Posicionamiento de CETUXIMAB en Cáncer de Cabeza y Cuello Recurrente y Metastásico

Ángel Rodríguez Sánchez

Valladolid, 9 de Noviembre de 2017

12a JORNADA DE CÀNCER DE CAP I COLL

Càncer de cap i coll en el pacient d'edat avançada

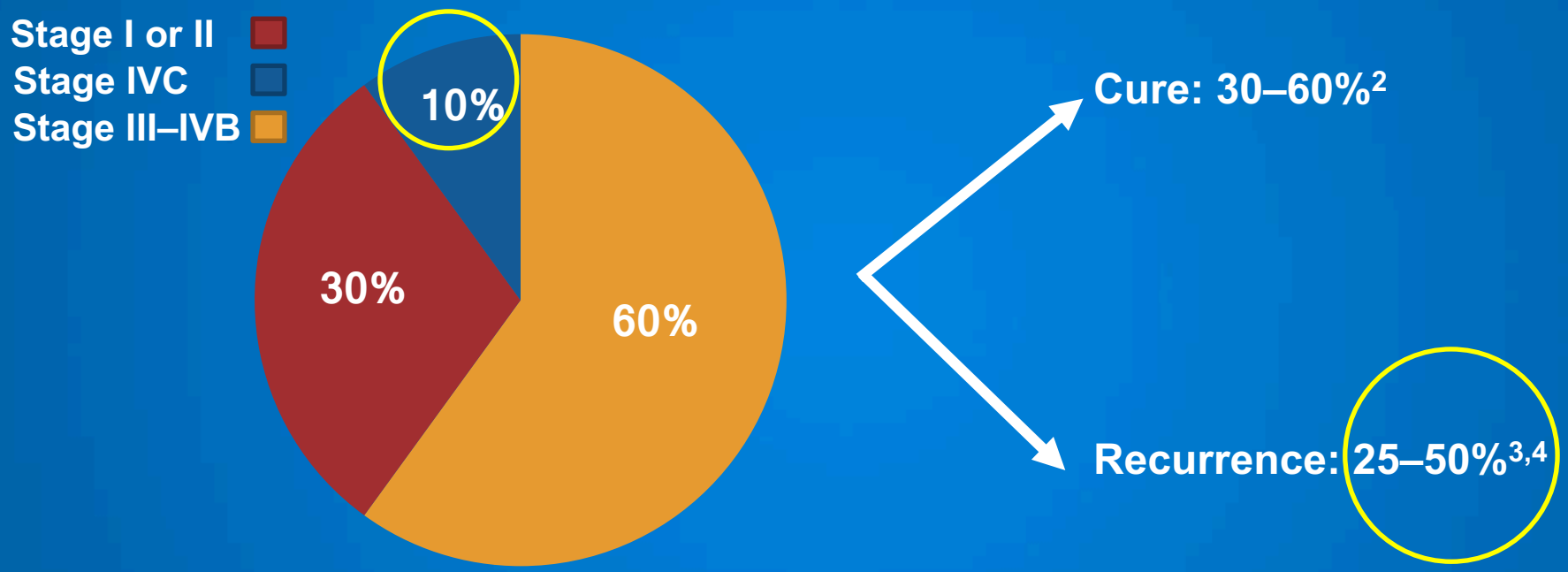
ICO l'Hospitalet

17 de novembre 2017

El divendres 17 de novembre l'ICO l'Hospitalet acollirà la 12ena edició de la Jornada de Càncer de cap i coll, que tractarà aquest tipus de tumor en pacients amb edat avançada.

A substantial proportion of patients with SCCHN will experience relapse or metastatic disease

Disease stage at diagnosis[1]



Stage I or II, early-stage resectable disease;
Stage III–IV, locoregionally advanced (sometimes unresectable)
Stage IVC, metastatic (incurable)

1. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hematology-oncology/head-and-neck-cancer/
2. Goodwin WJ. Laryngoscope 2000;110(3 Pt 2 Suppl 93):1–18;
3. Bernier J, et al. N Engl J Med 2004;350:1945–1952;
4. Cooper JS, et al. N Engl J Med 2004;350:1937–1944

Metotrexate

TREATMENT OF CARCINOMA OF THE HEAD AND NECK WITH INTRAVENOUS METHOTREXATE

LOUIS A. LEONE, MD, MAURICE M. ALBALA, MD, AND VISHRAM B. REGE, MD

Received for publication July 25, 1967.

Leone LA, Albala MM, Rege VB. Treatment of carcinoma of the head and neck with intravenous methotrexate. Cancer. 1968 May;21(5):828-37.

Development of Chemotherapy Regimens in R/M HNSCC

	N	Regimen	ORR (%)	Median OS (months)
Jacobs, et al[1]	249	Cisplatin 5-FU Cisplatin + 5-FU	17 13 32*	5.0 6.1 5.5
Forastiere, et al[2]	277	Cisplatin + 5-FU Carboplatin + 5-FU Methotrexate	32* 21 10	6.6 5.0 5.6
Clavel, et al[3]	382	Cisplatin, methotrexate, bleomycin, vincristine Cisplatin + 5-FU Cisplatin	34* 31* 15	7.3 7.3 7.3
Gibson, et al[4]	218	Cisplatin + 5-FU Cisplatin + paclitaxel	27 26	8.7 8.1
Vermorken, et al[5]	442	Platinum + 5-FU Platinum + 5-FU + Cetuximab	20 36*	7.4 10.1*

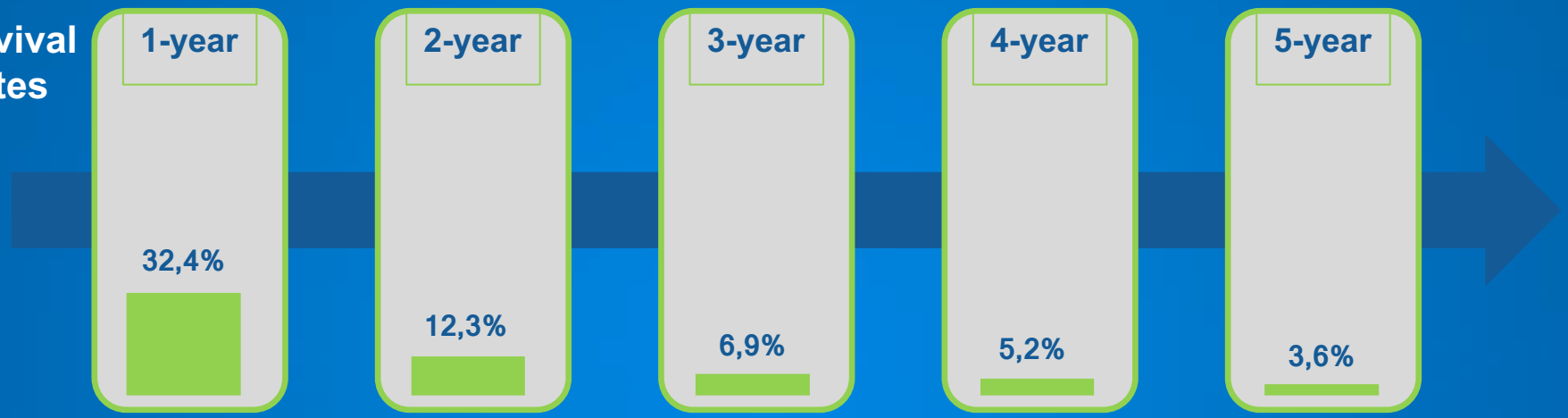
*Statistically significant; 5-FU, 5-fluorouracil

1. Jacobs C, et al. *J Clin Oncol.* 1992;10(2):257-263. 2. Forastiere A, et al. *J Clin Oncol.* 1992;10(8):1245-1251.
3. Clavel M, et al. *Ann Oncol.* 1994;5(6):521-526. 4. Gibson MK, et al. *J Clin Oncol.* 2005;23(15):3562-3567.
5. Vermorken JB, et al. *N Engl J Med.* 2008;359(11):1116-1127.

Long-term survival with CT* in R/M SCCHN: Analysis of two Phase III ECOG trials

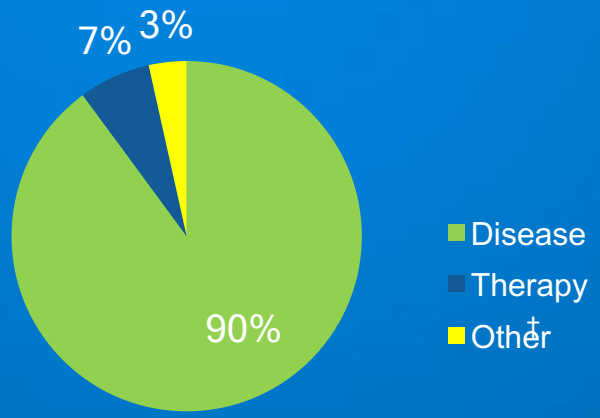
Analysis of 399 patients, with median follow-up 4.8 years

Survival rates



Median OS for all patients: 7.8 months

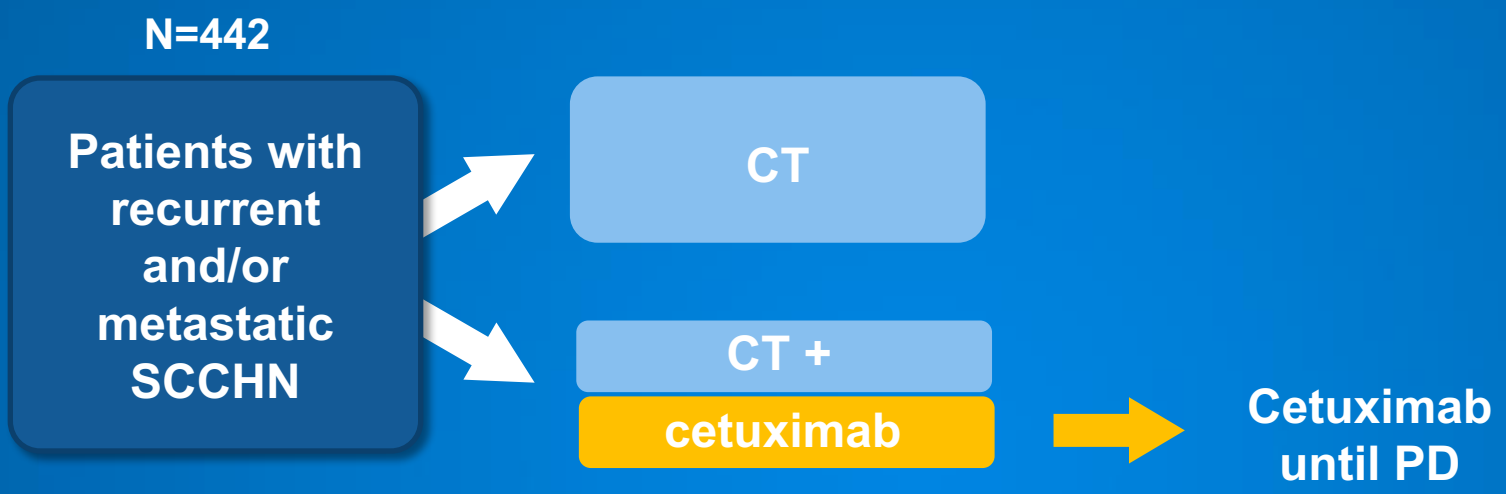
Causes of death:



*Cisplatin-based
E1393 study, n=201; E1395 study, n=198
†No further details provided in study

Argiris A, et al. Cancer 2004;101:2222–2229

EXTREME:
Estudio Fase III - aleatorizado



CT
Cisplatin (100mg/m^2 i.v., day 1)
[or **carboplatin** (AUC 5mg/mL/min, day 1)]
plus **5-FU** (1000mg/m^2 i.v., days 1–4)

Every 3 weeks, up to 6 cycles

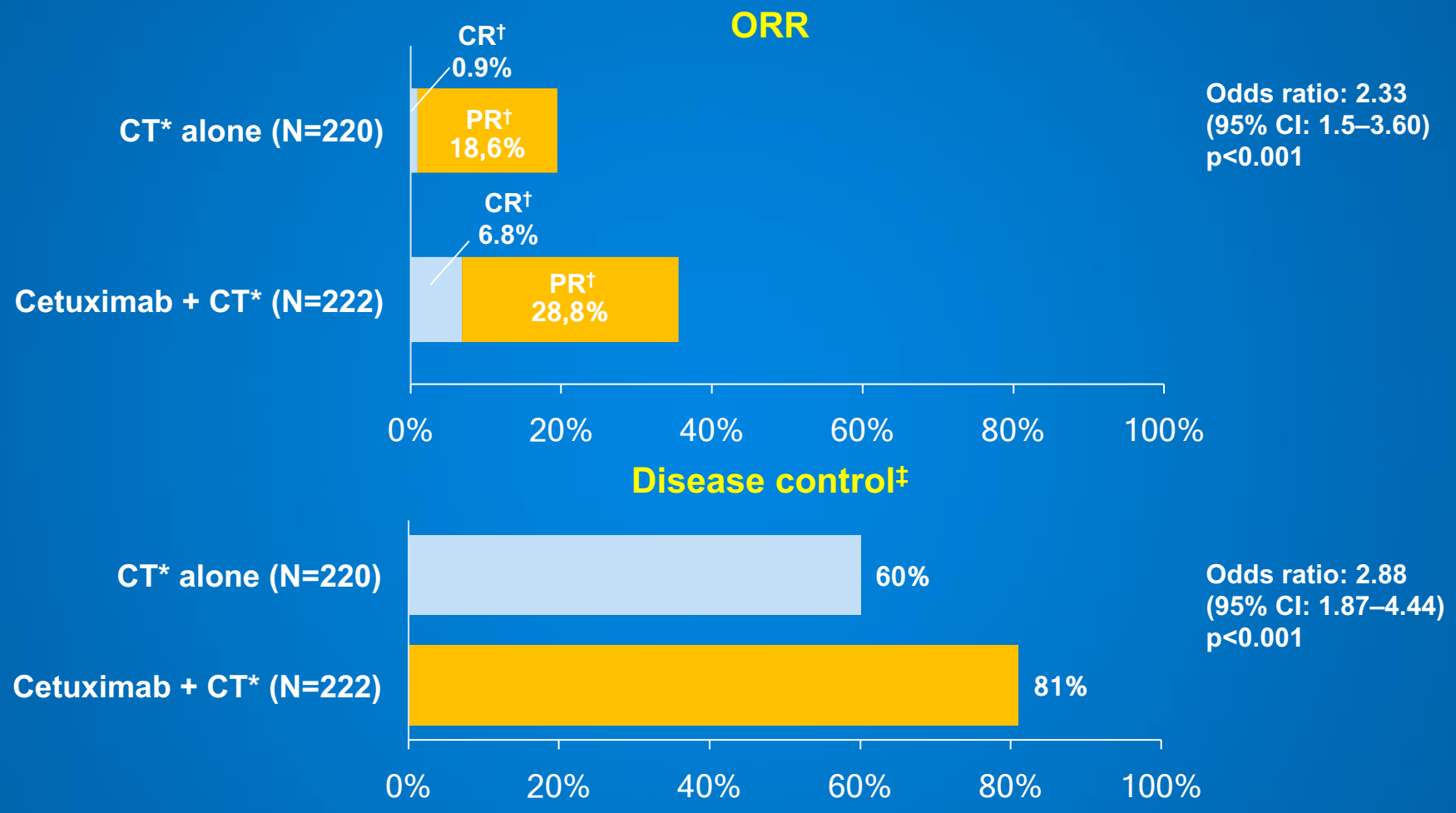
Cetuximab
Initial dose 400mg/m^2 i.v.
then 250mg/m^2 i.v. weekly
until PD

Primary endpoint: OS
Key secondary endpoints: PFS, relative risk, safety

AUC, area under the curve; PD, progressive disease

Vermorken JB, et al. N Engl J Med 2008;359:1116–1127

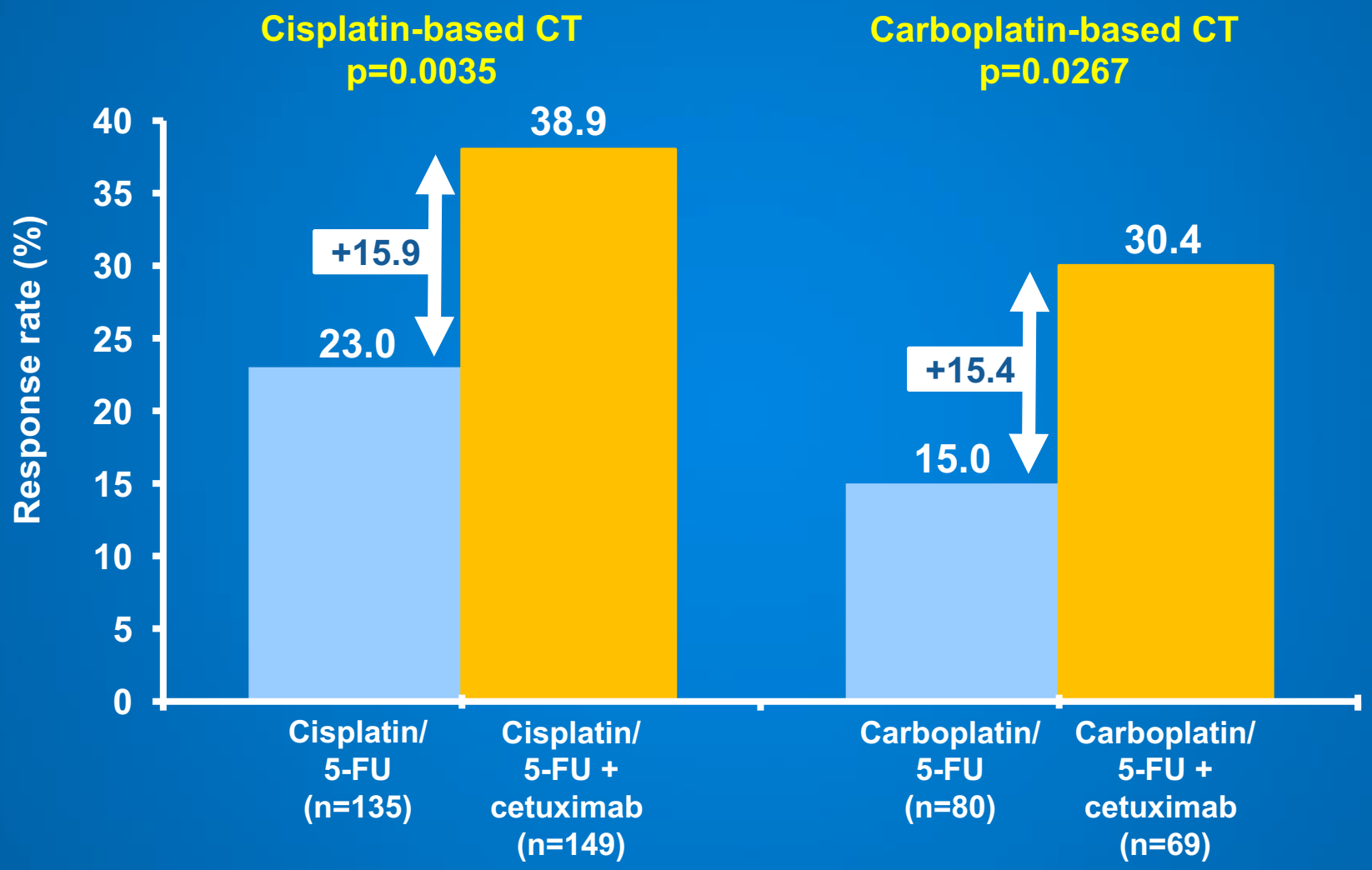
EXTREME:
Improved response rates and control of disease with cetuximab + CT* in R/M SCCHN



*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

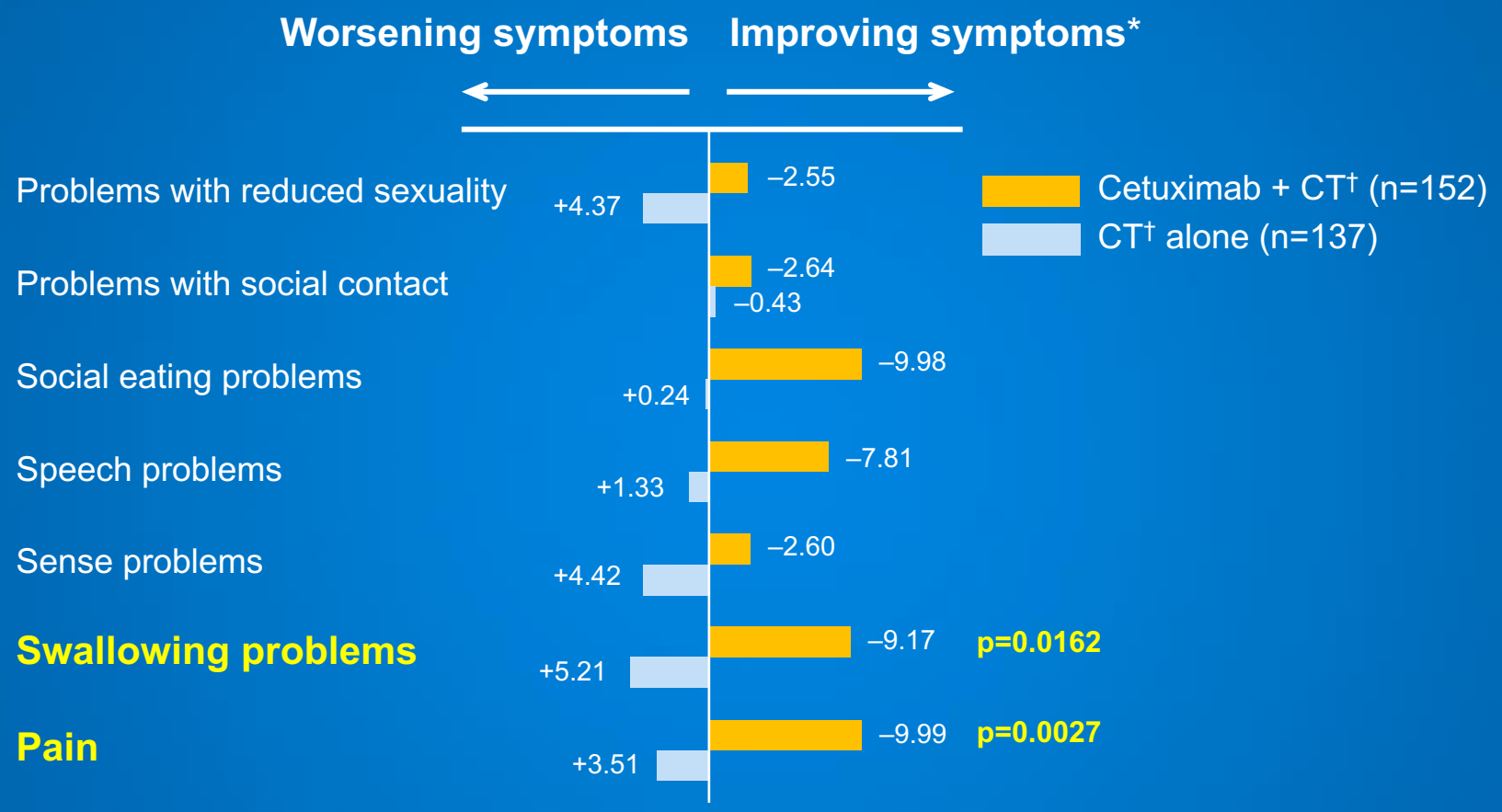
Vermorken JB, et al. N Engl J Med 2008;359:1116–1127
EMR 620202/002 study report (Tables 14.2-3.2 and 14.2-3.3)

EXTREME:
1st line treatment of R/M SCCHN: Cetuximab increases RR regardless of type of platinum CT



Vermorken JB. Springer Science+Business Media 2011:651–664

EXTREME: Significant improvement in swallowing problem and pain with cetuximab added to CT† vs CT† alone



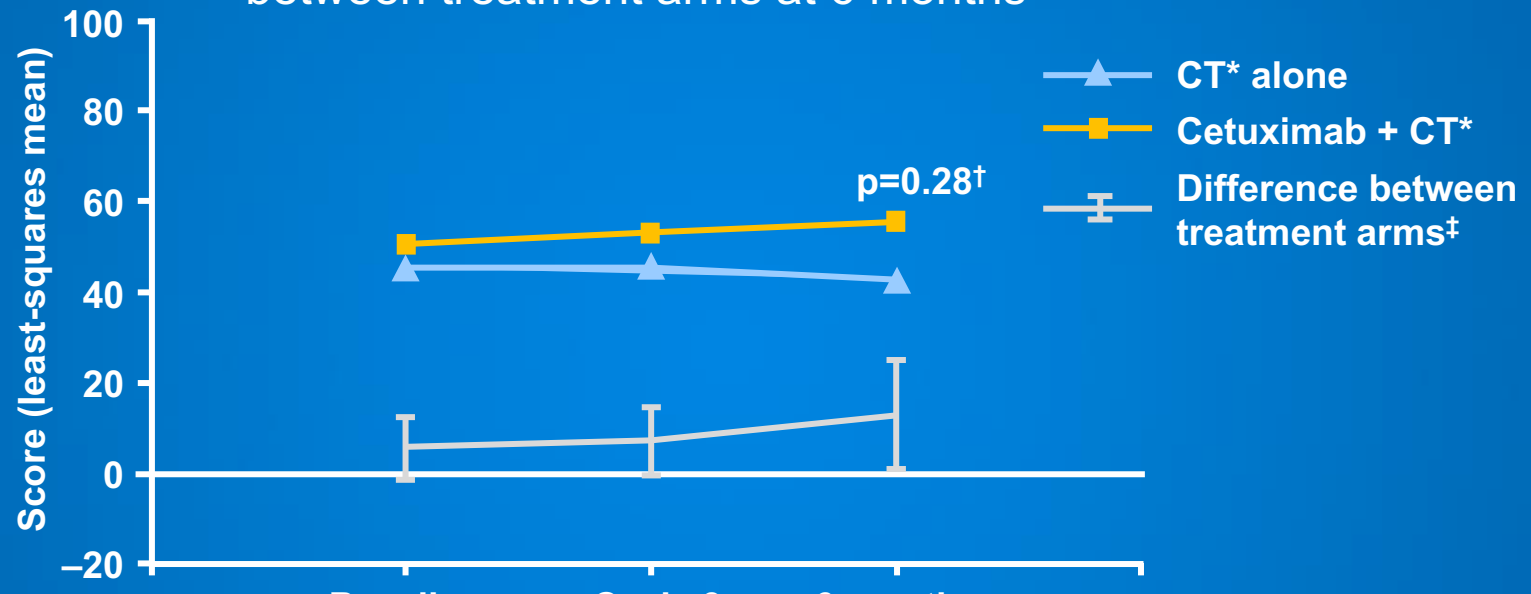
*Measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck 35

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

Mesía R, et al. Ann Oncol 2010;21:1967–1973

EXTREME: Adding cetuximab to CT* does not negatively affect QoL

Global health status/QoL was not statistically different between treatment arms at 6 months

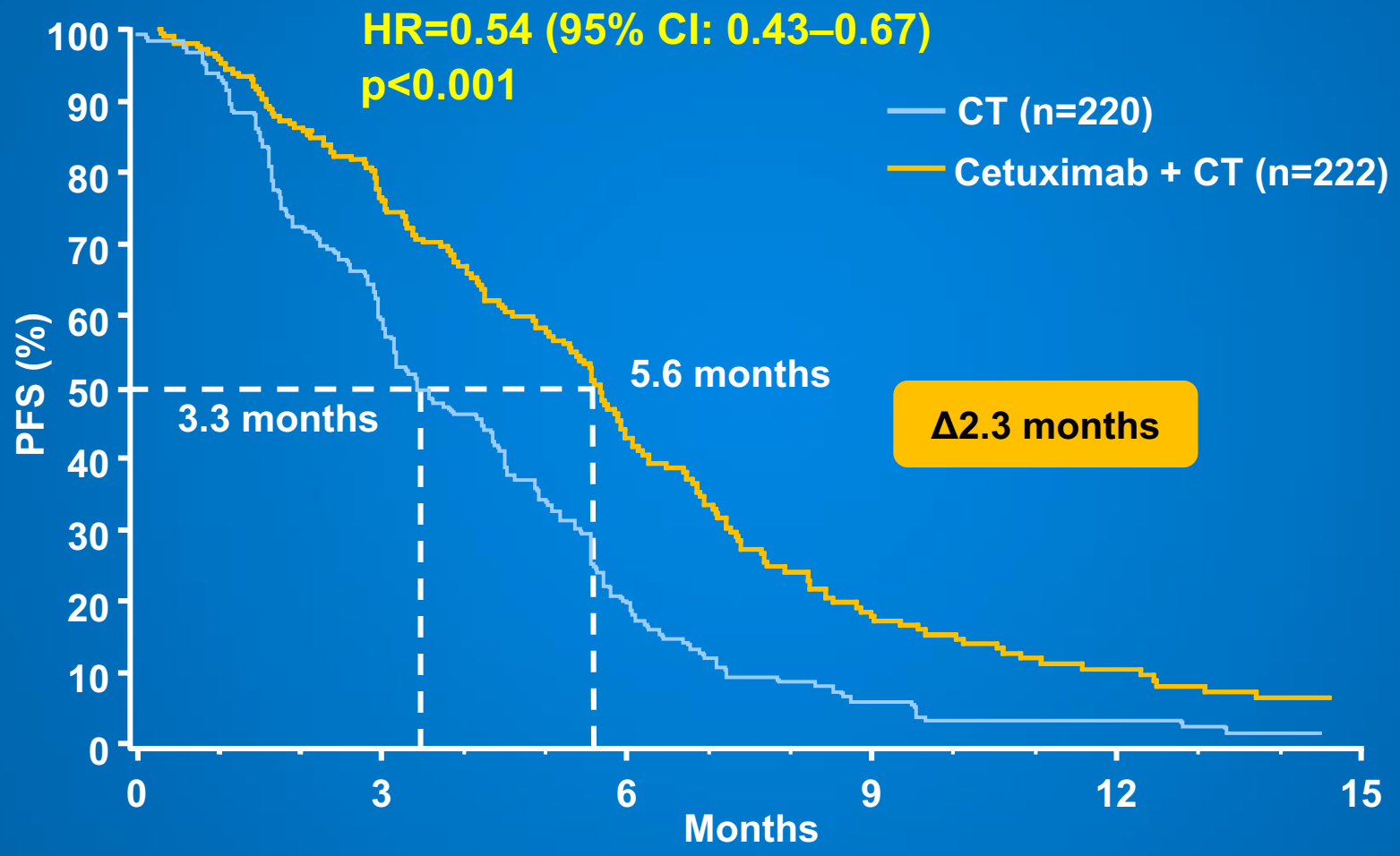


	Baseline	Cycle 3	6 months
CT alone:	n=94	n=63	n=20
Cetuximab + CT:	n=109	n=80	n=45

EORTC Quality of Life Questionnaire (QLQ)-C30; ≤55% of patients completed a baseline questionnaire
*Platinum-based CT, consisting of cisplatin/carboplatin + 5-FU
†At 6 months, after baseline adjustment
‡Bars show 95% CIs

Mesía R, et al. Ann Oncol 2010;21:1967–1973

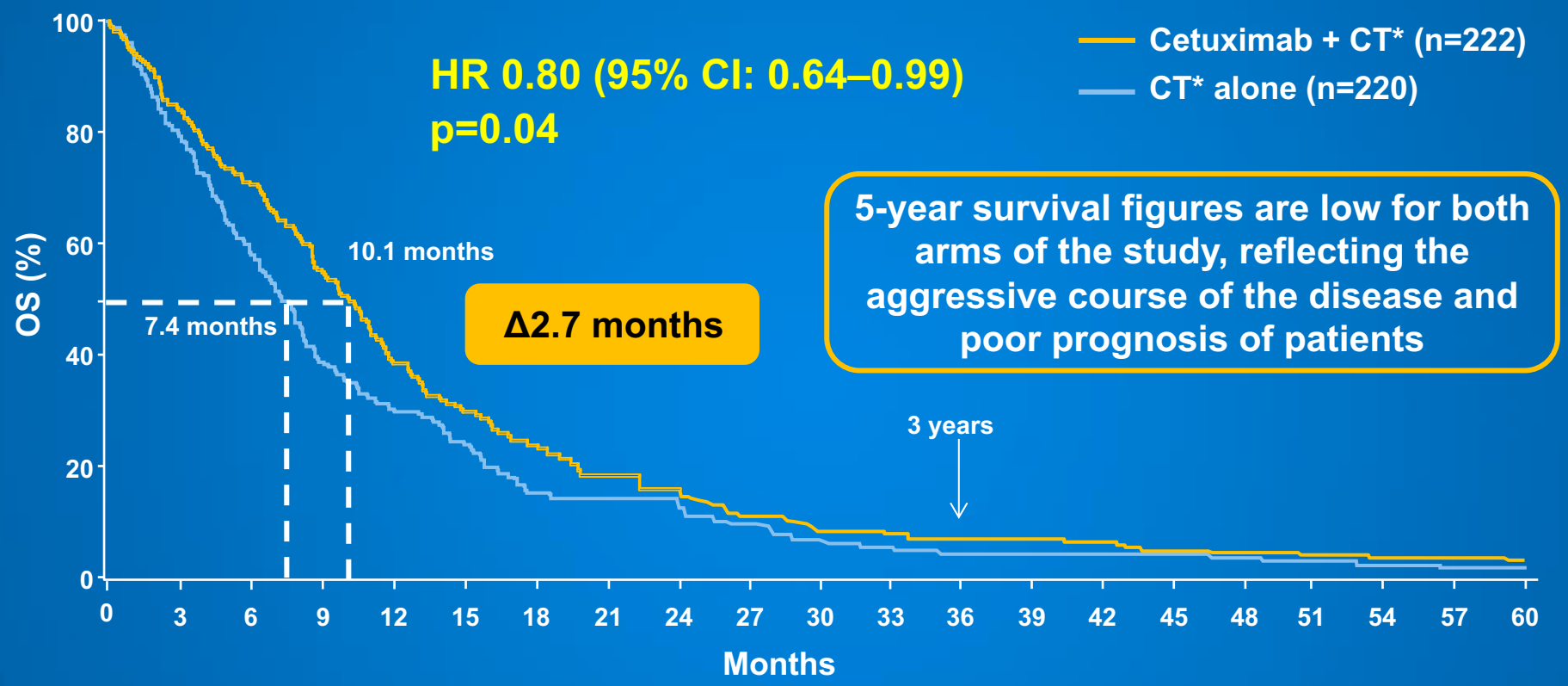
EXTREME: Cetuximab + QT* seguido de Cetuximab hasta PE prolonga la SLP vs QT exclusiva en 1L de tratamiento de tumores de CyC R/M



*Platinum-based QT, consisting of cisplatin/carboplatin + 5-FU
PD, progression of disease

Vermorken JB, et al. N Engl J Med 2008;359:1116–1127

EXTREME: Cetuximab + QT* seguido de Cetuximab hasta PE reduce el riesgo de muerte un 20% vs QT exclusiva

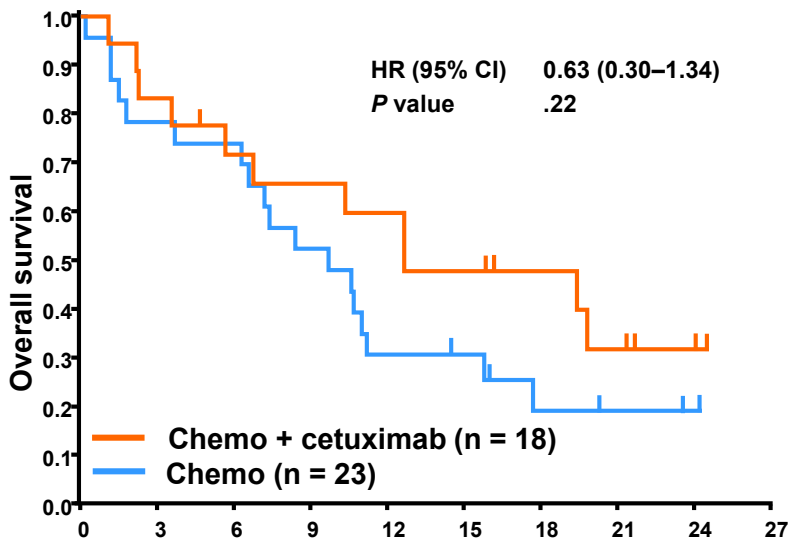


	CT* (n=220)	Cetuximab + CT* (n=222)
Long-term survivors (>2y)	25 (11%)	31 (14%)
Long-term responders (>12m)	3 (1%)	12 (5%)

*QT consisted of cisplatin/carboplatin + 5-FU

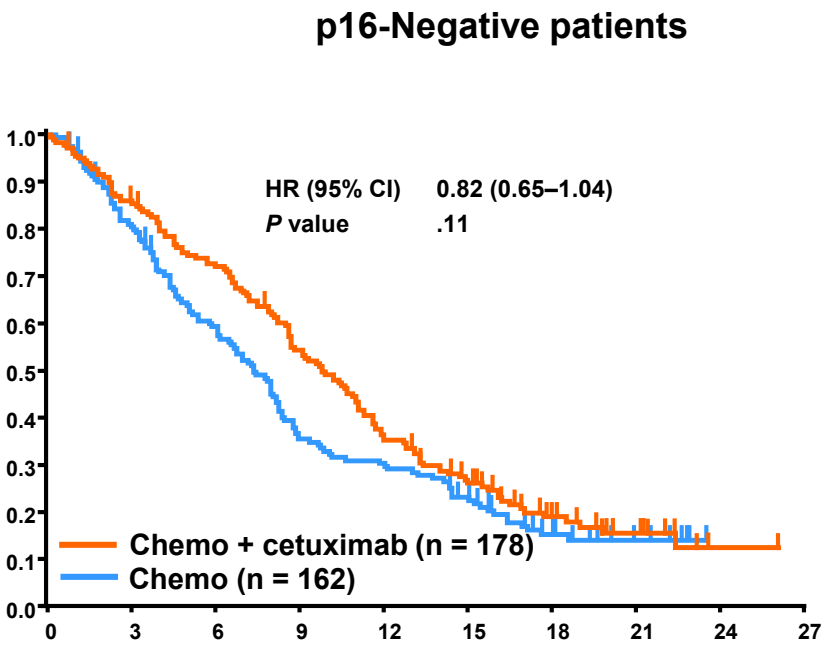
1. Vermorken JB, et al. N Engl J Med 2008;359:1116–1127
2. Vermorken JB, et al. Poster presented at ASCO 2014 (Abstract No. 6021)

Overall Survival in EXTREME by p16 Status



Number of patients at risk

18	15	12	11	10	8	6	4	1	0
23	18	17	12	7	6	3	2	1	0



Number of patients at risk

178	150	126	93	61	40	19	10	1	0
162	128	92	56	47	33	15	6	0	0

HRs are chemo + cetuximab vs chemo; CI, confidence interval; HR, hazard ratio

Vermorken JB, et al. *Ann Oncol.* 2014;25(4):801-807.

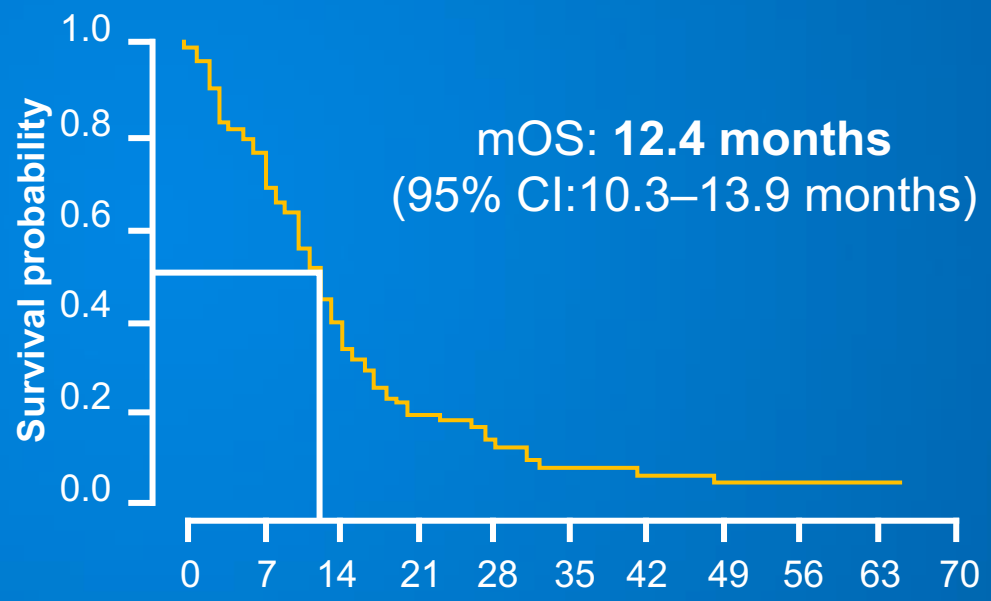
1st line overall survival in real-world clinical setting was consistent with outcomes from EXTREME

Single-center, retrospective analysis of 117 patients with R/M SCCHN[1]

- Patients were treated with cetuximab and platinum therapy in the 1st line

1st line systemic treatments received[1]	
Regimens	n (%)
Carboplatin + cetuximab	23 (44)
Cisplatin/cetuximab	15 (28)
Cisplatin/5-FU/cetuximab	7 (14)
Cisplatin/paclitaxel/cetuximab	6 (12)
Cetuximab monotherapy	1 (2)

1st line OS[1]



- These data provide real-world confirmation of the results of EXTREME, which found a median OS of 10.1 months with cetuximab + CT (vs 7.4 months with CT alone)[2]

1. Siano M, et al. ECC 2015 (Abstract 2865);
2. Vermorken JB, et al. N Engl J Med 2008;359:1116–1127

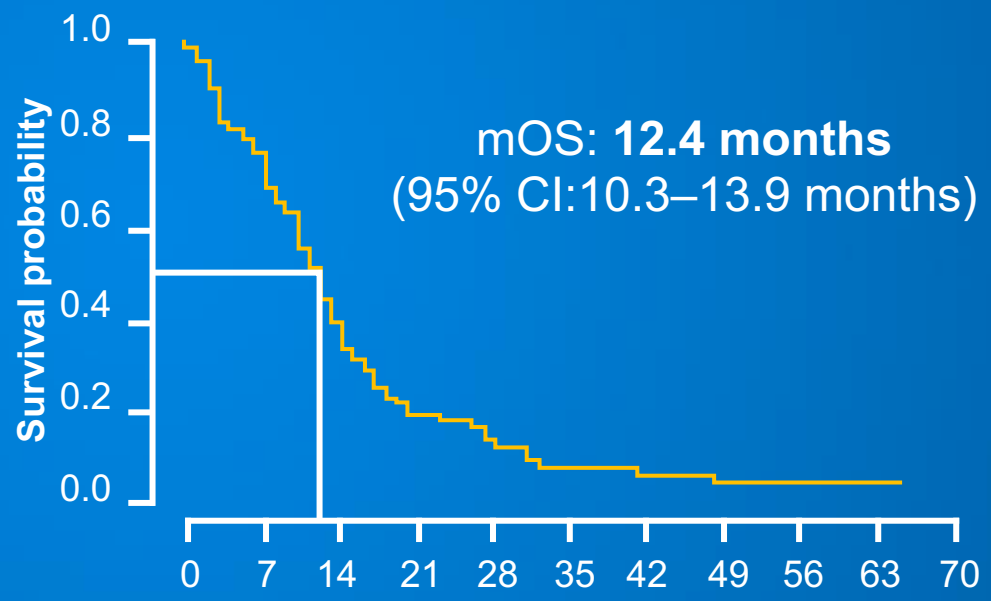
1st line overall survival in real-world clinical setting was consistent with outcomes from EXTREME

Single-center, retrospective analysis of 117 patients with R/M SCCHN[1]

- Patients were treated with cetuximab and platinum therapy in the 1st line

1st line systemic treatments received[1]	
Regimens	n (%)
Carboplatin + cetuximab	23 (44)
Cisplatin/cetuximab	15 (28)
Cisplatin/5-FU/cetuximab	7 (14)
Cisplatin/paclitaxel/cetuximab	6 (12)
Cetuximab monotherapy	1 (2)

1st line OS[1]



- These data provide real-world confirmation of the results of EXTREME, which found a median OS of 10.1 months with cetuximab + CT (vs 7.4 months with CT alone)[2]

1. Siano M, et al. ECC 2015 (Abstract 2865);
2. Vermorken JB, et al. N Engl J Med 2008;359:1116–1127

Datos de largos supervivientes

Resultados

La prevalencia de largos supervivientes es de un 2.7%. Todos los pacientes recibieron tratamiento con Cetuximab durante un periodo prolongado (mediana de tratamiento 22 m (6-29)). La mediana de supervivencia global es de 74,7 m (36-212)

Característica		
Edad al diagn mediana (ran		
Sexo (varón)		
Status de fum diagnóstico		
Estadio al dia		
Localización:		
Estadio en la tratamiento c		
Tratamiento a la recidiva/metástasis	ERBITAX	4
	EXTREME	3

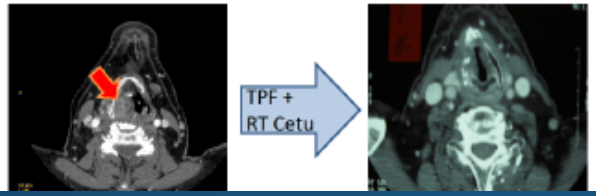
global (m)

Conclusiones

- Entre un 2-3 % de pacientes recurrentes/metastásicos pueden convertirse en largos supervivientes al añadirse Cetuximab al tratamiento con quimioterapia paliativa.
- Este fenómeno podría estar relacionado con el efecto de este anticuerpo sobre la respuesta inmune antitumoral.

Paciente nº 4

Diagnóstico Feb- 2008 RC Ago-2008



1. pT2N0M0 suelo de boca. IQ-RT adyuvante inicial. Recidiva con adenopatías mediastínicas. ERBITAX con respuesta completa (RC) y mantenimiento de cetuximab (primer paciente, ahora limitamos C mantenimiento a 24 m)
2. pT3N2cM0 supraglotis. IQ y QT-RT adyuvante. Recidiva local y M1 (adenopatías mediastínicas). EXTREME-Cilengitide en EC. RC. Se paro por progresión radiológica que posteriormente desapareció
3. T4N0M0 glotis. RT-C radical con RC al diagnóstico. Recidiva local tratada con ERBITAX con RC. Mantenimiento hasta 22m
4. cT4N0M0 amígdala. Inducción + QTRT al diagnóstico. 1ª recidiva IQ. 2ª recidiva EXTREME. 3ª recidiva ERBITAX con RC + RT-C consolidación, se suspendió cetuximab de mantenimiento por toxicidad.
5. cT3N2cM1 (pulmonar) de paladar blando. EXTREME*6 con Cilengitide en EC. RC
6. pT2N2bM0 de lengua. IQ + RT adyuvante al diagnóstico. Recidiva mediastínica. ERBITAX con RC y mantenimiento hasta 24m.
7. cT3N0M0 glotis. QT inducción + RT radical. 1ª recidiva tratada con IQ. 2ª recidiva. EXTREME (CDBCA)*6. RC. C mantenimiento hasta 24m.

OTRAS FORMAS DE CETUXIMAB: ERBITAX

Annals of Oncology 23: 1016–1022, 2012
doi:10.1093/annonc/mdr367
Published online 23 August 2011

Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck

R. Hitt[1]*, A. Irigoyen[2], H. Cortes-Funes[1], J. J. Grau[3], J. A. García-Sáenz[4] & J. J. Cruz-Hernandez[5] the Spanish Head and Neck Cancer Cooperative Group (TTCC)

Eur Arch Otorhinolaryngol
DOI 10.1007/s00405-013-2537-6

HEAD AND NECK

Outcome of patients treated with palliative weekly Paclitaxel plus Cetuximab in recurrent head and neck cancer after failure of platinum-based therapy

Aaron E. Sosa · Juan J. Grau · Luis Feliz ·
Verónica Pereira · Diego Alcaraz · Carmen Muñoz-García ·
Miguel Caballero

ERBITAX: Cetuximab + Paclitaxel en 1L de tratamiento de tumores de cabeza y cuello R/M

Estudio Fase II - aleatorizado

CECC Recurrente/mtx → **Cetuximab** (dosis inicial 400 mg/m^2, luego 250 mg/m^2 semanal) **+** **Paclitaxel** (80 mg/m^2) semanal → **Hasta progresión o toxicidad**

Objetivo primario: Tasa de respuesta objetiva

Objetivos secundarios: Duración de respuesta, SLP, SG, Seguridad.

Esquema fuera de indicación

Ricardo Hitt et al. Annals of Oncology 2011

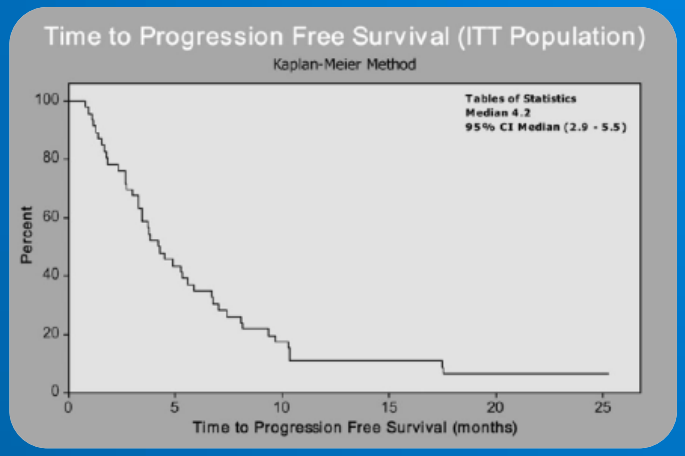
ERBITAX: Cetuximab + Paclitaxel demostró un aumento de la SG y la tasa de SLP

Mejor respuesta	n	%
RC	10	22
RP	15	33
EE	12	26
PE	5	11

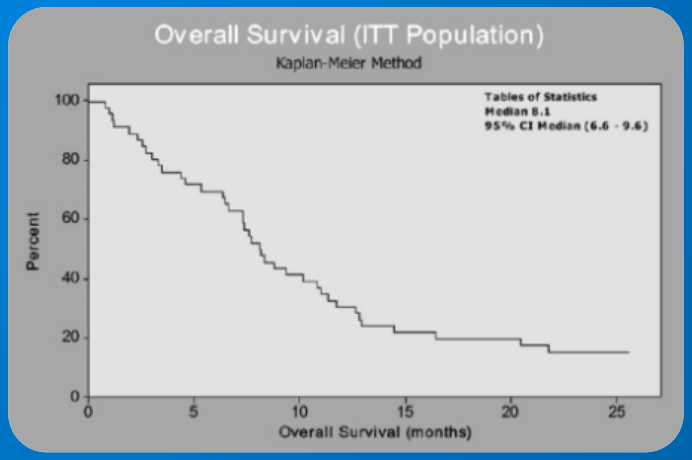
54% OR

80% DCR

Mediana SLP: 4.2 meses (95% IC 2.9–5.5)



Mediana SG: 8.1 meses (95% IC 6.6–9.6)



Ricardo Hitt et al. Annals of Oncology 2011

ERBITAX: datos en pacientes fuera de ensayo clínico

Estudio retrospectivo - 148 pacientes.

Objetivo: actividad de Paclitaxel + Erbitux (PCS) en pacientes con CECC R/M, analizando factores pronósticos de interés clínico.

64 pacientes (43,2%) recibieron además Erbitux de mantenimiento.

Resultados:

Tasa de respuesta (RR): 47,3% RC o RP - 20,3% EE - 32,4% PE.

SG 10 meses - SLP 7 meses.

Los factores pronósticos adversos significativos en el análisis univariante (AU) para SLP fueron:

- Progresión de la enfermedad, Albúmina basal de 1, IC Charlson >3, ECOG>1, intervalo libre de enfermedad (ILE) ≤20 meses y Albúmina basal <3gr/dl y Anemización durante el tratamiento.

En el análisis multivariante la presencia de progresión de la enfermedad y la disminución de Magnesio durante el tratamiento mayor de 10% resultaron significativos para SG.

Conclusiones:

Se confirma la actividad de PCS en pacientes RM-CECC no seleccionados, similar a los estudios previos, incluso con mejores resultados, y comparable al tratamiento basado en platino y Cetuximab.

Isabel Pajares Bernad et al. Comunicación oral SEOM 2015

Paclitaxel + Cetuximab for R/M SCCHN

Author (Year)	Phase	Line	N	RR (%)	PFS (Months)	OS (Months)
Sosa (2013)	Retrospective	Platinum refractory	33	55	4.0	10.0
Jiménez (2013)	Retrospective	Platinum refractory	22	55	5.4	9.1
Péron (2012)	Retrospective	Platinum refractory	42	38	3.9	7.6
Hitt (2012)	Phase II	First	46	54	4.2	8.1

PFS, progression-free survival; RR, relative response

Sosa AE, et al. *Eur Arch Otorhinolaryngol.* 2014;271(2):373-378. Jiménez B, et al. *Oral Oncol.* 2013;49(2):182-185. Péron J, et al. *Anticancer Drugs.* 2012;23(9):996-1001. Hitt R, et al. *Ann Oncol.* 2012;23(4):1016-1022.

Docetaxel + Cetuximab for R/M SCCHN

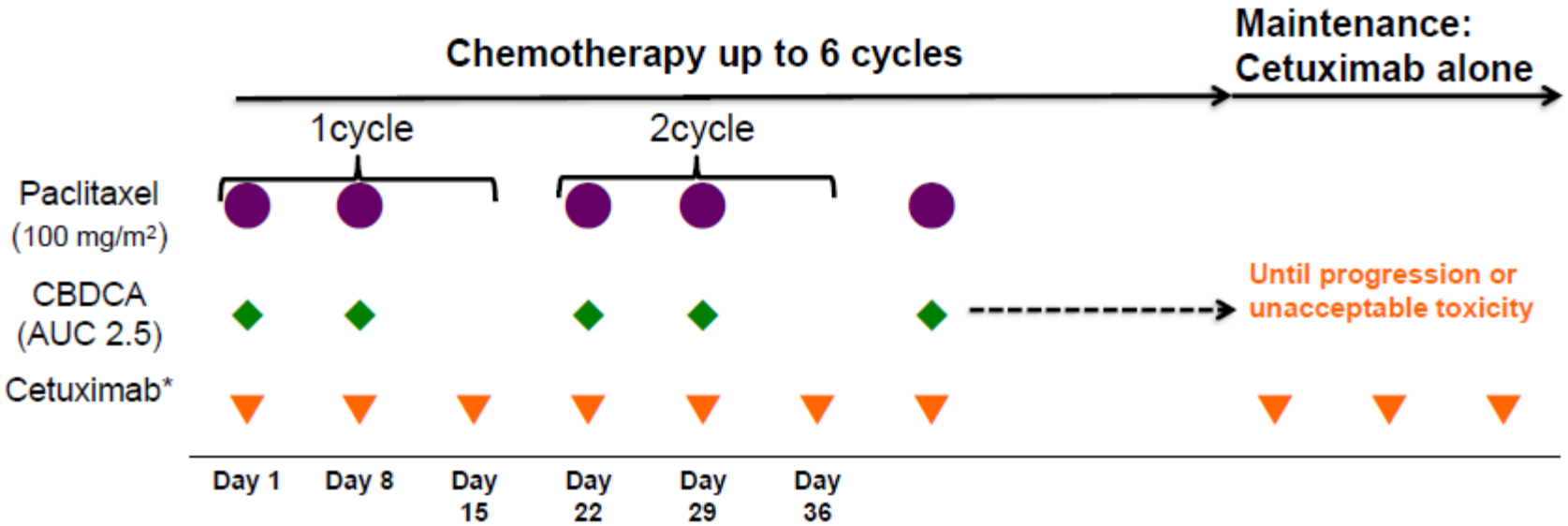
Author (Year)	Phase	N	RR (%)	SD (%)	PFS (Months)	OS (Months)
Knoedler (2013)	II*	84	11	40	3.1	6.7
Posch (2016)	Retrospective#	31	12.9	41.9	4.0	8.3

*docetaxel 35 mg/m² on day 1, 8, 15, every 4 weeks, 6 cycles
for patients not suitable for platinum: Docetaxel 50 mg/m², biweekly

Knoedler M, et al. *Oncology*. 2013;84(5):284-289. Posch D, et al. *Sci Rep*. 2016;6:32946.

CSPOR-HN02: Phase II Study of PCE

First-Line R/M SCCHN



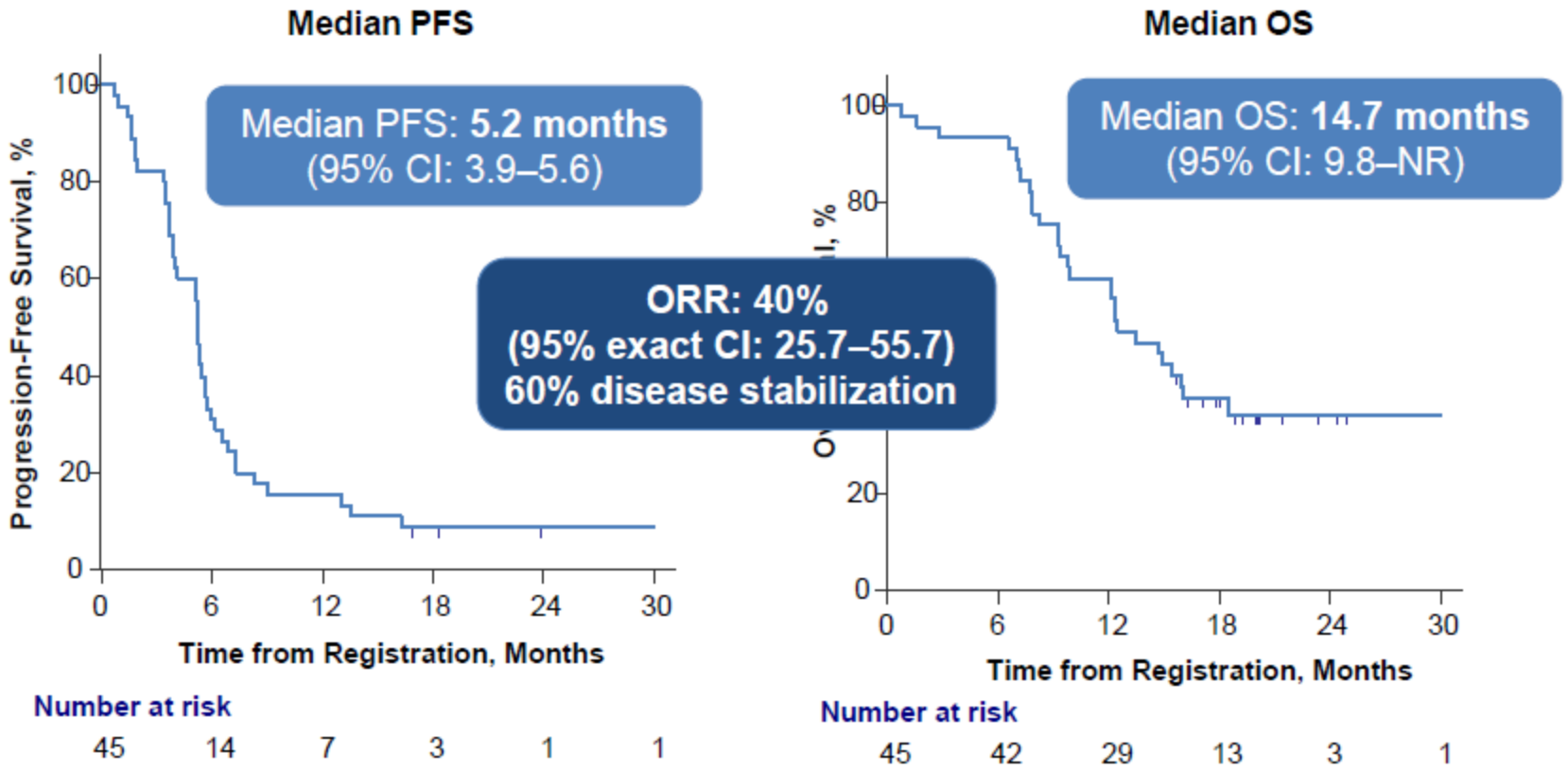
*initial dose of 400 mg/m², followed by 250 mg/m² weekly

Primary endpoint: Response rate according RECIST
Secondary endpoints: safety, PFS, OS, clinical benefit rate

Participating institutions: 23
Targeted accrual: N = 45

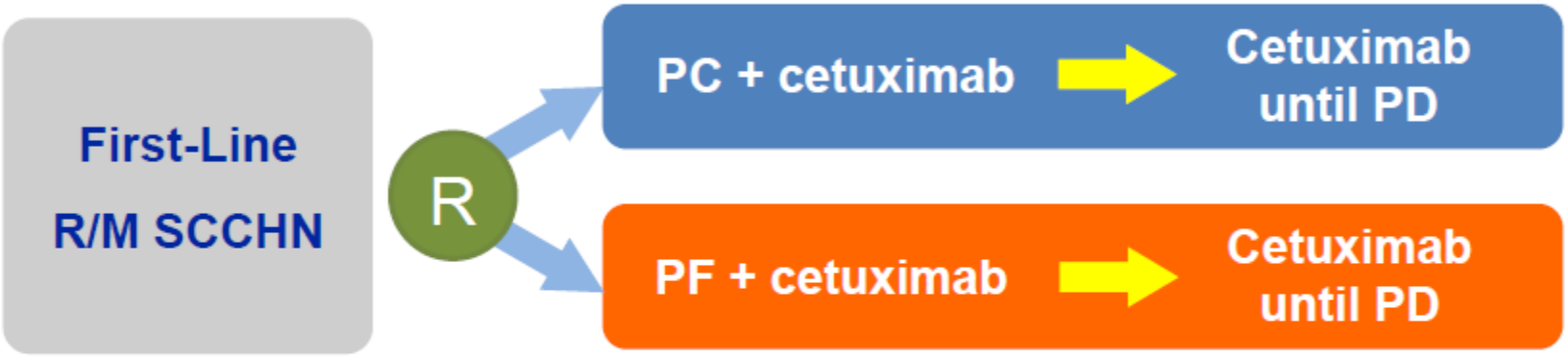
Tahara M, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 6026.

CSPOR-HN02: Efficacy (N = 47)



Tahara M, et al. *J Clin Oncol.* 2016;34(suppl):Abstract 6026.

Planned Phase III Trial of PCE vs PFE in R/M SCCHN (PEACE Trial)



PC
Paclitaxel (100 mg/m^2 IV, day 1, 8)
Carboplatin (AUC 2.5, day 1, 8)
every 3 weeks, up to 6 cycles

PF
Cisplatin (100 mg/m^2 IV, day 1)
5-FU (1000 mg/m^2 IV, days 1-4)
every 3 weeks, up to 6 cycles

Cetuximab
Initial dose 400 mg/m^2
then 250 mg/m^2 weekly
until progressive disease (PD)

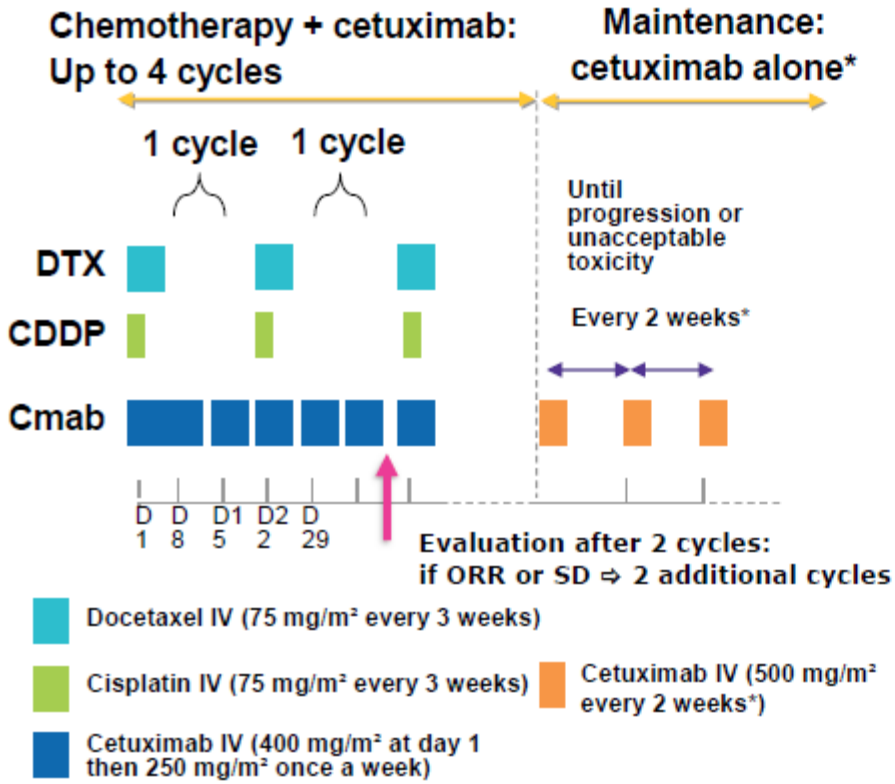
Primary endpoint: OS (non-inferiority)

PCE, paclitaxel + carboplatin + cetuximab; PFE, cisplatin + 5-FU + cetuximab

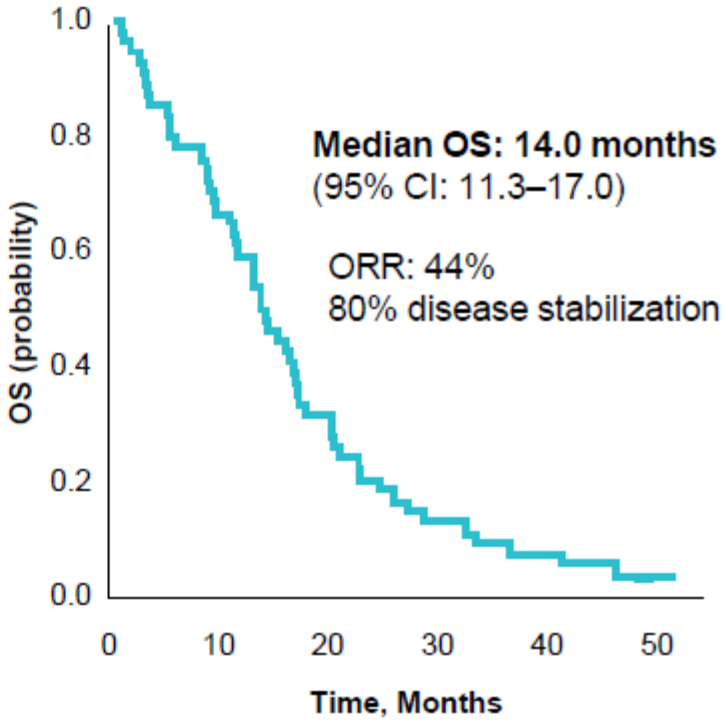
Tahara M. *Ann Oncol*. 2016;27(11): vii14. Tahara M. *Ann Oncol*. 2015;26(suppl 7): 14.

TPEx Demonstrated Promising Clinical Activity (GORTEC 2008-03)

Study Design



Efficacy



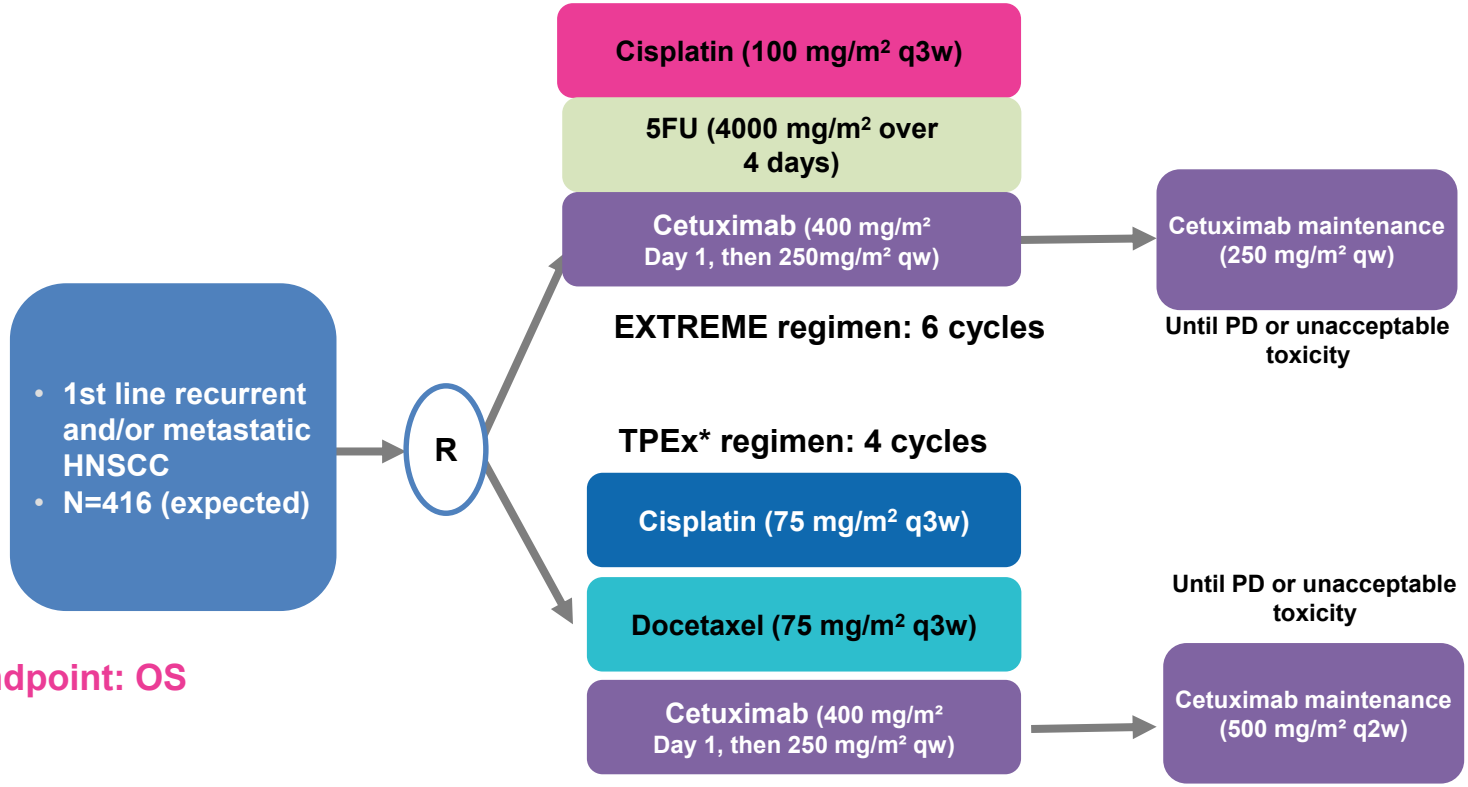
G-CSF (lenograstim) delivered after every cycle

*Off-label regimen for cetuximab
SD, stable disease

Guigay J, et al. *Ann Oncol.* 2015;26(9):1941-1947.

TPExtreme GORTEC Trial May Provide Further Insight Into the Optimal Chemotherapy Backbone to Combine With Cetuximab in First-Line R/M HNSCC

Phase III randomized study



Primary endpoint: OS

*Cetuximab in combination with taxanes is not approved in the EU[2].
†Cetuximab administered every 2 weeks at 500 mg/m² in the maintenance phase

National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT02268695. Accessed: July 10, 2017.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 00: 1–7, 2017
doi:10.1093/annonc/mdx439

ORIGINAL ARTICLE

A randomized, phase 2 study of cetuximab plus cisplatin with or without paclitaxel for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck

P. Bossi[1], R. Miceli[2], L. D. Locati[1], D. Ferrari[3], S. Vecchio[4], G. Moretti[5], N. Denaro[6], F. Caponigro[7], C. Moro[8], E. Vaccher[9], A. Sponghini[10], A. Caldara[11], G. Rinaldi[12], F. Ferrau[13], F. Nolè[14], S. Lo Vullo[2], F. Tettamanzi[15], L. Hollander[15] & L. Licitra[1*]

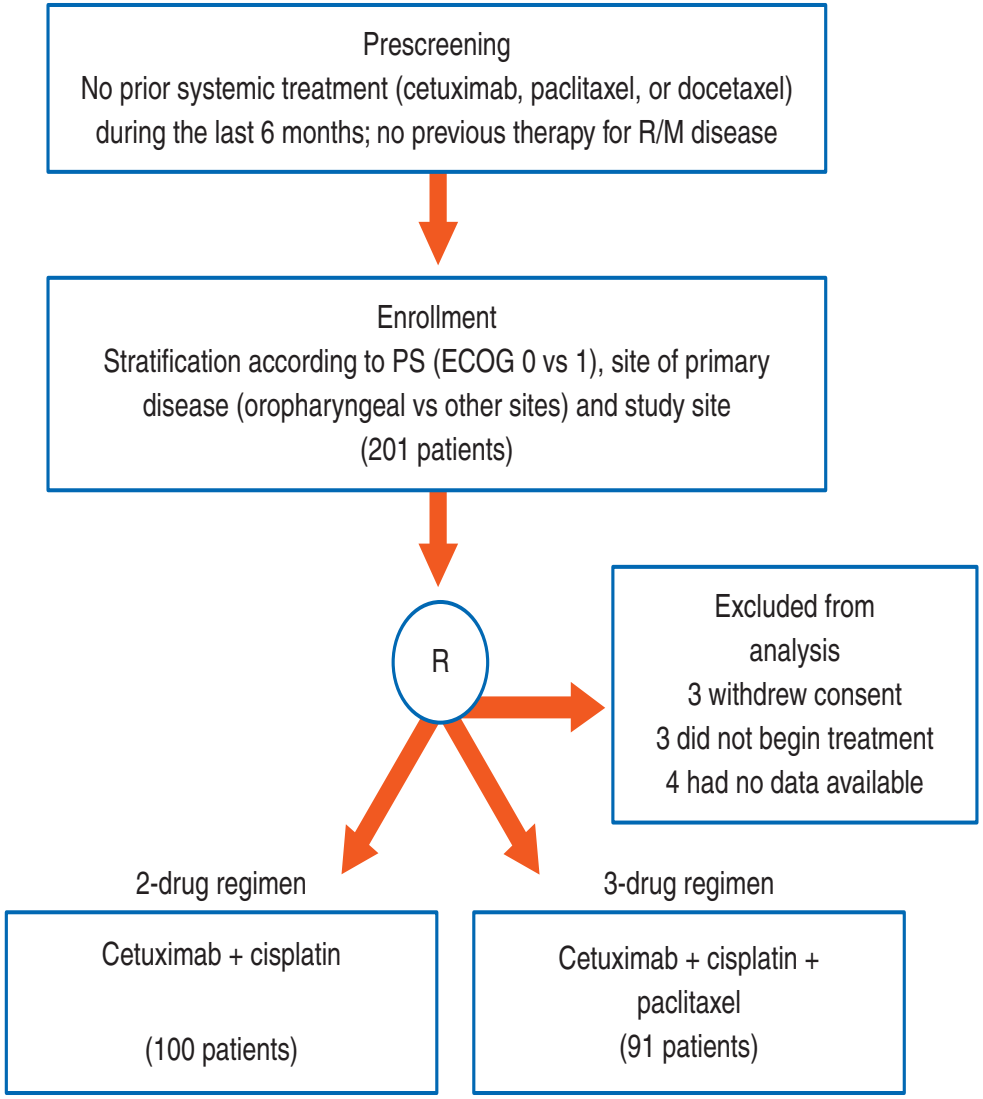
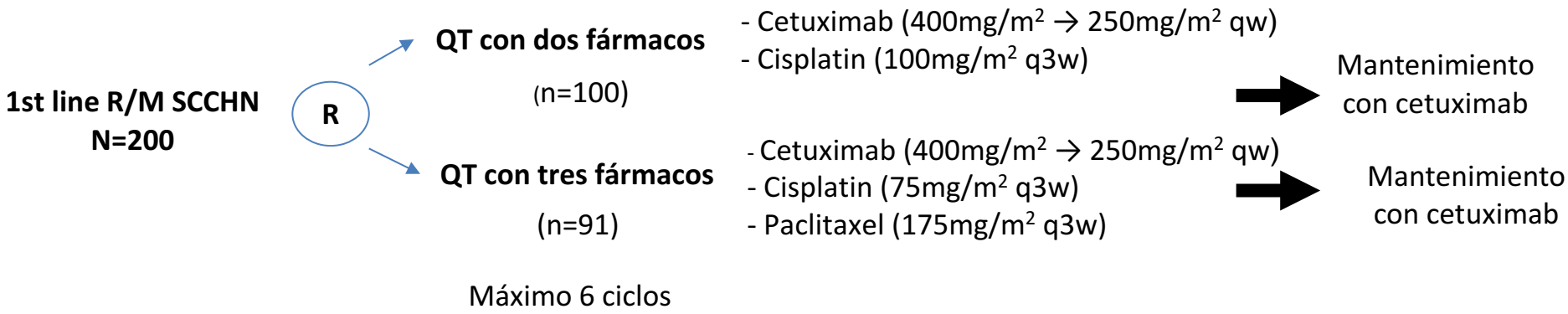


Figure 1. Patient disposition (CONSORT).

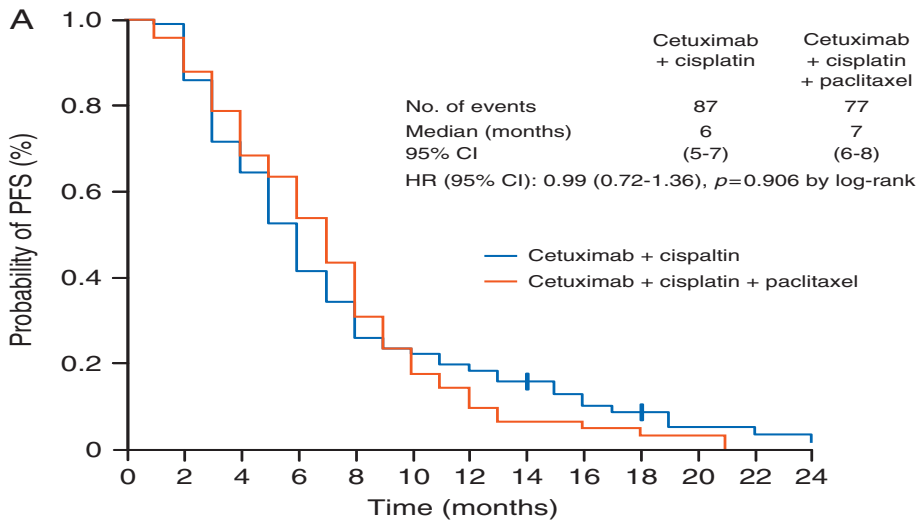
First line Cetuximab and Cisplatin with or without Paclitaxel in recurrent/metastatic head and neck cancer: a randomized phase IIb trial



Endpoints:†

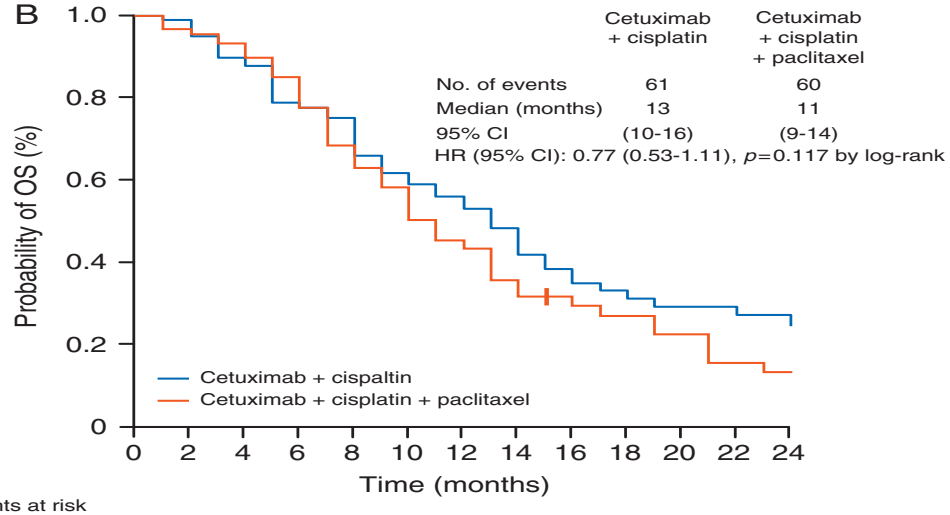
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, toxicity

Bossi, et al. ESMO 2017 (Abstract No. LBA47).



No. patients at risk

Cetuximab + cisplatin	100	97	70	47	29	19	15	12	9	6	3	3	2
Cetuximab + cisplatin + paclitaxel	91	85	68	52	31	16	9	4	4	3	2		



No. patients at risk

Cetuximab + cisplatin	100	97	86	66	58	44	37	30	23	18	14	14	12
Cetuximab + cisplatin + paclitaxel	91	86	80	70	49	37	24	18	14	12	10	7	4

The observational ENCORE study: cetuximab + platinum-based therapy (PBT) for first-line (1L) treatment of patients with R/M SCCHN

Estudio multicéntrico, observacional, prospectivo, abierto que pretende determinar cómo los oncólogos toman y ejecutan las decisiones terapéuticas relativas al tratamiento en 1L de pacientes con tumores R/M de cabeza y cuello en su práctica clínica habitual

Patients with 1st line R/M SCCHN)

N=225

Estudio en marcha: no hay datos de eficacia y/o seguridad

Le Tourneau C, et al. ESMO 2017 (Abstract No. 1068P).

The observational ENCORE study: cetuximab + platinum-based therapy (PBT) for first-line (1L) treatment of patients with R/M SCCHN

Baseline characteristics	cetuximab planned until PD (n=212)	cetuximab not planned until PD (n=13)
Median age, years (range)	64 (22–91)	60 (31–80)
Male, %	77.4	61.5
ECOG PS, %		
0	31.6	23.1
1	53.3	61.5
2	13.2	15.4
3	0.5	0
Missing	1.4	0

Role of MDT in decision-making	% patients planned for cetuximab until PD
Case discussed in MDT	77.8
Treatment decision by MDT	71.2
Treatment decision outside MDT	
Medical oncologist	23.6
Radiation specialist	4.7
Clinical radio-oncologist	0.5

CT agent to be included with cetuximab in planned regimen	% patients
Cisplatin	40.4
Carboplatin	59.1
5-FU	54.7
Taxane	3.1

Le Tourneau C, et al. ESMO 2017 (Abstract No. 1068P).

Phase III Randomized Trial of Platinum-based Chemotherapy With or Without Bevacizumab in Recurrent or Metastatic HNSCC (E1305)

Recurrent or metastatic HNSCC

ECOG Performance status 0-1

No prior therapy for recurrent or metastatic HNSCC

RANDOMIZE

Arm A
Platinum doublet*
Every 21 days until progression

Option to discontinue chemotherapy after 6 cycles if maximum response

Arm B
Platinum doublet*
+ Bevacizumab 15 mg/Kg IVIy
Every 21 days until progression

Option to discontinue chemotherapy after 6 cycles if maximum response. Bevacizumab continued until progression

Stratify by
a. Performance status
b. Weight loss
c. Prior radiotherapy
d. Chemotherapy regimen

** Choice of one of 4 chemotherapy regimens:*

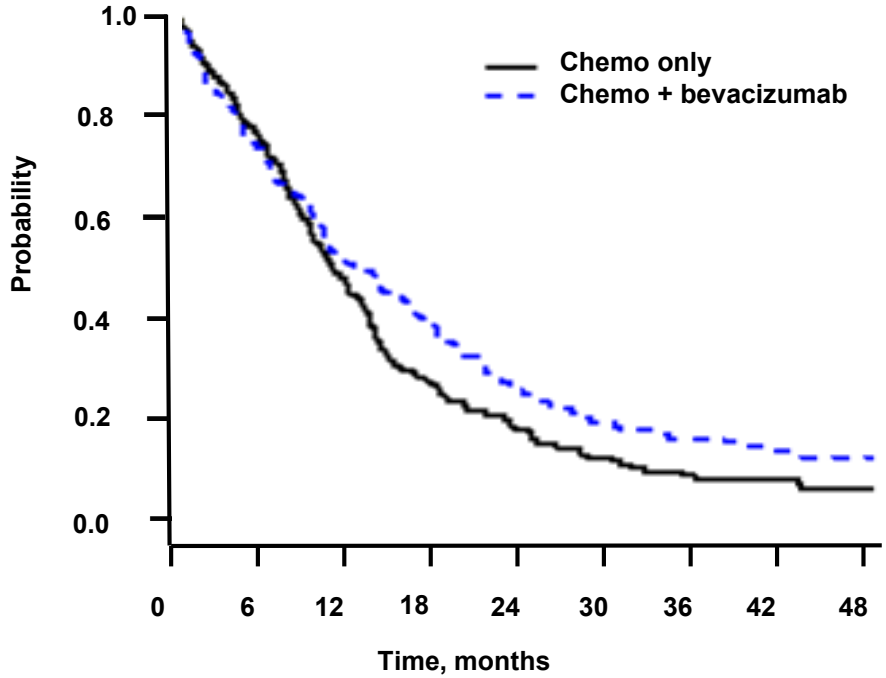
1. Cisplatin 100 mg/m^2 day 1 IV, 5-FU continuous infusion 1000 mg/m^2/day x 4 days.
2. Carboplatin AUC 6, day 1 IV, 5-FU continuous infusion 1000 mg/m^2/day x 4 days.
3. Cisplatin 75 mg/m^2 day 1 IV, docetaxel 75 mg/m^2, day 1, IV.
4. Carboplatin AUC 6, day 1 IV, docetaxel 75 mg/m^2, day 1, IV.

In regimens 1 and 3, carboplatin substitution was allowed for specific severe cisplatin-related toxicities.
All patients received prophylactic oral antibiotics (ciprofloxacin) on days 5-14.

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Argiris A, et al. *J Clin Oncol.* 2017;35(Suppl 4): Abstract 6000.

E1305: Overall Survival



No. at risk									
Chemo only	200	145	88	51	30	18	11	9	7
Chemo+Bev	203	144	98	73	41	26	18	13	11

	Median OS, months	*P* value	HR (95% CI)
Arm A: Chemo	11.0	.13	0.84 (0.67-1.05)
Arm B: Chemo + bevacizumab	12.6		

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Argiris A, et al. *J Clin Oncol.* 2017;35(Suppl 4): Abstract 6000.

E1305: Efficacy Results Summary

	Arm A: Chemo (N = 200)	Arm B: Chemo + Bev (N = 203)	*P* value
ORR, % (95% CI)	25 (19-32)	36 (30-44)	.013
Median PFS, months (95% CI)	4.4 (3.8-5.2)	6.1 (5.0-6.8)	.0012
HR for PFS (95% CI)	0.71 (0.58-0.87)		
Median OS, months (95% CI)	11.0 (9.5-13.0)	12.6 (10.3-16.5)	.13
HR for OS (95% CI)	0.84 (0.67-1.05)		
1-year OS, % (95% CI)	46 (39-53)	51 (44-58)	
2-year OS, % (95% CI)	18 (13-24)	26 (20-33)	
3-year OS, % (95% CI)	8 (5-13)	16 (11-22)	
4-year OS, % (95% CI)	6 (3-11)	13 (8-19)	

Argiris A, et al. *J Clin Oncol.* 2017;35(Suppl 4): Abstract 6000.

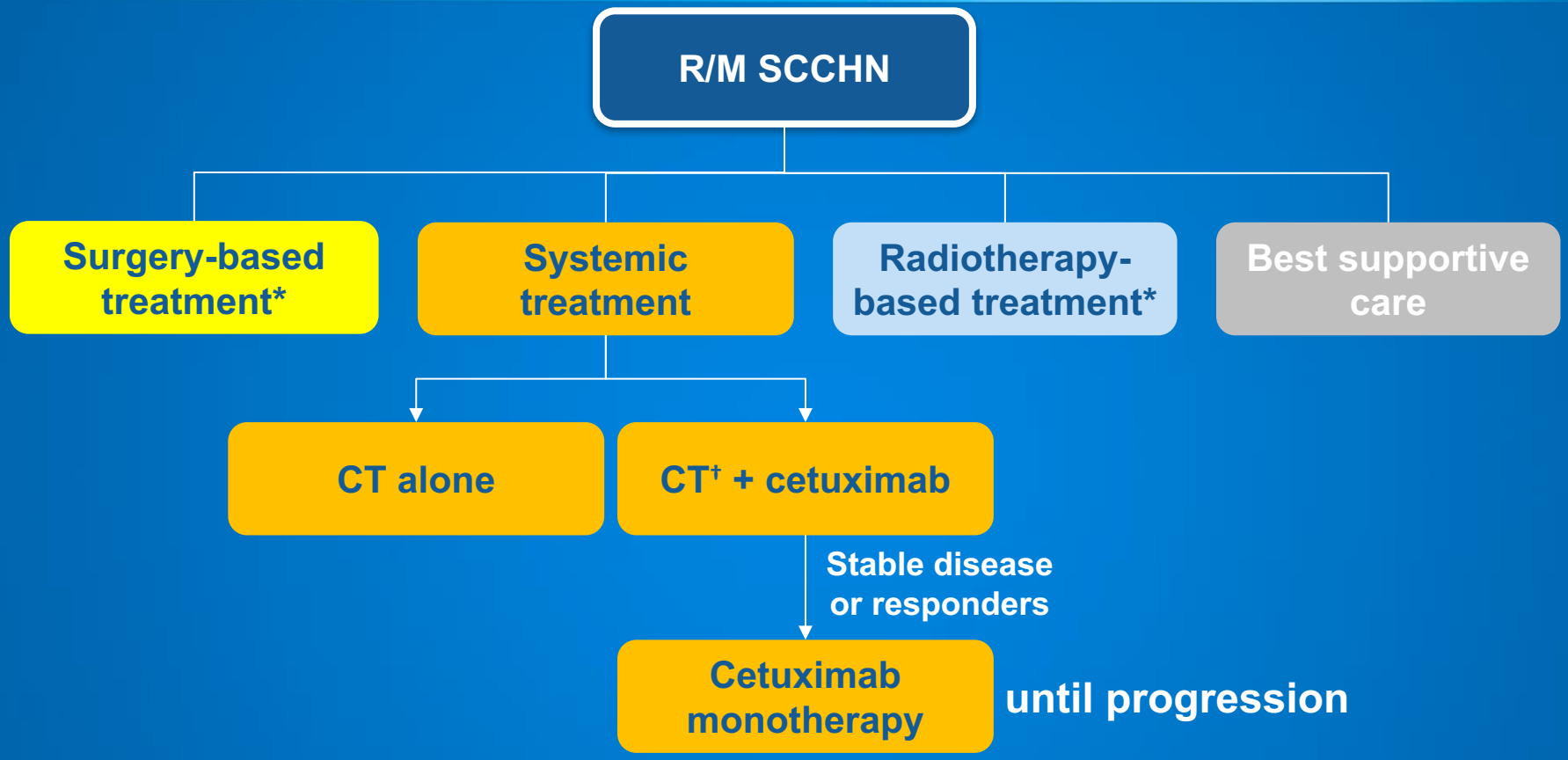
ECOG-ACRIN cancer research group
Reshaping the future of patient care

Cetuximab-Based Therapy Options for 1st-Line Treatment of Recurrent or Metastatic HNSCC

Regimen	Median PFS, mo	Median OS, mo	ORR, %
Cetuximab + cisplatin/carboplatin + 5FU (EXTREME)	5.6	10.1	36
Cetuximab + carboplatin + paclitaxel (PCE)	5.2	14.7	40
Cetuximab + cisplatin + docetaxel (TPE)	6.2	14	44.4
Cetuximab + cisplatin	4.2	9.2	26
Cetuximab + paclitaxel	4.2	8.1	54

AUC, area under the curve; IV, intravenous; PD, progressive disease

Treatment options in R/M SCCHN



- **The choice of 1st line therapy is key, as 2nd line options are limited**

*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 V1.2015

International Guidelines Recommend Cetuximab + Platinum-Based Chemotherapy Followed by Cetuximab Until Progression

- **The EXTREME regimen of cetuximab, used in combination with chemo, followed by cetuximab as maintenance therapy until disease progression in patients with r/m HNSCC, is recommended by international guidelines[1,2]**

The standard of care for recurrent, unresectable or metastatic non-nasopharyngeal cancer is considered to be the regimen from the EXTREME trial of cetuximab plus cisplatin/5FU or carboplatin/5-FU (category 1)[1]

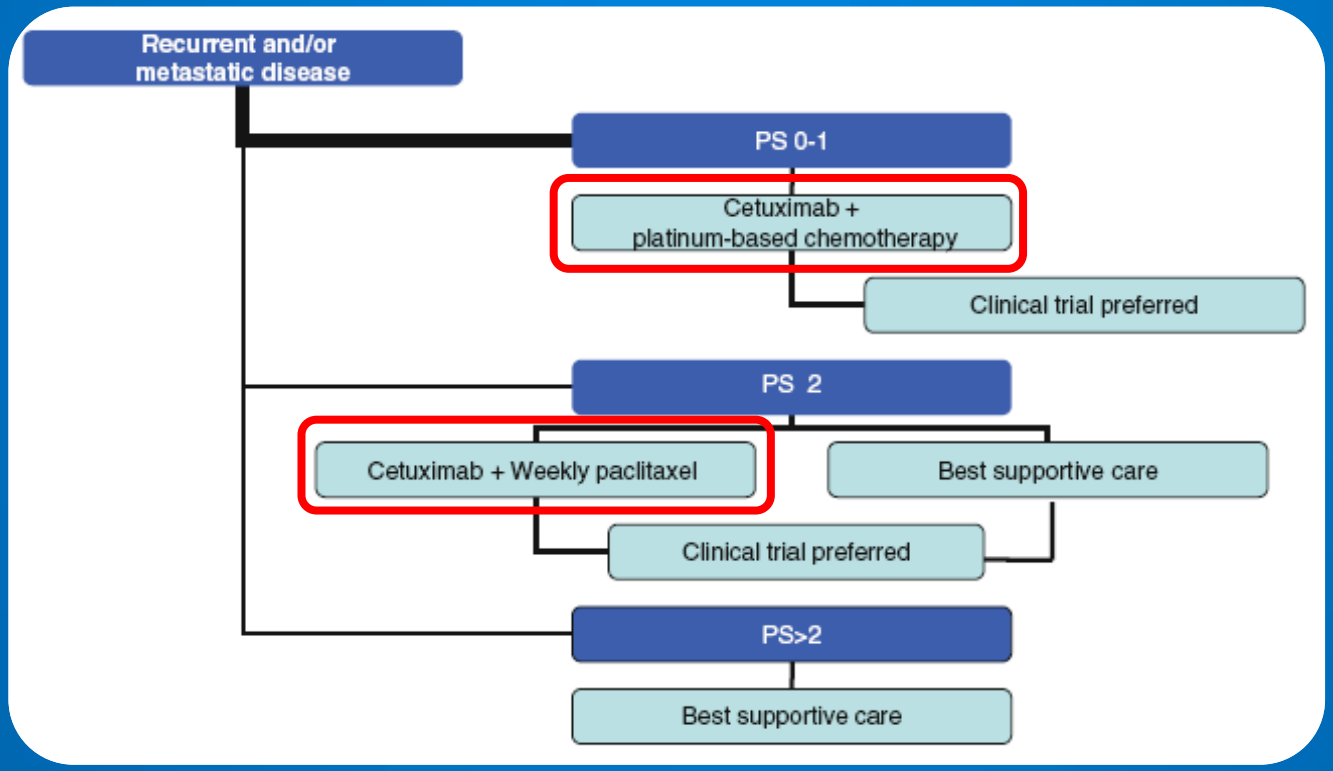
First-line option for fit patients should include the combination of cetuximab with cisplatin or carboplatin plus 5-FU (PF)… [II, A][2]

*Based on high-level evidence (randomized controlled trials)

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Head and Neck Cancer, V.2.2017. Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. 2. Grégoire V, et al. *Ann Oncol*. 2010;21:v184-v186.

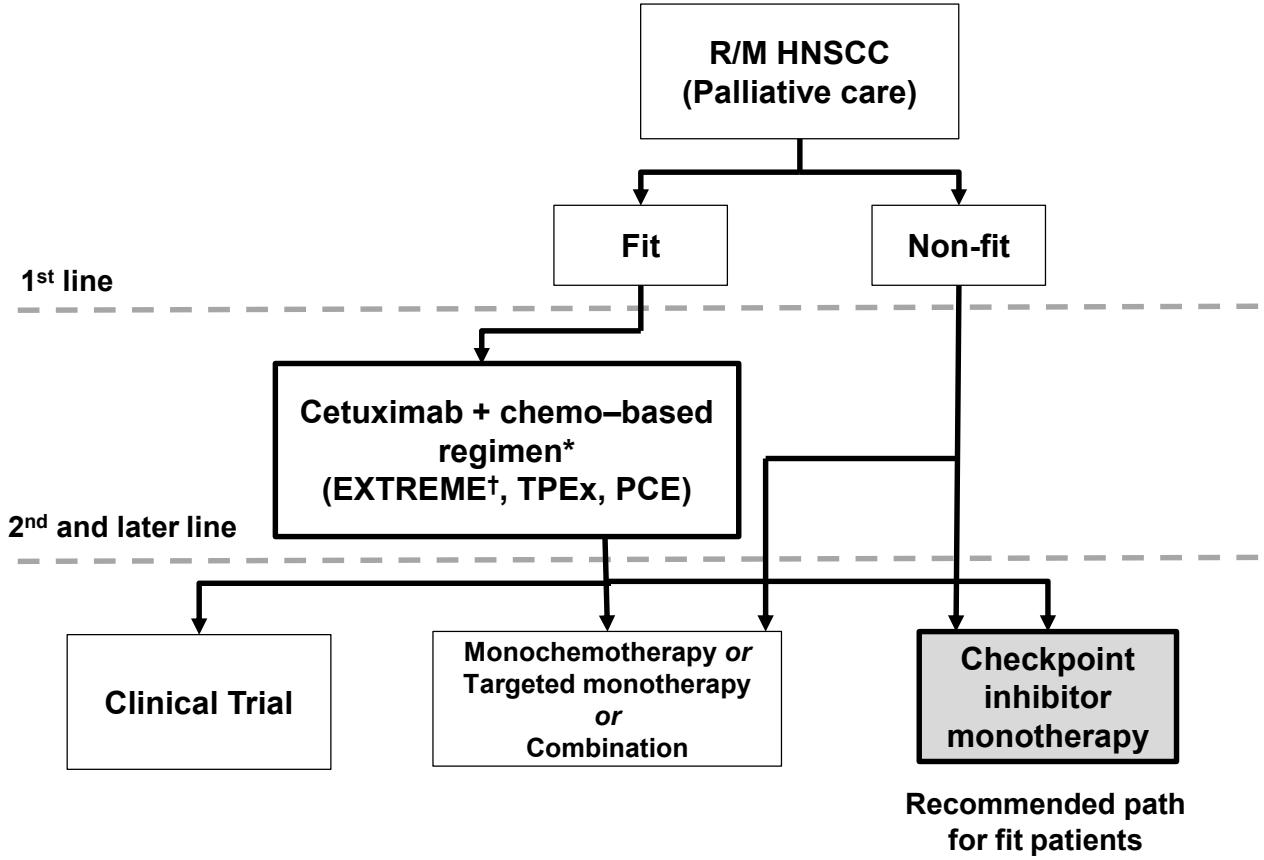
Guías SEOM

- Cetuximab + platinum + 5-FU recomendado como tratamiento estándar en pacientes con PS 0–1
- Cetuximab + paclitaxel semanal como 1ª opción de tratamiento en pacientes con PS 2



1. SEOM clinical guidelines for treatment of head and neck cancer (HNC) 2013. R. Mesia, M. Pastor, J.J. Grau, E. Del Barco

Continuum of Care in R/M HNSCC



*EXTREME regimen (platinum, 5-FU, cetuximab) is supported by phase III data

Argiris A, et al. *Front Oncol.* 2017;7:72.

Treatment Options for Patients With Disease That is Resistant to Platinum and Cetuximab

- Several cytotoxic drugs have demonstrated clinical activity for R/M SCCHN
- No evidence that second-line cytotoxic drugs prolong survival

	Phase	N	ORR (%)	Median OS (Months)
MTX	III[1]	152	4	7
Paclitaxel	II[2]	74	29	14.3
	II[3]	60	43.3	8.5
Docetaxel	II[4]	24	20.8	6.7
Gemcitabine	II[5]	54	13	-
S-1	II[6]	59	28.8	-

1. Stewart JS, et al. *J Clin Oncol.* 2009;27(11):1864-1871. 2. Tahara M, et al. *Cancer Chemo Pharmacol.* 2011;68(3):769-776. 3. Grau JJ, et al. *Acta Otolaryngol.* 2009;129(11):1294-1299. 4. Couteau C, et al. *Br J Cancer.* 1999;81(3):457-462. 5. Catimel G, et al. *Ann Oncol.* 1994;5(6):543-547. 6. Inuyama Y, et al. *Gan To Kagaku Ryoho.* 2001;28(10);1381-1390.

¿Propuesta de ensayo TTCC?

- Cetuximab 250 mg/m2 días 1-8 + Paclitaxel 80 mg/m2 días 1-8.
- Nivolumab 3 mg/Kg día 1 + Paclitaxel 80 mg/m2 días 1-8.

Right Treatment for Right Patient: Are Biomarkers the Answer?

Number of candidate biomarkers in SCCHN[1-3]

P16/HPV | P53 | EGFR

ERCC1 | RRM1 | ß-tubulin | TYMS | BRCA1

- **EXTREME trial:** EGFR copy number and EGFR expression level[4-5]

  predictive biomarkers ?
  - Only 11% of tumors: High-level amplification.
  - No association between copy number and OS, PFS, or best overall response
- EGFRvIII mutation: Not present at a meaningful frequency in HNSCC to consider it a useful biomarker[6]
- EGFR polymorphisms 58, 59: May predict outcome in HNSCC[7,8]

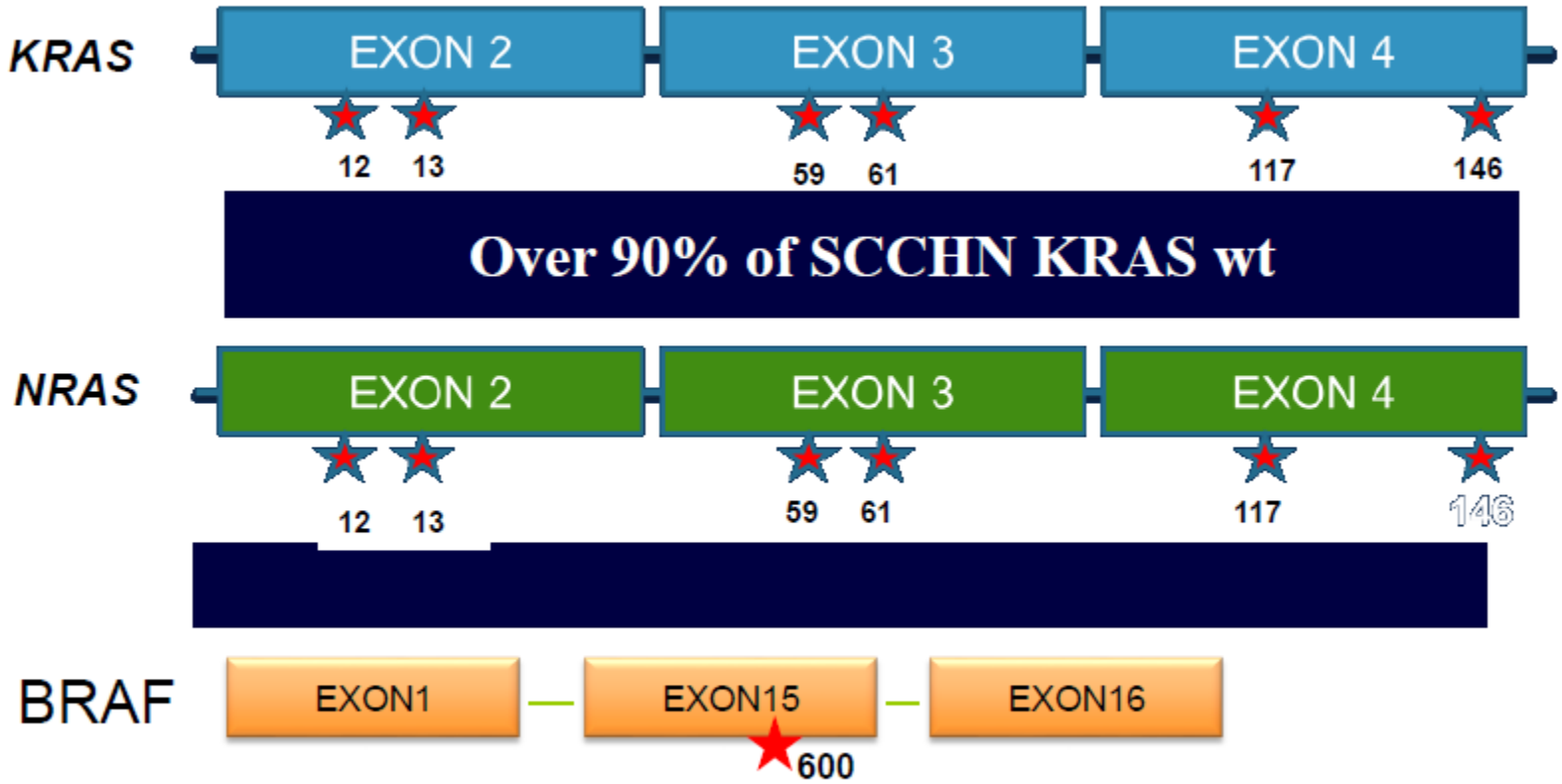
No predictive biomarker was found until now[1]

1. Langer CJ. Cancer. 2012;118(16):3882–3892. 2. Poeta ML, et al. N Eng J Med. 2007;357(25):2552–2561. 3. Smith EM, et al. Cancer Epidemiol Biomarkers Prev. 2008;17(2):421–427. 4. Licitra L, et al. Ann Oncol. 2011;22(5):1078-1087. 5. Licitra L, et al. Eur J Cancer. 2013;49(6):1161-1168. 6. Khattri A, et al. Oral Oncol. 2015;51(1):53-58. 7. Stoehlmacher-Williams J, et al. Anticancer Res. 2012;32(2):421-425. 8. Su NW, et al. Onco Targets Ther. 2014;7:2197-2204.

Most KRAS wt tumors are responsive to EGFR mAbs

Most KRAS mt tumors are resistant to EGFR mAbs

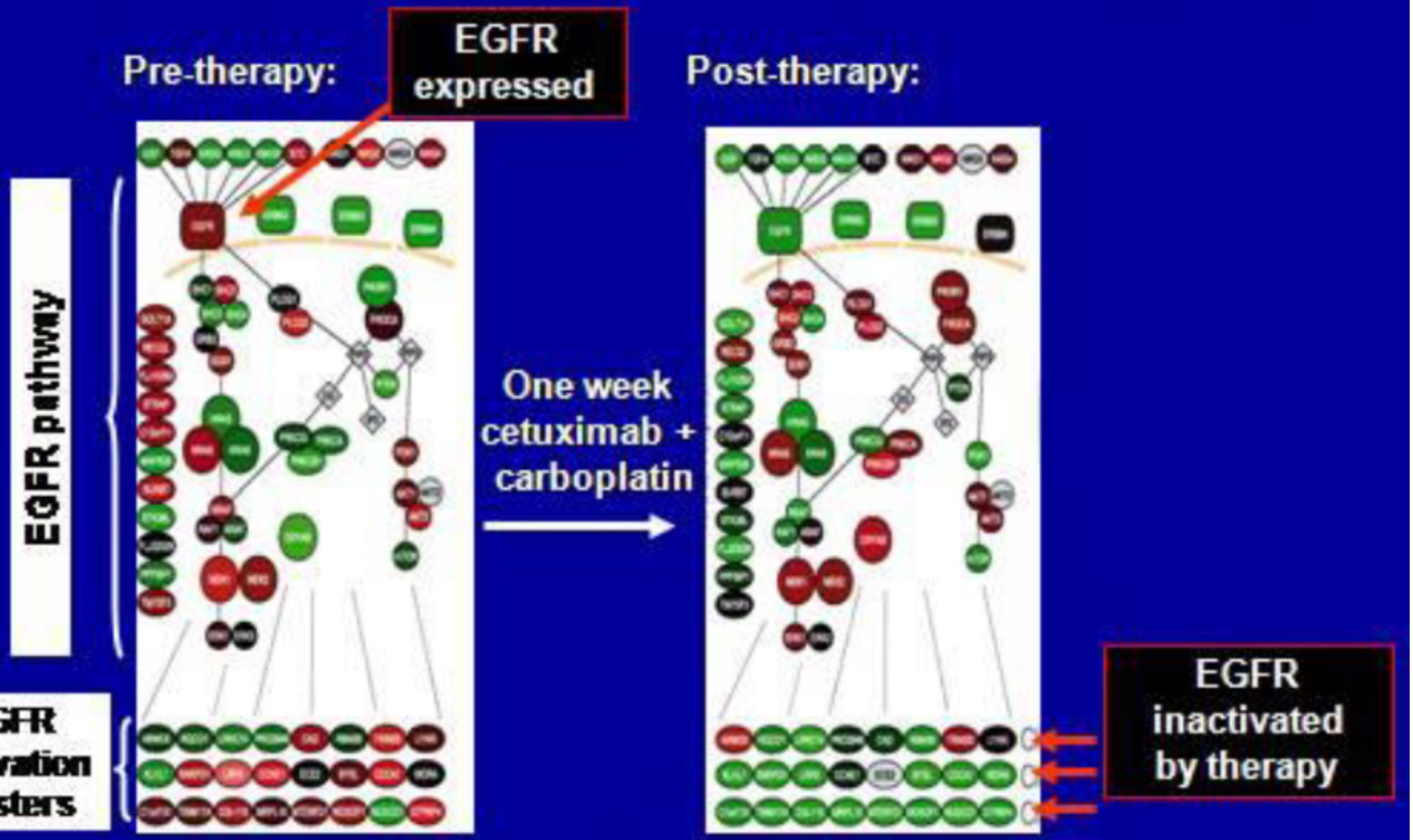
Mutations of RAS and BRAF



Detecting other alterations in the EGFR pathway that contribute to resistance may help select patients most likely to respond to treatment

Impact on EGFR Signaling

Clinical responder: Frozen biopsies of metastatic lesion, Agilent array

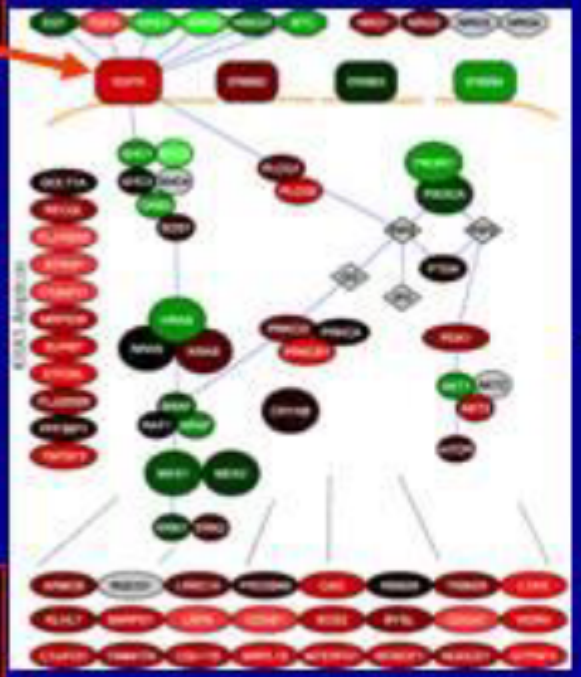


Courtesy of: Charles M. Perou, PhD.

Heterogeneous Impact on EGFR Signaling

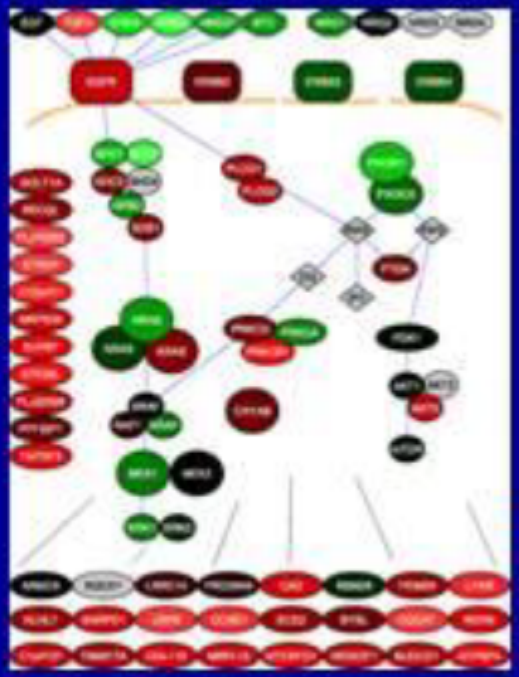
EGFR expressed

Pre-therapy



Rx

Post 1 wk cetux+carbo



Clinical non-responder

EGFR activated

BUT no change with Rx

- **16 tumors with serial biopsies from target lesion**

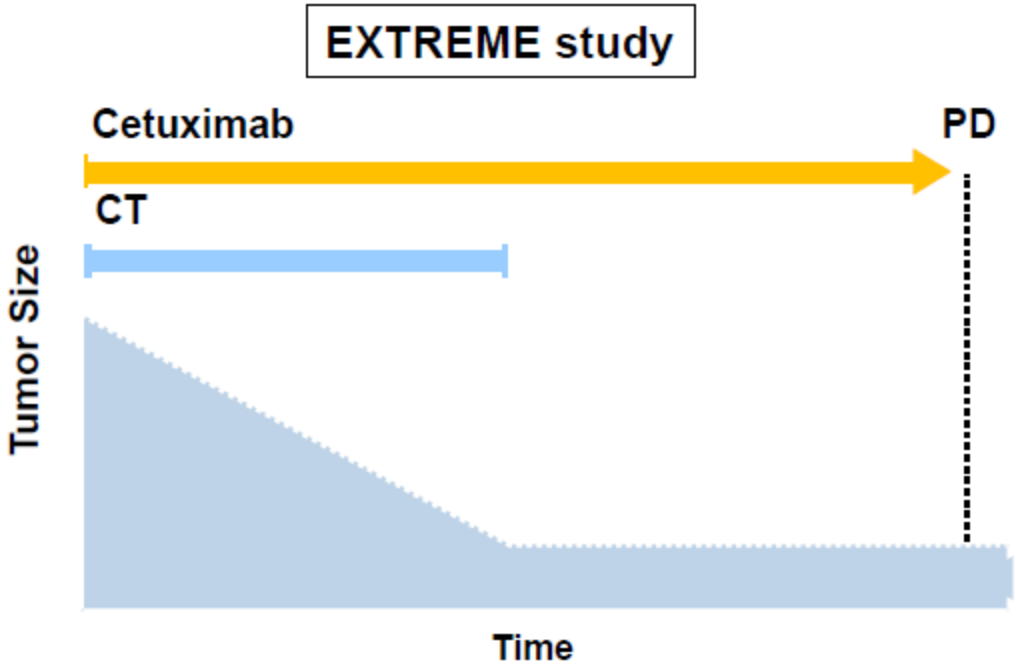
Targeted therapies require great understanding of all the players in a pathway.

Access to tumor tissue is critical!

- **8 no significant change (all PD)**

Role of Maintenance of Cetuximab

- Continuation of platinum-based CT is limited
- Response duration of platinum-based CT is limited
- Cetuximab administration should continue until PD

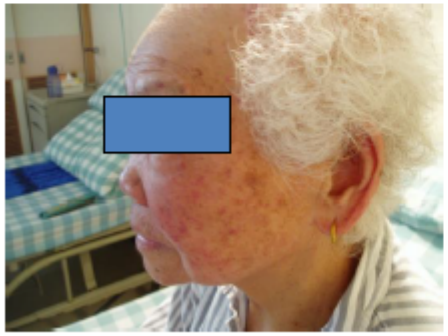


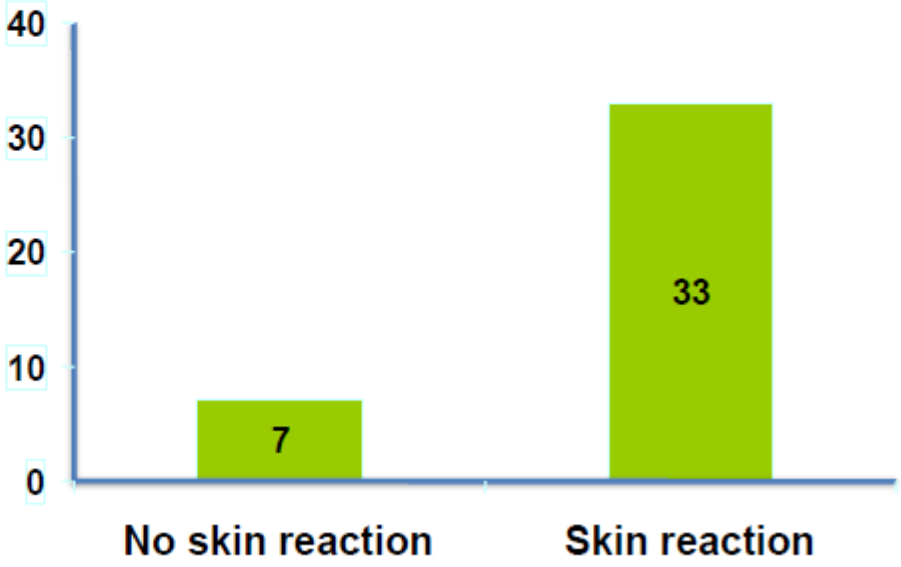
CT, chemotherapy

Vermorken JB, et al. *New Engl J Med.* 2008;359(11):1116-1127.

Skin Reaction and Efficacy in EGFR mAbs

Response rate for ERBITUX+ cisplatin patients % (n=57)





Limitations of Platinum + 5-FU (PF)

- **Patients' quality of life is impaired by the following issues:**

Continuous infusion of 5-FU for 4 days

Need for hospitalization

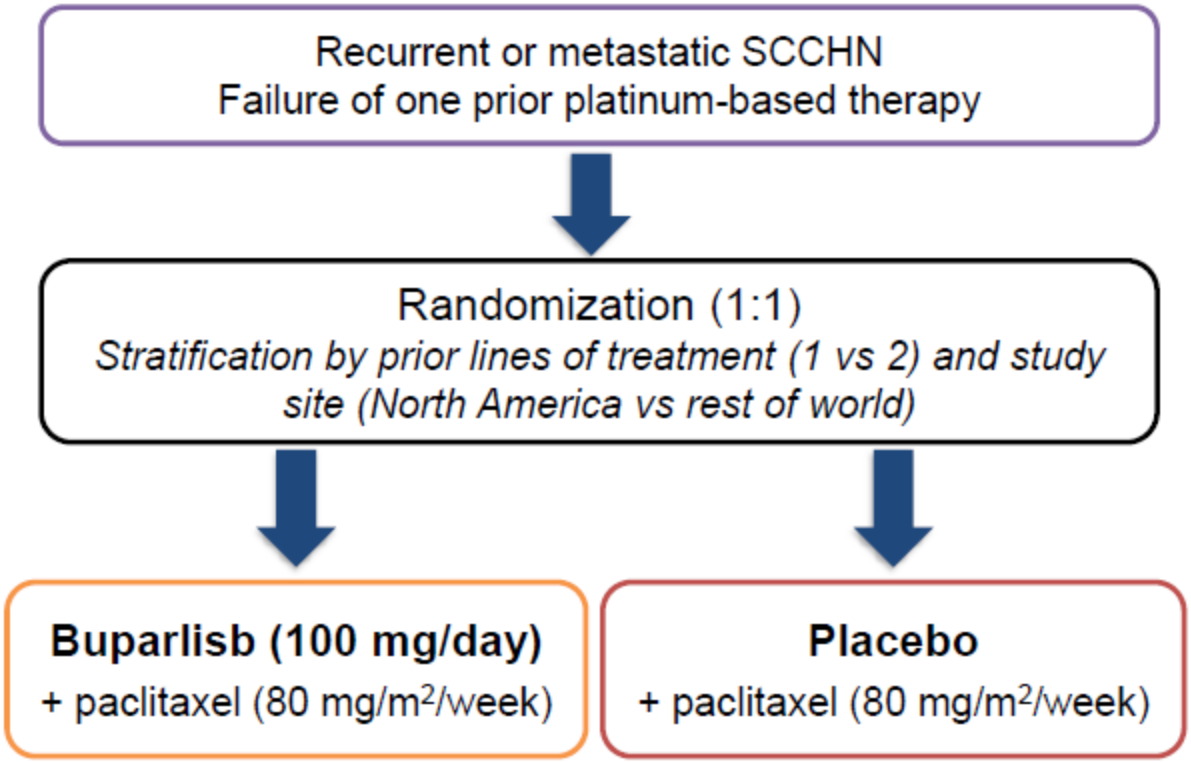
Concerning toxicities

Mucositis

Anorexia and fatigue

Renal dysfunction

BERIL-1: A Phase II, Randomized, Placebo-Controlled Study of Buparlisb and Paclitaxel in Platinum-Pretreated Advanced SCCHN



N = 150

Primary endpoint: PFS (local assessment RECIST v1.1)
Key secondary endpoint: OS

RECIST, Response Evaluation Criteria in Solid Tumors

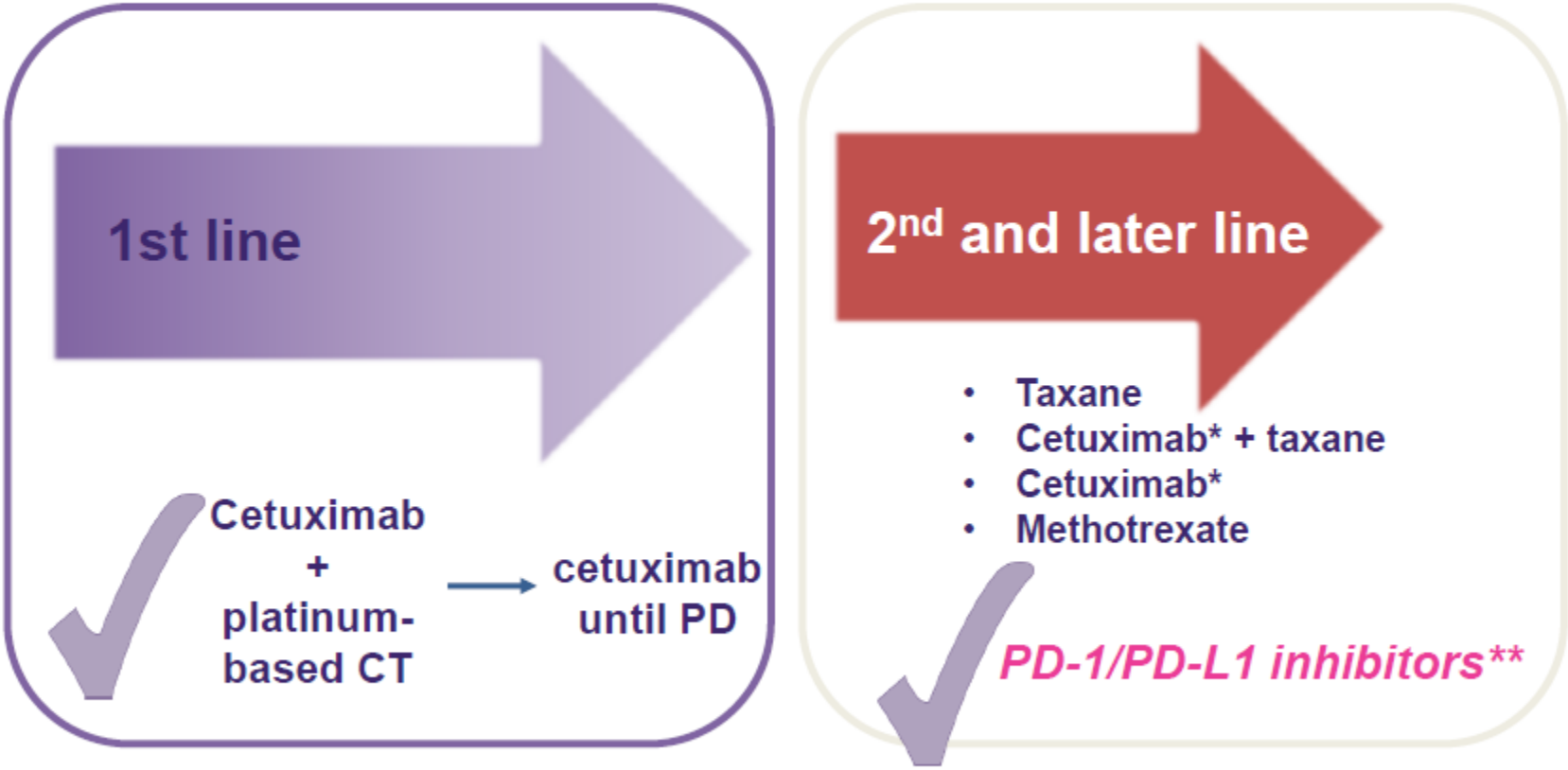
Soulières D, et al. *J Clin Oncol.* 2016;27(Suppl 6): Abstract 6008.

BERIL-1: A Phase II, Randomized, Placebo-Controlled Study of Buparlisb and Paclitaxel in Platinum-Pretreated Advanced SCCHN

		Buparlisb + Paclitaxel (n = 79)	Placebo + Paclitaxel (n = 79)	Hazard Ratio (95% CI)	One-Sided *P*-Value
ORR, %	Overall	39.2	13.9	-	<.001
	HPV- (n = 115)	39.6	11.3	-	
	HPV+ (n = 28)	35.3	27.3	-	
Median PFS, months		4.6	3.5	0.65 (0.45-0.95)	.011
Median OS, months		10.4	6.5	0.72 (0.56-0.92)	.041

Soulières D, et al. *J Clin Oncol.* 2016;27(Suppl 6): Abstract 6008.

New Evidence-Based Options in the Management of Recurrent or Metastatic SCCHN



*Cetuximab monotherapy or in combination with taxane is not approved for the treatment of SCCHN in the EU
** Pembrolizumab and nivolumab currently approved by the FDA for the treatment of SCCHN

CT, chemotherapy


MUCHAS
GRACIAS