19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

LARGOS SUPERVIVIENTES EN CECC

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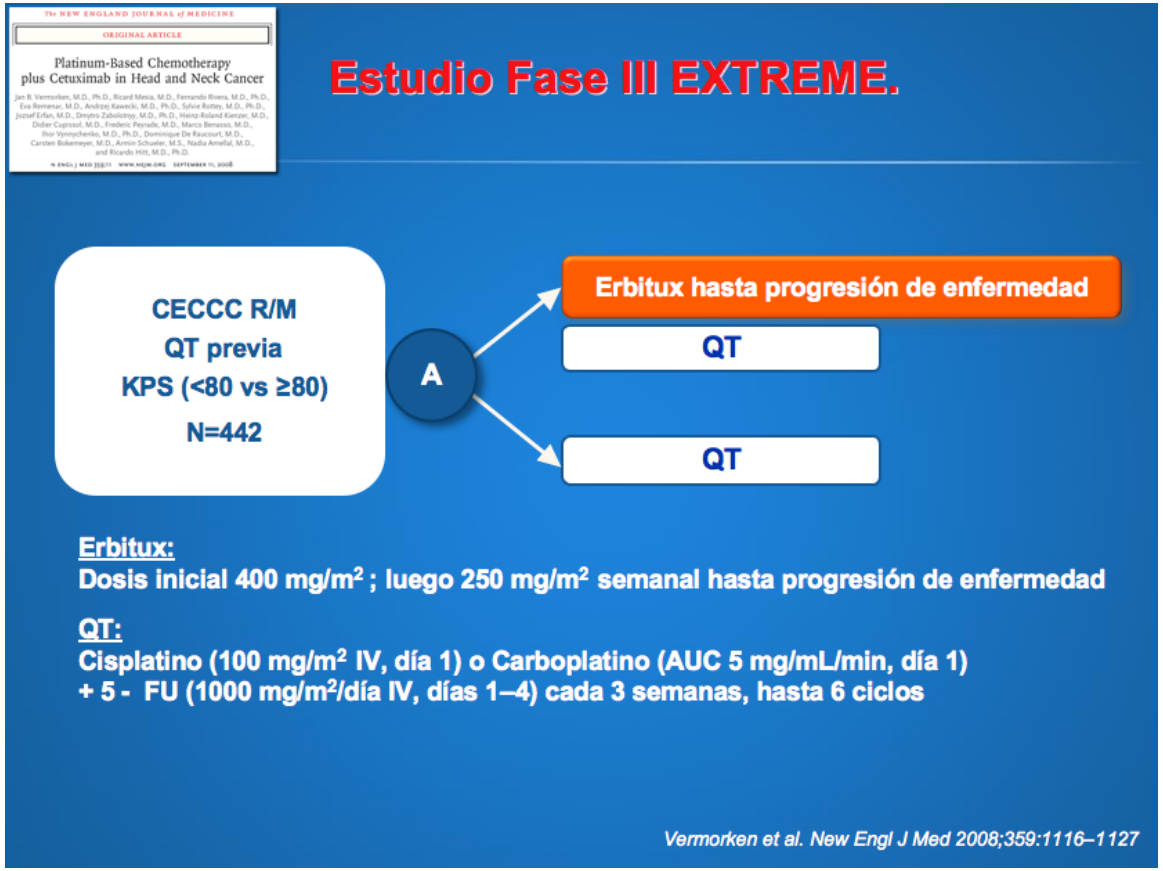
CONFLICTO DE INTERESES

- Situación laboral: Médico Adjunto en H.G.U GREGORIO MARAÑÓN
- Propiedad de acciones: NO
- Financiación de investigación: NO
- Subvención: NO
- Miembro de Advisory Board: Merck Serono, MSD, BMS, SANOFI
- Ponente en eventos científicos o docentes: Merck Serono, MSD, BMS, Bayer, Sanofi

Largos respondedores a Cetuximab en 1L: EXTREME y ERBITAX

EXTREME: Fundamento del mantenimiento y resultados del estudio

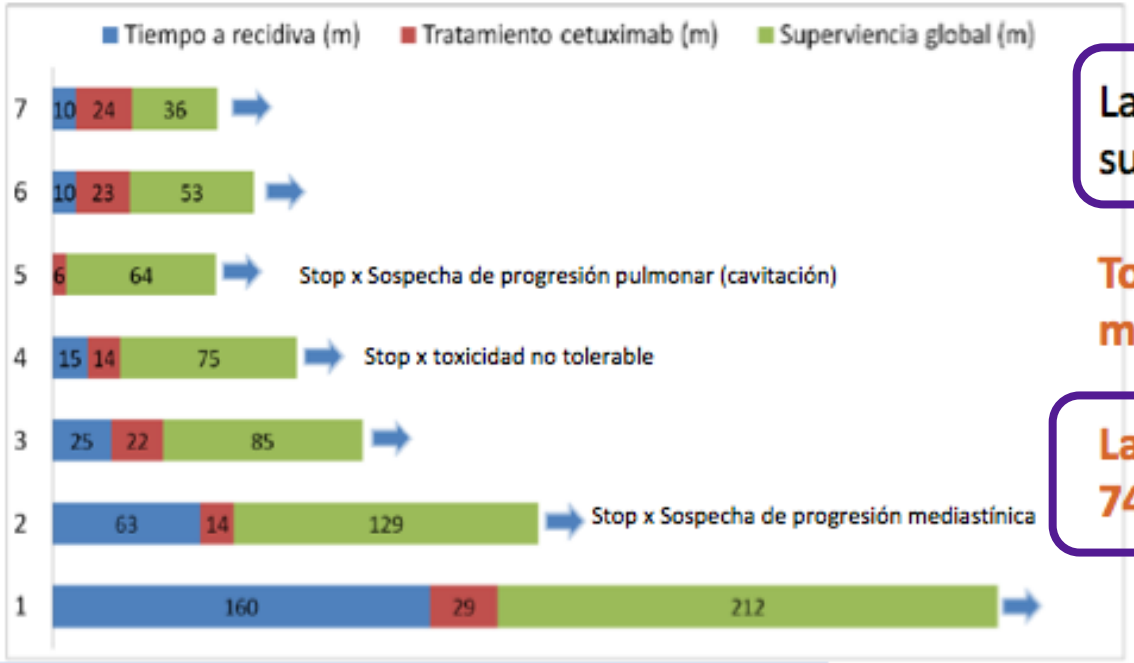


EXTREME: Conclusiones.

- Primer esquema en demuestra un aumento de SUPERVIVENCIA tras más de **30 años** de estancamiento[1]
- La adición de **ERBITUX** a la QT basada en platino aumenta significativamente la SG, la SLP y la tasa de respuesta ,con unos efectos adversos manejables y manteniendo la calidad de vida de los pacientes[1,2]
- **ERBITUX** + QT basada en platino es el **nuevo estándar de tratamiento** para la enfermedad recurrente y/o metastásica[1,2]
- Con este esquema mejoran el dolor los problemas de deglución/ habla y se reduce el deterioro físico y funcional del paciente[2]

1. Vermorken et al. New Engl J Med 2008;359:1116–1127. 2 Mesía R, et al. Ann Oncol 2010;21:1967–1973

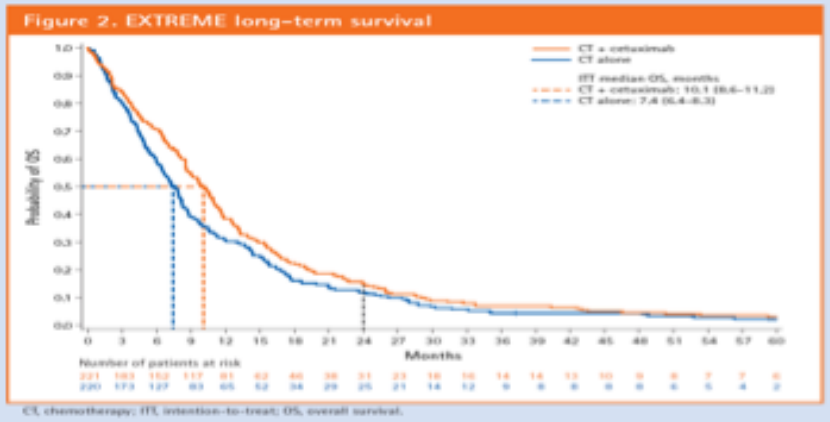
LARGOS SUPERVIVIENTES EN EL ICO – ESQUEMA EXTREME



La prevalencia de largos supervivientes es del 2.7%.

Todos recibieron Cetuximab mediana 22m (6-29m).

La mediana de SG es de 74.7m (36+-212+)



CT: 2/220 = <1%
CT+E: 6/221= 2.7%

❑ La misma proporción de ptes en ambas ramas recibieron 2ª línea de tto:
QT: 33% vs 32 % o Cetuximab 3% vs 6%

Linares J, Oral Oncology 2016

EXTREME trial: Platinum-based chemotherapy (CT) plus cetuximab in recurrent or metastatic squamous cell carc

A pivotal, open-label, randomized, multi-center, Phase III trial in patients with 1L R/M SCCHN

Stratification
- KPS (<80% vs ≥80%)
- Previous CT (receipt vs non-receipt)

Patients with 1L R/M SCCHN (N=442)

1:1 R

Cetuximab + platinum-based CT (n=222)

Platinum-based CT alone (n=220)

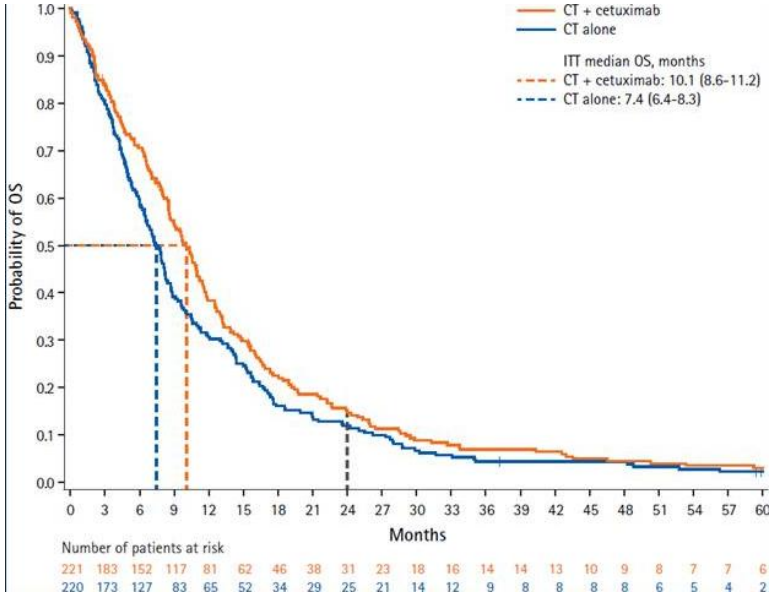
Up to 6 cycles (18 weeks)

If PR, CR, SD

Cetuximab maintenance treatment until disease progression or unacceptable toxicity

Platinum-based CT
- **Cisplatin** (100mg/m² i.v., day 1) [or **carboplatin** (AUC 5mg/mL/min, day 1)]
- **5-FU** (1000mg/m² i.v., days 1-4)

Primary endpoint: Overall survival
Key secondary endpoints: PFS, ORR and safety*



In the ITT population 12 patients **(5%)** in the CT+cetuximab arm were long term responders (**PFS>12 months**). Median treatment duration for cetuximab, **67.7 weeks.**

A **retrospective study** from cetuximab maintenance therapy for >6 months after first receiving platinum-based CT with cetuximab. Maintenance with cetuximab continued for **a mean duration of 11 months.** **PFS** and **OS** were **15.5 months** and **27.4 months**, respectively.

*Cetuximab was administered as a 400 mg/m² IV initial dose, then 250 mg/m² IV weekly + cisplatin OR carboplatin + 5-FU; Patients received cisplatin (100 mg/m² IV, day 1) OR carboplatin (AUC 5 mg/mL/min IV, day 1)† + 5-FU (1000 mg/m² IV, days 1-4) in 3-week cycles. †Cisplatin or carboplatin at investigator's discretion ‡Other secondary endpoints not listed
*Other secondary endpoints not listed. AUC, area under the curve; CR, complete response; IV, intravenous; KPS, Karnofsky performance score; PR, partial response; SD, stable disease. Vermorken JB, et al. J Clin Oncol. 2014;32:6021. Tardy MP, et al. J Clin Oncol. 2017;35:e17524

ERBITAX: Fase II y resultados

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/m², luego 250 mg/m² semanal) + Paclitaxel (80 mg/m²) 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

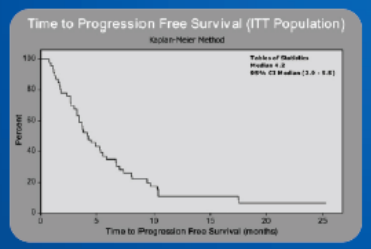
Mejor respuesta	n	%
RC	10	22
RP	15	33
EE	12	26
PE	5	11

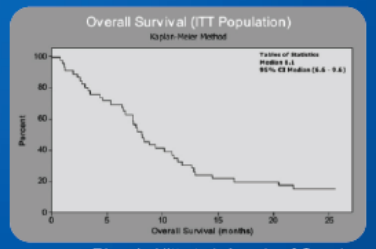
54% OR

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

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.

Real World Evidence of 1L Cetuximab + Paclitaxel (ERBITAX*) in R/M SCCHN - TTCC-2019-02

Retrospective, non-interventional, N=531 patients (16 centers from Spain)

Objective: To validate the efficacy and safety of cetuximab + paclitaxel* in 1L for the treatment of R/M HNSCC in real clinical practice.

Study design

Paclitaxel was administered weekly (days 1, 8, 15, 21...) and cetuximab could be switched to a bi-weekly schedule in the maintenance phase.

Enrolled patients received at least the first dose of cetuximab (400mg/m2 loading dose, then 250 mg/m2) and 80 mg/m2 paclitaxel between 2012 and 2018.

- **Primary endpoint:** PFS
- **Secondary endpoint**:
  - BOR, ORR, DCR, DoR, OS
  - Determine potential prognostic factors associated with survival
  - Safety profile (compliance and toxicity)

Inclusion criteria

- Patients on ERBITAX* regimen from January 2012 - December 2018
- Previously untreated patients for histologically confirmed R/M SCLC (oral cavity, oropharynx, hypopharynx, larynx)
- Age ≥ 18 years
- Ineligible for platinum-based CT:
  - PS
  - Comorbidities
  - High doses of cumulative platinum
  - Early progression after platinum (< 6 months in LA disease)

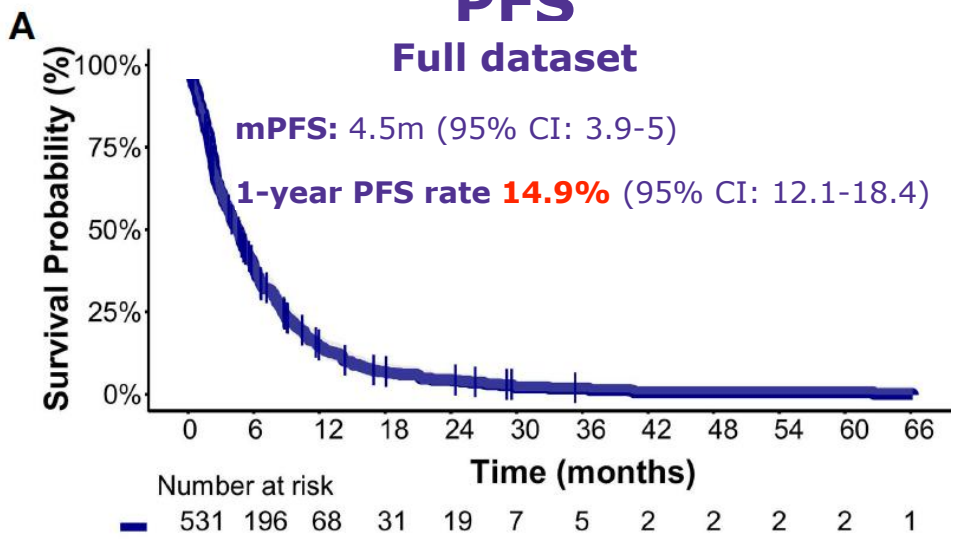
1L, first line; BOR, best overall response; CT, chemotherapy; DCR, disease control rate; DoR, duration of response;; R/M, recurrent and/or metastatic; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS: performance status; SCCHN: squamous cell carcinoma head and neck.
*Cetuximab is indicated in R/M SCCHN in combination with a platinum-based CT; Cetuximab in combination with taxanes only is currently not approved for R/M SCCHN.

Rubió-Casadevall J, et al., Front. Oncol. 13:1226939 (2023)

Real World Evidence of 1L Cetuximab + Paclitaxel (ERBITAX*) in R/M SCCH

PFS

Full dataset

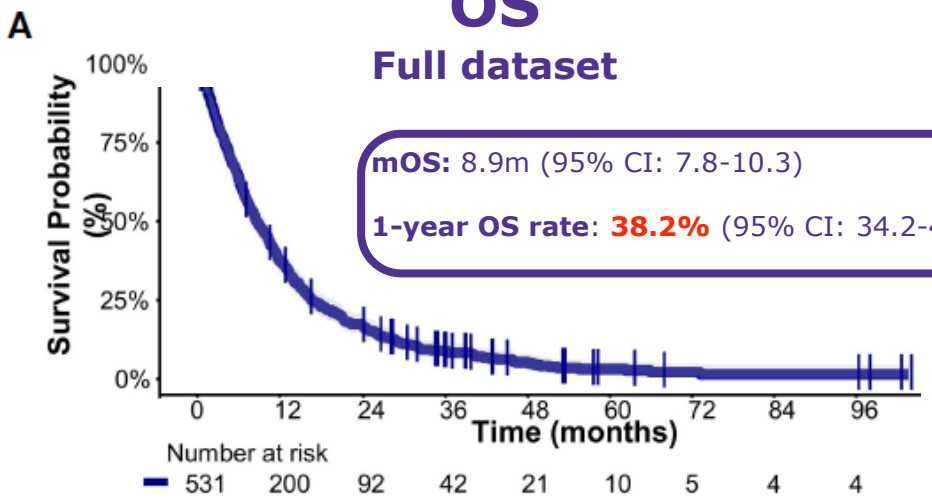


mPFS: 4.5m (95% CI: 3.9-5)

1-year PFS rate 14.9% (95% CI: 12.1-18.4)

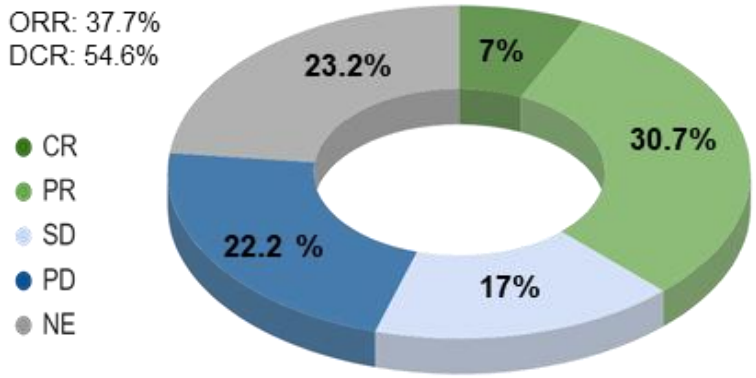
OS

Full dataset



mOS: 8.9m (95% CI: 7.8-10.3)

1-year OS rate: **38.2%** (95% CI: 34.2-42.6)



Overall, 497 (93.6%) patients died.

The most common cause of death was inexplorable progression of the disease (82.3%).

*Cetuximab is indicated in R/M SCCHN in combination with a platinum-based CT; Taxanes are currently not approved for R/M SCCHN.

Rubió-Casadevall J, et al., Front. Oncol. 13:1226939 (2023)

NIVOLUMAB en CECCR/M EN PROGRESION A PLATINO EN 6 O MENOS MESES DE INTERVALO

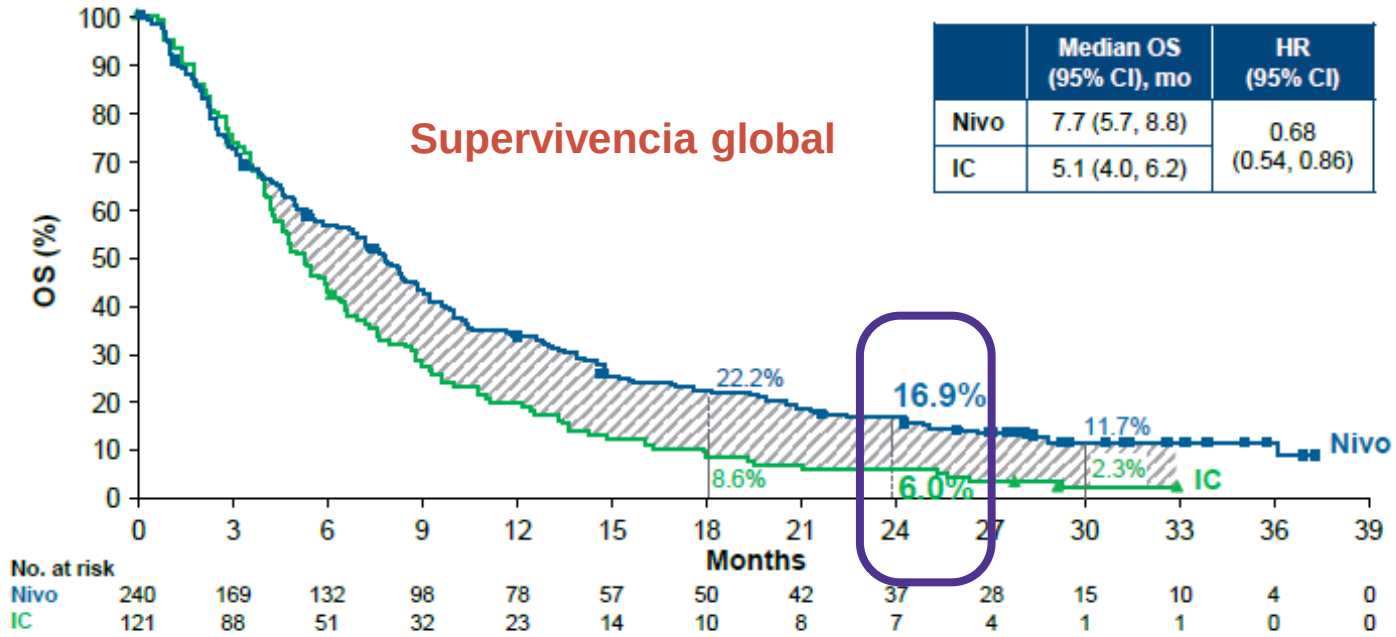
ESTUDIO CHECKMATE-141 PARA 2ª LÍNEA EN CECCRM

ELSEVIER
Oral Oncology
Volume 81, June 2018, Pages 45-51

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

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

- Nivolumab reduced the risk of death by 32% vs IC
- The 24-month OS rate was nearly tripled with nivolumab compared with IC



	Median OS (95% CI), mo	HR (95% CI)
Nivo	7.7 (5.7, 8.8)	0.68 (0.54, 0.86)
IC	5.1 (4.0, 6.2)	

Symbols represent censored observations. ITT = intent-to-treat; Nivo, nivolumab

ESTUDIO CHECKMATE-141 PARA 2ª LÍNEA EN CECCRM

Poster 6020

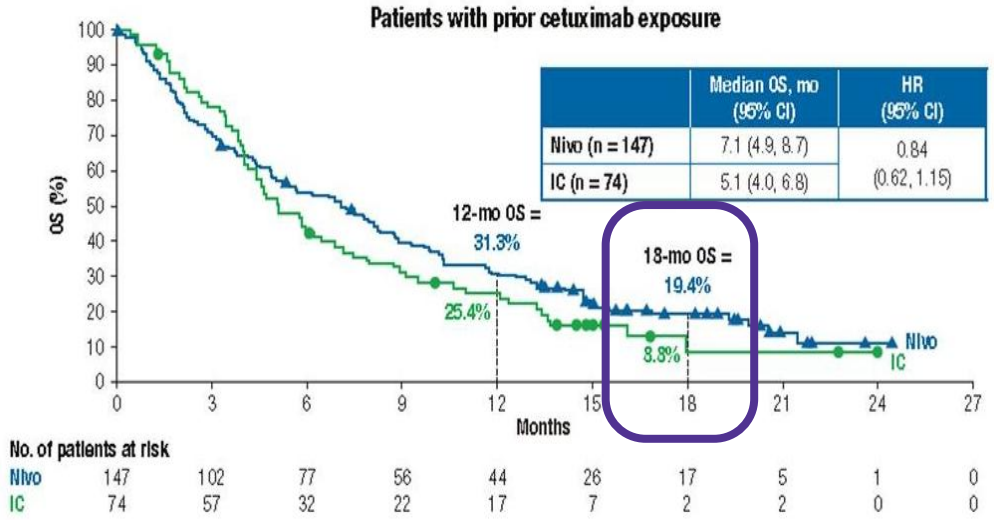
Nivolumab vs Investigator's Choice in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck: Efficacy and Safety in CheckMate 141 by Prior Cetuximab Use

Robert L. Ferris,[1] Lisa Licitra,[2] Jerome Fayette,[3] Caroline Even,[4] George Blumenschein Jr.,[5] Kevin Harrington,[6] Joel Guigay,[7] Everett E. Vokes,[8] Nabil F. Saba,[9] Robert Haddad,[10] Shanmugasundaram Ramkumar,[11] Jeffery Russell,[12] Peter Brossart,[13] Makoto Tahara,[14] Manish Monga,[15] Jin Zhu,[15] A. Dimitrios Colevas,[16] Maura L. Gillison[17]

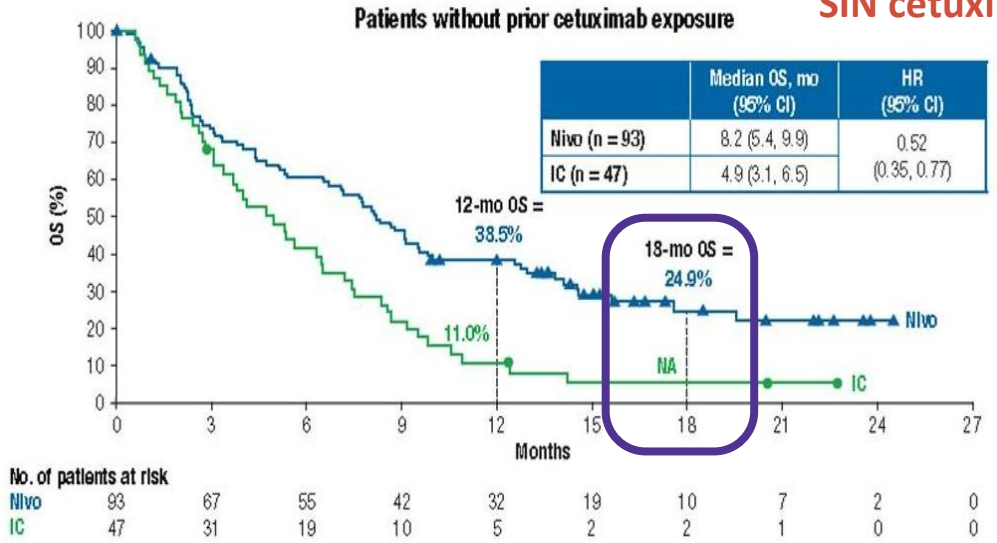
[1]University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA; [2]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; [3]Centre Leon Berard, Lyon, France; [4]Gustave Roussy, Villejuif Cedex, France; [5]MD Anderson Cancer Center, Houston, TX, USA; [6]Royal Marsden NHS Foundation Trust/The Institute of Cancer Research, London, UK; [7]Centre Antoine Lacassagne, FHU OncoAge, Nice, France; [8]University of Chicago Medical Center, Chicago, IL, USA; [9]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [10]Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [11]University Hospital Southampton/NHS Foundation Trust, Southampton, UK; [12]Moffitt Cancer Center, Tampa, FL, USA; [13]University Hospital of Bonn, Bonn, Germany; [14]National Cancer Center Hospital East, Kashiwa, Japan; [15]Bristol-Myers Squibb, Princeton, NJ, USA; [16]Stanford University, Stanford, CA, USA; [17]The Ohio State University, Columbus, OH, USA

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17

Con cetuximab



SIN cetuximab



NA = not available, minimum follow-up not reached

Patients with R/M SCCHN treated with nivolumab in the 1L+ settings in G

Updated results from a German prospective, observational, multicenter cohort study in patients with R/M SCCHN treated with nivolumab following progression during or after platinum-based therapy

Patients with R/M SCCHN

N=478

- Enrolled May 2017–July 2021
- ≥18 years
- Progression during or after platinum-based therapy
- Treatment decision for therapy with nivolumab already taken

Cohort 1 (n=255)*

Nivolumab (240 mg IV Q2W)†

≥2L treatment for R/M SCCHN, prior platinum-based therapy for LA or R/M SCCHN; patients were platinum-refractory or platinum-sensitive

Cohort 2 (n=223)

Nivolumab (240 mg IV Q2W)†

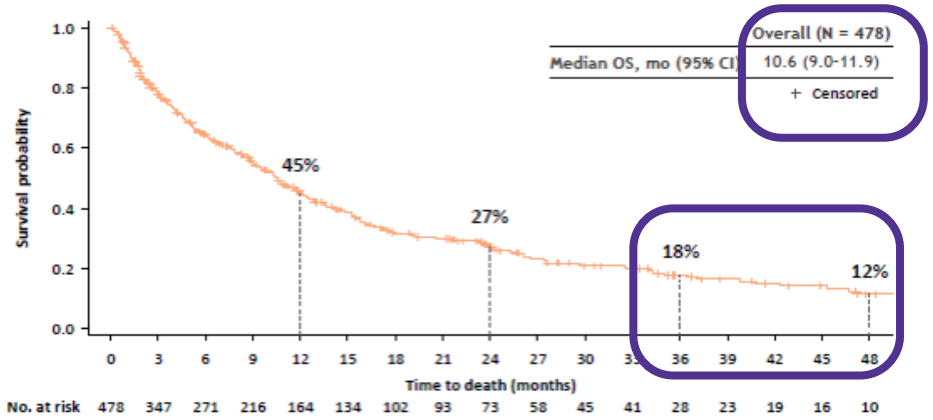
1L treatment for R/M SCCHN, prior platinum-based therapy for LA SCCHN adjuvant or primary setting; patients were platinum-refractory or platinum-sensitive

Primary endpoint: OS

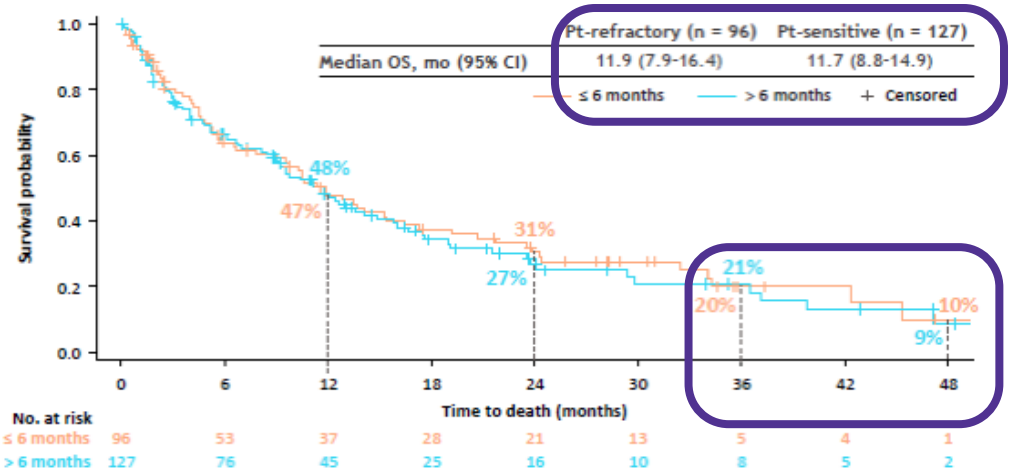
Secondary endpoints:
PFS, ORR, DoR, TTR, TTNT
DoT, patient characteristics, safety, QoL (EQ-5D)

Median potential follow-up: 57.2 months
Time since enrollment of each patient in study, regardless of patient's current status in study

OS in the overall population



OS by response to Pt-based therapy in 1L subset

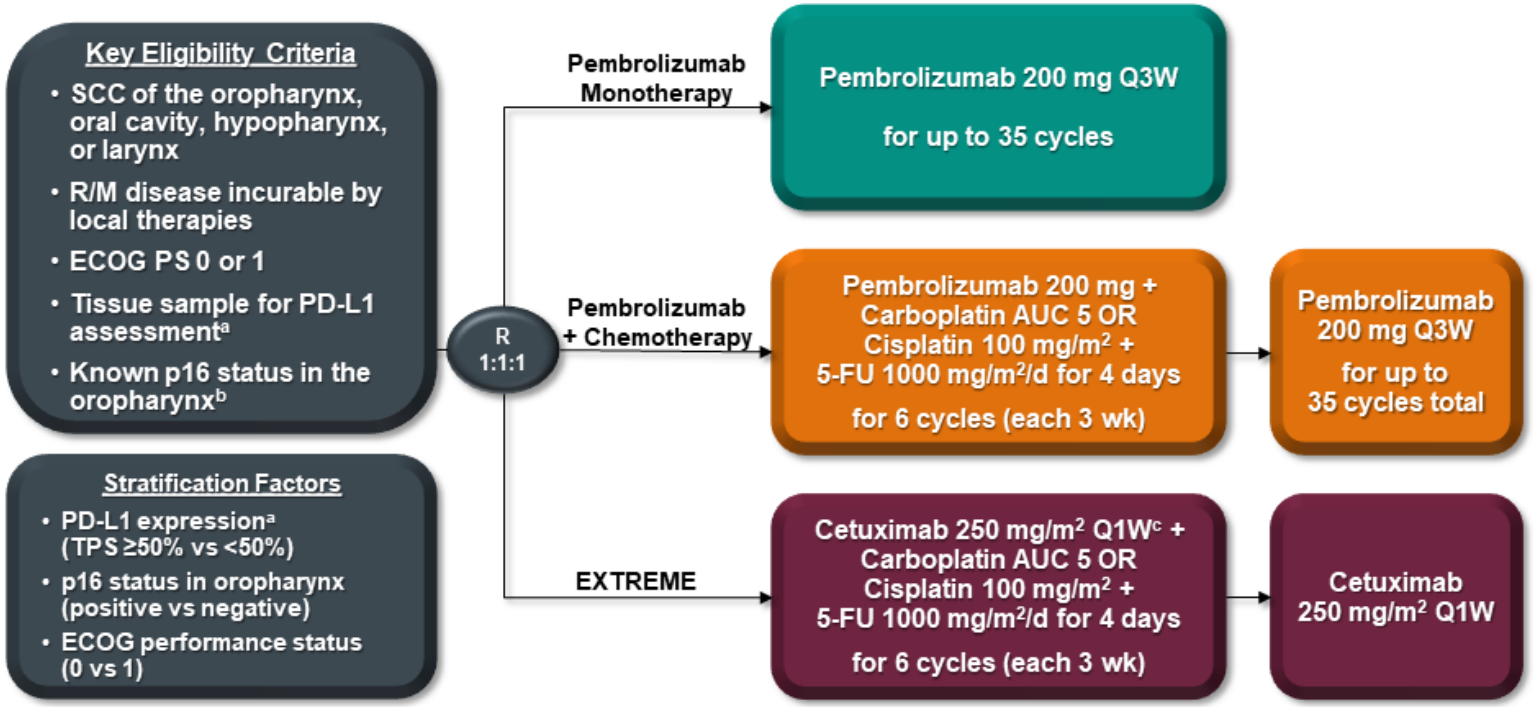


*Includes 3 patients with missing data on line of treatment; †Dosing according to current summary of product characteristics. 1L, first line; 2L, second line; DoR, duration of response; DoT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IRAE, immune-related adverse event; IV, intravenous; LA, locally advanced; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PT, platinum-based therapy; Q2W, every 2 weeks; QoL, quality of life; R/M, recurrent and/or metastatic; TTNT, time to next treatment; TTR, time to response.

PEMBROLIZUMAB EN 1ª LÍNEA PARA CECCR/M

Burtness KN048 ESMO 2018

KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

PEMBROLIZUMAB EN 1ª LÍNEA PARA CECCR/M

Pembrolizumab plus a platinum and 5-FU vs EXTREME:

Superior OS for pembrolizumab + chemotherapy in the **PD-L1 CPS ≥20** and **CPS ≥1** and **total populations**
Longer duration of response for pembrolizumab + chemotherapy
Comparable safety profiles for pembrolizumab + chemotherapy and EXTREME

Pembrolizumab monotherapy vs EXTREME:

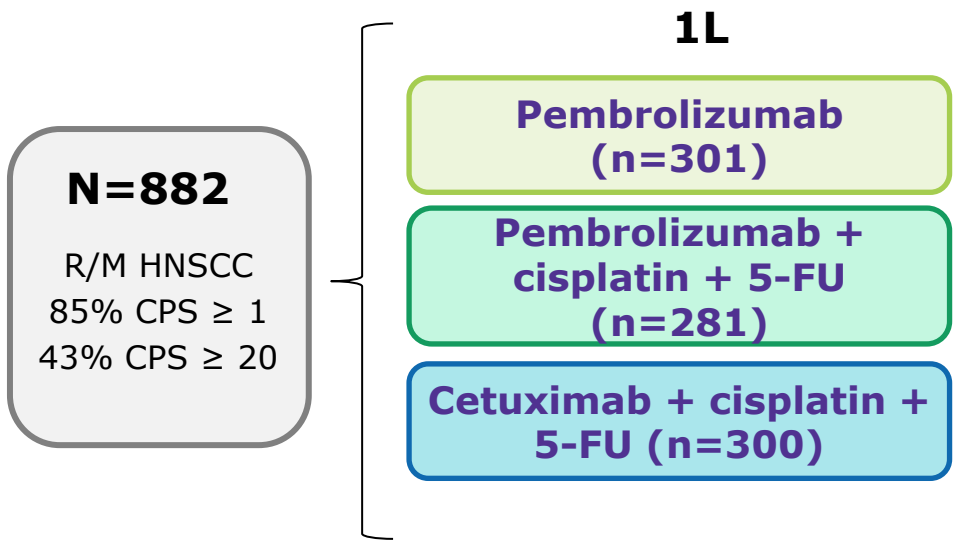
Superior OS for pembrolizumab in the **CPS ≥20 and CPS ≥1** populations
Noninferior OS for pembrolizumab in the **total population**
Substantially **longer duration** of response for pembrolizumab
Favorable safety profile for pembrolizumab

Data support **pembrolizumab plus platinum-based** chemotherapy and **pembrolizumab monotherapy** as **new first-line standard-of-care therapies for R/M HNSCC**

Rischin KN048 ASCO 2019

Pembrolizumab ± chemotherapy vs. cetuximab with chemotherapy for R/M S

Randomised, **open-label, phase 3 study** with patients who were diagnosed with **R/M HNSCC** at 200 sites in 37 countries.



Primary endpoints

- **OS and PFS**

Secondary endpoints

- **Safety and tolerability**
- **Participants with ORR**
- **Progression-free at 6 &12 months**

Stratification factors:

- PD-L1 expression (≥50% or ≤ 50%)
- P16 status for oropharyngeal cancers (+/-)
- ECOG PS 0 or 1

Kevin J. Harrington et al., Journal of Clinical Oncology **2023** 41:4, 790-802

OS benefit with pembrolizumab monotherapy was driven by patients with CPS ≥20

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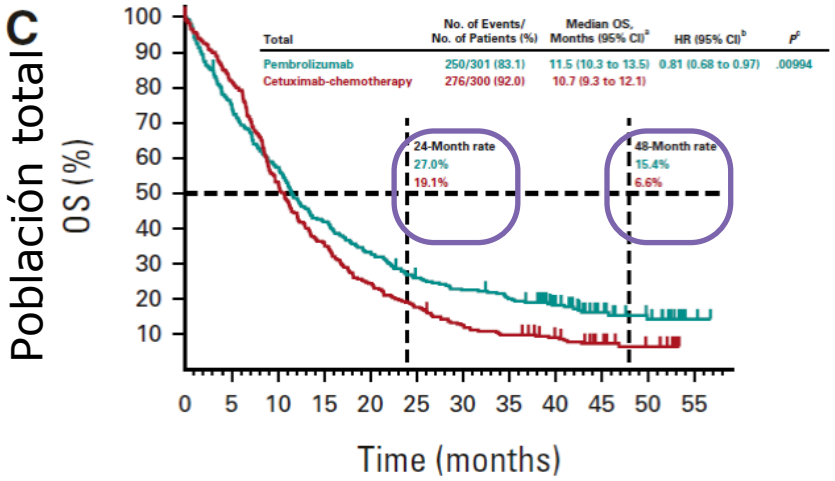

No. at risk:

Pembrolizumab	301	226	172	126	100	76	66	58	43	24	13	2
Cetuximab-chemotherapy	300	245	159	108	73	53	37	29	22	13	7	0

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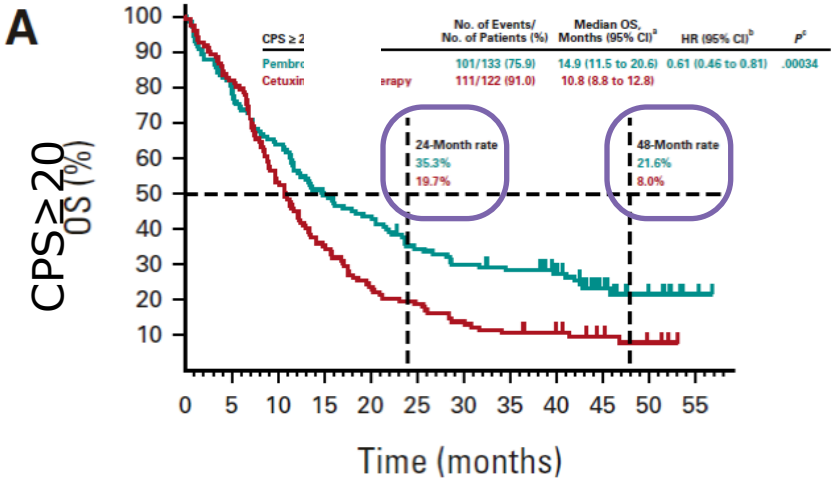
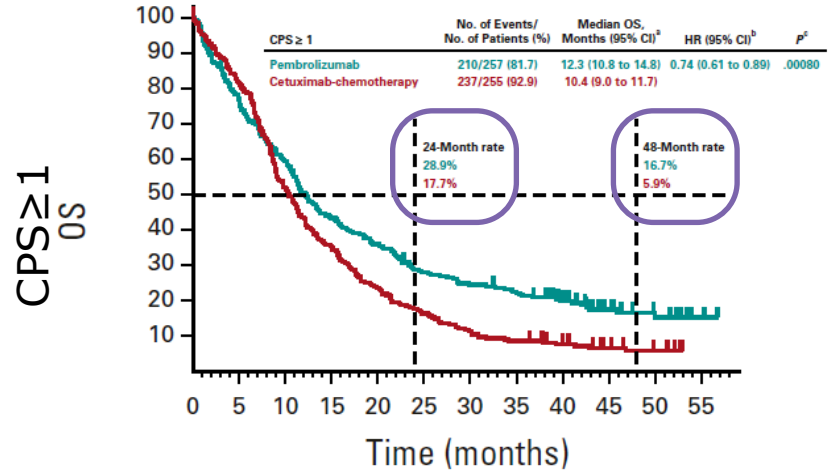


No. at risk:

Pembrolizumab	133	107	85	66	58	45	39	36	30	17	9	2
Cetuximab-chemotherapy	122	100	65	43	29	23	17	13	11	7	4	0



No. at risk:

Pembrolizumab	257	197	152	111	92	71	62	55	40	22	12	2
Cetuximab-chemotherapy	255	207	132	90	60	42	29	22	16	10	6	0

Kevin J. Harrington et al., Journal of Clinical Oncology **2023** 41:4, 790-802

mOS benefit with pembrolizumab + platinum + 5-FU was highest in patients with CPS ≥20

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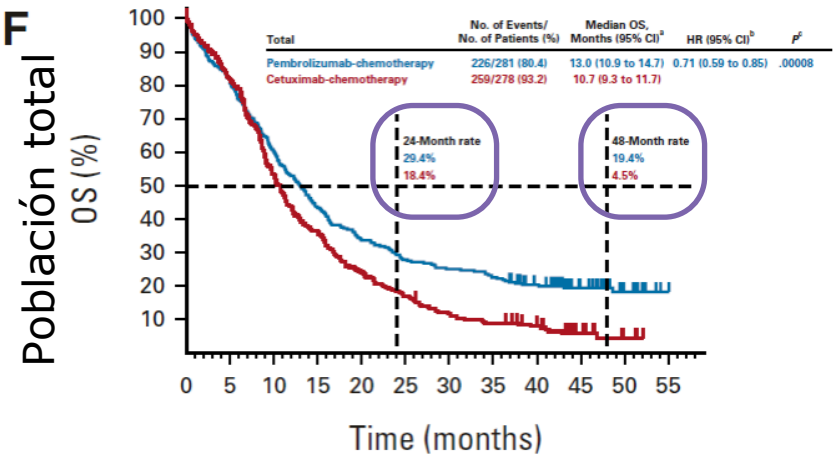

No. at risk:

Pembrolizumab-chemotherapy	281	227	169	122	94	78	70	63	49	30	9	1
Cetuximab-chemotherapy	278	227	148	101	67	47	32	24	17	8	2	0

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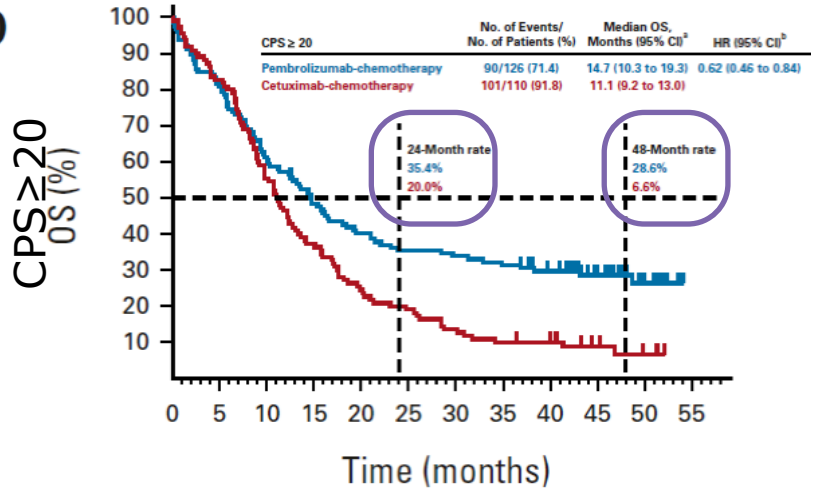
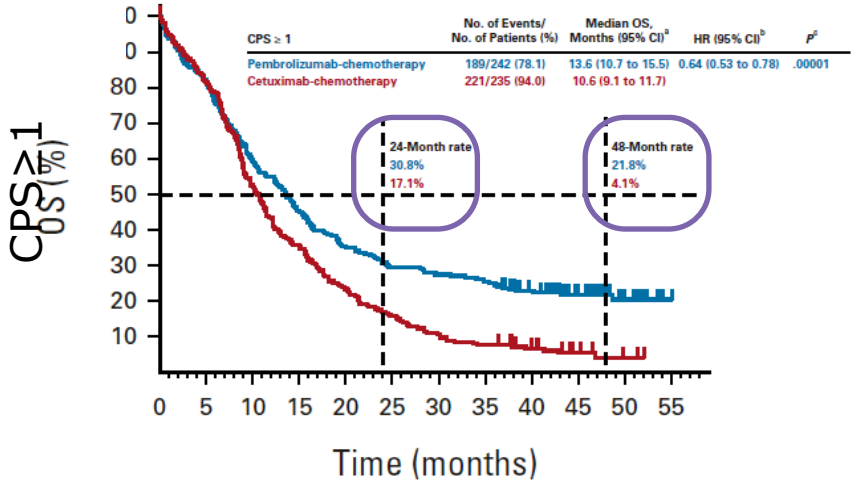


No. at risk:

Pembrolizumab-chemotherapy	126	102	77	60	50	44	42	39	33	22	7	0
Cetuximab-chemotherapy	110	91	61	41	27	21	15	11	9	5	2	0



No. at risk:

Pembrolizumab-chemotherapy	242	197	144	109	84	71	66	61	48	29	9	1
Cetuximab-chemotherapy	235	191	123	84	55	37	25	18	12	6	2	0

Kevin J. Harrington et al., Journal of Clinical Oncology 2023 41:4, 790-802

¿ES POSIBLE MEJORAR LOS DATOS DE SUPERVIVENCIA DE LAS PRIMERAS LÍNEAS DE TRATAMIENTO DEL CECCR/M?

SECUENCIA TERAPÉUTICA

Secuencia de QT con Cetuximab seguida de IO: ERBITAX-IO, EXTREME-IO (KESTREL) y TPEXTREME-IO

Real World Evidence of 1L Cetuximab + Paclitaxel (ERBITAX*) in R/M SCCHN - TTCC-2019-02

Baseline characteristics for patients who received ulterior immunotherapies or other treatments

ON

Characteristics; unit		Post Immunotherapy N = 43	Post other therapy N =142	TTCC-2019-02 ≥1 post therapy N = 185	*p*-value
Median age (range); years		66 (35–91)	65 (44–90)	65 (35–91)	0.855
Sex, *n* (%)	Male	32 (74.4)	118 (83.1)	150 (81.1)	0.203
ECOG PS; *n* (%)	0	7 (16.3)	2 (2.1)	10 (5.4)	0.002
	1	17 (39.5)	82 (57.7)	99 (53.5)	
	2	19 (44.2)	57 (40.1)	76 (41.1)	
Stage at diagnosis; *n* (%)	I	3 (7)	7 (4.9)	10 (5.4)	0.784
	II	2 (4.7)	10 (7)	12 (6.5)	
	III	7 (16.3)	28 (19.7)	35 (18.9)	
	IV	29 (67.4)	94 (66.2)	123 (66.5)	
	UK	2 (4.7)	3 (2.1)	5 (2.7)	
Metastasis; *n* (%)		2 (4.7)	13 (9.2)	15 (8.1)	0.526
Smoking habit; *n* (%)	Never smoker	8 (18.6)	13 (9.2)	21 (11.4)	0.301
	Former	20 (46.5)	64 (45.1)	84 (45.4)	
	Current smoker	12 (27.9	54 (38)	66 (35.7)	
	UK	3 (7)	11 (7.7)	14 (7.6)	
PD-L1	Positive	13 (30.2)	5 (3.5)	18 (9.7)	< 0.001
	Negative	7 (16.3)	25 (17.6)	32 (17.3)	
	Not determined	23 (53.5)	112 (78.9)	135 (73)	
Previous surgery; *n* (%)	Yes	32 (74.4)	82 (57.7)	114 (61.6)	0.049
	No	11 (25.6)	60 (42.3)	71 (38.4)	
Cetuximab paclitaxel median treatment duration (range); months		9.1 (0.7–46.4)	5.9 (0.2–27.2)	6.2 (0.2–46.4)	0.002
ORR cetuximab paclitaxel; *n* (%)		32 (74.4)	70 (49.3)	102 (55.1)	0.004
DCR cetuximab paclitaxel; *n* (%)		38 (88.4)	99 (69.7)	137 (74.1)	0.014
Median DoR cetuximab paclitaxel (range); months		6.9 (1.9–19.2)	4.6 (0–35.9)	5.6 (0–35.9)	0.04

Only patients with one or more treatment lines after cetuximab paclitaxel. Those patients who died or had no longer follow-up and did not receive other treatment lines were excluded from the analysis to avoid bias.
DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate.

Patients who received subsequent treatment with ICI had a better ECOG and better ERBITAX* outcomes.

After ERBITAX*, the **median duration of response was 6.9 months (95% CI 5.3-9.8)** for patients who were subsequently **treated with ICI** and **4.6 months (95% CI 3.7-6.5) for other treatments (p=0.04).**

Patients treated with other treatments:

Carboplatin (43%)

Methotrexate (43%)

Rubió-Casadevall J, et al., Front. Oncol. 13:1226939 (2023)

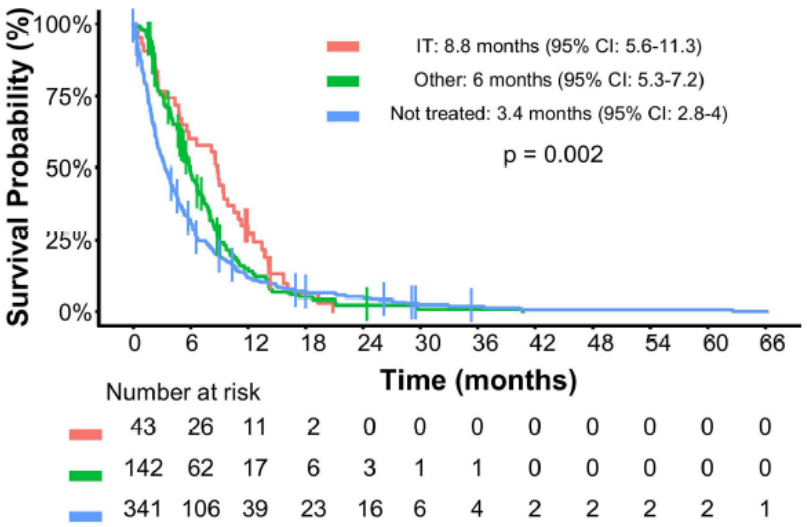
*Cetuximab is indicated in R/M SCCHN in combination with a platinum-based CT; Taxanes are currently not approved for R/M SCCHN.

Efficacy results according to subsequent treatment

ONCOLOGICOS: MEJOR DE 2024

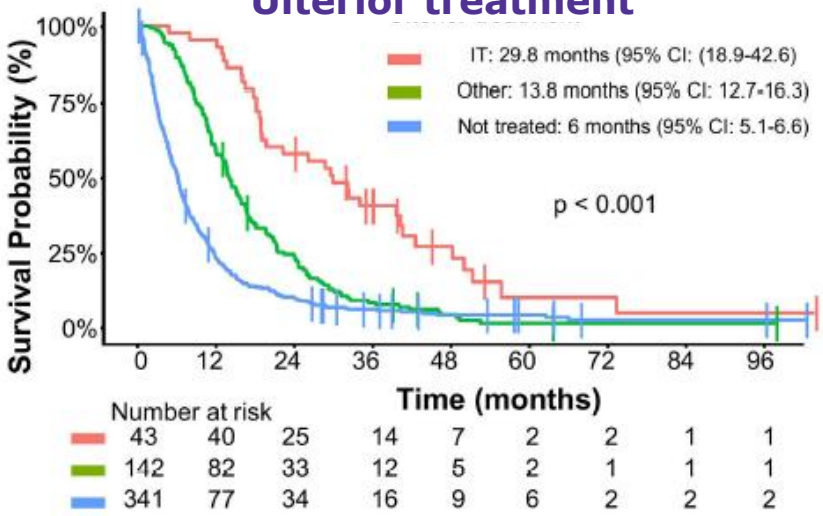
Stratified PFS

Ulterior treatment



Stratified OS

Ulterior treatment



Patients who **received ICI** in any **subsequent line** of treatment had an **mPFS of 8.8 months**, while patients who received subsequent treatments **other than ICI** had an **mPFS of 6 months**.

Patients treated with **ICI (nivolumab)** in subsequent lines also had **better survival**, with a **median OS of 29.8 months** and **13.8 months for other treatments**.

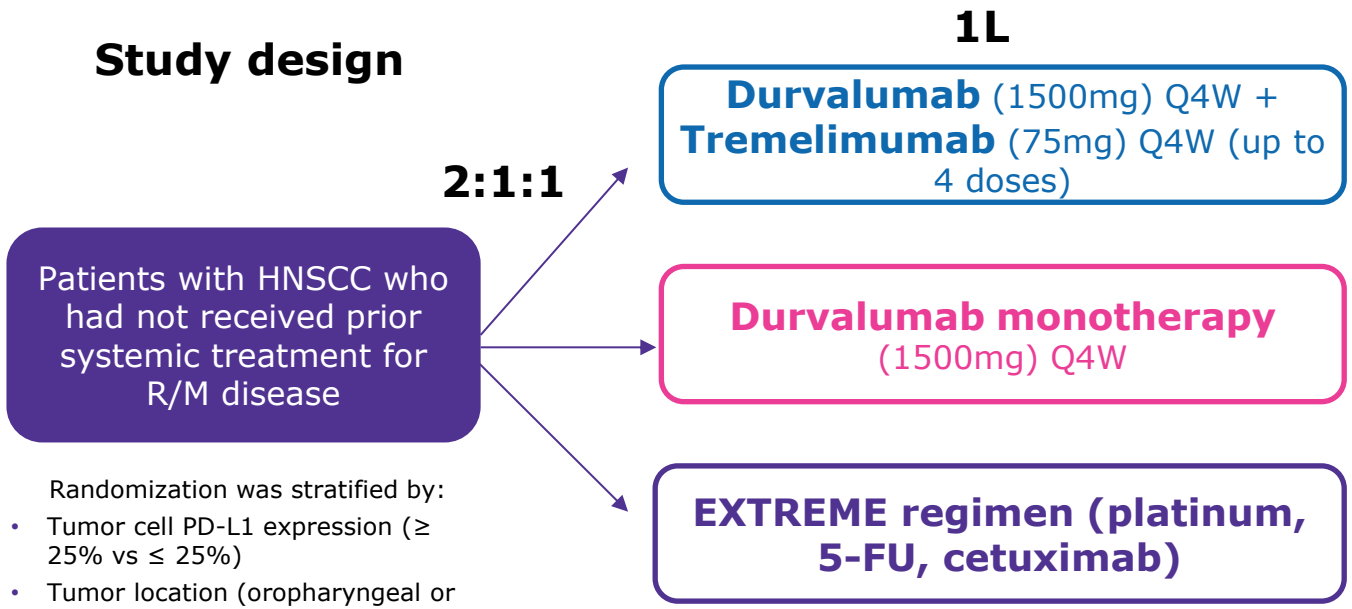
*Cetuximab is indicated in R/M SCCHN in combination with a platinum-based CT; Taxanes are currently not approved for R/M SCCHN.

Rubió-Casadevall J, et al., Front. Oncol. 13:1226939 (2023)

KESTREL: Durvalumab with or without tremelimumab versus the EXTREME regimen as 1L treatment for R/M SCCHN

Phase III randomized open-label study: Evaluate the efficacy of **durvalumab** (PD-L1 antibody) with or without **tremelimumab** (CTLA-4 antibody) vs the **EXTREME regimen** in patients with **R/M SCCHN.**

Study design



Randomization was stratified by:

- Tumor cell PD-L1 expression (≥ 25% vs ≤ 25%)
- Tumor location (oropharyngeal or non-oropharyngeal)
  - Patients with OPC were stratified by HPV status (+/-)
- Smoking history (>10 or ≤ 10 pack years)

Table S1. Patients receiving subsequent therapy after study discontinuation

	Durvalumab		Durvalumab + tremelimumab		EXTREME	
	PD-L1-high[a] (*n* = 99)	All randomized patients (*n* = 204)	PD-L1-high[a] (*n* = 190)	All randomized patients (*n* = 413)	PD-L1-high[a] (*n* = 94)	All randomized patients (*n* = 206)
Patients receiving any subsequent therapy after study discontinuation, *n* (%)	52 (52.5)	110 (53.9)	68 (35.8)	167 (40.4)	61 (64.9)	134 (65.0)
Patients receiving subsequent immunotherapy, *n* (%)	3 (3.0)	13 (6.4)	5 (2.6)	14 (3.4)	23 (24.5)	50 (24.3)
Patients receiving non-immunotherapy subsequent therapy, *n* (%)	49 (49.5)	97 (47.5)	63 (33.2)	153 (37.0)	38 (40.4)	84 (40.8)

EXTREME, cetuximab, 5-fluorouracil, and either carboplatin or cisplatin; IC, immune cell; PD-L1, programmed cell death ligand-1; TC, tumor cell.

[a]PD-L1-high, TC≥50% or IC≥25%.

Until PD, initiation of alternative therapy, unacceptable toxicity, withdrawal of consent or until any other treatment discontinuation criterion was met.

Primary objective: OS of durvalumab monotherapy compared to EXTREME in patients with R/M SCCHN whose tumors express high PDL1 (PD-L1 TC ≥50% or immune cells (IC)≥ 25%

Secondary objectives:

- Efficacy of durvalumab monotherapy compared to EXTREME in all patients
- Efficacy of durvalumab + tremelimumab compared to EXTREME in both patients with PDL1 high tumors and in all patients

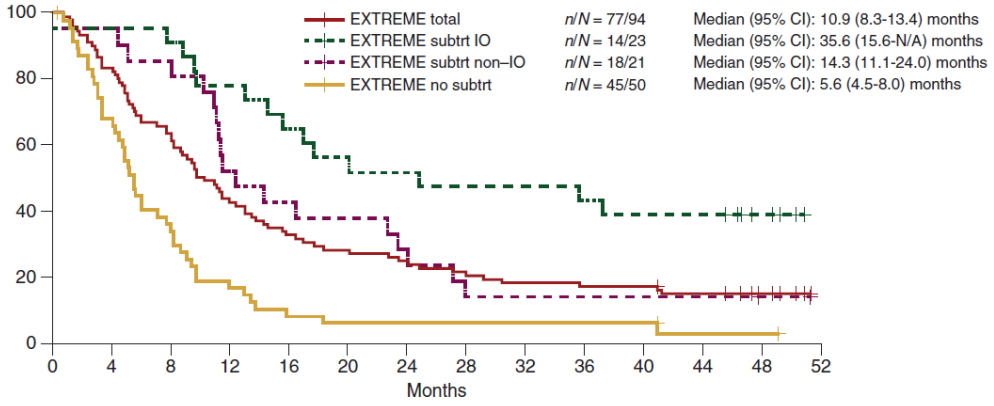
1L, first line; 2L, second line; CI, confidence interval; CT, chemotherapy; IO, immunotherapy; R/M, recurrent and/or metastatic SCCHN: squamous cell carcinoma head and neck.

Psyrri A, et al. Ann Oncol 2023;34:262–274.

Overall survival according to subsequent treatment

PD-L1 high patients

A



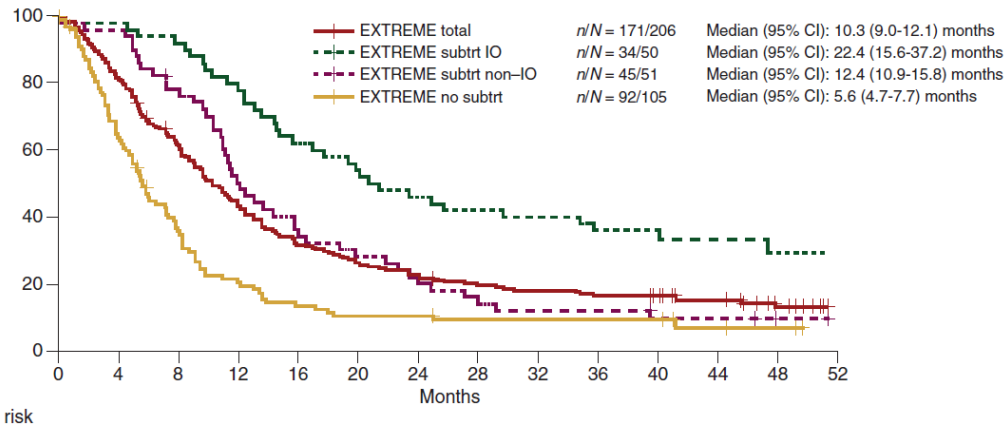
Number of patients still at risk

EXTREME total	94	77	59	40	31	27	24	20	18	17	16	13	7	0
EXTREME subtrt IO	23	23	22	19	16	14	13	12	12	11	10	9	5	0
EXTREME subtrt non–IO	21	21	19	12	10	9	7	4	3	3	3	3	1	0
EXTREME no subtrt	50	33	18	9	5	4	4	4	3	3	3	1	1	0

mOS EXTREME subtrt IO: **35.6** (95% CI 15.6-N/A) months
mOS EXTREME subtrt non-IO: 14.3 (95% CI 11.1-24.0) months

All patients

B



Number of patients still at risk

EXTREME total	206	168	123	87	64	53	46	39	36	33	28	21	11	0
EXTREME subtrt IO	50	50	47	40	32	28	24	22	21	19	15	13	8	0
EXTREME subtrt non–IO	51	50	40	26	18	15	12	8	7	6	5	5	1	0
EXTREME no subtrt	105	68	36	21	14	10	10	9	8	8	8	3	2	0

mOS EXTREME subtrt IO: **22.4** (95% CI 15.6-37.2) months
mOS EXTREME subtrt non-IO: 12.4 (95% CI 10.9-15.8) months

Conclusions

- High proportion of patients in the EXTREME arm received 2L ICI
- **Subsequent ICI following the EXTREME regimen improved OS**
- The EXTREME may be an appropriate choice of 1L therapy for those patients with a high tumor burden and life-threatening disease, followed by ICI upon PD or following disease stabilization

CI, confidence interval; CT, chemotherapy; IO, immunotherapy; ICI, immune checkpoint inhibitor; mOS, median overall survival; Psyrri A, et al. Ann Oncol 2023;34:262–274.

TPExtreme*#: A large randomized study comparing TPEx (ce

Study design

1L R/M SCCHN (N=539)

- No prior systemic CT for R/M SCCHN except if completed >6 months prior if given as part of multimodal treatment for LA disease
- ECOG PS 0–1

EXTREME (reference arm)
6 cycles Q3W CT
Cetuximab + cisplatin + 5-FU

→ **Maintenance Cetuximab 250 mg/m2 QW**

TPEx (experimental arm)
4 cycles Q3W CT Cetuximab + cisplatin + docetaxel + G CSF after each cycle

→ **Maintenance Cetuximab 500 mg/m² Q2W†**

Until PD or unacceptable toxicity

Primary endpoint:
OS

Secondary endpoints:
PFS, ORR at 12 weeks, safety, compliance

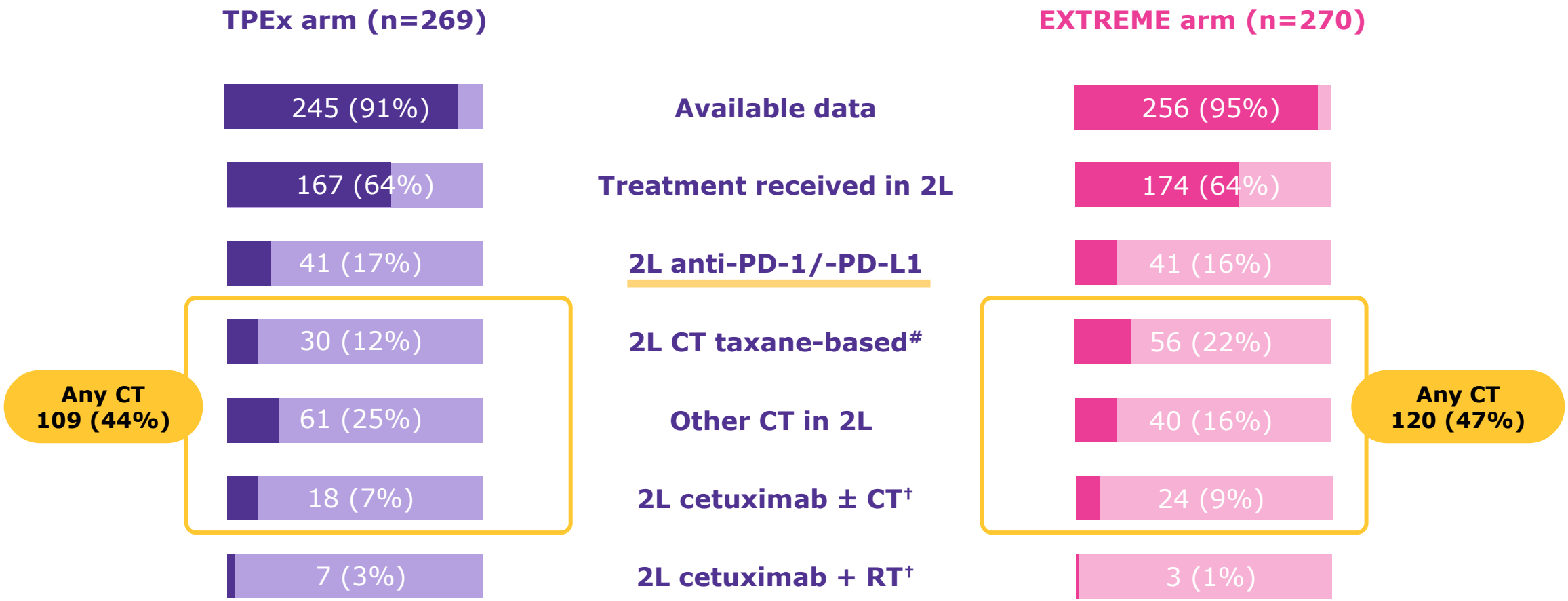
Cisplatin was replaced by intravenous carboplatin in case of cisplatin-related nephrotoxicity of grade 1 or worse, ototoxicity of grade 3 or worse, or neurotoxicity of grade 3 or worse.

*The TPEx regimen is Cetuximab + cisplatin + docetaxel. #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;

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

Guigay J, et al. The Lancet 2021;Vol. 22(4)pp.463-475

In the TPExtreme* trial, the majority of patients received CT or ICI in 2L

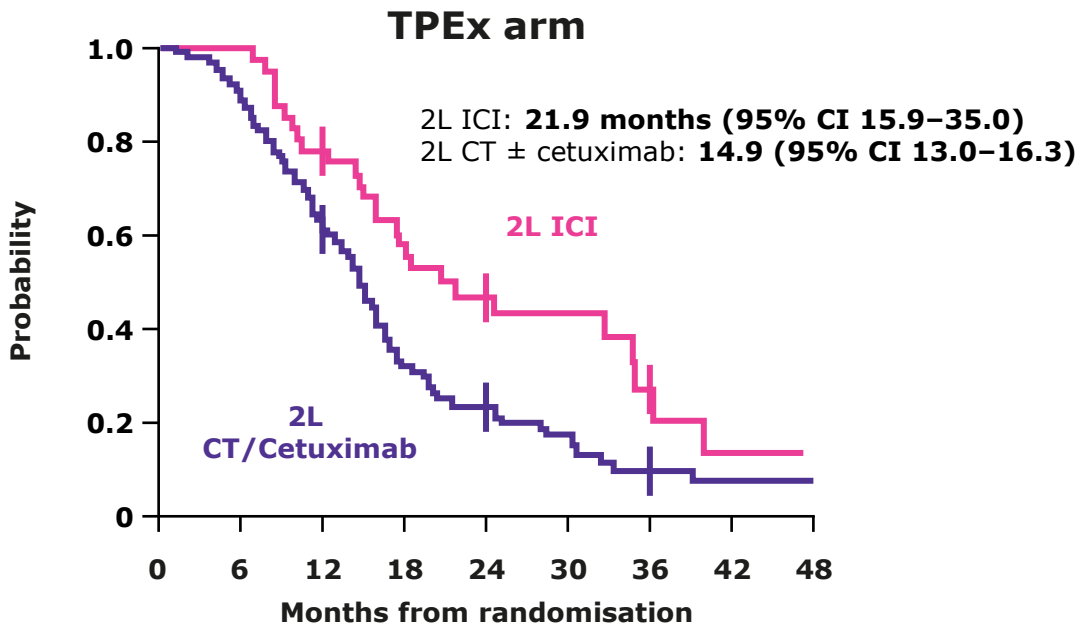


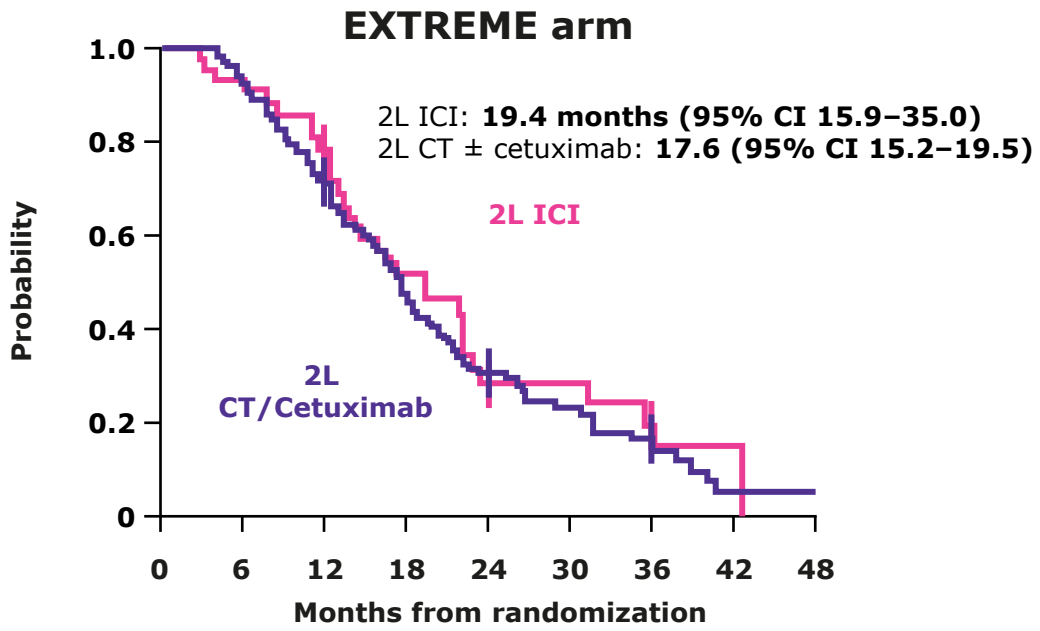
*The TPEx regimen is Cetuximab + cisplatin + docetaxel. The TPExtreme study did not meet its primary endpoint of significantly improving OS in the TPEx regimen vs the EXTREME regimen. Cetuximab is administered Q2W in this study arm during maintenance, whereas the EU SmPC stipulates weekly administration;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

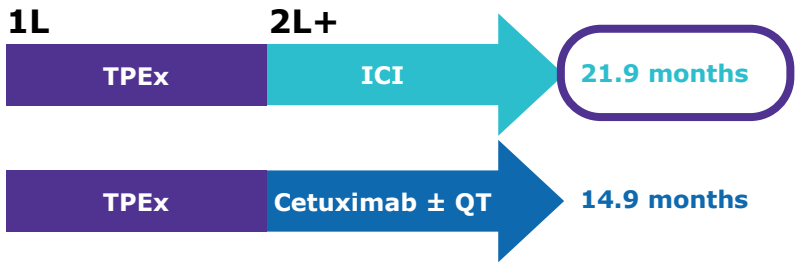
Guigay J, et al. The Lancet 2021;Vol. 22(4)pp.463-475

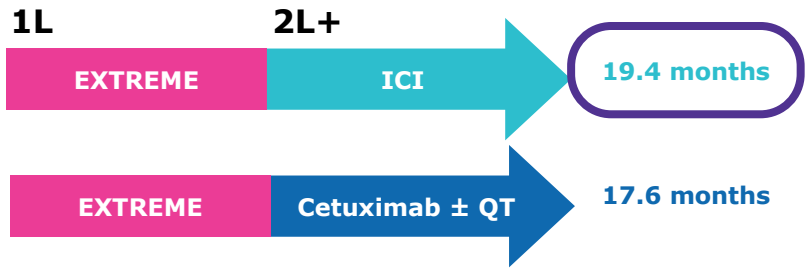
Treatment in 1L with TPEx*# or EXTREME followed by ICI in 2L was associated with

mOS from randomization[1]









1L, first line; 2L, second line; CI, confidence interval; CT, chemotherapy; IO, immune checkpoint inhibitor; mOS: median overall survival.

*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;

1. Guigay J, et al. The Lancet 2021;Vol. 22(4)pp.463-475

Secuencia IO seguida de QT:

Pembro/PembroQT – QT (KEYNOTE-048)

Subsequent anticancer therapies in KEYNOTE-048 long-term study.

TABLE 1. Summary of Subsequent Anticancer Therapy

Subsequent Anticancer Therapy	Pembrolizumab *v* Cetuximab-Chemotherapy, No. (%)		Pembrolizumab-Chemotherapy *v* Cetuximab-Chemotherapy, No. (%)	
	Pembrolizumab (n = 301)	Cetuximab-Chemotherapy (n = 300)	Pembrolizumab-Chemotherapy (n = 281)	Cetuximab-Chemotherapy (n = 278)
Any[a]	150 (49.8)	161 (53.7)	119 (42.3)	147 (52.9)
Chemotherapy	138 (45.8)	121 (40.3)	100 (35.6)	110 (39.6)
Taxane	83 (27.6)	94 (31.3)	72 (25.6)	86 (30.9)
Nontaxane	134 (44.5)	71 (23.7)	65 (23.1)	65 (23.4)
Antimetabolite	100 (33.2)	39 (13.0)	45 (16.0)	34 (12.2)
Platinum-based	122 (40.5)	47 (15.7)	45 (16.0)	43 (15.5)
EGFR inhibitor	74 (24.6)	20 (6.7)	52 (18.5)	18 (6.5)
Chemotherapy plus EGFR inhibitor	67 (22.3)	13 (4.3)	44 (15.7)	11 (4.0)
Kinase inhibitor	5 (1.7)	3 (1.0)	7 (2.5)	3 (1.1)
ICI	19 (6.3)	76 (25.3)	23 (8.2)	70 (25.2)
Anti–PD-1/PD-L1	19 (6.3)	75 (25.0)	21 (7.5)	69 (24.8)
Anti–B7-H3	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Anti–CTLA-4	1 (0.3)	6 (2.0)	1 (0.4)	5 (1.8)
Anti-TIGIT	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Other immunotherapy	3 (1.0)	6 (2.0)	1 (0.4)	5 (1.8)
Other therapy	2 (0.7)	7 (2.3)	4 (1.4)	5 (1.8)

Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated protein 4; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TIGIT, T-cell immunoreceptor with Ig and ITIM domains.

[a]Patients could have received more than one subsequent anticancer therapy overall or of a specific category.

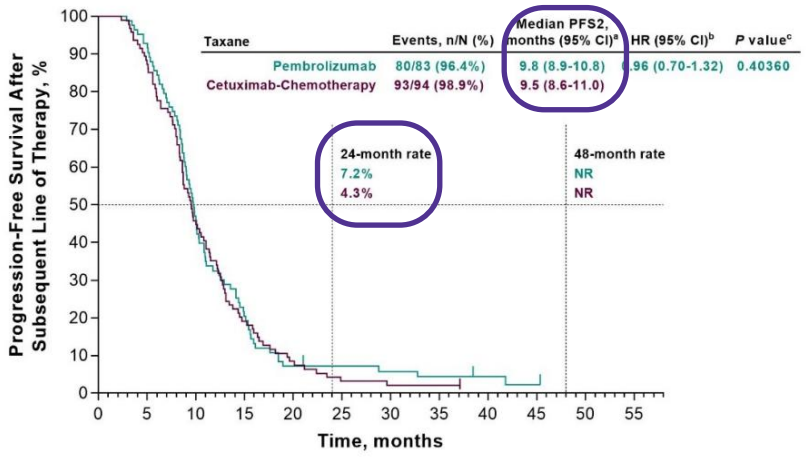
Most patients received chemotherapy in 2L

Kevin J. Harrington et al., Journal of Clinical Oncology 2023 41:4, 790-802

Taxane-containing 2nd line therapies

Pembrolizumab monotherapy vs. Cetuximab + CT*

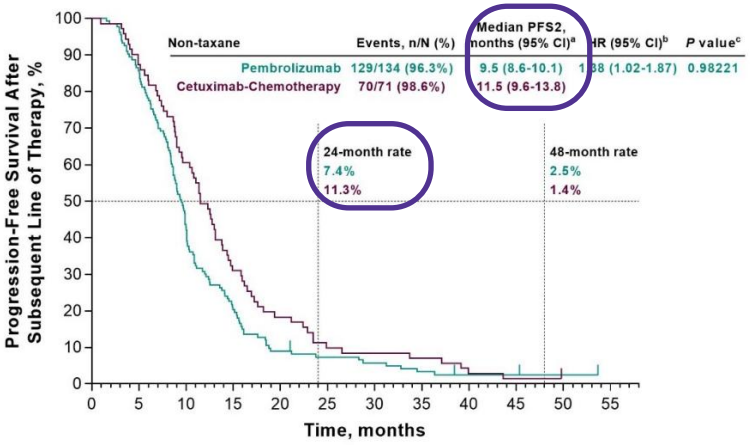
Taxane



No. at Risk

Pembrolizumab	83	77	39	17	6	5	4	3	2	1	0	0
Cetuximab-Chemotherapy	94	82	43	18	8	3	2	2	0	0	0	0

Non-Taxane



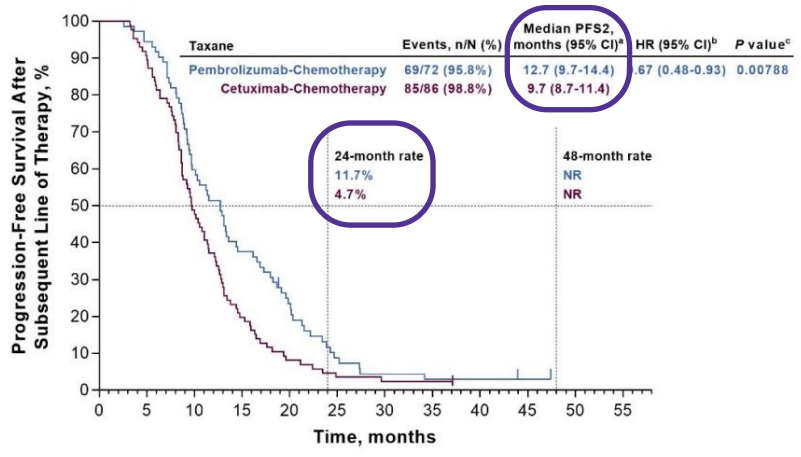
No. at Risk

Pembrolizumab	134	114	57	27	12	9	7	4	2	2	1	0
Cetuximab-Chemotherapy	71	62	43	22	13	7	6	5	2	1	0	0

PFS2 on taxane-containing 2nd line therapy was similar for pembrolizumab alone versus cetuximab-CT* whereas on non-taxane-containing 2nd line therapy was numerically shorter for pembrolizumab alone versus cetuximab-CT

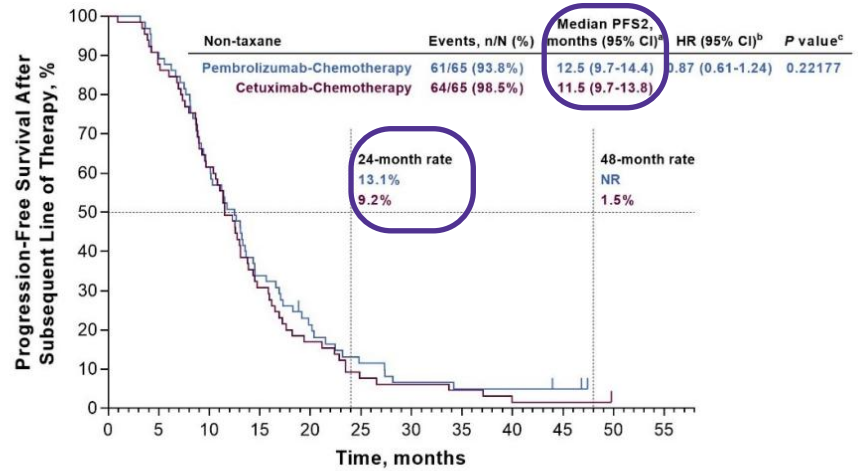
PFS2 on taxane-containing 2nd line therapy was longer for pembrolizumab-CT versus cetuximab-CT* whereas on non-taxane-containing 2nd line therapy was similar for pembrolizumab alone versus cetuximab-CT

Pembrolizumab chemotherapy vs. Cetuximab + CT*



No. at Risk

Pembrolizumab-Chemotherapy	72	68	43	27	16	6	3	2	2	1	0	0
Cetuximab-Chemotherapy	86	77	42	17	7	3	2	2	0	0	0	0



No. at Risk

Pembrolizumab-Chemotherapy	65	58	40	22	13	7	4	3	3	2	0	0
Cetuximab-Chemotherapy	65	57	40	20	11	5	4	3	1	1	0	0

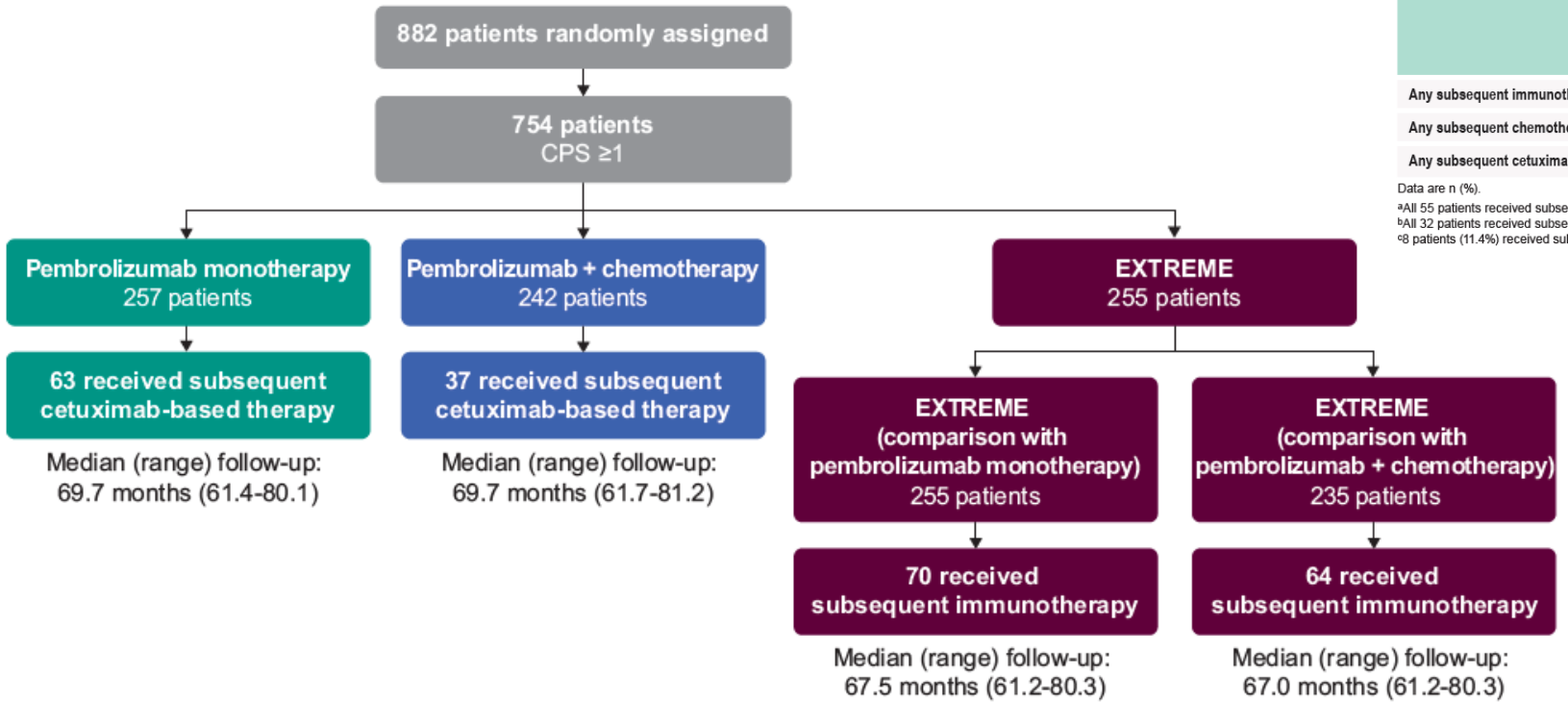
*Cetuximab is indicated in combination with a platinum-based CT in R/M SCCHN; Cetuximab + taxanes only are currently not approved for R/M SCCHN.

Kevin J. Harrington et al., Journal of Clinical Oncology 2023 41:4, 790-802

Treatment sequencing in PD-L1 Positive R/M SCCHN: Exploratory Analysis of the Phase 3 KEYNOTE-048 Study

Post-hoc exploratory analysis of **OS** in patients with R/M SCCHN who had tumors that expressed PD-L1 (**CPS ≥ 1**) and received:

- **1L Pembrolizumab monotherapy → cetuximab-based therapy** (87% cetuximab + CT, 13% cetuximab monotherapy)
- **1L Pembrolizumab + platinum-based QT + 5-FU → cetuximab-based therapy** (86% cetuximab + CT, 14% cetuximab monotherapy)
- **1L EXTREME → IO**



Subsequent therapy

Table 2. Summary of any subsequent therapy following treatment discontinuation

	Pembrolizumab→ Cetuximab-Based Therapy n = 63	Pembrolizumab + Chemotherapy→ Cetuximab-Based Therapy n = 37	EXTREME→IO n = 70
Any subsequent immunotherapy	13 (21)	10 (27)	70 (100)
Any subsequent chemotherapy	55 (87)[a]	32 (86)[b]	40 (57)[c]
Any subsequent cetuximab monotherapy	8 (13)	5 (14)	1 (1.4)

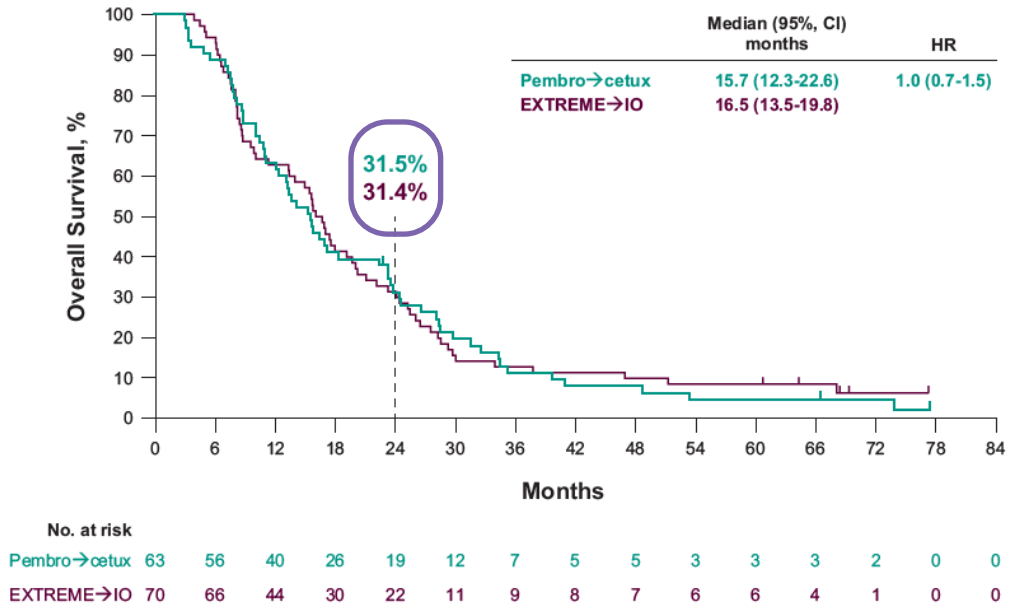
Data are n (%).

[a]All 55 patients received subsequent chemotherapy + cetuximab.
[b]All 32 patients received subsequent chemotherapy + cetuximab.
[c]8 patients (11.4%) received subsequent chemotherapy + cetuximab.

Greil R, Burtness B et al. Presented at ESMO Immuno-Oncology December 6-8 2023

Treatment sequencing in PD-L1 Positive R/M SCCHN: Exploratory Analysis of the Ph

A



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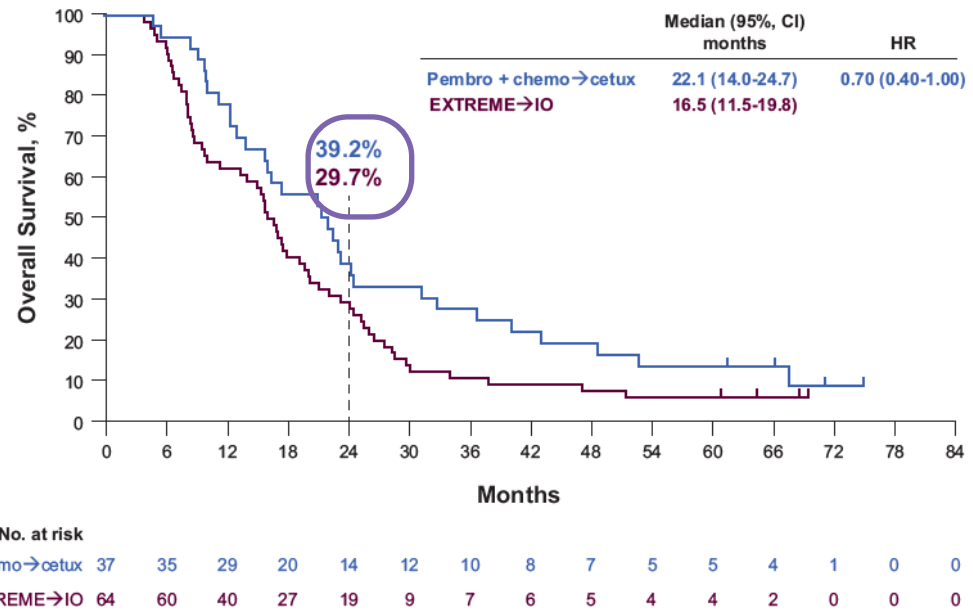

Conclusions[1]

- **OS** was **similar** for patients who received **Pembrolizumab monotherapy → cetuximab-based regimen** (**15,7 months**) compared with patients who received **EXTREME→IO** (**16,5 months**); HR 1.0 (0.7-1.5)
- **OS** was **numerically superior** in **Pembro + CT → cetuximab-based regimen** (**22,1 months**) compared with **EXTREME → IO** (**16,5 months**), HR 0.70 (0.40-1.0)
- Findings from this exploratory post-hoc analysis of KEYNOTE-048 should be interpreted with caution

1. Greil R, Burtness B et al. Presented at ESMO Immuno-Oncology December 6-8 2023

CONCLUSIONES

- **Datos actualizados de los estudios con QT (EXTREME, ERBITAX, TPEX) que mostraban los primaros hallazgos**
- Resultados a largo plazo del CHECKMATE140 **con nivolumab (HANNA) muestran tasas de LS tanto para pacientes plat**
- **Datos del KEYNOTE 048 con Pembrolizumab en seguimiento a 48 meses también nos muestran LS.**
- El uso de **tratamientos en SECUENCIA** aumenta las SLP y las SG de forma notable con la aplicacion de la segunda línea
- La secuencia funciona en **ambos sentidos**: QT (con cetuximab) seguida de IO e IO (sola o con QT) seguida de QT
- La **optimización** de la secuencia terapéutica depende de factores clínicos y moleculares que nos hagan priorizar un esque

¡MUCHAS GRACIAS POR VUESTRA ATENCIÓN!