

# Integrazione di cetuximab nella strategia terapeutica combinata dei tumori del testa-collo: la realtà italiana

Cetuximab in associazione alla radioterapia

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*Discussant: G. Numico*



Con il contributo educativo di

 Merck Serono

 MERCK

***Conflitto di interessi: presentazione a simposio sponsorizzato. Inoltre, un altro conflitto...***

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## ***Magrini vs Magrini***

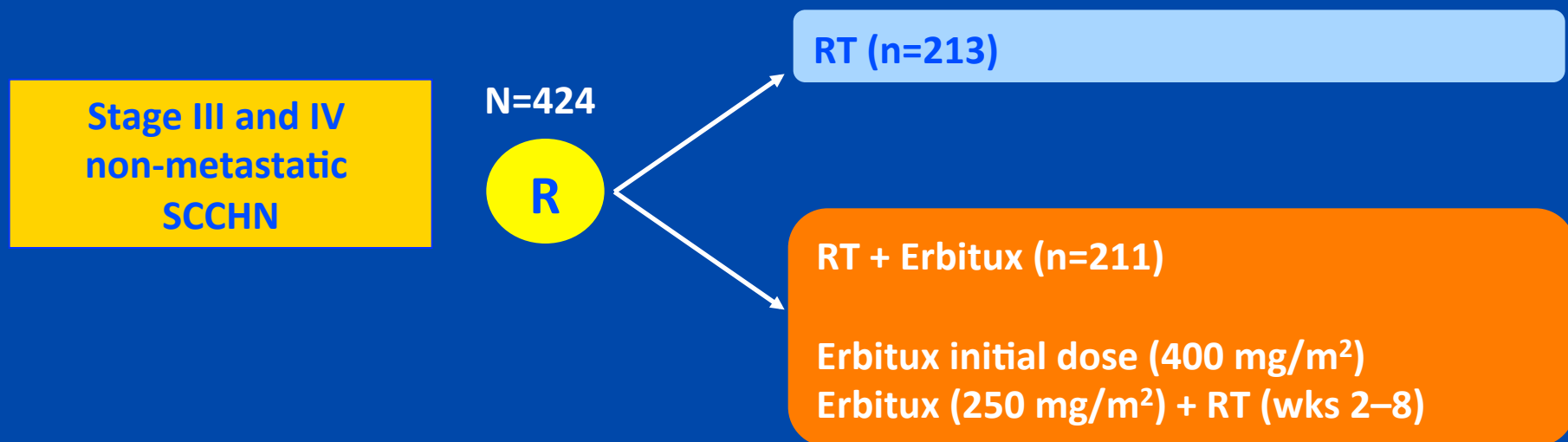
***Perplessità sul “Bonner” e ricerca di un razionale per un impiego logico degli anti-EGFR nel trattamento del carcinoma squamocellulare localmente avanzato del distretto cervico-cefalico (LAHNSCC).***



*La perplessità di riproporre problematiche già discusse in ambito AIRO... e delle possibili reazioni...*



# Erbitux in locally advanced SCCHN: Bonner Phase III study

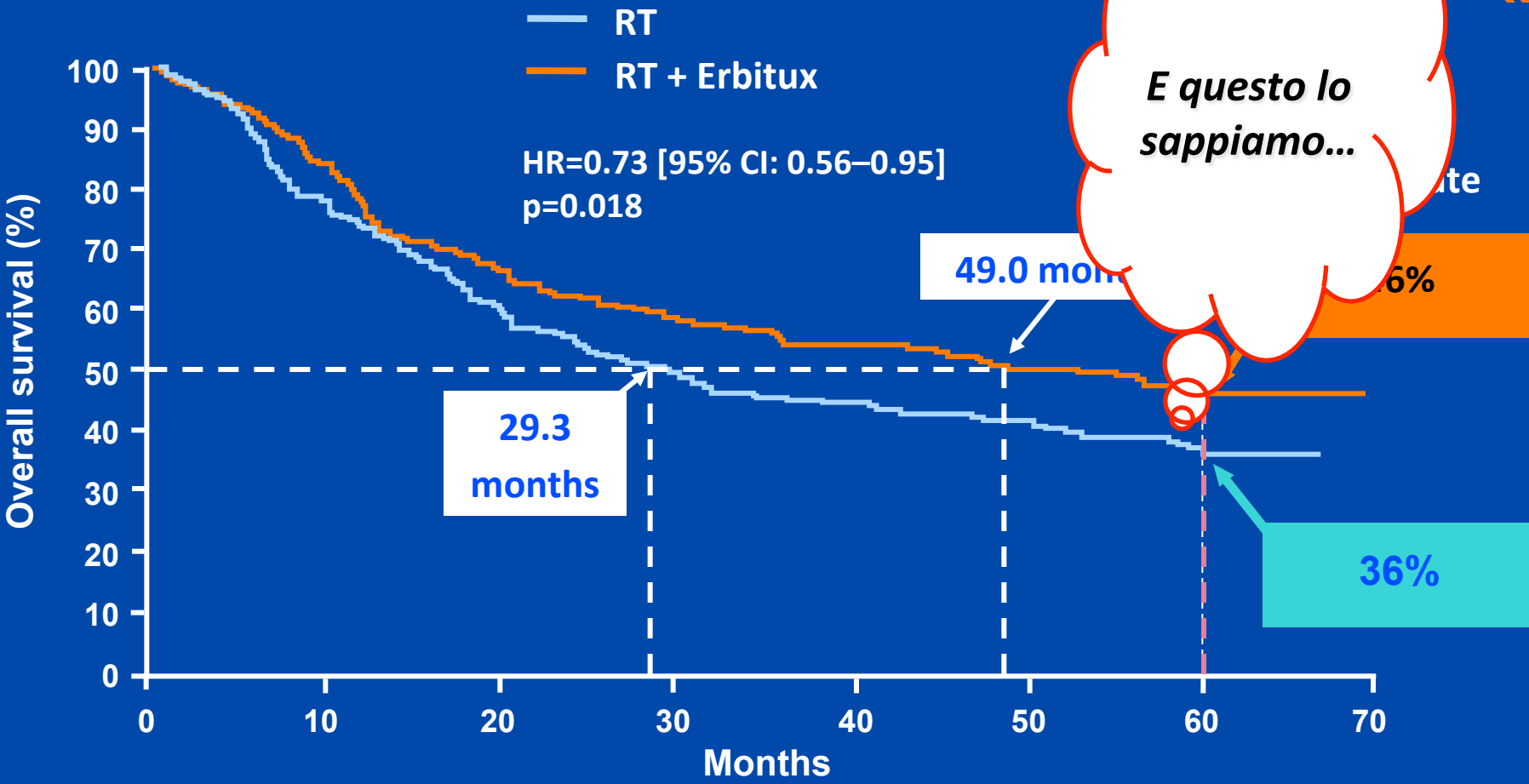


**Primary endpoint:** duration of locoregional control

**Secondary endpoints:** OS, PFS, RR, QoL, and safety

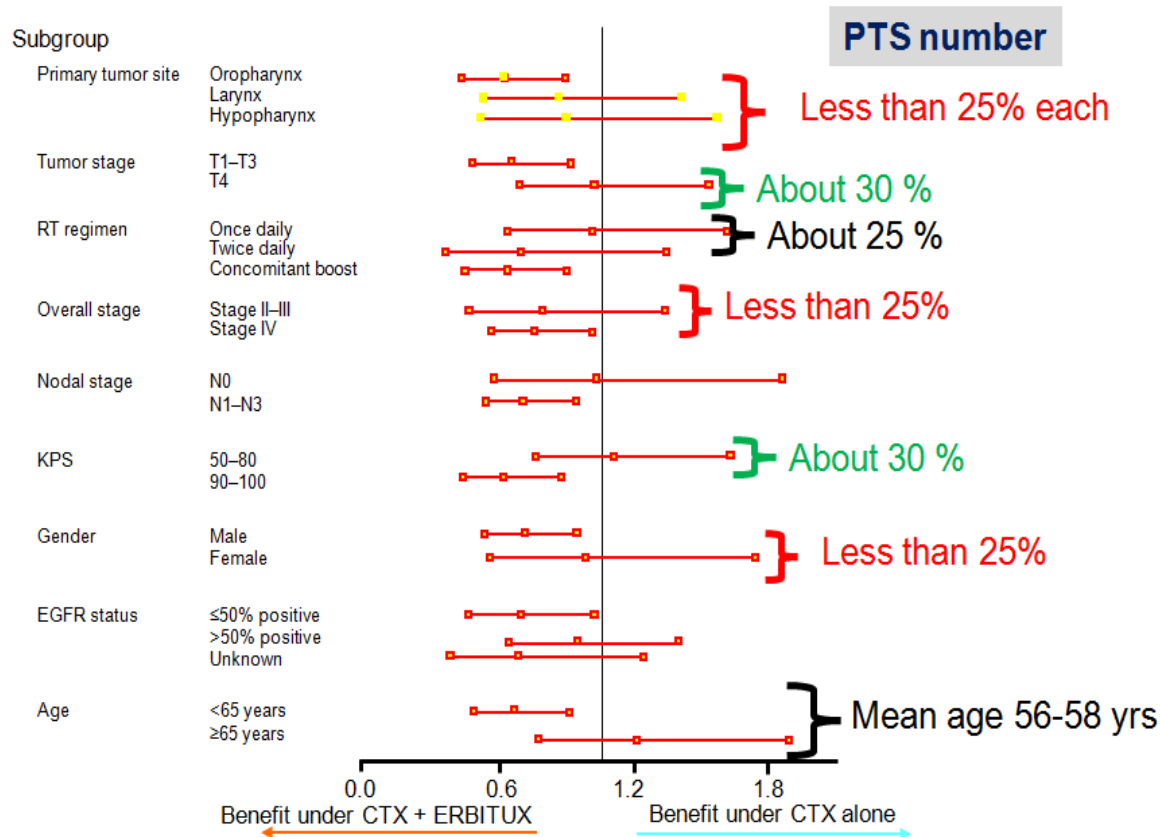


# Erbix in locally advanced SCCHN: 5 years survival update



# Problemi aperti... dopo 2 anni

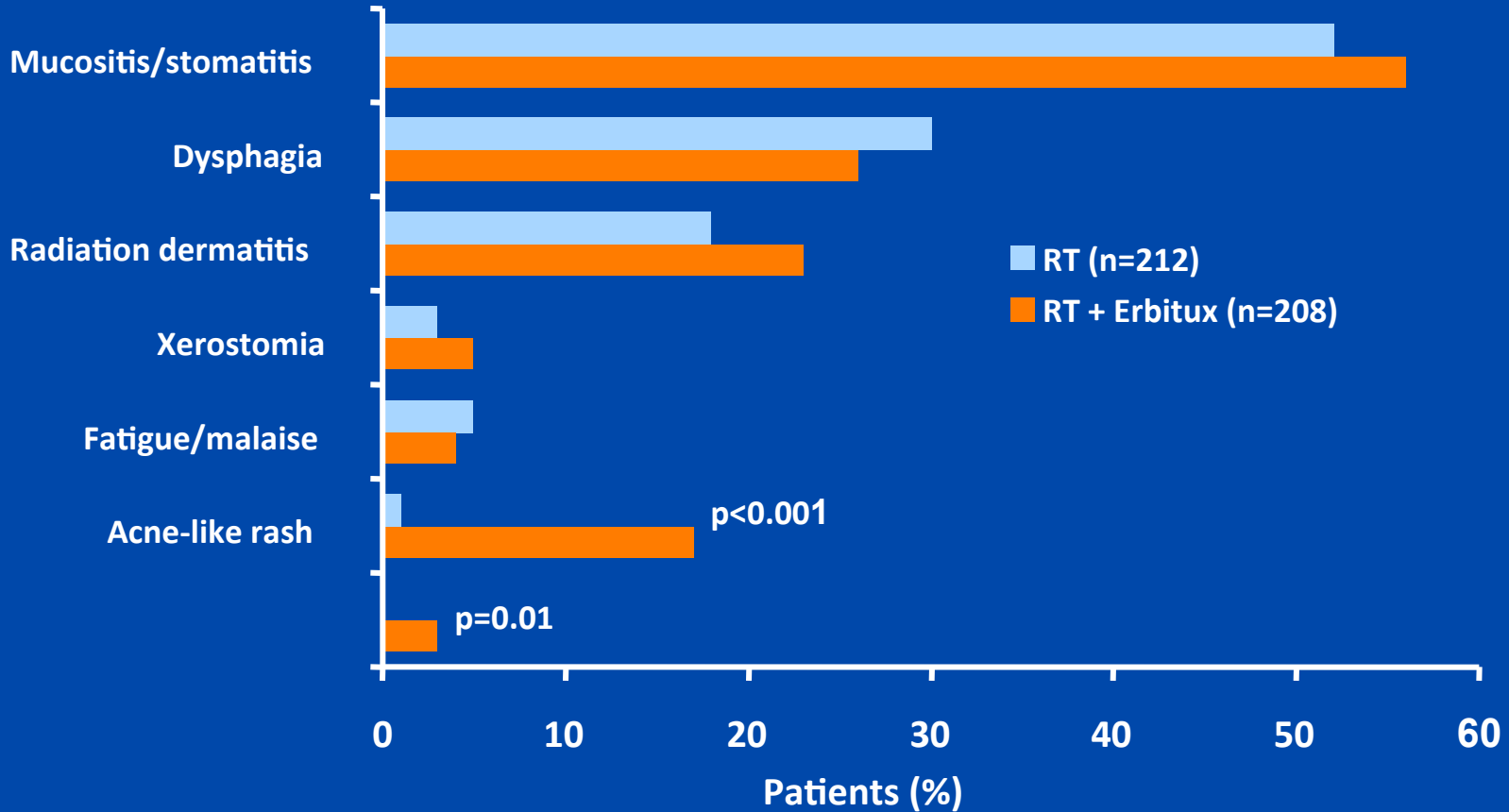
## Forest Plot of the Hazard Ratios by Pre-Treatment Characteristics – 5-year Update



Bonner J.A, et al. as presented ASTRO 2008

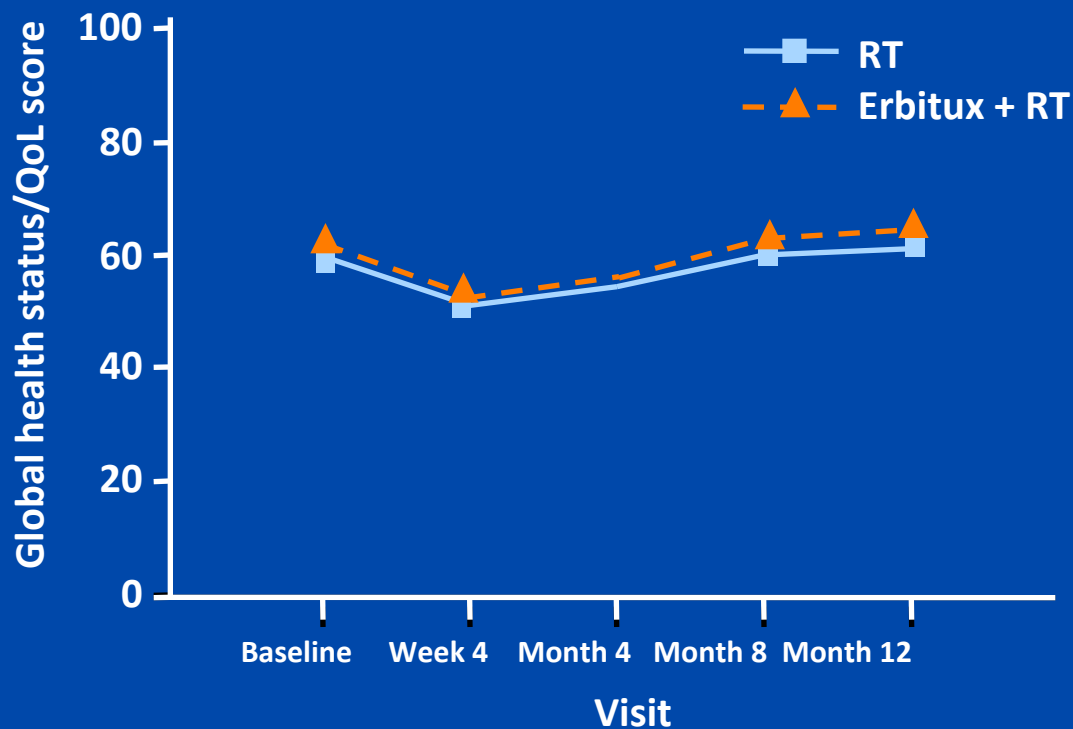
- ✓ **Funziona in tutte le fasce di età ?**
- ✓ **Funziona solo con RT iper-frazionata ?**
- ✓ **Funziona solo in chi ha un buon IK ?**
- ✓ **E' tossico ?**

# Erbix+RT: Relevant grade $\geq 3$ adverse events





# Adding Erbitux+RT does not adversely affect QoL



## Management of radiation dermatitis in patients receiving cetuximab and radiotherapy for locally advanced squamous cell carcinoma of the head and neck: proposals for a revised grading system and consensus management guidelines

J. Bernier<sup>1\*</sup>, E. G. Russi<sup>2</sup>, B. Homey<sup>3</sup>, M. C. Merlano<sup>4</sup>, R. Mesía<sup>5</sup>, F. Peyrade<sup>6</sup> & W. Budach<sup>7</sup>



It is recognized that the management of radiation dermatitis associated with cetuximab plus radiotherapy is an evolving area ... While a few of the trials that have investigated approaches designed to prevent radiation dermatitis have demonstrated some degree of efficacy, *there are currently no validated prevention strategies and this is an area that requires continued investigation.*

## **Dermatologic Infections in Cancer Patients Treated With Epidermal Growth Factor Receptor Inhibitor Therapy**

R. E. Eilers Jr, M. Gandhi, J. D. Patel, M. F. Mulcahy, M. Agulnik, T. Hensing, Mario E. Lacouture

**Patients with dermatologic toxic effects following treatment with EGFRIs have a *high prevalence of cutaneous infections*. Most notably, bacterial infections developed at sites previously affected by dermatologic toxic effects, with leukopenic patients being at greater risk.**

***J Natl Cancer Inst 2010; 102: 47 – 53***





# Erbitux+RT in locally advanced SCC HN: Summary

Probably very useful .....

Erbitux +

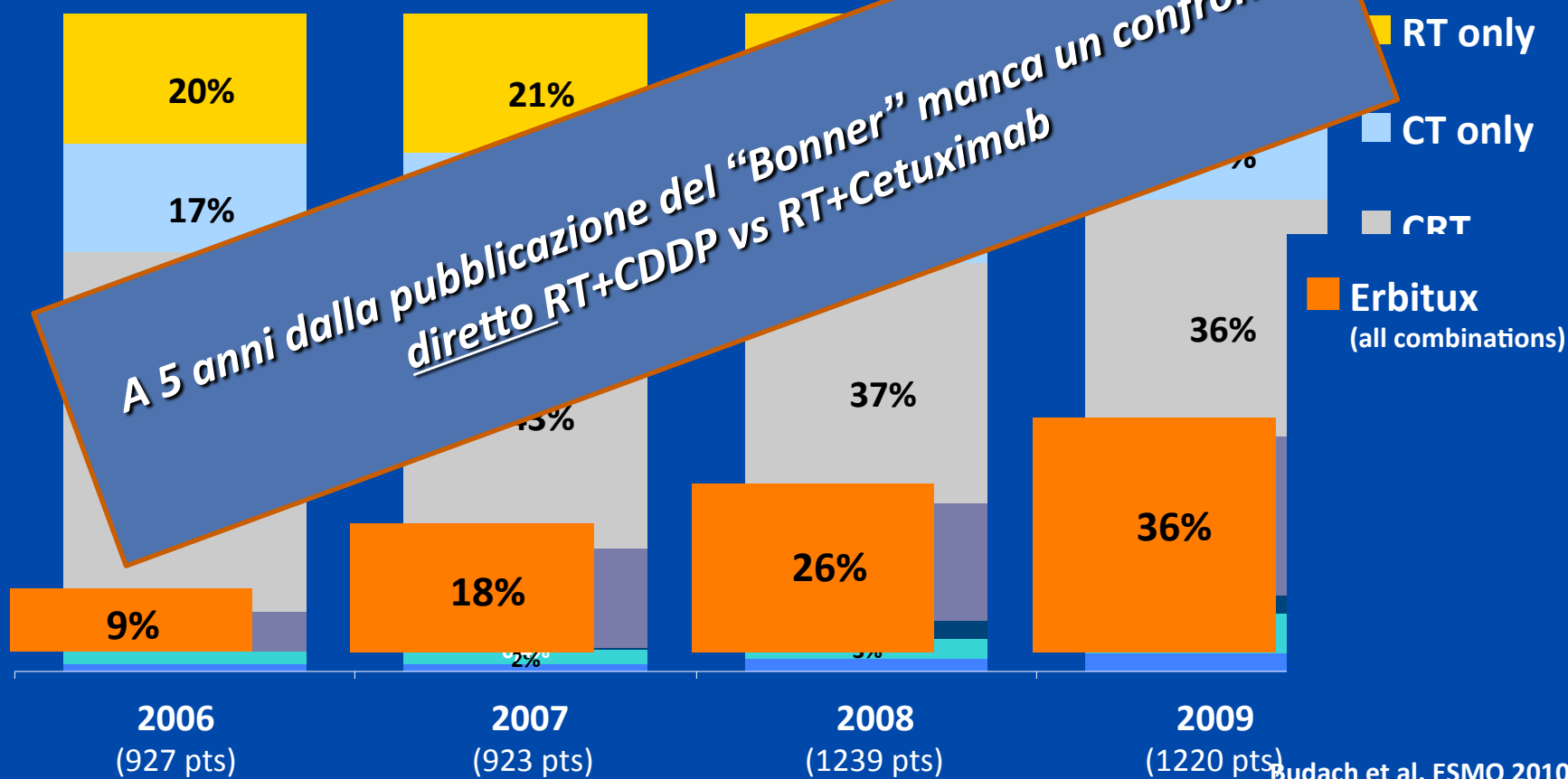
- A ... approach to CRT

Probably better ..... In  
some cases.

- Fav ... toxicity profile

# Erbitux usage in locally advanced SCCHN

Treatment patterns in Europe\*  
(incl. RT only, excluding surgery)



\*Europe: France, Germany, Italy, Spain

# Efficacy: only indirect comparison with CRT available

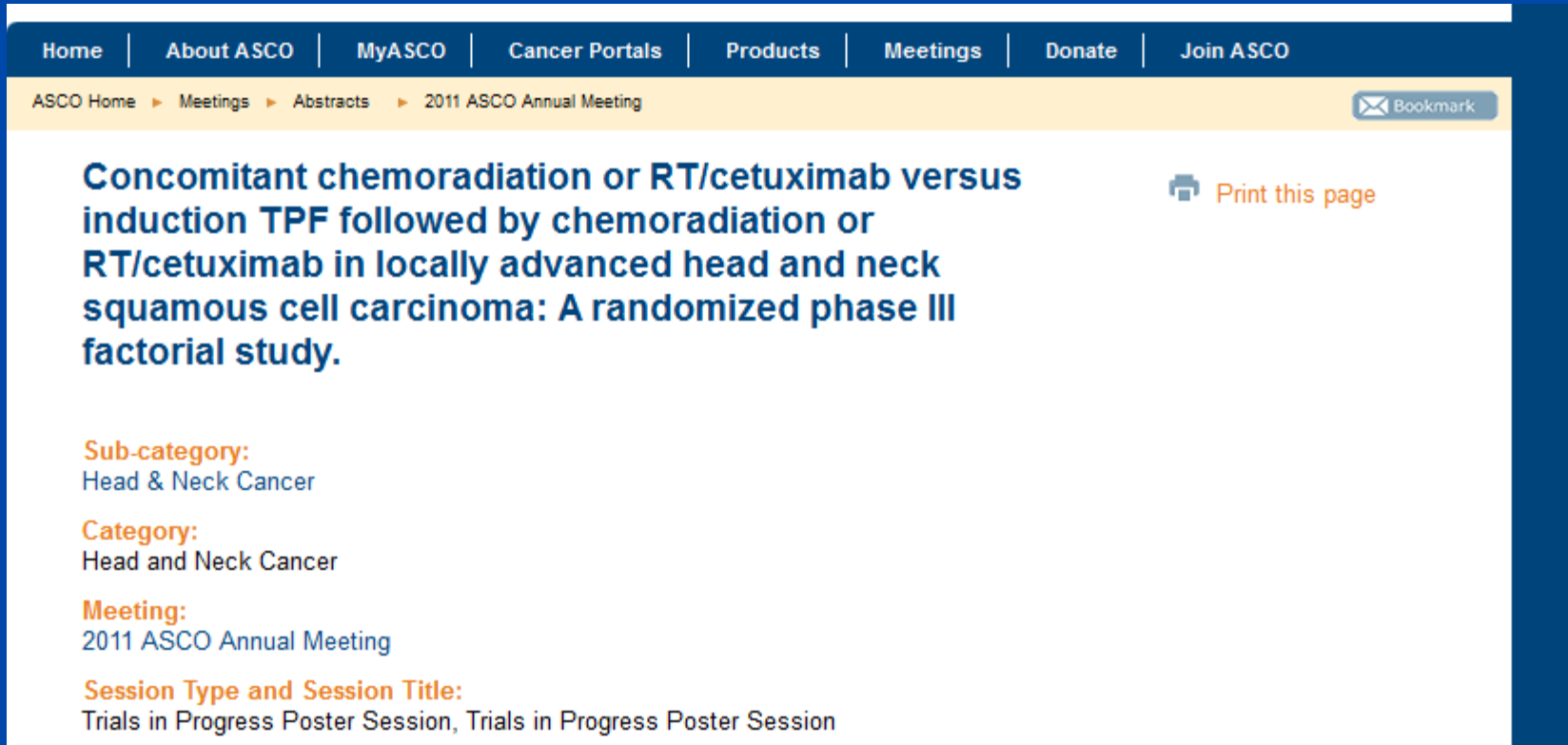
Rx regimens	HR	Absolute Benefit
	(95% CI)	5-Year
RT + concurrent CT <sup>1</sup> vs RT alone	0.81 (0.76–0.88)	8%
Cisplatin + 5-FU	0.77 (0.69–0.85)	10%
Cisplatin alone	<b>0.73</b> (0.56–0.95)	11%
RT + Erbitux vs RT alone <sup>2,3</sup>	<b>0.73</b> (0.56–0.95)	9%
TPF (vs PF) → RT <sup>4</sup>	<b>0.73</b> (0.56–0.94)	
TPF (vs PF) → RT + Carboplatin <sup>5</sup>	<b>0.70</b> (0.54–0.90)	

<sup>1</sup>Pignon et al. Lancet 2000; <sup>2</sup>Bonner et al. NEJM 2006; <sup>3</sup>Bonner et al. Lancet Oncol 2010;

<sup>4</sup>Vermorken et al. NEJM 2007; <sup>5</sup>Posner et al. NEJM 2007



# Di quali nuovi dati disponiamo ?



The screenshot shows the ASCO website interface. At the top, there is a navigation menu with links: Home, About ASCO, MyASCO, Cancer Portals, Products, Meetings, Donate, and Join ASCO. Below the navigation menu is a breadcrumb trail: ASCO Home > Meetings > Abstracts > 2011 ASCO Annual Meeting. On the right side of the breadcrumb trail, there is a 'Bookmark' button. The main content area features a large blue heading for the abstract: 'Concomitant chemoradiation or RT/cetuximab versus induction TPF followed by chemoradiation or RT/cetuximab in locally advanced head and neck squamous cell carcinoma: A randomized phase III factorial study.' To the right of the heading is a 'Print this page' button. Below the heading, there are three sections: 'Sub-category: Head & Neck Cancer', 'Category: Head and Neck Cancer', and 'Meeting: 2011 ASCO Annual Meeting'. At the bottom, there is a section for 'Session Type and Session Title: Trials in Progress Poster Session, Trials in Progress Poster Session'.

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## Concomitant chemoradiation or RT/cetuximab versus induction TPF followed by chemoradiation or RT/cetuximab in locally advanced head and neck squamous cell carcinoma: A randomized phase III factorial study.

[Print this page](#)

**Sub-category:**  
Head & Neck Cancer

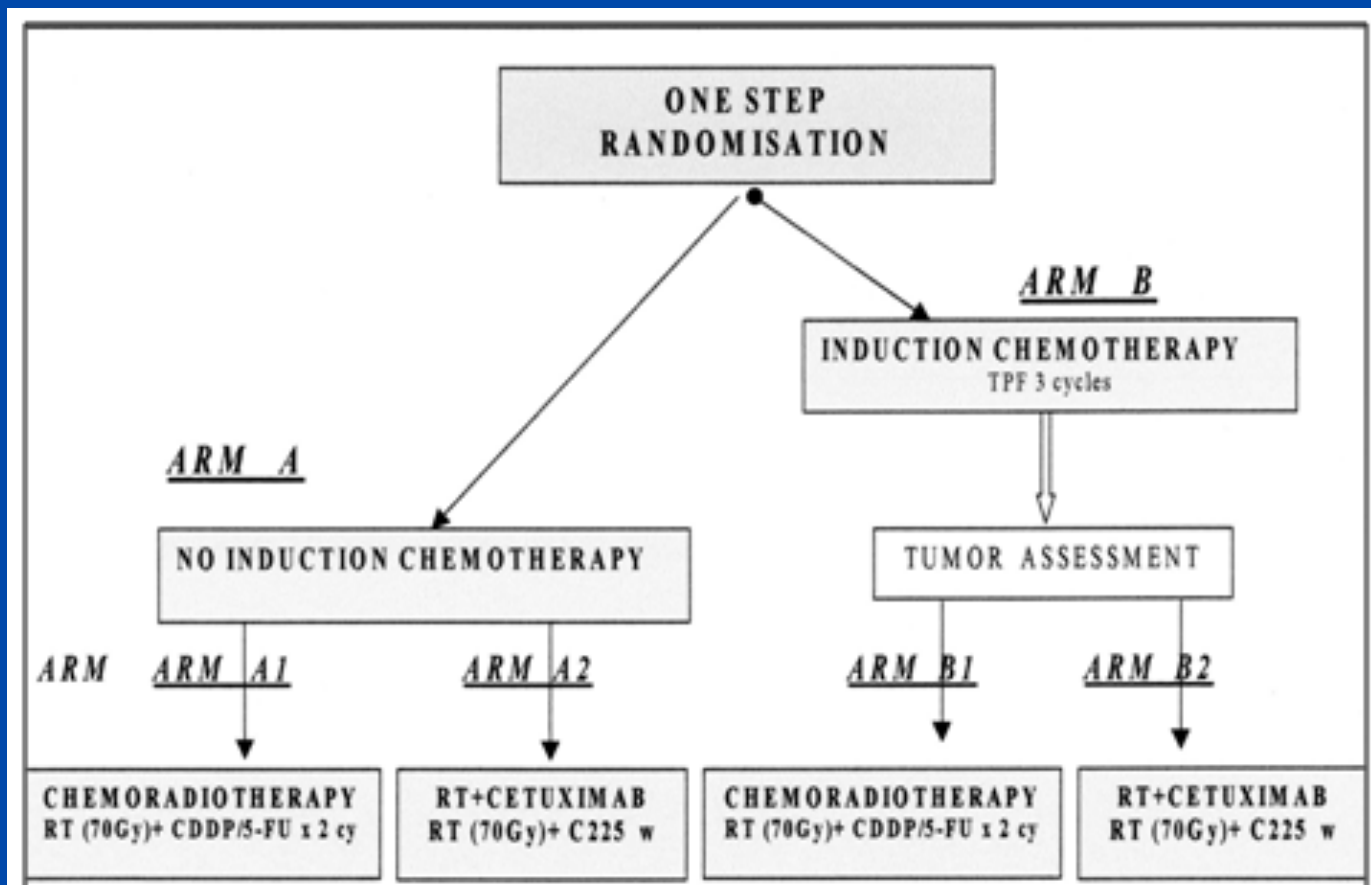
**Category:**  
Head and Neck Cancer

**Meeting:**  
2011 ASCO Annual Meeting

**Session Type and Session Title:**  
Trials in Progress Poster Session, Trials in Progress Poster Session

***Paccagnella et al. , ASCO 2011 : evidenze indirette ... da confermare***

# Disegno studio ....



### Abstract:

**Background:** Concomitant chemoradiation (CRT) is the standard treatment for locally advanced squamous cell carcinoma (LASCC). RT plus cetuximab is superior to RT alone and it is an alternative treatment to CRT (Bonner, NEJM 2006). The efficacy of induction chemotherapy when added to standard treatment has never been demonstrated, however, induction cisplatin/fluorouracil [PF] plus docetaxel combination (TPF) is superior to PF when added to CRT or RT alone (Posner, NEJM 2005; Vermorken, NEJM 2005). **Methods:** This ongoing factorial phase III study is the implementation of a previous phase II randomized trial evaluating the efficacy of CRT with or without induction TPF. At the end of the phase II study a Monitoring Committee decided to continue the study as a phase III, as initially planned, based on the efficacy and safety data of the phase II study. This phase III four arm factorial study has now randomized 352 patients (target 420) with LASCC unresectable stage III-IVM0 of oral cavity, oropharynx, hypopharynx, age > 18 years, ECOG PS 0-1, measurable disease by RECIST, adequate organ function. One step randomization is adopted to assign patients to concomitant treatment alone CRT (arm A1) or RT/cetuximab (arm A2) or to 3 cycles of induction TPF followed by CRT (arm B1) or RT/cetuximab (arm B2). Two concomitant PF cycles are administered in the CRT arm. Primary endpoints are the comparison of 3-year overall survival (OS) between induction vs no induction and the incidence of G3-4 in-field toxicity between CRT and RT/cetuximab. During the planned ad-interim analysis, the Independent Data and Safety Monitoring Committee decided to increase the sample size from the initially planned 350 patients to 420 to detect an absolute difference of 12% in 3 years OS in favour of the induction arm. Assuming an hazard ratio of 0.675 this study will have 80% statistical power with a two-sided type I error of 0.05. The total number of 420 patients will also be able to detect a difference of 10%, in grade 3-4 in-field toxicity between CRT vs RT/cetuximab with a power of 80%.

# 3 meglio di 2 ? Forse no....

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### **RTOG 0522 Initial Results Reported at ASCO**

posted on June 07, 2011 04:50

**Initial Results of RTOG Clinical Trial Show No Survival Benefits by the Addition of Cetuximab to Chemoradiation Treatment for Patients with Locally Advanced Head and Neck Cancer**

*The randomized trial conducted by the Radiation Therapy Oncology Group (RTOG) sought to determine if adding cetuximab to a chemoradiotherapy treatment regimen would improve progression-free and overall survival for patients with Stage III-IV head and neck squamous cell cancers. The initial results will be presented at the 2011 American Society of Clinical Oncology Annual Meeting on June 6.*

Head and neck cancer is the sixth most common cancer worldwide, with 36,540 new cases and 7,880 deaths estimated in the United States for 2010. Ninety percent of cases are head and neck cancers squamous cell carcinomas (HNSCC), and many patients are first diagnosed with locally advanced (Stage III-IV) disease that is associated with a poor prognosis.

## ***3 meglio di 2 ? Forse no .. Ma bisogna capire per chi ...***



**“Kian Ang, MD (MD Anderson Cancer Center), the principal investigator for the recently completed RTOG 0522 states, “The next step was to assess whether adding cetuximab to a chemoradiation treatment regimen would further improve both progression-free and overall survival without added adverse side effects. The initial results, however, show that the addition of cetuximab to the radiation-cisplatin platform did not improve progression-free or overall survival and was associated with higher rates of mucositis and cetuximab-induced skin reactions. The rate of mucositis was, however, within the range of that reported in other prospective trials testing various combined therapy regimens.”**

***Further analysis is underway to determine if tumor human papillomavirus status affects the relative efficacy of the chemoradiotherapy plus cetuximab regimen.***

Tornate tutti a casa! Non se ne fa niente!  
Il Papa, da Roma l'ha proibito: lo  
spettacolo è finito!"

**"Ed io lo faccio lo stesso! - disse prete  
Liprando -  
ma le fascine, quaranta!- io non ce le  
ho!..."**

...La gente portava le fascine fin da  
Biandrate;  
facevano un sacco di fumo: la gente  
tossiva,  
tossiva e piangeva, ma non si muoveva!  
Che popolo pio! Voleva vedere il Giudizio  
di Dio!

"Eccolo là!... Liprando è già pronto..."

"Dove l'è?"

**Liprando** (... -1113) era un prete milanese, diventato famoso per una disputa con l'arcivescovo Grossolano, che lo portò a passare attraverso due pire infuocate per dimostrare l'accusa di simonia che aveva rivolto contro l'arcivescovo..



# Attivazione di Studio Fase II di confronto diretto RT+CHT vs RT+Erbitux

National Cancer Institute

at the National Institutes of Health

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**Trial Status:** Active

**Trial Investigators:** Stefano Magrini

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1. [Cetuximab Plus Radiotherapy Versus Cisplatin Plus Radiotherapy in Locally Advanced Head and Neck Cancer](#)

# “Real world” conditions ...

Phase	Type	Status	Age	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	Other	eudract 2010-021552-26 NCT01216020

## Trial Description

### Summary

#### BACKGROUND:

Concomitant radiotherapy and cisplatin (CDDP) based chemotherapy is the standard treatment for LA-NHSCC. This combined modality treatment is linked with considerable acute local and systemic toxicity. EGFR is overexpressed in 90-100% of the HNSCC cases and is considered an unfavourable prognostic marker. EGFR constitutive activation is linked with HNSCC pathogenesis.

Cetuximab is a monoclonal anti-EGFR antibody blocking the activation of the receptor and signal transduction. Cetuximab combined with radiotherapy is superior to radiotherapy only in the treatment of LA-HNSCC and is characterized by an acceptable toxicity profile.

# “Real world” conditions ...



## RATIONALE:

A direct comparison between concomitant chemoradiotherapy with Cisplatin and the concomitant treatment with radiotherapy associated to cetuximab does not exist.

## STUDY DESIGN:

Arm A: Radical radiotherapy (doses and volumes) concomitant with chemotherapy with Cisplatin (40 mg/mq/week) Arm B: Radical radiotherapy (doses and volumes) concomitant with therapy with the monoclonal antibody Cetuximab (400 mg/m<sup>2</sup> ["loading dose"] and subsequently 250 mg /m<sup>2</sup>/week)

# *Further Study Information...*



## ***PRIMARY OBJECTIVES:***

***Evaluation and comparison of the compliance of the two treatments***

## ***SECONDARY OBJECTIVES:***

***Evaluation and comparison of the grade and incidence of acute toxicity;***

***Evaluation and comparison of local control;***

***Evaluation and comparison of event free survival (both local control and distant metastases);***

***Evaluation and comparison of cause specific / overall survival.***

# ***Centri partecipanti***

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- ✓ ***Arezzo***
- ✓ ***Brescia***
- ✓ ***Firenze***
- ✓ ***Genova***
- ✓ ***Pistoia***
- ✓ ***Prato***
- ✓ ***Siena***
- ✓ ***Torino***

# ***In corso....***



- ✓ ***Reclutati 16 pazienti...***
- ✓ ***Conclusi i primi trattamenti...***
- ✓ ***Emendamenti per stratificazione per determinanti biologici ... (HPV, EGFR...)***
- ✓ ***Aumento numero Centri partecipanti ...***
- ✓ ***Difficoltà per assicurazione (studio no profit)***



# Concludendo...



1. L'associazione Cetuximab / RT è meglio di sola RT
2. Mancano confronti diretti RT+Cetux vs RT + CDDP
3. Cetuximab è stato spesso usato in serie sfavorite per condizioni generali e patologia concomitante
4. In queste condizioni la sua tollerabilità è risultata soddisfacente



5. E' necessario definire le diverse indicazioni di Cetuximab e CDDP in associazione a RT, sulla base delle caratteristiche dei pazienti e dei principali fattori biologici che caratterizzano la malattia
6. Sono necessari studi di confronto diretto con analisi dei possibili determinanti biologici dell'*outcome* per rispondere a questi quesiti di indubbia rilevanza clinica.