Cetuximab e radioterapia: gli studi italiani

Trattamento concomitante (CRT or Cetuximab/RT) con o senza chemioterapia di induzione: studio randomizzato di fase III

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RADIOTERAPIA ONCOLOGICA TREVISO

Disclosure

The randomized phase II part of the study was sponsored by Sanofi- Aventis, Italy.

I have no conflicts of interest to disclose .

Background

- The efficacy of induction CT in prolonging OS when added to locoregional treatment has not been proven .

- TPF is superior to induction PF in OS[1].

- CRT w/wo induction CT has been recently investigated in three phase III trials:

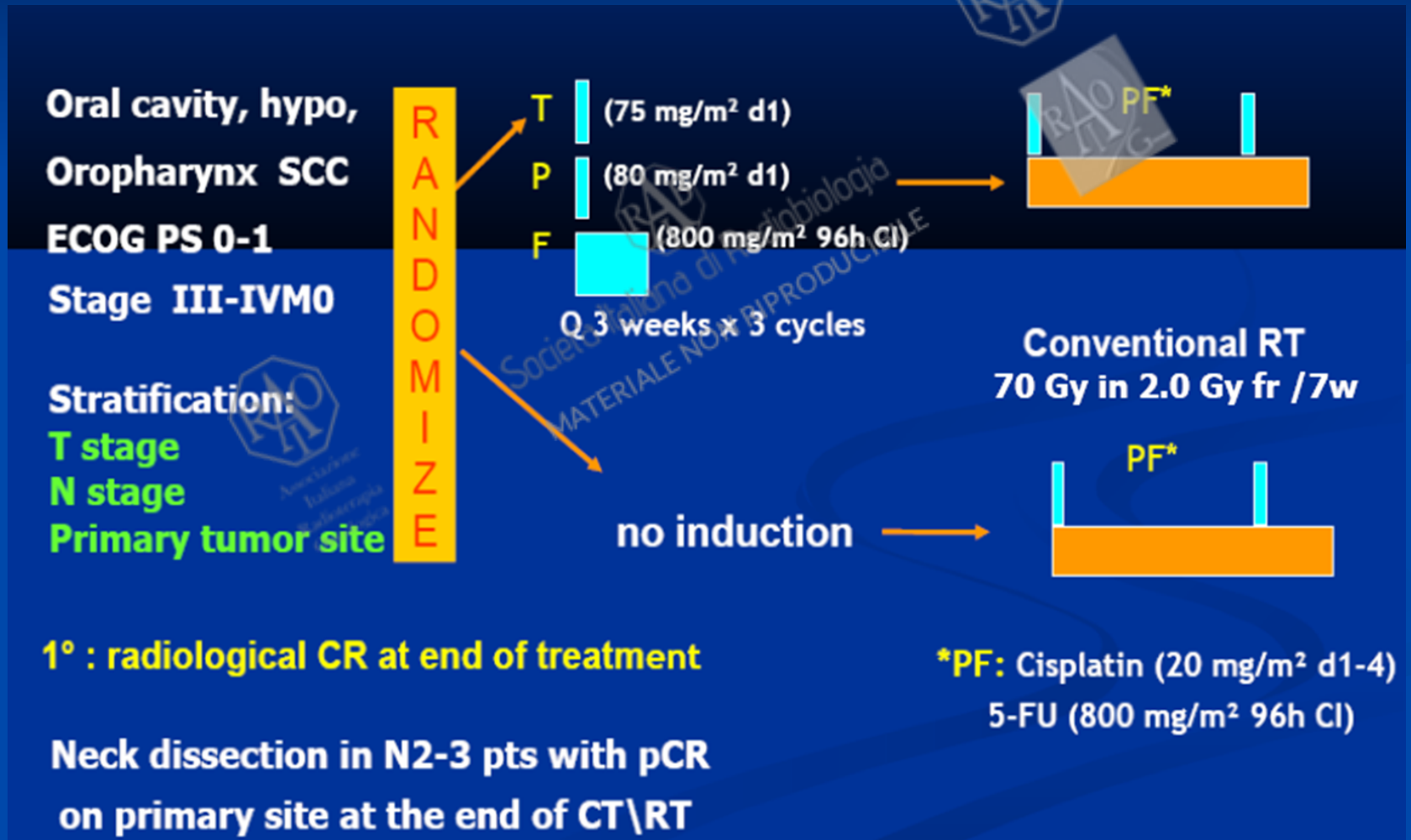
  - two trials were prematurely terminated due to slow accrual[2,3]

  - one trial was negative[4]

1. Blanchard et al, J Clin Oncol 2013; 31: 2854- 2860
2. Cohen et al, J Clin Oncol 2014; 32: 2735-2543
3. Haddad et al, Lancet Oncol 2013 14:257-264
4. Hitt et al, Ann Oncol 2014; 25: 216-225

STUDIO H&N07

For the randomized phase II part of the study the activity and feasibility of induction TPF followed by concomitant CRT was compared to CRT alone.



Complete Response: primary endpoint

Paccagnella et al, Annals of Oncology 2010

Response	CT/RT (arm A) ($N = 47$), n (%)	TPF + CT/RT (arm B) ($N = 46$), n (%)
Complete response (95% CI)	10 (21.3) (10.7% to 35.7%)	23 (50.0) (34.9% to 65.1%)
Partial response	29 (61.7)	13 (28.2)
Stable disease	0	1 (2.2)
Progressive disease	8 (17.0)	9 (19.5)
Overall response rate	39 (83.0)	36 (78.2)

p=0.004

Three cycles of induction TPF is a feasible treatment and does not compromise the delivery of subsequent CRT.

The difference in CR in favor of TPF induction CT (p=0.004) justifies the starting of the Phase III part of the study.

Annals of Oncology

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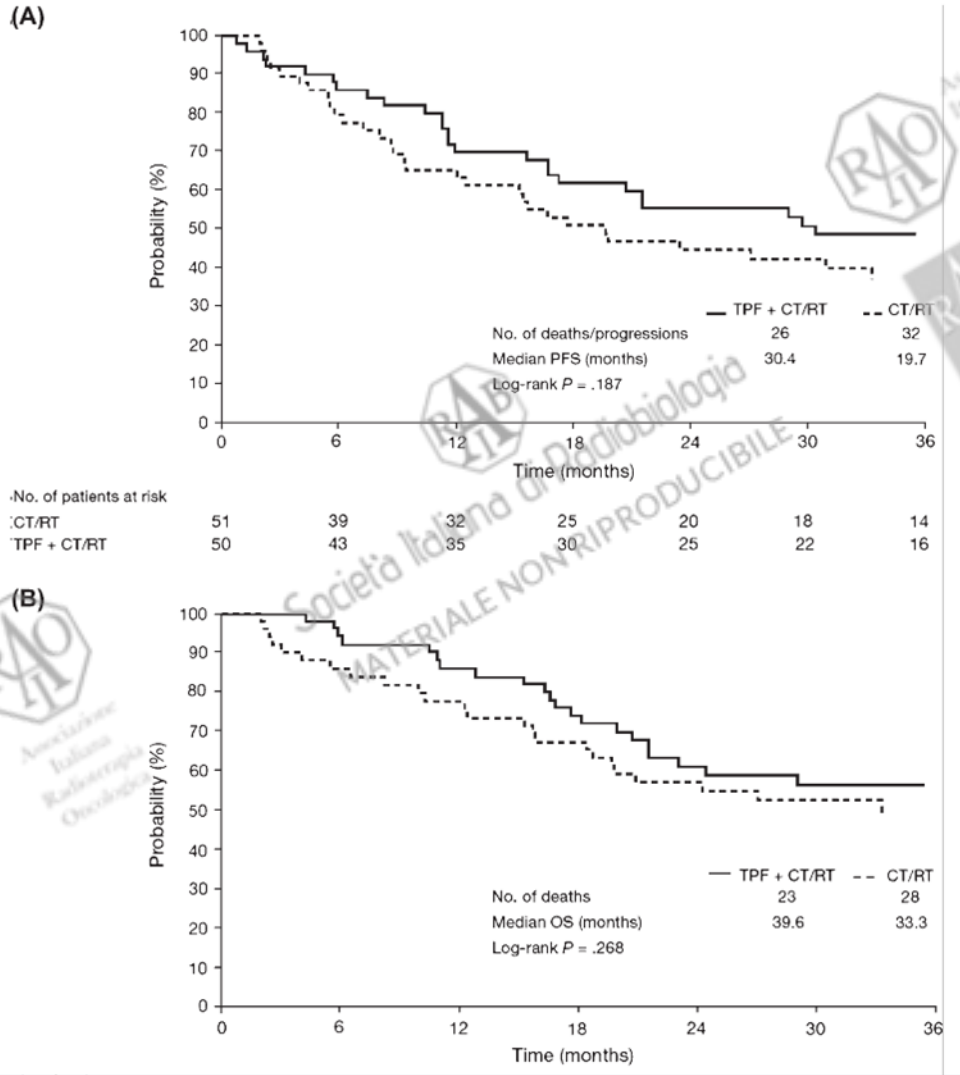

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Received 5 June 2009; revised 31 August 2009 & 15 October 2009; accepted 11 November 2009

PHASE II-III STUDY DESIGN
Phase II part of the study

studio H&N07

For the randomized phase II part of the study the activity and feasibility of induction TPF followed by CRT was compared to CRT alone.

Targeted Therapies

The NEW ENGLAND JOURNAL of MEDICINE

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.*

ABSTRACT

BACKGROUND

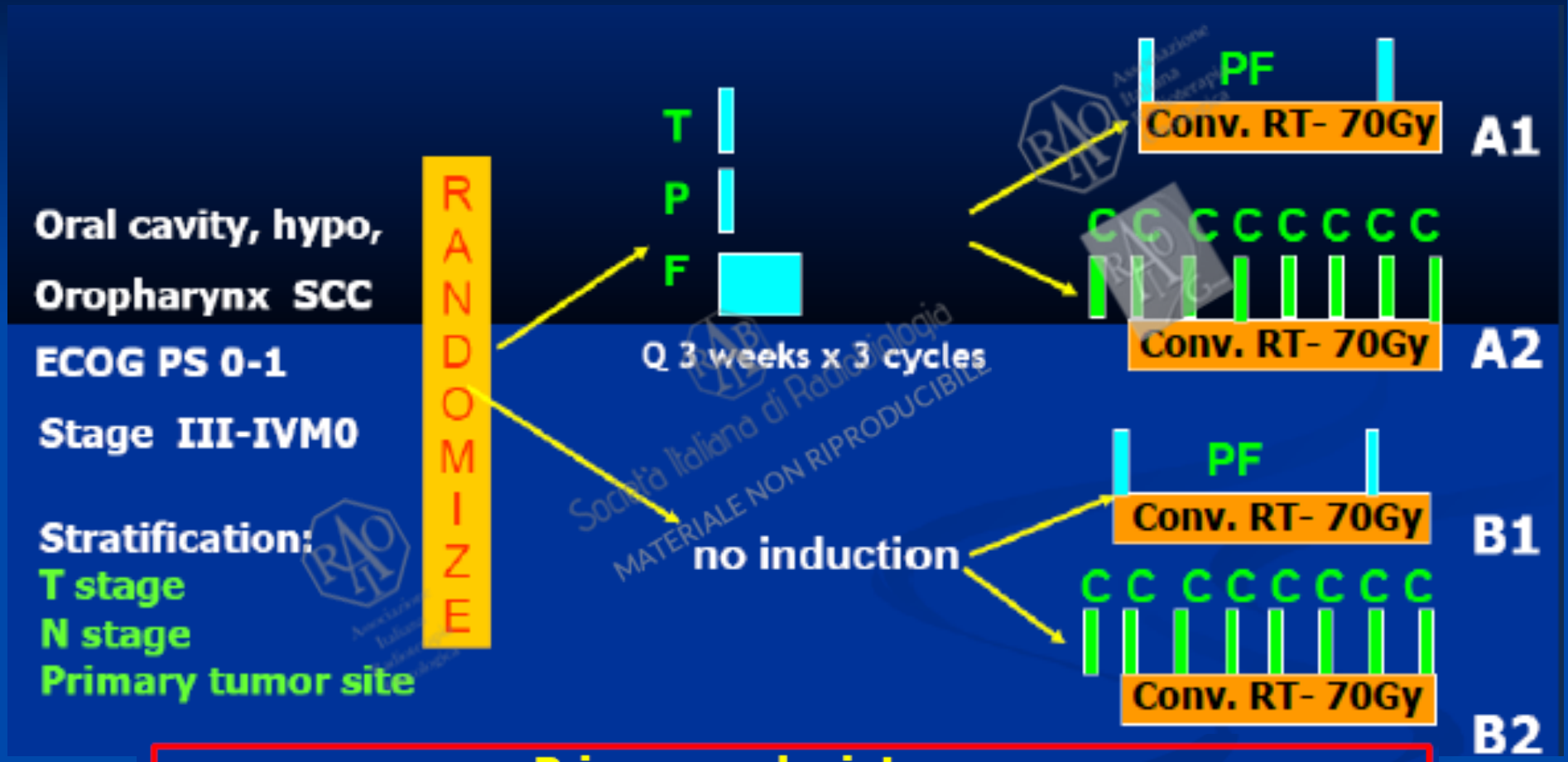
We conducted a multinational, randomized study to compare radiotherapy alone with radiotherapy plus cetuximab, a monoclonal antibody against the epidermal growth factor receptor, in the treatment of locoregionally advanced squamous-cell carcinoma of the head and neck.

PHASE II-III STUDY DESIGN
Phase III part of the study

- For the phase III part of the study, the cetuximab/ RT treatment option was added in both arms in a 2x2 factorial design .

- The cetuximab/RT arms were numerically not balanced by design.

PHASE III PART: 2 X 2 FACTORIAL DESIGN



Primary endpoints:

1) 3y OS Induction vs no induction: A1+A2 vs B1+B2

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

MG Ghi et al, ASCO 2013 and ASCO 2014

Statistical considerations:
OS endpoint: induction vs no-induction (A1+A2 vs B1+B2)

420 (210 per arm) pts required to detect a difference of 12% in 3 year overall survival in favor of the induction arm (from 52.5% to 64.5%). Power=0.85; HR=0.675; type I error of 0.05, two-sided.

- Accrual 4y + 2y follow-up

Toxicity endpoint: CRT vs cetuximab/RT

(A1+B1 vs A2+B2)

A number of 420 patients will provide a power of 80% to detect a difference of 10% (from 45% to 35%) in grade 3-4 in-field toxicity in favor of RT/Cetuximab arm.

- Cetuximab arm numerically unbalanced by design

Statistical considerations:

OS endpoint: induction vs no-induction (A1+A2 vs B1+B2)

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Main inclusion criteria

- SCC of the oral cavity, oroph, hypopharynx (no larynx)
- Stage III or IV–M0 (AJCC 6th edition) unresectable
- At least one measurable lesion
- Age ≥18 years
- ECOG PS: 0–1
- Life expectancy >6 months
- Adequate haematological, hepatic and renal function
- Written informed consent

Treatments

Induction TPF*:

- docetaxel 75 mg/sqm d 1
- cisplatin 80 mg/sqm d1
- 5Fluorouracil 800 mg/sqm/d 96h c.i.

Antibiotics starting on day 5 for 10 days

CRT*:

- RT 70 Gy (2 Gy/day, 5 d per week for 7 wks)
- CT cisplatin 20 mg/sqm d 1-4
  5-Fluorouracil 800mg/sqm/d 96h c.i.
  on weeks 1 and 6

cetuximab/RT:

- RT 70 Gy (2 Gy/day, 5 d per week for 7 wks)
- Cetuximab 400 mg/sqm d -7, 250 mg/sqm w x 7 wks

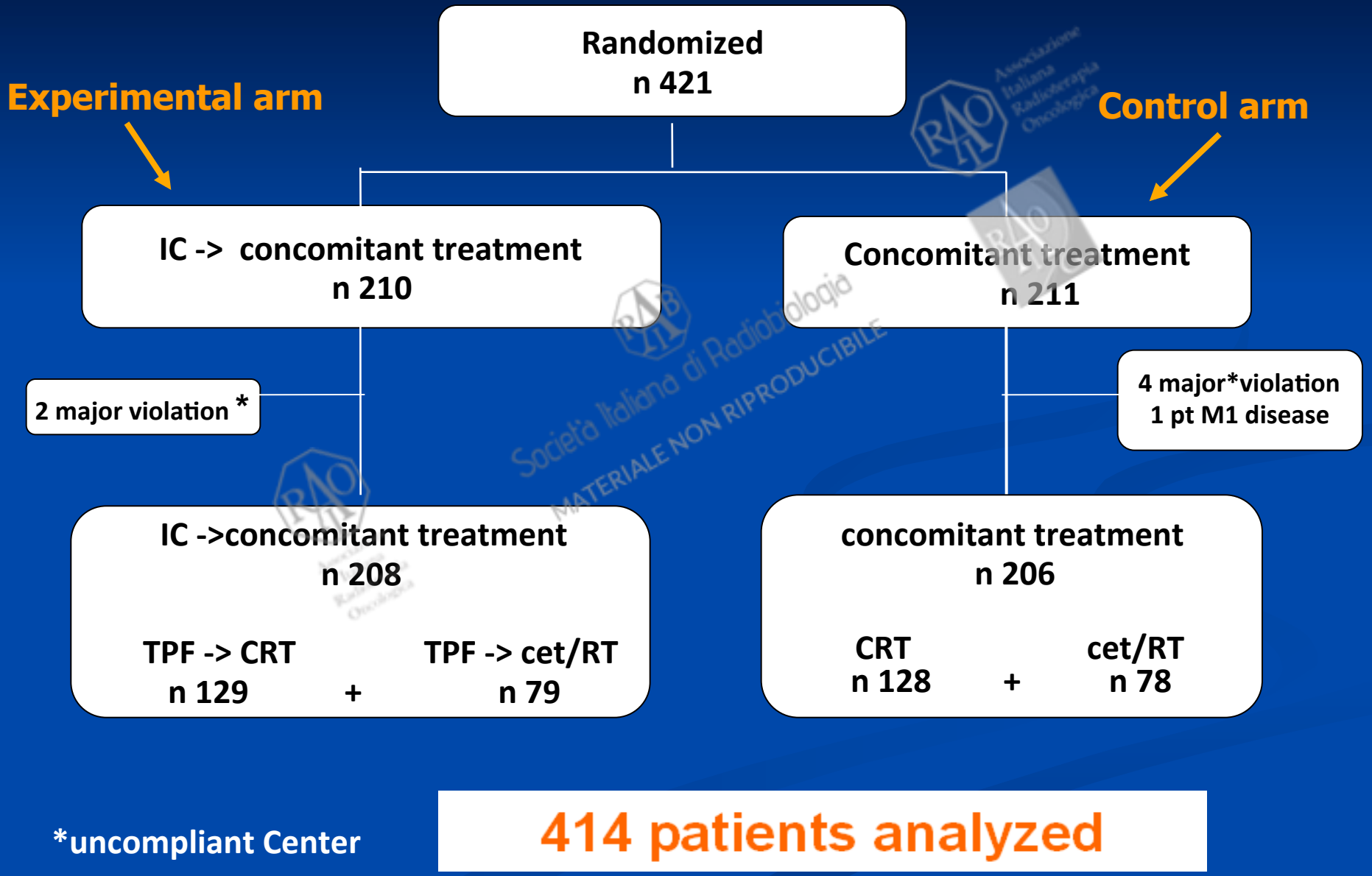
* Ghi et al, IJROBP 2004: vol 59 (2): 481-487

Patient Characteristics

	TPF + concomitant n=208	concomitant n= 206
Age, median (range)	61 (37- 78)	60 (27-81)
Gender % Male / Female	82% / 18%	81.5%/ 18.5%
ECOG PS % 0 1	 78% 22%	 83% 17%
Tumor site Oropharynx* Hypopharynx Oral cavity Multiple site	 119 (57%) 49 (23.5%) 38 (18.5%) 2 (1%)	 114 (55%) 48 (23.5%) 44 (21.5%) 0
T stage Tx T1 T2 T3 T4	 1(0.5%) 12 (6%) 45 (22%) 55 (26%) 95 (45.5%)	 2 (1%) 12 (6%) 36 (17.5%) 75 (36.5%) 81 (39%)
N stage Nx N0 N1 N2 N3	 3 (1.5%) 22 (10.5%) 31 (15%) 134 (64.5%) 18 (8.5%)	 3 (1.5%) 22 (10.5%) 32 (15.5%) 135 (65.5%) 14 (7%)
AJCC clinical stage III IV	 60 (29%) 148 (71%)	 71 (34%) 134 (65.5%)

*HPV analysis in progress

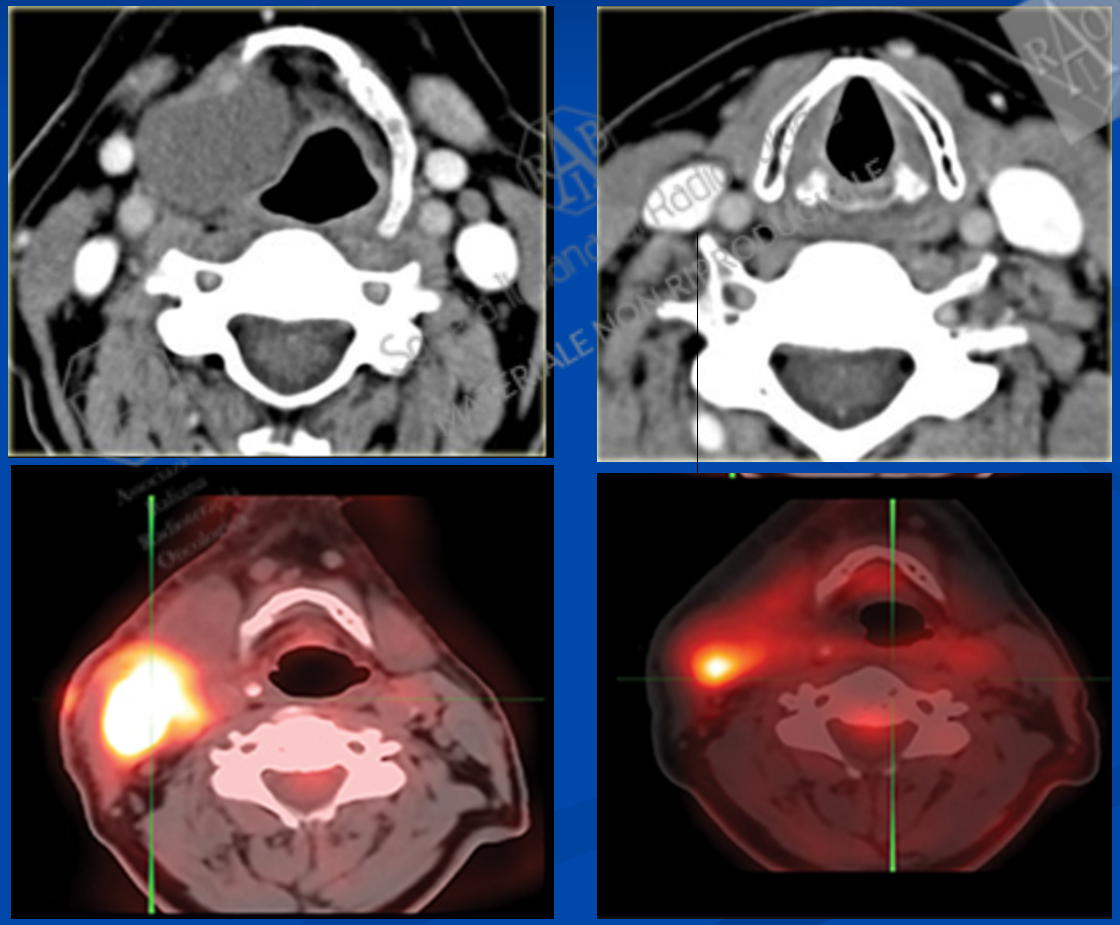
Study population



*uncompliant Center

414 patients analyzed

RESULTS



RESPONSE RATE AFTER INDUCTION TPF

Response rate

RR	TPF n=196
Complete Response	16 (8%)
Partial Response	133 (68%)
Stable Disease	34 (17.5%)
Progressive Disease	13 (6.5%)

ORR 76%

Not evaluable	12 (6%)
Never started Consent withdrawn Missing data	5 1 6

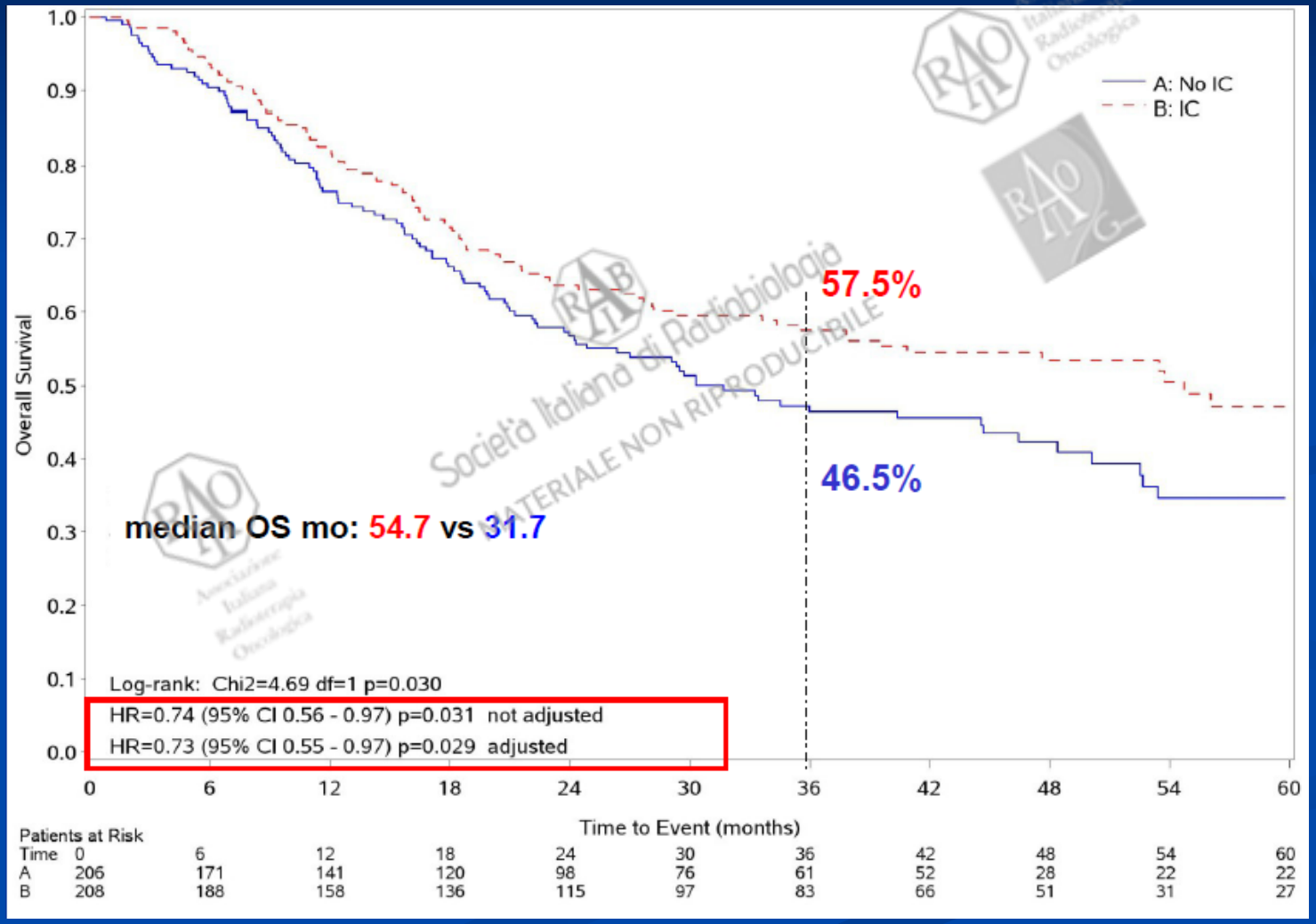
G3-4 toxicity

	TPF n=204
leukopenia	24 (12%)
neutropenia	56 (27.5%)
febrile neutropenia	23 (11%)
anemia	5 (2.5%)
thrombocitopenia	2 (1%)
nausea/vomiting	8 (4%)
diarrhoea	4 (2%)
stomatitis	10 (5%)
cardiac	1 (0.5%)
liver	4 (2%)
renal	2 (1%)

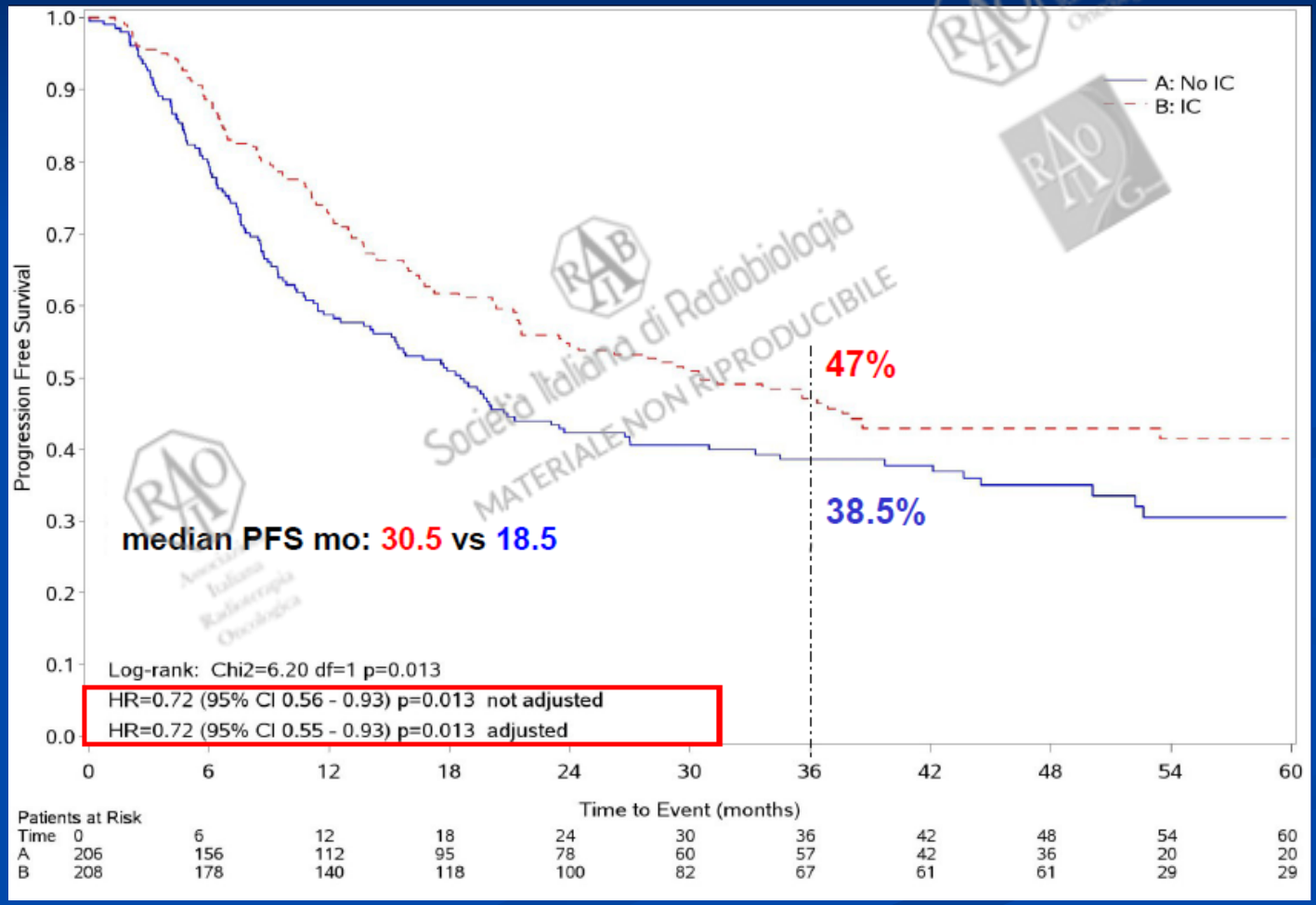
RESPONSE RATE AFTER CONCOMITANT TREATMENT

	TPF + concomitant n=181	concomitant n= 191	p value
Overall RR	145 (80%)	155 (81%)	
Complete Response	77 (42.5%)	53 (28%)	0.0028
Partial Response	68 (38%)	102 (53%)	
Stable Disease	8 (4%)	8 (4%)	
Progressive Disease	28 (15.5%)	28 (15%)	

OVERALL SURVIVAL

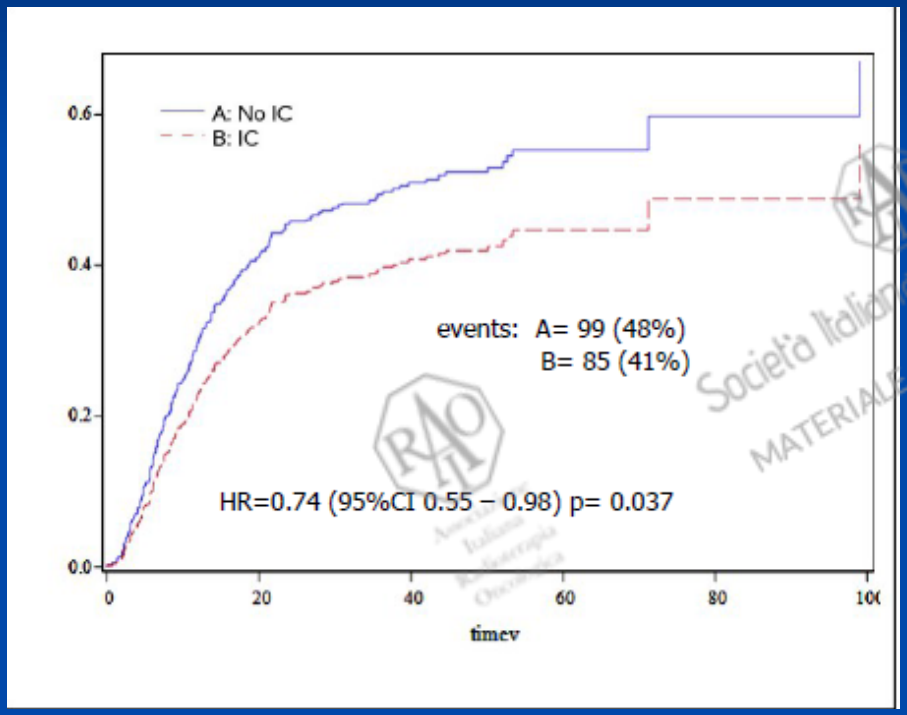


PROGRESSION FREE SURVIVAL

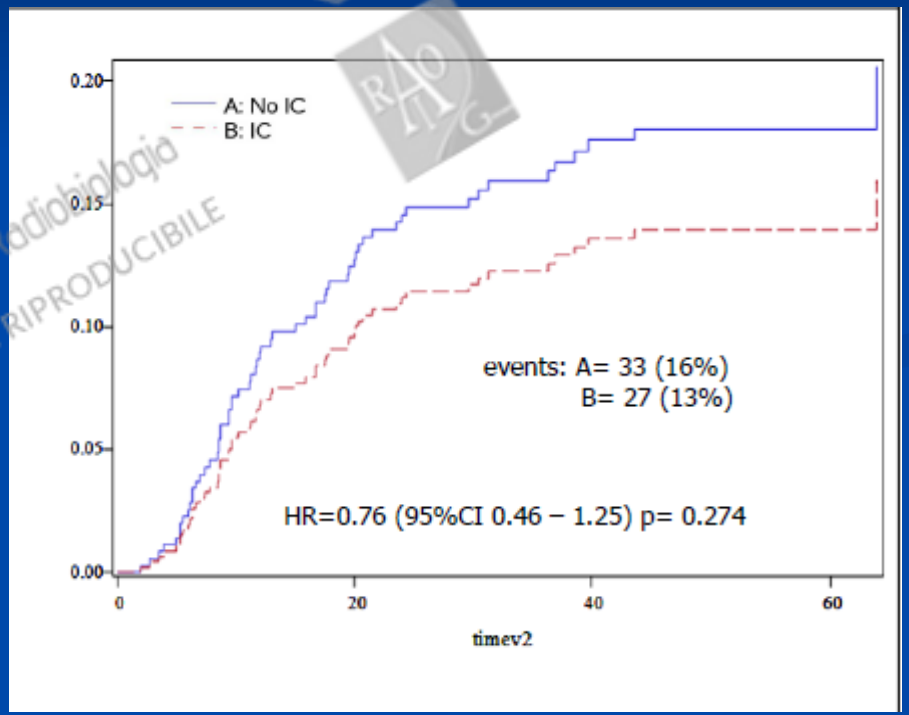


LOCOREGIONAL AND DISTANT FAILURE

Locoregional failure



Distant failure



Locoregional progression, death related to disease without a documented progression or death from an unknown cause were considered loco-regional failure

COMPLIANCE WITH CONCOMITANT TREATMENTSì

	TPF + concomitant n=183	concomitant n= 201	p value
PF 2 cy/cetuximab 7 wks - no modifications	85% 56%	87.5% 57%	0.860
RT completion - no modifications	93% 62%	89% 63%	0.986
Median RT dose, Gy (range)	70 (8-73)	70 (18-70)	0.119
Median RT duration, weeks (range)	7.3 (0.4-13)	7.4 (0.3-11)	0.951
Pts with Rt interruption > 3 consecutive days (%)	50 (27.5%)	59 (29.5%)	0.639

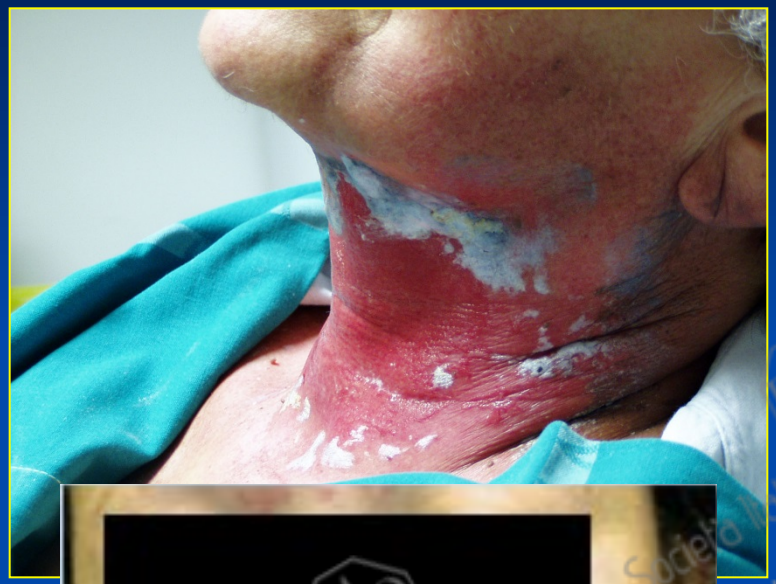
	TPF + concomitant n=204	concomitant n= 201
Death from any cause within 30 days after treatments	5 (2.5%) [2 during TPF= 1% 3 during conc= 1.5%]	7 (3.5.%)

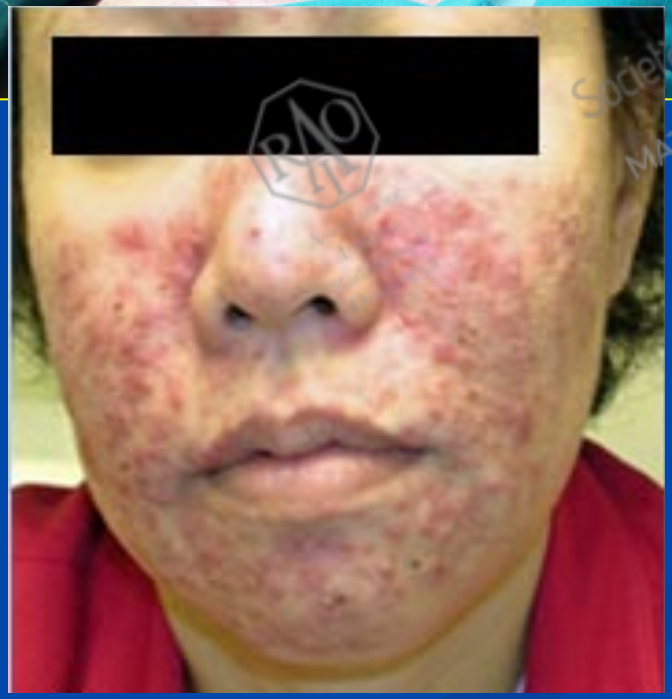
	TPF + concomitant n=208	concomitant n= 206
Never started RT	21 (10%)	6 (3%)
PD before concomitant tr./early death	10	1
Consent withdrawn/pts refusal	4	2
Toxicity*	5*	1§
Unknown	0	2
Lost	1	0
Surgery after IC	1	na

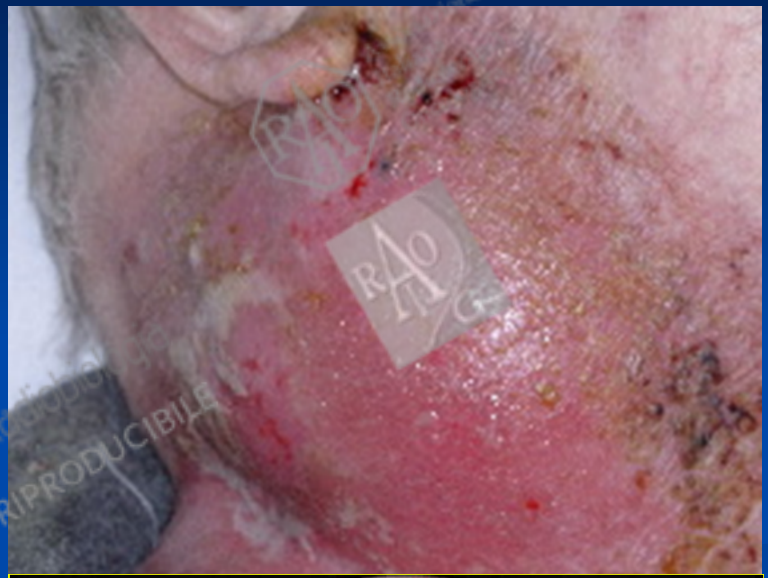
* 1 renal toxicity G2, 1 intestinal occlusion, 1 diarrhea G4, 2 Unk

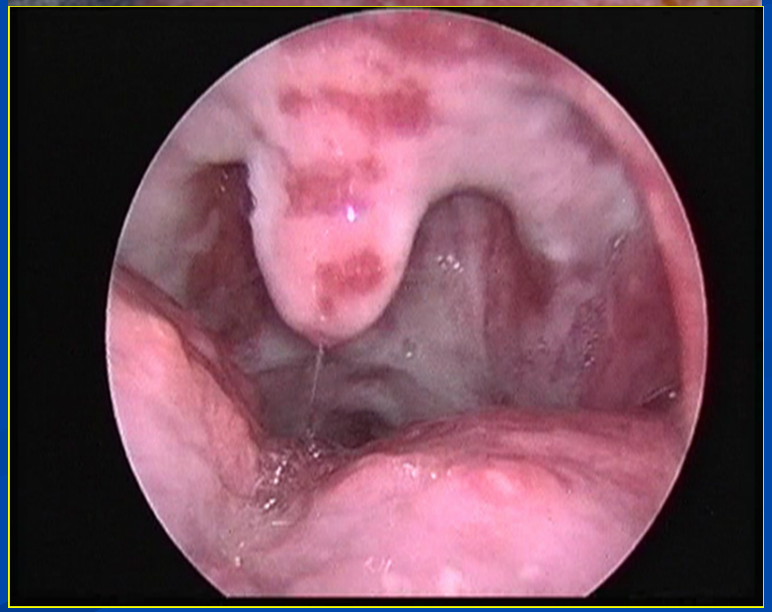
§ 1 Allergic reaction G3 (cetuximab)

TOXICITY









GRADE 3-4 HAEMATOLOGICAL TOXICITY DURING CONCOMITANT TREATMENT

	TPF + concomitant n=183	concomitant n= 201	p value
leukopenia	4 (2%)	3 (1.5%)	0.396
neutropenia	8 (4%)	2 (1%)	0.038
Febrile neutropenia	0	2 (1%)	0.200
anemia	4 (2%)	1 (0.5%)	0.145
thrombocitopenia	2 (1%)	0	0.137

GRADE 3-4 NON HAEMATOLOGICAL TOXICITY DURING CONCOMITANT TREATMENT

	TPF + concomitant n=183	concomitant n= 201	p value
nausea/vomiting	0	0	
diarrhea	0	0	
in-field stomatitis	63 (34.5%)	83 (41%)	0.166
in-field dermatitis	26 (14%)	30 (15%)	0.842
skin rash	3 (1.5%)	12 (6%)	0.028
liver	0	1 (0.5%)	0.340
renal G2-4	2 (1%)*	1(0.5%)*	0.508
neurological	0	1 (0.5%%)	0.269
allergy	1 (0.5%)	1 (0.5%)	0.947
fever w/o neutropenia	2 (1%)	6 (3%)	0.195

* all Grade 2

Toxicity EP: G3-4 in-field mucosal toxicity

CT/RT vs Cet/RT (+/- IC)

	CRT n= 233 (%)	Cet /RT n= 158 (%)	p value
Mucositis			
any grade	182 (78)	114 (72)	0.177
Grade 3	81 (35)	54 (34)	0.670
Grade 4	8 (3) 38%	3 (2) 36%	
Skin			
any grade	134 (58)	105 (66)	0.075
Grade 3	28 (12)	30 (19)	0.120
Grade 4	4 (2)	1 (0.6)	
Mucositis + Skin in-field per pts			
any grade	192 (82)	125 (79)	0.415
Grade 3-4	102 (44)	74 (47)	0.551

MG Ghi et al for GSTTC, ASCO 2013

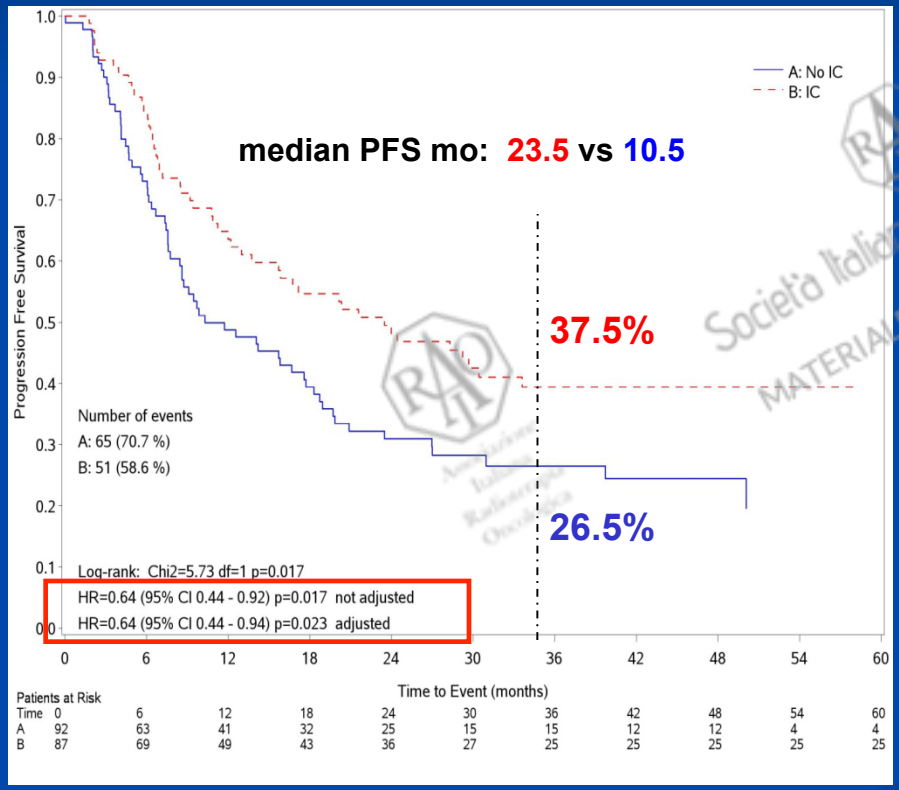
ANALISI IN CORSO

PER SEDE: orofaringe vs non orofaringe

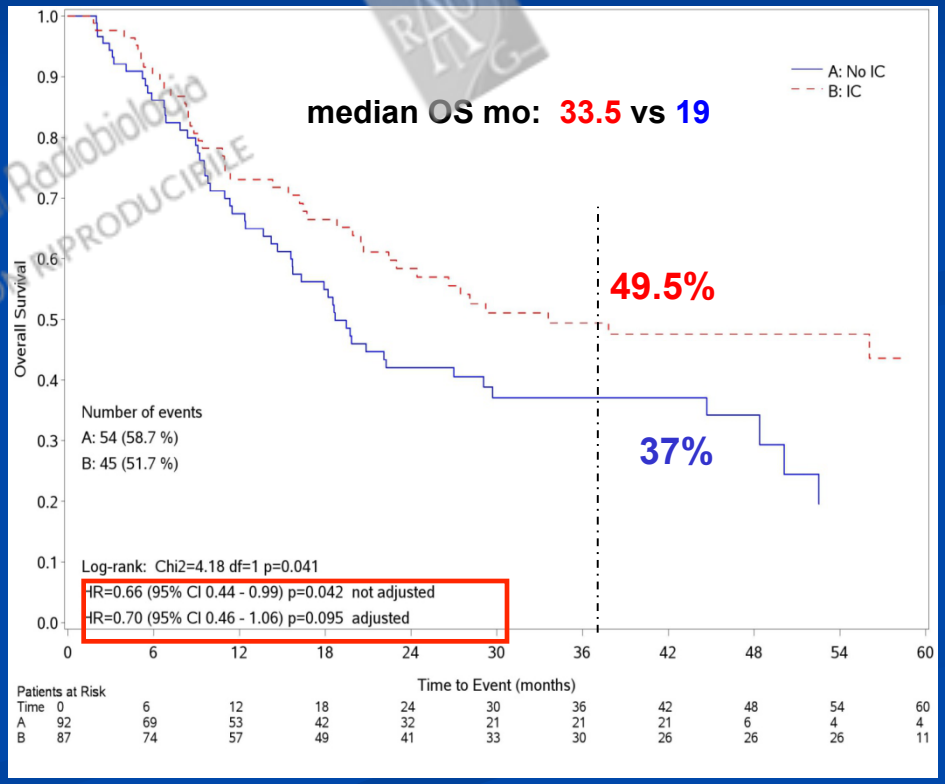
NON OPC: PFS and OS (unplanned)

(IC vs no-IC)

Progression Free Survival



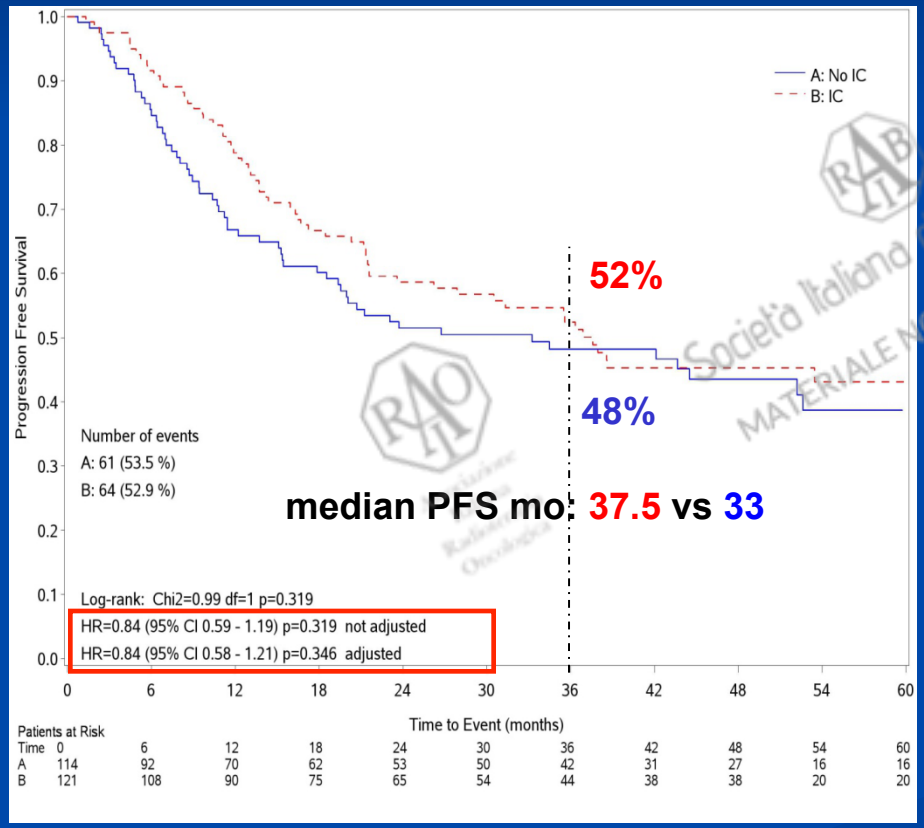
Overall Survival



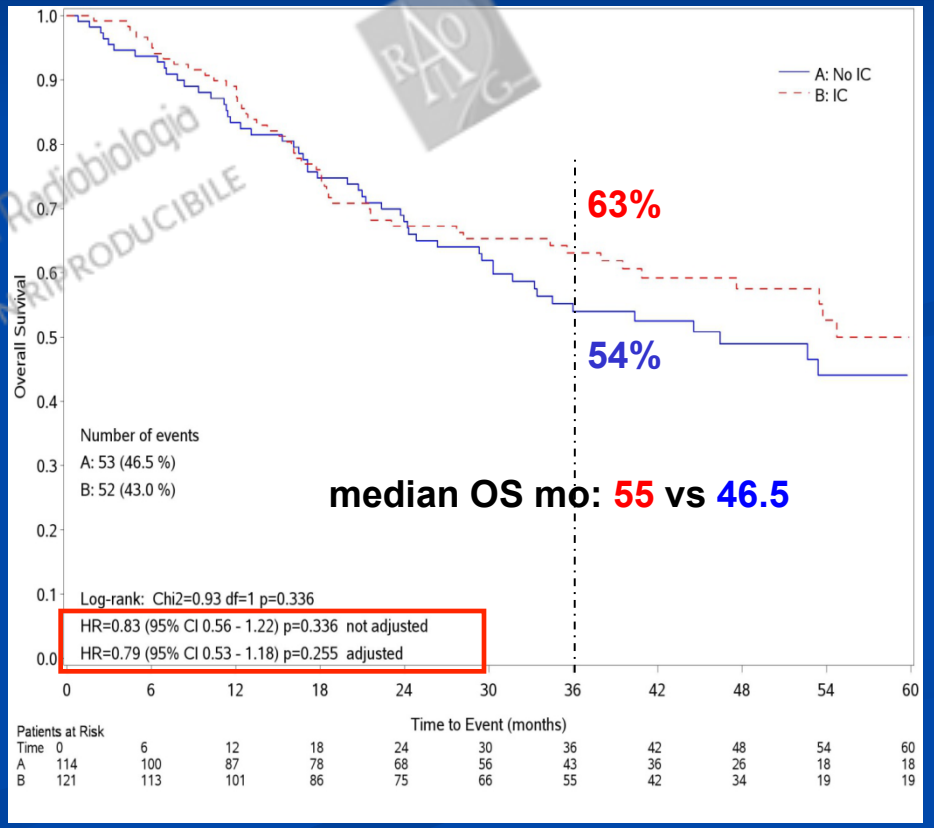
OPC : PFS and OS (unplanned)

(IC vs no-IC)

Progression Free Survival



Overall Survival



*HPV analysis in progress

ANALISI IN CORSO

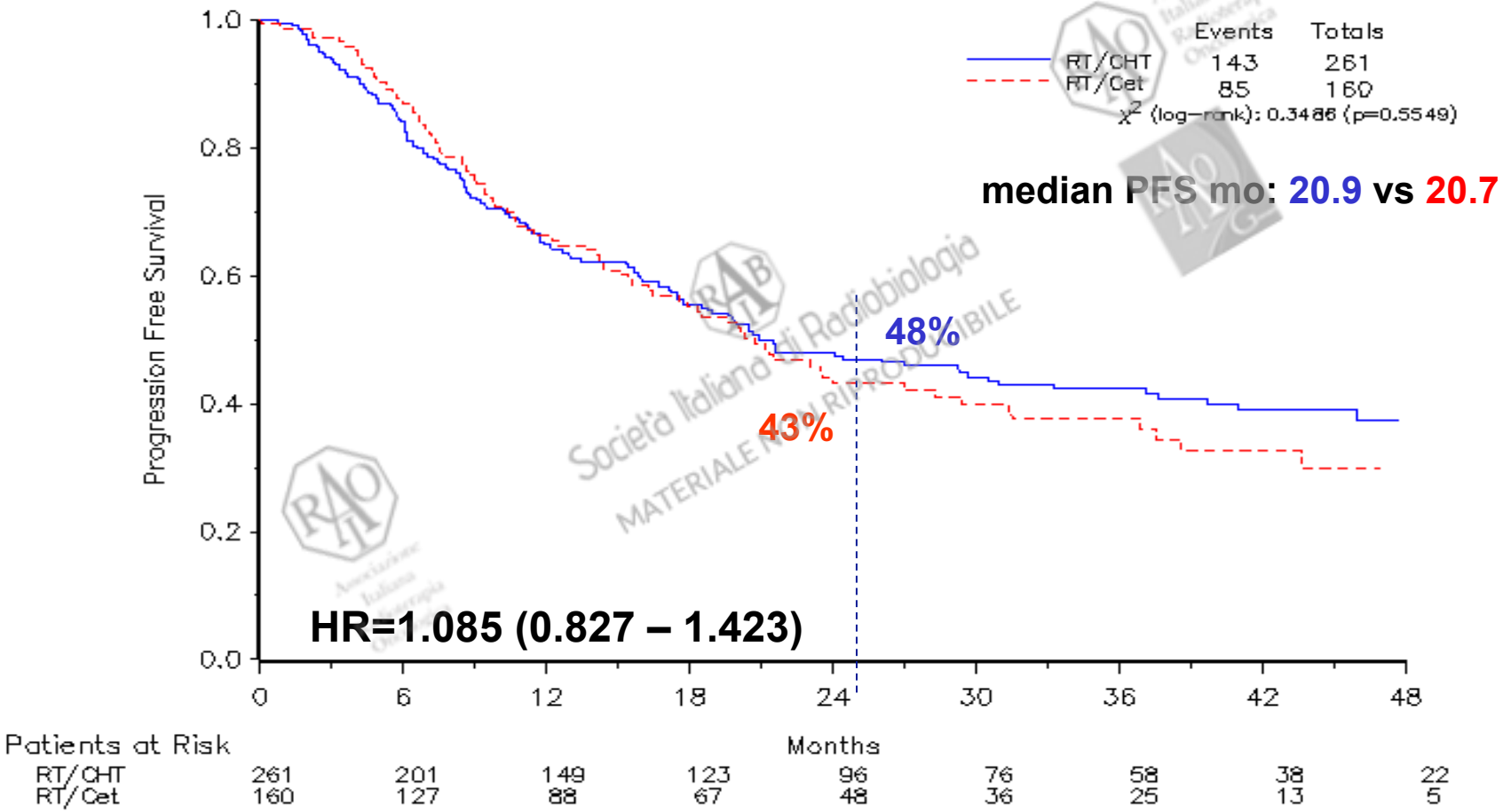
PER FARMACI ASSOCIATI: CRT vs CET-RT

Response Rate after concomitant treatment

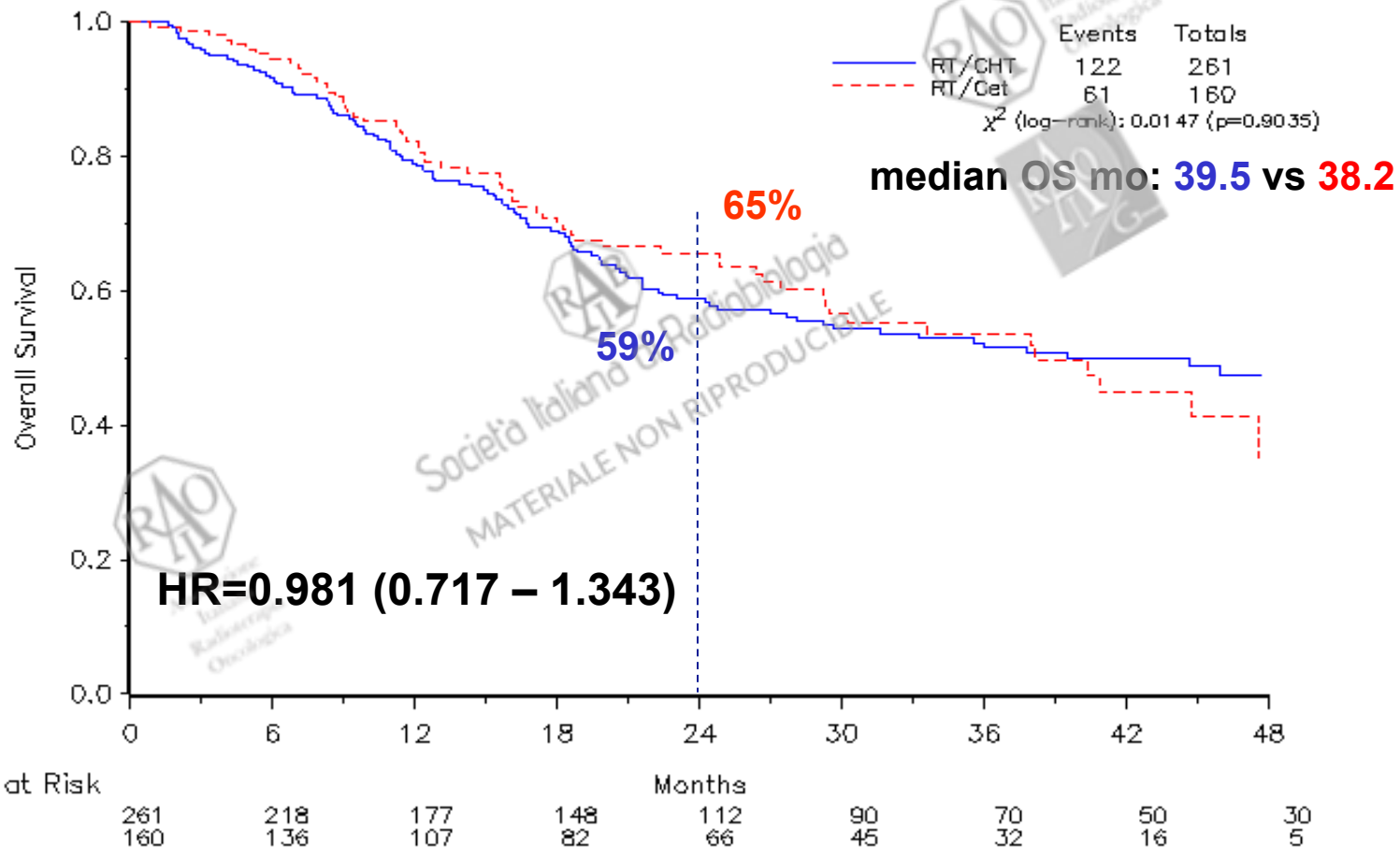
	CRT n= 223 (%)	RT/cet. n= 142 (%)	p value
Complete Response	75 (34%)	54 (38%)	0.392
Partial Response	105 (47%)	65 (46%)	
Stable Disease	11 (5%)	8 (6%)	
Progressive Disease	32 (14%)	15 (11%)	

Not evaluable	38/261 (14.5%)	18/160(11%)
withdrawn before treat.	14/261 (5%)	9/160 (5.5%)
missing data	24/261 (9%)	9/160 (5.5%)

PFS by concomitant treatment
(Intention To Treat analyses)



OS by concomitant treatment
(Intention To Treat analyses)



CONCLUSIONS

- TPF followed by concomitant treatments is superior to concomitant treatments alone in CR, PFS and OS (primary endpoint) with a significant reduction in locoregional failure.
This has to be intended as a proof of principle.

-The beneficial effect of induction TPF may weight differently according to the primary tumor site and to the subsequent concomitant strategy.

- Since this is a 2x2 factorial study with 2 different concomitant treatments and 2 different experimental arms, these phase III results are difficult to transpose into clinical practice.

GRAZIE PER L'ATTENZIONE