For Recurrent/Metastatic Head and Neck Cancer patients.. How do we maximize patient benefit?

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First Priority: Surgical Treatment

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Locally advanced squamous cell carcinoma of the head and neck: A systematic review and Bayesian network meta-analysis of the currently available treatment options

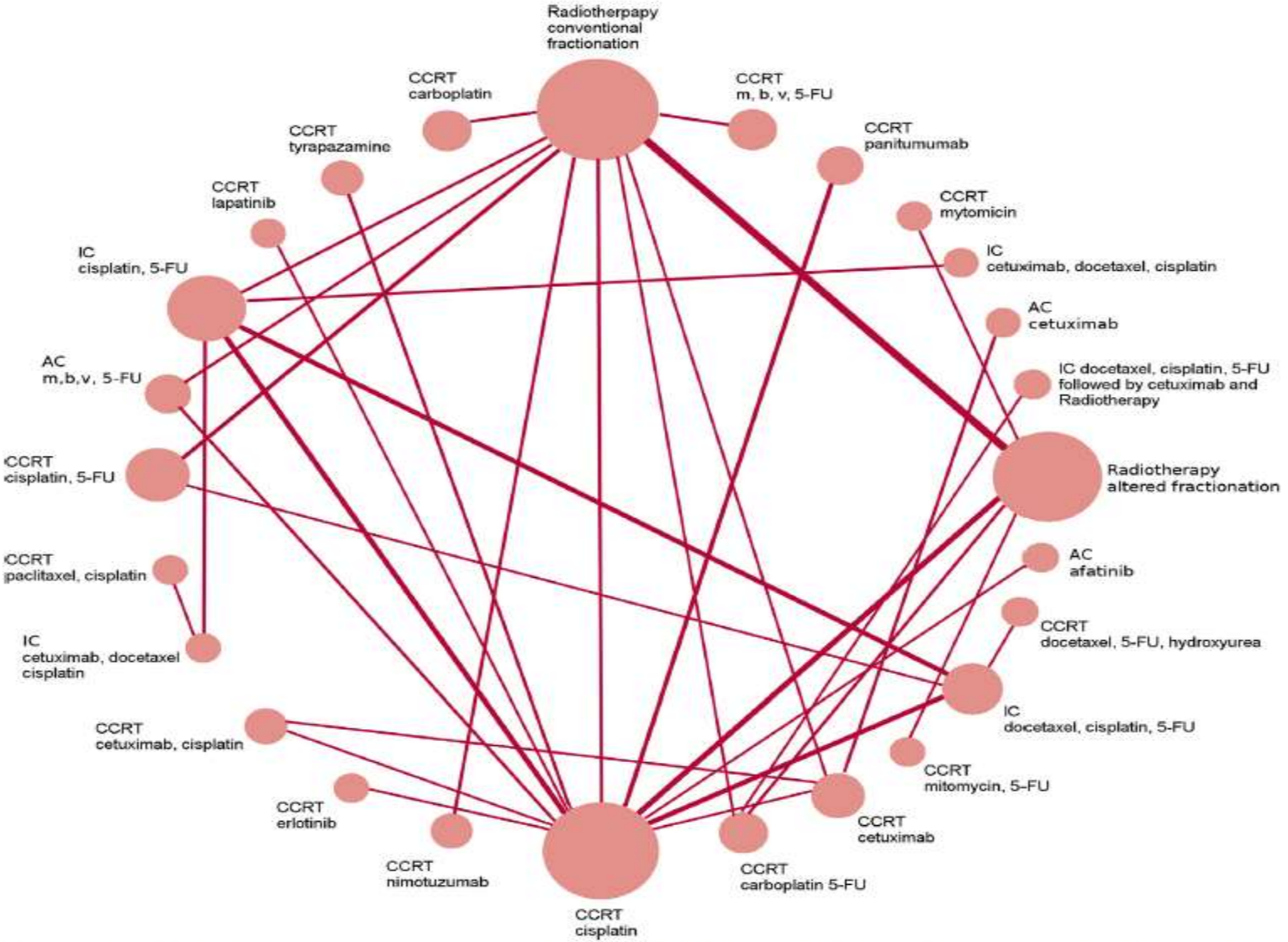


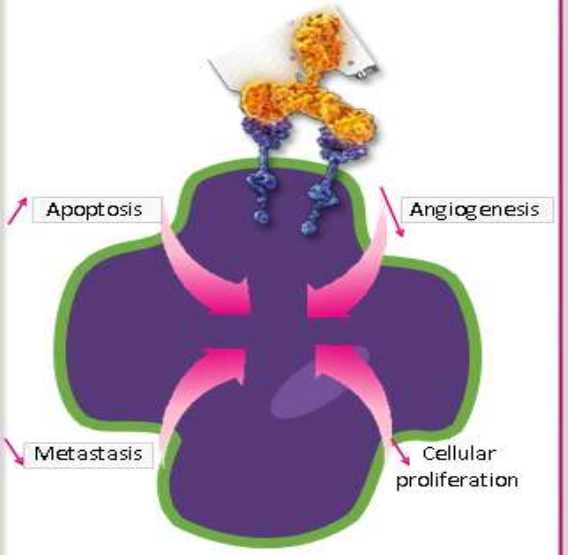
Fig. 2. Network of treatments available for comparison of Overall Survival. Dimensions of nodes and thickness of lines corresponds respectively to the number of studies evaluating a given treatment and the number of studies comparing the two connected treatments.

Table 2
Synthesis of the significant comparisons in the network and the pairwise meta-analyses.

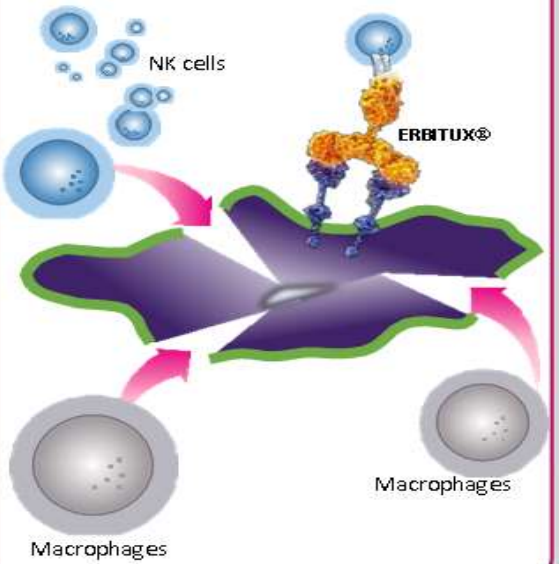
Comparison Overall Survival	Network meta-analysis HR (Random effects, 95% CrI)	Pairwise Meta-analysis HR (IV
CCRT cpt vs RT	0.70(0.62–0.78)	0.74(0.57–0.95)
CCRT carbopt vs RT	1.11(0.81–1.46)	0.67 (0.50–0.90)
CCRT cetuximab vs RT	0.69(0.5–0.97)	0.75(0.59–0.95)
CCRT cpt vs. altered fractionation RT	0.74(0.64–0.84)	0.74 (0.65–0.85)
CCRT cpt vs CCRT carbopt	0.63(0.48–0.86)	Not compared directly
IC docetaxel, cpt, FU vs IC cpt, FU	0.88(0.74–1.06)	0.72 (0.62–0.84)
IC paclitaxel, cpt, FU vs IC cpt, FU	0.74(0.48–1.14)	0.76(0.58–1.00)
IC docetaxel, cpt, FU vs CCRT cpt, fu	0.76(0.58–1.00)	0.73(0.55–0.97)
IC docetaxel, cpt, FU vs RT	0.74(0.59–0.92)	Not compared directly
IC paclitaxel, cpt, FU vs RT	0.65(0.52–0.82)	Not compared directly
IC docetaxel, cpt, cetuximab vs RT	0.55(0.34–0.89)	Not compared directly

Erbitux®: Summary of antitumor action

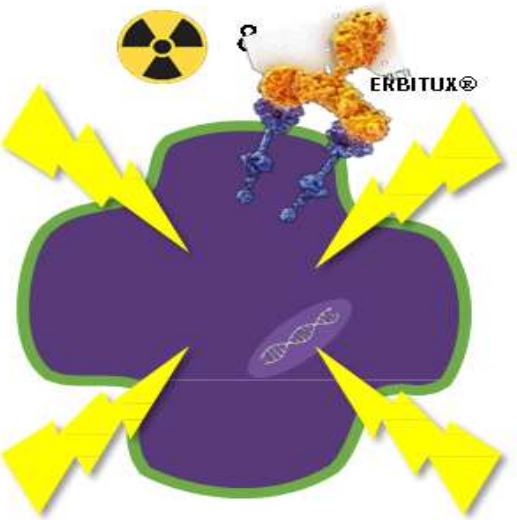
Intracellular action
Blockage of EGFR signaling [1,2,3,4]



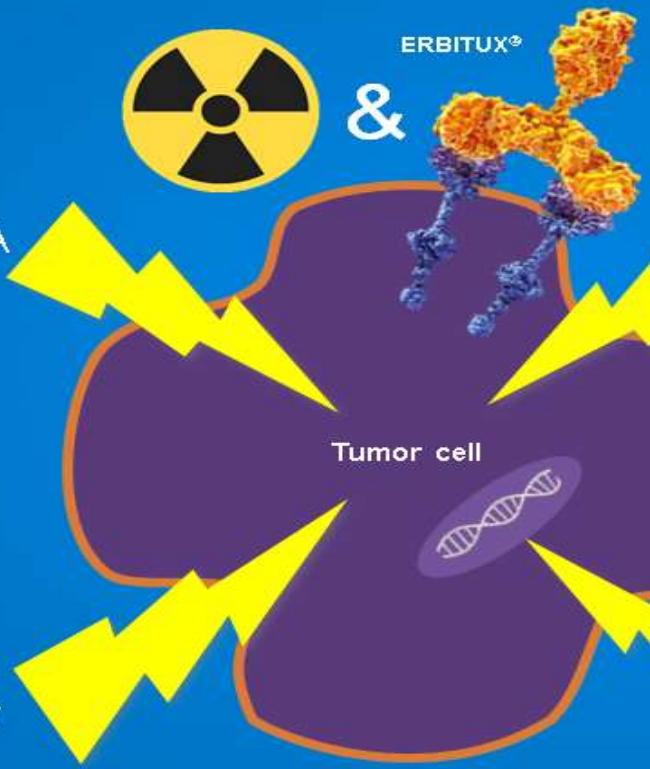
Extracellular action
ADCC [5]



Synergistic action with RT
[6]



Radiotherapy and Erbitux combine to destroy tumor cells



Inhibition of DNA damage repair

Augmention of radiosensitivity (increase of radiosensitive G1 phase cells and reduction of S phase radioresistant cells)

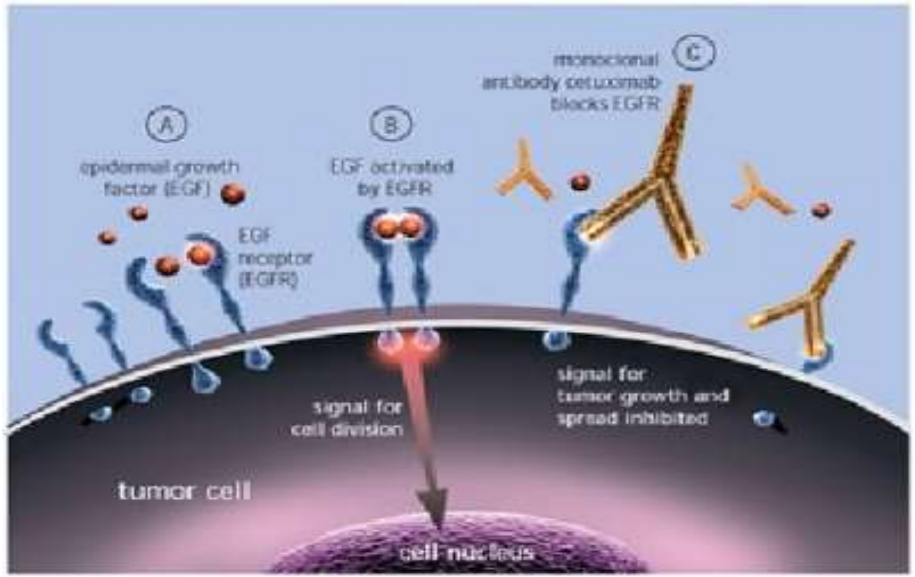
Inhibition of tumor angiogenesis

Augmentation of radiation-induced apoptosis

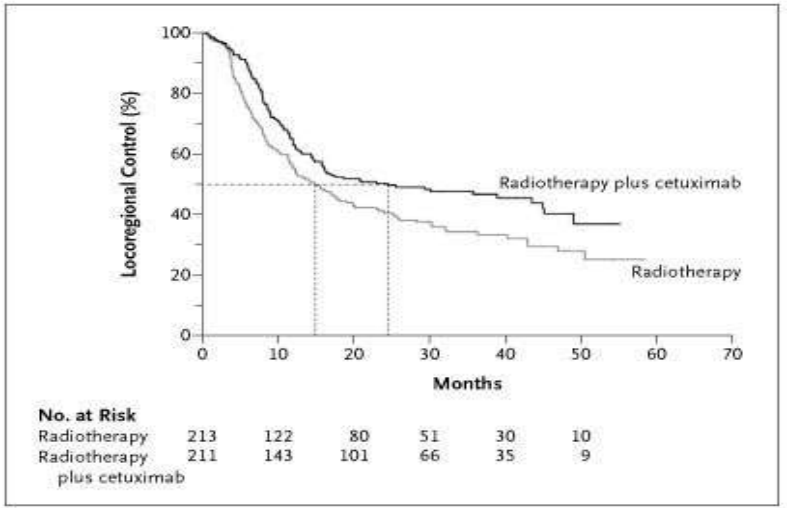
Bio-RT- Cetuximab with RT

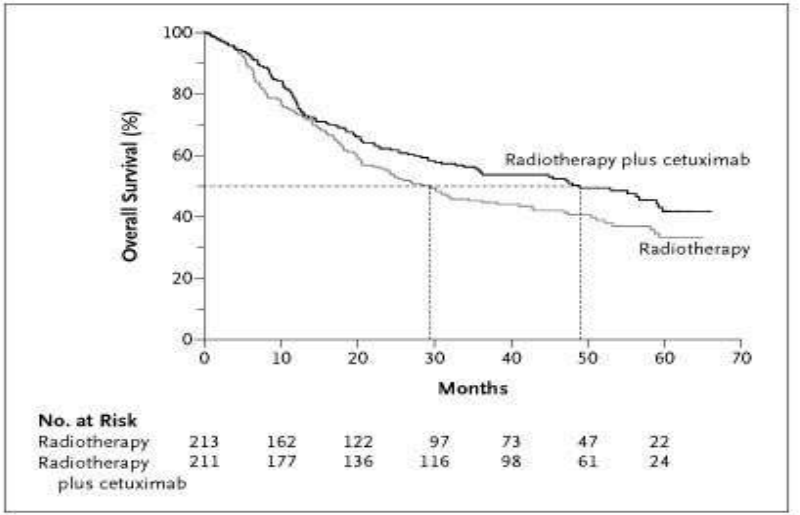
- James A. Bonner, NEJM 2006

Modulation of radiation response following EGFR blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics and tumor angiogenesis.



Bio-RT > RT





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

Oncology

Clinical Study

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

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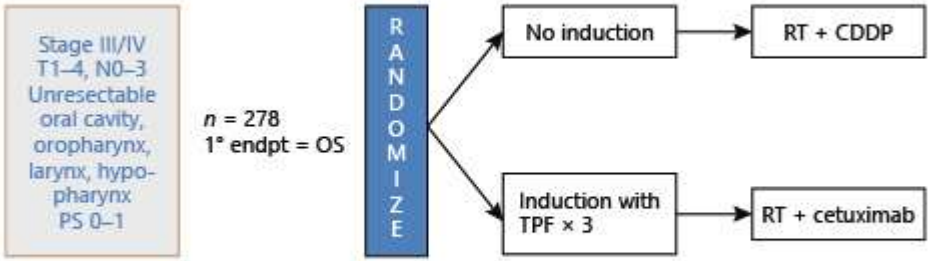
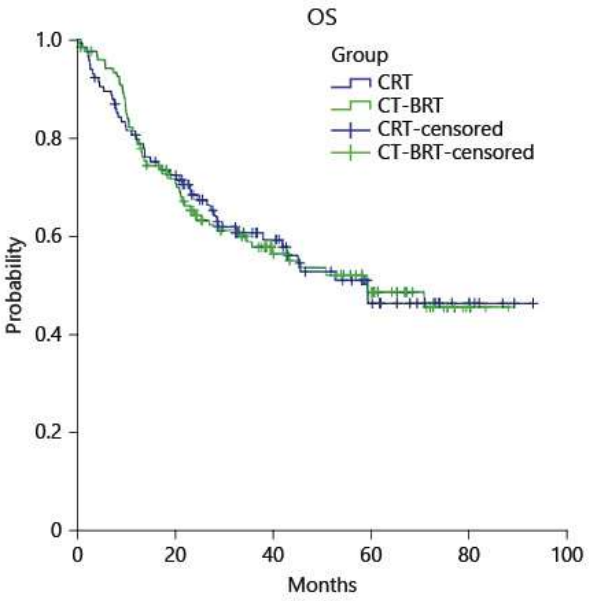
Accepted: March 25, 2020
Published online: July 6, 2020

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)

GONO INTERCEPTOR NCT 00999700



ARM A: Induction TPF (Docetaxel 75 mg/mq d1, Cisplatin 75 mg/mq d1, 5FU 750 mg/mq/die c.i. 96 hours) → Cetuximab 400 mg/mq → 250 mg/mq weekly +RT
ARM B: Cisplatin 100 mg/mq d1 q 21+ (RTOG)



Warwick
Medical School
CLINICAL TRIALS UNIT

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

DESIGN

Unblinded, randomised controlled trial

Radiotherapy 70Gy in 35F over 7 weeks

All centres underwent rigorous RT QA

Trial Treatments: 1:1 allocation

Cisplatin IV 100mg/m2 day - day 1, 22, 43

Cetuximab IV 400mg pre treatment loading dose then weekly 250mg

Stratification: by Centre, T stage, N stage, Radiotherapy laterality (uni/bilateral), Planned PEG use

Follow-up: minimum 24 months

SURVIVAL

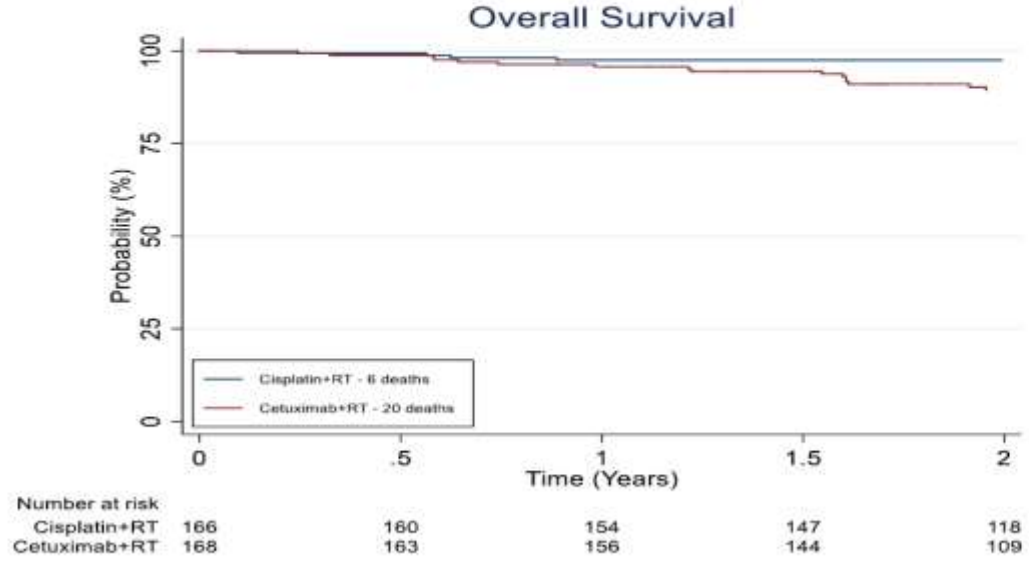
Worse overall survival with cetuximab

2 yr OS:
97.5% vs 89.4%
p= 0.001

HR=4.99
95% CI: 1.70 to 14.67

Adjusted HR: 5.94,
95% CI: 1.98-17.79, p=0.001

NNT for harm
12



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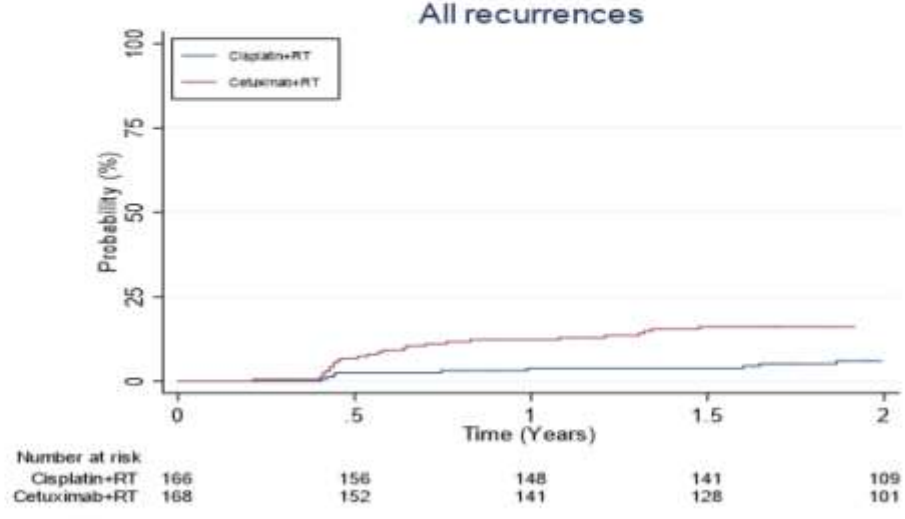
RECURRENCE

Significantly higher recurrence rates with cetuximab



2 yr RR
6.0% vs 16.1%

HR=3.39
(1.61 to 7.19)

p=0.0007

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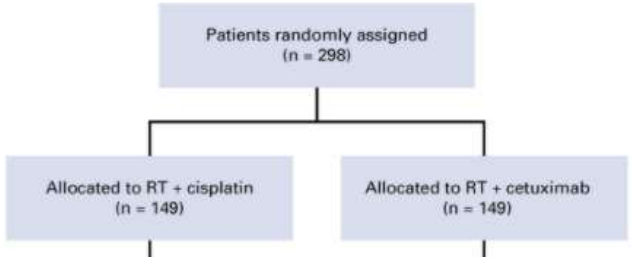
original reports

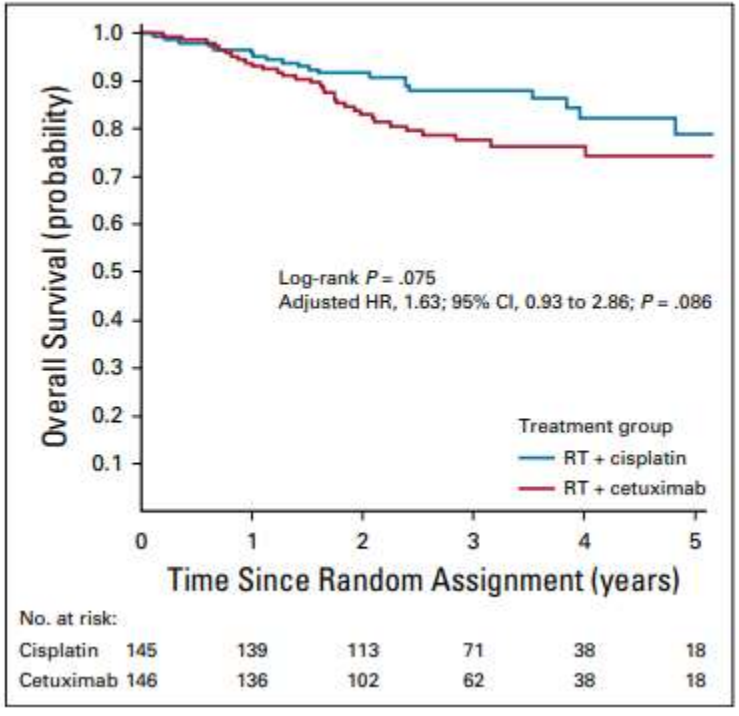
ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer

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

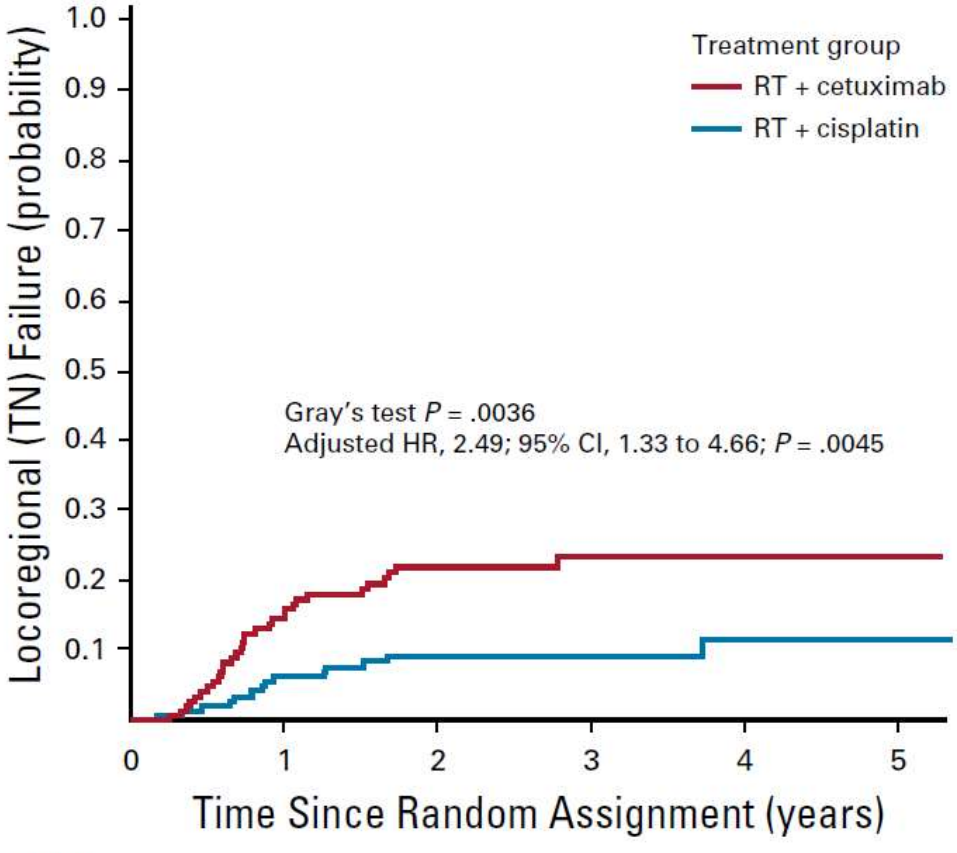


J Clin Oncol 2021 Jan 1;39(1):38-47.

Primary tumor site[a]		
Oropharynx	123 (85)	125 (86)
Oral cavity	7 (5)	8 (5)
Larynx	6 (4)	6 (4)
Hypopharynx	9 (6)	7 (5)
T stage[a]		
T1	21 (14)	22 (15)
T2	55 (38)	55 (38)
T3	25 (17)	31 (21)
T4	44 (30)	38 (26)
Nodal status		
N0	9 (6)	17 (12)
N1	10 (7)	10 (7)
N2a	12 (8)	7 (5)
N2b	81 (56)	79 (54)
N2c	29 (20)	27 (18)
N3	4 (3)	6 (4)
Clinical stage		
III	14 (10)	16 (11)
IV	131 (90)	130 (89)
p16 (patients with oropharyngeal cancer)		
Positive	108 (88)	113 (90)
Negative	14 (11)	11 (9)
Missing	1 (1)	1 (1)



A



No. at risk:

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

Locoregional failures at 3Y

- 23% (cetuximab) VS
- 9% (cisplatin) , P = .0036

in ***HPV+*** oropharyngeal ca….

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Pembrolizumab *versus* cetuximab, concomitant with radiotherapy (RT) in locally advanced head and neck squamous cell carcinoma (LA-HNSCC):

Results of the **GORTEC 2015-01 "PembroRad"** randomized trial (NCT 02707588)

YG Tao[1], XS Sun[2], C Sire[3], L Martin[4], M Alfonsi[5], JB Prevost[6], M Rives[7], C Lafond[8], JM Tourani[9], J Biau[10], L Geoffrois[11], A Coutte[12], X Liem[13], E Vauleon[14], F Drouet[15], G Waksi[16], A Péchery[16], J Guigay[17], M Wanneveich[16], A Auperin[1], J Bourhis[18]

on behalf of GORTEC

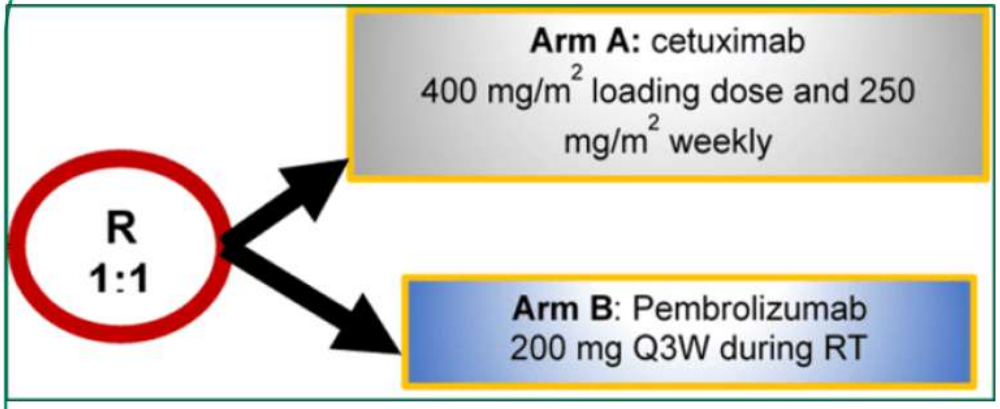
GORTEC
Groupe Oncologie Radiothérapie Tête Et Cou
Radiotherapy oncology group for head & neck

[1]Villejuif, [2] Besançon & Montbeliard, France, [3]Lorient, [4]Le Havre, [5]Avignon, [6]Beuvry, [7]Toulouse, [8]Le Mans, [9]Poitiers, [10]Clermont-Ferrand, [11]Nancy, [12]Amiens, [13]Lille, [14]Rennes, [15]Saint Nazaire, [16]Tours, [17]Nice, [18] Lausanne, Switzerland;

1. Tao YG et al. ESMO 2020. Presentation LBA38

Patients & Methods

Randomization



Stratification : N Stage (N0-1 vs N2-3)

P16 status & tumor site

OPC p16 positive vs OPC negative or non OPC

In both arms : IMRT (69.96 Gy in 33 fractions)

Main Inclusion criteria

- Patients unfit for receiving high dose cisplatin
- Non operated stage III-IVa-b
- SCC of oral cavity, oro/hypopharynx and larynx
- Non metastatic

1. Tao YG et al. ESMO 2020. Presentation LBA38

Primary endpoint

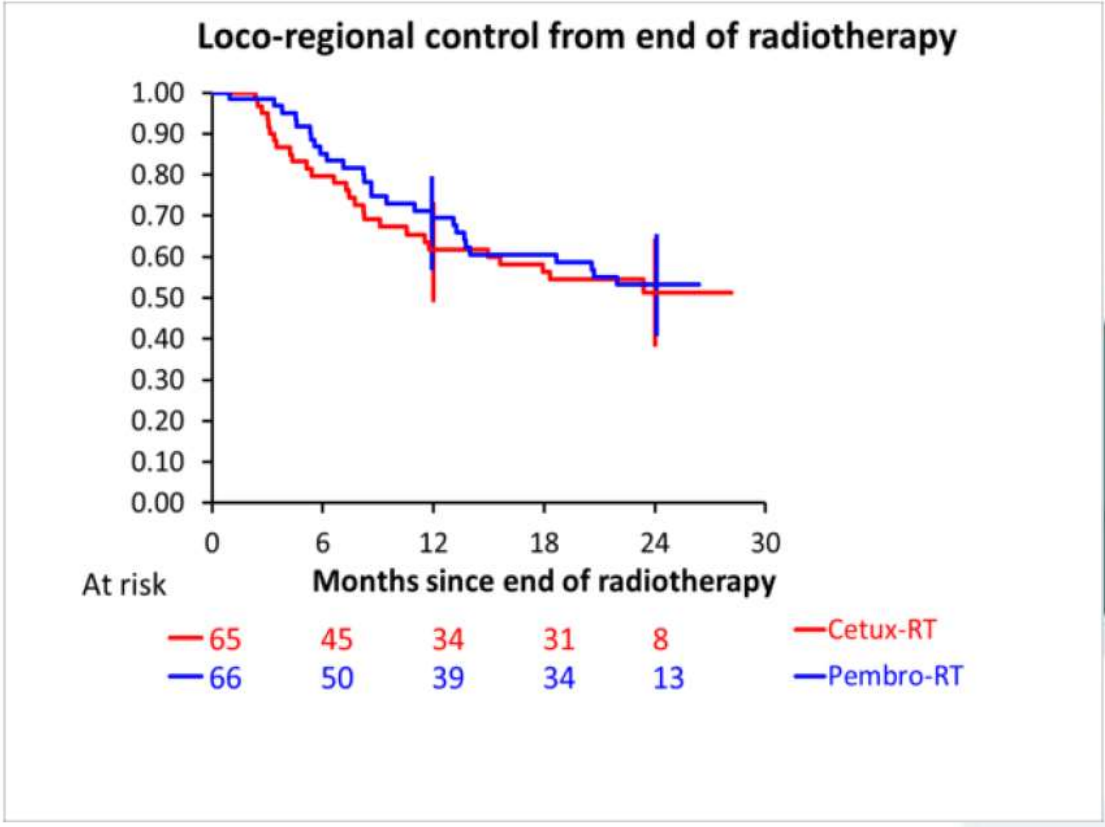
Loco-regional control at 15 months after radiotherapy

- **Median Follow-up: 25.6** months (9.0-30.2 months)
- **LRC at 15 months after RT:**

Cetux-RT : 59% (95%CI 45%-72%)

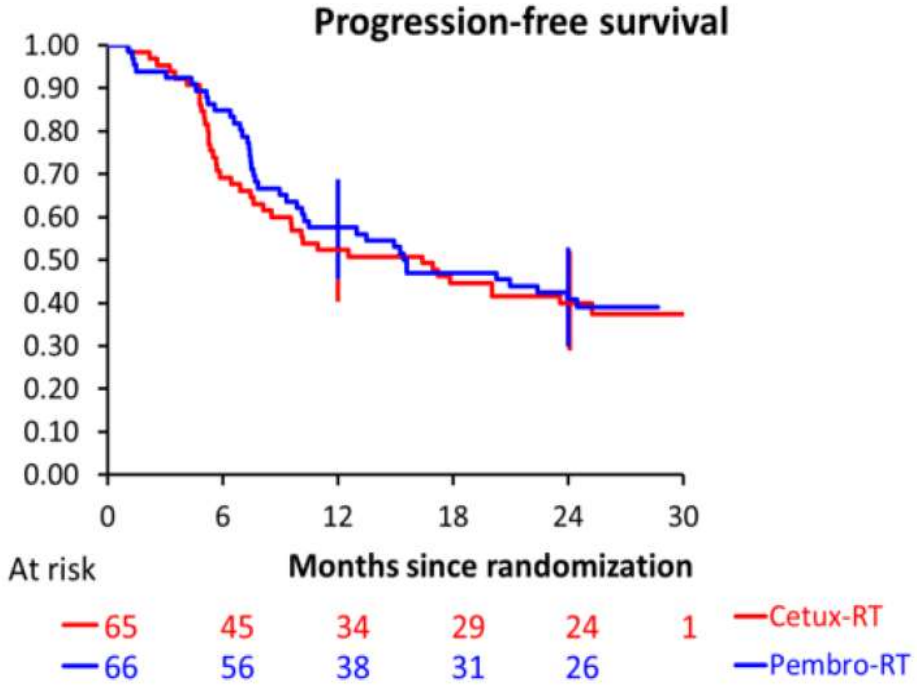
Pembro-RT : 60% (95%CI 46%-72%)

OR = 1.05, (95%CI 0.43-2.59); **p = 0.91**



1. Tao YG et al. ESMO 2020. Presentation LBA38

Progression free survival

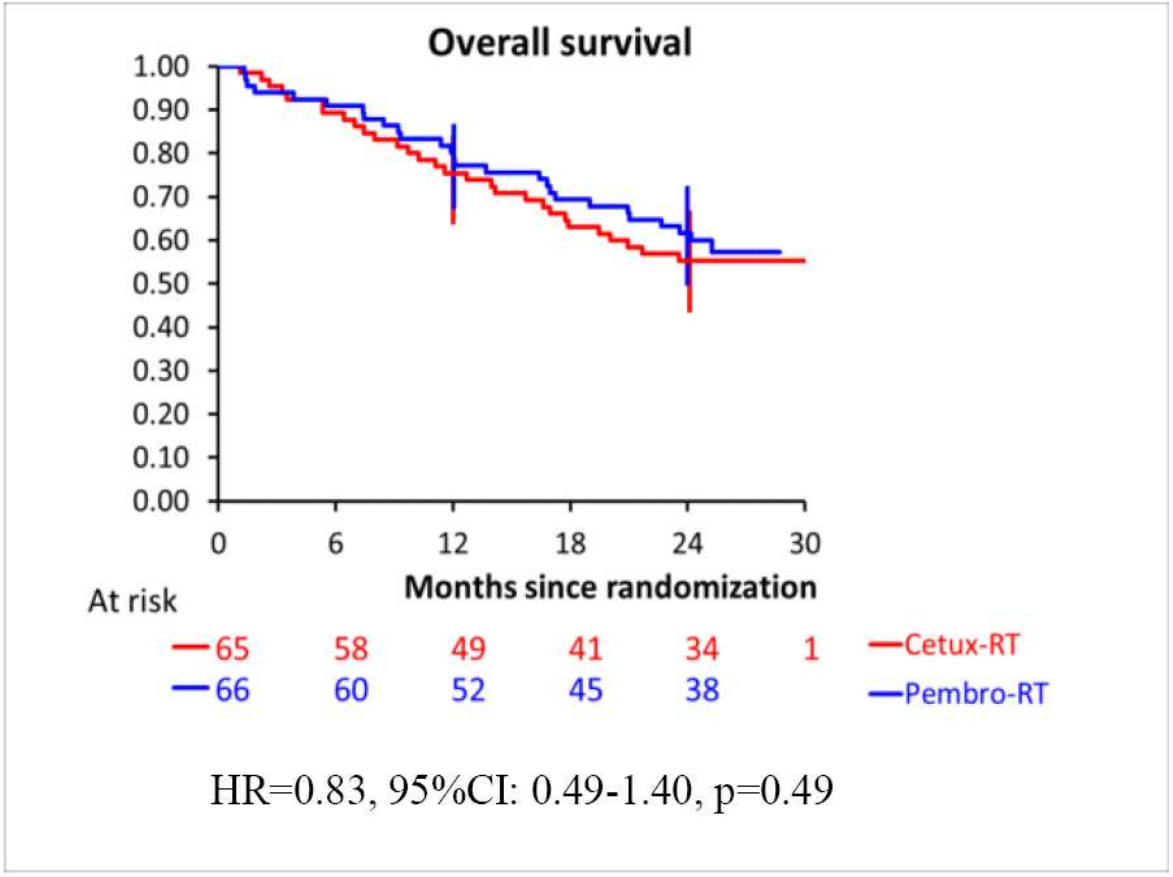


2-year PFS

Cetux-RT : 40%
Pembro-RT : 42%;

1. Tao YG et al. ESMO 2020. Presentation LBA38

Overall survival



2-year OS

Cetux-RT : 55%

Pembro-RT : 62%

1. Tao YG et al. ESMO 2020. Presentation LBA38

Conclusion

- **Primary end-point not met** : No difference of **loco-regional control** at 15 months between concomitant pembro–RT vs cetux-RT
- No difference in **OS or PFS** between the two arms
- **The toxicity profiles were different** (dysthyroidism vs mucosal & skin reactions)
- Significantly **more G>=3 with cetuximab**, essentially due to **skin** and **mucosal** reactions

1. Tao YG et al. ESMO 2020. Presentation LBA38

BioRT = PembroRT ?

VIRTUAL 2020 ESMO congress

Primary results of the phase 3 JAVELIN Head & Neck 100 trial: avelumab plus chemoradiotherapy (CRT) followed by avelumab maintenance vs CRT in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN)

E.W. Cohen,[1*] R.L. Ferris,[2*] A. Psyrri,[3] R.I. Haddad,[4] M. Tahara,[5] J. Bourhis,[6] K. Harrington,[7] P. M-H. Chang,[8] J-C. Lin,[9] M. A. Razaq,[10] M. M. Teixeira,[11] J. Lovey,[12] J. Chamois,[13] A. Rueda,[14] C. Hu,[15] M. V. Dvorkin,[16] S. De Beukelaer,[17] D. Pavlov,[18] H. Thurm,[18] and N. Lee[19*]

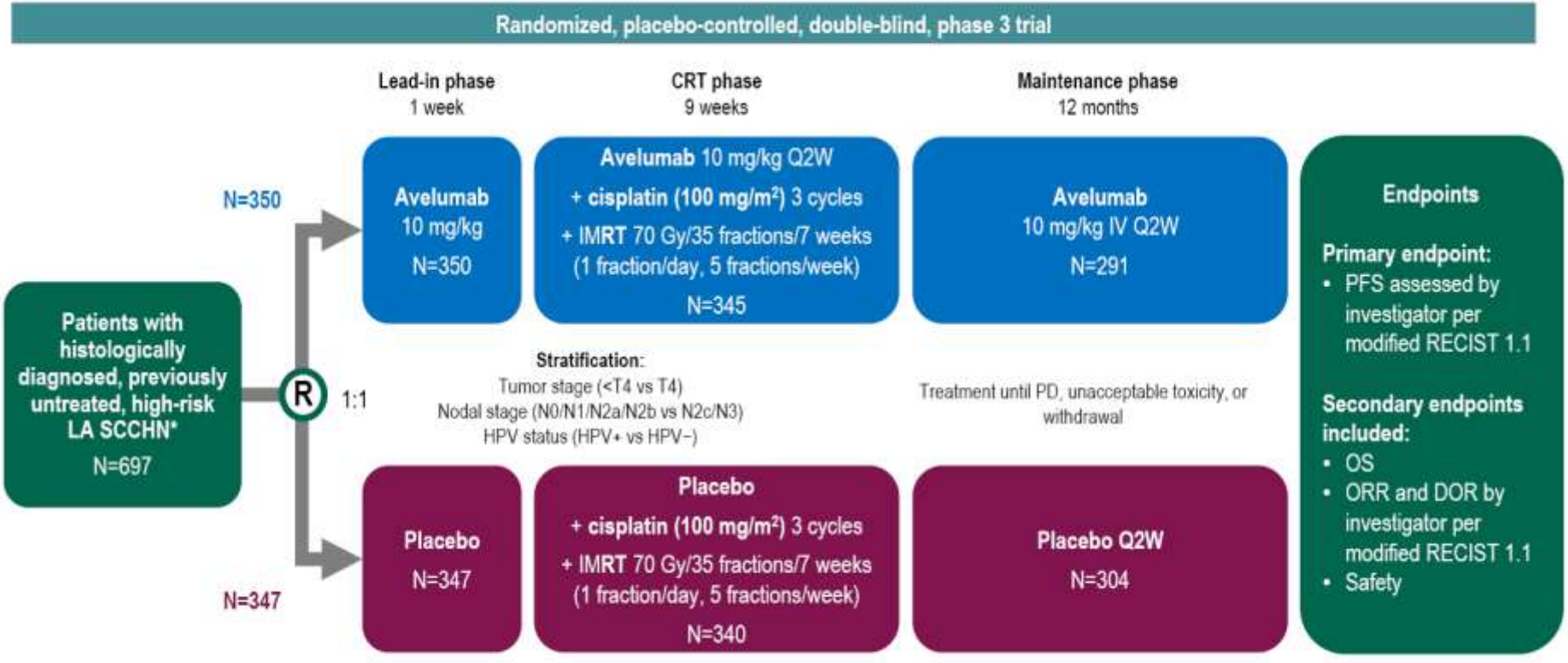
[1]Moores Cancer Center, UC San Diego Health, La Jolla, California, USA, [2]UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, USA; [3]Attikon University Hospital, National Kapodistrian University of Athens, Athens, Greece; [4]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Centre Hospitalier Universitaire Vaudois, Lausanne, Vaud, Switzerland; [7]Institute of Cancer Research, London, United Kingdom; [8]Taipei Veterans General Hospital, Taipei, Taiwan; [9]Changhua Christian Hospital, Changhua, Taiwan; [10]Stephenson Cancer Center, University of Oklahoma, Oklahoma City, Oklahoma, USA; [11]Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E, Coimbra, Portugal; [12]Országos Onkológiai Intézet, Sugárterápiás Osztály, Budapest, Hungary; [13]Centre Hospitalier Prive Saint Gregoire, Saint Gregoire, France; [14]Area of Oncology, Costa del Sol Hospital, IBIMA, Málaga, Spain; [15]Fudan University Shanghai Cancer Center, Xuhui, Shanghai, China; [16]Budgetary Institution of Healthcare of the Omsk region, Clinical Oncology Dispensary, Omsk, Russia; [17]Pfizer AG, Zürich, Switzerland, [18]Pfizer, Inc, La Jolla, California, USA; [19]Memorial Sloan Kettering Cancer Center, New York, New York, USA

* Study co-chairs

1. Cohen EW et al. ESMO 2020. Presentation 9100

This indication has not been register

JAVELIN Head & Neck 100: study design



DOR, duration of response; **HPV**, human papillomavirus; **IMRT**, intensity-modulated radiation therapy; **IV**, intravenously; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomized; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

1. Cohen EW et al. ESMO 2020. Presentation 910O

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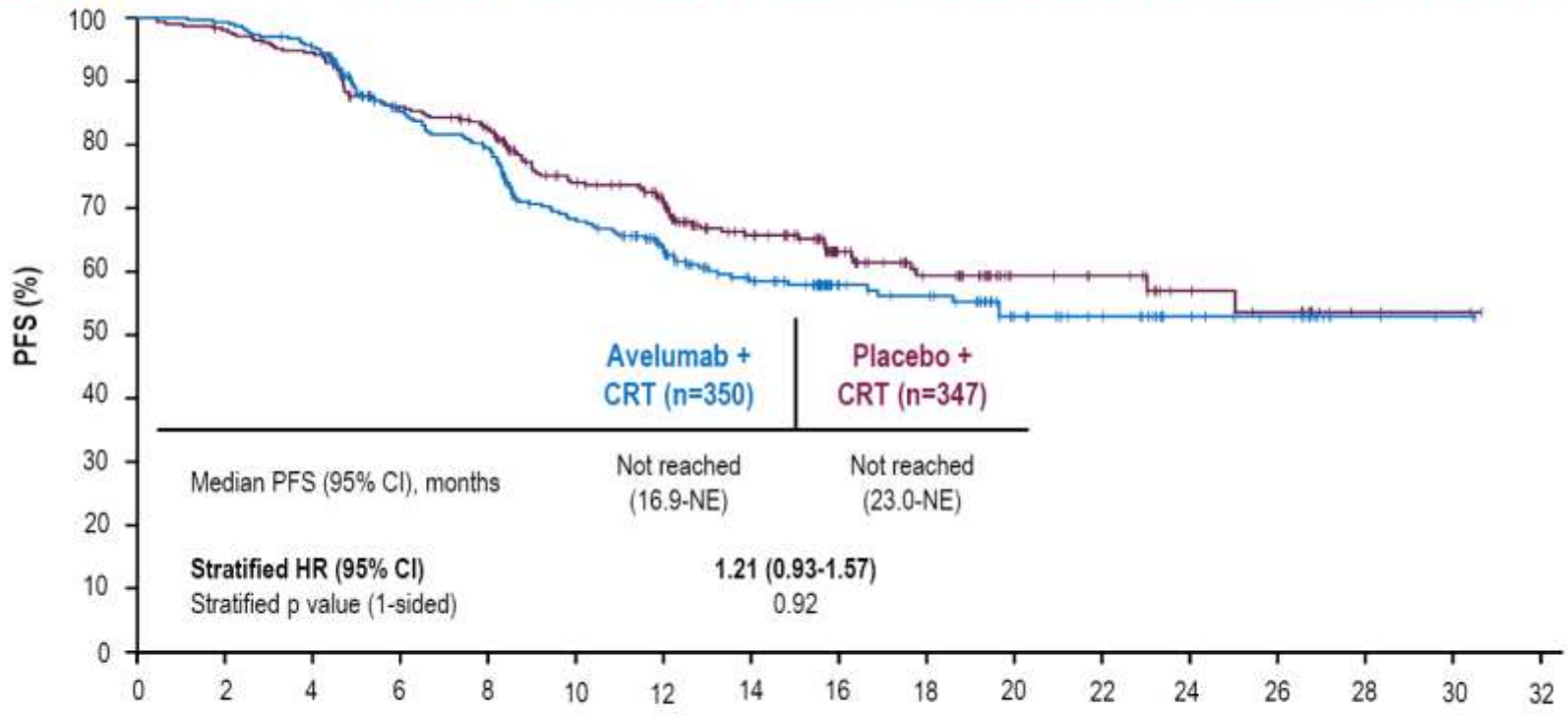
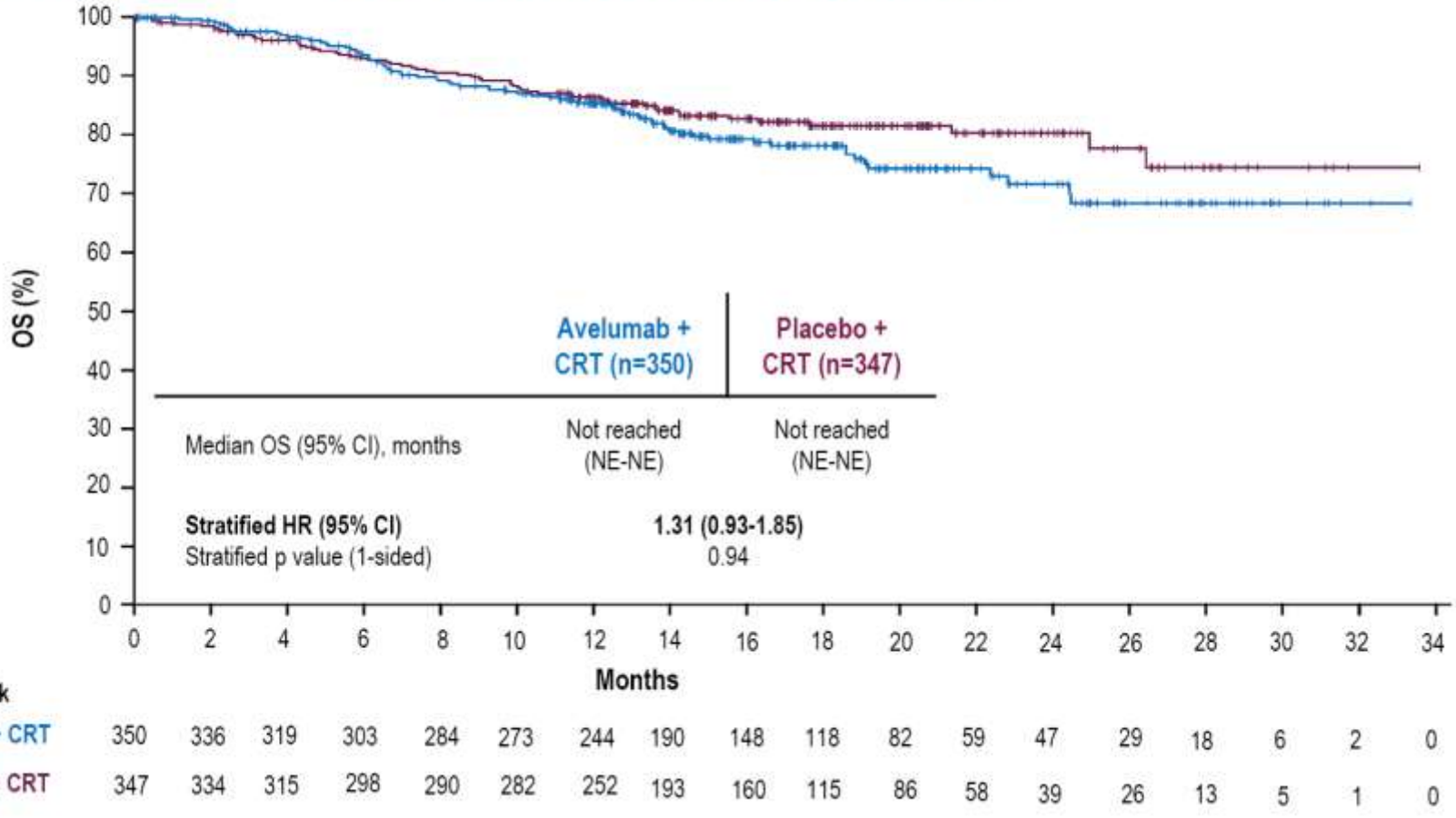
Primary endpoint: PFS by investigator per modified RECIST 1.1



NE, not estimable.

1. Cohen EW et al. ESMO 2020. Presentation 9110

OS: overall patient population



1. Cohen EW et al. ESMO 2020. Presentation 9110

Locally Advanced HNCa

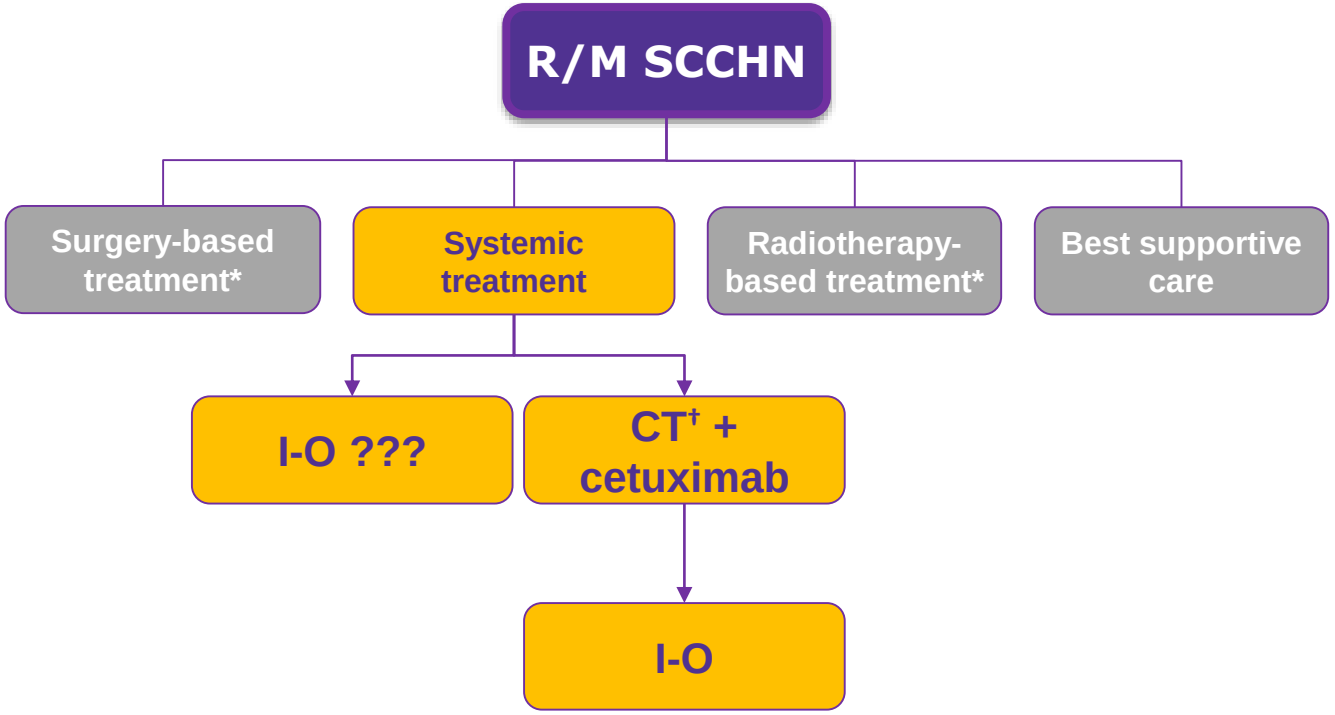
=

CCRT with ***Cisplatin*** or

BioRT with ***Cetuximab*** (flare pt)

Recurrence/ Metastasis HNCa.

Recurrent/ Metastatic SCCHN treatment landscape



*In metastatic disease: selected patients with limited metastases, good PS

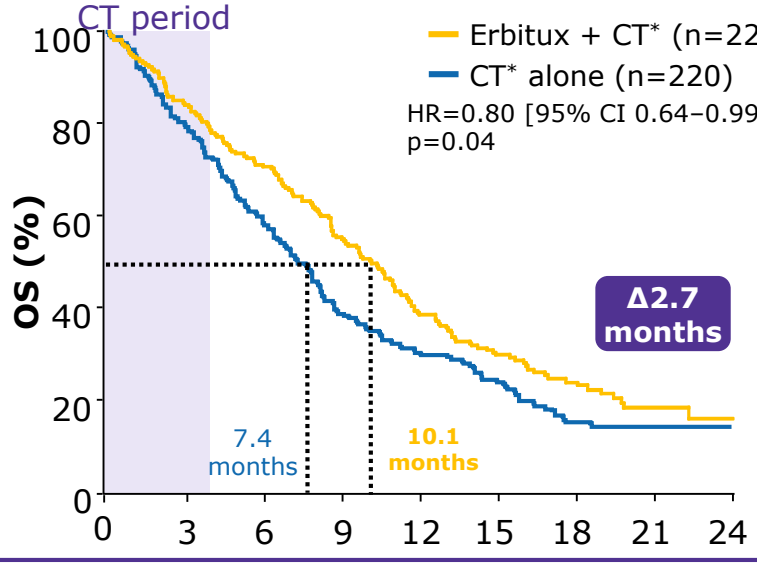
†Platinum-based CT, consisting of cisplatin/carboplatin + 5-FU

CT, chemotherapy; PS, performance status;
QoL, quality of life; R/M, recurrent and/or metastatic

National Comprehensive Cancer Network Clinical (NCCN) Practice Guidelines in Oncology: Head and Neck Cancers V1.2019

The EXTREME regimen significantly prolongs survival compared with CT alone, and achieves long survival outcomes in RWD

EXTREME Phase III study[1]



*Platinum-based CT, consisting of cisplatin/carboplatin + 5-FU
HR, hazard ratio; NR, not reached (due to limited follow-up)

Real-world data support the use of the EXTREME regimen in 1st line R/M SCCHN[2–4]

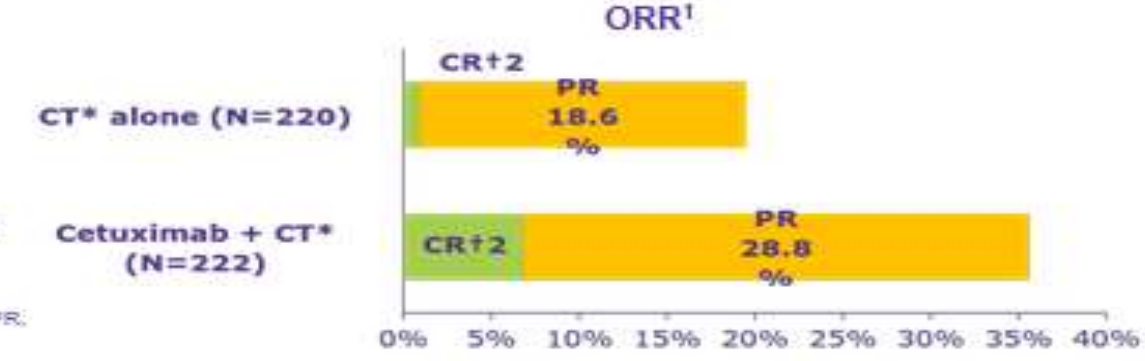
Phase III
Median OS **10.1 months;**
Median PFS **5.6 months**(N=121)[1]

Asian data
Median OS **14.1 months;**
Median PFS **4.1 months** (N=33)[2]

Real-world
Median OS **11.8 months;**
Median PFS **5.0 months**(n=37)[3]

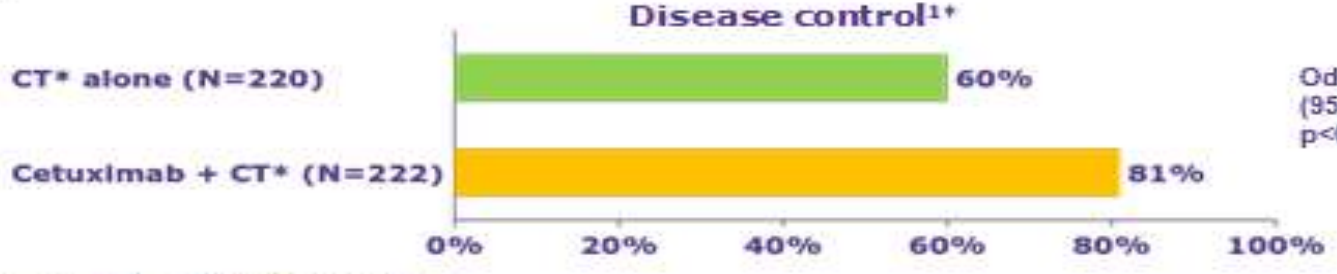
Real-world
Median OS **NR;**
Median PFS **5 months** (N=154)[4]

EXTREME study:
Improved response rates and control of disease with Erbitux + CT* in R/M SCCHN



Odds ratio: 2.33
(95% CI: 1.5–3.60)
p<0.001

*Platinum-based CT, consisting of cisplatin/carboplatin + 5-FU
†ORR is published data but breakdown of CR and PR is unpublished
‡Disease control includes CR, PR, and SD
CR, complete response;
PR, partial response;
SD, stable disease



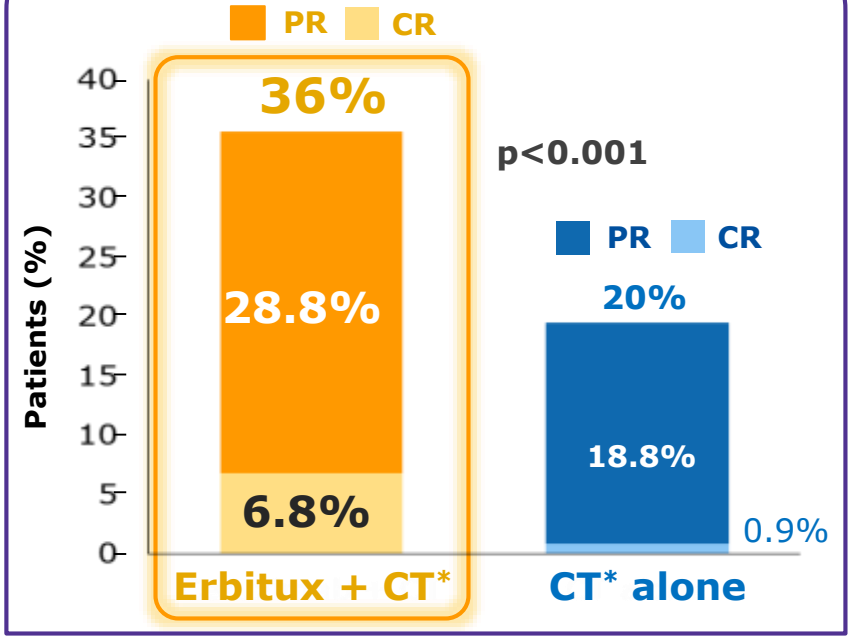
Odds ratio: 2.88
(95% CI: 1.87–4.44)
p<0.001

Ref:
1. Vermorken JB, et al. N Engl J Med 2008;359:1116–1127.
2. EMR 62020/002 study report (Tables 14.2.3.2 and 14.2.3.3)

Merck

The EXTREME regimen provides disease control for over 80% of patients, with benefit vs CT seen within 3 months

Response rates in the EXTREME study[1,2]



Disease control rates in the EXTREME study[1]

81% disease control rate

with the **EXTREME** regimen
(compared with 60% treated with CT* alone; p<0.001)[1]

Early PFS benefit with the EXTREME regimen[2]

3-month PFS:

Erbitux + CT*: 74% (95% CI 68–80)

CT* alone: 56% (95% CI 49–63)

*Platinum-based CT, consisting of cisplatin/carboplatin + 5-FU
CT, chemotherapy; CR, complete response; PR, partial response

cetuximab + CT in Japanese SCCHN population

- open-label, single-arm, multicenter, phase II study in Japan
- 33 patients with confirmed recurrent and/or metastatic SCCHN

↓

CT
(day 1: cisplatin 100 mg/m^2,
day 1-4: 5-fluourouracil 1000 mg/m^2/day;
every 3 weeks)
+
cetuximab
(initial dose 400 mg/m^2, 250 mg/m^2 weekly)

↓

cetuximab until PD

↓

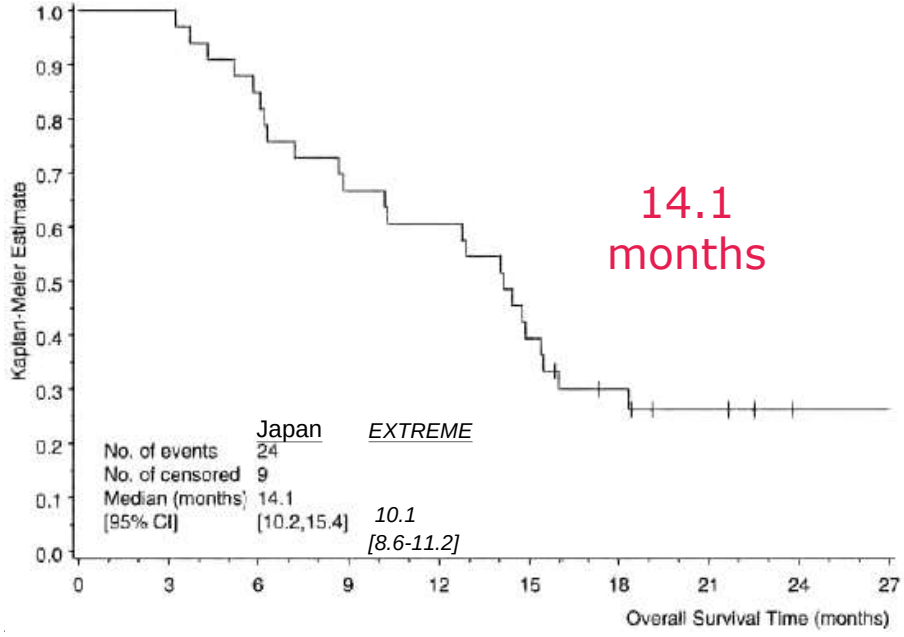
- Primary end point: ORR with WHO criteria
- Secondary end points: ORR with RECIST criteria, disease control rate, duration of response, time-to-treatment failure, PFS, OS

CT, chemotherapy; OS, overall survival; ORR, overall response rate; PFS, progression-free survival

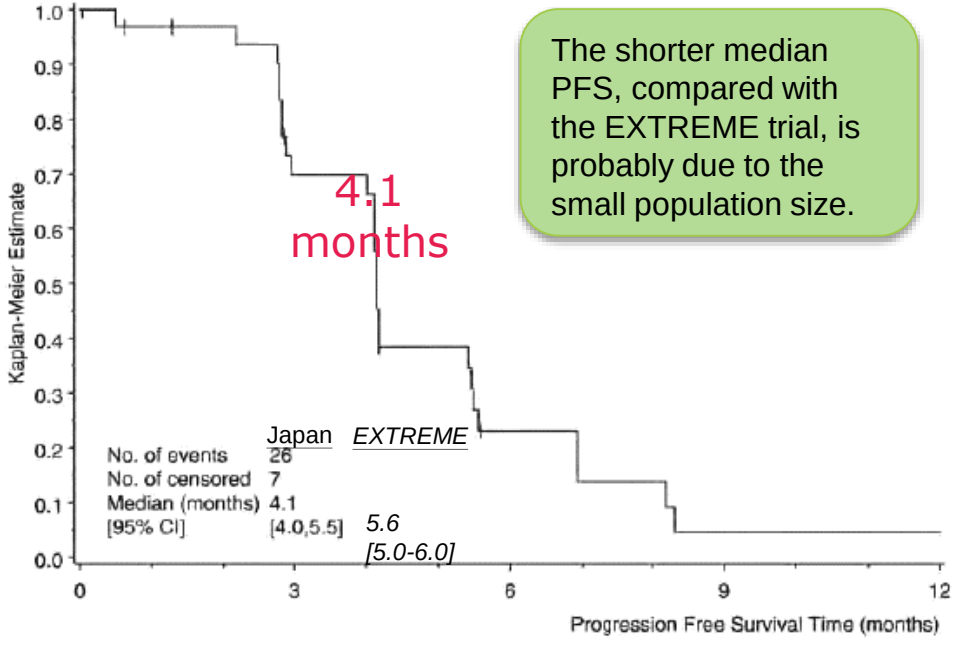
Ref: Yoshino T, et al. Jpn J Clin Oncol 2013;43:524-31.

Promising OS was reported in Japanese patients

OS in Japanese patients



PFS in Japanese patients



The shorter median PFS, compared with the EXTREME trial, is probably due to the small population size.

OS, overall survival; PFS, progression-free survival.

Ref: Yoshino T, et al. Jpn J Clin Oncol 2013;43:524-31.

In E-DA hospital

From Feb,2017~Mar,2021

Total 54 patients

- 20 pts: 2017~2018
- 34 pts: 2019~2021
- Mostly male (53: 1)
- Age: ~56 y/o (32~71)

RM distributions

- 19 patients: local recurrence.
- 35 patients: distant metastasis. (mostly lung mets ~90%)

Baseline patient characteristics

Characteristic	N=54
Age (years)	56 (32–71)
Gender	
Male	53 (95%)
Female	1 (5%)
The extent of disease	
Local recurrent, not metastatic	19 (35%)
Metastatic, including recurrent	35 (65%)
Location of primary tumor	
Oral cavity	18 (33%)
Hypopharynx	14 (26%)
Oropharynx	16 (30%)
Double cancer (/ esophageus)	6 (11%)

Chemotherapy Regimen

Mostly “EXTREME” regimen

- Cetuximab 400mg/m2 → 250mg/m2 weekly
- PF (Cisplatin 70~80 mg/m2 , D1 and 5FU 700-800mg/m2 D2~D4 total 4 days) q4 weeks.

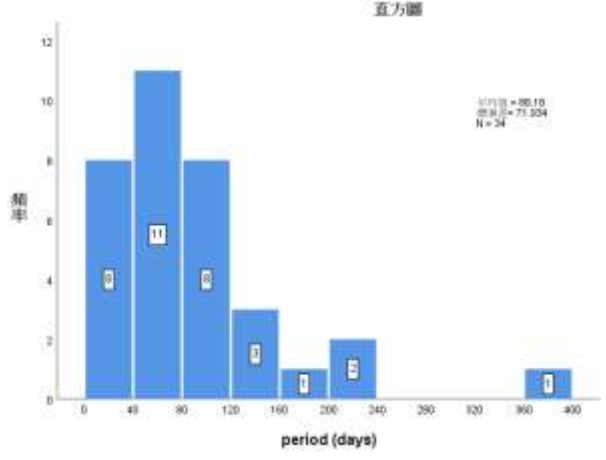
Single Cetuximab +/- ufur if poor performance. (2 pts)

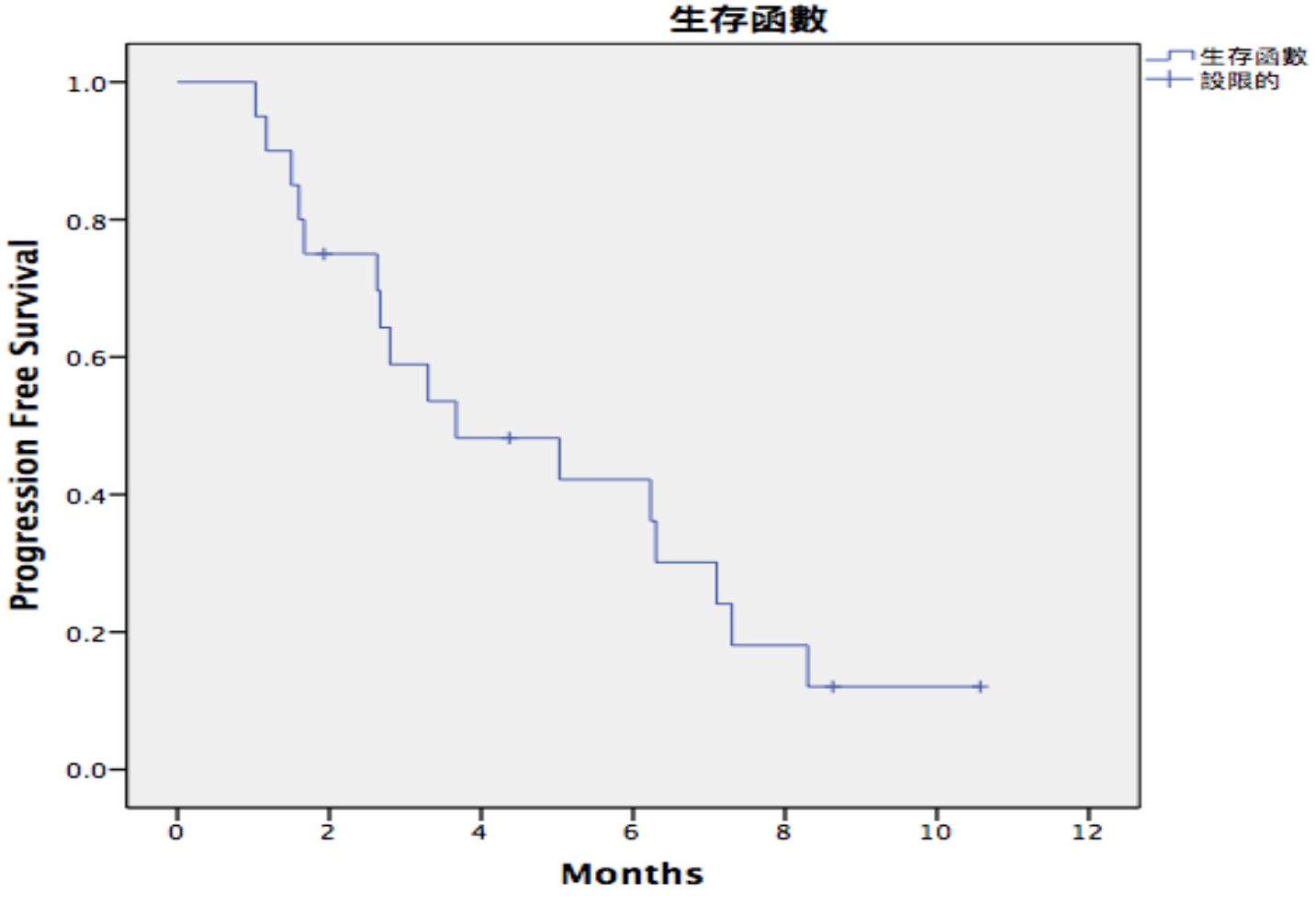
No other combinations such as TPEx or other regimen

- 2 pts receive Pembro-Cetuximab do not count

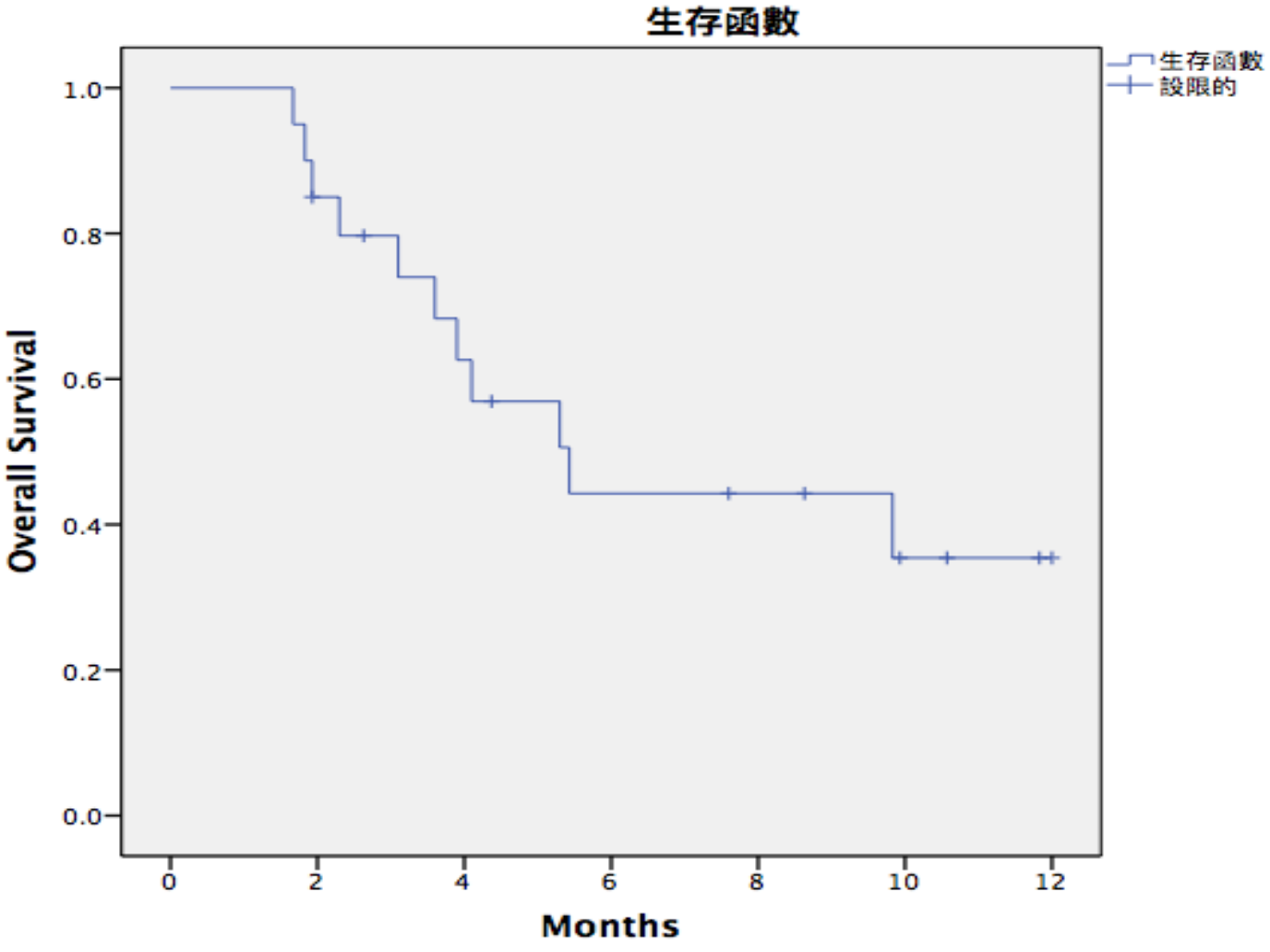
Cohort 2 (34 pts):

- 平均使用時間 ： 3.0 months +/- 2.5months (12.5 weeks +/- 7.8 weeks)
- 平均使用藥物： 44 vials +/- 20 vials (11 weeks +/- 5 weeks)





估計	標準誤差	95% 信賴區間	
		下界	上界
4.856	.712	3.460	6.252

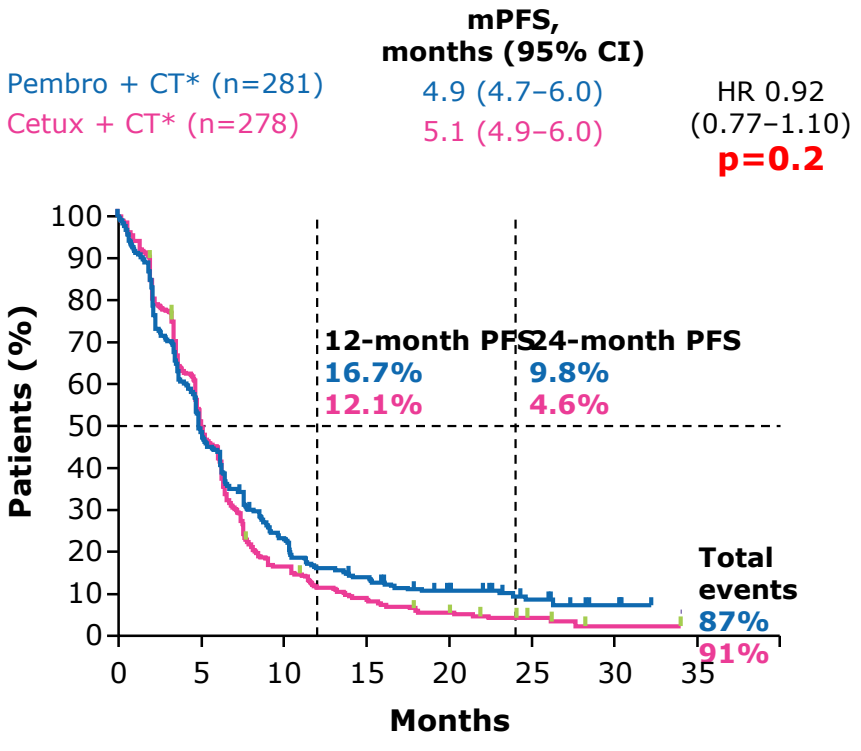


估計	標準誤差	95% 信賴區間	
		下界	上界
7.029	1.000	5.069	8.989

	EXTREME	JAPAN (33)	E-DA (54)
OS (month)	**10 (8.6~11.2)**	**14.1 (10.2~15.4)**	**7.0 (5.1~9.0)**
PFS (month)	**5.6 (5.0~6.0)**	**4.1 (4.0~5.5)**	**4.8 (3.5 ~6.2)**
Response Rate	**35%**	**36%**	**38%**
DCR	**81%**	**85%**	**65%**

Pembrolizumab + platinum + 5-FU did not improve PFS vs EXTREME in any patient population

PFS (ITT)[19]



PFS (CPS subgroups)[21]

	CPS ≥20		CPS ≥1	
	Pembro + platinum + 5-FU (n=126)	EXTREME (n=110)	Pembro + platinum + 5-FU (n=242)	EXTREME (n=235)
mPFS, months (95% CI)	5.8 (4.7–7.6)	5.2 (4.8–6.2)	5.0 (4.7–6.2)	5.0 (4.8–5.8)
HR (95% CI)	HR 0.73 (0.55–0.97), p=0.0162†		HR 0.82 (0.67–1.00), p=NS*	

*Not significant as per hierarchical statistical testing;
†Not statistically significant at superiority threshold of p=0.0017.

19. Burtness B, et al. ESMO 2018 (Abstract No. LBA8_PR – presentation);
21. Rischin D, et al. ASCO 2019 (Abstract No. 6000 – presentation).

mOS was 10.8 for pembrolizumab vs 10.1 for EXTREME in CPS 1-19, suggesting the OS benefit in CPS≥1 may be driven by CPS≥20

OS and ORR (CPS subgroups)

	CPS ≥20		CPS ≥1		CPS 1–19	
	Pembro mono (n=133)	EXTREME (n=122)	Pembro mono (n=257)	EXTREME (n=255)	Pembro mono (n=NR)	EXTREME (n=NR)
mOS, months (95% CI)	14.8 (11.5–20.6)	10.7 (8.8–12.8)	12.3 (10.8–14.3)	10.3 (9.0–11.5)	10.8 (9.0–12.6)	10.1 (8.7–12.1)
HR (95% CI)	0.58 (0.44–0.78), p=NR		0.74 (0.61–0.90), p=NR		0.90 (0.68–1.18)	
ORR, %	23.3	36.1	19.1	34.9	NR	NR
mDOR, months (range)	20.9 (2.7+ to 34.8+)	4.2 (1.2+ to 22.3+)	20.9 (1.5+ to 34.8+)	4.5 (1.2+ to 28.6+)	NR	NR

Package Insert - Keytruda - FDA

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.90 (95% CI: 0.68, 1.18).

Package Insert - Keytruda - FDA

Pembrolizumab + CT showed similar OS vs EXTREME in patients of Asian subgroup regardless of PD-L1 status[1]

Pembrolizumab + platinum + 5-FU vs EXTREME

	Asia Subgroup[a]						Non-Asia Subgroup[a]					
	CPS ≥20		CPS ≥1		Total Subgroup		CPS ≥20		CPS ≥1		Total Subgroup	
	P+C	E	P+C	E	P+C	E	P+C	E	P+C	E	P+C	E
n	22	21	45	43	57	49	104	89	197	192	224	229
OS,[b] HR (95% CI)	0.80 (0.41–1.58)		1.13 (0.71–1.79)		1.03 (0.68–1.58)		0.75 (0.54–1.04)		0.76 (0.61–0.95)		0.87 (0.71–1.06)	
PFS,[b,c] HR (95% CI)	1.07 (0.58–1.99)		1.14 (0.74–1.76)		1.12 (0.75–1.66)		0.65 (0.47–0.89)		0.74 (0.60–0.92)		0.82 (0.67–1.00)	
Objective responses, n	**10**	**7**	**14**	**16**	**18**	**20**	**44**	**35**	**74**	**68**	**82**	**81**
ORR, % (95% CI)	45.5 (24.4–67.8)	33.3 (14.6–57.0)	31.1 (18.2–46.6)	37.2 (23.0–53.3)	31.6 (19.9–45.2)	40.8 (27.0–55.8)	42.3 (32.7–52.4)	39.3 (29.1–50.3)	37.6 (30.8–44.7)	35.4 (28.7–42.6)	36.6 (30.3–43.3)	35.4 (29.2–41.9)
mDoR,[b] month (range)	6.1 (2.4–18.1+)	4.3 (2.6–22.3+)	6.1 (2.4–18.0+)	4.2 (2.6–27.9+)	5.7 (2.4–18.0+)	4.1 (2.0–27.9+)	8.5 (2.1–30.4+)	4.1 (1.2+–22.1+)	6.9 (1.6+–30.4+)	4.4 (1.2+–22.1+)	6.9 (1.6+–30.4)	5.0 (1.2+–22.7+)

'+' indicates there was no progressive disease at the time of last disease assessment; [a]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate; [b]From product-limit (Kaplan-Meier) method for censored data; [c]PFS assessed per RECIST v1.1 by blinded independent central review.

1. Tahara J, et al. ESMO 2019 (Abstract No. 1136P – poster).

Treatment choices for 1L R/M SCCHN should be guided by need for rapid response, and by PD-L1 expression[19,21]

Tumor and/or symptom burden factors

- Bulky disease
- High symptom burden
- Proximity to organs
- Fast progression

Rapid response needed

ORR with cetuximab + CT* remains consistent regardless PD-L1 status and race

PD-L1 expression factors

CPS

- **≥20**: Clear evidence for OS benefit with pembrolizumab monotherapy vs EXTREME
  Pembrolizumab + CT vs EXTREME showed comparable OS in Asian
- **<20–1**: No significant benefit with pembrolizumab monotherapy vs EXTREME; Unclear evidence for benefit with pembrolizumab + CT vs EXTREME
- **<1**: Lack of evidence for benefit with pembrolizumab ± CT vs EXTREME
- **Unknown**: Cetuximab + CT* data are consistent, regardless of CPS

*Platinum-based CT; Symptom burden icon by lastspark, RU from the Noun Project; Fast icon by Alexander Wiefel from the Noun Project.

In Taiwan, Erbitux could be reimbursed for R/M SCCHN until PD and no more than 18 weeks

局部晚期之口咽癌、下咽癌及喉癌	復發及/ 或轉移性頭頸部鱗狀細胞癌
口咽癌、下咽癌及喉癌治療部分：(98/7/1) (1)限與放射線療法合併使用於局部晚期之口咽癌、下咽癌及喉癌患者，且符合下列條件之一： 1. 年齡 ≧ 70歲 2. Ccr ＜50ml/min 3. 聽力障礙者(聽力障礙定義為500Hz、1000Hz、2000Hz平均聽力損失大於25分貝) (99/10/1) 4. 無法耐受platinum-based化學治療 (2)使用總療程以接受8次輸注為上限 (3)需經事前審查核准後使用	頭頸癌部分(106/1/1)： (1)限無法接受局部治療之復發及/ 或轉移性頭頸部鱗狀細胞癌，且未曾申報cetuximab 之病患使用。 (2)使用總療程以18 週為限，每9週申請一次，**需無疾病惡化情形方得繼續使用**。 **→ 可給付於 CR+PR+SD**  **SD, PR or CR → DCR** (**81%** of patients could benefit from reimbursed EXTREME[1])

[1]https://www.nhi.gov.tw/Content_List.aspx?n=E70D4F1BD029DC37&topn=3FC7D09599D25979

EXTREME as first line…

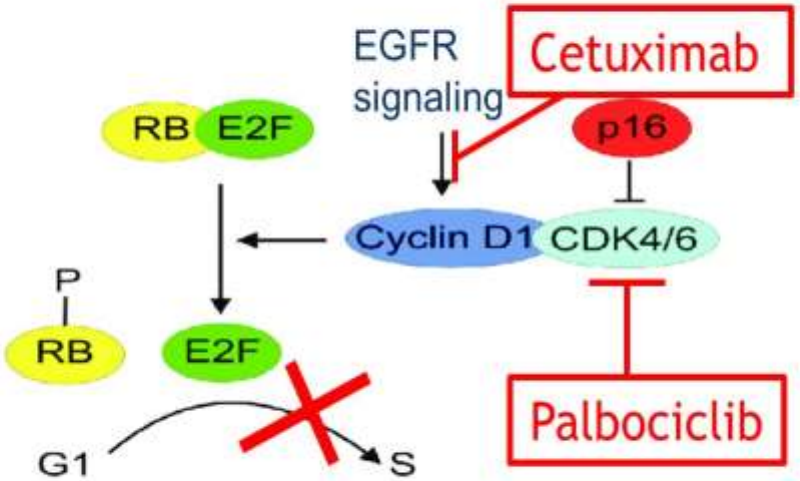
- PFS: 4.1 M ~ 5.5 M
- OS : 7M ~ 14.1 M
- Further questions
  - Combo?
  - Sequential?

	EXTREME	JAPAN (33)	E-DA (54)
OS (month)	10 (8.6~11.2)	14.1 (10.2~15.4)	7.0 (5.1~9.0)
PFS (month)	5.6 (5.0~6.0)	4.1 (4.0~5.5)	4.8 (3.5 ~6.2)
Response Rate	35%	36%	38%
DCR	81%	85%	65%

Other possible combination regimen?

Rationale for CDK4/6 inhibition with palbociclib and cetuximab in HPV-unrelated HNSCC

- *CCND1* amplification (in 30%) and frequent *CDNK2A* mutations/deletion result in cell cycle dysregulation in HPV (-) HNSCC
- Cyclin D1 suggested as mechanism of resistance to cetuximab



Phase II study of Palbociclib + cetuximab in HPV-unrelated HNSCC: Comparison with historical cohorts

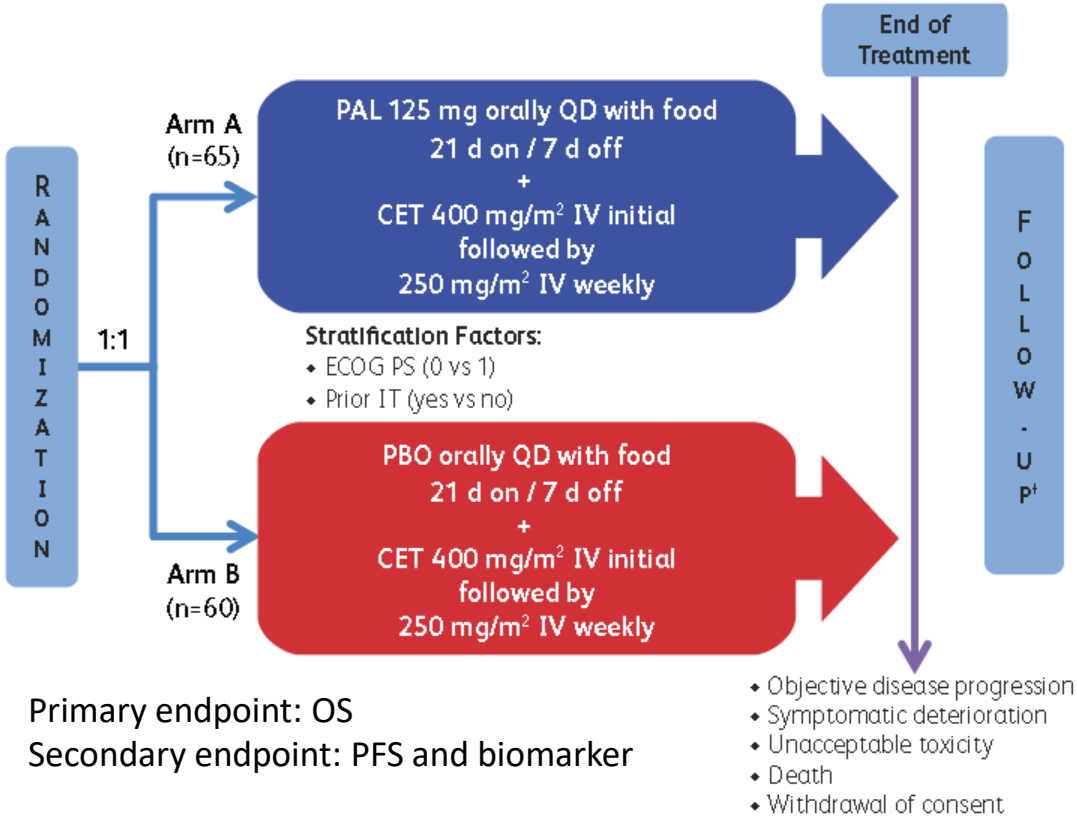
	Palbociclib + Cetuximab	Cetuximab	Nivolumab	Pembrolizumab
Response Rate	39%	13%	13%	14.6%
Progression Free Survival	5.4 M (3.4-7.0)	2.3M	2.0M	2.1M
Overall Survival	9.4 M (5.3-16.5)	6.0M	7.5M	8·4 M (6·4-9·4)

JCO 2007; NEJM 2016; Lancet 2019

PALATINUS: Study design (NCT02499120)[1]

PALATINUS (N=125)

- **Key inclusion criteria:**
  - Age ≥18 y (or ≥20 y per local regulations)
  - **Recurrent or metastatic HPV-unrelated HNSCC***
  - PD (per RECIST v1.1) after ≥2 cycles platinum-containing CT
  - ECOG PS 0 or 1
- **Key exclusion criteria:**
  - Prior nasopharyngeal cancer, salivary gland, or sinus tumors
  - >1 CT regimen for R/M disease
  - PD ≤3 mo after completion of treatment with curative intent
  - Known active, uncontrolled, or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease
  - Prior CET for R/M disease



Primary endpoint: OS
Secondary endpoint: PFS and biomarker

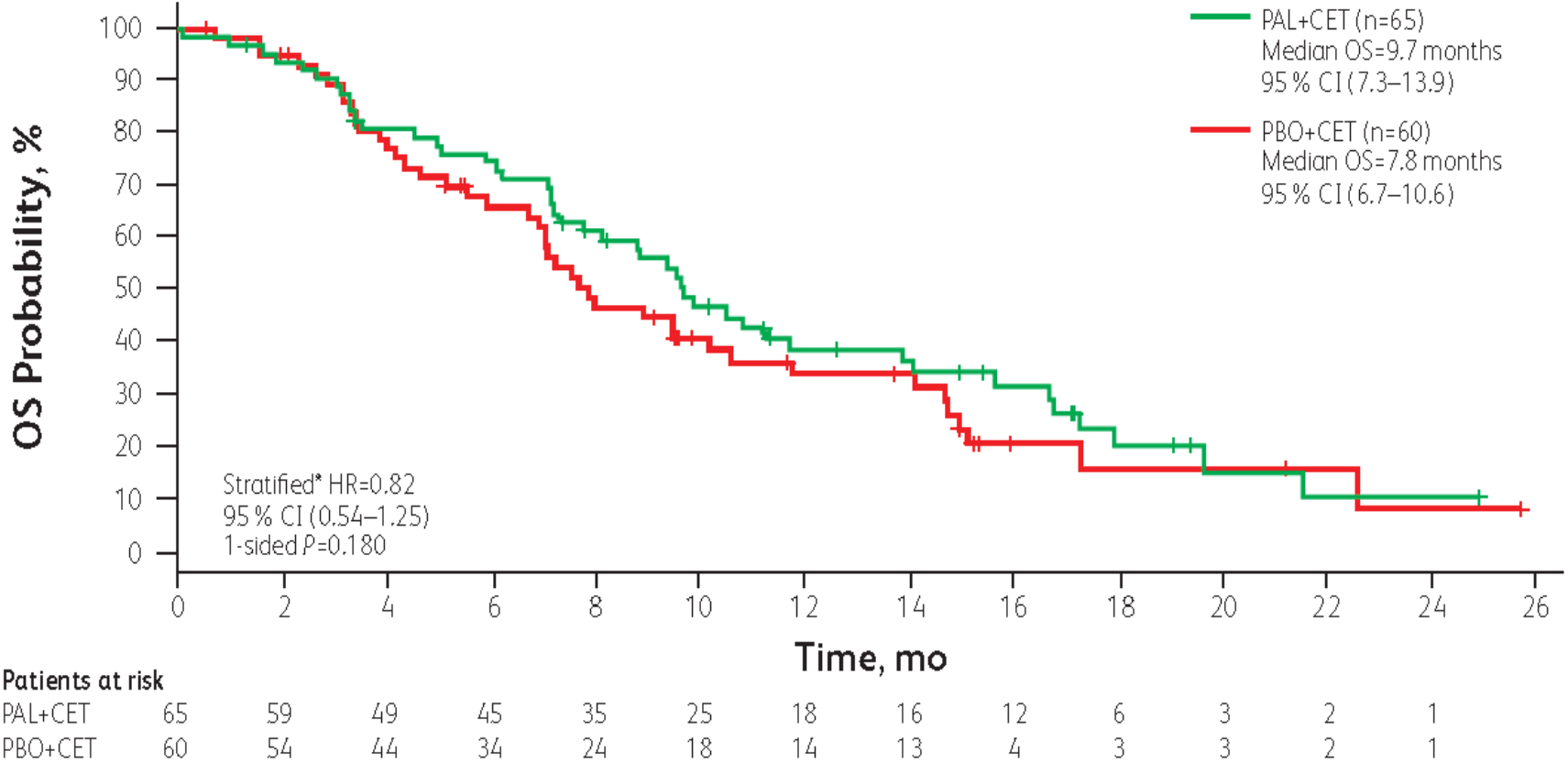
CET=cetuximab; CNS=central nervous system; CT=chemotherapy; ECOG PS=Eastern Cooperative Oncology Group performance status; HNSCC=head and neck squamous cell carcinoma; HPV=human papilloma virus; IT=immunotherapy; IV=intravenous; PAL=palbociclib; PBO=placebo; PCR=polymerase chain reaction; PD=progressive disease; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; R/M=recurrent/metastatic

***Definition of HPV-unrelated HNSCC was determined per institutional standard (p16 immunohistochemistry, multiplex nucleic acid sequence-based amplification or other PCR-based assays).**

†Follow-up period concluded at the time of final OS analysis.

1. Adkins D, et al. 2019 ASCO, Abs. 6013

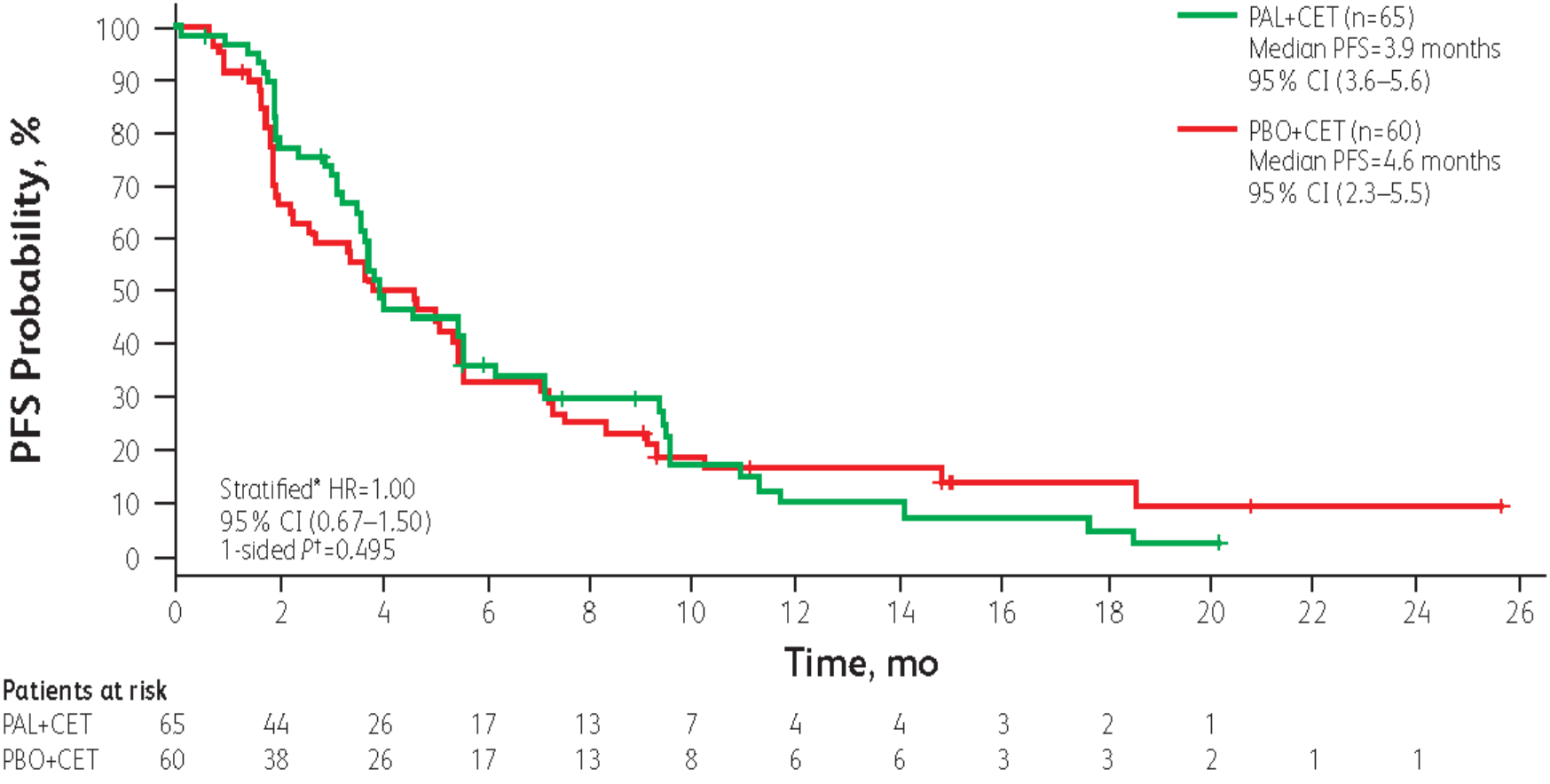
A numerical trend in favor of Arm A but did not meet the statistical threshold[1]



Median follow-up for OS was 15.9 months
Significance level: 0.10

1. Adkins D, et al. 2019 ASCO, Abs. 6013

PFS[1]



Patients at risk

PAL+CET	65	44	26	17	13	7	4	4	3	2	1		
PBO+CET	60	38	26	17	13	8	6	6	3	3	2	1	1

1. Adkins D, et al. 2019 ASCO, Abs. 6013

An open-label, non-randomized, multi-arm, phase II trial evaluating pembrolizumab combined with cetuximab in patients with recurrent/ metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): results of cohort 1 interim analysis.

Assuntina G Sacco MD,[1] Ruifeng Chen MS,[1] Debanjali Ghosh MA,[1] Deborah JL Wong MD,[2] Francis P Worden MD,[3] Douglas Adkins MD,[4] Emily Pittman PhD,[1] Karen Messer PhD,[1] Kathryn Gold MD,[1] Gregory Daniels MD,[1] Paul Swiecicki MD,[3] Valeria Estrada MD,[1] Alfredo Molinolo MD,[1] Brian Sutton MMS, PA-C,[1] Amanda Natsuhara BS,[1] Ezra EW Cohen, MD[1]

[1]University of California, San Diego Moores Comprehensive Cancer Center, La Jolla, CA; [2]University of California, Los Angeles Jonsson Comprehensive Cancer Center, Los Angeles, CA; [3]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, [4]Washington University Siteman Comprehensive Cancer Center, Saint Louis, MO

1. Sacco AG, et al. 2019 ASCO, Abs. TPS6033

THE LANCET
Oncology

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Pembrolizumab plus cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma: an open-label, multi-arm, non-randomised, multicentre, phase 2 trial

Assuntina G Sacco, MD • Ruifeng Chen, MS • Prof Francis P Worden, MD • Deborah J L Wong, MD • Prof Douglas Adkins, MD • Paul Swiecicki, MD • et al. Show all authors

Published: May 11, 2021 • DOI: https://doi.org/10.1016/S1470-2045(21)00136-4 • Check for updates

Cetuximab + Pembrolizumab – R/M HNSCC

Study design[1] (NCT03082534)

Open-label, non-randomised, multi-arm, phase II trial

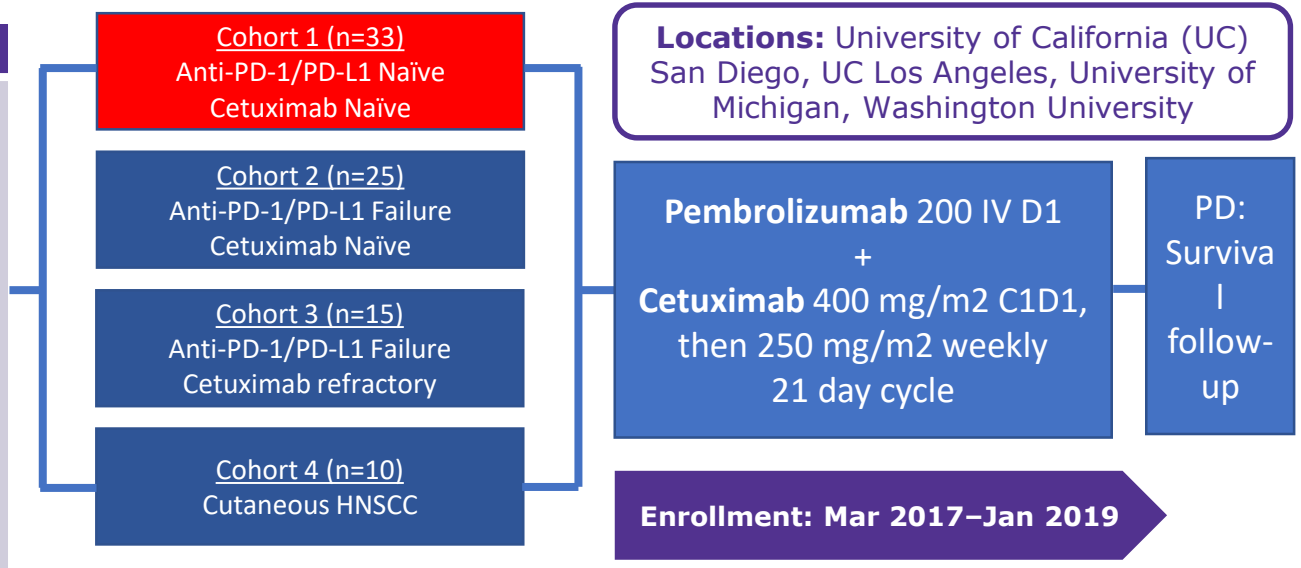
key eligibility criteria

Inclusion criteria

- Incurable HNSCC (lip, oral cavity, oropharynx, larynx, hypopharynx, non-EBV nasopharynx, sinonasal, skin)
- Platinum-refractory or ineligible
- ECOG 0-1

Exclusion criteria

- Salivary gland primary
- Chemotherapy, RT or investigational agent within 4 weeks
- Prior grade ≥ 3 irAE or any unresolved irAE > Grade 1
- Known active, uncontrolled CNS metastases
- Cohort 1 and 4: prior anti-PD-1/PD-L1 therapy



- Primary endpoint: 6-month ORR based on RECIST
- Secondary endpoints include: 12-month PFS, OS, DOR, safety and tolerability, correlation between molecular markers and disease outcome

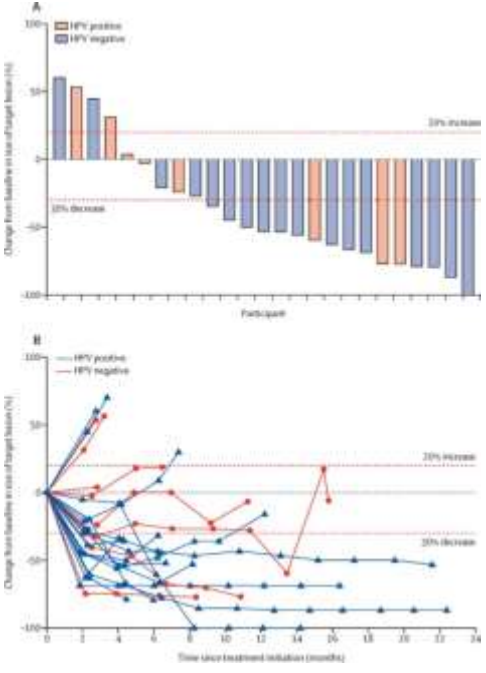
1. Sacco AG, et al. 2019 ASCO, Abs. 6033

Results of cohort 1 interim analysis[1]

15 pts enrolled Mar 2017 – Jan 2019

Characteristic	N (Total = 15)
Median age (range), year	58 (47 - 86)
Gender (Male : Female)	7:8
Race	
White	11
Asian	2
More than 1 race	2
Tumour site	
Oral cavity	9
Oropharynx	3 (all HPV-mediated)
Nasopharynx	2
Larynx	1
ECOG 0 : 1	2:13
Disease recurrence pattern	
Local only	4
Locoregional	2
Locoregional, distant	1
Local and distant	1
Regional and distant	1
Distant only	6
Prior lines of systemic therapy for R/M disease	
None	11
1	4

Response/Survival data				
Response type by 6 mo	Out of 15 pts	Mean DOR	DCR	Median PFS
CR	0		67 %	189 days (6.3 mo)
PR	7 (47%)	192 days (6.4 mo)		
SD	3 (20%)	205 days (6.8 mo)		
PD	5 (33%)*			

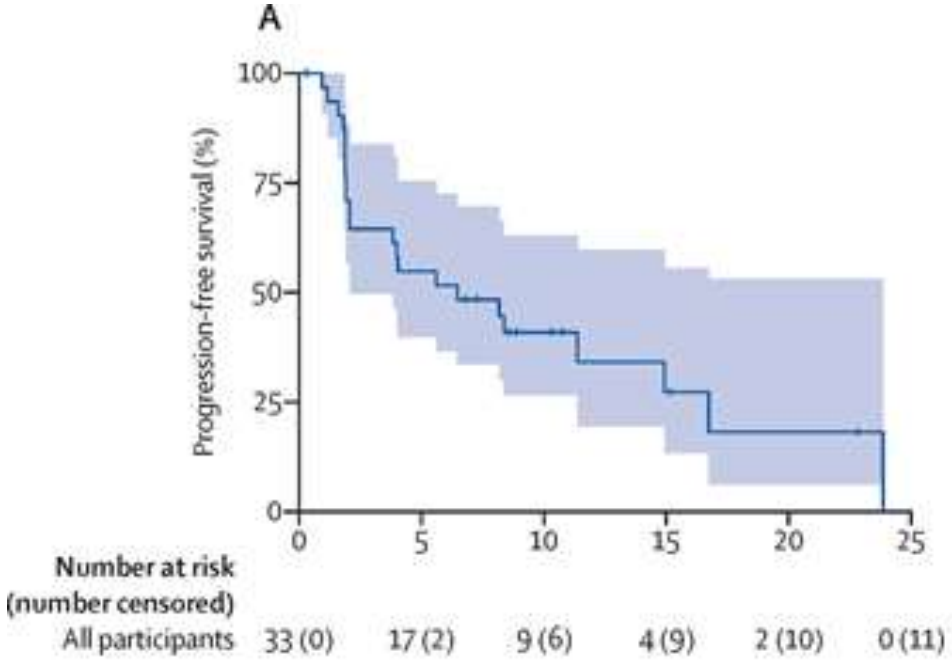


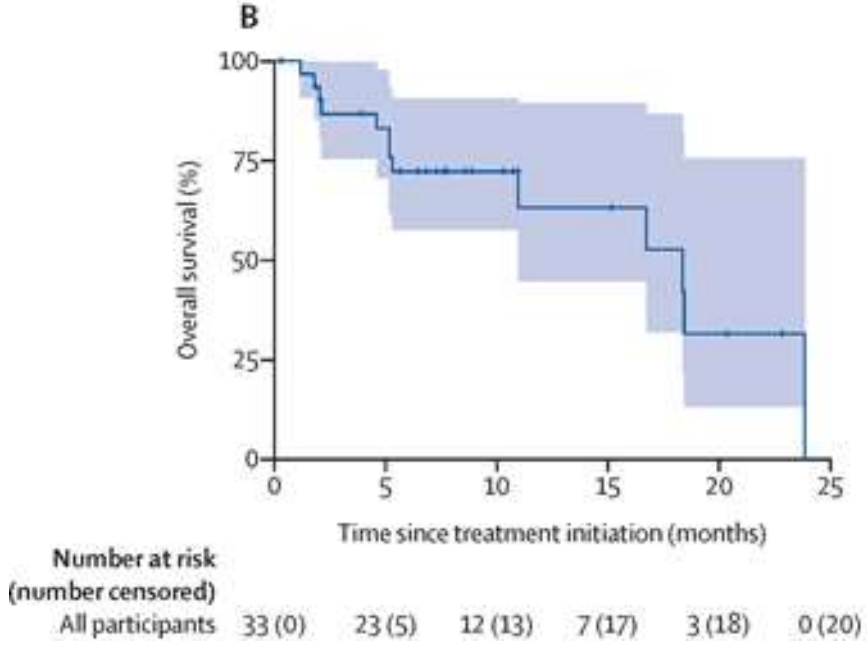
Safety

- 7 grade 3 TRAE
  - Colitis (n=2)
  - Oral mucositis (n=2)
  - Fatigue (n=1)
  - Laryngeal edema (n=1)
  - Hypomagnesemia
- 3 pts discontinued cetuximab due to toxicity
- 1 pt discontinued pembrolizumab due to toxicity

1. Sacco AG, et al. **2019 ASCO**, Abs. 6033

PFS : ~ 5.5 M and OS: ~17M





Conclusion[1]

- By 6 months, the overall response rate was 45% (95% CI 28-62), with 15 of 33 participants achieving a partial response.
  - The most common grade 3-4 treatment-related adverse event was **oral mucositis** (three [9%] of 33 participants)
  - SAEs occurred in five (15%) participants.
  - No treatment-related deaths occurred.

- Interim analysis indicates that pembrolizumab plus cetuximab is potentially active for platinum-refractory/ineligible pts with R/M HNSCC.

- These results meet protocol specifications for trial continuation.

1. Sacco AG, et al. 2019 ASCO, Abs. 6033

Efficacy of concurrent cetuximab (CTX) and nivolumab (NIVO) in previously untreated recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)[1]

Abstract #6017: Efficacy of concurrent cetuximab (CTX) and nivolumab (NIVO) in previously untreated recurrent (R) and/or metastatic (M) head and neck squamous cell carcinoma (HNSCC)

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[1]Moffitt Cancer Center, [2]Emory University, [3]Ohio State University

1. Chung CH et al. ASCO 2021. Abs. 6017 (Poster)

Cetuximab + Nivolumab – R/M SCCHN

First-line

Key eligibility criteria

- SCC of oral cavity, oropharynx, paranasal sinuses, nasal cavity, hypopharynx, or larynx. SCC of unknow primary in cervical lymph node can be included only if p16 status is positive.
- R/M HNSCC that is amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
- Patient must not have any systemic therapy for R/M disease except if given as a part of a multimodality treatment (re-irradiation and systemic therapy for curable intent of locally recurrent disease)
- Persistent disease or platinum-refractory recurrent disease (recurs within 6 months of last dose of chemotherapy given as sensitizer to definitive radiation) are included

D-14: Cetuximab 500 mg/m^2 x1

Cetuximab 500 mg/m^2 Q2W +
Nivolumab 240 mg Q2W
(1 cycle = 4 weeks)

Until PD, intolerable toxicity, withdrawal of consent, or up to 24 cycles

- **Primary objective: 1-y OS**

1. Chung CH et al. ASCO 2021. Abs. 6017 (Poster)

Patient characteristics (n=54)

RESULTS: PATIENT CHARACTERISTICS (DATA LOCK 01/28/2021)

Variable	N=54 (%)	Primary Site	
Median Age	62 (42,85)	Hypopharynx	3 (6)
Gender: M/F	38 (70)/16 (30)	Larynx	9 (17)
Race		Oral Cavity	19 (35)
White	48 (89)	Oropharynx	22 (41)
Black	3 (6)	Unknown Primary (UP)	1 (2)
Other	3 (6)	**Prior Therapy**	
ECOG		Cisplatin + RT	20 (37)
0	20 (37)	Carboplatin/Cisplatin + Paclitaxel + RT	9 (17)
1	30 (56)	Carboplatin + RT	3 (6)
2	4 (7)	Docetaxel + 5-FU → Carboplatin + Paclitaxel + RT	1 (2)
Smoking		Cisplatin + Docetaxel + 5-FU → Carboplatin + Paclitaxel + RT	1 (2)
Current	6 (11)	Carboplatin + Paclitaxel → Cisplatin + RT	1 (2)
Never	17 (32)	Cisplatin + RT → Carboplatin + Paclitaxel + Cetuximab → Carboplatin + Paclitaxel + re-RT	1 (2)
Former	31 (57)	Definitive RT alone	4 (7)
p16 IHC status		Surgery → RT alone	5 (9)
OP+UP pos	18 (33)	Surgery → unknown chemo + RT	1 (2)
OP neg	5 (9)	Surgery → Carboplatin + Paclitaxel + RT	1 (2)
Non-OP pos	4 (7)	RT alone → unknown chemo + re-RT	1 (2)
Non-OP neg	27 (50)	RT alone → re-RT alone	1 (2)
PD-L1 CPS		No prior treatment	5 (9)
0	6 (11)		
>/= 1	26 (48)	***Persistent Disease after definitive CRT (N=36)**	5 (9)
Unknown	22 (41)	*On treatment within 3 months from the last dose of RT	

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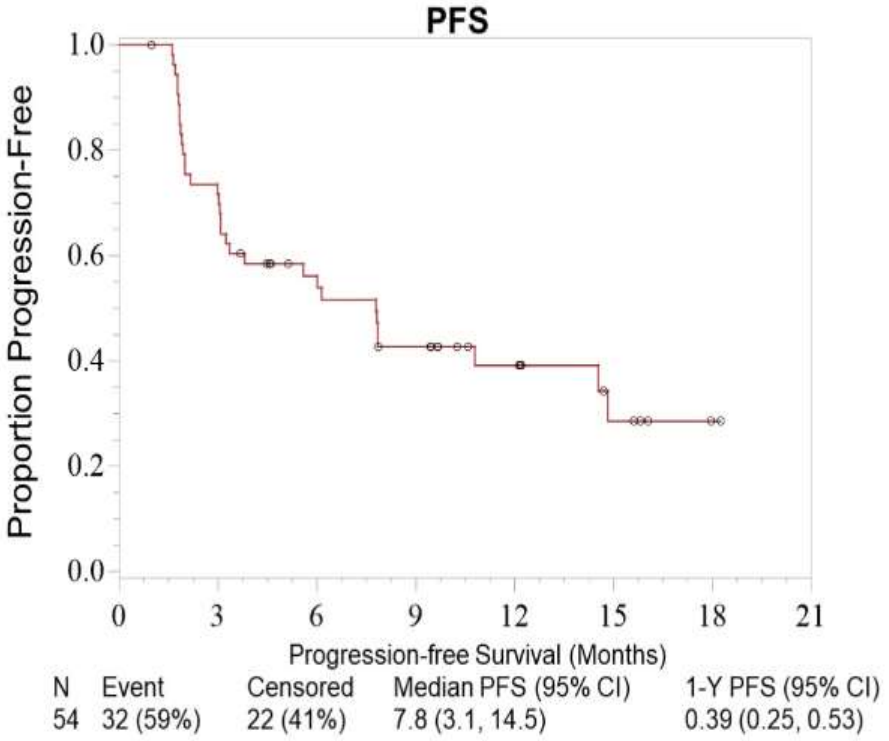
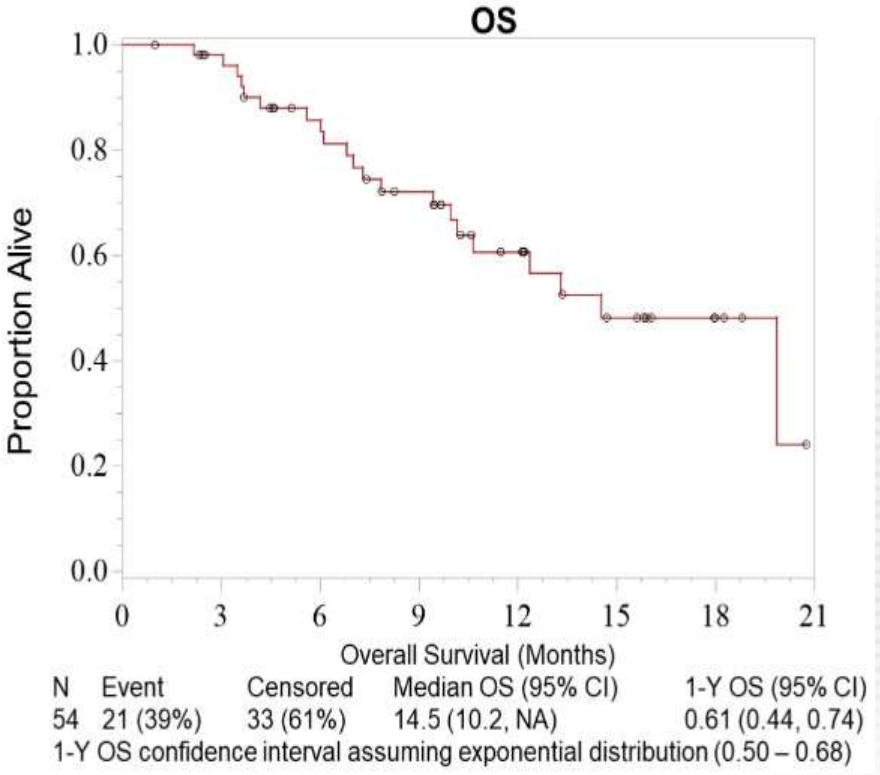
Efficacy – PFS and OS[1]

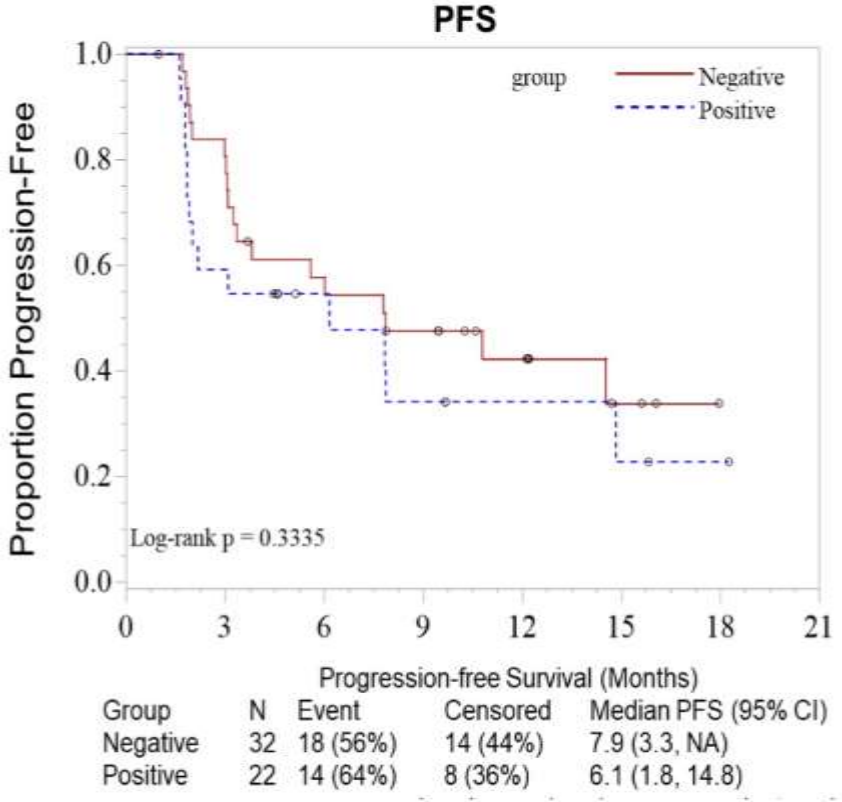
- **Median follow-up: 12.2 mo (95% CI: 9.67 – 15.81)**



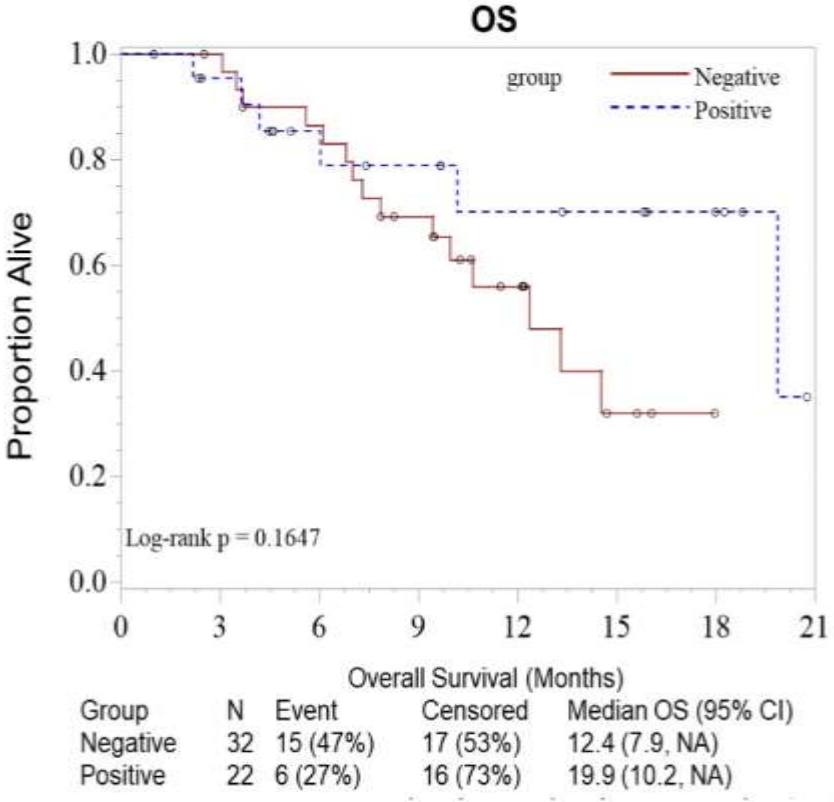


1. Chung CH et al. ASCO 2021. Abs. 6017 (Poster)

Efficacy – PFS and OS by p16 status[1]



Group	N	Event	Censored	Median PFS (95% CI)
Negative	32	18 (56%)	14 (44%)	7.9 (3.3, NA)
Positive	22	14 (64%)	8 (36%)	6.1 (1.8, 14.8)



Group	N	Event	Censored	Median OS (95% CI)
Negative	32	15 (47%)	17 (53%)	12.4 (7.9, NA)
Positive	22	6 (27%)	16 (73%)	19.9 (10.2, NA)

1. Chung CH et al. ASCO 2021. Abs. 6017 (Poster)

Summary

- 1-year OS with median OS 14.5 months.

- CTX and NIVO is safe and effective
- The response rate was suggested to be ***higher in p16-neg*** than p16-pos patients (48% vs. 24%), but there was no significant difference in PFS and OS.

- These preliminary results support further evaluation in previously untreated patients with R/M HNSCC.

1. Chung CH et al. ASCO 2021. Abs. 6017 (Poster)

Combo with Cetuximab..other then Chemo.

- Target therapy..
- Immune Check-point inhibitor (PD1/PDL-1 Mab)
- Anti-angiogenesis..?

Promising… but need more data

Afatinib and pembrolizumab for recurrent or metastatic head and neck squamous cell carcinoma (ALPHA Study): A phase II study with biomarker analysis[1]

Afatinib and pembrolizumab for recurrent or metastatic head and neck squamous cell carcinoma (ALPHA Study): A phase II study with biomarker analysis

Hsiang-Fong Kao[1,4], Bin-Chi Liao[1,4], Yen-Lin Huang[2,5], Huai-Cheng Huang[1,4], Chun-Nan Chen[3], Tseng-Cheng Chen[3], Yuan-Jing Hong[1], Ching-Yi Chang[1], Ruey-Long Hong[1]

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1. Kao HF et al. ASCO 2021. Abs. 6024 (Poster)

ALPHA study– R/M SCCHN

Phase II trial design – Second-line

ALPHA study[1,2] (NCT03695510)

Phase II, single-arm trial

Key inclusion criteria:

- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- The recurrent disease is not suitable for curative surgery or definitive chemoradiation, and/or metastatic diseases which are not amenable to surgery and/or curative radiotherapy.
- ECOG ≤2
- Tumor progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant, primary, recurrent, or metastatic setting

Key exclusion criteria:

- Nasopharyngeal carcinoma or nasal cavity malignancies other than HNSCC
- Prior exposure to anti-PD-1, anti-PD-L1, anti-CTLA-4, or other ICI
- Prior exposure to EGFR TKIs (e.g. afatinib)

N=29

→

Afatinib 40 mg PO QD
+
Pembrolizumab 200 mg IV Q3W
(for 35 cycles)

- Primary endpoint: ORR
- Biomarker analysis:
  - PD-L1 IHC: 22C3
  - TMB: Roche Foundation One CDx
  - Nanostring

1. Kao HF et al. ASCO 2021. Abs. 6024 (Poster); 2. NCT03695510

Baseline characteristics (n=29)[1]

- Mean age: 53.4 years
- 27 Male, 2 Female
- Tumor types:
  - 19 Oral cavity
  - 6 oropharynx
  - 2 hypopharynx
  - 2 larynx
- PD-L1
  - TPS ≥50%: 7/29 (24.1%)
  - CPS ≥20: 8/29 (27.6%)
- TMB >10: 0%

1. Kao HF et al. ASCO 2021. Abs. 6024 (Poster)

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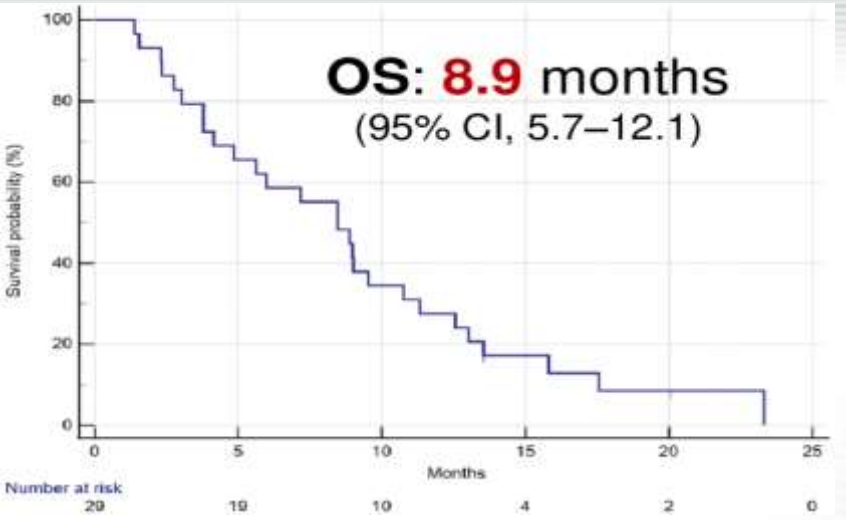

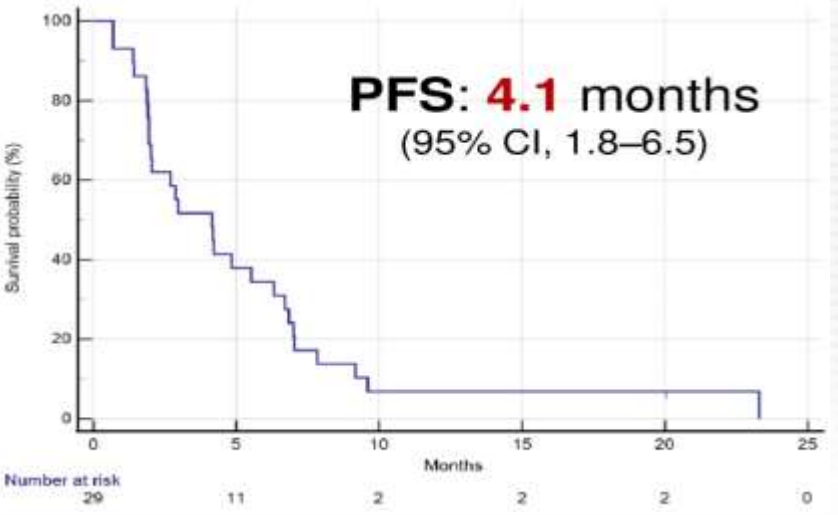

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1. Kao HF et al. ASCO 2021. Abs. 6024 (Poster)

Summary

- Afatinib plus pembrolizumab showed promising anti-tumor activity in HNSCC patients.

- Possible predicting factors: MTAP loss or mutation, and EGFR amplification.

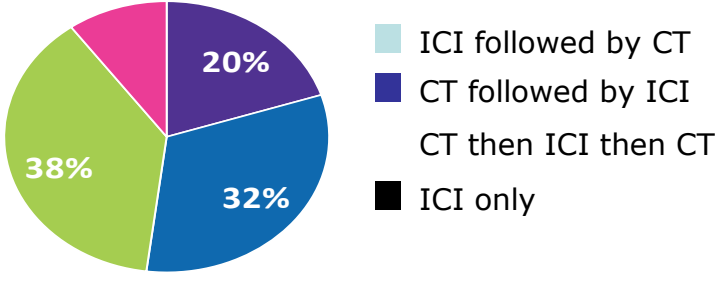
1. Kao HF et al. ASCO 2021. Abs. 6024 (Poster)

How about 2nd line Tx after Cetuximab ?

Patients who received ICIs in the 2L had a similar OS to 1L and a prolonged mDoR[1]

Retrospective study of patients treated with ICI for R/M SCCHN in 1L or 2L in four hospitals in France (N=192)

Treatment received:



ECOG PS		1L ICI (n=57)	2L ICI (n=135)
ECOG at ICI start, %	0	44	24
	1	51	69
	2	5	7

Efficacy	1L ICI (n=57)	2L ICI (n=135)	p-value
ICI given as monotherapy, %	23	66	
ICI given in combination, %	77	34	
ORR, %	17.5	17.9	
mDoR, months	7.3	15.2	
mPFS, months	3.3	2.7	0.7
mOS from start of ICI, months	12.2	11.6	0.7
mOS from diagnosis of advanced disease*, months	15.9	22.1	0.11
Patients receiving salvage CT after progression on ICI, n (%)	38 (67)	73 (53)	
ORR to salvage CT, %	44	34	

*After median follow-up of 28.5 months.

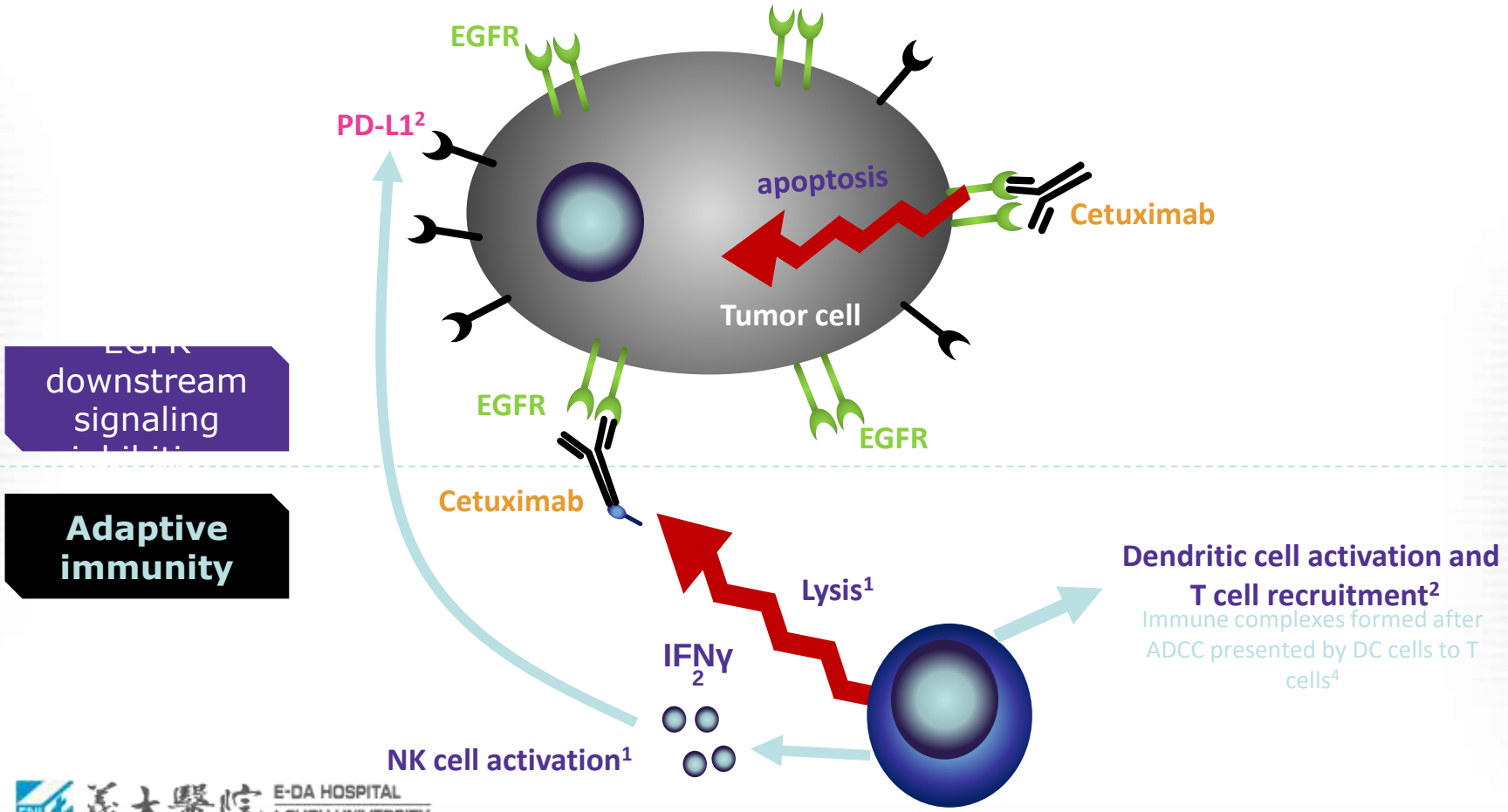
1. Even C et al. ESMO 2019 (Abstract No. 1138P – poster).

Summary of current sequential treatment evidences

Study	Cetuximab -> CPI	CPI -> Cetuximab
TPExtreme	21.9 m (OS from cet regimen)	-
Lien MY, 2020	20.6 m (OS from cet regimen)	-
Sano D, 2019	20.0 m (PPS from cet PD)	-
Park JC, 2020	13.6 m (OS from cet regimen); worse outcomes vs no prior cet	11.3 m (OS from CPI PD) Similar OS vs no prior CPI
CheckMate-141	7.1 m (OS from nivo treatment) Similar OS vs no prior cet	-
Keynote-040	NA; Similar OS vs no prior cet	-
Chung CH, 2021	14.7 m (OS from CPI treatment) Similar OS vs no prior cet	6.7 m (OS from cet mono) worse OS vs no prior CPI
Shin K, 2021	8.4 m (OS from nivo treatment) Similar OS vs no prior cet	-

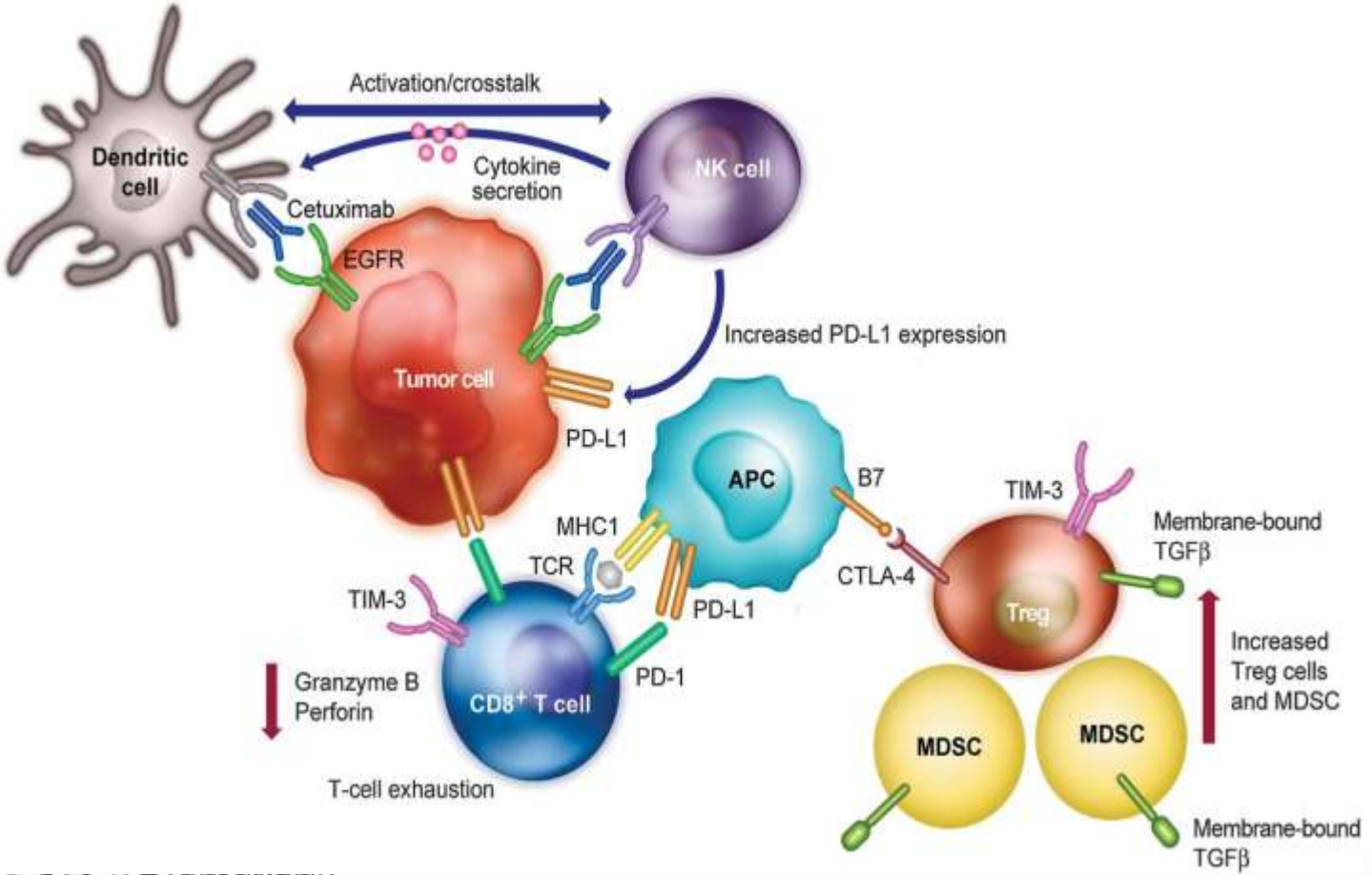
Does previous cetuximab reduce the efficacy of later-line CPI?

Cetuximab is not only a targeted therapy but also an immune modulator which potential synergy with subsequent I-O therapy



1. Trivedi S, et al. Ann Oncol 2015;26:40–47;2. Bellucci R, et al. OncoImmunol 2015;4:6,e1008824;3. Lo Nigro C, et al. Cancer Res 2015;75:1327.

There are some reports that cet mediates ADCC and adaptive immunity may lead to immunosuppressive feedback loops and counterregulation



Ferris RL et al. Clin Cancer Res. 2019 Sep 1;25(17):5221-5230

Effectiveness of nivolumab affected by prior cetuximab use and neck dissection in Japanese patients with recurrent or metastatic head and neck cancer: results from a retrospective observational study in a real-world setting

Shin Kariya[1] · Yasushi Shimizu[2] · Nobuhiro Hanai[3] · Ryuji Yasumatsu[4] · Tomoya Yokota[5] · Takashi Fujii[6] · Kiyoaki Tsukahara[7] · Masafumi Yoshida[8] · Kenji Hanyu[9] · Tsutomu Ueda[10] · Hitoshi Hirakawa[11] · Shunji Takahashi[12] · Takeharu Ono[13] · Daisuke Sano[14] · Moriyasu Yamauchi[15] · Akihito Watanabe[16] · Koichi Omori[17] · Tomoko Yamazaki[18] · Nobuya Monden[19] · Naomi Kudo[20] · Makoto Arai[21] · Shuji Yonekura[22] · Takahiro Asakage[23] · Akinori Fujiwara[24] · Takayuki Yamada[25] · Akihiro Homma[26]

Received: 22 December 2020 / Accepted: 13 March 2021

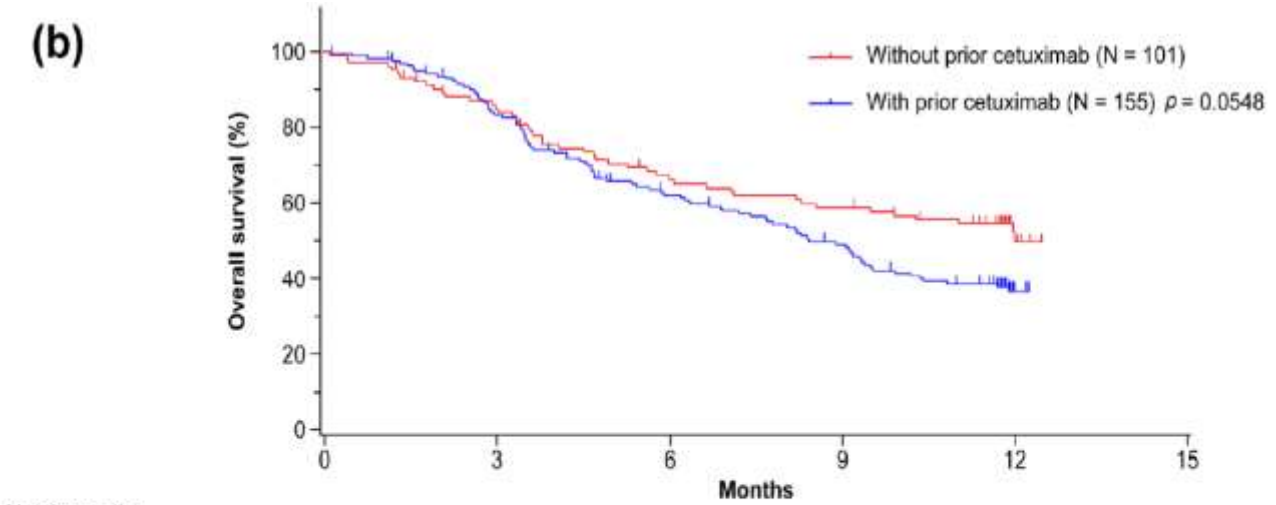
With prior Cetuximab

Without prior Cetuximab

→ Received Nivolumab

Shin K., et al. Int J Clin Oncol. 2021 Jun;26(6):1049-1056.

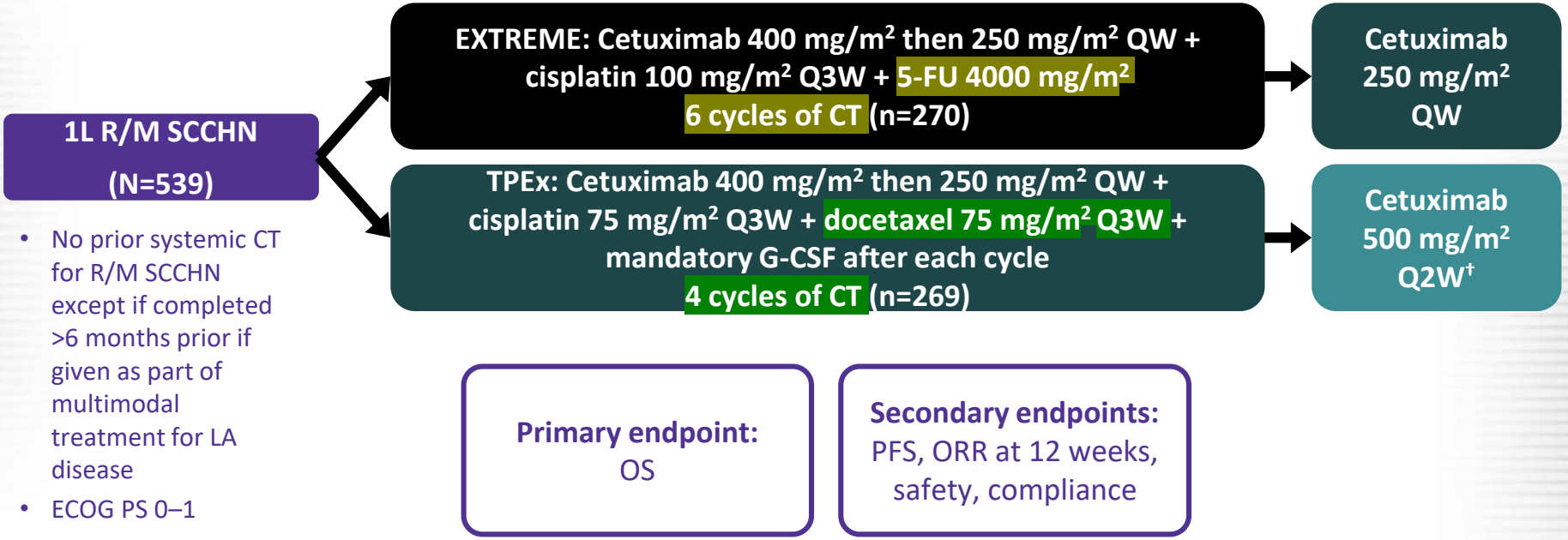
OS was not statistical different between patient with vs without prior Cet exposure



Prior cetuximab use	N	Median OS (95% CI), (months)	6-month OS rate (%) (95% CI)	12-month OS rate (%) (95% CI)
With	155	8.4 (6.9 – 9.9)	62.1 (53.8 – 69.4)	36.9 (28.9 – 44.9)
Without	101	12 (8.3 – NE)	66.2 (55.8 – 74.6)	52.5 (41.7 – 62.2)

Shin K., et al. Int J Clin Oncol. 2021 Jun;26(6):1049-1056.

TPExtreme* study has fulfilled part of data gap in the treatment sequence [7,31]



➤ *The TPExtreme study did not meet its primary endpoint of significantly improving OS in the TPEx regimen vs the EXTREME regimen. Cetuximab is administered Q2W in this study arm during maintenance, whereas the EU SmPC stipulates weekly administration. Cetuximab is indicated in R/M SCCHN in combination with a platinum-based CT. Taxanes are currently not approved for R/M SCCHN; †The EU SmPC stipulates weekly administration for cetuximab.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; G-CSF, granulocyte-colony stimulating factor; LA, locally advanced; QW, weekly; Q2W, every 2 weeks; Q3W, every 3 weeks.

7. Guigay J, et al. ASCO 2019 (Abstract No. 6002 – Presentation); 31. ClinicalTrials.gov (NCT02268695). Available at: https://clinicaltrials.gov/ct2/show/NCT02268695 Last accessed July 2020.

64% of patients received 2L treatments after 1L progression in the TPExtreme study*[37]

Post-hoc exploratory analysis based on 2L treatment

n (%)	EXTREME arm	TPEx arm
2L data available	256	245
2L received	164 (64%)	157 (64%)
Type of 2L treatment		
IO (anti PD-1/PDL-1)	41 (16%)	41 (17%)
Taxane-based CT	56 (22%)	30 (12%)
Other CT	40 (16%)	61 (25%)
Cetuximab ± CT	24 (9%)	18 (7%)
Radiotherapy	3 (1%)	7 (3%)

Tx sequence Analysis

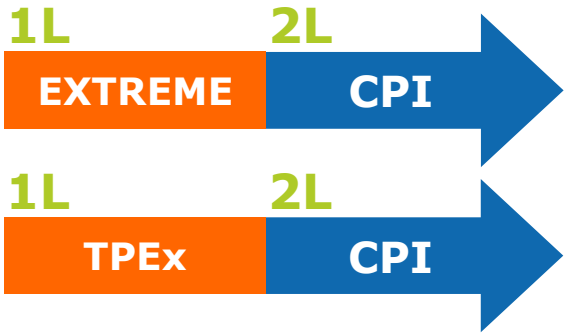
47% of patients in the EXTREME arm and 44% of patients in the TPEx arm received 2L CT ± cetuximab, based on the post-hoc analysis

- *The TPExtreme study did not meet its primary endpoint of significantly improving OS in the TPEx regimen vs the EXTREME regimen. Cetuximab is administered Q2W in this study arm during maintenance, whereas the EU SmPC stipulates weekly administration. Cetuximab is indicated in R/M SCCHN in combination with a platinum-based CT. Taxanes are currently not approved for R/M SCCHN.

IO, immunotherapy; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1.

37. Guigay J, et al. ASCO 2020 (Abstract No. 6507 – Presentation).

Rather than antagonistic action, 1L cetuximab + CT followed by 2L CPI MAY have an OS benefit in TPExtreme study

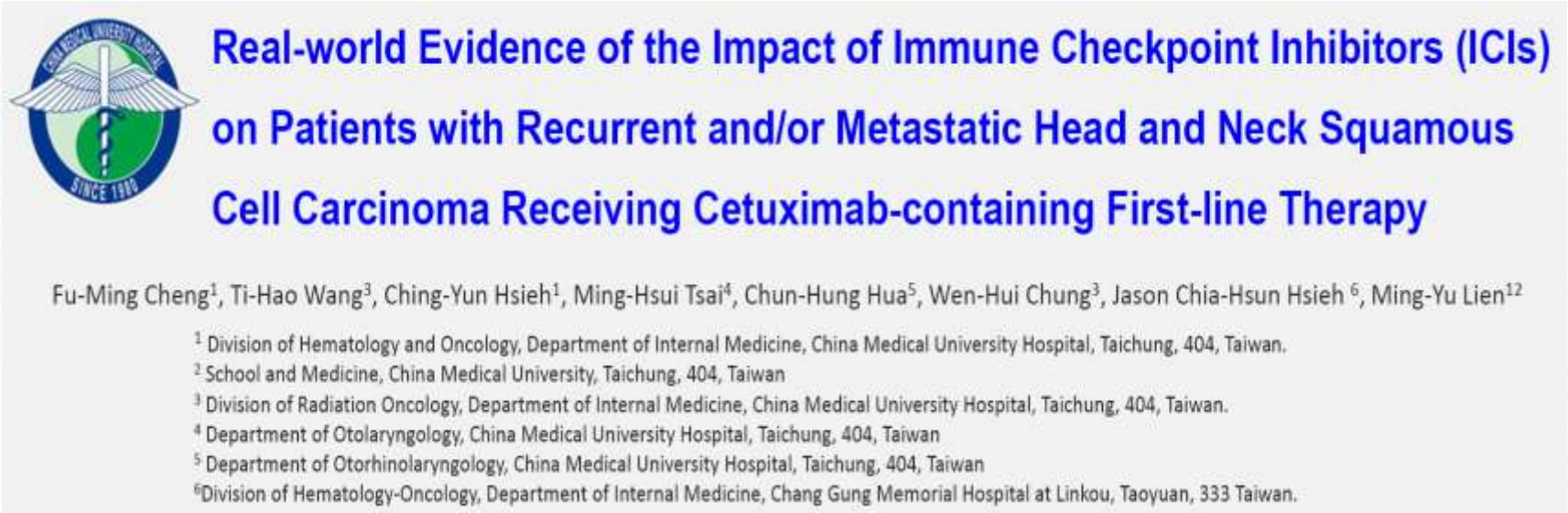


mOS since randomization in each arm, 2L CPI vs 2L CT ± cetuximab (interaction test

2L treatment	Patients with PD, n (%)	2L CPI		
		n (%)	mOS from randomization, mo (95% CI)	mOS from 2L, mo (95% CI)
EXTREME (n=256)	213 (79)	41 (16)	**19.4 (13.4–22.3)**	8.3 (5.0–15.0)
TPEx (n=245)	208 (85)	41 (17)	**21.9 (15.9–35.0)**	11.6 (6.0–21.4)

1L TPEx followed by IO has the longest mOS (21.9m)

Real-world Evidence of the Impact of Immune Checkpoint Inhibitors (ICIs) on Patients with Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma Receiving Cetuximab containing First line Therapy[1]



Real-world Evidence of the Impact of Immune Checkpoint Inhibitors (ICIs) on Patients with Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma Receiving Cetuximab-containing First-line Therapy

Fu-Ming Cheng[1], Ti-Hao Wang[3], Ching-Yun Hsieh[1], Ming-Hsui Tsai[4], Chun-Hung Hua[5], Wen-Hui Chung[3], Jason Chia-Hsun Hsieh [6], Ming-Yu Lien[12]

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1. Cheng FM et al. ESMO 2020. Poster 926P For medical external reactive use only

CMU RWE[1]

Retrospective observational study at two tertiary medical centers in Taiwan:

- RM HNSCC who received cetuximab plus chemotherapy as first line therapy.
- Between January 2017 and July 2019.

Table 1. Demographic of patients undergoing cetuximab and chemotherapy (n=290)

Characteristics	n	(%) or standard deviation
Mean Age (years)	56.1	+/-10.4
Male Gender	272	93.8
ECOG		
0-1	232	80.0
Tumor primary site		
Oral cavity	172	59.3
Oropharynx	46	15.9
Hypopharynx	49	16.9
others	23	7.9
Initial clinical stage		
Stage I-II	56	19.3
Stage III-IV	205	70.7
unknown	29	10.0
Status at recurrence		
Locally advanced	208	71.8
Metastatic	82	28.3
HPV positive*	10	21.7
Prior radical operation (Yes)	164	56.6
Prior radiotherapy (Yes)	247	85.2
Interval between previous platinum (months)		
<6	128	44.1
>=6	162	55.9
Combination chemotherapy regimen(*)		
Platinum base	214	73.8
5FU base	216	74.5
Taxane base	55	19.0
Best response to cetuximab		
CR	26	9.0
PR	97	33.5
ICI (Yes)	93	32.1
ICI in combination with cetuximab	64	22.1
ICI after progression on cetuximab	29	10.0

* p16 data available only for oropharyngeal cancer patients.
** May receive more than 1 chemotherapy regimen for a patient.

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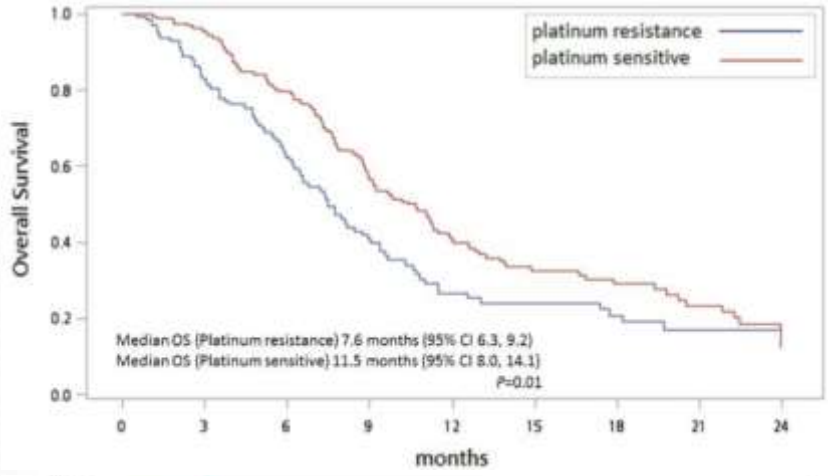
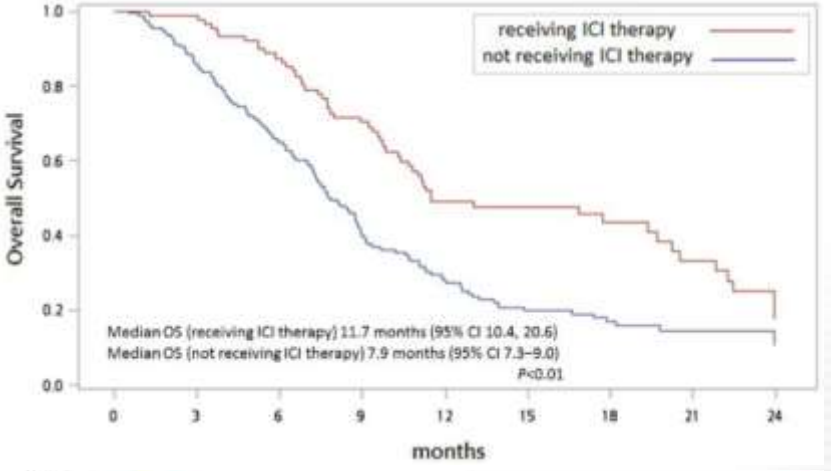
1. Cheng FM et al. ESMO 2020. Poster 926P For medical external reactive use only

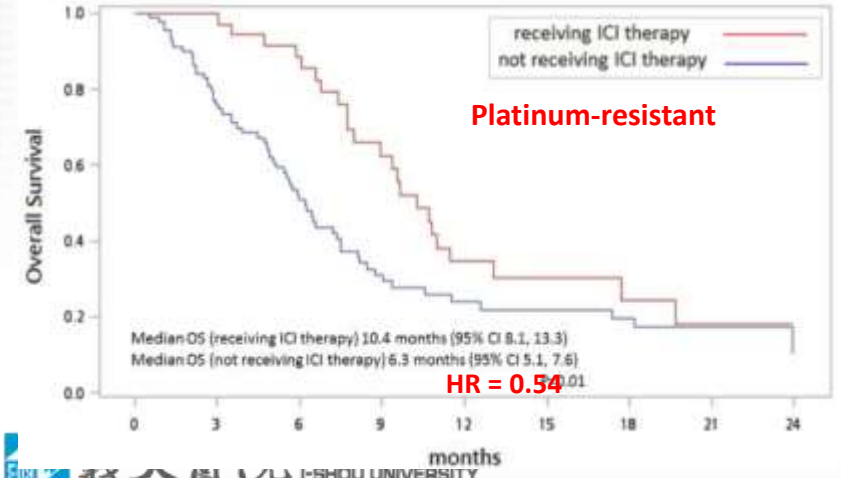
Result[1]

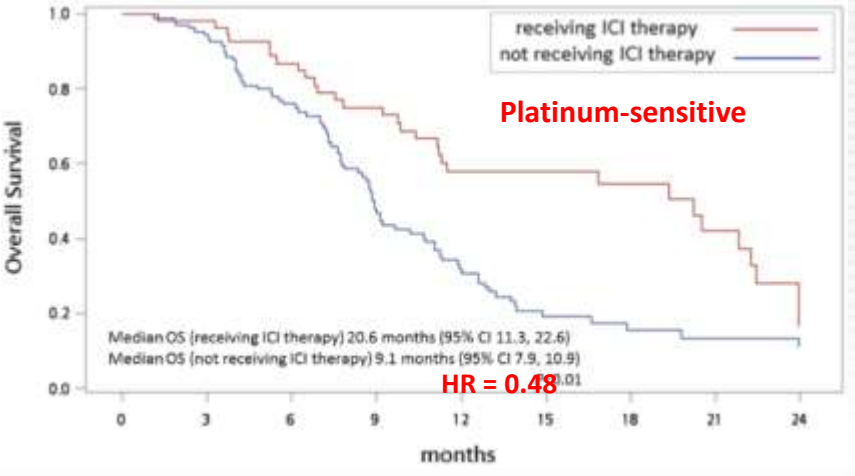
mOS: 9.1 mo (95% CI: 8.2 to 10.4)
mPFS: 5.0 mo (95% CI 4.3 to 5.7)

Similar OS benefit between patients received ICIs after progression on cetuximab and patients received cetuximab in combination with ICIs.









1. Cheng FM et al. ESMO 2020. Poster 926P For medical external reactive use only

Result[1]

- ICIs appeared to improve OS, **even in platinum resistant populations**, which supporting its use in patients with RM HNSCC who treated cetuximab plus chemotherapy as first-line therapy.

- ***The reduction in risk of death with ICIs was similar regarding the combination or sequencing of Cetuximab.***


Care