ACTUALIZACIÓN SOBRE INMUNOTERAPIA EN CÁNCER DE CABEZA Y CUELLO

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ORIGINAL ARTICLE

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L. Gillison

N Engl J Med 2016;375:1856-67.

Ferris RL et al. N Engl J Med 2016; (Epub ahead of print)

Nivolumab Versus Investigator's Choice (IC) for Recurrent or Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (SCCHN): CheckMate-141

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AACR 2016

CheckMate 141 Study Design

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab versus investigator's choice in patients with R/M SCCHN

Key Eligibility Criteria

- R/M SCCHN of the oral cavity, pharynx, or larynx
- Not amenable to curative therapy
- Progression on or within 6 months of last dose of platinum-based therapy
- ECOG PS 0–1
- Documentation of p16 to determine HPV status
- No active CNS metastases

Stratification factor

- Prior cetuximab treatment

R 2:1

Nivolumab
3 mg/kg IV q2w

Investigator's Choice

- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly)

Primary endpoint

- OS

Other endpoints

- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomized; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck; Clinicaltrials.gov. NCT02105636.

Statistical Analysis for Primary Endpoint

- Planned sample size of 360 patients
- **90% power for a hazard ratio of nivolumab to investigator's choice therapy of 0.667**
- Total of 278 deaths were required
  - Two-sided test procedure with one interim analysis
- Interim analysis was planned after 195 (70%) events

Demographics (1)

	Nivolumab (n = 240) n (%)	Investigator's Choice (n = 121) n (%)	Total (N = 361) n (%)
Median age (years)	**59.0**	**61.0**	**60.0**
< 65	172 (71.7)	76 (62.8)	248 (68.7)
≥ 65	68 (28.3)	45 (37.2)	113 (31.3)
Gender			
Male	197 (82.1)	103 (85.1)	300 (83.1)
Race			
White	196 (81.7)	104 (86.0)	300 (83.1)
Asian	29 (12.1)	14 (11.6)	43 (11.9)
Other	15 (6.3)	3 (2.5)	18 (5.0)
Smoking/tobacco use			
Current/former	191 (79.6)	85 (70.2)	276 (76.5)
Never	39 (16.3)	31 (25.6)	70 (19.4)

Demographics (2)

	Nivolumab (n = 240) n (%)	Investigator's Choice (n = 121) n (%)	Total (N = 361) n (%)
ECOG performance status			
0	49 (20.4)	23 (19.0)	72 (19.9)
1	189 (78.8)	94 (77.7)	283 (78.4)
≥ 2	1 (0.4)	3 (2.5)	4 (1.1)
Not reported	1 (0.4)	1 (0.8)	2 (0.6)
Number of prior lines of systemic cancer therapy			
1	105 (43.8)	58 (47.9)	163 (45.2)
2	81 (33.8)	45 (37.2)	126 (34.9)
≥ 3	54 (22.5)	18 (14.9)	72 (19.9)
Site of primary tumor			
Oral cavity	108 (45.0)	67 (55.4)	175 (48.5)
Pharynx	92 (38.3)	36 (29.8)	128 (35.5)
Larynx	34 (14.2)	15 (12.4)	49 (13.6)
Other	6 (2.5)	3 (2.5)	9 (2.5)

Demographics (3)

	Nivolumab (n = 240) n (%)	Investigator's Choice (n = 121) n (%)	Total (N = 361) n (%)
Context of previous systemic therapy regimen — no. (%)‖			
Adjuvant therapy	37 (15.4)	21 (17.4)	58 (16.1)
Neoadjuvant therapy	17 (7.1)	16 (13.2)	33 (9.1)
Primary disease	173 (72.1)	83 (68.6)	256 (70.9)
Metastatic disease	112 (46.7)	59 (48.8)	171 (47.4)
Previous receipt of cetuximab — no. (%)	150 (62.5)	72 (59.5)	222 (61.5)

Baseline PD-L1 Expression and p16 Status

	Nivolumab (n = 240) n (%)	Investigator's Choice (n = 121) n (%)	Total (N = 361) n (%)
PD-L1 quantifiable	161 (67.1)	99 (81.8)	260 (72.0)
≥ 1%	88 (54.7)	61 (61.6)	149 (57.3)
< 1%	73 (45.3)	38 (38.4)	111 (42.7)
PD-L1 not evaluable	79 (32.9)	22 (18.2)	101 (28.0)
p16 status[a,b]			
Positive	63 (26.3)	29 (24.0)	92 (25.5)
Negative	50 (20.8)	36 (29.8)	86 (23.8)
Not tested	127 (52.9)	56 (46.3)	183 (50.7)

[a]Required from oropharyngeal cancer patients only.
[b]Determined via p16 immunohistochemistry.

Treatment Administration

	Nivolumab (n = 240)	Investigator's Choice (n = 121)	Total (N = 361)
Patients receiving ≥ 1 dose, n (%)	236 (98.3)	111 (91.7)	347 (96.1)
Investigator's choice therapy, n (%)			
Methotrexate	–	46 (38.0)	–
Docetaxel	–	52 (43.0)	–
Cetuximab	–	13 (10.7)	–
Median time on therapy, mo (95% CI)	1.9 (1.6–2.3)	1.9 (1.6–2.0)	–
Median duration of follow-up, mo (range)	5.3 (0–16.8)	4.6 (0–15.2)	–
Number of deaths, n (%)	133 (55.4)	85 (70.2)	218 (60.4)
Ongoing treatment, n (%)	41 (17.4)	3 (2.7)	44 (12.7)

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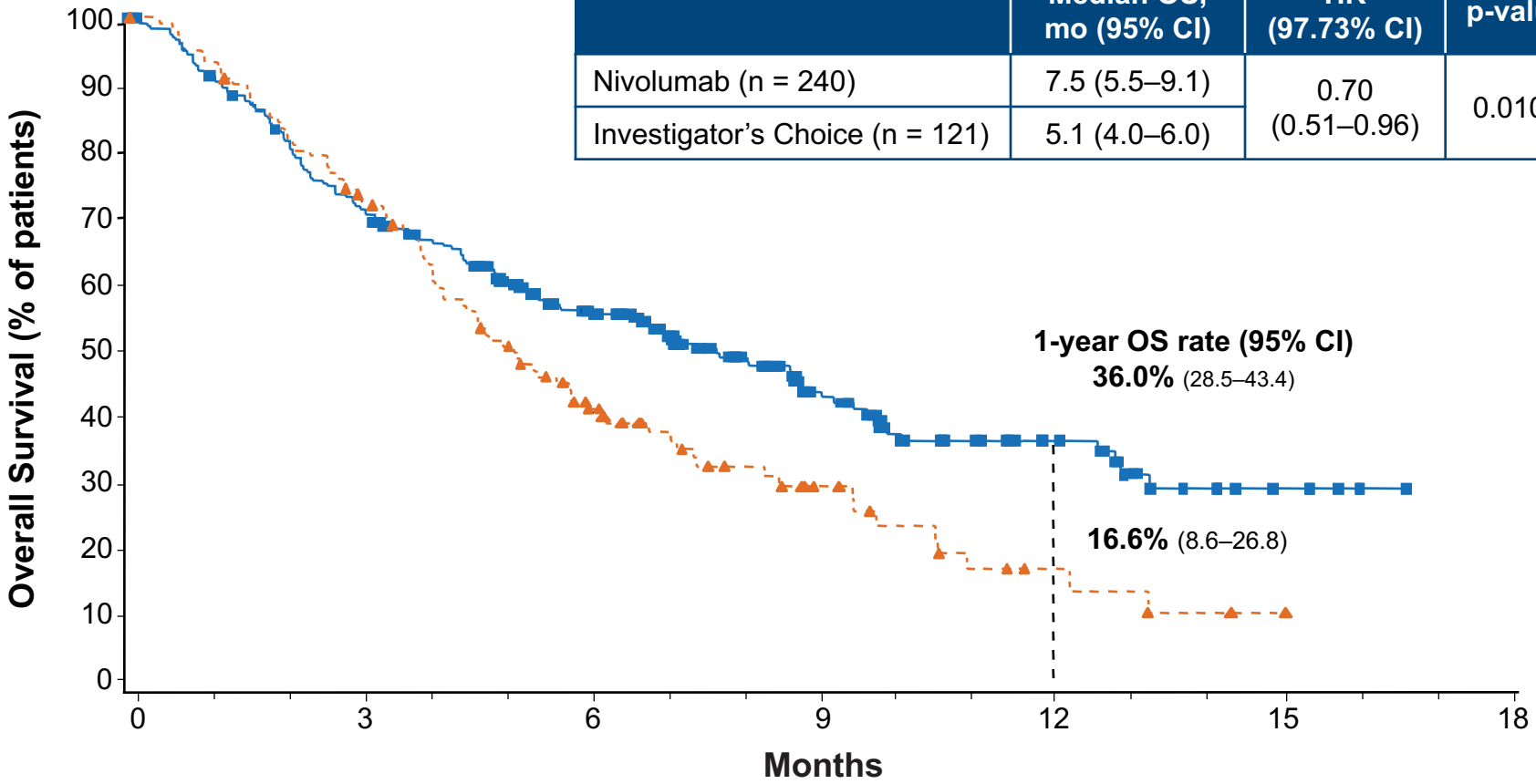
Overall Survival

	Median OS, mo (95% CI)	HR (97.73% CI)	p-value
Nivolumab (n = 240)	7.5 (5.5–9.1)	0.70 (0.51–0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0–6.0)		



No. at Risk

Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

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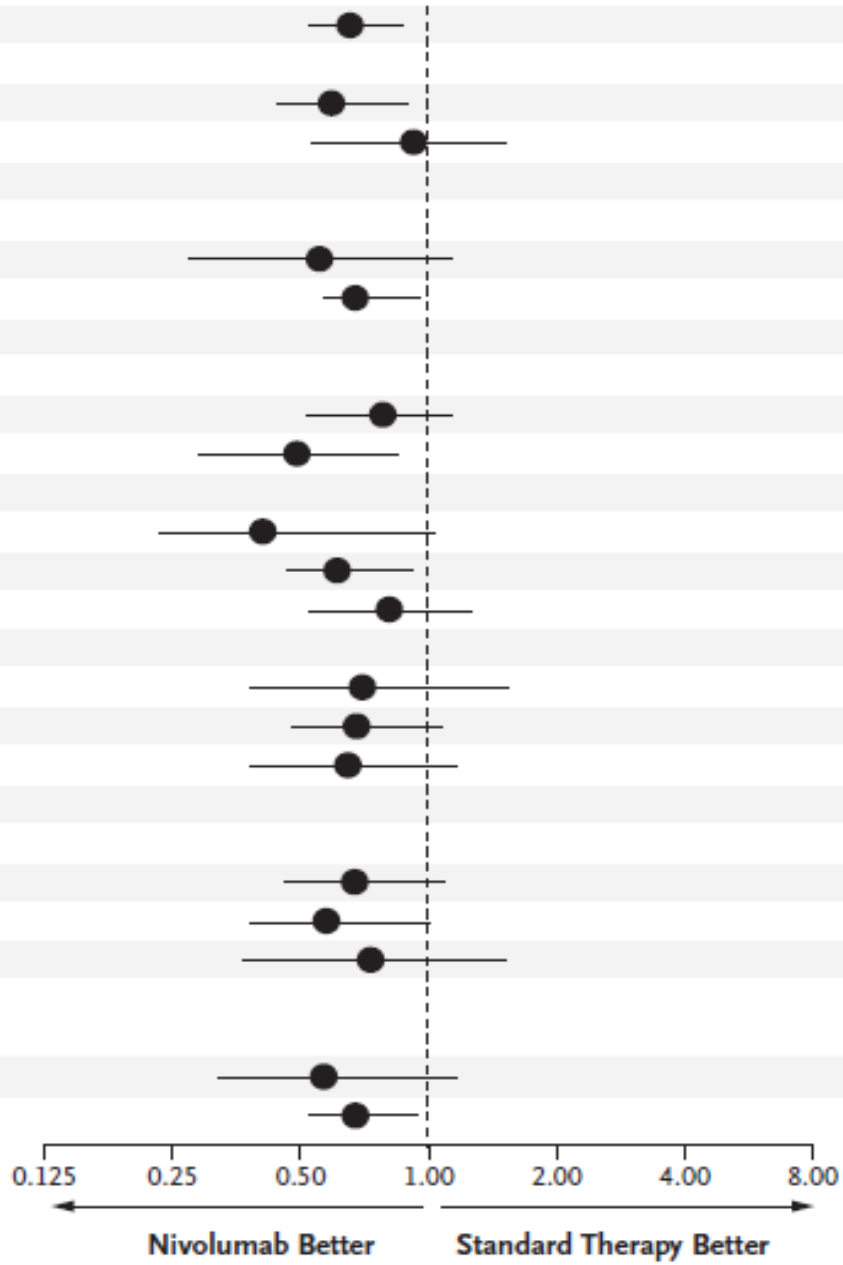
C Treatment Effect on Overall Survival, According to Subgroup

Subgroup	Nivolumab	Standard Therapy	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall	240	121	0.69 (0.53–0.91)
Age			
<65 yr	172	76	0.64 (0.45–0.89)
≥65 yr and <75 yr	56	39	0.93 (0.56–1.54)
≥75 yr	12	6	—
ECOG performance-status score			
0	49	23	0.60 (0.30–1.23)
≥1	190	97	0.71 (0.53–0.96)
Not reported	1	1	—
Previous cetuximab use			
Yes	147	74	0.81 (0.57–1.15)
No	93	47	0.55 (0.35–0.86)
Intended standard therapy			
Cetuximab	33	15	0.47 (0.22–1.01)
Methotrexate	119	52	0.64 (0.43–0.96)
Docetaxel	88	54	0.82 (0.53–1.28)
Site of primary tumor			
Larynx	34	15	0.75 (0.36–1.59)
Oral cavity	108	67	0.73 (0.51–1.07)
Pharynx	92	36	0.71 (0.42–1.19)
Other	6	3	—
No. of previous lines of systemic therapy			
1	106	58	0.72 (0.48–1.07)
2	80	45	0.64 (0.40–1.00)
≥3	54	18	0.77 (0.38–1.57)
Platinum-refractory disease in context of primary therapy			
Yes	52	26	0.63 (0.35–1.12)
No	188	95	0.71 (0.52–0.97)



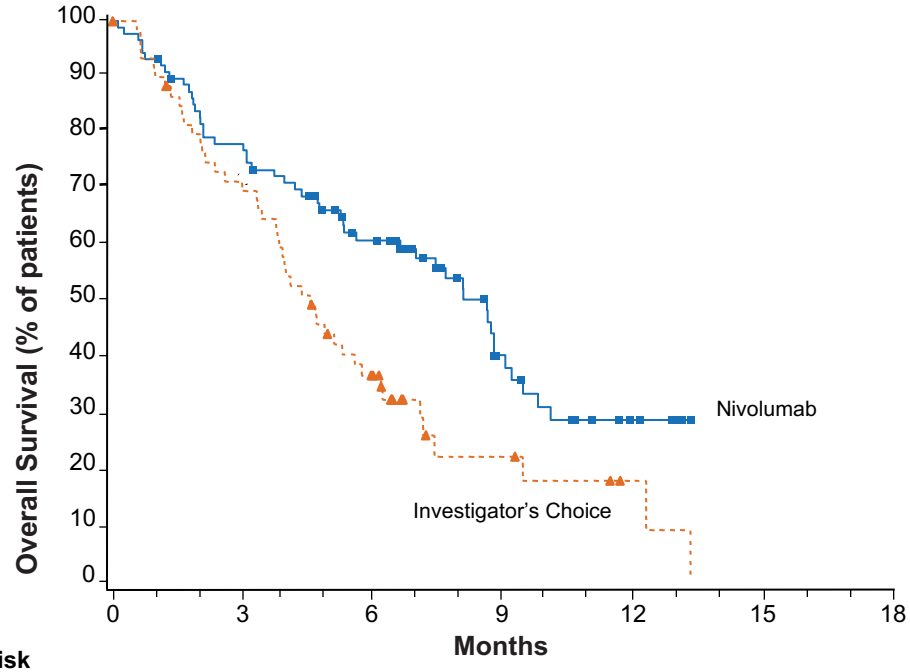
Overall Survival by PD-L1 Expression

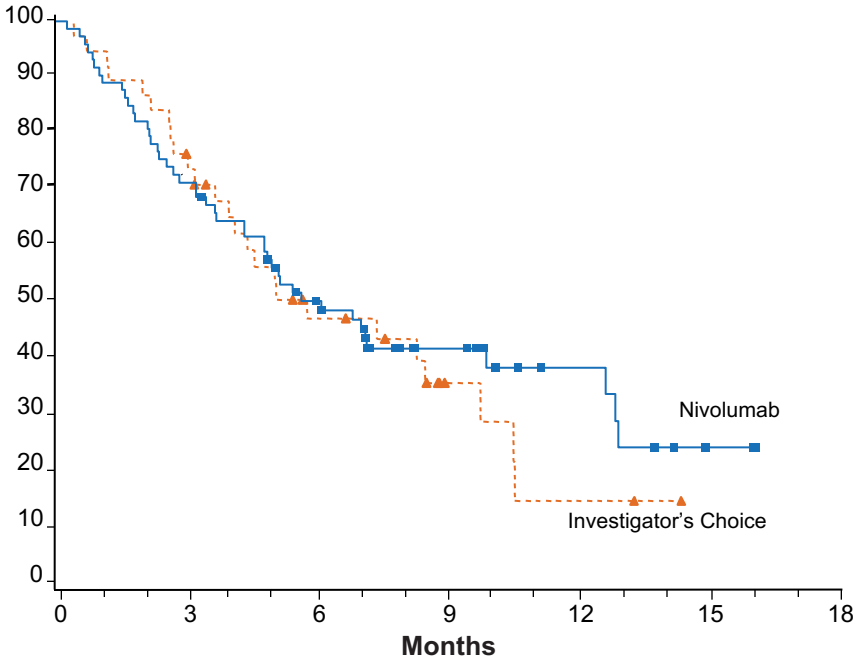
PD-L1 Expression ≥ 1%

	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 88)	8.7 (5.7–9.1)	0.55 (0.36–0.83)
Investigator's Choice (n = 61)	4.6 (3.8–5.8)	

PD-L1 Expression < 1%

	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 73)	5.7 (4.4–12.7)	0.89 (0.54–1.45)
Investigator's Choice (n = 38)	5.8 (4.0–9.8)	





No. at Risk

Nivolumab	88	67	44	18	6	0	73	52	33	17	8	3	0
Investigator's Choice	61	42	20	6	2	0	38	29	14	6	2	0	0

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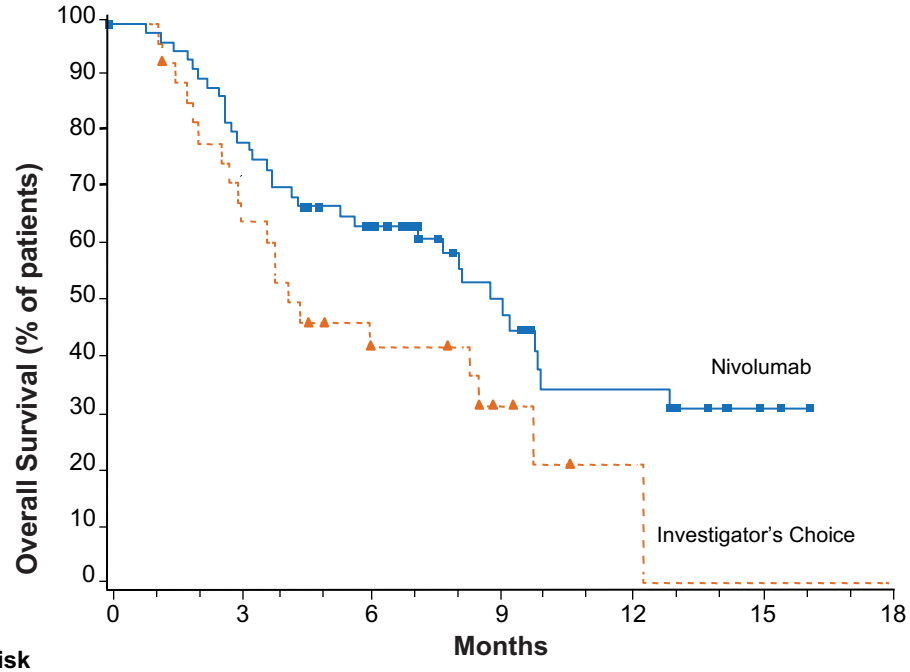
Overall Survival by p16 Status

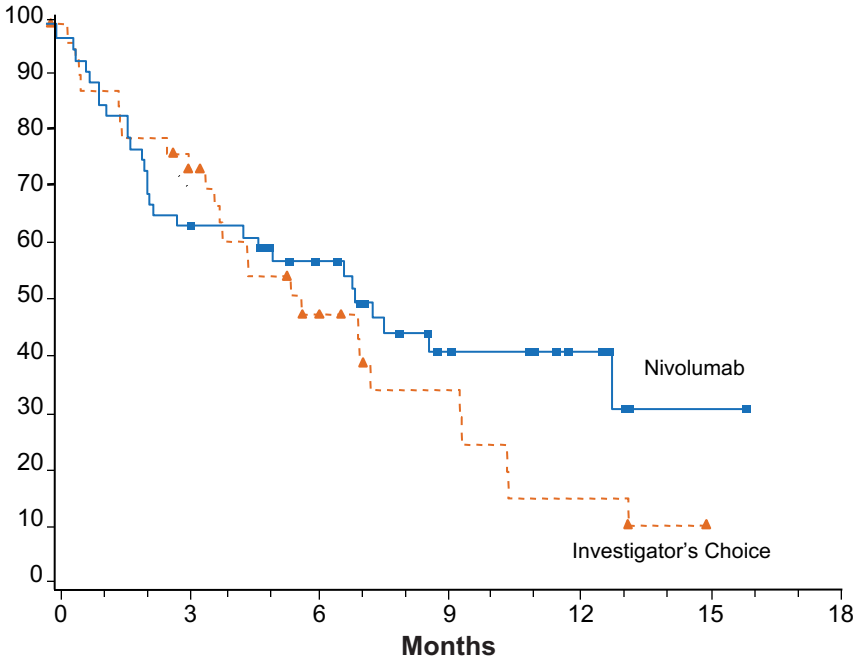
p16-Positive

	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 63)	9.1 (7.2–10.0)	0.56 (0.32–0.99)
Investigator's Choice (n = 29)	4.4 (3.0–9.8)	

p16-Negative

	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 50)	7.5 (3.0–NA)	0.73 (0.42–1.25)
Investigator's Choice (n = 36)	5.8 (3.8–9.5)	





No. at Risk

Nivolumab	63	49	35	18	10	3	0	50	32	25	12	6	1	0
Investigator's Choice	29	20	11	4	1	0	0	36	26	13	7	3	1	0

AACR 2016

Overall Survival Summary

	Nivolumab		Investigator's Choice		Comparison of Nivolumab to Investigator's Choice
	n	Median, mo	n	Median, mo	HR (95% CI)
All patients	240	7.5	121	5.1	0.70 (0.51–0.96)[a]
PD-L1 ≥1%	88	8.7	61	4.6	0.55 (0.36–0.83)
PD-L1 <1%	73	5.7	38	5.8	0.89 (0.54–1.45)
p16-positive	63	9.1	29	4.4	0.56 (0.32–0.99)
p16-negative	50	7.5	36	5.8	0.73 (0.42–1.25)

[a]HR and 97.73% CI

Table 2. Exploratory Analysis of Overall Survival According to Tumor PD-L1 Expression and p16 Status Subgroups.*

Variable	Nivolumab (N=240)		Standard Therapy (N=121)		Hazard Ratio for Death (95% CI)
	Patients	Median Survival	Patients	Median Survival	
	no. (%)	*mo*	*no. (%)*	*mo*	
All patients	240 (100.0)	7.5	121 (100.0)	5.1	0.69 (0.53–0.91)
PD-L1 expression level					
≥1%	88 (36.7)	8.7	61 (50.4)	4.6	0.55 (0.36–0.83)
≥5%	54 (22.5)	8.8	43 (35.5)	4.6	0.50 (0.30–0.83)
≥10%	43 (17.9)	8.7	34 (28.1)	5.2	0.56 (0.31–1.01)
<1%	73 (30.4)	5.7	38 (31.4)	5.8	0.89 (0.54–1.45)
<5%	107 (44.6)	7.0	56 (46.3)	5.1	0.81 (0.55–1.21)
<10%	118 (49.2)	7.2	65 (53.7)	4.6	0.73 (0.50–1.06)
Not quantifiable	79 (32.9)	7.8	22 (18.2)	5.8	0.79 (0.44–1.44)
p16 status					
Positive	63 (26.2)	9.1	29 (24.0)	4.4	0.56 (0.32–0.99)
Negative	50 (20.8)	7.5	36 (29.8)	5.8	0.73 (0.42–1.25)
Combined subgroup					
PD-L1 ≥1% and p16-positive	23 (9.6)	8.8	14 (11.6)	3.9	0.50 (0.21–1.19)
PD-L1 ≥1% and p16-negative	17 (7.1)	8.8	16 (13.2)	5.6	0.44 (0.18–1.10)
PD-L1 <1% and p16-positive	24 (10.0)	10.0	10 (8.3)	6.4	0.55 (0.22–1.39)
PD-L1 <1% and p16-negative	14 (5.8)	7.1	12 (9.9)	7.4	0.82 (0.31–2.19)

NIVOLUMAB

CHECKMATE 141 – FASE 3

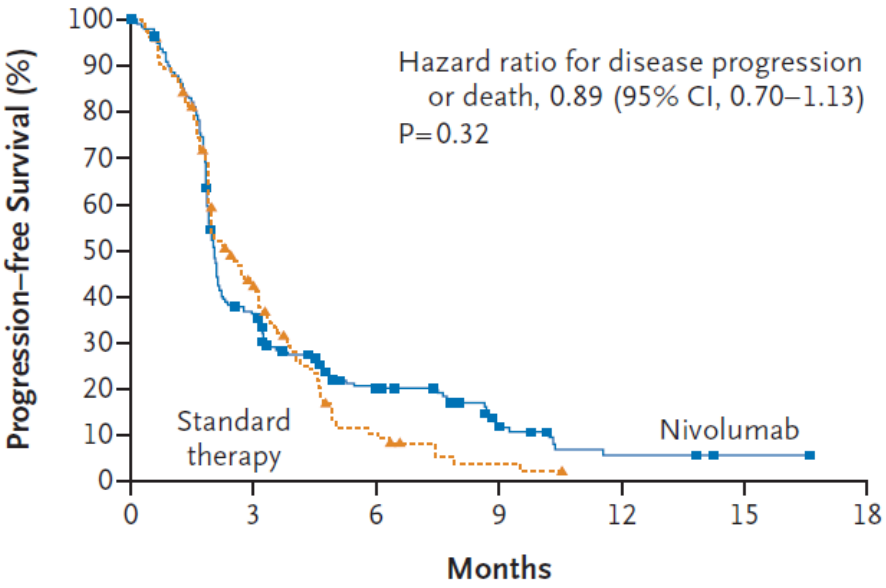
TASA DE RESPUESTAS

	Nivolumab	Terapia estándar
TR, n(%)	**32 (13.3%)**	**7 (5.8%)**
RC	6 (2.5)	1 (0.8)
RP	26 (10.8)	6 (5)
EE	55 (22.9)	43 (35.5)
EP	100 (41.7)	42 (34.7)
Tº a respuesta	**2.1 meses**	**2.0 meses**
Duración respuesta	**9.7 meses**	**4 meses**

Más respuesta y más duraderas con NIVO

Beneficio retardado de NIVO (SLP a 6 meses: 19.7% vs 9.9%)

SUPERVIVENCIA LIBRE DE PROGRESIÓN



Ferris RL et al. N Engl J Med 2016; 375:1856-67; Gillison M et al. ASCO 2017:#6019

Treatment-Related AEs in ≥ 10% of Patients

Event	Nivolumab (n = 236)		Investigator's Choice (n = 111)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Any[a]	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Alopecia	0	0	14 (12.6)	3 (2.7)

[a]One Grade 5 event (hypercalcemia) in the nivolumab arm and one Grade 5 event (lung infection) in the investigator's choice arm were reported. A second death occurred in the nivolumab arm subsequent to pneumonitis.

Treatment-Related Select AEs

Event	Nivolumab (n = 236)		Investigator's Choice (n = 111)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/Infusion reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)

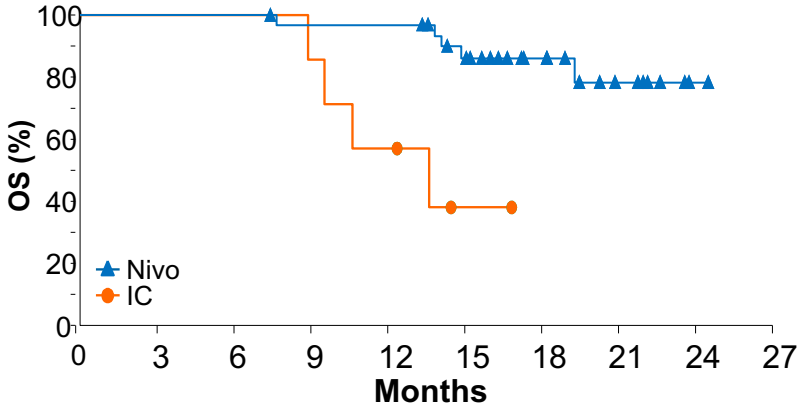
Select AEs: AEs with potential immunologic etiology that requires monitoring/intervention

NIVOLUMAB

CHECKMATE 141 – SUBANÁLISIS

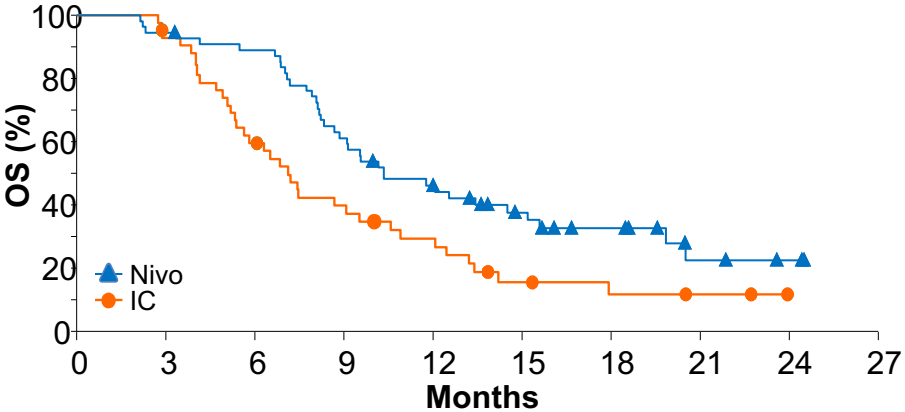
¿LOS PACIENTES SIN RESPUESTA OBJETIVA OBTIENEN BENEFICIO EN SUPERVIVENCIA?

RESPUESTA COMPLETA/PARCIAL



	Nivolumab (n = 32)	IC (n = 7)
Median OS (95% CI), months[a]	NR (NR, NR)	13.6 (8.9, NR)
HR (95% CI)[b]	0.12 (0.03, 0.51)	
12-month OS rate (95% CI), %	96.8 (79.2, 99.5)	57.1 (17.2, 83.7)
18-month OS rate (95% CI), %	86.1 (67.0, 94.6)	38.1 (6.1, 71.6)

ENFERMEDAD ESTABLE



	Nivolumab (n = 55)	IC (n = 43)
Median OS (95% CI), months[a]	10.4 (8.7, 15.2)	7.1 (5.4, 9.5)
HR (95% CI)[b]	0.54 (0.34, 0.86)	
12-month OS rate (95% CI), %	46.1 (32.4, 58.7)	29.4 (16.4, 43.7)
18-month OS rate (95% CI), %	32.6 (20.0, 45.8)	11.7 (3.6, 25.0)

NIVOLUMAB PROLONGA LA SG TANTO EN PACIENTES CON RC/RP COMO CON EE

Licitra L et al. ESMO 2017:#1055P

NIVOLUMAB

CHECKMATE 141 – SUBANÁLISIS

¿PUEDE SER BENEFICIOSO MANTENER NIVOLUMAB TRAS LA PROGRESIÓN?

SELECCIÓN DE PACIENTES

- Beneficio clínico a juicio del investigador
- Ausencia de progresión rápida
- Buena tolerancia a NIVO
- PS estable
- No retraso de intervenciones inminentes para prevenir complicaciones serias de la EP

n=57

NIVO TRAS LA PROGRESIÓN

- Supervivencia más prolongada (**12.7 vs 6.1 meses**)
- Reducción del tumor en un **23%** de los pacientes
- Tiempo entre la EP y la respuesta (mediana): 5.6 meses
- Sin incremento de la toxicidad

UN SUBGRUPO DE PACIENTES SELECCIONADOS PUEDE BENEFICIARSE DE CONTINUAR CON NIVO TRAS LA PROGRESIÓN

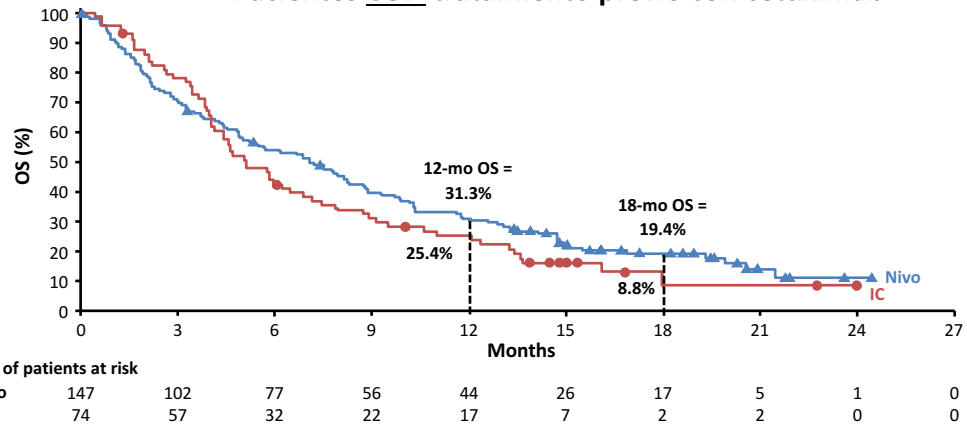
Haddad R et al. AACR 2017:#CT157

NIVOLUMAB

CHECKMATE 141 – SUBANÁLISIS

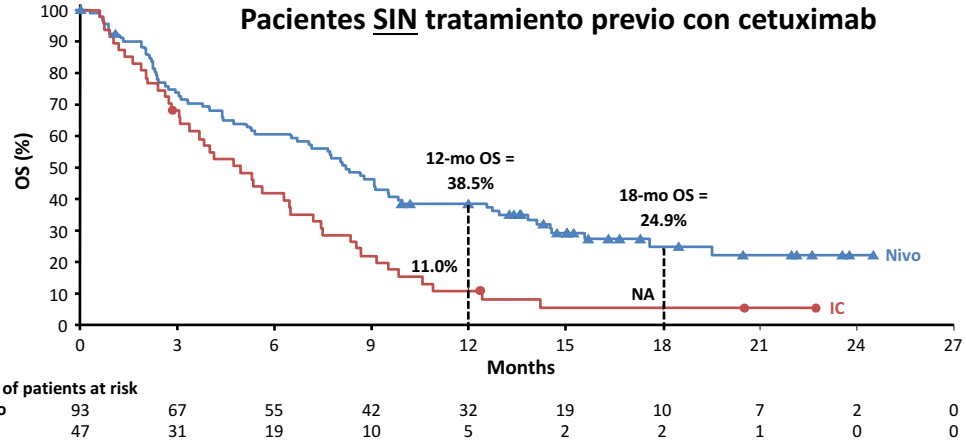
¿EL BENEFICIO ES INDEPENDIENTE DEL TRATAMIENTO PREVIO CON CETUXIMAB?

Pacientes CON tratamiento previo con cetuximab



	Median OS, mo (95% CI)	HR (95% CI)
Nivo (n = 147)	7.1 (4.9, 8.7)	0.84 (0.62, 1.15)
IC (n = 74)	5.1 (4.0, 6.8)	

Pacientes SIN tratamiento previo con cetuximab



	Median OS, mo (95% CI)	HR (95% CI)
Nivo (n = 93)	8.2 (5.4, 9.9)	0.52 (0.35, 0.77)
IC (n = 47)	4.9 (3.1, 6.5)	

Ferris RL et al. ASCO 2017:#6020

Conclusions

- Nivolumab is the first agent to demonstrate a significant improvement in survival in patients with SCCHN who progress after platinum-based therapy in a randomized, phase 3 comparative trial
- Nivolumab doubled the 1-year survival rate compared to investigator's choice therapy
  - 36% with nivolumab vs 17% with investigator's choice
- Nivolumab demonstrated a survival benefit in the overall study population, regardless of PD-L1 expression or p16 status
- Safety profile for nivolumab was favorable compared to investigator's choice therapy, and consistent with prior studies
- Nivolumab represents a new standard of care option for patients with R/M SCCHN after platinum-based therapy

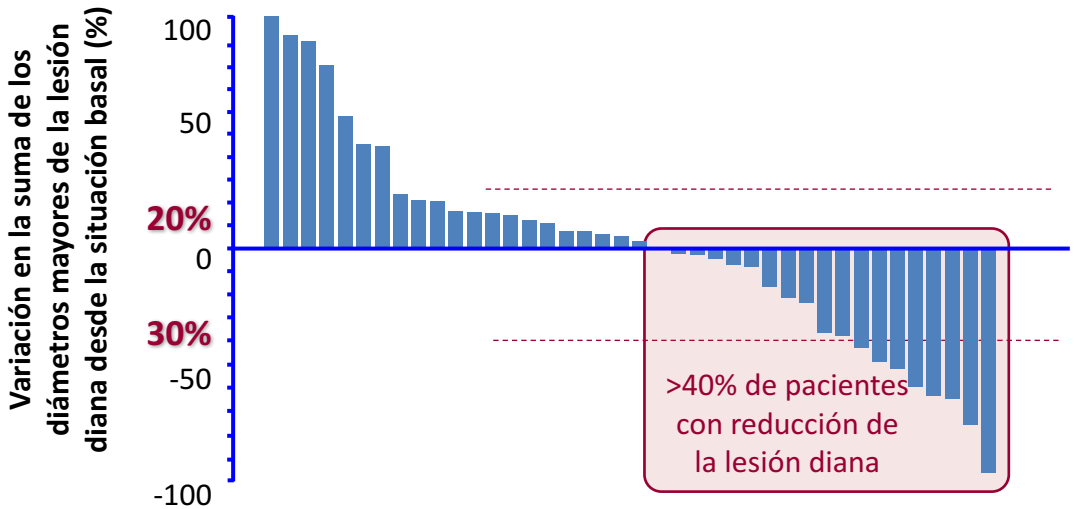
NIVOLUMAB

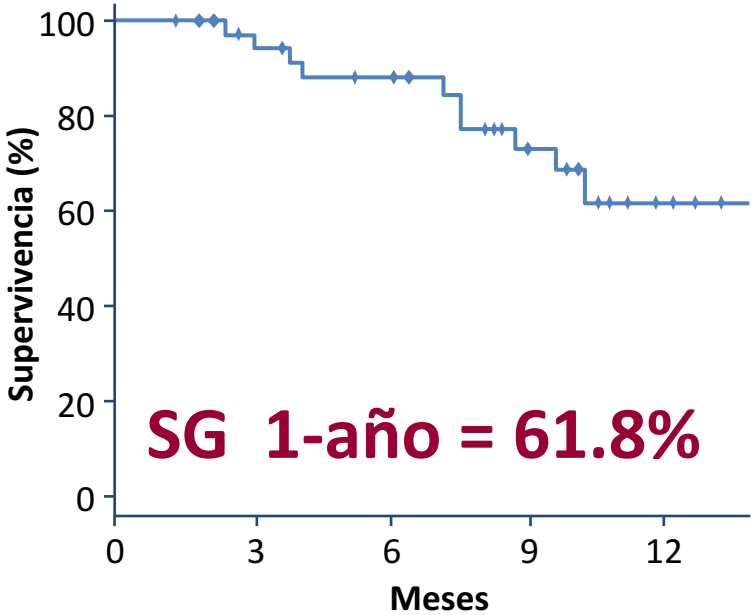
NCT02339558 – FASE 2

¿EXISTEN DATOS EN CARCINOMA DE NASOFARINGE?

CNF no queratinizante recurrente/M1, > 1 línea de tratamiento previo → **n=40** → **NIVOLUMAB 3 mg/kg c/2 sem** → Hasta EP o toxicidad inaceptable

Objetivo 1º: TR (RECIST)





RESPUESTAS DURADERAS Y SUPERVIVENCIA COMPARABLE A CONTROLES HISTÓRICOS CON QT

Ma B et al. AACR 2017:#CT076

NIVOLUMAB

ANEXO I

FICHA TÉCNICA O RESUMEN DE LAS CARACTERÍSTICAS DEL PRODUCTO

4. DATOS CLÍNICOS

4.1 Indicaciones terapéuticas

Cáncer de Células Escamosas de Cabeza y Cuello (CCECC)

OPDIVO en monoterapia está indicado para el tratamiento de pacientes adultos con cáncer de células escamosas de cabeza y cuello que progresa durante o después de un tratamiento basado en platino (ver sección 5.1).

** Aprobado por la EMA y a la espera de precio y reembolso en España*

PEMBROLIZUMAB

KEYNOTE 040 – FASE 3

MADRID 2017 ESMO congress

E Cohen_ESMO 2017

Pembrolizumab vs Standard of Care For Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Phase 3 KEYNOTE-040 Trial

Ezra EW Cohen,[1] Kevin J. Harrington,[2] Christophe Le Tourneau,[3] José Dinis,[4] Lisa Licitra,[5] Myung-Ju Ahn,[6] Ainara Soria,[7] Jean-Pascal Machiels,[8] Nicolas Mach,[9] Ranee Mehra,[10] Barbara Burtness,[11] Yang Wang,[12] Alba Tuozzo,[12] Jonathan D Cheng,[12] Ramona Swaby,[12] Denis Soulières[13]

[1]University of California, San Diego Moores Cancer Center, La Jolla, CA, USA; [2]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust, London, UK; [3]Institut Curie, Paris, France; [4]Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal; [5]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; [6]Samsung Medical Center, Seoul, South Korea; [7]Hospital Universitario Ramón y Cajal, Madrid, Spain; [8]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [9]Hôpitaux Universitaires de Genève, Geneva, Switzerland; [10]Fox Chase Cancer Center, Philadelphia, PA, USA (currently at Sidney Kimmel Cancer Center of Johns Hopkins University, Baltimore, MD, USA); [11]Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA; [12]Merck & Co., Inc., Kenilworth, NJ, USA; [13]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada

Cohen E et al. ESMO 2017:#LBA45_PR

E Cohen_ESMO 2017

Phase 3 KEYNOTE-040 Study (NCT02252042)

Key Eligibility Criteria

- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence or PD within 3-6 mo of multimodal therapy using platinum[a]
- ECOG PS 0 or 1
- Known p16 status (oropharynx)[b]
- Tissue sample[c] for PD-L1 assessment[d]

Stratification Factors

- ECOG PS (0 vs 1)
- p16 status[b] (positive vs negative)
- PD-L1 TPS[d] (≥50% vs <50%)

R 1:1

Pembrolizumab
200 mg IV Q3W
for 2 y

Methotrexate 40 mg/m² QW[e]
OR
Docetaxel 75 mg/m² Q3W
OR
Cetuximab 250 mg/m² QW[f]

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%.
[c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[e]Could be increased to 60 mg/m² QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m².

Analysis Populations and End Points

Analysis Populations

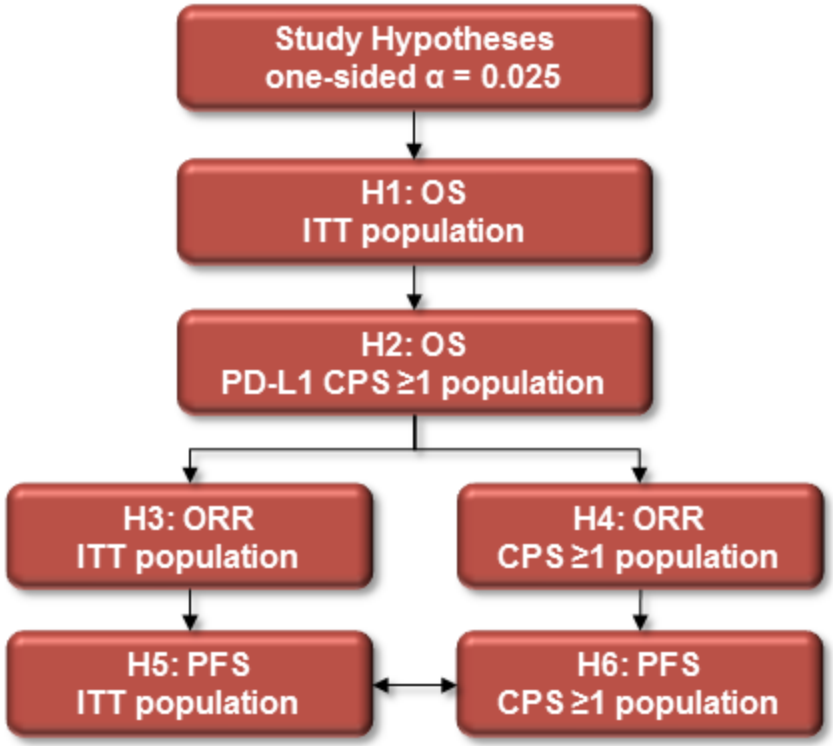
- Intention-to-treat (ITT)
- PD-L1 combined positive score (CPS) ≥1[a]
  - Previously reported as and equivalent to CPS ≥1%
  - CPS = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100
- PD-L1 tumor proportion score (TPS) ≥50%[a]
  - TPS = percentage of tumor cells with membranous PD-L1 expression

Key End Points

- Primary: OS in the ITT population
- Secondary
  - OS in the CPS ≥1 population
  - PFS[b] in the ITT and CPS ≥1 populations
  - ORR[b] in the ITT and CPS ≥1 populations
  - DOR[b] in the ITT and CPS ≥1 populations
  - Safety and tolerability
- Predefined exploratory
  - OS, PFS,[b] ORR,[b] and DOR[b] in the TPS ≥50% population

[a]PD-L1 assessed at a central laboratory in newly collected (preferred) or archival tumor samples using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies).
[b]Assessed per RECIST v1.1 by blinded, independent radiology review.

Statistical Considerations



- Multiplicity strategy
  - Family-wise alpha strictly controlled at **0.025 (one sided)**
  - Alpha allocated in stepwise fashion
- Final analysis
  - Performed after **380 OS** events in 495 patients
  - Data cutoff date: May 15, 2017
  - **Efficacy boundary**
    - OS, ITT: one-sided **α = 0.0175**, HR ~0.80
    - OS, CPS ≥1: one-sided α = 0.0178, HR ~0.78
      - Tested only if efficacy boundary in ITT population reached

Data cutoff date: May 15, 2017.

Baseline Characteristics

Characteristic, n (%)	Pembro N = 247	SOC N = 248
Age, median (range)	60 (19-85)	60 (34-78)
Male	207 (83.8)	205 (82.7)
ECOG PS 1	176 (71.3)	180 (72.6)
Current/former smoker	179 (72.5)	182 (73.4)
Region of enrollment		
Europe + Russia	158 (64.0)	177 (71.4)
North America	73 (29.6)	60 (24.2)
Asia Pacific	16 (6.5)	11 (4.4)

Characteristic, n (%)	Pembro N = 247	SOC N = 248
p16 positive (oropharynx)	61 (24.7)	58 (23.4)
PD-L1 TPS ≥50%	64 (25.9)	65 (26.2)
PD-L1 CPS ≥1	196 (79.4)	191 (77.0)
Prior therapy		
(Neo)adjuvant or definitive	34 (13.8)	40 (16.1)
First line	141 (57.1)	141 (56.9)
Second line	69 (27.9)	64 (25.8)
Third line	3 (1.2)	3 (1.2)

Data cutoff date: May 15, 2017.

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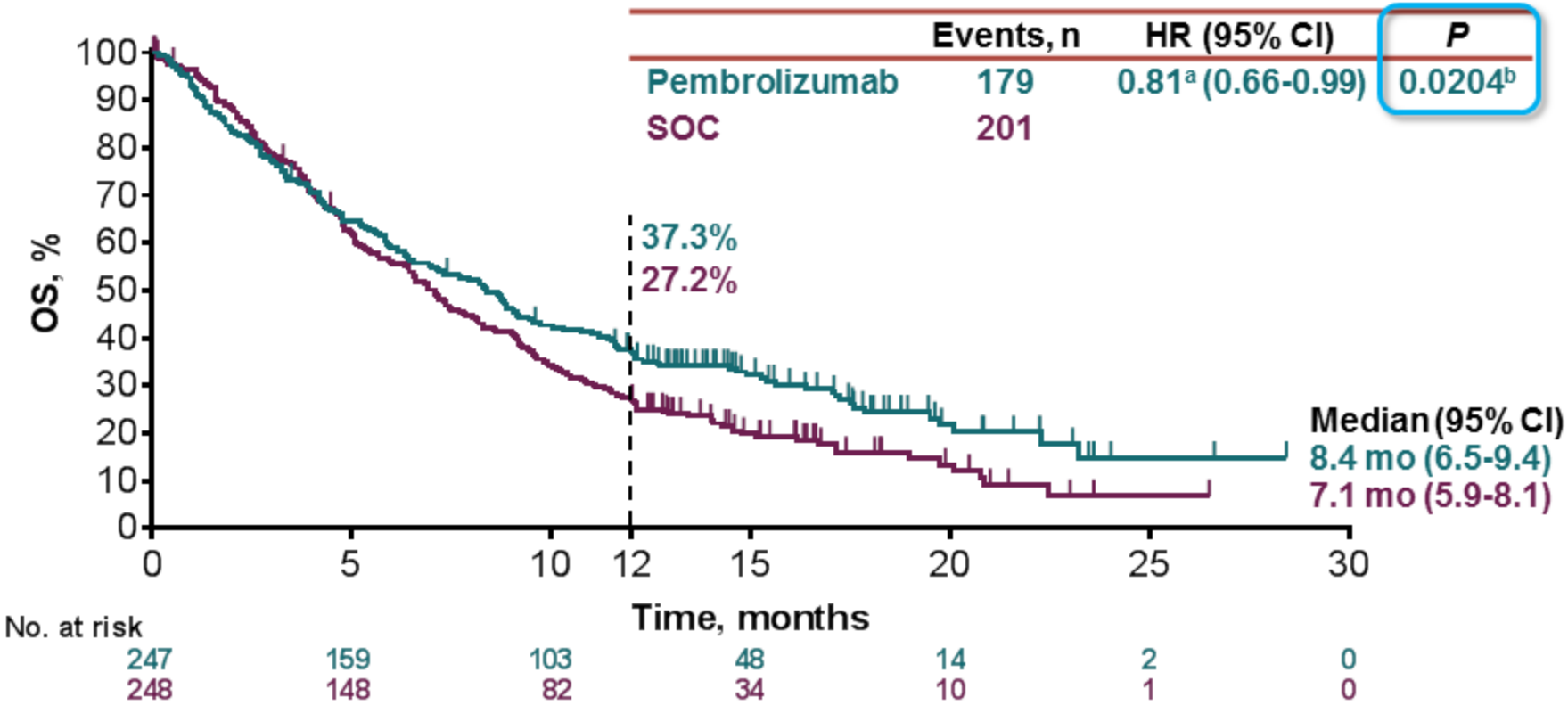
Overall Survival in ITT Population



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 0.67-1.01), $P = 0.0316$. After the initial report, updated survival data were obtained for 4 patients. [b]One-sided P value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

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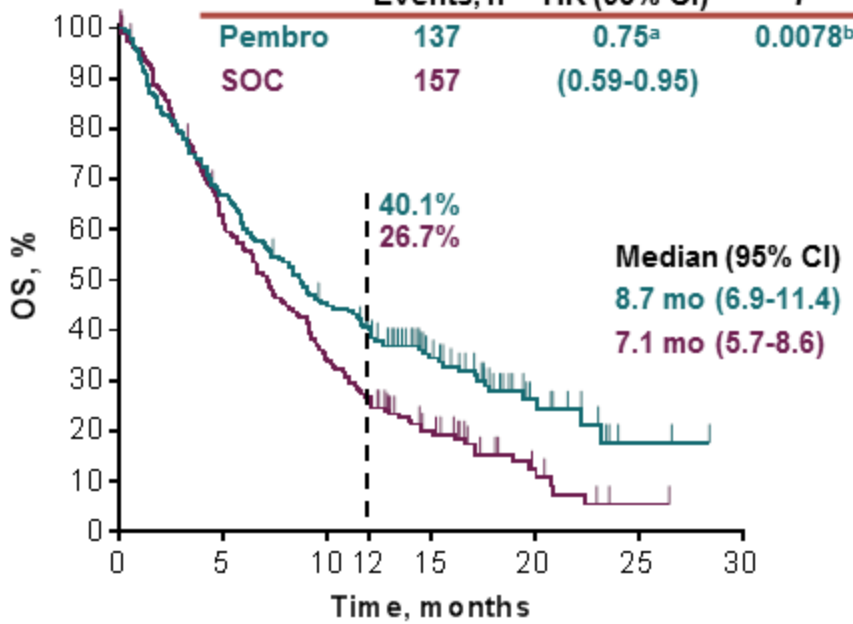
Overall Survival by PD-L1 Expression

PD-L1 CPS ≥1

	Events, n	HR (95% CI)	*P*
Pembro	137	0.75[a]	0.0078[b]
SOC	157	(0.59-0.95)	

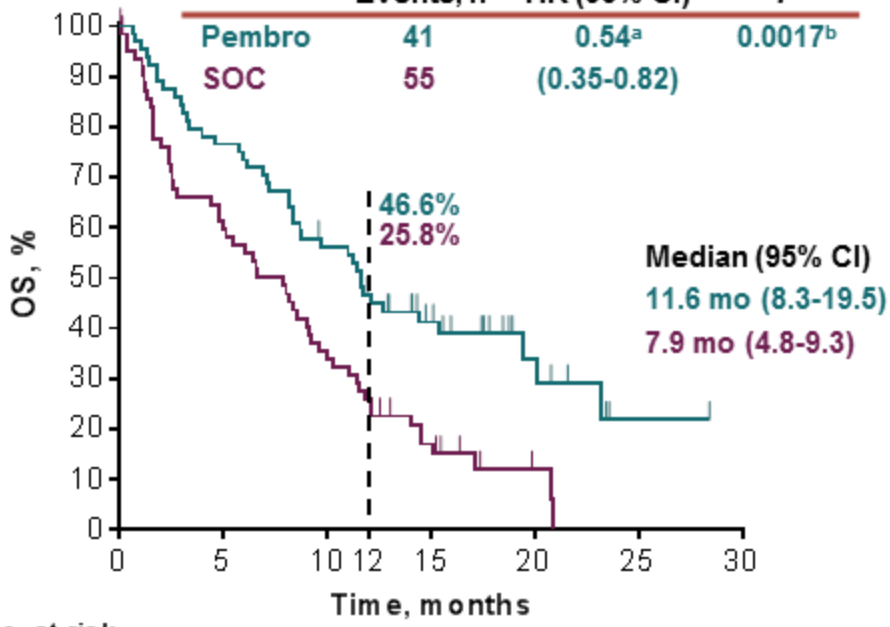


No. at risk

196	131	87	43	14	2	0
191	113	63	28	8	1	0

PD-L1 TPS ≥50%

	Events, n	HR (95% CI)	*P*
Pembro	41	0.54[a]	0.0017[b]
SOC	55	(0.35-0.82)	



No. at risk

64	49	35	19	7	1	0
65	38	22	9	2	0	0

[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.
[b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors.
Data cutoff date: May 15, 2017.

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Objective Response Rate
(RECIST v1.1, Blinded Independent Radiology Review)

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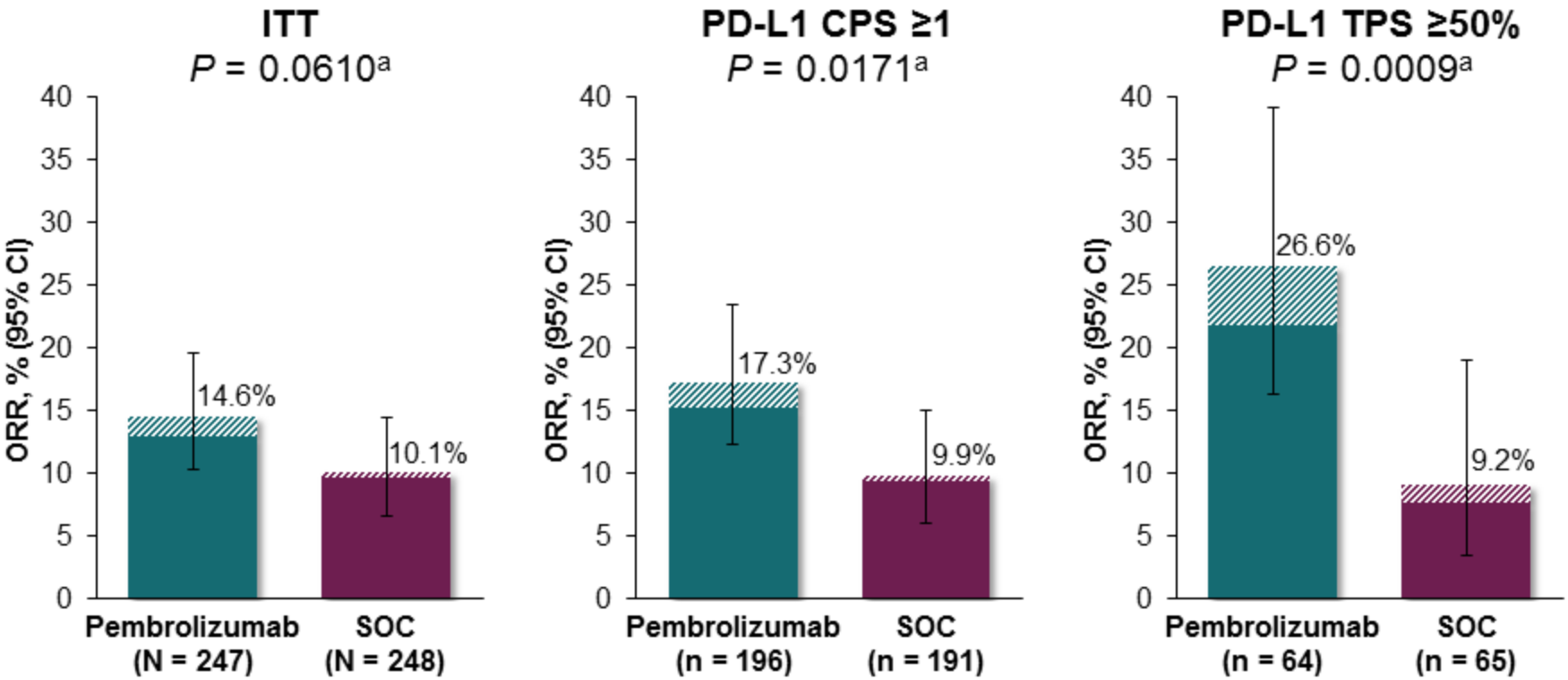

[a]Nominal one-sided *P* value based on the Miettinen and Nurminen method stratified by the randomization stratification factors.
Data cutoff date: May 15, 2017.

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Best Overall Response
(RECIST v1.1, Blinded Independent Radiology Review)

	ITT		CPS ≥1		TPS ≥50%	
Best Response, (%)	Pembro N = 247	SOC N = 248	Pembro n = 196	SOC n = 191	Pembro n = 64	SOC n = 65
CR	4 (1.6)	1 (0.4)	4 (2.0)	1 (0.5)	3 (4.7)	1 (1.5)
PR	32 (13.0)	24 (9.7)	30 (15.3)	18 (9.4)	14 (21.9)	5 (7.7)
SD	56 (22.7)	65 (26.2)	46 (23.5)	53 (27.7)	15 (23.4)	15 (23.1)
PD	108 (43.7)	97 (39.1)	77 (39.3)	72 (37.7)	22 (34.4)	23 (35.4)
NonCR/nonPD[a]	2 (0.8)	1 (0.4)	2 (1.0)	0	1 (1.6)	0
Not evaluable or assessable[b]	45 (18.2)	60 (24.2)	37 (18.9)	47 (24.6)	9 (14.1)	21 (32.3)

[a]Patients without measurable disease at baseline per RECIST v1.1 by independent radiology review who did not experience CR or PD.
[b]Not evaluable: patients who had ≥1 postbaseline tumor assessment, none of which were evaluable (n = 9); not assessable: patients who had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy (n = 96).
Data cutoff date: May 15, 2017.

Progression-Free Survival
(RECIST v1.1, Blinded Independent Radiology Review)

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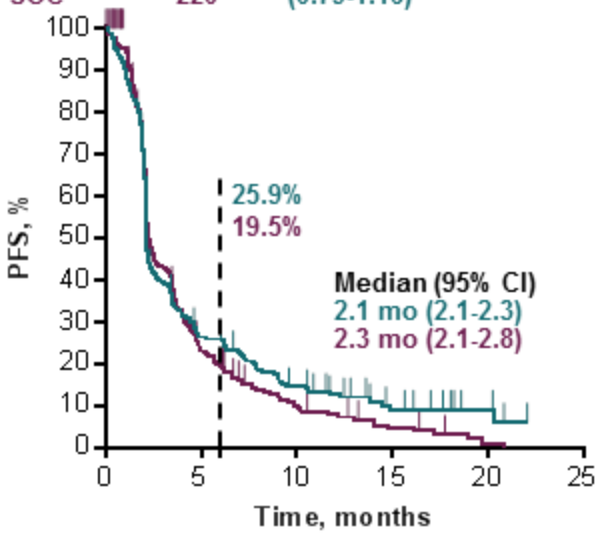
ITT

	Events, n	HR[a] (95% CI)	P^b
Pembro	217	0.95	0.3037
SOC	220	(0.79-1.16)	

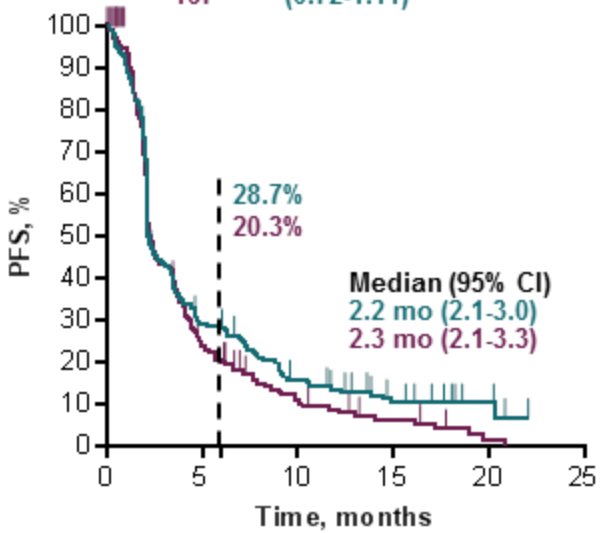


No. at risk

247	62	32	11	4	0
248	52	19	7	1	0

PD-L1 CPS ≥1

	Events, n	HR[a] (95% CI)	P^b
Pembro	170	0.89	0.1526
SOC	167	(0.72-1.11)	

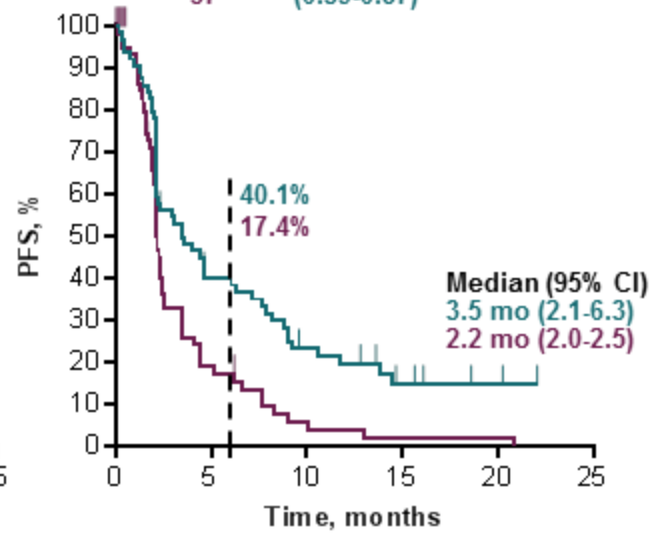


No. at risk

196	55	28	11	4	0
191	41	16	7	1	0

PD-L1 TPS ≥50%

	Events, n	HR[a] (95% CI)	P^b
Pembro	52	0.58	0.0034
SOC	57	(0.39-0.87)	



No. at risk

64	24	13	5	2	0
65	11	3	1	1	0

[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.
[b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

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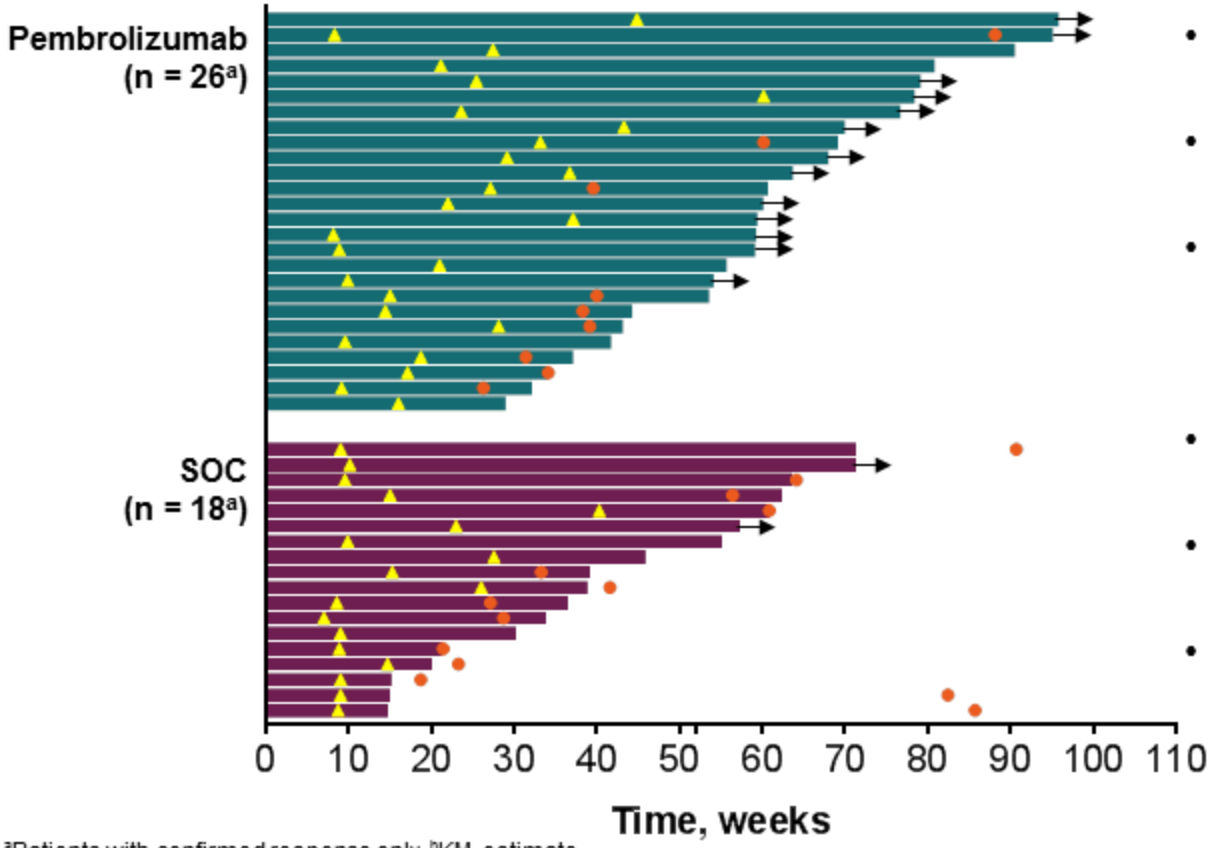
Time to and Duration of Response: ITT
(RECIST v1.1, Blinded Independent Radiology Review)

E Cohen
ESMO 2017



- Median (range) time to response: 4.5 mo (1.9-13.8)
- Median[b] (range) duration of response: **18.4 mo** (2.7-18.4)
- Response duration ≥6 mo[b]: **71.5%**

- Median (range) time to response: 2.2 mo (1.6-9.3)
- Median[b] (range) duration of response: **5.0 mo** (1.4+-14.4+)
- Response duration ≥6 mo[b]: **47.1%**

First response
Radiologic PD or death[c]
Ongoing treatment

[a]Patients with confirmed response only. [b]KM estimate.
[c]Whichever occurred first. Data cutoff date: May 15, 2017.

Overall Survival in Subgroups, ITT Population

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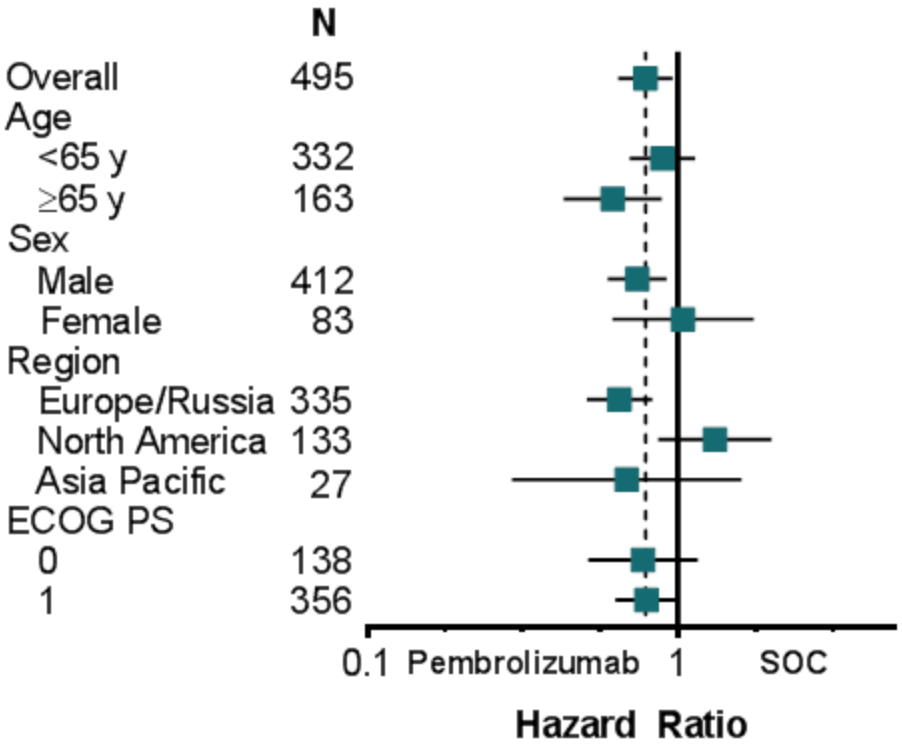

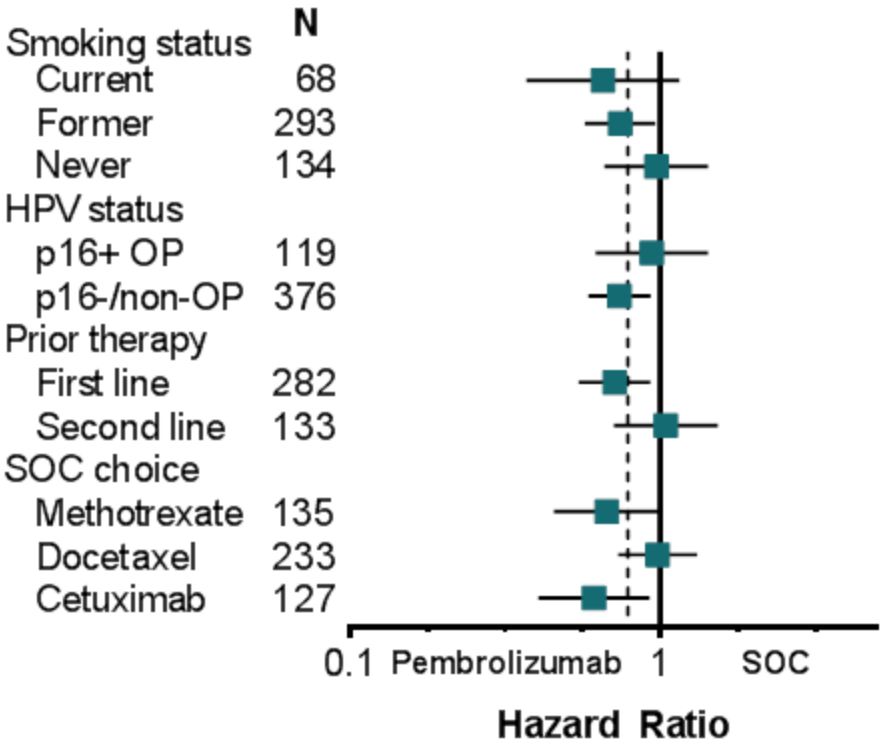

Unstratified Cox proportional hazards model with treatment as a covariate.
Data cutoff date: May 15, 2017.

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Summary

- Pembrolizumab provided a 19% reduction in the risk of death over investigator's choice of SOC in patients with R/M HNSCC
  - HR 0.81, $P = 0.0204$
  - Prespecified efficacy boundary was not reached
  - Post-study crossover in the SOC arm appears to have confounded the OS analysis
- Responses more frequent and more durable in the pembrolizumab arm
  - ORR: 14.6% vs 10.1%
  - Median DOR: 18.4 mo vs 5.0 mo
- Pembrolizumab benefit greater in patients with PD-L1–expressing tumors
  - CPS ≥1: 0.75 HR for OS, ORR 17.3% with pembrolizumab vs 9.9% with SOC
  - TPS ≥50%: 0.54 HR for OS, ORR 26.6% with pembrolizumab vs 9.2% with SOC
  - All CRs with pembrolizumab observed in CPS ≥1 population

Summary

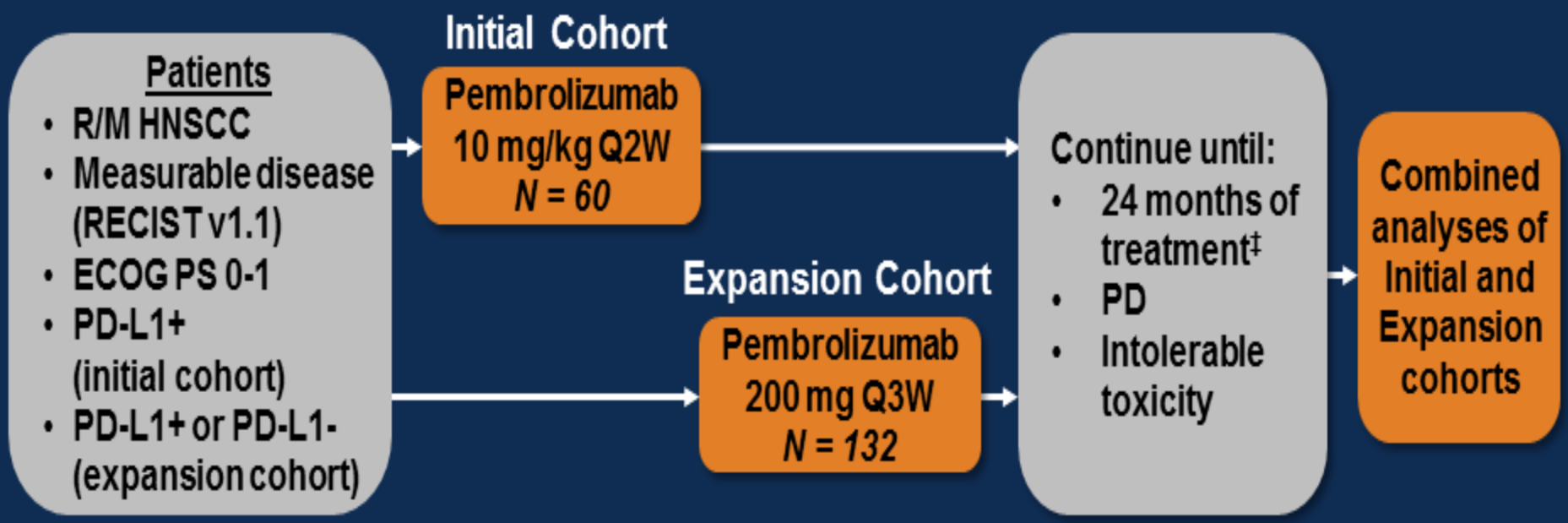
- Incidence of treatment-related AEs of any grade and grade 3-5 severity lower with pembrolizumab
  - Any grade: 63.0% vs 83.8%
  - Grade 3-5: 13.4% vs 36.3%
- Ongoing phase 3 studies of pembrolizumab in HNSCC
  - KEYNOTE-048: pembrolizumab monotherapy vs pembrolizumab + platinum + 5-FU vs cetuximab + platinum + 5-FU as first-line therapy for R/M HNSCC (NCT02358031)
  - KEYNOTE-412: pembrolizumab + chemoradiation vs placebo + chemoradiation for locally advanced HNSCC (NCT03040999)

Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): pooled analyses after long-term follow-up in KEYNOTE-012

Ranee Mehra,[1] Tanguy Y. Seiwert,[2] Amit Mahipal,[3] Jared Weiss,[4] Raanan Berger,[5] J. Paul Eder,[6] Barbara Burtness,[6] Makoto Tahara,[7] Bhumsuk Keam,[8] Dung T. Le,[9] Kei Muro,[10] Ravit Geva,[11] Hyun Cheol Chung,[12] Chia-Chi Lin,[13] Amy Meister,[14] Kumudu Pathiraja,[14] Jonathan Cheng,[14] Laura Q. Chow,[15] Robert Haddad[16]

[1]Fox Chase Cancer Center, Philadelphia, PA; [2]University of Chicago, Chicago, IL; [3]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [4]Lineberger Comprehensive Cancer Center at the University of North Carolina, Chapel Hill, NC; [5]Sheba Medical Center, Tel Hashomer, Israel; [6]Yale Cancer Center, New Haven, CT; [7]National Cancer Center Hospital East, Chiba, Japan; [8]Seoul National University Hospital, Seoul, Republic of Korea; [9]Johns Hopkins University, Baltimore, MD; [10]Aichi Cancer Center Hospital, Nagoya, Japan; [11]Sourasky Medical Center, Tel Aviv, Israel; [12]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [13]National Taiwan University Hospital, Taipei, Taiwan; [14]Merck & Co., Inc., Kenilworth, NJ; [15]University of Washington, Seattle, WA; [16]Dana-Farber Cancer Institute, Boston, MA

HNSCC Cohorts of Nonrandomized, Phase 1b, Multi-cohort KEYNOTE-012 Trial†



Response assessment: Every 8 weeks

Primary end points: ORR (RECIST v1.1, central imaging vendor), safety

Secondary end points: ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients§

†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§Initial cohort only.

Baseline Characteristics All HNSCC Patients

Characteristic	N = 192† n (%)
Median age (range), years	60 (20–84)
Male	159 (83)
ECOG performance status	
0	57 (30)
1	135 (70)
Metastatic stage M1	165 (86)
HPV status‡	
Positive	45 (23)
Negative	147 (77)

Characteristic	N = 192† n (%)
Median prior systemic therapies (range)	2 (0-7)
Prior lines of systemic therapy§	
1	47 (24)
2	56 (29)
≥3	86 (45)
Prior platinum therapy	174 (91)
Prior platinum and cetuximab therapy	110 (57)

Data cutoff date: Apr 26, 2016. †Includes patients who received ≥1 dose of pembrolizumab in the initial or expansion cohort. ‡HPV status was determined by the local institution. Cancers outside the oropharynx, identified from primary diagnosis/prior radiation/prior surgery, were considered HPV negative. §3 patients received 0 systemic therapies.

Overall Response Rate

Best Overall Response	Total N = 192†			HPV+ n = 45‡			HPV− n = 147‡		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
ORR	34	18	13–24	11	24	13–40	23	16	10–23
CR	8	4	–	4	9	–	4	3	–
PR	26	14	–	7	16	–	19	13	–
SD	33	17	–	7	16	–	26	18	–
PD	93	48	–	19	42	–	74	50	–
NA§	32	17	–	8	18	–	24	16	–

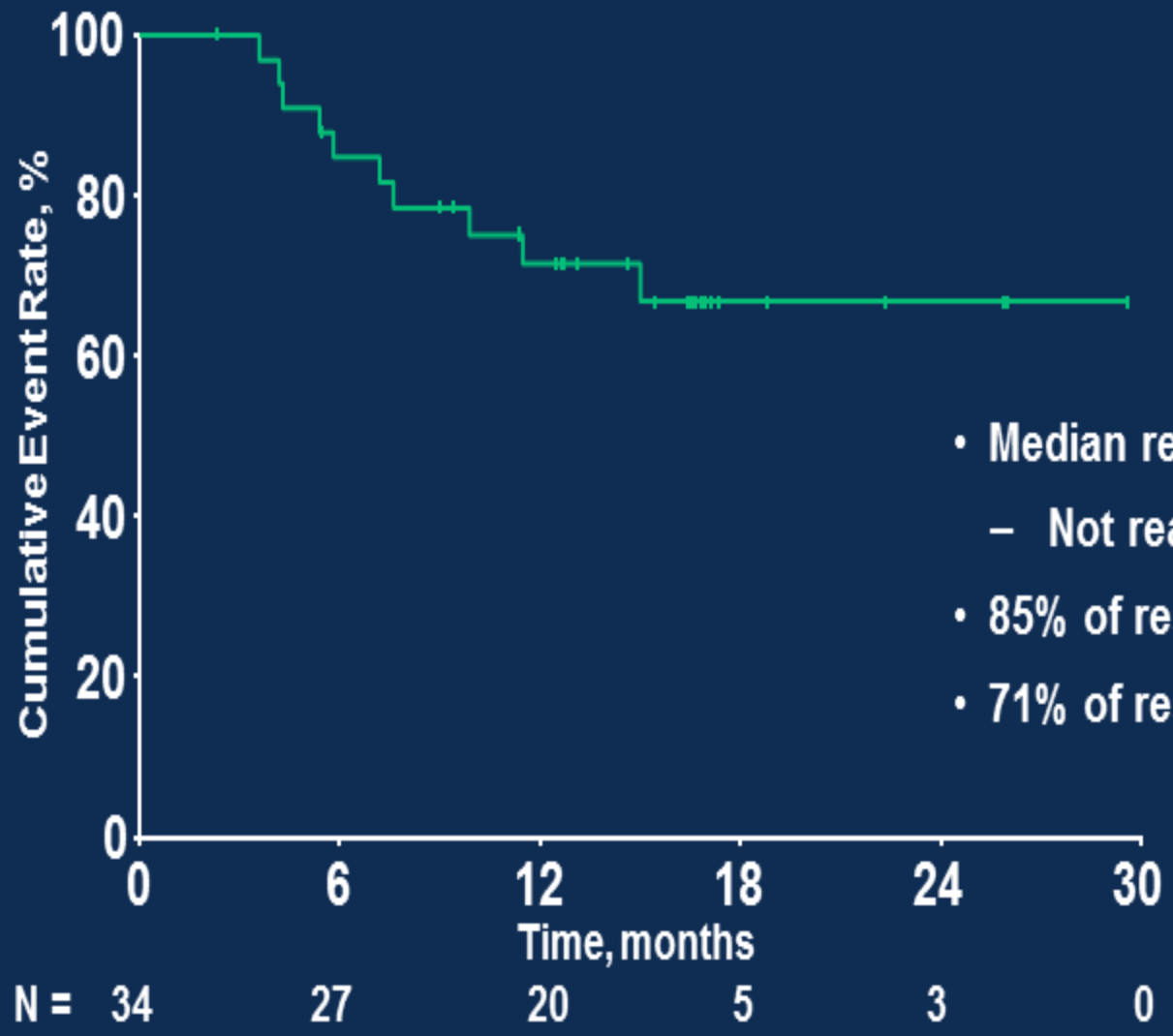
Data cutoff date: Apr 26, 2016. Response assessed per RECIST v1.1 (central imaging vendor review, all patients as treated). Only confirmed responses are included.
†Includes patients who received ≥1 dose of pembrolizumab in the initial or expansion cohort.
‡HPV status was determined by the local institution. Cancers outside the oropharynx, identified from primary diagnosis/prior radiation/prior surgery, were considered HPV negative.
§No assessment because patient did not have central imaging review data or images were not evaluable.

Overall Response Rate by Prior Treatment

Best Overall Response	Prior Platinum n = 174			Prior Platinum and Cetuximab† n = 110		
	n	%	95% CI	n	%	95% CI
ORR	29	17	12–23	16	15	9–23
CR	8	5	–	5	5	–
PR	21	12	–	11	10	–
SD	31	18	–	18	16	–
PD	86	49	–	57	52	–
NA‡	28	16	–	19	17	–

Data cutoff date: Apr 26, 2016. Response assessed per RECIST v1.1 (central imaging vendor review). Only confirmed responses are included. †Subset of "prior platinum" patients. ‡No assessment because patient did not have central imaging review data or images were not evaluable.

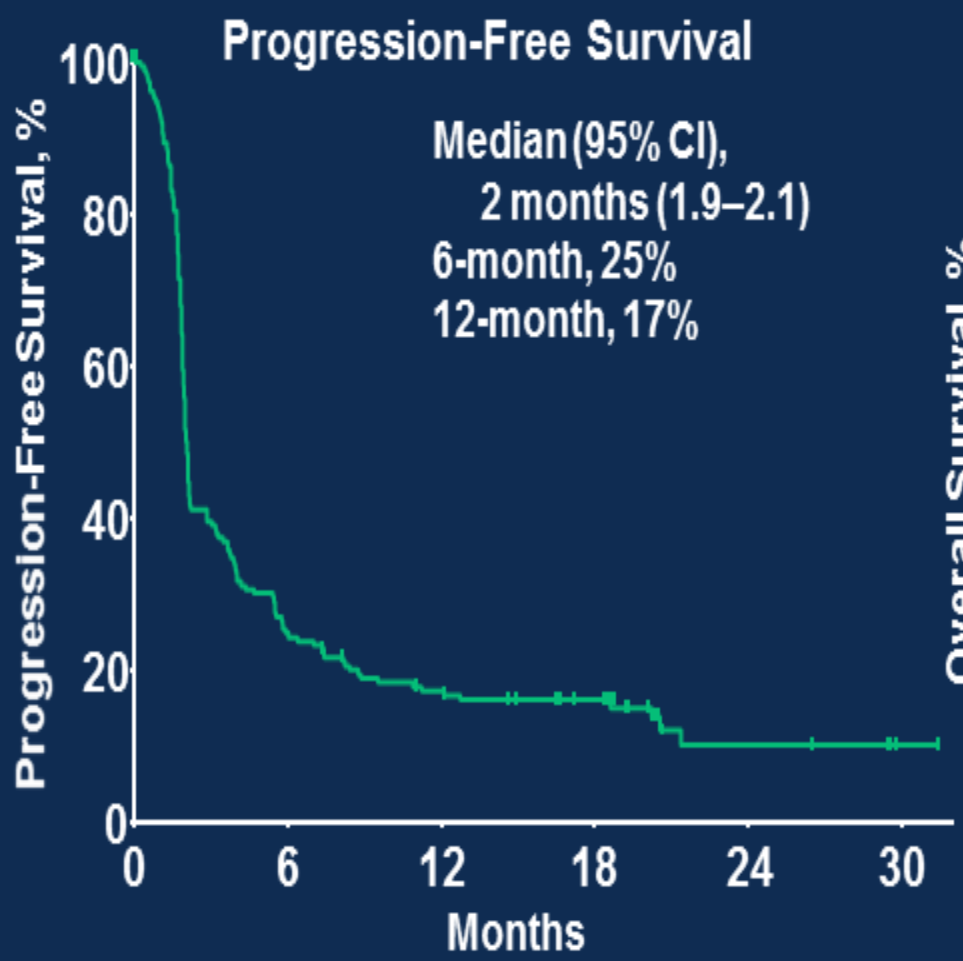
Objective Response Duration

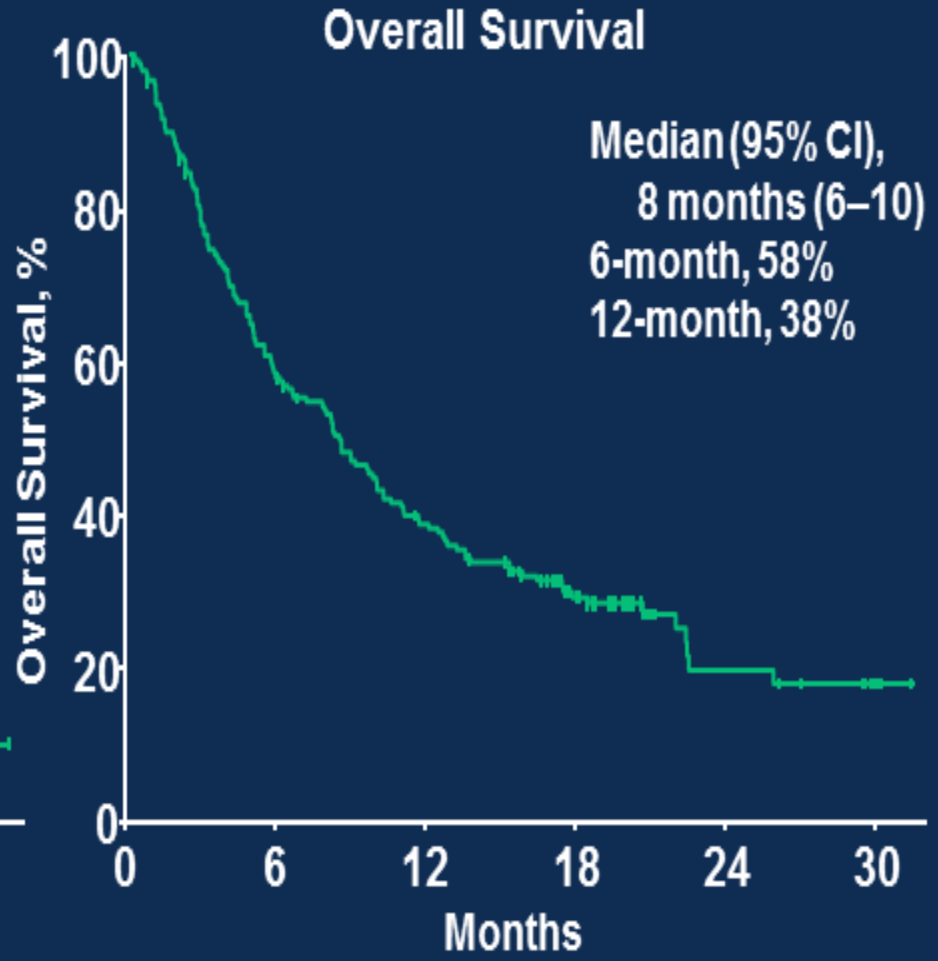


- Median response duration
  - Not reached (range, 2+ to 30+ months)
- 85% of responses lasted for ≥6 months
- 71% of responses lasted for ≥12 months

Data cutoff date: Apr 26, 2016.
Based on patients with confirmed response per RECIST v1.1 by central imaging vendor review.

Progression-Free Survival† and Overall Survival





N =	192	47	30	21	5	1	192	109	69	37	11	2

Data cutoff date: Apr 26, 2016.
†RECIST v1.1 by central imaging vendor review.

Summary and Conclusions

- Pembrolizumab had robust, durable antitumor activity in heavily pretreated patients with R/M HNSCC (>16 months since last patient enrolled)
  - Promising ORR
    - Overall, 18%; Pts with prior platinum, 17%; Pts with prior platinum and cetuximab, 15%
  - Durable responses
    - Median response duration not reached
    - 65% of responders remain in response
    - 85% of responses was ≥6 months and 71% was ≥12 months
  - Encouraging survival
    - 6-month OS, 58%; 12-month OS, 38%
- Pembrolizumab was well tolerated
  - 6% discontinued due to a treatment-related AE
  - No treatment-related deaths

PEMBROLIZUMAB

KEYNOTE 055 – FASE 2

CECC recurrente/M1 (cavidad oral, faringe, laringe), **en progresión tras platino y cetuximab** → **n=171** → **PEMBROLIZUMAB 200 mg c/3 sem** → Hasta 24 meses, EP o toxicidad inaceptable

Objetivo 1º: TR (RECIST v1.1)

Characteristic	All Patients N = 171
Age, years, median (range)	61 (33-90)
Male, n (%)	138 (81)
ECOG performance status, n (%)	
0	48 (28)
1	120 (70)
2†	3 (2)
HPV status, n (%)‡	
Positive	37 (22)
Negative	131 (77)
History of tobacco use, n (%)	
Yes	117 (68)
No	54 (32)
Previous systemic therapies, median (range)	2 (1-6)
Previous lines for recurrent/metastatic disease, n (%)	
1	39 (23)
2	68 (40)
≥3	61 (36)
PD-L1 status,§ n (%)	
CPS ≥1%	140 (82)
CPS <1%	26 (15)
CPS ≥50%	48 (28)
CPS <50%	118 (69)

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PEMBROLIZUMAB

KEYNOTE 055 – FASE 2

Response Evaluation	All Patients‡ N = 171		HPV-Positive§ n = 37		HPV-Negative§ n = 131	
	n	% (95% CI)‖	n	% (95% CI)‖	n	% (95% CI)‖
Overall response	28	16 (11-23)	6	16 (6-32)	20	15 (10-23)
Complete response	1	1 (0-3)	0	0 (0-10)	1	1 (0-4)
Partial response	27	16 (11-22)	6	16 (6-32)	19	15 (9-22)
Stable disease	33	19 (14-26)	6	16 (6-32)	26	20 (13-28)
Progressive disease	87	51 (43-59)	21	57 (40-73)	66	50 (42-59)

Mediana de tiempo a respuesta (rango):
2 meses (7-17 meses)

Mediana de duración de la respuesta (rango):
8 meses (2+ - 12+ meses)

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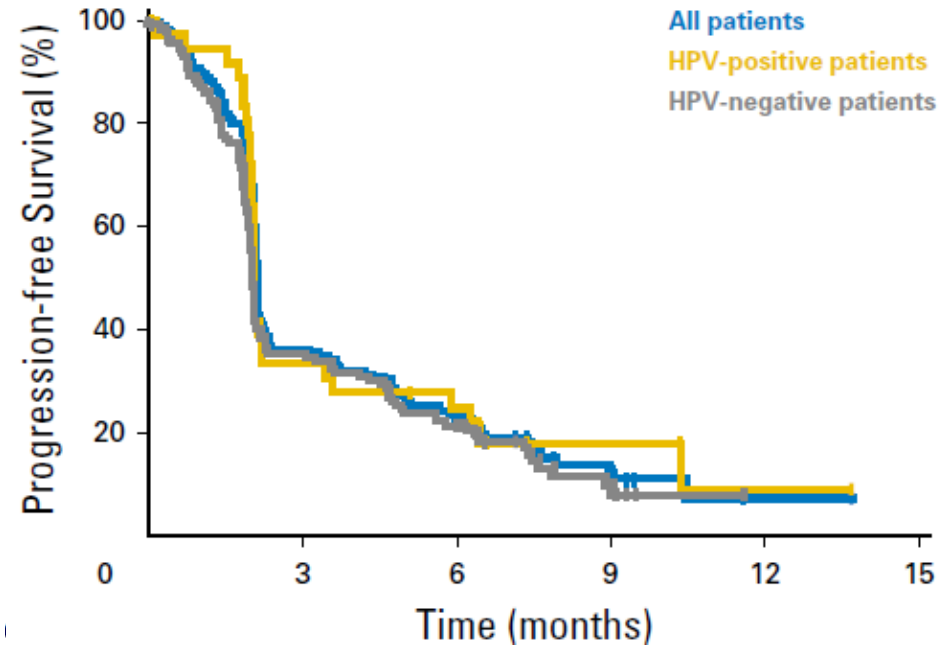
PEMBROLIZUMAB

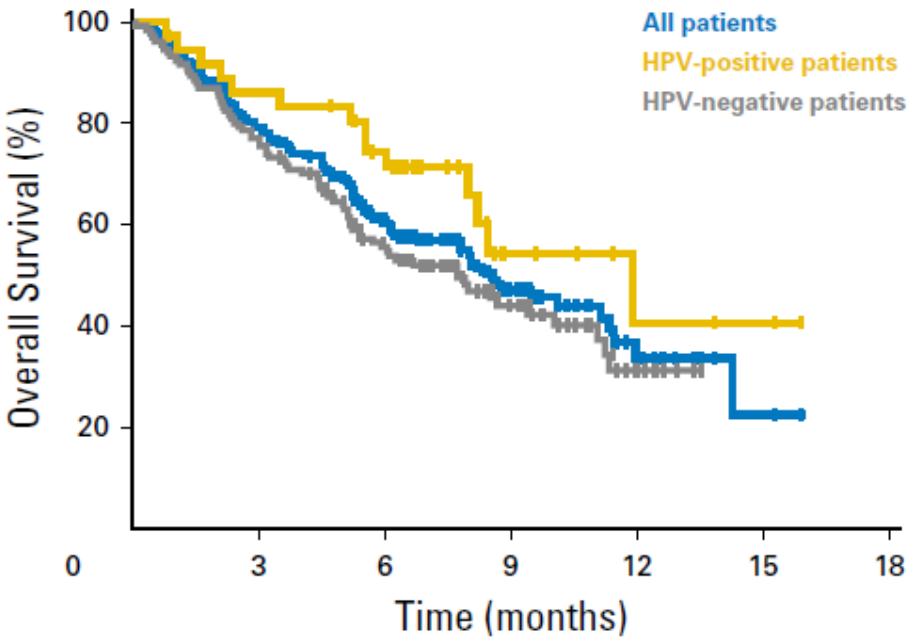
KEYNOTE 055 – FASE 2

SUPERVIVENCIA LIBRE DE PROGRESIÓN



Mediana **SLP**: 2.1 meses

SUPERVIVENCIA GLOBAL



Mediana **SG**: 8 meses

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PEMBROLIZUMAB

KEYNOTE 055 – FASE 2

TASA DE RESPUESTAS SEGÚN LA EXPRESIÓN DE PD-L1

PD-L1 ≥ 1% | **PD-L1 < 1%** | **PD-L1 ≥ 50%** | **PD-L1 < 50%**

Antitumor Activity on the Basis of PD-L1 Expression Status

	CPS ≥ 1% (n = 140)		CPS < 1% (n = 26)		CPS ≥ 50% (n = 48)		CPS < 50% (n = 118)	
Response Evaluation	No.	% (95% CI)*	No.	% (95% CI)*	No.	% (95% CI)*	No.	% (95% CI)*
Overall response rate	25	18 (12 to 25)	3	12 (2 to 30)	13	27 (15 to 42)	15	13 (7 to 20)
Complete response	1	1 (0 to 4)	0	0 (0 to 13)	1	2 (0 to 11)	0	0 (0 to 3)
Partial response	24	17 (11 to 24)	3	12 (2 to 30)	12	25 (14 to 40)	15	13 (7 to 20)
Stable disease	23	16 (11 to 24)	7	27 (12 to 48)	7	15 (6 to 28)	23	20 (13 to 28)
Progressive disease	73	52 (44 to 61)	13	50 (30 to 70)	18	38 (24 to 53)	68	58 (48 to 67)
Nonevaluable	2	1 (0 to 5)	2	8 (1 to 25)	0	0 (0 to 7)	4	3 (1 to 9)
Data unavailable	17	12 (7 to 19)	1	4 (0 to 20)	10	21 (11 to 35)	8	7 (3 to 13)

LA EXPRESIÓN DE PD-L1 SE ASOCIA A MAYOR TASA DE RESPUESTAS CON PEMBROLIZUMAB
(análisis en células tumorales y células inflamatorias peritumorales)

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PEMBROLIZUMAB

"On August 5, 2016, the U. S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA injection, Merck Sharp & Dohme Corp.) for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy."

DURVALUMAB

ESTUDIO HAWK - FASE 2

CECC recurrente/M1
(cavidad oral, faringe o laringe)
Tratamiento previo con platino
PD-L1 > 25%

→ **n=112** → **DURVALUMAB 10 mg/kg c/2 sem** → Hasta 12 meses, EP o toxicidad inaceptable

Objetivo 1º: TR (RECIST v1.1)

Treatment-related AEs[a] (>5%)	N=112 Any grade, n (%)
Any treatment-related AE	64 (57.1)
Nausea	11 (9.8)
Fatigue	11 (9.8)
Hypothyroidism	10 (8.9)
Asthaenia	9 (8.0)
Pruritus	7 (6.3)
Diarrhoea	6 (5.4)
Decreased appetite	6 (5.4)
Grade 3/4 treatment-related AEs	**9 (8.0)**
GGT increased	3 (2.7)

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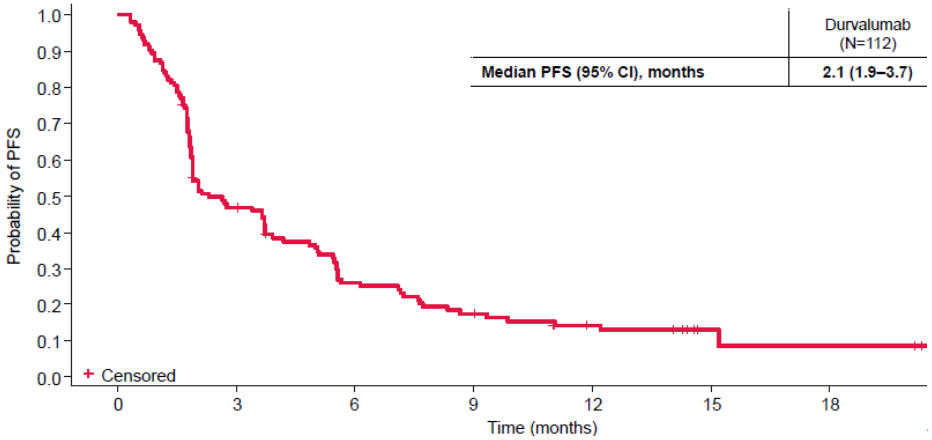
DURVALUMAB

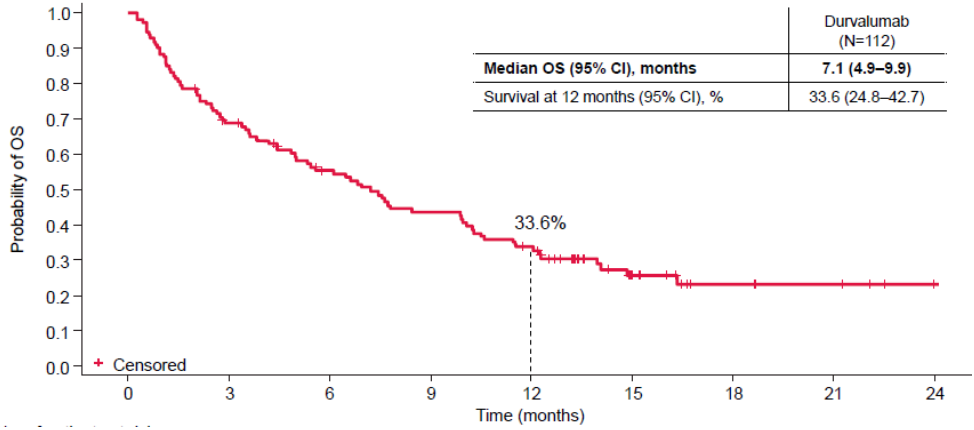
ESTUDIO HAWK - FASE 2

	N=111
ORR[a], n (%)	18 (16.2 [95% CI, 9.90–24.41])
Complete response	1 (0.9)
Partial response	17 (15.3)
Stable disease	10 (9.0)
Disease control rate at 24 weeks[b], n (%)	26 (23.4)

SUPERVIVENCIA LIBRE DE PROGRESIÓN



SUPERVIVENCIA GLOBAL

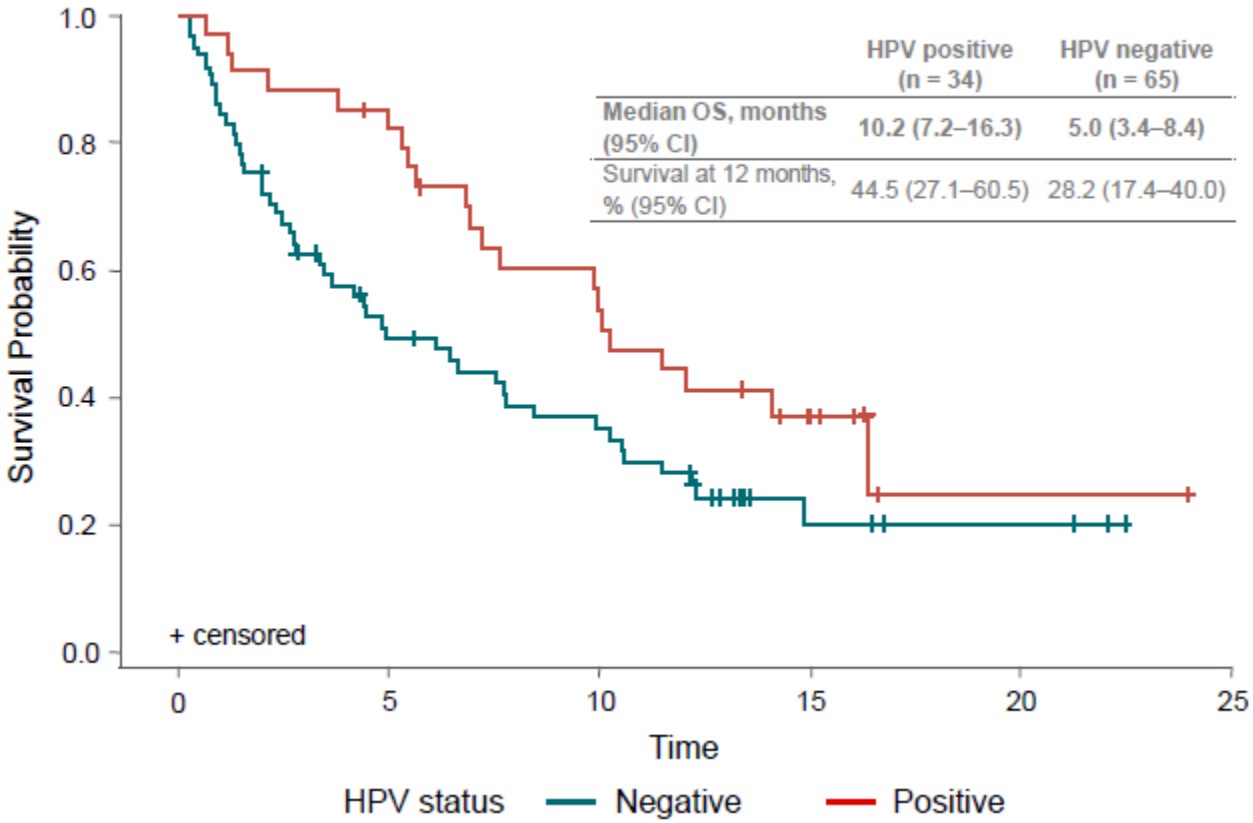


Zandberg D et al. ESMO 2017

DURVALUMAB

ESTUDIO HAWK - FASE 2

SUPERVIVENCIA GLOBAL SEGÚN HPV



	HPV positive (n = 34)	HPV negative (n = 65)
Median OS, months (95% CI)	10.2 (7.2–16.3)	5.0 (3.4–8.4)
Survival at 12 months, % (95% CI)	44.5 (27.1–60.5)	28.2 (17.4–40.0)

MEJORES RESULTADOS CON DURVALUMAB EN PACIENTES CON HPV+

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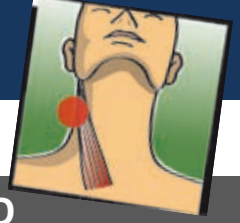
INHIBIDORES DE PUNTOS DE CONTROL INMUNOLÓGICO



ESTUDIO	TRATAMIENTOS	LÍNEA	N	ESTADO
ANTI-PD-1				
CHECKMATE 651[1]	NIVOLUMAB + IPILIMUMAB *vs* CDDP/CBP + 5FU + CETUXIMAB	1ª L	490	Abierto
KEYNOTE 048[2]	PEMBROLIZUMAB *vs* PEMBROLIZUMAB + CDDP/CBP + 5FU *vs* CDDP/CBP + 5FU + CETUXIMAB	1ª L	780	Reclutamiento cerrado
KEYNOTE 412[3]	PEMBROLIZUMAB + CDDP/RT *vs* CDDP/RT	LA	780	Abierto
ANTI-PD-L1				
EAGLE[4]	DURVALUMAB + TREMELIMUMAB *vs* DURVALUMAB *vs* TRATAMIENTO ESTÁNDAR	2ª L	720	Abierto
KESTREL[5]	DURVALUMAB + TREMELIMUMAB *vs* DURVALUMAB *vs* CDDP/CBP + 5FU + CETUXIMAB	1ª L	628	Reclutamiento cerrado
NCT03258554[6]	DURVALUMAB + IMRT *vs* CETUXIMAB + IMRT	LA	533	Próxima apertura

www.clinicaltrials.org:1-NCT02741570;2-NCT02358031;3-NCT03040999;4-NCT02369874;5-NCT02551159;6-NCT03258554

CONCLUSIONES

ACTUALMENTE LOS DATOS MÁS SÓLIDOS PROVIENEN DE LOS **INHIBIDORES DE PUNTOS DE CONTROL INMUNOLÓGICO**

BENEFICIO DEMOSTRADO EN **PACIENTES PREVIAMENTE TRATADOS**, CON **RESPUESTAS MÁS DURADERAS** Y **MEJOR PERFIL DE TOLERANCIA** QUE LA QUIMIOTERAPIA

AUSENCIA DE BIOMARCADORES VALIDADOS

DATOS A FAVOR DE PD-L1, PERO CON MUCHAS LIMITACIONES (¿dónde medirlo? ¿cuándo? ¿con qué método? ¿punto de corte?)