Jornada sobre Cáncer de Cabeza y Cuello

Miércoles,
12 de diciembre de 2018
Hotel Melía Recoletos I Valladolid

Cáncer de Cabeza y Cuello Recurrente y Metastásico: Inmunoterapia en primera línea.

Dr. Carlos García Girón.
Hospital Universitario de Burgos.

Organiza

Asociación Castellano-Leonesa de Oncología

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Colabora

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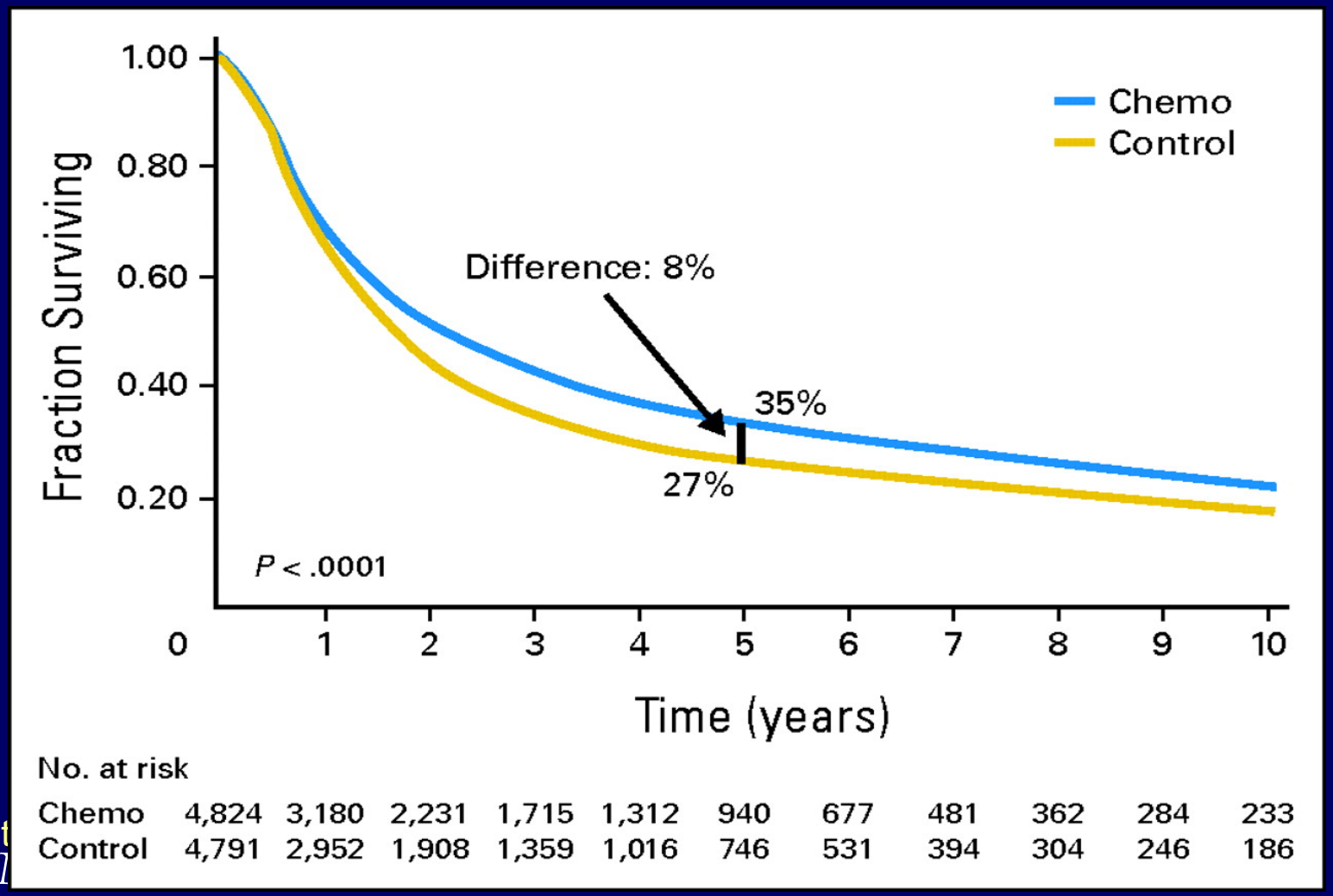
Secretaría Técnica I Información

menycep

meta-análisis en ccc
VALOR DE LA QUIMIOTERAPIA



MACH-1

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Pignon JP, et al. Lancet 2000;355:949-55. ASCO 2004: # 5.505

Population-Based Study of Competing Mortality in Head and Neck Cancer

Brent S. Rose, Jong-Hyeon Jeong, Sameer K. Nath, Sharon M. Lu, and Loren K. Mell

Cumulative incidences of competing causes of death in patients with head and neck cancer.

Characteristic	No.	%
Total No. of patients	34,568	
Age, years		
Mean	62.5	
Range	18-103	
Stage		
Localized	11,125	32.2
Regional	23,443	67.8
Site		
Hypopharynx	2,744	7.9
Larynx	12,652	36.6
Nasopharynx	1,776	5.1
Oral cavity	6,276	18.2
Oropharynx	11,120	32.2
Postoperative	16,218	46.9

JCO 2011;29:3503-3509

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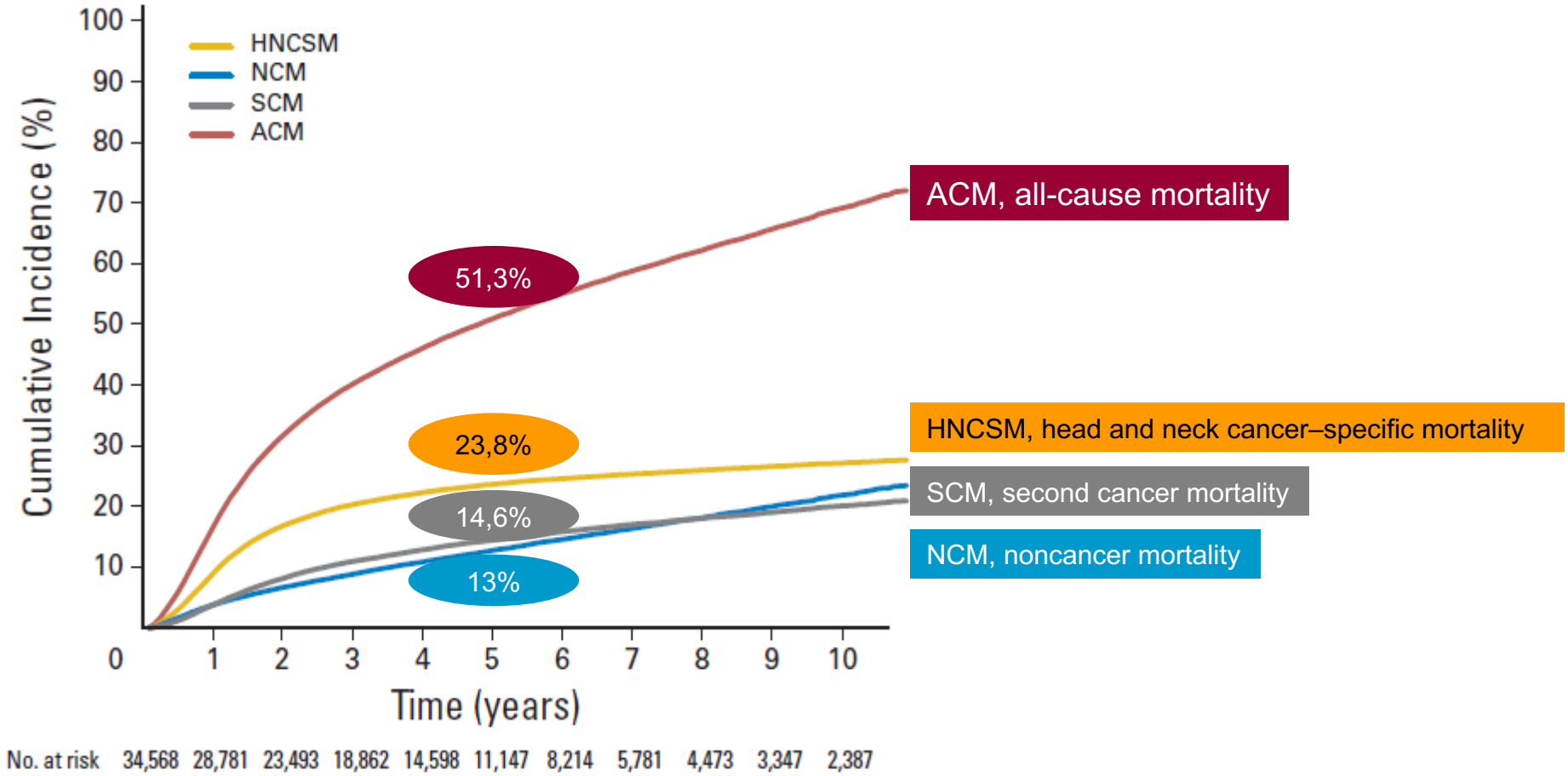
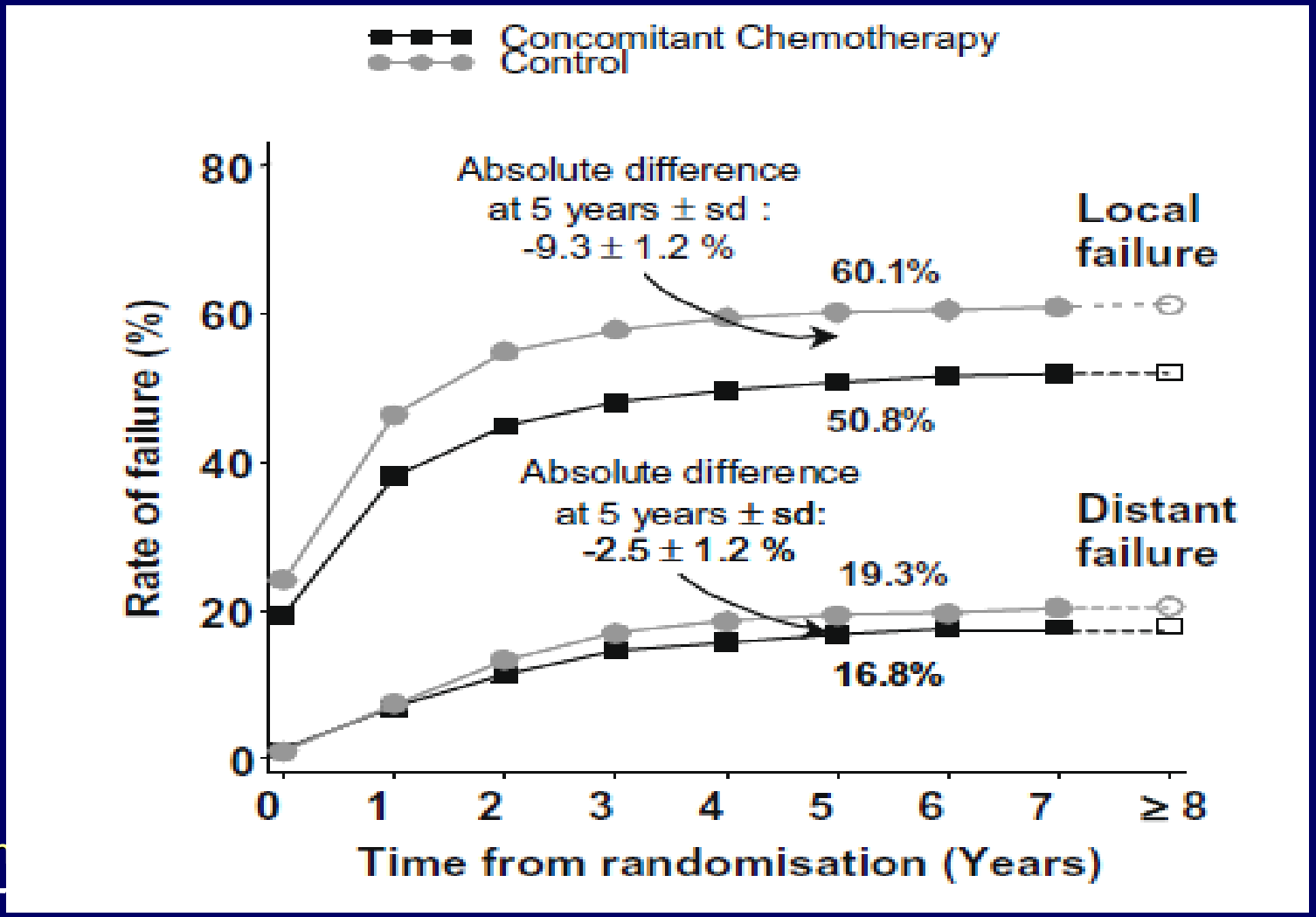


JCO 2011;29:3503-3509

meta-análisis en ccc
VALOR DE LA QUIMIOTERAPIA



MACH-

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Pignon JP, et al. Lancet 2000;355:949-55. ASCO 2004: # 5.505

meta-análisis en ccc
VALOR DE LA QUIMIOTERAPIA

Category		No. Deaths / No. Entered LRT + CT	LRT
Stage			
I-II	53%	133/251	155/286
III	58%	661/1140	699/1094
IV	69%	2268/3266	2430/3261
Site			
Oral cavity	68%	680/997	754/1020
Oropharynx	65%	1123/1723	1219/1681
Larynx	60%	607/1013	644/1012
Hypopharynx	72%	546/760	563/757
Others		187/264	183/256

MACH

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Pignon JP, et al. Lancet 2000;355:949-55. ASCO 2004: # 5.505

CÁNCER DE CABEZA Y CUELLO RECURRENTE Y/O METASTÁSICO

- Metastásico de inicio: 5%.

- Recaída o Progresión: 95%
  - Estadios I-II: 10%.
  - Estadios III: 20%.
  - Estadios IV A-B: 70%.

MONOTERAPIA EN CÁNCER DE CABEZA Y CUELLO RECURRENTE Y/O METASTÁSICO

FÁRMACO	Nº PACIENTES	R.O. (%)
CISPLATINO	288	28
CARBOPLATINO	169	22
FLUOROURACILO	118	15
METOTREXATE	988	31
PEMETREXED	35	26
GEMCITABINA	54	13
IXABEPILONE	50	10
TAXOL	174	26
TAXOTERE	161	29
VINORELBINA	102	18
IFOSFAMIDA	120	23
TOPOTECAN	43	14
BLEOMICINA	347	21
SORAFENIB	27	4 (EE: 37%)
ERLOTINIB	115	4 (EE: 38%)
GEFITINIB	526	1-11 (EE: 26-43%)
CETUXIMAB	103	13 (EE: 33%)
LAPATINIB	42	0 (EE: 20-37%)

PLATINO-FU EN CÁNCER DE CABEZA Y CUELLO RECURRENTE Y/O METASTÁSICO

Autor, año	Nº Pacientes	TRATAMIENTO	R.O. (%)	MST (mes)
Jacobs, 92	249	CDDP-FU	32*	5,5
		CDDP	17	5
		FU	13	6,1
Forastiere, 92	277	CDDP-FU	32*	6,6
		CBDCA-FU	21	5
		MTX	10	5,6
Liverpool, 92	200	CDDP-FU	12	NA
		CDDP-MTX	11	NA
		CDDP	14	NA
		MTX	6	NA

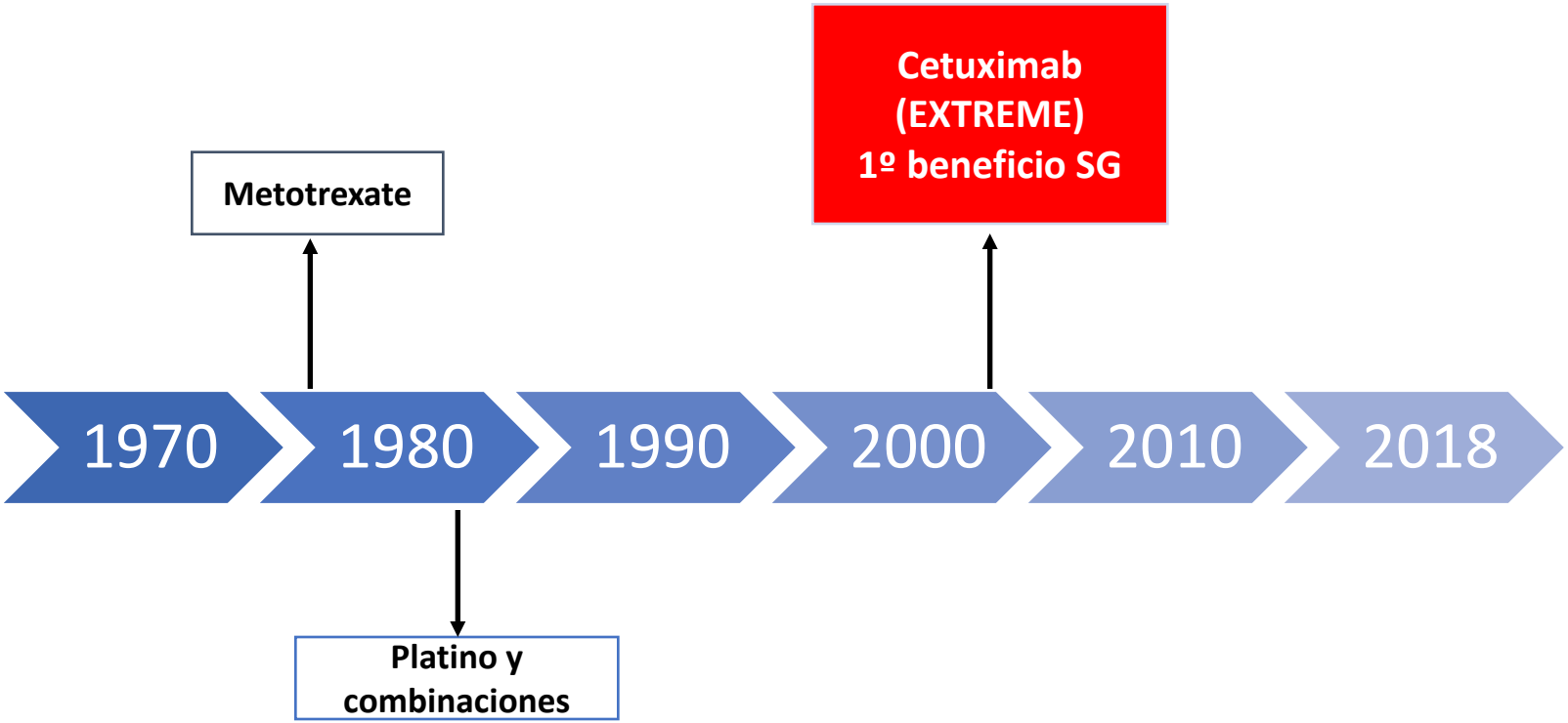
PLATINO-FU EN CÁNCER DE CABEZA Y CUELLO RECURRENTE Y/O METASTÁSICO

Autor, año	Nº Pacientes	TRATAMIENTO	R.O. (%)	MST (mes)
Clavel, 94	382	CDDP-MTX-BLEO-VCR	34*	8,2
		CDDP-FU	31*	6,2
		CDDP	15	5,3
Schrijvers, 98	122	CDDP-FU-IFN	38	6
		CDDP-FU	47	6,3
Gibson, 05	218	CDDP-FU	30	8,7
		CDDP-TAXOL	26	8,1

PLATINO-FU EN CÁNCER DE CABEZA Y CUELLO RECURRENTE Y/O METASTÁSICO

- **CÁNCER DE CABEZA Y CUELLO RECURRENTE O METASTÁSICO:**
  - **QT PALIATIVA.**
    - **R.O.: 30-50% (R.C.: 5-10%).**
    - **MST: 6-8 meses.**

Evolución del tratamiento del CECC recurrente/metastásico



Cetuximab plus platinum/5-FU is active in first-line R/M SCCHN

- **Phase I/II study in 53 patients**
- **3-weekly cycles of:**
  - Cisplatin or carboplatin
  - 5-FU at dose escalation
  - Cetuximab
- **Overall response rate = 36%**
- **Median overall survival = 9.8 mo (95 % CI : 8.0 ; 13.7)**
- **Treatment was generally well tolerated with the highest doses of platinum and 5-FU. The most common grade 3/4 adverse events were:**
  - Leucopenia 38%
  - Asthenia 25%
  - Thrombocytopenia 15%

Bourhis et al. J Clin Oncol 2006;24:2866-2872

EXTREME

The NEW ENGLAND JOURNAL of MEDICINE

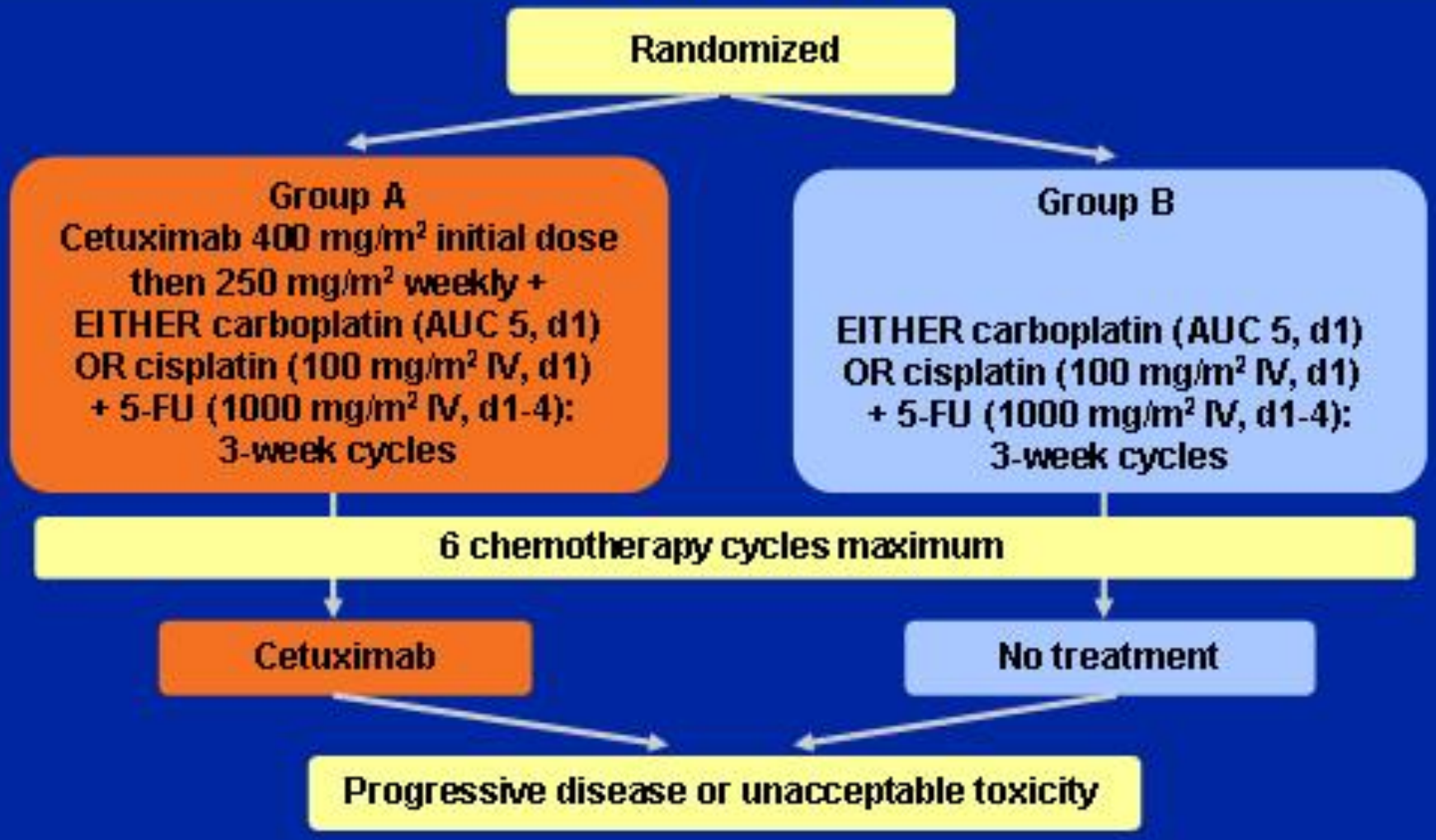
ORIGINAL ARTICLE

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Ricard Mesia, M.D., Fernando Rivera, M.D., Ph.D., Eva Remenar, M.D., Andrzej Kawecki, M.D., Ph.D., Sylvie Rottey, M.D., Ph.D., Jozsef Erfan, M.D., Dmytro Zabolotnyy, M.D., Ph.D., Heinz-Roland Kienzer, M.D., Didier Cupissol, M.D., Frederic Peyrade, M.D., Marco Benasso, M.D., Ihor Vynnychenko, M.D., Ph.D., Dominique De Raucourt, M.D., Carsten Bokemeyer, M.D., Armin Schueler, M.S., Nadia Amellal, M.D., and Ricardo Hitt, M.D., Ph.D.

N Engl J Med 2008;359:1116-27.

EXTREME
Study design



ASCO 2007

EXTREME
Main inclusion and exclusion criteria

- **Inclusion criteria:**
  - R/M SCCHN, unsuitable for local therapy
  - KPS ≥70 at study entry
  - ≥ 1 bi-dimensionally measurable lesion (by MRI or CT scan)
  - Adequate hematologic, hepatic and renal function

- **Exclusion criteria:**
  - Surgery or irradiation within 4 weeks of study entry
  - Prior chemotherapy (except if given as part of treatment for locally advanced disease >6 months before study entry)
  - Nasopharyngeal carcinoma
  - Other concomitant anticancer therapies

ASCO 2007

EXTREME
Study endpoints

- **Primary endpoint:**
  - overall survival time (OS)
- **Secondary endpoints:**
  - duration of response
  - time to progression
  - response rate
  - assessment of quality of life (QoL)
  - safety

ASCO 2007

EXTREME

Table 1. Baseline Characteristics of the Patients.*

Variable	Cetuximab plus Platinum–Fluorouracil (N=222)	Platinum–Fluorouracil Alone (N=220)
Sex — no. (%)		
Male	197 (89)	202 (92)
Female	25 (11)	18 (8)
Age		
Median age — yr	56	57
<65 yr — no. (%)	183 (82)	182 (83)
≥65 yr — no. (%)	39 (18)	38 (17)
Karnofsky score		
Median score	80	80
Primary tumor site — no. (%)		
Oropharynx	80 (36)	69 (31)
Hypopharynx	28 (13)	34 (15)
Larynx	59 (27)	52 (24)
Oral cavity	46 (21)	42 (19)
Other	9 (4)	23 (10)
Extent of disease — no. (%)		
Only locoregionally recurrent	118 (53)	118 (54)
Metastatic with or without locoregional recurrence	104 (47)	102 (46)
Previous treatment — no. (%)		
Chemotherapy	90 (41)	80 (36)
Radiotherapy	189 (85)	190 (86)

N Engl J Med 2008;359:1116-27.

EXTREME

Table 1. Baseline Characteristics of the Patients.*

Variable	Cetuximab plus Platinum–Fluorouracil (N=222)	Platinum–Fluorouracil Alone (N=220)
Previous treatment — no. (%)		
Chemotherapy	90 (41)	80 (36)
Radiotherapy	189 (85)	190 (86)

170 ptes QT previa:

-RT+QT: 76%.

-QT neoadyuvante: 33%.

-Ambos: 9,5%

N Engl J Med 2008;359:1116-27.

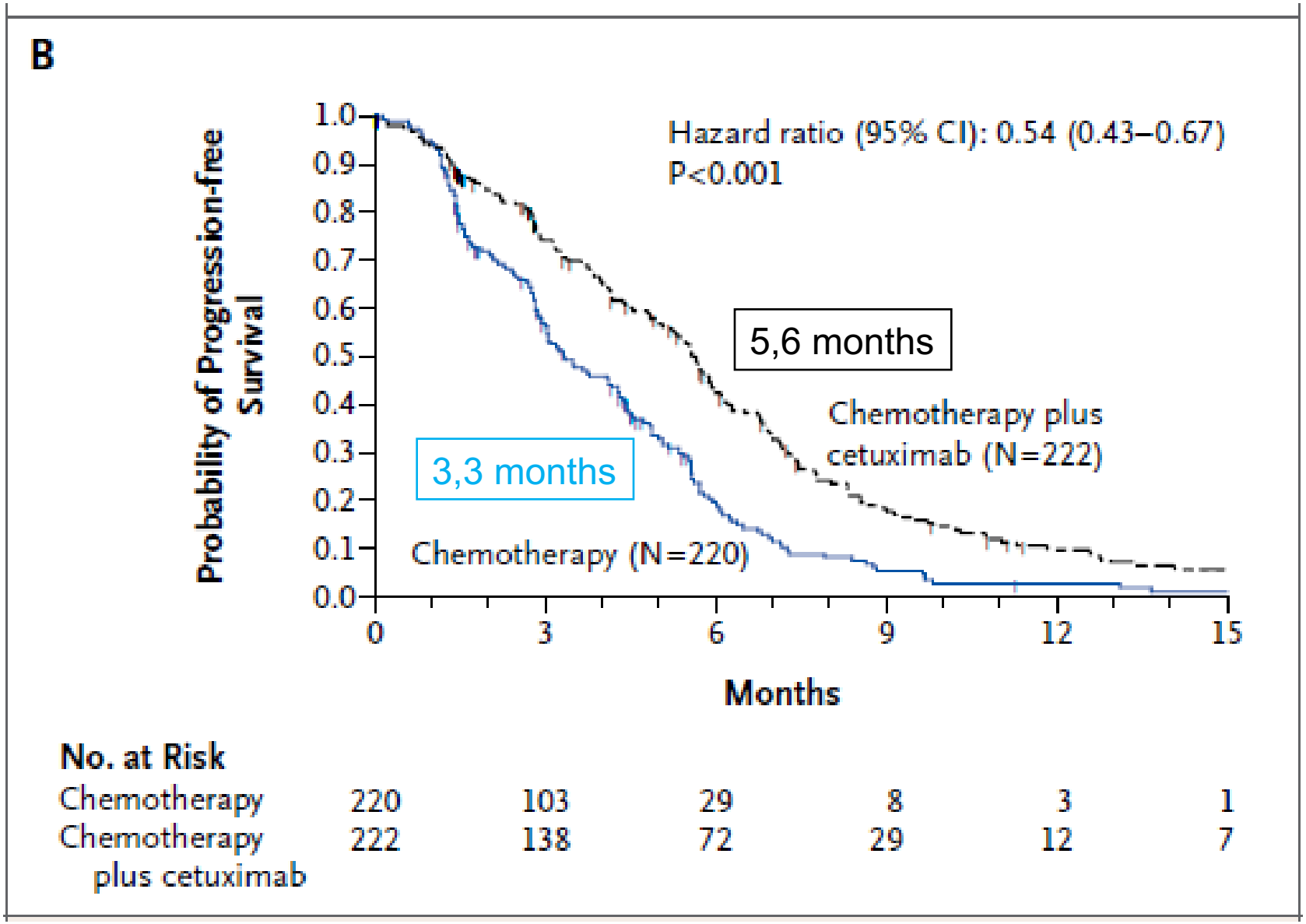
EXTREME

Table 2. Responses to Treatment and Survival.*

Variable	Cetuximab plus Platinum–Fluorouracil (N=222)	Platinum–Fluorouracil Alone (N=220)	Hazard Ratio or Odds Ratio (95% CI)	P Value
Survival — mo†				
Overall	10.1 (8.6–11.2)	7.4 (6.4–8.3)	Hazard ratio, 0.80 (0.64–0.99)	0.04‡
Progression-free	5.6 (5.0–6.0)	3.3 (2.9–4.3)	Hazard ratio, 0.54 (0.43–0.67)	<0.001‡
Best response to therapy — %				
Overall	36 (29–42)	20 (15–25)	Odds ratio, 2.33 (1.50–3.60)	<0.001§
Disease control¶	81 (75–86)	60.0 (53–67)	Odds ratio, 2.88 (1.87–4.44)	<0.001§
Time to treatment failure — mo†	4.8 (4.0–5.6)	3.0 (2.8–3.4)	Hazard ratio, 0.59 (0.48–0.73)	<0.001‡
Duration of response — mo‖	5.6 (4.7–6.0)	4.7 (3.6–5.9)	Hazard ratio, 0.76 (0.50–1.17)	0.21‡

N Engl J Med 2008;359:1116-27.

EXTREME



N Engl J Med 2008;359:1116-27.

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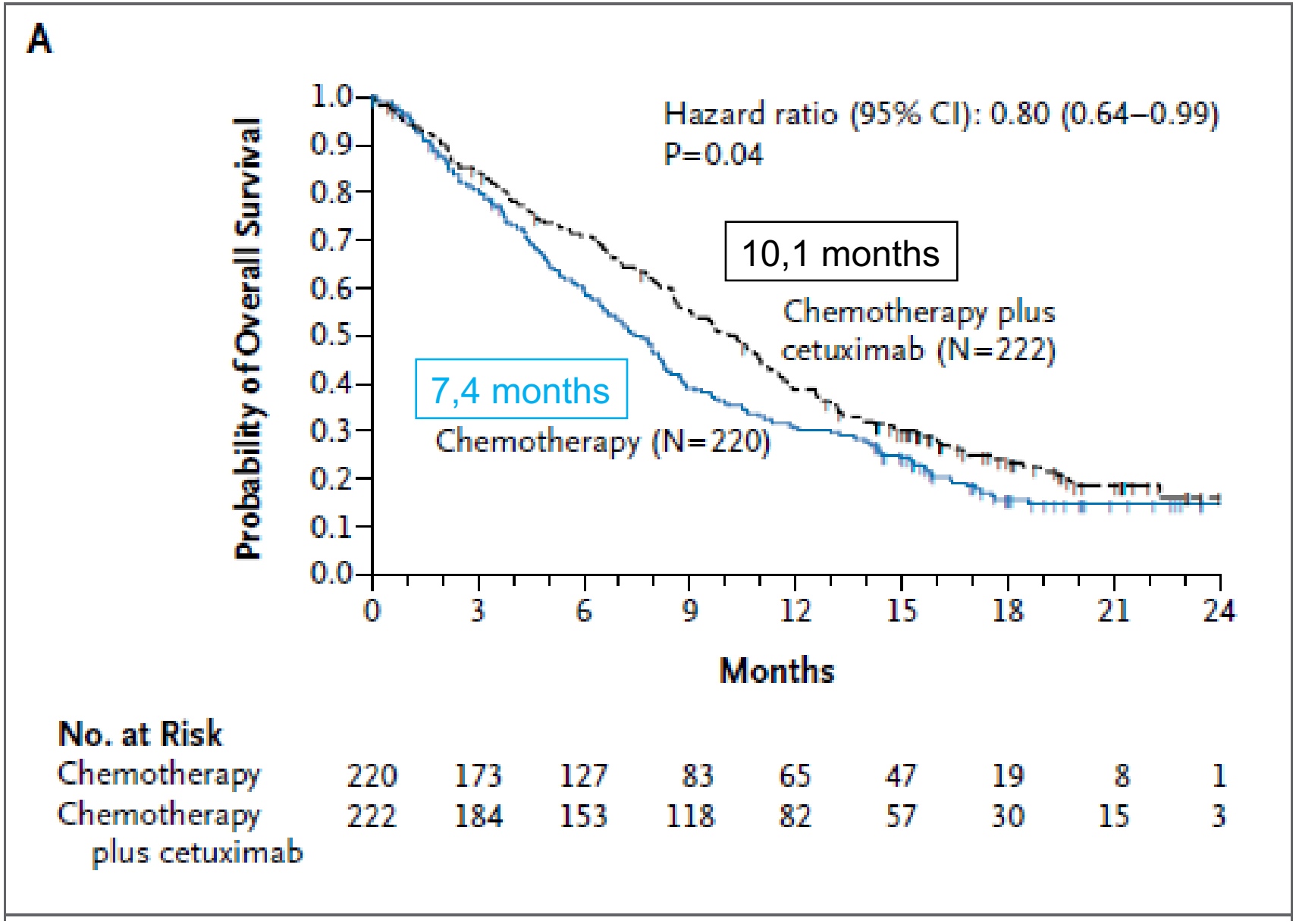

N Engl J Med 2008;359:1116-27.

Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial

Jan B Vermorken, Jan Stöhlmacher-Williams, Irina Davidenko, Lisa Licitra, Eric Winquist, Cristian Villanueva, Paolo Foa, Sylvie Rottey, Krzysztof Skladowski, Makoto Tahara, Vasant R Pai, Sandrine Faivre, Cesar R Blajman, Arlene A Forastiere, Brian N Stein, Kelly S Oliner, Zhiying Pan, Bruce A Bach, on behalf of the SPECTRUM investigators

Findings Between May 15, 2007, and March 10, 2009, we randomly assigned 657 patients: 327 to the panitumumab group and 330 to the control group. Median overall survival was 11·1 months (95% CI 9·8–12·2) in the panitumumab group and 9·0 months (8·1–11·2) in the control group (hazard ratio [HR] 0·873, 95% CI 0·729–1·046; p=0·1403). Median progression-free survival was 5·8 months (95% CI 5·6–6·6) in the panitumumab group and 4·6 months (4·1–5·4) in the control group (HR 0·780, 95% CI 0·659–0·922; p=0·0036). Several grade 3 or 4 adverse events

Lancet Oncol 2013; 14: 697–710

CLINICAL PROGNOSTIC FACTORS IN PATIENTS (PTS) WITH RECURRENT AND/OR METASTATIC (RM) HEAD AND NECK CARCINOMA (HNC) TREATED WITH CETUXIMAB PLUS CHEMOTHERAPY.

Bossi P.[1], Depenni R.[2], Cossu Rocca M.[3], Ferrari D.[4], Azzarello G.[5], Pugliese G.[2], Alù M.[6], Nole' F[3], Codecà' C[4], Boscolo G[5], Piccininni M.[7], Cavalieri S.[1], Licitra L[1].

297 ptes R-M

In non-selected RM HNC pts, we obtained a median PFS and OS of 4.8 and 10.8 months, very similar to 5.6 and 10.1 months reported in Extreme trial (Vermorken et al. 2008).

At baseline, PS > 0, residual tumor at primary site and platinum resistance could be used to define patient prognosis.

Response to the treatment is a strong prognostic indicator.

ESMO, 2018

original article

Annals of Oncology 00: 1–7, 2015
doi:10.1093/annonc/mdv268

Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study

J. Guigay[1,2*], J. Fayette[3], A. F. Dillies[4], C. Sire[5], J. N. Kerger[6], I. Tennevet[7], J. P. Machiels[8], S. Zanetta[9], Y. Pointreau[10], L. Bozec Le Moal[11], S. Henry[12], A. Schilf[13] & J. Bourhis[14]

Patients and methods: Patients with a histologically confirmed HNSCC with metastasis or recurrence unsuitable for locoregional curative treatment received docetaxel and cisplatin (75 mg/m^2 both) at day 1 and weekly cetuximab 250 mg/m^2 (loading dose of 400 mg/m^2), repeated every 21 days for four cycles, followed by maintenance cetuximab 500 mg/m^2 every 2 weeks until progression or unacceptable toxicity. Prophylactic administration of granulocyte colony-stimulating factor was done systematically after each chemotherapy cycle. Patients had a good general status (performance status $\leq$1) and were under 71 years. Prior total doses of cisplatin exceeding 300 mg/m^2 were not allowed. The primary end point was objective response rate (ORR) after four cycles.

Results: Fifty-four patients were enrolled. The primary end point was met with an ORR of 44.4% (95% CI 30.9–58.6). Median overall and progression-free survivals were, respectively, 14 months (95% CI 11.3–17.3) and 6.2 months (95% CI 5.4–7.2). The most common grade 3/4 adverse events were skin rash (16.6%) and non-febrile neutropenia (20.4%).

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Clinical Trial Results

Weekly Docetaxel, Cisplatin, and Cetuximab in Palliative Treatment of Patients with Squamous Cell Carcinoma of the Head and Neck

Vanessa Trieu,[a] Harlan Pinto,[b] Jonathan W. Riess,[c] Ruth Lira,[d] Richard Luciano,[e] Jessie Coty,[e] Derek Boothroyd,[f] A. Dimitrios Colevas[b]

curative treatment. Patients received cisplatin 30 mg/m^2 or carboplatin area under the curve (AUC) 2, docetaxel 30 mg/m^2, and cetuximab 250 mg/m^2 weekly for 3 weeks, followed by a break during the fourth week, for a 28-day cycle. Planned intrapatient dose modifications were based on individual toxicity.

Results. Twenty-seven patients received TPC and were evaluable for response and toxicity. Rates of complete response (CR), partial response (PR), and confirmed PR were 3%, 52%, and 30%, respectively. The overall objective response rate was 56%. Estimated median PFS and OS were 4.8 and 14.7 months,

The Oncologist 2018;23:764-e86

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 1004–1009, 2018
doi:10.1093/annonc/mdy040
Published online 2 February 2018

ORIGINAL ARTICLE

Phase II trial of combination treatment with paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CSPOR-HN02)

M. Tahara[1*], N. Kiyota[2], T. Yokota[3], Y. Hasegawa[4], K. Muro[5], S. Takahashi[6], T. Onoe[7], A. Homma[8], J. Taguchi[9], M. Suzuki[10], K. Minato[11], K. Yane[12], S. Ueda[13], H. Hara[14], K. Saijo[15] & T. Yamanaka[16]

Patients and methods: Eligibility criteria included recurrent and/or metastatic, histologically proven SCC of the oropharynx, oral cavity, hypopharynx or larynx; PS 0-1; adequate organ function; no suitable local therapy for R/M SCCHN; and no prior systemic chemotherapy for R/M SCCHN. Chemotherapy consisted of paclitaxel 100 mg/m^2 on days 1, 8; carboplatin area under the blood concentration-time curve 2.5 on days 1, 8, repeated every 3 weeks for up to 6 cycles; and cetuximab at an initial dose of 400 mg/m^2, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicities. Primary end point was overall response rate. Secondary end points were safety, treatment completion rate, progression-free survival, overall survival, and clinical benefit rate. Planned sample size was 45 patients.

Results: Forty-seven subjects were accrued from July 2013 to October 2014. Of 45 evaluable, 40 were male; median age was 63 years; Eastern Cooperative Oncology Group Performance Status was 0/1 in 23/22 cases; site was the hypopharynx/oropharynx/oral cavity/larynx in 17/11/10/7 cases; and 36/9 cases were smokers/nonsmokers, respectively. Overall response rate, the primary end point, was 40%. Median overall survival was 14.7 months and progression-free survival was 5.2 months.

CCC R-M: 1ª línea de tratamiento

	RO	**SLP** (mes)	**SG** (mes)
Platino-Fu-Cetuximab (Extreme)	36%	5-6	10-11
Cisplatino-Taxano-Cetuximab (TPEx)	40-50%	5-6	11-14

Randomized phase II multicenter study comparing modified PFE regimen with modified TPEx regimen in recurrent or metastatic squamous cell carcinoma of the head and neck: TEMPER study

Mototsugu Shimokawa[1], Motoyuki Suzuki[2], Masashi Sugasawa[3], Kiyoto Shiga[4], Taroh Satoh[5], Hidenori Inohara[2]

Recurrent or metastatic squamous cell carcinoma of the head and neck, PS 0-1, Age ≥ 20

R 1:1

Stratification factors
- PS (ECOG)
- p16-positive oropharynx carcinoma
- History of chemotherapy

n = 180

Group A (modified PFE group)
- CDDP 75 mg/m²/3 weeks
- 5-FU 750 mg/m²/3 weeks days 1-5
- CEX (Initial dose: 400 mg/m²
  Maintenance dose: 250mg/m²/week)
  × 6 cycles

n = 180

Group B (modified TPEx group)
- DTX 60 mg/m²/3 weeks
- CDDP 60 mg/m²/3 weeks
- CEX (Initial dose: 400 mg/m²
  Maintenance dose: 250 mg/m²/week)
  × 4 cycles

Cases for which the "response better than SD" was achieved.

Maintain CEX at a dose of 250 mg/m2/week

Treatment until progression (PD) or unacceptable toxicity emerges.
If treatment cannot be continued,
track outcome (1 year after last patient registered).

- **Actual accrual: Oct.2017 -**
- **Enrollment: 14 (31.Aug, 2018)**

ESMO, 2018

Phase II study of combination cetuximab and weekly paclitaxel in patients with recurrent and/or metastatic squamous cell carcinoma of head and neck (SCCHN)

R. Hitt, A. Irigoyen, J. Nuñez, J. Grau, J. García Saenz, M. Pastor, C. Jara, C. García Girón, M. Hidalgo, J. Cruz Hernández

Spanish Head and Neck Cancer Group (TTCC)

ASCO 2007

Cetuximab/paclitaxel in recurrent/metastatic SCCHN

Study design

Eligibility:

- KPS ≥ 70%
- Prior systemic chemotherapy is only allowed if given as part of a multimodal treatment for locally advanced disease which was completed > 6 months prior to study entry

Dosing schedule up to PD/toxicity:

- Paclitaxel 80 mg/m² IV weekly
- Cetuximab 400/250 mg/m² IV weekly

Response assessment (RECIST):

- CT/MRI every 6 weeks

ASCO 2007

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)

Best response	Number of patients (n = 46)	Percentage
CR	10	22
95% CI		11% to 36%
PR	15	33
95% CI		20% to 48%
Stable disease	12	26
95% CI		14% to 41%
Progressive disease	5	11
95% CI		4% to 23.6%
Not evaluable	4	9
Overall response rate	25	54
95% CI		39% to 69%
Disease control rate (CR + PR + stable disease)	37	80
95% CI		66% to 91%

Annals of Oncology 23: 1016–1022, 2012
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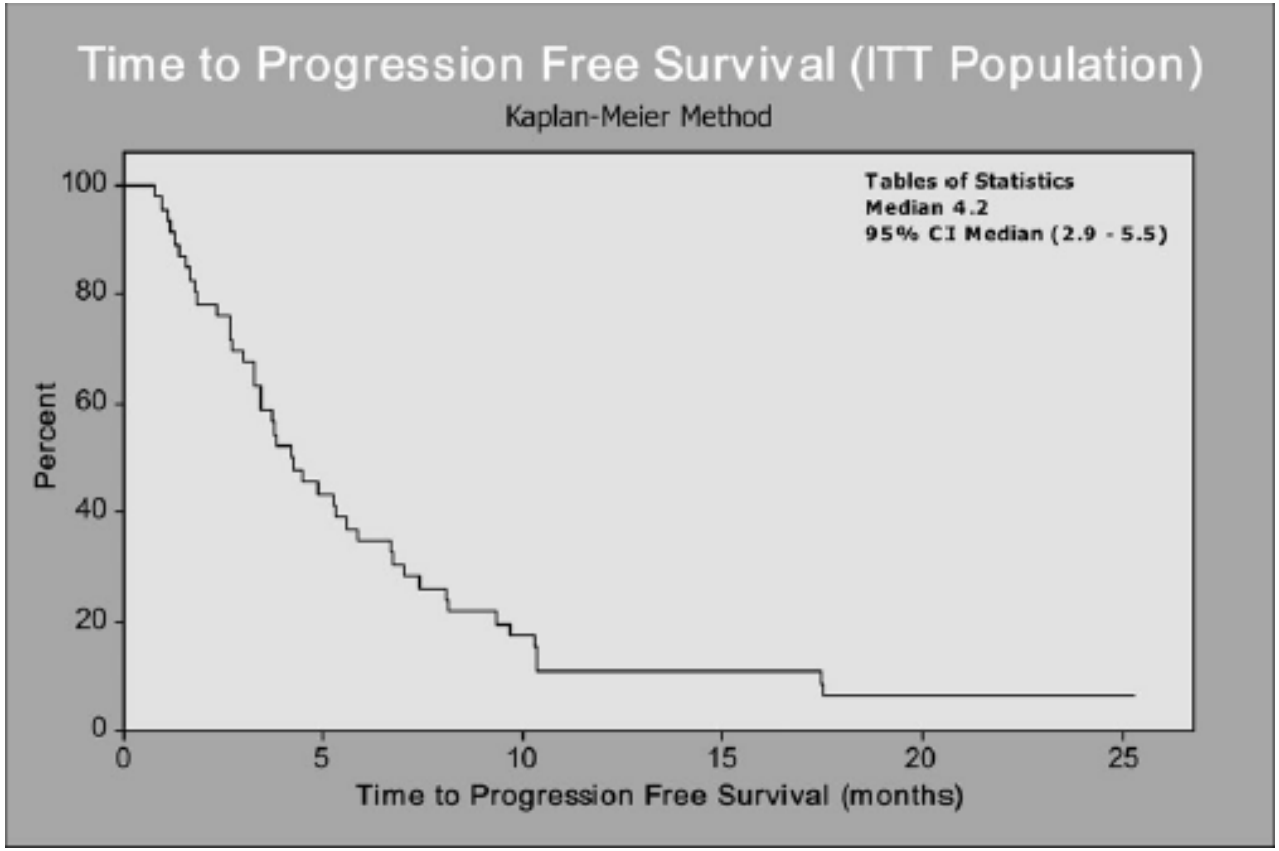

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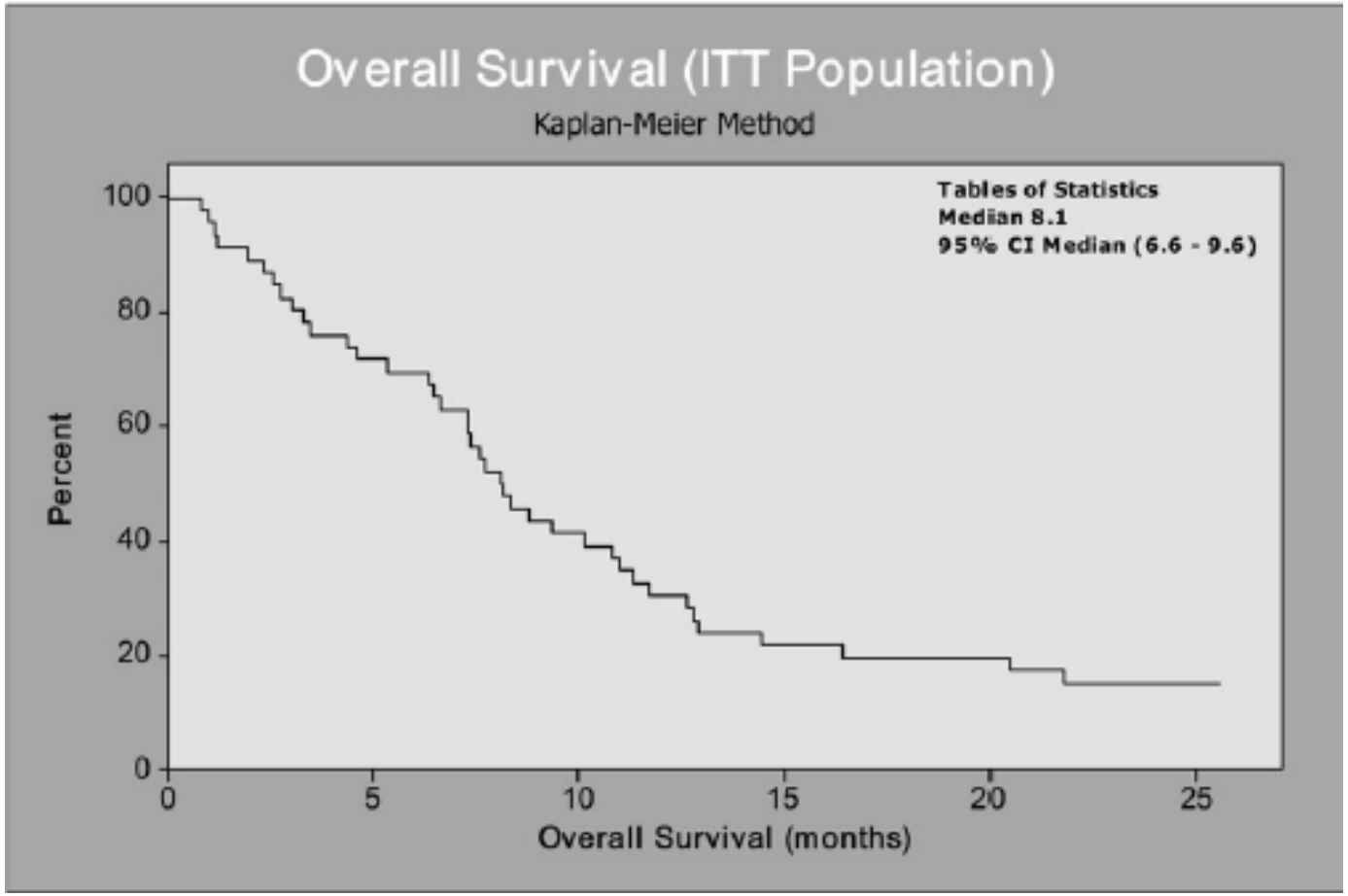


CCC R-M: 1ª línea de tratamiento

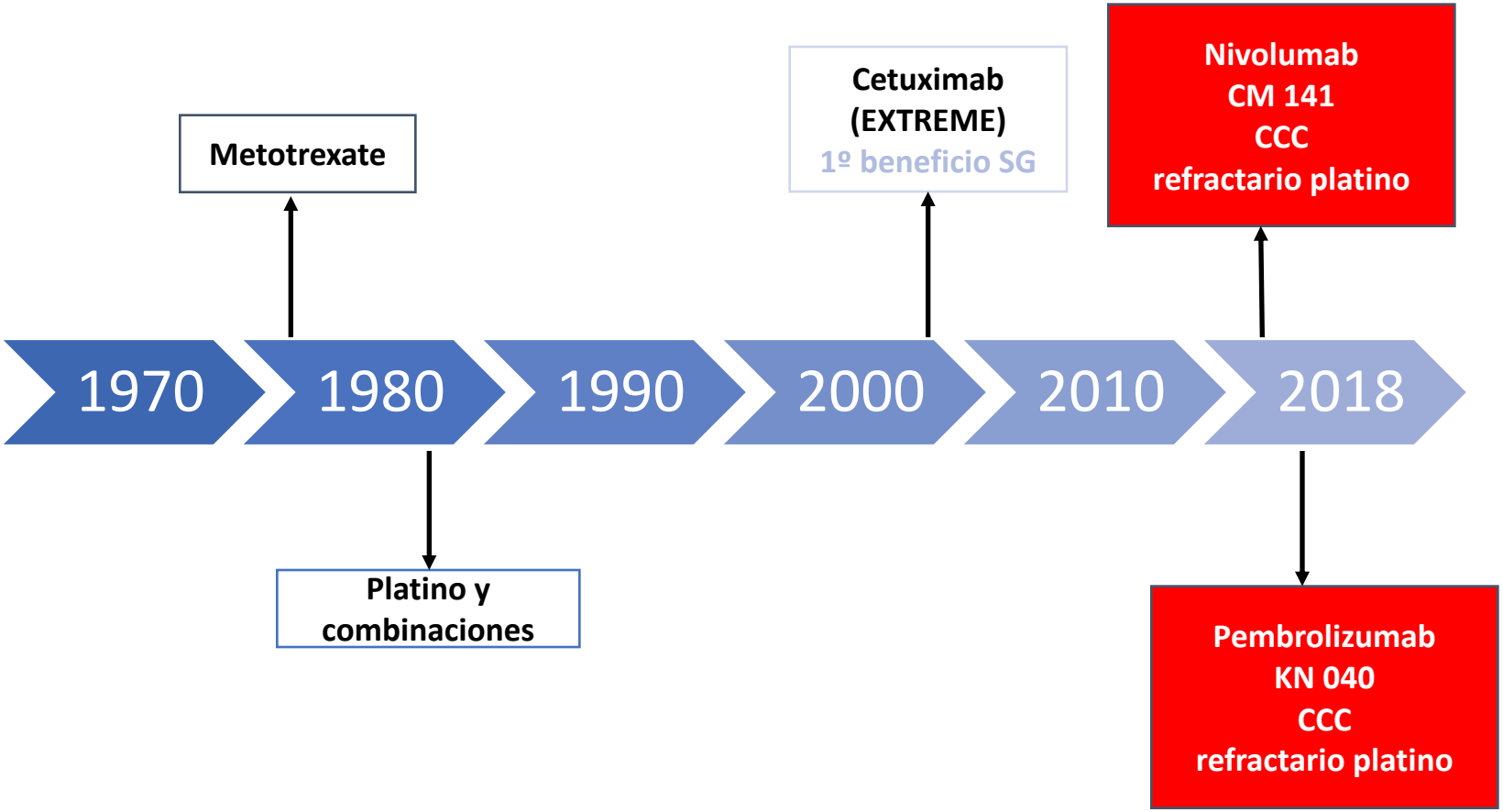
PE > 6 meses a QT (**Platino** neoadyuvante, concomitante, adyuvante): **Platino-sensible**.

-Platino-Fu-Cetuximab (Extreme)

-Platino-Taxano-Cetuximab (TPEx)

-Paclitaxel-Cetuximab (Erbitax)

Evolución del tratamiento del CECC recurrente/metastásico



CCC R-M: 1ª línea de tratamiento

PE > 6 meses a QT (**Platino** neoadyuvante, concomitante, adyuvante): **Platino-sensible**.

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-Platino-Taxano-Cetuximab (TPEx)

-Paclitaxel-Cetuximab (Erbitax)

PE ≤ 6 meses a QT (**Platino** neoadyuvante, concomitante, adyuvante y 1ª línea): **Platino-resistente**.

-Nivolumab (ChM 141)

-Pembrolizumab (PD-L1 ≥ 50%) (KN 040)

CCC R-M: 2ª línea de tratamiento

PE > 6 meses a 1ª línea QT con **Platino** (PF, PF+Cetuximab (Extreme), P-Taxano-Cetuximab (PTEx): **Platino-sensible**.

-Paclitaxel-Cetuximab (Erbitax)

-Cetuximab.

-Paclitaxel, Docetaxel.

-Metotrexate

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

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Burtness KN048 ESMO 2018

KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification Factors

- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R 1:1:1

Pembrolizumab Monotherapy → Pembrolizumab 200 mg Q3W for up to 35 cycles

Pembrolizumab + Chemotherapy → Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 35 cycles total

EXTREME → Cetuximab 250 mg/m^2 Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk) → Cetuximab 250 mg/m^2 Q1W

[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/m^2.

Burtness KN048 ESMO 2018

Study End Points: Pembrolizumab vs EXTREME and Pembrolizumab + Chemotherapy vs EXTREME

Primary

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - OS
  - PFS[b]

Secondary

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - PFS[b] rates at 6 and 12 mo
  - ORR[b]
  - Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)[c]
- Total population
  - Safety and tolerability

Key Exploratory

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - Duration of response[b]

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
[b]Assessed per RECIST v1.1 by blinded, independent central review.
[c]To be presented at a later date.

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Baseline Characteristics, ITT Population

Characteristic, n (%)	Pembro Alone vs EXTREME		Pembro + Chemo vs EXTREME	
	Pembro N = 301	EXTREME N = 300	Pembro + Chemo N = 281	EXTREME N = 278[a]
Age, median (range), yrs	62 (22-94)	61 (24-84)	61 (20-85)	61 (24-84)
Male	250 (83.1)	261 (87.0)	224 (79.7)	242 (87.1)
ECOG PS 1	183 (60.8)	183 (61.0)	171 (60.9)	170 (61.2)
Current/former smoker	239 (79.4)	234 (78.0)	224 (79.7)	215 (77.3)
p16 positive (oropharynx)	63 (20.9)	67 (22.3)	60 (21.4)	61 (21.9)
PD-L1 status				
TPS ≥50%	67 (22.3)	66 (22.0)	66 (23.5)	62 (22.3)
CPS ≥20	133 (44.2)	122 (40.7)	126 (44.8)	110 (39.6)
CPS ≥1	257 (85.4)	255 (85.0)	242 (86.1)	235 (84.5)
Disease status[b]				
Metastatic	216 (71.8)	203 (67.7)	201 (71.5)	187 (67.3)
Recurrent only[c]	82 (27.2)	94 (31.3)	76 (27.0)	88 (31.7)

[a]Patients randomized to EXTREME during the pembro + chemo enrollment hold were excluded from all pembro + chemo vs EXTREME efficacy comparisons.
[b]3 patients in the pembro arm, 3 patients in the EXTREME arm, and 4 patients in the pembro + chemo arm had neither metastatic nor recurrent disease.
[c]Includes locally recurrent disease and disease that spread to cervical lymph nodes. Data cutoff date: Jun 13, 2018.

Burtness KN048 ESMO 2018

KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification Factors

- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R (1:1:1)

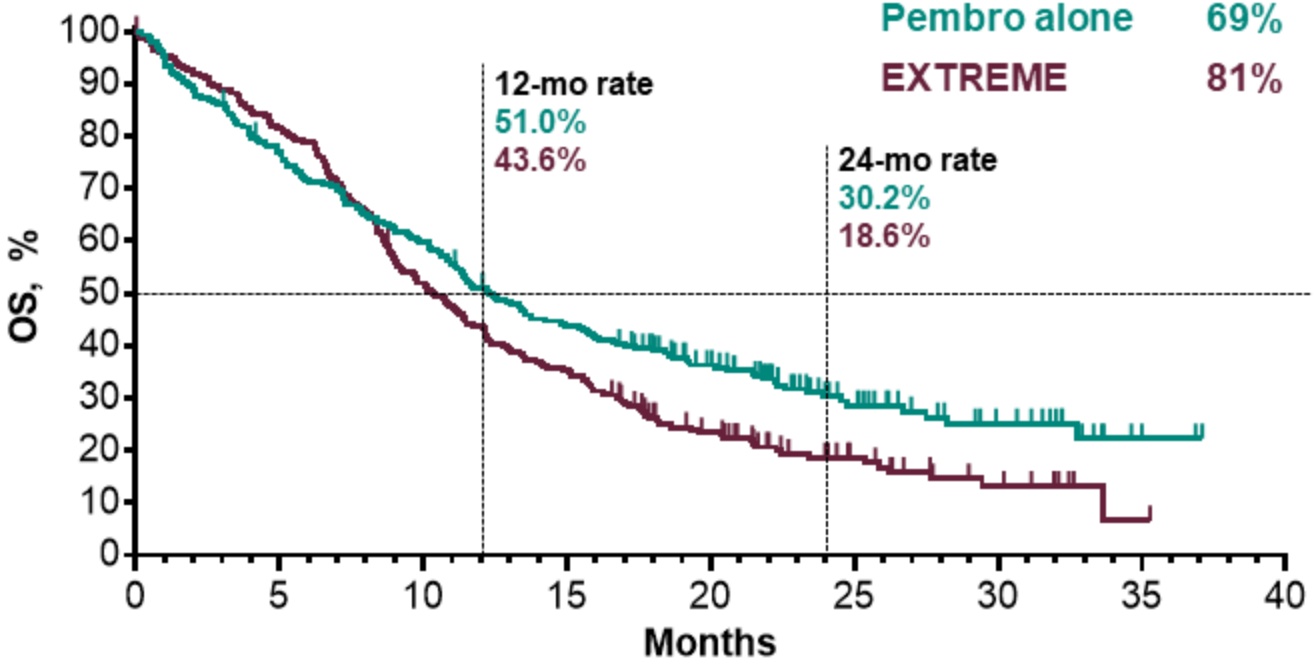
- Pembrolizumab 200 mg Q3W for up to 35 cycles
- Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 29 cycles
- Cetuximab 250 mg/m^2 Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk) → Cetuximab 250 mg/m^2 Q1W

[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/m^2.

Burtness KN048 ESMO 2018

Overall Survival: P vs E, CPS ≥1 Population

	Events	HR (95% CI)	*P*
Pembro alone	69%	0.78 (0.64-0.96)	0.0086
EXTREME	81%		



Median (95% CI)
12.3 mo (10.8-14.9)
10.3 mo (9.0-11.5)

No. at Risk

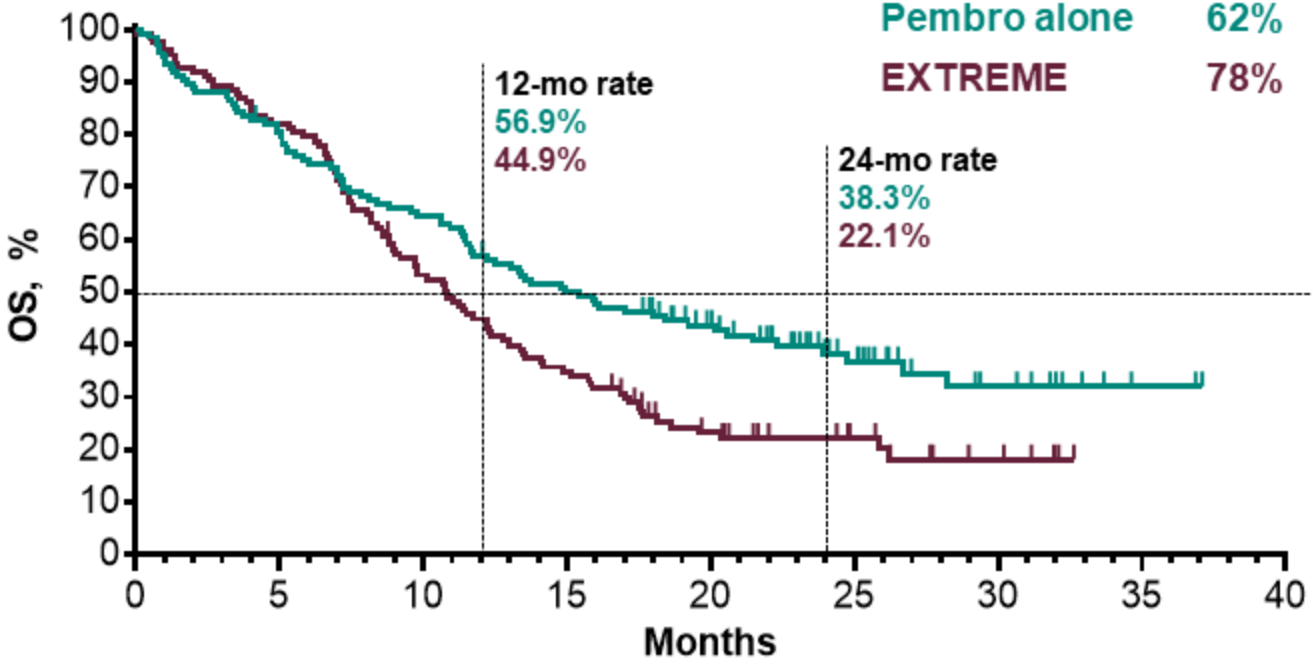
257	196	152	110	74	34	17	2	0
255	207	131	89	47	21	9	1	0

Data cutoff date: Jun 13, 2018.

Burtness KN048 ESMO 2018

Overall Survival: P vs E, CPS ≥20 Population

	Events	HR (95% CI)	*P*
Pembro alone	62%	0.61 (0.45-0.83)	0.0007
EXTREME	78%		



Median (95% CI)
14.9 mo (11.6-21.5)
10.7 mo (8.8-12.8)

No. at Risk

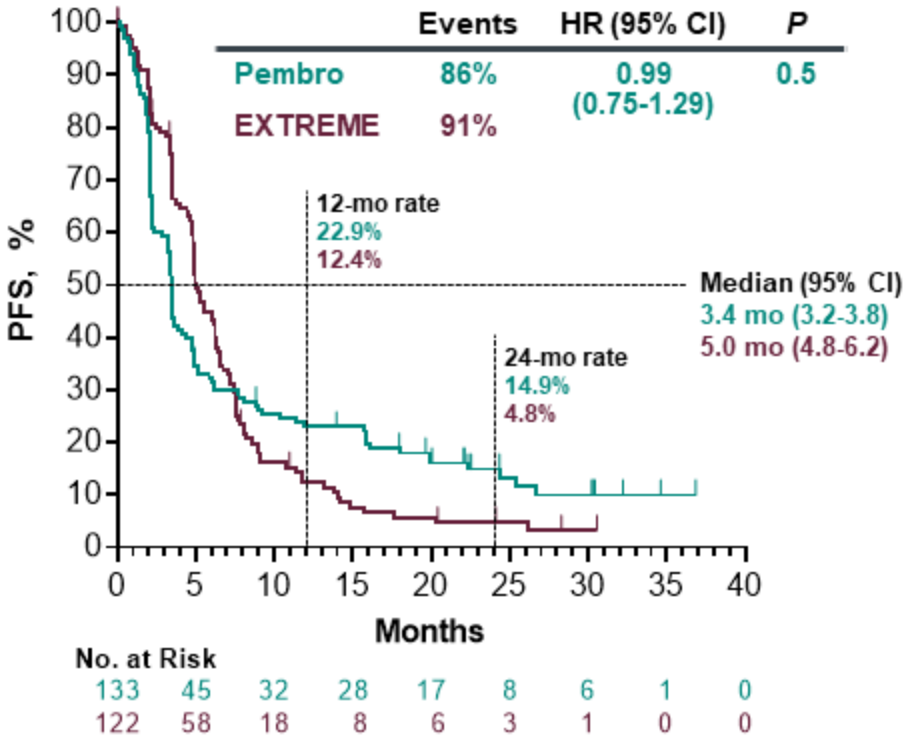
133	106	85	65	47	24	11	2	0
122	100	64	42	22	12	5	0	0

Data cutoff date: Jun 13, 2018.

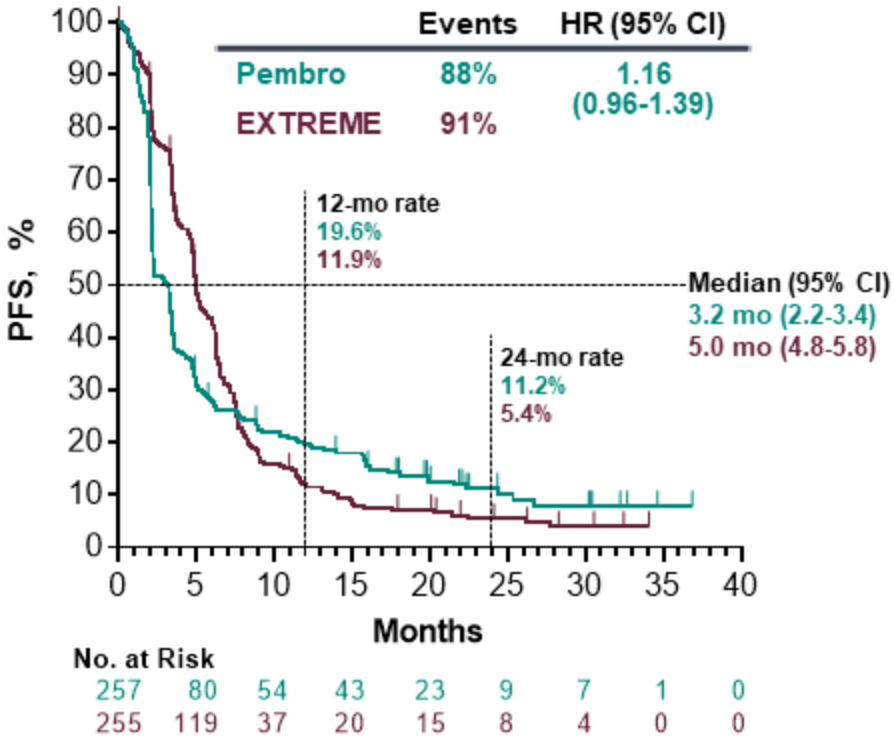
Burtness KN048 ESMO 2018

Progression-Free Survival: P vs E

CPS ≥20



CPS ≥1



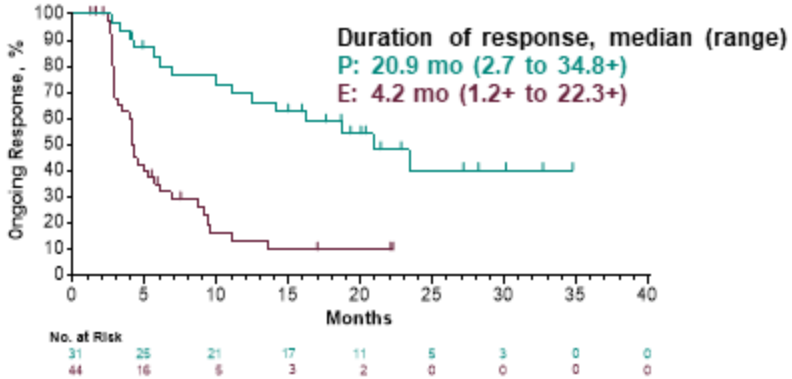
Progression-free survival assessed per RECIST v1.1 by blinded, independent central radiologic review.
Data cutoff date: Jun 13, 2018.

Burtness KN048 ESMO 2018

Response Summary, P vs E

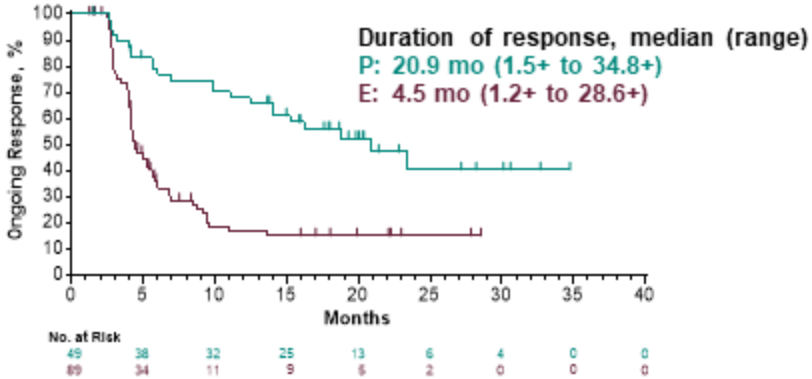
CPS ≥20

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



CPS ≥1

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

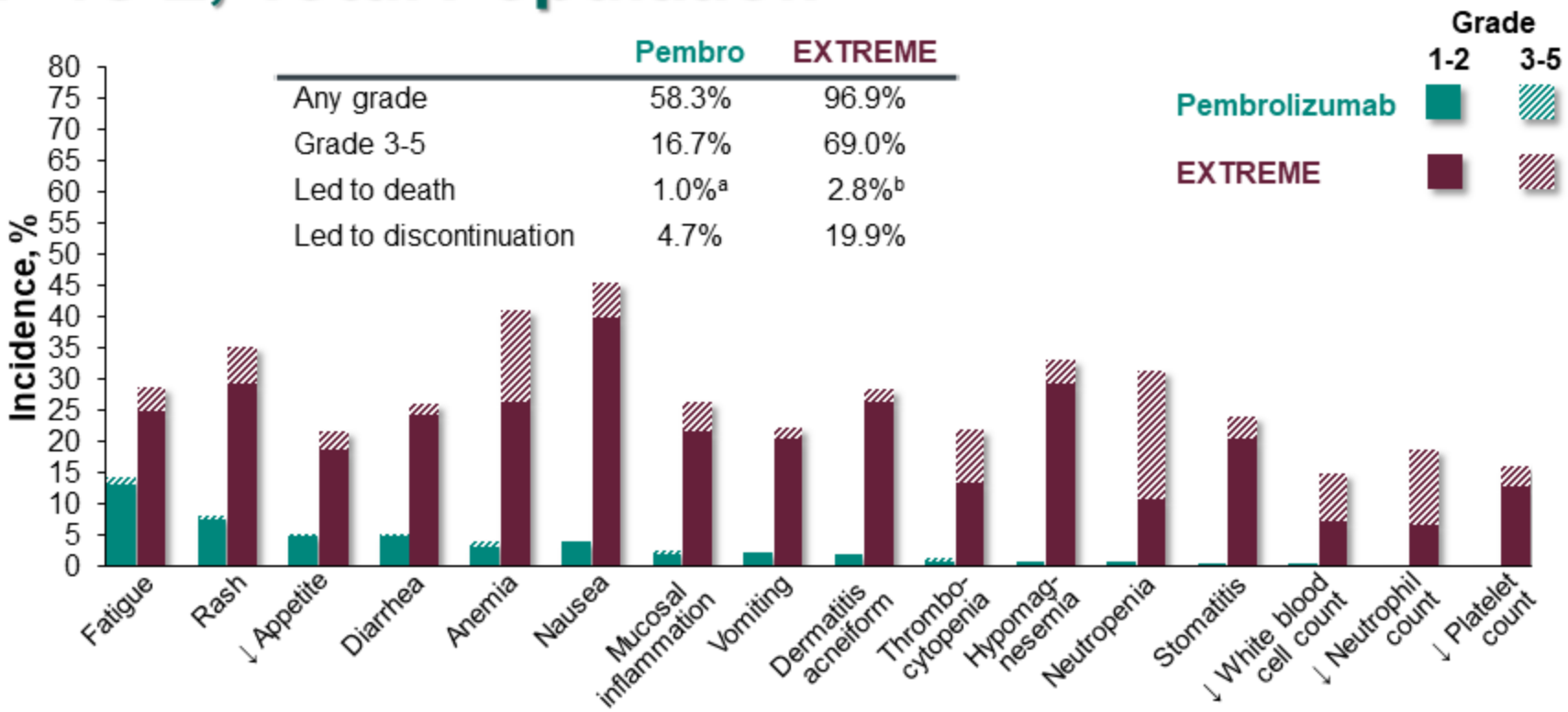


[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cutoff date: Jun 13, 2018.

Burtness KN048 ESMO 2018

Treatment-Related AEs With Incidence ≥15%, P vs E, Total Population

	Pembro	EXTREME
Any grade	58.3%	96.9%
Grade 3-5	16.7%	69.0%
Led to death	1.0%[a]	2.8%[b]
Led to discontinuation	4.7%	19.9%



Median (range) treatment duration was 3.5 mo (0.03-24.2) for pembrolizumab and 4.9 mo (0.03-35.3) for EXTREME.

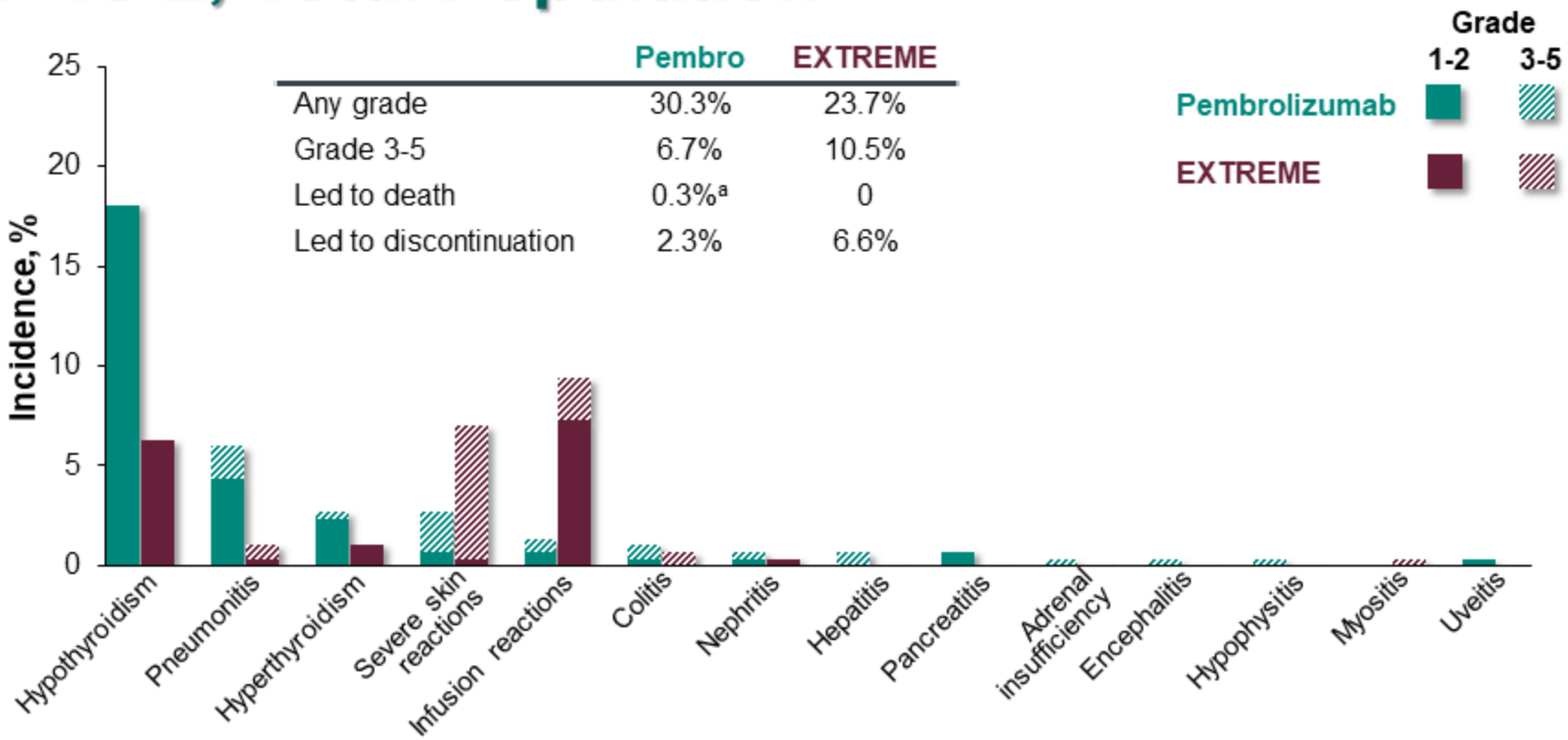
[a]Autoinflammatory disease, disseminated intravascular coagulation, and pneumonitis (n=1 each).

[b]Pneumonia (n=3), sepsis (n=2), and hypoxia, osteomyelitis, and pulmonary artery thrombosis (n=1 each). Data cutoff date: Jun 13, 2018.

Burtness KN048 ESMO 2018

Immune-Mediated AEs and Infusion Reactions, P vs E, Total Population

	Pembro	EXTREME
Any grade	30.3%	23.7%
Grade 3-5	6.7%	10.5%
Led to death	0.3%[a]	0
Led to discontinuation	2.3%	6.6%



[a]Pneumonitis (n=1).

Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: Jun 13, 2018.

Summary and Conclusions: Pembrolizumab Monotherapy vs EXTREME

- Pembrolizumab significantly improved OS vs EXTREME in the PD-L1 CPS ≥20 (HR 0.61, P = 0.0007) and CPS ≥1 (HR 0.78, P = 0.0086) populations
  - No PFS benefit for pembrolizumab
  - Although pembrolizumab had a lower ORR, responses were substantially more durable
- Pembrolizumab had a favorable safety profile vs EXTREME
  - Lower incidence of any-grade, grade 3-4, and grade 5 treatment-related AEs
  - Lower incidence of treatment-related AEs leading to discontinuation
  - Safety profiles as expected for pembrolizumab and EXTREME
- Data support pembrolizumab monotherapy as a new first-line standard-of-care for R/M HNSCC that expresses PD-L1

Burtness KN048 ESMO 2018

KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification Factors

- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R (1:1:1)

Pembrolizumab 200 mg Q3W for up to 35 cycles

Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 29 cycles

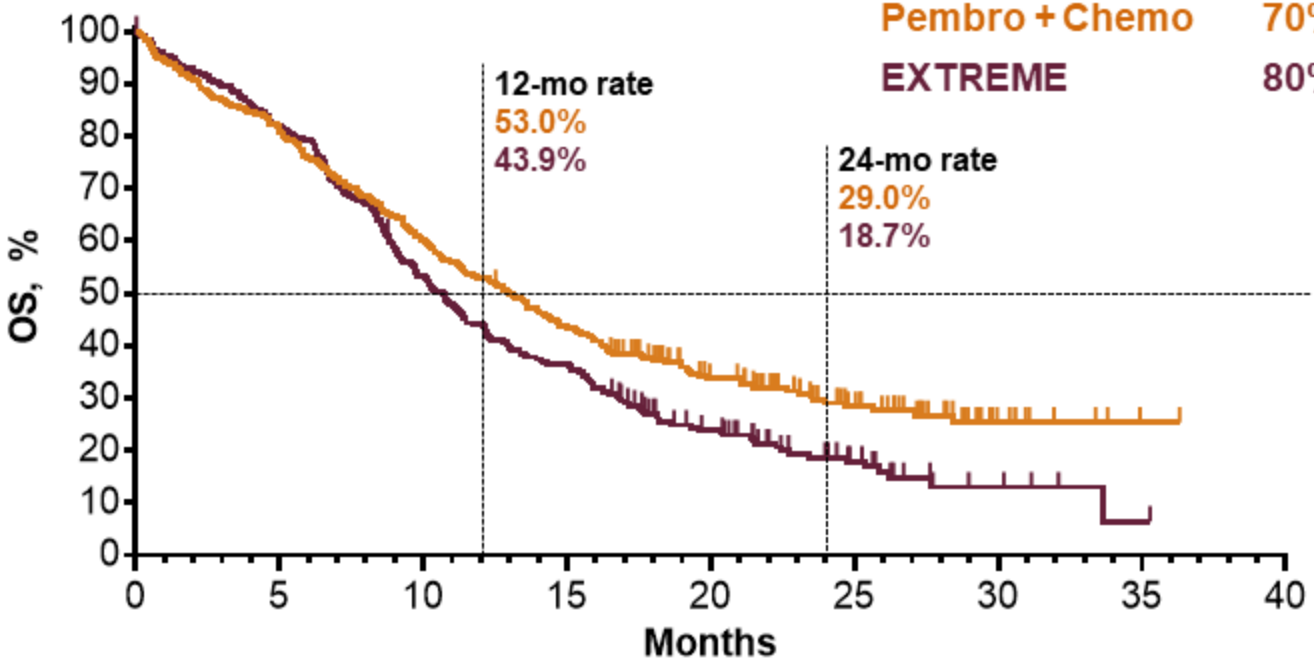
Cetuximab 250 mg/m^2 Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk) → Cetuximab 250 mg/m^2 Q1W

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score; % of tumor cells with membrane PD-L1 expression. [b]Assessed using the CINtec® p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m^2.

Burtness KN048 ESMO 2018

Overall Survival: P+C vs E, Total Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	70%	0.77 (0.63-0.93)	0.0034
EXTREME	80%		



Median (95% CI)
13.0 mo (10.9-14.7)
10.7 mo (9.3-11.7)

No. at Risk

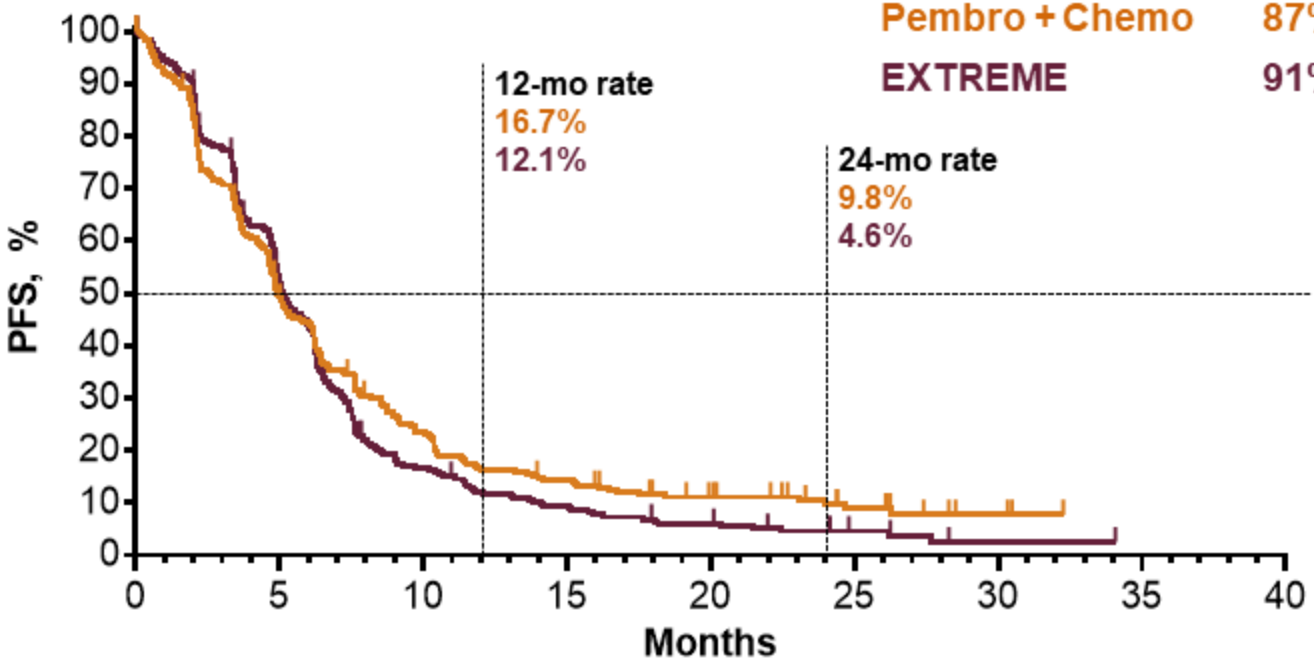
281	227	169	122	75	40	10	1	0
278	227	147	100	51	20	5	1	0

Data cutoff date: Jun 13, 2018.

Burtness KN048 ESMO 2018

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

	Events	HR (95% CI)	*P*
Pembro + Chemo	87%	0.92 (0.77-1.10)	0.2
EXTREME	91%		



Median (95% CI)
4.9 mo (4.7-6.0)
5.1 mo (4.9-6.0)

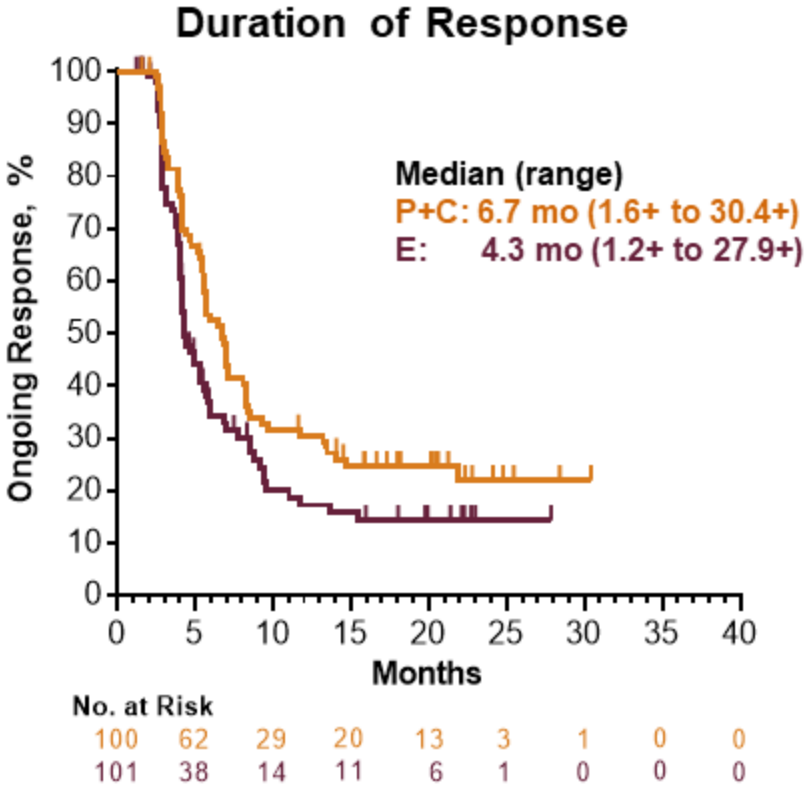
No. at Risk

281	134	62	37	22	11	3	0	0
278	136	42	23	14	6	1	0	0

Progression-free survival assessed per RECIST v1.1 by blinded, independent central radiologic review.
Data cutoff date: Jun 13, 2018.

Response Summary, P+C vs E, Total Population

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

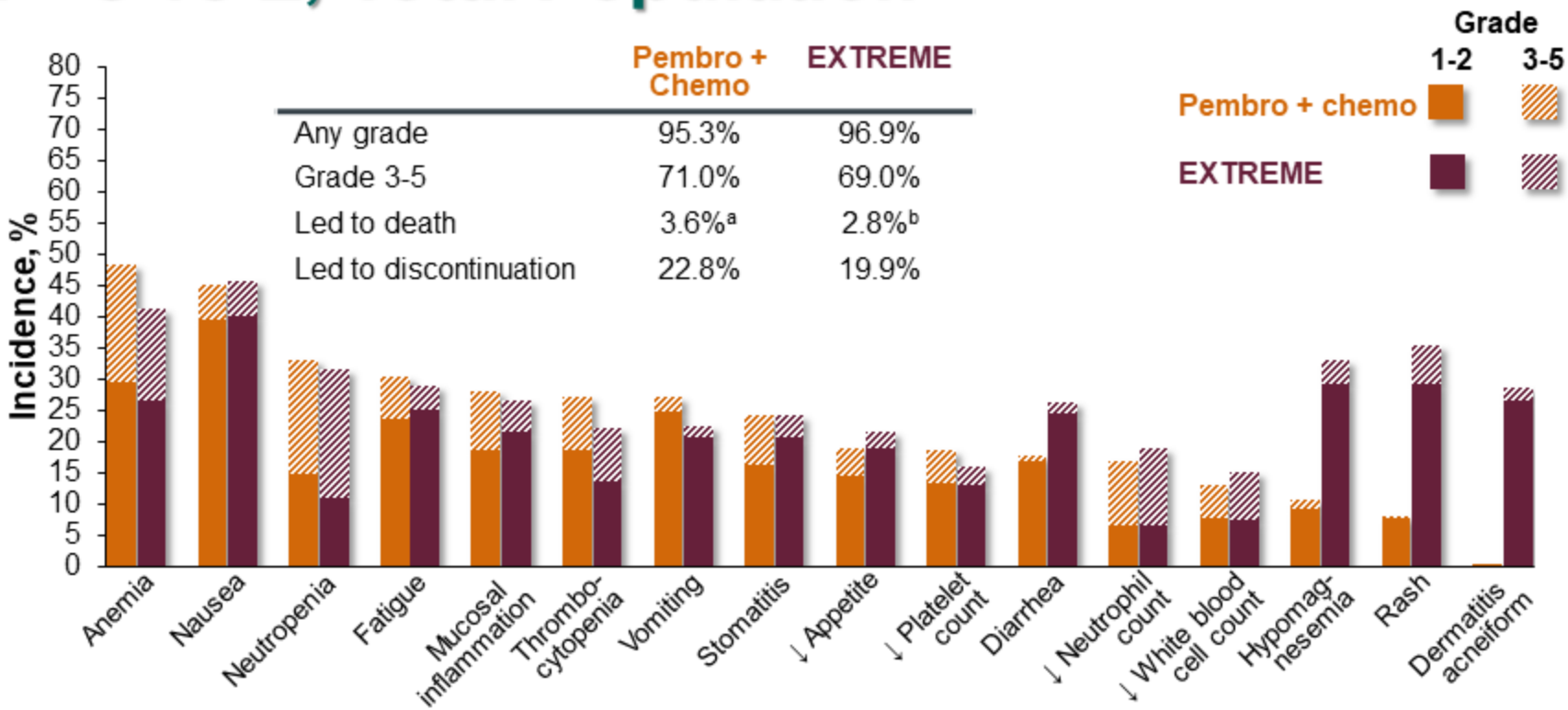


[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cutoff date: Jun 13, 2018.

Burtness KN048 ESMO 2018

Treatment-Related AEs With Incidence ≥15%, P+C vs E, Total Population

	Pembro + Chemo	EXTREME
Any grade	95.3%	96.9%
Grade 3-5	71.0%	69.0%
Led to death	3.6%[a]	2.8%[b]
Led to discontinuation	22.8%	19.9%

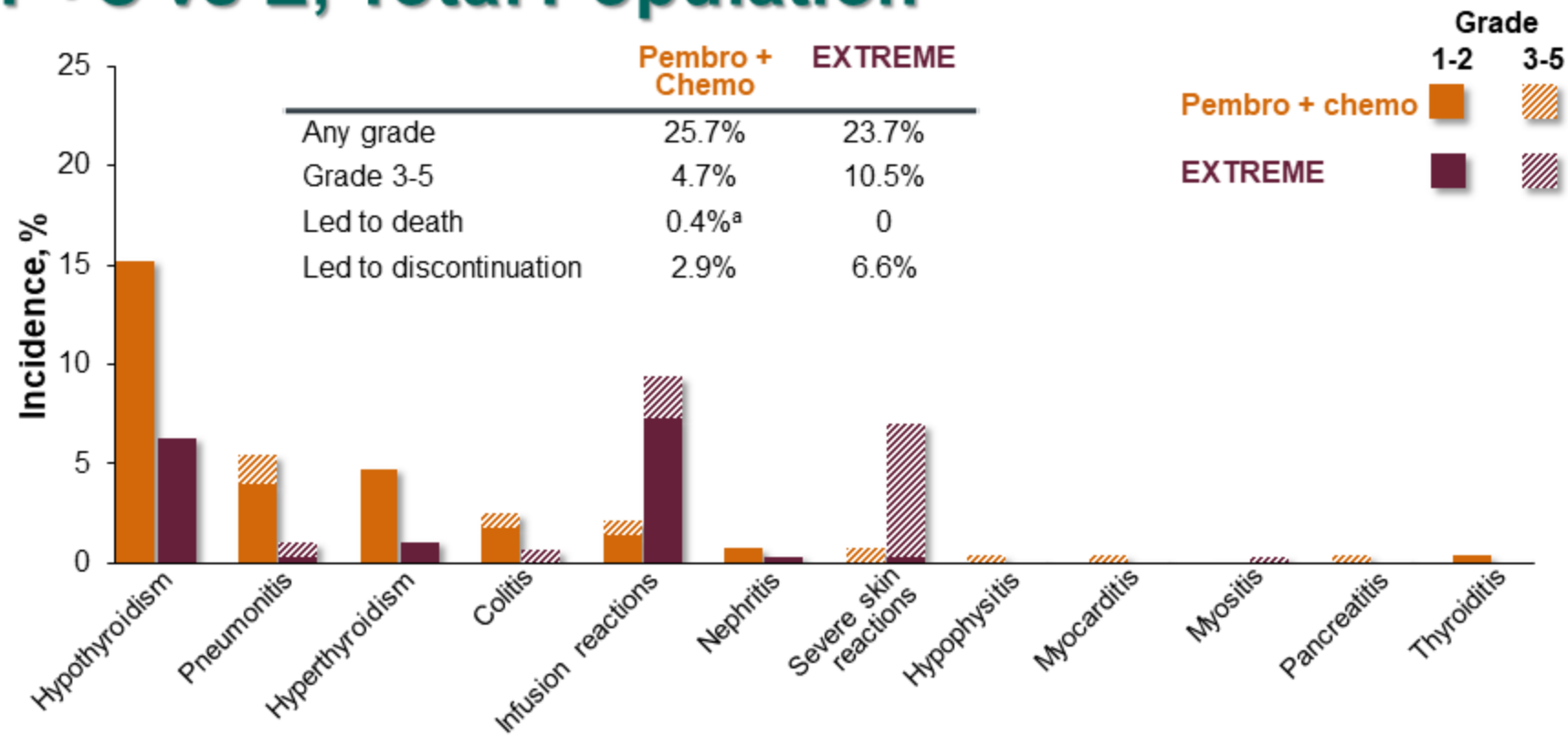


Median (range) treatment duration was 5.8 mo (0.1-24.2) for pembrolizumab + chemotherapy and 4.9 mo (0.03-35.3) for EXTREME.
[a]Septic shock (n=5) and cerebral ischemia, hemorrhage, interstitial lung disease, sepsis, and tumor hemorrhage (n=1 each).
[b]Pneumonia (n=3), sepsis (n=2), and hypoxia, osteomyelitis, and pulmonary artery thrombosis (n=1 each). Data cutoff date: Jun 13, 2018.

Burtness KN048 ESMO 2018

Immune-Mediated AEs and Infusion Reactions, P+C vs E, Total Population

	Pembro + Chemo	EXTREME
Any grade	25.7%	23.7%
Grade 3-5	4.7%	10.5%
Led to death	0.4%[a]	0
Led to discontinuation	2.9%	6.6%



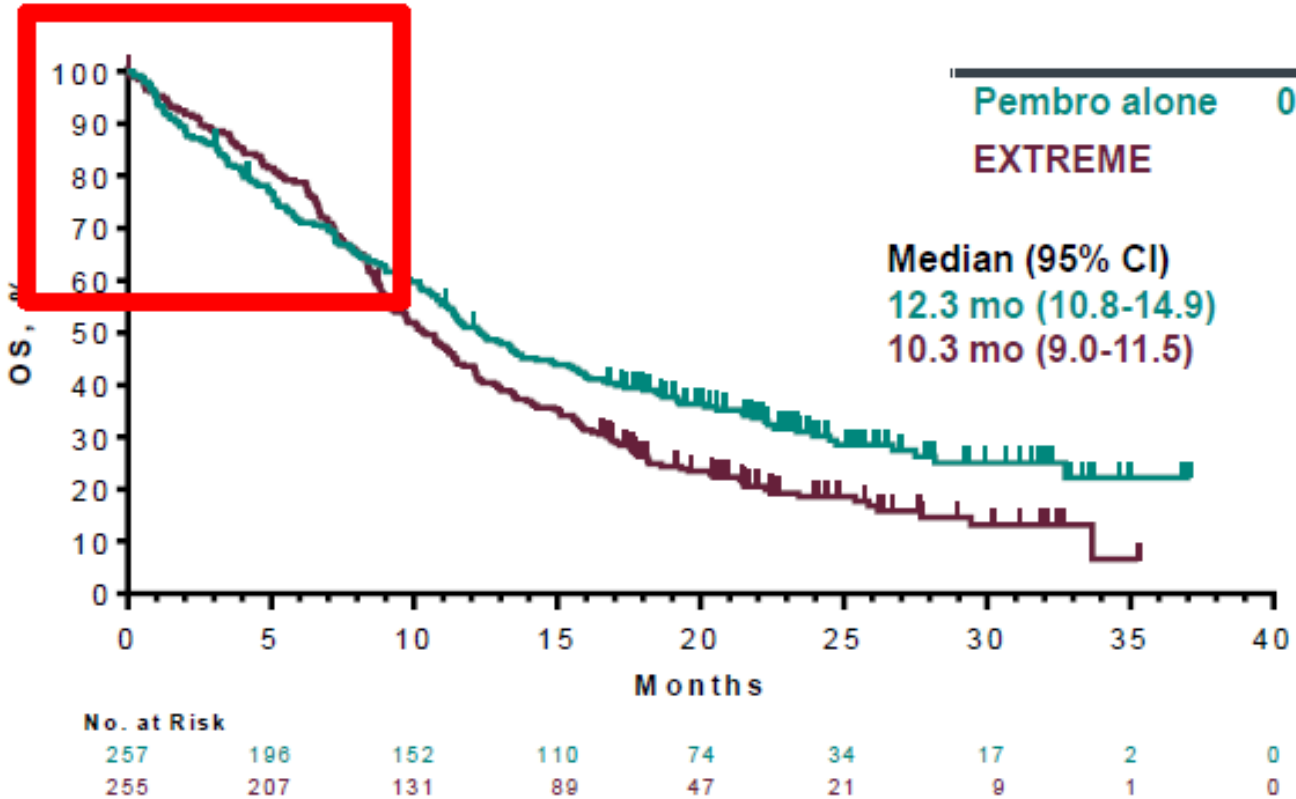
[a]Pneumonitis (n=1).

Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: Jun 13, 2018.

Summary and Conclusions: Pembrolizumab + Chemotherapy vs EXTREME

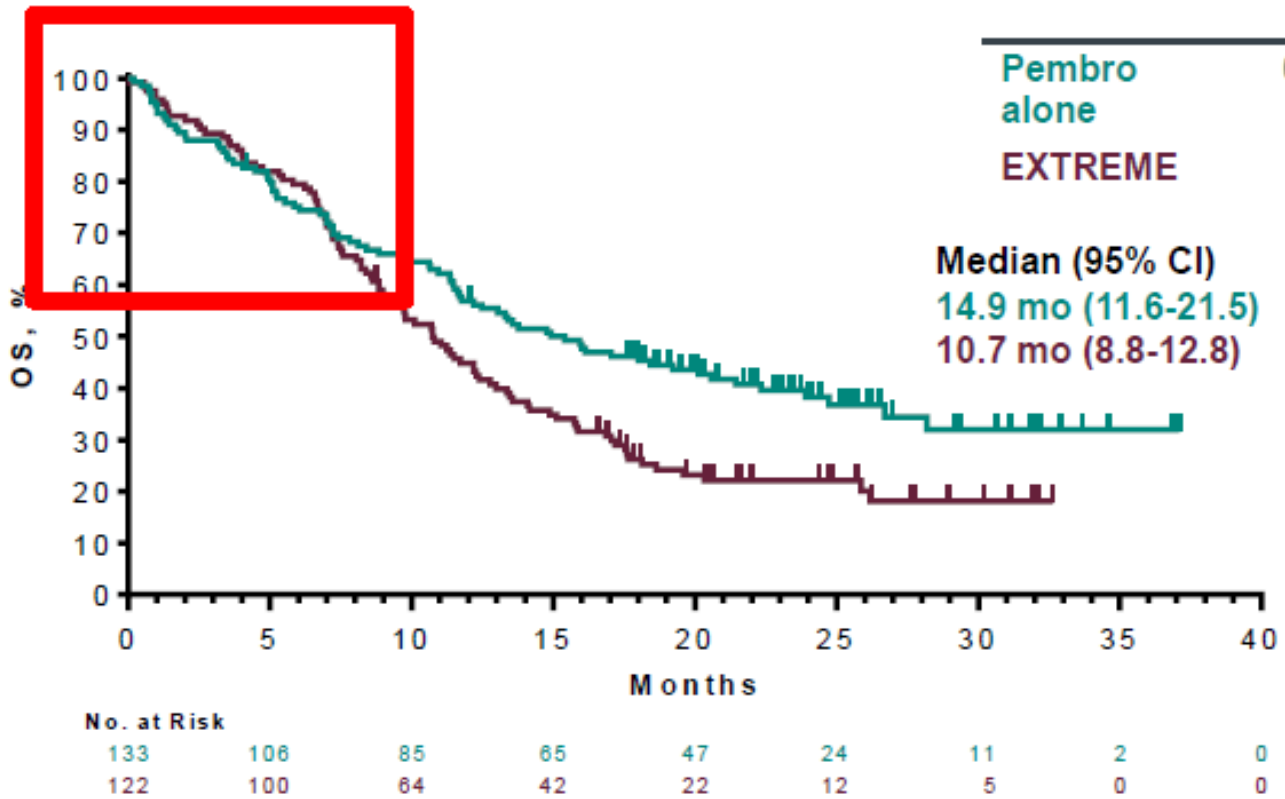
- Pembrolizumab plus chemotherapy with a platinum and 5-FU significantly improved OS vs EXTREME in the total population (HR 0.77, $P = 0.0034$)
  - No PFS or ORR benefit for pembrolizumab plus chemotherapy
  - Responses to pembrolizumab plus chemotherapy were more durable
- Pembrolizumab plus chemotherapy had a comparable safety profile vs EXTREME
  - Similar incidence of any-grade, grade 3-4, and grade 5 treatment-related AEs
  - No unexpected toxicity in the pembrolizumab + chemotherapy arm
- Data support pembrolizumab plus platinum-based chemotherapy as a new first-line standard-of-care for R/M HNSCC

WHAT ABOUT CPS ≥ 1 ?



	HR (95% CI)	*P*
Pembro alone	0.78 (0.64-0.96)	0.0086
EXTREME		

ARE WE TAKING RISKS IN CPS ≥ 20 ?



	HR (95% CI)	*P*
Pembro alone	0.61 (0.45-0.83)	0.0007
EXTREME		

Median (95% CI)

14.9 mo (11.6-21.5)

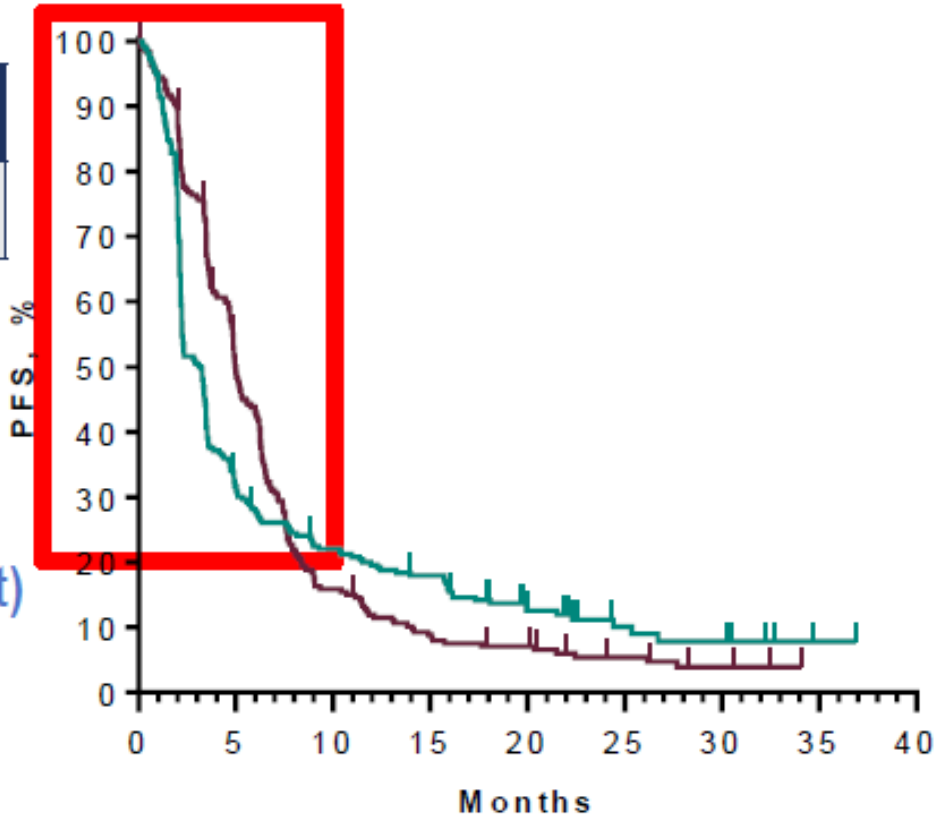
10.7 mo (8.8-12.8)

ARE WE TAKING RISKS IN CPS ≥ 1 ?

	Pembro	EXTREME
ORR	19%	35%

ORR: +16 % in favor of EXTREME

PFS in favor of EXTREME (at the start)



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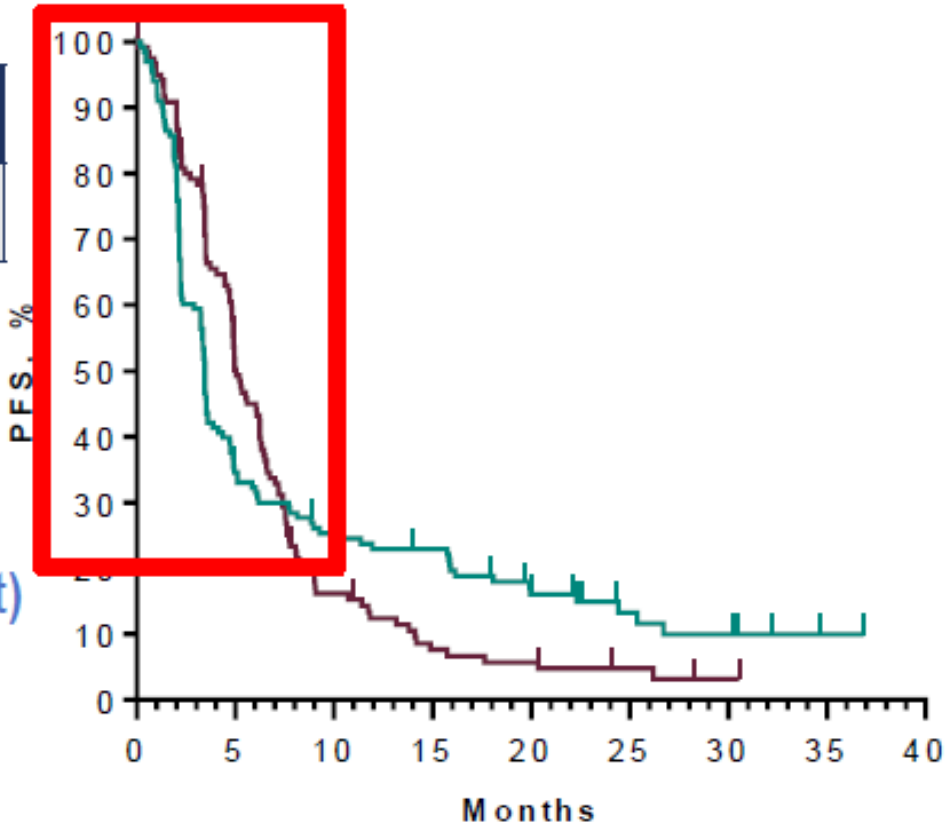
ARE WE TAKING RISKS IN CPS ≥ 20 ?

	Pembro	EXTREME
ORR	23%	36%

ORR: +13 % in favor of EXTREME

PFS in favor of EXTREME (at the start)



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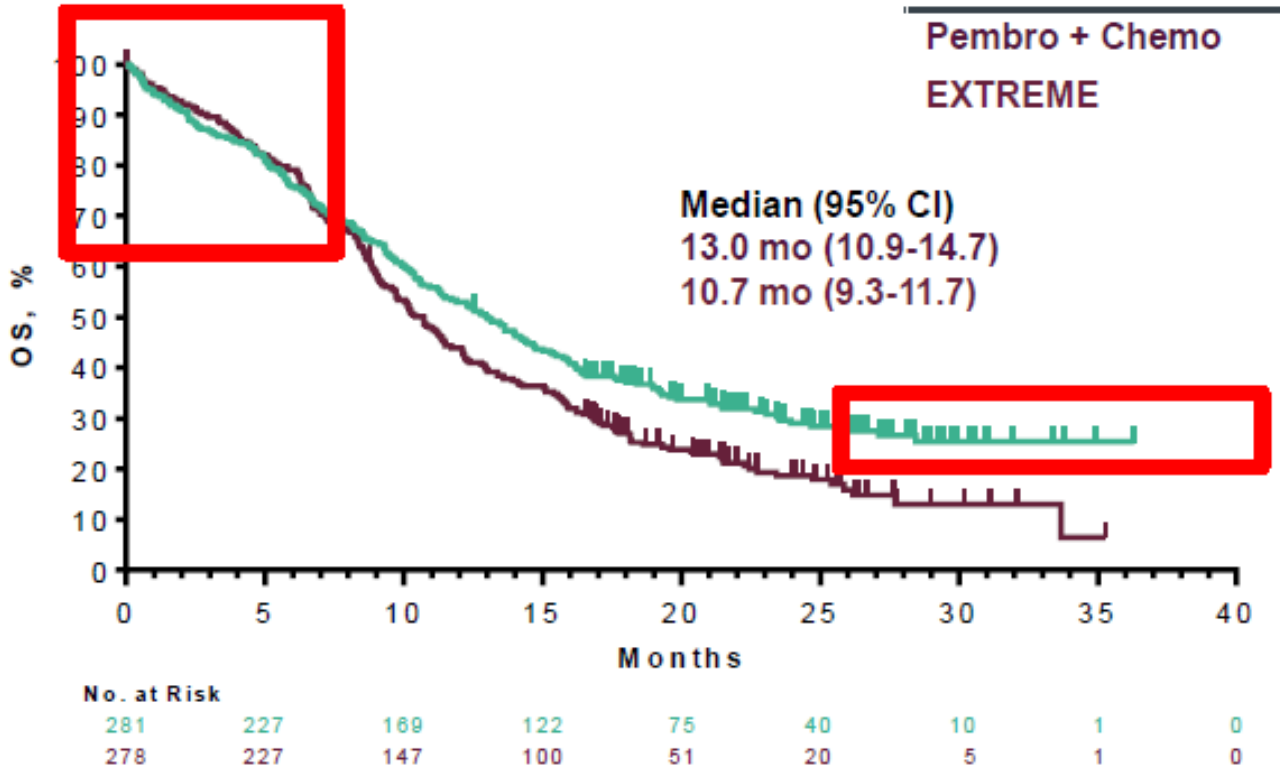
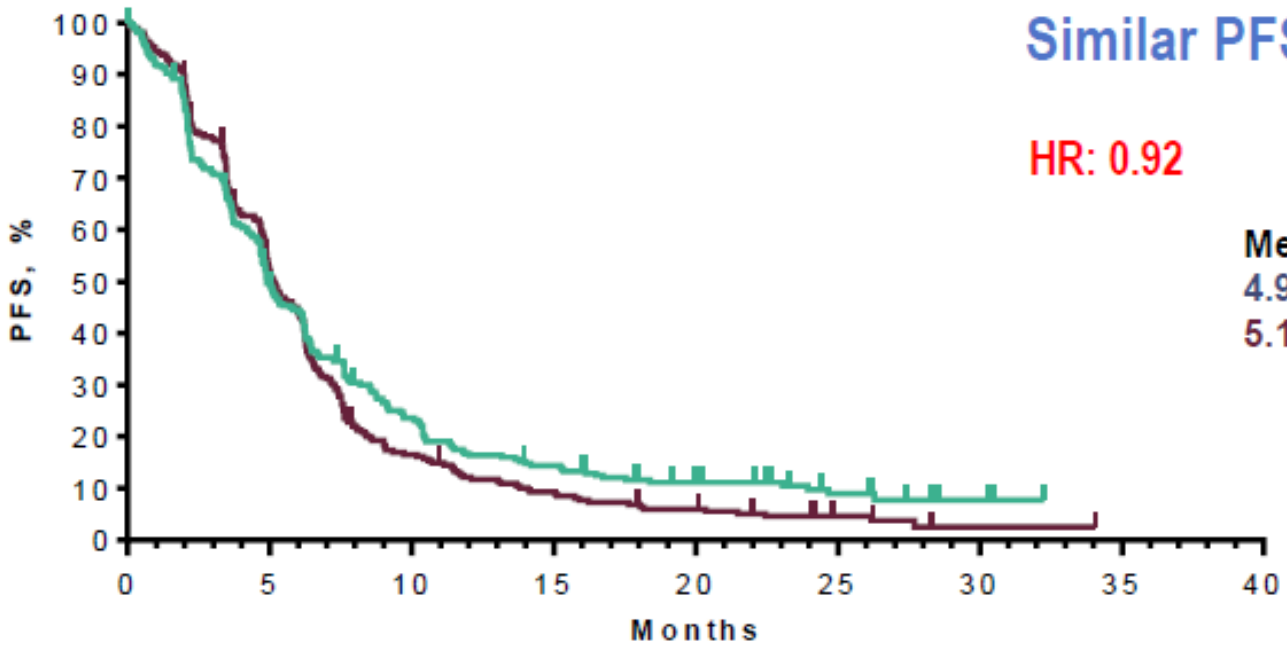
TOTAL POPULATION: SURVIVAL

	HR (95% CI)	*P*
Pembro + Chemo	0.77 (0.63-0.93)	0.0034
EXTREME		



TOTAL POPULATION: PFS



No. at Risk								
281	134	62	37	22	11	3	0	0
278	136	42	23	14	6	1	0	0

Similar PFS

HR: 0.92

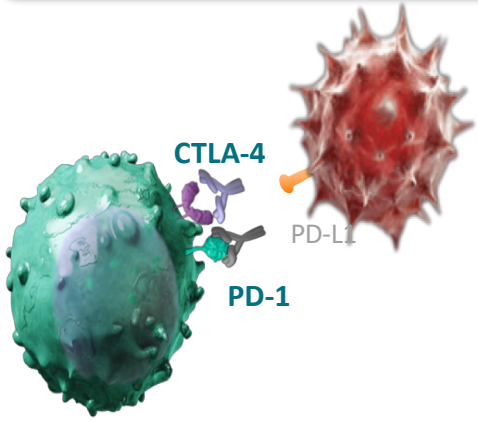
Median (95% CI)
4.9 mo (4.7-6.0)
5.1 mo (4.9-6.0)

KN 048

		Todos	CPS <1	CPS ≥1	CPS ≥1-<20	CPS ≥20	TPS ≥ 50
		100%	15%	85%	40-45%	40-45%	20-25%
Pembrolizumab	SG(mes)	?	?	12,3 (+2)	?	14,9 (+4,2)	?
	PFS(mes)	?	?	3,2 (-1,8)	?	3,4 (-1,6)	?
	RO(%)	?	?	19,1 (-15,8)	?	23,3 (-12,8)	?
	DRO(mes)	?	?	20,9 (+16,4)	?	20,9 (+16,7)	?
Pembrolizumab + Platino-Fu	SG(mes)	13 (+2,3)	?	?	?	?	?
	PFS(mes)	4,9 (-0,2)	?	?	?	?	?
	RO(%)	35,6 (=)	?	?	?	?	?
	DRO(mes)	6,7 (+2,4)	?	?	?	?	?

Trial: NCT02741570

CHECKMATE-651: Phase III randomized, open-label study of nivolumab + ipilimumab compared to the EXTREME regimen as 1L treatment in patients with R/M SCCHN[1]



Adapted from Mellman I et al 2011.[2]

Start Date: August 2016

Primary Endpoints: OS, PFS

Other Endpoints: ORR, time to deterioration, PD-L1 expression as biomarker

Key Eligibility Criteria

- No prior systemic therapy for R/M disease except if chemotherapy was part of multimodal treatment ≤6 months prior to enrollment
- Tumor tissue required for HPV p16 (for OPC) and PD-L1 testing prior to randomization

Randomized

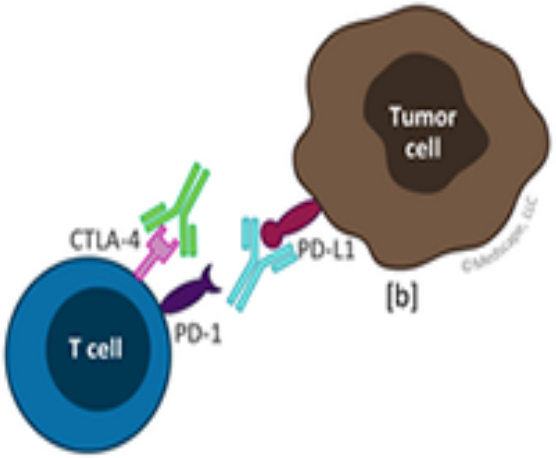
Nivolumab + Ipilimumab	EXTREME Cetuximab + cisplatin/carboplatin + 5-FU

1L, first line; 5-FU, 5-fluorouracil; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HPV, human papillomavirus; OPC, oropharyngeal cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck.

1. Clinicaltrials.gov. NCT02741570. Accessed June 10, 2016. 2. Mellman I et al. *Nature.* 2011;480(7378):480-489.

KESTREL: PHASE 3 RANDOMIZED, OPEN-LABEL STUDY OF EFFICACY AND SAFETY OF DURVALUMAB ± TREMELIMUMAB VS ACTIVE COMPARATOR IN THE TREATMENT OF FIRST-LINE R/M HNSCC

Platinum-Sensitive



Start Date: October 2015

Primary Endpoint: PFS, OS (durvalumab + tremelimumab vs SoC)

Other Endpoints: ORR, PFS2, DoR, APF12, OS24, PFS (durvalumab vs SoC), OS (durvalumab vs SoC), PK, immunogenicity, QoL

Key Eligibility Criteria

- No prior systemic chemotherapy for R/M disease
- No progression or recurrence ≤ 6 mo since last Pt therapy
- Fresh or archival tumor biopsy

Randomized (1:1:1)
Stratification factor: PD-L1, HPV, and smoking status

- Durvalumab + tremelimumab
- Durvalumab
- Active comparator (cetuximab, 5FU, cisplatin/ carboplatin)

a. ClinicalTrials.gov. NCT02551159; b. Mellman I, et al. *Nature*. 2011;480:480-489.

CCC R-M: 1ª línea de tratamiento

PE > 6 meses a QT (**Platino** neoadyuvante, concomitante, adyuvante): **Platino-sensible**.

-**Platino-Fu-Cetuximab (Extreme) + Pembrolizumab**

-"Necesidad" de RO.

-**Pembrolizumab**

-CPS ≥ 1%, CPS ≥ 20%.

-No "necesidad" de RO.