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

Cetuximab dopo terapia di induzione

U. Ricardi

Discussant: S. M.Magrini

Con il contributo educazionale di

Merck Serono

MERCK

CHEMIOTERAPIA DI INDUZIONE SEGUITA DA RADIOTERAPIA CONCOMITANTE A CETUXIMAB NEL TRATTAMENTO INTEGRATO DELLE NEOPLASIE LOCALMENTE AVANZATE DEL DISTRETTO CERVICO-CEFALICO: STUDIO CLINICO MULTICENTRICO DI FASE II

Principal Investigator: **U. Ricardi**, Radiation Oncology, University of Torino

Efficacy and feasibility of induction chemotherapy and radiotherapy plus Cetuximab in head and neck cancer

ANTICANCER RESEARCH
International Journal of Cancer Research and Treatment

Efficacy and feasibility of induction chemotherapy and radiotherapy plus Cetuximab in head and neck cancer.

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Locally advanced SCCHN:
CERCEFA Study: TPF followed by Erbitux + RT

INCLUSION CRITERIA:

> non-metastatic, histologically proven, stage III or IV squamous-cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx;

> age between 18 and 75 years old;

> measurable disease according to World Health Organization criteria;

> Performance Status ECOG 0-2;

> adequate haematological, hepatic, cardiac and renal functions.

EXCLUSION CRITERIA:

> distant metastases,

> previous malignancies,

> previous CT and/or RT.

Locally advanced SCCHN:
CERCEFA Study: TPF followed by Erbitux + RT

Taxotere 75 mg/m2 day 1, 21
5-Fluorouracil 2500 mg/m2/day 1, 2, 3
5-Fluorouracil 250 mg/m2 day 1, 2, 3

→ evaluation

RT (70 Gy)+ weekly Erbitux (Bonner 2006)

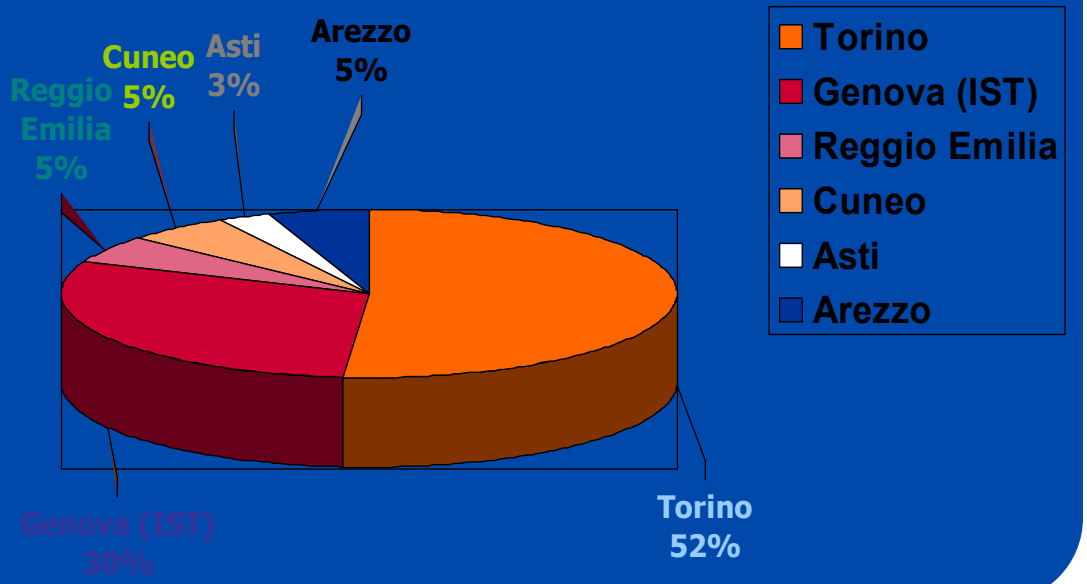
the whole treatment) and toxicity.

- **Secondary endpoints**: objective response rate at the end of
survival and overall survival. locoregional control, progression-free
survival and overall survival.

Patient and tumour characteristics

Age (years)	
Median	62
Range	45-74
Gender	n (%)
Male	29 (80.6%)
Female	7 (19.4%)
PS	
0	22 (61%)
1	12 (33%)
III/IV	19%/81%
Tumour site	
Oral cavity	5 (14%)
Oropharynx	17 (47%)
Hypopharynx	10 (28%)
Larynx	4 (11%)

From November 2007 to November 2009, 36 patients were enrolled onto this phase-II trial from 6 centers in Italy.



Locally advanced SCCHN:
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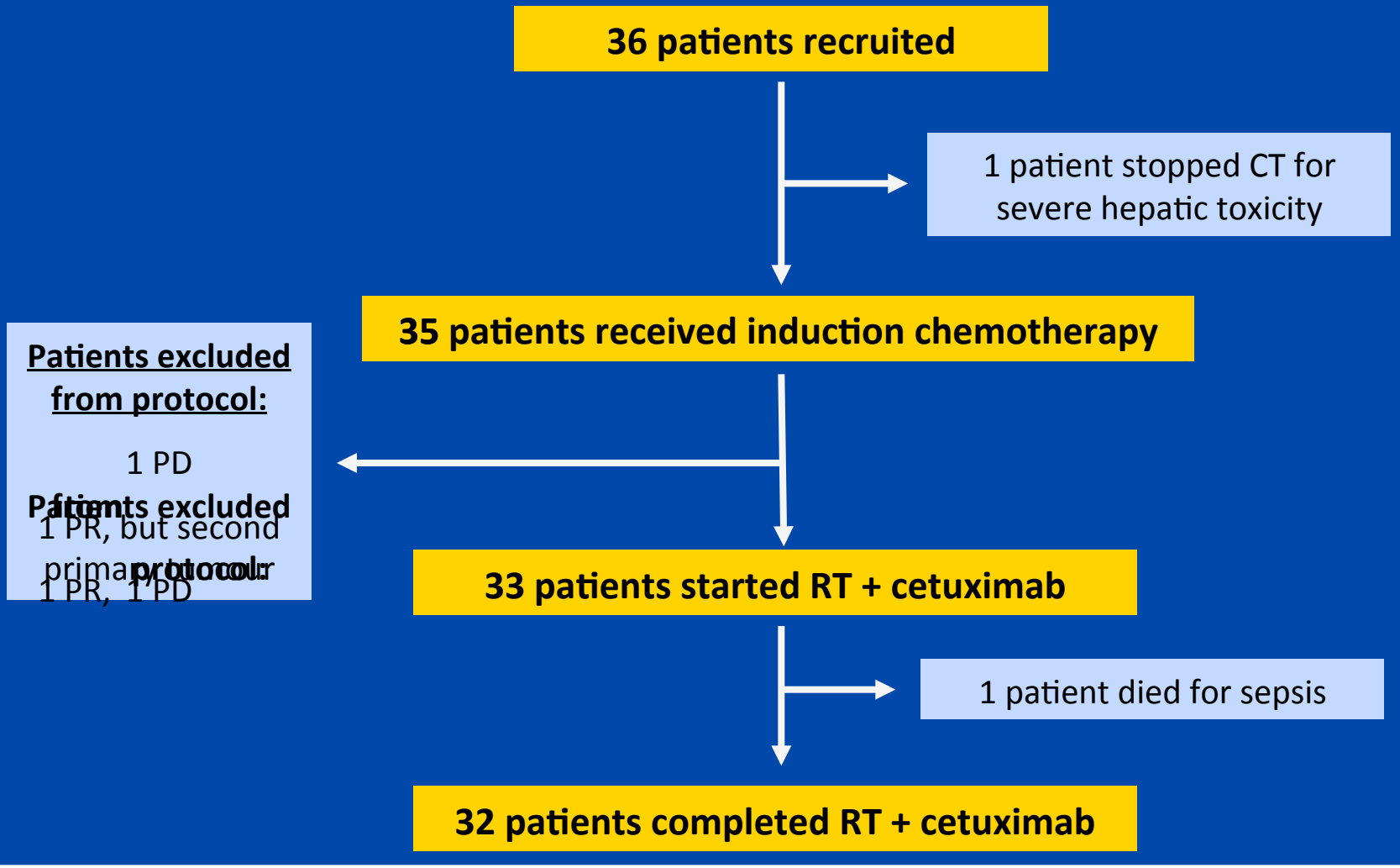


Severe Toxicities per Treatment Period

	Induction TPF (n=35)	RT-cetuximab(n=33)	
	G3-4	G3-4	G5
	No. (%)	No. (%)	No. (%)
Anaemia	-	-	-
Thrombocytopenia	-	-	-
Neutropenia	11 (31.4%)	-	-
Febrile neutropenia	2 (5.7%)	-	-
Hepatic toxicity	1 (2.8%)	-	-
Infection	-	-	1 (3%)
Cetuximab infusion reaction	-	1 (3%)	-
Acneiform rash	-	2 (6%)	
Nail toxicity	-	6 (18%)	-
Radiodermatitis	-	16 (48%)	-
Mucositis	-	11 (33%)	-
Dysphagia	-	4 (12%)	-

Most pts (97.2%) completed two cycles of ICT

Thirty-two out of 33 pts completed the whole RT treatment

Most pts (97.2%) completed two cycles of ICT as planned

RTOG 0522: Acute Toxicity

RT + Cisplatin	Cetuximab	
	No (448)	Yes (447)
Mucositis ($P = 0.004$)		
None	126 (28%)	85 (19%)
Grade 1-2	174 (39%)	172 (38%)
Grade 3-4	148 (33%)	190 (43%)
Skin Reactions - In-field ($P < 0.001$)		
None	98 (22%)	104 (23%)
Grade 1-2	285 (64%)	231 (52%)
Grade 3-4	65 (15%)	112 (25%)
Skin Reactions - Out-field ($P < 0.001$)		
None	385 (86%)	87 (19%)
Grade 1-2	60 (13%)	273 (61%)
Grade 3-4	3 (1%)	87 (19%)

Our trial can thus be considered successful because we achieved 81.8% ORR after completion of the whole protocol and severe toxicity rate was maintained under 50%, that is in line with the statistical endpoints.

Response rate after induction and concomitant therapy

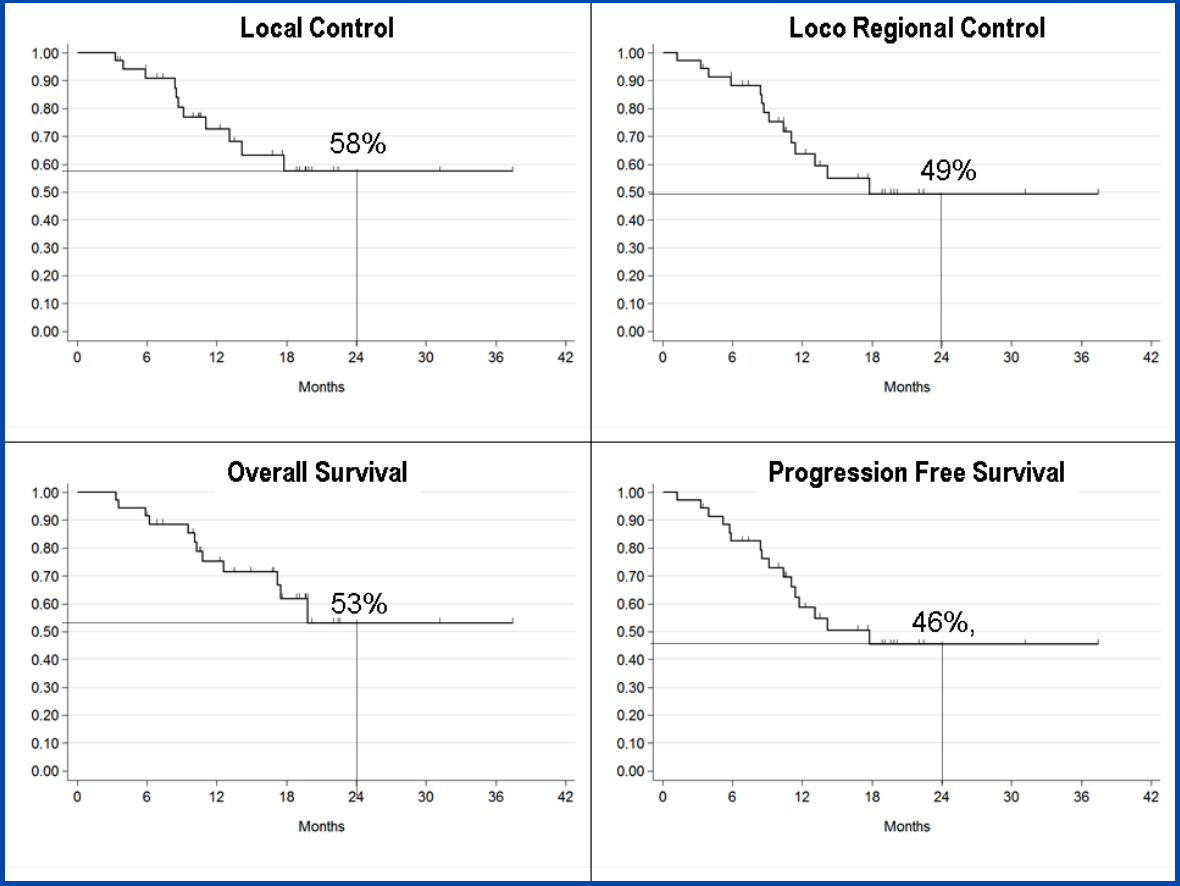
Induction phase response (n. 35)	N.	%	
CR	2	5.7%	
PR	27	77.1%	
OR	29	82.8%	95% C.I.: 66.4%-93.4%
SD	4	11.4%	
PD	1	2.9%	
Not assessable	1	2.9%	
Concomitant phase response (n. 33)			
CR	16	48.5%	
PR	11	33.3%	
OR	27	81.8%	95% C.I.: 66.4%-93.4%
SD	2	6.1%	
PD	2	6.1%	
Not assessable	2	6.1%	

Results

		C.I. 95%
LOCAL CONTROL	57.5%	35.2%-74.5%
LOCOREGIONAL CONTROL	49.4%	28.7%-67%
PROGRESSION FREE SURVIVAL	45.5%	26.2%-62.9%
OVERALL SURVIVAL	53%	28.9%-72.3%

Twenty-four months actuarial LC, LRC, PFS and OS
median follow-up: 17.5 months (range: 4-35)

Locally advanced SCCHN:
CERCEFA Study: Erbitux after induction chemotherapy



median follow-up: 17.5 months (range: 4-35)

CERCEFA Study: Erbitux after induction chemotherapy: discussion

- **"Modified" TPF** (2 cycles , dose variation): The post-induction **ORR** obtained in our study was similar to those of other authors, who adopted more intensive ICT

- Post-induction **CR rate** was lower (5.7%) in our study than in Vermorken (8.5%) or Posner (17%) studies. However, the final CR rate in our study was 48.5%, roughly comparable with the results of therapeutic strategies including more intensive TPF regimens

-OS and PFS were inferior to those reported in trials*with more intensive TPF schedule (but…unfavorable selection of patients in our study, with 81% stage IV)

•Posner, *N Engl J Med*. 2007.
•Vermorken, *N Engl J Med*. 2007.
•Lefebvre J, TREMPLIN study. 2009.
•Paccagnella, *Ann. Oncol*. 2010.

CERCEFA Study: Erbitux after induction chemotherapy

Conclusions

After induction TPF, Erbitux + RT

- Achieves high ORR
- Shows an excellent toxicity profile

Valide alternative to standard chemo-radiotherapy?

INTERCEPTOR

INTERCEPTOR TRIAL

INduction chemo**T**h**ER**apy followed by **CE**tuximab **P**lus defini**T**ive radi**O**the**R**apy versus radiation plus cisplatin

Studio randomizzato di fase III

Trattamento

>CT neoadiuvante con TXT, CDDP, 5-FU (Vermorken) per 3 cicli

seguiti da

>Radioterapia 70 Gy

associata a

>Cetuximab 400 mg/mq, poi 250 mg/mq/w

Versus

>Radioterapia 70 Gy

>Cisplatino 100 mg/mq g1 q 21 (RTOG)

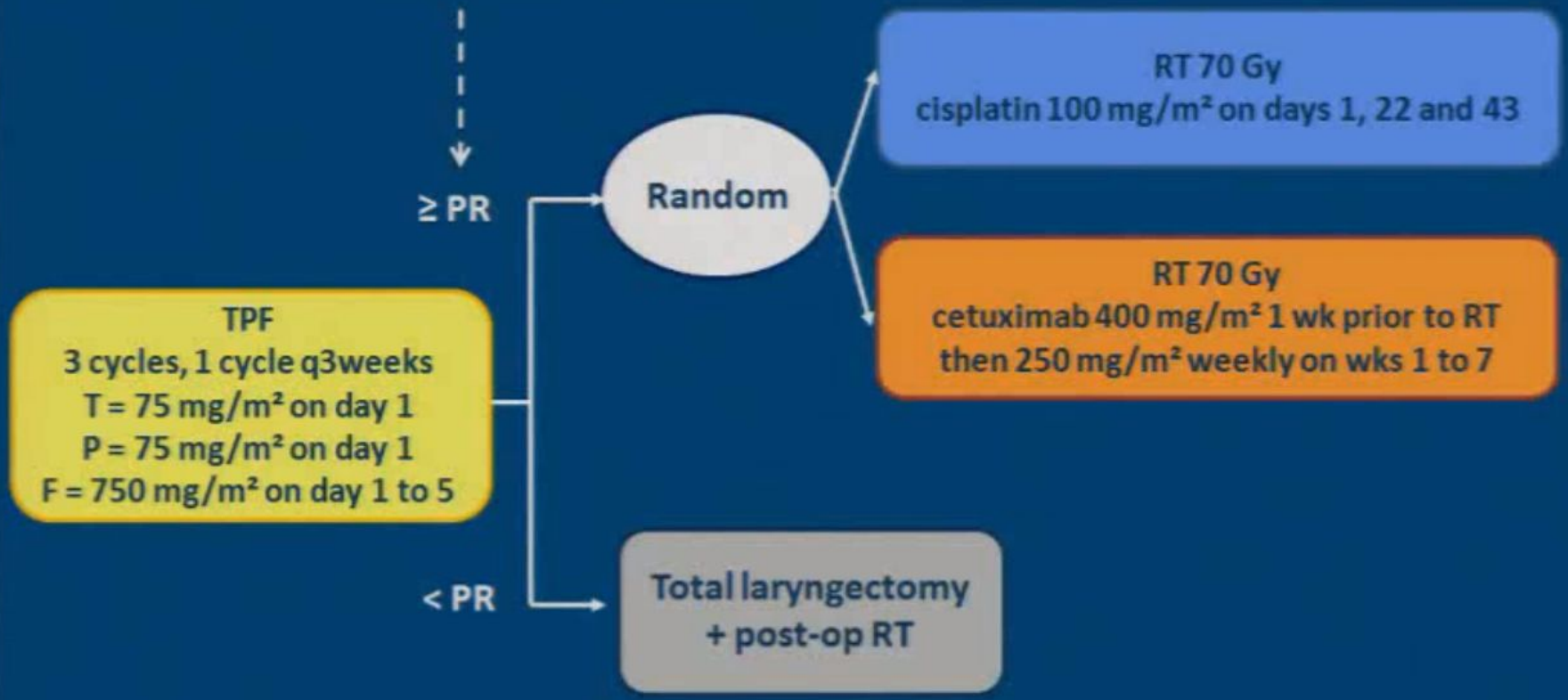
Sequential chemoradiotherapy for larynx preservation: results of the randomized phase II TREMPLIN study

JL Lefebvre, Y Pointreau, F Rolland, M Alfonsi, A Baudoux, C Sire, D de Raucourt, E Bardet, C Tuchais, P Garaud and G Calais

ASCO 2011

ASCO Annual '11 Meeting

The randomized phase II study: TREMPLIN



P = cisplatin, F = 5-fluorouracil, T = docetaxel, TL = total laryngectomy, PR = partial response
RT = radiotherapy, CT = computed tomography, Tx = treatment

PRESENTED AT: ASCO Annual '11 Meeting

Demographics

	Cisplatin n = 60	ERBITUX n = 56	p-value
Gender, n			0.03
Male	52	55	
Female	8	1	
Mean age, years	57 (45 – 73)	57 (44 – 70)	0.78
PS			0.42
0	46	39	
1	13	17	
Missing data	1		
Primary site			0.41
Larynx	27	20	
hypopharynx	33	36	
Stage			0.21
2	9	4	
3	35	30	
4	16	22	

Compliance to treatment

Radiotherapy	cisplatin arm 60 pts	cetuximab arm 56 pts
Not done	2*	0
Mean dose (Gy)	69 (24**-74)	69.5 (56-76)

Nb. of cycles administered	cisplatin arm 60 pts	cetuximab arm 56 pts
7	-	40 (71 %)
6	-	4
5	-	4
4	-	1
3	26 (43 %)	1
2	24	2
1	8	2
0	2*	3***

* 1 refusal and 1 rapid evolution
** another rapid evolution
*** 3 infusion-related reactions

Acute toxicity during RT

	cisplatin arm 58 pts*	cetuximab arm 56 pts	p value
Grade 3 mucositis **Grade 4 mucositis**	**25 (43 %)** **2**	**24 (43 %)** **1**	*NS*
Grade 3 in field skin toxicity **Grade 4 in field skin toxicity**	**14 (24 %)** **1**	**29 (52 %)** **3**	**< 0.001**
Other toxicities, any grade, justifying a protocol modification Renal toxicity Hematological toxicity Poor general condition Infusion-related reaction	 9 (15.5 %) 8 (14 %) 7 (12 %) 0	 0 0 1 (1.7 %) 3 (5 %)	
Protocol modification due to acute toxicity	**33 (57 %)**	**19 (29 %)**	**0.02**

***2 patients did not start the treatment in the cisplatin arm**

Severe Toxicities per Treatment Period

	Induction TPF (n=35)	RT-cetuximab(n=33)	
	G3-4	**G3-4**	**G5**
	No. (%)	No. (%)	No. (%)
Anaemia	-	-	-
Thrombocytopenia	-	-	-
Neutropenia	11 (31.4%)	-	-
Febrile neutropenia	2 (5.7%)	-	-
Hepatic toxicity	1 (2.8%)	-	-
Infection	-	-	1 (3%)
Cetuximab infusion reaction	-	1 (3%)	-
Acneiform rash	-	2 (6%)	
Nail toxicity	-	6 (18%)	-
Radiodermatitis	-	16 (48%)	-
Mucositis	-	11 (33%)	-
Dysphagia	-	4 (12%)	-

Late toxicity

	cisplatin arm 58 pts*	cetuximab arm 56 pts	p value
Residual renal dysfuntion at last evaluation (all grade 1)	**13 (22.4 %)**	**0**	**< 0.001**
1 cycle of cisplatin during RT *2 cycles of cisplatin during RT* *3 cycles of cisplatin during RT*	*3 %* *5 %* *14 %*		
Grade 3-4 mucosal toxicity	**2 (3.5 %)**	**1 (1.8 %)**	
Grade 3-4 osteoradionecrosis	**1 (1.7%)**	**1 (1.8 %)**	
Grade 3-4 xerostomia	**6 (10.3 %)**	**5 (8.9 %)**	
Grade 3-4 subcutaneous fibrosis	**4 (7 %)**	**1 (2 %)**	
Grade 3-4 neuropathy	**2 (3.5 %)**	**0**	
Grade 3-4 laryngoesophageal toxicity	**5 (8.6 %)**	**5 (9 %)**	

***2 patients did not start the treatment in the cisplatin arm**

Endpoints (ITT):

Primary endpoint (3 months after end of Tx)	**cisplatin arm 60 pts**	**cetuximab arm 56 pts**	**p value**
Larynx preservation (larynx in place without tumor)	57/60 (95 %)	52/56 (93 %)	*0.63*

Secondary endpoints (18 months after end of Tx)	**cisplatin arm 60 pts**	**cetuximab arm 56 pts**	**p value**
Larynx function preservation (larynx in place without tumor/ trach/feeding tube) *NB: at 18 months or at death*	52/60 (87 %)	46/56 (82 %)	*0.68*
Overall survival *NB: since randomization*	92 %	89 %	*Log-rank: 0.44*

NB: 1 pt lost to FU in the cisplatin arm is considered as failure

Clinical situation at randomization

	cisplatin arm 60 pts	cetuximab arm 56 pts
Larynx mobility		
Normal	54	51
Still impaired	5	5
Missing data	1	0
Primary site		
CR	41	36
PR	19	20
Nodal status		
No palpable LN	49	42
PR	9	12
SD	1	1
PD	1	0
Missing data	0	1

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease
LN = Lymph Node

- **TPF followed by cisplatin-containing regimens are difficult to deliver because of their high levels of toxicity, while induction chemotherapy followed by bioradiation is more feasible**

Bioradiation is probably a better option than chemoradiation during the second phase of sequential treatments for organ and function preservation programs