Targeted therapy in HNSCC

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Targeted therapy

Anti EGFR agents

Immunotherapy

Inhibitor of Apoptosis Proteins

Anti EGFR therapy in LAHNSCC

- Radiotherapy Vs RT + Anti EGFR therapy
- CCRT Vs CCRT plus Anti EGFR
- RT + Cetuximab Vs Chemo + Cetuximab + RT
- CCRT Vs RT + Anti EGFR therapy
- IC followed by RT + Cetuximab Vs CCRT
- RT + Cetuximab Vs CDDP+ RT after TPF

N Engl J Med 2006;354:567-78.

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.*

Articles

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

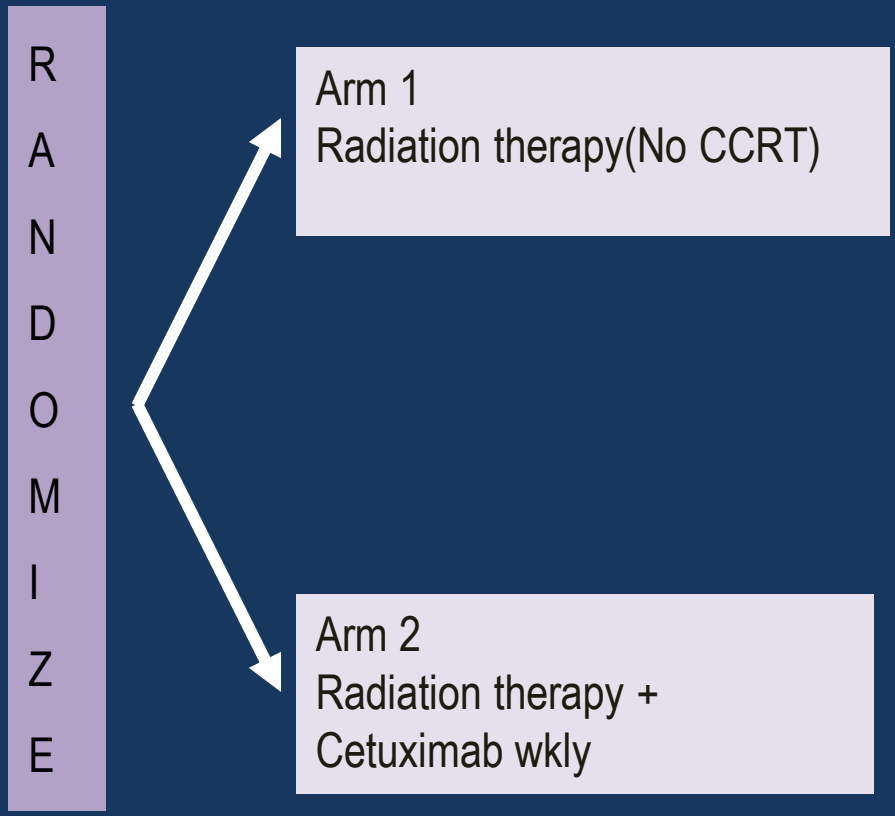
Lancet Oncol 2010; 11: 21–28

James A Bonner, Paul M Harari, Jordi Giralt, Roger B Cohen, Christopher U Jones, Ranjan K Sur, David Raben, Jose Baselga, Sharon A Spencer, Junming Zhu, Hagop Youssoufian, Eric K Rowinsky, K Kian Ang

Phase III Study Design

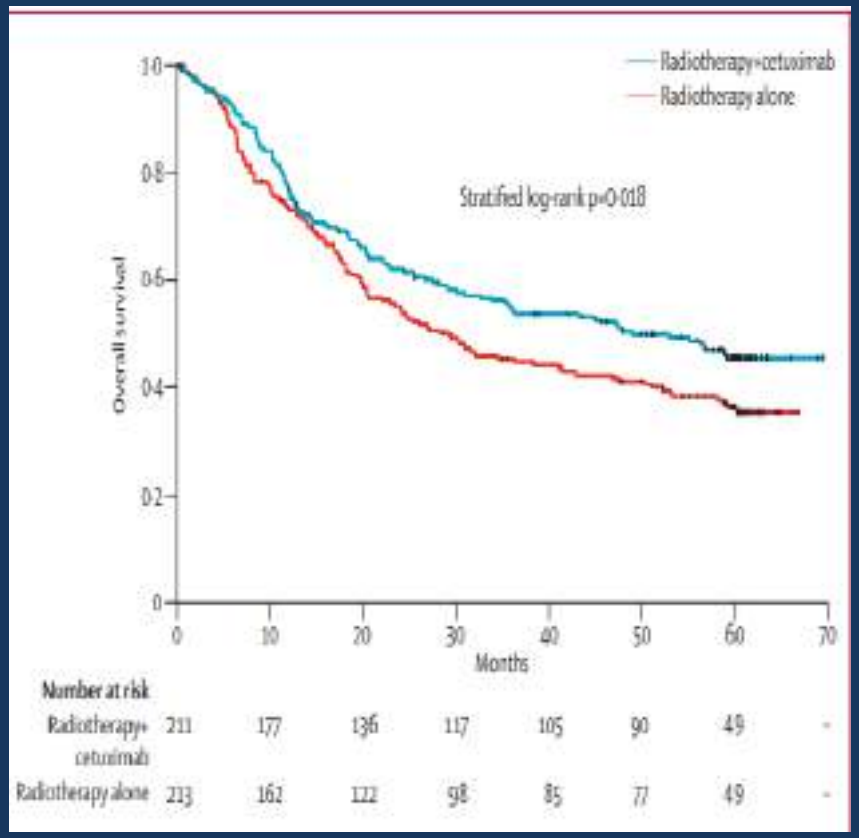
Stratified by

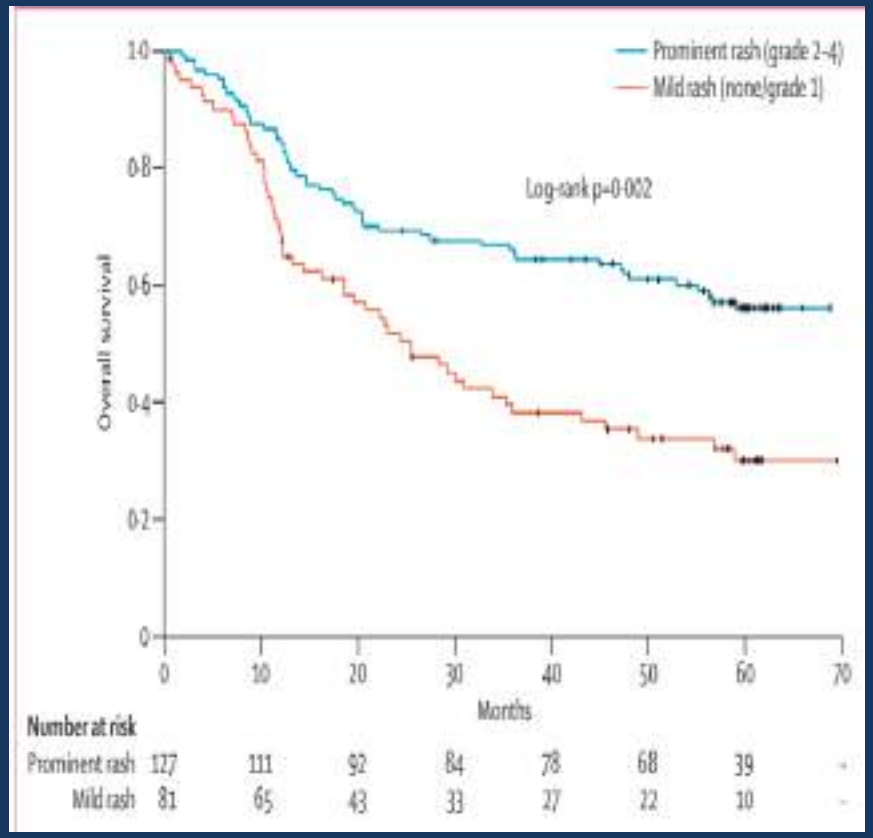
- Karnofsky score: 90-100 vs 60-80
- Regional nodes: negative vs positive
- Tumor stage: AJCC T1-3 vs T4
- RT fractionation: concomitant boost vs once daily vs twice daily



N Engl J Med 2006;354:567-78.

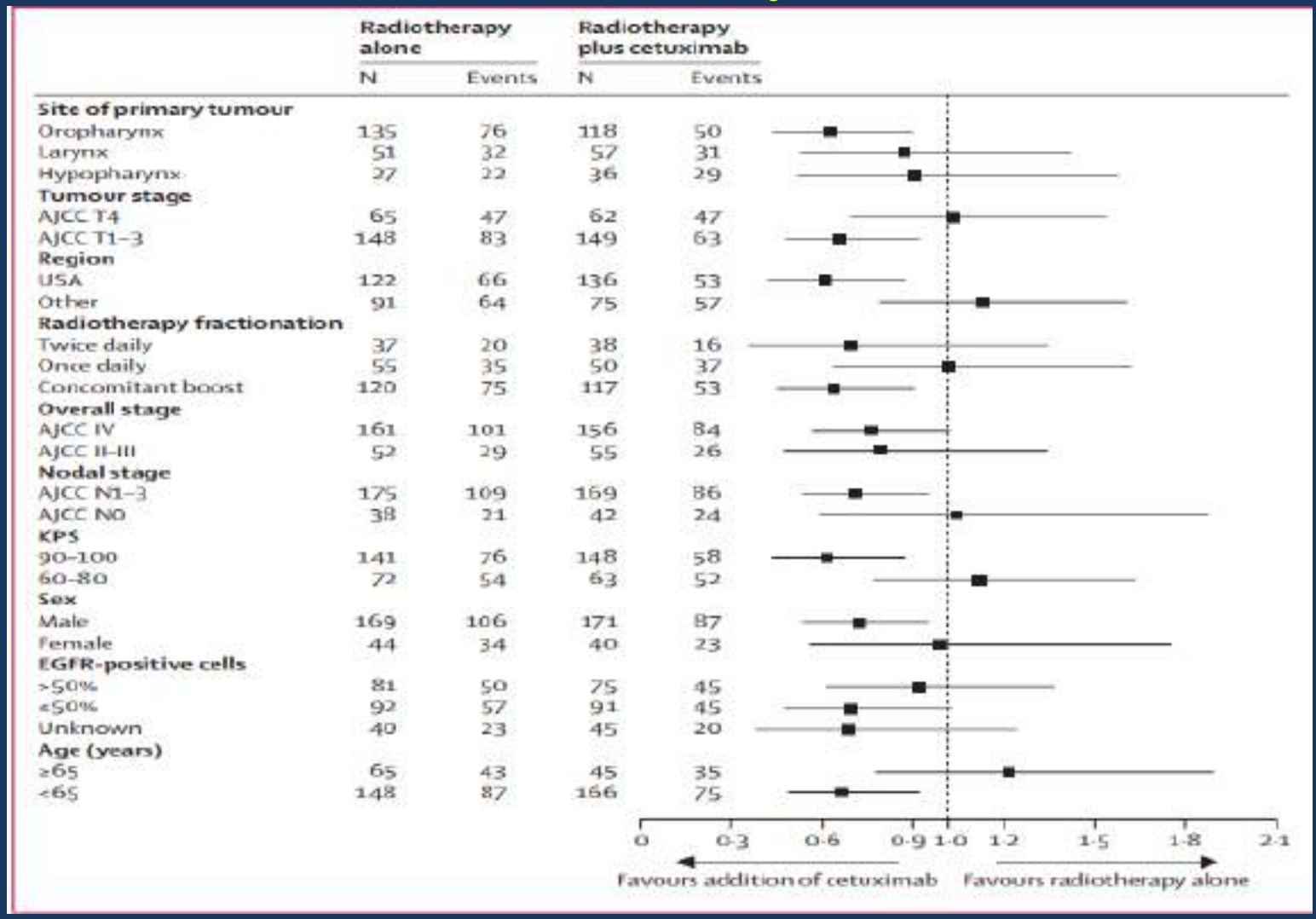
5yr update





Lancet Oncol 2010; 11: 21–28

Subset analysis



Lancet Oncol 2010; 11: 21–28

Most Common Adverse Events

Toxicity, %	RT (n = 212)		RT + C (n = 208)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Skin reaction	91	18	97†	34‡
Mucositis/stomatitis	93	52	91	54
Dysphagia	63	30	64	25
Xerostomia	70	3	64	4
Fatigue/Malaise	50	5	52	4
Infusion reaction*	--	–	14‡	3†

*Listed for its relationship to cetuximab.
†$P < .05$
‡$P < .001$, Fisher's exact test.

Bonner JA, et al. N Engl J Med. 2006;354:567-578.

Cetuximab and Radiotherapy for Head and Neck Cancer

Marshall R. Posner, M.D. and Lori J. Wirth, M.D.

et al. found with cetuximab. Whether cetuximab plus radiotherapy is a better therapy than platinum-based chemoradiotherapy and whether cetuximab can be added to platinum-based chemoradiotherapy are important questions, the answers to which require randomized phase 3 studies. These are already under way. At present, for patients who can tolerate it, chemoradiotherapy with cisplatin remains the standard of care. Patients who cannot tolerate platinum-based chemotherapy for any of a variety of reasons should be expected to benefit from the addition of cetuximab to radiotherapy.

Anti EGFR therapy in LAHNSCC

- Radiotherapy Vs RT + Anti EGFR therapy
- CCRT Vs CCRT plus Anti EGFR
- RT + Cetuximab Vs Chemo + Cetuximab + RT
- CCRT Vs RT + Anti EGFR therapy
- IC followed by RT + Cetuximab Vs CCRT
- RT + Cetuximab Vs CDDP+ RT after TPF

CCRT Vs CCRT plus Anti EGFR

- RTOG 0522
- Nimozutumab TMH trial
- DHANCA 19

Published Ahead of Print on August 25, 2014 as 10.1200/JCO.2013.53.5633
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.53.5633

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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. Konski, Wade L. Thorstad, Andy Trotti, Jonathan J. Beitler, Adam S. Garden, William J. Spanos,† Sue S. Yom, and Rita S. Axelrod

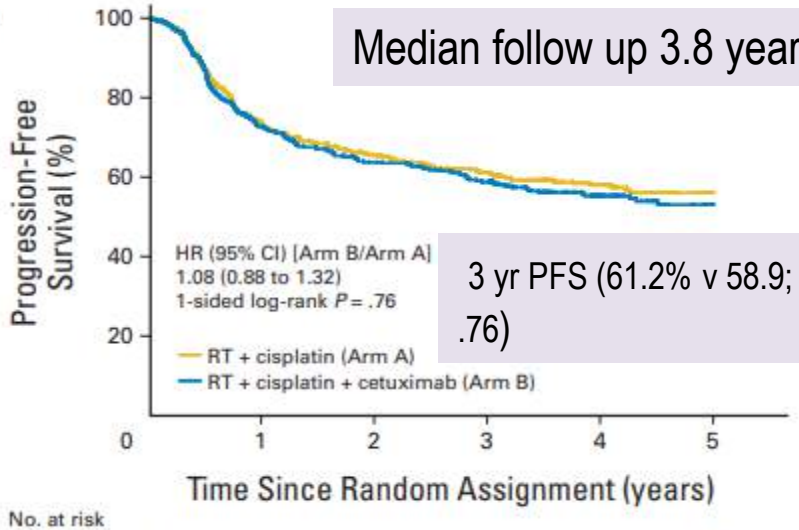
Advanced head and neck cancer(N-940)
Primary end point - PFS

Concurrent chemoRT

Concurrent chemoRT+ Cetuximab

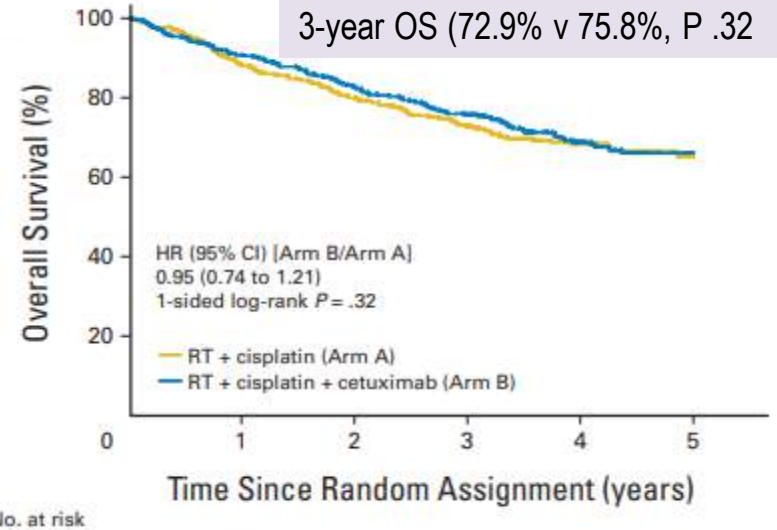
follow-up

J Clin Oncol 2014 ;32:2940-2950.

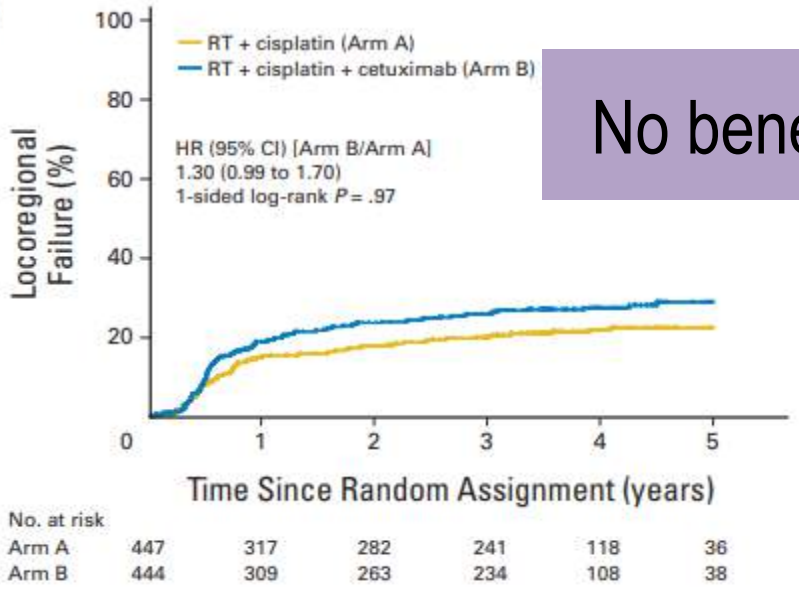


Median follow up 3.8 years

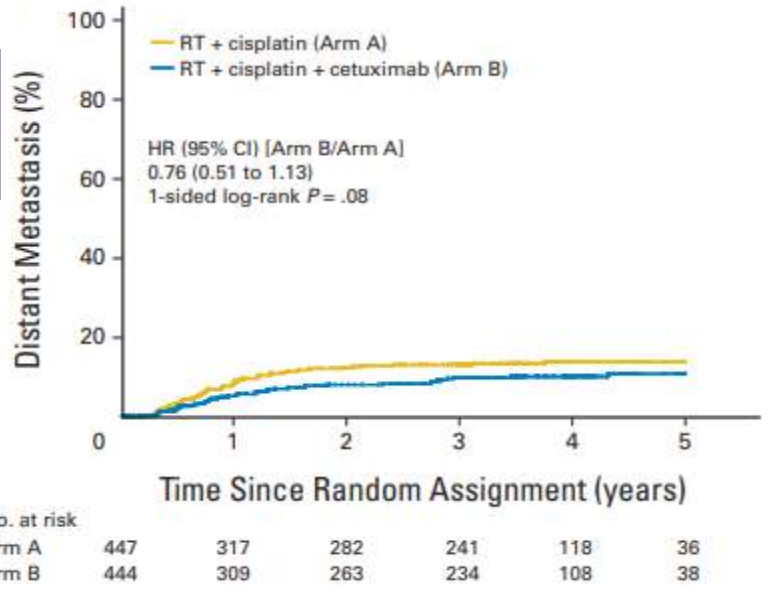
3 yr PFS (61.2% v 58.9; P .76)



3-year OS (72.9% v 75.8%, P .32



No benefit



J Clin Oncol 2014 ;32:2940-2950.

Toxicity

Adverse Event*	% of Patients					
	Arm A: RT + Cisplatin		Arm B: RT + Cisplatin + Cetuximab		*P*†	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Acute period‡						
No. of patients	447		444			
Any event	97	87	97	89	.70	.61
Dysphagia	86	57	82	53	.08	.25
Radiation mucositis	72	33	82	43	< .001	.002
Skin reaction outside portal§	14	1	82	20	< .001	< .001
Skin reaction inside portal‖	79	15	78	25	.87	< .001
Fatigue	60	9	65	14	.17	.03
Nausea	57	14	59	18	.59	.08
Hemoglobin	53	4	51	6	.55	.30
Weight decreased	50	2	52	2	.74	.80
Leukopenia NOS	49	19	50	19	.79	.80
Mucositis/stomatitis (clinical exam): pharynx	49	24	43	28	.11	.29
Vomiting NOS	38	9	42	10	.17	.56
Hyponatremia	34	10	42	13	.01	.29
Dysgeusia	39	0	36	0	.33	—
Dehydration	36	15	37	18	.63	.24
Dry mouth	35	6	37	7	.53	.28
Hypomagnesemia	21	2	36	3	< .001	.26
Neutrophil count	33	16	33	17	.89	.65
Pharyngolaryngeal pain	32	8	26	7	.05	.70
Anorexia	32	11	32	16	.89	.04
Salivary gland disorder NOS	31	2	27	4	.24	.07
Hypoalbuminemia	25	1	30	2	.11	.09
Oral pain	24	7	28	10	.17	.19
Hypocalcemia	16	1	26	3	< .001	.09
Hyperglycemia NOS	23	3	25	3	.48	.84
Hypokalemia	18	5	25	10	.007	.005

J Clin Oncol 2014 ;32:2940-2950.

Original Article

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

Vijay Maruti Patil, MD[1]; Vanita Noronha, MD[1]; Amit Joshi, MD[1]; Jaiprakash Agarwal, MD[2]; Sarbani Ghosh-Laskar, MD[2]; Ashwini Budrukkar, MD[2]; Vedang Murthy, MD[2]; Tejpal Gupta, MD[2]; Manoj Mahimkar, MD[3]; Shashikant Juvekar, MD[4]; Supreeta Arya, MD[4]; Abhishek Mahajan, MD[4]; Archi Agarwal, MD[5]; Nilendu Purandare, MD[5]; Venkatesh Rangarajan, MD[5]; Arun Balaji, MASLP[6]; Sameer Vasant Chaudhari, MD[7]; Shripad Banavali, MD[1]; Sadhana Kannan, MD[8]; Atanu Bhattacharjee, PhD[9]; Anil K. D'Cruz, MS[10]; Pankaj Chaturvedi, MS[10]; Prathamesh S. Pai, MS[10]; Devendra Chaukar, MS[10]; Gouri Pantvaidya, MS[10]; Deepa Nair, MS[10]; Sudhir Nair, MS[10]; Anuja Deshmukh, MS[10]; Shivakumar Thiagarajan, MS[10]; Vijayalakshmi Mathrudev, MBA[1]; Aparna Manjrekar, PGDCR[1]; Sachin Dhumal, MSc[1]; Kamesh Maske, PGDCR[1]; Arti Sanjay Bhelekar, MSc[1]; Kavita Nawale, MBA[1]; Arun Chandrasekharan, MD[1]; Nikhil Pande, MD[1]; Alok Goel, MD[1]; Vikas Talreja, MD[1]; Vijai Simha, MD[1]; Sujay Srinivas, MD[1]; Rohit Swami, MD[1]; Dilip Harindran Vallathol, MD[1]; Hollis Dsouza, MD[1]; Sameer Shrirangwar, MD[1]; Siddharth Turkar, MD[1]; George Abraham, MD[1]; Aditi Harsh Thanky, MD[1]; Usha Patel, MSc[3]; Manish Kumar Pandey, MSc[3]; and Kumar Prabhash, MD[1]

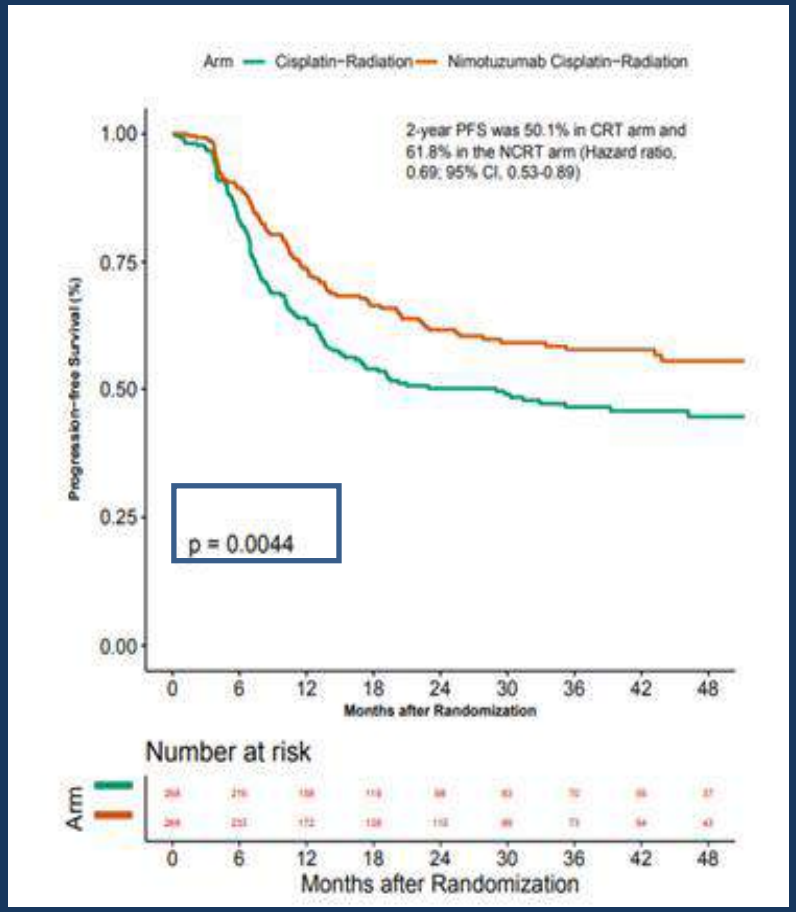
Advanced head and neck cancer(N=536)
Primary end point -PFS

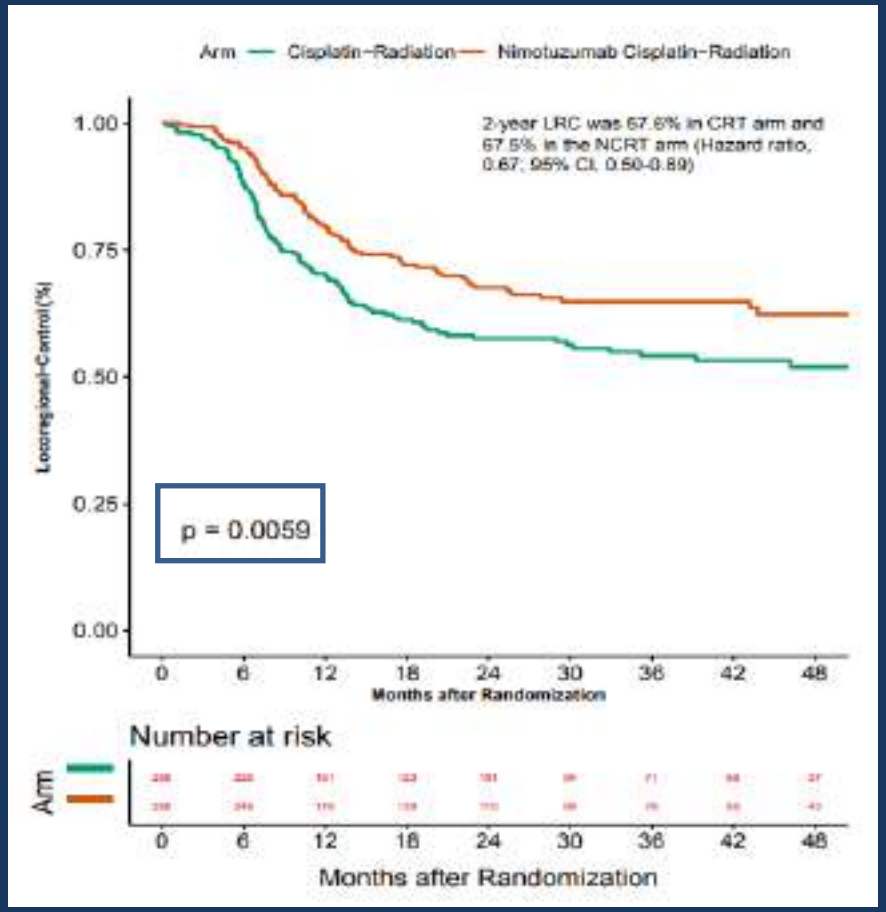
Concurrent chemoRT
(66-70Gy+30 mg/m2 CDDP Weekly)

Concurrent chemoRT+ Nimozutumab 200mgq1wk

Cancer 2019;125:3184-3197.

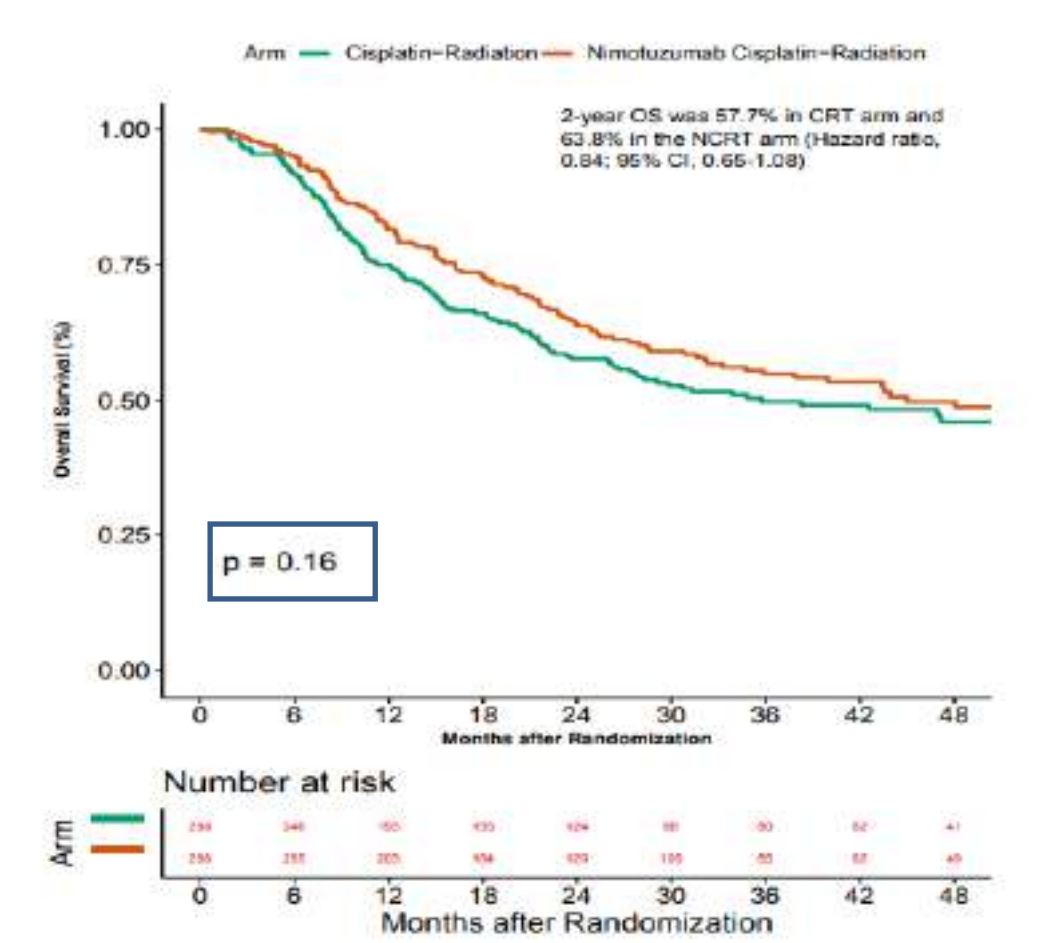
Results – Median FU -39 Months





Cancer 2019;125:3184-3197.

OS



Cancer 2019;125:3184-3197.

Toxicity

Variable	No. of Patients (%)				P
	CRT Arm		NCRT Arm		
	All Grades	Grade 3-5	All Grades	Grade 3-5	Grade 3-5
Hematologic adverse events					
Anemia	211 (80.5)	4 (1.5)	229 (86.1)	3 (1.1)	.689
Neutropenia	45 (17.2)	9 (3.4)	45 (16.9)	6 (2.3)	.415
Febrile neutropenia	—	5 (1.9)	—	4 (1.5)	.737
Thrombocytopenia	64 (24.4)	4 (1.5)	46 (17.3)	3 (1.1)	.689
Biochemical adverse events					
Increased serum creatinine	26 (9.9)	0 (0.0)	24 (9.0)	2 (0.8)	.16
Increased AST	48 (18.3)	3 (1.1)	41 (15.4)	2 (0.8)	.641
Increased ALT	75 (28.6)	3 (1.1)	85 (32.0)	4 (1.5)	.719
Electrolyte disturbance					
Hyponatremia	236 (90.1)	82 (31.3)	237 (89.1)	89 (33.5)	.596
Hypokalemia	10 (3.8)	3 (1.1)	16 (6.0)	2 (0.8)	.641
Hypomagnesemia	79 (30.2)	—	89 (33.5)	—	—
Local radiation adverse events					
Mucositis	252 (96.9)	145 (55.8)	256 (97)	176 (66.7)	.01
Radiation dermatitis	238 (91.5)	76 (29.2)	234 (88.6)	73 (27.7)	.689
Odynophagia	252 (96.9)	96 (37.7)	257 (97.3)	109 (41.3)	.4
Dysphagia	226 (86.9)	75 (28.8)	229 (86.7)	80 (30.3)	.715
Gastrointestinal adverse events					
Nausea	124 (47.7)	2 (0.8)	127 (48.1)	4 (1.5)	.422
Vomiting	78 (30.0)	4 (1.5)	77 (29.2)	3 (1.1)	.689
Weight loss	133 (51.2)	2 (0.8)	160 (60.6)	3 (1.1)	.666
Other adverse events					
Maculopapular rash	6 (2.3)	—	19 (17.2)	—	—
Stroke	—	—	4 (1.5)	2 (0.8)	.16
Tinnitus	3 (1.2)	—	3 (1.1)	—	—
Long-term side effects, >90 d					
Xerostomia	186 (97.4)	4 (2.1)	181 (95.8)	8 (4.2)	.233
Dysgeusia	151 (79.1)	—	143 (75.7)	—	—
Subcutaneous fibrosis	183 (95.8)	48 (25.1)	178 (94.2)	55 (29.1)	.384
Decreased shoulder range of motion	7 (3.7)	—	7 (3.7)	2 (1.1)	.154
Dysphagia	79 (41.4)	6 (3.1)	79 (41.8)	12 (6.3)	.141
Impaired hearing caused by SNHL	33 (17.3)	9 (4.7)	31 (16.4)	11 (5.8)	.629

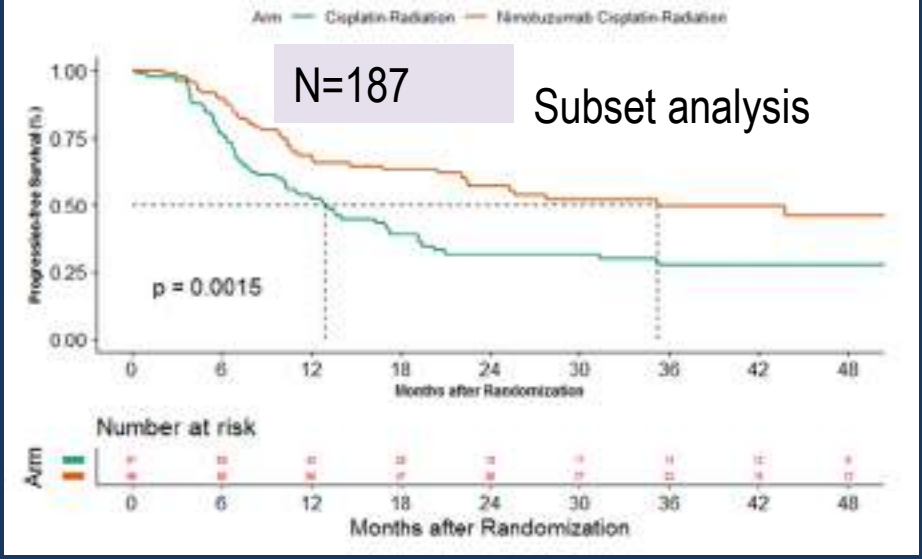
Cancer 2019;125:3184-3197.

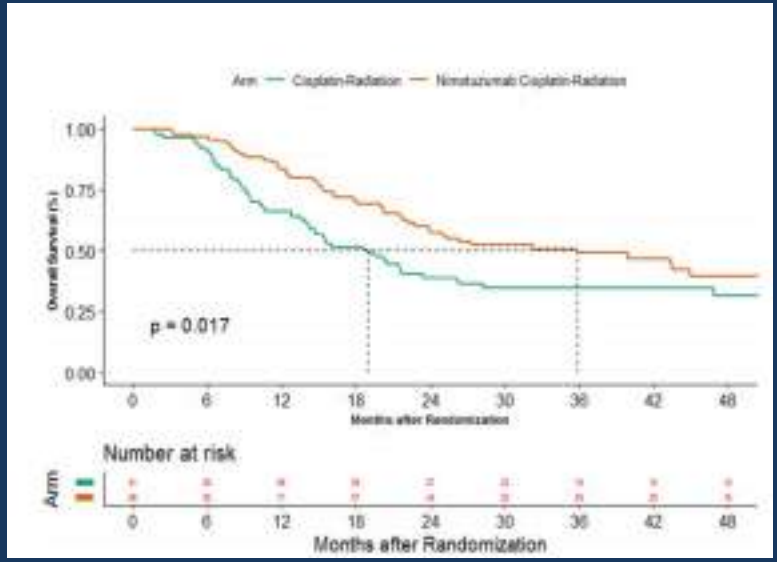
www.oncotarget.com Oncotarget, 2020, Vol. 11, (No. 4), pp: 399-408

Research Paper

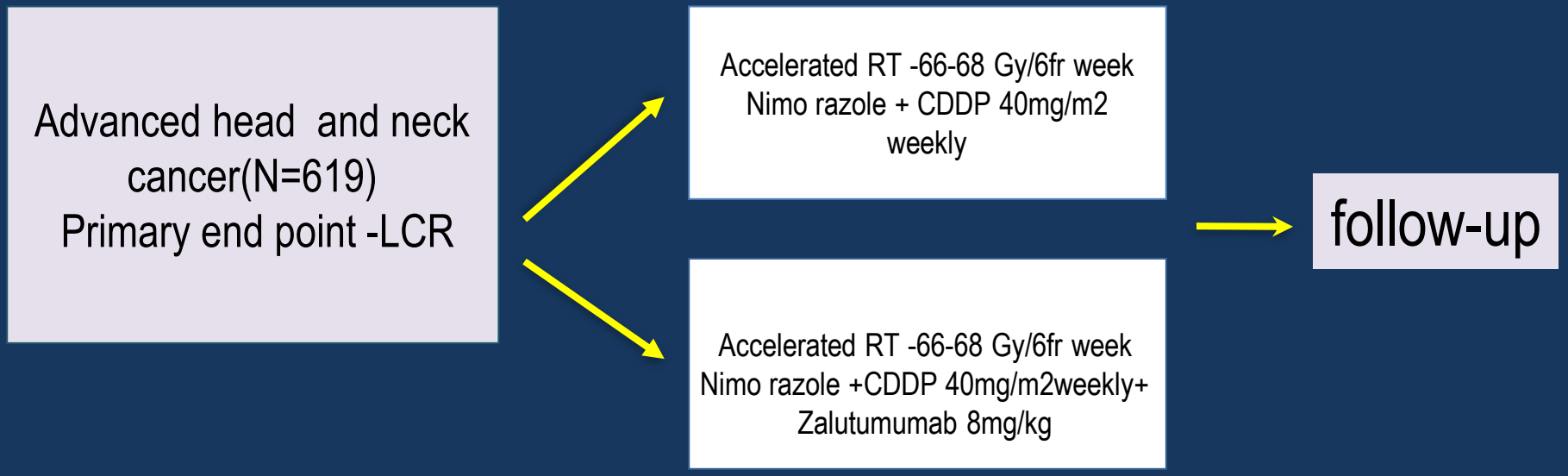
Nimotuzumab-cisplatin-radiation versus cisplatin-radiation in HPV negative oropharyngeal cancer

Vanita Noronha[1,*], Vijay Maruti Patil[1,*], Amit Joshi[1], Manoj Mahimkar[2], Usha Patel[2], Manish Kumar Pandey[2], Arun Chandrasekharan[1], Hollis Dsouza[1], Atanu Bhattacharjee[3], Abhishek Mahajan[1], Nilesh Sabale[1], Jai Prakash Agarwal[4], Sarbani Ghosh-Laskar[4], Ashwini Budrukkar[4], Anil K. D'Cruz[5], Pankaj Chaturvedi[5], Prathamesh S. Pai[5], Devendra Chaukar[5], Sudhir Nair[5], Shivakumar Thiagarajan[5], Shripad Banavali[1] and Kumar Prabhash[1]





Oncotarget, 2020, Vol. 11, (No. 4), pp: 399-408



Median follow up 36 months

29% increase in grade 3/4 rash

3 year LCR 78% Vs 79%(NS)

Volume 88, Issue 2 , P 465, February 01, 2014 IJROBP

Conclusions – ChemoRT +Anti EGFR agents

- None of the trials did not show any survival benefit
- There is an increase in toxicity
- One trial showed improvement in PFS, DFS.
- More robust data- required to accept as the standard

Anti EGFR therapy in LAHNSCC

- Radiotherapy Vs RT + Anti EGFR therapy
- CCRT Vs CCRT plus Anti EGFR
- RT + Cetuximab Vs Chemo + Cetuximab + RT
- CCRT Vs RT + Anti EGFR therapy
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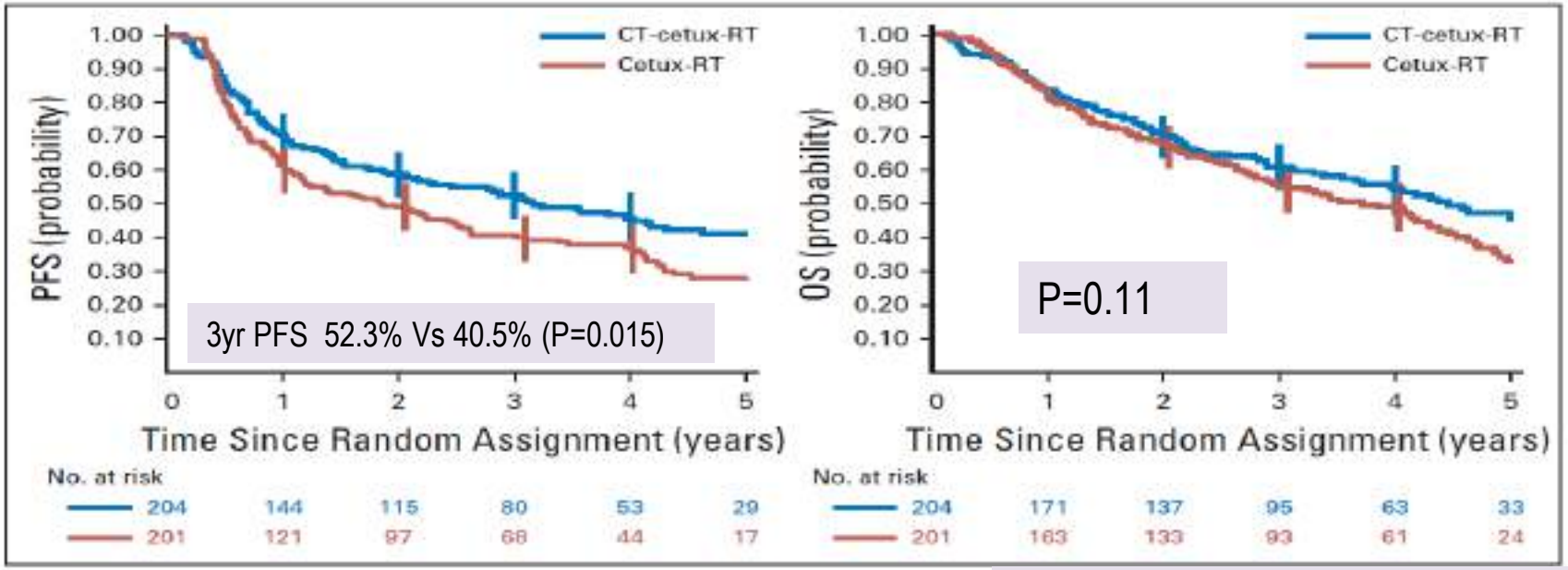
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

N=406
N0-N2b
Primary endpoint - PFS

Median FU-4.4YRS

Improved Outcome by Adding Concurrent Chemotherapy to Cetuximab and Radiotherapy for Locally Advanced Head and Neck Carcinomas: Results of the GORTEC 2007-01 Phase III Randomized Trial

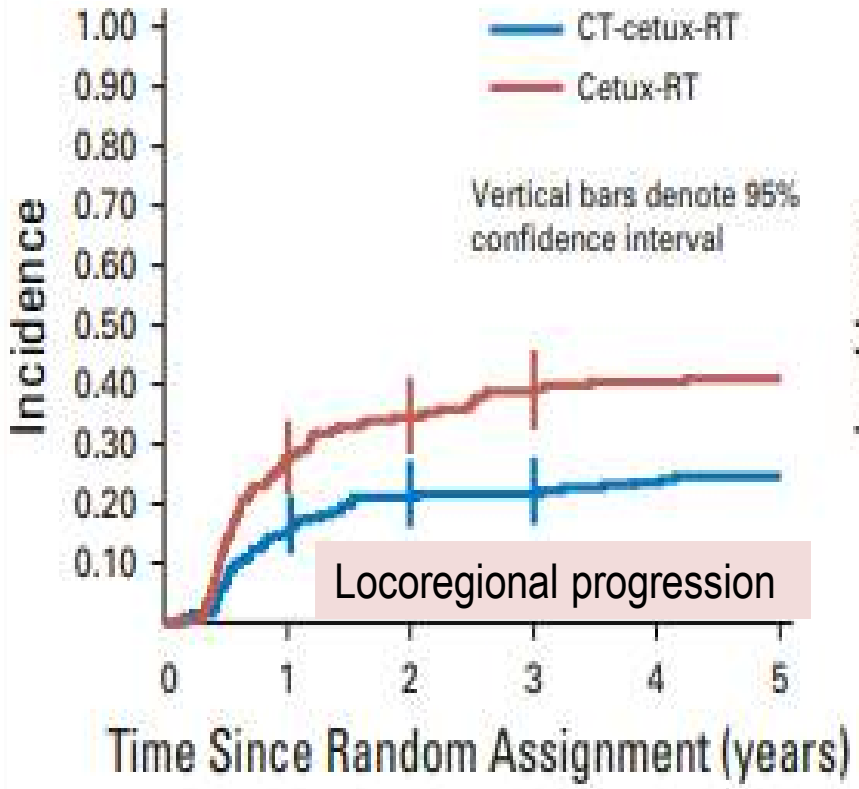
Yungan Tao, Anne Auperin, Christian Sire, Laurent Martin, Cedric Khoury, Philippe Maingon, Etienne Bardet, Marie-Christine Kaminsky, Michel Lapeyre, Thierry Chatellier, Marc Alfonsi, Yoann Pointreau, Eric Jaulmé, Bernard Géry, Ayman Zawadi, Jean-Marc Tourani, Brigitte Laguerre, Alexandre Coutte, Séverine Racadot, Ali Hasbini, Emanuelle Malaurie, Christian Borel, Nicolas Meert, Alexandre Cornely, Nathalie Ollivier, Odile Casiraghi, Xu Shan Sun, and Jean Bourhis

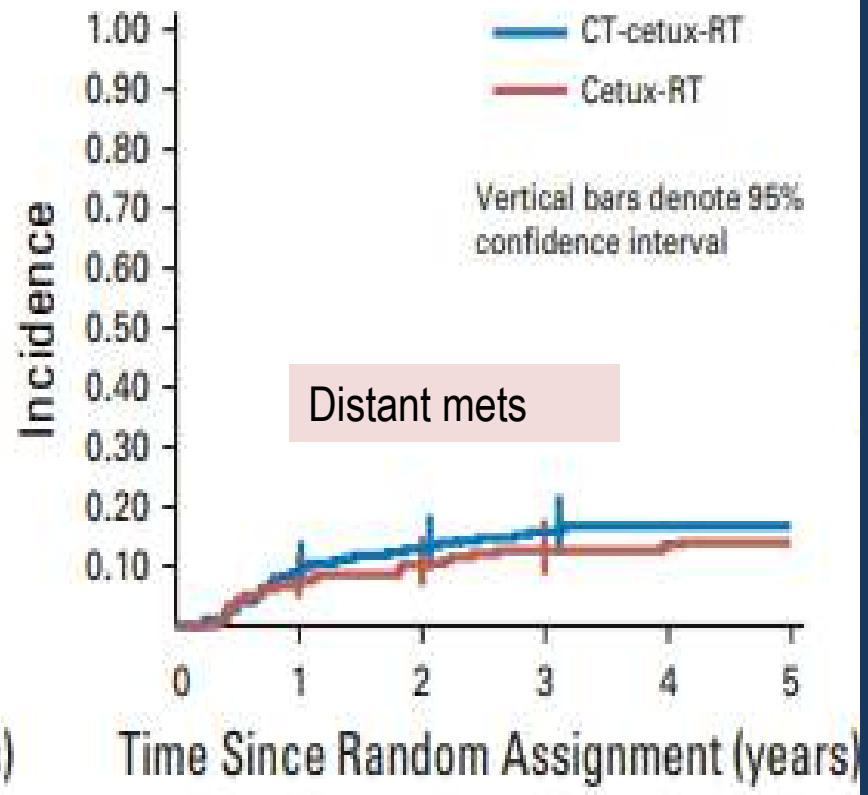


J Clin Oncol 2018 36:3084-3090

Median FU-4.4 Years

The HR for loco regional control was 0.54 ,P .001)





J Clin Oncol 2018 36:3084-3090

Anti EGFR therapy in LAHNSCC

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- RT + Cetuximab Vs CDDP+ RT after TPF

CCRT Vs RT + Anti EGFR therapy

- ARTSCAN III trial
- HN6 Trial

HPV positive patients

- De- ESCALaTE
- RTOG 1016
- TROG 12.01

original reports

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, PhD[1]; Eva Brun, MD, PhD[1]; Per Engström, PhD[1]; Hedda Haugen Cange, MD, PhD[2]; Lalle Hammarstedt-Nordenvall, MD, PhD[3]; Johan Reizenstein, MD[4]; Jan Nyman, MD, PhD[2]; Edvard Abel, MD[2]; Signe Friesland, MD, PhD[5,6]; Helena Sjödin, MD[2]; Henrik Carlsson, MD[1]; Karin Söderkvist, MD, PhD[7]; Marcus Thomasson, MD, PhD[7]; Björn Zackrisson, MD, PhD[7]; and Per Nilsson, PhD[1]

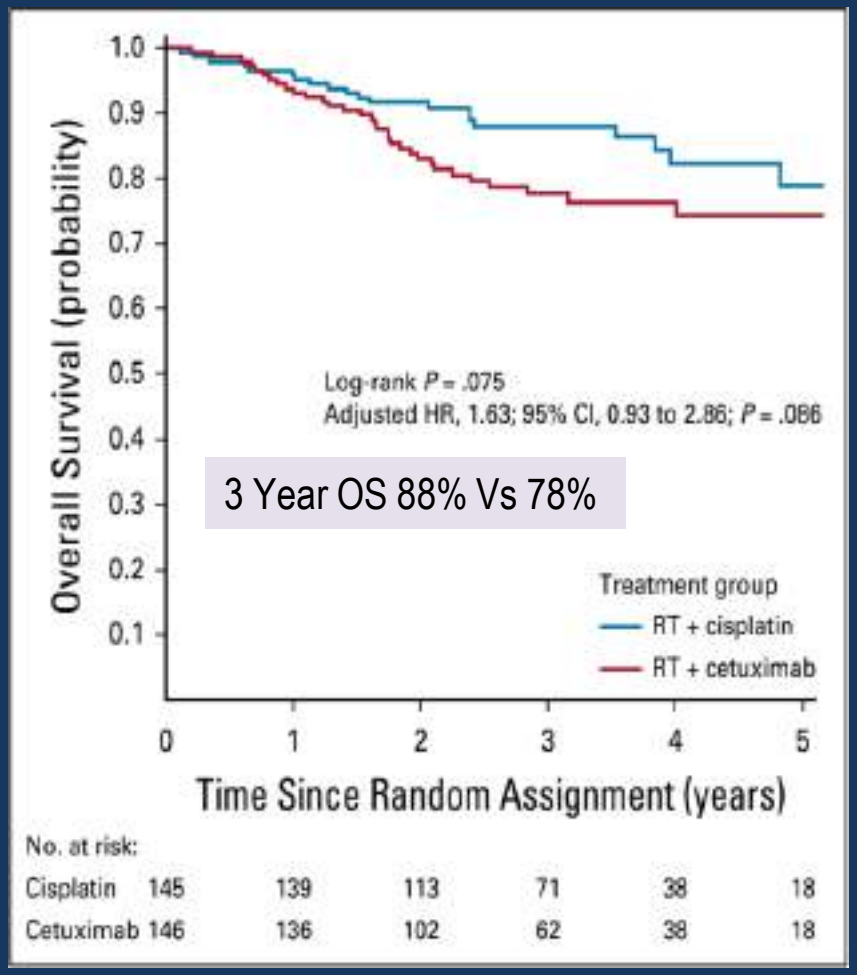
Advanced head and neck cancer(N= 298)
Primary end point – OS

Arm 1
CCRT

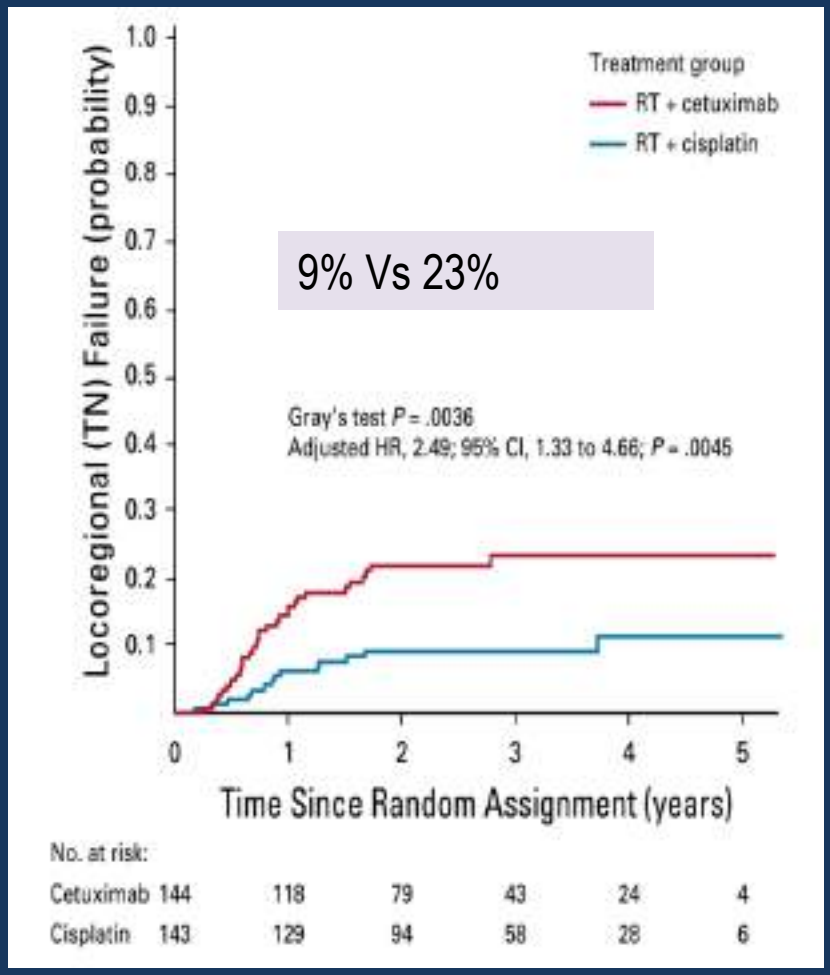
Arm 2
Radiation therapy +
Cetuximab wkly

J Clin Oncol 2020,39:38-47

3 year results



Prematurely closed



J Clin Oncol 2020 ,39:38-47

Acute Toxicity	Scale/Scores	RT + Cisplatin[a]	RT + Cetuximab[a]	P
Early deaths[b]	Within 30 days	2/145 (1)	1/145 (1)	1.00
Weight loss	CTCAE gr 3	6/143 (4)	8/144 (6)	.79
PEG[b]	Yes (used)	90/145 (62)	73/145 (50)	.06
Tracheostomy[b]	Yes	3/145 (2)	3/145 (2)	1.00
Pain	RTOG gr 3	113/145 (78)	117/145 (81)	.66
Dysphagia	RTOG gr 3-4	47/145 (32)[c]	30/145 (21)	**.033**
Mucositis	RTOG gr 3-4	87/145 (60)	105/145 (72)[c]	**.035**
Skin reactions	RTOG gr 3-4	11/145 (8)	32/145 (22)[c]	**.001**
Rash acneiform	CTCAE gr 3-4	0/145 (0)	31/145 (21)[c]	**< .001**
Allergic reactions	CTCAE gr 3-4	0/145 (0)	5/145 (3)	.06
Anemia	CTCAE gr 3-4	1/145 (1)	0/144 (0)	1.00
Hearing impaired	CTCAE gr 3-4	5/145 (3)	4/145 (3)	1.00
Hypomagnesemia	CTCAE gr 3-4	0/145 (0)	0/144 (0)	1.00
Nausea	CTCAE gr 3	40/145 (28)[c]	16/145 (11)	**.001**
Vomiting	CTCAE gr 3-4	7/145 (5)[c]	0/145 (0)	**.015**
Acute kidney injury	CTCAE gr 2-4	19/145 (13)[c]	1/145 (1)	**< .001**
Paronychia	CTCAE gr 3	0/145 (0)	0/145 (0)	1.00
Neuropathy	CTCAE gr 3	1/145 (1)	0/145 (0)	1.00
Neutropenia	CTCAE gr 3-4	16/145 (11)[c]	1/144 (1)	**< .001**
Tinnitus	CTCAE gr 2-3	15/145 (10)[c]	2/145 (1)	**.002**
Thrombocytopenia	CTCAE gr 3-4	4/145 (3)	0/144 (0)	.12
Infection	CTCAE gr 3-4	14/145 (10)	16/145 (11)	.85
Mean raw T score		2.66	2.54	.71

J Clin Oncol 2020 ,39:38-47

Research

JAMA Oncology | Original Investigation

Effect of Standard Radiotherapy With Cisplatin vs Accelerated Radiotherapy With Panitumumab in Locoregionally Advanced Squamous Cell Head and Neck Carcinoma

A Randomized Clinical Trial

Lillian L. Siu, MD, FRCPC; John N. Waldron, MD; Bingshu E. Chen, PhD; Eric Winquist, MD; Jim R. Wright, MD; Abdenour Nabid, MD; John H. Hay, MD; Jolie Ringash, MD; Geoffrey Liu, MD; Ana Johnson, PhD; George Shenouda, MD; Martin Chasen, MD; Andrew Pearce, MD; James B. Butler, MD; Stephen Breen, PhD; Eric Xueyu Chen, MD; T. J. FitzGerald, MD; T. J. Childs, MD; Alexander Montenegro, MSc; Brian O'Sullivan, MD; Wendy R. Parulekar, MD

Advanced head and neck cancer(N=326)
Primary end point - PFS

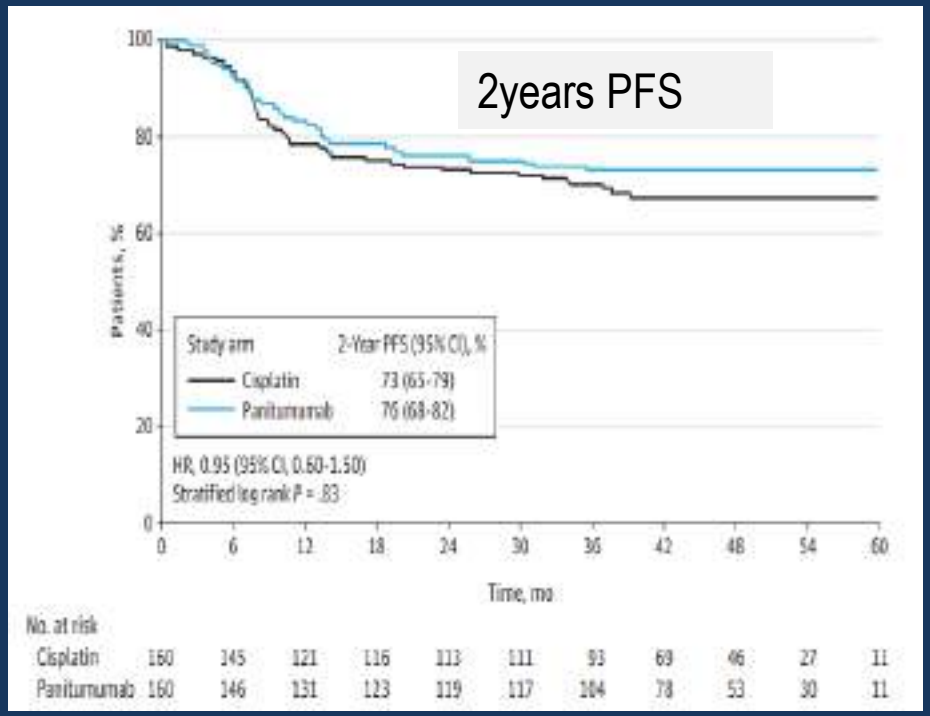
Concurrent chemoRT
70Gy/35fr,7 weeks +CDDP100 mg/m2

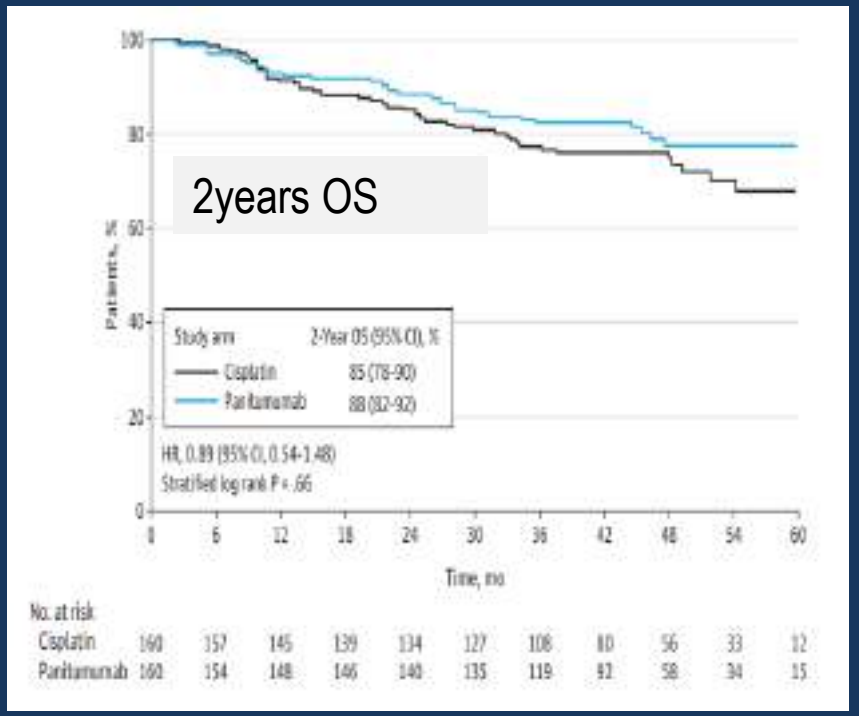
Accelarated RT 70Gy/35fr,6weeks
+
Panitumumab 9mg/kg q3weeks

follow-up

JAMA Oncol. 2017;3(2):220-226

Results- Median follow up 46 months





JAMA Oncol. 2017;3(2):220-226

Lancet 2019; 393:51–60

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

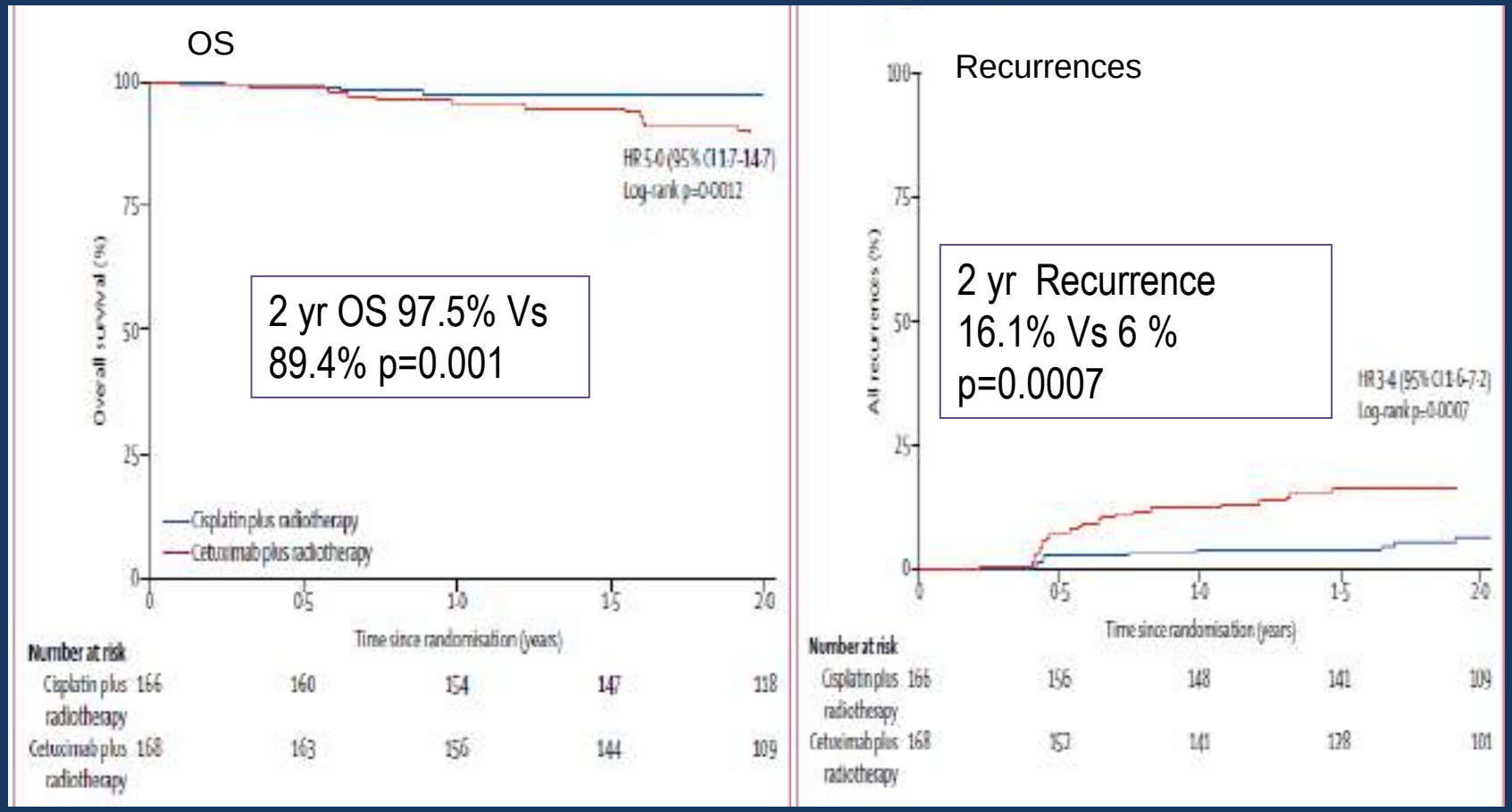
Hisham Mehanna, Max Robinson, Andrew Hartley, Anthony Kong, Bernadette Foran, Tessa Fulton-Lieuw, Matthew Dalby, Pankaj Mistry, Mehmet Sen, Lorcan O'Toole, Hoda Al Booz, Karen Dyker, Rafael Moleron, Stephen Whitaker, Sinead Brennan, Audrey Cook, Matthew Griffin, Eleanor Aynsley, Martin Rolles, Emma De Winton, Andrew Chan, Devraj Srinivasan, Joanna 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*

Lancet 2019; 393:40–50

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

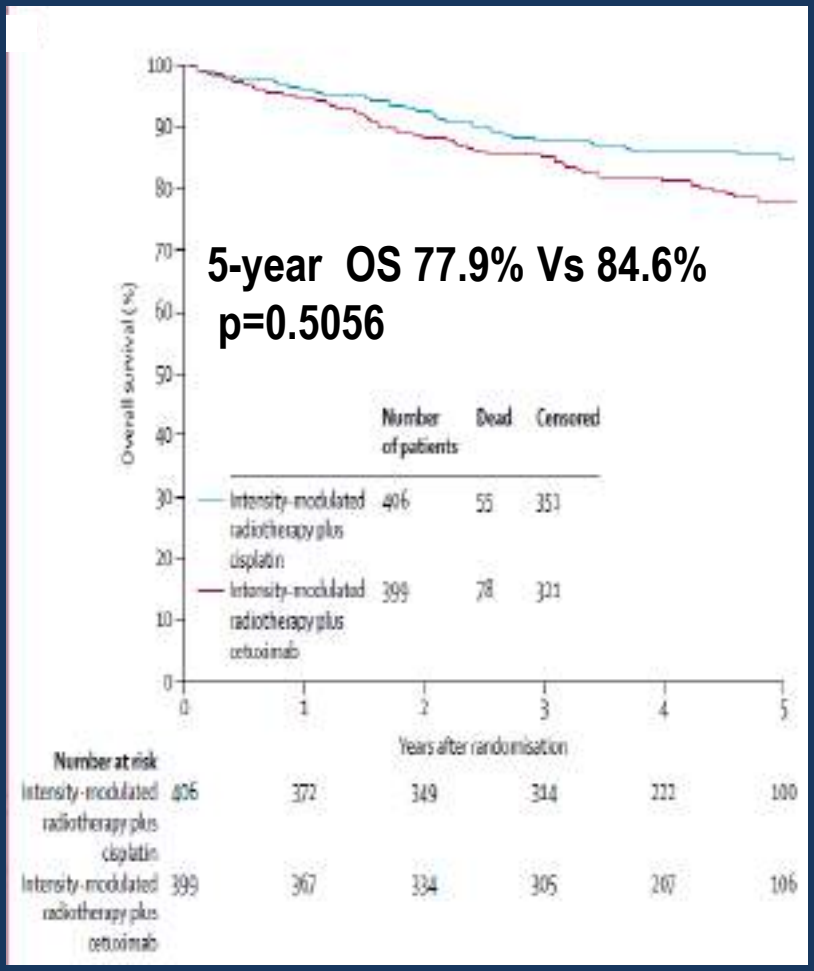
Maura L Gillison*, Andy M Trotti*, Jonathan Harris, Avraham Eisbruch, Paul M Harari, David J Adelstein, Erich M Sturgis, Barbara Burtness, John A Ridge, Jolie Ringash, James Galvin, Min Yao, Shlomo A Koyfman, Dukagjin M Blakaj, Mohammed A Razaq, A Dimitrios Colevas, Jonathan J Beitler, Christopher U Jones, Neal E Dunlap, Samantha A Seaward, Sharon Spencer, Thomas J Galloway, Jack Phan, James J Dignam, Quynh Thu Le

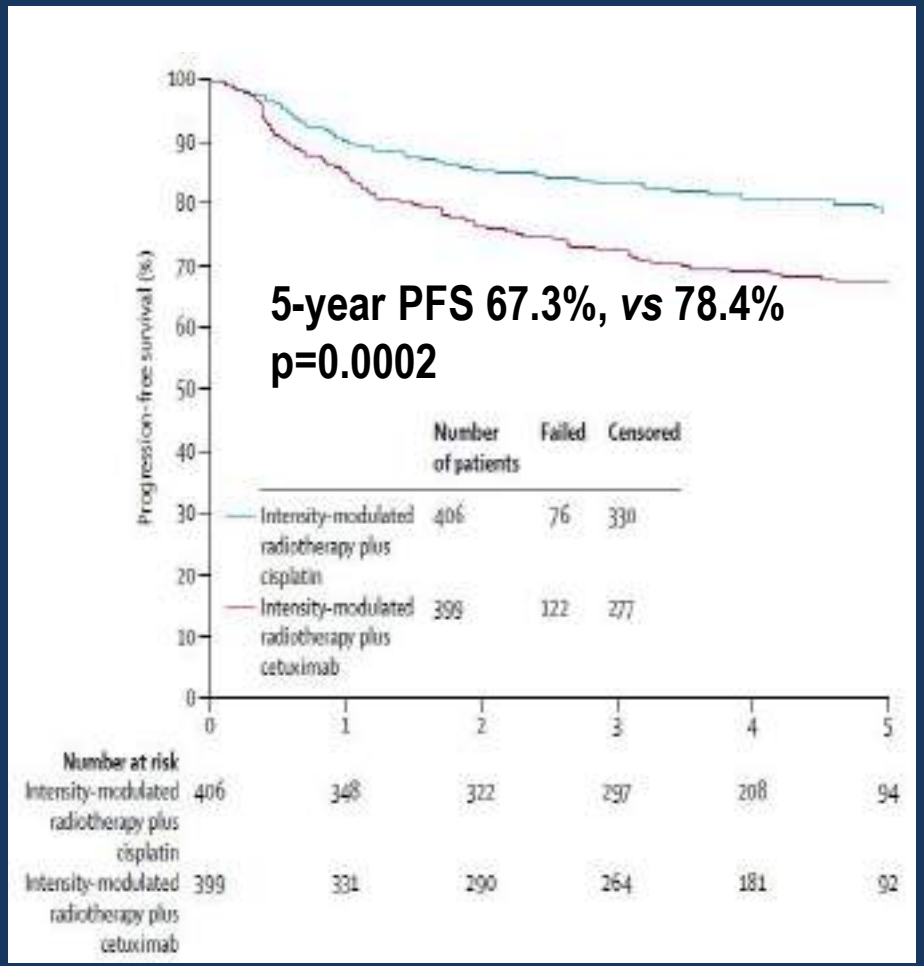
Results- Median follow up 22 months



Lancet 2019; 393:51–60

Median follow up 4.5 yrs





Lancet 2019; 393:40–50

Comparison

RTOG 1016	De- ESCALaTE
▪ Low risk and intermediate	▪ Only low risk
▪ Primary end point – OS	▪ Primary end point -Toxicity
▪ More long term follow up 4.5 yrs	▪ Median follow up 22 months
▪ Number of patients-987	▪ Number of patients -348
▪ Difference in toxicity	▪ No difference in toxicities
▪ OS better with CDDP plus RT	▪ OS better with CDDP plus RT

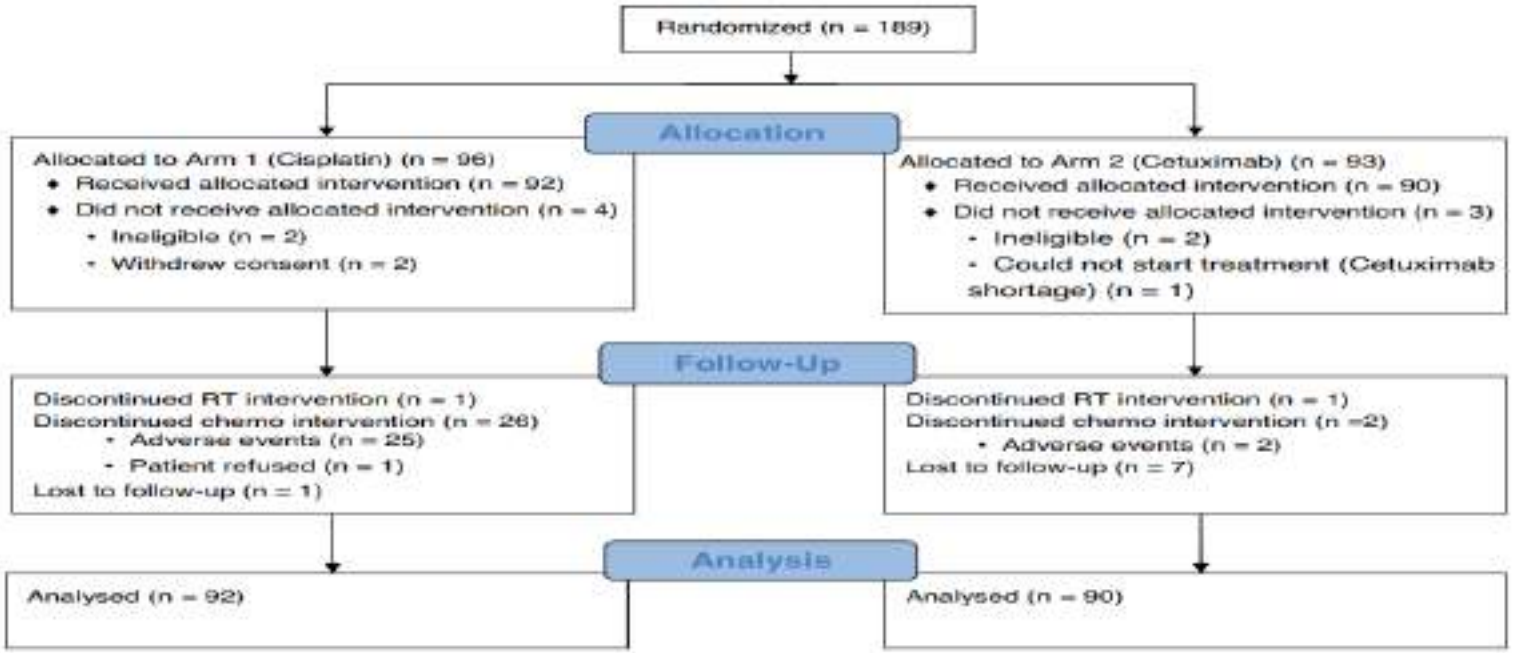
MD Anderson Symptom Inventory Head and Neck Symptom Severity Scale

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

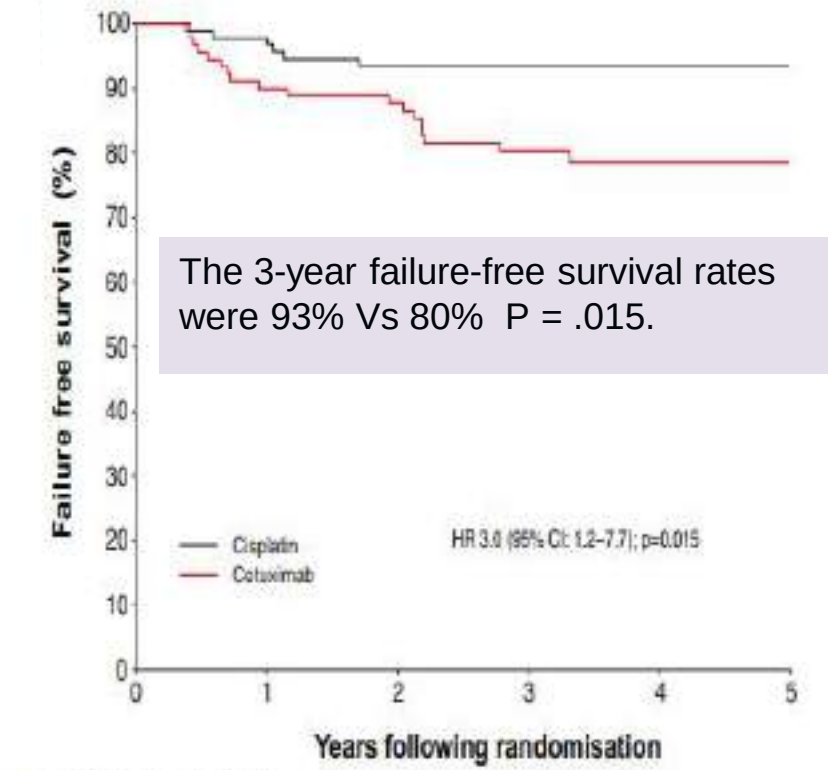
Randomized Trial of Radiation Therapy With Weekly Cisplatin or Cetuximab in Low-Risk HPV-Associated Oropharyngeal Cancer (TROG 12.01) — A Trans-Tasman Radiation Oncology Group Study

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[†††,‡‡‡]

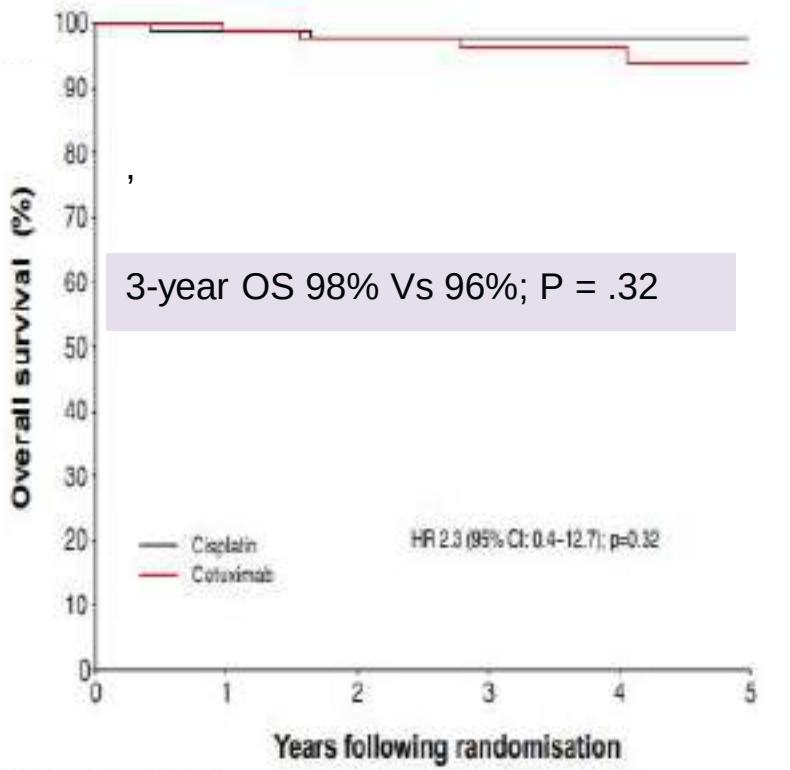


Int J Radiation Oncol Biol Phys, Vol. 111, No. 4, pp. 876–886, 2021

Median follow up- 4.1 yrs



The 3-year failure-free survival rates were 93% Vs 80% P = .015.



3-year OS 98% Vs 96%; P = .32

Int J Radiation Oncol Biol Phys, Vol. 111, No. 4, pp. 876−886, 2021

Anti EGFR therapy in LAHNSCC

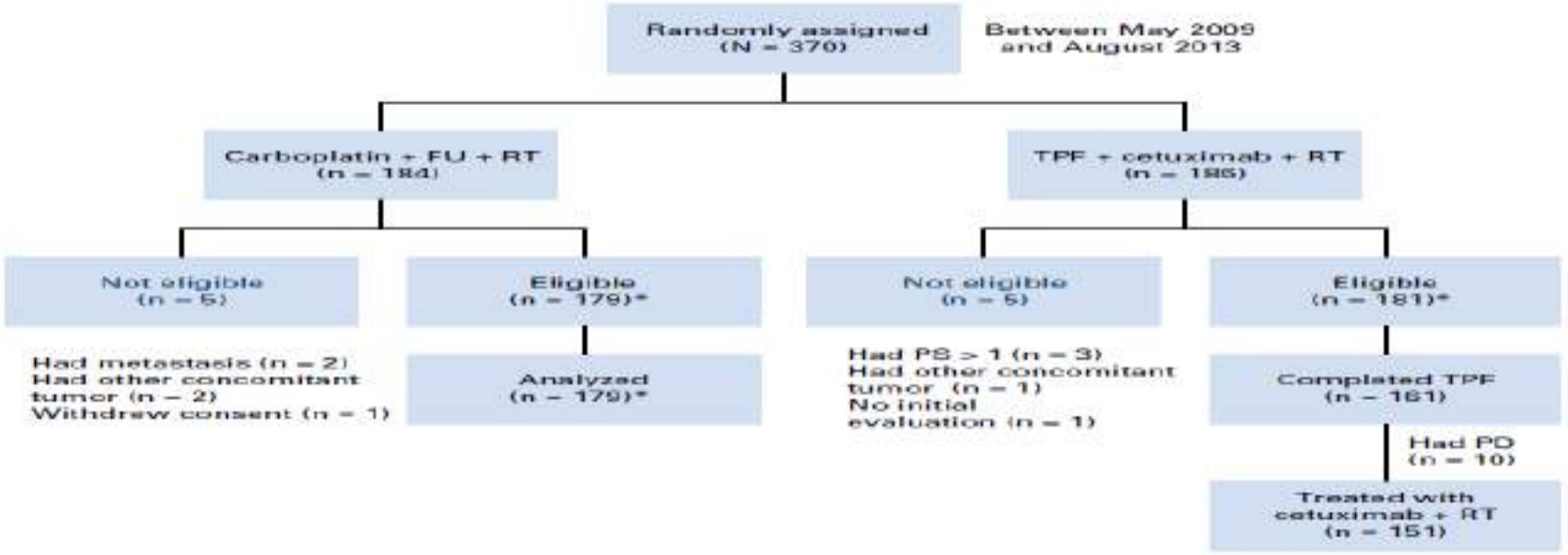
- Radiotherapy Vs RT + Anti EGFR therapy – Increased OS, LCR with toxicity
- CCRT Vs CCRT plus Anti EGFR – No OS benefit , toxicity , LCR & PFS benefit in one study
- RT + Cetuximab Vs Chemo + Cetuximab + RT – Added benefit
- CCRT Vs RT + Anti EGFR therapy- Inferior outcomes with different toxicity
- IC followed by RT + Cetuximab Vs CCRT
- RT + Cetuximab Vs CDDP+ RT after TPF

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

N=370
N2& N3 patients
Primary end point-PFS

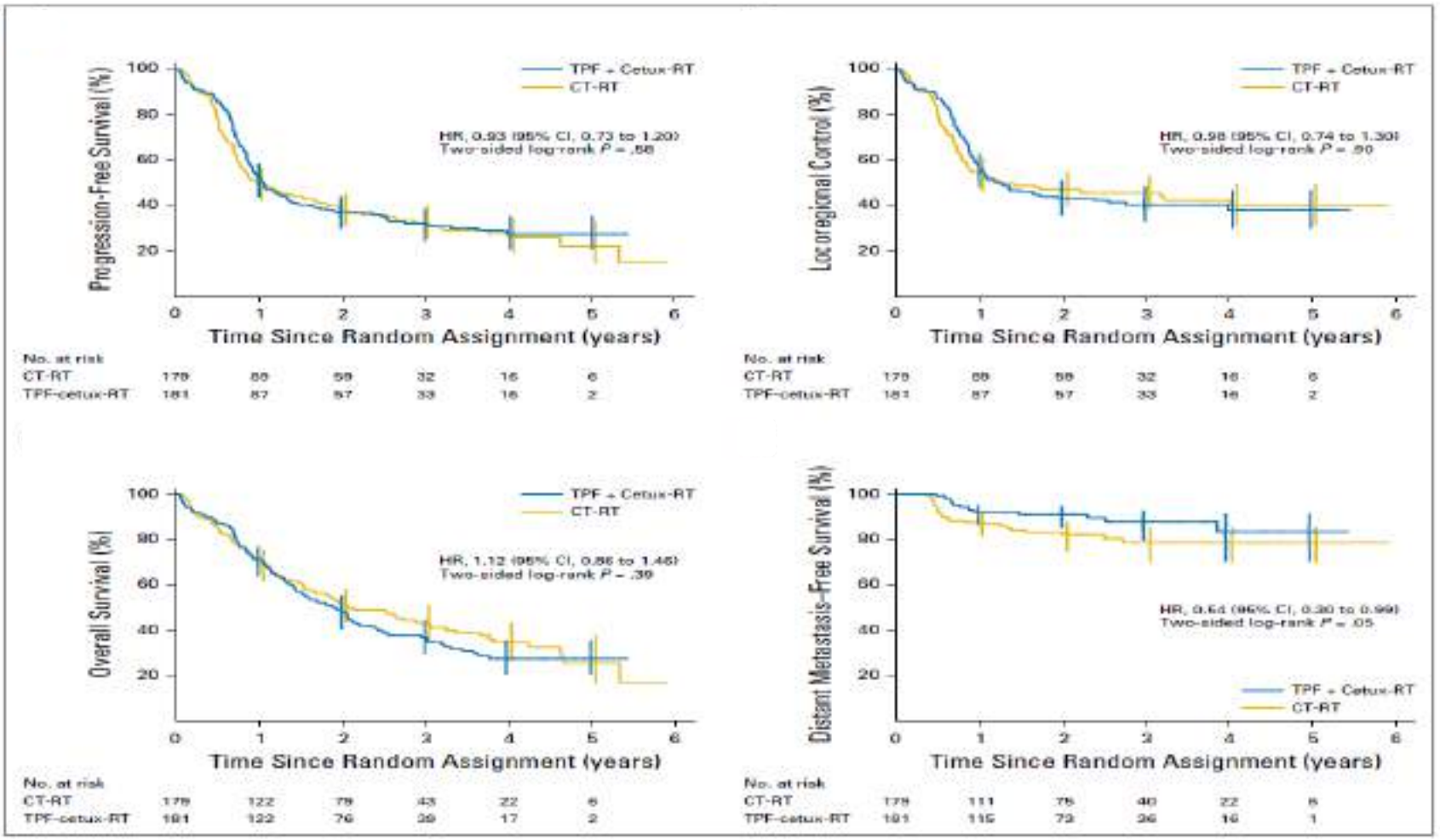
Induction Chemotherapy Followed by Cetuximab Radiotherapy Is Not Superior to Concurrent Chemoradiotherapy for Head and Neck Carcinomas: Results of the GORTEC 2007-02 Phase III Randomized Trial

Lionnel Geoffrois, Laurent Martin, Dominique De Raucourt, Xu Shan Sun, Yungan Tao, Philippe Maingon, Joëlle Buffet, Yoann Pointreau, Christian Sire, Claude Tuchais, Emmanuel Babin, Alexandre Coutte, Frédéric Rolland, Marie-Christine Kaminsky, Marc Alfonsi, Michel Lapeyre, Marie Salion, Cédric Lafond, Eric Jadaud, Bernard Gery, Ayman Zawadi, Jean-Marc Tourani, Cédric Khoury, Anne Rose Henry, Ali Hasbini, François Guichard, Christian Borel, Nicolas Meert, Pierre Guillet, Marie-Hélène Calais, Pascal Garaud, and Jean Bourhis



J Clin Oncol 2018;36:3077-3083

Median follow up 2.8 yrs



J Clin Oncol 2018;36:3077-3083

Oncology

Clinical Study

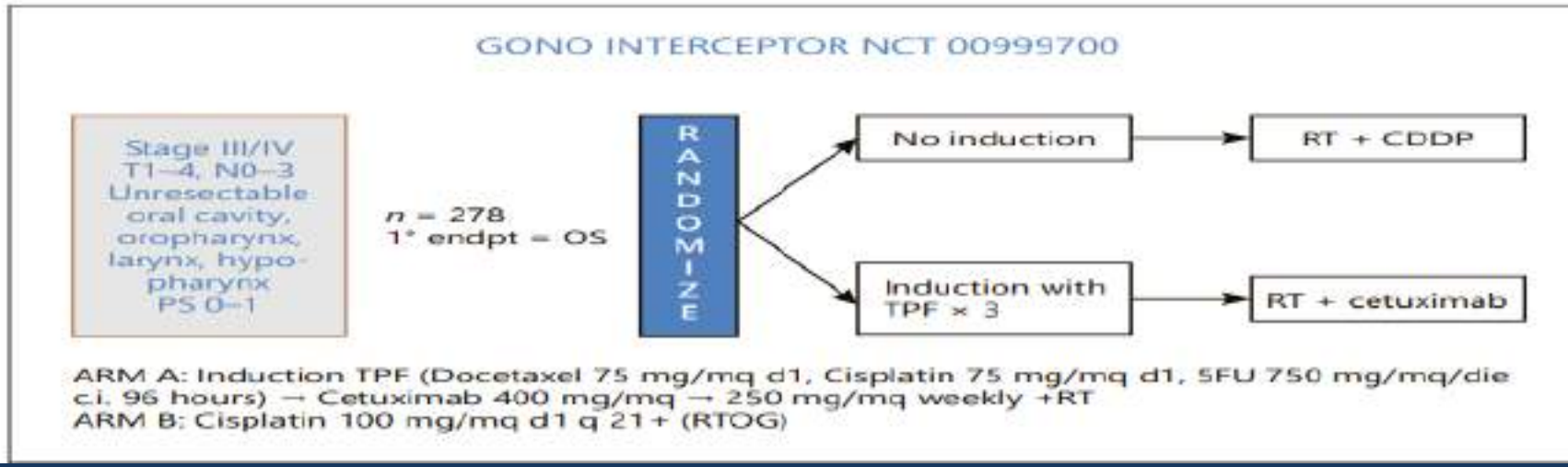
Oncology 2020;98:763–770
DOI: 10.1159/000507733

Received: March 10, 2020
Accepted: March 25, 2020
Published online: July 6, 2020

Phase III Randomized Study of Induction Chemotherapy Followed by Definitive Radiotherapy + Cetuximab Versus Chemoradiotherapy in Squamous Cell Carcinoma of Head and Neck: The INTERCEPTOR-GONO Study (NCT00999700)

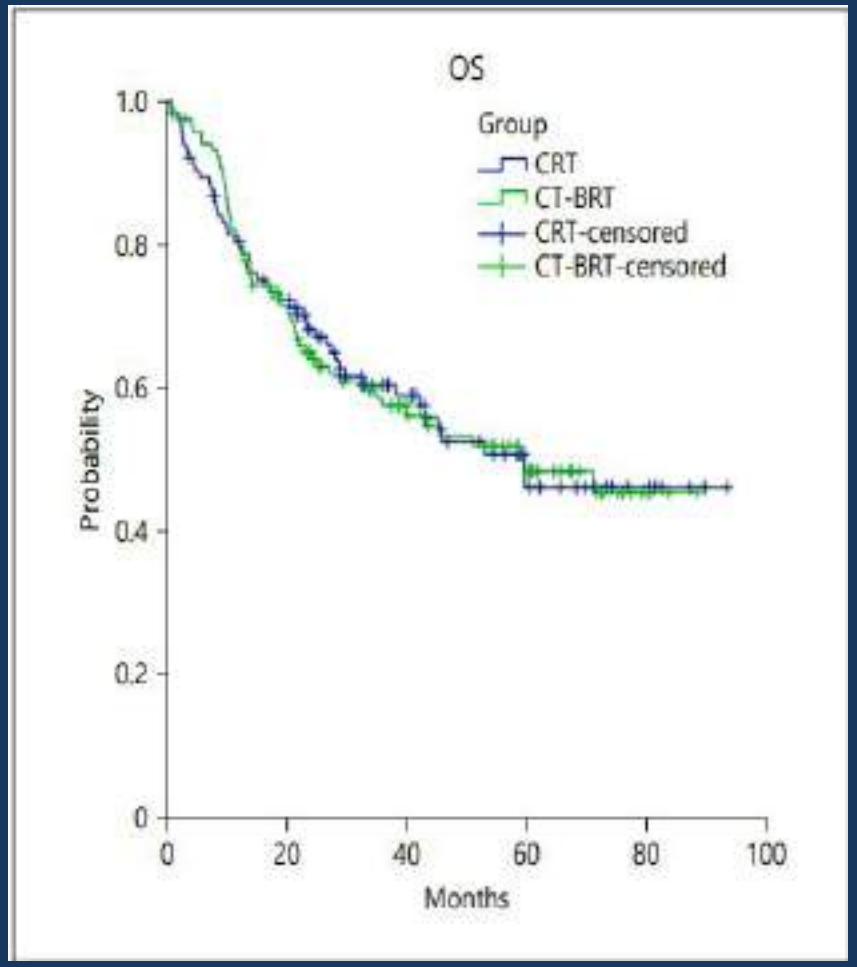
Marco Carlo Merlano[a] Nerina Denaro[a] Stefania Vecchio[b] Lisa Licitra[c]
Paola Curcio[d] Marco Benasso[e] Almalina Bagicalupo[f] Gianmauro Numico[g]
Elvio Russi[h] Renzo Corvo'[b, f] Paolo Bruzzi[i] on behalf of INTERCEPTOR trialists

[a]Medical Oncology, St. Croce & Carle University Teaching Hospital and ARCO Foundation, Cuneo, Italy; [b]Medical Oncology, IRCCS San Martino, IST National Cancer Institute and University of Genova, Genova, Italy; [c]Head and Neck Medical Oncology, Fondazione IRCCS – Istituto Nazionale dei Tumori, University of Milan, Milan, Italy; [d]Trials Office, Medical Oncology, St. Croce & Carle University Teaching Hospital, Cuneo, Italy; [e]Medical Oncology, San Paolo General Hospital, Savona, Italy; [f]Radiation Oncology, San Martino Hospital, Genova, Italy; [g]Medical Oncology, SS Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; [h]Radiation Oncology, St. Croce & Carle University Teaching Hospital, Cuneo, Italy; [i]Statistic Unit, Genova University, Genova, Italy



Oncology 2020;98:763–770

Efficacy and toxicity



Toxicity data on 228 patients

Toxicity	Arm A (115 patients)	Arm B (113 patients)	*p*
WBC G3-4	14	11	NS
Neutropenia G3	10	2	0.04*
Anemia G3	3	3	NS
Mucositis G3-4	48	43	NS
TPN	30	34	NS
Median TPN duration (range), days	7.7 (3–59)	8.9 (3–48)	
Body weight loss G2-3	21	36	0.017
Skin toxicity G2-3	73	42	0.00007
Infection/pneumonitis	6/0	9/2	NS

Oncology 2020;98:763–770

Anti EGFR therapy in LAHNSCC

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Oral Oncology 134 (2022) 106087

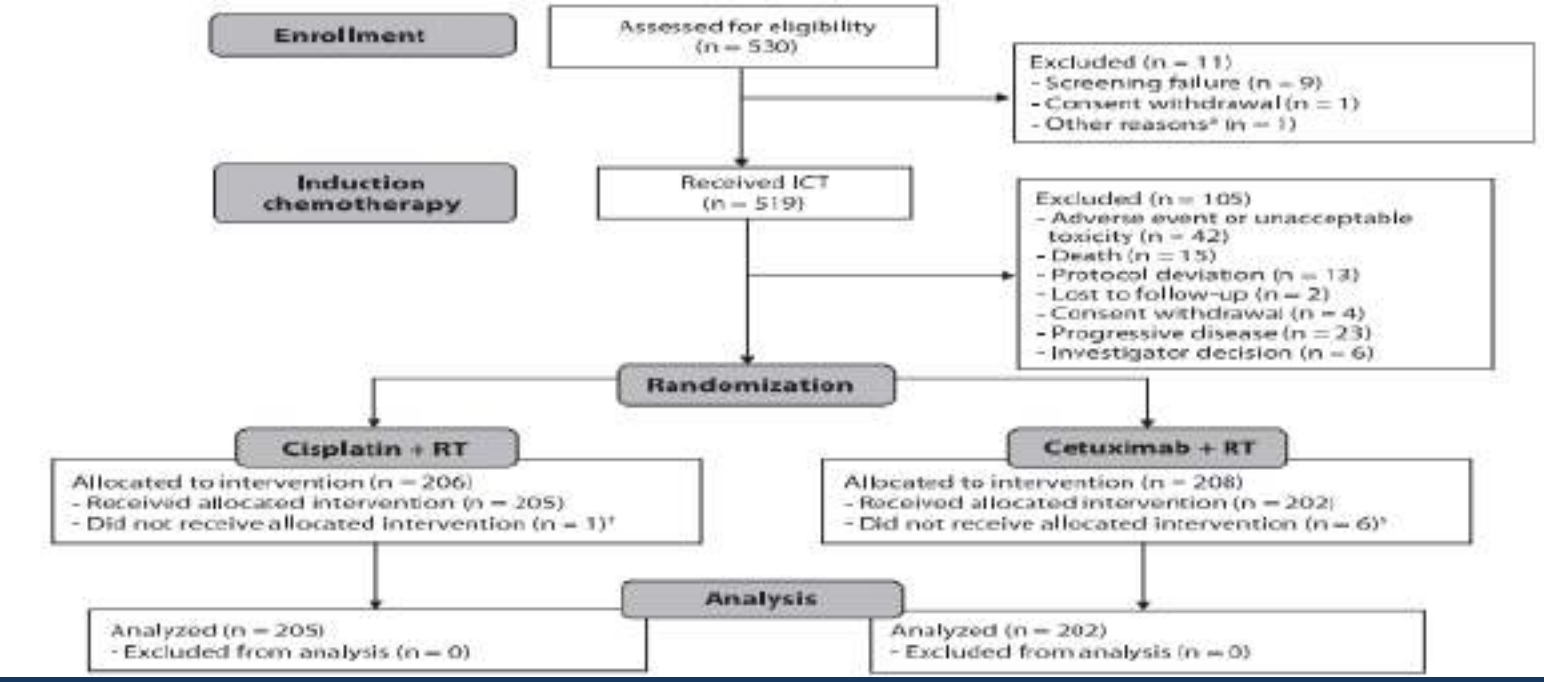
Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

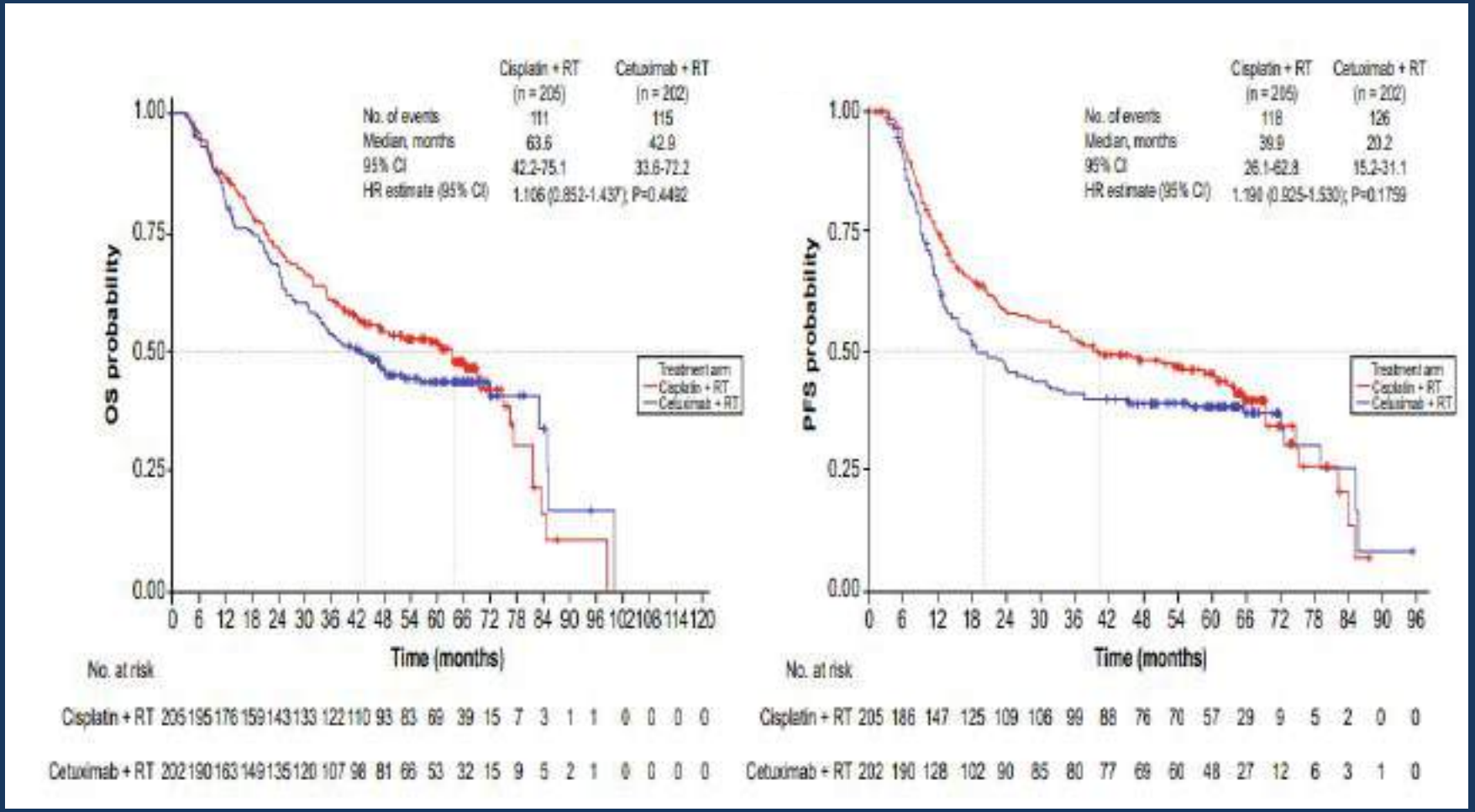
Randomized phase 3 noninferiority trial of radiotherapy and cisplatin vs radiotherapy and cetuximab after docetaxel-cisplatin-fluorouracil induction chemotherapy in patients with locally advanced unresectable head and neck cancer

Ricardo Hitt [a,*], Ricard Mesía [b], Alicia Lozano [c], Lara Iglesias Docampo [d], Juan J. Grau [e], Miren Taberna [f], Jordi Rubió-Casadevall [g], Javier Martínez-Trufero [h], Edel del Barco Morillo [i], Carlos García Girón [j], Sergio Vázquez Estévez [k], Beatriz Cirauqui [l], Juan Jesús Cruz-Hernández [m]



Oral Oncology 134 (2022) 1060-87

Efficacy



Oral Oncology 134 (2022) 106087

Anti EGFR therapy in LAHNSCC

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- CCRT Vs CCRT plus Mob– No OS benefit , toxicity ,LCR & PFS benefit (1study)
- RT + Cetuximab Vs Chemo + Cetuximab + RT – Added benefit
- CCRT Vs RT + Anti EGFR therapy- Inferior outcomes with different toxicity
- IC followed by RT + Cetuximab Vs CCRT- No benefit
- RT + Cetuximab Vs CDDP+ RT after TPF- Not non inferior

CANCER STUDIES AND MOLECULAR MEDICINE

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Research

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Volume 3 : Issue 1
Article Ref. #: 1000CSMMOJ3114

Current Status of Anti Epidermal Growth Factor Receptor Therapy in the Curative Treatment of Head and Neck Squamous Cell Carcinoma

Cessal Thommachan Kainickal, MD*; Aparna M. P., MD; Rejnish Kumar Ravi Kumar, MD; Malu Rafi, DNB; Kunnambath Ramadas, MD, PhD

Department of Radiation Oncology, Regional Cancer Centre, Trivandrum, Kerala, India

Anti EGFR- Adjuvant setting

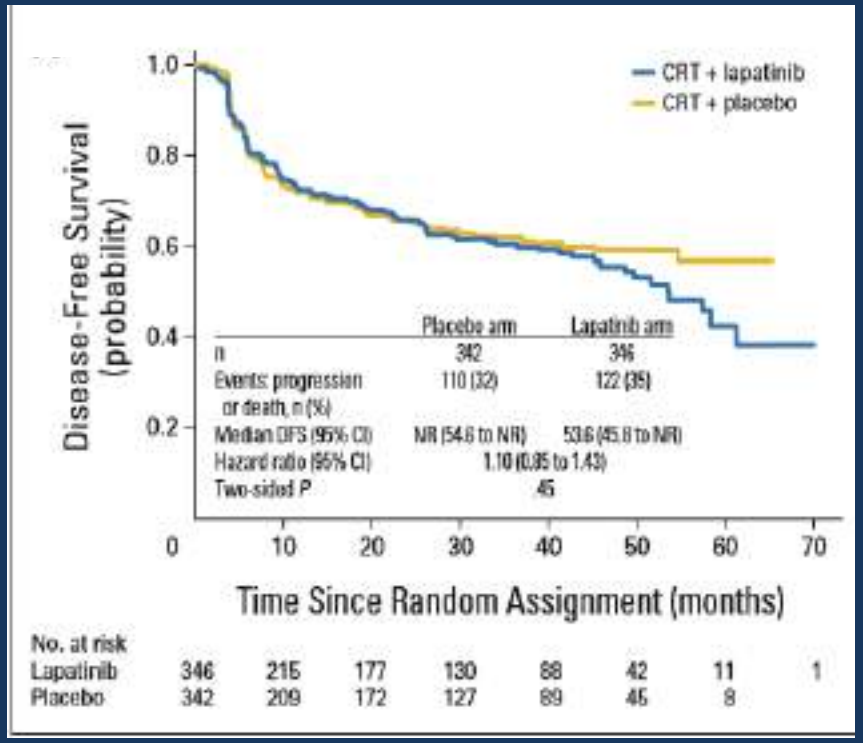
VOLUME 33 · NUMBER 35 · DECEMBER 10 2015

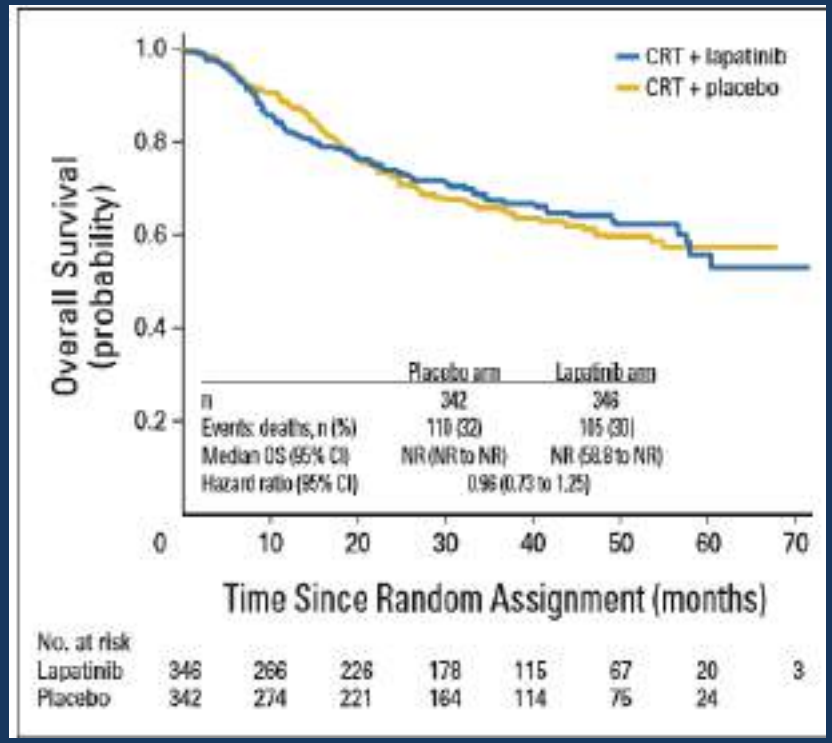
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Postoperative Adjuvant Lapatinib and Concurrent Chemoradiotherapy Followed by Maintenance Lapatinib Monotherapy in High-Risk Patients With Resected Squamous Cell Carcinoma of the Head and Neck: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study

Kevin Harrington, Stephane Temam, Hisham Mehanna, Anil D'Cruz, Mitish Jain, Ida D'Onofrio, Georgy Manikhas, Zsuzsanna Horvath, Yan Sun, Stefan Dietzsch, Pavol Dubinsky, Petra Holeckova, Iman El-Hariry, Natalie Franklin, Nigel Biswas-Baldwin, Philippe Legenne, Paul Wissel, Thelma Netherway, John Farrell, Catherine Ellis, Jing Wang-Silvanto, Mayur Amonkar, Nazma Ahmed, Sergio Santillana, and Jean Bourhis

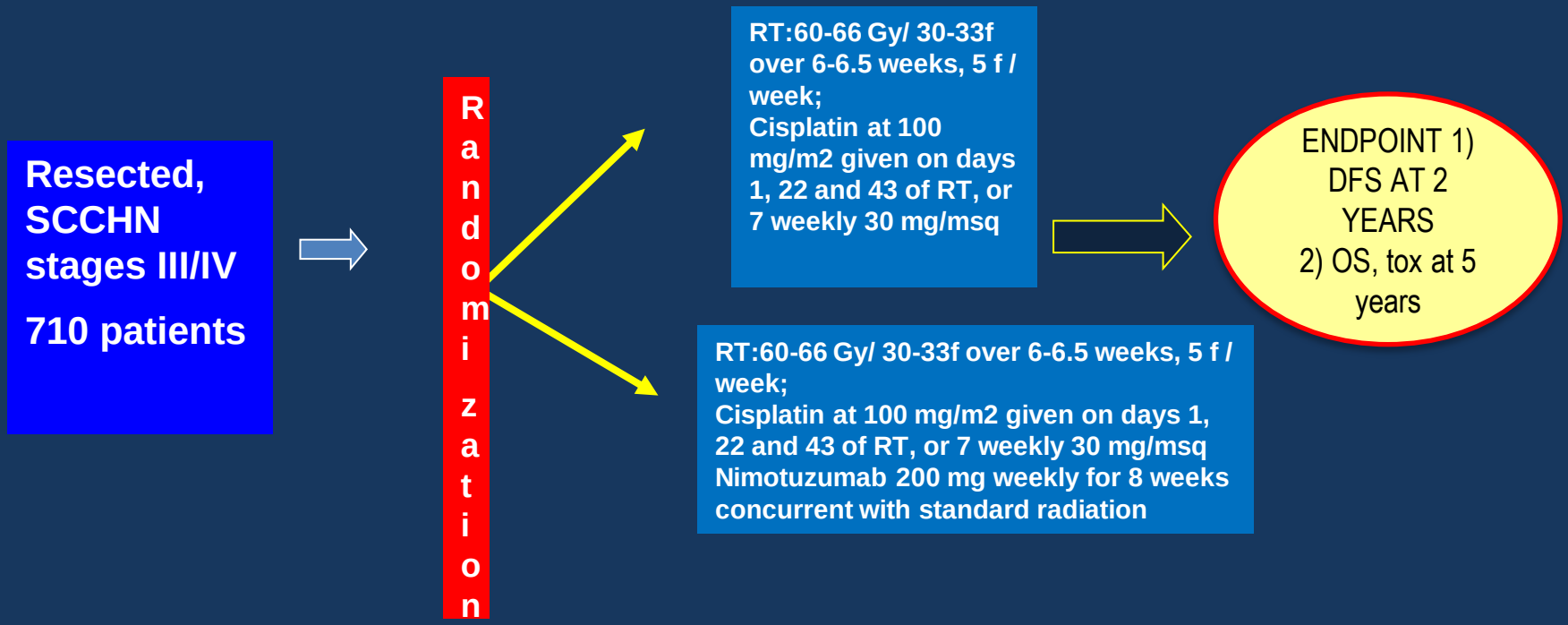




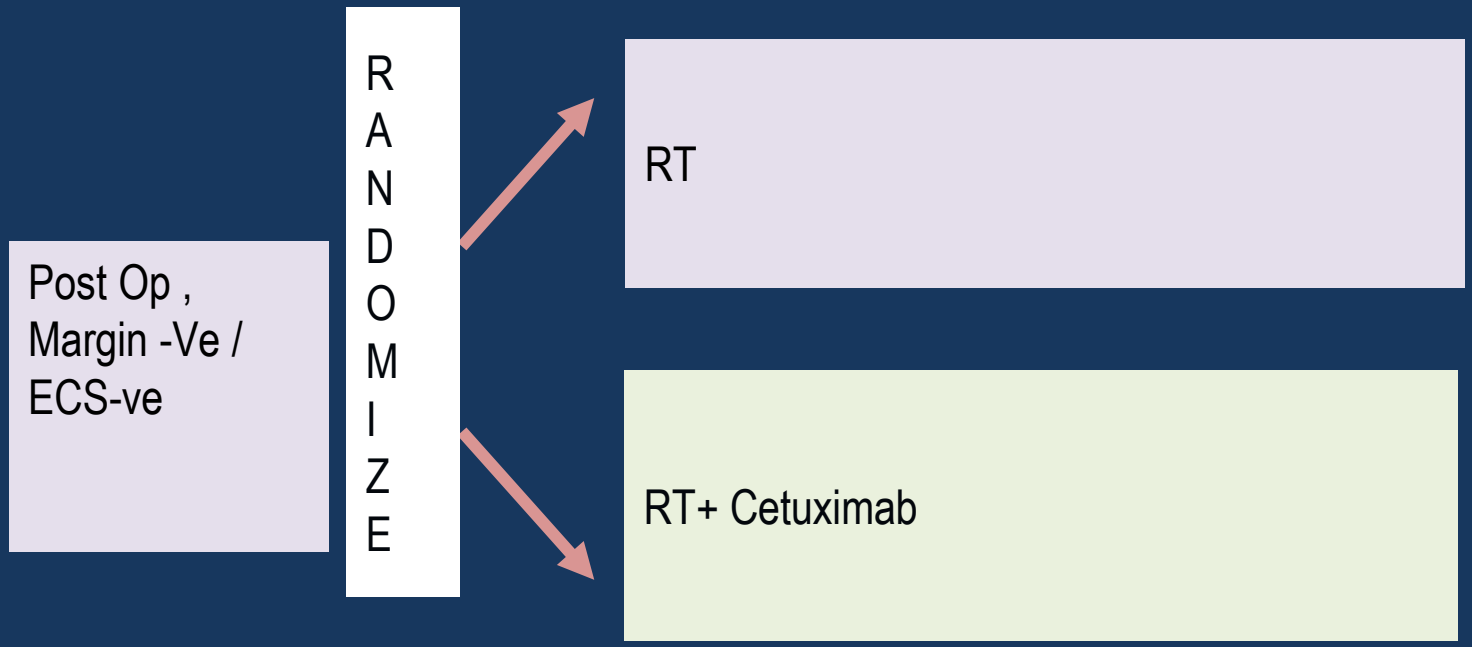
Clinical trial design

Phase III , multicentric , randomized, two arms, controlled study.

- Stratified according to tumor primary site, nodal status, presence/absence of microscopic margins/adverse features and investigator center
- Patients pool: Post-curative surgery: stages III, IV SCCHN



Phase III Trial comparing adjuvant RT +/- Cetuximab RTOG 0920



One or more of the following:

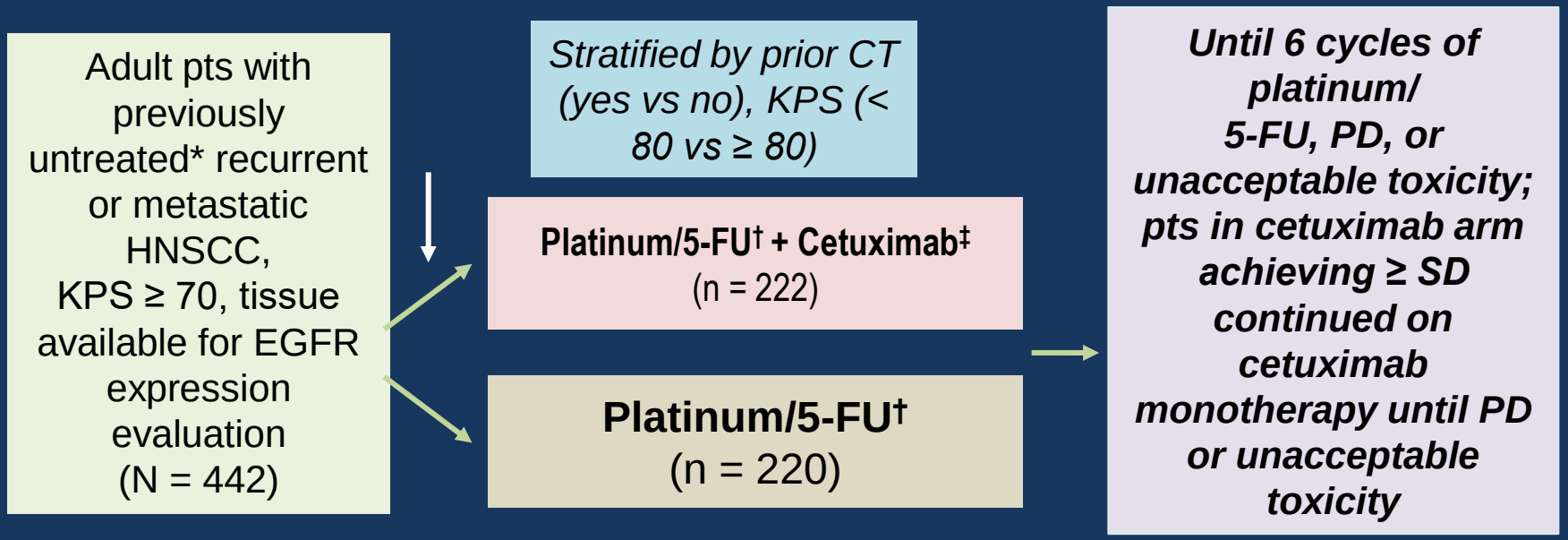
- PNI
- LVI
- 1 LN > 3cm
- 2 more more LN < 6 cm
- Close Margins
- T3 or T4a primary tumor
- T2 with > 5mm depth

Primary end point - OS

https://clinicaltrials.gov/ct2/show/NCT00956007

Anti EGFR - recurrent /metastatic HNSCC

EXTREME: Phase III Trial of Platinum/5-FU ± Cetuximab in First-line R/M HNSCC

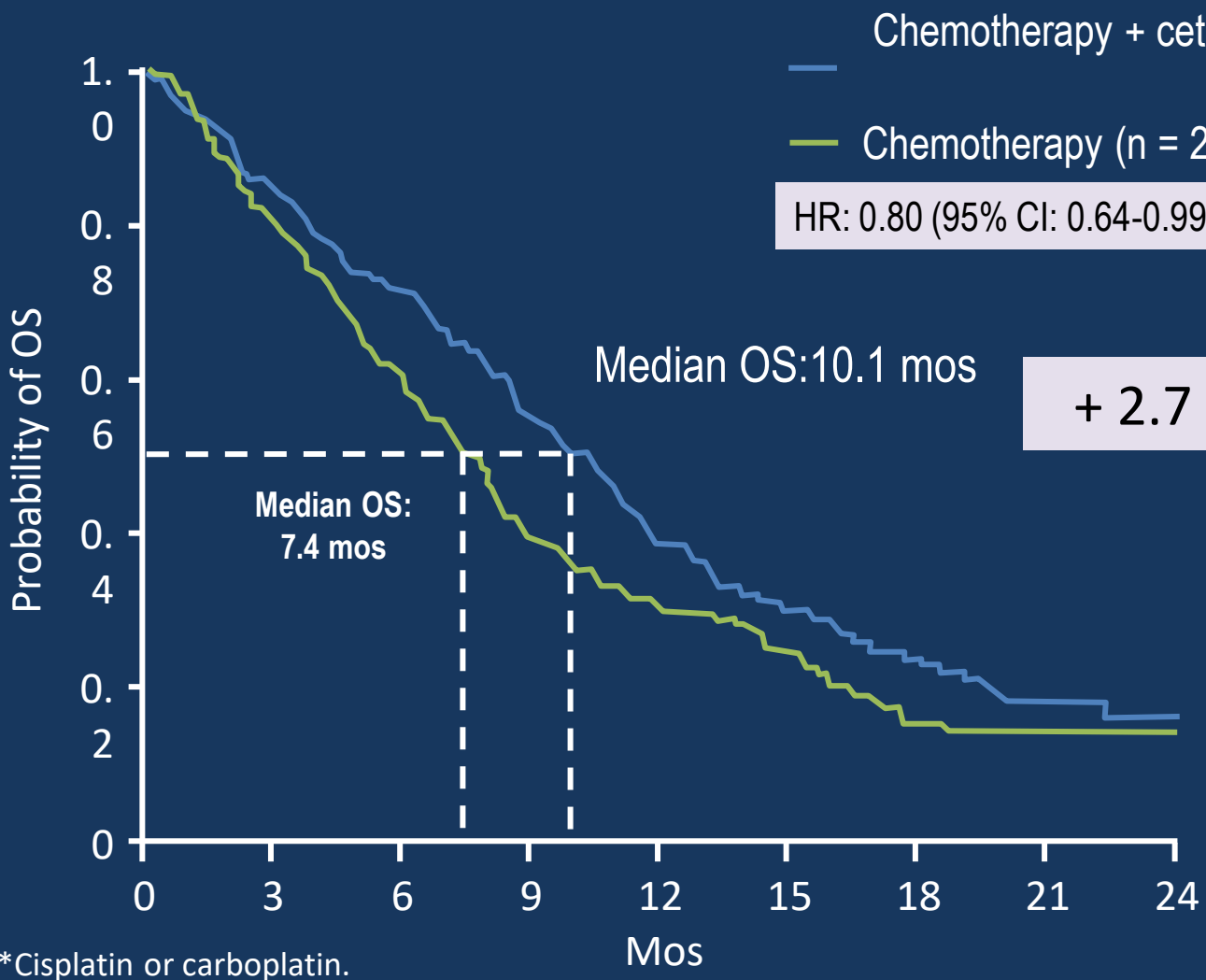


*Prior systemic CT permitted if component of multimodal treatment for locally advanced disease completed > 6 mos before entering study.
†Platinum agent either cisplatin 100 mg/m^2 IV on Day 1 or carboplatin AUC 5 mg/mL/min IV on Day 1 + 5-FU at 1000 mg/m^2/day x 4 days Q3W. ‡Cetuximab given at initial dose of 400 mg/m^2 IV followed by 250 mg/m^2 weekly administered ≥ 1 h prior to CT.

- Primary endpoint: OS
- Secondary endpoints: best overall response, DoR, TTF, safety

Vermorken JB, et al. N Engl J Med. 2008;359:1116-1127.
ClinicalTrials.gov. NCT00122460.

EXTREME Chemotherapy* + Cetuximab: OS



*Cisplatin or carboplatin.

Vermorken JB, et al. N Engl J Med. 2008;359:1116-1127.
ClinicalTrials.gov. NCT00122460.

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Targeted Therapy in Recurrent or Metastatic Head and Neck Carcinoma

Abstract

This review article is trying to high light the current evidence to support the use of targeted therapy for the best management practices for patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Platinum based chemotherapy is the cornerstone of palliation for patients with R/M HNSCC .Platinum doublets induce higher response rates at the cost of toxicity, but do not demonstrate a survival advantage. EGFR inhibitors, including monoclonal antibodies and tyrosine kinase inhibitors, have achieved only modest success in R/M HNSCC. Immunotherapy represents an attractive treatment strategy for R/M HNSCC, with promising preliminary results. Despite therapeutic advances, prognosis remains poor for patients with R/M HNSCC, illustrating the importance of identifying predictive biomarkers and finding ways to overcome mechanisms of resistance.

Keywords: Targeted therapy; Head and neck carcinoma; Metastatic or recurrent disease

Review Article

Volume 2 Issue 3 - 2018

Cessal Thommachan Kainickal, Aparna MP, Rejnish Ravi Kumar, Malu Rafi and Kunnambath Ramadas*

Department of Radiation Oncology, Regional Cancer Center, India

***Corresponding author:** Kunnambath Ramadas, Professor, Department of Radiation Oncology, Regional Cancer Centre, Trivandrum, Kerala, India -695011, Email: ramdasrcc@gmail.com

Received: January 25, 2018 | **Published:** February 09, 2018

Targeted therapy

Anti EGFR agents

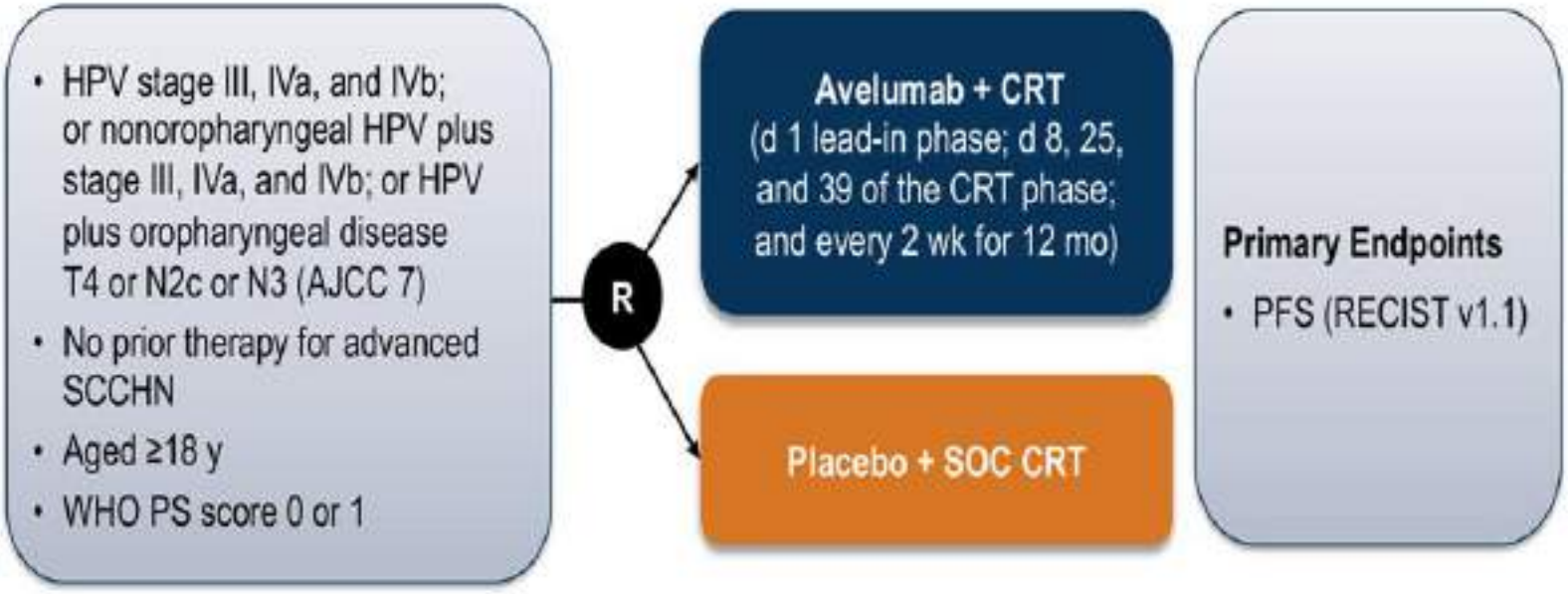
Immunotherapy

Inhibitor of Apoptosis Proteins

LAHNSCC

JAVELIN Head and Neck 100: Schema[1]

Phase 3, randomized, double-blind, placebo-controlled study

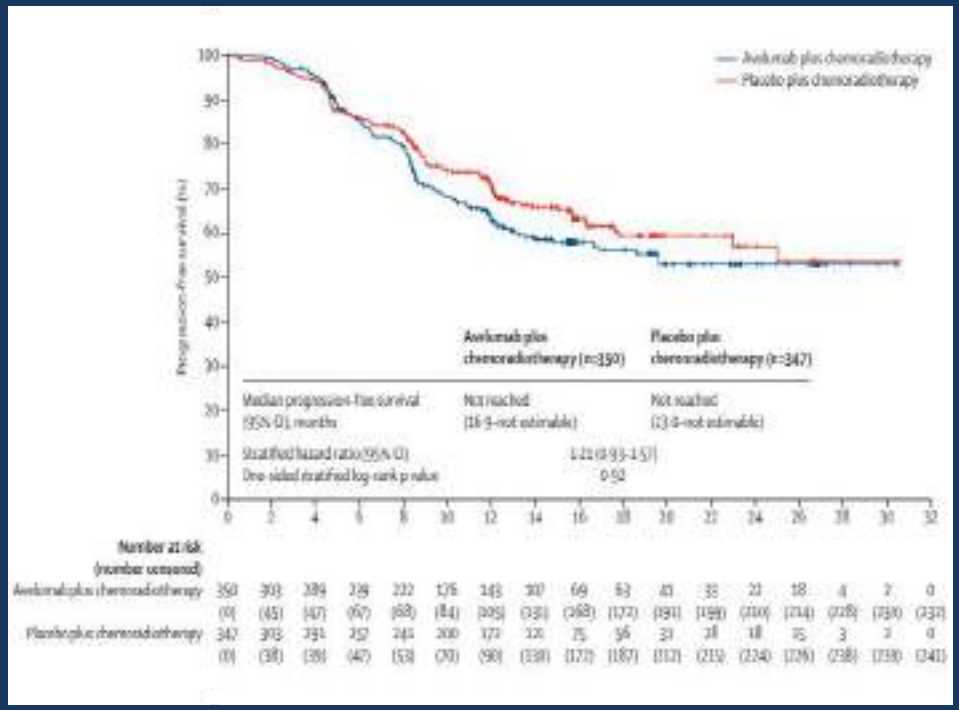


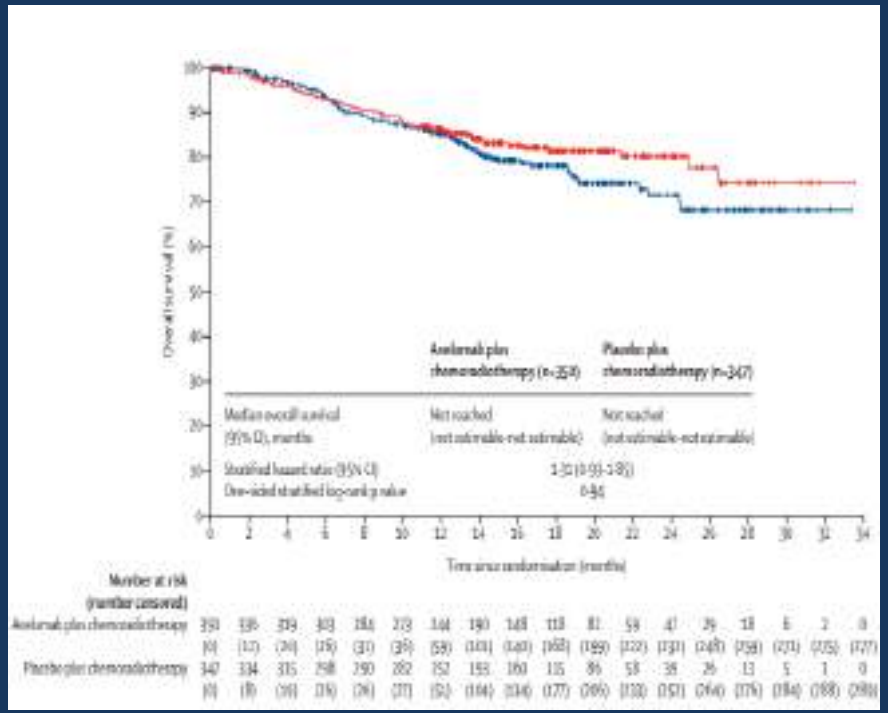
1. Lee N et al. *Lancet Oncol*. 2021;22:450-462.

Lancet Oncol 2021; 22: 450–62

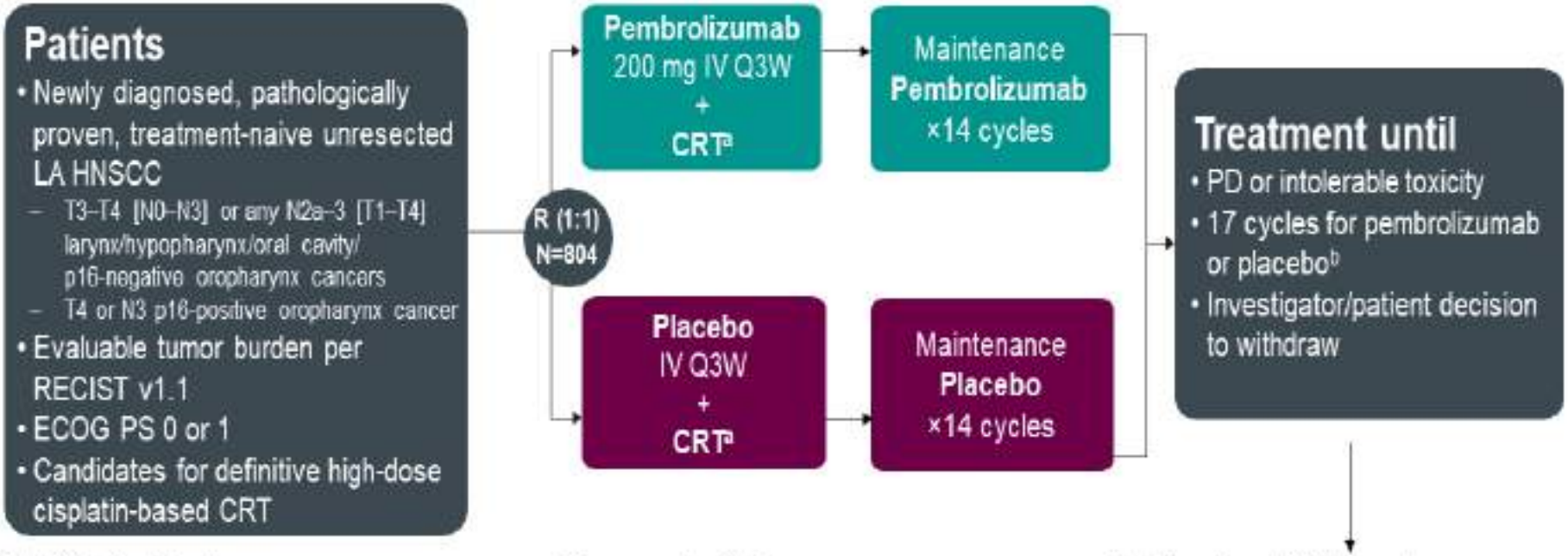
Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial

Nancy Y Lee, Robert L Ferris*, Amanda Psyrri, 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**





KEYNOTE-412 Study Design (NCT03040999)



Stratification Factors
- Radiotherapy regimen (AFX vs SFX)
- Tumor site/p16 status (oropharynx [p16+ vs p16-] or larynx/hypopharynx/oral cavity)
- Disease stage (III vs IV)

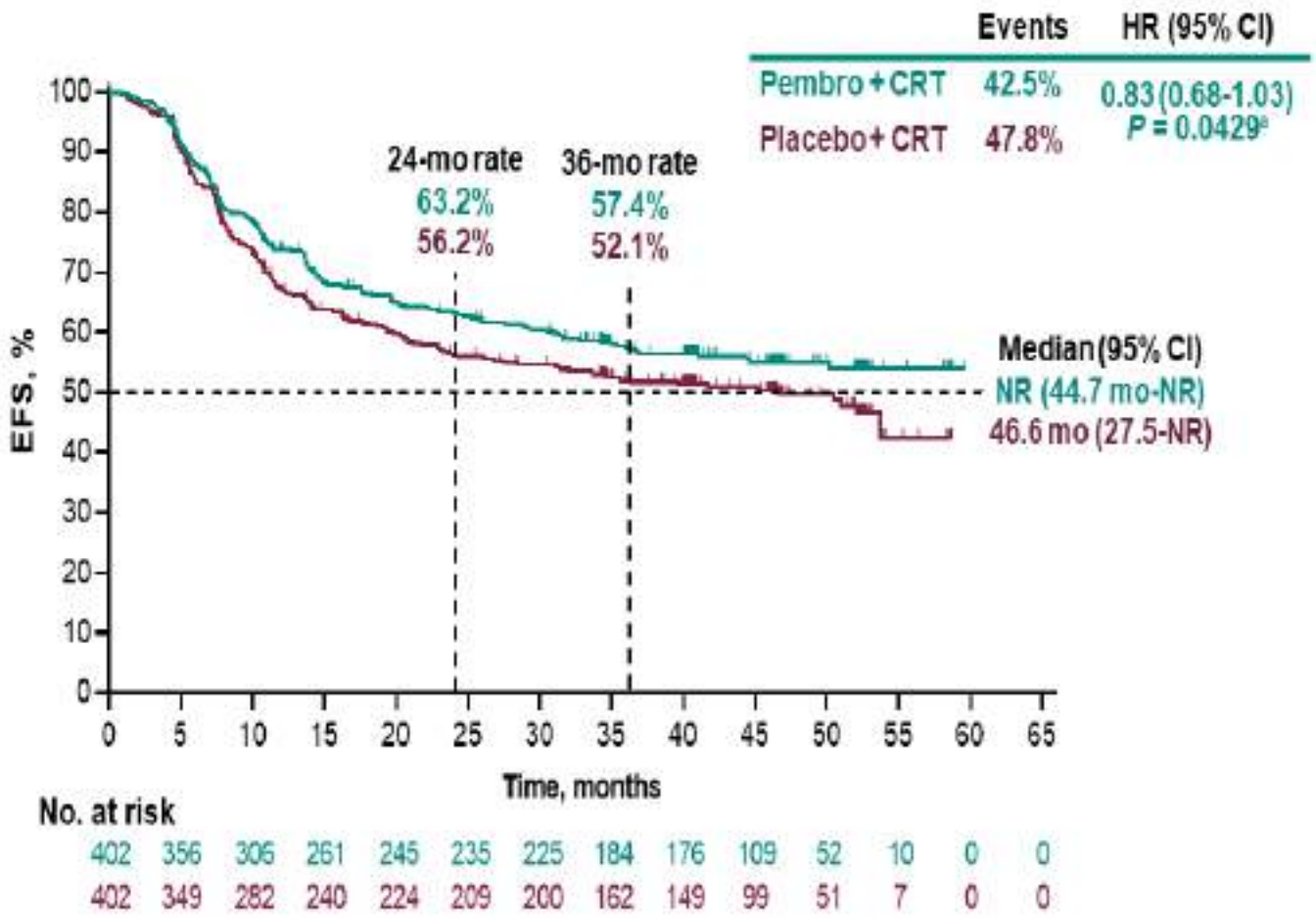
Primary endpoint
- Event-free survival (EFS)

Secondary endpoints included:
- OS
- Safety/tolerability

Post-treatment follow-up to assess
- Safety
- Disease status
- Survival

[a]CRT included cisplatin (100 mg/m^2, Q3W) and accelerated fractionation (AFX) (70 Gy, 6 fractions/week for 5 weeks and then 5 fractions for the 6th week, 35 fractions in total) or standard fractionation (SFX) (70 Gy, 5 fractions/week for 7 weeks, 35 fractions in total). [b]A pembrolizumab/placebo priming dose was given 1 week before CRT, followed by 2 doses during CRT and 14 doses of maintenance therapy after CRT, for a total of 17 doses.

Event-Free Survival, ITT Population

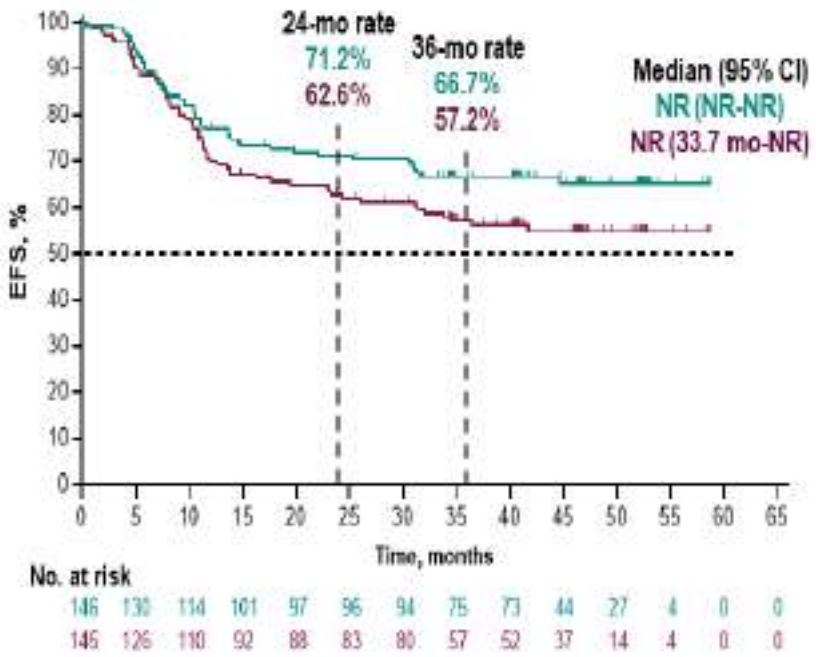


[a]P value did not meet the superiority threshold of one-sided α of 0.0242.
Data cutoff date: May 31, 2022.

EFS and OS in Patients With PD-L1 CPS ≥20 (Post Hoc Analysis)

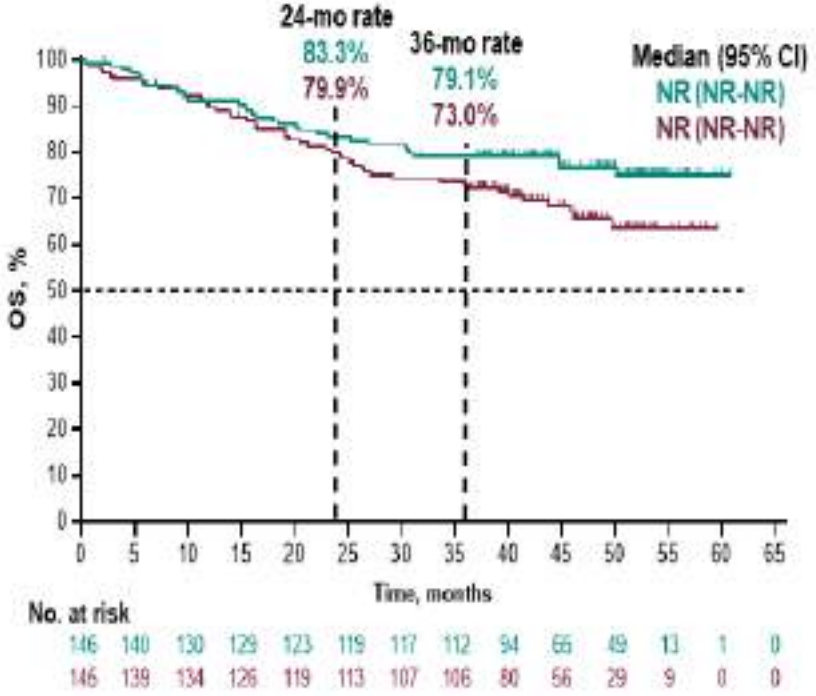
EFS

	Events	HR (95% CI)
Pembro + CRT	32.2%	0.73 (0.49-1.06)
Placebo + CRT	42.1%	



OS

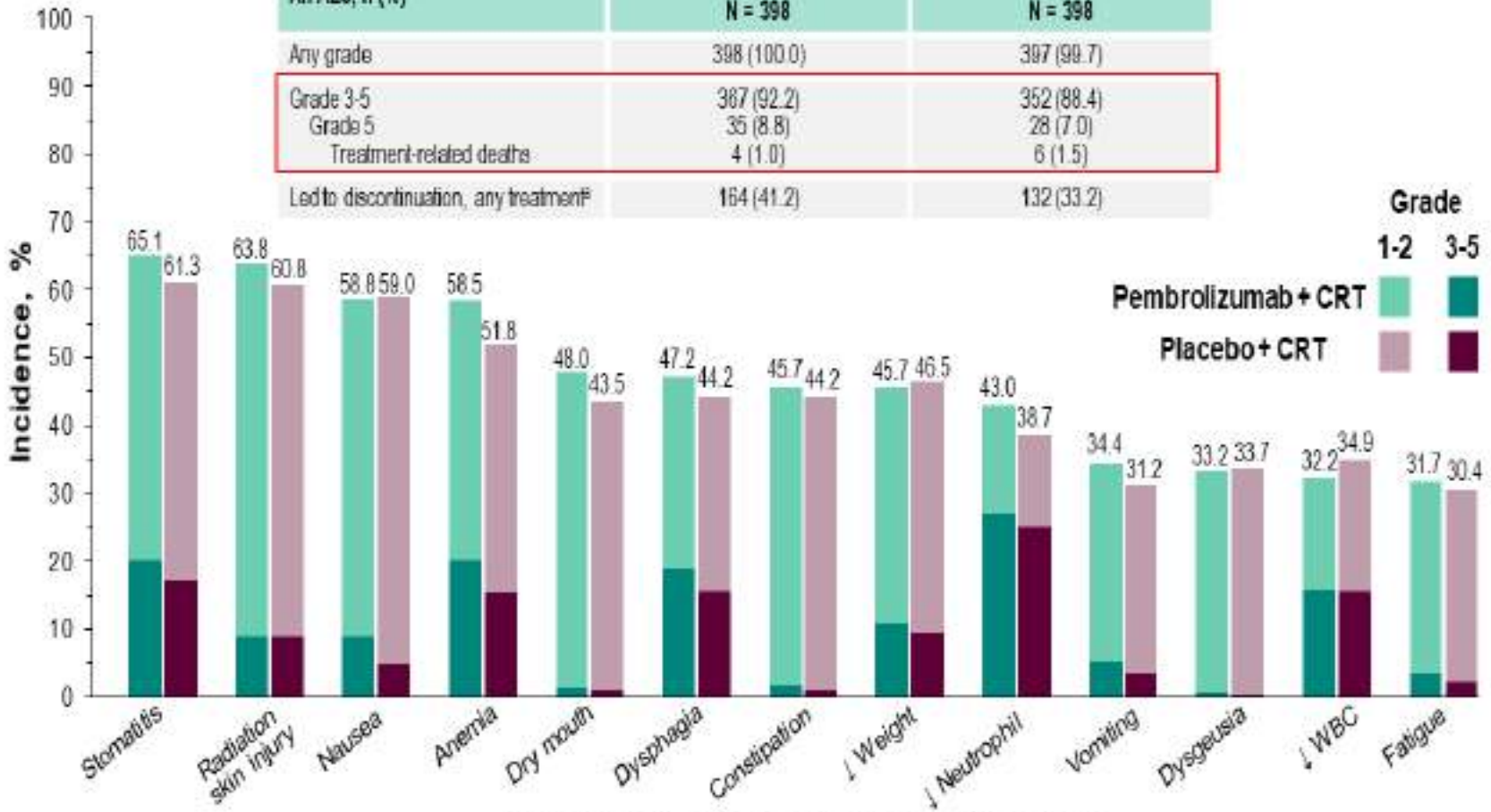
	Events	HR (95% CI)
Pembro + CRT	22.6%	0.67 (0.43-1.04)
Placebo + CRT	32.4%	



Data cutoff date: May 31, 2022.

All-Cause AEs Across Both Treatment Phases, As Treated

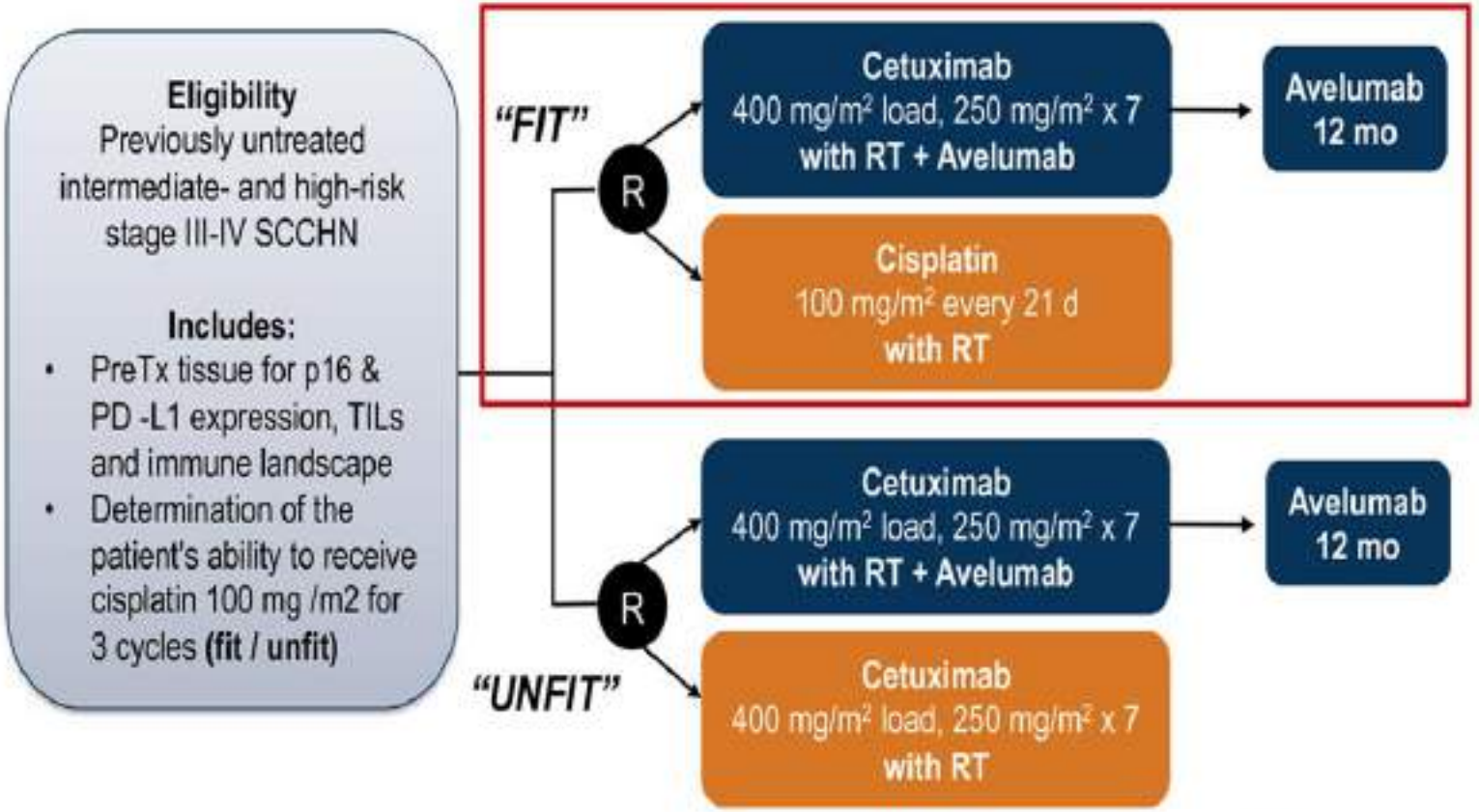
All AEs, n (%)	Pembro + CRT N = 398	Placebo + CRT N = 398
Any grade	398 (100.0)	397 (99.7)
Grade 3-5	367 (92.2)	352 (88.4)
Grade 5	35 (8.8)	28 (7.0)
Treatment-related deaths	4 (1.0)	6 (1.5)
Led to discontinuation, any treatment[a]	164 (41.2)	132 (33.2)



AEs With Incidence ≥30% in Either Arm

[a]Cisplatin, RT, and/or pembrolizumab/placebo.
Data cutoff date: May 31, 2022.

GORTEC 2017-01 (REACH): Phase 3 Trial of Avelumab-Cetuximab-RT vs SOC in LA-HNSCC[1]



1. Bourhis J et al. ESMO Virtual Congress 2021. LBA35.

GORTEC- 2017-01

Fit cohort
Primary endpoint: Kaplan Meier estimate of progression free survival

430 patients randomized

The number of PFS events was not reached, at the time of analysis

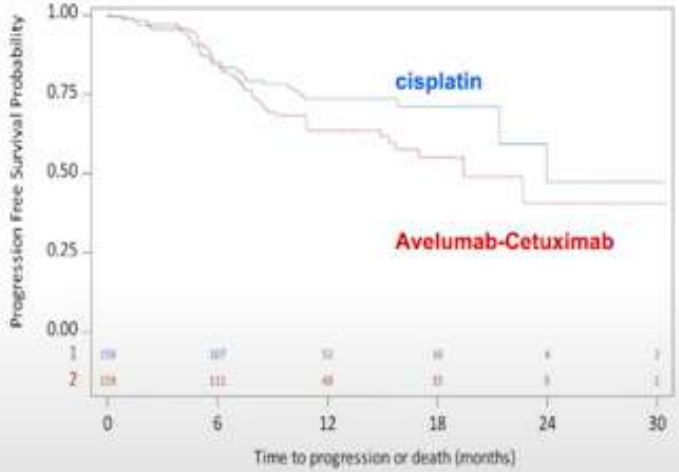
The planned interim analysis for futility based on 89 events in 317 patients showed a 1-year PFS rate of :

73% (95%CI 65%-81%) in SOC-cisplatin-RT

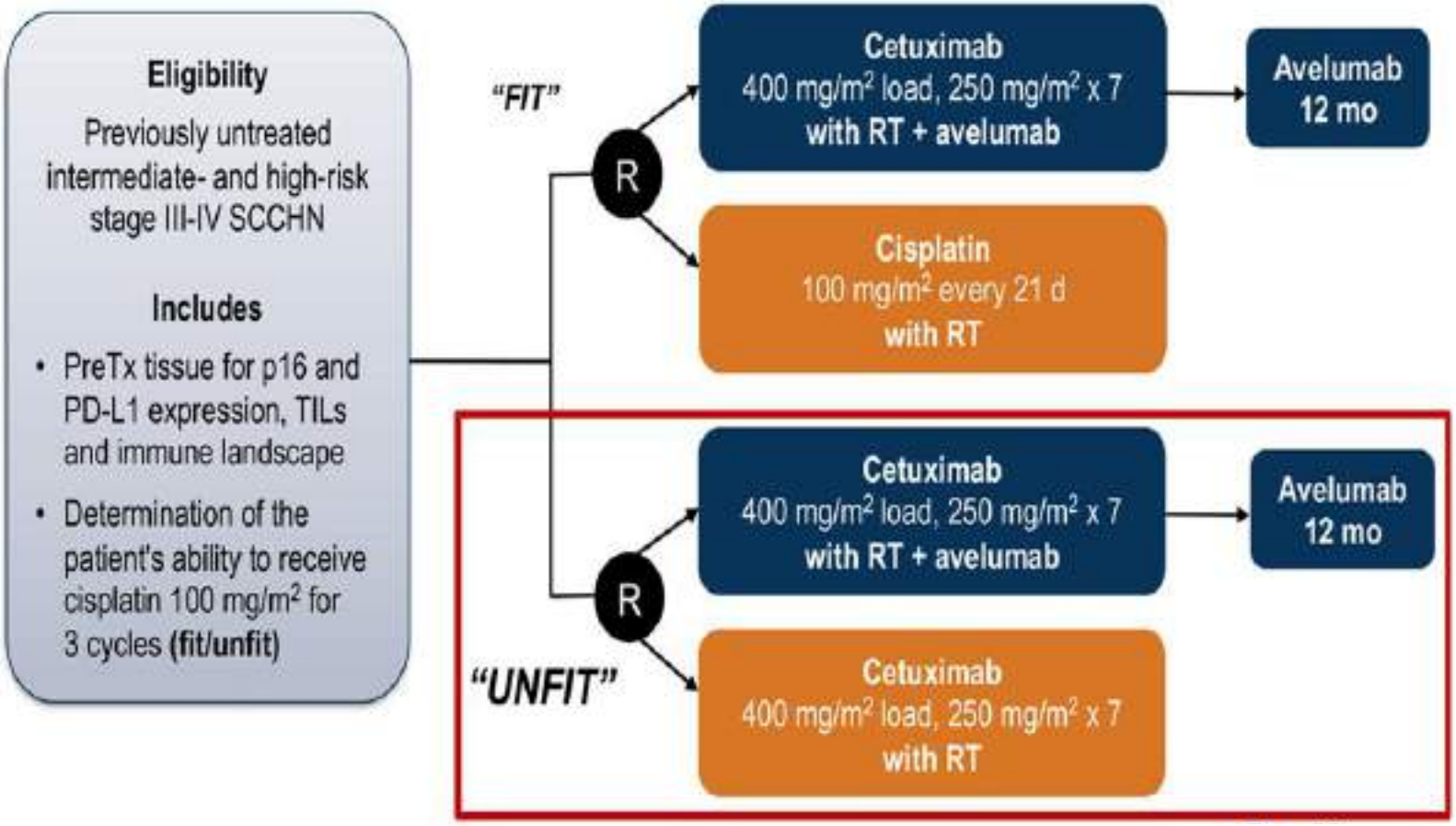
vs

64% (95%CI 54%-72%) in Avelumab-Cetuximab-RT

→ **HR 1.27 (95%CI 0.83-1.93), crossing the futility boundary**



GORTEC 2017-01 (REACH): Phase 3 Trial of Avelumab-Cetuximab-RT vs SOC in LA-HNSCC[1]

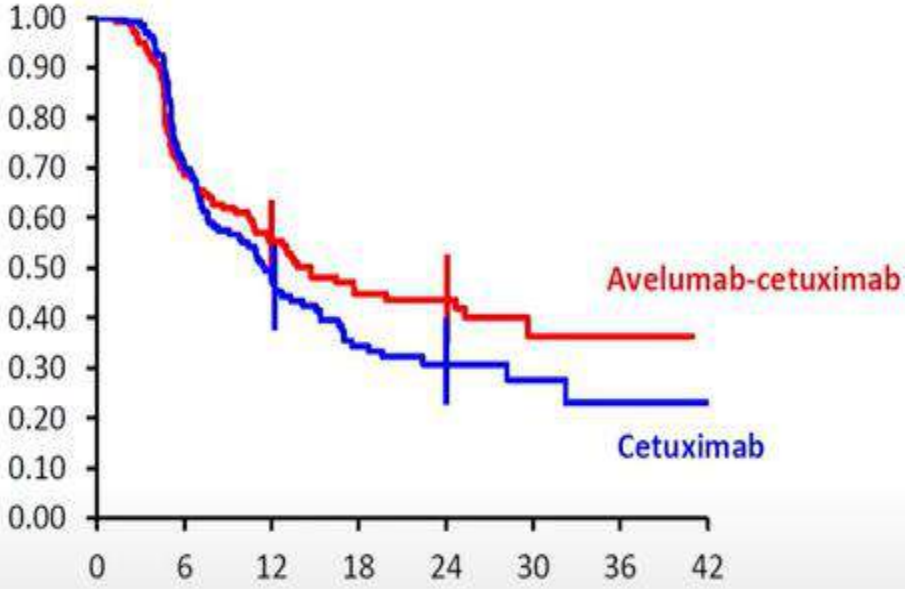


1. Bourhis J et al. ESMO Virtual Congress 2021. LBA35.

GORTEC- 2017-01

Unfit cohort
Primary endpoint: Kaplan Meier estimate of progression free survival

Median follow-up = 21.3 months (IQR 14.6-28.3)(similar in both arms)



At risk							
140	95	68	39	27	9	4	
135	92	56	32	20	6	4	1

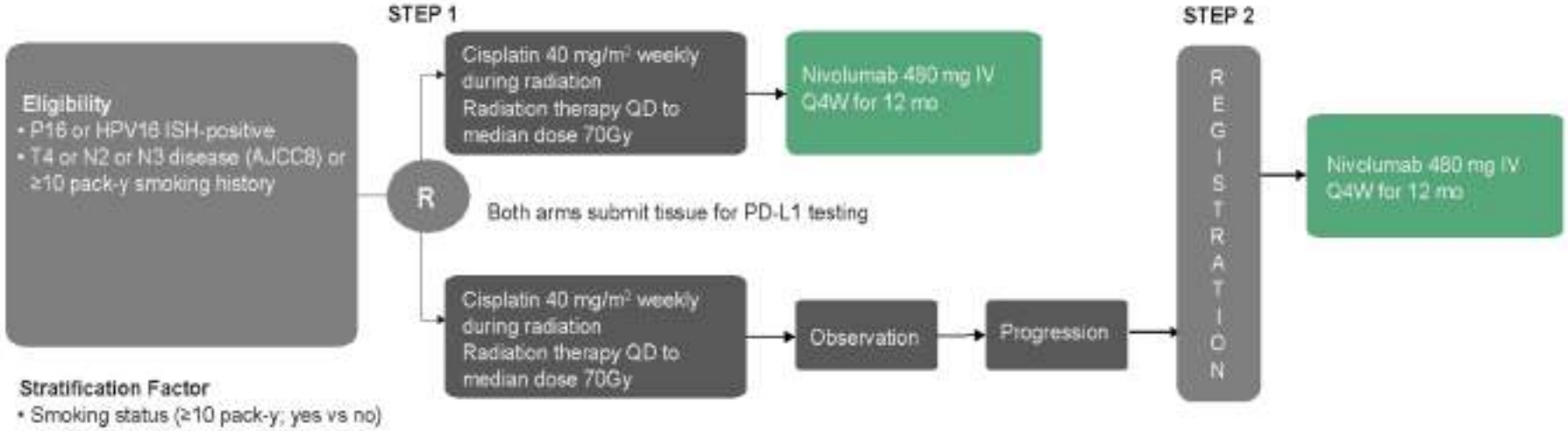
PFS at 2 years

44% (95%CI 35%-53%)
in **Avelumab-Cetuximab**
vs
31% (95%CI 23%-40%)
in **Cetuximab**

Adjusted* HR 0.84 for PFS
(95% CI 0.62-1.15)
one-sided p-value=0.14

EA3161: Intermediate-Risk HPV+ Oropharynx Cancer

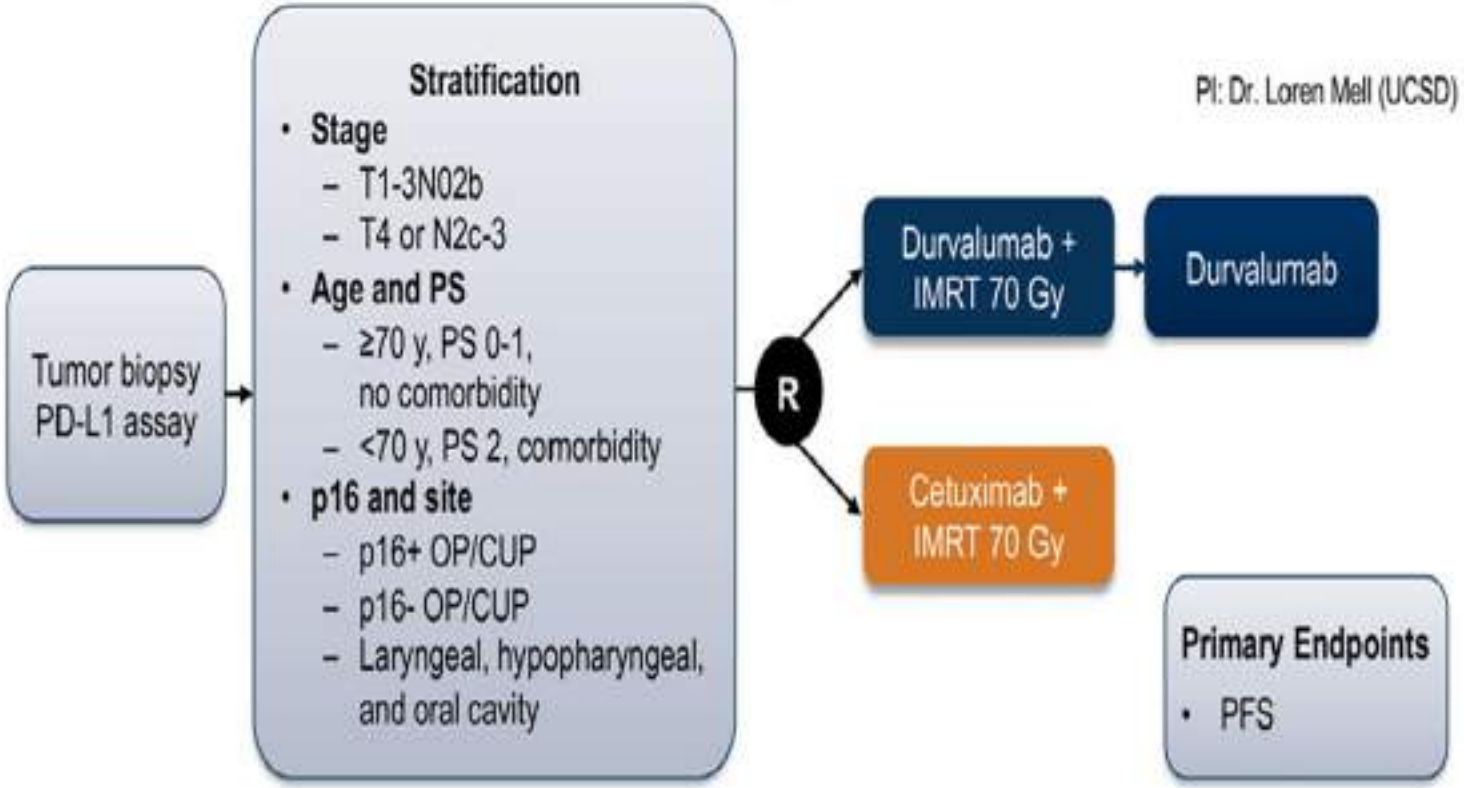
- CR rate remains high in this group
- Is there a role for immunotherapy in subclinical disease?
- Radiation known to upregulate PD-L1 expression and TIL
- Avoids radiating newly recruited TIL
- However, regional lymph nodes may have reduced capacity to participate in immune response



ISH: in situ hybridization; TIL: tumor-infiltrating lymphocyte.
https://www.clinicaltrials.gov/ct2/show/NCT03811015. Accessed June 3, 2023.

HN004: NRG Phase 2/3 Trial[1]

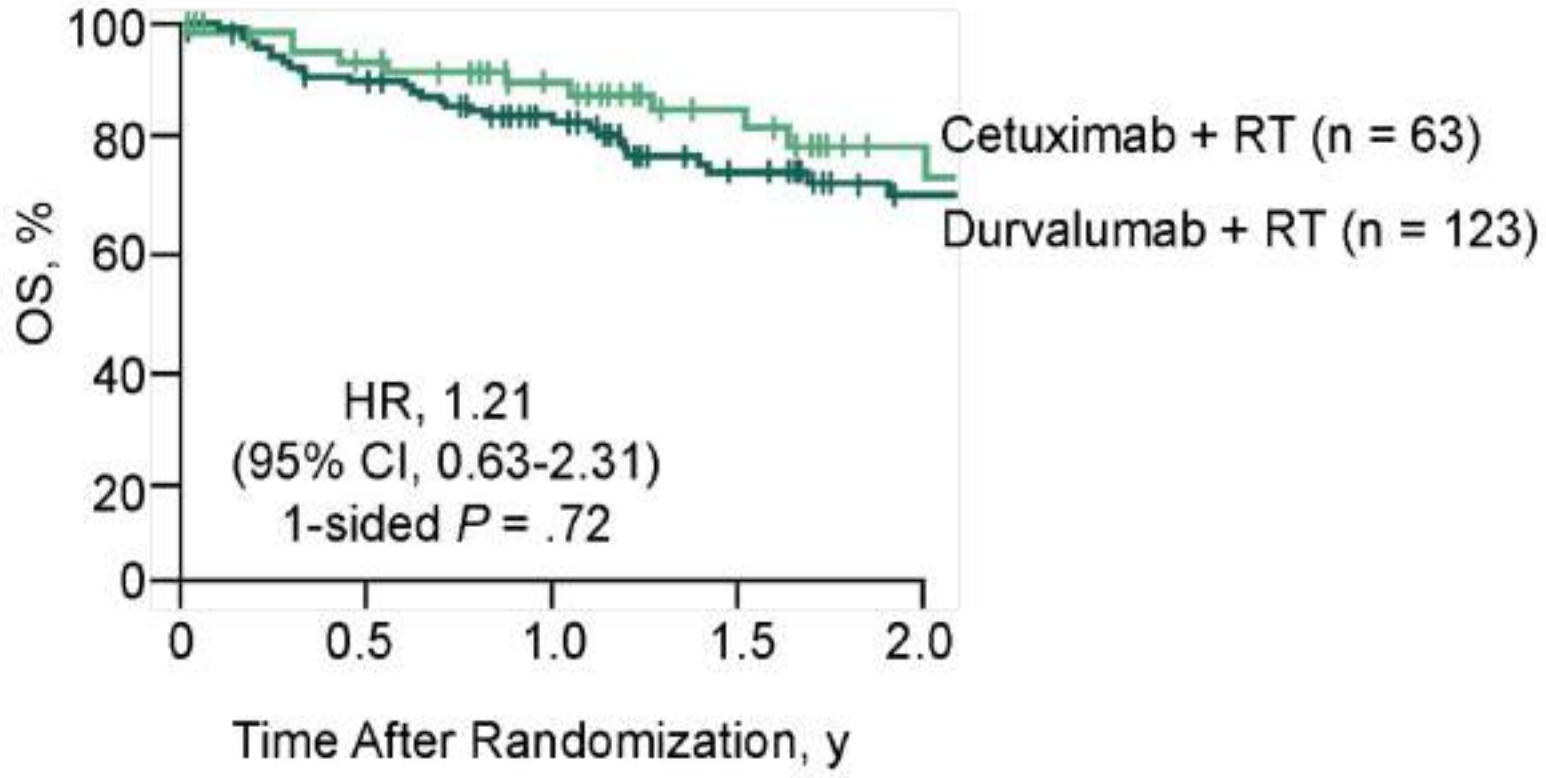
Cisplatin Unfit or Age ≥70 y With Poor Performance Status or Comorbidities (Intermediate-Risk and High-Risk Patients)



N = 533 (phase 2-3 with phase 1 run-in)

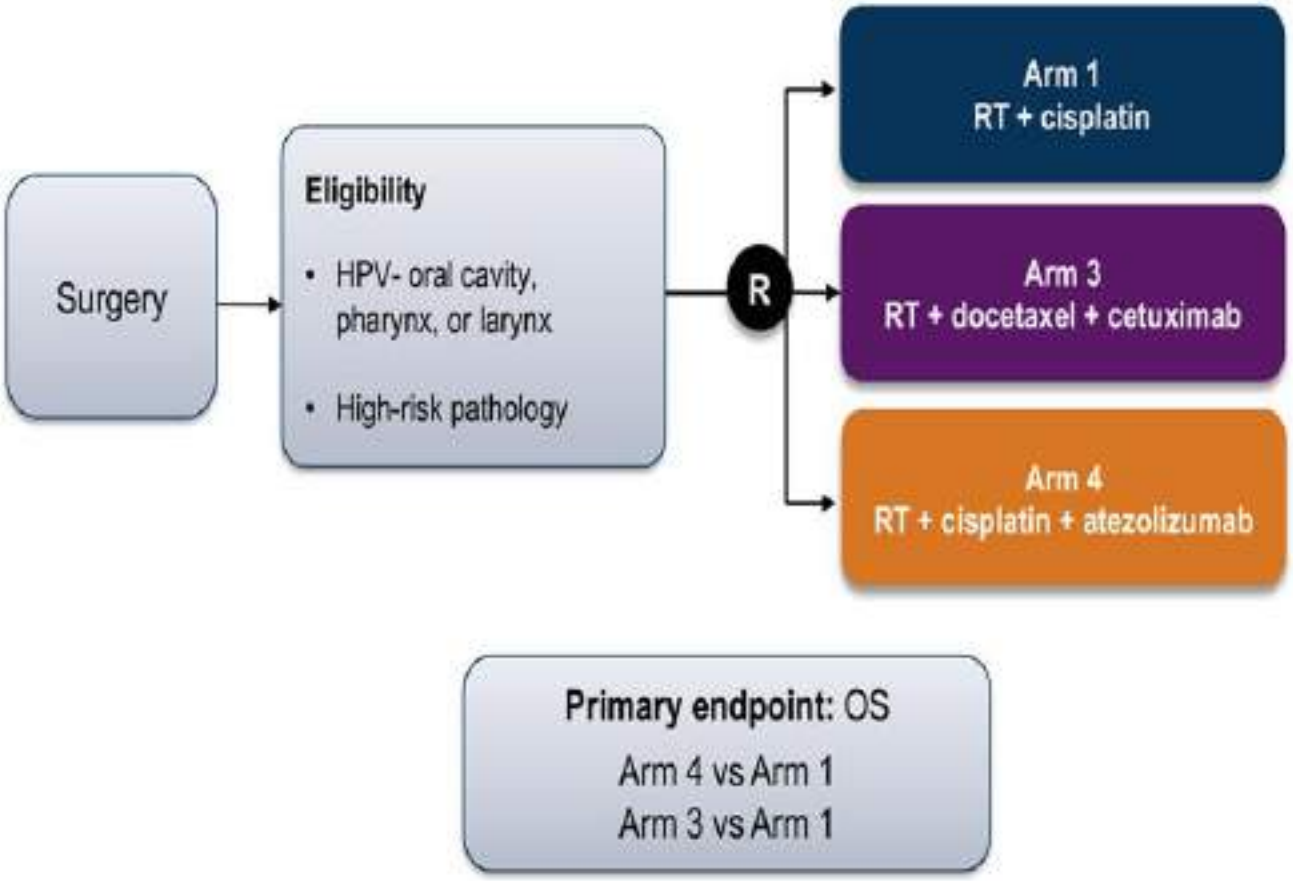
1. Mell L et al. *J Clin Oncol*. 2019;37(suppl 15):6065.

NRG-HN004: Outcomes



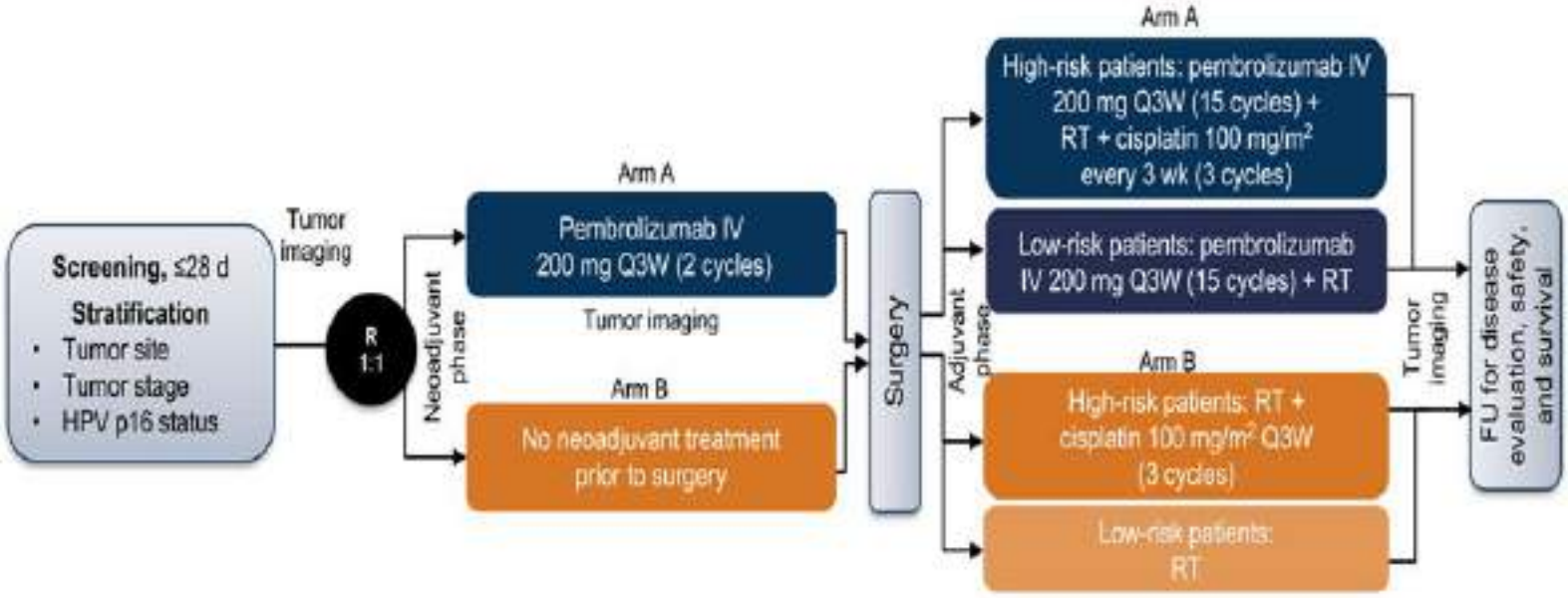
Mell LK et al. ASTRO 2022.

HN003/RTOG 1216: Postoperative Adjuvant CisRT + Atezolizumab or Docetaxel-Cetuximab + RT vs CisRT in High-Risk SCCHN[1]



1. https://clinicaltrials.gov/ct2/show/NCT01810913

KEYNOTE-689: Phase 3 Study of Pembrolizumab in Stage III-IVA Resectable LA SCCHN[1]

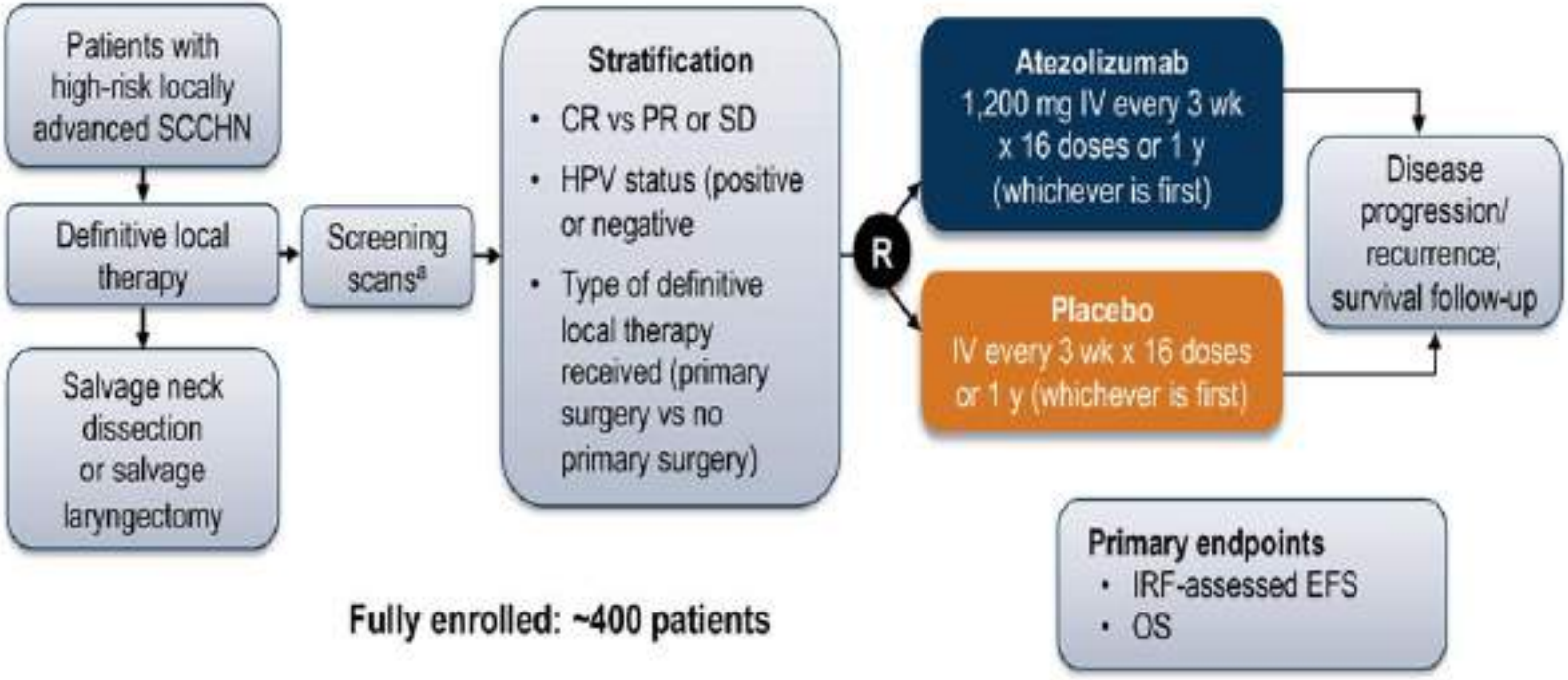


- Randomized study will test pembrolizumab as neoadjuvant therapy and in combination with SOC as adjuvant therapy
- Approximately 600 patients will be enrolled
- Primary objectives: mPR and EFS

1. Uppaluri R et al. J Clin Oncol. 2019;37(suppl 15):TPS6090.

Atezolizumab as Adjuvant Therapy in Patients With High-Risk Locally Advanced SCCHN[1]

A phase 3, multicenter, randomized, double-blind, placebo-controlled study



Fully enrolled: ~400 patients

[a] Must be done ≥8 wk after completing definitive local therapy and within 28 d prior to initiation of study drug.

1. Haddad R et al. *Ann Oncol*. 2018;29(suppl 8):VIII397.

ICI in LAHNSCC - No proven benefit

ICI - recurrent /metastatic HNSCC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L. Gillison

Oral Oncology 81 (2018) 45–51

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression

Robert L. Ferris[a,*], George Blumenschein Jr.[b], Jerome Fayette[c], Joel Guigay[d], A. Dimitrios Colevas[e], Lisa Licitra[f], Kevin J. Harrington[g], Stefan Kasper[h], Everett E. Vokes[i], Caroline Even[j], Francis Worden[k], Nabil F. Saba[l], Lara Carmen Iglesias Docampo[m], Robert Haddad[n], Tamara Rordorf[o], Naomi Kiyota[p], Makoto Tahara[q], Mark Lynch[r], Vijayvel Jayaprakash[r], Li Li[r], Maura L. Gillison[b]

Phase III CheckMate 141: Nivolumab in Recurrent/Metastatic HNSCC After Platinum Therapy

Patients with recurrent or metastatic HNSCC (oral cavity, pharynx, or larynx), progression or recurrence in ≤ 6 mos after last dose of platinum-based chemotherapy, p16 documented for determining HPV status (oropharyngeal cancer only), any prior tx experience, any PD-L1 status
(N = 361)

Stratified by prior cetuximab

Active brain metastases, Autoimmune disease, or systemic immunosuppression; known human immunodeficiency virus or hepatitis B or C virus infection- Excluded

Randomized 2:1

Nivolumab 3 mg/kg IV Q2W
(n = 240)

Investigator's Choice of methotrexate 40 mg/m^2 IV weekly, docetaxel 30 mg/m^2 IV weekly, or cetuximab 400 mg/m^2 IV once followed by 250 mg/m^2 weekly
(n = 121)

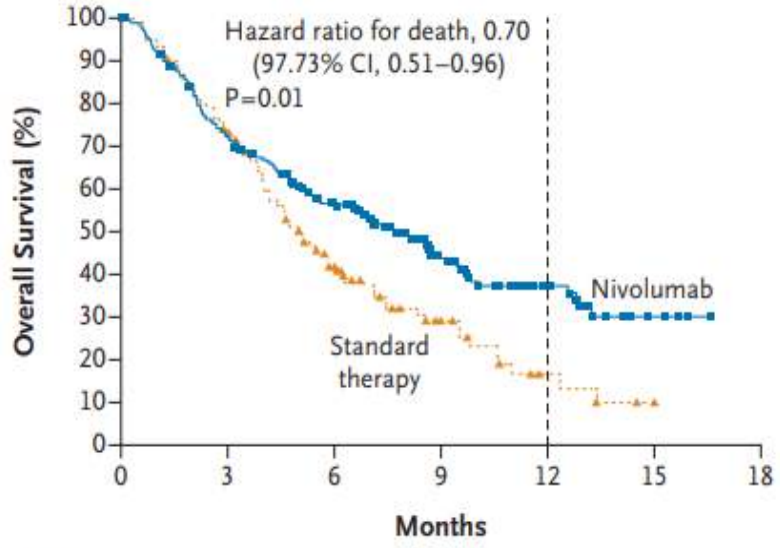
- Primary endpoint: OS
- Other endpoints: PFS, ORR, DoR, safety, biomarkers, QoL

Ferris. NEJM. 2016;375:1856.

Checkmate 141

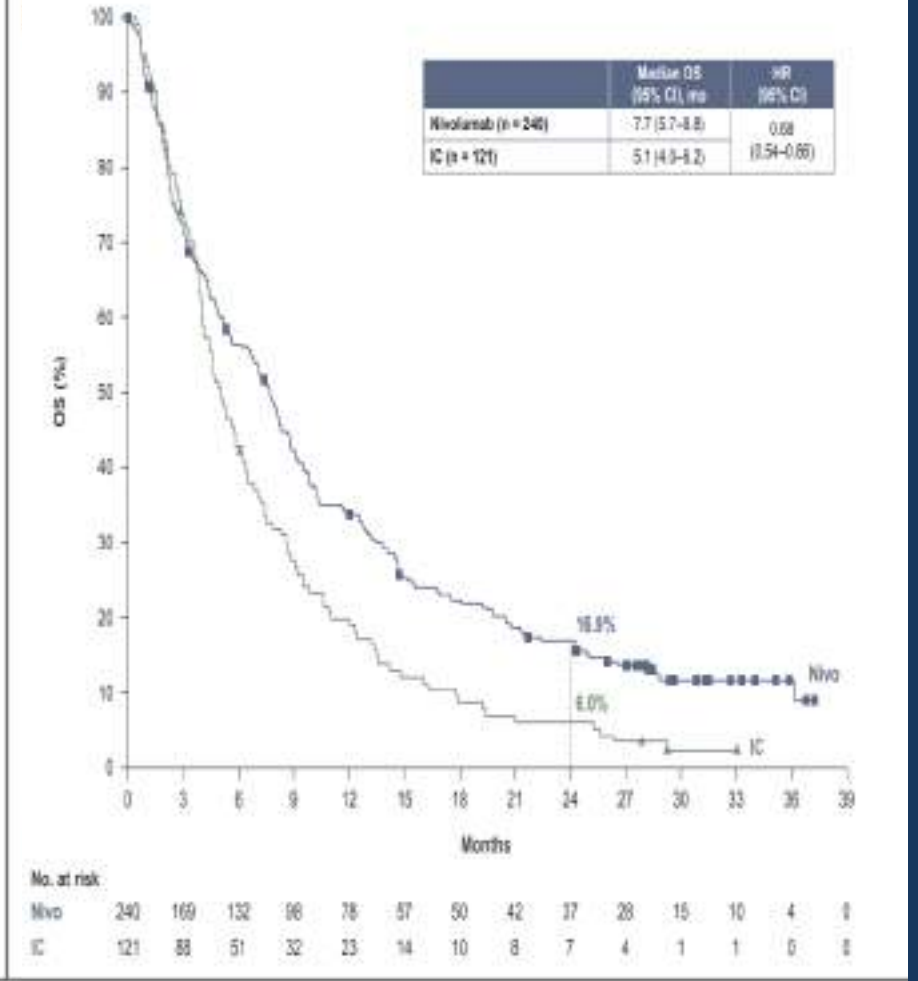
Overall Survival

	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk

Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

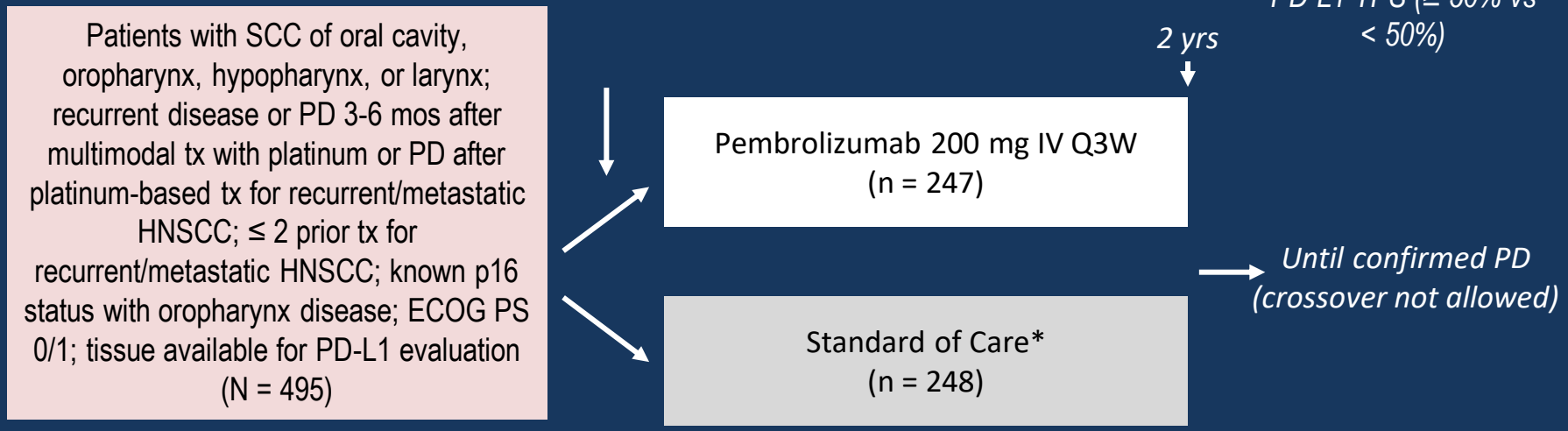


Ferris. NEJM. 2016;375:1856-1867

Ferris. Oral Oncol. 2018;81:45.

KEYNOTE-040: Pembrolizumab vs Standard of Care in Recurrent/ Metastatic HNSCC

Stratified by ECOG PS (0 vs 1), p16 status (pos vs neg), PD-L1 TPS (≥ 50% vs < 50%)

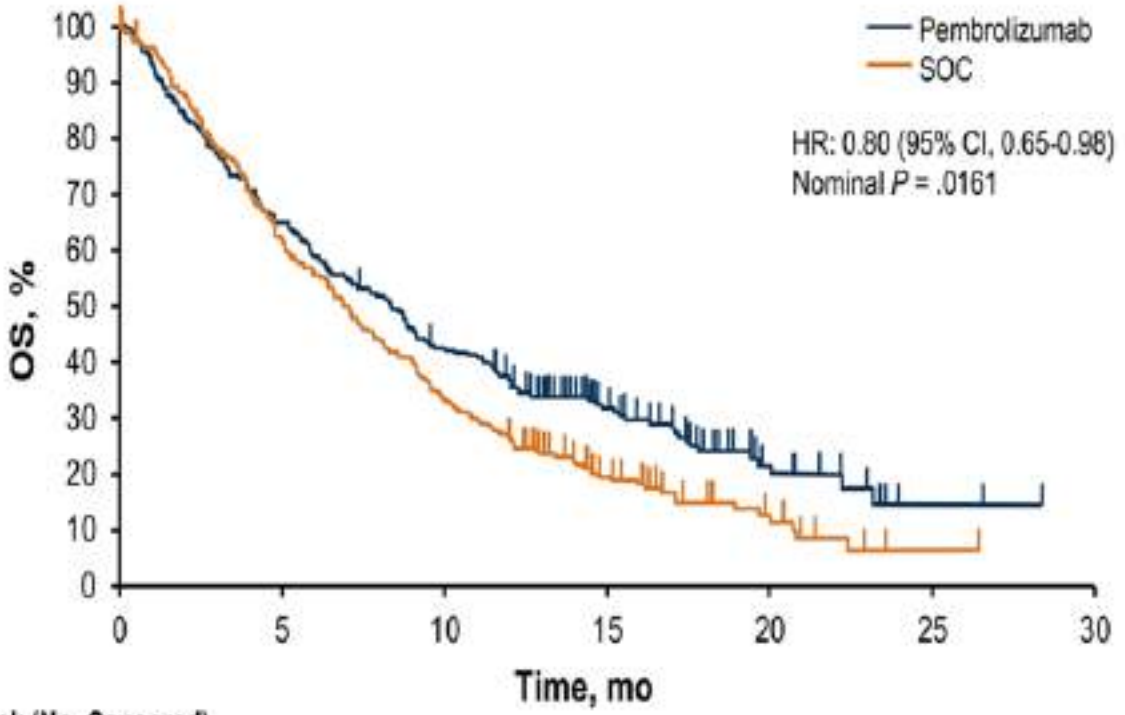


*Investigator's choice of methotrexate 40 mg/m^2 weekly (in absence of toxicity could increase to 60 mg/m^2), docetaxel 75 mg/m^2 Q3W, or cetuximab loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly.

- Primary endpoint: OS in ITT population
- Secondary endpoints: OS in PD-L1–positive subgroups, PFS, ORR, DoR, safety, tolerability

Cohen. Lancet. 2019;393:156-167

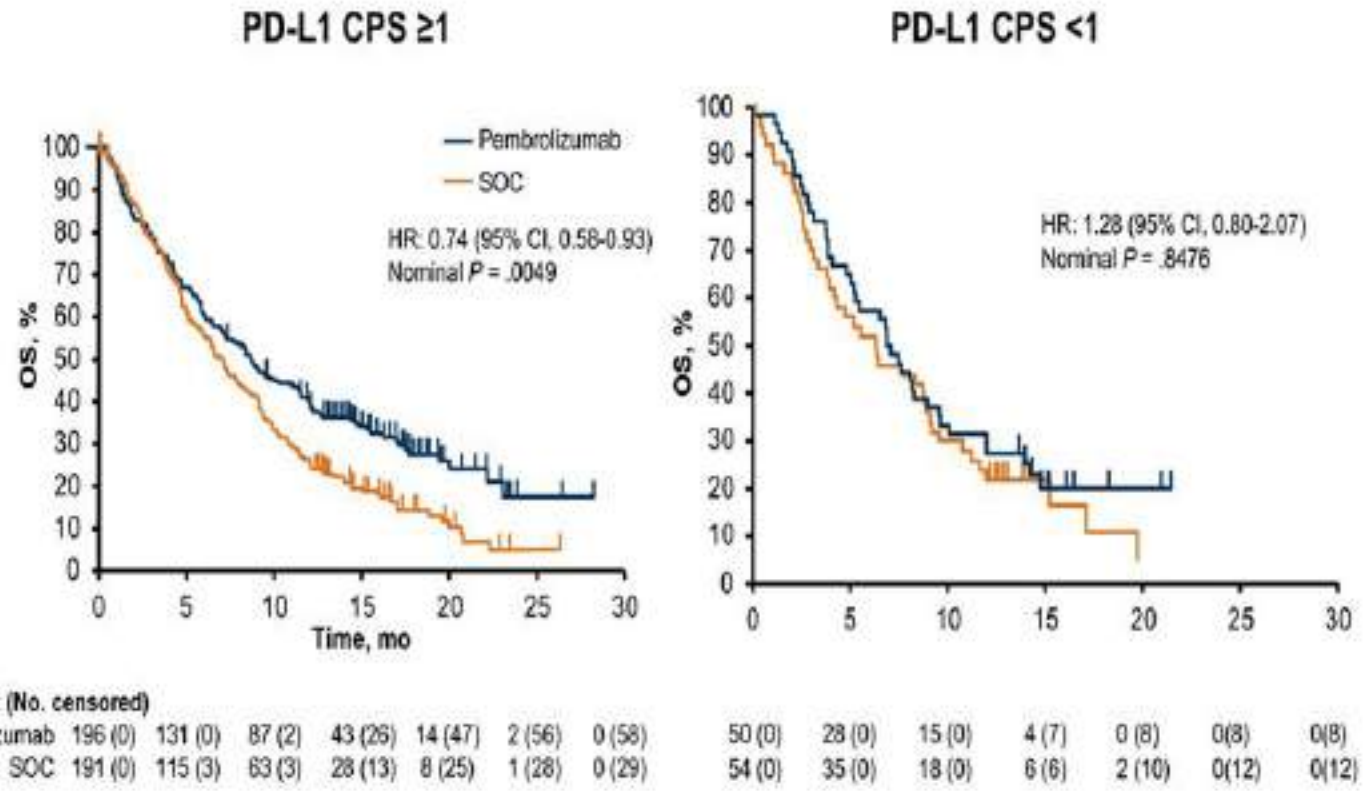
KEYNOTE-040: Overall Survival[1]



No. at Risk (No. Censored)							
Pembrolizumab	247 (0)	160 (0)	103 (2)	48 (33)	14 (55)	2 (64)	0 (66)
SOC	248 (0)	151 (3)	82 (3)	34 (19)	10 (35)	1 (40)	0 (41)

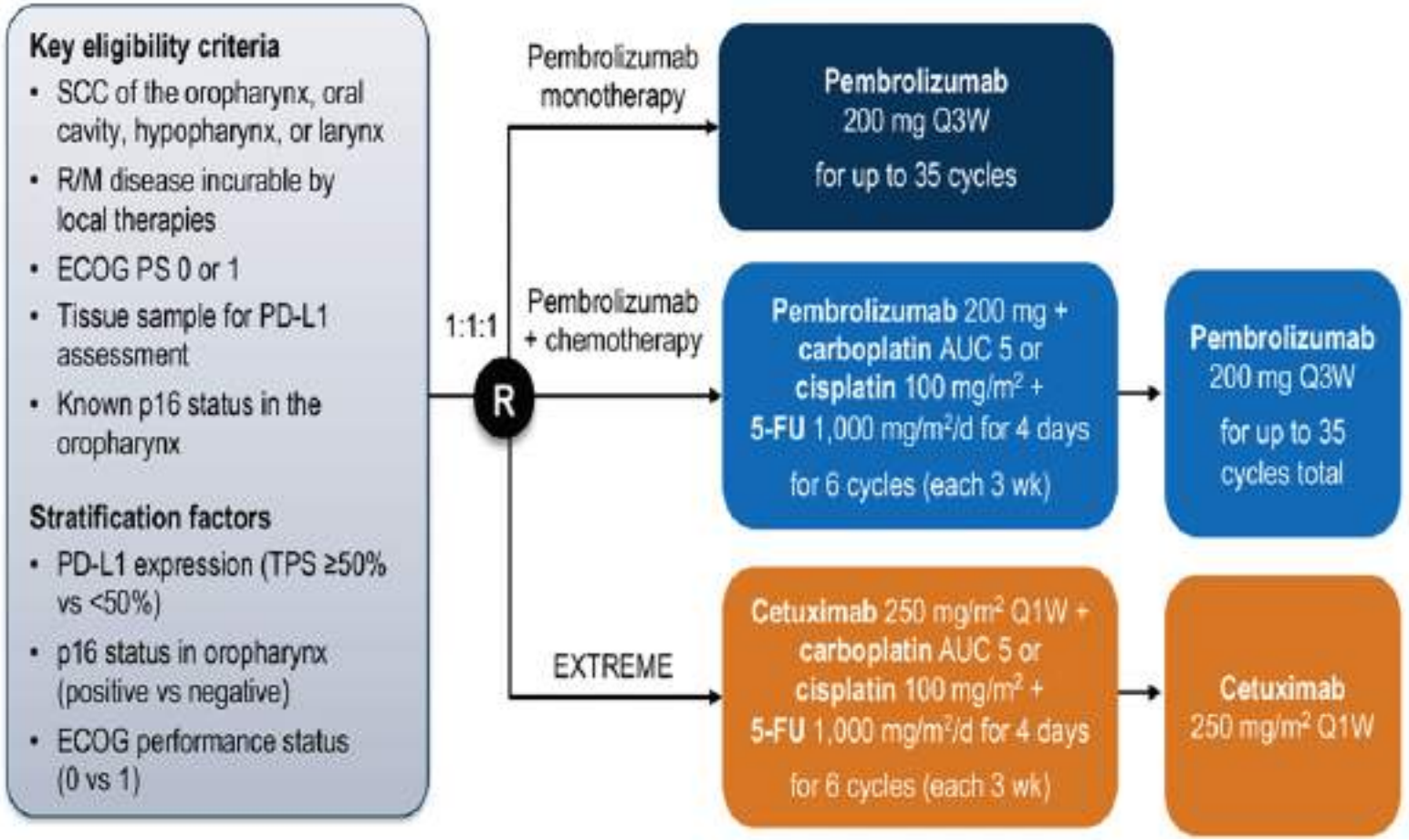
1. Cohen EE et al. *Lancet*. 2019;393:156-167.

Overall Survival According to PD-L1 Expression[1]



1. Cohen EE et al. *Lancet*. 2019;393:156-167.

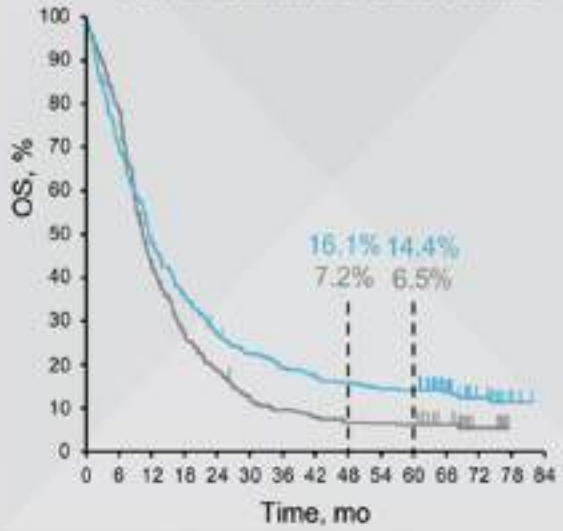
KEYNOTE-048: Study Design[1]



1. Burtness B et al. Lancet. 2019;394:1915-1928.

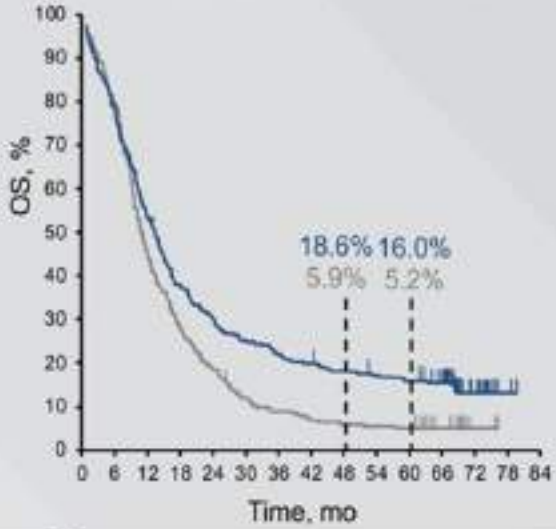
KEYNOTE-048: 5-Year OS in ITT Population

Pembrolizumab vs EXTREME



	Median OS, mo	HR
Pembrolizumab (n = 301)	11.5	0.82 (0.69-0.97)
EXTREME (n = 300)	10.7	

Pembrolizumab + ChT vs EXTREME



	Median OS, mo	HR
Pembrolizumab + ChT (n = 281)	13.0	0.72 (0.60-0.86)
EXTREME (n = 278)	10.7	

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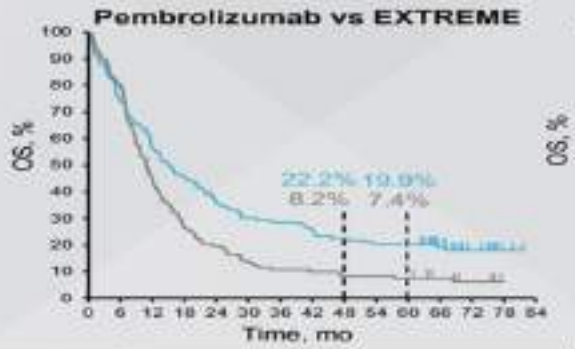
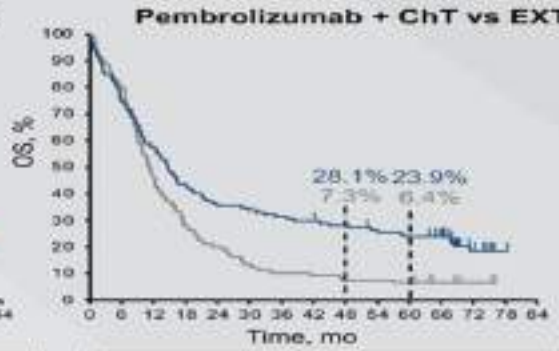
KEYNOTE-048: 5-Year OS in CPS ≥20 Population

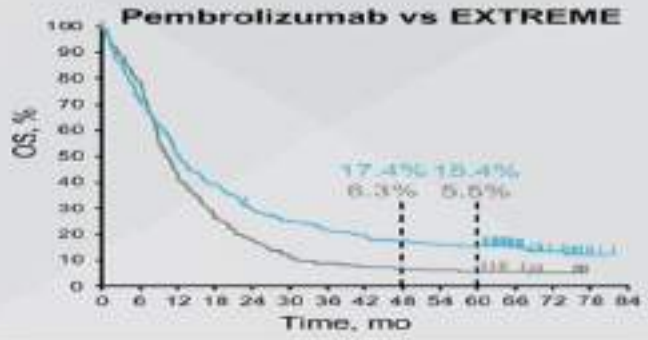


	Median OS, mo	HR
Pembrolizumab (n = 133)	14.9	0.61 (0.46-0.81)
EXTREME (n = 122)	10.8	

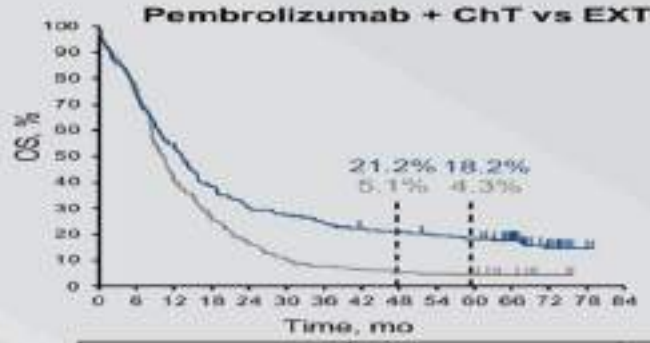


	Median OS, mo	HR
Pembrolizumab + ChT (n = 126)	14.7	0.63 (0.47-0.84)
EXTREME (n = 110)	11.1	

KEYNOTE-048: 5-Year OS in CPS ≥1 Population



	Median OS, mo	HR
Pembrolizumab (n = 257)	12.3	0.74 (0.61-0.89)
EXTREME (n = 255)	10.4	



	Median OS, mo	HR
Pembrolizumab + ChT (n = 242)	13.6	0.65 (0.53-0.79)
EXTREME (n = 235)	10.6	

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Outcome	Pembrolizumab vs EXTREME		Pembrolizumab + ChT vs EXTREME	
	Pembrolizumab (n = 301)	EXTREME (n = 300)	Pembrolizumab + ChT (n = 281)	EXTREME (n = 278)
ORR, %	16.9	36.0	37.0	36.3
Median DOR, mo	22.6	4.5	6.7	4.3

TRAE, %	Pembrolizumab vs EXTREME		Pembrolizumab + ChT vs EXTREME	
	Pembrolizumab	EXTREME	Pembrolizumab + ChT	EXTREME
Grade 1/2	41.3	27.5	23.9	27.5
Grade 3-5	17.0	69.3	71.7	69.3

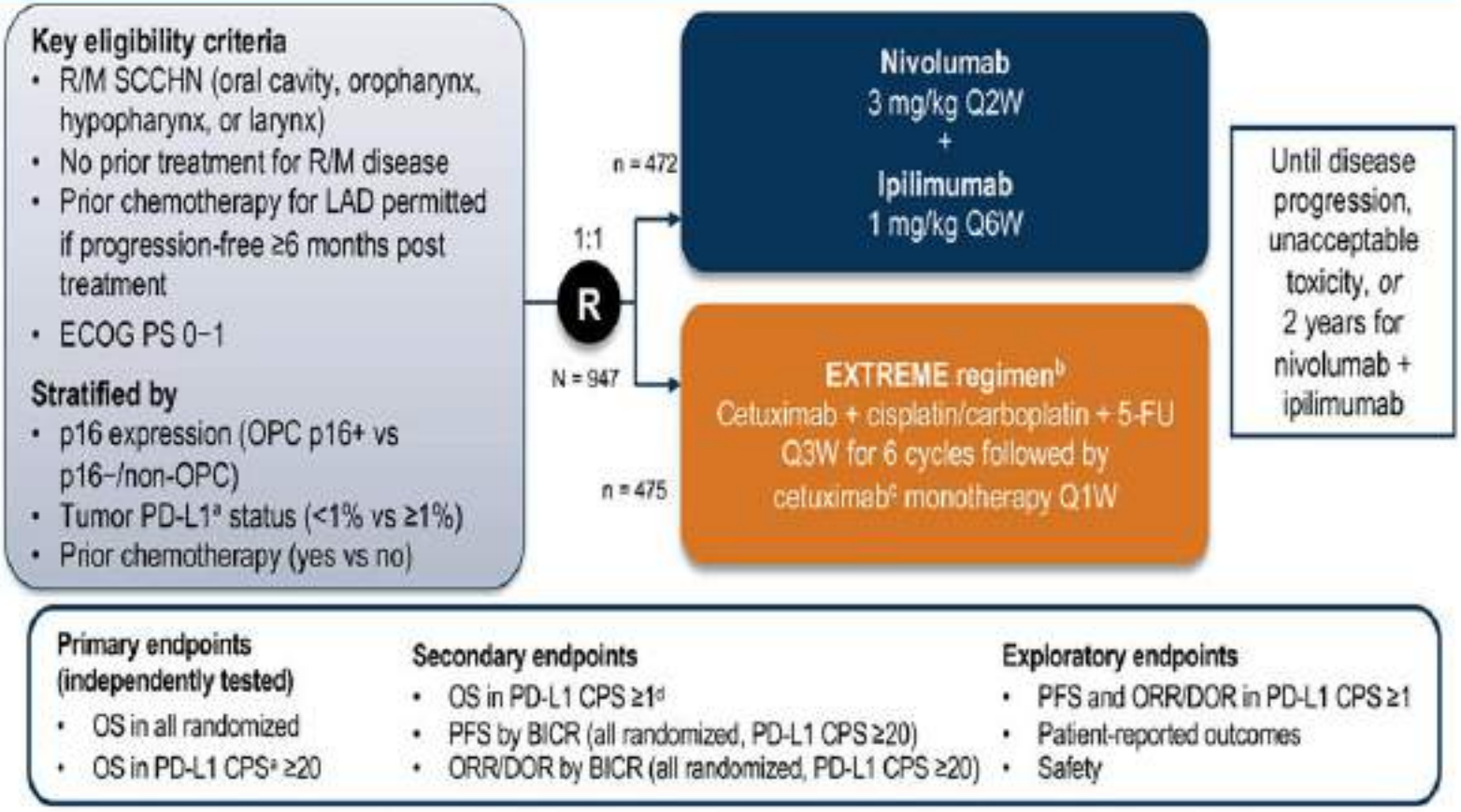
KEYNOTE-048 Post-hoc/Exploratory Outcomes of PD-L1 CPS Subgroups: Pembrolizumab vs EXTREME

Survival	PD-L1 CPS <1		PD-L1 CPS 1-19		PD-L1 CPS ≥20	
	Pembrolizumab (n = 44)	Cetuximab-ChT (n = 45)	Pembrolizumab (n = 124)	Cetuximab-ChT (n = 133)	Pembrolizumab (n = 133)	Cetuximab-ChT (n = 122)
Median OS, mo	7.9	11.3	10.8	10.1	14.8	10.7
OS HR (95% CI)	1.51 (0.96-2.37)		0.86 (0.66-1.12)		0.58 (0.44-0.78)	
P	.96241		.12827		.00010	
12-mo OS rate, %	38.6	48.9	44.0	42.4	56.4	44.9
Median PFS, mo	2.1	6.2	2.2	4.9	3.4	5.3
PFS HR (95% CI)	4.31 (2.63-7.08)		1.25 (0.96-1.61)		0.99 (0.76-1.29)	
P	1.000		.95093		.46791	

KEYNOTE-048 Post-hoc/Exploratory Outcomes of PD-L1 CPS Subgroups: Pembrolizumab + ChT vs EXTREME

Survival	PD-L1 CPS <1		PD-L1 CPS 1-19		PD-L1 CPS ≥20	
	Pembrolizumab-ChT (n = 39)	Cetuximab-ChT (n = 43)	Pembrolizumab-ChT (n = 116)	Cetuximab-ChT (n = 125)	Pembrolizumab-ChT (n = 126)	Cetuximab-ChT (n = 110)
Median OS, mo	11.3	10.7	12.7	9.9	14.7	11.0
OS HR (95% CI)	1.21 (0.76-1.94)		0.71 (0.54-0.94)		0.60 (0.45-0.82)	
P	.78932		.00726		.00044	
12-mo OS rate, %	41.0	46.5	52.6	41.1	57.1	46.1
Median PFS, mo	4.7	6.2	4.9	4.9	5.8	5.3
PFS HR (95% CI)	1.46 (0.93-2.30)		0.93 (0.71-1.21)		0.76 (0.58-1.01)	
P	.94898		.29189		.02951	

CheckMate -651 Study Design[1]

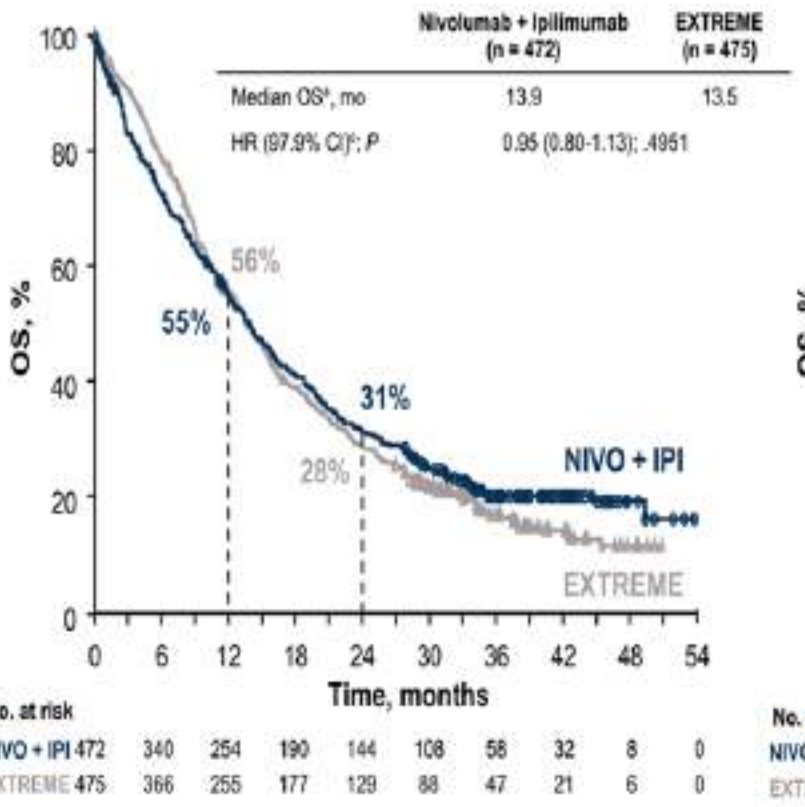


[a] Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [b] Initial cetuximab dose of 400 mg/m² once only, then cetuximab 250 mg/m² Q1W plus cisplatin 100 mg/m² or carboplatin AUC 5 on day 1, plus fluorouracil 1,000 mg/m²/d for 4 days for 6 cycles (Q3W). [c] Cetuximab 250 mg/m² Q1W; Q2W maintenance was allowed per local prescribing information. [d] Part of statistical testing hierarchy.

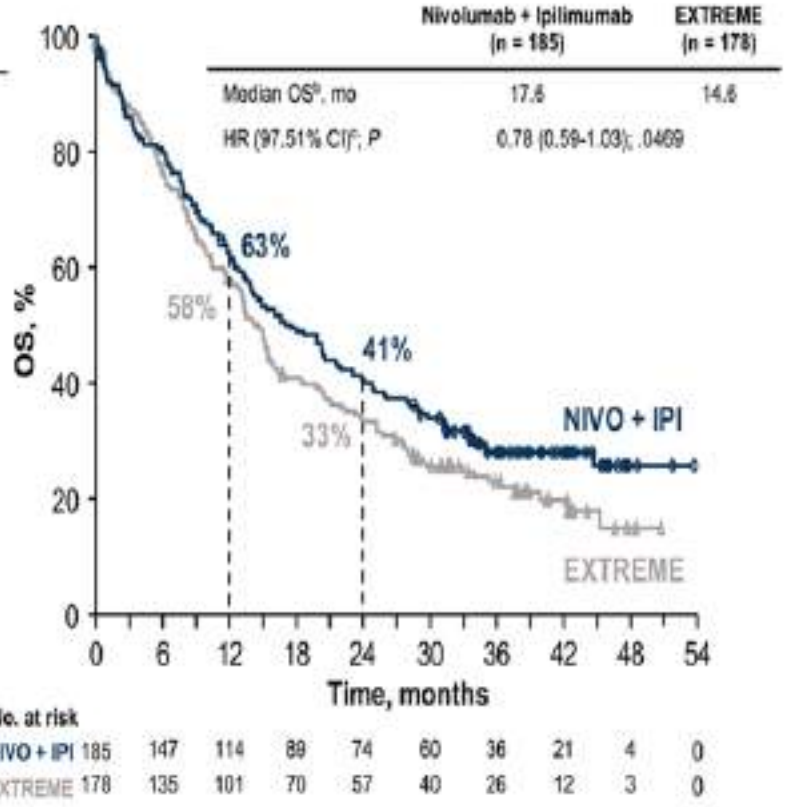
1. Agiris A et al. 2021 ESMO 2021. Abstract LBA36.

Primary Endpoints:
OS With Nivolumab + Ipilimumab vs EXTREME[1]

All Randomized



PD-L1 CPS ≥20



Minimum follow-up: 27.3 months.

[a] 95% CI = 12.1-15.8 (nivolumab + ipilimumab) and 12.6-15.2 (EXTREME). [b] 95% CI = 13.8-22.0 (nivolumab + ipilimumab) and 12.3-16.0 (EXTREME).

[c] Confidence intervals are adjusted based on the final α levels for each primary endpoint.

1. Agiris A et al. 2021 ESMO 2021. Abstract LBA36.

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original reports

Low-Dose Immunotherapy in Head and Neck Cancer: A Randomized Study

Vijay Maruti Patil, MBBS, MD, DM[1]; Vanita Noronha, MBBS, MD, DM[1]; Nandini Menon, MBBS, MD, DNB[1]; Rahul Rai, MBBS, MD[1]; Atanu Bhattacharjee, PhD[2]; Ajay Singh, MBBS, MD, DM[1]; Kavita Nawale, PDCR[1]; Shweta Jogdhankar, MSc[1]; Rupali Tambe, BCom[1]; Sachin Dhumal, BHMS[1]; Riddhi Sawant, PDCR[1]; Mitali Alone, MSc[1]; Devanshi Karla, MSc[1]; Zoya Peelay, MSc[1]; Shruti Pathak, MSc[1]; Arun Balaji, MASLP[3]; Suman Kumar, MBBS, DNB[4]; Nilendu Purandare, MBBS, DNB[5]; Archi Agarwal, MBBS, DNB[5]; Ameya Puranik, MBBS, DNB[5]; Abhishek Mahajan, MBBS, DNB[4]; Amit Janu, MBBS, DNB[4]; Gunjesh Kumar Singh, MBBS, MD, DM[1]; Neha Mittal, MBBS, MD[6]; Subhash Yadav, MBBS, MD[6]; Shripad Banavali, MBBS, MD[1]; and Kumar Prabhash, MBBS, MD, DM[1]

Relapsed -recurrent or newly diagnosed advanced HNSCC being treated with palliative intent with ECOG PS 0-1

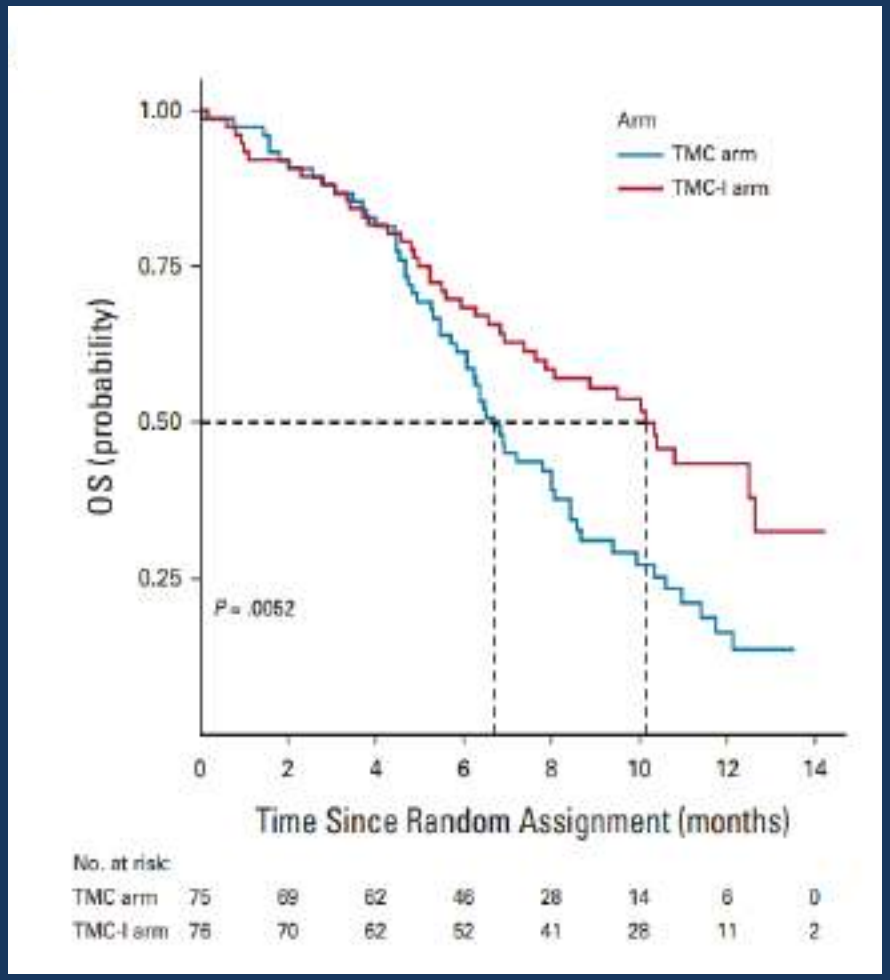
Primary endpoint – 1 yr survival

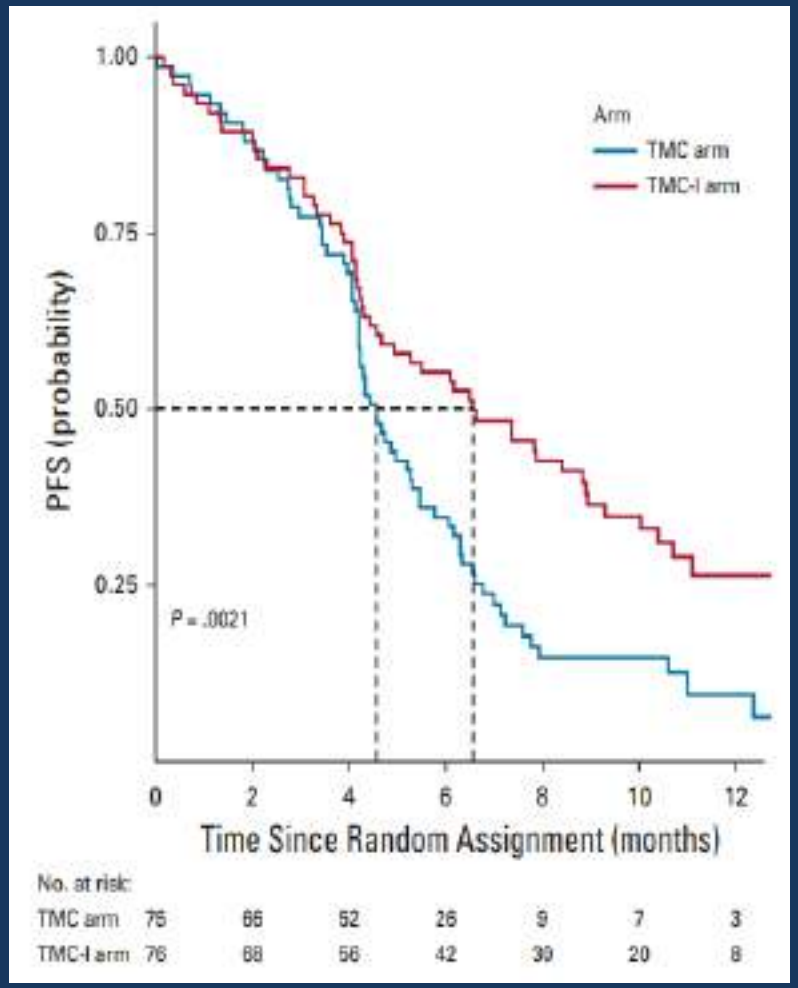
Nivolumab 20mg IVq3weeks + MC(N=76) → Until confirmed PD or Toxicity

- MC-methotrexate 15 mg/m2 PO weekly, celecoxib 200 mg PO
- daily and erlotinib 150 mg PO daily(N=75)

J Clin Oncol 41:222-232 ; 2022

Median follow up – 10.6 months





J Clin Oncol 41:222-232 ; 2022

ICI - recurrent /metastatic HNSCC

1ST line treatment – Pembro and low dose Nivo
2nd line – Pembro and Nivo

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2022 May 24; 13(5): 388-411

DOI: 10.5306/wjco.v13.i5.388

ISSN 2218-4333 (online)

SYSTEMATIC REVIEWS

Immune checkpoint inhibitors in head and neck squamous cell carcinoma: A systematic review of phase-3 clinical trials

Jissy Vijo Poulose, Cessal Thommachan Kainickal

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Jissy Vijo Poulose, National Fellowship in Palliative Medicine (Training Program), Institute of Palliative Medicine, Calicut 673008, Kerala, India

Cessal Thommachan Kainickal, Department of Radiation Oncology, Regional Cancer Centre, Thiruvananthapuram 695011, Kerala, India

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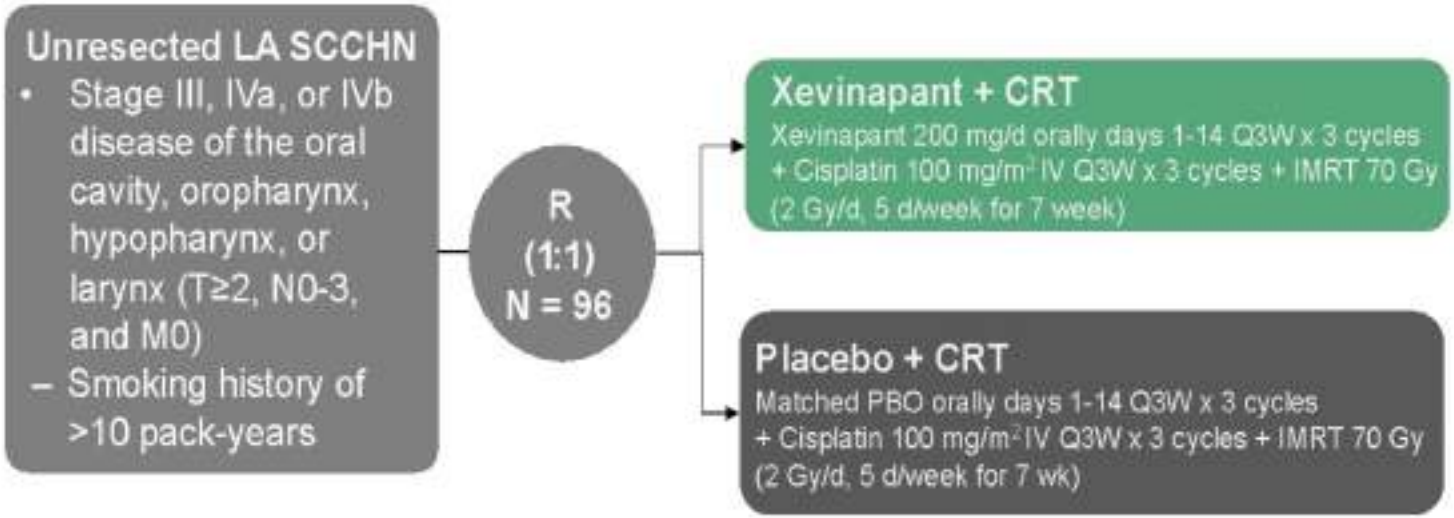
Targeted therapy

Anti EGFR agents

Immunotherapy

Inhibitor of Apoptosis Proteins

DEBIO 1143: Study Design



Stratification Factors

- Stage (N0-N1 vs N2-N3)
- Primary tumor site (OPC vs non-OPC; if OPC, by HPV-16 status)

Primary endpoint

- LRC rate at 18 months from end of CRT

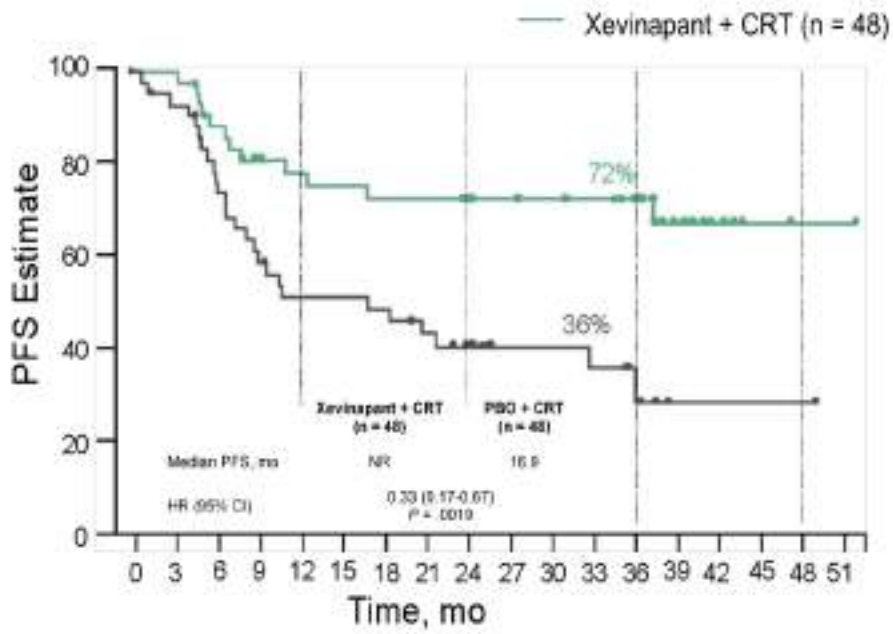
Selected secondary endpoints

- PFS, OS, DOR, Safety

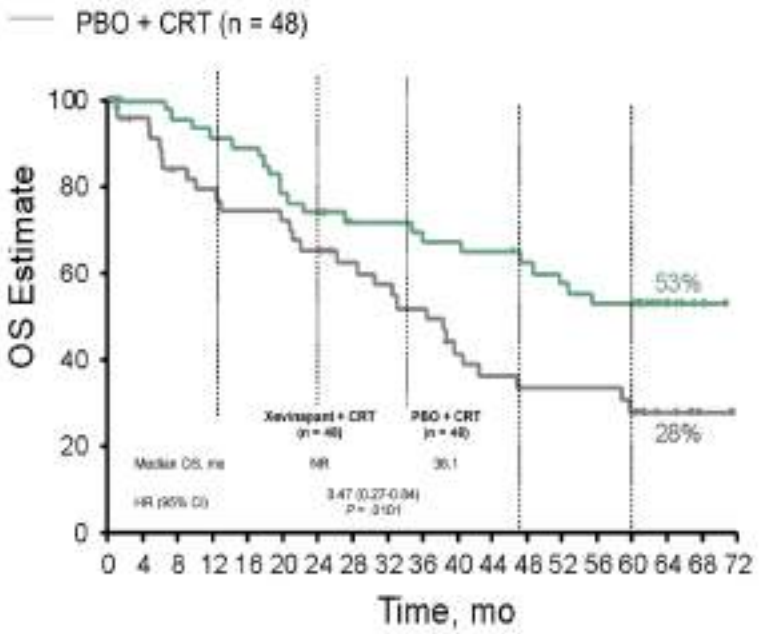
Sun XS et al. *Lancet Oncol*. 2020;21:1173-1184. Bourhis J et al. *Ann Oncol*. 2022;33(suppl 7): S808-S869.

DEBIO 1143: Outcomes

PFS (3-Year Analysis)



OS (5-Year Analysis)



Sun XS et al. *Lancet Oncol*. 2020;21:1173-1184. Bourhis J et al. *Ann Oncol*. 2022;33(suppl 7): S808-S869.

DEBIO 1143: Safety

TEAEs, % (Grade 3-4 in >10% of Patients)	Xevinapant + CRT (n = 48)			PBO + CRT (n = 47)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Mucositis	44	31	0	47	21	0
Dysphagia	21	50	0	40	21	0
Anemia	25	35	0	32	23	0
Neutropenia	8	15	8	9	23	4
ALT increased	15	13	0	13	4	0

- Late toxicities were recorded 73% of patients in the xevinapant + CRT treatment arm and 66% of the PBO + CRT arm

TEAE: treatment-emergent AE

Sun XS et al. *Lancet Oncol*. 2020;21:1173-1184.

Xevinapant/PBO + CRT in LA-SCCHN: TrilynX Study Design

N = 700
Phase 3 (ongoing)

Eligibility criteria:
- Histologically confirmed, unresected, locally advanced SCCHN
- Stage III, IVa or IVb tumour of the oropharynx (HPV-neg), hypopharynx, or larynx
- ECOG PS 0 or 1

R 1:1

Combination treatment
- **Xevinapant** 200 mg/d (days 1-14, Q3W for 3 cycles)
- **Cisplatin** 100 mg/m^2 Q3W for 3 cycles (day 2)
- **IMRT** 70 Gy (2 Gy/d, 5d/wk for 7 wks)

Monotherapy
- **Xevinapant** 200 mg/d (days 1-14, Q3W for 3 cycles)

Combination treatment
- **Matched PBO** (days 1-14, Q3W for 3 cycles)
- **Cisplatin** 100 mg/m^2 Q3W for 3 cycles (day 2)
- **IMRT** 70 Gy (2 Gy/d, 5d/wk for 7 wks)

Monotherapy
- **Matched PBO** (days 1-14, Q3W for 3 cycles)

Primary endpoint
- EFS by BIRC

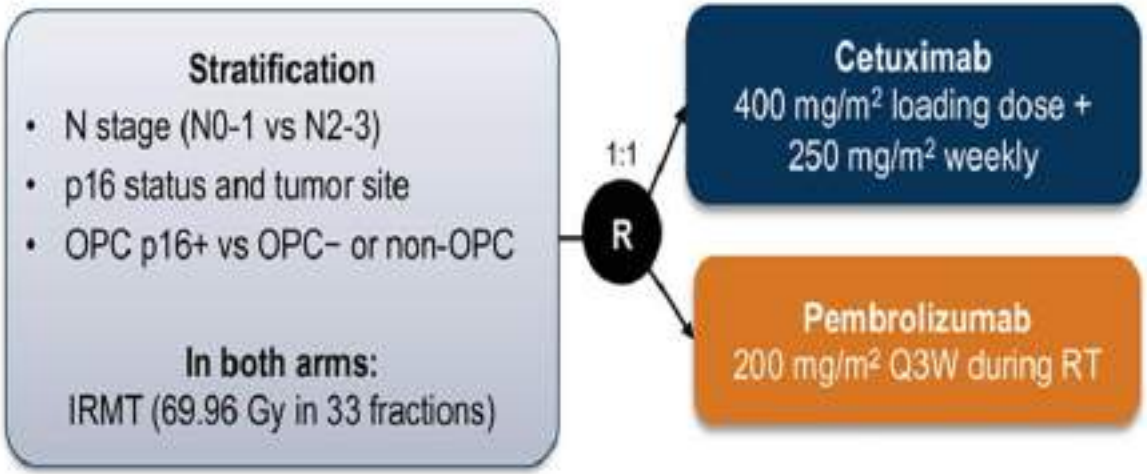
Secondary endpoints
- OS
- DOR
- PFS by BIRC
- ORR LRC
- Safety
- HRQOL

Clinicaltrials.gov: NCT04459715.

Thank you

drcessalthomas@gmail.com

GORTEC 2015-01 (PembroRad) Randomized Trial in Cisplatin-Unfit Patients[1]



Conclusions

- No difference in LRC
- No differences in PFS or OS

1. Bourhis J et al. *Ann Oncol*. 2020;31(suppl 4):S1168.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

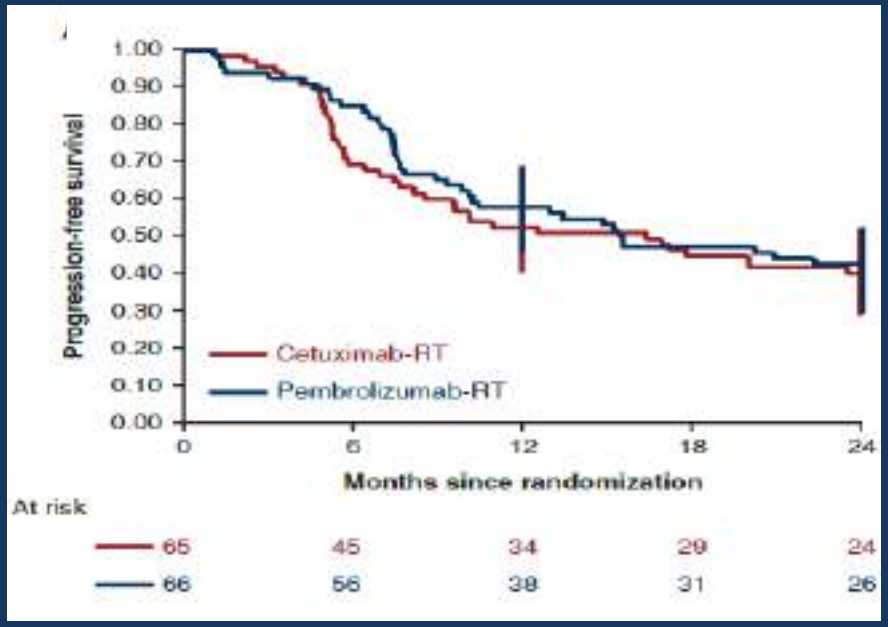
ANNALS OF ONCOLOGY driving innovation in oncology

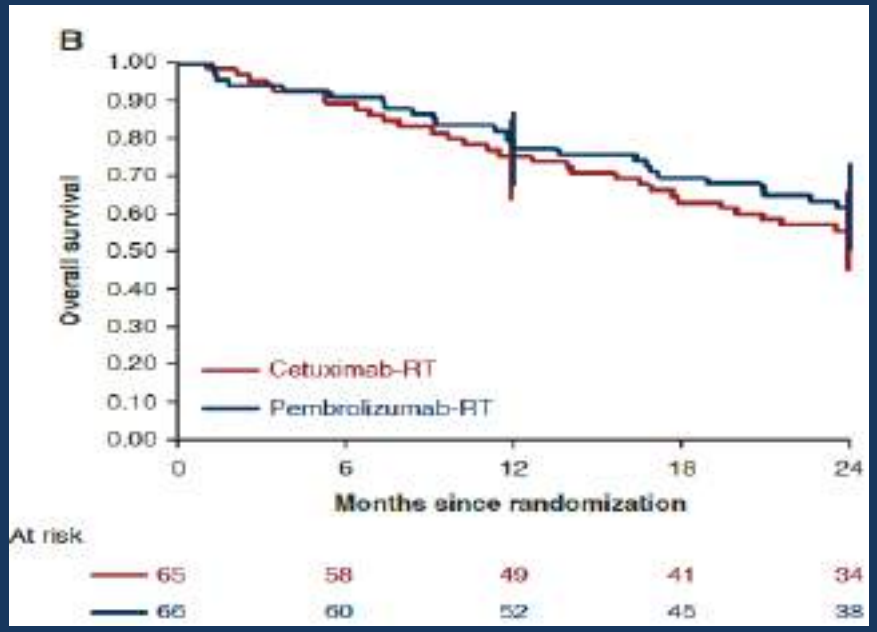
ORIGINAL ARTICLE

Pembrolizumab versus cetuximab concurrent with radiotherapy in patients with locally advanced squamous cell carcinoma of head and neck unfit for cisplatin (GORTEC 2015-01 PembroRad): a multicenter, randomized, phase II trial

Y. Tao[1], J. Biau[2], X. S. Sun[3], C. Sire[4], L. Martin[5], M. Alfonsi[6], J. B. Prevost[7], A. Modesto[8], C. Lafond[9], J. M. Tourani[10], J. Miroir[2], M. C. Kaminsky[11], A. Coutte[12], X. Liem[13], E. Chautard[2], E. Vauleon[14], F. Drouet[15], A. Ruffier[1,9], J. F. Ramee[16], G. Waksi[17], A. Péchery[17], M. Wanneveich[17], J. Guigay[18], A. Aupérin[19] & J. Bourhis[20]*

[1]Gustave-Roussy Institute, Villejuif; [2]Centre Jean Perrin, Clermont Ferrand; [3]Hôpital Nord Franche-Comté, Montbéliard and CHU Besançon, Montbéliard; [4]Centre Hospitalier de Bretagne Sud, Lorient; [5]Clinique des Ormeaux, Le Havre; [6]Clinique Sainte Catherine, Avignon; [7]Centre Pierre Curie, Beuvry; [8]Institut Claudius Regaud, Toulouse; [9]Clinique Victor Hugo-Centre Jean Bernard, Le Mans; [10]Centre Hospitalier Universitaire de Poitiers, Poitiers; [11]Institut de Cancérologie de Lorraine, Nancy; [12]Centre Hospitalier Universitaire Amiens-Picardie, Amiens; [13]Centre Oscar Lambret, Lille; [14]Centre Eugène Marquis, Rennes; [15]Clinique Mutualiste de l'estuaire, Saint-Nazaire; [16]Centre Hospitalier Départemental de Vendée, La Roche sur Yon; [17]GORTEC, Tours; [18]Centre Antoine Lacassagne, FHU OncoAge, University Côte d'Azur, Nice; [19]Unit of Biostatistics and Epidemiology, Gustave Roussy, Oncostat 1018 INSERM, labeled Ligue Contre le Cancer, Université Paris-Saclay, Villejuif, France, [20]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland





https://doi.org/10.1016/j.annonc.2022.10.006

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Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study

Kevin J. Harrington, PhD[1]; Barbara Burtness, MD[2]; Richard Greil, MD[3,4]; Denis Soulières, MD[5]; Makoto Tahara, MD[6]; Gilberto de Castro Jr, MD[7]; Amanda Psyrri, MD[8]; Irene Brana, MD[9]; Neus Basté, MD[3]; Prakash Neupane, MD[10]; Åse Bratland, PhD[11]; Thorsten Fuereder, MD[12]; Brett G.M. Hughes, MBBS[13]; Ricard Mesia, PhD[14]; Nuttapong Ngamphaiboon, MD[15]; Tamara Rordorf, MD[16]; Wan Zamaniah Wan Ishak, MD[17]; Jianxin Lin, MS[18]; Burak Gumuscu, MD[18]; Ramona F. Swaby, MD[18]; and Danny Rischin, MD[19,20]

J Clin Oncol 41:790-802;2022

J Clin Oncol 40:2321-2332;2022.

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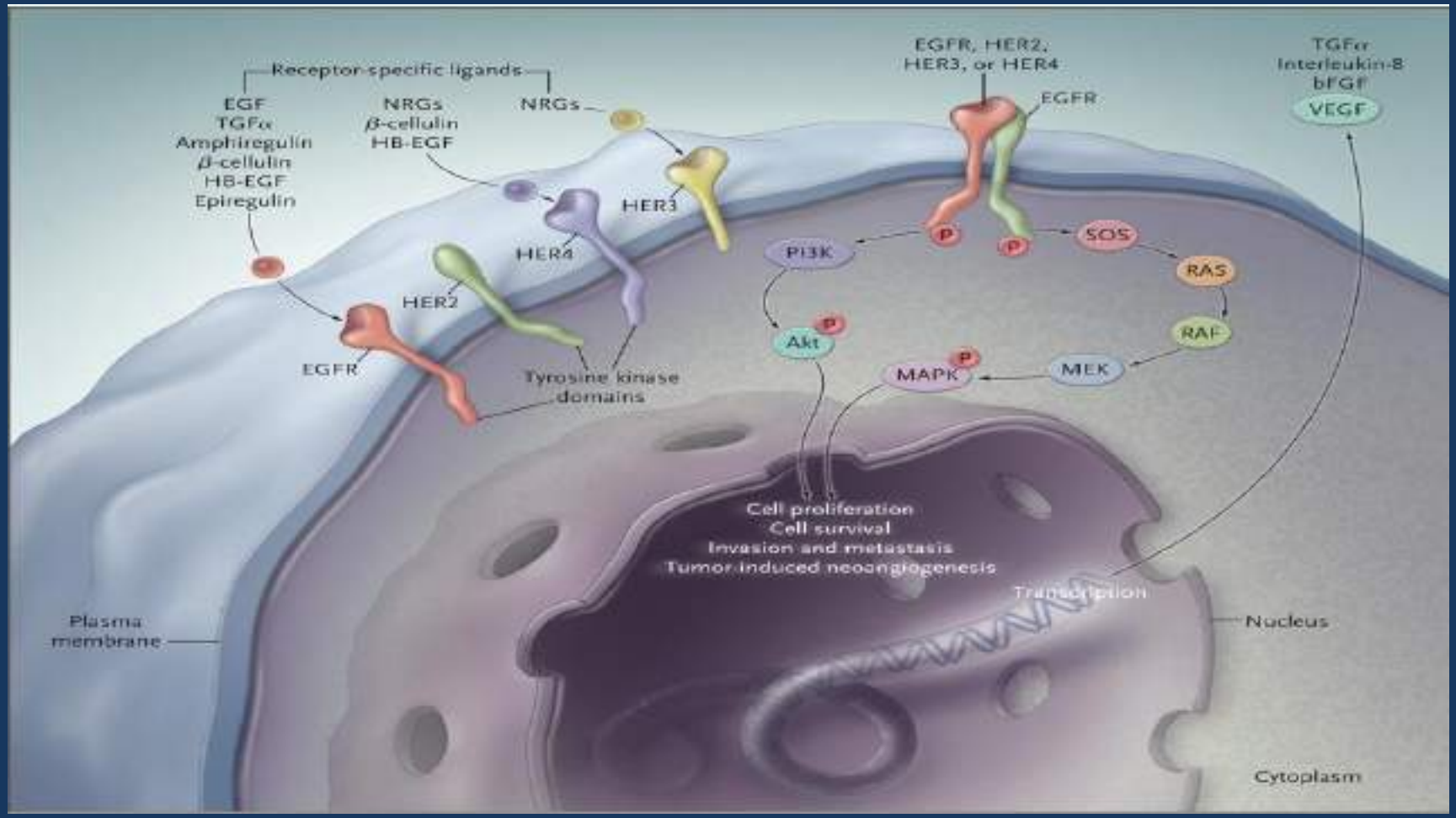
original reports

Pembrolizumab Alone or With Chemotherapy for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma in KEYNOTE-048: Subgroup Analysis by Programmed Death Ligand-1 Combined Positive Score

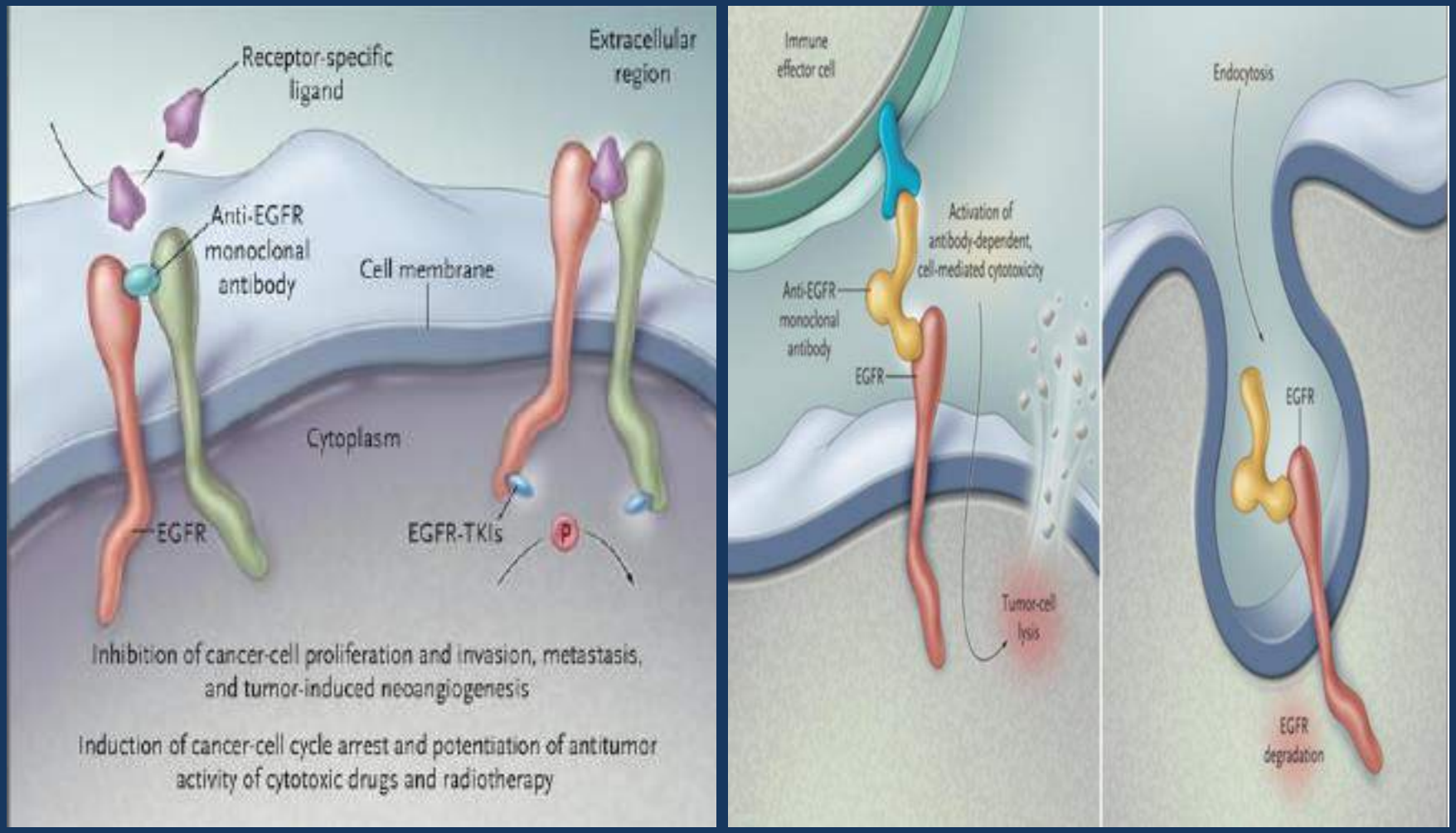
Barbara Burtness, MD[1]; Danny Rischin, MBBS, FRACP, MD[2]; Richard Greil, MD[3]; Denis Soulières, MD, MSc, FRCPC[4]; Makoto Tahara, MD, PhD[5]; Gilberto de Castro Jr, MD, PhD[6]; Amanda Psyrri, MD, PhD[7]; Irene Brana, MD, PhD[8]; Neus Basté, MD[9]; Prakash Neupane, MD[9]; Åse Bratland, MD, PhD[10]; Thorsten Fuereder, MD[11]; Brett G.M. Hughes, BSc, MBBS[12]; Ricard Mesia, MD[13]; Nuttapong Ngamphaiboon, MD[14]; Tamara Rordorf, MD[15]; Wan Zamaniah Wan Ishak, MD[16]; Joy Ge, PhD[17]; Ramona F. Swaby, MD[17]; Burak Gumuscu, MD, PhD[17]; and Kevin Harrington, MBBS, PhD, FRCP, FRCR[18]

Mechanism of action



N Engl J Med 2008; 358:1160-1174

Anti EGFR drugs – MOA



N Engl J Med 2008; 358:1160-1174