LE NEOPLASIE DEL DISTRETTO TESTA COLLO
BEST OF THE YEAR 2018

Roma 19 dicembre 2018

Marco Ciaparrone

Dipartimento di Oncologia

Ospedale“S.Giovanni Calibita”

Isola Tiberina – Roma

Presentation outline

- ✓ Locally advanced disease
- ✓ Recurrent/metastatic disease
- ✓ Platinum refractory disease

Locally advanced disease:standard treatments

Locally advanced stage (III-IV M0; TNM 7°ed): T3-4a N0-1; any T, N2-3

Multimodal:

Resectable disease with conservative surgery:

- Surgery followed by RT or concomitant RT/CT in high risk patients (extranodal disease, positive margins)

Combined:

Unresectable disease or demolitive surgery (oropharynx)

- Concomitant RT/CT

Larynx preservation program (larynx; hypopharynx)

- Induction CT followed by RT
- Concomitant RT/CT

Locally advanced disease: standard treatments

- ✓ Concomitant platinum based therapy (CRT) is the treatment of choice for medically fit patients with locally advanced unresectable disease

  (Evidence level: I)[1]
- ✓ RT + Cetuximab is an alternative option to CRT

  (Evidence level: I-IIB) [1]
- ✓ Decreased efficacy for pts (MACH-NC data)[2]:

  ≥ 70 years→ HR: 1

  PS≥ 2 → HR: 0.93

[1] NCCN Head and Neck guidelines 2018; [2] Pignon et al, Radiot and oncology 2009

Locally advanced disease: Cisplatin concomitant treatment

- ✓ Two schedule: high dose triweekly cisplatin (100 mg/mq; 3 doses) and low dose weekly (40 mg/mq; 7 doses)
- ✓ Triweekly is the most used schedule, no prospective comparison
- ✓ Several meta-analisys showed no difference in LRC, PFS and OS[1-3]
- ✓ Weekly cisplatin is less toxic [1]
- ✓ Requested cumulative dose to significantly improve OS and PFS is ≥ 200 mg/mq[4-5]

[1]Szturz et al, The Oncologist, 2017; [2]Guan J et al, Oncotarget, 2016; [3]Jacinto JK et al, British Institute of Radiology; 2017; [4]Strojan P et al, Head and Neck 2016; [5]Ang KK et al, Abs 5507; ASCO 2010

Locally advanced disease: intensification strategies

OS: 54% at 2 years, 34% at 5 years

INTENSIFICATION

Increase efficacy, with acceptable toxicity

Anti-EGFR

- CDDP/RT + anti-EGFR

Immunocheckpoint inhibitors (ICIs)

- CRT^{1} + ICIs

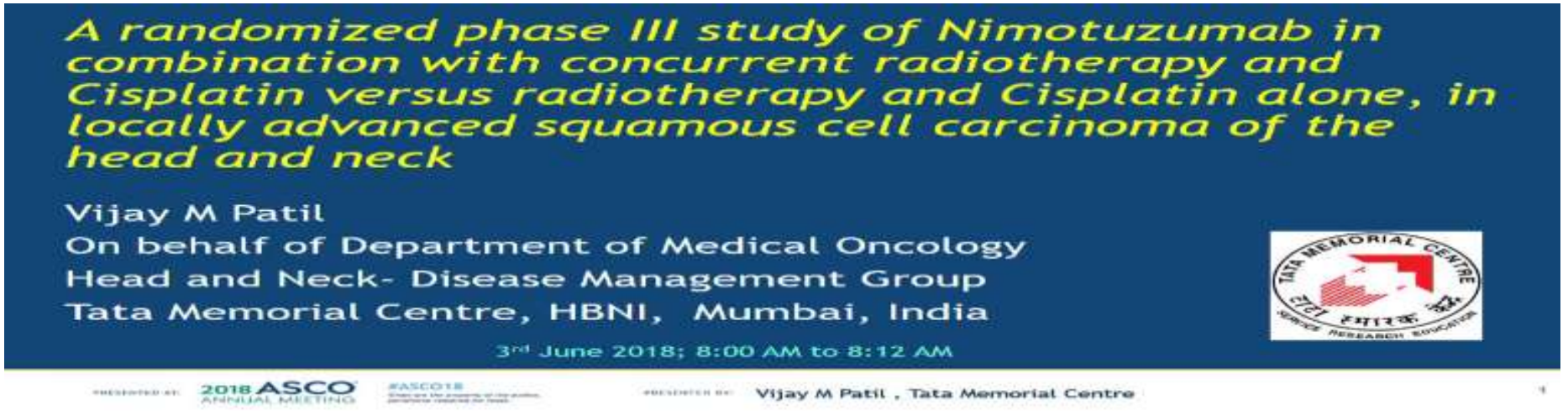
CRT^{1}: CDDP/RT or CET/RT

Intensification strategies
CRT+antiEGFR vs CRT

Group	Phase	Regimen	End point
RTOG 0522[1]	III	CRT (CDDP) + ERB vs CRT (CDDP)	OS no difference
CONCERT 1[2]	II Ran	CRT (CDDP) + Panitumumab vs CRT (CDDP)	LRC no difference
US Study[3]	II Ran	CRT (CDDP) + Erlotinib vs CRT (CDDP)	RR no difference PFS no difference

[1] Ang KK et al, JCO 2014; [2] Mesia et al, Lancet Oncol 2015; [3] Martins RG, JCO 2013

Intensification strategies
CRT+Nimotuzumab *vs* CRT



Stage III/IV
T1–4, N0-3
Unresectable
oral cavity, oropharynx, larynx, hypopharynx

R

N=268

Nimotuzumab[1]+ weekly cisplatin 30 mg/m²+ RT

RT: 70 Gy in 35 fractions/7 weeks

Weekly cisplatin 30 mg/m² + RT

N=268

Primary endpoint:

- Progression free survival

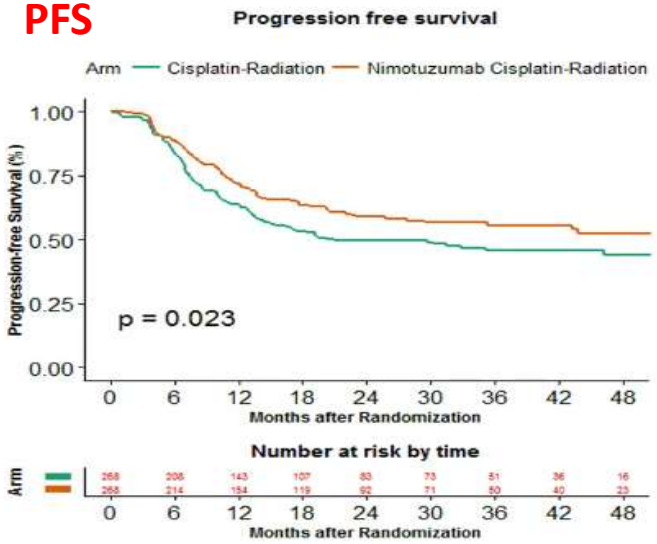
Secondary endpoints:

- Locoregional control
- Overall survival
- Toxicity

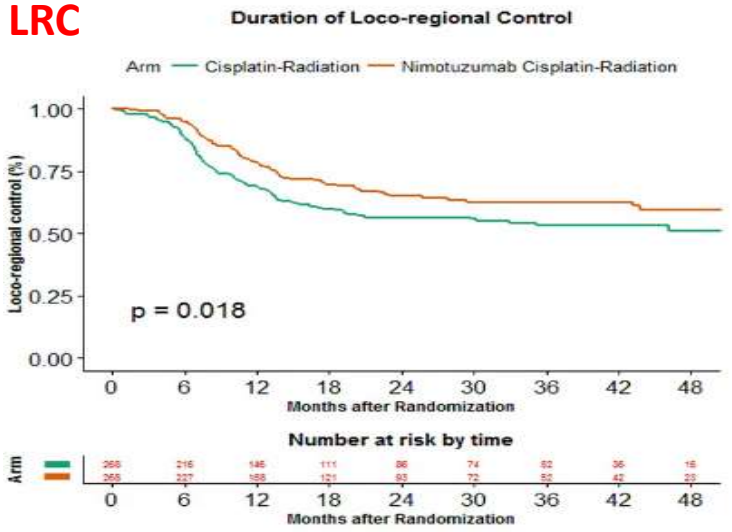
[1]Humanized IgG1 anti EGFR monoclonal antibody

Intensification strategies
CRT+Nimotuzumab *vs* CRT

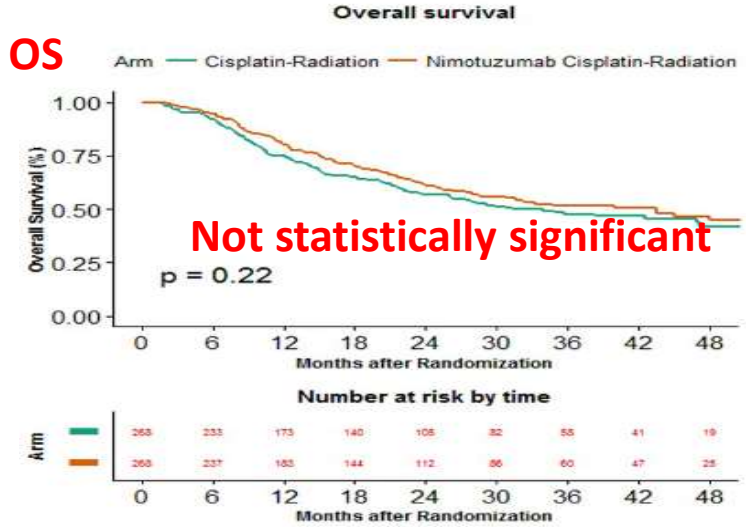
PFS



LRC

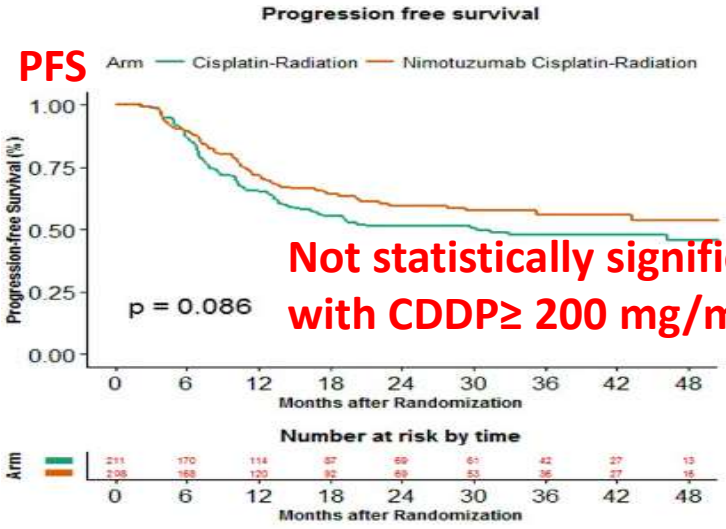


OS



Not statistically significant

PFS



Not statistically significant with CDDP≥ 200 mg/mq

Intensification strategies
CRT+Nimotuzumab *vs* CRT

Results

- ✓ Increase in PFS and LCR statistically significant in favour of the experimental arm
- ✓ No difference in OS
- ✓ No significant increase of toxicities

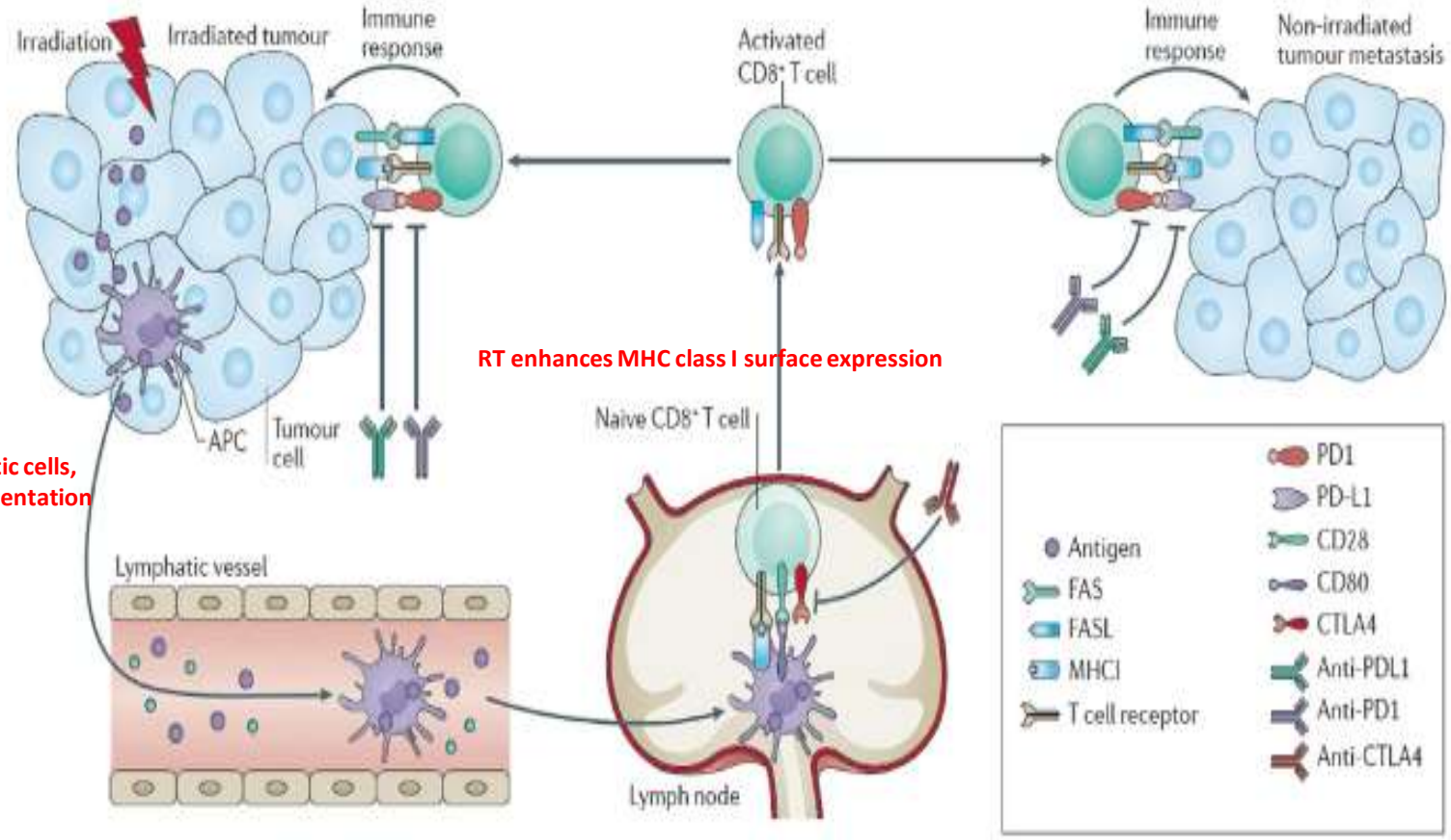
Comments

- ✓ Monocentric study
- ✓ Not applicable to oral cancer (1% in total; 0 pts in experimental arm!)
- ✓ The gain in the experimental arm is probably due to the ability of Nimotuzumab to overcome the suboptimal CT of control arm (30 mg/mq)
- ✓ Insufficient evidence to introduce Nivo+CRT in clinical practice

Intensification strategies
Rationale for immunocheckpoints inhibitors (ICIs) and RT

RT increases the density of tumor–infiltrating lymphocytes

RT modulates the expression of immune checkpoint molecules



RT enhances MHC class I surface expression

RT activates dendritic cells, enhances cross presentation

Intensification strategies
Immunocheckpoints inhibitors (ICIs) and RT

In platinum fit patients

- CDDP/RT *vs* CDDP/RT + ICIs
- CDDP/RT *vs* CetRT + ICIs

In platinum unfit patients

- CetRT *vs* CetRT+ ICIs
- CetRT *vs* RT + ICIs

Intensification strategies
Immunocheckpoints inhibitors (ICIs) and RT

RTOG FOUNDATION

Safety and early efficacy of Nivolumab (Anti-PD1) added to cisplatin- or cetuximab-radiotherapy platforms for patients with intermediate and high-risk local-regionally advanced head and neck squamous cell carcinoma

Robert L Ferris, Maura L Gillison, Jonathan Harris, A Dimitrios Colevas, Loren K Mell, Christina Kong, Richard C Jordan, Kevin Moore, Minh-Tam Truong, Claudia Kirsch, David A Clump, James P Ohr, Kai He, Dukagjin M Blakaj, John F Deeken, Mitchell Machtay, Walter J Curran, Jr., Quynh-Thu Le

Support for this project was provided by Bristol-Myers Squibb Company.

RTOG Foundation 3504

High-Risk SCC
OC, Larynx, Hypopharynx,
p16-negative OP
AJCC 7th edition
T1-2N2a-3,
T3-4N0-3

Intermediate-Risk SCC
p16-positive OP
>10 pack-years
T1-2N2b-3,
T3-4N0-3
≤10 pack-years
T4N0-3,
T1-3N3

SEQUENTIALLY ENROLL

Arm 1:
Nivolumab 240 mg q14D X 10
Cisplatin 40 mg/m²/wk X 7
70 Gy/35 Fx/7 weeks

Arm 2:
Nivolumab 240 mg q14D X 1 then 360 mgs q21D X 6
Cisplatin 100 mg/m² q21D X 3
70 Gy/35 Fx/7 weeks

Arm 3:
Nivolumab 240 mg q14D X 10
Cetuximab 250/400 mg/m²/wk X 7
70 Gy/35 Fx/7 weeks

Adjuvant: Nivolumab 480 mg q28D X 7

RTOG FOUNDATION

Intensification strategies
Immunocheckpoints inhibitors (ICIs) and RT

1 dose limiting toxicity (DLT) nivolumab related (oral mucositis)
2 pts discontinued RT (nivolumab unrelated)
2 pts discontinued cetuximab (nivolumab unrelated)

Immune-related Adverse Events*

Event	Arm 1: RT + cis q7 + nivo (n = 10)		Arm 2: RT + cis q21 + nivo (n = 9)		Arm 3: RT + cetux + nivo (n = 10)	
	Grade 1-2 (n)	Grade 3–4 (n)	Grade 1-2 (n)	Grade 3–4 (n)	Grade 1-2 (n)	Grade 3–4 (n)
Endocrine						
Hypothyroidism	3	0	3	0	2	0
Hyperthyroidism	2	0	2	0	1	0
Gastrointestinal						
Colitis	1	0	0	0	1	0
Diarrhea	4	1	0	2	4	0
Hepatic						
Transaminitis	3	0	2	0	2	0
Pancreatic						
Lipase	0	2	2	1	1	1
Amylase	3	1	1	1	0	0
Renal	0	0	1	0	0	0

*Additional grade ≥ 3 events attributable to nivolumab: adrenal insufficiency, neutropenia, lymphopenia, oral mucositis, fatigue, anorexia, hyponatremia.

RTOG FOUNDATION 12

44 vs 5% (Checkmate 141)

27 vs 7% (Checkmate 141)

Caution for overlapping toxicities (diarrea, dysthyroidism, oral mucositis, dermatitis, fatigue, infusion reaction)

Limited data on general and in field (dermatitis) toxicities

Intensification strategies
Immunocheckpoints inhibitors (ICIs) and RT

- ✓ Concurrent cetuximab+nivo/RT is safe
  - No new safety concerns were identified with cetuximab+nivo/RT
  - Cetuximab and RT delivery were not compromised by the addition of nivo

Previously reported DLT rates for cisplatin+nivo/RT also acceptable

- ✓ Adjuvant treatment is considered feasible
  - 2/8 pts discontinued treatment due to nivo adverse events

- ✓ Oncologic outcome appears promising at early follow up (1 recurrence at 10 months)

ICIs and combined treatments
Current landscape of Phase III trials

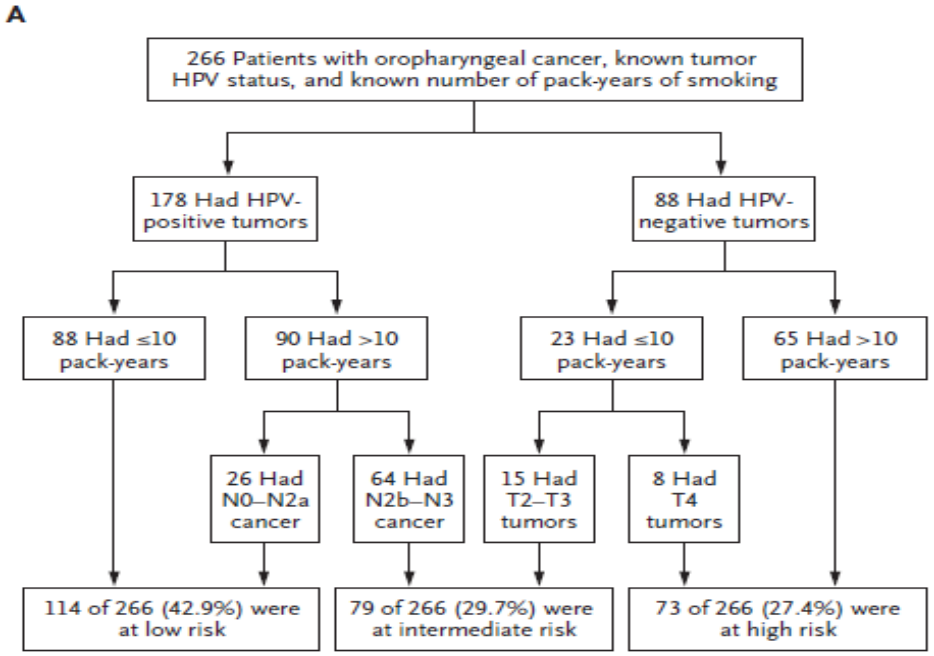
Agent	Study	Investigational arm	Control arm
Avelumab	JAVELIN HN 100 (NCT02952586)	RT+Cisplatin+Avelumab	RT+Cisplatin
Pembrolizumab	KEYNOTE-412 (NCT03040999)	RT+Cisplatin+Pembrolizumab	RT+Cisplatin
Nivolumab	CA209-9TM (NCT03349710)	RT+Cisplatin+Nivolumab (Cis fit) RT+Cetuximab+Nivolumab (Cis unfit)	RT+Cisplatin (Cis fit) RT+Cetuximab (Cis unfit)
Durvalumab	NRG HN-004 (NCT03258554)	RT+Durvalumab (Cis unfit)	RT+Cetuximab (Cis unfit)
Avelumab	REACH (NCT02999087)	RT+Avelumab +Cetuximab (Cis fit) RT+Avelumab +Cetuximab (Cis unfit)	RT+Cisplatin (Cis fit) RT+Cetuximab (Cis unfit)

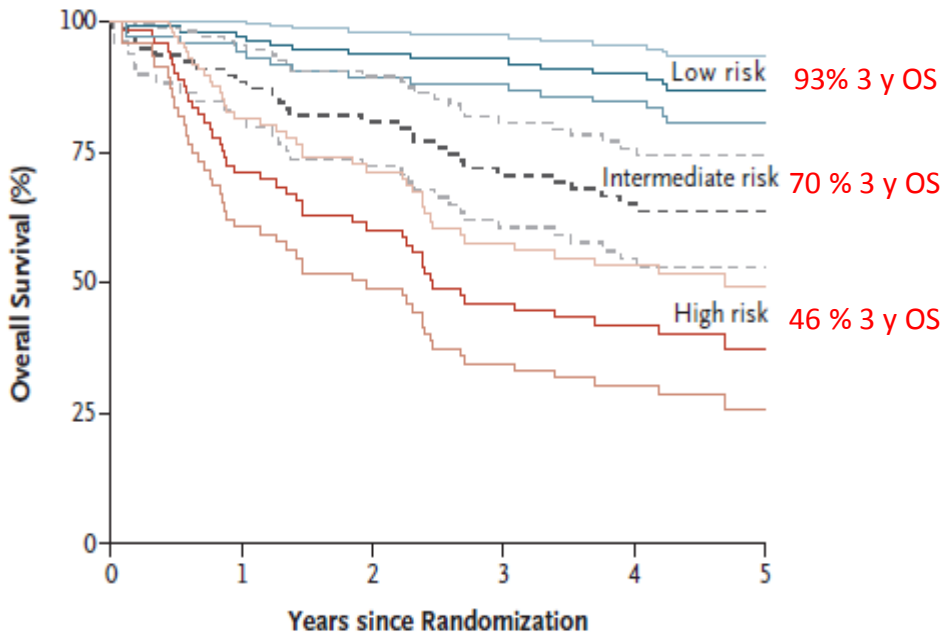
Maintenance therapy or not: ongoing trials do not isolate this question, all continue immunotherapy beyond RT

Deintensification strategies
Rationale and pts selection

Reducing toxicity without compromising efficacy

- HPV positive tumor status is a strong, independent predictor of good prognosis among pts with locally advanced oropharyngeal cancer[1]
- HPV positive oropharyngeal cancer pts are candidates for deintensification
- Risk-stratification models incorporating HPV expression, tobacco use, nodal status and T stage categorize patients into a low, intermediate or high probability of poor prognosis





[1]Ang et al, NEJM, 2010

Deintensification strategies

1. Cetuximab as an alternative to cisplatin in concomitant radiation
2. Induction chemotherapy followed by decreased chemo-radiotherapy dose in good responders
3. Surgical resection with or without adjuvant chemo-radiotherapy (based on histopathology risk factors)

Table 1. Deintensification Clinical Trials in Locally Advanced HPV-Positive OPC

Trial	Phase	No. of Patients	Inclusion Criteria	Treatment
Radiation deintensification trials				
ECOG 1308 (NCT01084083)	II	80	Resectable stages IIIA/IIIB and IVA/IVB HPV-positive OPC (p16-high or HPV-16 ISH positive)	IC, then response-adapted RT (54 or 66-70 Gy) with cetuximab
The Quarterback Trial (NCT01706939)	III	365	Stage III/IV (M0) HPV-positive OPC/ unknown primary/nasopharynx. Excludes active smokers/> 20 PY	IC with TPF: patients with CR/PR randomly assigned 2:1 to carboplatin with RT (56 *v* 70 Gy) per week. Nonresponders receive standard RT
ECOG 3311 (NCT01898884)	II	377	Resectable stage III-IVB p16-positive OPC	TORS then risk-adapted postoperative treatment (observation/50 *v* 60/66 Gy with platinum once per week)
Chemotherapy deintensification trials				
ADEPT (NCT01687413)	III	500	Transoral resected p16-positive OPC (R0 margin), T1-4a, pN positive with ECE	Postoperative adjuvant 60-Gy RT with or without weekly cisplatin
RTOG 1016 (NCT01302834)	III	987	T1-2, N2a-3, or T3-4, any N, HPV-positive OPC	Cetuximab *v* high-dose cisplatin concurrent with accelerated IMRT (70 Gy in 6 weeks)
TROG 12.01 (NCT01855451)	III	200	Stage III (excluding T1-2, N1) or IV (excluding T4, N3, or M1) HPV-positive OPC if ≤ 10 PY. If > 10 PY, only N0-2a	Cetuximab *v* cisplatin concurrent with RT (70 Gy) once per week
De-ESCALATE (NCT01874171)	III	304	Stage III-IVA HPV-positive OPC (T3N0-T4N0, T1N1-T4N3). Excludes ≥ N2b, > 10 PY	Cetuximab *v* high-dose cisplatin concurrent with RT (70 Gy)
NRG-HN002 (NCT02254278)	II	296	T1-2, N1-2b, or T3, N0-2b disease and < 10 PY HPV-positive OPC	Reduced-dose IMRT (60 Gy) with/without weekly cisplatin

Bhatia et al, JCO 2015

Deintensification strategies
De-ESCALaTE HPV TRIAL

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**

Determination of **E**pidermal growth factor receptor-inhibitor (cetuximab) versus Standard chemotherapy (**C**isplatin) early **A**nd **La**te **T**oxicity **E**vents in human papillomavirus-positive oropharyngeal squamous cell carcinoma
De-ESCALaTE HPV

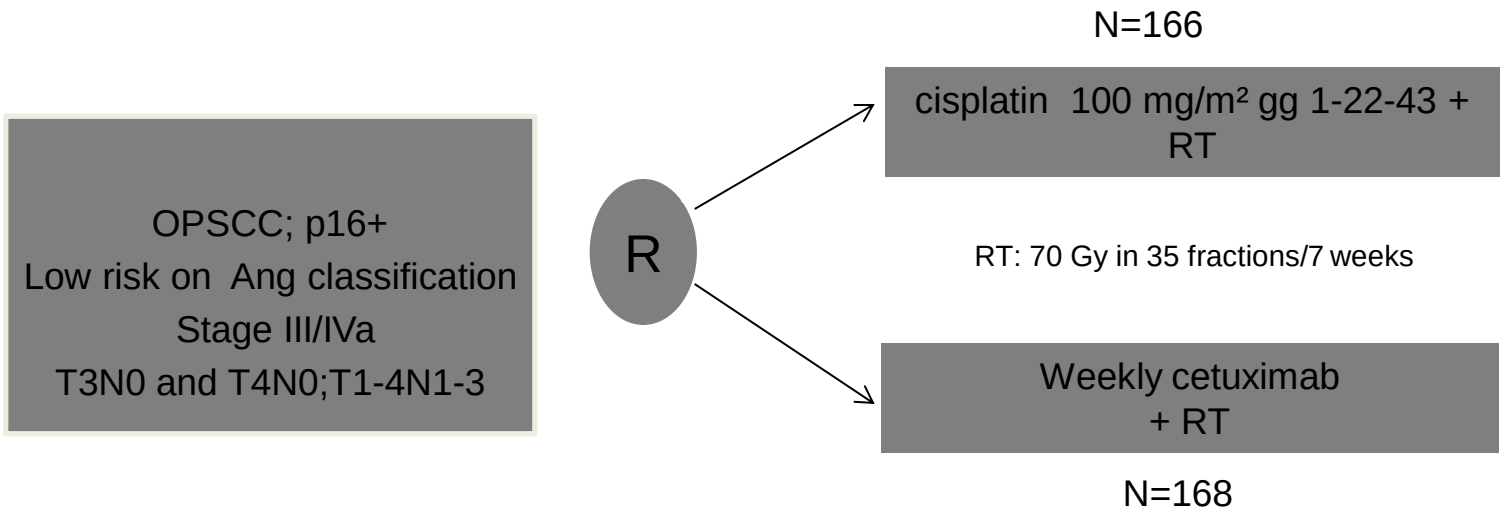
Prof Hisham Mehanna
Director, Institute of Head and Neck Studies and Education
University of Birmingham

On behalf of M. Robinson, A. Kong, A. Hartley, P. Mistry, M. Dalby, T. Fulton-Lieuw, A. Gray, B. Foran, M. Sen, L. O'Toole, K. Dyker, H. Al Booz, R. Moleron, S. Brennan, E. Aynsley, A. Chan, D. Srinivasan, R. Leemans, De-escalate trial group, J. Dunn

MUNICH 2018 ESMO congress

UNIVERSITY OF BIRMINGHAM

Deintensification strategies
De-ESCALaTE HPV TRIAL



Primary endpoint:

- Overall severe toxicity (CTCAE v4 G3-5)

Secondary endpoints:

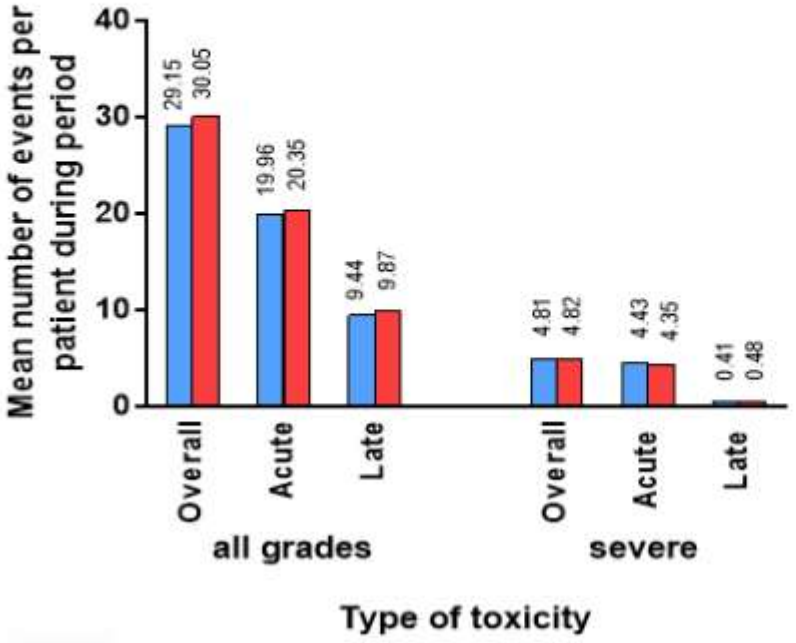
- Overall survival and recurrence
- Overall number of acute severe events
- Overall number of late severe events
- QoL
- Swallowing

POPULATION OF LOW RISK HPV +

Deintensification strategies
De-ESCALaTE HPV TRIAL

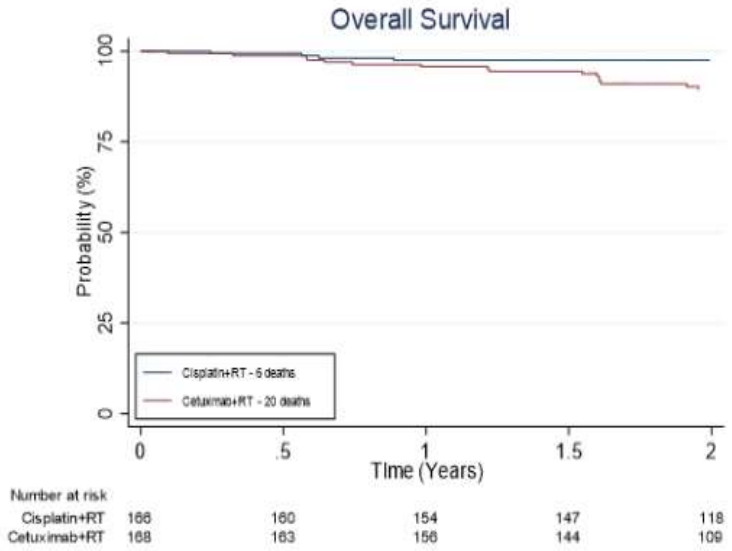
PRIMARY OUTCOME: TOXICITY

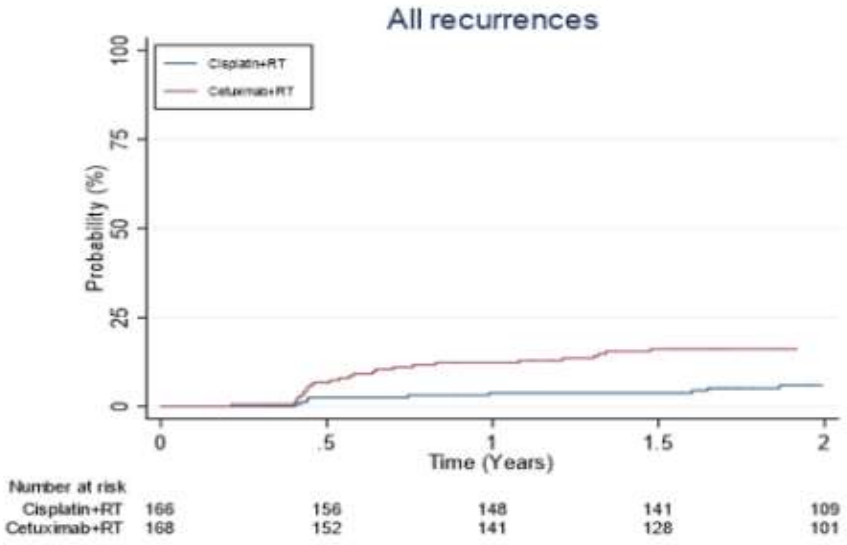
Same rates of severe (G3-5) and all-grade (G1-5) toxicity between arms



No difference in swallowing
No difference in QoL
Cisplatin causes more adverse events

Deintensification strategies
De-ESCALaTE HPV TRIAL





Significantly worse survival with cetuximab
2 y OS: 97.5 vs 89.4%; p=0.001
HR:4.99; 95% CI 1.70-14.7

Significantly worse recurrence rate with cetuximab
2 y OS: 6 vs 16%; p=0.0007
HR:3.39; 95% CI 1.61-7.19

Deintensification strategies
RTOG-1016

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

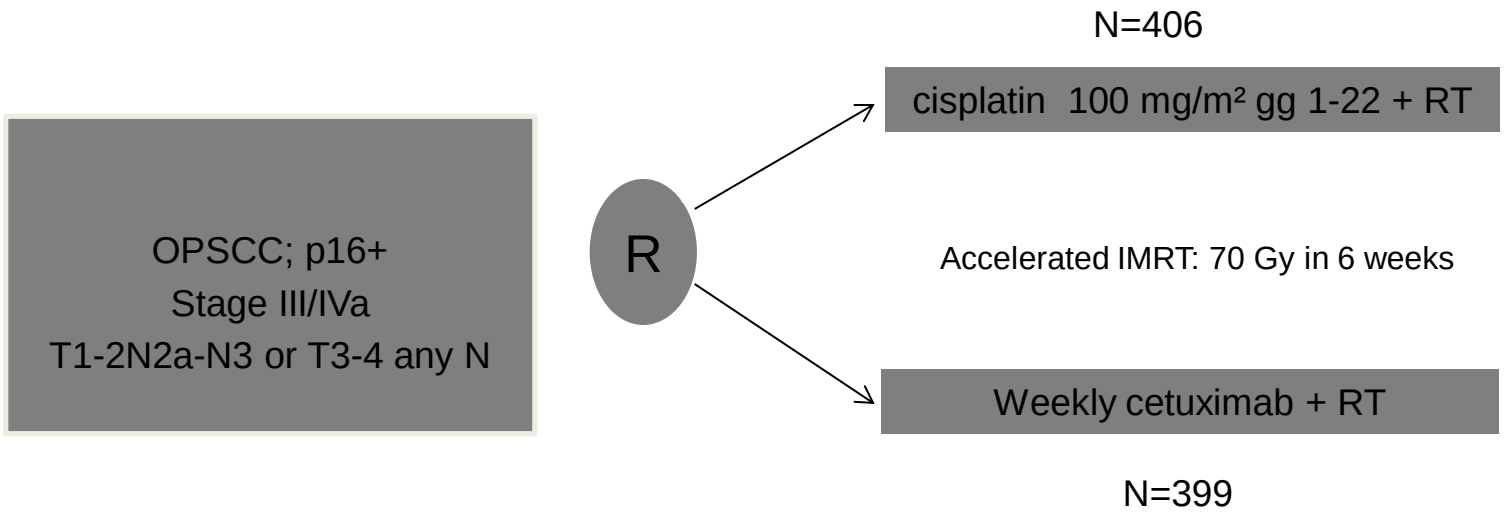
Maura L Gillison, Andy M Trotti*, Jonathan Harris, Avraham Eisbruch, Paul M Harari, David J Adelstein, Erich M Sturgis, Barbara Burtness, John A Ridge, Jolie Ringash, James Galvin, Min Yao, Shlomo A Koyfman, Dukagjin M Blakaj, Mohammed A Razaq, A Dimitrios Colevas, Jonathan J Beitler, Christopher U Jones,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

NRG-RTOG 1016: Phase III Trial Comparing Radiation/Cetuximab to Radiation/Cisplatin in HPV-related Cancer of the Oropharynx

A. Trotti[1], J. Harris[2], M. Gillison[3], A. Eisbruch[4], P. M. Harari[5], D. J. Adelstein[6], E. M. Sturgis[3], J. M. Galvin[7], S. Koyfman[6], D. Blakaj[8], M. A. Razaq[9], A. D. Colevas[10], J. J. Beitler[11], C. U. Jones[12], N. E. Dunlap[13], S. A. Seaward[14], S. A. Spencer[15], J. A. Ridge[16], J. Phan[3], and Q. T. Le[17]

[1]Moffitt Cancer Center and Research Institute, Tampa, FL, [2]RTOG, Philadelphia, PA, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, [4]University of Michigan, Ann Arbor, MI, [5]University of Wisconsin, Madison, WI, [6]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [7]IROC, Philadelphia, PA, [8]The Ohio State University, Columbus, OH, [9]University of Oklahoma, Oklahoma City, OK, [10]Stanford University, Palo Alto, CA, [11]Emory University, Atlanta, GA, [12]Sutter Medical Group and Cancer Center, Sacramento, CA, [13]University of Louisville Hospital, Louisville, KY, [14]Kaiser Permanente, Vallejo, CA, [15]University of Alabama at Birmingham, Birmingham, AL, [16]Fox Chase Cancer Center, Philadelphia, PA, [17]Stanford Cancer Institute, Stanford, CA

Deintensification strategies
RTOG-1016



Primary endpoint:

- Non inferiority of cetuximab vs cisplatin at 5 y OS

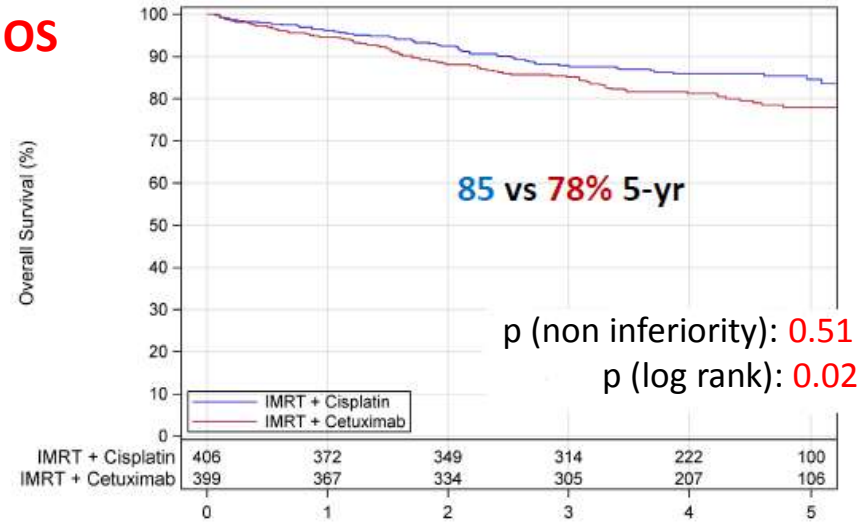
Secondary end points:

- PFS
- Locoregional failure
- Distant metastases
- Toxicity

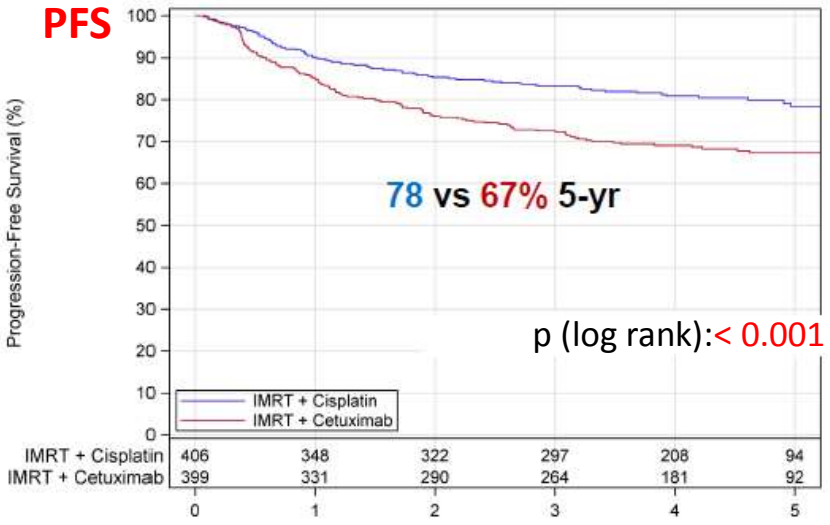
POPULATION OF LOW AND INTERMEDIATE RISK HPV +

Deintensification strategies
RTOG-1016

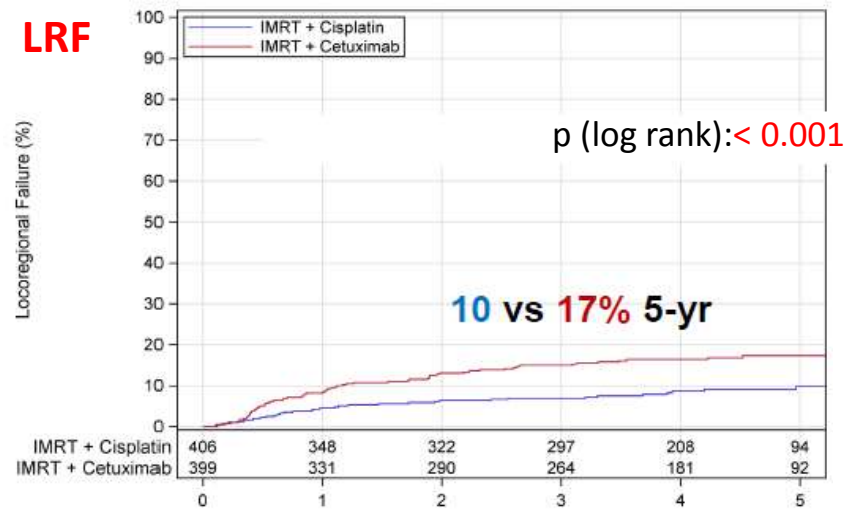
OS



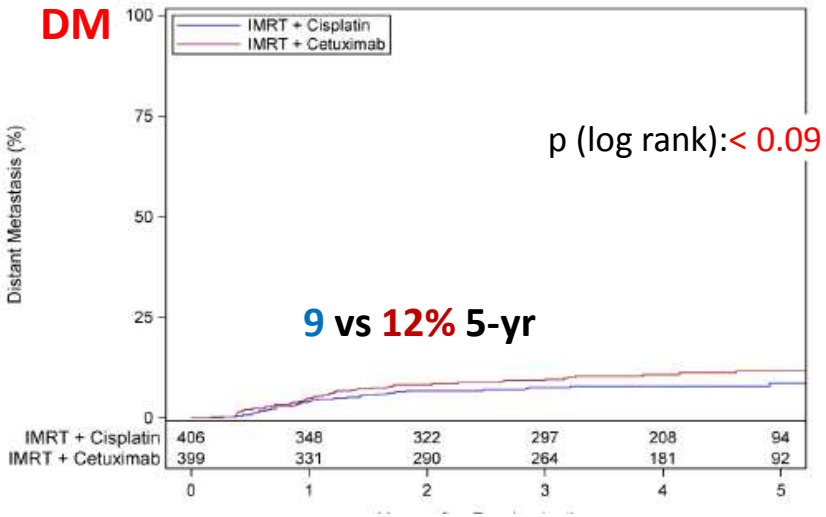
PFS



LRF



DM



Statistically significant difference in OS, PFS and locoregionagional failure in favour of cisplatin

Locally advanced disease

Intensification

- Insufficient data for CDDP/RT + anti EGFR
- Promising data for CRT+ICIs

Deintensification

- Negative data for substitution of cisplatin with cetuximab in good prognosis pts

Platinum based CRT remain the standard in locally advanced disease also in good prognosis pts

RT+CET is an alternative option in platinum unfit pts

Standard treatments in recurrent/metastatic disease

- Resectable disease

  Surgery if possible with postoperative reirradiation (± CT)

- Unresectable disease

  Reirradiation (± CT)

- No surgery or RT

  CT with PF+cet (in fit patients; PS 0-1); median OS: 10 months

Pembro ± CT in recurrent/metastatic disease

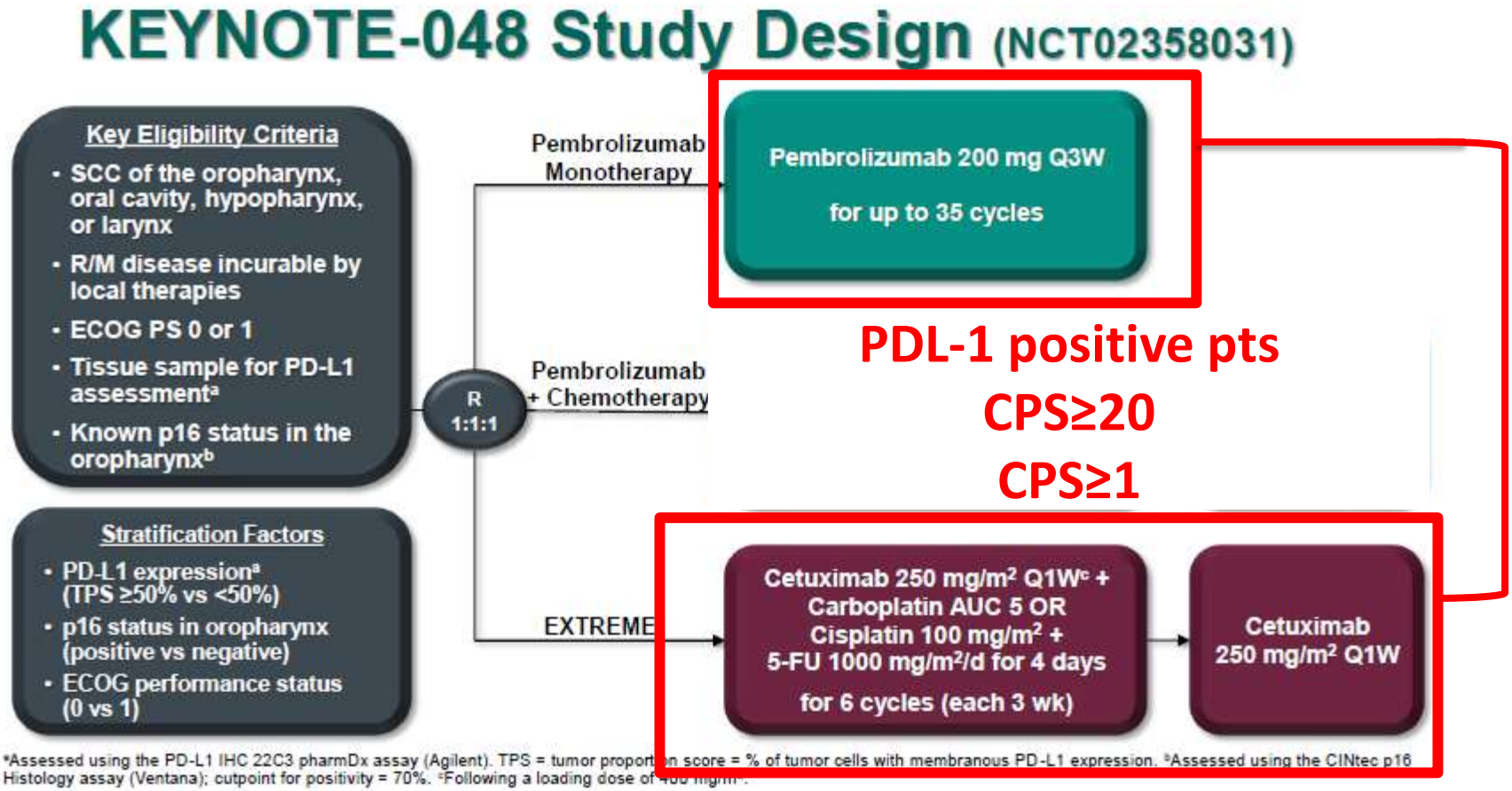
MUNICH 2018 ESMO congress

KEYNOTE-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Barbara Burtness,[1] Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5] Gilberto de Castro,[6] Amanda Psyrri,[7] Neus Basté Rotllan,[8] Prakash Neupane,[9] Åse Bratland,[10] Thorsten Fuereder,[11] Brett GM Hughes,[12] Ricard Mesia,[13] Nuttapong Ngamphaiboon,[14] Tamara Rordorf,[15] Wan Zamaniah Wan Ishak,[16] Ananya Roy,[17] Jonathan Cheng,[17] Fan Jin,[17] Danny Rischin[18]

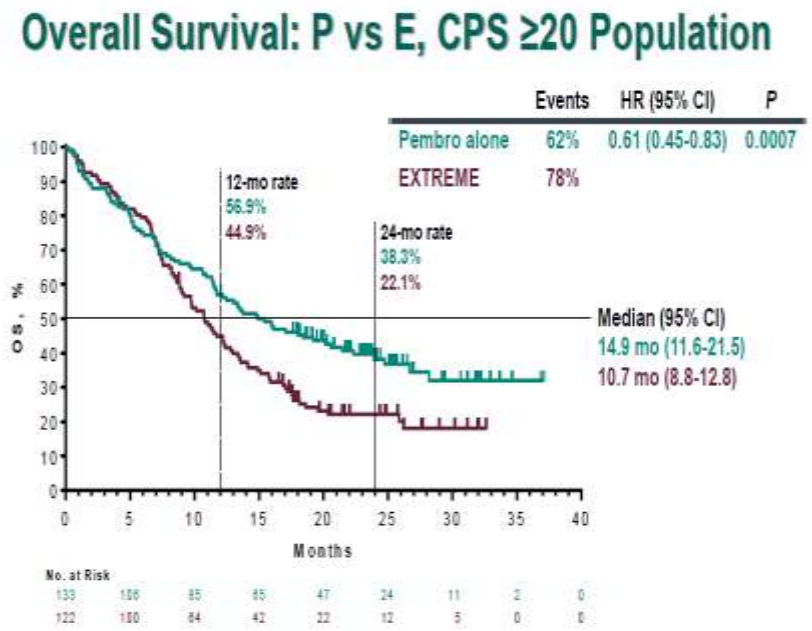
[1]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA; [2]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, UK; [3]Paracelsus Medical University, Salzburg Cancer Research Institute, and Cancer Cluster Salzburg, Salzburg, Austria; [4]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]National Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [8]Vall d'Hebron University Hospital, Barcelona, Spain (currently at Institut Gustave Roussy, Paris, France); [9]University of Kansas Medical Center, Kansas City, KS, USA; [10]Oslo University Hospital, Oslo, Norway; [11]Medical University of Vienna, Vienna, Austria; [12]Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, QLD, Australia; [13]Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [14]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [15]University Hospital, Zurich, Switzerland; [16]University Malaya, Kuala Lumpur, Malaysia; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

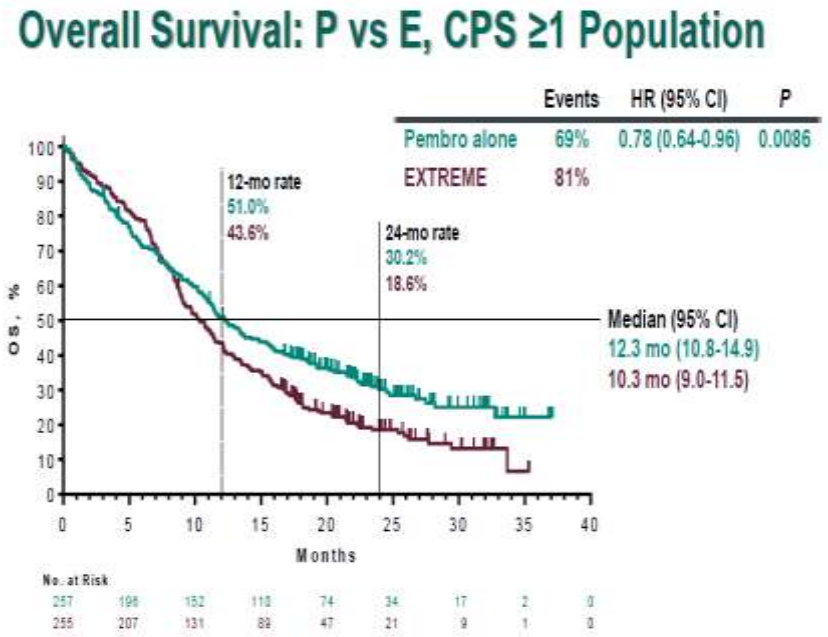
Pembro in recurrent/metastatic disease



PRIMARY END POINTS: OS and PFS

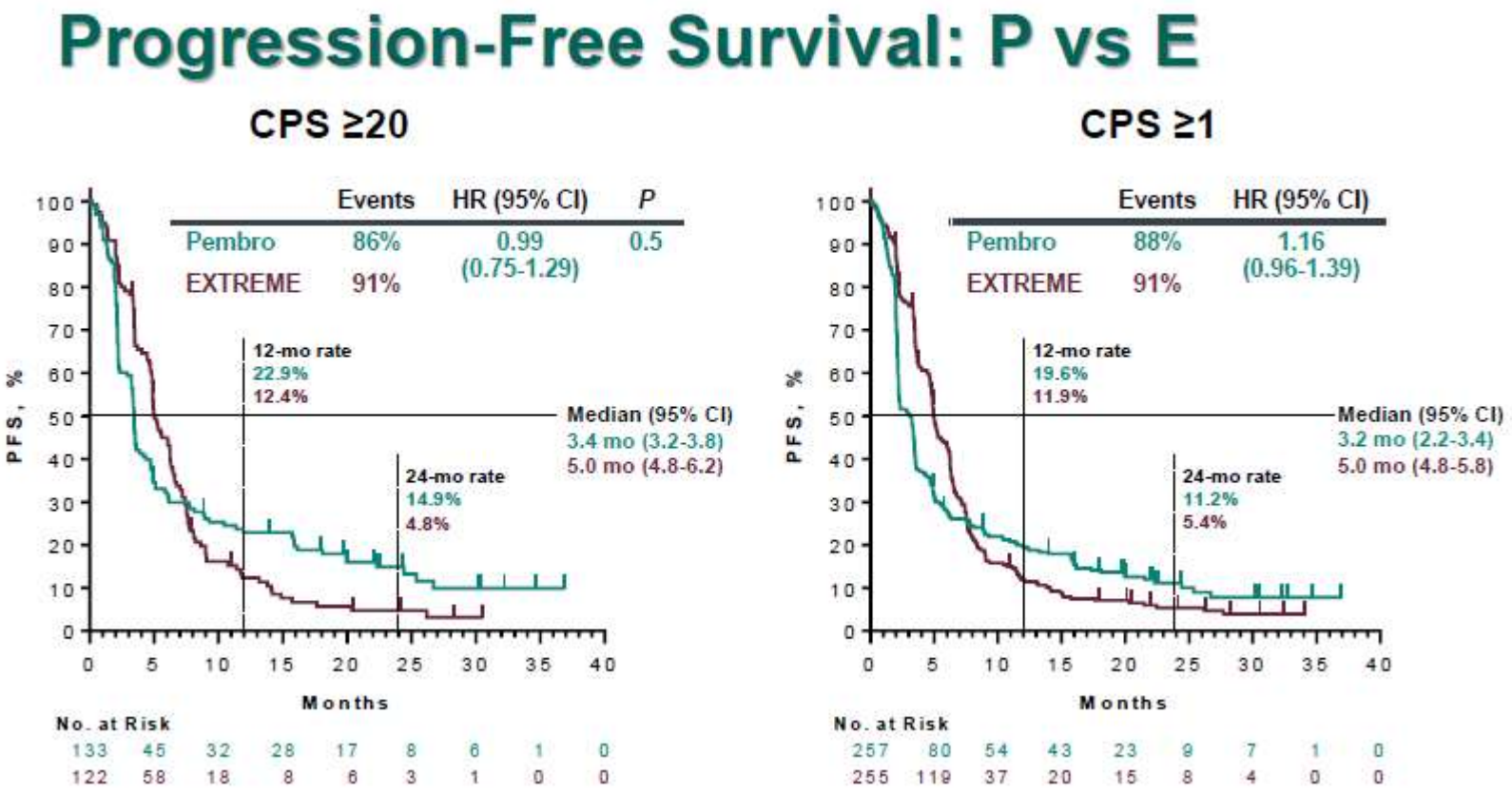
Pembro monotherapy in recurrent/metastatic disease





Statistically significant difference in OS in favour of pembro monotherapy in both populations

Pembro monotherapy in recurrent/metastatic disease



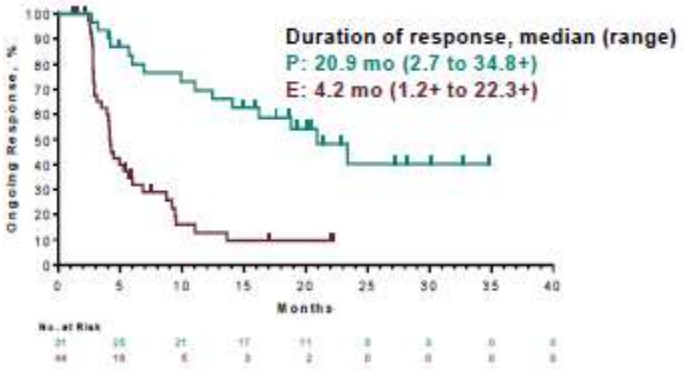
No significant difference in PFS in both populations

Pembro monotherapy in recurrent/metastatic disease

Response Summary, P vs E

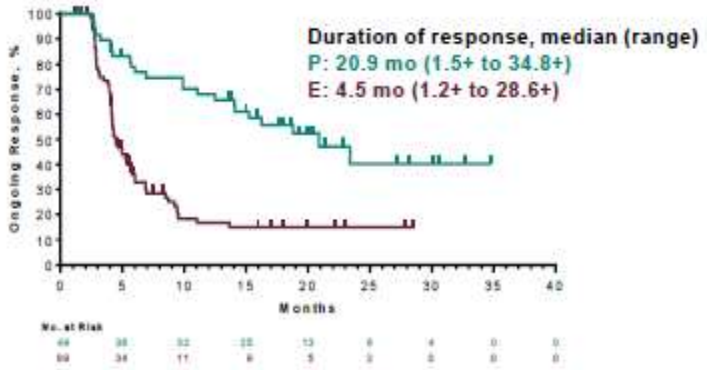
CPS ≥20

Confirmed Response, n (%)	Pembro N = 133	EXTREME N = 122
ORR	**31 (23.3)**	**44 (36.1)**
CR	10 (7.5)	4 (3.3)
PR	21 (15.8)	40 (32.8)
SD	40 (30.1)	42 (34.4)
PD	42 (31.6)	13 (10.7)
Non-CR/non-PD[a]	8 (6.0)	6 (4.9)
Not evaluable or assessed[b]	12 (9.0)	17 (13.9)



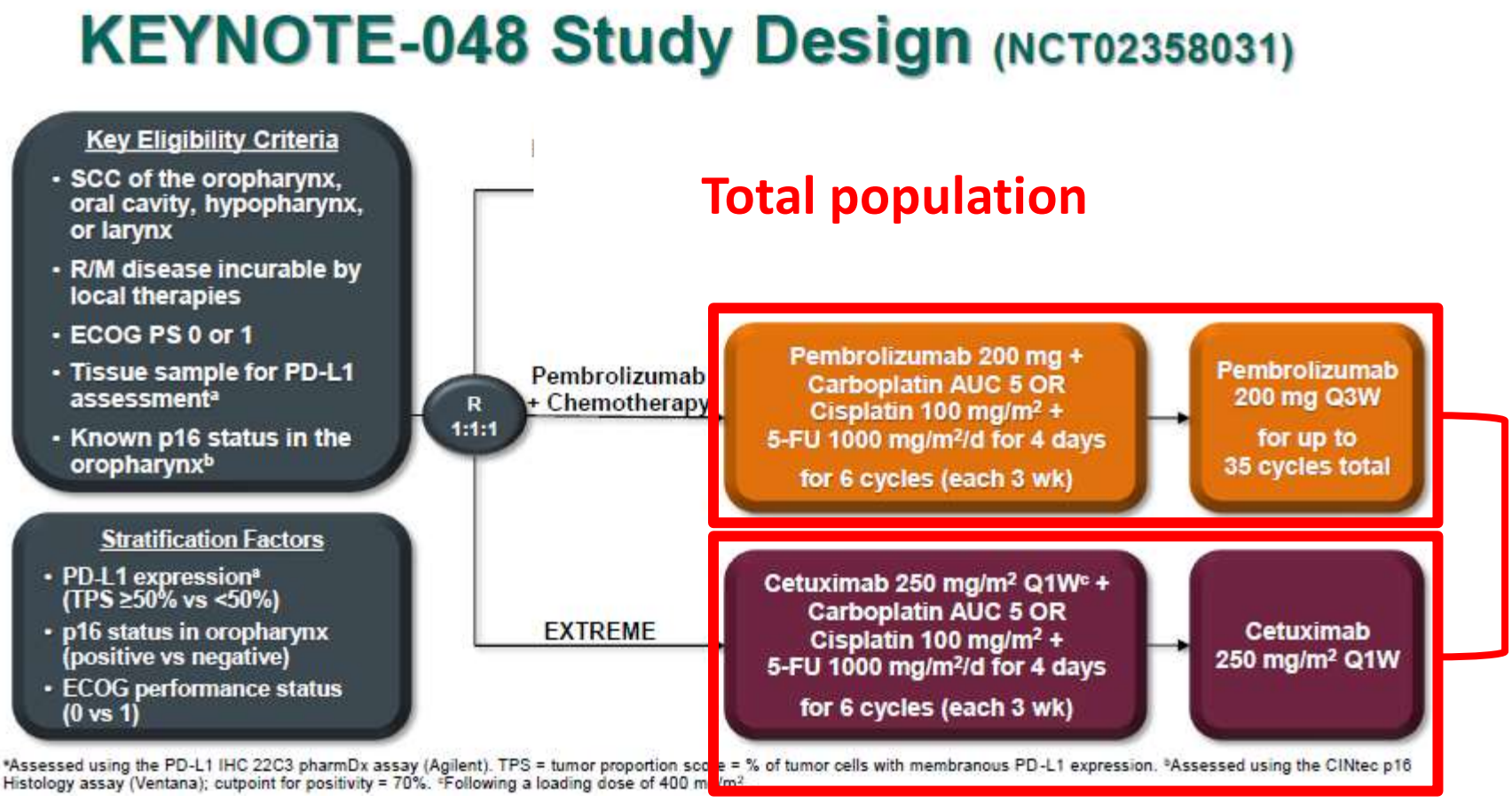
CPS ≥1

Confirmed Response, n (%)	Pembro N = 257	EXTREME N = 255
ORR	**49 (19.1)**	**89 (34.9)**
CR	14 (5.4)	7 (2.7)
PR	35 (13.6)	82 (32.2)
SD	72 (28.0)	83 (32.5)
PD	100 (38.9)	34 (13.3)
Non-CR/non-PD[a]	11 (4.3)	11 (4.3)
Not evaluable or assessed[b]	25 (9.7)	38 (14.9)



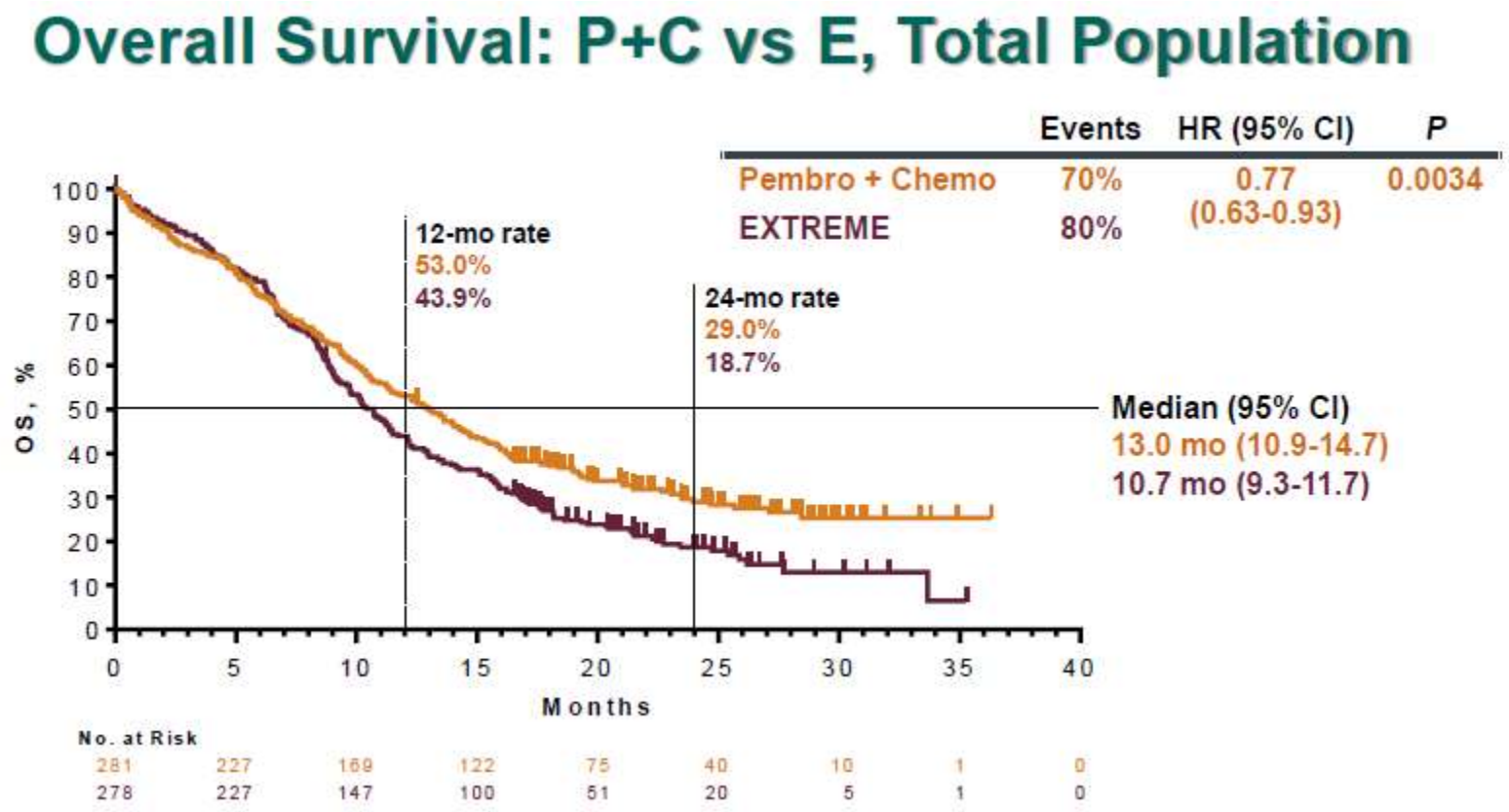
Better RR for CT, but more durable response for pembro monotherapy in both populations

Pembro + CT in recurrent/metastatic disease



PRIMARY END POINT: OS and PFS

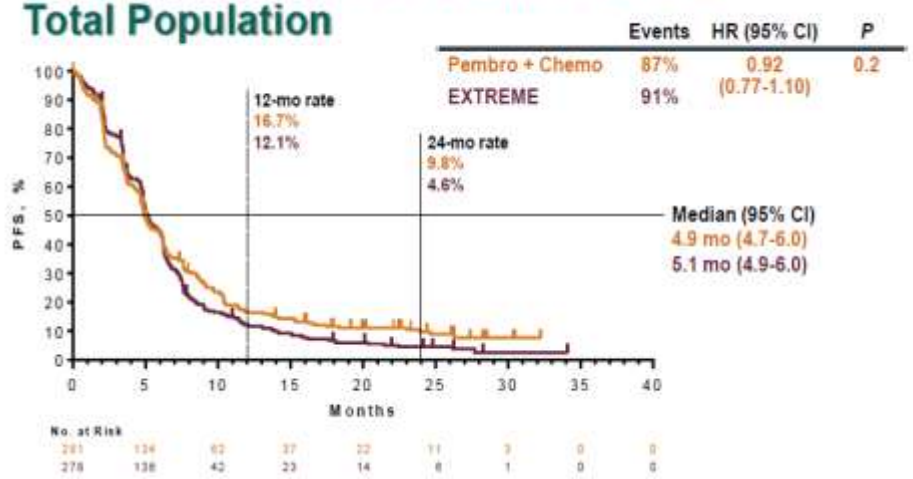
Pembro + CT in recurrent/metastatic disease



Statistically significant difference in OS in favour of pembro + CT

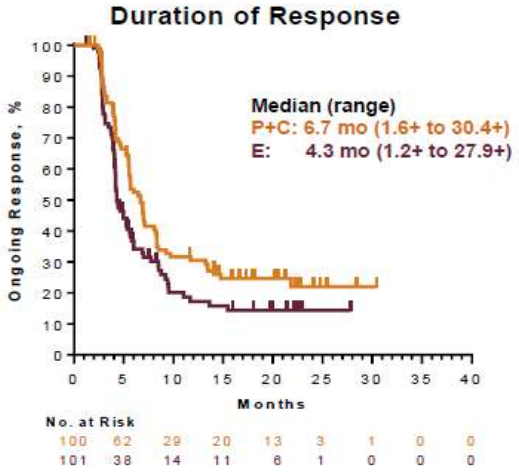
Pembro + CT in recurrent/metastatic disease

Progression-Free Survival: P+C vs E, Total Population



Response Summary, P+C vs E, Total Population

Confirmed Response, n (%)	Pembro + Chemo N = 281	EXTREME N = 278
ORR	**100 (35.6)**	**101 (36.3)**
CR	17 (6.0)	8 (2.9)
PR	83 (29.5)	93 (33.5)
SD	78 (27.8)	94 (33.8)
PD	48 (17.1)	34 (12.2)
Non-CR/non-PD[a]	13 (4.6)	9 (3.2)
Not evaluable or assessed[b]	42 (14.9)	40 (14.4)



No significant difference in PFS and RR, but more durable responses for pembro+CT

Pembro ± CT in recurrent/metastatic disease

- ✓ Pembrolizumab significantly improved OS vs Extreme in the PDL-1 CPS≥20 (HR: 0.61, p= 0.0007) and CPS≥1 (HR: 0.78, p= 0.0086) populations

  -Reduced toxicity

  - No difference in PFS

  - Although pembrolizumab had a lower ORR, responses were more durable

- ✓ Pembrolizumab plus chemotherapy with platinum/5-FU significantly improved OS vs Extreme in the total population (HR: 0.77, p= 0.0034)

  - No difference in PFS and ORR and toxicity

  - Responses to pembrolizumab plus chemotherapy were more durable

Data support

Pembrolizumab monotherapy as a new first line standard for R/M head and neck cancer that express PDL-1

Pembrolizumab plus platinum based-chemotherapy as a new first line standard for R/M head and neck cancer

Standard treatment in cisplatin refractory disease

Pts with PD within 6 mo after platinum-based CT administered as: adjuvant or in the context of primary or recurrent/metastatic disease

✓ **Standard treatment :**

Nivolumab (Checkmate 141)[1]; 2 years follow up:

- OS: 7.7 *vs* 5.1 mo in all pts; HR: 0,68
- OS: 6,5 vs 5,5 mo in PDL < 1; HR: 0,73

AIFA reimbursable irrespective of PDL-1 expression

✓ **Next:**

Pembrolizumab (Keynote 040)[2]

- OS: 8,4 *vs* 6.9 mo in all pts; HR: 0,8
- OS: 11,6 *vs* 6,6 mo in TPS (tumor proportion score) ≥ 50% for PDL-1; HR: 0,53
- OS: 6,3 vs 7 mo in CPS (combined proportion score) < 1; HR:1,28

EMA approved on July 2018 for pts with TPS ≥ 50% for PDL-1

[1]Ferris et al Oral Oncol, 2018; [2]Cohen et al Lancet, 2018

Take home messages

- ✓ **Locally advanced disease :**

  At present: Platinum based CRT remain the standard

  Next : Ongoing trials with CRT+ICIs

- ✓ **Recurrent/metastatic disease :**

  At present: Extreme

  Next: Platinum based therapies with ICIs

  ICIs monotherapy in positive PDL-1 pts

  Treatment choice based on predictive factors and pts characteristics

- ✓ **Platinum refractory disease:**

  At present: Nivolumab

  Next: Nivolumab or Pembrolizumab (PDL-1 ≥ 50%)