Cetuximab e Radioterapia: gli studi internazionali

Pierluigi Bonomo
Radioterapia Oncologica
Azienda Ospedaliero – Universitaria Careggi
Firenze

DICHIARAZIONE

Relatore: Pierluigi Bonomo

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board **NIENTE DA DICHIARARE**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**

One size fits all:
a winding road for progress

A *Is more….BETTER?* ?

- **Gortec 2007-02** randomized phase 3 trial
- **TTCC 2007-01** randomized phase 3 trial
- **Gortec 2007-01** randomized phase 3 trial

Gortec 2007-02

- Oral cavity, oro/hypopharynx, larynx
- T2–T4
- N2b (clinically palpable), N2c or N3
- M0
- Non-operable

GORTEC 2007-02

R

No induction

Carboplatin 70mg/m²/d +
5-FU 600mg/m²/d D1–D4, Weeks 1, 4 and 7

RT
70 Gy, 35 fractions,
5 fractions/wk

T
P
F

x 3 cycles

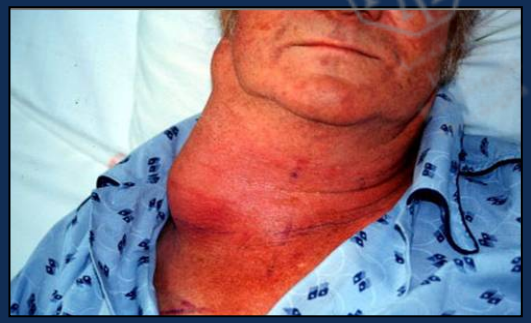
If CR, PR or SD

Docetaxel 75mg/m² D1 (T)
+ **cisplatin** 75mg/m² D1 (P)
+ **5-FU** 750mg/m² D1–5 (F)

Supportive therapy:
lenograstim and ciprofloxacin

Cetuximab
400mg/m² D-8 then 250mg/m²/w x 7 weeks

RT
70Gy, 35 fractions,
5 fractions/weeks



Geoffrois L, ASCO annual meeting, 2016

Gortec 2007-02

	CT-RT n=179 n (%)	TPF → Cetux-RT n=181 n (%)
Male	153 (85)	157 (87)
Age (median)	56.5	56
PS = 0	63 (35)	71 (39)
PS = 1	116 (65)	110 (61)
T2	29 (16)	30 (17)
T3	64 (36)	59 (33)
T4	86 (48)	91 (50)
N2b	57 (32)	46 (26)
N2c	81 (45)	98 (54)
N3	41 (23)	37 (21)
Oral cavity	24 (14)	18 (10)
Oropharynx *	108 (60)	123 (68)
Larynx	8 (5)	12 (7)
Hypopharynx	39 (22)	28 (15)

> 80% Bulky

> 65%

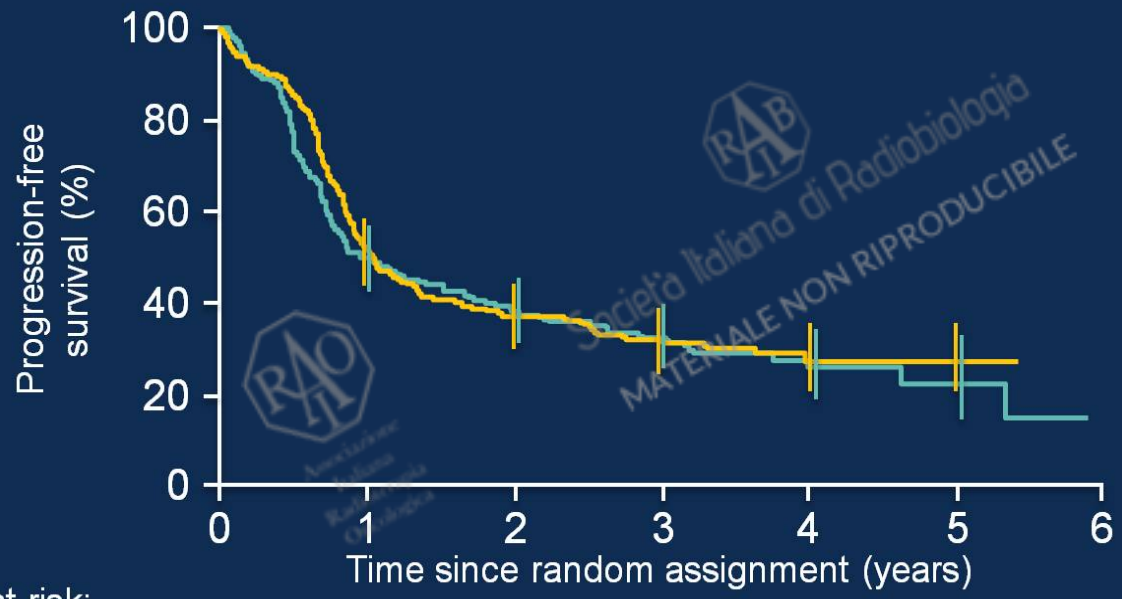
60%

p16: 80% neg

Geoffrois L, ASCO annual meeting, 2016

Gortec 2007-02

Progression-free survival



TPF + cetux-RT
CT-RT

HR (95% CI): 0.93 (0.73 to 1.20)
2-sided log-rank ***p*=0.58**

No. at risk:

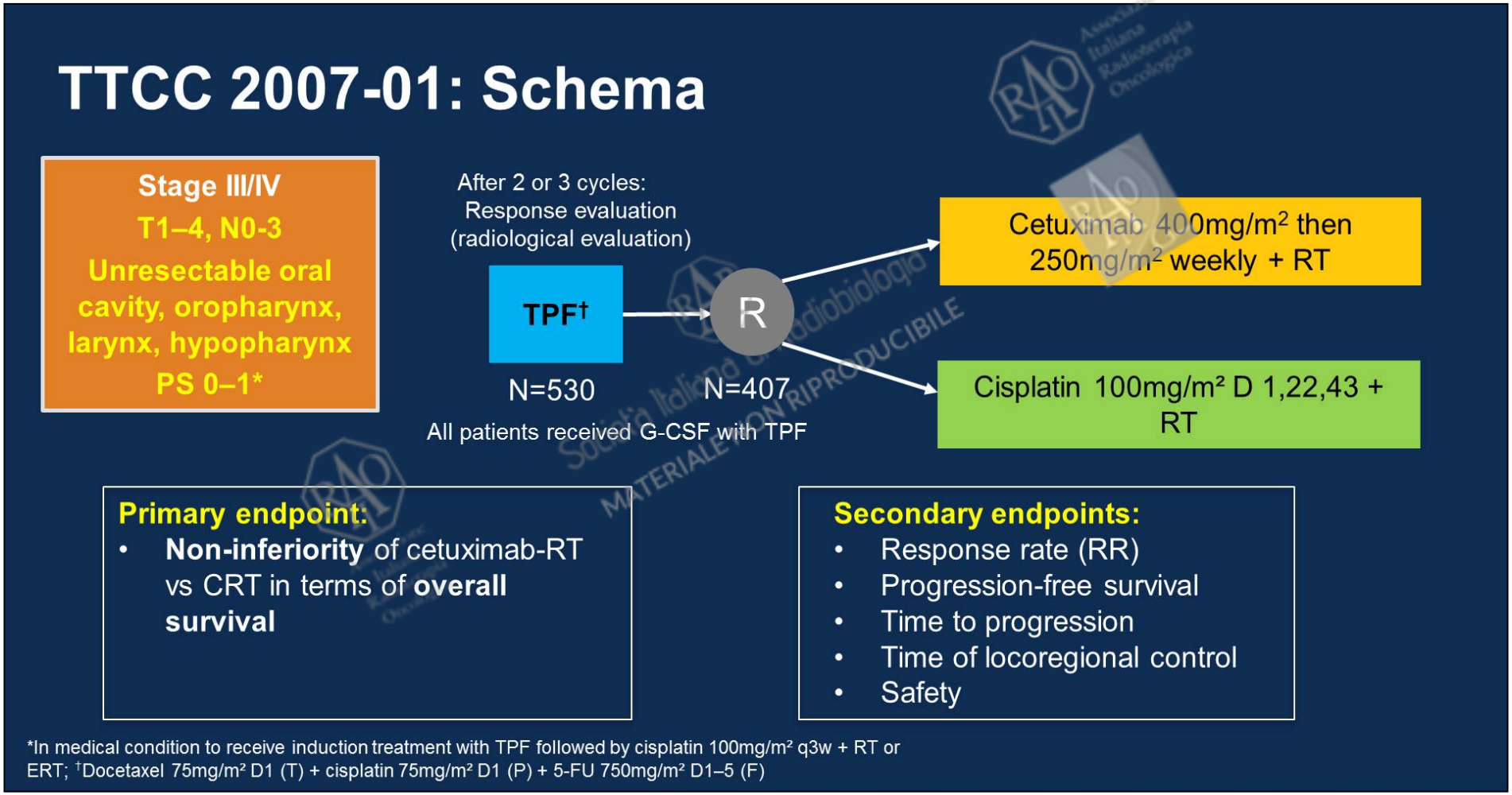
CT-RT	179	89	59	32	16	6
TPF-cetux-RT	181	87	57	33	16	2

Geoffrois L, ASCO annual meeting, 2016

Is more….BETTER?

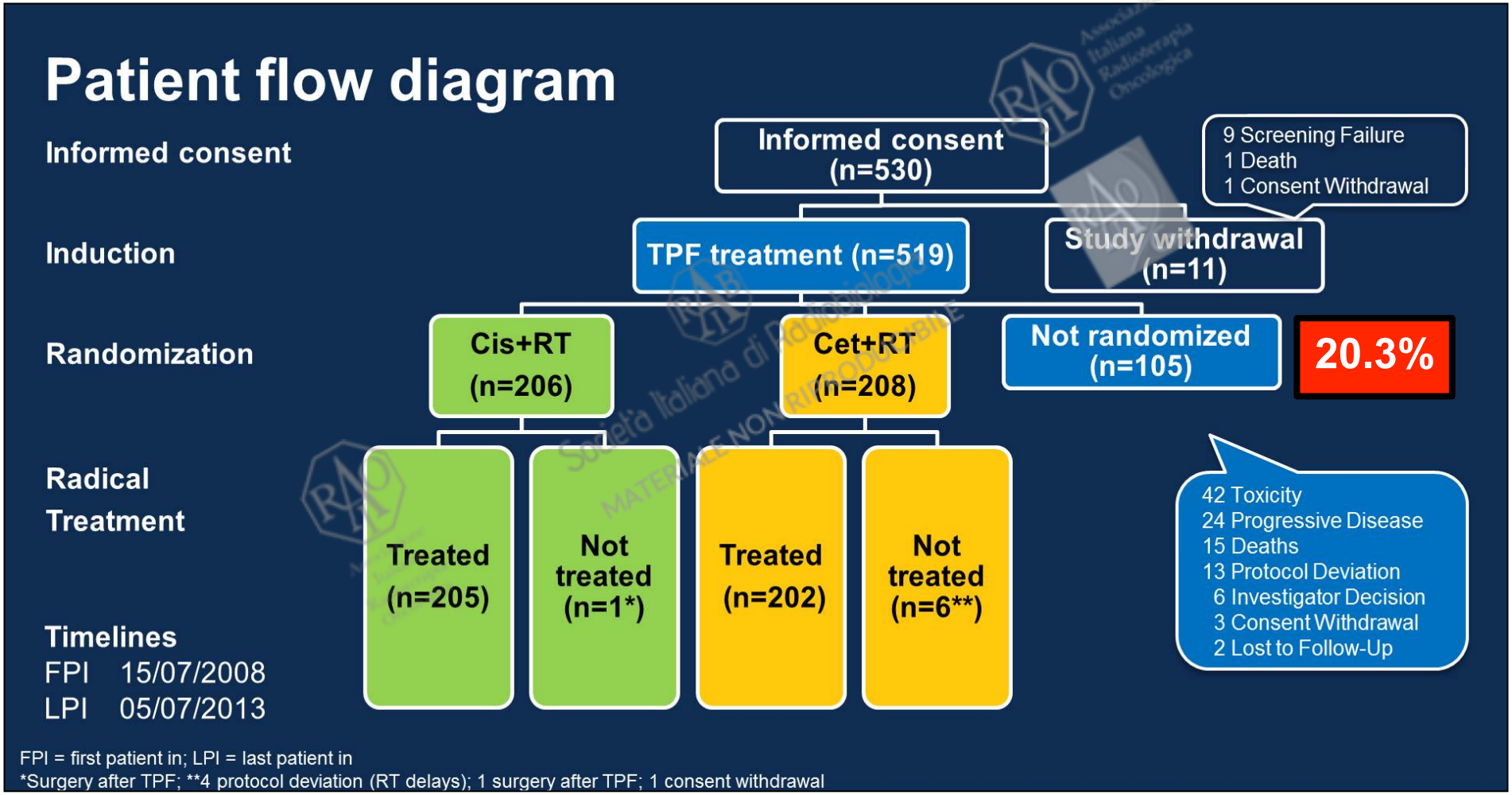
- **Gortec 2007-02** randomized phase 3 trial
- **TTCC 2007-01** randomized phase 3 trial
- **Gortec 2007-01** randomized phase 3 trial

TTCC 2007-01



Hitt R, ASCO annual meeting, 2016

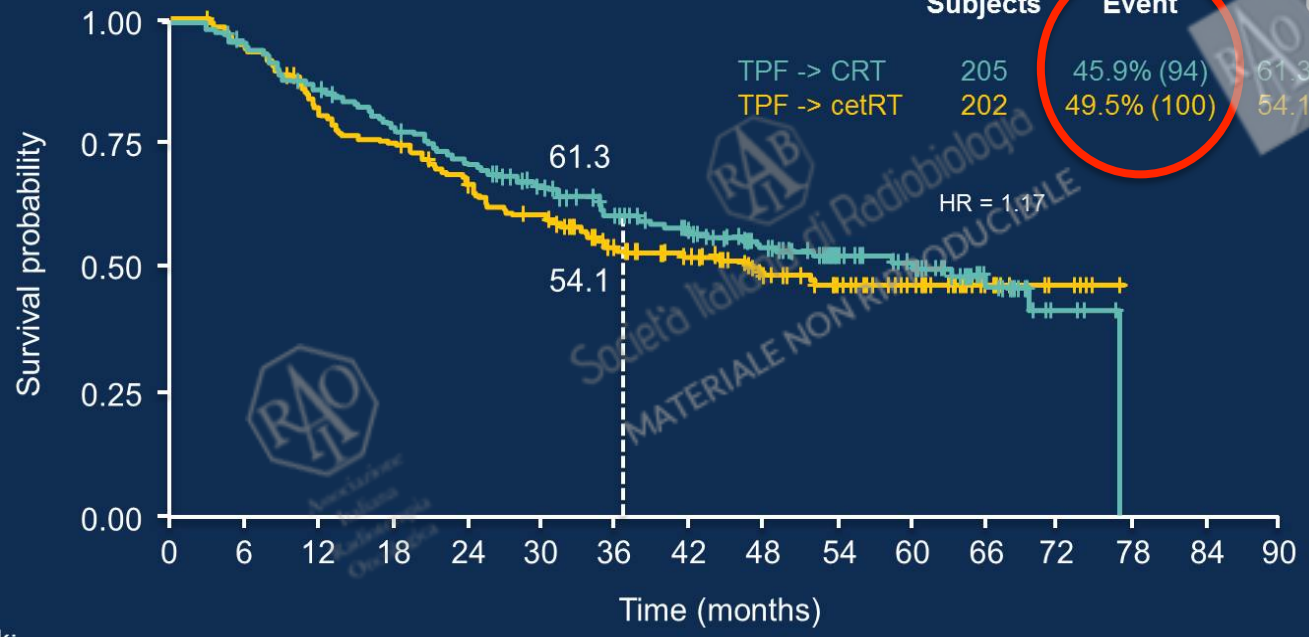
TTCC 2007-01



Hitt R, ASCO annual meeting, 2016

TTCC 2007-01

Overall Survival (after randomization)



	Subjects	Event	OS Rate 36 m	Median (95%CI)
TPF -> CRT	205	45.9% (94)	61.3 (54.1–67.8)	63.6 (43.6, 77.5)
TPF -> cetRT	202	49.5% (100)	54.1 (46.8–60.8)	47.1 (33.7, NA)

At risk:

TPF -> CRT	205	195	175	159	143	126	104	93	70	54	42	23	4	0	0	0
TPF -> cetRT	202	191	163	149	134	117	92	76	59	48	34	17	6	0	0	0

Hitt R, ASCO annual meeting, 2016

Sequential vs concurrent treatment: randomized trials

Group	Reference	Regimen	Survival benefit
TTCC (Spain)	Hitt R, Ann Oncol 2013	TPF (or PF) x 3 + CCRT (cisplatin) **vs** CCRT (cisplatin)	**NO**
Boston (US)	Haddad R, Lancet Oncol 2013	TPF x 3 + CCRT (cisplatin or docetaxel) **vs** CCRT (cisplatin)	**NO**
Chicago (US)	Cohen EE, J Clin Oncol 2014	TPF x 2+ CCRT (docetaxel, 5FU, HU) **vs** CCRT (docetaxel, 5FU, HU)	**NO**
GGTCC (Italy)	Ghi MG, Asco 2014	CCRT (carbo/5FU) w/without foregoing TPF **vs** CCRT (cetuximab) w/without foregoing TPF	**YES**
GORTEC (France)	Geoffrois L, Asco 2016	TPF x 3 + CCRT (cetuximab) **vs** CCRT (carbo/5FU)	**NO**
GONO (Italy)	Merlano MC, Ecco 2015	TPF x 3 + CCRT (cetuximab) **vs** CCRT (cisplatin)	**?**

Is more….BETTER?

- **Gortec 2007-02** randomized phase 3 trial
- **TTCC 2007-01** randomized phase 3 trial
- **Gortec 2007-01** randomized phase 3 trial

Gortec 2007-01

- Squamous cell carcinoma, Stage III/IV
- Oral cavity, oro/hypopharynx, larynx
- T0–T4
- N0–N2a (N2b allowed if non-palpable)
- M0
- Non-operable

GORTEC 2007-01

R*

Carboplatin[1,2] 70mg/m²/d +
5-FU 600mg/m²/d D1–D4, Weeks 1, 4 and 7

Cetuximab
400mg/m² D-8, then 250mg/m²/w x 7 weeks

RT
70Gy in 35 fractions,
5 fractions/week

Cetuximab[3]
400mg/m² D-8, then 250mg/m²/w x 7 weeks

RT
70Gy in 35 fractions,
5 fractions/week

p16:
79% neg

*Randomization 1:1, by minimization on N stage, T stage and center

1. Bourhis J, et al. Lancet Oncol 2012;13:145–153;
2. Calais G, et al. J Natl Cancer Inst 1999;91:2081–2086;
3. Bonner J, et al. N Engl J Med 2006;354:567–578.

Bourhis J, ASCO annual meeting, 2016

Gortec 2007-01

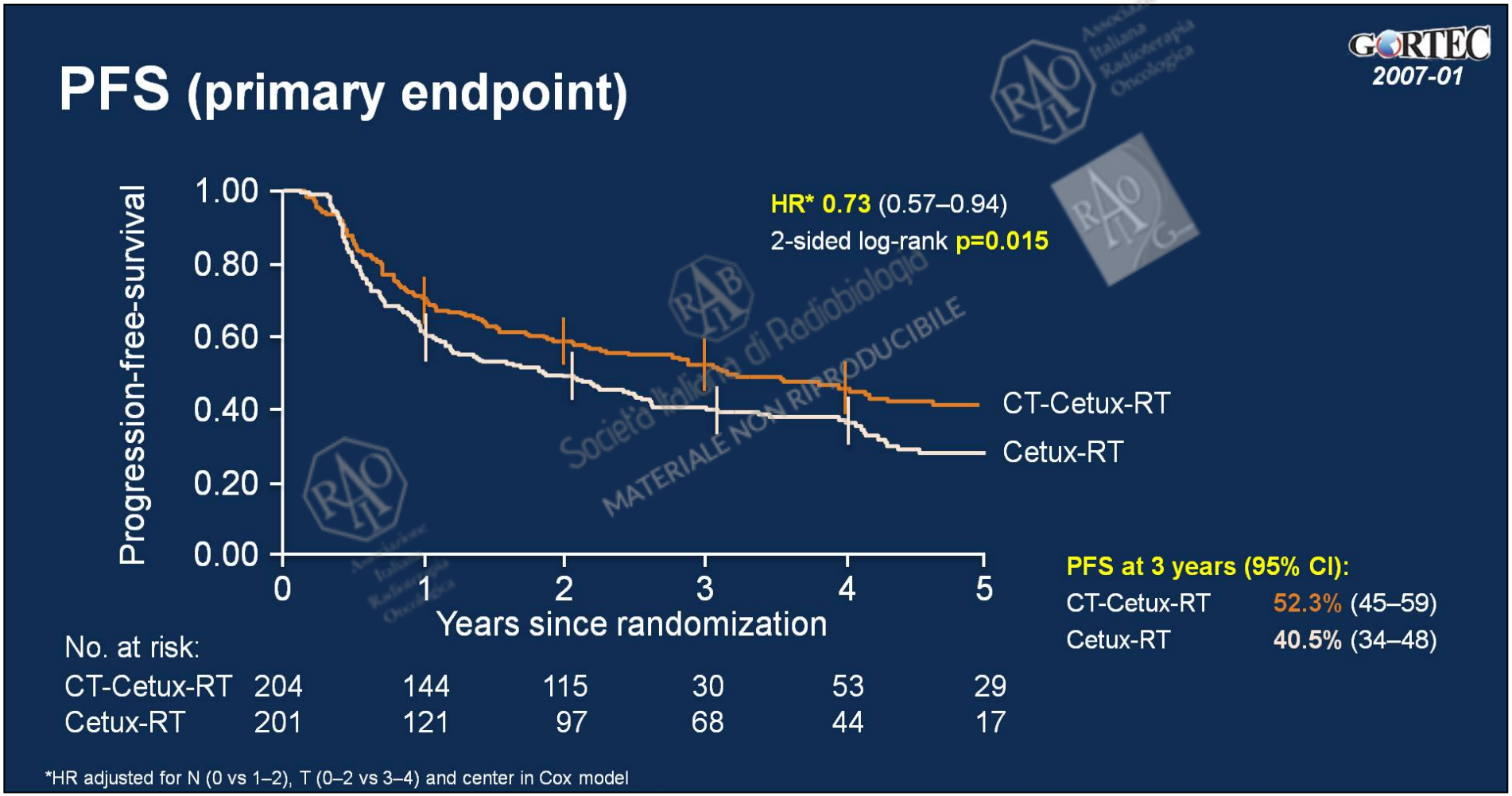
Tolerance

GORTEC 2007-01

	CT-Cetux-RT n=202	Cetux-RT n=201	P-value
At least one grade ≥3 toxicity	91%	91%	
Feeding tube use	67%	54%	0.01
Hospitalization during treatment	42%	22%	<0.0001
Early death (<30 days post-treatment)	4.9%	1.5%	

Bourhis J, ASCO annual meeting, 2016

Gortec 2007-01



Bourhis J, ASCO annual meeting, 2016

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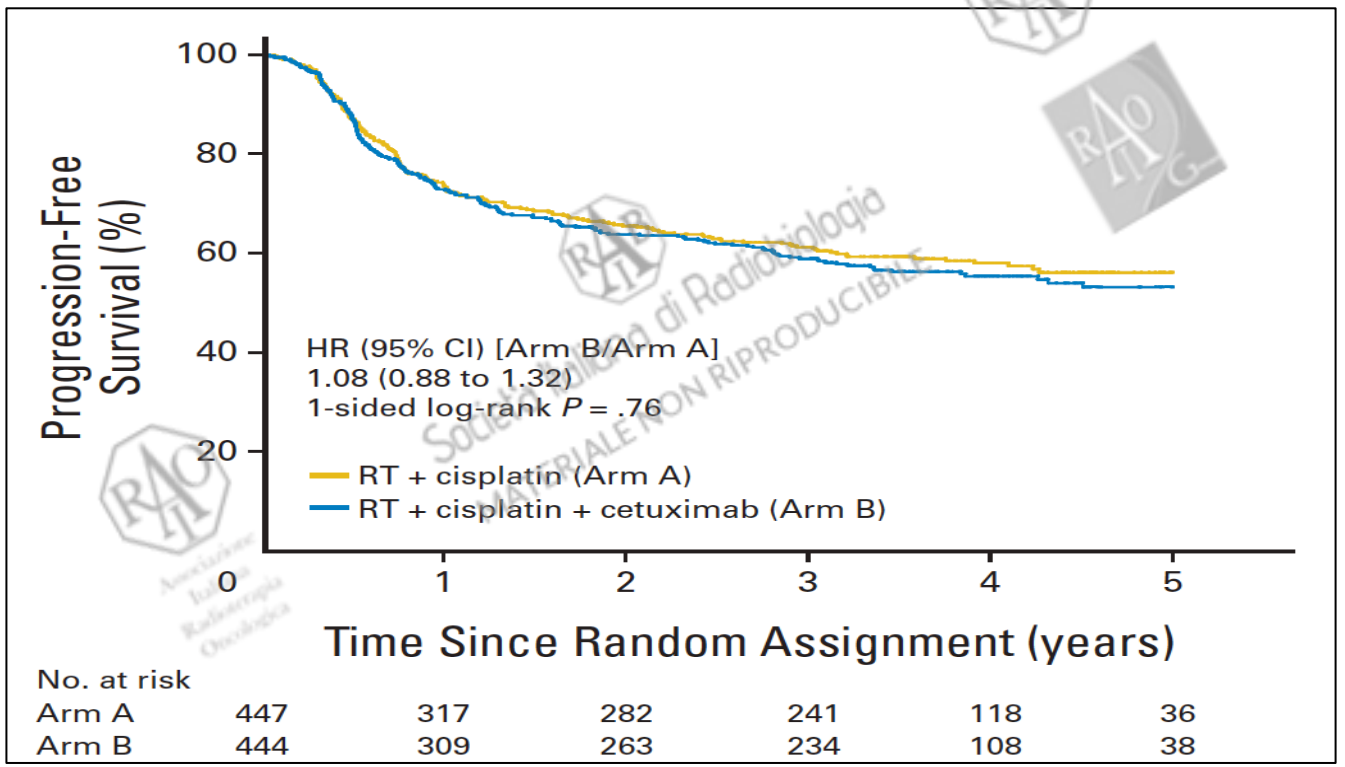
JOURNAL OF CLINICAL ONCOLOGY E D I T O R I A L

Combining Cetuximab With Chemoradiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma: Is More Better?



- more RT interruptions (27% vs 15%)
- more G3/G4 mucositis (43% vs 33%)

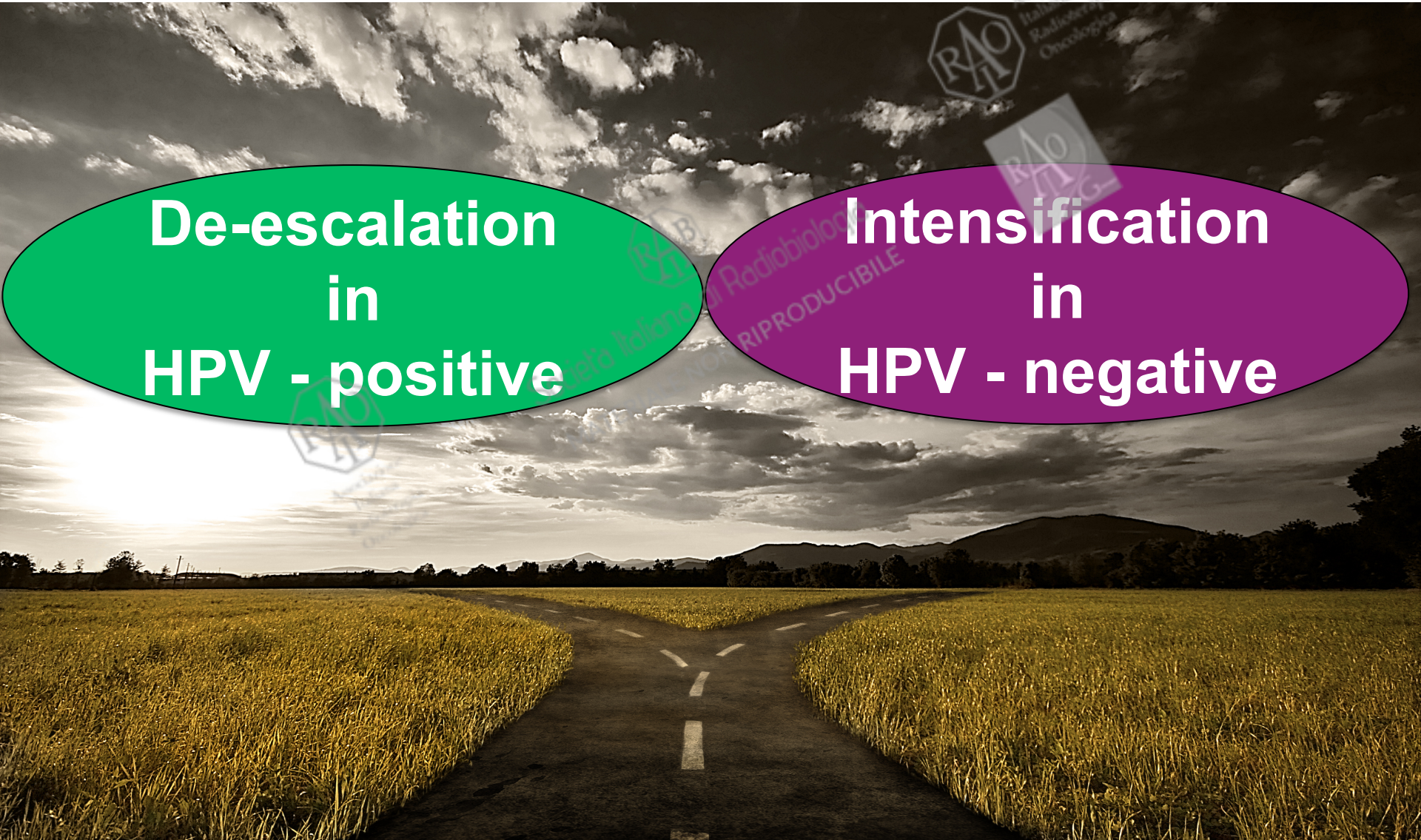
Ang KK, J Clin Oncol 2014

More is not always better

- Cave: rt-dermatitis with 5-FU + Cetuximab (AlteRCC phase 2[1])
- Failure with cisplatin-RT
  - Panitumumab (Concert-1 rdm phase 2[2])
  - Zalutumumab (Dahanca 19 rdm phase 3[3])
  - Lapatinib (adjuvant rdm phase 3[4])
- Promising with cetuximab-RT
  - Docetaxel (RTOG 0234 rdm phase 2[5], ongoing RTOG 1216 phase 2/3)
  - Ipilimumab phase 1b just completed[6]

[1]Merlano M, Ann Oncol 2010; [2]Mesia R, Lancet Oncol 2015; [3]Eriksen J, 5th ICHNO 2015; [4]Harrington K, J Clin Oncol 2015; [5]Harari PM J Clin Oncol 2016; [6]Ferris RL, NCT01935921

The world has changed after RTOG 0129



De… in loca…rynx

Is less….MORE?

Trial (phase)	N	Smoke	Design	Due date
ECOG 1308 (II)	80	all pts	IC with PCC, then response adapted RT (54-70 Gy) + Cetuximab	pending
QUARTERBACK (III)	365	> 20 PY	IC with TPF, then response adapted RT (56-70 Gy) + weekly carboplatin	2021
ECOG 3311 (II)	377	> 10 PY	TORS, then risk adapted RT (50-66 Gy) ± weekly cisplatin	2017
ADEPT (III)	500	all pts	TORS + post-op 60 Gy ± weekly cisplatin	2021
RTOG 1016 (III)	987	all pts	accelerated 70 Gy + 3w cisplatin or cetuximab	2020
TROG 12.01 (III)	200	< 10 PY	70 Gy + weekly cisplatin or cetuximab	2018
De-ESCALATE (III)	304	< 10 PY	70 Gy + 3w cisplatin or cetuximab	2019
NRG-HN002 (II rdm)	296	< 10 PY	60 Gy ± weekly cisplatin	2018

Genetic landscape in HNSCC

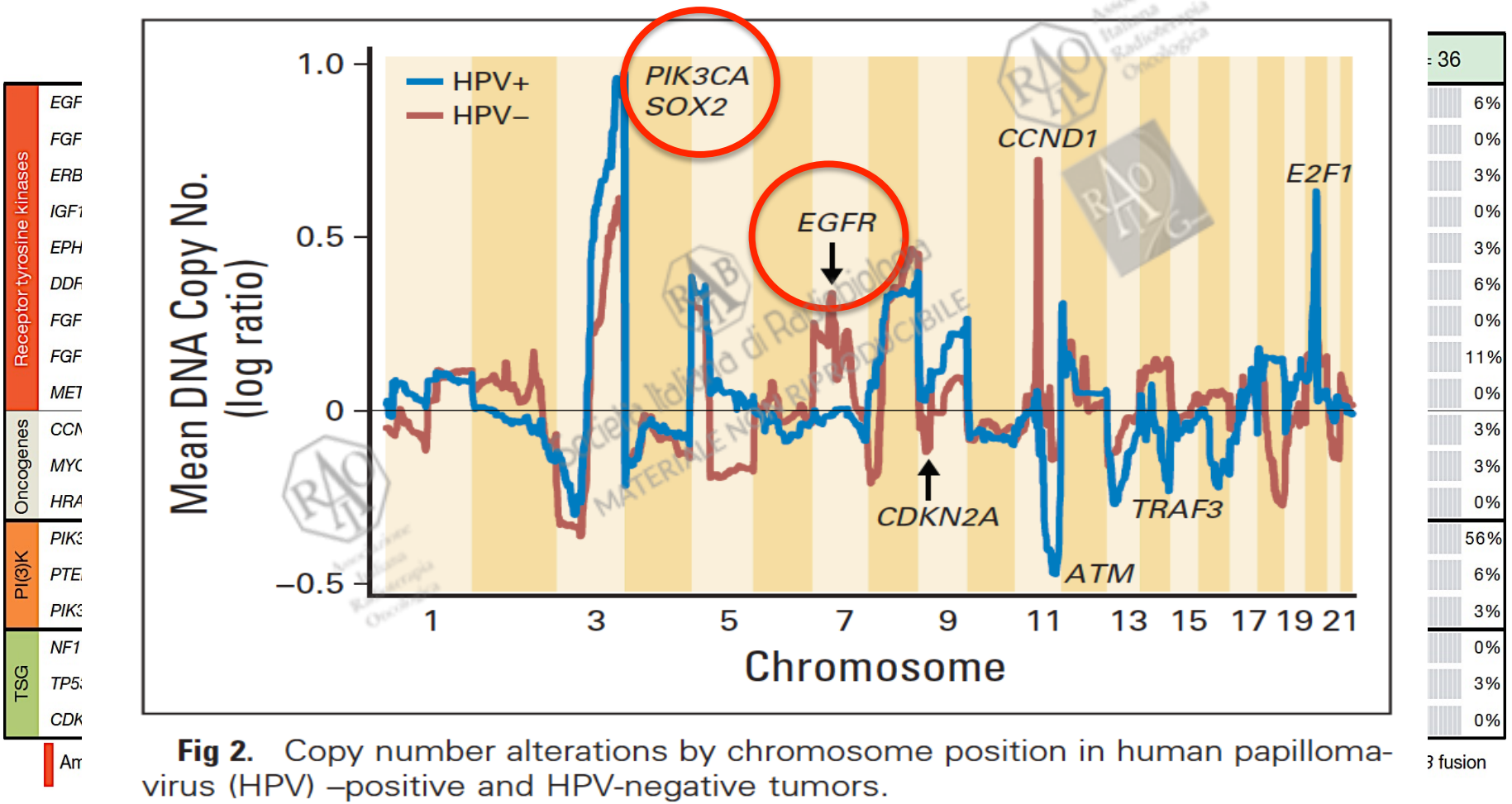


Fig 2. Copy number alterations by chromosome position in human papillomavirus (HPV) –positive and HPV-negative tumors.

TCGA Network, Nature 2015
Hayes DN, J Clin Oncol 2015

Anti-EGFR and HPV status: a continuing debate

- No difference in efficacy by HPV status:
  - Cetuximab, EXTREME trial[1]
  - Cetuximab, Bonner trial[2]
- Anti-EGFR work better in HPV negative:
  - Panitumumab, SPECTRUM trial[3]
  - Afatinib, LUX-H&N1 trial[4]

[1]Vermorken JB, Ann Oncol 2014; [2]Rosenthal DI, J Clin Oncol 2016;
[3]Vermorken JB, Lancet Oncol 2013; [4] Cohen EE, ASCO 2015

Summary

- **Role of cetuximab in the treatment of LASSCHN yet to be fully defined**
  - warrants further investigation in neoadjuvant setting & non-cisplatin based CTRT
  - bioRT still holds promise in HPV +
- **Critical lack of EGFR-sensitivity signature**
  - ≥ G2 skin rash weak prognosticator

Associazione Italiana Radioterapia Oncologica

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