Institut de cancérologie
GUSTAVE ROUSSY
VILLEJUIF - www.igr.fr

Poster discussion : Head & Neck cancers

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Disclosure slide

no Conflicts of Interest to declare

Modulation of the peritumoral microenvironment by cetuximab: a window pre-operative study in patients with squamous cell carcinoma of the head and neck

S Schmitz, M Hamoir, H Reycher, M Magremanne, B Weynand, JF Hanin, R Lhommel, Th. Duprez, N Michoux, D Rommel, M Lonneux, N Cappoen, A Gillain, JP Machiels

Brussels, Belgium

VIENNA 2012 ESMO congress

www.esmo2012.org

Primary objective : safety

N=32 (pts phase I/II)	Grade 1-2	Grade 3-4
Dermatologic (Rash)	29(66%)	3(9%)
Diarrhea	1(3%)	0%
Hypocalcemia	12(37,5%)	0%
Hypomagnesium	2(6%)	0%
Hypophosphorus	5(16%)	0%
Stomatitis	2(6%)	0%
Nail changes	1(3%)	0%

Does preoperative time is a good window for phase I/II studies for targeted therapies ?

- YES
  - HNSCC : fast growing tumors
  - Tumor size and Accessibility to the tumor allow multiple biopsies
- NO
  - No need for additional treatment for early stages
  - Tumor shrinkage can make difficult to perform the planned surgery
  - Toxicity or protocol organisation can delay curative treatment
  - Ethical issues : right explanations to the patient (expect high rate of refusal) and not the surgeon for inclusion (afraid to say no)

Similar studies in HNSCC

- **Cetuximab : 32 pts. 18FDG-PET EORTC guidelines: 90% of partial Pet response**
- Erlotinib : 31 pts 3wks 29% Partial response 18% FDG PET partial response *(CCR 2007, 2010)* → *no active dvpt*
- GA201 (Roche glycoengineered ADCC anti-EGFR mAb): 2 wks, 77% PMR PET (ASCO2012) → phase II
- Afatinib (ongoing)
- Lapatinib (preCXRT) : 107 pts, 2 wks, Objective Response : 17% (CCR2010) → PIII postoperative study (results pending)

Which Biomarkers need to be tested ?

- Singles markers
  - Dowregulation of Ki67, pEGFR and pErk expression after cetuximab
  - p21 for erlotinib
  - Ki67 for lapatinib
- Gene expression profile : cetuximab→ modifications of the microenvironment: upregulation of fibrosis and downregulation of hypoxia and proliferation gene signatures
- Immune system : ADDC system with GA201

PI in Preoperative time

- Toxicity evaluation
- Looking for signs of clinical activity in naïve patients
- Translational: Modifications of the target
- But need also to be compared with serial biopsies in a real situation of treatment like during radiotherapy

Cetuximab/RT versus concomitant CT/RT with or without induction TPF in locally advanced unresecable H&NSCC.

Preliminary toxicity results of a randomized, 2x2 factorial, phase II-III study

(GSTTC) – Italy

MG Ghi, A Paccagnella, D Ferrari, M Cossu Rocca, E Verri, F Morelli, G Azzarello, C D'Ambrosio, C Casanova, IC Floriani.

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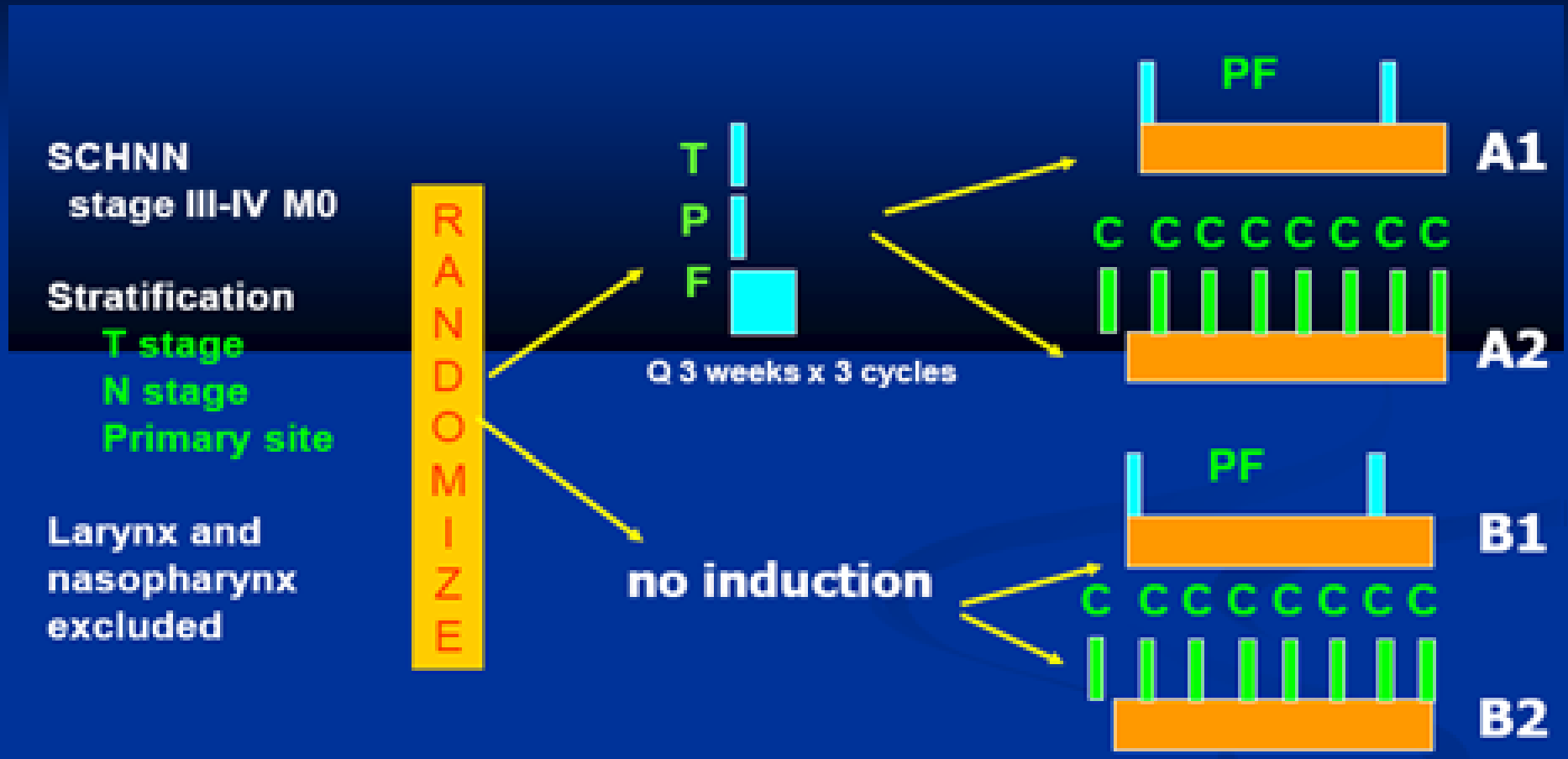
PHASE III PART: 2 X 2 FACTORIAL DESIGN



Primary Endpoints:

3y OS Induction vs no induction: A1+A2 vs B1+B2

G3-4 in field toxicity : A1+B1 vs A2+B2

	CT/RT N 215	CET/RT N 133	p
In-field mucositis Grade 3 Grade 4	37% 4%	35% 2%	0.79 0.45
In-field skin reaction Grade 3 Grade 4	13% 1%	20% 1%	0.07 0.58
RT median dose, Gy (range)	70 (8-70)	70 (14-70)	0.32
RT median duration, weeks (range)	7 (1-13)	8 (1-14)	<0.01
Pts with RT interruption >3days	32%	38%	0.22
RT modification due to acute toxicity	37%	40%	0.58

→No difference in toxicity for CET/RT over CT/RT

Discussion

- Are both arms comparable ?
- Total rate of any kind of RT modifications ?
- Rate of chemotherapy or Cetuximab modifications in both arms?

MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

TPF before CT-RT … ?

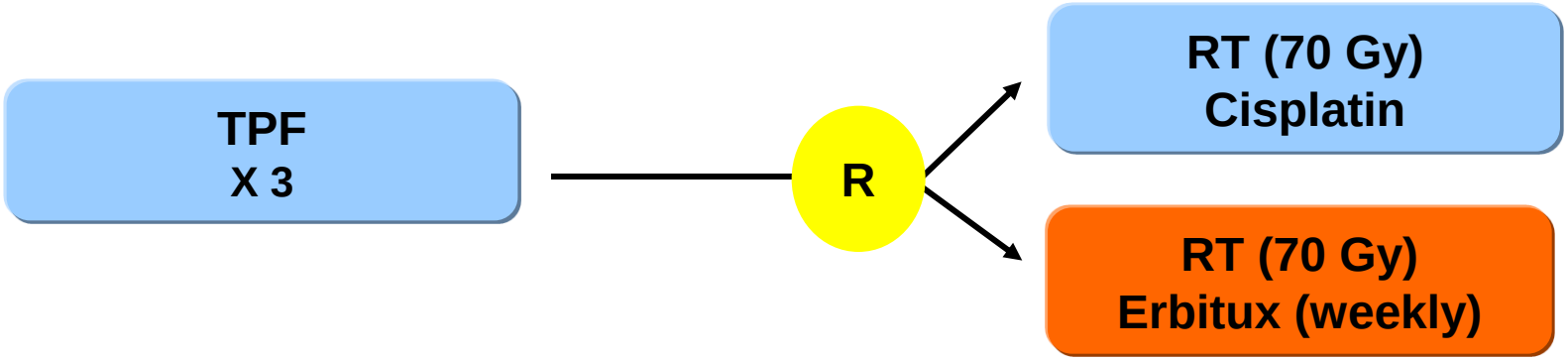
TPF may compromise the RT-CT phase

Compliance to concomitant cisplatin after TPF x 3 cycles

= only 43% in the TREMPLIN larynx preservation randomised study (JCO submitted)

TREMPLIN : Organ preservation

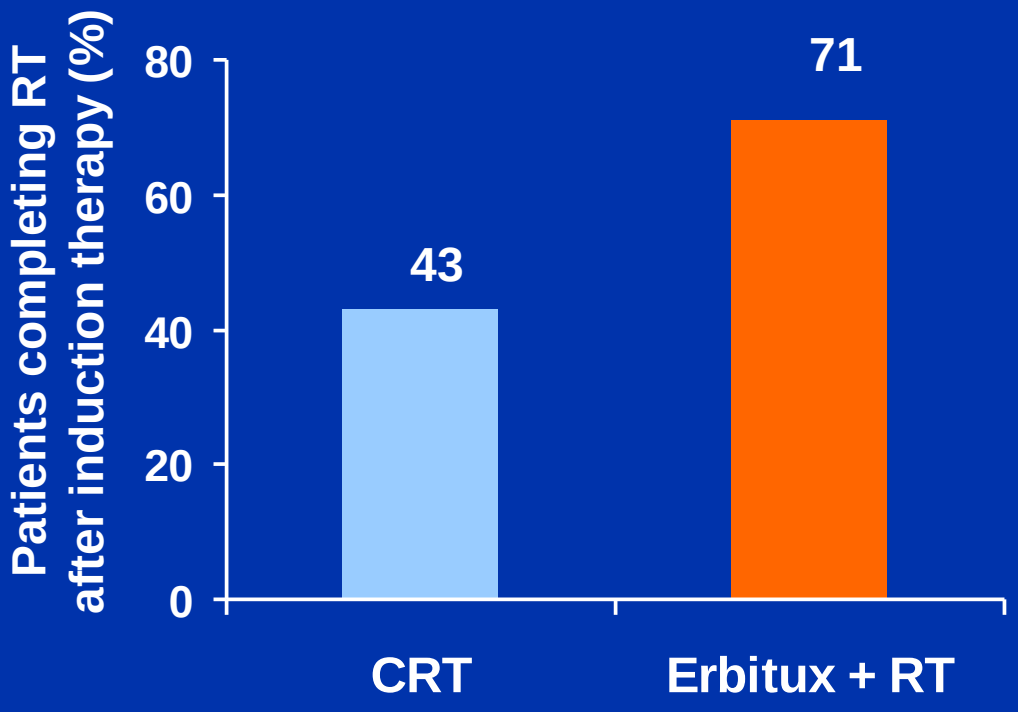
Cetuximab + RT *versus* CDDP + RT



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

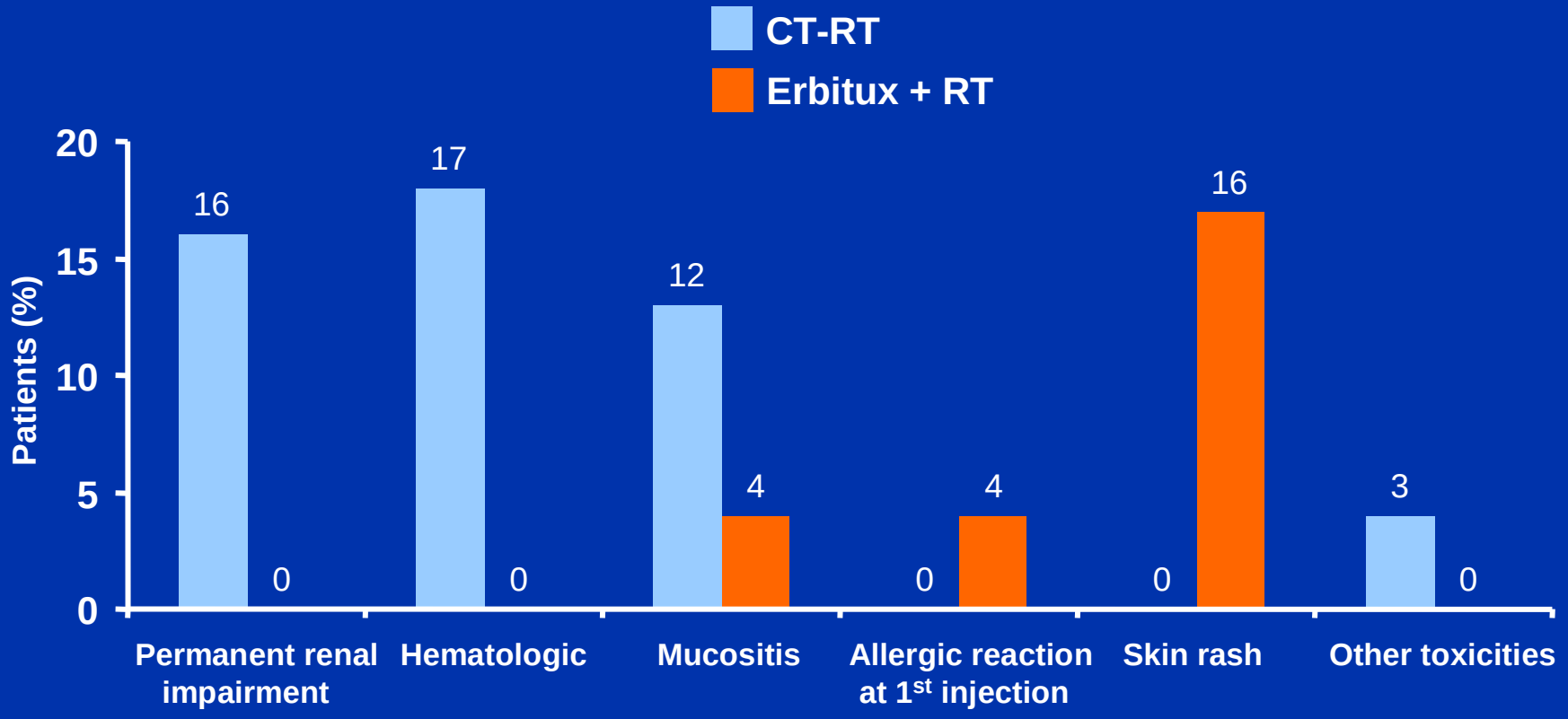
Lefebvre et al. JCO 2011

Erbitux + RT *versus* Cisplatin-RT : compliance



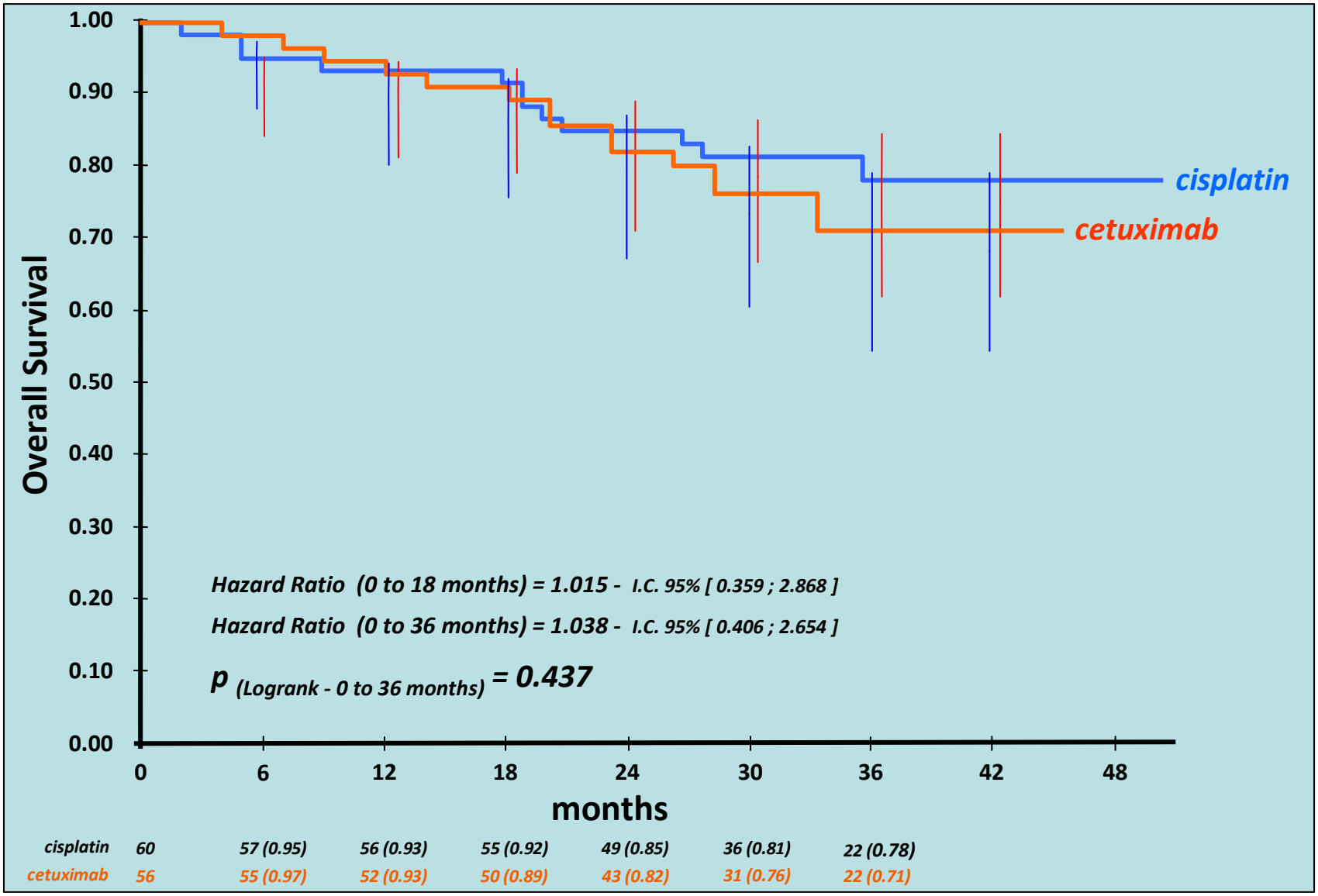
Lefebvre et al. JCO 2009

Erbitux + RT has a better toxicity profile than than CT-RT



Lefebvre et al. JCO 2009

Overall survival *(N = 153 patients randomized)*



Lefebvre JCO in press

Induction TPF *before* concomitant CT-RT ?

Randomized trials

Group	Regimen
TTCC (Sp)	TPF (or PF) x 3 → CRT (Cisplatin)
	CRT (cisplatin)
Boston (US)	TPF x 3 → CRT (carboplatin)
	CRT (cisplatin)
Chicago (US)	TPF x 2 → THFX
	THFX
GCTCC (It)	TPF x 3 → XRT (cetuximab)
	TPF x 3 → XRT (PF)
	XRT (cetuximab)
	XRT (PF)

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Definitive results pending

Induction TPF *before* concomitant CT-RT ?

Group	Regimen
TTCC (Sp)	TPF (or PF) x 3 → CRT (Cisplatin)
	CRT (cisplatin)
Paradigm (US)	TPF x 3 → CRT
	CT-RT (cisplatin)
DeCIDE (US)	TPF x 2 → THFX
	THFX
GCTCC (It)	TPF x 3 → XRT (cetuximab)
	TPF x 3 → XRT (PF)
	XRT (cetuximab)
	XRT (PF)

ASCO 2012 Negative

Induction TPF *before* concomitant CT-RT ?

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TTCC (Sp)	TPF (or PF) x 3 → CRT
	CRT (cisplatin)
Paradigm (US)	TPF x 3 → CRT
	CT-RT (cisplatin)
DeCIDE (US) 245 pts	TPF x 2 → THFX
	THFX
GCTCC (It)	TPF x 3 XRT (cetuximab) XRT (PF)

Restricted to N2-N3

ASCO 2012

Negative except

Benefit for M+

XRT (cetuximab)
XRT (PF)

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TTCC (Sp)	TPF (or PF) x 3 → CRT (Cisplatin)
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Ongoing phase III