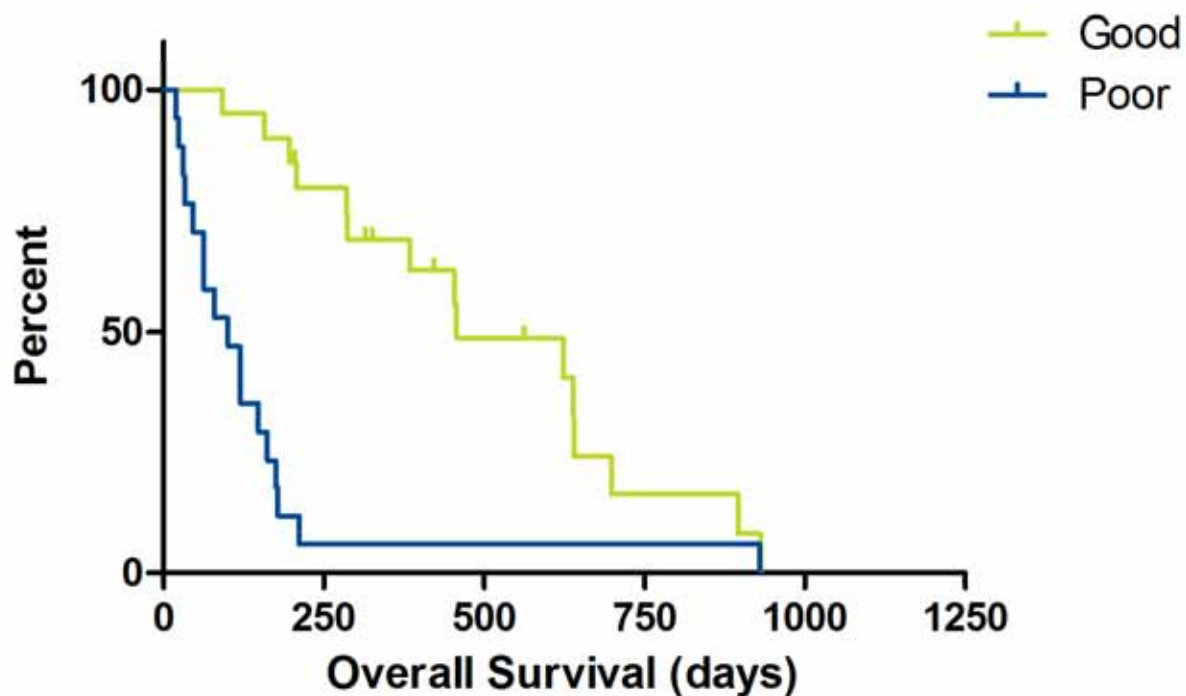
# Current Biomarkers for EGFR Inhibitor Therapy

- EGFR tyrosine kinase domain mutations associated with response in lung cancer is extremely rare in HNSCC (Chung, et al. JCO 2006)
- KRAS mutations associated with resistance in colon cancer are present in only 3.5% of HNSCC (Bissada, et al. ASCO 2008)
- Increased EGFR gene copy number does not predict response to cetuximab in HNSCC (Licitra, et al. ASCO 2009)
- Currently there is no validated biomarker that predicts clinical benefits of EGFR inhibitors in HNSCC

## Background

- In a previous study, a mass spectrometry (MS) profile from serum and plasma samples from non-small cell lung cancer (NSCLC) patients can predict the overall survival after the treatments with EGFR TK inhibitors, gefitinib or erlotinib (Taguchi, *et al.* JNCI, 2007)
- The profile contains 8 distinguishing MS peaks
- The assay is currently commercialized as VeriStrat<sup>R</sup>

# Subset Analysis of NSCLC Patients with Squamous Cell Histology treated with EGFR-TKIs



**N=37 (20 Good, 17 Poor)**

**Median survival  
65.3 weeks (Good)  
14.4 weeks (Poor)**

**$p < 0.0001$ , HR=0.17**

## HNSCC Study

- Hypothesis: The MS profile is reflective of EGFR dependency of the tumor regardless of the histology
- Therefore, the profile may be predictive of overall survival in HNSCC patients with the tumors dependent on EGFR pathway, treated with various types of EGFR inhibitors

# HNSCC Sample Description

- EGFR inhibitor treated cohorts
  - N= 55, Phase II recurrent and/or metastatic (R/M) patients, Gefitinib 250 mg once daily
  - N= 32, Phase II R/M patients, Erlotinib 150 mg once daily and Bevacizumab 15 mg/kg every three weeks
  - N= 21, R/M patients, Cetuximab 400 mg/m<sup>2</sup> loading dose and 250 mg/m<sup>2</sup> once a week

# HNSCC Sample Description

- Control cohorts
  - N= 78, HNSCC patients at the time of diagnosis treated with surgery as a primary therapy
  - N= 34, Two phase II clinical trials with identical eligibility criteria, R/M HNSCC treated with docetaxel/bortezomib or docetaxel/irinotecan combinations

# Classification based on the MALDI MS Algorithm

Cohorts	Gefitinib (n=55)	Erlotinib/Bev (n=32)	Cetux (n=21)	Control #1 surgical (n=78)	Control #2 no EGFRI (n=34)
<b>Good (%)</b>	<b>31 (56)</b>	<b>24 (75)</b>	<b>16 (76)</b>	<b>77 (99)</b>	<b>22 (65)</b>
<b>Poor (%)</b>	<b>23 (42)</b>	<b>6 (19)</b>	<b>5 (24)</b>	<b>1 (1)</b>	<b>12 (35)</b>
<b>Undefined (%)</b>	<b>1 (2)</b>	<b>1 (3)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>0 (0)</b>
<b>Failed MS (%)</b>	<b>0 (0)</b>	<b>1 (3)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>0 (0)</b>

# Overall Survival based on the MS Profile

## Gefitinib

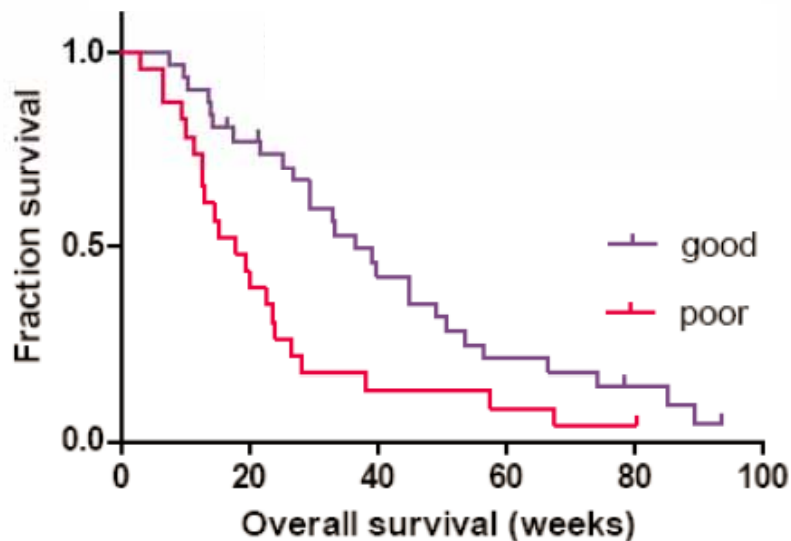
**P=0.007**

**HR=0.41, 95% CI 0.22-0.79**

**Median time to death:**

**Good 36.7 weeks**

**Poor 18.0 weeks**



## Erlotinib/bevacizumab

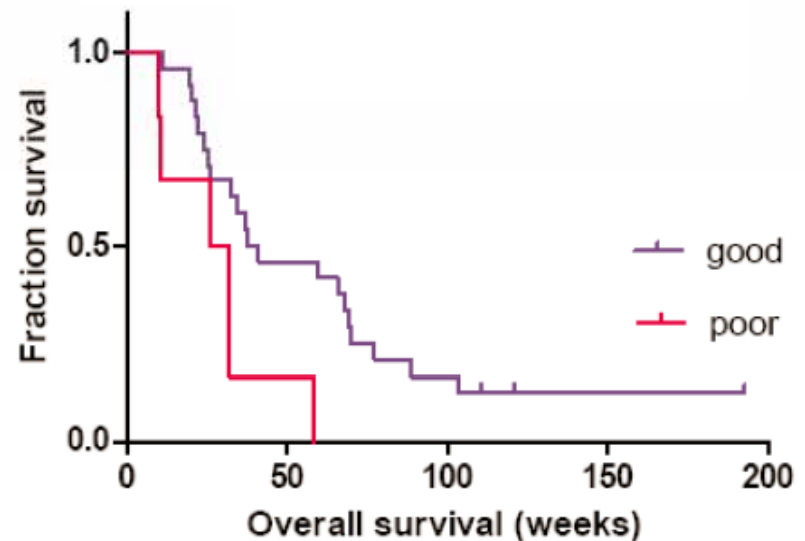
**P=0.02**

**HR=0.20, 95% CI 0.05-0.78**

**Median time to death:**

**Good 39.5 weeks**

**Poor 29.1 weeks**



# Overall Survival based on the MS Profile

## Cetuximab

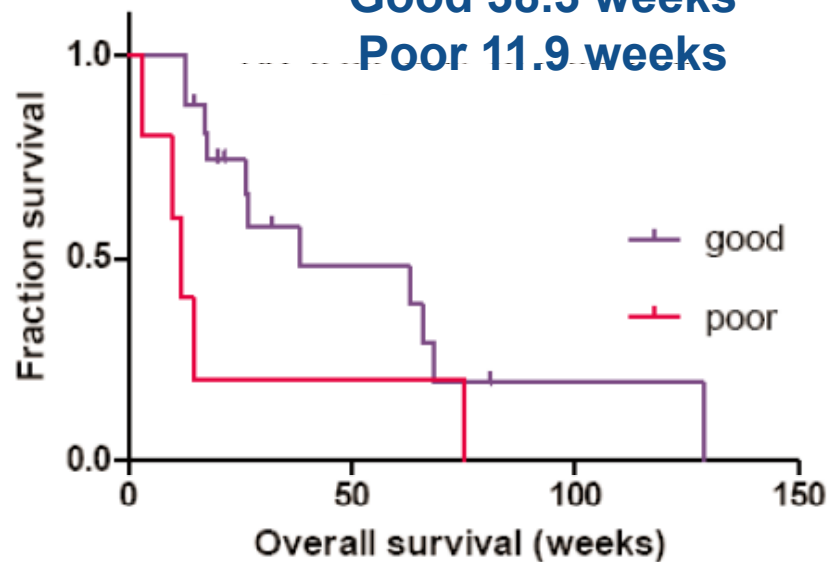
**P=0.06**

**HR= 0.26, 95% CI 0.06-1.06**

**Median time to death:**

**Good 38.3 weeks**

**Poor 11.9 weeks**



## Chemotherapy

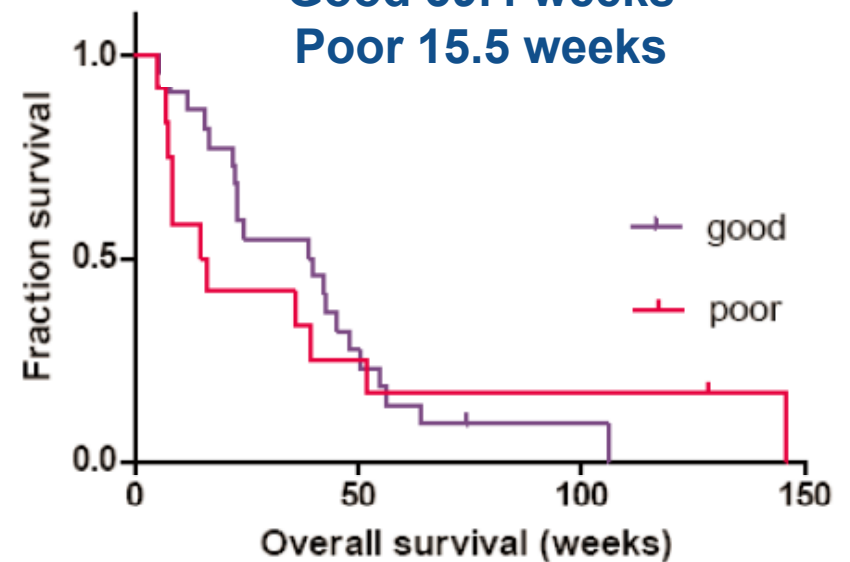
**P=0.76**

**HR= 0.88, 95% CI 0.4-1.94**

**Median time to death:**

**Good 39.4 weeks**

**Poor 15.5 weeks**



# Conclusions

- This study suggests that;
  - The same predictive algorithm for MALDI-MS (VeriStrat<sup>R</sup>) generated from EGFR TKI-treated patients with NSCLC is also predictive of survival outcome in HNSCC patients
  - The profile is predictive in both small molecule EGFR TKI- and cetuximab-treated patients
- Application of the proteomic profile may allow rational selection of patients most likely to benefit from an EGFR Monotherapy and EGFR-containing combination therapy

# **Chemotherapy in SCCHN**

## **Abstract 6009**

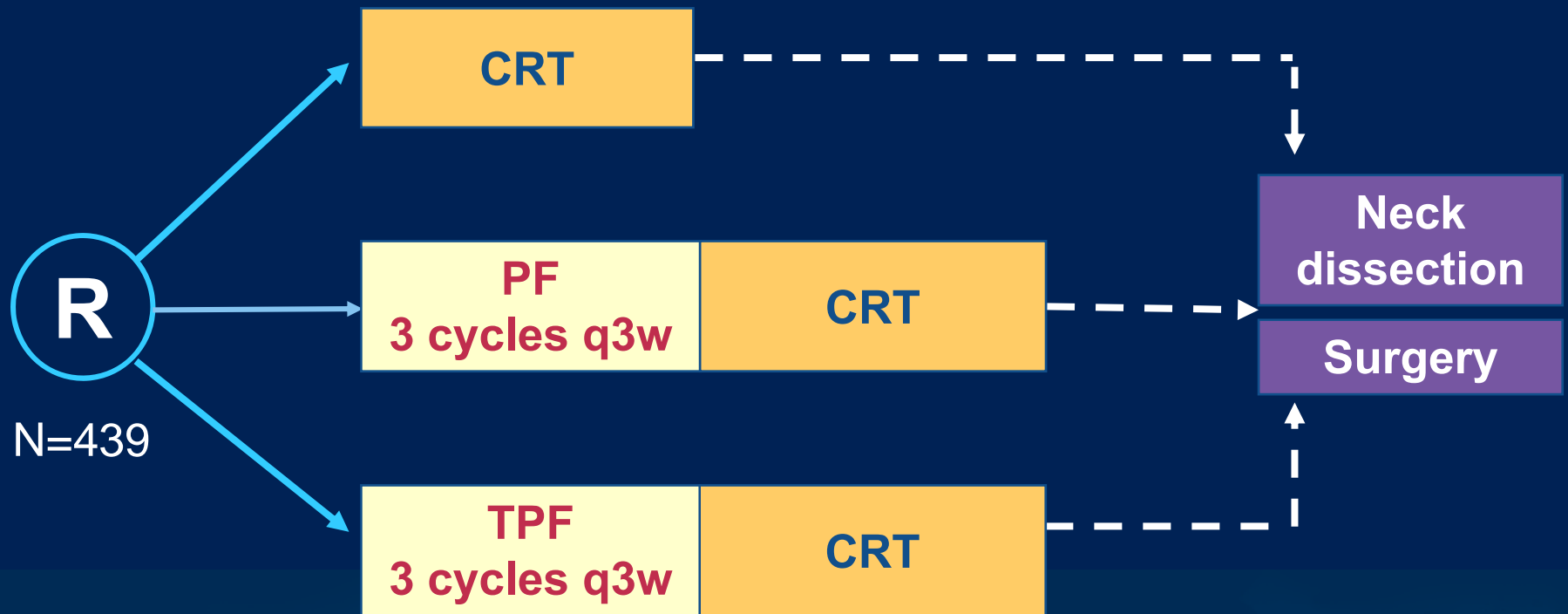
**Final Results Of A Phase III Trial Comparing  
Induction Chemotherapy PF or TPF Followed By  
Chemoradiotherapy vs CRT Alone for Unresectable  
Locally Advanced Head And Neck Cancer**

**Hitt et al**

# Curative Treatment of SCCHN:

- TPF is the Standard of Care for Induction Chemotherapy
- Which is the Better Therapy for Survival?
  - Sequential Therapy or Chemoradiotherapy
- Which is the Better Therapy for Organ Preservation?
  - Sequential Therapy, Induction Therapy (Followed by RT), or Chemoradiotherapy

# Study Design



# Statistical hypothesis

- Planned sample size: 438 patients
  - To show an increase of 50% in median TTF\* for ICT/CRT versus CRT, 8 to 12 months, HR=0.67,  $\alpha=0.05$ ; power=80%
- Analysis Populations:
  - Efficacy ITT: All randomized patients
  - Efficacy Evaluable: Patients with at least 1 cycle of CRT and/or ICT and all early progressions and deaths due to tumor
  - Safety: All patients with at least 1 dose of study treatment

# Tumor characteristics

Characteristic	CRT (N=128)	PF plus CRT (N=156)	TPF plus CRT (N=155)
Primary tumor site, %			
Oropharynx	42	43	43
Hypopharynx	18	18	17
Larynx	20	17	19
Oral cavity	20	22	21
TN stage (primary), %			
T4 N0	15	17	17
T4 N1	20	13	14
T4 N2	34	44	44
T4 N3	5	6	1
Total T4 (N0/1/2/3), %	74	80	76

# Summary of efficacy

Median HR (95% CI) vs CRT	CRT (N=119)	PF plus CRT (N=123)	TPF plus CRT (N=111)	Total ICT (TPF + PF) (N=234)
TTF	5.0	12.3 0.60 (0.44–0.80)	13.4 0.55 (0.41–0.75)	12.5 0.57 (0.45–0.74)
TTP	13.1	18.5 0.83 (0.61–1.13)	20.4 0.74 (0.53–1.02)	18.5 0.79 (0.60–1.03)
OS	27.1	33.6 0.87 (0.62–1.24)	37.2 0.82 (0.57–1.18)	37.1 0.85 (0.63–1.15)

86 Patients Missing in  
the Analysis

Hitt

## Conclusions

- Further Analysis and Review of the Data Are Needed and Conclusions are Limited Due to:
  - End Point Selection (TTF)
  - Missing Patients in All Arms (ITT Analysis)
- The Question: Which is the Better Treatment for Survival in LAHNC - Sequential Therapy (ICT + CRT) or Bolus Cisplatin-CRT – Remains Open

# **Toxicity/Supportive Care**

## **Abstract 6007**

**Randomized Study of Darbepoetin Alpha as a  
Modifier of radiotherapy in Patients with HNC:  
Final Outcome of the DAHANCA 10 Trial**

**Overgaard et al**

# Goal

The study aimed to evaluate if correction of low hemoglobin levels by means of the erythropoietin stimulating agent: Darbepoetin alpha (Aranesp) during radiotherapy (RT) improves outcome in patients with HNSCC

## Design and Treatment

- Pts with HNSCC , eligible for primary RT alone.
- Hgb values below 14.0 g/dl
- Randomized to receive Aranesp together with accelerated fractionated RT.
- Pts. were stratified according to gender, T and N staging, tumor site, and institution.
- Aranesp was given subcutaneously in a dose of 150 micrograms weekly during RT, or stopped earlier if the Hgb exceeded 15.5 g/dl

# Results

- Planned interim analysis showed inferiority of the experimental treatment and the trial was stopped in November 2006
- Poorer outcome in 5-year loco-regional control (59% vs. 68% ( $p = 0.04$ , RR: 1.47 [1.14-1.94]) for the Aranesp vs. control arm.
- This was also seen for the endpoint of disease-free survival (37% vs. 47%,  $p = 0.02$ , RR: 1.32 [1.04-1.68])
- No significant difference in overall survival (40% vs. 51%,  $p = 0.16$ , RR: 1.20 [0.93-1.55]).
- There were no differences in radiation related morbidity

# Conclusions

- There is a Significant Negative Effect On Survival And LRC For Darbepoetin During Radiotherapy For HNC

## ASCO 2009 : Practical Implications in HNC

- HPV related Oropharynx ; new Entity, different disease. ? Different therapy
- Sequential vs Concurrent chemoradiotherapy: Await phase III trials: Remains an open question
- Sorafenib is active in thyroid cancer : Phase III starting