Jornada sobre Cáncer de Cabeza y Cuello

# Cáncer de Cabeza y Cuello Recurrente y Metastásico :

# Inmunoterapia en segunda línea.

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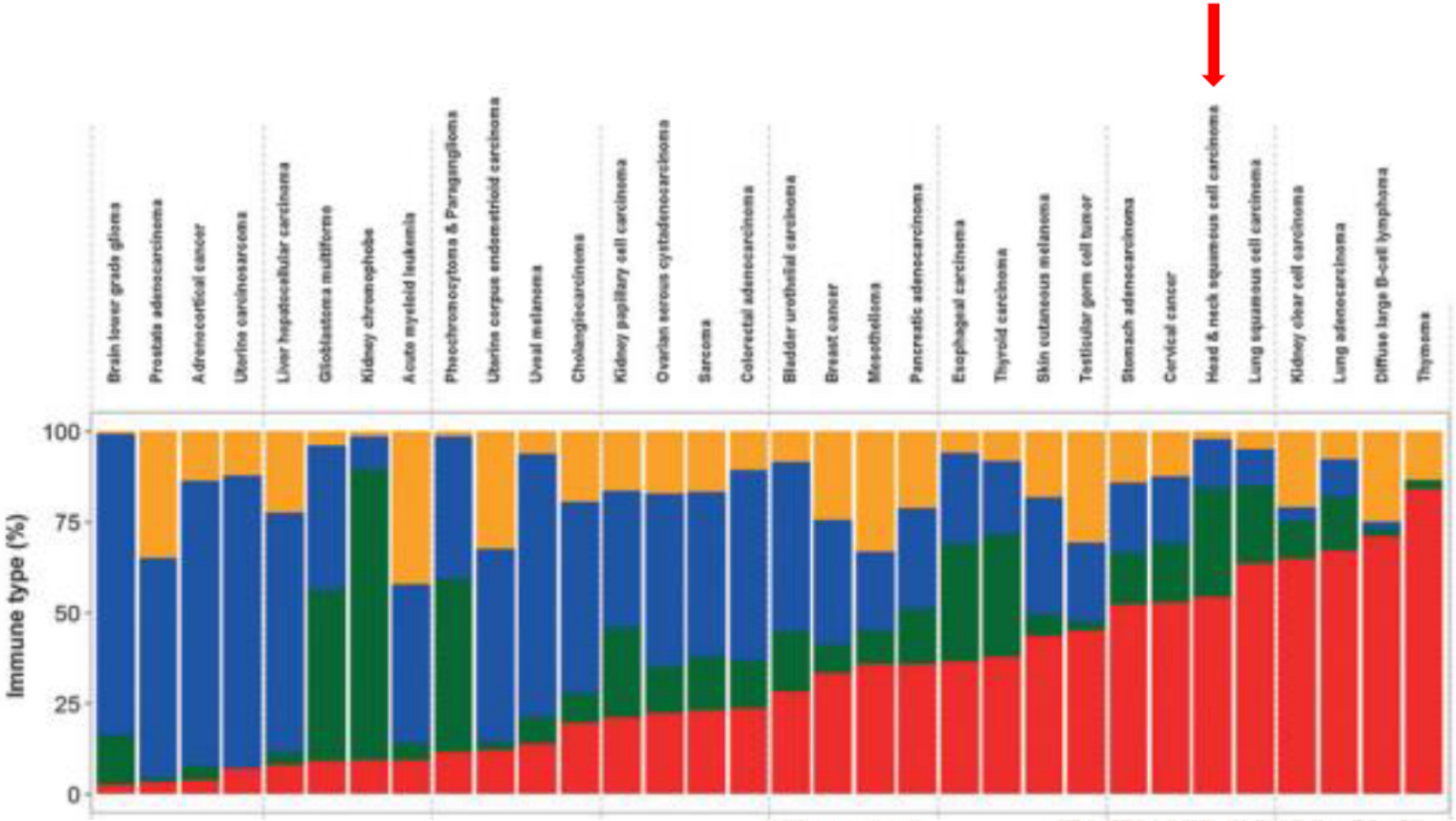
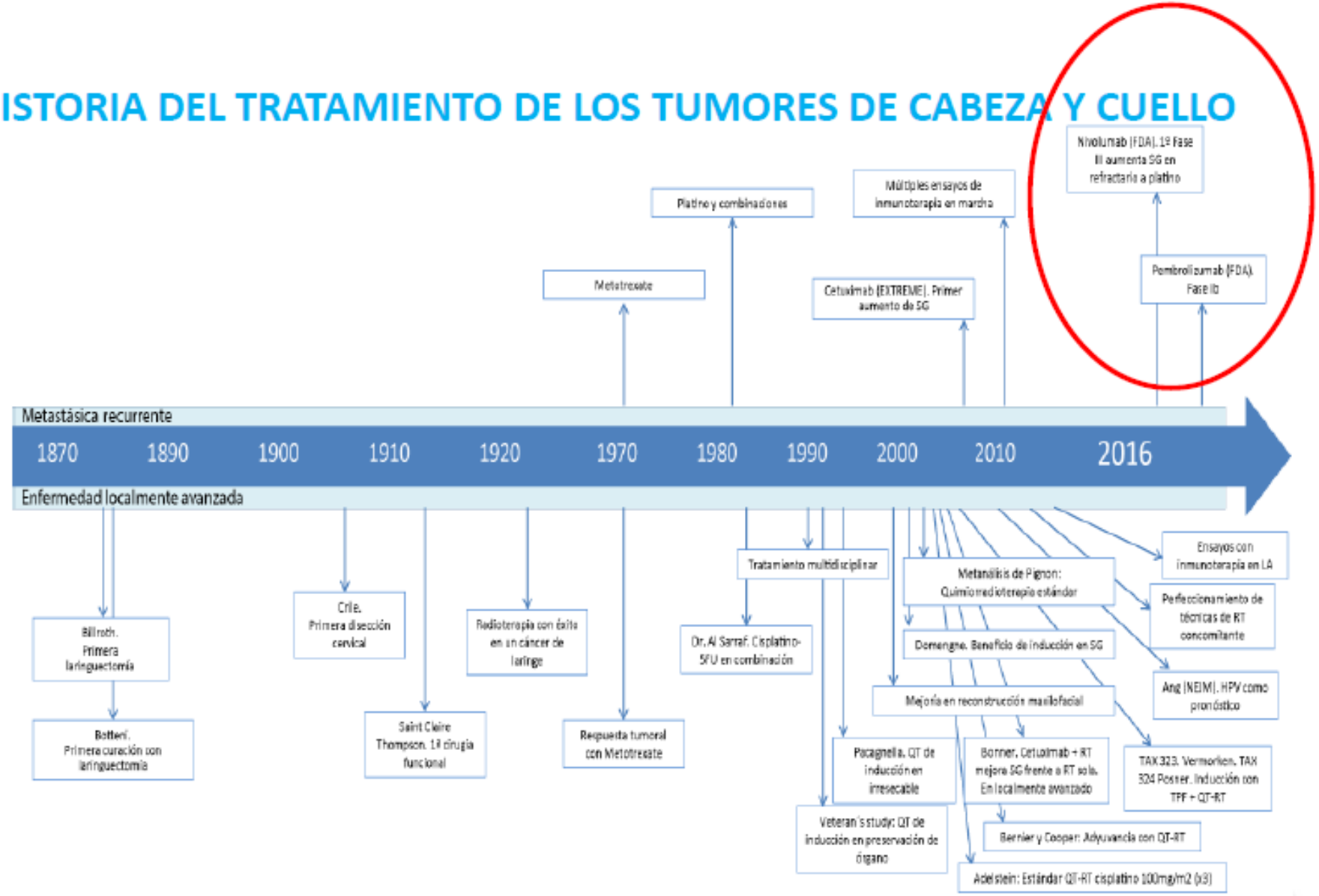
Miércoles,
12 de diciembre de 2018
Hotel Melía Recoletos I Valladolid

# SCCHN tiene microambiente “inflamatorio”



# HISTORIA DEL TRATAMIENTO DE LOS TUMORES DE CABEZA Y CUELLO



# Expresión de PD-L1 en SCCHN

**Table 2**
PD-L1 expression in SCCHN.

| Study | Primary site | Sample size | Percent of tumors with PD-L1 expression | Percent of tumors with PD-L1 expression in HPV positive cases | Percent of tumors with PD-L1 expression in HPV negative cases |
|---|---|---|---|---|---|
| Strome et al. [46] | OC, HP, L, PNS | 24 | 66 | NA | NA |
| Ukpo et al. [47] | OP | 181 | 46.4 | 49.2 | 34.1 |
| Lyford-pike et al. [45] | OP | 27 | 59 | 70 | 29 |
| Badoual et al. [41] | OC, OP, HP | 64 | 51.5 | 62.5 | 40 |
| Cho et al. [50] | OC | 45 | 87 | NA | NA |
| Zhang et al. [48] | NP | 59 | 67.8 | NA | NA |
| Hsu et al. [49] | NP | 25 | 100 | NA | NA |

OC – oral cavity; OP – oropharynx; NP – nasopharynx; HP – hypopharynx; PNS – paranasal sinus; L – larynx.
NA – non-applicable.

**HPV +: 50-70%**

**HPV –: 30-40%**

| | |
|---|---|
| Nivolumab | Tumor PD-L1 – Dako 28-8 |
| Pembrolizumab | Tumor and inflammatory cells PD-L1 – Dako 22C3 – Tumor cells PD-L1 |
| Durvalumab | Tumor PD-L1. VENTANA SP263 |
| Atezolizumab | Immune cells PD-L1 – VENTANA SP142 |

Extraído de: Zandberg DP, Strome SE. The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck. Oral

# Ongoing Randomized 2nd-line Trials with Checkpoint Inhibitors in R/M-SCCHN as of April 2017 (≥100 pts)

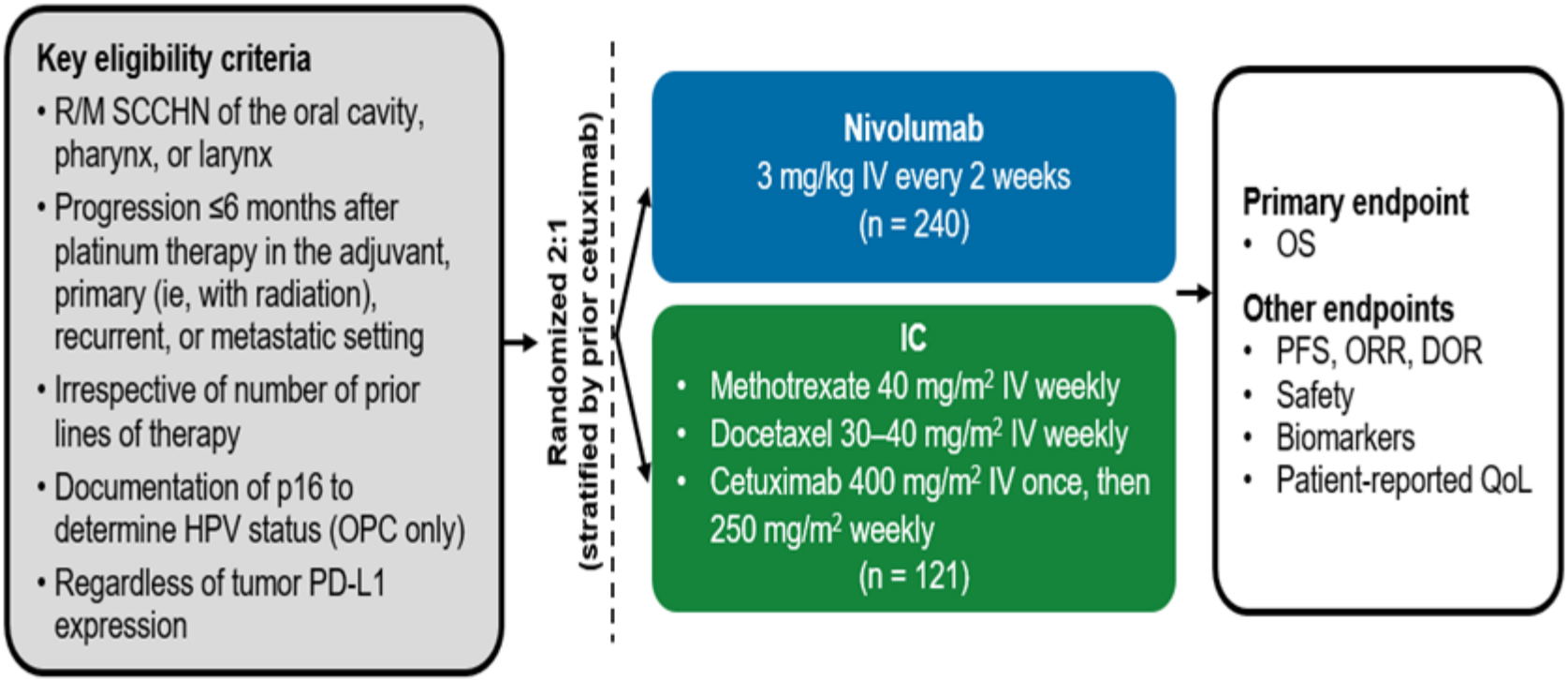
| Trial | Setting | No | Regimens |
|---|---|---|---|
| CheckMate-141 | III | 361 | Nivo vs SoC |
| CONDOR | IIR | 240 | Durva vs Treme vs Combination |
| KEYNOTE-040 | III | 466 | Pembro vs SoC |
| EAGLE | III | 720 | Durva vs Durva+Treme vs SoC |
| KEYNOTE-122 | IIR | 160 | Pembro vs SoC |

*Modified from Szturz and Vermorken, BMC Medicine, 2017*

*Nivo= nivolumab (anti-PD1); Durva= durvalumab (anti-PD-L1); Treme= tremelimumab (anti-CTLA-4)*
*Pembro= pembrolizumab (anti-PD1); SoC= standard of care*

# CheckMate 141 Study Design

- Randomized, open-label, phase 3 trial (NCT02105636)




- Data cutoff: September 2017 (minimum follow-up of 24.2 months)

DOR = duration of response; HPV = human papillomavirus; IV = intravenous; OPC = oropharyngeal cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; QoL = quality of life

# *Nivolumab in R/M SCCHN After Platinum Therapy*

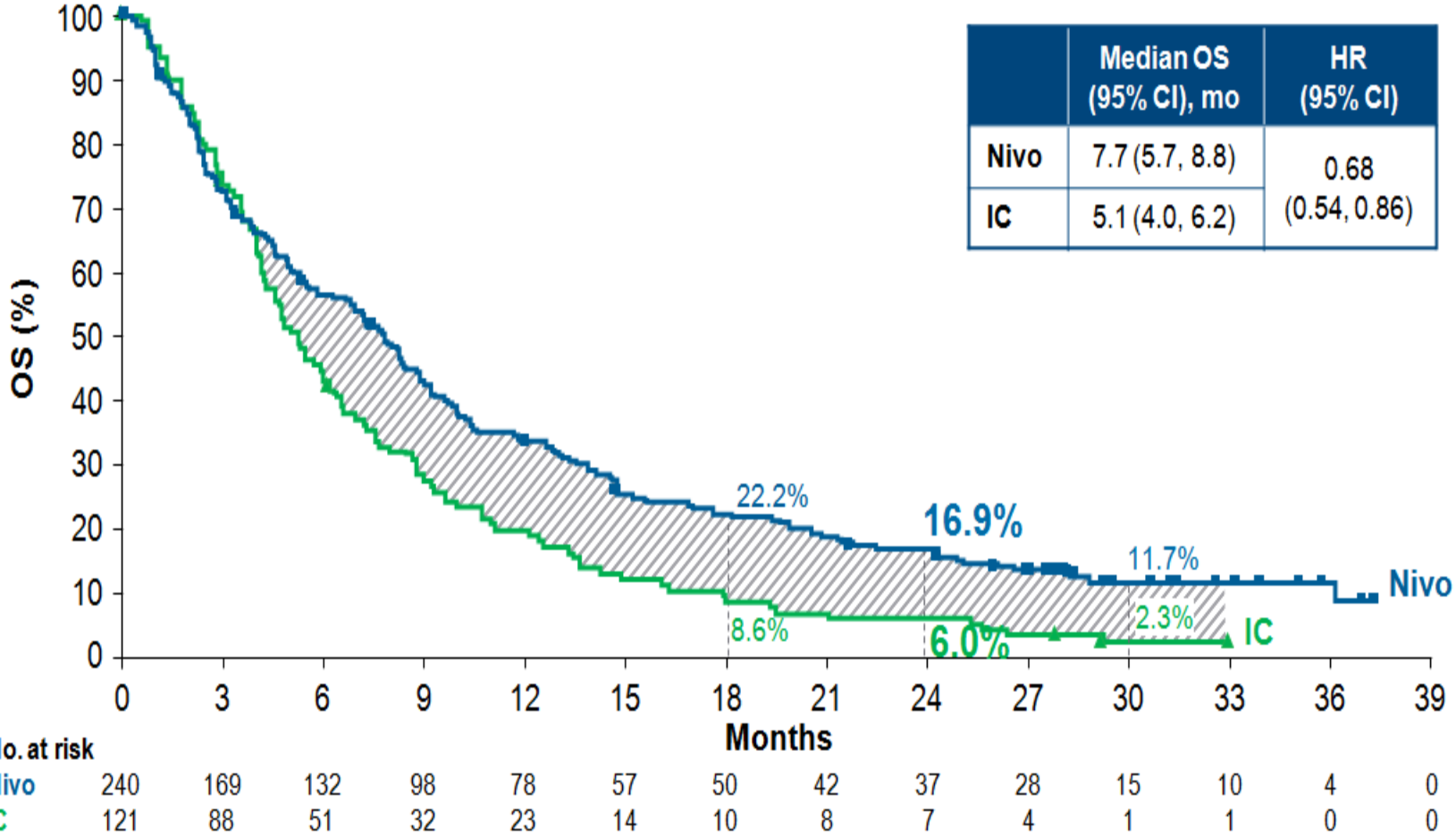
| | Nivolumab (n = 240) | Investigator's Choice (n = 121) | Total (N = 361) |
|---|---|---|---|
| **Median age, years** | **59.0** | **61.0** | **60.0** |
| <65, n (%) | 172 (71.7) | 76 (62.8) | 248 (68.7) |
| **Smoking/tobacco use, n (%)** | | | |
| Current/former | 191 (79.6) | 85 (70.2) | 276 (76.5) |
| 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) |

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

ECOG = Eastern Cooperative Oncology Group

# Sustained OS Benefit in the Overall (ITT) Population

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

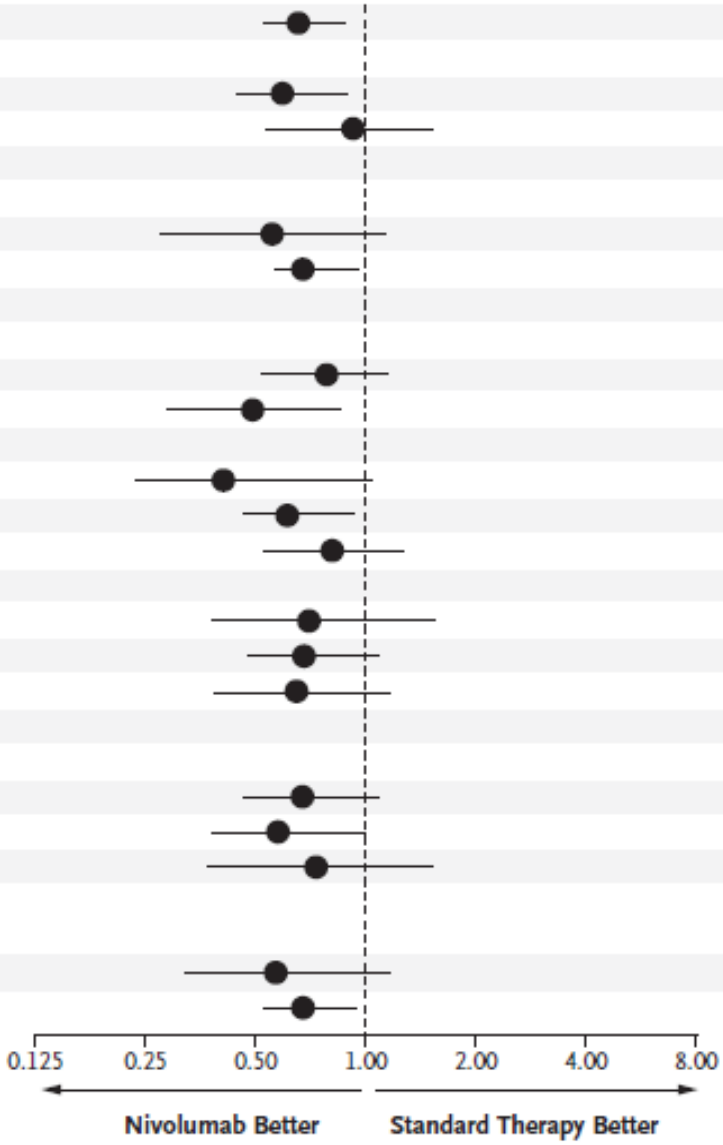



| | Median OS (95% CI), mo | HR (95% CI) |
|---|---|---|
| Nivo | 7.7 (5.7, 8.8) | 0.68 (0.54, 0.86) |
| IC | 5.1 (4.0, 6.2) | |

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

**C Treatment Effect on Overall Survival, According to Subgroup**

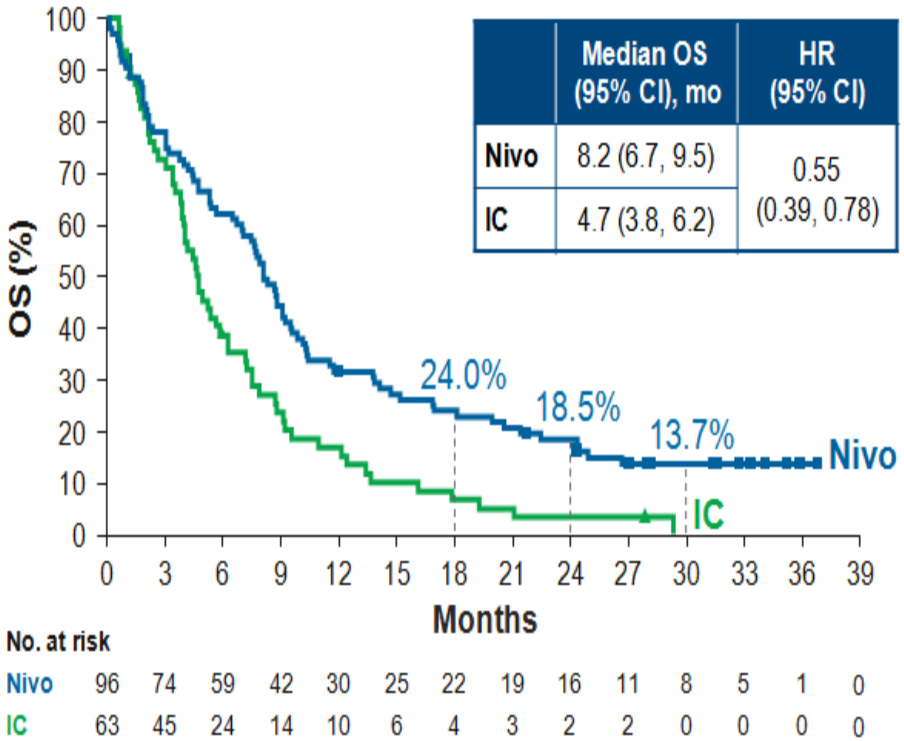
| Subgroup | Nivolumab | Standard Therapy | Unstratified Hazard Ratio (95% CI) |
|---|---|---|---|
| | *no. of patients* | | |
| Overall | 240 | 121 | 0.69 (0.53–0.91) |
| Age | | | |
| <65 yr | 172 | 76 | 0.64 (0.45–0.89) |
| ≥65 yr and <75 yr | 56 | 39 | 0.93 (0.56–1.54) |
| ≥75 yr | 12 | 6 | — |
| 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) |



# OS Benefit Across PD-L1 Expressors and Non-Expressors

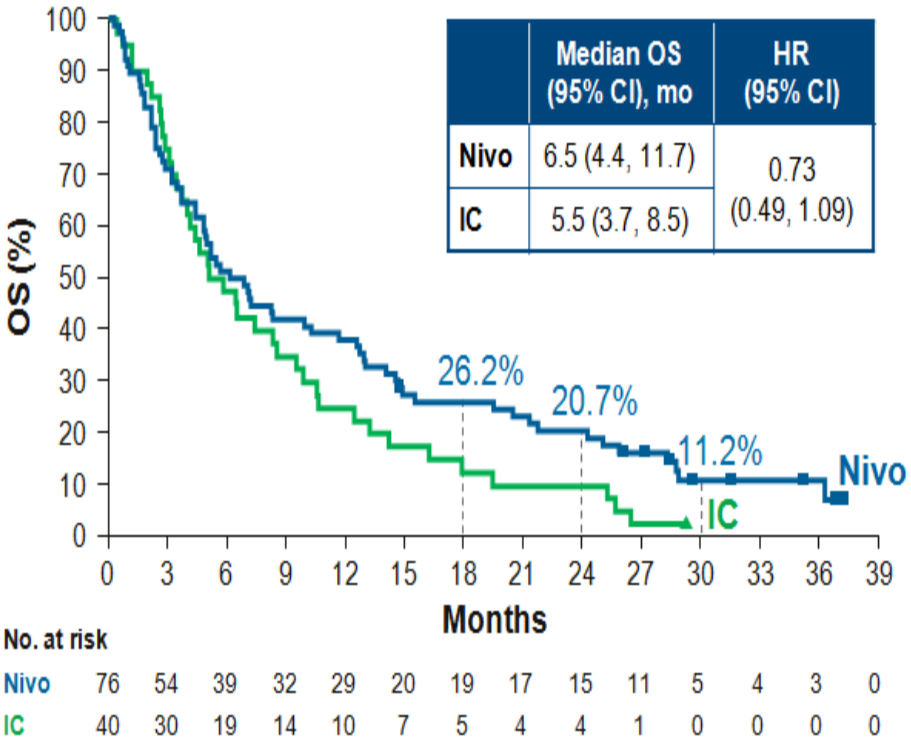
- OS rates at 18, 24, and 30 months were similar in both groups
  - PD-L1 expressors: nivolumab continued to provide OS benefit, with 45% reduction in risk of death vs IC
  - PD-L1 non-expressors: nivolumab resulted in 27% reduction in risk of death vs IC

## PD-L1 Expressors (≥1%)




| | Median OS (95% CI), mo | HR (95% CI) |
|---|---|---|
| Nivo | 8.2 (6.7, 9.5) | 0.55 (0.39, 0.78) |
| IC | 4.7 (3.8, 6.2) | |

## PD-L1 Non-Expressors (<1%)




| | Median OS (95% CI), mo | HR (95% CI) |
|---|---|---|
| Nivo | 6.5 (4.4, 11.7) | 0.73 (0.49, 1.09) |
| IC | 5.5 (3.7, 8.5) | |

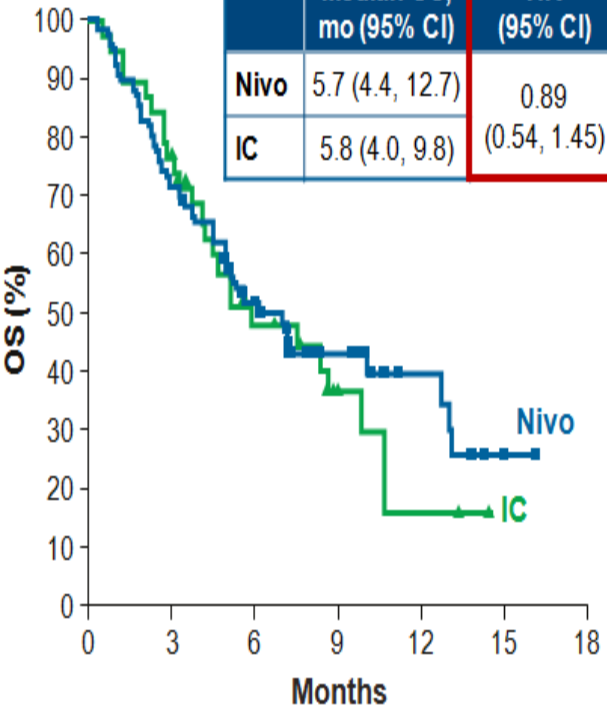
Symbols represent censored observations

# OS in PD-L1 Non-Expressors (<1%)

- In PD-L1 non-expressors, the HR for risk of death with nivolumab vs IC consistently trended lower with longer follow-up

## Primary Analysis[a] (Dec 2015 data cutoff)

| | Median OS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| Nivo | 5.7 (4.4, 12.7) | 0.89 (0.54, 1.45) |
| IC | 5.8 (4.0, 9.8) | |

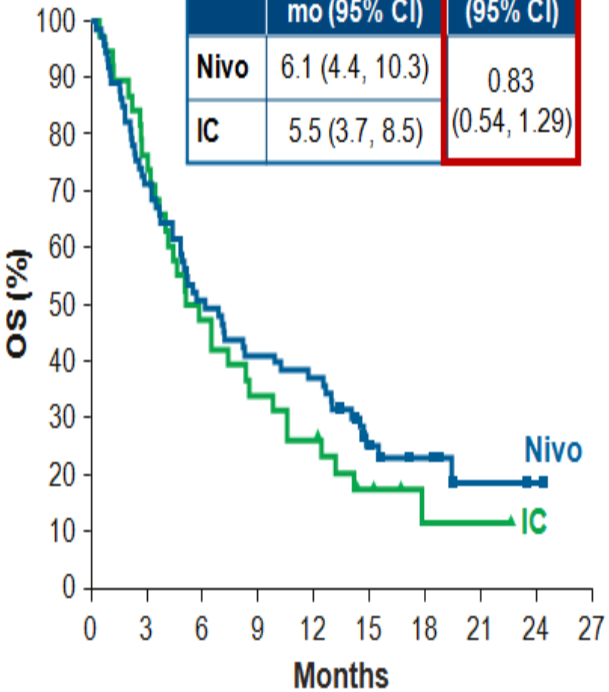



No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nivo | 73 | 52 | 33 | 17 | 8 | 3 | 0 |
| IC | 38 | 29 | 14 | 6 | 2 | 0 | 0 |

## 1-Year Follow-up (Sept 2016 data cutoff)

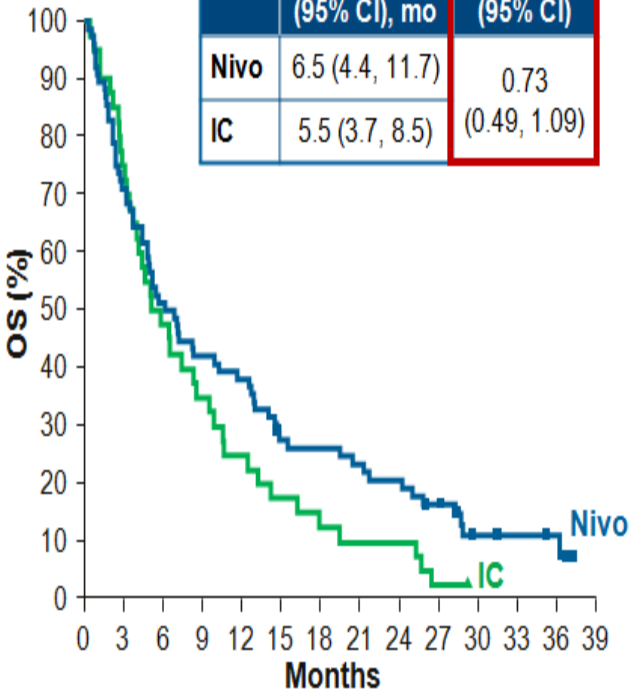
| | Median OS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| Nivo | 6.1 (4.4, 10.3) | 0.83 (0.54, 1.29) |
| IC | 5.5 (3.7, 8.5) | |




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Nivo | 73 | 52 | 37 | 30 | 27 | 13 | 8 | 3 | 1 | 0 |
| IC | 38 | 29 | 18 | 13 | 10 | 5 | 2 | 2 | 0 | 0 |

## 2-Year Follow-up (Sept 2017 data cutoff)

| | Median OS (95% CI), mo | HR (95% CI) |
|---|---|---|
| Nivo | 6.5 (4.4, 11.7) | 0.73 (0.49, 1.09) |
| IC | 5.5 (3.7, 8.5) | |



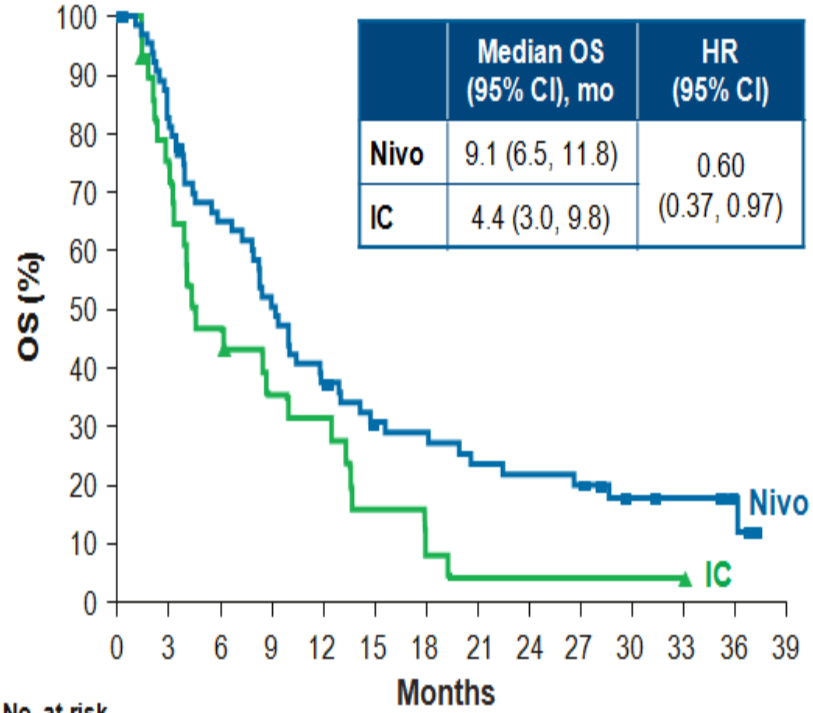

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivo | 76 | 54 | 39 | 32 | 29 | 20 | 19 | 17 | 15 | 11 | 5 | 4 | 3 | 0 |
| IC | 40 | 30 | 19 | 14 | 10 | 7 | 5 | 4 | 4 | 1 | 0 | 0 | 0 | 0 |

Symbols represent censored observations; [a]From NEJM, Ferris RL et al., Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck, 375, 1856-67, Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

# OS by HPV Status[a]

- Nivolumab demonstrated survival benefit in patients with HPV-positive and HPV-negative tumors, with comparable HRs for risk of death vs IC

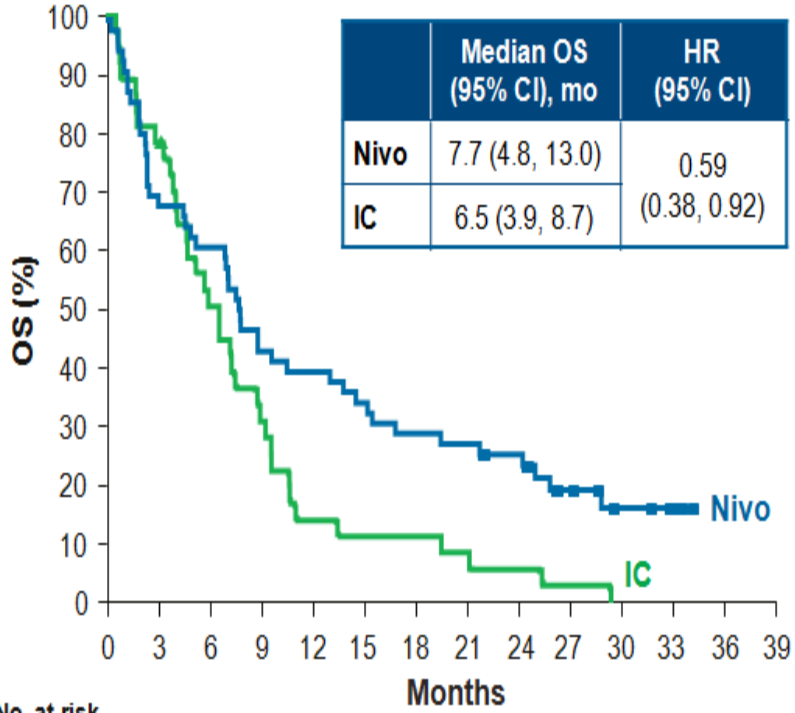
## HPV-Positive




| | Median OS (95% CI), mo | HR (95% CI) |
|---|---|---|
| Nivo | 9.1 (6.5, 11.8) | 0.60 (0.37, 0.97) |
| IC | 4.4 (3.0, 9.8) | |

| No. at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivo | 64 | 50 | 40 | 31 | 23 | 17 | 16 | 13 | 12 | 11 | 7 | 6 | 3 | 0 |
| IC | 29 | 20 | 13 | 9 | 8 | 4 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |

## HPV-Negative




| | Median OS (95% CI), mo | HR (95% CI) |
|---|---|---|
| Nivo | 7.7 (4.8, 13.0) | 0.59 (0.38, 0.92) |
| IC | 6.5 (3.9, 8.7) | |

| No. at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivo | 56 | 38 | 34 | 24 | 22 | 19 | 16 | 15 | 13 | 8 | 4 | 2 | 0 | 0 |
| IC | 37 | 28 | 18 | 11 | 5 | 4 | 4 | 3 | 2 | 1 | 0 | 0 | 0 | 0 |

[a]HPV testing was required only for patients with OPC; symbols represent censored observations

# Subsequent Therapies Among Patients Who Discontinued Treatment

- Nivolumab continued to improve in OS vs IC in spite of subsequent immunotherapy in 10.1% of patients in the IC arm

| Patients, n (%) | Nivolumab (n = 228) | IC (n = 109) |
|---|---|---|
| **Any therapy**[a] | 91 (39.9) | 43 (39.4) |
| **Radiotherapy** | 30 (13.2) | 14 (12.8) |
| **Surgery** | 2 (0.9) | 3 (2.8) |
| **Systemic therapy** | 82 (36.0) | 36 (33.0) |
| Taxanes | 35 (15.4) | 11 (10.1) |
| Monoclonal antibodies (bevacizumab, cetuximab) | 31 (13.6) | 8 (7.3) |
| Other – approved agents | 31 (13.6) | 12 (11.0) |
| Folic acid analogue | 22 (9.6) | 7 (6.4) |
| Platinum-based chemotherapy | 16 (7.0) | 11 (10.1) |
| Other – experimental agents | 15 (6.6) | 3 (2.8) |
| Immunotherapy (nivolumab, pembrolizumab, durvalumab, urelumab) | 12 (5.3) | 11 (10.1) |
| PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, durvalumab) | 9 (3.9) | 10 (9.2) |
| Unassigned | 1 (0.4) | 0 |

[a]Patients may have received more than 1 type of subsequent therapy, which was defined as non-study anticancer therapy started on or after first dosing date (or randomization date, if patient was not treated)

# Tumor Response

- In the nivolumab arm, complete responses were observed in both PD-L1 expressors and PD-L1 non-expressors
  - Seven complete responders (2 PD-L1 expressors, 2 PD-L1 non-expressors, and 3 with no data on tumor PD-L1 expression)
  - One patient had a partial response, which later converted to a complete response

| | Nivolumab (n = 240) | IC (n = 121) |
|---|---|---|
| **ORR, % (95% CI)** | 13.3 (9.3, 18.3) | 5.8 (2.4, 11.6) |
| **Time to response, median (range), months** | 2.1 (1.8 to 7.4) | 2.0 (1.9 to 4.6) |
| **Duration of response, median (range), months** | 9.7 (2.8 to 32.8+) | 4.0 (1.5+ to 11.3) |

# LA EXPRESIÓN DE PD-L1 AUMENTA LA TASA DE RESPUESTAS

| PD-L1 Expression Level | Objective Response Rate | | | |
|---|---|---|---|---|
| | Nivolumab | | Investigator's Choice | |
| | n/N | % | n/N | % |
| ≥ 1% | 15/88 | 17.0 | 1/61 | 1.6 |
| ≥ 5% | 12/54 | 22.2 | 1/43 | 2.3 |
| ≥ 10% | 12/43 | 27.9 | 1/34 | 2.9 |
| < 1% | 9/73 | 12.3 | 4/38 | 10.5 |
| < 5% | 12/107 | 11.2 | 4/56 | 7.1 |
| < 10% | 12/118 | 10.2 | 4/65 | 6.2 |

# Treatment-Related Adverse Events

- The safety profile of nivolumab remained consistent with previous analyses,[1,2] and manageable
  - Fewer grade 3–4 events in the nivolumab arm vs the IC arm
  - No new safety signals were reported
- The incidence of serious TRAEs was lower in the nivolumab arm (7.2%) vs the IC arm (15.3%)
- Rates of death due to drug toxicity remained unchanged from the primary analysis[1]

| | Nivolumab (n = 236) | | IC (n = 111) | |
|---|---|---|---|---|
| | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| **Any TRAE, n (%)** | 146 (61.9) | 36 (15.3) | 88 (79.3) | 41 (36.9) |
| **TRAEs in ≥15% of patients, n (%)** | | | | |
| Fatigue | 37 (15.7) | 5 (2.1) | 20 (18.0) | 3 (2.7) |
| Nausea | 22 (9.3) | 0 | 23 (20.7) | 1 (0.9) |
| Anemia | 12 (5.1) | 3 (1.3) | 19 (17.1) | 6 (5.4) |
| Asthenia | 10 (4.2) | 1 (0.4) | 17 (15.3) | 2 (1.8) |

1. Ferris RL, et al. *N Engl J Med* 2016;375:1856–1867. 2. Gillison ML, et al. *The Oncologist* 2018; In Press.
TRAE = treatment-related adverse event

# Patient Disposition

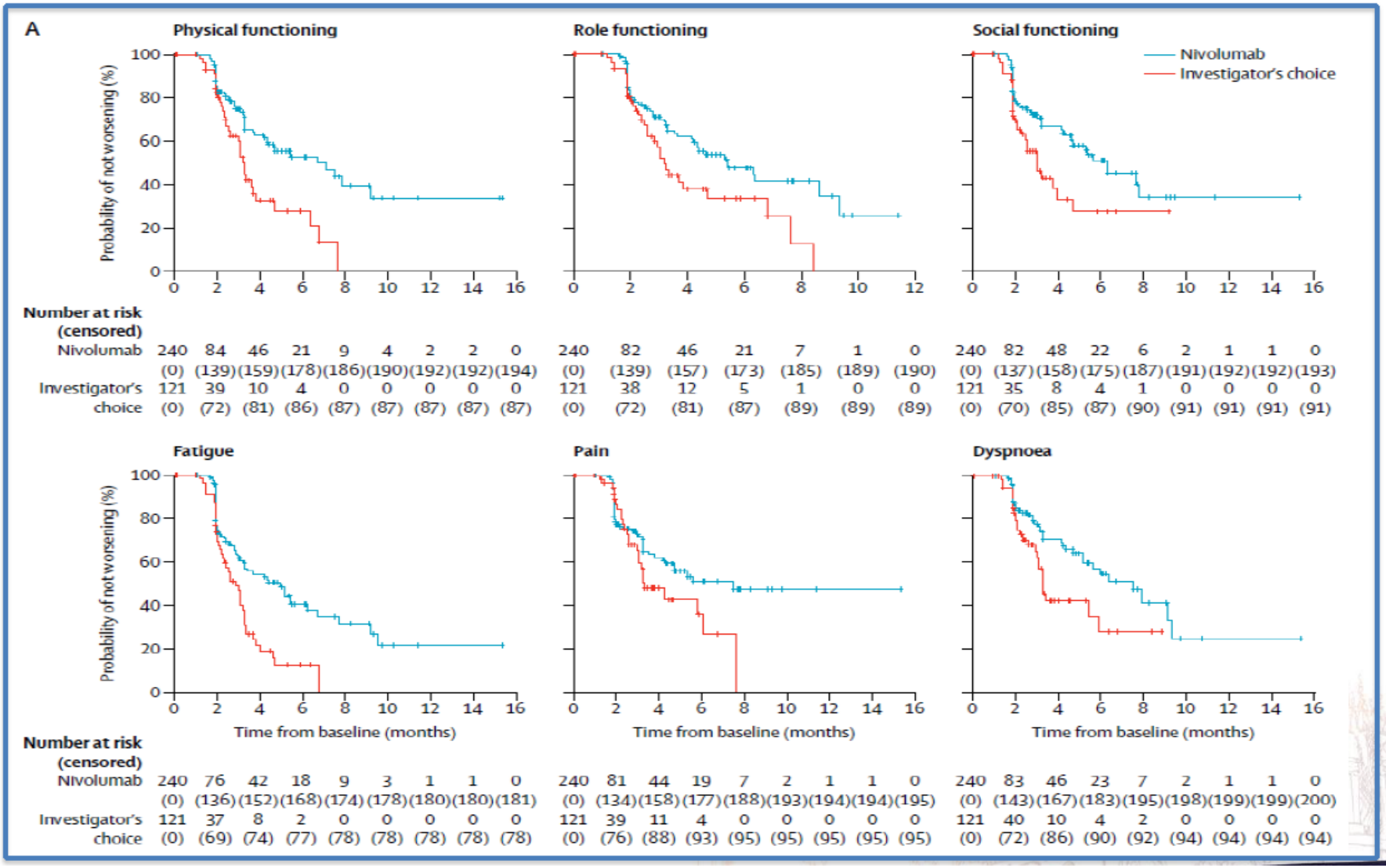
| Patients, n (%) | Nivolumab (n = 236) | IC (n = 111) |
|---|---|---|
| **Continuing treatment** | 8 (3.4) | 0 |
| **Not continuing treatment** | 228 (96.6) | 111 (100.0) |
| Disease progression | 182 (77.1) | 87 (78.4) |
| AEs unrelated to study drug | 19 (8.1) | 3 (2.7) |
| Study drug toxicity | 12 (5.1) | 10 (9.0) |
| Patient request/withdrawal of consent | 12 (5.1) | 7 (6.3) |
| Other[a] | 3 (1.3) | 4 (3.6) |

[a]Other included loss to follow-up, poor/noncompliance, maximum clinical benefit, and patient no longer meeting study criteria
AE = adverse event

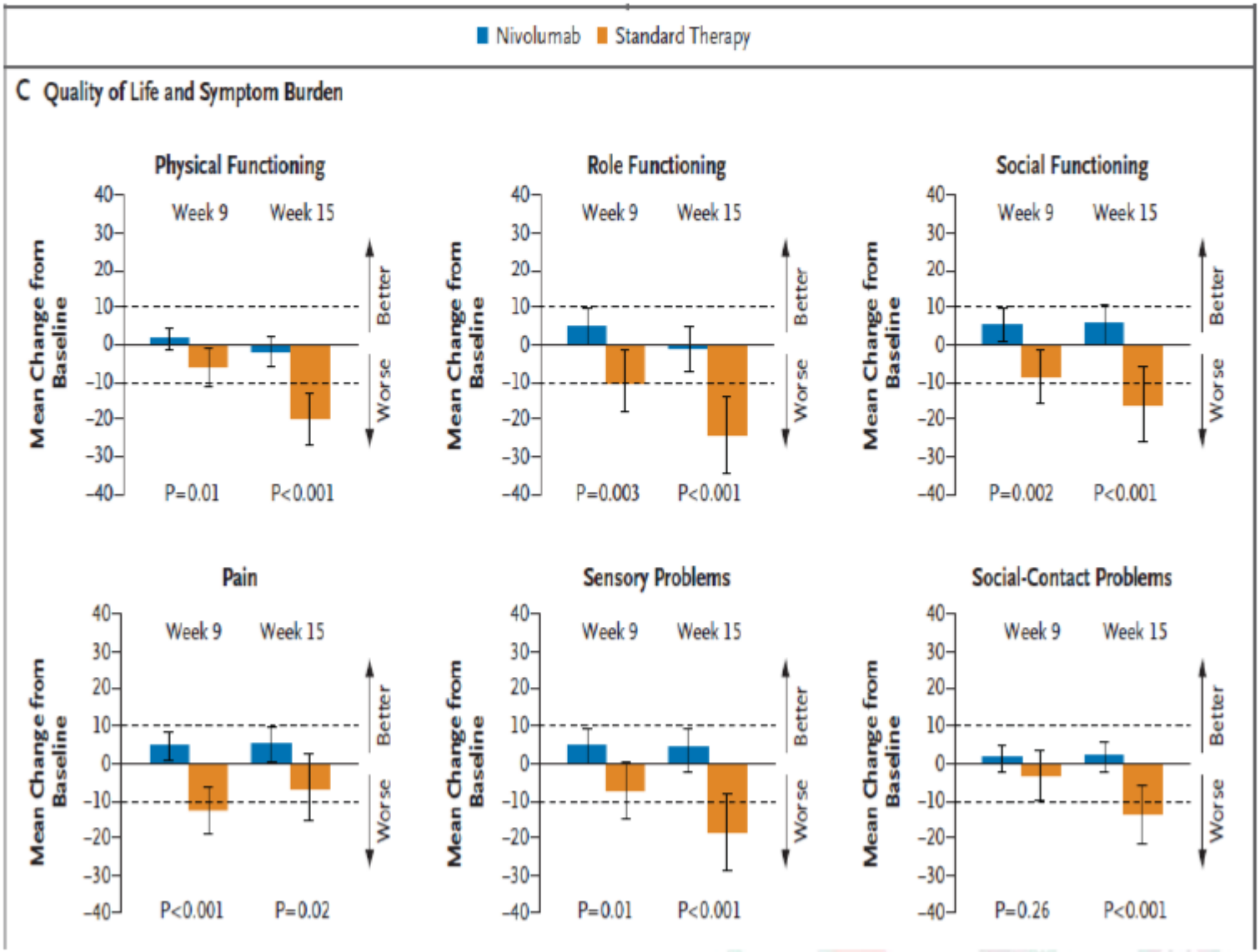
# Conclusions

- Nivolumab is the only immunotherapy to significantly improve OS vs IC in patients with R/M SCCHN post–platinum therapy, in the primary analysis of a randomized, phase 3 study (CheckMate 141)
  - Primary analysis: HR = 0.70 (97.73% CI: 0.51, 0.96); $P = 0.01$
  - 2-year follow-up: HR = 0.68 (95% CI: 0.54, 0.86)
- With long-term (2-year) follow-up, nivolumab demonstrated prolonged OS benefit compared with IC in the overall population with
  - Efficacy across PD-L1 expressors and non-expressors
  - Efficacy regardless of tumor HPV status
  - A favorable safety profile compared with IC maintained; no new safety signals observed
  - No observed differences in baseline characteristics or safety profile among long-term survivors in the nivolumab arm compared with the overall nivolumab population
- Nivolumab is an established therapeutic option in R/M SCCHN post–platinum therapy, with demonstrated long-term benefits in OS and safety compared with monotherapy options

# EORTC QLQ - Time To Deterioration
# CheckMate 141: Nivolumab vs IC in R/M SCCHN After Platinum Therapy

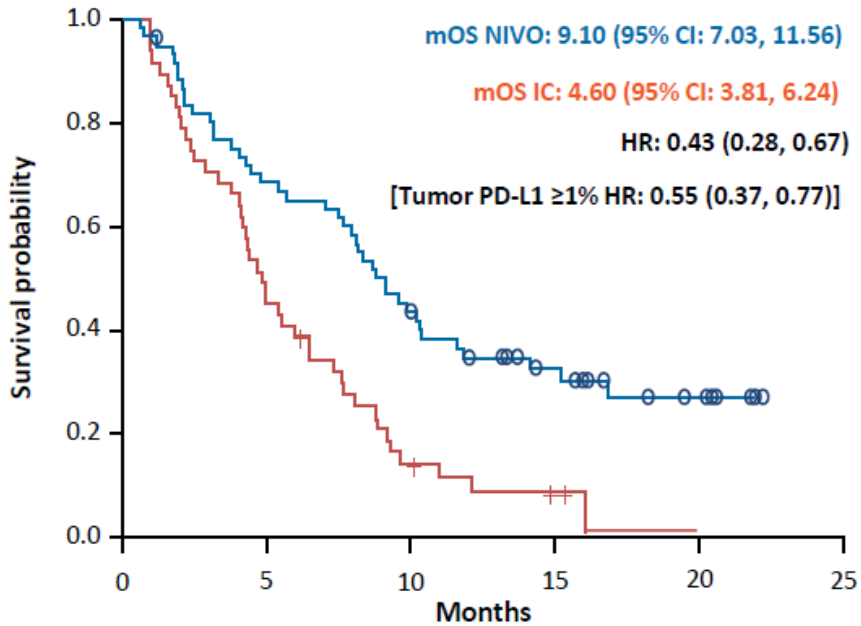


# Quality of Life and Symptom Burden



# Overall Survival by Tumor PD-L1 Expression and PD-L1⁺ TAIC Abundance

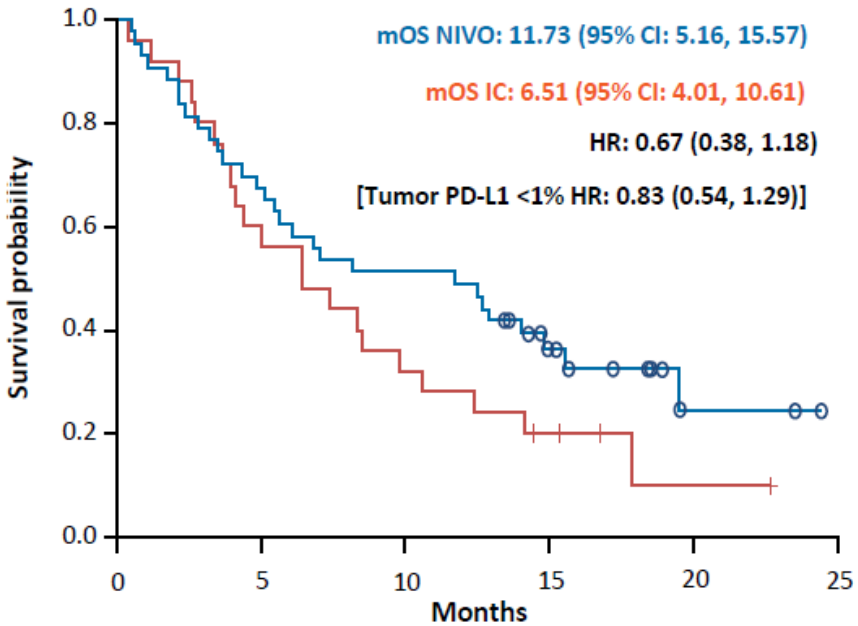
## Tumor PD-L1 ≥1% & PD-L1⁺ TAIC Abundance




Patients at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| NIVO | 61 | 41 | 25 | 14 | 6 | 0 |
| IC | 47 | 21 | 6 | 2 | 0 | |

## Tumor PD-L1 <1% & PD-L1⁺ TAIC Abundance

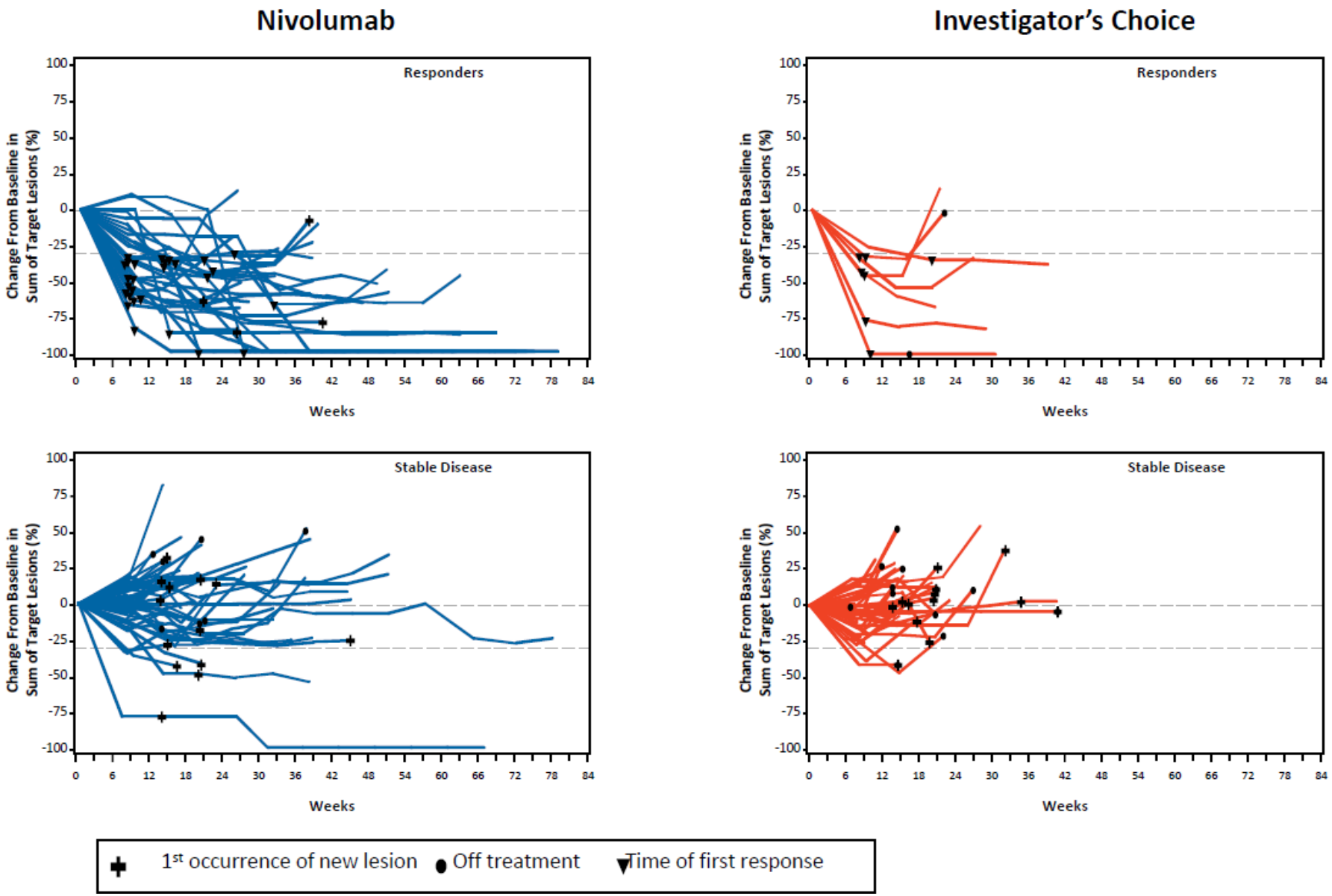



Patients at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| NIVO | 43 | 29 | 22 | 11 | 2 | 0 |
| IC | 25 | 15 | 8 | 4 | 1 | 0 |

- Tumor PD-L1 ≥1% and rare PD-L1⁺ TAICs: mOS increased with NIVO vs IC (6.7 vs 4.9 months, HR 0.89 [0.44, 1.80])
- Tumor PD-L1 <1% and rare PD-L1⁺ TAICs: no difference mOS with NIVO vs IC (3.7 vs 4.9 months, HR 1.09 [0.50, 2.36])

# Patrones respuesta Checkmate 141



*Subestudios **Checkmate 141: NIVOLUMAB EN RECURRENTE / METASTÁSICO.***

*Poster Discussion.*

.

## Nivolumab vs Investigator's Choice For Platinum-Refractory Recurrent or Metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (Checkmate 141): Outcomes in First-Line R/M Patients and Updated Safety and Efficacy

Maura L Gillison,[1] George Blumenschein Jr.,[2] Jerome Fayette,[3] Joel Guigay,[4] Alexander D Colevas,[5] Lisa Licitra,[6] Kevin J Harrington,[7] Stefan Kasper,[8] Everett E Vokes,[9] Caroline Even,[10] Francis Worden,[11] Nabil F Saba,[12] Lara Carmen Iglesias Docampo,[13] Robert Haddad,[14] Tamara Rordorf,[15] Naomi Kiyota,[16] Makoto Tahara,[17] Mark Lynch,[18] Justin Kopit,[18] Robert L Ferris[19]

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Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 2–6, 2017; Chicago, IL, USA

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Presenter: Nabil F Saba

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Email: mgillison@mdanderson.org

Poster 6020

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

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

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

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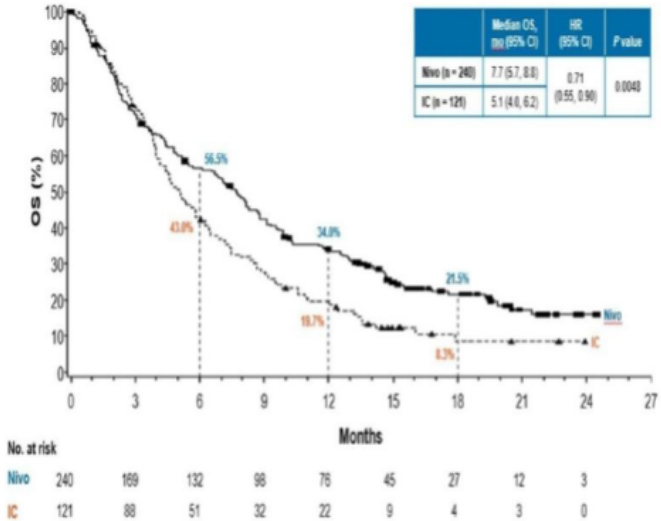
# *Subestudios Checkmate 141: NIVOLUMAB EN RECURRENTE / METASTÁSICO*

## Población Global

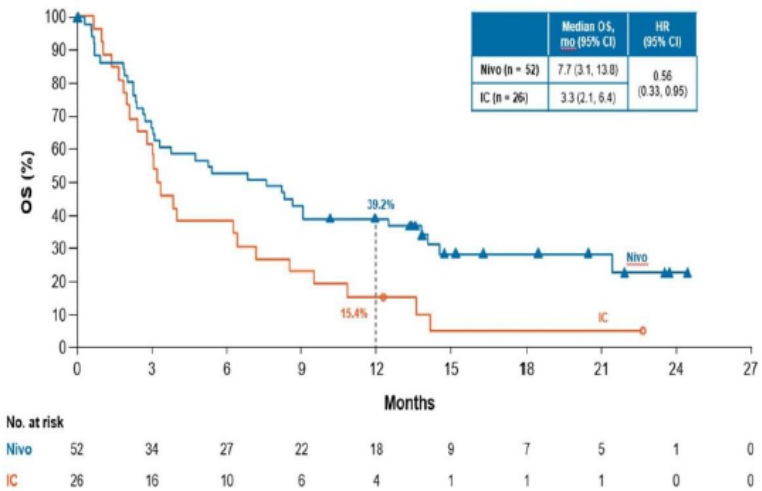
**Overall survival, CheckMate 141 full study population**




| | Median OS, mo (95% CI) | HR (95% CI) | *P* value |
|---|---|---|---|
| Nivo (n = 240) | 7.7 (5.7, 8.8) | 0.71 (0.55, 0.90) | 0.0043 |
| IC (n = 121) | 5.1 (4.0, 6.2) | | |

## *Primera línea*

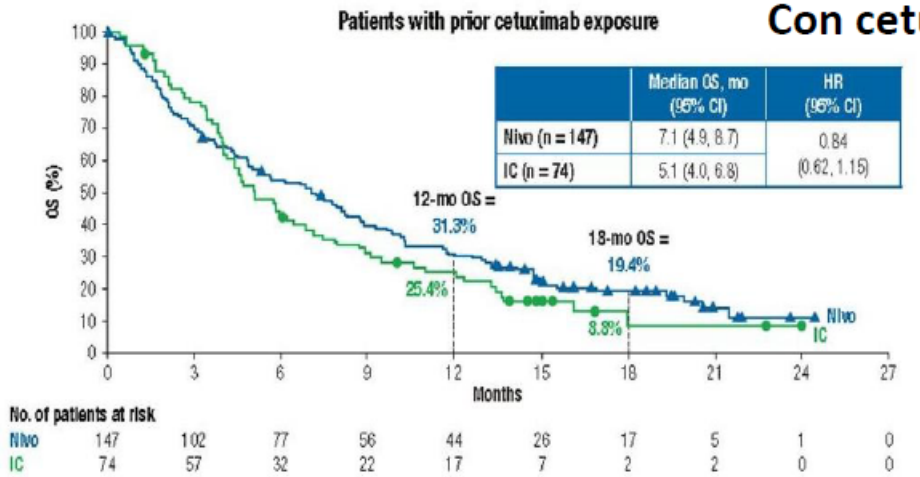
**Overall survival among patients treated in the 1L R/M setting**




| | Median OS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| Nivo (n = 52) | 7.7 (3.1, 13.8) | 0.56 (0.33, 0.95) |
| IC (n = 26) | 3.3 (2.1, 6.4) | |

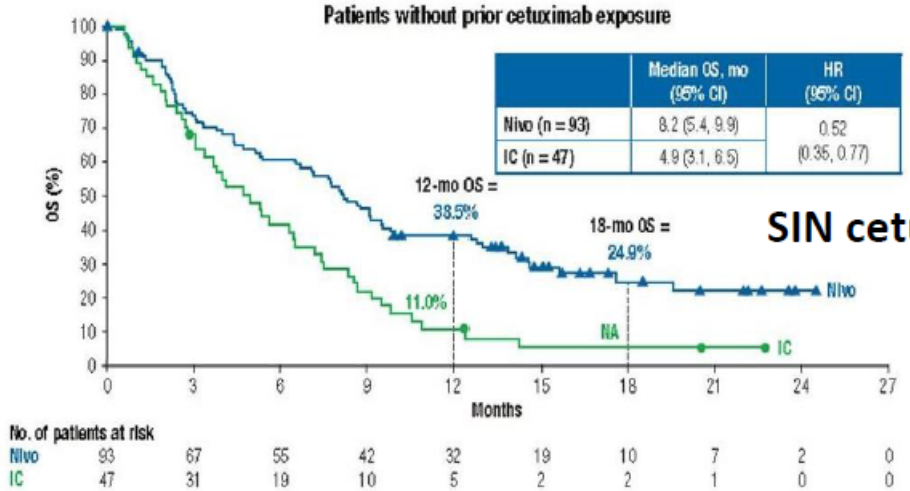
# Exposición previa a cetuximab

## 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) | |

## SIN 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) | |

NA = not available, minimum follow-up not reached

# ¿HASTA CUANDO TRATAR?

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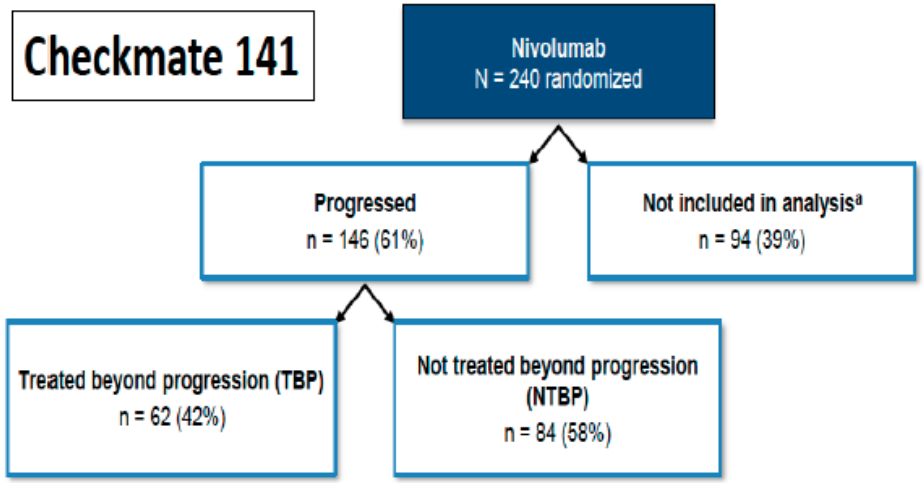
## Treatment Beyond Progression With Nivolumab in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck in the Phase 3 CheckMate 141 Study: A Biomarker Analysis and Updated Clinical Outcomes

Robert Haddad,[1] George Blumenschein, Jr.,[2] Jerome Fayette,[3] Joel Guigay,[4] A. Dimitrios Colevas,[5] Lisa Licitra,[6] Stefan Kasper,[7] Everett E. Vokes,[8] Francis Worden,[9] Nabil F. Saba,[10] Makoto Tahara,[11] Fernando Concha-Benavente,[12] Manish Monga,[13] Mark Lynch,[13] Li Li,[13] James W. Shaw,[13] Maura L. Gillison,[2] Kevin J. Harrington,[14] Robert L. Ferris[12]

[1]Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Centre Leon Berard, Lyon, France; [4]Centre Antoine Lacassagne, Université Côte d'Azur, Nice, France; [5]Stanford University, Stanford, CA, USA; [6]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; [7]West German Cancer Center, University Hospital, Essen, Germany; [8]University of Chicago Medical Center, Chicago, IL, USA; [9]University of Michigan, Ann Arbor, MI, USA; [10]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA, USA; [13]Bristol-Myers Squibb, Princeton, NJ, USA; [14]Royal Marsden NHS Foundation Trust/The Institute of Cancer Research, London, UK

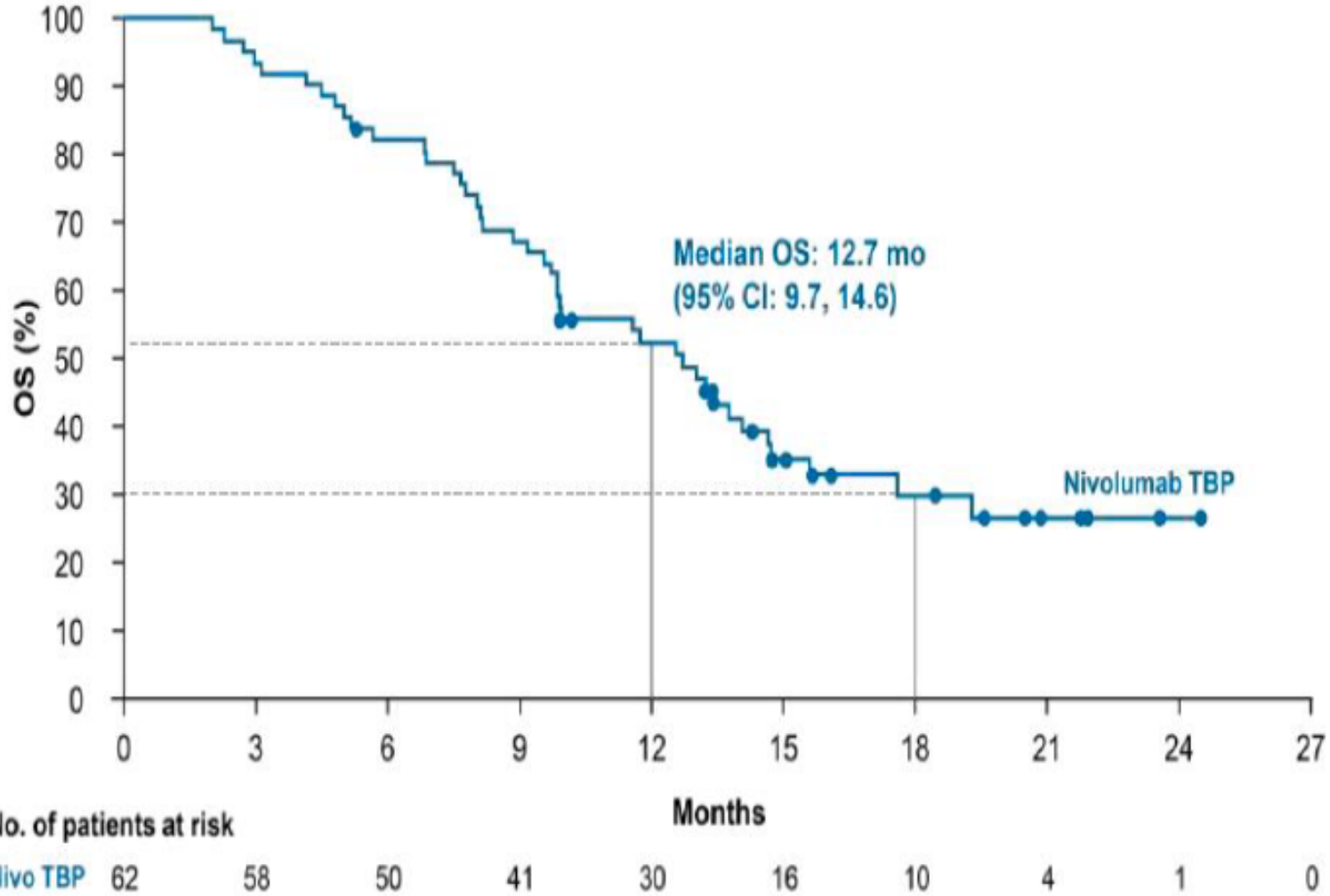
## Treatment beyond progression with nivolumab




Haddad et al 1043O

# Overall Survival, Patients Treated Beyond Progression

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

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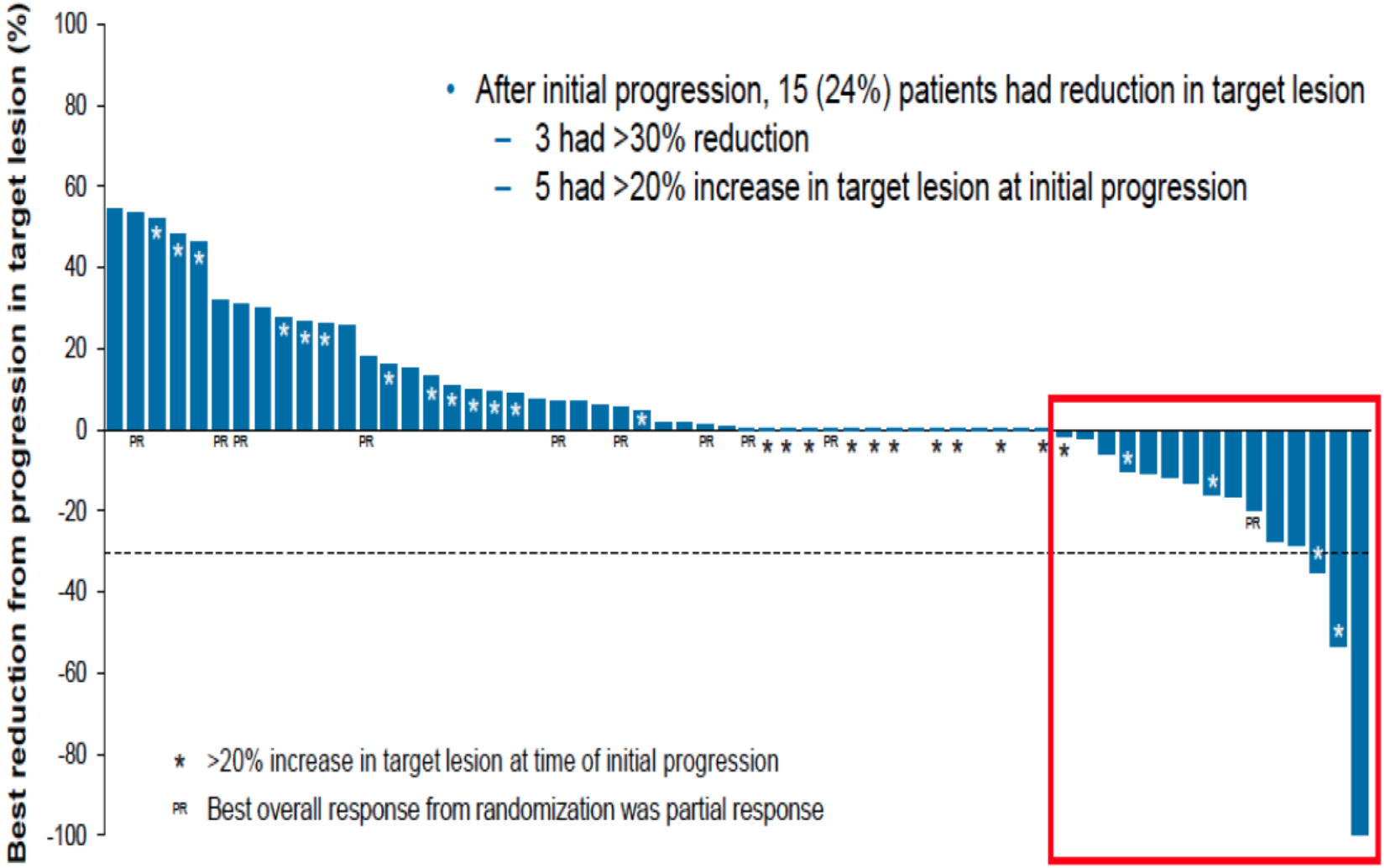
# Tumor Reduction in Patients Treated Beyond Progression

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




- After initial progression, 15 (24%) patients had reduction in target lesion
  - 3 had >30% reduction
  - 5 had >20% increase in target lesion at initial progression

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# PEMBROLIZUMAB

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Articles

## Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial

Dr Tanguy Y Seiwert, MD, Barbara Burtness, MD, Ranee Mehra, Jared Weiss, MD, Raanan Berger, MD, Joseph Paul Eder, MD, Karl Heath, MPH, Terrill McClanahan, PhD, Jared Lunceford, PhD, Christine Gause, PhD, Jonathan D Cheng, MD, Laura Q Chow, MD

Published: 27 May 2016

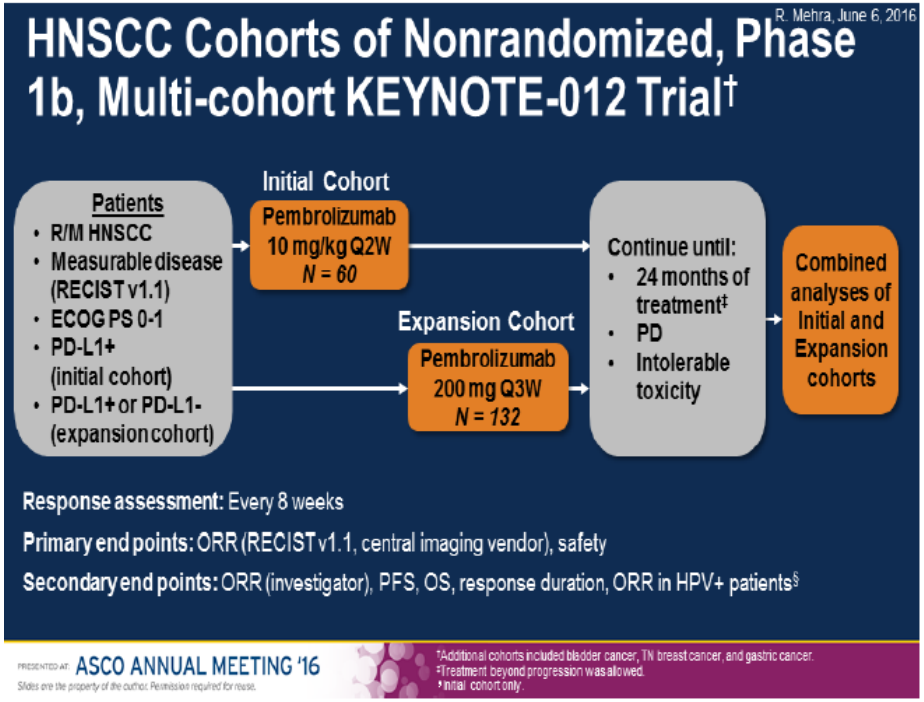
JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

## Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort

Laura Q.M. Chow[1*], Robert Haddad[2], Shilpa Gupta[3], Amit Mahipal[3], Ranee Mehra[4], Makoto Tahara[10], Raanan Berger[12], Joseph Paul Eder[5], Barbara Burtness[5], Se-Hoon Lee[14], Bhumsuk Keam[14], Hyunseok Kang[6], Kei Muro[11], Jared Weiss[7], Ravit Geva[13], Chia-Chi Lin[16], Hyun Cheol Chung[15], Amy Meister[8], Marisa Dolled-Filhart[8], Kumudu Pathiraja[8], Jonathan D. Cheng[8], and Tanguy Y. Seiwert[9]

*Journal of Clinical Oncology* - published online before print September 30, 2016




| | |
|---|---|
| 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) |

R. Mehra, June 6, 2016

# Progression-Free Survival† and Overall Survival

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

R. Mehra, June 6, 2016

## 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 25, 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.

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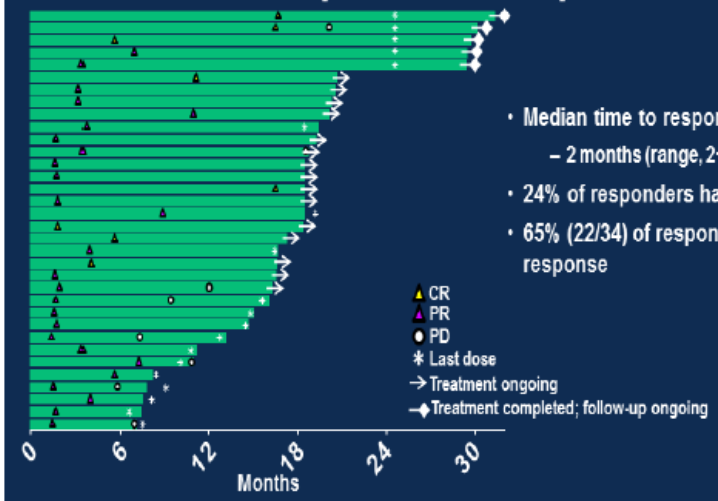
## Duration of Response in Responders




- Median time to response
  - 2 months (range, 2–17)
- 24% of responders had CR
- 65% (22/34) of responders remain in response

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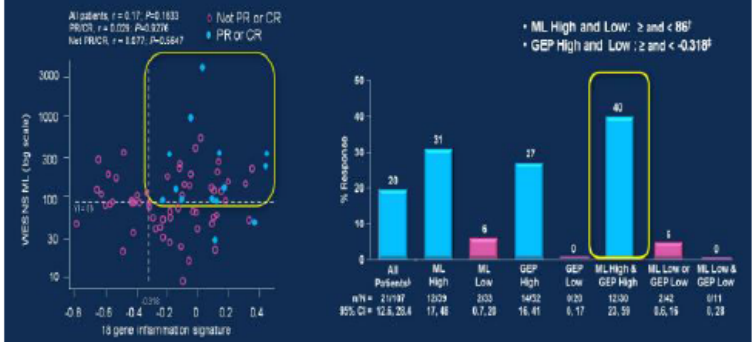
Data cutoff date: Apr 25, 2016.
Based on RECIST v1.1 per central imaging vendor review (swimlane plot).
Only confirmed responses shown.

## ML and GEP Associated BOR: HPV/EBV⁻ WES




- ML and GEP were weakly correlated and remained significant predictors in a multivariate model adjusted for each measure (ML $P$=0.0349; GEP $P$=0.0056)
- Response was higher in patients with high ML or GEP; highest in those with both high ML and GEP

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†Cutoff associated with ROC Youden Index; ‡Cutoff selected via analysis of pan-cancer data; equivalent but numerically different clinical assay cutoff is currently under evaluation in same Merck trials: IB1+B2, WES cohorts

J. Bauml, June 6, 2016

# Preliminary Results From KEYNOTE-055: Pembrolizumab After Platinum and Cetuximab Failure in Head and Neck Squamous Cell Carcinoma (HNSCC)

*Joshua Bauml*,[1] Tanguy Seiwert,[2] David G. Pfister,[3] Francis Worden,[4] Stephen V. Liu,[5] Jill Gilbert,[6] Nabil F. Saba,[7] Jared Weiss,[8] Lori Wirth,[9] Ammar Sukari,[10] Hyunseok Kang,[11] Michael K. Gibson,[12] Erminia Massarelli,[13] Steven Powell,[14] Amy Meister,[15] Xinxin Shu,[15] Jonathan Cheng,[15] Robert Haddad[16]

[1]University of Pennsylvania, Philadelphia, PA; [2]University of Chicago, Chicago, IL; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; [5]Georgetown University Hospital, Washington, DC; [6]Vanderbilt University School of Medicine, Nashville, TN; [7]Winship Cancer Institute/Emory University, Atlanta, GA; [8]Lineberger Comprehensive Cancer Center at the University of North Carolina, Chapel Hill, NC; [9]Massachusetts General Hospital, Boston, MA; [10]Karmanos Cancer Institute, Wayne State University, Detroit, MI; [11]Johns Hopkins University School of Medicine, Baltimore, MD; [12]University Hospitals Case Medical Center, Cleveland, OH; [13]The University of Texas MD Anderson Cancer Center, Houston, TX; [14]Sanford Health, Sioux Falls, SD; [15]Merck & Co., Inc., Kenilworth, NJ; [16]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

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JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

## Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study

*Joshua Bauml, Tanguy Y. Seiwert, David G. Pfister, Francis Worden, Stephen V. Liu, Jill Gilbert, Nabil F. Saba, Jared Weiss, Lori Wirth, Ammar Sukari, Hyunseok Kang, Michael K. Gibson, Erminia Massarelli, Steven Powell, Amy Meister, Xinxin Shu, Jonathan D. Cheng, and Robert Haddad*

Author affiliations and support information (if applicable) appear at the end of this article.

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J.B. and T.Y.S. are co-primary authors.

Clinical trial information: NCT02255097.

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0732-183X/17/35599-1/$20.00

### ABSTRACT

**Purpose**

There are no approved treatments for recurrent/metastatic head and neck squamous cell carcinoma refractory to platinum and cetuximab. In the single-arm, phase II KEYNOTE-055 study, we evaluated pembrolizumab, an anti–programmed death 1 receptor antibody, in this platinum- and cetuximab-pretreated population with poor prognosis.

**Methods**

Eligibility stipulated disease progression within 6 months of platinum and cetuximab treatment. Patients received pembrolizumab 200 mg every 3 weeks. Imaging was performed every 6 to 9 weeks. Primary end points: overall response rate (Response Evaluation Criteria in Solid Tumors v1.1, central review) and safety. Efficacy was assessed in all dosed patients and in subgroups on the basis of programmed death ligand 1 (PD-L1) expression and human papillomavirus (HPV) status.

**Results**

Among 171 patients treated, 75% received two or more prior lines of therapy for metastatic disease, 82% were PD-L1 positive, and 22% were HPV positive. At the time of analysis, 109 patients (64%) experienced a treatment-related adverse event; 26 patients (15%) experienced a grade ≥ 3 event. Seven patients (4%) discontinued treatment, and one died of treatment-related adverse events. Overall response rate was 16% (95% CI, 11% to 23%), with a median duration of response of 8 months (range, 2+ to 12+ months); 75% of responses were ongoing at the time of analysis. Response rates were similar in all HPV and PD-L1 subgroups. Median progression-free survival was 2.1 months, and median overall survival was 8 months.

**Conclusion**

Pembrolizumab exhibited clinically meaningful antitumor activity and an acceptable safety profile in recurrent/metastatic head and neck squamous cell carcinoma previously treated with platinum and cetuximab.

*J Clin Oncol 35. © 2017 by American Society of Clinical Oncology*

J. Bauml, June 6, 2016

# KEYNOTE-055: Single Arm, Phase 2 Trial in R/M HNSCC After Progression on Platinum/Cetuximab

**Patients**
- Recurrent/ metastatic HNSCC
- Resistant to platinum and cetuximab†
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1

→ **Pembrolizumab 200 mg Q3W Flat Dose** →

Continue until:
- 24 months of treatment
- PD
- Intolerable toxicity
- Investigator/patient decision

→ **Safety and Survival Follow-up**

**Response assessment:** Every 6-9 weeks

**Primary end points:** ORR (RECIST v1.1, central imaging vendor) in all patients and PD-L1+ patients, safety

**Secondary end points:** ORR in HPV+ patients, PFS, OS, duration of response

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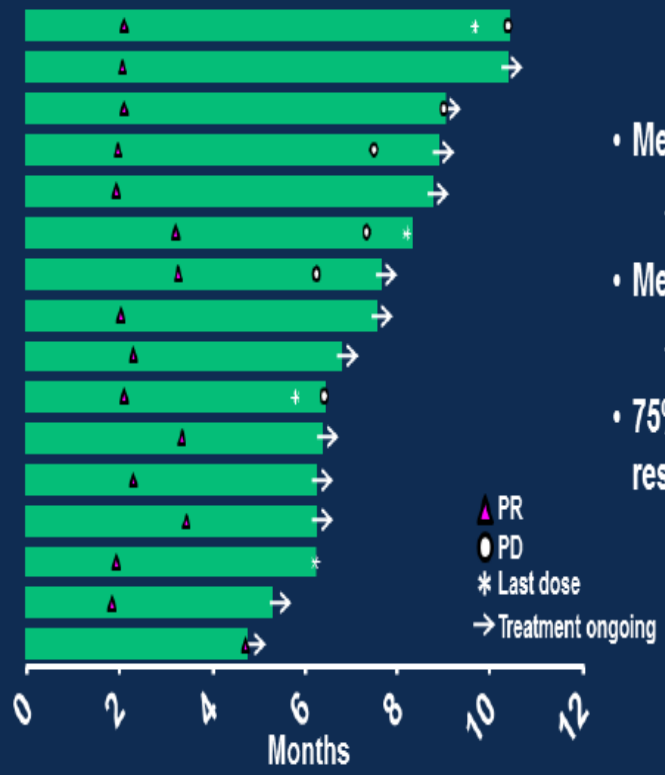
†Resistance defined as tumor progression or recurrence within 6 months of last platinum and cetuximab dose.

| Characteristic | N = 171† n (%) |
|---|---|
| Median prior systemic therapies (range) | 2 (1–6) |
| Prior lines of systemic therapy | |
| 1 | 28 (16) |
| 2 | 71 (42) |
| ≥3 | 72 (42) |

# Duration of Exposure in Responders Patients With ≥6 Months Follow-up

J. Bauml, June 6, 2016




- Median follow-up duration
  - 7 (range, 0–14) months
- Median time to response
  - 2 (range, 2–5) months
- 75% of responders remain in response



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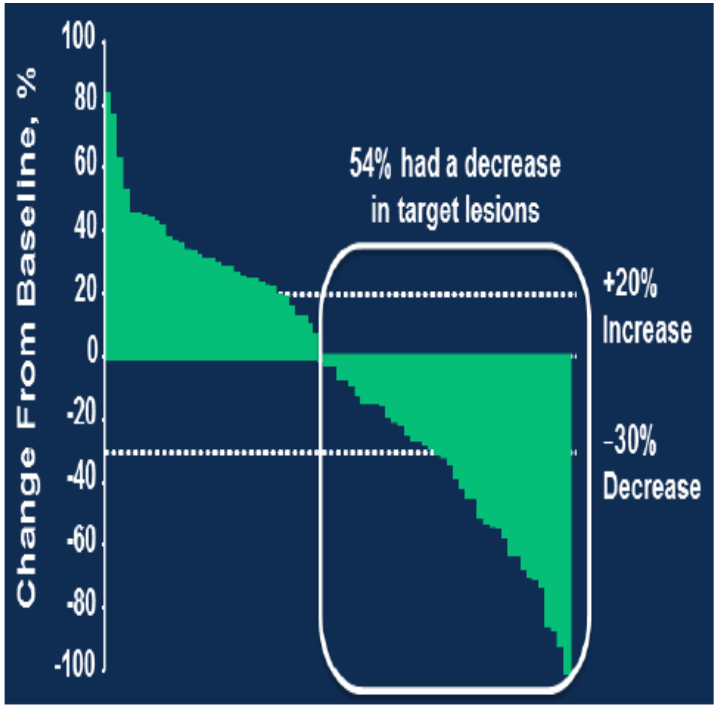
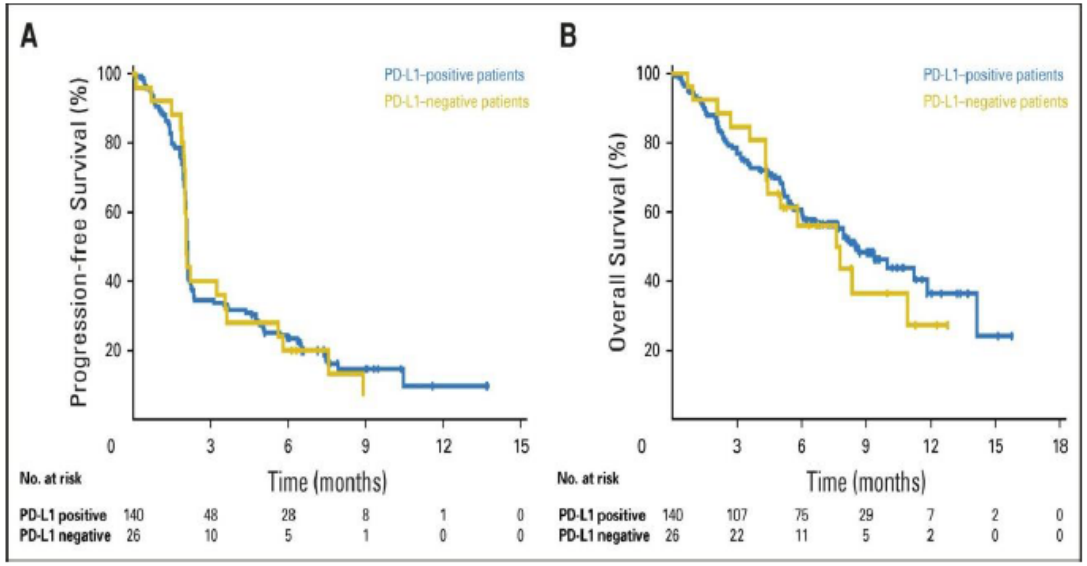
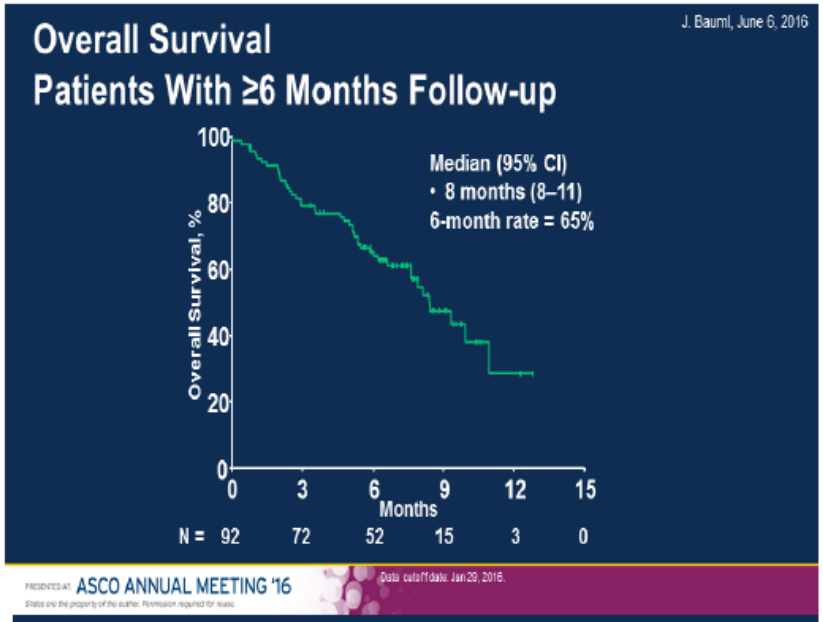
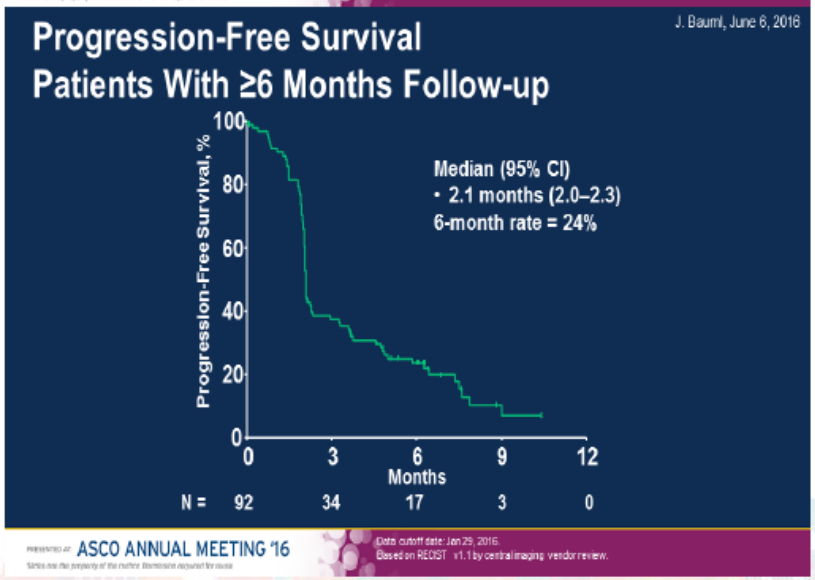
Data cutoff date: Jan 29, 2016. Based on RECIST v1.1 by central imaging vendor review (waterfall plot). Only confirmed responses are shown.




A
Progression-free Survival (%)
PD-L1-positive patients
PD-L1-negative patients
Time (months)
No. at risk
PD-L1 positive 140 48 28 8 1 0
PD-L1 negative 26 10 5 1 0 0
B
Overall Survival (%)
PD-L1-positive patients
PD-L1-negative patients
Time (months)
No. at risk
PD-L1 positive 140 107 75 29 7 2 0
PD-L1 negative 26 22 11 5 2 0 0


J. Bauml, June 6, 2016
Overall Survival
Patients With ≥6 Months Follow-up
Median (95% CI)
• 8 months (8–11)
6-month rate = 65%
Overall Survival, %
Months
N = 92 72 52 15 3 0
ASCO ANNUAL MEETING '16
Data cutoff date: Jan 29, 2016.


J. Bauml, June 6, 2016
Progression-Free Survival
Patients With ≥6 Months Follow-up
Median (95% CI)
• 2.1 months (2.0–2.3)
6-month rate = 24%
Progression-Free Survival, %
Months
N = 92 34 17 3 0
ASCO ANNUAL MEETING '16
Data cutoff date: Jan 29, 2016.
Based on RECIST v1.1 by central imaging vendor review.

MADRID 2017 ESMO congress

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

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# Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study

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# 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]
  - 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
  - Efficacy boundary: one-sided $\alpha = 0.0175$
- 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.

# 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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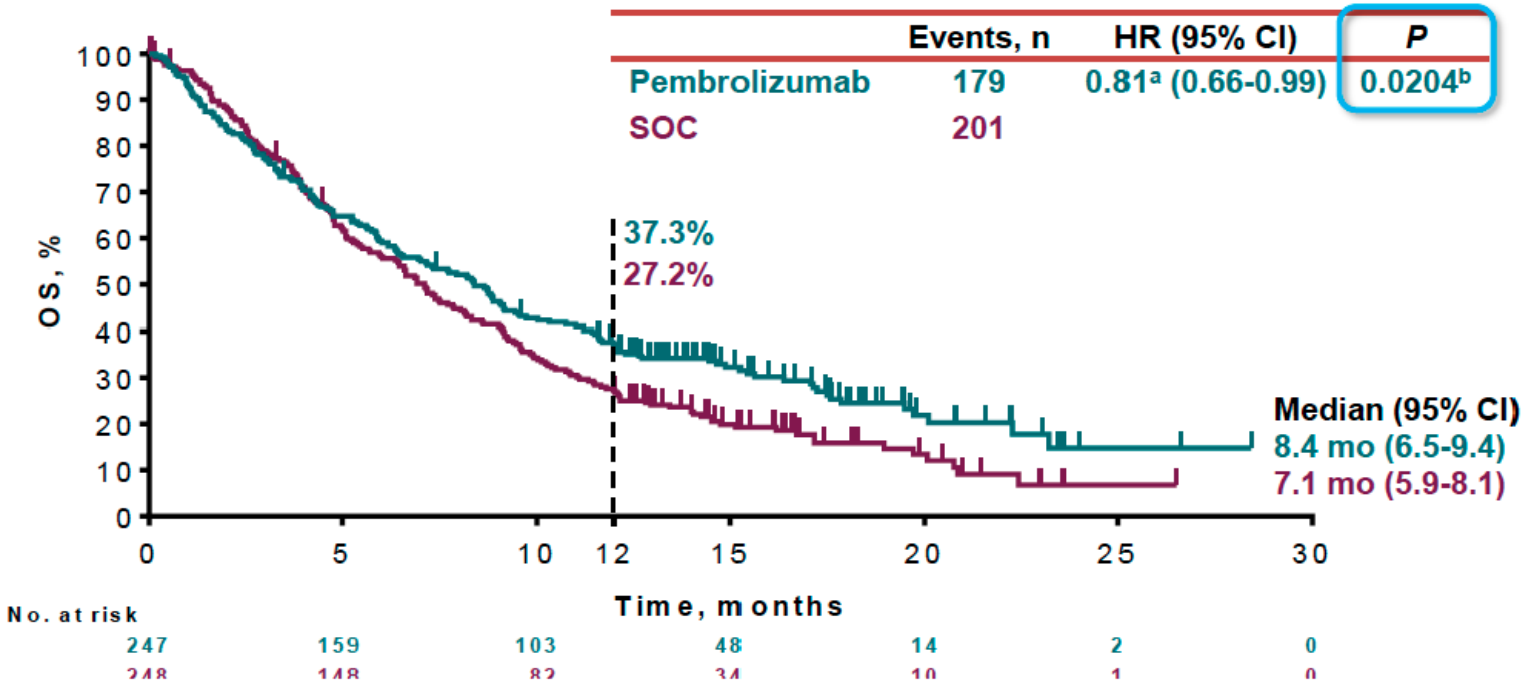
# Overall Survival in ITT Population




[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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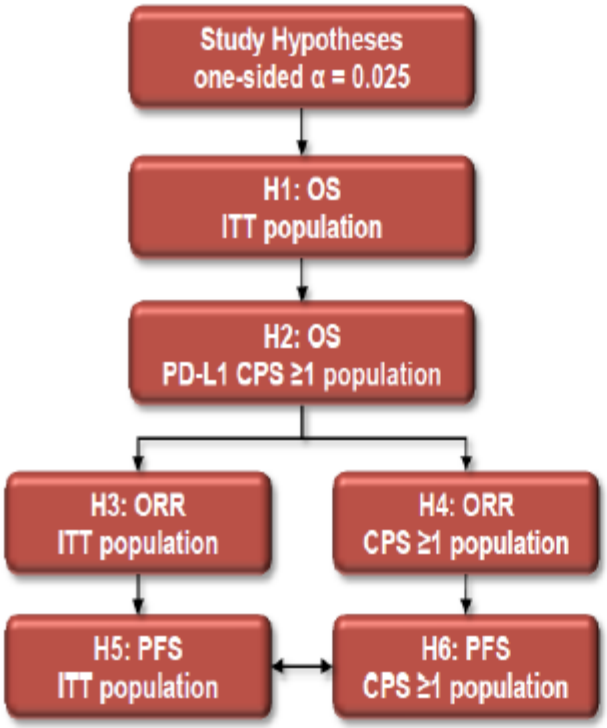
# Statistical Considerations




- 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.

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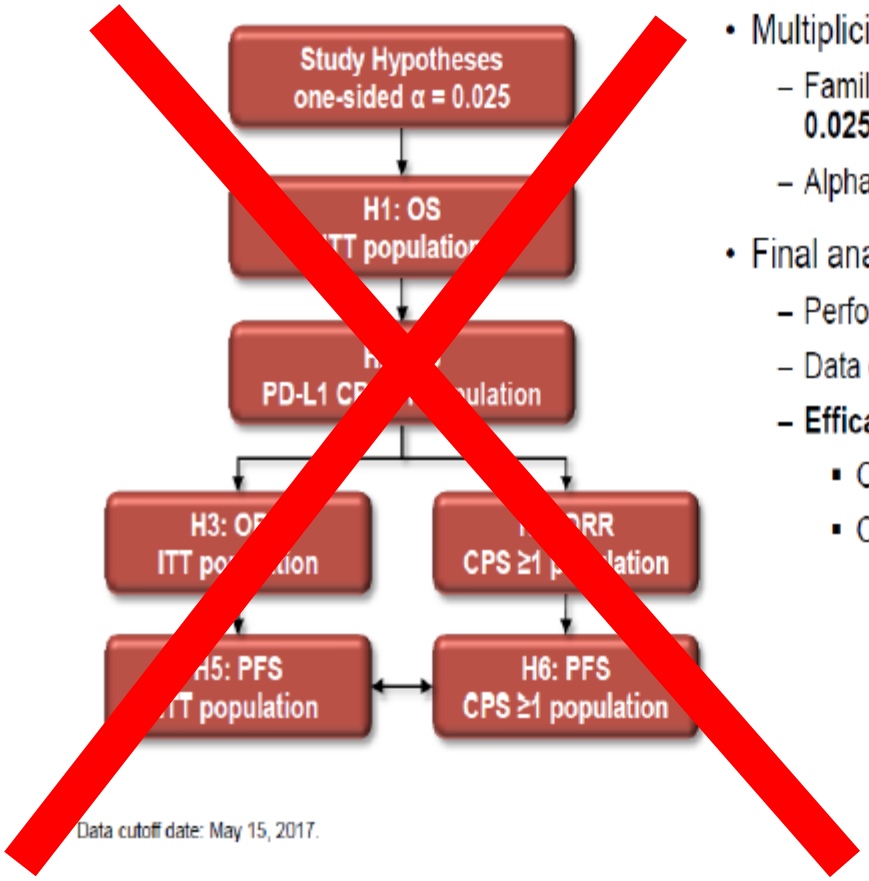
| | Events, n | HR (95% CI) | *P* |
|---|---|---|---|
| Pembrolizumab | 179 | 0.81[a] (0.66-0.99) | 0.0204[b] |
| SOC | 201 | | |

# Statistical Considerations




Data cutoff date: May 15, 2017.

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      - Tested only if efficacy boundary in ITT population reached

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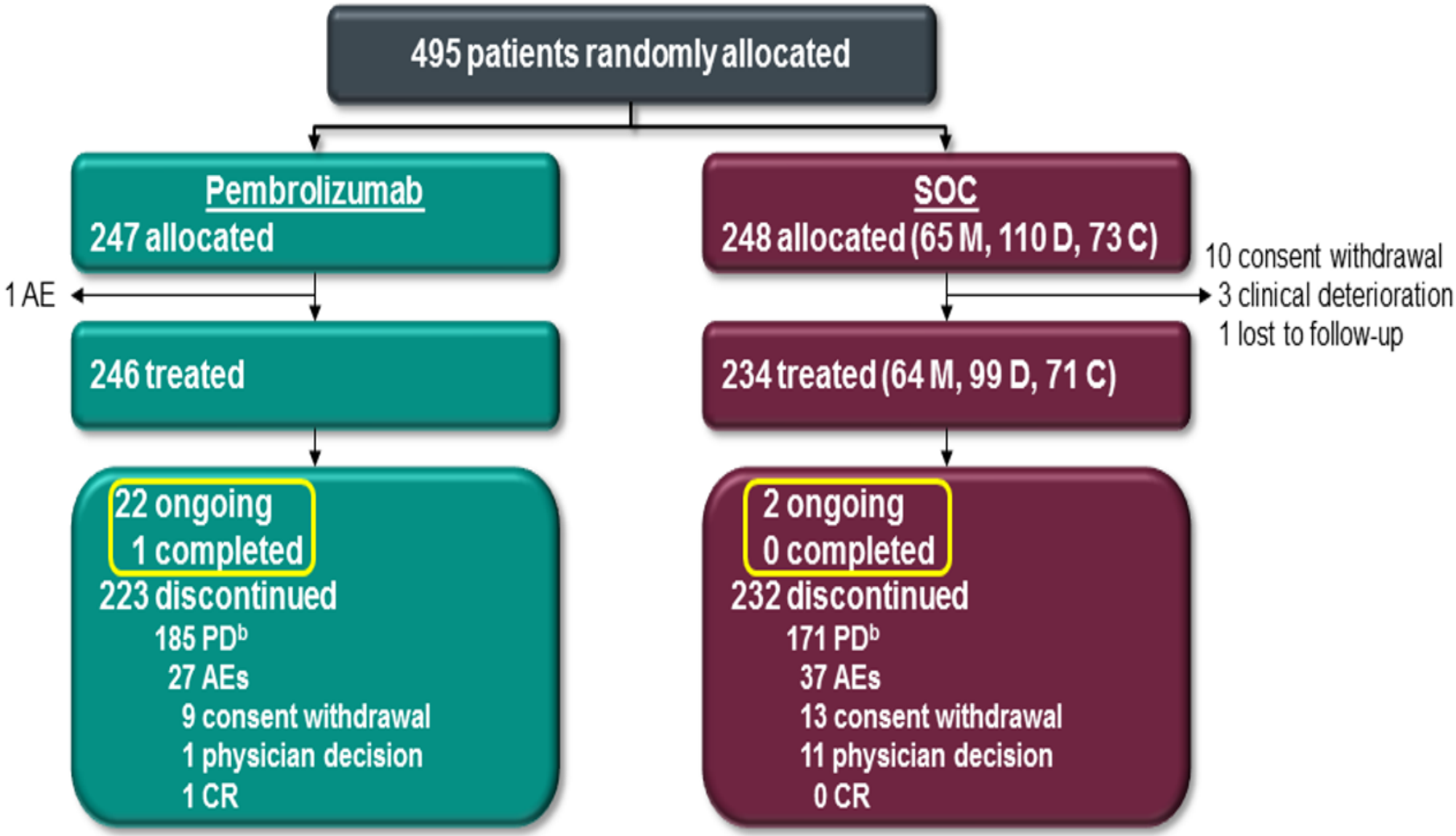
# KEYNOTE-040: Primary and Updated Analyses

- Primary analysis presented at ESMO 2017[1]
  - Prespecified significance boundary: $P = 0.0175$
  - Data cutoff date: May 15, 2017
  - No. of deaths: 380
    - Data outstanding for 11 patients
  - OS: HR 0.81 (95% CI 0.66-0.99), $P = 0.02024$
- Updated analysis presented here
  - Same data cutoff date: May 15, 2017
    (i.e., update achieved without extending follow-up duration)
  - Full acquisition of survival status, including the 11 patients previously outstanding
  - No. of deaths after full acquisition of survival status: 388

Cohen E et al. ESMO 2017 Congress; Madrid, Spain; Sep 8-12, 2017; Abstr LBA45.

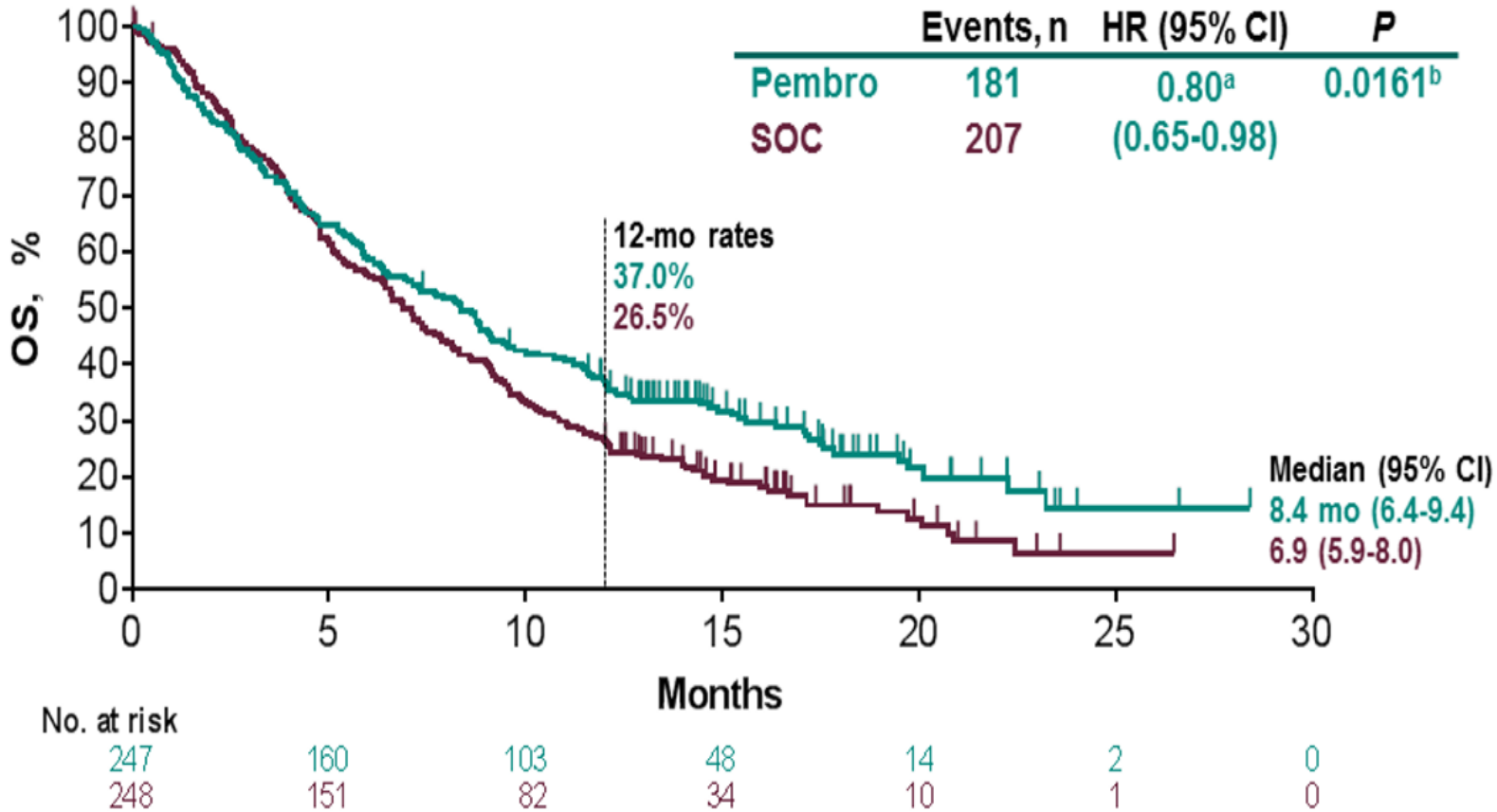
# Disposition of Assigned Study Treatment

## Median Follow-Up[a]: 7.3 mo (range, 0.03-28.4)



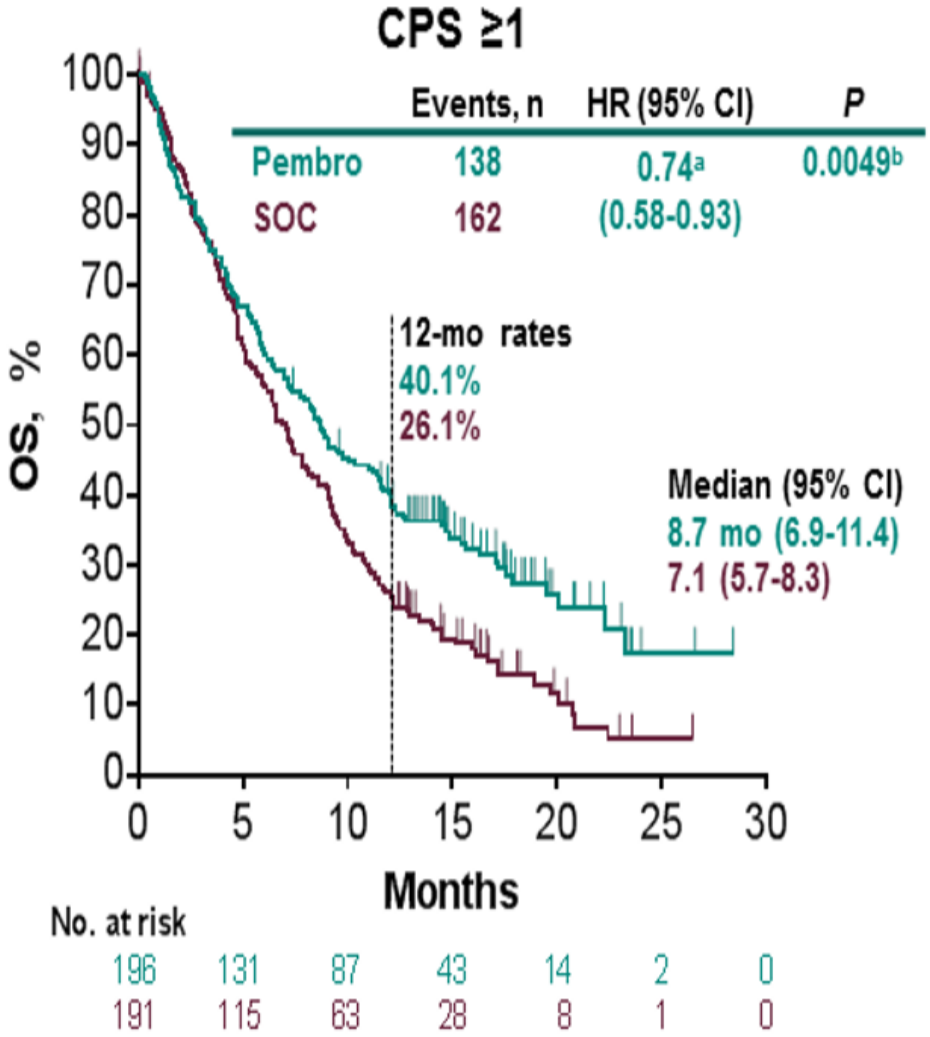

C, cetuximab; D, docetaxel; M, methotrexate. [a]Defined as time from randomization to death or last known survival. [b]Includes clinical progression.
Data cutoff date: May 15, 2017.

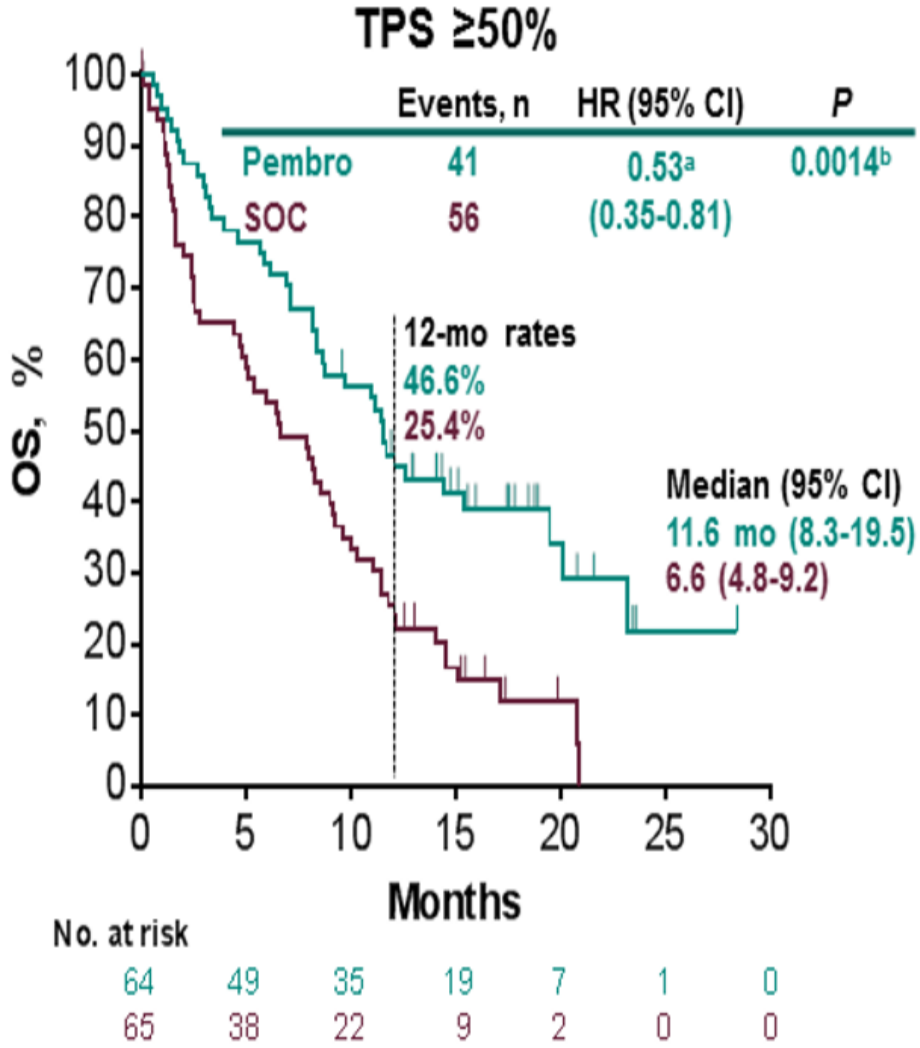
# Updated Overall Survival: ITT




[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.

# Updated Overall Survival by PD-L1 Expression




[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.

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

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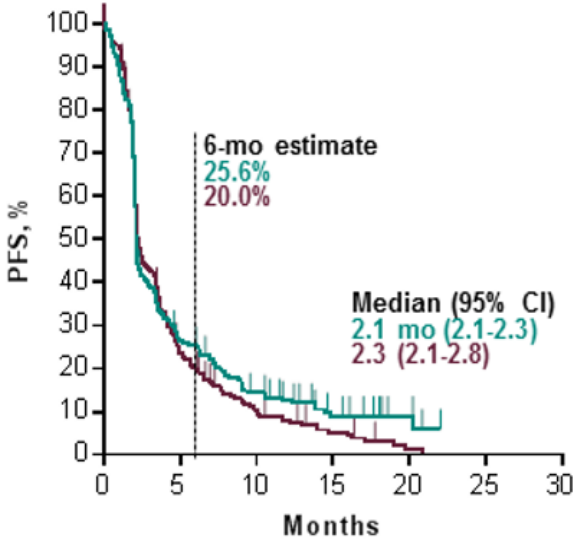
### ITT

| | Events, n | HR[a] (95% CI) | $P^b$ |
|---|---|---|---|
| Pembro | 218 | 0.96 | 0.3250 |
| SOC | 224 | (0.79-1.16) | |

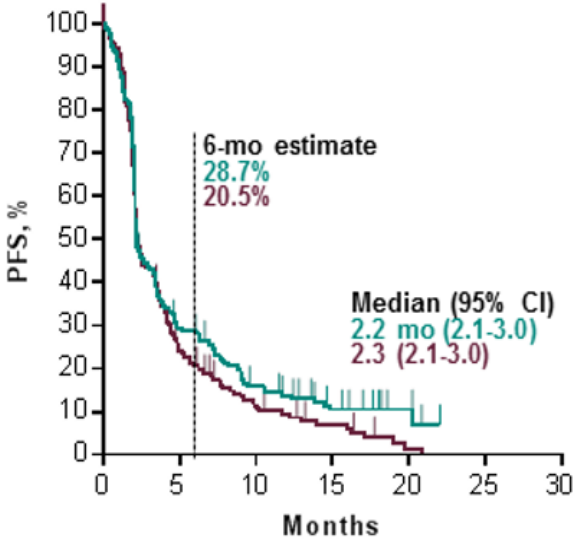



No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| 247 | 63 | 32 | 11 | 4 | 0 | 0 |
| 248 | 54 | 20 | 8 | 1 | 0 | 0 |

### PD-L1 CPS ≥1

| | Events, n | HR[a] (95% CI) | $P^b$ |
|---|---|---|---|
| Pembro | 170 | 0.86 | 0.0774 |
| SOC | 170 | (0.69-1.06) | |

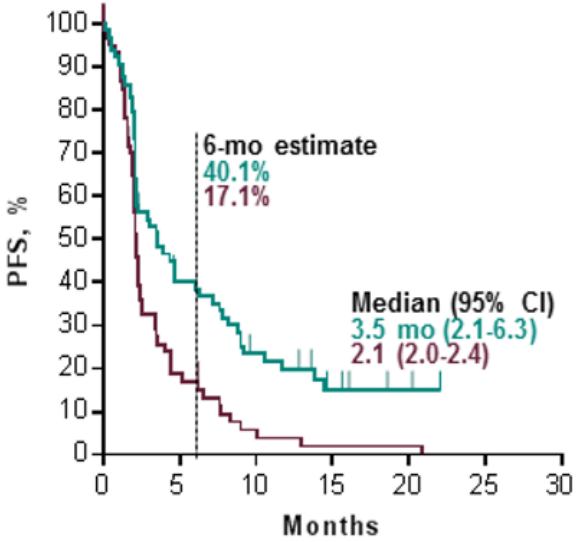



No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| 196 | 55 | 28 | 11 | 4 | 0 | 0 |
| 191 | 42 | 17 | 8 | 1 | 0 | 0 |

### PD-L1 TPS ≥50%

| | Events, n | HR[a] (95% CI) | $P^b$ |
|---|---|---|---|
| Pembro | 52 | 0.58 | 0.0028 |
| SOC | 58 | (0.39-0.86) | |

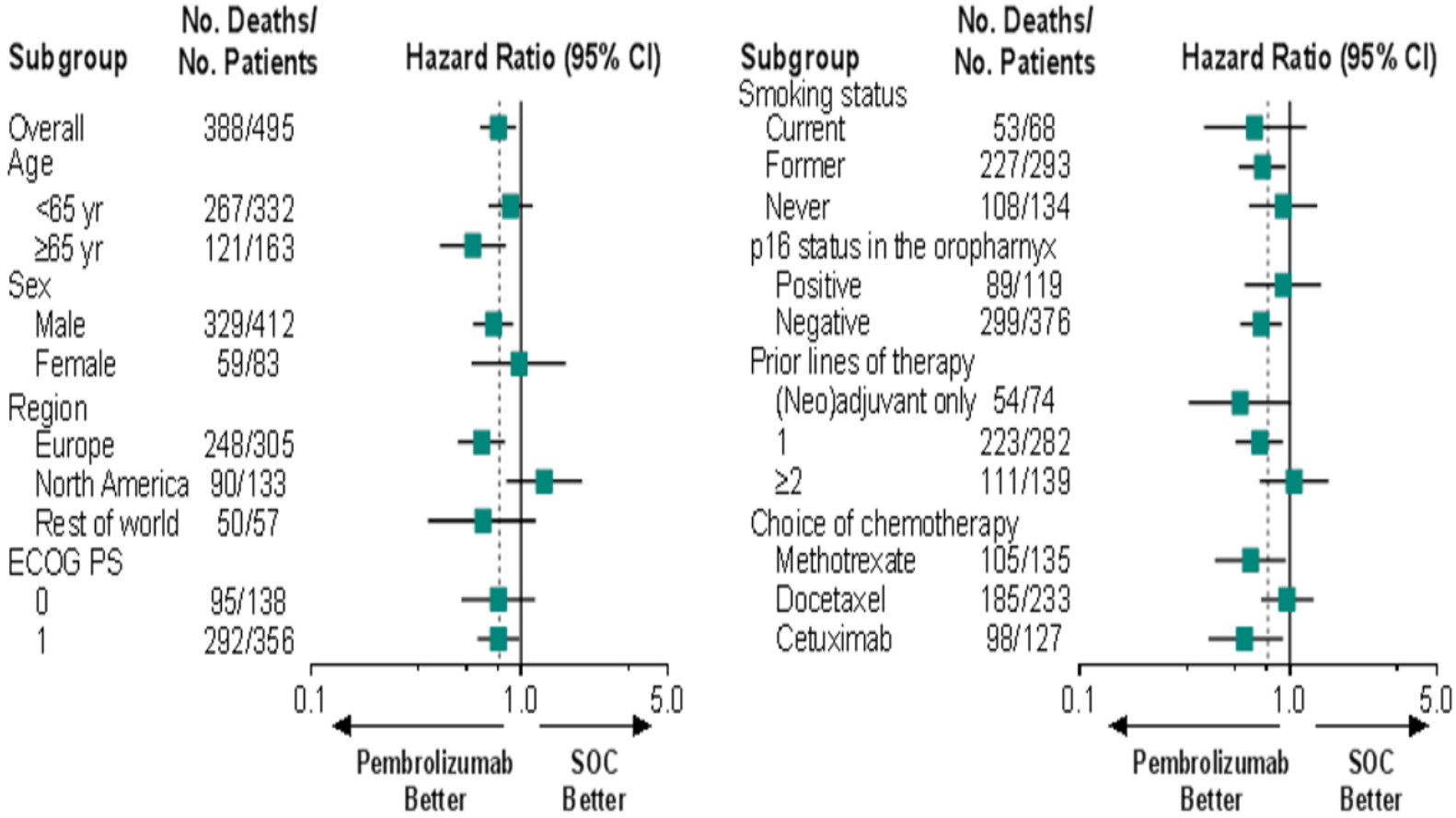



No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| 64 | 24 | 13 | 5 | 2 | 0 | 0 |
| 65 | 11 | 3 | 1 | 1 | 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.

# Updated Overall Survival: Subgroups



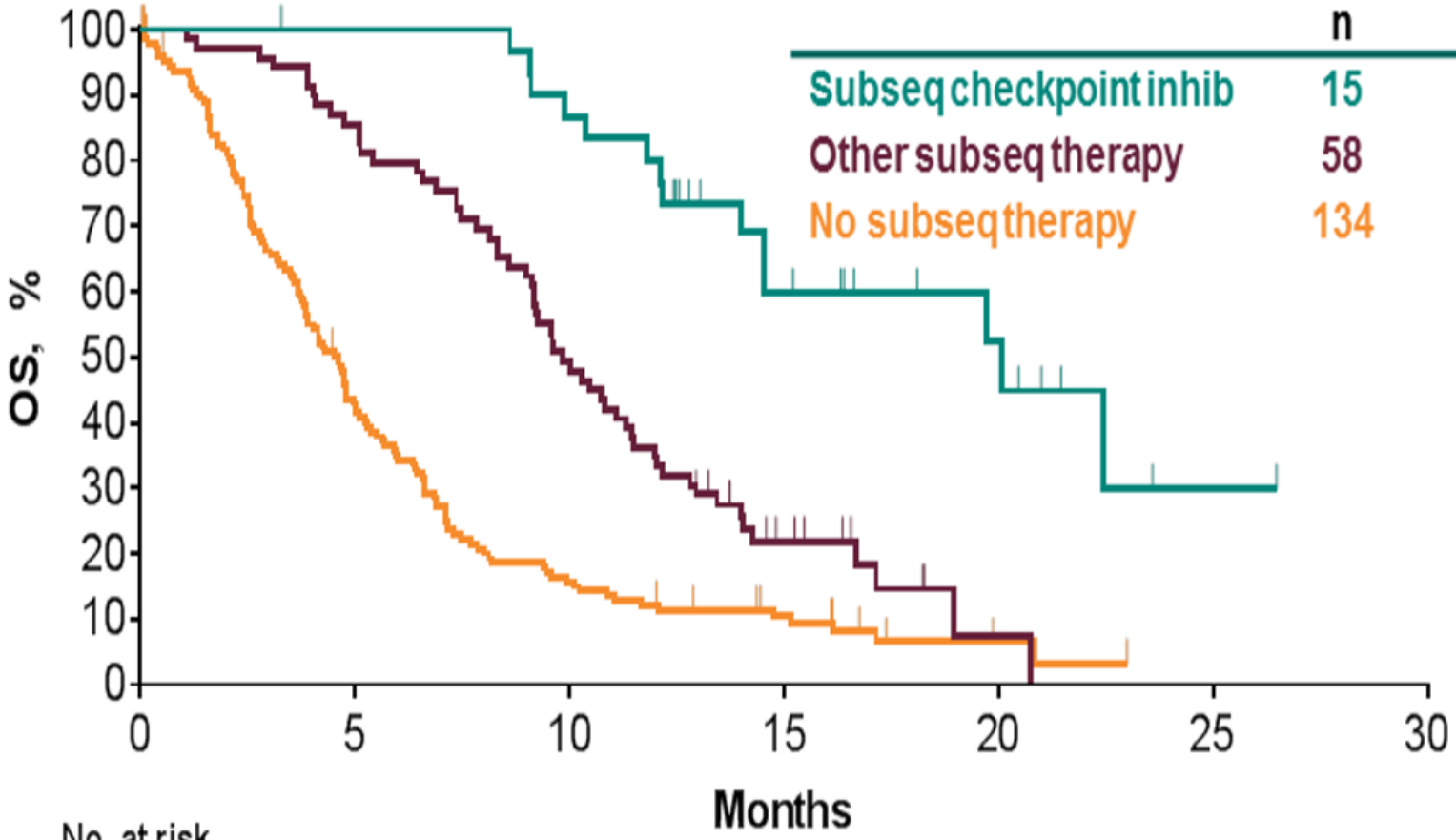

Unstratified Cox proportional hazards model with treatment as a covariate.
Data cutoff date: May 15, 2017.

# Updated Subsequent Therapy

| Type, n (%) | Pembrolizumab N = 247 | SOC N = 248 |
|---|---|---|
| Any[a] | 84 (34.0) | 101 (40.7) |
| Chemotherapy | 70 (28.3) | 77 (31.0) |
| EGFR inhibitor | 20 (8.1) | 19 (7.7) |
| Kinase inhibitor | 3 (1.2) | 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.

# Updated Overall Survival: Effect of Subsequent Immune Checkpoint Inhibitors in the SOC Arm




| | Events, n | Median (95% CI), mo |
|---|---|---|
| Subseq checkpoint inhib | 15 | 20.1 (14.0-NE) |
| Other subseq therapy | 58 | 9.7 (9.0-11.3) |
| No subseq therapy | 134 | 4.5 (3.7-5.0) |

No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| 31 | 30 | 26 | 13 | 7 | 1 | 0 |
| 69 | 59 | 34 | 10 | 1 | 0 | 0 |
| 148 | 59 | 22 | 11 | 2 | 0 | 0 |

Data cutoff date: May 15, 2017.

# Updated Overall Survival: Effect of Subsequent Immune Checkpoint Inhibitors in the SOC Arm

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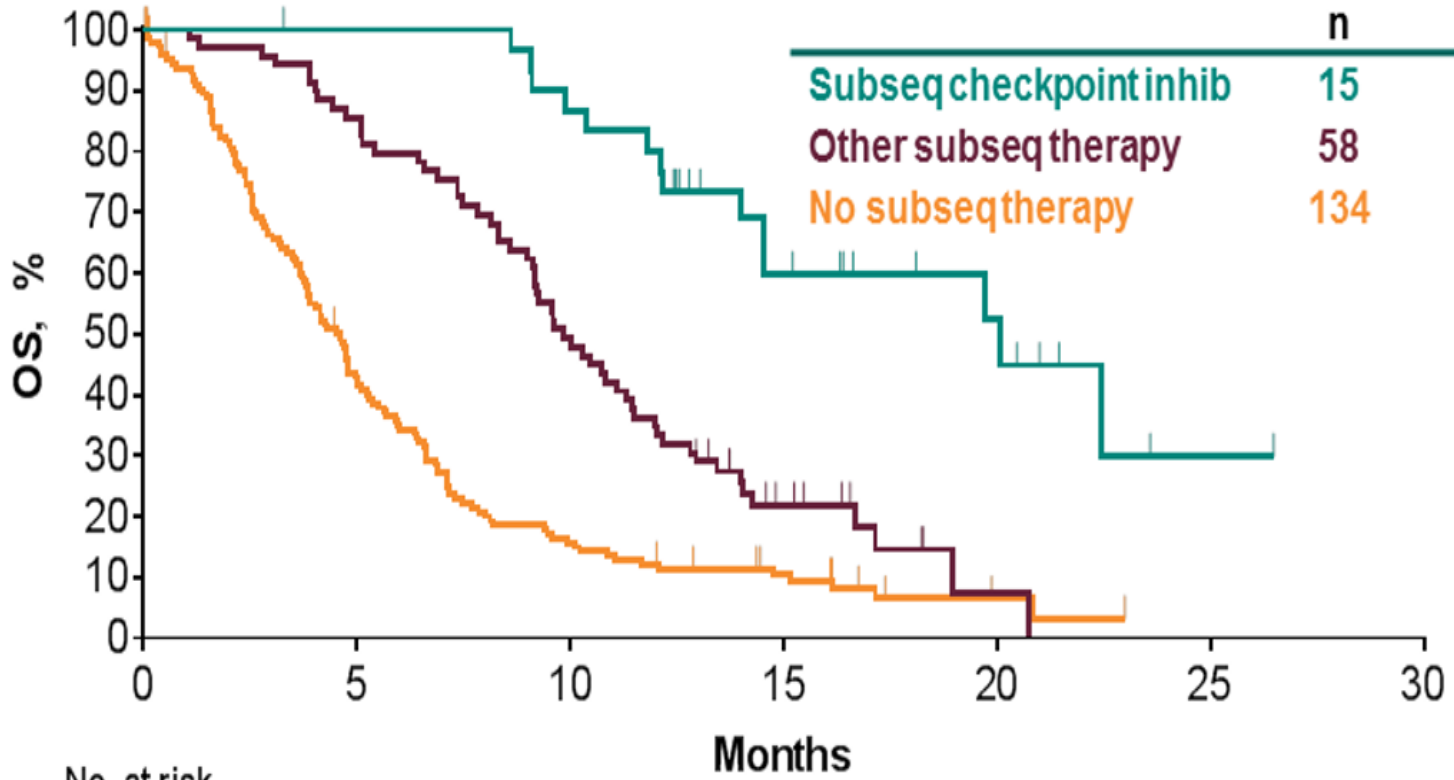


| | Events, n | Median (95% CI), mo |
|---|---|---|
| Subseq checkpoint inhib | 15 | 20.1 (14.0-NE) |
| Other subseq therapy | 58 | 9.7 (9.0-11.3) |
| No subseq therapy | 134 | 4.5 (3.7-5.0) |

No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| 31 | 30 | 26 | 13 | 7 | 1 | 0 |
| 69 | 59 | 34 | 10 | 1 | 0 | 0 |
| 148 | 59 | 22 | 11 | 2 | 0 | 0 |

Data cutoff date: May 15, 2017.

# Best Overall Response[a]
## (RECIST v1.1, Blinded Independent Radiology Review)

| Best Response, (%) | ITT | | CPS ≥1 | | TPS ≥50% | |
|---|---|---|---|---|---|---|
| | Pembro N = 247 | SOC N = 248 | Pembro n = 196 | SOC n = 191 | Pembro n = 64 | SOC n = 65 |
| ORR | 36 (14.6) | 25 (10.1) | 34 (17.3) | 19 (9.9) | 17 (26.6) | 6 (9.2) |
| 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[b] | 2 (0.8) | 1 (0.4) | 2 (1.0) | 0 | 1 (1.6) | 0 |
| Not evaluable or assessable[c] | 45 (18.2) | 60 (24.2) | 37 (18.9) | 47 (24.6) | 9 (14.1) | 21 (32.3) |

[a]Best overall response did not change with the updated analysis. [b]Patients without measurable disease at baseline per RECIST v1.1 by independent radiology review who did not experience CR or PD. [c]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.

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

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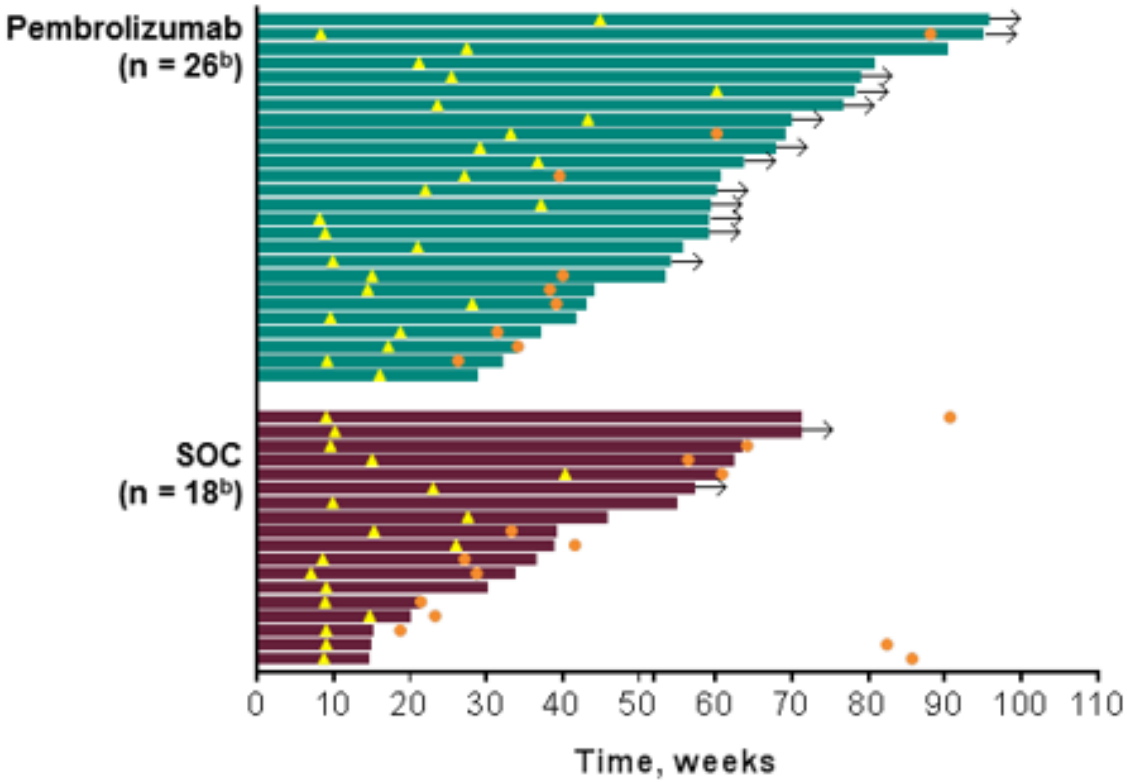


- Median (range) time to response: 4.5 mo (1.9-13.8)
- Median[b] (range) duration of response: **18.4 mo** (2.7-18.4)
- Response duration ≥6 mo[c]: **71.5%**

- 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[c]: **47.1%**

△ First response
● Radiologic PD or death[d]
→ Ongoing treatment

[a]Time to and duration of response did not change with the updated analysis. [b]Patients with confirmed response only. [c]KM estimate. [d]Whichever occurred first. Data cutoff date: May 15, 2017.

# Exposure and AE Summary[a]

| | Pembrolizumab N = 246 | SOC N = 234 |
|---|---|---|
| Exposure, median (range) | 2.8 mo (1 d-24.0 mo) | MTX: 1.4 mo (1 d-9.2 mo)<br>CET: 2.3 mo (1 d-18.0 mo)<br>DOC: 1.7 mo (1 d-13.2 mo) |
| Treatment-related AEs,[b] n (%) | | |
| Any | 155 (63.0) | 196 (83.8) |
| Grade 3-5 | 33 (13.4) | 85 (36.3) |
| Led to discontinuation | 15 (6.1) | 12 (5.1) |
| Led to death | 4[c] (1.6) | 2[d] (0.9) |

[a]Exposure and AEs did not change in updated analysis. [b]As determined by the investigator. [c]One case each of death, large intestine perforation, malignant neoplasm progression, and Stevens-Johnson syndrome. [d]One case each of malignant neoplasm progression and pneumonia.
Data cutoff date: May 15, 2017.

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# Treatment-Related AEs With Incidence ≥10%

| | Pembrolizumab (N = 246) | | SOC (N = 234) | |
|---|---|---|---|---|
| Event, n (%) | Any Grade | Grade 3-5 | Any Grade | Grade 3-5 |
| Hypothyroidism | 33 (13.4) | 1 (0.4) | 2 (0.9) | 0 |
| Fatigue | 31 (12.6) | 4 (1.6) | 43 (18.4) | 2 (0.9) |
| Diarrhea | 20 (8.1) | 4 (1.6) | 24 (10.3) | 1 (0.4) |
| Rash | 19 (7.7) | 1 (0.4) | 34 (14.5) | 1 (0.4) |
| Asthenia | 18 (7.3) | 1 (0.4) | 28 (12.0) | 4 (1.7) |
| Anemia | 17 (6.9) | 1 (0.4) | 33 (14.1) | 9 (3.8) |
| Nausea | 12 (4.9) | 0 | 29 (12.4) | 1 (0.4) |
| Mucosal inflammation | 9 (3.7) | 1 (0.4) | 30 (12.8) | 5 (2.1) |
| Stomatitis | 6 (2.4) | 1 (0.4) | 28 (12.0) | 11 (4.7) |
| Neutrophil count decreased | 3 (1.2) | 1 ().4) | 25 (10.7) | 20 (8.5) |
| Alopecia | 1 (0.4) | 0 | 25 (10.7) | 0 |

Es did not change in updated analysis. Relationship to treatment was determined by the investigator.
ta cutoff date: May 15, 2017.

# Summary and Conclusions

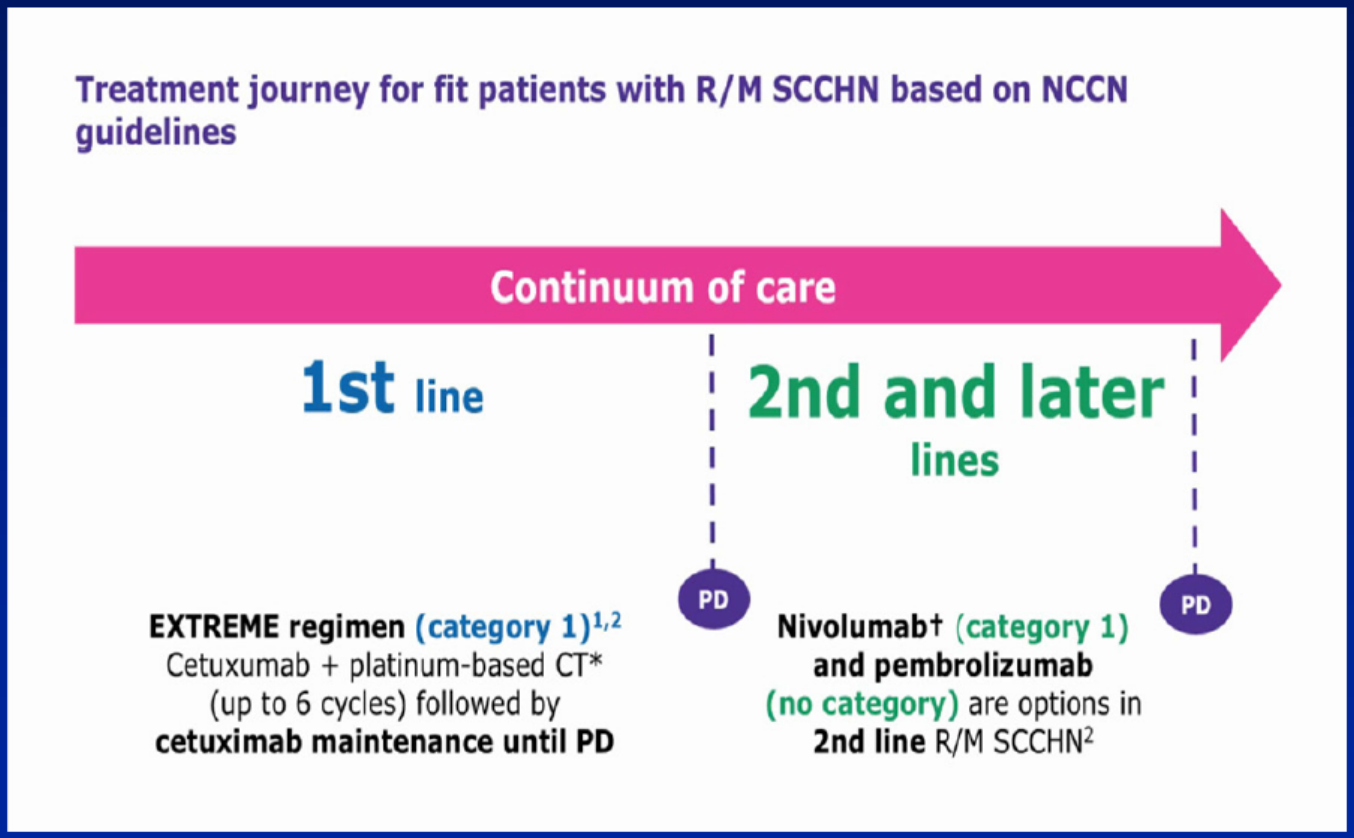
- With full acquisition of survival data using the same data cutoff date and comparing with the primary analysis:
  - Hazard ratio for OS decreased from 0.81 to 0.80
  - *P* value for OS decreased from 0.0204 to 0.0161
  - Treatment effect for pembrolizumab continued to be greater in patients with PD-L1–expressing tumors
  - Apparent confounding effect of subsequent immune checkpoint inhibitors in SOC arm continued to be observed
- Along with the more durable responses and favorable safety profile, updated survival data provide stronger support for the benefit of pembrolizumab in patients with R/M HNSCC

# Anti-PD-1 MoAb in Second-line R/M-SCCHN

| Parameter | Second-line Chemother[1] | Nivolumab Checkmate 141[1] | Pembrolizumab KEYNOTE 040[2] | Second-line Chemother[2] |
|---|---|---|---|---|
| ORR | 5.8% | 13.3% | 14.6% | 10.1% |
| CR | 0.8% | 2.5% | 1.6% | 0.4% |
| PR | 5.0% | 10.8% | 13.0% | 9.7% |
| Median PFS | 2.3 months | 2.0 months | 2.1 months | 2.3 |
| 6-month PFS | 9.0% | 19.7% | 25.9% | 19.5% |
| Median OS | 5.1 months | 7.5 months | 8.4 months | 7.1 months |
| 12-months | 16.6% | 36.0% | 37.3.0% | 27.2% |

[1] *From Checkmate 141 study (Ferris et al, NEJM 2016; DOI: 10.1056/NEJMMoa1602252)*
[2] *From KEYNOTE-040 (Cohen et al, ESMO abstract LBA-45, 2017)*

# New NCCN Guidelines for R/M-SCCHN



# MUCHAS GRACIAS