



Definitive Chemo + Mabs+ RT in LAHNSCC

Dr Vineeta Goel

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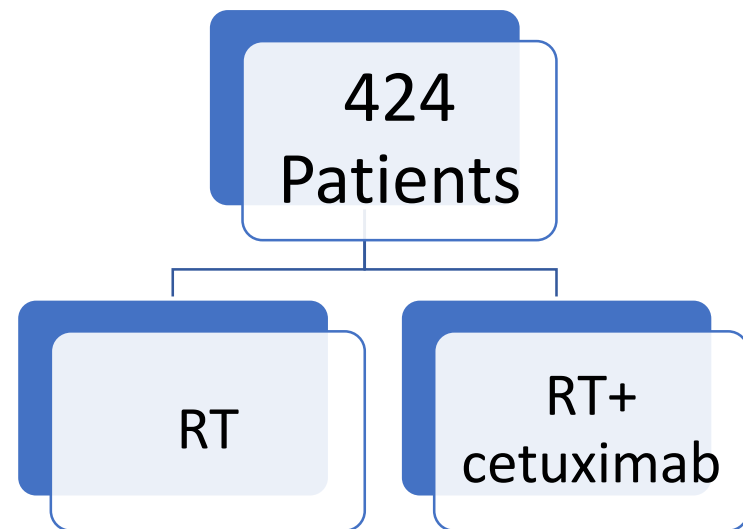
CETUXIMAB

- Human –murine chimeric Monoclonal Antibody against EGFR
- MOA : Binds to 2nd domain of EGFR
 - cause receptor internalization and degradation
 - downregulation of receptors
 - reduced EGFR signaling
- Cell cycle specific : arrests cells in G1 phase
- Radiation increases the expression of EGFR in cancer cells, and blockade of EGFR signalling sensitizes cells to the effects of radiation.

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.*



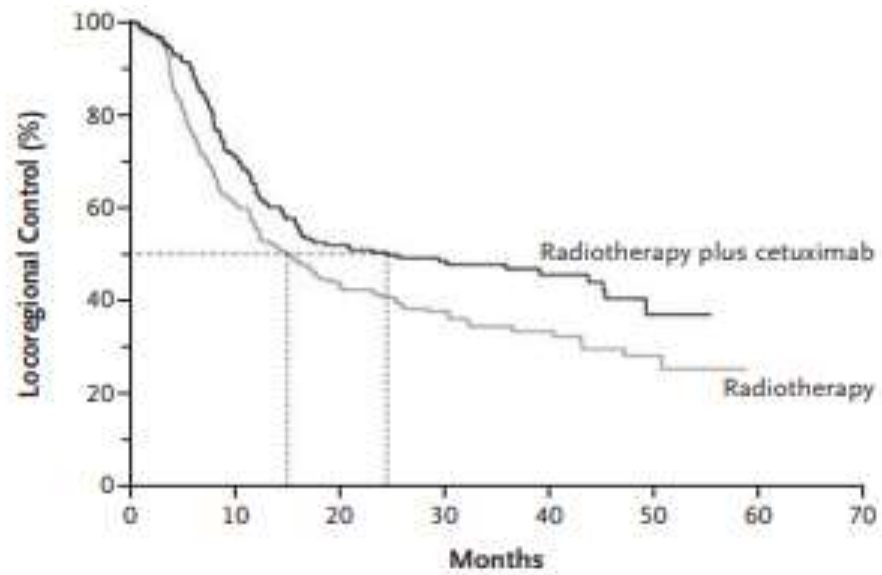
- Multinational , randomised study to compare RT Vs RT + Cetuximab in LA HNSCC
- Stage III – IV Oropharynx, Larynx and Hypopharynx
- **Bonner Trial 2004**

- Investigators were required to select one of the three RT fractionation regimens before patient registration.

Regimen	Total RT Dose	Once-Daily Fractions	Twice Daily Fractions
Once daily (26%)	70 Gy/ 35 frs	2.0 Gy/fr; 5 fr/ wk over 7 wks	NA
Twice daily (18%)	72–76.8 Gy /60–64 frs	NA	1.2 Gy/fr; 10 fractions/wk for 6.0–6.5 wks
Concomitant boost (MC used 56% pts)	72 Gy/ 42 frs	32.4 Gy; 1.8 Gy/fr; 5 fractions/wk for 3.6 wk	Morning dose: 21.6 Gy; 1.8 Gy/ fr; 5 frs/wk for 2.4 wks Afternoon dose: 18.0 Gy; 1.5 Gy/ fr; 5 frs/wk for 2.4 wks

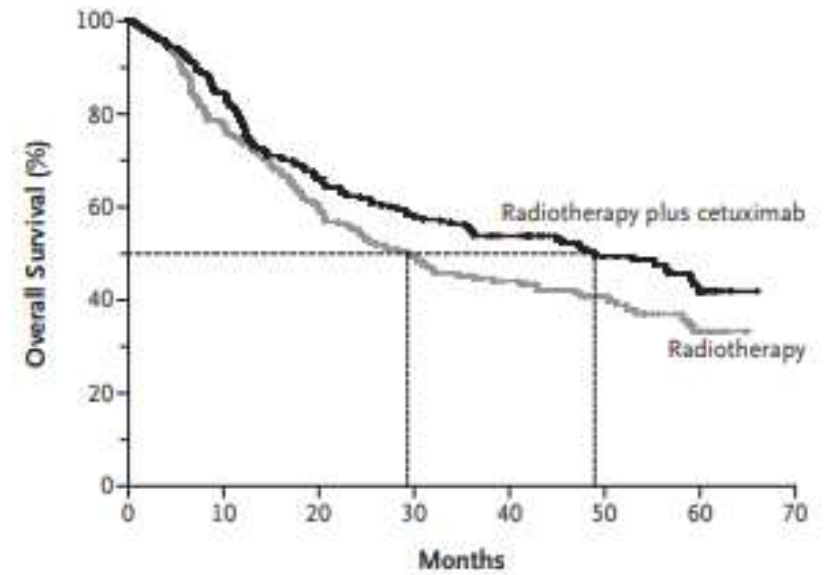
In the group assigned to receive RT+ Cetuximab- loading week -1 dose 400 m/m² followed by weekly @ 250 mg/m²

- **Primary end point - LRCR**
- **Secondary end points – OS, PFS, ORR and safety**
- Required 208 patients per treatment group for 90 % power for primary end point
- Balanced between both treatment groups with respect to- Compliance, Type of RT chosen, Subsequent neck dissections, subsequent salvage surgery and subsequent chemotherapy



No. at Risk	0	10	20	30	40	50	60	70
Radiotherapy	213	122	80	51	30	10		
Radiotherapy plus cetuximab	211	143	101	66	35	9		

LOCO-REGIONAL CONTROL



No. at Risk	0	10	20	30	40	50	60	70
Radiotherapy	213	162	122	97	73	47	22	
Radiotherapy plus cetuximab	211	177	136	116	98	61	24	

OVER ALL SURVIVAL

Median FU - 54 mo	Cetuximab + RT	RT	HR	p
Median duration of LRC	24.4 Mo	14.9 Mo	0.68	0.005
Median OS	49 Mo	29.3 Mo	0.74	0.03
3 Y OS	55%	45%		0.05

SAFETY

- 13 patients discontinued cetuximab
 - 4 due to hypersensitivity reactions after the test dose
 - 8 due to grade 3 acneiform rash.
- Cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck, including mucositis, xerostomia, dysphagia, pain, weight loss, and performance-status deterioration
- **Acneiform rash and Infusion reactions**

CONCLUSION

- Cetuximab plus RT is superior to RT alone
- Improvement in LRCR and OS
- Without increasing toxic side effects

Criticism

- CTRT Vs RT + Cetuximab was not compared; standard arm of RT alone is an inferior treatment
- Use of altered fractionation

Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival



James A Bonner, Paul M Harari, Jordi Giralt, Roger B Coher, Junming Zhu, Hagop Youssoufian, Eric K Rowinsky, K Kian

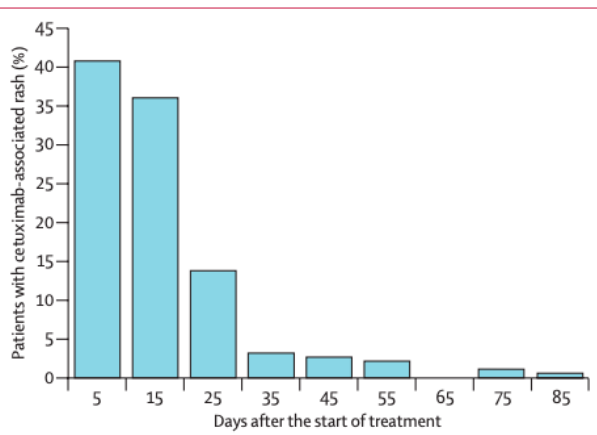


Figure 4: The onset of cetuximab-induced rash following the initiation of first treatment

	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94.3%)	45 (21.2%)	3 (1.4%)	204 (98.1%)	73 (35.1%)	4 (1.9%)
Mucositis/stomatitis†	199 (93.9%)	110 (51.9%)	9 (4.2%)	194 (93.3%)	116 (55.8%)	13 (6.3%)
Dysphagia	134 (63.2%)	63 (29.7%)	3 (1.4%)	136 (65.4%)	54 (26.0%)	1 (0.5%)
Xerostomia‡	150 (70.8%)	6 (2.8%)	0 (0%)	150 (72.1%)	10 (4.8%)	0 (0%)
Acneiform rash§	21 (9.9%)	3 (1.4%)	0 (0%)	174 (83.7%)	35 (16.8%)	1 (0.5%)
Infusion reaction¶	4 (1.9%)	0 (0%)	0 (0%)	32 (15.4%)	6 (2.9%)	2 (1.0%)

*Skin reaction includes all Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) terms in the Skin and Appendages body system. †Mucositis/stomatitis includes COSTART terms aphthous stomatitis; gingivitis; glossitis; mouth ulceration; mucous membrane disorder; stomatitis; and ulcerative stomatitis. ‡Xerostomia is COSTART term dry mouth. §Acneiform rash includes COSTART terms acne; rash; maculopapular rash; exfoliative dermatitis. ¶Infusion reaction includes COSTART terms allergic reaction; anaphylactoid reaction; and/or fever; chills; or dyspnoea on the first day of treatment. ||Statistically significant ($p < 0.05$) difference between the treatment groups; Fisher's exact test.

Table 2: Most common adverse events

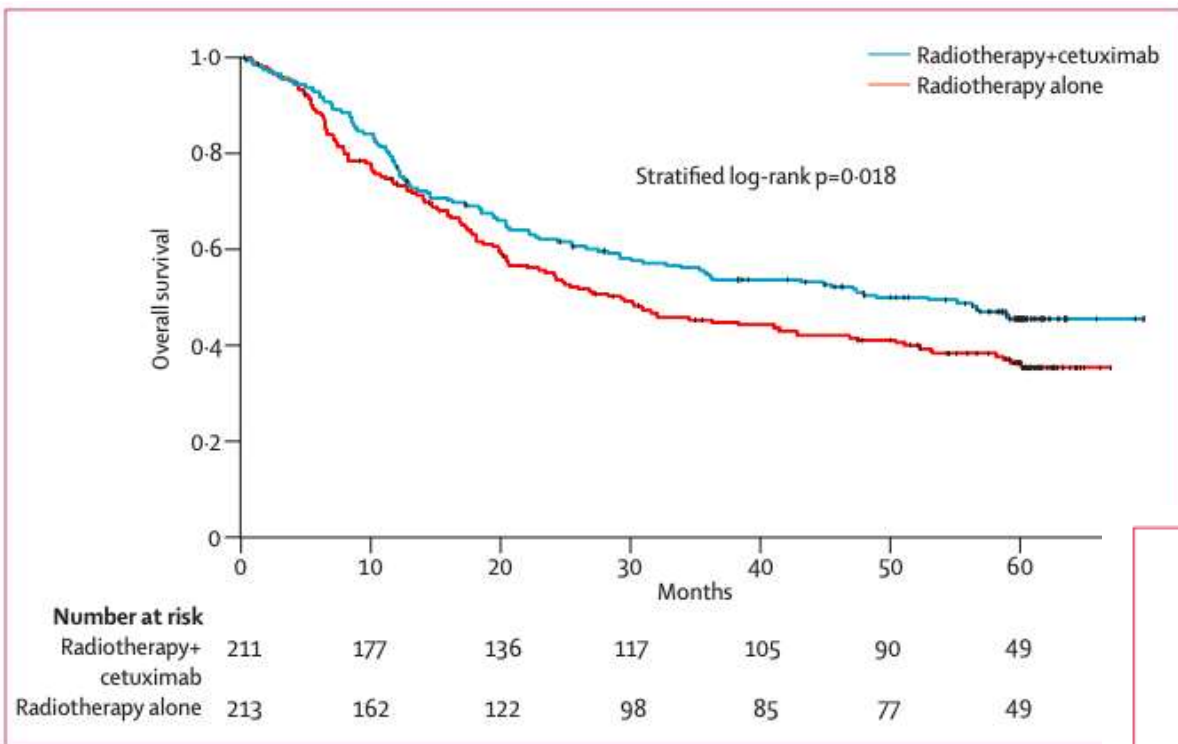


Figure 2: Overall survival by treatment: 5-year update (median follow-up 60 months)

Patients continued to show benefit in OS with Cetuximab + RT

Patients with rash had better OS as compared to pts who did not get rash- “Welcome Rash”- indicated drug efficacy

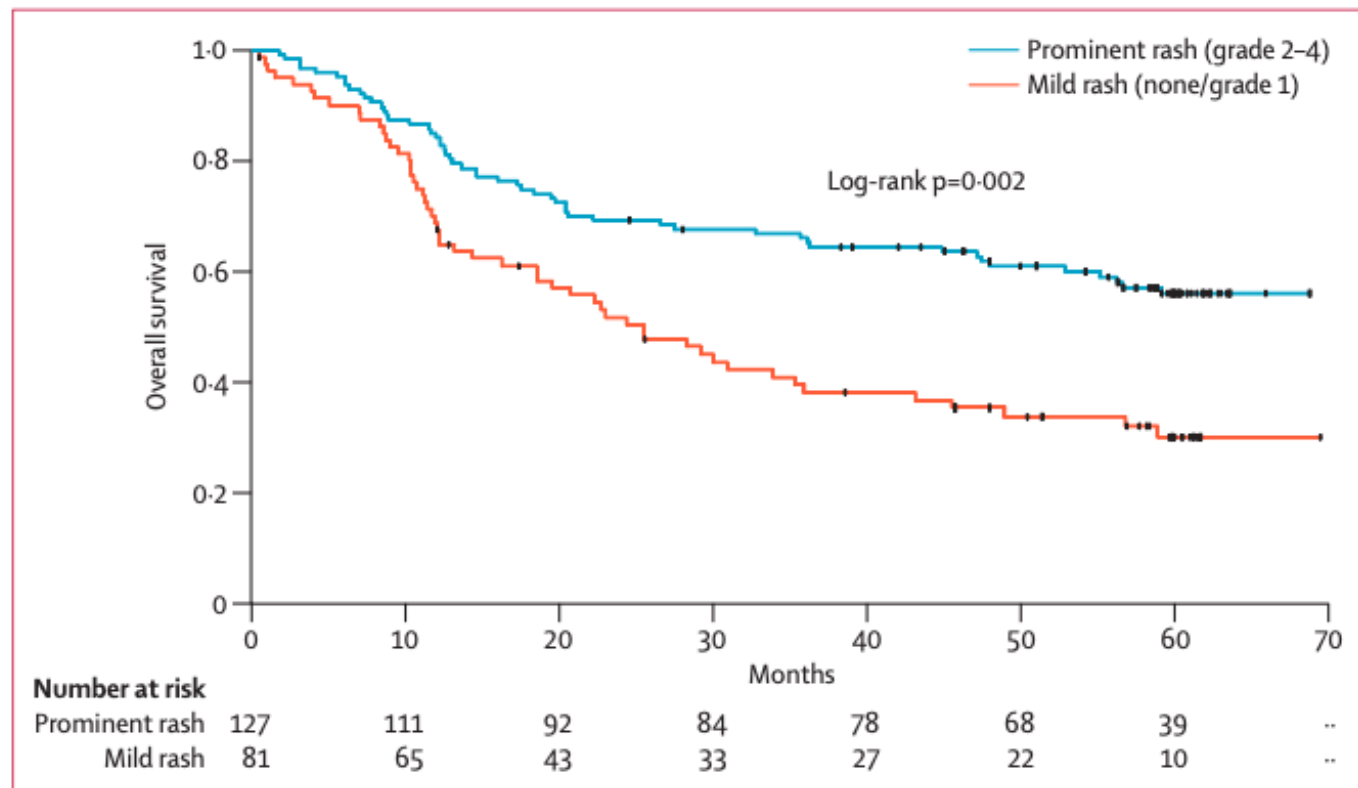


Figure 5: Overall survival by severity of rash in cetuximab-treated patients

ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer



Maria Gebre-Medhin, MD, PhD¹; Eva Brun, MD, PhD¹; Per Engström, PhD¹; Hedda Haugen Cange, MD, PhD²;
Lalle Hammarstedt-Nordenvall, MD, PhD³; Johan Reizenstein, MD⁴; Jan Nyman, MD, PhD²; Edvard Abel, MD²;
Signe Friesland, MD, PhD^{5,6}; Helena Sjödin, MD⁵; Henrik Carlsson, MD¹; Karin Söderkvist, MD, PhD⁷; Marcus Thomasson, MD, PhD⁷;
Björn Zackrisson, MD, PhD⁷; and Per Nilsson, PhD¹

- Randomized trial comparing curative treatment with RT plus cisplatin versus RT plus cetuximab in pts with LA SCC HNC
- Primary end point : OS
- Secondary end point: Locoregional control
 - Patterns of failure
 - Acute and late adverse effects
 - Quality of life

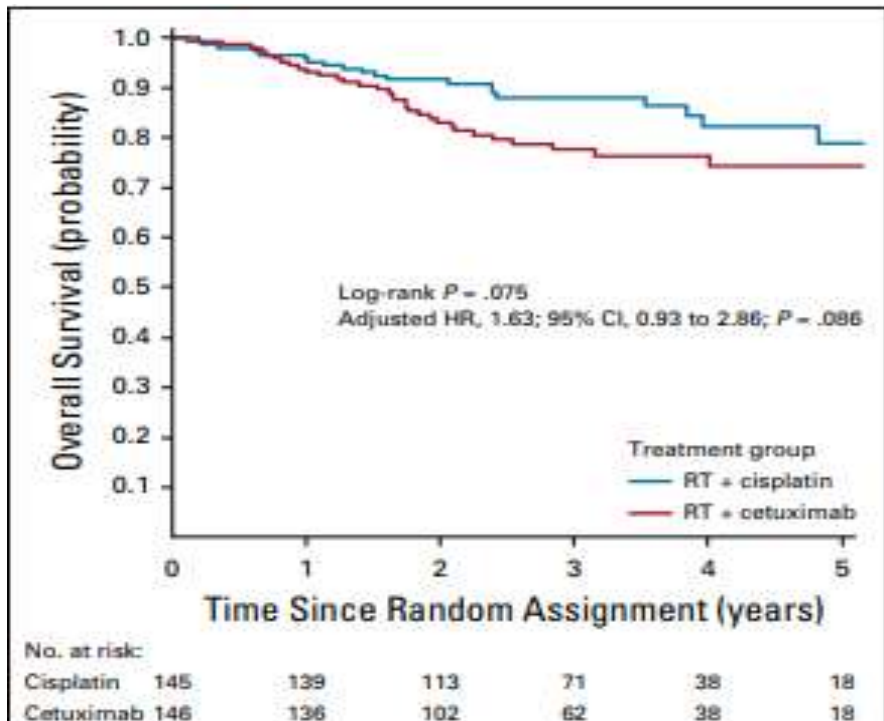
Eligibility

INCLUSION :

- Previously untreated SCC of oropharynx, hypopharynx or larynx
- Stage III-IV (7th edition)
- No distant metastases
- **Oral cavity cancers** (unresectable or not amenable for surgery)

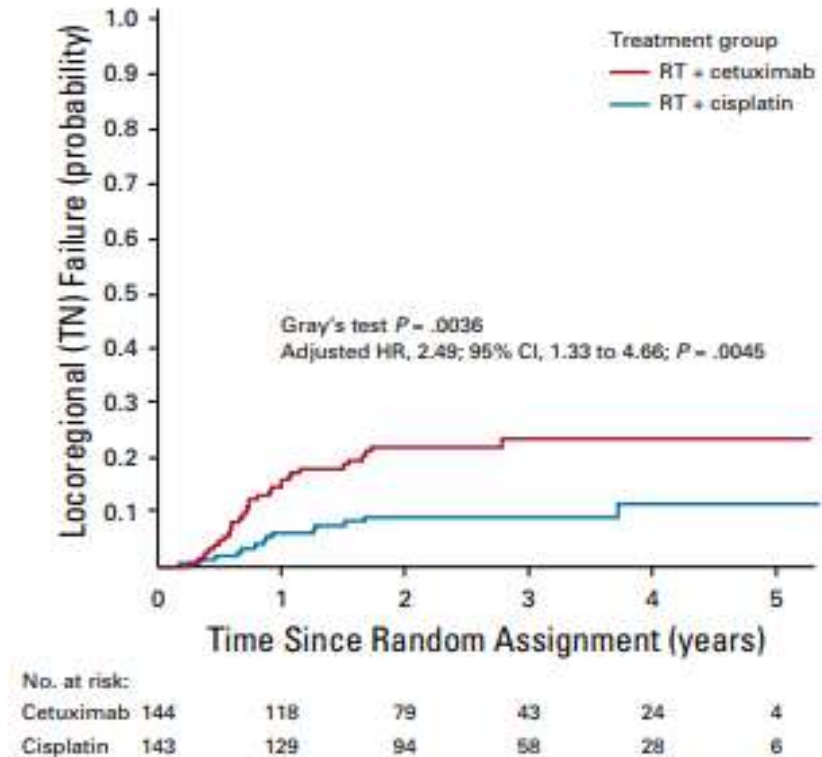
- Cisplatin @ 40mg/m², maximum dose 70mg, weekly during 7 weeks.
- Cetuximab iv loading dose of 400mg/m² 1 week before start of RT followed by seven weekly doses of 250mg/m².
- RT Doses - Standard
- Patients with T3-T4 tumors underwent second random assignment between standard radiation dose of 68Gy to primary tumor or dose escalation to 73.1Gy.

OVERALL SURVIVAL (OS)



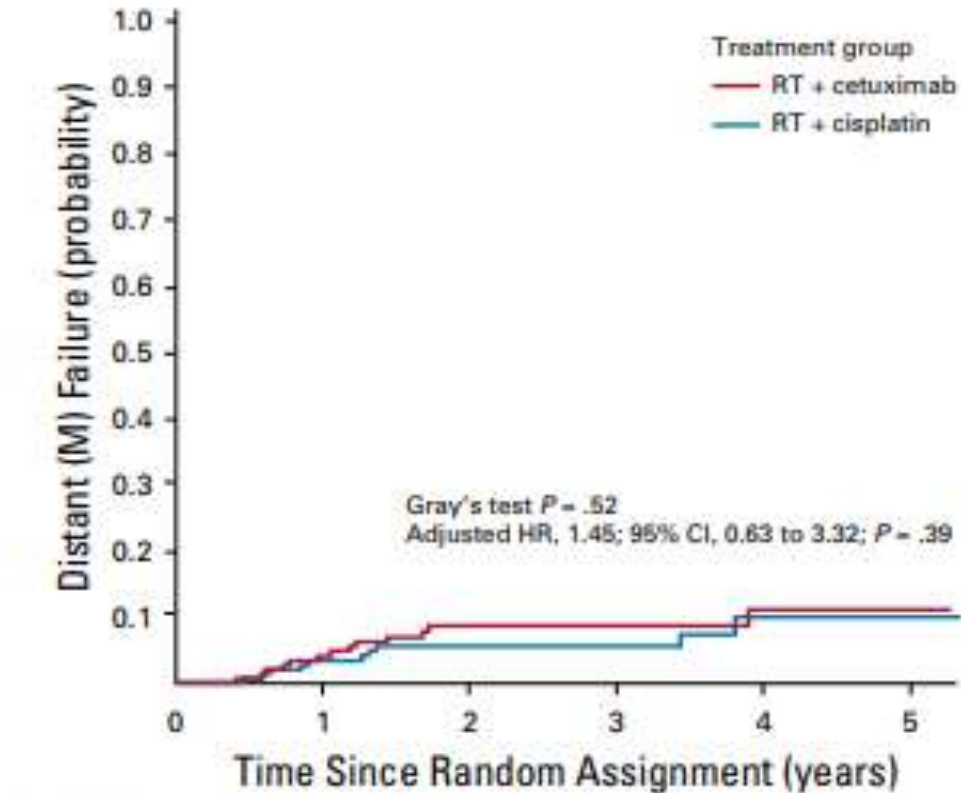
- 3 years, OS was 88%(95% CI, 83%-94%) in cisplatin group and 78% (95% CI, 71%-85%) in cetuximab group
- HR 1.63
- $P = 0.086$

LOCOREGIONAL FAILURE



- 3 years, locoregional failure was more than twice in cetuximab group, 23% (95% CI, 16%-31%) compared to 9% (95%CI, 4%-14%) in cisplatin group.
- $P = 0.0036$

DISTANT METASTASES



No. at risk:

Cetuximab	144	118	79	43	24	4
Cisplatin	143	129	94	58	28	6

The cumulative incidence of distant metastases did not differ between treatment groups.

CONCLUSION

- This randomised phase III study comparing concurrent cisplatin with concurrent cetuximab in patients with locoregionally advanced HNSCC showed a significantly better locoregional control with concurrent cisplatin, which should remain the standard treatment for patients with p16 positive or p16 negative HNSCC.

Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522

K. Kian Ang,† Qiang Zhang, David I. Rosenthal, Phuc Felix Nguyen-Tan, Eric J. Sherman, Randal S. Weber, James M. Galvin, James A. Bonner, Jonathan Harris, Adel K. El-Naggar, Maura L. Gillison, Richard C. Jordan, Andre A. Kanski, Wade L. Thorstad, Andy Trotti, Jonathan J. Beitler, Adam S. Garden, William J. Spanos,† Sue S. Yom, and Rita S. Axelrod

RTOG 0522

Hypothesis- Most HNC have high expressions of EGFR; High EGFR expression is a/w with poor response to RT or CRT. EGFR inhibitors sensitized tumours to RT or CRT

Eligibility- Stage III /IV SCC HNC- Oropharynx, Larynx and Hypopharynx

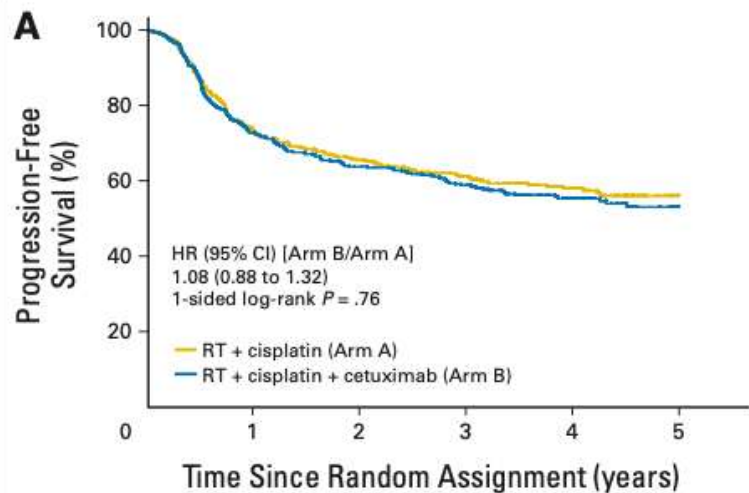
Control Arm- RT + Cisplatin

Experimental arm - RT + Cisplatin + Cetuximab

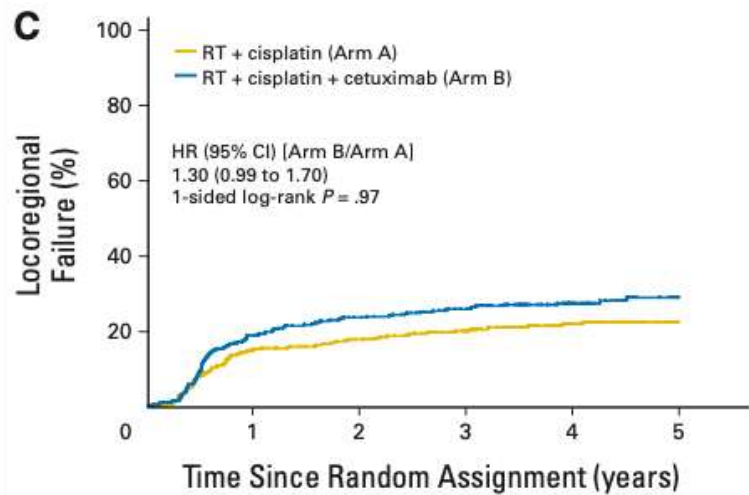
Primary end point- PFS, LRCR, DM

Secondary end points- OS, Adverse effects, compliance, P16 and EGFR expression

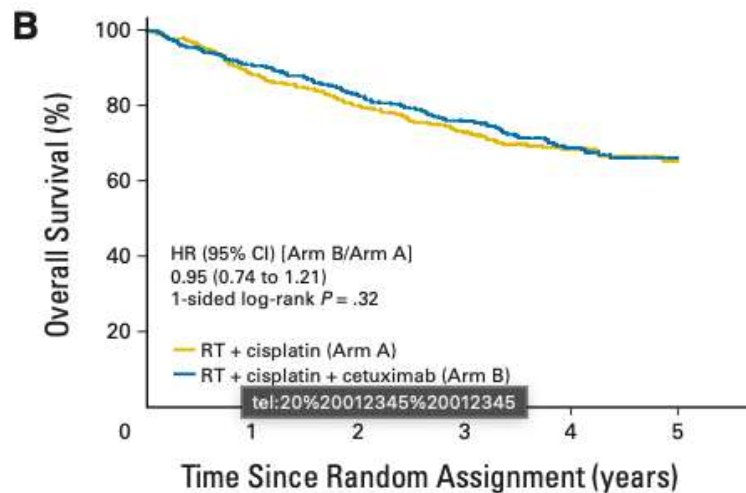
N=891	RT + Cis	RT+ Cis+ Cetuximab
T/t interruptions	15.1%	26.9%
Grade III- IV mucositis	33.3%	43.2%
Rash, fatigue, anorexia, hypokalemia		More
30 day mortality	Similar	
Cisplatin delivery	Similar	
Late toxicity	Similar	



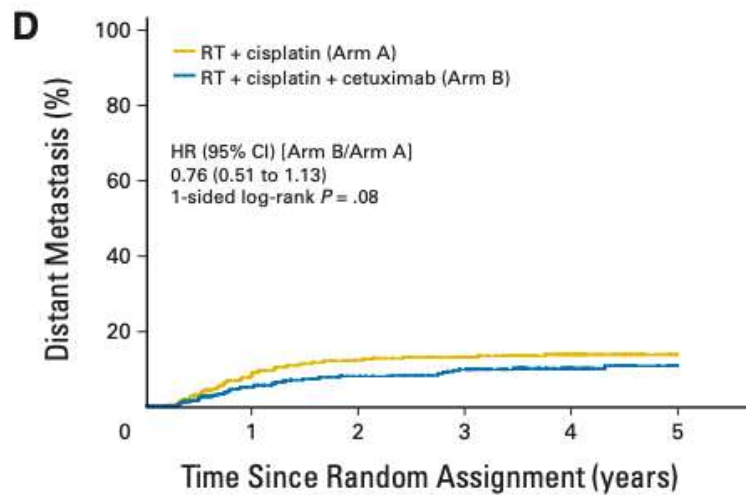
No. at risk						
Arm A	447	317	282	241	118	36
Arm B	444	309	263	234	108	38



No. at risk						
Arm A	447	317	282	241	118	36
Arm B	444	309	263	234	108	38



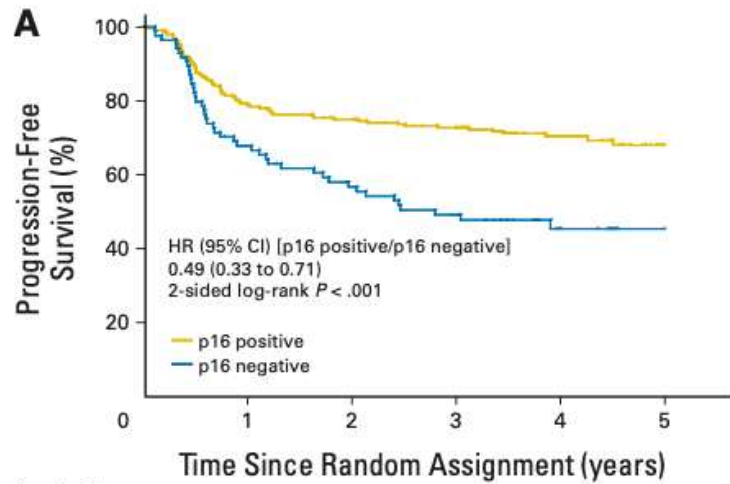
No. at risk						
Arm A	447	386	344	287	138	41
Arm B	444	383	339	295	134	43



No. at risk						
Arm A	447	317	282	241	118	36
Arm B	444	309	263	234	108	38

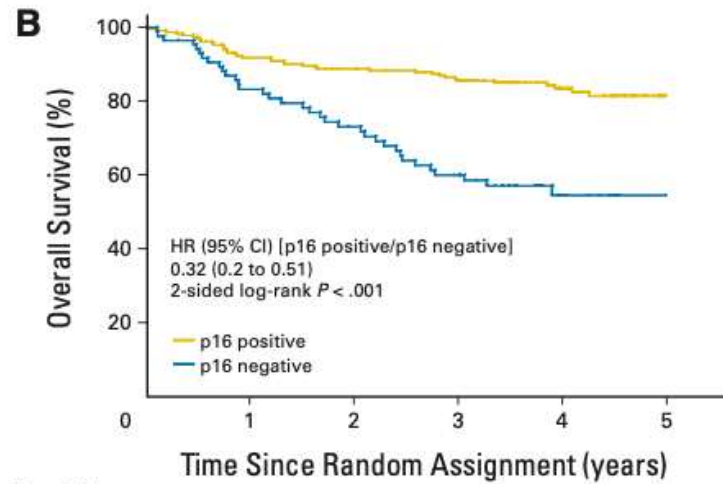
	RT + Cis	RT + Cis + Cetuximab	p
3 YPFS	61.2%	58.9%	0.76
3 YOS	72.9%	75.8%	0.32
3 YLRF	19.9%	25.9%	0.97
3 YDM	13%	9.7%	0.08

No advantage of Cetuximab in any of the oncological end points



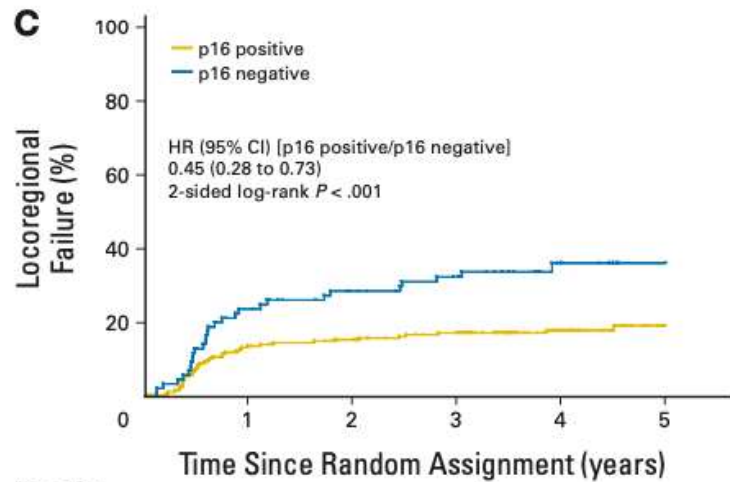
No. at risk

	0	1	2	3	4	5
p16 positive	235	183	171	156	84	31
p16 negative	86	56	45	38	17	8



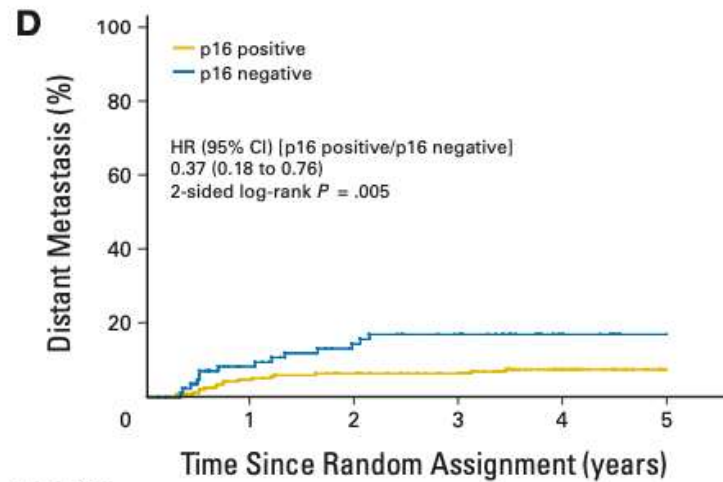
No. at risk

	0	1	2	3	4	5
p16 positive	235	212	202	183	99	34
p16 negative	86	68	56	45	19	8



No. at risk

	0	1	2	3	4	5
p16 positive	235	183	171	156	84	31
p16 negative	86	56	45	38	17	8



No. at risk

	0	1	2	3	4	5
p16 positive	235	183	171	156	84	31
p16 negative	86	56	45	38	17	8

	P16+ OPC	P16 - OPC	p
3 YPFS	72.8%	49.2%	<0.001
3 YOS	85.6%	60.1%	<0.001

Patients with P16 positive tumours had better outcomes

Tumour EGFR expression did not affect outcomes

Conclusion

Adding cetuximab to radiation-cisplatin did not improve outcome and hence should not be prescribed routinely. PFS and OS were higher in patients with p16-positive OPC, but outcomes did not differ by EGFR expression.

J Clin Oncol 32. © 2014 by American Society of Clinical Oncology

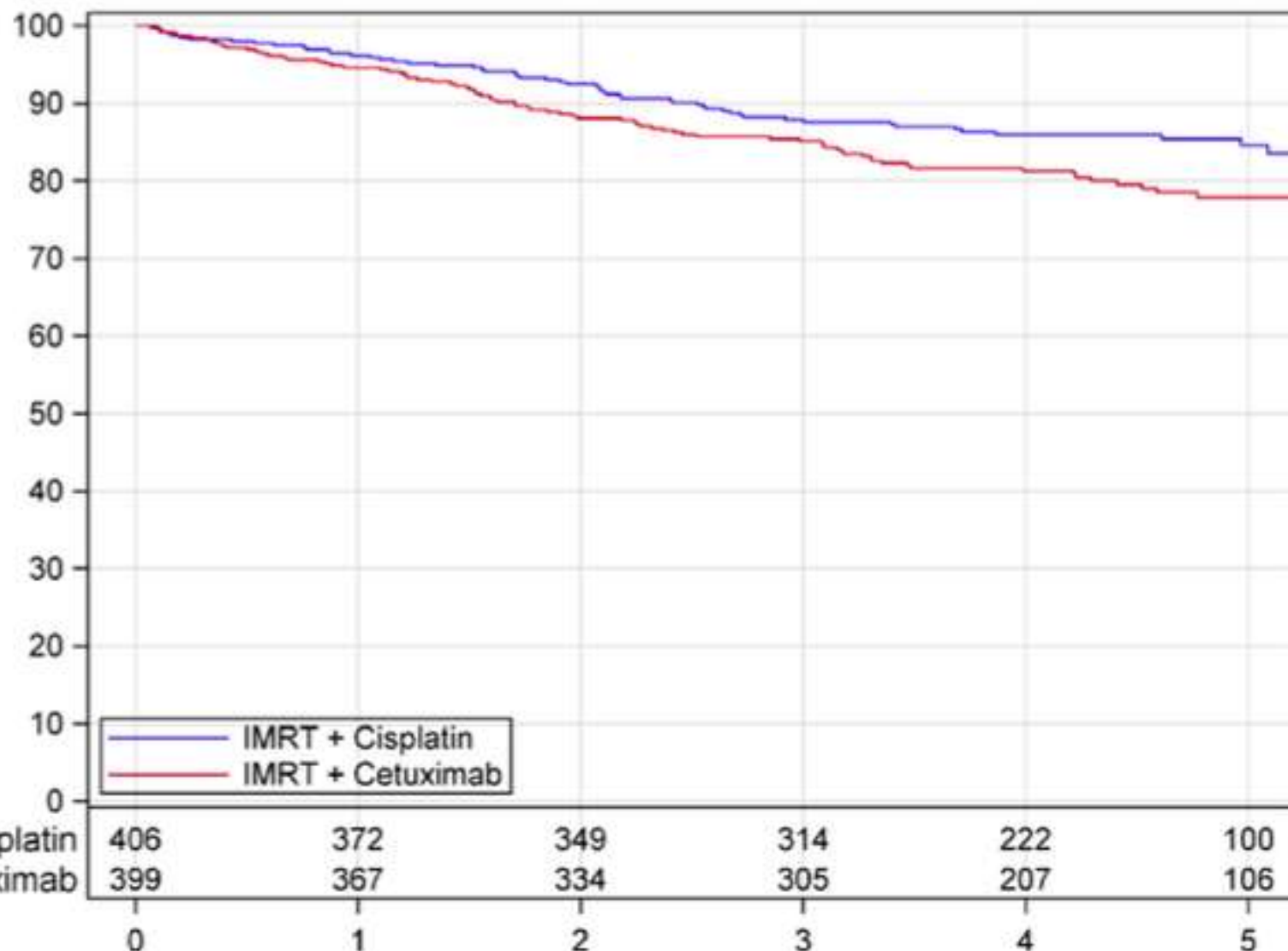
Radiotherapy plus cetuximab or cisplatin for human papillomavirus (HPV)-positive oropharyngeal cancer: a randomized, multicenter, non-inferiority clinical trial

Maura L Gillison*,

Department of Thoracic Head and Neck Medical Oncology, MD Anderson Cancer Center,
Houston, TX, USA

- Survival rates of HPV positive tumours are higher than HPV negative tumours
- High survival rates with young age at diagnosis – raised concerns about late treatment related toxicity for HPV positive OPC
- Randomized, **Non inferiority** multi centre randomized trial
- **P16 positive Locally advanced oropharyngeal SCC –849 pts randomized**
- **RT+ Cisplatin Vs RT + Cetuximab**

Overall Survival (%)



IMRT + Cisplatin
IMRT + Cetuximab

— IMRT + Cisplatin
— IMRT + Cetuximab

Years after Randomization

	No. of Patients	Dead	Censored
IMRT + Cisplatin	406	55	351
IMRT + Cetuximab	399	78	321

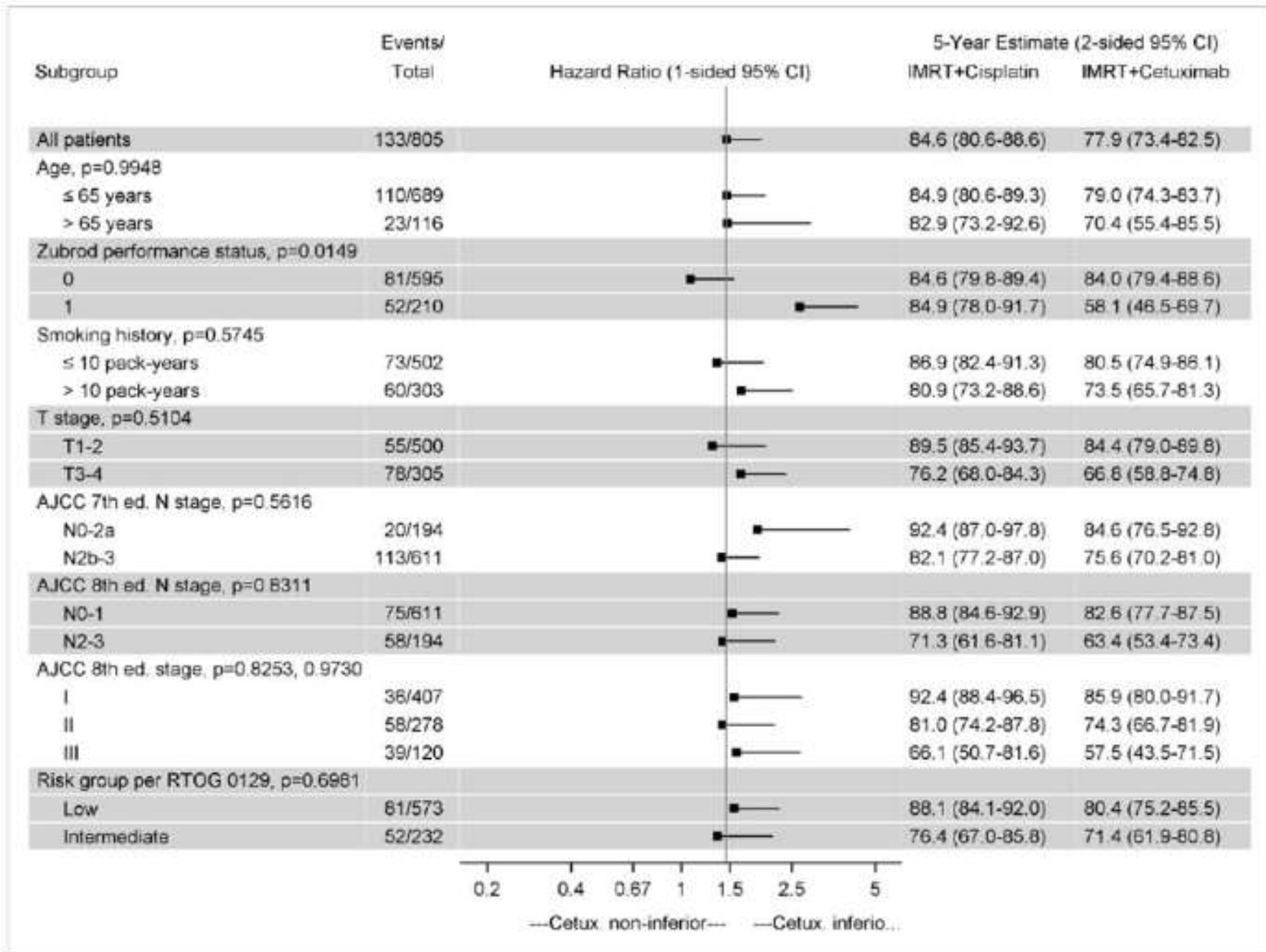
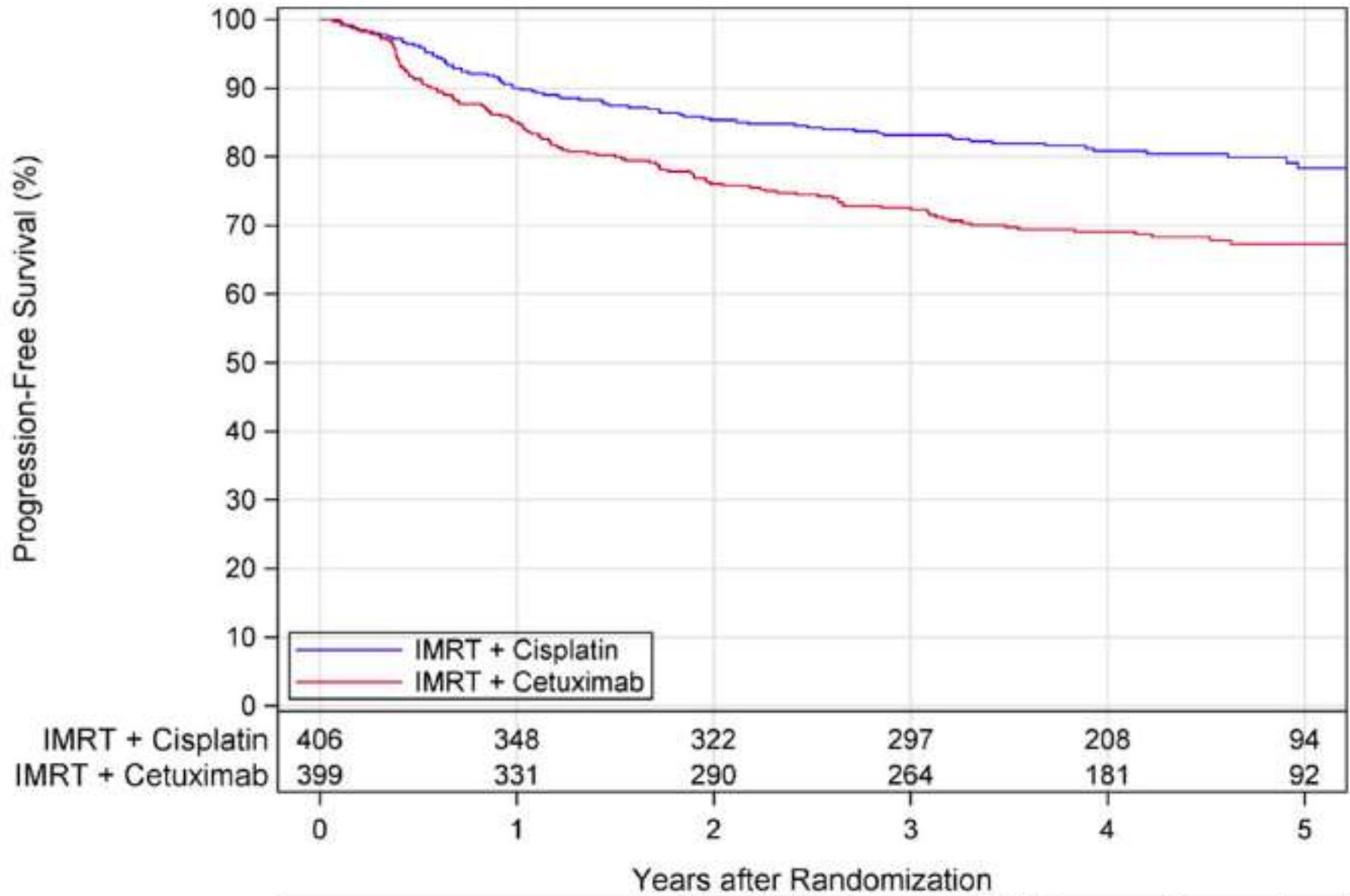


Figure 1B. Overall Survival Treatment Effect in Subgroups.



	No. of Patients	Failed	Censored
IMRT + Cisplatin	406	76	330
IMRT + Cetuximab	399	122	277

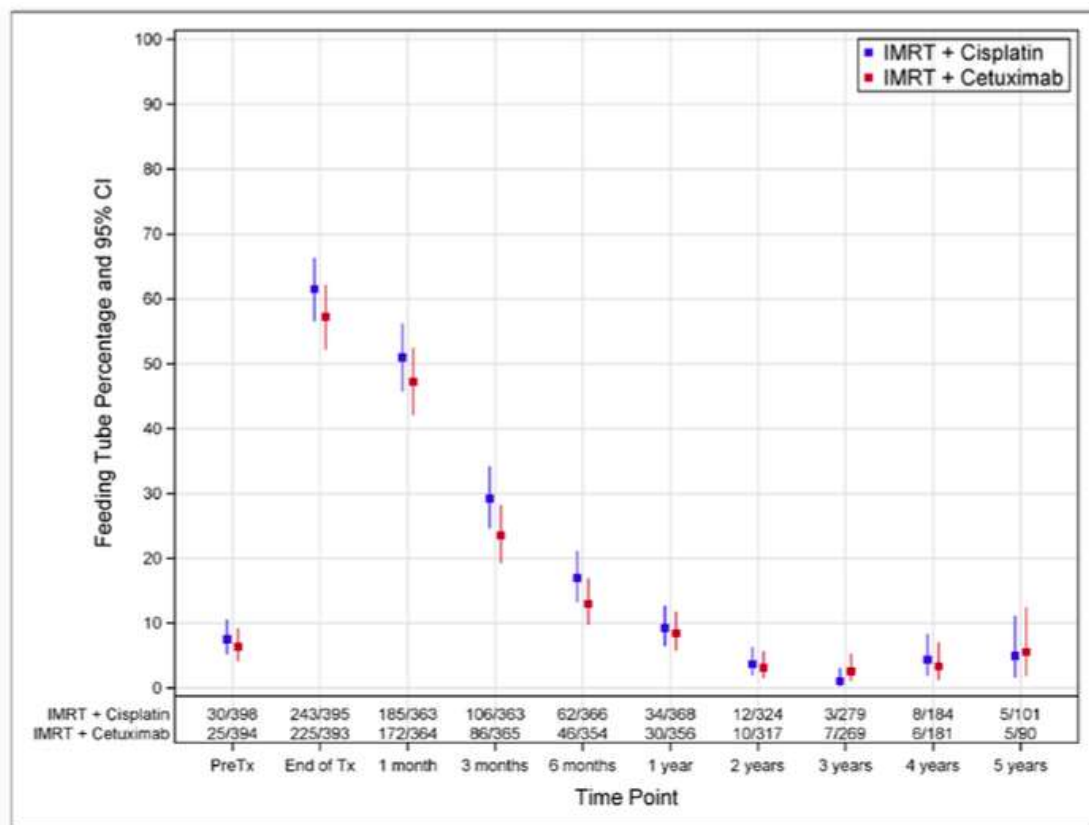


Figure 3B. Feeding Tube Rates Over Time According to Assigned Treatment.

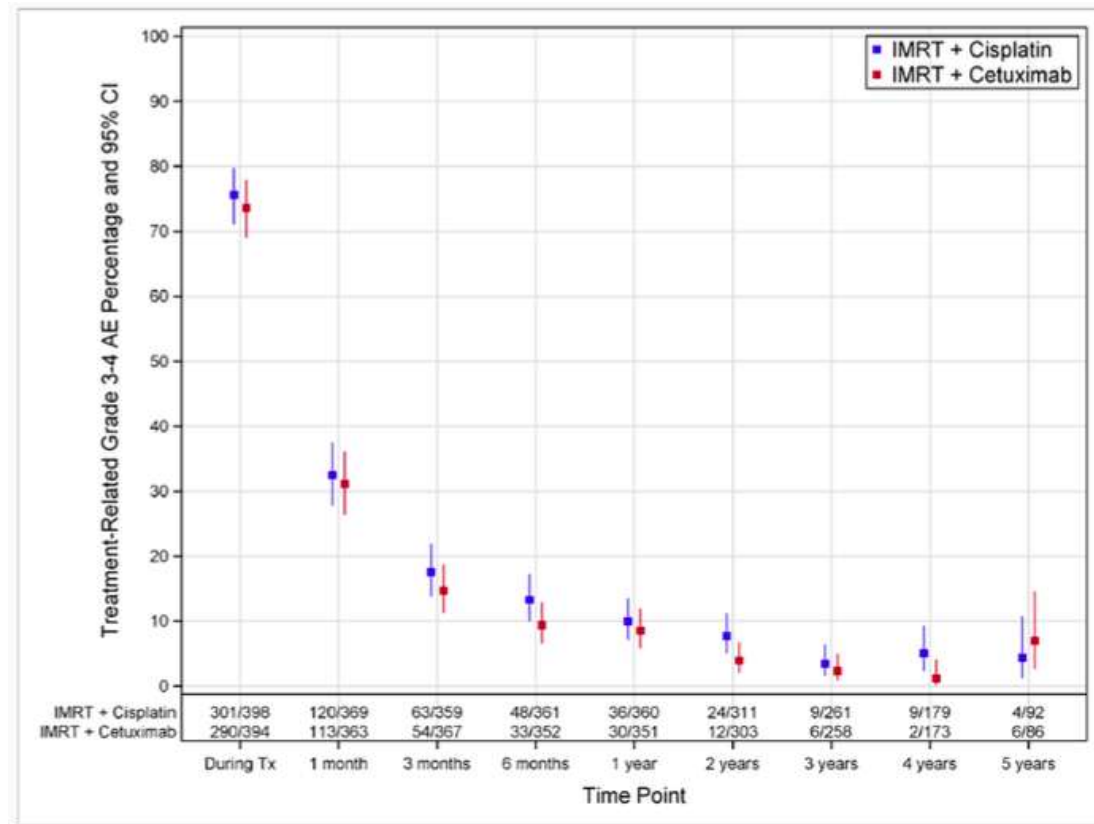


Figure 3A. Treatment-Related Grade 3-4 Adverse Event Rates Over Time According to Assigned Treatment.

Interpretation—For patients with HPV-positive OPC, radiotherapy plus cetuximab demonstrated inferior OS and PFS compared to radiotherapy plus cisplatin; toxicity rates were similar ([NCT01302834](#)).

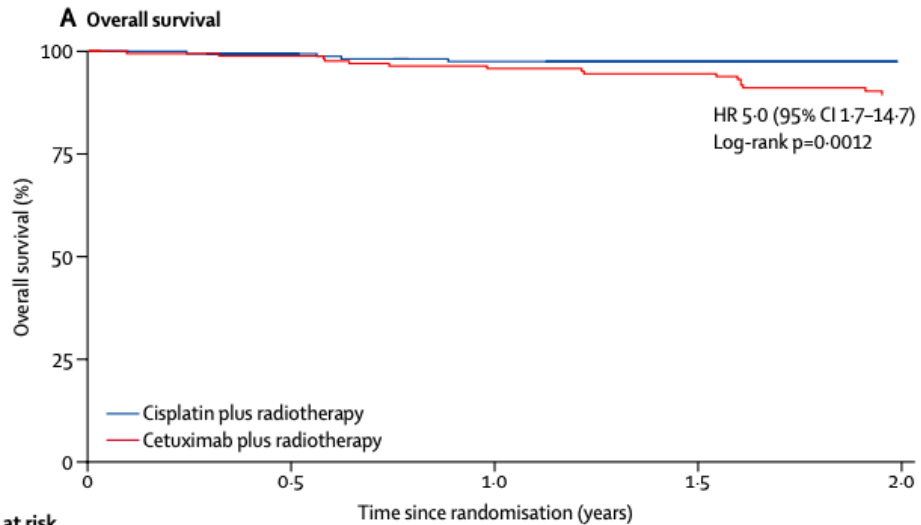
Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial



*Hisham Mehanna, Max Robinson, Andrew Hartley, Anthony Kong, Bernadette Foran, Tessa Fulton-Lieuw, Matthew Dalby, Pankaj Mistry, Mehmet Sen, Lorcan O'Toole, Hoda Al Booz, Karen Dyker, Rafael Moleron, Stephen Whitaker, Sinead Brennan, Audrey Cook, Matthew Griffin, Eleanor Aynsley, Martin Rolles, Emma De Winton, Andrew Chan, Devraj Srinivasan, Ioanna Nixon, Joanne Grumett, C René Leemans, Jan Buter, Julia Henderson, Kevin Harrington, Christopher McConkey, Alastair Gray, Janet Dunn, on behalf of the De-ESCALaTE HPV Trial Group**

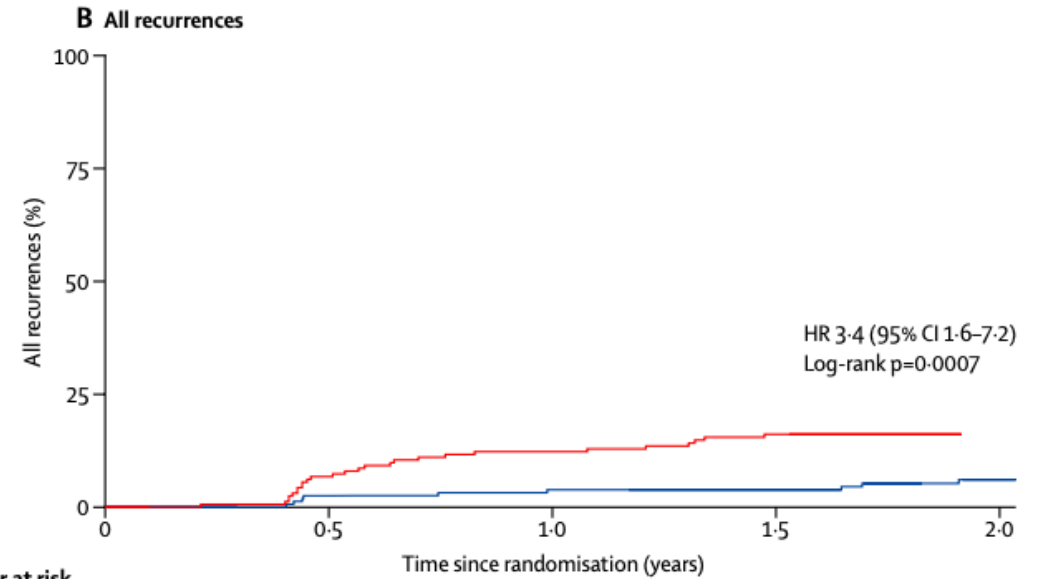


Randomized Ph III trial- 32 centres across Ireland, Netherland, UK
HPV positive low risk oropharyngeal ca (Non Smokers or <10 pack years somkers)
RT+ Cis Vs RT + Cetuximab
334 pts
No significant difference b/w acute or late (24 months) severe (Grade 3-5) toxicity b/w 2 arms
2 YOS 97.5% Vs 89.4% with Cisplatin vs Cetuximab (p= 0.001)
2 YLRR 6% Vs 16 % with Cisplatin vs Cetuximab (p= 0.007)



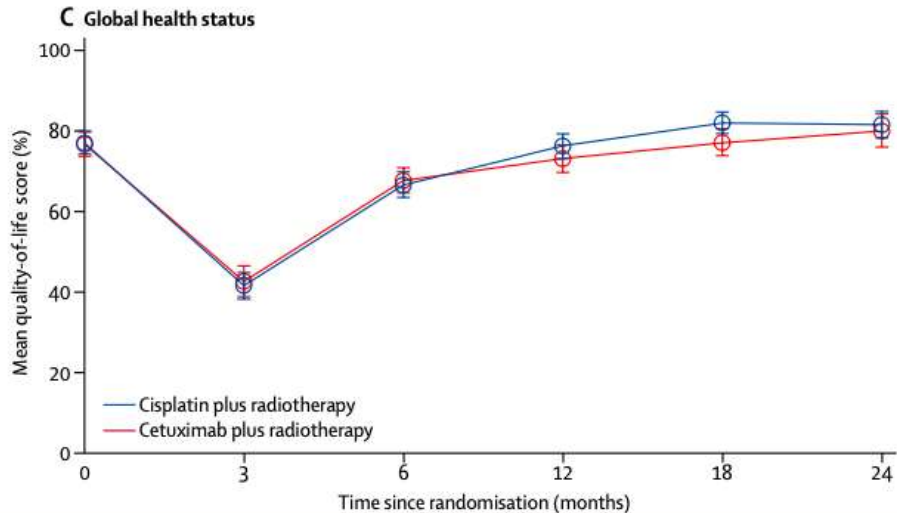
Number at risk

	0	0.5	1.0	1.5	2.0
Cisplatin plus radiotherapy	166	160	154	147	118
Cetuximab plus radiotherapy	168	163	156	144	109



Number at risk

	0	0.5	1.0	1.5	2.0
Cisplatin plus radiotherapy	166	156	148	141	109
Cetuximab plus radiotherapy	168	152	141	128	101



Cetuximab shows no benefit in reducing toxicity

Rather tumour control decreases

Clinical Investigation

Randomized Trial of Radiation Therapy With Weekly Cisplatin or Cetuximab in Low-Risk HPV-Associated Oropharyngeal Cancer (TROG 12.01) — A Trans-Tasman Radiation Oncology Group Study

Danny Rischin, MD,^{*,†} Madeleine King, PhD,[‡] Lizbeth Kenny, MBBS,^{§,||}
Sandro Porceddu, MD,^{||,#} Christopher Wratten, MBBS,^{*,*}
Andrew Macann, MBChB,^{††} James E. Jackson, MBBS,^{††}
Mathias Bressel, MSc,^{§§} Alan Herschtal, PhD,^{§§} Richard Fisher, PhD,^{§§}
Tsien Fua, MBBS,^{||,||} Charles Lin, MBBS,[§] Chen Liu, MBBS,^{||,||}
Brett G.M. Hughes, MBBS,^{||,##} Margaret McGrath, MBBS,^{***}
Lachlan McDowell, MBBS,^{†,||,||} and June Corry, MD^{†††,†††}

^{*}Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [†]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia; [‡]University of Sydney, School of Psychology, Sydney Quality of Life Office, Sydney, Australia; [§]Department of Radiation Oncology, Royal Brisbane & Women's Hospital, Brisbane, Australia; ^{||}Faculty of Medicine, University of Queensland, Brisbane, Australia; [#]Department of Radiation Oncology, Princess Alexandra Hospital, Brisbane, Australia; ^{**}Department of Radiation Oncology, Calvary Mater Hospital and University of Newcastle, Newcastle, Australia; ^{††}Department of Radiation Oncology, Auckland City Hospital and University of Auckland, Auckland, New Zealand; ^{†††}Icon Cancer Centres, Gold Coast, Australia; ^{§§}Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, Australia; ^{||,||}Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne,

Methods and Materials

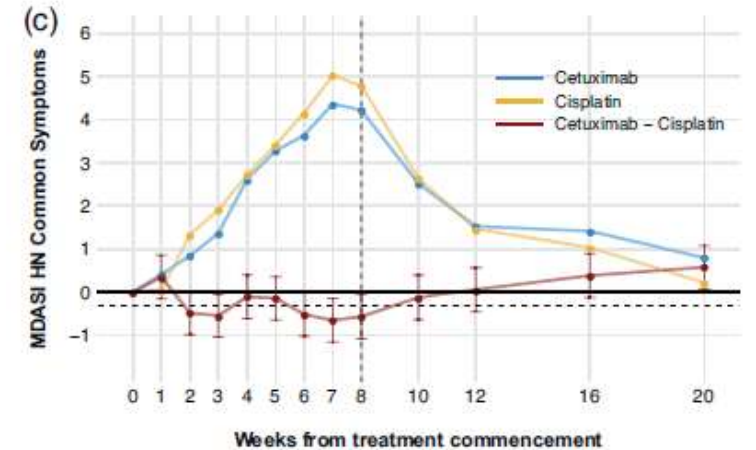
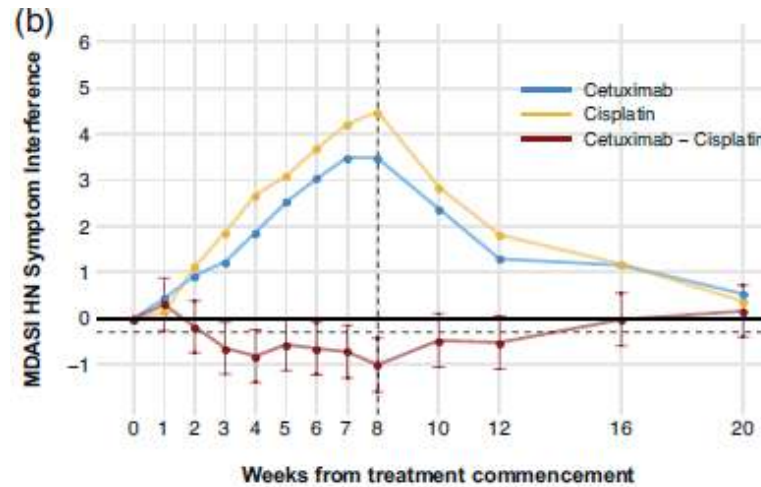
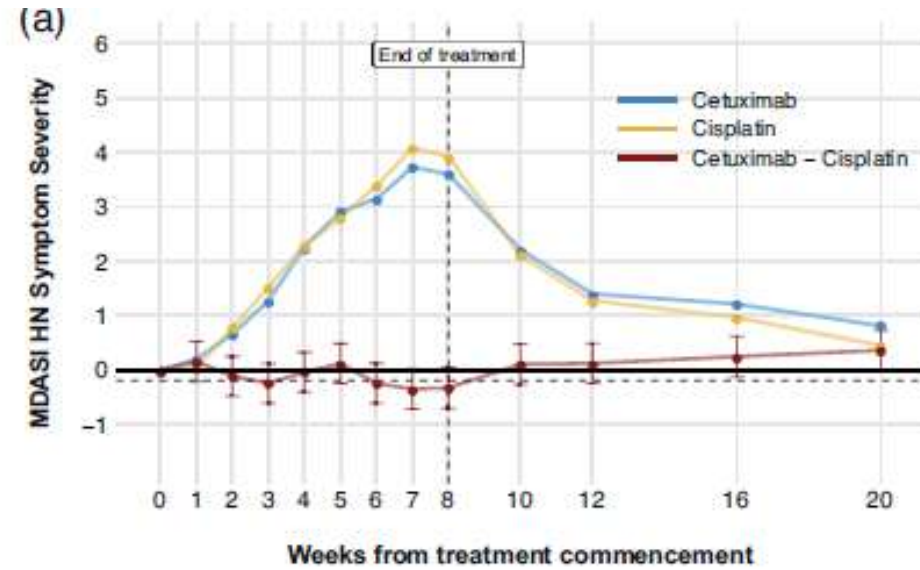
- Randomized phase 3 trial with a patient-reported outcome (PROM) primary endpoint, conducted under the TROG in 15 hospitals in Australia and New Zealand
- Tumors p16-positive defined by grade 2 (moderate) or 3 (strong) nuclear and cytoplasmic staining in $\geq 70\%$ of the tumor cells

Eligibility criteria

- AJCC 7th edition stage III (excluding T1-2N1) or stage IV (excluding T4 and/or N3 and/or N2b-c if h/o smoking > 10 pack yrs/ or distant metastases)

Outcome

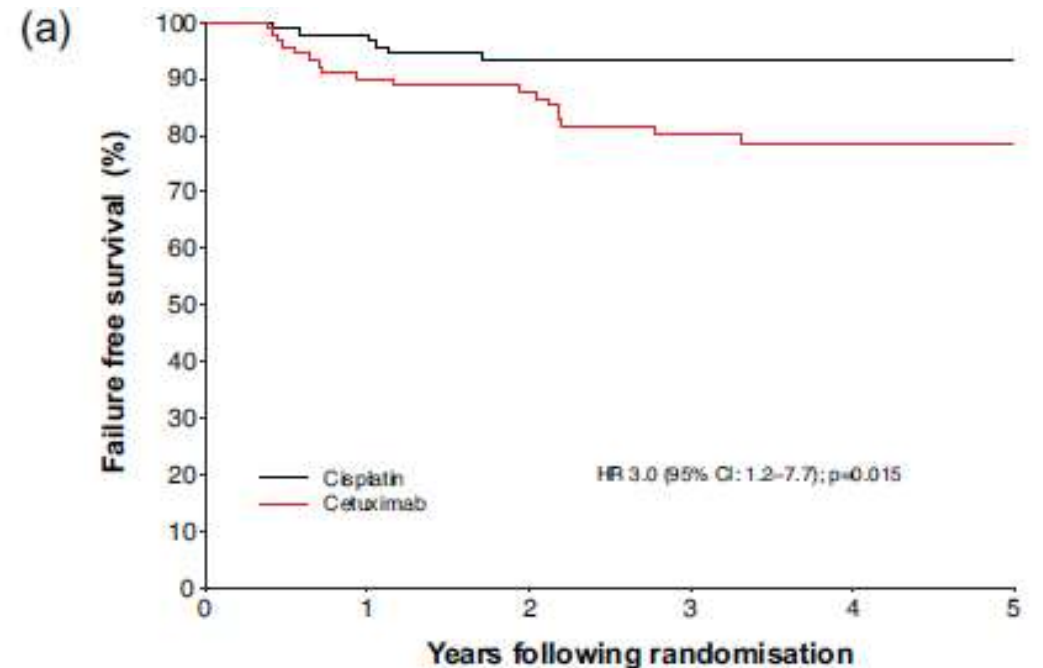
- No significant difference in primary endpoint of symptom severity between 2 arms
- Also no significant difference in secondary endpoints
 - Modified symptom severity
 - Mucositis symptoms



Results (FFS)

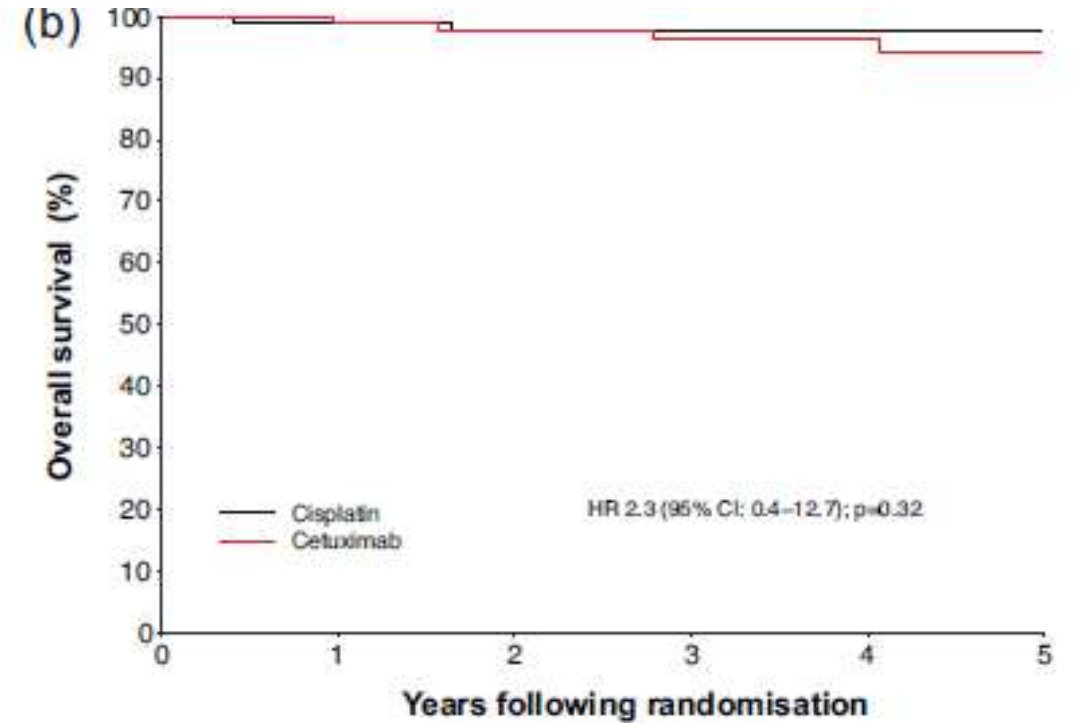
- FFS was superior in the cisplatin arm
- 3 year FFS rates were 93% in cisplatin arm
- 80% in cetuximab arm

HR, 3.0; 95%, P = .015



Results

- There was no significant difference in OS;
 - 3-year OS was 98% (95% CI, 92%-99%) in the cisplatin arm
 - 96% (95% CI, 89%-99%) in the cetuximab arm
 - HR, 2.3; 95% CI, 0.4-12.7; P = .32)



Results – Adverse Events

- Grade 3/4 AEs, there was more radiation dermatitis and acneiform rash in the cetuximab arm
- More febrile neutropenia, emesis, dry mouth, and fatigue in the cisplatin arm
- There were no statistically significant differences in late toxicity between the two arms

Conclusion

- The key findings from this trial were that cetuximab and radiation, compared with weekly cisplatin and radiation, had inferior efficacy with similar overall symptom burden and toxicity.
- TROG 12.01 trial reinforced that 70Gy RT and Cisplatin remains the standard of care for low risk HPVOPSCC

SUMMARY CETUXIMAB TRIALS

1. Bonner Trial- RT Vs RT + Cetuximab- Survival advantage

RT is not SoC; SoC is CRT for LA SCC HNC

2. RTOG 0522- Cis + RT Vs Cis + RT+ Cetuximab- No advantage of adding Cetuximab





3 ARTSCAN III- LA SCCHNC- RT + Cis Vs RT + Cetuximab- favours Cisplatin

4. RTOG 1016- P16 + OPC- RT + Cis Vs RT+ Cetuximab- No advantage of Cetuximab over Cisplatin

5 De ESCALATE- Low risk HPV positive OPC- RT + Cis Vs RT+ Cetuximab- No advantage of Cetuximab over Cisplatin

6 TROG 12.01-Low risk HPV positive OPC- RT + Cis Vs RT+ Cetuximab- No advantage of Cetuximab over Cisplatin

A Randomized Phase 3 Trial Comparing Nimotuzumab Plus Cisplatin Chemoradiotherapy Versus Cisplatin Chemoradiotherapy Alone in Locally Advanced Head and Neck Cancer

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Nimotuzumab (h-R3) is a humanized immunoglobulin G1 isotype monoclonal antibody directed against the extracellular domain of EGFR.

Materials and methods

Phase 3 randomized study comparing outcomes

- between patients who received nimotuzumab plus CTRT Vs CTRT

Inclusion criteria

- Nonmetastatic, stage III or IV LAHNSCC arising in the oropharynx, larynx, hypopharynx, or oral cavity were eligible.

Exclusion Criteria

- Patients with tumors originating in the nasopharynx, salivary gland, or nasal cavity and those who had received immunotherapy or prior RT to the head and neck region were excluded.

Study Procedures – Chemotherapy

- In both arms, cisplatin was dosed at 30 mg/m² weekly
- Nimotuzumab was administered weekly in the NCRT arm intravenously as a 200-mg flat dose in 250 mL normal saline over 60 minutes without premedication
- Between 2012 and 2018, 536 patients were randomized equally between both arms
- Median duration of follow-up was 39.13 months

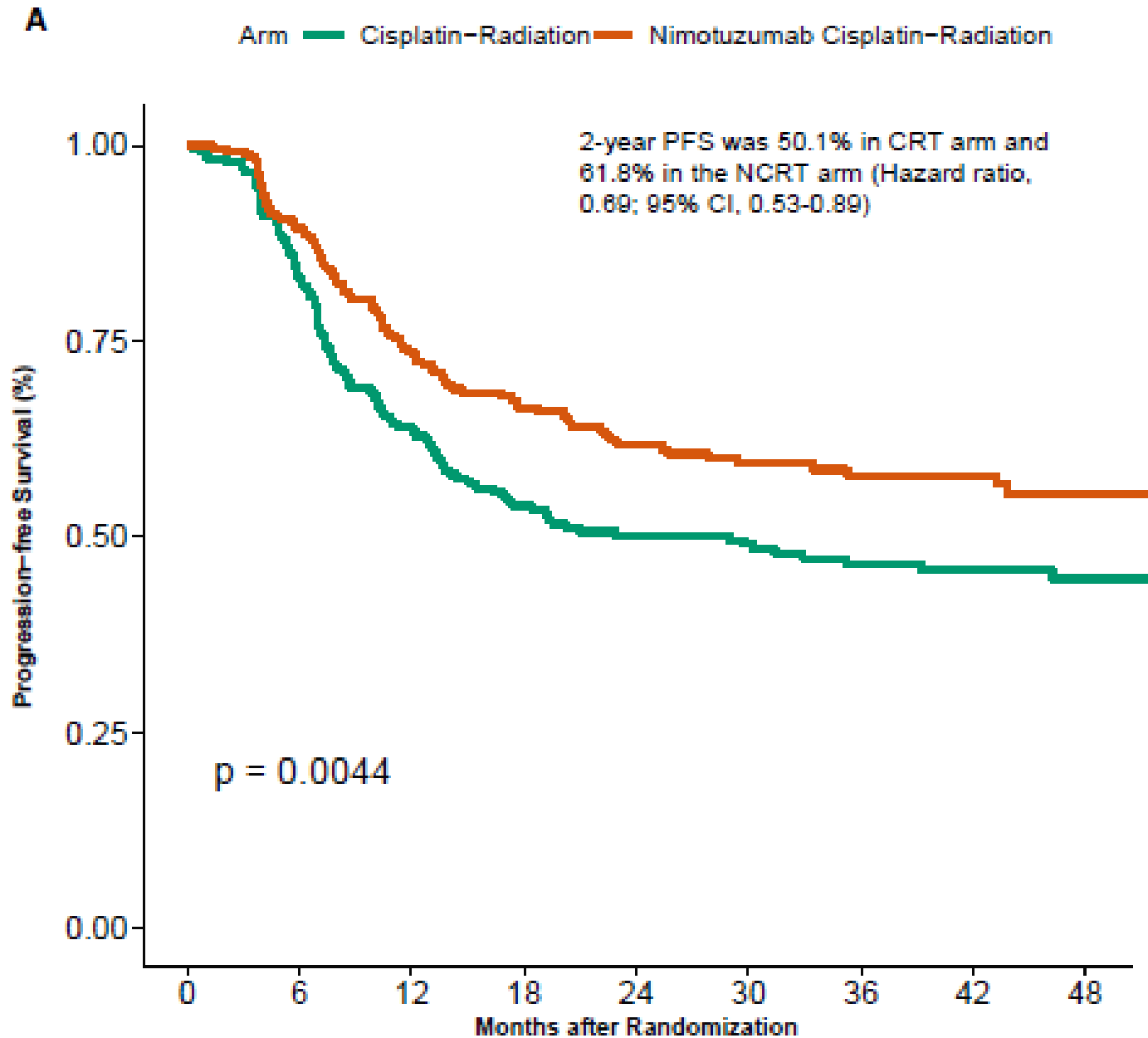
Treatment Details

- A cumulative cisplatin dose ≥ 200 mg/m² was administered to 78.7% patients in the CRT arm and to 77.6% pts in NCRT arm (P = .754)

Variable	No. of Patients (%)		P
	CRT Arm, n = 268	NCRT Arm, n = 268	
Radiotherapy details			
Radiotherapy dose: Median [IQR], Gy	70 [70-70]	70 [70-70]	.713 ^a
100% of planned radiotherapy dose completed	252 (94.0)	250 (93.3)	.723
Dose <100%	16 (6.0)	18 (6.7)	
Reasons for dose <100%			
Never started radiation	1 (0.4)	1 (0.4)	—
Default	9 (3.3)	7 (2.6)	
Toxicity	2 (0.7)	6 (2.2)	
Progression	2 (0.7)	2 (0.7)	
Others	2 (0.7)	1 (0.4)	
Neurosis/mania	—	1 (0.4)	
Technique			
Conventional	229 (85.4)	238 (88.8)	.240 ^b
Intensity modulated	38 (14.2)	29 (10.8)	
Radiotherapy	—	—	
Not received	1 (0.4)	1 (0.4)	
Chemotherapy details			
Cisplatin			
No. of cycles: Median [IQR]	7 [7-7]	7 [7-7]	.389 ^a
No. of cycles completed			.421 ^d
≥7	219 (81.7)	226 (84.3)	
6	20 (7.5)	23 (8.6)	
5	12 (4.5)	4 (1.5)	
<5	17 (6.3)	15 (5.6)	
Nimotuzumab			
No. of cycles: Median [IQR]	Not applicable	7 [7-7]	—
No. of cycles completed	Not applicable		—
≥7		226 (84.3)	
6		23 (8.6)	
5		4 (1.5)	
<5		15 (5.6)	
Patients who had dose reductions	Not applicable	—	—

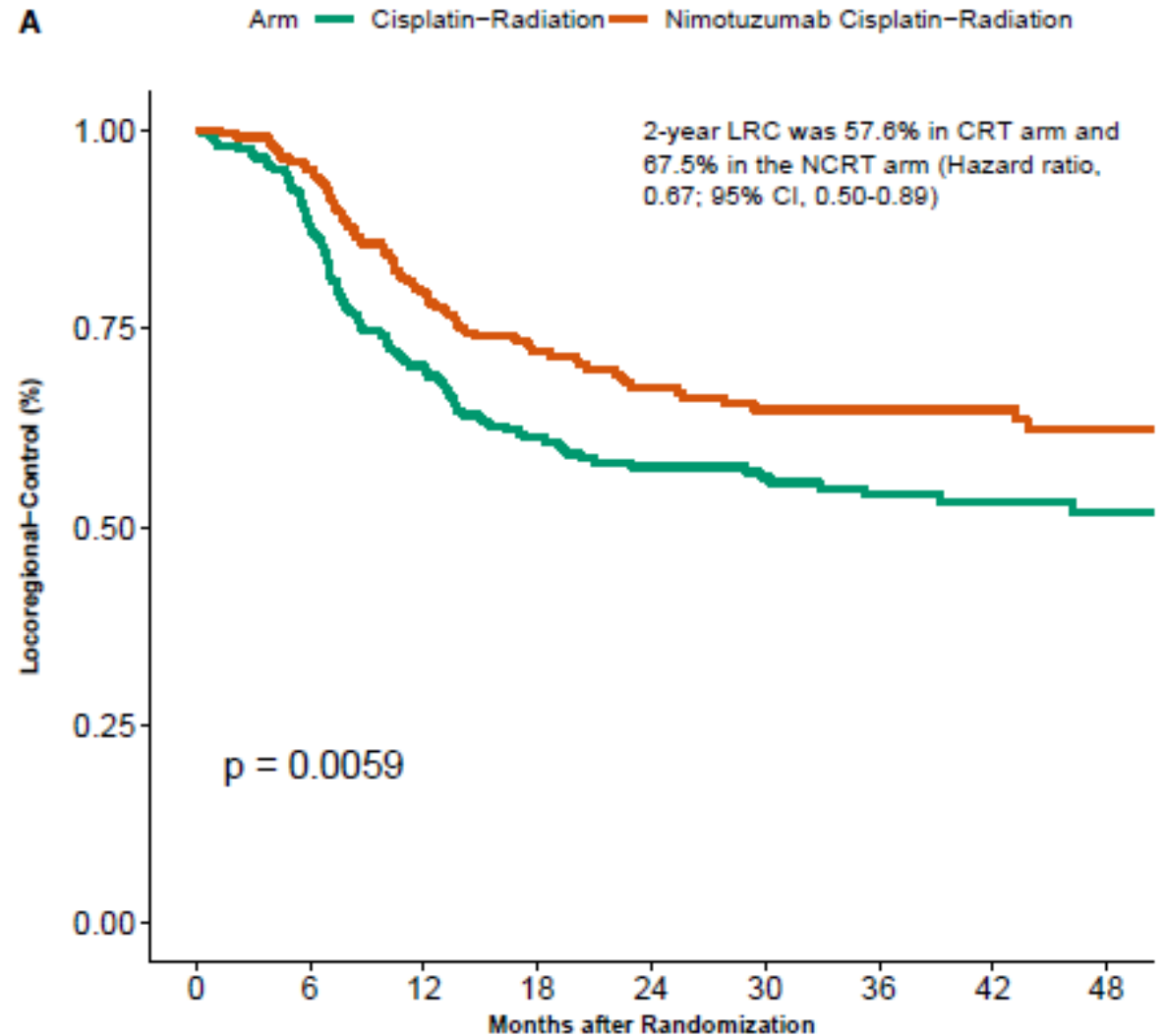
Progression free survival

- The 2-year PFS was 50.1% (95% CI, 43.7-56.2) in the CRT arm and 61.8% (95% CI, 55.2- 67.7) in the NCRT arm.
- The addition of nimotuzumab led to a consistent benefit across all subgroups



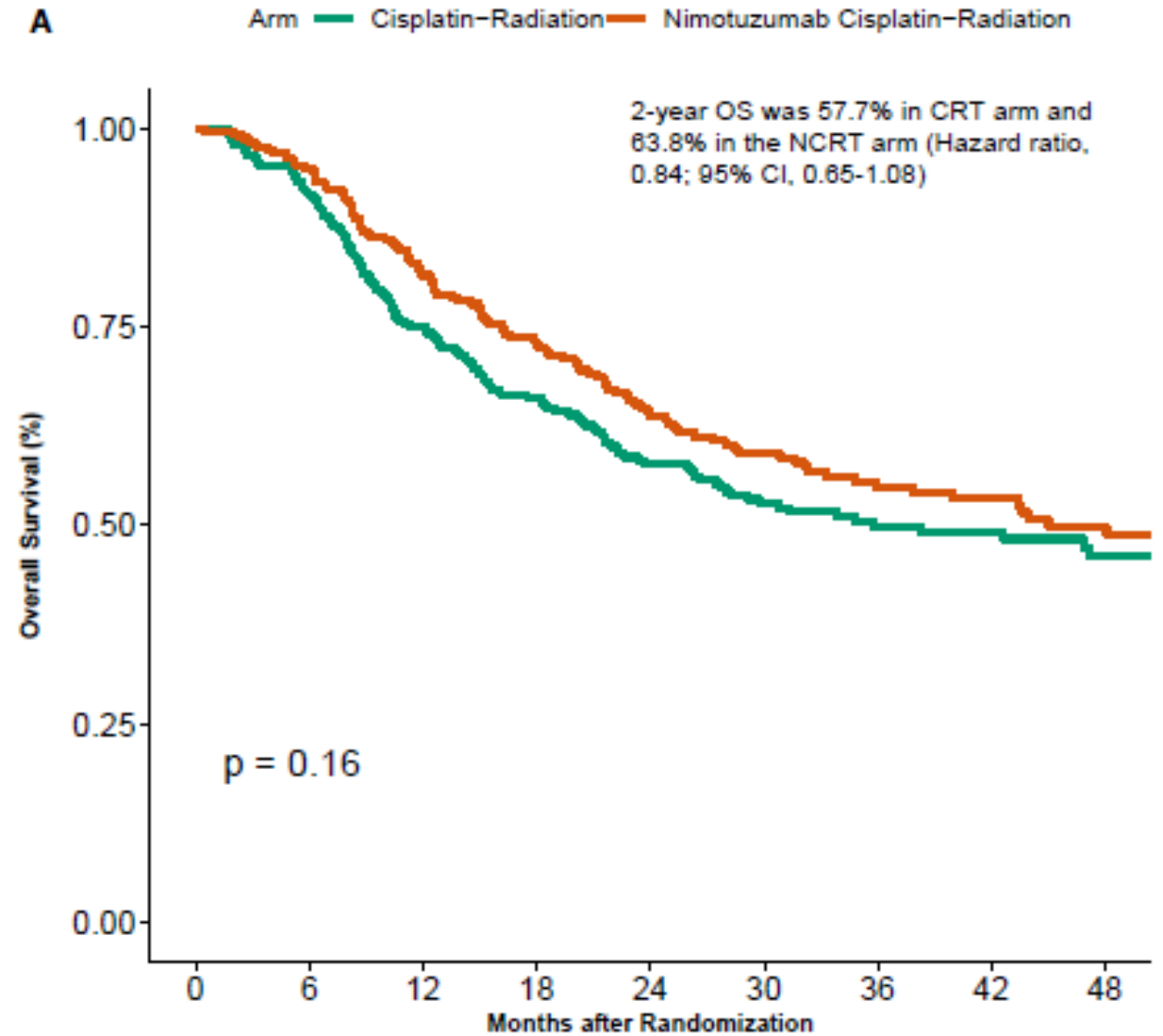
Disease free survival

- The addition of nimotuzumab decreased the hazard of disease recurrence by 29% (hazard ratio, 0.71; 95% CI, 0.55-0.92; P = .008).
- The 2-year DFS was higher in the NCRT arm (60.2%; 95% CI 53.6%-66.3%) compared with the CRT arm (48.5%; 95% CI, 42.1%-54.7%)



Overall Survival

- There were 128 deaths in the CRT arm and 113 in the NCRT arm (hazard ratio, 0.84; 95% CI, 0.65-1.08; P = .163).
- The 2-year OS was 63.8% (95% CI, 57.3%-69.6%) and 57.7% (95% CI, 51.3%-63.6%) in the NCRT and CRT arms,



Locoregional control

- The increment in PFS from the addition of nimotuzumab was largely because of a decrease in locoregional failures (P = .006)
- The 2-year LRC rate was significantly better in the NCRT arm (67.5%; 95% CI, 60.9%-73.3%) than in the CRT arm (57.6%; 95% CI, 50.9%-63.6%).
- The addition of nimotuzumab led to a 33% reduction (hazard ratio, 0.67; 95% CI, 0.50-0.89; P = .006) in the risk of locoregional failure, and the reduction was consistent across all subgroups, inclusive of the patients who received a cumulative cisplatin dose ≥ 200 mg/m² (P = .016; hazard ratio, 0.66; 95% CI, 0.48-0.93)

Adverse Events

- All adverse events occurred with similar frequency in the 2 arms except mucositis and thrombocytopenia.
- Hospitalization because of toxicities was higher in the NCRT arm (58 patients; 21.6%) versus the CRT arm (41 patients; 15.3%; $P = .058$).
- Nasogastric tubes were placed in 97 patients (36.2%) in CRT arm versus 102 patients (38.1%) in the NCRT arm ($P = .655$).

HPV Status and Outcomes

- There was a significant interaction between HPV status and treatment outcomes
- The hazard ratio for PFS in p16-negative oropharyngeal cancers was 0.54 (95% CI, 0.36-0.79), whereas hazard ratio for p16-positive cancers was 2.6 (95% CI, 0.57-11.9).
- The 2-year PFS was 31.5% (95% CI, 21.5%-42.0%) in the CRT arm and 57.2% (95% CI, 45.8%-67.1%) in the NCRT arm in patients with p16-negative oropharyngeal cancers (P = .001).
- A similar higher magnitude of benefit was observed with regard to DFS (hazard ratio, 0.55; 95% CI, 0.37-0.82; P = .006), LRC (hazard ratio, 0.61; 95% CI, 0.4-0.94; P = .024), and OS (hazard ratio, 0.63; 95% CI, 0.43-0.92; P = .018).
- The 2-year OS was 39% (95% CI, 28.3%-49.6%) in the CRT arm and 57.6% (95% CI, 46.3%-67.4%) in the NCRT arm in patients with p16-negative oropharyngeal cancers.

Conclusion

- The addition of nimotuzumab to concurrent weekly cisplatin and chemoradiotherapy improves PFS, LRC, and DFS.

- Immunotherapy Trials

JAVELIN Head and Neck 100: A phase III trial



Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial

Nancy Y Lee, Robert L Ferris*, Amanda Psyrry, Robert I Haddad, Makoto Tahara, Jean Bourhis, Kevin Harrington, Peter Mu-Hsin Chang, Jin-Ching Lin, Mohammad Abdul Razaq, Maria Margarida Teixeira, József Lövey, Jerome Chamois, Antonio Rueda, Chaosu Hu, Lara A Dunn, Mikhail Vladimirovich Dvorkin, Steven De Beukelaer, Dmitri Pavlov, Holger Thurm, Ezra Cohen**

Summary

Lancet Oncol 2021; 22: 450–62

*These authors contributed
equally

Background Chemoradiotherapy is the standard of care for unresected locally advanced squamous cell carcinoma of the head and neck. We aimed to assess if addition of avelumab (anti-PD-L1) to chemoradiotherapy could improve treatment outcomes for this patient population.

Background

- Outcomes for pts with LA HNSCC are suboptimal
- ICP inhibitors have activity for platinum-refractory recurrent and metastatic HNSCC, including both p16-positive and -negative ds.
- Preclinical and clinical evidences in **other** diseases sites suggest potential synergies for combination therapy with ICP inhibitors and CRT

- Avelumab

- Fully human monoclonal IgG1 antibody against PD-L1.
- The US FDA approved for Merkel cell carcinoma and urothelial carcinoma.
- Well tolerated across many solid tumor types.

JAVELIN Head and neck 100

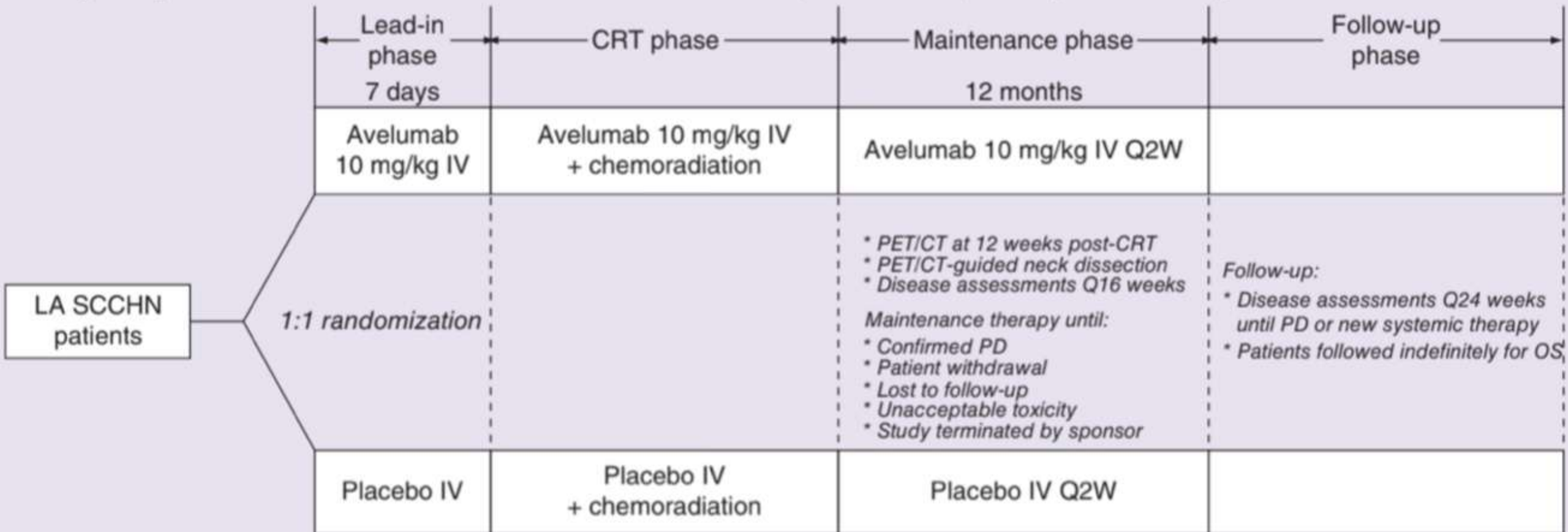
- Double-blind, placebo-controlled, Phase III prospective clinical trial.
- 196 hospitals across 22 countries
- Inclusions- high-risk LA HNSCC of the oral cavity, oropharynx, larynx and hypopharynx.
- High-risk patients include:
 - • p16-negative stage III-IVb disease.
 - • p16-positive stage III-IVb non-oropharyngeal SCC
 - • p16-positive T4 or N2c-N3 oropharyngeal SCC

- Patients randomized to cisplatin-based CRT combined with concurrent and 12 months of adjuvant avelumab or placebo.
- Patients stratified by T-stage, N-stage and p16 status.
- Standard IMRT 70 Gy/35 fractions/7 weeks.
- Cisplatin 100 mg/m² 3weekly
- Avelumab- 10 mg/kg – Loading dose day -7 followed by every 2 weekly for 12 months

STUDY DESIGN

Study design

Randomized, double-blind, 2-arm phase III study

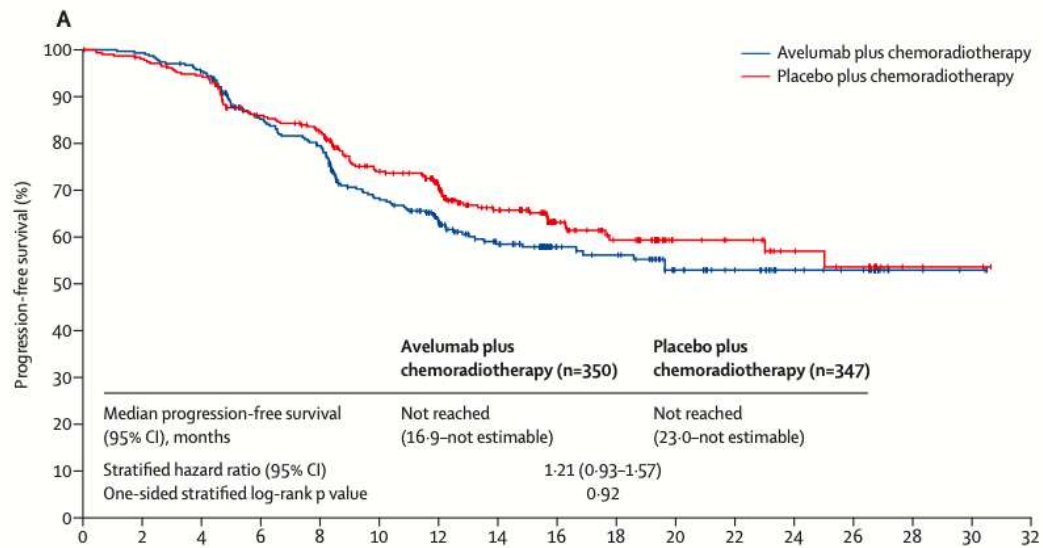


Objective

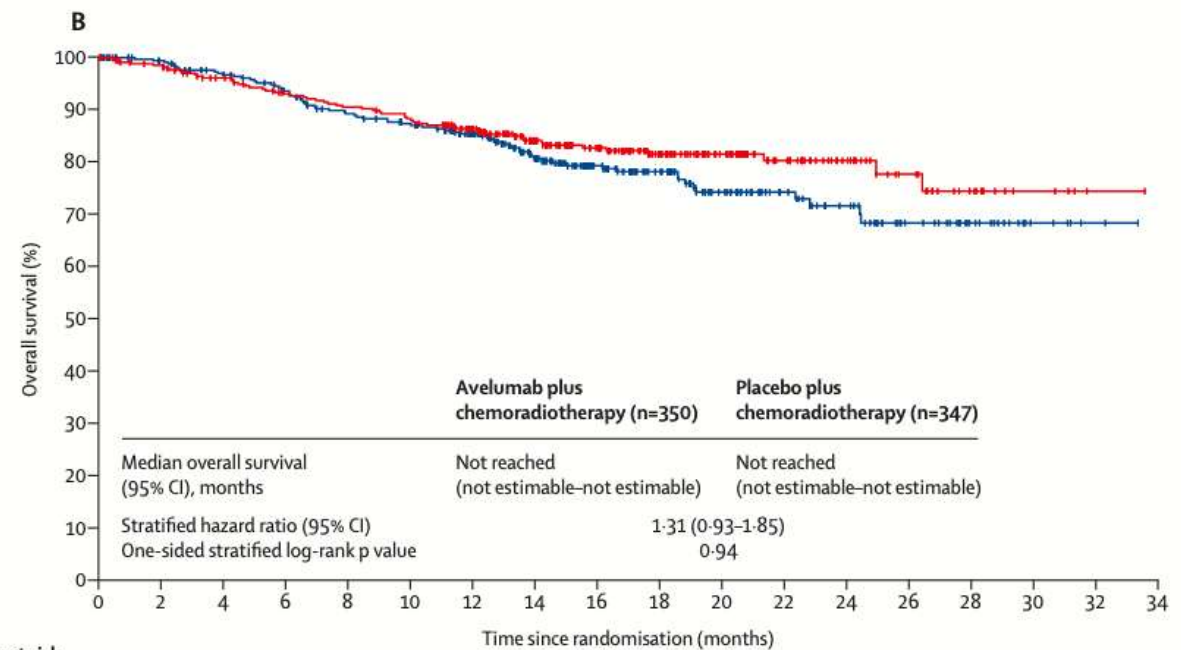
- 697 patients.
- Primary end point is **progression-free survival**.
- Secondary end points include **overall survival, objective response and patient-reported outcomes, and predictive tissue biomarkers**.

RESULTS- TOXICITY

	Avelumab	Placebo	
Median FU	14.6 Mo	14.8 Mo	
Median PFS	Not reached (95% CI- 16.9 mo)	Not reached (95% CI- 23 mo)	HR 1.21 favouring placebo arm
MC grade III toxicity- Neutropenia	16%	15%	
Gr III mucositis	14%	13%	
SAE	36%	32%	
T/t related death	1%	1%	



	Number at risk (number censored)														
Avelumab plus chemoradiotherapy	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4
	(0)	(45)	(47)	(67)	(68)	(84)	(105)	(131)	(168)	(172)	(191)	(199)	(210)	(214)	(228)
Placebo plus chemoradiotherapy	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3
	(0)	(38)	(39)	(47)	(53)	(70)	(90)	(130)	(172)	(187)	(212)	(215)	(224)	(226)	(238)



	Number at risk (number censored)																	
Avelumab plus chemoradiotherapy	350	336	319	303	284	273	244	190	148	118	82	59	47	29	18	6	2	0
	(0)	(12)	(20)	(26)	(31)	(36)	(59)	(101)	(140)	(168)	(199)	(222)	(232)	(248)	(259)	(271)	(275)	(277)
Placebo plus chemoradiotherapy	347	334	315	298	290	282	252	193	160	115	86	58	39	26	13	5	1	0
	(0)	(8)	(19)	(26)	(26)	(27)	(51)	(104)	(134)	(177)	(206)	(233)	(252)	(264)	(276)	(284)	(288)	(289)

Conclusion

- The primary objective of improvement in PFS with CTRT + Avelumab was not achieved
- Exploratory analysis- Potential PFS benefit of Avelumab in pts with high PD L 1 expressing tumours
- **Why should you know this trial?**
- JAVELIN Head neck 100 is the first randomized ph 3 study of ICI combined with CTRT in any solid cancer including LA HNSCC
- Possible explanation for negative outcome- In HNSCC RT (Unlike lung cancer) , we also radiate- Prophylactic LN volumes – which possibly lead to depletion/dysfunction of T cells which negatively impacts ability of immune system to eradicate microscopic ds

Pembrolizumab given concomitantly with chemoradiation and as maintenance therapy for locally advanced head and neck squamous cell carcinoma: KEYNOTE-412

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Randomized, double-blind, Phase III study evaluating the efficacy and safety of Pembrolizumab or placebo given concomitantly with CRT followed by maintenance pembrolizumab or placebo therapy in patients with locally advanced HNSCC.

Pembrolizumab-Anti PD 1

- The antitumor activity and safety of Pembrolizumab monotherapy in HNSCC -established in recurrent and/or metastatic disease in the Phase III KEYNOTE-040 and KEYNOTE-048 studies, as well as for pembrolizumab given concurrently with platinum-based chemotherapy in the KEYNOTE-048 study.
- Interim data from a Phase IB single-arm trial investigating the safety and tolerability of pembrolizumab in combination with CRT in patients with stage III–IVB HNSCC revealed that the treatment regimen is tolerable and feasible.
- The therapeutic combination of concomitant Pembrolizumab and CRT, followed by maintenance pembrolizumab, may be beneficial for patients with locally advanced HNSCC.

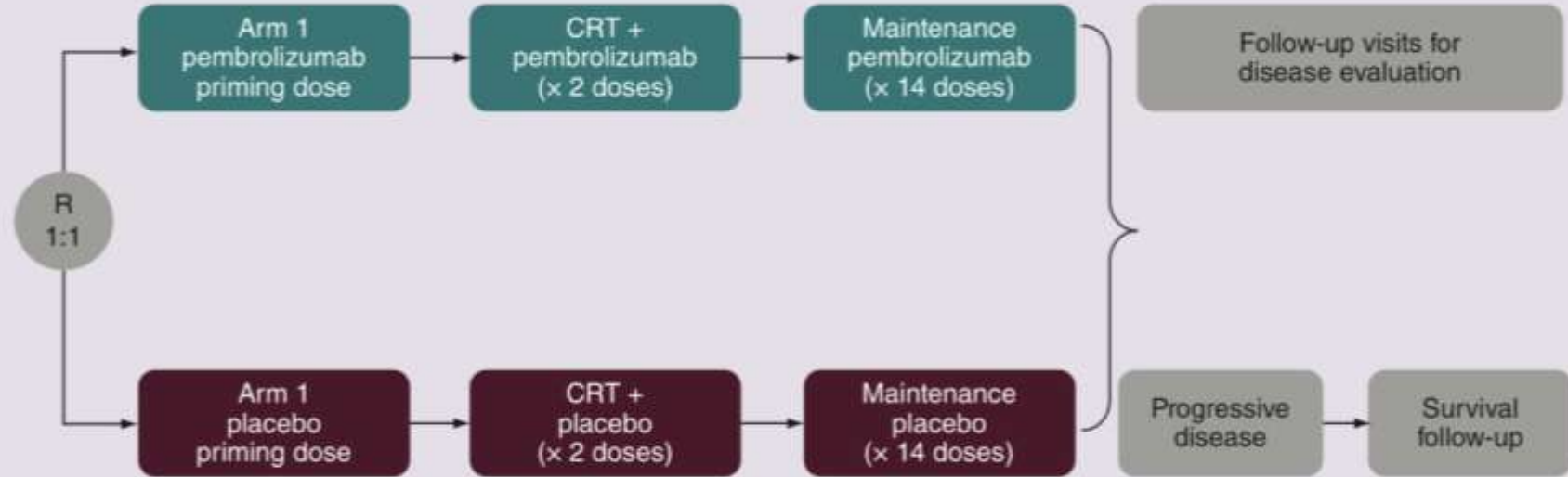
Patients and treatment

- Approximately 780 patients with previously untreated, locally advanced HNSCC have been enrolled; efficacy and safety data are awaited.
- Eligible patients were randomly assigned to receive pembrolizumab or placebo in combination with the current standard treatment of CRT (cisplatin plus fractionated radiation).

Local testing for p16⁺

Patient population

- Oropharyngeal p16 positive
 - T4 (N0–N3), M0
 - N3 (T1–T4), M0
- Oropharyngeal p16 negative
 - Any T3–T4 (N0–N3), M0
 - Any N2a–N3 (T1–T4), M0
- Larynx/hypopharynx/oral cavity (independent of p16)
 - Any T3–T4 (N0–N3), M0
 - Any N2a–N3 (T1–T4), M0



Stratification factors

1. Radiotherapy regimen (AFX or SFX)
2. Tumor site/p16 status (oropharynx – p16 positive vs oropharynx – p16 negative or larynx/hypopharynx/oral cavity)
3. Stage (III vs IV)

151 sites, 21 countries

CDDP 100 mg/2 3 weekly

Pembrolizumab 200 mg/m²

Accelerated RT 70 Gy/35 fr/ 6 weeks

Standard RT 70 Gy/ 35 fr/7 weeks

• Study end points

- The primary end point is event-free survival using RECIST 1.1
- The key Secondary end point is OS.
- Other secondary outcomes include: patient reported outcomes, potential Predicted biomarkers and immune dynamics in the subgroup of patients with oropharyngeal p16 negative or larynx, hypo pharynx, oral cavity head and neck cancers and the overall population.

Conclusion

- **Despite currently available treatment options for locally advanced head and neck cancer, there is a need for better therapies in the curative setting.**
- **The KEYNOTE-412 (NCT03040999) trial was designed to evaluate the clinical utility of pembrolizumab in combination with CRT and as maintenance therapy in patients with locally advanced HNSCC.**



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Open label, randomized , Multicentre phase III study of
LA SCCHN- France, Monaco and switzerland

Original Research

Avelumab—cetuximab—radiotherapy versus standards of
care in locally advanced squamous-cell carcinoma of the
head and neck: The safety phase of a randomised phase
III trial GORTEC 2017-01 (REACH)



Yungan Tao ^a, Anne Aupérin ^a, Xushan Sun ^b, Christian Sire ^c,

Safety of combining Avelumab and Cetuximab has been tested
Avelumab is the only PD-1/PD L1 inhibitor that can induce antibody dependent cell mediated cyto
toxicity (ADCC)
This could synergies with ADCC induced by Cetuximab- which is its key mechanism of action
Both drugs are known to enhance high affinity natural killer cell killing of SCCHN cells

This effect can increase the tumour control but also aggravate adverse reactions especially radiation
dermatitis

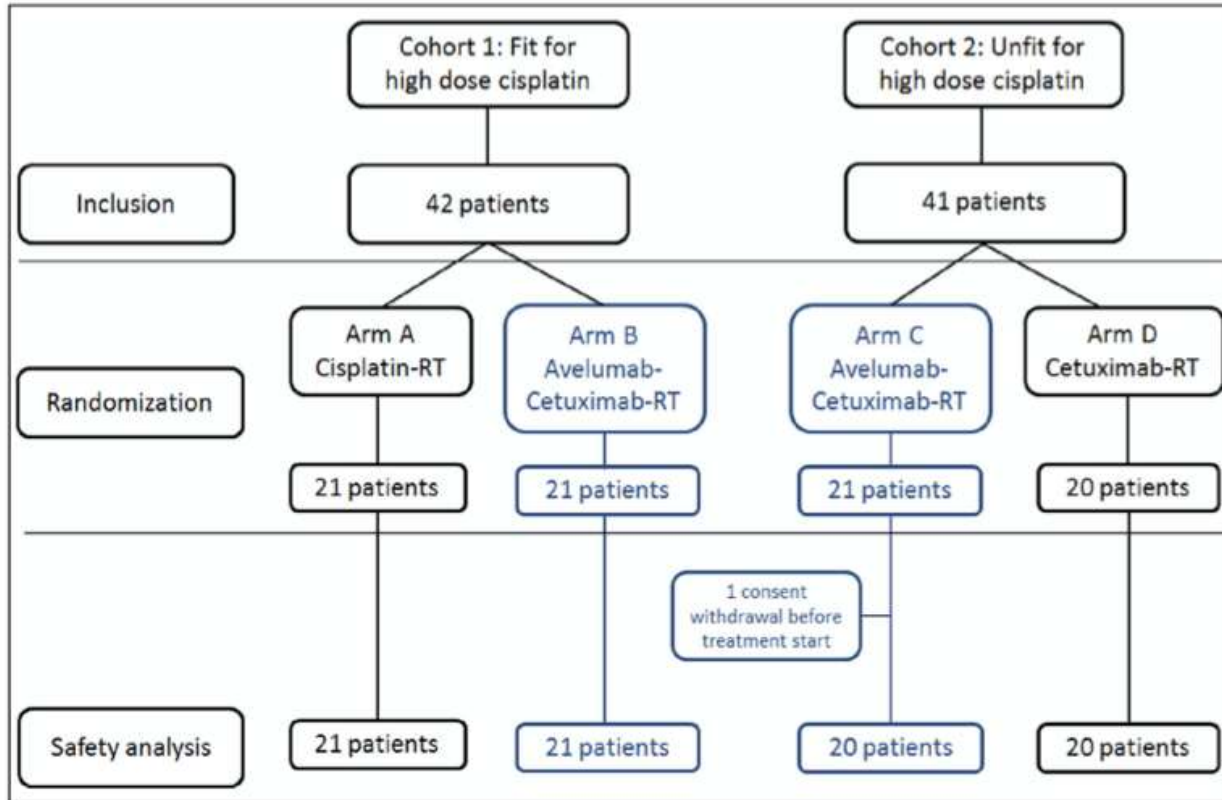


Fig. 1. Trial profile.

Experimental Arm- RT + Cetuximab + Avelumab (arm B and C)
 RT – IMRT 70/Gy33 Fr+ 53Gy/33 fr for HR and LR TV
 Cetuximab 250 mg/m²
 Avelumab 10 mg/kg - 2 weekly concomitant and maintenance for 12 months
 CDDP 100 mg/2- 3 weekly

Results-

Compliance to treatment- all patients completed planned RT except for 1

MC AE were- Mucositis, radio dermatitis and dysphagia

Grade \geq IV AE – 12% patients- all in arm C

Conclusion- The Avelumab + Cetuximab + RT combination was tolerable

Approval granted for continuing this trial without modification

Alone these drugs did not work– you never know synergy might work- watch out for this space

Acknowledgement

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Dr Swati Virmani

Thank you!

