

ERBITUX extends survival in locally advanced SCCHN



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MACH-NC analysis: effect of chemotherapy according to platin and/or 5-FU: yes / no

Chemotherapy	Absolute survival benefit at 5 years
P+ F+	10%
P+ F-	11% p<0.04
P- F+	7%
P- F-	4%

MACH-NC analysis: effect of chemotherapy according to the type of local treatment

Absolute survival benefit at 5 years

Definitive RT

- | | |
|----------------------------|--------------------------------|
| - Conventional RT | + 8% in favor of chemotherapy |
| - Modified-fractionated RT | + 11% in favor of chemotherapy |
-

Chemoradiotherapy (CRT) in the treatment of locally advanced SCCHN

- CRT has greater efficacy than RT alone

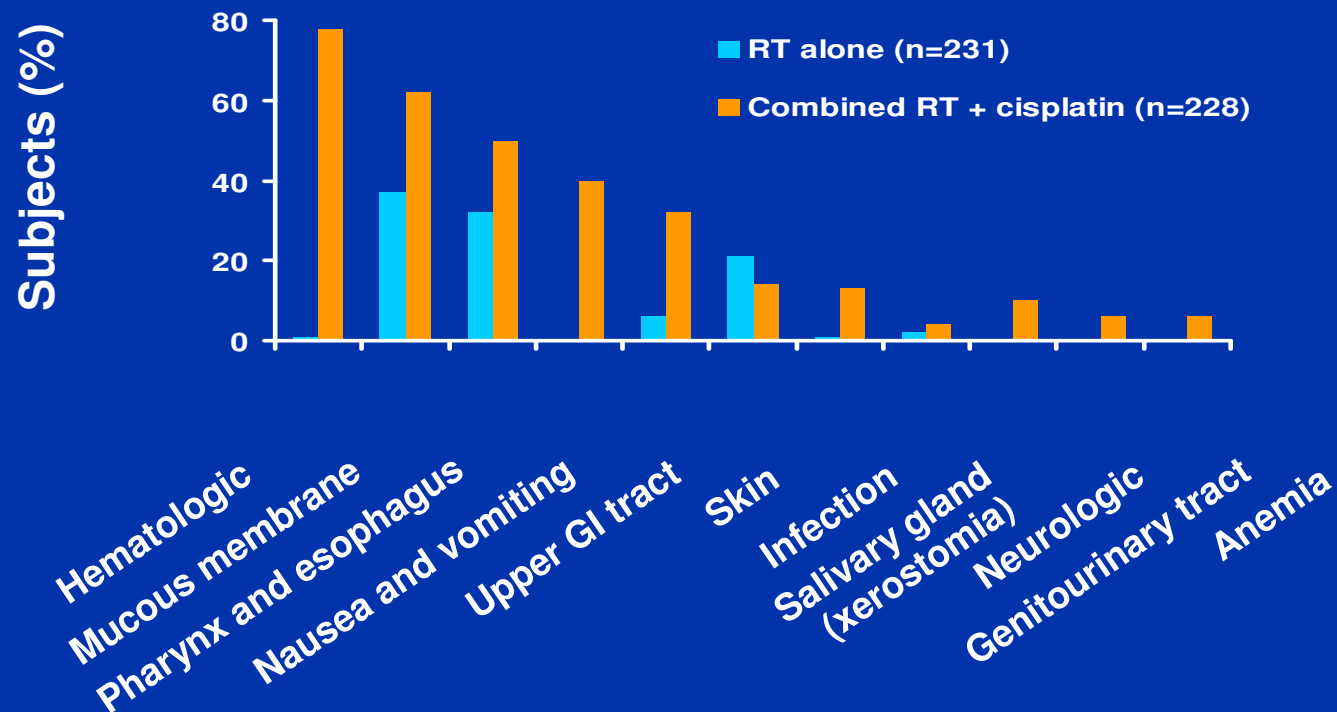
However:

- CRT results in:
 - Significant increases in acute toxicity
 - Compromised adherence to chemotherapy over treatment cycles
 - Patients often receiving suboptimal doses of chemotherapy in an attempt to keep toxicity at acceptable levels
- Maximum tolerable toxicity may have been reached with dose intensities currently used in platinum-based CT



CRT results in significant increases in acute toxicity

**Acute adverse effects: grade 3 or higher
77% with CRT vs 34% with RT alone (p<0.001)**



MACH-NC analysis: treatment-related mortality (n = 10, 741)

	Control	Chemotherapy
Adjuvant	0.5 %	1.3 %
Neoadjuvant	0.4 %	1.5 %
Concomitant	0.9 %	2.1 %

 + 1% toxic death

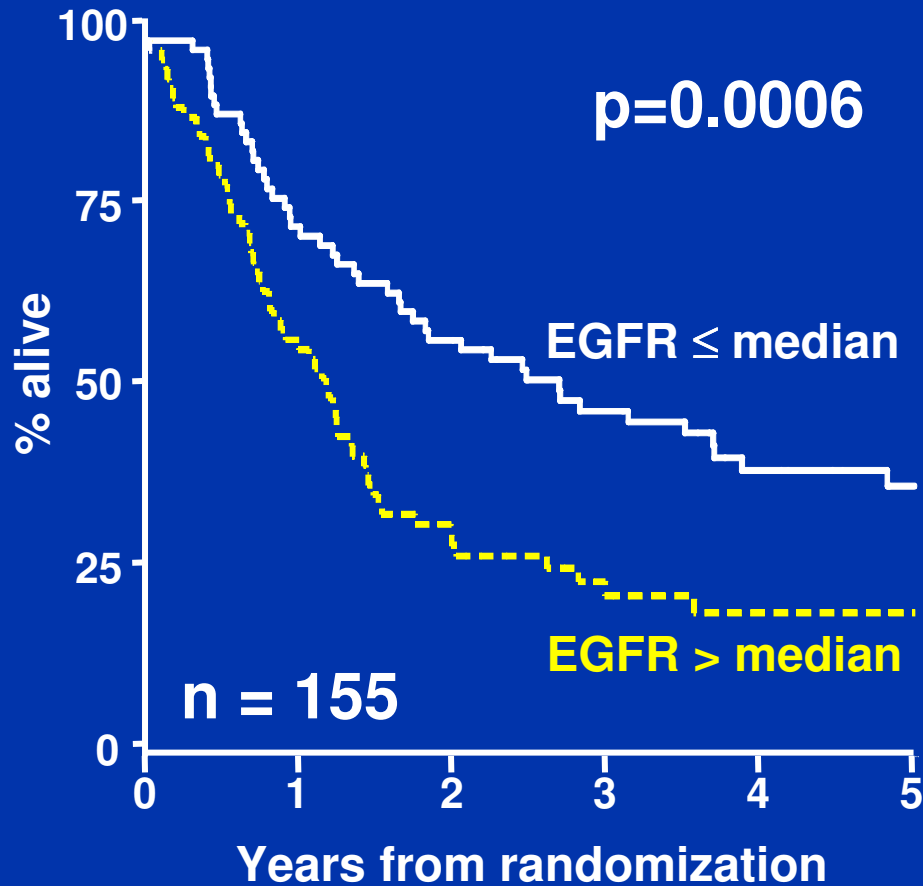
Future prospects

- **New drugs: taxanes**
- **New schedules: induction CT followed by CT/RT**
- **New biologically targeted therapies:**
 - **anti-EGFR**
 - **cyclin-dependent kinase inhibitors**
 - **farnesyl transferase inhibitors**
 - **anti-angiogenesis gene therapy**

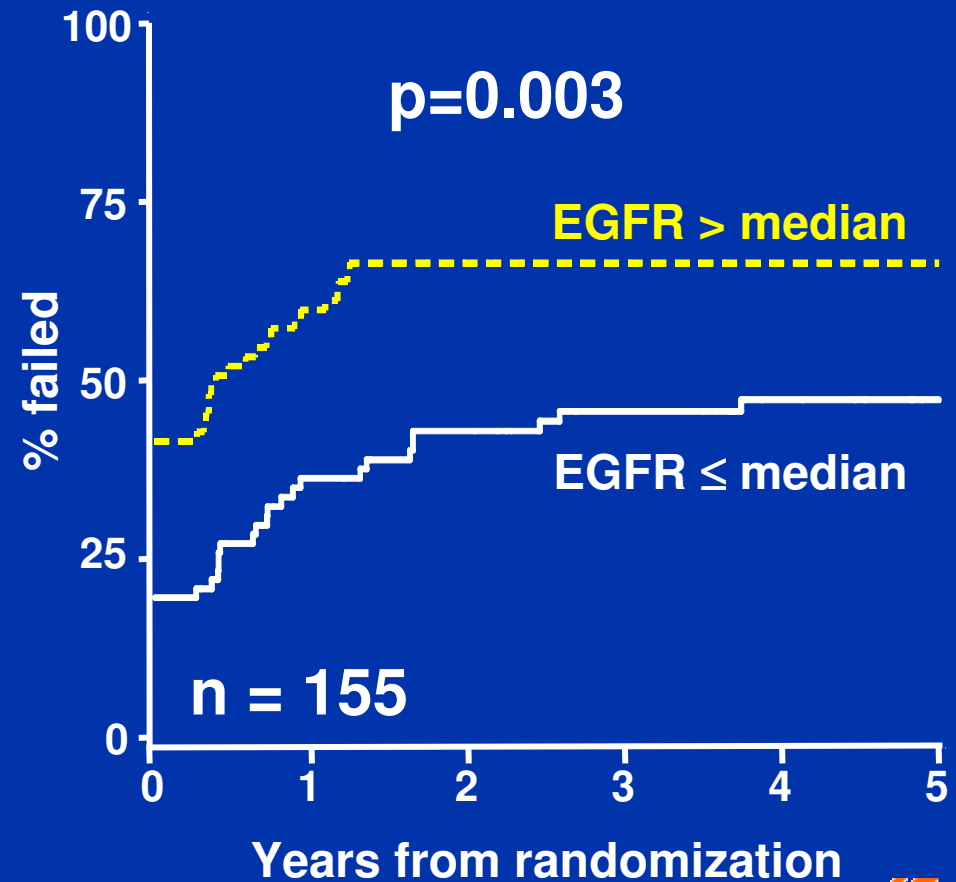


EGFR: a marker for response to radiation (SCCHN)

Overall survival



Locoregional relapse



Can we target selective pathways to improve outcomes and reduce toxicity?



A phase III study of high-dose RT ± ERBITUX

The NEW ENGLAND JOURNAL of MEDICINE
354:567-78, 2006

ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous- Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D.,
Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D.,
Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D.,
Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D.,
Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D.,
Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*



Study design

Stratified by

- **KPS:** 90–100 vs 60–80
- **Regional nodes:** N0 and N+
- **Tumor stage:** AJCC T1–3 and T4
- **RT fractionation^a:** concomitant boost, once daily, twice daily

Randomized patients with
stage III or IV, nonmetastatic,
measurable SCCHN
(n = 424)



Arm 1: RT (n = 213)

Arm 2: ERBITUX + RT (n = 211)
ERBITUX initial dose (400 mg/m²)
1 week before RT
ERBITUX (250 mg/m²) + RT
(weeks 2–8)^b

Primary endpoint: duration of locoregional control

Secondary endpoints: OS, PFS, RR and safety

^aInvestigators' choice

^bUAB regimen: Robert F. J Clin Oncol (2001)

Patient randomization

	RT	ERBITUX + RT
Patients randomized	213	211
Stratification factors		
KPS: 90–100 / 60–80	67% / 33%	70% / 30%
N stage: N0 / N+	18% / 82%	20% / 80%
T stage: T1–3/T4^a	69% / 31%	71% / 29%
RT fractionation		
Concomitant boost	56%	56%
Once daily	26%	26%
Twice daily	18%	18%

^aT3–4: 69%

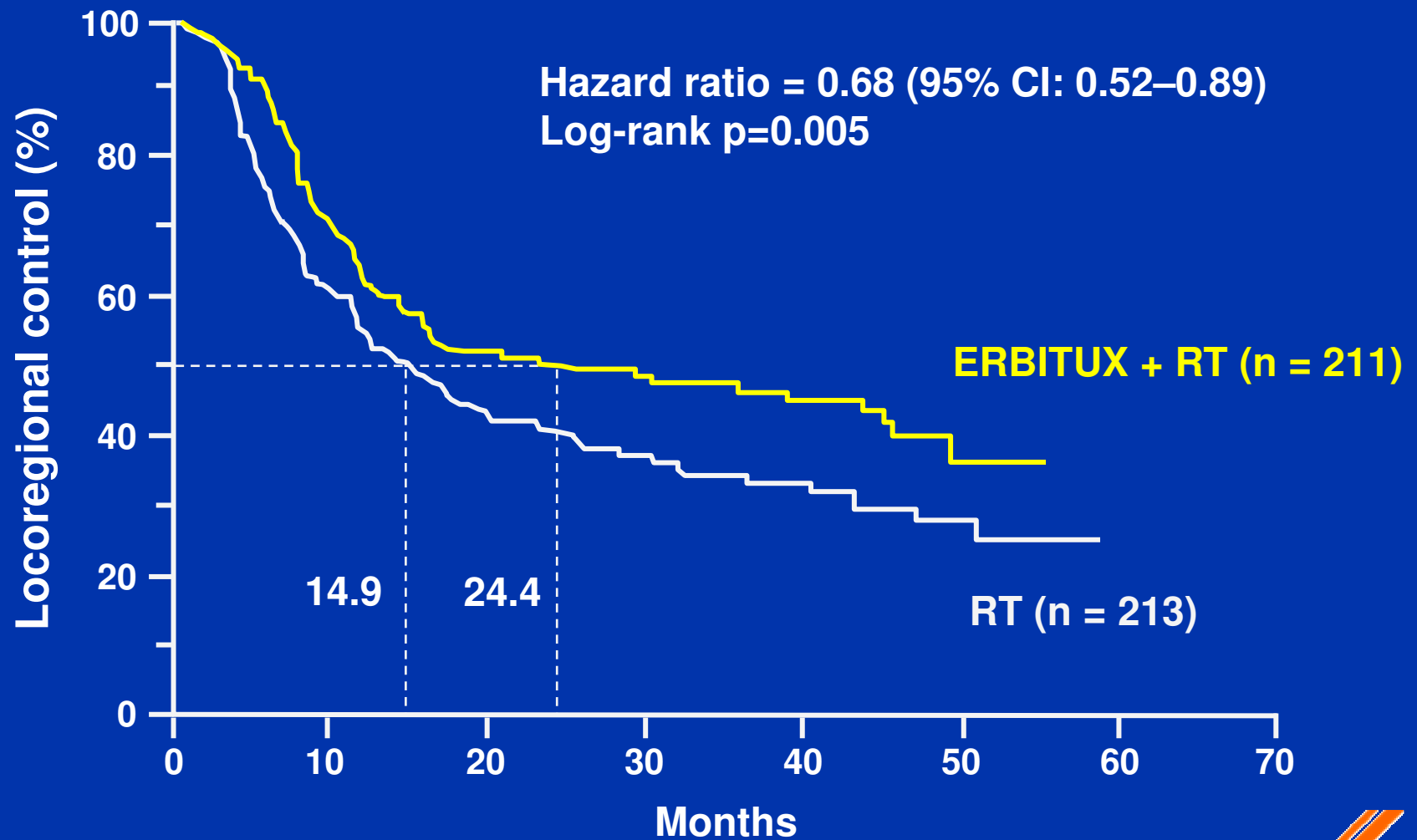


Patient characteristics

	RT	ERBITUX + RT
Median age, years (range)	58 (35–83)	56 (34–81)
Male / female	79% / 21%	81% / 19%
Primary tumor site		
Oropharynx	63%	56%
Hypopharynx	13%	17%
Larynx	24%	27%



Locoregional control

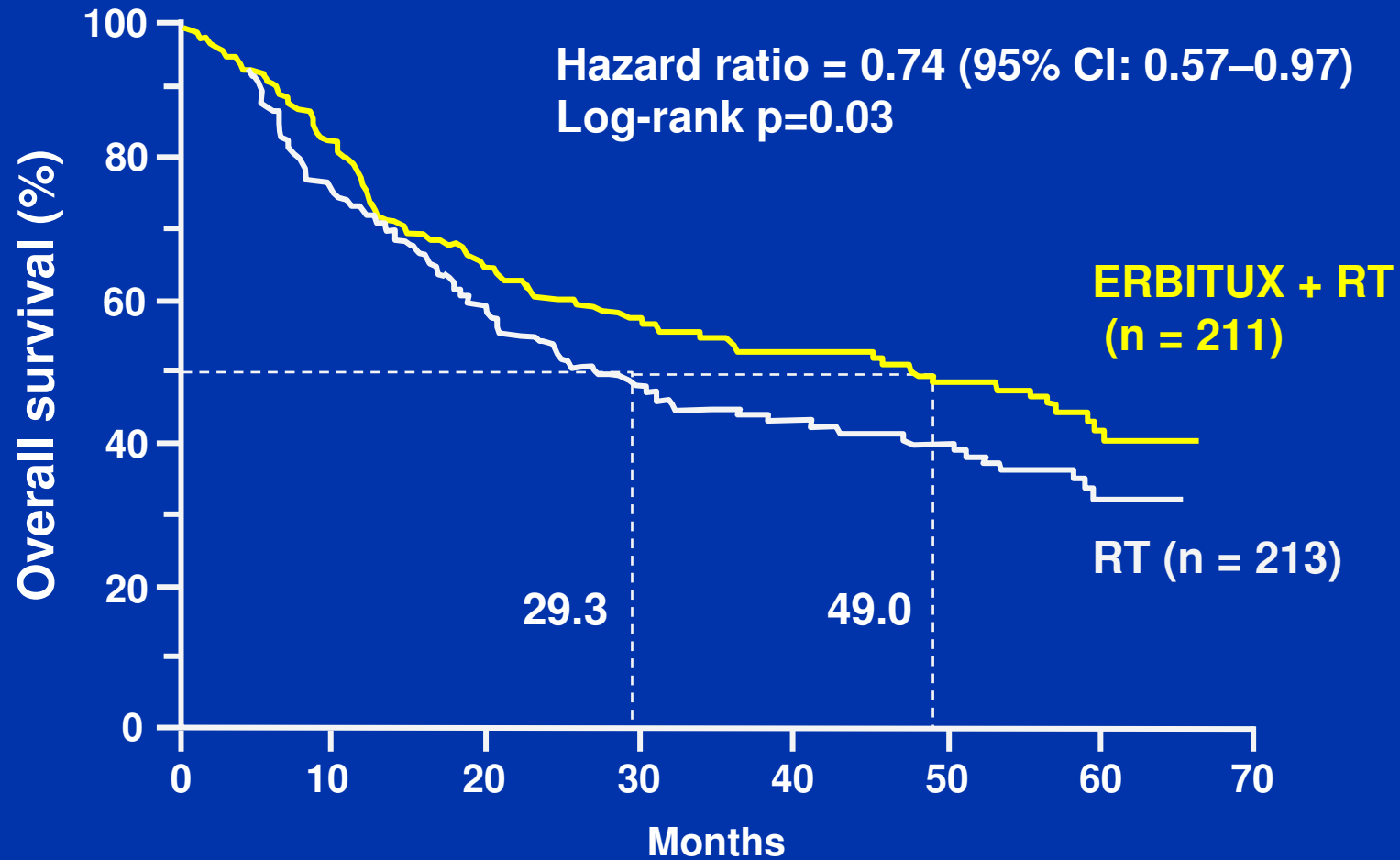


Locoregional control

	RT (n = 213)	ERBITUX + RT (n = 211)	p-value
Median duration	14.9 months	24.4 months	0.005
Locoregional control rate			
1-year	55%	63%	
2-year	41%	50%	
3-year	34%	47%	<0.01



Overall survival



Overall survival

	RT (n = 213)	ERBITUX + RT (n = 211)	p-value
Median overall survival	29.3 months	49.0 months	0.03
Survival rate 3-year	45%	55%	0.05



Relevant grade 3–5 side effects

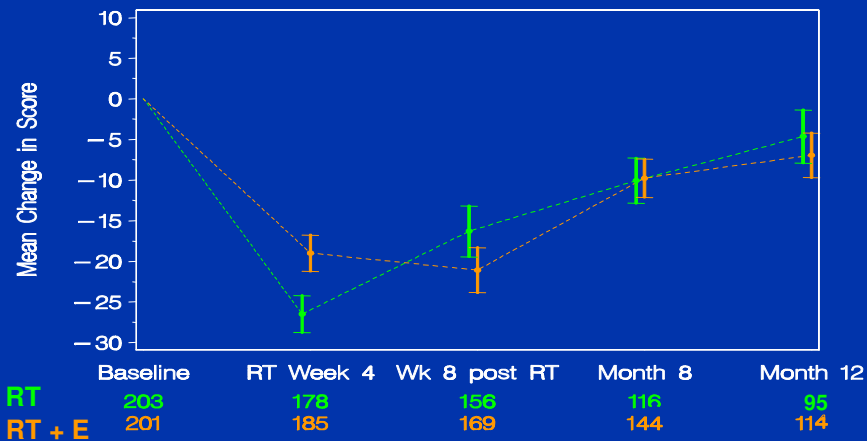
Side effect	RT (n = 212)	ERBITUX + RT (n = 208)	p-value ^a
Mucositis / stomatitis	52%	56%	0.44
Dysphagia	30%	26%	0.45
Radiation dermatitis	18%	23%	0.27
Xerostomia	3%	5%	0.32
Fatigue / malaise	5%	4%	0.64
Acne-like rash	1%	17%	<0.001
Infusion-related reactions ^b	0%	3%	0.01

^aFisher's exact test

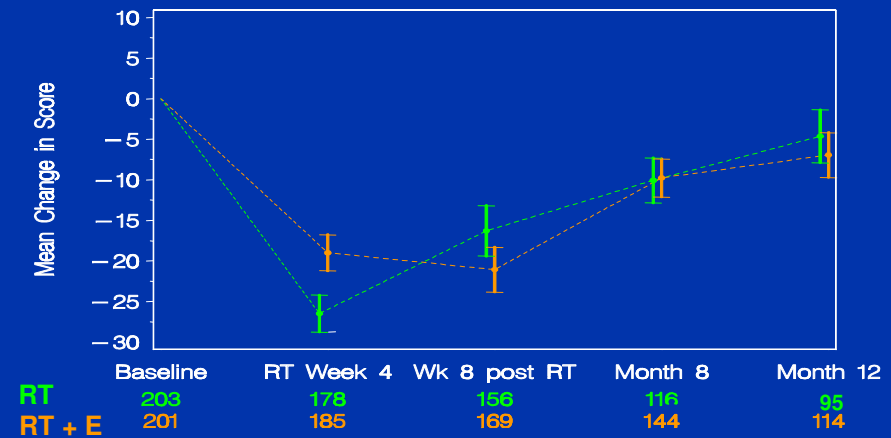
^bListed for its relationship to ERBITUX

Phase III study: RT vs ERBITUX + RT

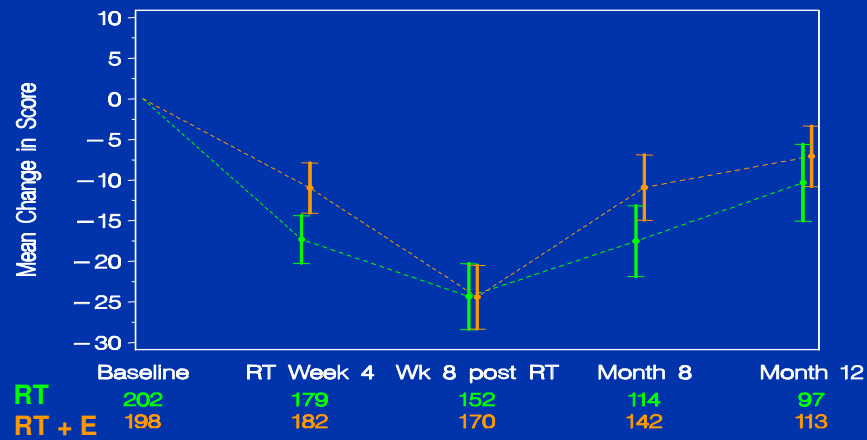
Global health



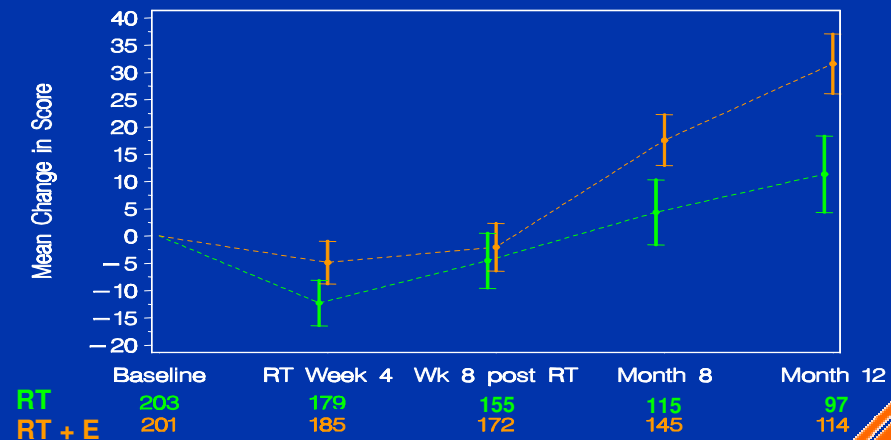
Swallowing



Feeding tube



Painkillers



Modified from Curran D, et al. J Clin Oncol 2007 (in press)

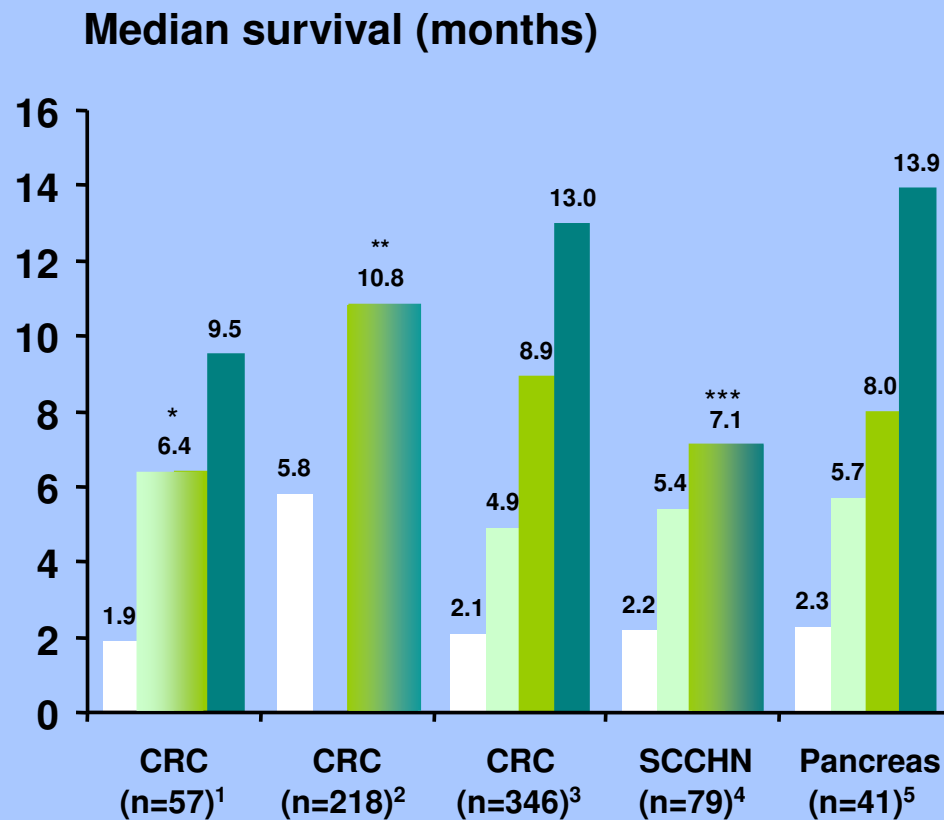
Follow-up analysis from the Bonner study: duration of mucositis and dysphagia

- The duration of adverse events (AEs) was investigated
- Median duration of any mucositis or dysphagia in the overall population (n = 424) was 3 months
 - 28% of patients with mucositis experienced this AE for 3 months
 - 31.5% of patients with dysphagia experienced this AE for 3 months
 - Less than 10% of patients suffered these AEs for >15 weeks
- Findings were similar for the two treatment arms

Summary

- Addition of ERBITUX to RT does not affect the duration of the primary acute side effects of RT

ERBITUX: correlation between skin rash and survival



¹ERBITUX monotherapy

²ERBITUX + irinotecan

³ERBITUX monotherapy

⁴ERBITUX + cisplatin

⁵ERBITUX + gemcitabine

■ No rash

■ Grade 1

■ Grade 2

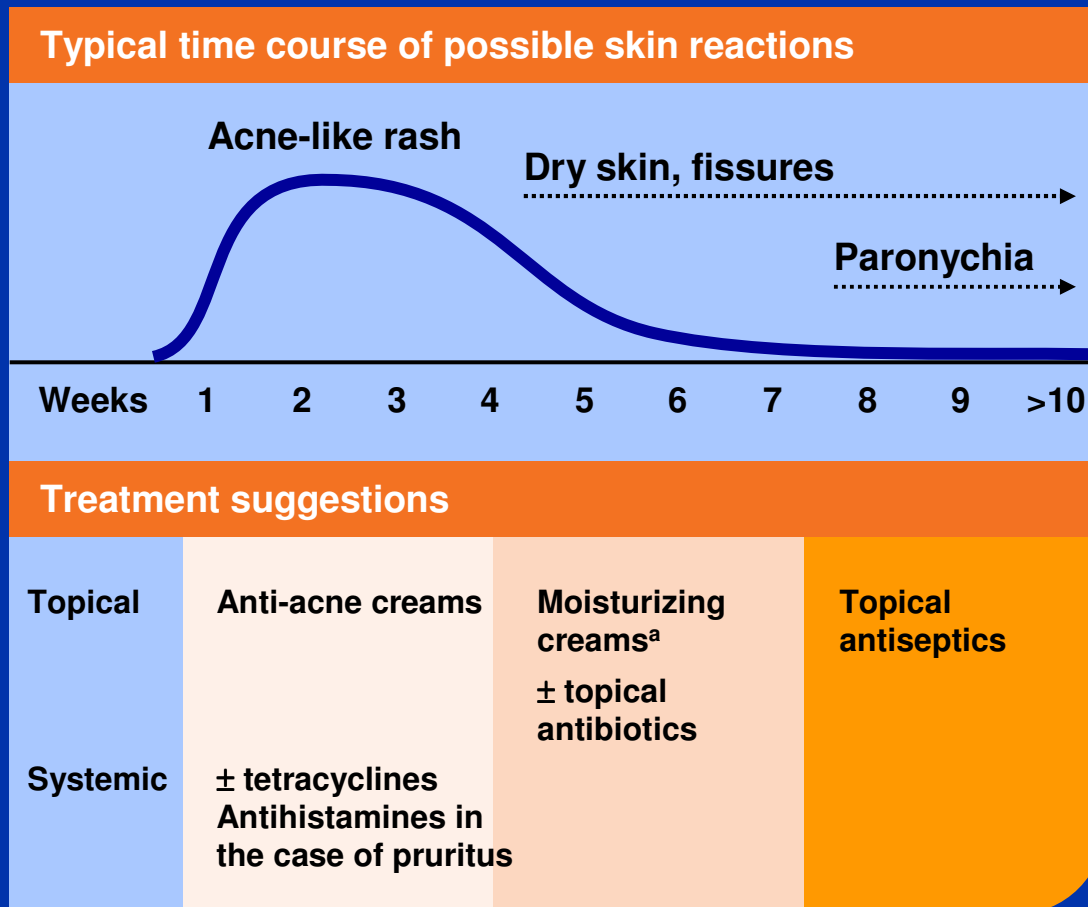
■ Grade 3

* Grades 1 and 2

** ≥Grade 2

*** Grades 2 and 3

Management of EGFR inhibitor-related skin reactions



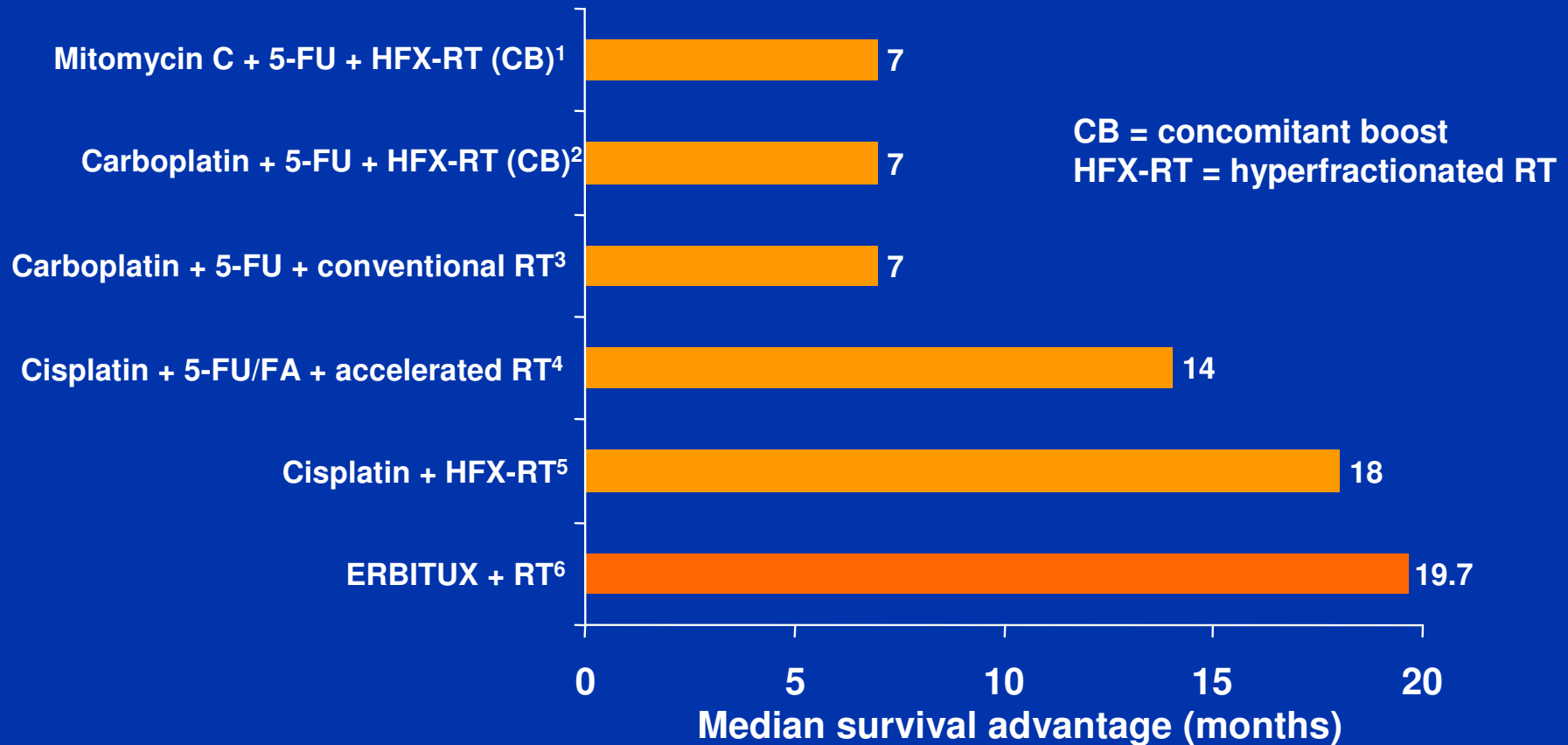
^aTopical corticosteroids if necessary



**Efficacy of ERBITUX + RT in the
context of chemoradiotherapy in
locally advanced SCCHN**



CRT vs RT: survival time advantage



¹Budach V, et al. J Clin Oncol (2005); ²Semrau R, et al. Int J Radiat Oncol Biol Phys 2006;

³Denis F, et al. J Clin Oncol (2004); ⁴Wendt TG, et al. J Clin Oncol 1998;

⁵Huguenin P, et al. J Clin Oncol (2004); ⁶Bonner JA, et al. N Engl J Med 2006

RTOG 0522: phase III trial CRT vs CRT + ERBITUX

Stratified by:

- Larynx vs others
- **KPS**: 60–80 vs 90–100
- **Regional nodes**: N0~N1, 2a, 2b~N2c-3
- 3-D vs IMRT^b

Randomized patients with stage
III or IV^a SCC of oropharynx,
hypopharynx or larynx
(n = 720)



Arm 1:
Accelerated FX^b +
CDDP: 100 mg/m², q3w x 2

Arm 2:
Accelerated FX^b +
CDDP: 100 mg/m², q3w x 2
ERBITUX: 400 mg/m², week -1
250 mg/m²/week, weeks 2–8

^aExclude T1, any N, and T2N1

^b3-D: AFX-CB (72 Gy/42 F/6 w) IMRT: 70
Gy/35 F/6w (bid x 5d)



RTOG 0234 phase II trial: surgery followed by chemoradiation + ERBITUX for advanced SCCHN

Stratified by

- KPS: 80–100 vs 60–70

Risk category:

Positive margins

High risk (≥ 2 positive nodes or extranodal spread)

Randomization
(n = 230)



Arm 1:

60 Gy / 6 weeks
+ weekly ERBITUX
+ weekly CDDP

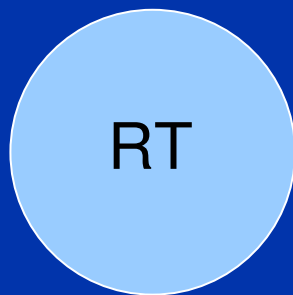
Arm 2:

60 Gy / 6 weeks
+ weekly ERBITUX
+ weekly docetaxel



ERBITUX in locoregionally advanced SCCHN: efficacy summary

- ERBITUX + high-dose RT demonstrated significant efficacy benefits over high-dose RT alone



+ ERBITUX



20-month increase in
median survival

26% reduction in
risk of death

10-month increase in
median LR control

32% reduction in
locoregional relapse

ERBITUX in locally advanced SCCHN: safety summary

- ERBITUX did not significantly increase acute RT-related side effects
 - >95% of all patients received the full dose of ERBITUX
- The main side effect associated with ERBITUX was acne-like rash characteristic of EGFR-targeting therapies



FDA News

FOR IMMEDIATE RELEASE

P06-34

March 1, 2006

Media Inquiries:

Laura Alvey, 301-827-6242

Consumer Inquiries:

888-INFO-FDA

FDA Approves First Head & Neck Cancer Treatment in 45 Years Data Shows Treatment with Erbitux Extends Survival

The Food and Drug Administration (FDA) today announced the approval of Erbitux (cetuximab) for use in combination with radiation therapy to treat patients with squamous cell cancer of the head and neck (SCCHN) that can not be removed by surgery (unresectable SCCHN). This is the first drug approved for head and neck cancer that has shown a survival benefit in this population. Erbitux was also approved today for use alone (monotherapy) to treat patients whose head and neck cancer has spread (metastasized) despite the use of standard chemotherapy.

"Patients suffering from all forms of cancer have a common goal – to treat the disease and prolong life," said Steven Galson, MD, Director of FDA's Center for Drug Evaluation and Research. "We consider this approval an important advance in the treatment of head and neck cancer because it has been shown to help some patients live longer. The approval of Erbitux monotherapy to shrink tumors in patients with metastatic disease who no longer respond to other forms of treatment is also important. Patients need as many effective treatment options as possible."



Clinical application of ERBITUX + RT in locally advanced SCCHN

- ERBITUX + RT replaces RT alone for the treatment of locally advanced SCCHN
- ERBITUX + RT offers an alternative to concurrent chemotherapy + RT for patients with locally advanced SCCHN
- Studies are ongoing to further improve outcomes for patients with locally advanced SCCHN

