Le associazioni con i nuovi farmaci biologici

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Larynx preservation: a dilemma

“Ideal” goal of non-surgical approaches:
disease control+organ preservation+function preservation

“**Ideal” composite endpoint**:
survival and preservation of organ function
-heterogeneity among published trials
-standardization of assessment of speech and swallowing functions

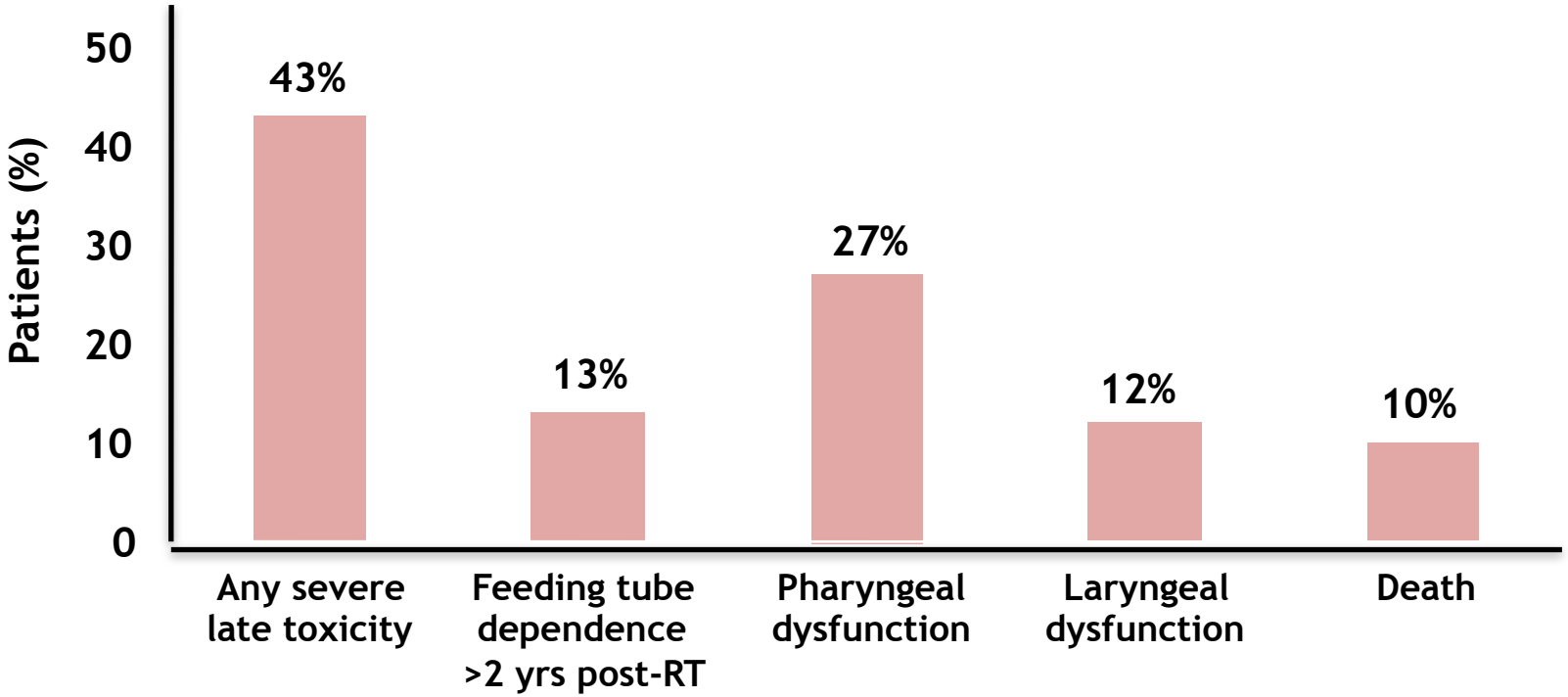
“Ideal” patient:
T2 or T3 laryngeal (glottic or supraglottic) or hypopharyngeal SCC without laryngeal dysfunction aged ≤70

Larynx preservation: current evidence

- Concomitant CT/RT gives higher **LP** rate and is considered the preferred approach in most cases. *(RTOG 91-11, 2003-2013)*
- Similar **LFS** and **DFS** with lower toxicity may be achieved with induction CT followed by RT for responders or alternating CT/RT. *(RTOG 91-11, 2003) (EORTC 24954, 2009)*
- **TPF** should be considered the standard regimen when an induction therapy is chosen. *(GORTEC, 2009)*

Concurrent RT + CDDP 100mg/mq: real standard?

Analysis of late toxicity in 230 patients receiving CRT in 3 studies (RTOG 91-11, 97-03, 99-14)



[a] Chronic grade 3-4 pharyngeal/laryngeal toxicity and/or requirement for feeding tube >2 years after registration and/or potential treatment-related death within 3 years

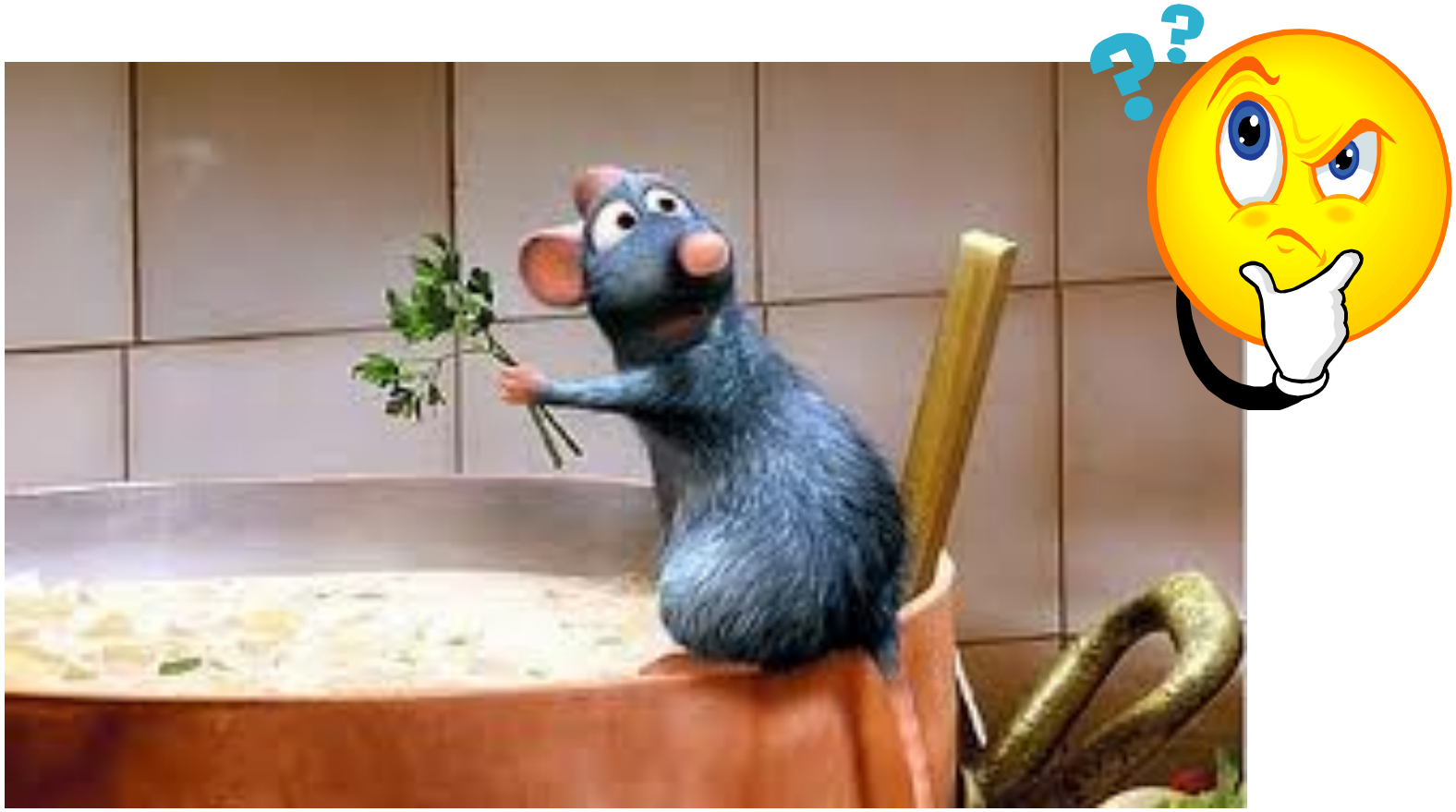
Machtay et al. J Clin Oncol 2008

RTOG 91-11
larynx preservation trial update

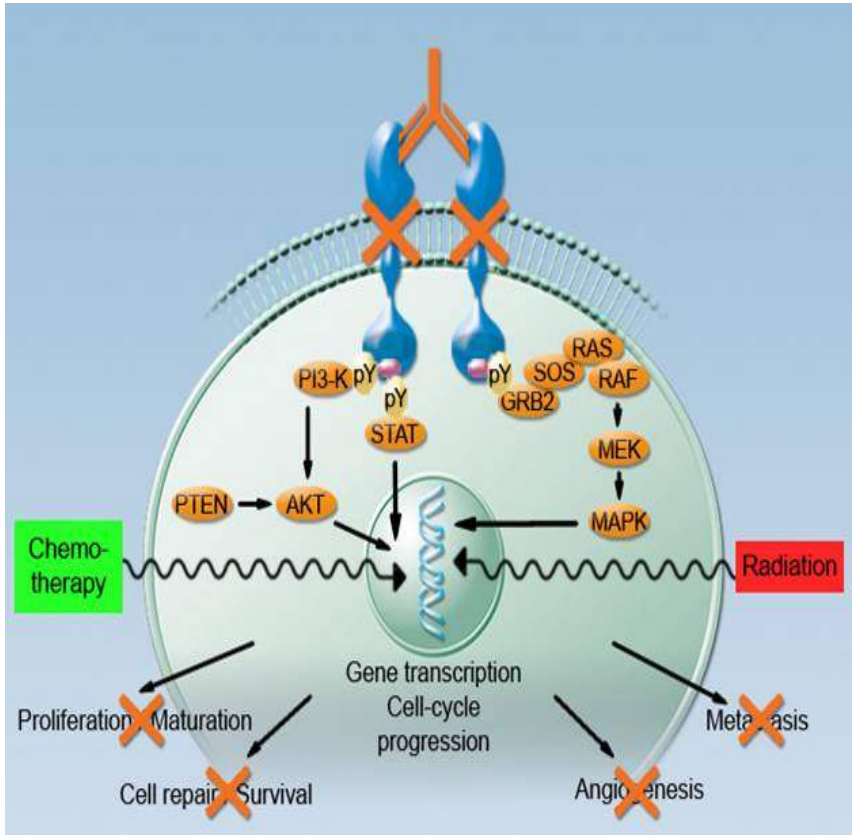
	Induction *(n=173)*	Concurrent *(n=172)*	Radiation *(n=173)*
Laryngectomy free survival **5 ys**	**44.1% (p=.011)**	**47 (p=.011)**	**34%**
Laryngectomy free survival **10 ys**	**28.9%**	**23.5%**	**17.2%**
Overall survival **5 ys**	**58.1%**	**55.1%**	**53.8%**
Overall survival **10 ys**	**38.8%**	**27.5%**	**31.5%**
Local control **5 ys**	**58.2%**	**71.1%**	**53.6%**
Local control **10 ys**	**53.7%**	**69.2%**	**50.1%**
Laryngeal preservation **5ys**	**70.8%**	**83.6%**	**65.8%**
Laryngeal preservation **10ys**	**67.5%**	**81.7%**	**63.8%**

Forastiere jco 2013

Larynx Preservation: can we do better?

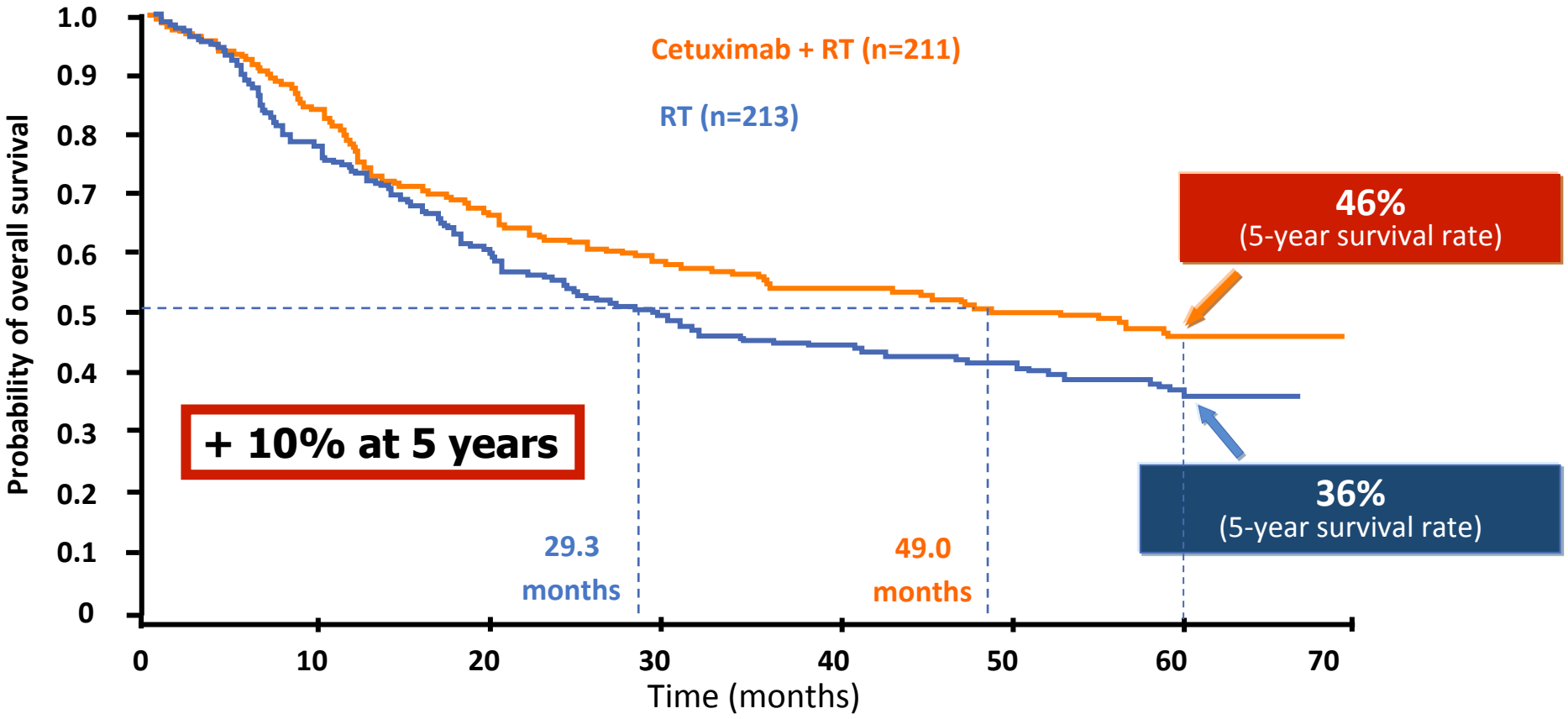


… adding targeted therapies…



- TGFa, EGF interaction with EGFR: increased cell proliferation/neoplastic trigger
- EGFR promotes accelerated repopulation of the tumor when neoplastic cells are hit by radiation (**EGFR-mediated radioresistance**)
- Cetuximab blocks EGFR downstream signals and **potentiates radiation and chemotherapy effects** resulting in decreased proliferation

Cetuximab + RT: Overall Survival



Hazard ratio=0.73 (95% CI: 0.56–0.95); p=0.018

Bonner JA et al, Lancet Onc 2010

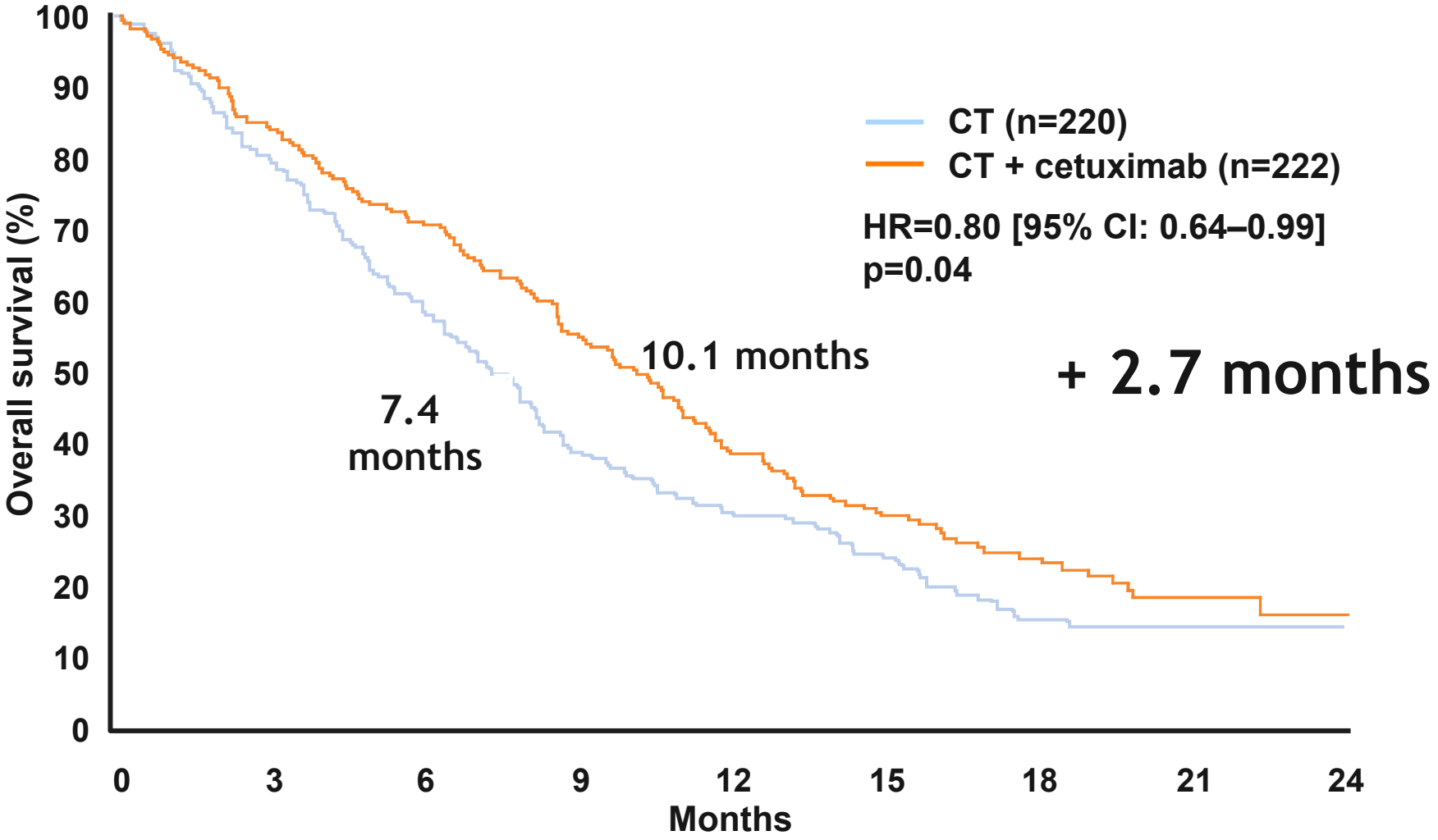
Cetuximab + RT: Organ preservation

Subset of 171 patients with laryngeal and hypopharyngeal SCC

	Laryngeal preservation	
Treatment	**2-year rate**	**3-year rate**
RT alone (n=78)	**80%**	**77%**
cetuximab + RT (n=93)	**90%**	**87%**

Bonner J et al. J Clin Oncol 2005;23(Suppl. 16):Abstract No. 5533

Cetuximab in 1st-line SCCHN EXTREME: significant OS benefit



Vermorken et al. NEJM 2008

Potential role of Cetuximab in laryngeal preservation strategies

- **Cetuximab + RT significantly improves survival and locoregional control over RT alone in locally advanced SCCHN**
- **Laryngeal preservation is directly linked to local control**
- **Cetuximab + RT causes fewer adverse events that could compromise the function of the preserved larynx**

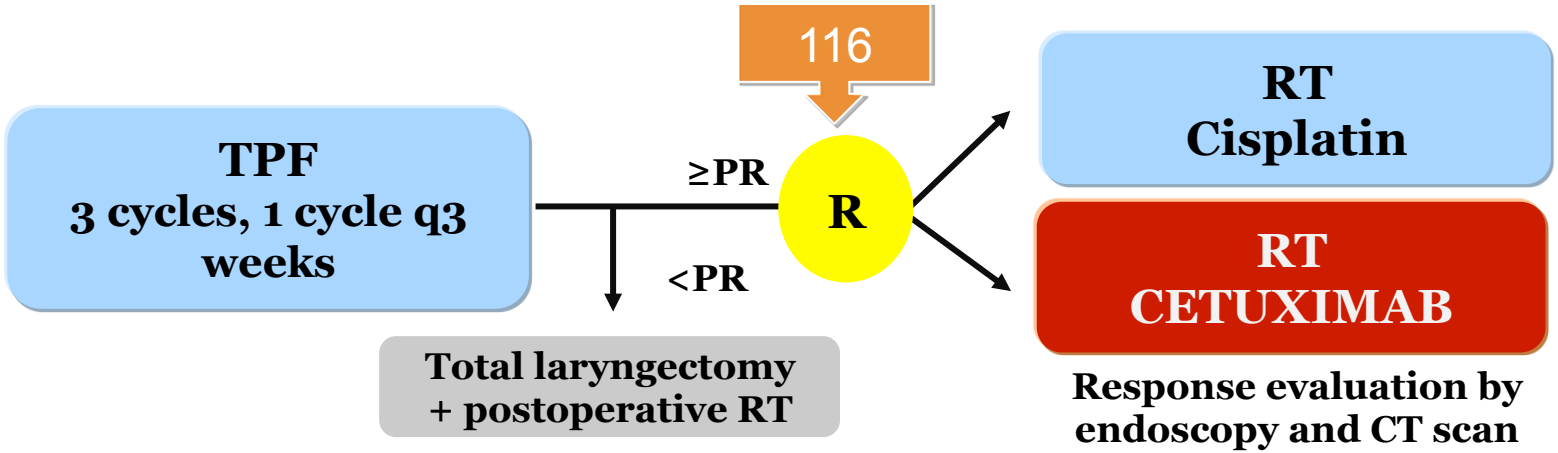
Improving strategies for larynx preservation

- **Improving ICT?**
- **Improving CRT?**
- **Sequencing ICT and CRT?**

cetuximab

TREMPLIN study

Previously untreated SCC larynx/hypopharynx suitable for total laryngectomy (n=153)



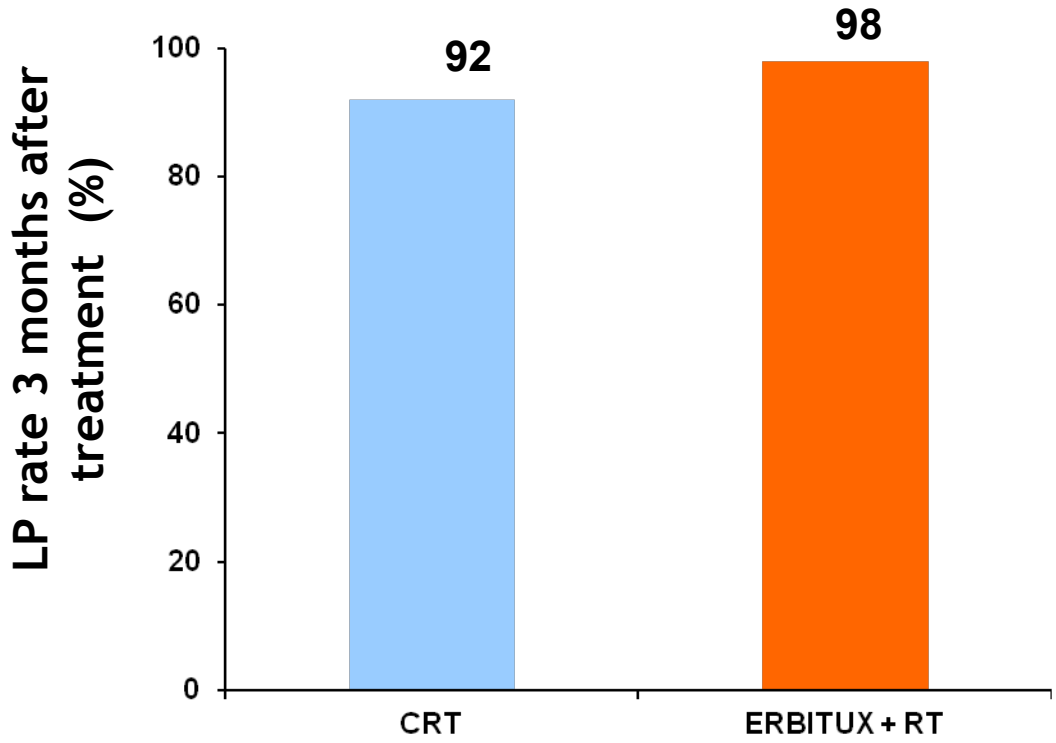
TPF Docetaxel: Cisplatin: 5-FU:	 75 mg/m^2, day 1 in each induction cycle 75 mg/m^2 day 1 in each induction cycle 750 mg/m^2 days 1–5 in each induction cycle
RT:	70 Gy
CETUXIMAB	400 mg/m^2 1 week prior to RT then 250 mg/m^2 weekly on weeks 1–7
Cisplatin:	100 mg/m^2 and day 1, 22, 43 post-randomization

- **Primary endpoint:** larynx preservation 3 months after treatment
- **Secondary endpoints:** larynx function preservation and survival 18 months after treatment

Lefebvre J et al. J Clin Oncol 2013

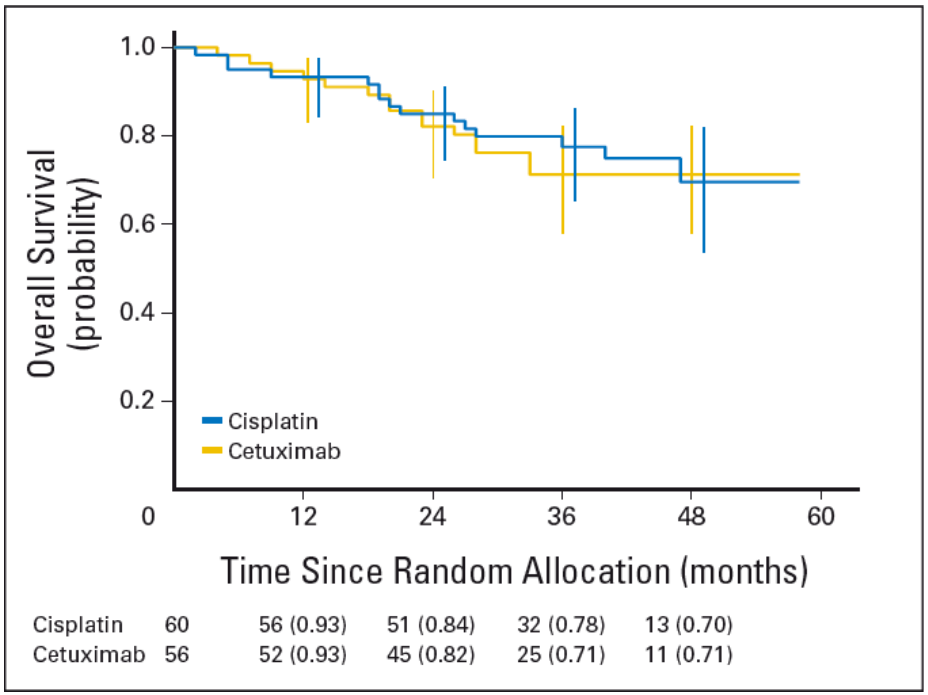
Adding cetuximab to RT provides similar efficacy to concomitant CRT

The immediate larynx preservation (LP) rate after TPF followed by cetuximab + RT is similar to TPF followed by cisplatin + RT



Lefebvre J et al. J Clin Oncol 2013

Tremplin study: secondary endpoints



- No difference in OS: 92% CRT vs 89% Cetuximab + RT (18 months)
- No difference in LFP: 87% CRT VS 82% Cetuximab + RT (18 months)

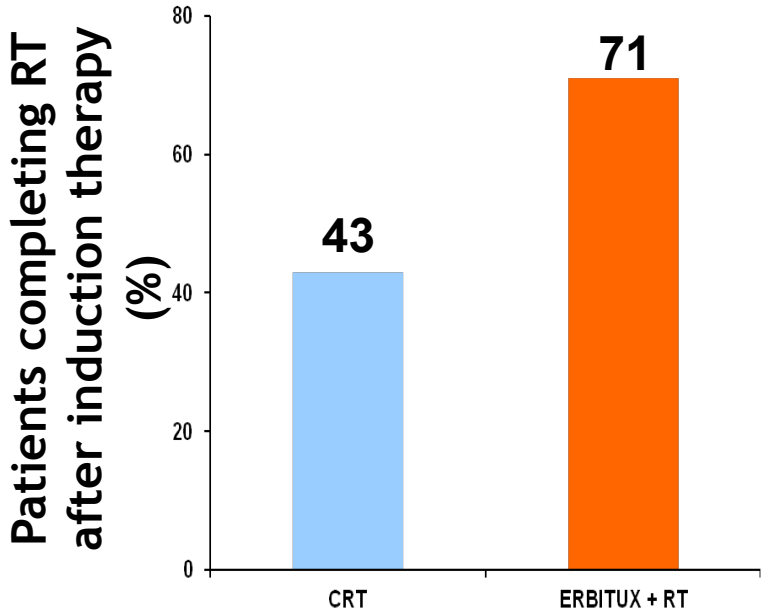
cetuximab + RT: more patients treated as planned

More patients were able to complete their cetuximab + RT course compared with patients receiving CRT

Table 3. Acute Toxicity

Variable	Cisplatin No.	Cisplatin %	Cetuximab No.	Cetuximab %
No. of patients	58*		56	
Mucositis grade				
3	25	43	24	43
4	2	3	1	2
In-field skin toxicity grade				
3	14	24	29	52
4	1	2	3	5
Other toxicity, any grade, justifying protocol modification				
Renal	9	15.5	0	
Hematologic	8	14	0	
Poor performance	7	12	1	1.7
Infusion-related reaction	0		3	5
Protocol modification due to acute toxicity	33	57	19	34

*Two patients did not start treatment.



Lefebvre J et al. J Clin Oncol 2013

TREMPLIN study: summary

- **After TPF induction chemotherapy, an 85% ORR allowed continuation of the LP protocol**
- **TPF-induced toxicity precluded further cisplatin in some cases (but would not have precluded cetuximab)**
- **TPF followed by RT + cisplatin had substantial toxicity**
- **TPF followed by RT + cetuximab had lower toxicity and improved compliance**
- **The immediate LP and delayed LFP were similar in each treatment arm**

Lefebvre J et al. J Clin Oncol 2013

Improving strategies for larynx preservation

- **Improving ICT?**
- **Improving CRT**
- **Sequencing ICT and CRT?**

cetuximab

cetuximab

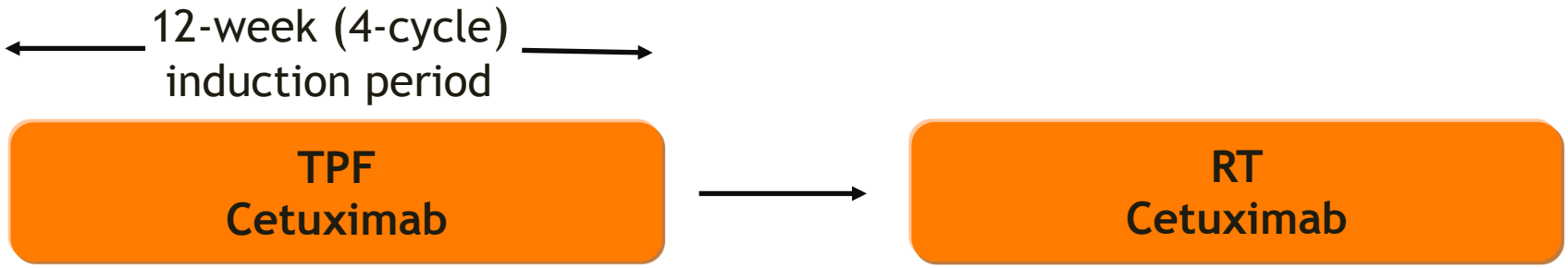
Phase I/II Studies assessing the addition of Cetuximab in ICT ±CRT

Study	#	CT regimen	CR	RR	CT–RT regimen	Survival
Posner et al. [4]	255	DCF	17%	72%	RT + Cb	3y OS: 62%
Vermorken et al. [5]	177	DCF	8.5%	68%	RT	3y OS: 37%
Pointreau et al. [6]	110	DCF	42%	80%	RT	3y OS: 60%
Hitt et al. [8]	189	PCF	33%	80%	RT + C	2y OS: 66%
Haddad et al. [9]	28	DCF + Cet	80% (T)	100%	RT + CT	1y OS: 85%
Kies et al. [12]	47	P Cb + Cet	19%	96%	RT + C	3y OS: 91%
Mesia et al. [10]	50	DCF + Cet	24%	78%	RT + Cet	n.r.
Argiris et al. [15]	39	DC + Cet	5.4%	86%	RT + wC + Cet	3y OS: 74%
Wanebo et al. [16]	61	Cb + P + Cet	59% (T)	n.r.	RT + Cb + P + Cet	2y OS: 82%
Siewert et al. [17]	54	Cb + P + Cet	n.r.	92%	RT + HU + F + Cet	2y OS: 89%
Siewert et al. [17]	56	Cb + P + Cet	n.r.	92%	RT + P + Cet	2y OS: 91%

CT: chemotherapy; RT: radiotherapy; OS: overall survival; CR: complete response rate; RR: overall response rate; D: docetaxel; C: Cisplatin; wC: weekly Cisplatin; F: Fluorouracil; P: paclitaxel; Cb: Carboplatin; Cet: Cetuximab; n.r.: not reported; (T): response rate on the T-site.

Phase II study (NEO-TPFE-TTCC): Sequential therapy with Cetuximab

Stage IV LA HNC (n=50); 30% Stage IVb



TPF (4 cycles) Docetaxel: Cisplatin: 5-FU:	 75 mg/m^2 day 1 75 mg/m^2 day 1 750 mg/m^2 days 1–5
Cetuximab	Initial dose 400 mg/m^2 on cycle 1, day 1, then 250 mg/m^2 day 1, 8, 15 in induction period 250 mg/m^2 weekly with RT
RT:	Accelerated RT with concomitant boost (70 Gy)

Primary endpoint: objective response rate after 2 and 4 cycles
Secondary endpoints: complete response rate, safety and toxicity, compliance rate

Mesia R et al. J Clin Oncol 2009;27(Suppl. 15):Abstract 6015

Phase II study: Efficacy and toxicity

ERBITUX + TPF induction chemotherapy gives a high response rate

Efficacy (n=47)[a]	
Complete response, %	26
Partial response, %	57
Stable disease, %	6
Progressive disease, %	3

ORR = 83%

Disease control = 89%

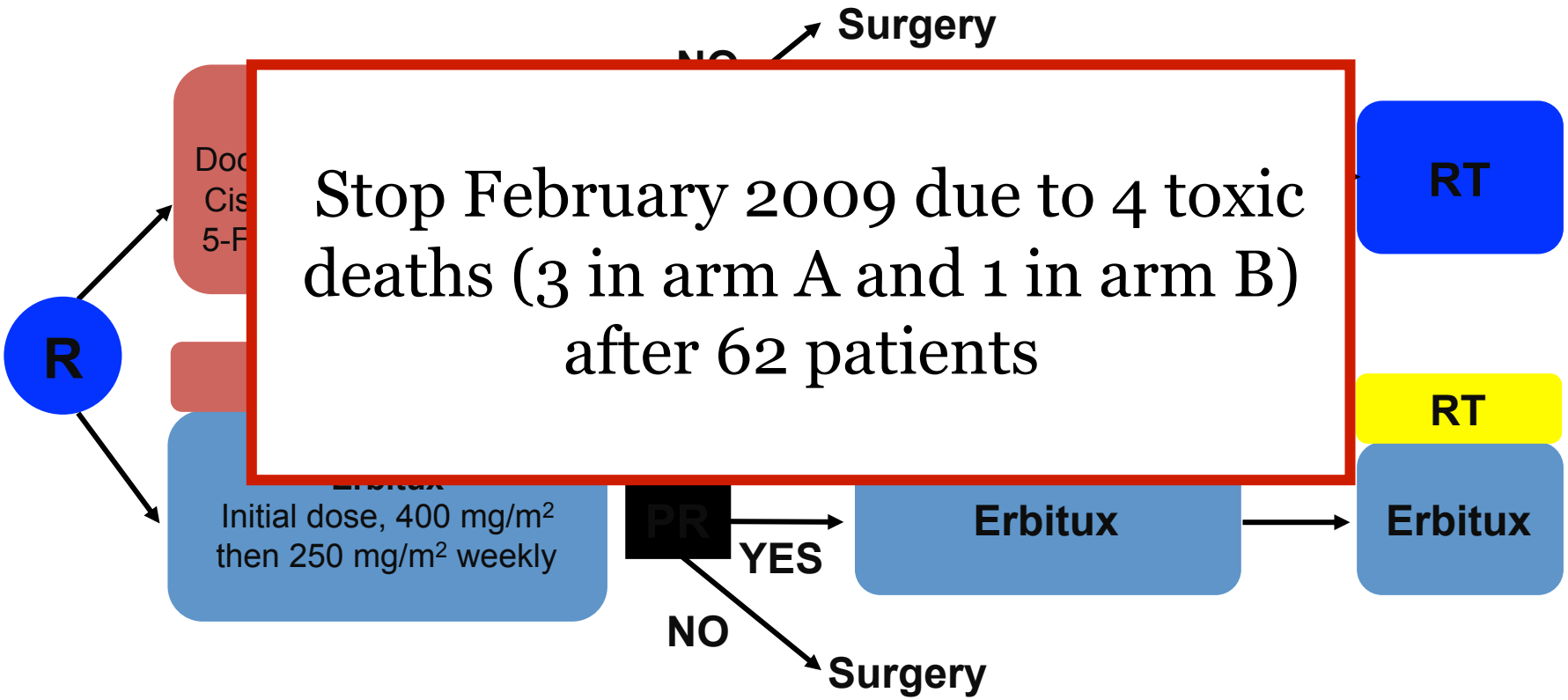
Toxicity[a]

- **Most common grade ≥3 toxicities:**
  - **Neutropenia, 26%; febrile neutropenia, 24%; diarrhea, 14%; stomatitis, 14%**

[a]Data shown after 4 cycles of ERBITUX + TPF induction

Mesia R et al. J Clin Oncol 2009;27(Suppl. 15):Abstract 6015 (updated information presented)

DeLOS-II-Protocol



DeLOS = German larynx organ preservation study group (25 centers)

Dietz et al. JCO 2010

Targeted drugs in larynx preservation protocols

CAUTION!!!!!!

Radiotherapy and Oncology 105 (2012) 238–240

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.c

Head and neck cancer

EORTC 24051: Unexpected side effects i… study of TPF induction chemotherapy followed by chem… with lapatinib, a dual EGFR/ErbB2 inhibitor, in patients with l… ced resectable larynx and hypopharynx squamous cell carcin…

Yassine Lalami [a,*] …ier [b], Ahmad Awada [a], Denis Lacombe [c], Cecilia Liberatoscioli [c], Catherine … El-Hariry [d], Jan Bogaerts [c], Guy Andry [a], J.A. Langendijk [e], Jan B. Vermorken [b]

[a] Insti… Antwerp University Hospital, Edegem; [c] EORTC Headquarters, Brussels, Belgium; [d] Glaxo Wellcome Research and Development, Greenford, …ent of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Lapatinib cannot be combined safetely with full dose TPF

Conclusions: a bio-failure?

- Cetuximab + RT: superior to RT alone (but never been directly tested vs standard CRT!)
- Cetuximab + CT: superior to CT alone (Cisplatin – 5 FU) in the metastatic setting

BUT in larynx preservation:

- the Tremplin study failed to identify a role for it
- no other definitive prospective data are available

TAKE HOME MESSAGE

- Larynx preservation: optimal non-surgical approach not yet clearly identified
- In clinical practice, if an organ preservation approach is pursued, the choice should be either induction or concomitant therapy but not both
- Absence of reliable biomarkers doesn’t allow to identify who may benefit