II CURSO DE RESIDENTES DE SAOM

13 y 14 DE ABRIL 2018
GRANADA

Organizado por:

SAOM
Sociedad Andaluza de Oncología Medica

VENTAJAS E INCONVENIENTES DE LA INMUNOTERAPIA EN TUMORES DE CABEZA Y CUELLO.

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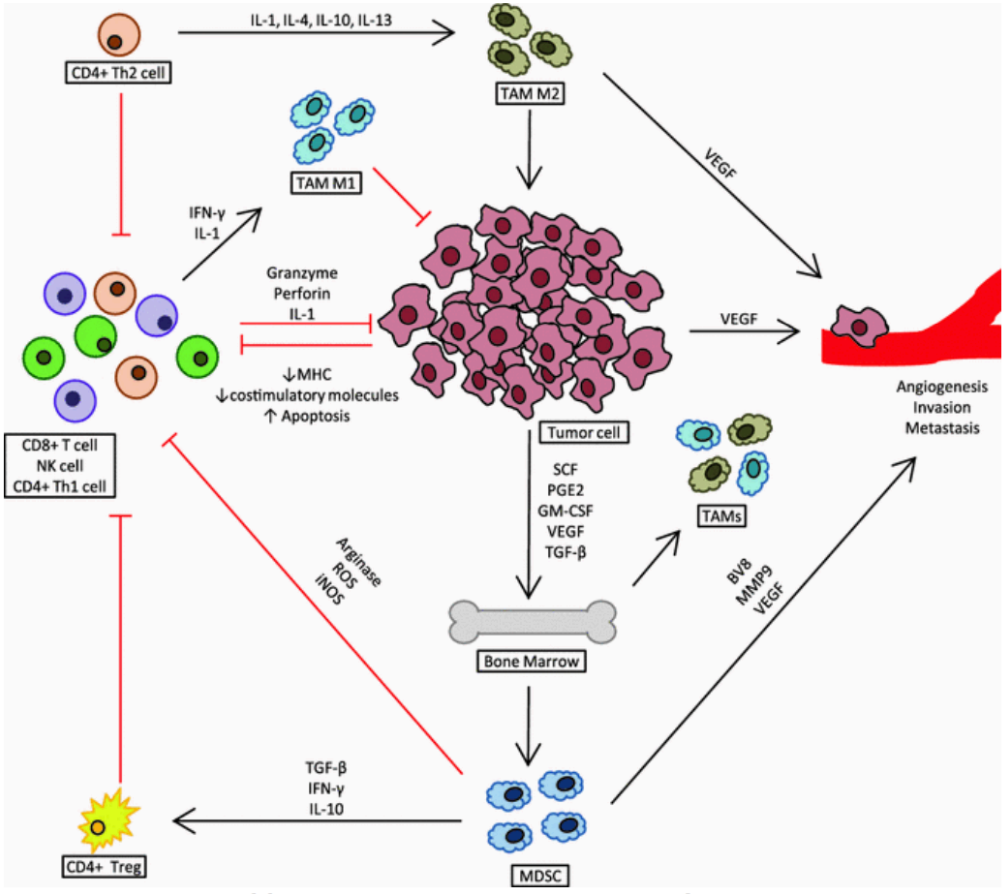
INDICE

INTRODUCCIÓN

- 5% nuevos casos de cáncer en España.
- 2/3 enf localmente avanzada.
- Tasa de Recurrencia (localización): 25- 50% a los 2 años.
- mOS 10 meses para enf R/M
- Factores de riesgo
  - VPH

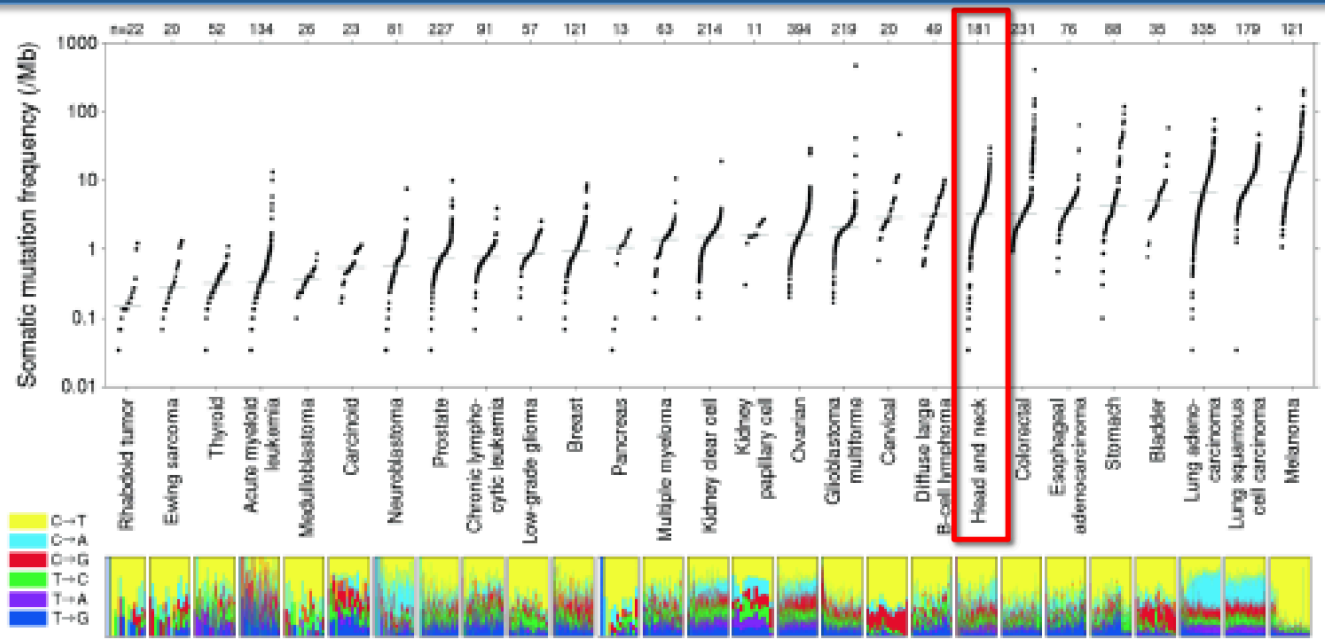
MICROAMBIENTE INMUNOSUPRESIVO DEL TUMOR CYC

- Suppressives/Regulatory inmunocytes:
  - Regulatory T cells (Treg)
  - Myeloid derived suppressor cells (MDSC)
  - Tumor associated macrophagues (TAMs)
- Checkpoint molecules
  - CTLA-4
  - PD1/PDL1
  - LAG3
  - TIM
- Inmunosuppresives citokynes
  - TGF-B, IL- 10
- Others
  - IDO, iNOS, arginase…



Tong CC, et al. Immunol Res. 2012:54(1-3):266-274.

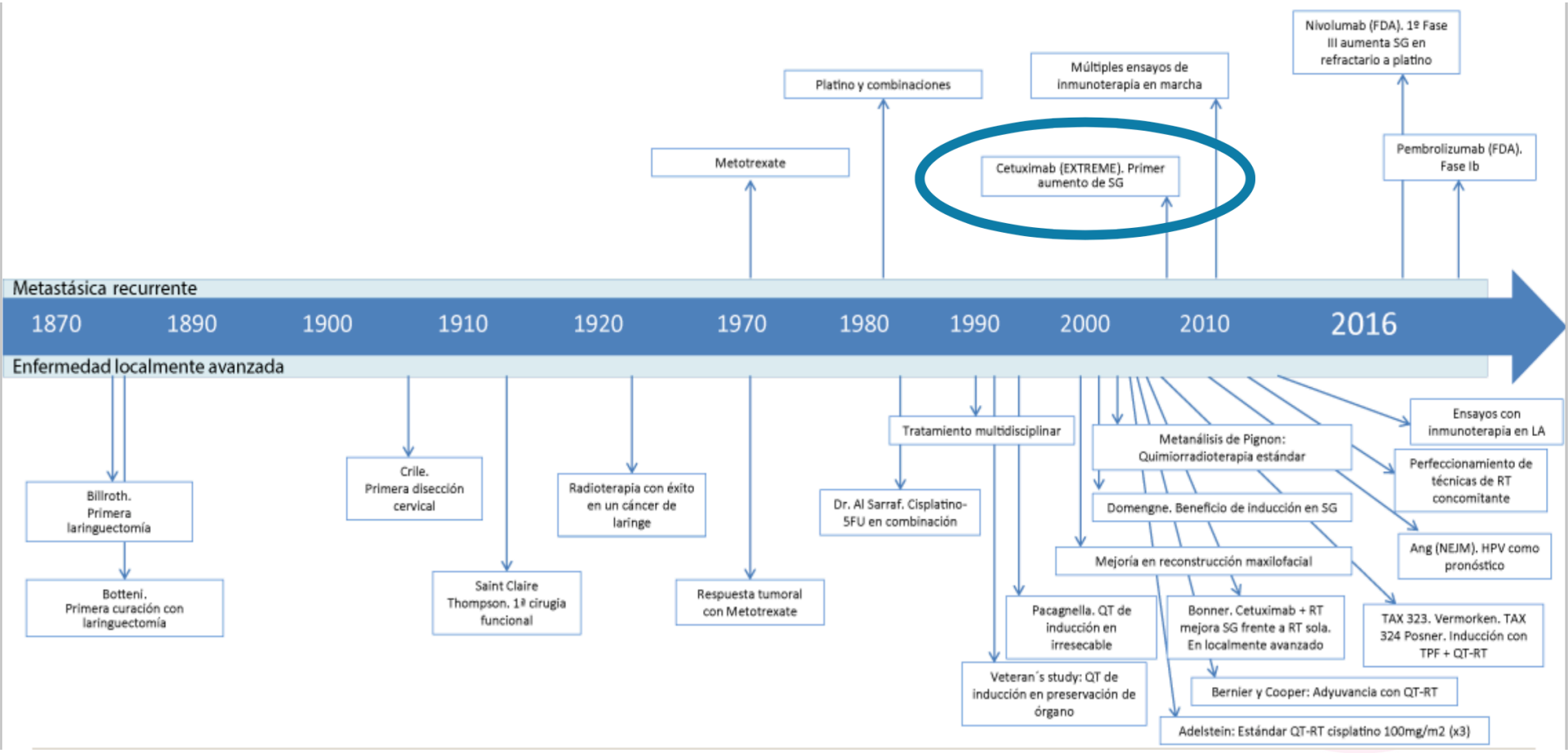
CARGA MUTACIONAL DE HNC



- Higher responses rate to PD-1/PDL-1 inhibitor in former and current smokers in lung cancer patients.
- Higher mutational load in smoking-associated lung cancer, leading to more tumor neoantigens and increased immunogenicity.

Nature. 2013 July 11; 499(7457): 214–218

ENFERMEDAD RECURRENTE / METASTÁSICA



1ª LÍNEA

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 359;11 WWW.NEJM.ORG SEPTEMBER 11, 2008

Annals of Oncology Advance Access published August 23, 2011

original article

Annals of Oncology
doi:10.1093/annonc/mdr367

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)

[1]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid; [2]Department of Medical Oncology, Hospital Universitario, Granada; [3]Department of Medical Oncology, Hospital Clinic I Provincial, Barcelona; [4]Department of Medical Oncology, Hospital Clínico Universitario, Madrid; [5]Department of Medical Oncology, Hospital Universitario, Salamanca, Spain

EXTREME

- 1º: OS: 10,1 vs 7,4 meses
- PFS 5,6 vs 3,3 meses
- Tasa Rpta: 36 vs 20%

ERBITAX

- 1º Tasa Rpta: 54%
- PFSm 4,2 meses
- SGm 8,1 meses
- → PS 2

1.Vermoken, J. et al.N Eng J Med 2008. 2.Hitt, R. Ann Oncology 2011, Apr

TERAPIAS EN 2ª LÍNEA HASTA EL MOMENTO

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Head and Neck Cancers
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

- The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy).
- Unless otherwise specified, regimens listed below can be used for either nasopharyngeal or non-nasopharyngeal cancer.

Recurrent, Unresectable, or Metastatic
(with no surgery or RT option)

- Combination therapy
  - Cisplatin or carboplatin/5-FU/cetuximab[30] (non-nasopharyngeal) (category 1)
  - Cisplatin or carboplatin/docetaxel[31] or paclitaxel[32]
  - Cisplatin/cetuximab[33] (non-nasopharyngeal)
  - Cisplatin/5-FU[32,34]
  - Cisplatin or carboplatin/docetaxel/cetuximab[35] (non-nasopharyngeal)
  - Cisplatin or carboplatin/paclitaxel/cetuximab[36,37] (non-nasopharyngeal)
  - Carboplatin/cetuximab[38] (nasopharyngeal)
  - Cisplatin/gemcitabine[39] (nasopharyngeal)
  - Gemcitabine/vinorelbine[40] (nasopharyngeal)

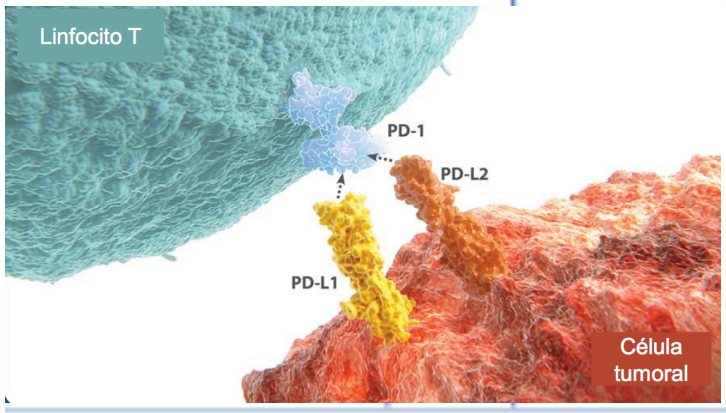
- Single agents
  - Cisplatin[33,41]
  - Carboplatin[42]
  - Paclitaxel[43]
  - Docetaxel[44,45]
  - 5-FU[41]
  - Methotrexate[46,47]
  - Cetuximab[48] (non-nasopharyngeal)
  - Gemcitabine[49] (nasopharyngeal)
  - Capecitabine[50]
  - Afatinib[51] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 2B)
  - Pembrolizumab[52,53] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy)
  - Nivolumab[54] (non-nasopharyngeal, if disease progression on or after platinum-containing chemotherapy) (category 1)

INMUNOTERAPIA TRAS PROGRESIÓN A PLATINO

Nivolumab (FDA). 1º Fase III aumenta SG en refractario a platino

Múltiples ensayos de inmunoterapia en marcha

Pembrolizumab (FDA). Fase Ib



2000 2010 2016

- **Pembrolizumab**
  - FDA, Agosto 2016
- **Nivolumab**
  - FDA, Noviembre 2016
  - EMA, Abril 2017

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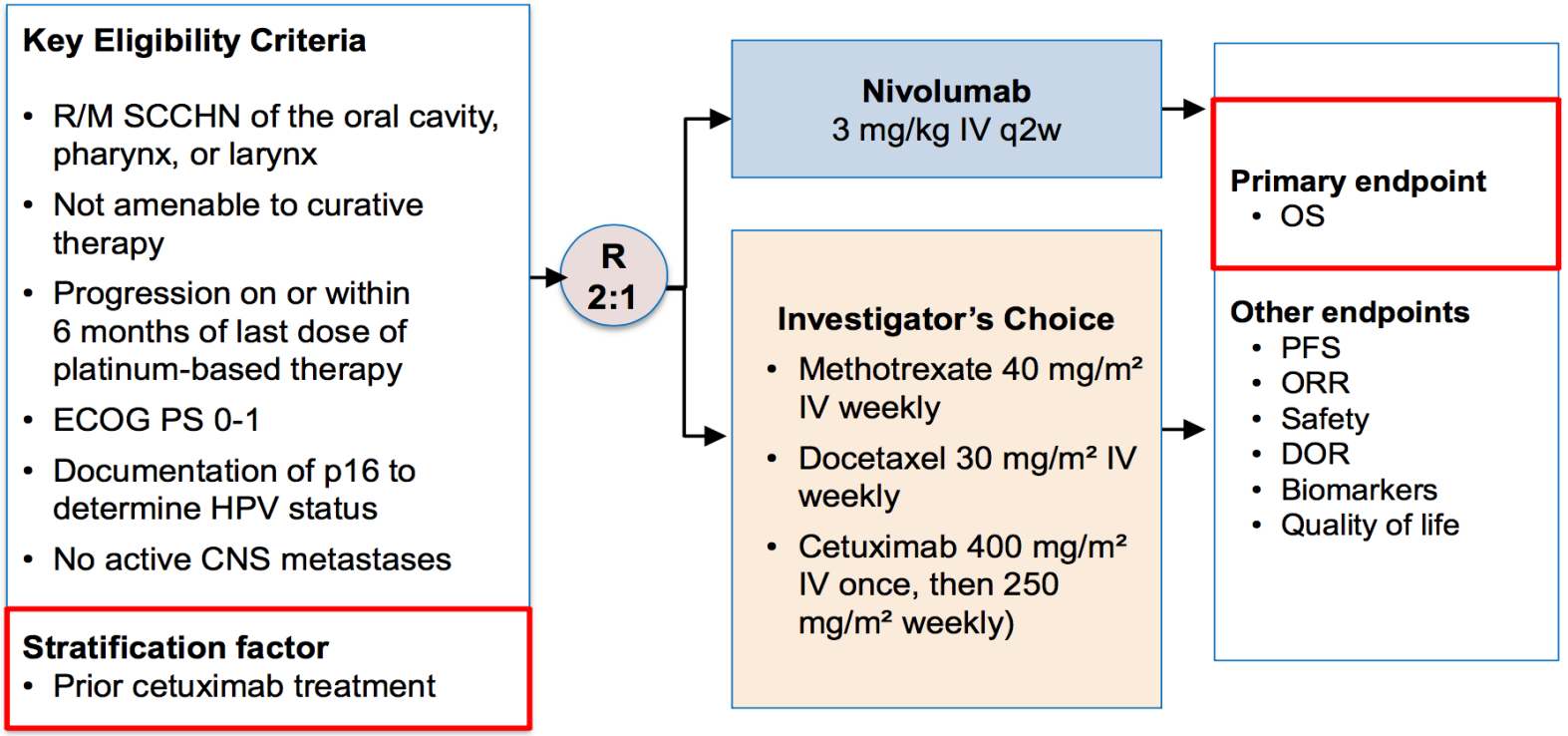
NIVOLUMAB

NIVOLUMAB

CheckMate 141: Study Design

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



CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; IV, intravenous; ORR, objective response rat
OS, overall survival; PFS, progression-free survival; PS, performance status

Ferris RL et al. N Engl J Med 2016;375:1856-1867

CARÁCTERÍSTICAS DE LOS PACIENTES CHECKMATE 141

	Nivolumab (n = 240)	Investigator's Choice (n = 121)	Total (N = 361)
Median age, years	**59.0**	**61.0**	**60.0**
<65, n (%)	172 (71.7)	76 (62.8)	248 (68.7)
Smoking/tobacco use, n (%)			
Current/former	191 (79.6)	85 (70.2)	276 (76.5)
Never	39 (16.3)	31 (25.6)	70 (19.4)
ECOG performance status, n (%)			
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, n (%)			
1	106 (44.2)	58 (47.9)	164 (45.4)
2	80 (33.3)	45 (37.2)	125 (34.6)
≥3	54 (22.5)	18 (14.9)	72 (19.9)
p16 status[a,b], n (%)			
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)

ECOG = Eastern Cooperative Oncology Group.
[a]Required from patients with oropharyngeal cancer only. [b]Determined via p16 immunohistochemistry.

Ferris RL et al. N Engl J Med 2016;375:1856-1867

Treatment Administration and Patient Disposition

Nivolumab in R/M SCCHN After Platinum Therapy

	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, months (95% CI)	1.9 (1.6-2.3)	1.9 (1.6-2.0)	–
Median duration of follow-up, months (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)

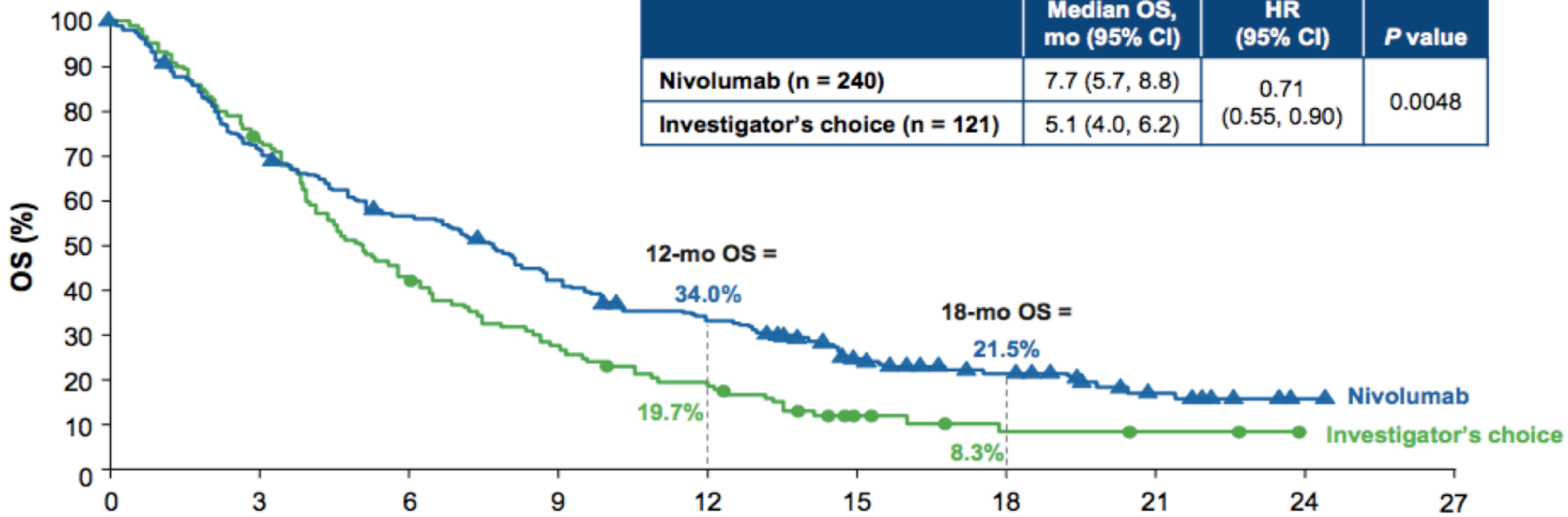
Ferris RL et al. N Engl J Med 2016;375:1856-1867

RESULTADOS: SUPERVIVENCIA GLOBAL

Overall Survival, Minimum Follow-up: 11.4 Months

CheckMate 141: Nivolumab in R/M SCCHN After Platinum Therapy

	Median OS, mo (95% CI)	HR (95% CI)	*P* value
Nivolumab (n = 240)	7.7 (5.7, 8.8)	0.71 (0.55, 0.90)	0.0048
Investigator's choice (n = 121)	5.1 (4.0, 6.2)		



No. of patients at risk

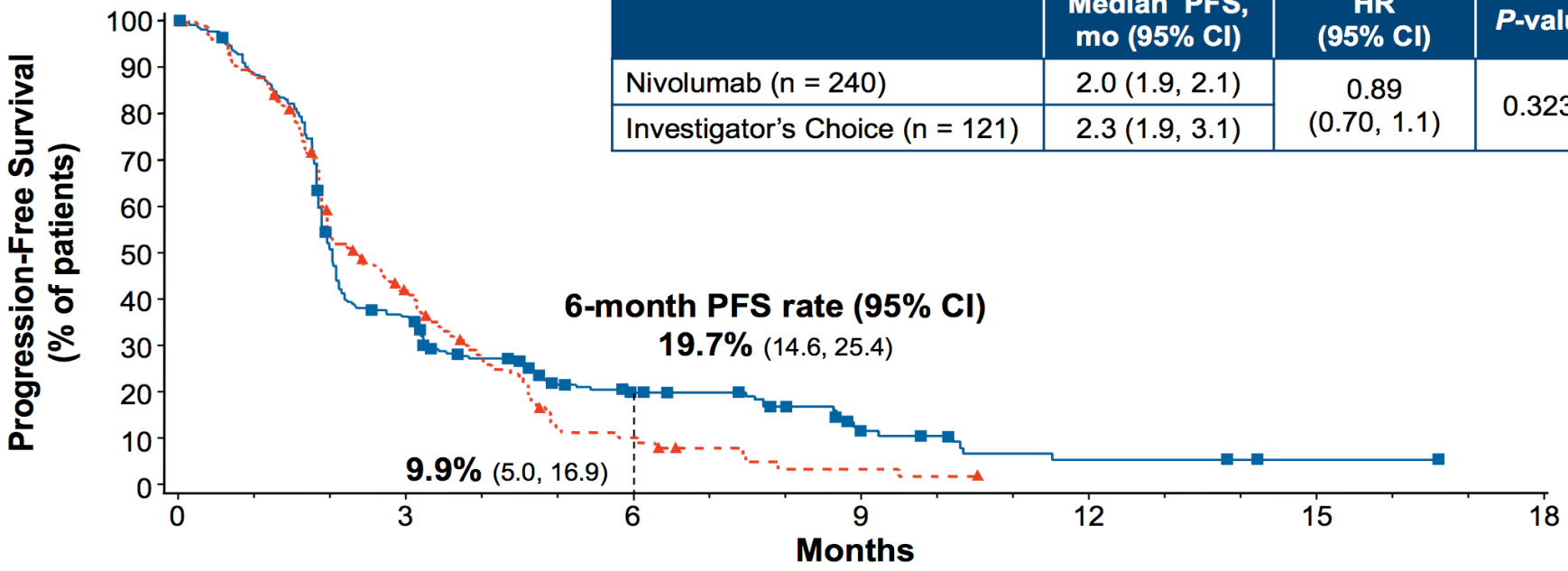
Nivo	240	169	132	98	76	45	27	12	3	0
IC	121	88	51	32	22	9	4	3	0	0

Ferris RL et al. N Engl J Med 2016;375:1856-1867

Progression-Free Survival

Nivolumab in R/M SCCHN After Platinum Therapy

	Median PFS, mo (95% CI)	HR (95% CI)	*P*-value
Nivolumab (n = 240)	2.0 (1.9, 2.1)	0.89 (0.70, 1.1)	0.3236
Investigator's Choice (n = 121)	2.3 (1.9, 3.1)		



No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Investigator's Choice	121	43	9	2	0	0	0

Ferris RL et al. N Engl J Med 2016;375:1856-1867

EFECTOS ADVERSOS: OCURRIDOS EN >10% PACIENTES

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.

Ferris RL et al. N Engl J Med 2016;375:1856-1867

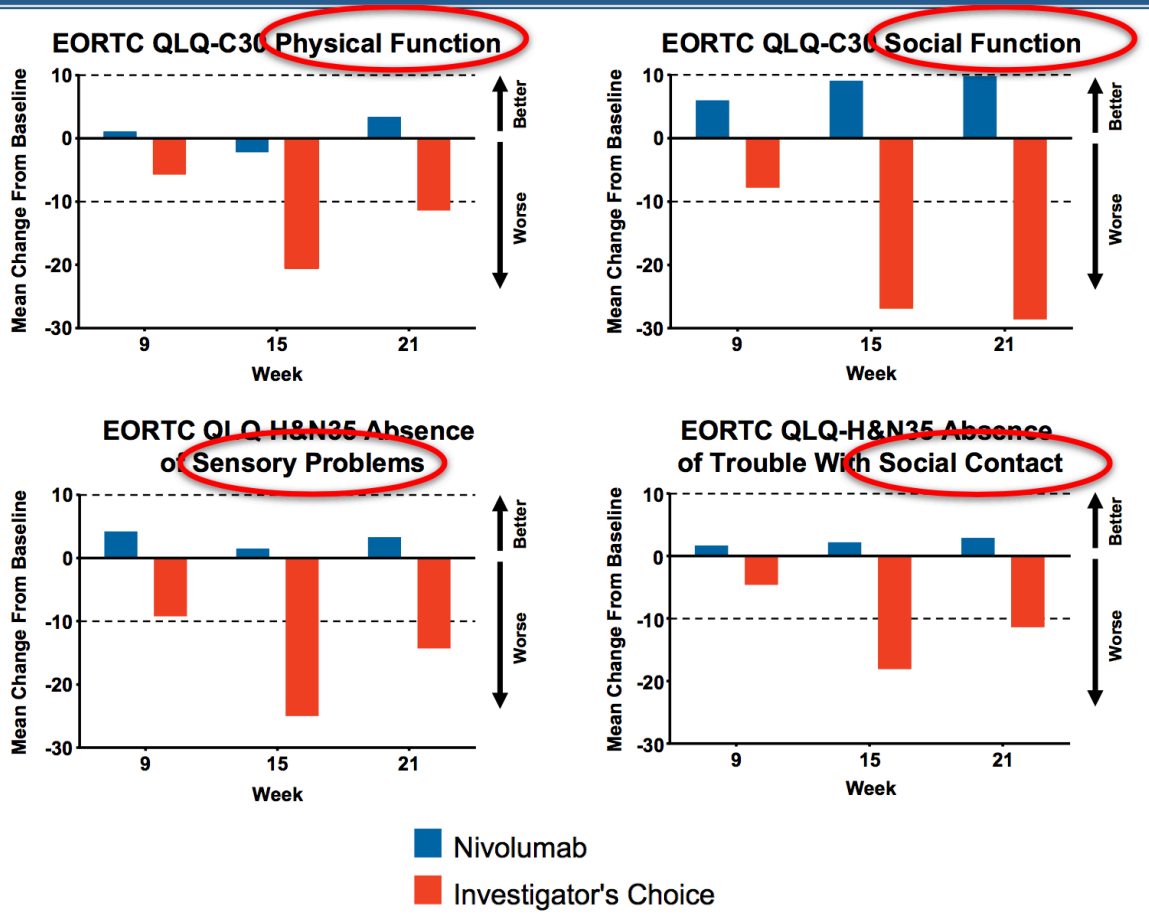
EFECTOS ADVERSOS EN RELACIÓN A INMUNOTERAPIA

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

Ferris RL et al. N Engl J Med 2016;375:1856-1867

CALIDAD DE VIDA



Nivolumab mantuvo estable la calidad de vida de los pacientes (3 escalas diferentes), y retraso en el deterior del paciente, mientras que el tto comparador dió lugar a un empeoramiento relevante de las funciones y de los síntomas.

Ferris RL et al. N Engl J Med 2016;375:1856-1867

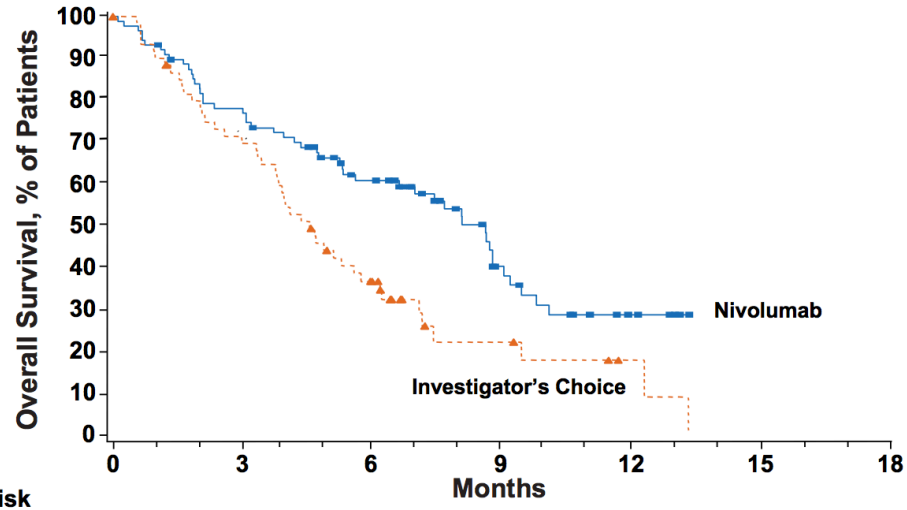
ANÁLISIS DE BIOMARCADORES

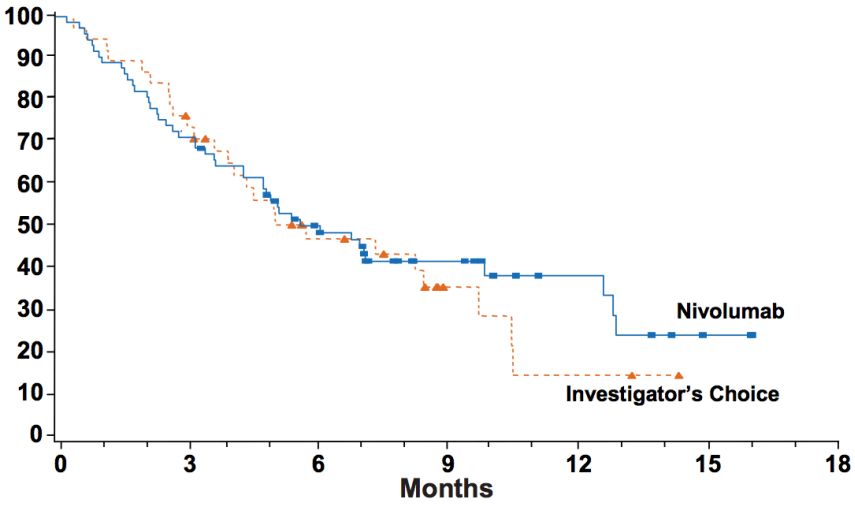
PD-L1 Expression ≥1%

	Median OS, Months (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, Months (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

Ferris RL, et al. *N Engl J Med.* 2016.375(19):1856-1867.

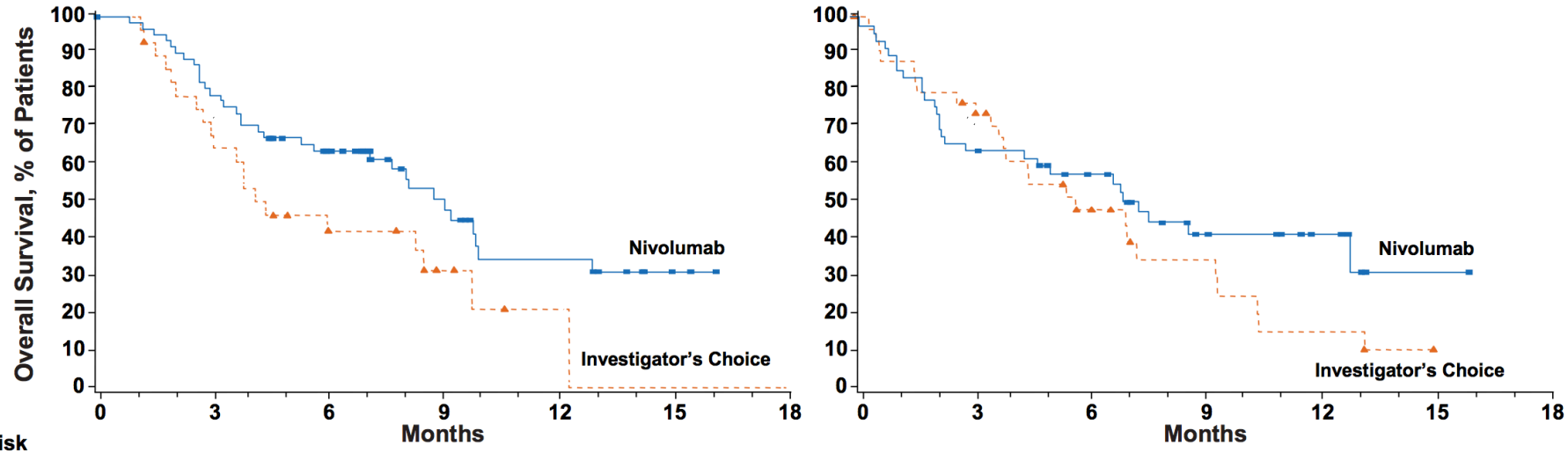
ANÁLISIS DE BIOMARCADORES

p16-Positive

	Median OS, Months (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
Investigator's Choice	29	20	11	4	1	0	0
Nivolumab	50	32	25	12	6	1	0
Investigator's Choice	36	26	13	7	3	1	0

Ferris RL, et al. *N Engl J Med.* 2016.375(19):1856-1867.

CONCLUSIONES CHECKMATE 141

- Nivolumab primer agente en demostrar un aumento de la supervivencia significativo en pacientes R/M SCCHN con progresión a platino.
  - beneficios en supervivencia independientemente del nivel de expresión de PD-L1 o del estado p16.

- Menos efectos adversos grado 3 o 4 que la terapia estándar.
- Mantuvo estable la calidad de vida.
- Necesidad de seleccionar a los pacientes.

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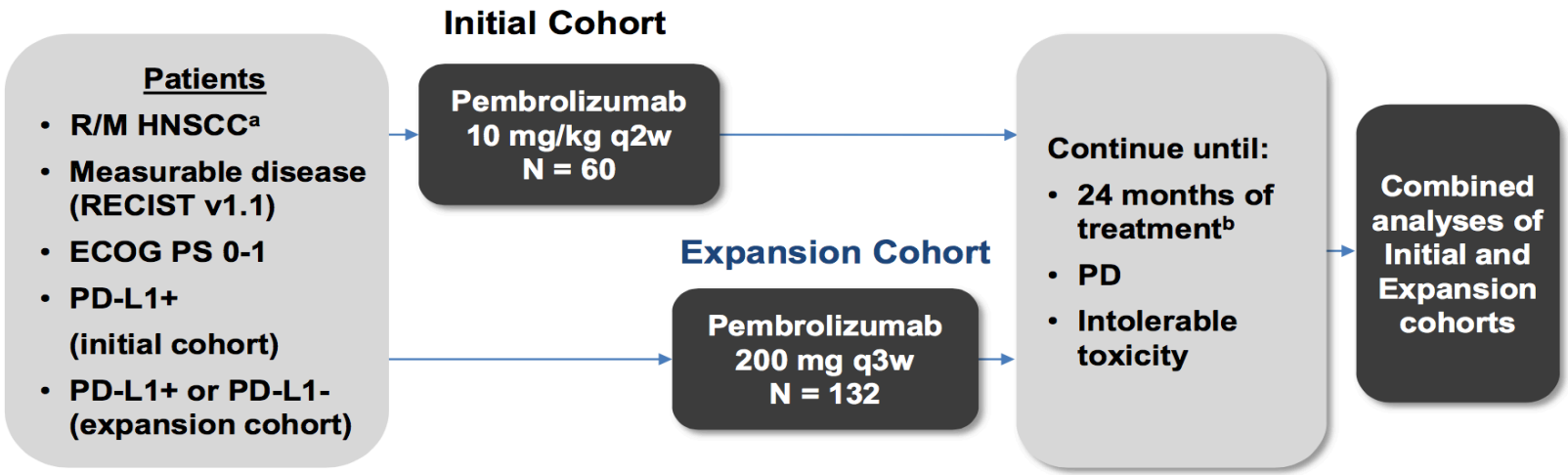
PEMBROLIZUMAB

KEYNOTE-012: Study Design



Response assessment: Every 8 weeks

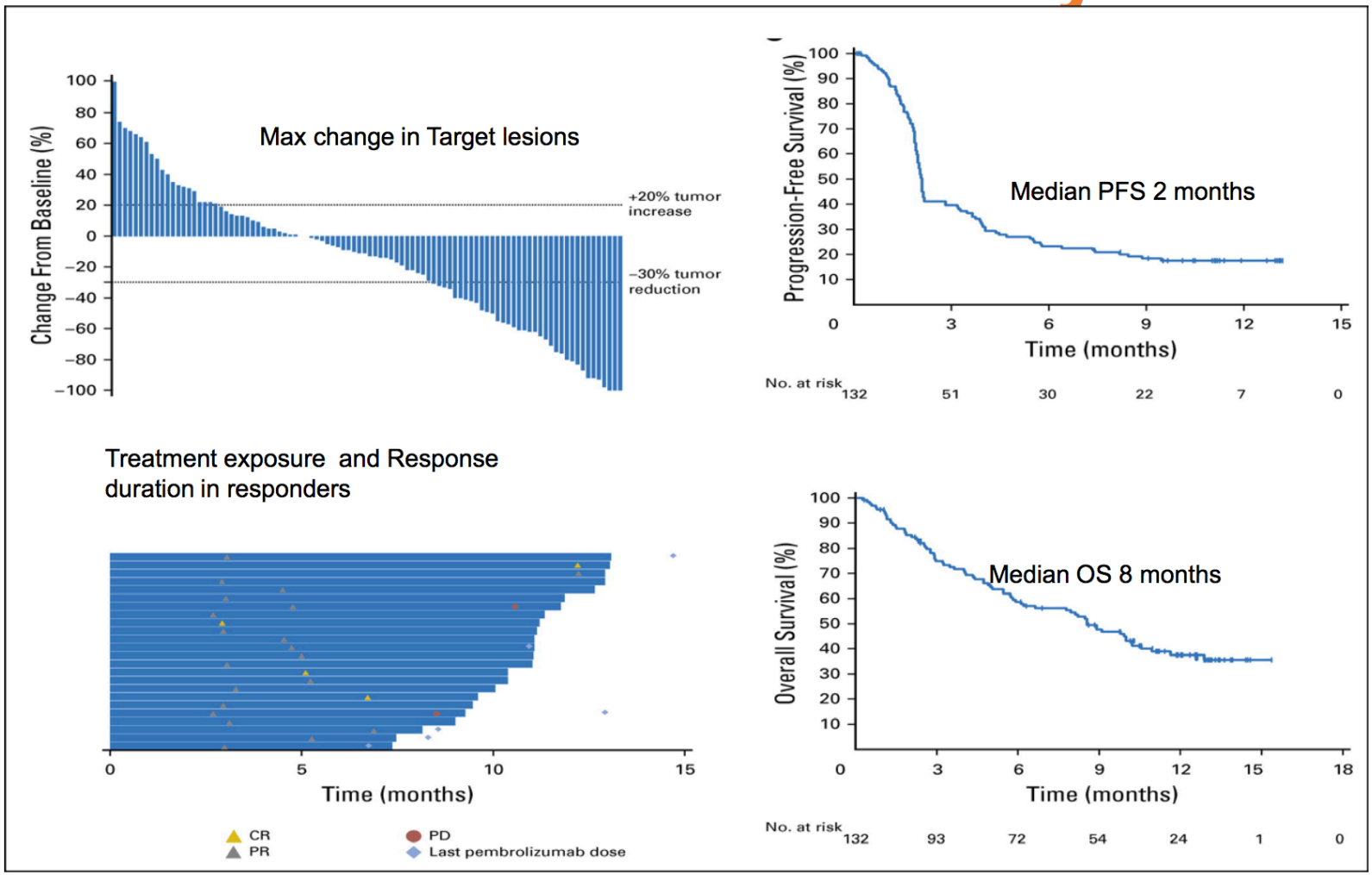
Primary end points: ORR (RECIST v1.1, central imaging vendor), safety

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

[a]Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer
[b]Treatment beyond progression was allowed
[c]Initial cohort only

Chow LQ, et al. *J Clin Oncol.* 2016;34(32):3838-3845.

KEYNOTE-012: Efficacy



Phase III 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]

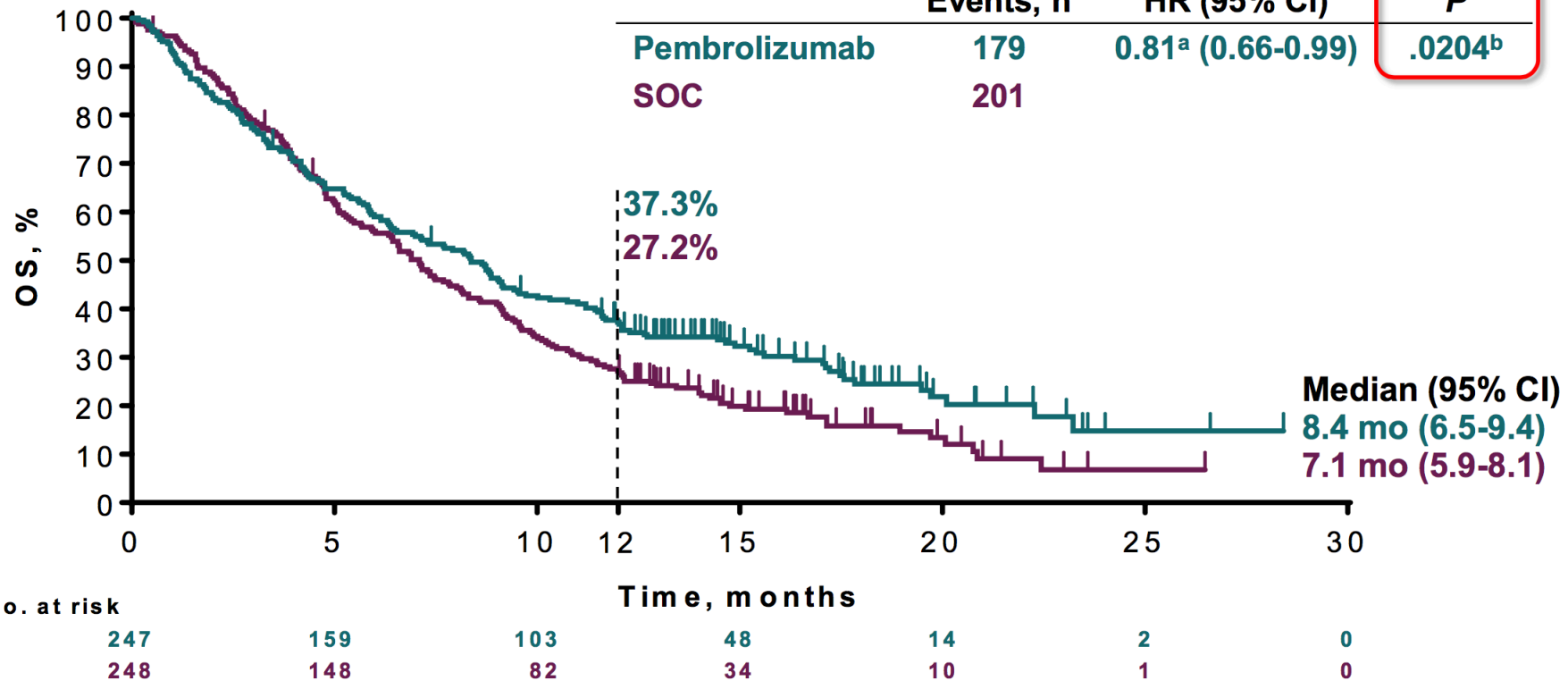
- **Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD**
- **Crossover not permitted**

[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. 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.

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

OVERALL SURVIVAL IN ITT POPULATION

	Events, n	HR (95% CI)	*P*
Pembrolizumab	179	0.81[a] (0.66-0.99)	.0204[b]
SOC	201		

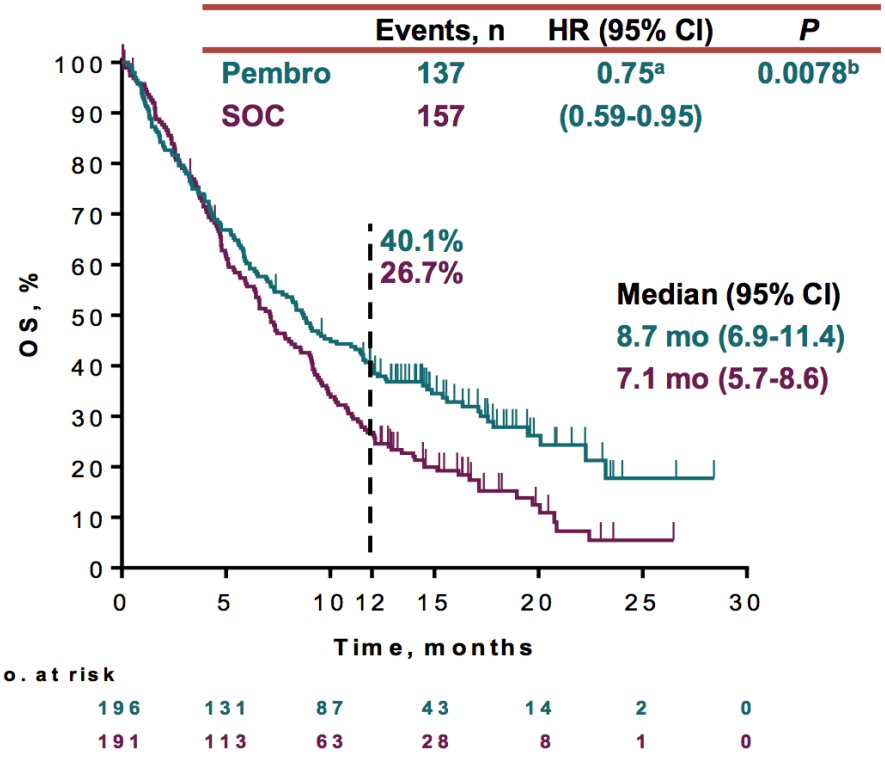


[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 0.67-1.01), *P* = 0.0316. After the initial report, updated survival data were obtained for 4 patients. [b]One-sided *P* value based on the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

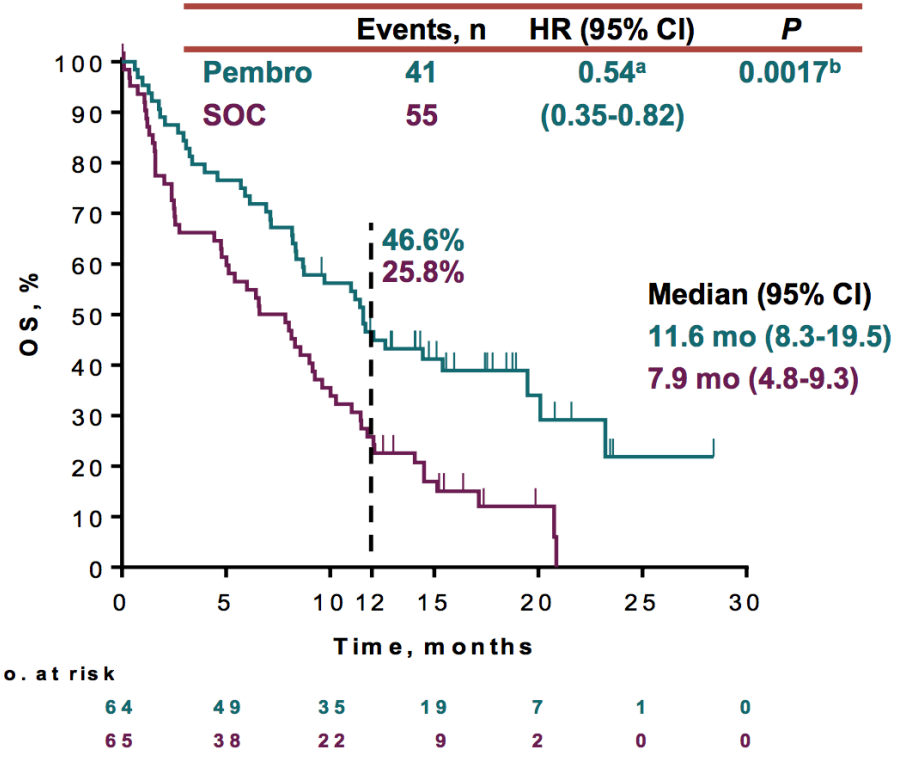
Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

Overall Survival by PD-L1 Expression

PD-L1 CPS ≥1

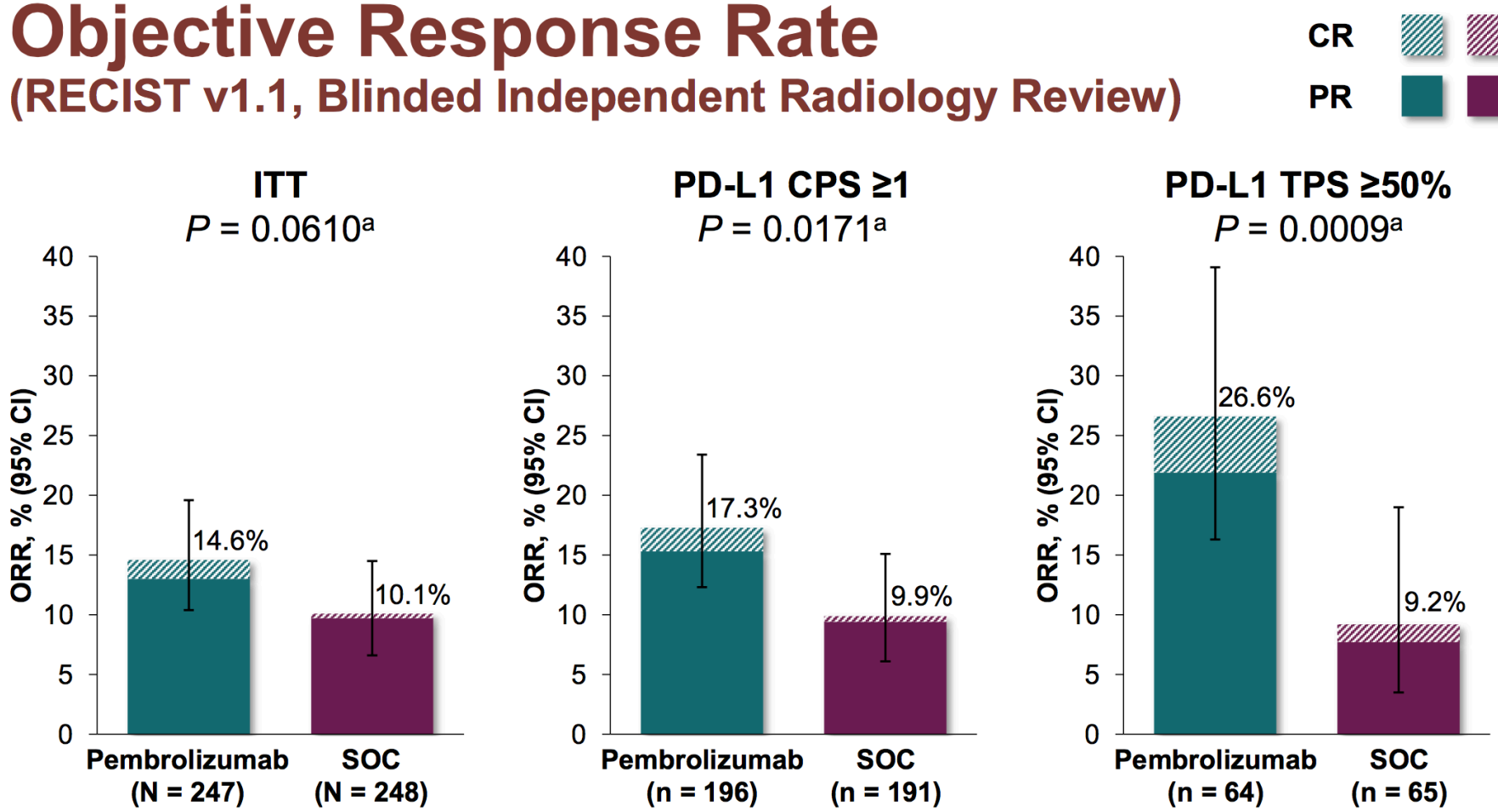


PD-L1 TPS ≥50%



[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.

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

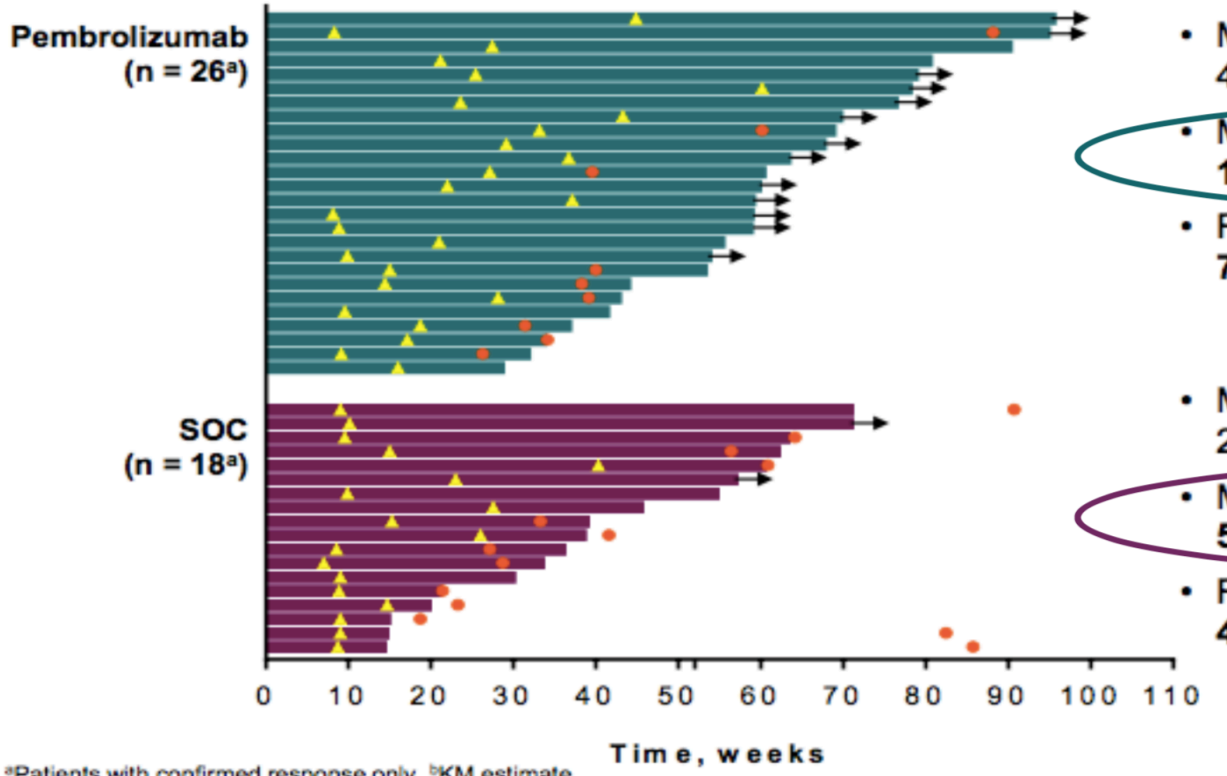


[a]Nominal one-sided *P* value based on the Miettinen and Nurminen method stratified by the randomization stratification factors.
Data cutoff date: May 15, 2017.

MADRID 2017 ESMO congress

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

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



- 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%**

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

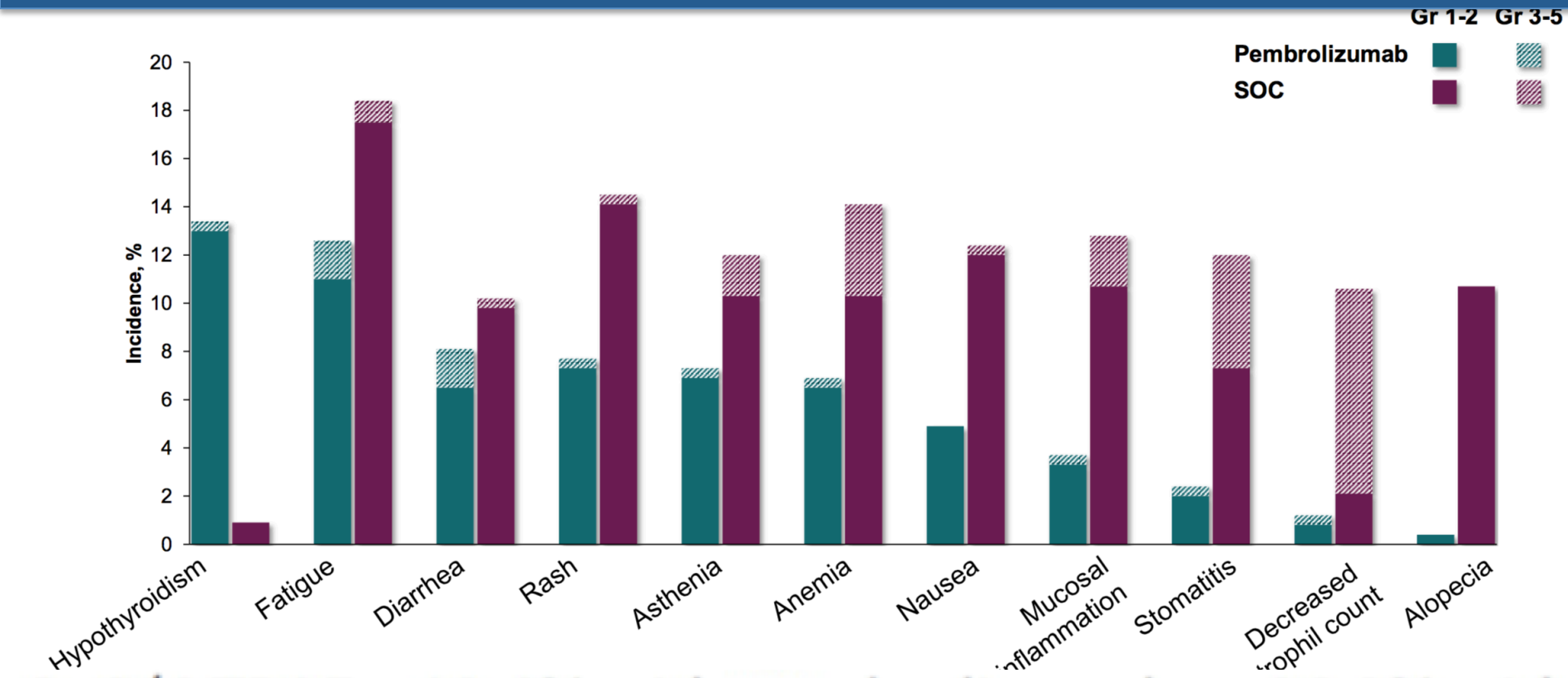
TERAPIA POSTERIOR

Type, n (%)	Pembrolizumab N = 247	SOC N = 248
Any[a]	84 (34.0)	100 (40.3)
Chemotherapy	70 (28.3)	76 (30.6)
EGFR inhibitor	20 (8.1)	19 (7.7)
Kinase inhibitor	4 (1.6)	8 (3.2)
Immune checkpoint inhibitor	11 (4.5)	31 (12.5)
Other immunotherapy	5 (2.0)	1 (0.4)
Other	2 (0.8)	2 (0.8)

[a]Patients may have received ≥1 subsequent therapy. Data cutoff date: May 15, 2017.

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

EFECTOS ADVERSOS: OCURRIDOS EN >10% PACIENTES



Gr 3/4 TRAEs: 13.4% with pembrolizumab vs 36.3% with standard of care

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

CONCLUSIONES KEYNOTE 040

- Pembrolizumab proporciona una reducción del 19% en el riesgo de muerte en comparación con SOC en pacientes con R/M HNSCC.
  - No cumple el objetivo principal pre-especificado para ser estadisticamente signiticativo.
  - Autores defienden como tto activo podría ser una buena opción frente a SOC.
    - Superior en términos de toxicidad
    - Tto posterior con IT (brazo SOC) pudo confundir el análisis OS .
    - La magnitud de la efectividad del tto fue mayor en pacientes con CPS>50%, sugiere que podría ser una mejor opción en este subgrupo.

NIVOLUMAB vs PEMBROLIZUMAB

- Resultados similares en sí mismos. Aunque SOC en ensayo Pembrolizumab, resultados sorprendentemente altos.

	Nivolumab[a]	Pembrolizumab[b]
mOS, mo	7.5	8.4
mPFS, mo	2.0	2.1
ORR, %	13.3	14.6
Gr 3/4 TRAEs, %	13.1	13.4

- Diferencias entre los ensayos:
  - Esquema de docetaxel
  - Randomización
    - 1:1 (Pembrolizumab), 2:1 (Nivolumab)
  - Eligibilidad:
    - >3m PFS en Pembrolizumab, cualquier progresión Nivolumab.

II CURSO DE RESIDENTES DE SAOM

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DURVALUMAB

FASE II: HAWK TRIAL

Patients

- R/M HNSCC of the oral cavity,oropharynx, larynx, hypopharynx
- Failure of 1 platinum-based chemotherapy in the R/M setting
- Measurable disease
- PD-L1 high: TC≥25% (Ventana SP 263)

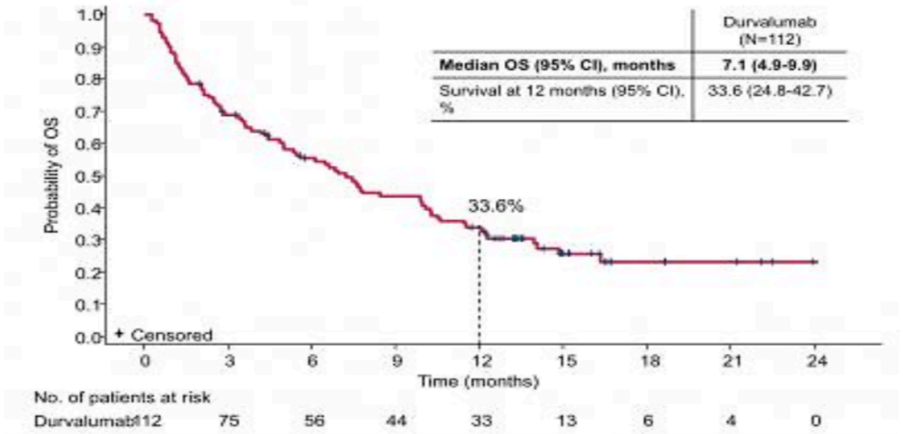
DURVALUMAB (10 mg/kg, i.v., Q2W) → Continue until 12 months, PD, toxicity, or patient decision to stop therapy → **Safety and survival follow-up**

Study endpoints:
- Primary: ORR (BICR assessment by RECIST v1.1)
- Secondary: DoR, DCR, PFS, OS, Quality of Life

ORR by Blinded Independent Central Review

	N=111
ORR, n (%)	18 (16.2)
CR	1 (0.9)
PR	17 (15.3)
SD	10 (9.0)
Disease control rate at 24 weeks, n (%)	26 (23.4)

Overall Survival



BICR, blinded independent central review; DCR, disease control rate; i.v., intravenous; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; Q2W, every 2 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TC, tumor cell

Zandberg D, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract 1042O.

FASE II: CONDOR TRIAL

PATIENTS

- R/M HNSCC
  (oral cavity, oropharynx, hypopharynx, larynx)
- ≥1 measurable lesion per RECIST v1.1
- Failure of 1 platinum-based chemotherapy in the R/M setting
- PD-L1 low/negative (<25% TC)
- Stratified by HPV status and smoking status

R

- 2 → **Durvalumab + tremelimumab** (D 20 mg/kg Q4W + T 1 mg/kg Q4W) for 4 cycles then durvalumab 10 mg/kg Q2W for up to 12 months
- 1 → **Durvalumab** (10 mg/kg Q2W) for up to 12 months
- 1 → **Tremelimumab** (10 mg/kg Q4W) for 7 doses then Q12W for 2 additional doses

PRIMARY ENDPOINTS	SECONDARY ENDPOINTS
- **ORR** by RECIST v1.1 by BICR assessment (durvalumab + tremelimumab)	- DoR, DCR, BOR, PFS, OS (durvalumab/tremelimumab) - ORR, PFS, and OS for combination vs monotherapies - Safety and tolerability - Quality of Life: EORTC QLQ-HN35 and QLQ-C30

L.L Siu, et al. 2018 Multidisciplinary Head and Neck Cancers Symposium, Arizona

OBJETIVO 1º: ORR

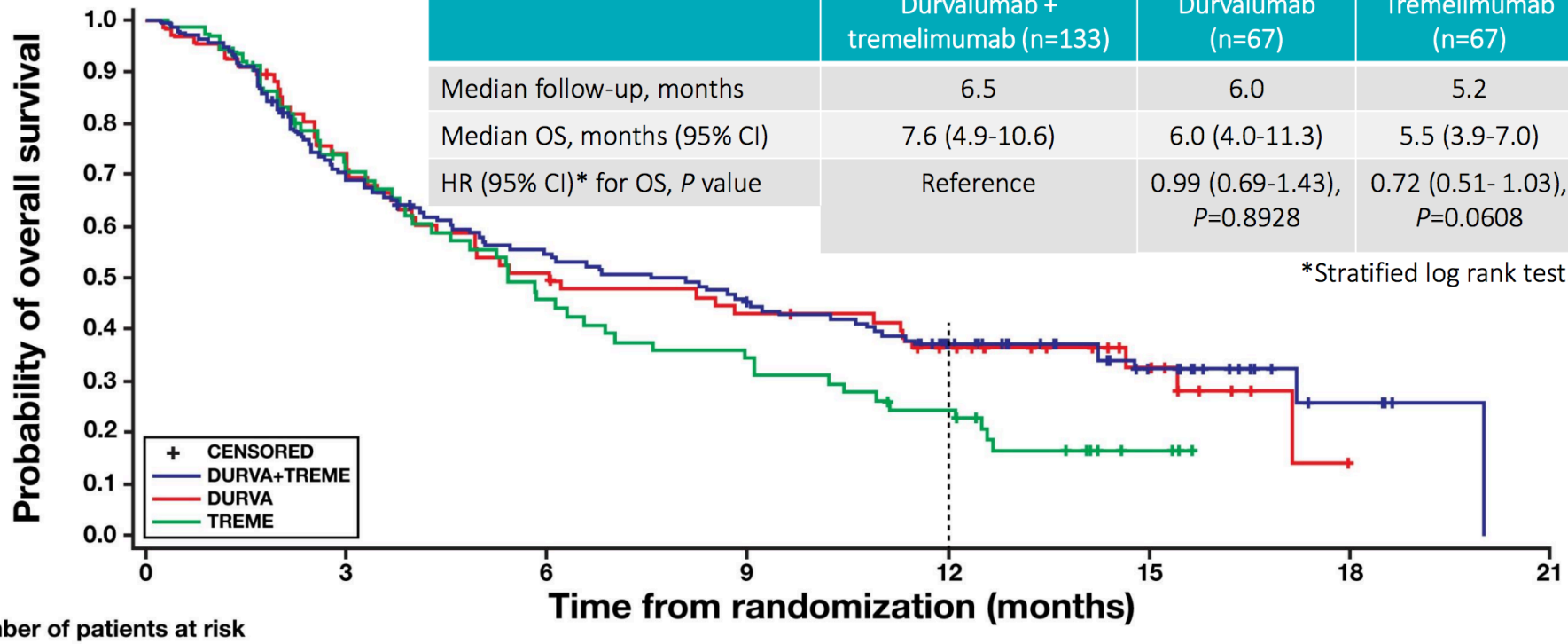
	Durvalumab + tremelimumab (n=129)	Durvalumab (n=65)	Tremelimumab (n=63)
ORR, % (n) [95% CI]	7.8 (10) [3.8–13.8]	9.2 (6) [3.5–19.0]	1.6 (1) [0.04–8.5]
Odds ratio (95% CI), *P*-value	Reference	0.83 (0.29–2.53), *P*=0.728	5.21 (0.96–96.70), *P*=0.056
Complete response, n	0	0	0
Partial response, n	10	6	1
Stable disease ≥6 months,† n (%)	7 (5.4)	4 (6.2)	0 (0.0)
Disease control rate at 6 months,‡ n (%)	17 (13.2)	14 (21.5)	1 (1.6)
Median duration of response, months	9.4	NA	NA
Ongoing response at data cutoff, n	5	4	1

L.L Siu, et al. 2018 Multidisciplinary Head and Neck Cancers Symposium, Arizona

SUPERVIVENCIA GLOBAL

	Durvalumab + tremelimumab (n=133)	Durvalumab (n=67)	Tremelimumab (n=67)
Median follow-up, months	6.5	6.0	5.2
Median OS, months (95% CI)	7.6 (4.9-10.6)	6.0 (4.0-11.3)	5.5 (3.9-7.0)
HR (95% CI)* for OS, *P* value	Reference	0.99 (0.69-1.43), *P*=0.8928	0.72 (0.51- 1.03), *P*=0.0608

*Stratified log rank test.



Number of patients at risk

DURVA+TREME	133	89	69	57	37	17	3	0
DURVA	67	48	33	27	19	9	0	0
TREME	67	43	28	21	14	3	0	0

L.L Siu, et al. 2018 Multidisciplinary Head and Neck Cancers Symposium, Arizona

CONCLUSIONES CONDOR

- Durvalumab muestra una tasa de respuesta del 9,2%, consistente con otros PD-1 en la segunda línea.
- Tanto D en monoterapia con D + T muestra OS clinicamente relevante, pero no se observa diferencia en eficacia entre las 2.
- Perfil seguridad tolerable

FASE III EAGLE

Key Eligibility Criteria

- PD-L1+/- as determined by Ventana SP263 (cutoff: 25%)
- Failure of exactly one Pt-tx for recurrent/metastatic disease, or progression within 6 months of completing platinum-containing multimodality therapy with curative intent
- No prior exposure to immune-mediated therapy

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

Durvalumab	Durvalumab + Tremelimumab	Active Comparator

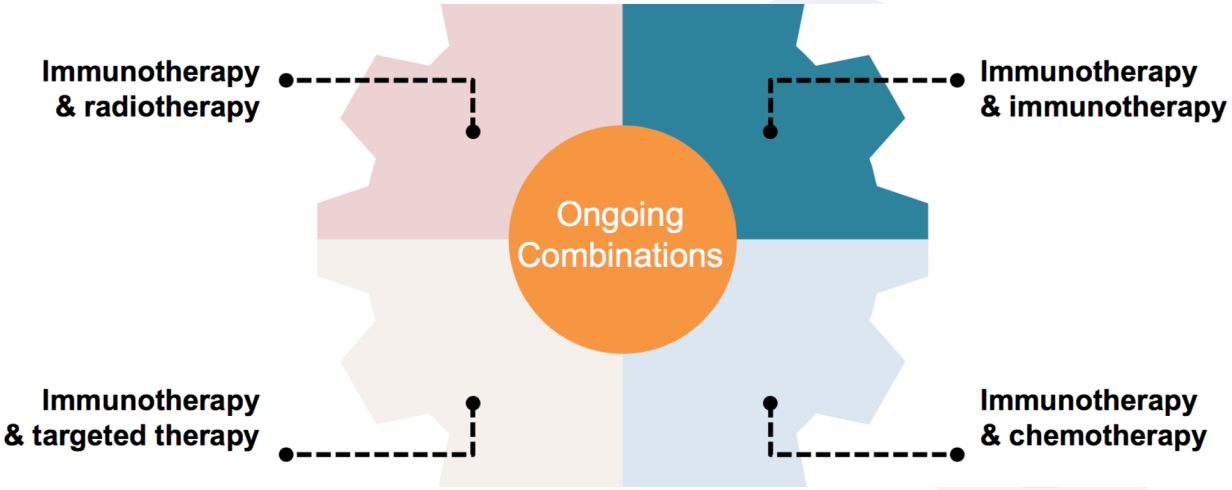
Primary Endpoint: OS
Other Endpoints: OS (PD-L1+), OS (PD-L1-), PFS, ORR, DOR, DCR, APF, safety and tolerability

1ª LÍNEA

Trial Name (NCT #)	Immunotherapy Agent(s) in Study	Phase	Population	Treatment Arms
CheckMate 651 (NCT02741570)	Nivolumab, Ipilimumab	III	Previously untreated R/M HNSCC, ≥6 months since last dose of platinum	Nivolumab + Ipilimumab vs EXTREME
KEYNOTE-048 (NCT02358031)	Pembrolizumab	III		Pembrolizumab vs Pembrolizumab + Platinum/5FU vs EXTREME
KESTREL (NCT02551159)	Durvalumab Tremelimumab	III		Durvalumab vs Durvalumab + tremelimumab vs EXTREME

OTRAS ESTRATEGIAS EN COMBINACIÓN

- **Anti–PD-1 + anti-CD137 (nivolumab + urelumab)**
- **Anti–PD-1 + anti-KIR (nivolumab + lirilumab)**
- **Anti–PD-1 + anti-LAG3 (nivolumab + BMS986016)**
- **Anti-PD-1 + anti-CSF-1R (nivolumab + FPA008)**
- **Oncolytic virus/GM-CSF + anti–PD-1 (TVEC + pembrolizumab)**
- **Anti–PD-1 + anti-EGFR (multiple)**
- **Anti–PD-1 + IDO1 inhibitor**



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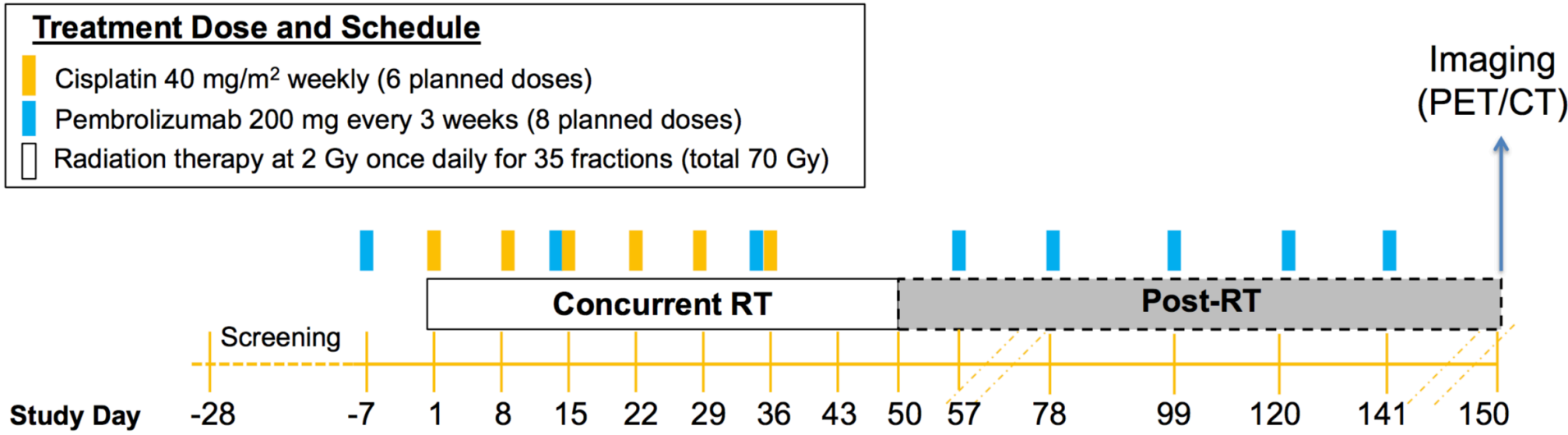
ENFERMEDAD LOCALMENTE AVANZADA

FASE III: KEYNOTE 412



Primary endpoints:

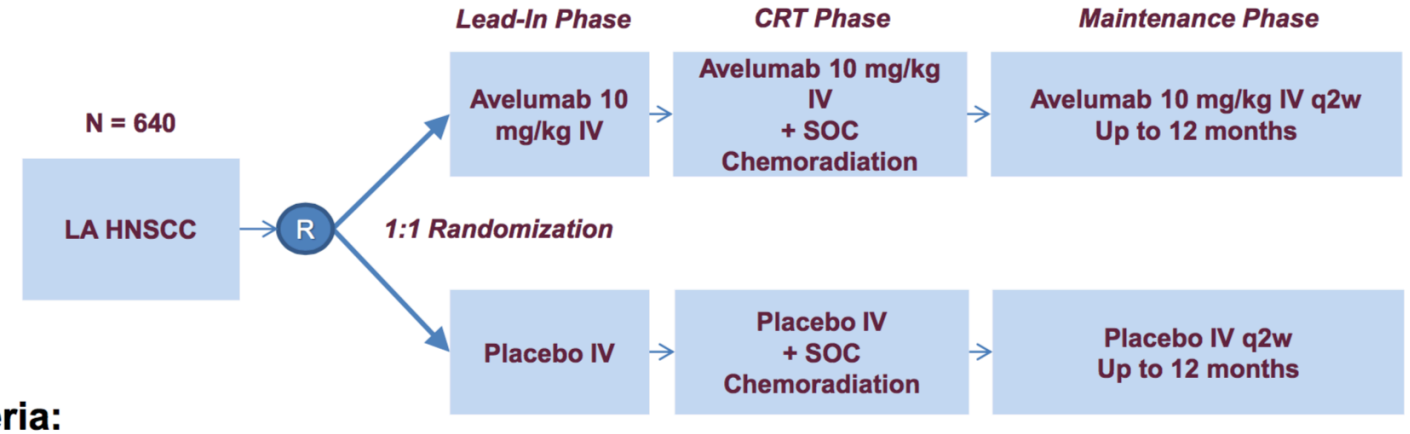
- **Safety - dose-limiting AEs and immune-related AEs (irAEs)**
- **Efficacy - CR rate on imaging or salvage surgery at day 150**

Secondary endpoints: PFS, OS, locoregional control, distant metastasis rate, QoL (FACT H&N)

Powell S, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 6011.

JAVELIN

- **A randomized double-blind phase III study of avelumab in combination with standard of care (SOC) chemoradiotherapy versus SOC chemoradiotherapy in the front-line treatment of HNSCC**



Inclusion criteria:

- LA SCC oral cavity, oropharynx, larynx, hypopharynx
- HPV-; stage II, IVa, IVb
- HPV+: T4 or N2c (AJCC 7) or N3
- ECOG PS = 0 or 1
- No prior therapy

Primary Endpoint: PFS by investigator per modified RECIST v1.1

Stratification Factors

- T stage (<T4 vs T4)
- N stage (N0/N1/2b vs N2c/N3)
- HPV (+ vs -) as measured by p16 IHC

National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT02952586. Accessed: April 19, 2017

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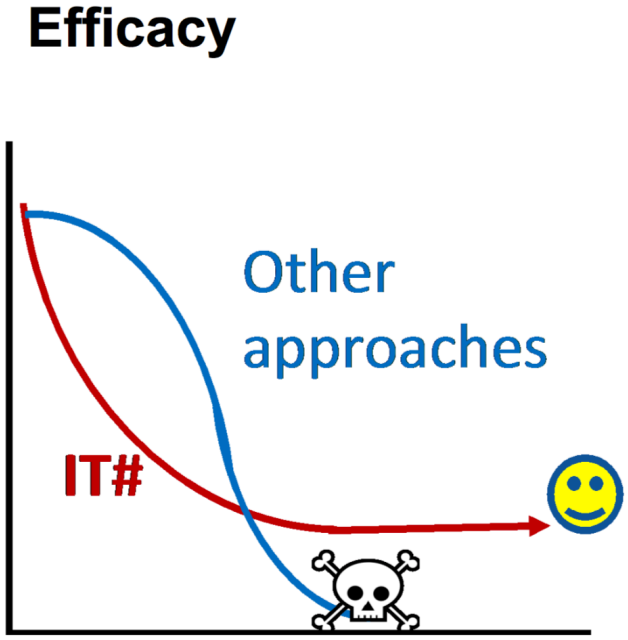
CONCLUSIONES

VENTAJAS

- Nueva era: opción nueva de tratamiento en enfermedad recurrente o metastásica en progresión a platino.
- Principal beneficio es la larga supervivencia de los pacientes respondedores.
- Menos tóxico. Perfil de toxicidad, manejable y que no se superpone a los efectos 2º de otros ttos.
- Mantiene la calidad de vida de los pacientes.
  - Incluso mejor de algunas funciones.

VENTAJAS (II)

- No vemos el mismo efecto en rápidez de respuesta que con citostáticos estándar.
- Patrón de respuesta diferente. Un aumento de pacientes largos supervivientes.
- Pacientes seleccionados tratados con Nivolumab más allá de la 1ªevidencia de PD, han demostrado RP/EE (24%).



INCONVENIENTES

- Queda mucho camino por recorrer.
- A pesar de los nuevos avances, los resultados siguen siendo pobres.
- Seleccionar mejor los pacientes que más se podrían beneficiar.
  - Clínicamente: refractarios (<6m) a tratamiento con Platino para enfermedad metastásica, o progresión a tratamiento multimodal en enf avanzada.
  - Muy sintomáticos. ECOG 0-1 vs 2
  - Biomarcadores: PDL1,p16.

INCONVENIENTES (II)

- Pacientes incluídos en EECC no representan el mundo real.
- Multitud de ensayos clínicos ongoing de IT en monoterapia y combinaciones que mejoren la eficacia de los ttos, vencer mecanismos de resistencia y consigan respuestas más duraderas.

- Necesidad de integración en estadíos más precoces de la enfermedad.
  - Escenario 1ªL, neoadyuvante, LA.