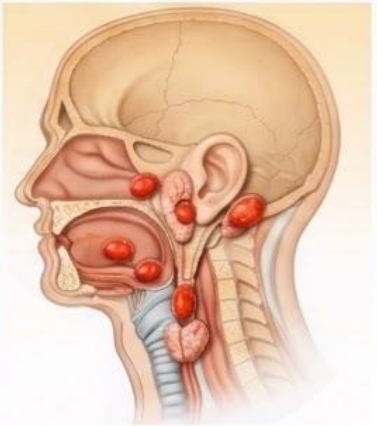
Inducción y estratificación por PDL1: Evidencia Actual y Controversias



Gudiño Natalia
30/07/26

Jornada de Actualización Integral y Abordaje Multidisciplinario

HOSPITAL ONCOLÓGICO

delacañada
sanatorio privado

GENERALIDADES

Comprende **4%** de los tumores malignos y **2%** de las muertes por cáncer.

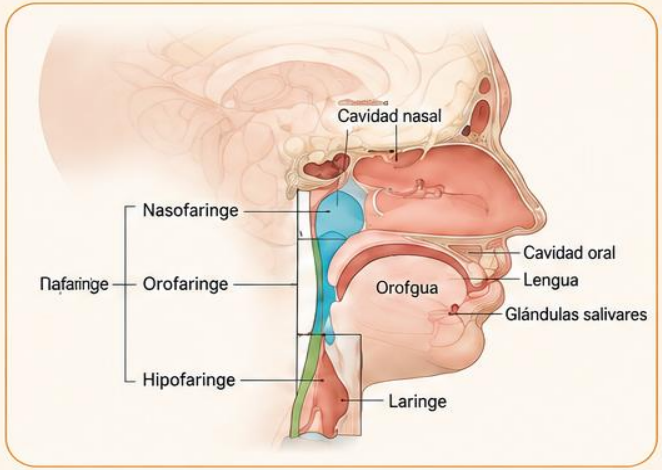
7mo cáncer en el mundo.

90% cáncer epidermoide.

La edad al diagnóstico es después de los **50** años, relación hombre-mujer es **2:1 a 5:1**.

75-85% asociado al tabaco y alcohol.

30-35% prevalencia de HPV.



TRATAMIENTO DEL CÁNCER EPIDERMOIDE DE CABEZA Y CUELLO

Aproximadamente el **60%** de los pacientes diagnosticados con cáncer epidermoide de cabeza y cuello se presentan inicialmente en estadios localmente avanzados.

El estándar de tratamiento oscila entre dos pilares fundamentales:

- **Cirugía primaria** seguida de radioterapia o quimiorradioterapia adyuvante.
- **Protocolos de preservación de órgano** mediante QT RT concurrente definitiva.

Terapia de inducción continua siendo **controvertida**.

EVIDENCIA MACH-NC (ACTUALIZACIÓN 2021)

Meta-análisis de quimioterapia en cáncer de cabeza y cuello

107 ensayos randomizados | **19.805** pacientes

Principalmente pacientes con estadios III–IV (~90%)

Quimiorradioterapia concomitante (QT-RT) mostró el mayor beneficio en supervivencia

Beneficio absoluto en supervivencia global a 5 años: **≈6,5%**

La quimioterapia de inducción no mostró superioridad consistente

Confirmó la superioridad de QT-RT concomitante sobre inducción

METANÁLISIS MACH-NC

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group

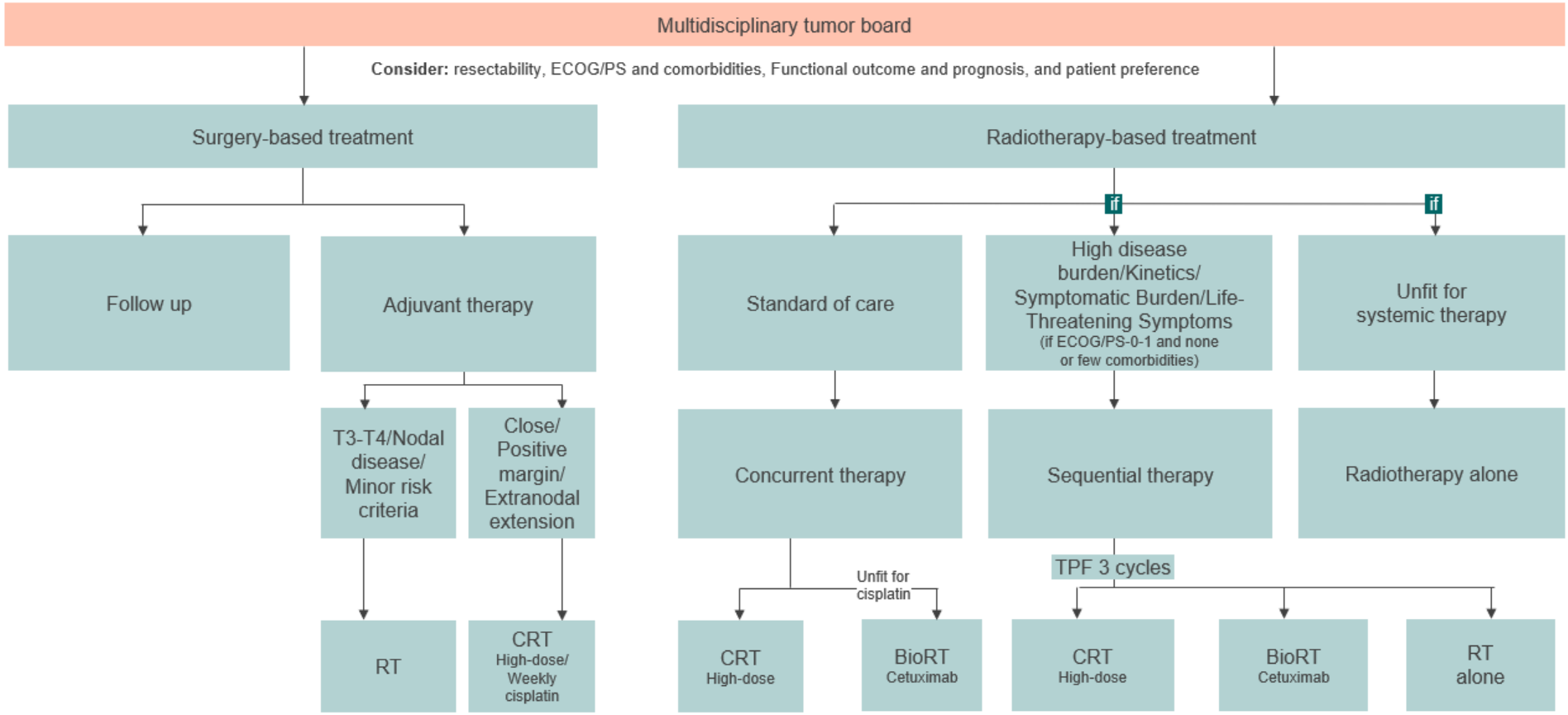
Radiother Oncol. 2021 Mar;156:291–293.
doi: 10.1016/j.radonc.2021.01.013.

CONCLUSIONES CLAVE

- La QT-RT concomitante es el estándar de tratamiento en enfermedad localmente avanzada.
- Aporta un beneficio absoluto de supervivencia a 5 años **Beneficio de la quimioterapia concurrente 6,5% a los 5 años y del 3,6% a los 10 años.**
- El rol de la terapia de inducción continúa siendo motivo de debate y no se recomienda de rutina.

La evidencia actual respalda la QT-RT concomitante como estrategia estándar en cáncer de cabeza y cuello localmente avanzado.

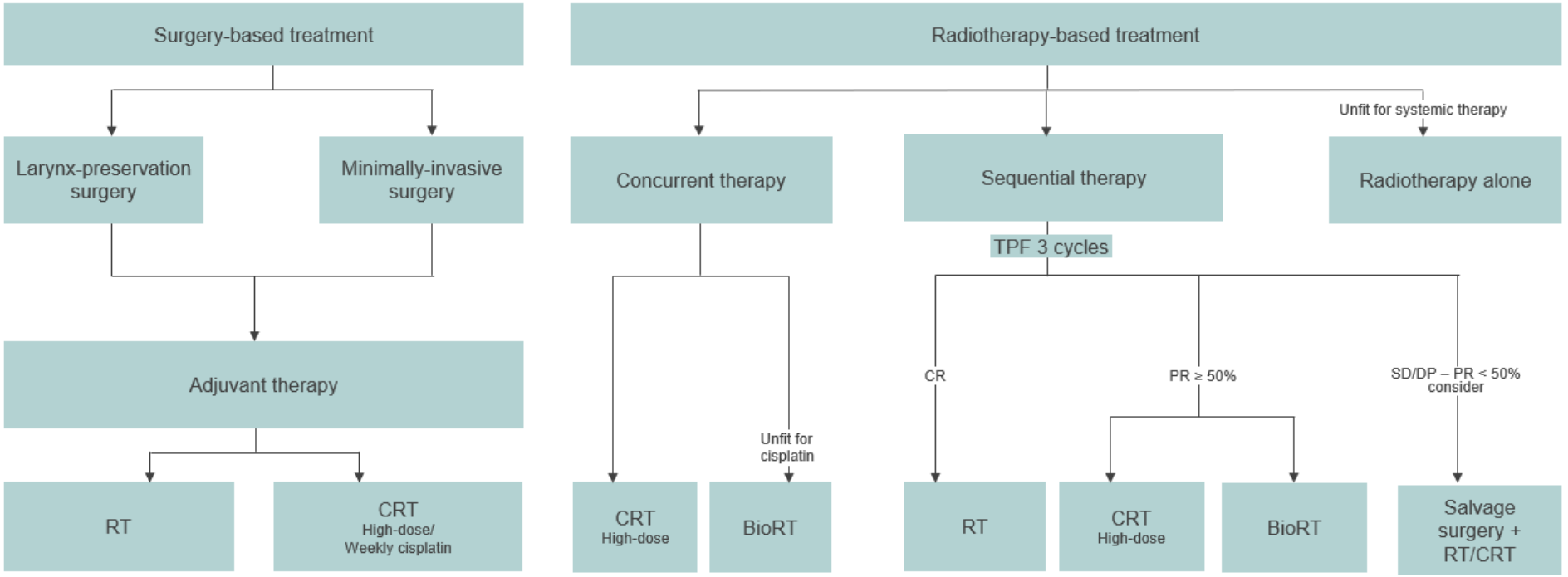
Locally advanced squamous cell carcinoma of the head and neck (Stage III, IVA-IVB)



IORT: bioradiotherapy; CRT: chemoradiotherapy; PS: performance status; RT; radiotherapy; TPF: docetaxel/cisplatin/5-fluorouracil..

Sociedad Española de Oncología Médica | SEOM

Candidate for organ preservation



BIORT: bioradiotherapy; CR: complete response; CRT: chemoradiotherapy; DP: disease progression; PR: partial response; PS: performance status; RT: radiotherapy; TPF: docetaxel/cisplatin/5-fluorouracil; SD: stable disease.

The NEW ENGLAND JOURNAL of MEDICINE

Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer. N Engl J Med. 2007;357(17):1695–1704.

TAX 323

Ensayo fase III: inducción con TPF vs PF en cáncer de cabeza y cuello localmente avanzado

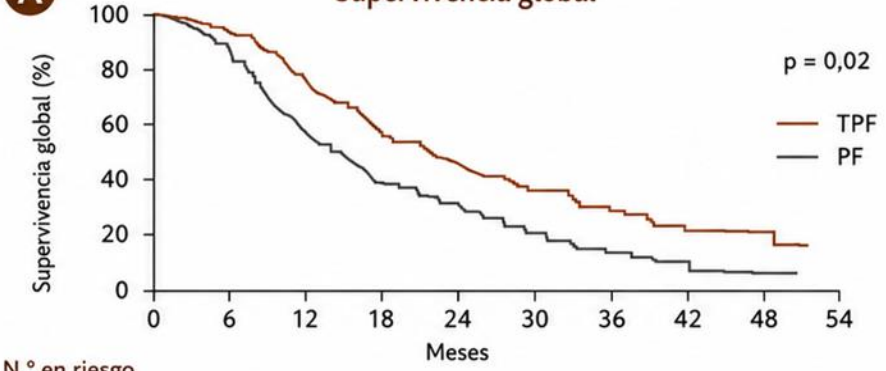
DISEÑO DEL ESTUDIO

- 358 pacientes, 18–70 años.
- Estadio III–IV (sin metástasis), PS 0–1.
- TPF (docetaxel 75 mg/m² día 1, cisplatino 75 mg/m² día 1 y 5–fluorouracilo 750 mg/m² día 1 a 5) vs PF (cisplatino 100 mg/m² día 1 y 5–fluorouracilo 1 g/m² día 1 a 5) por 4 ciclos.
- Seguido de radioterapia en pacientes que no progresaron.

RESULTADOS PRINCIPALES

- Mayor tasa de respuesta: **68% vs 54%** (p = 0,006)
- Reducción del riesgo de muerte del **27%** (p = 0,02)
- Supervivencia global: **18,8 vs 14,5 meses** (p = 0,02)
- Supervivencia libre de progresión: **11 vs 8,2 meses** (p = 0,007)
- Toxicidad
  - Mayor neutropenia y leucopenia grado 3–4 con TPF.
  - Mayor anemia y trombocitopenia graves con PF.
  - Neutropenia febril: **5,2%** con TPF.

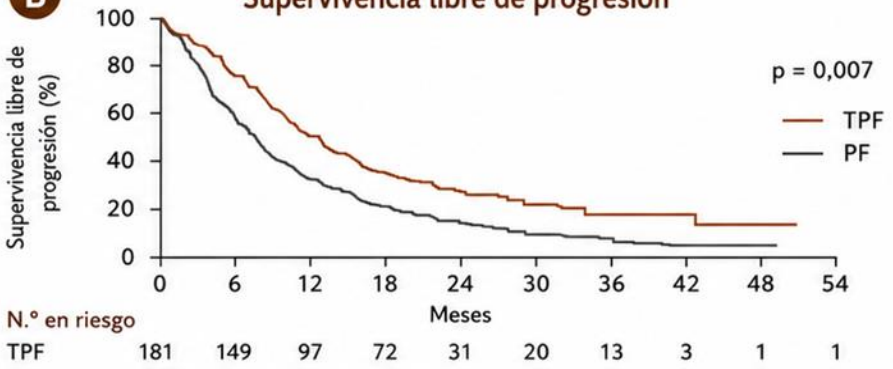
A Supervivencia global



N.° en riesgo

TPF	181	169	112	82	37	25	13	6	3	1
PF	177	149	97	72	25	16	5	3	2	1

B Supervivencia libre de progresión



N.° en riesgo

TPF	181	149	97	72	31	20	13	3	1	1
PF	177	112	73	49	21	13	5	3	2	1

TPF: docetaxel, cisplatino y 5–fluorouracilo; PF: cisplatino y 5–fluorouracilo.

TAX 324

Ensayo fase III: inducción con TPF vs PF en cáncer de cabeza y cuello localmente avanzado

DISEÑO DEL ESTUDIO

501 pacientes.

Estadio III–IV (sin metástasis), ECOG 0–1.

TPF × 3 ciclos

- Docetaxel 75 mg/m² (día 1)
- Cisplatino 100 mg/m² (día 1)
- 5-FU 1.000 mg/m²/día (días 1–4)

PF × 3 ciclos

- Cisplatino 100 mg/m² (día 1)
- 5-FU 1.000 mg/m²/día (días 1–5)

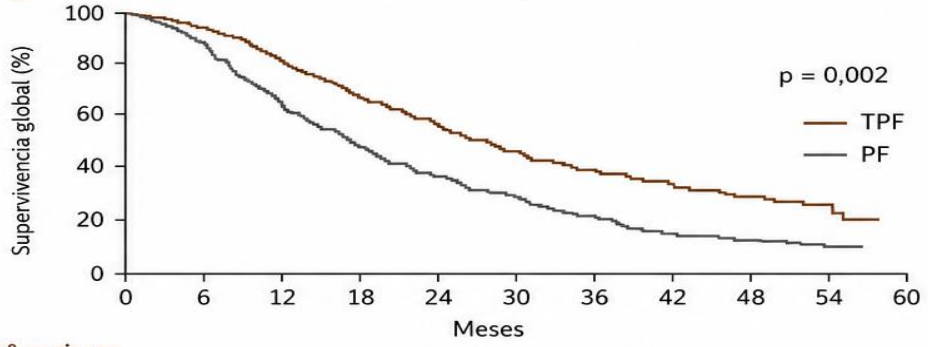
Ambos grupos recibieron radioterapia + carboplatino.

RESULTADOS PRINCIPALES

- Supervivencia global (SG) a 3 años: **62%** vs **48%** (p = 0,002)
- Mediana de SG: **71** vs **30 meses** (p = 0,006)
- Supervivencia libre de progresión (SLP) a 2 años: **53%** vs **42%** (p = 0,01)
- Mediana de SLP: **36** vs **13 meses** (p = 0,004)
- Tasa de respuesta: **72%** vs **64%** (p = 0,07)
- **Toxicidad hematológica:**
  - Mayor neutropenia grado 3–4 con TPF: **83%** vs **56%** (p < 0,001)
  - Mayor trombocitopenia grado 3–4 con PF: **11%** vs **4%** (p = 0,005)

TPF: docetaxel, cisplatino y 5-fluorouracilo; PF: cisplatino y 5-fluorouracilo; 5-FU: 5-fluorouracilo; RT: radioterapia.

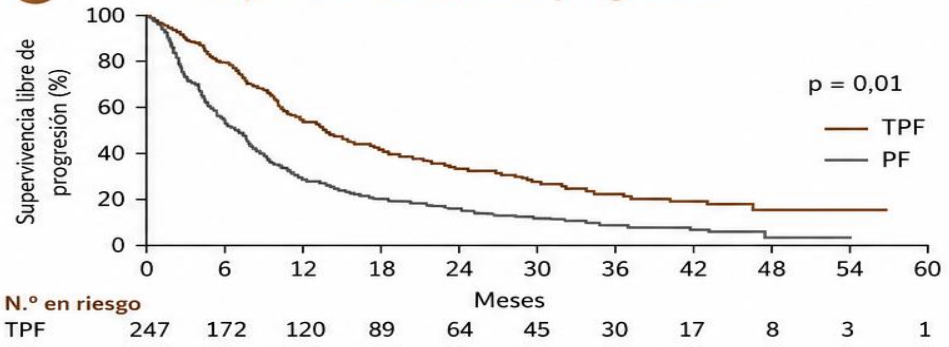
A Supervivencia global



N.º en riesgo

TPF	247	221	191	160	126	96	68	42	24	10	2
PF	254	200	151	111	78	55	38	20	8	3	1

B Supervivencia libre de progresión



N.º en riesgo

TPF	247	172	120	89	64	45	30	17	8	3	1
PF	254	131	83	47	32	21	14	8	3	1	1

Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. ***N Engl J Med***. 2007;357(17):1695-1704.

RTOG 91-11

Ensayo fase III: preservación de la laringe con distintas estrategias en cáncer de laringe localmente avanzado

ARTÍCULO

A Phase III Trial to Preserve the Larynx – Induction Chemotherapy Followed by Concurrent Chemoradiotherapy vs Chemoradiotherapy Alone in Patients With Resectable Stage III–IV Head and Neck Cancers (RTOG 91-11)

Forastiere AA, Goepfert H, Maor M, et al.
N Engl J Med. 2003;349(22):2091-2098.

DISEÑO DEL ESTUDIO

547 pacientes con carcinoma epidermoide de laringe resecable, estadios III–IV.

18–70 años; KPS ≥ 70.

Aleatorización (3 brazos):

1. Radioterapia (RT) + cisplatino concomitante.
2. Quimioterapia de inducción con PF (cisplatino 100 mg/m² día 1 + 5-FU 1000 mg/m²/día días 1–5) × 3 ciclos → RT.
3. Radioterapia sola.

Objetivo primario: preservación laríngea.

No respondedores después de la inducción: cirugía.

RESULTADOS PRINCIPALES

Mayor tasa de preservación laríngea con **RT + cisplatino concomitante** a los 2 y 5 años.

PF (inducción) → RT mejoró la preservación laríngea comparado con RT sola, aunque fue inferior a la quimiorradioterapia concomitante.

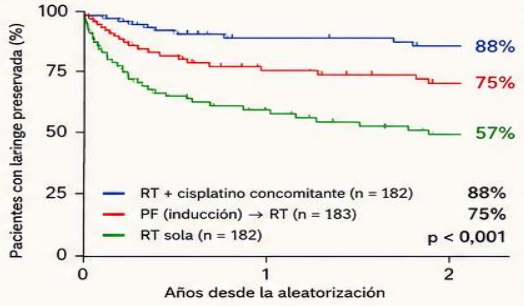
No hubo diferencias significativas en supervivencia global entre los tres brazos.

Mayor toxicidad aguda con RT + cisplatino concomitante (neutropenia y mucositis grado 3–4).

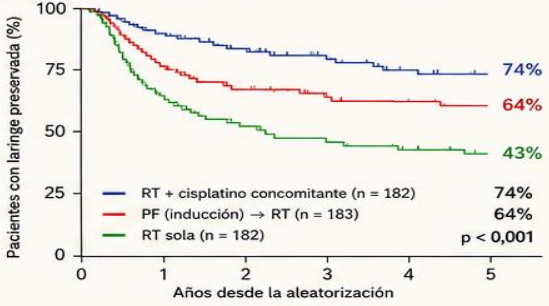
Conclusión: la quimiorradioterapia concomitante con cisplatino se estableció como el tratamiento estándar para la preservación de la laringe en pacientes seleccionados con cáncer de laringe localmente avanzado.

RESULTADOS (curvas de Kaplan–Meier)

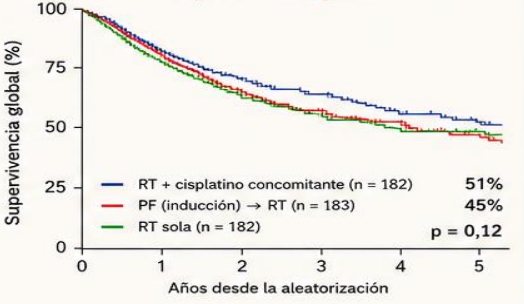
A



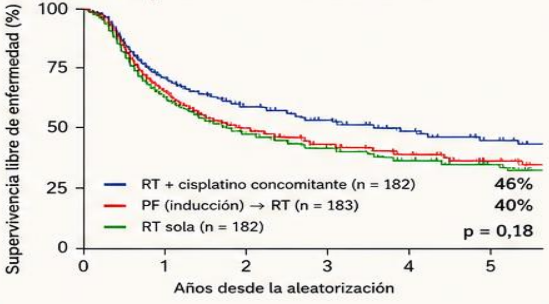
B



C



D



- Todos los pacientes recibieron radioterapia con fraccionamiento convencional (aprox. 70 Gy). Los respondedores completos o parciales después de la inducción recibieron radioterapia.

PF: cisplatino + 5-fluorouracilo; RT: radioterapia; KPS: Karnofsky Performance Status.

GORTEC 2000-01

Ensayo fase III: inducción con TPF vs PF en cáncer de laringe e hipofaringe operables (estadios III–IV)

ARTÍCULO

Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation

Temam S, Poissonnet G, Noubhani A, et al.
J Clin Oncol. 2007;25(7):843-849.

DISEÑO DEL ESTUDIO

Pacientes con cáncer de laringe o hipofaringe operables, estadios III–IV.

18–75 años, KPS igual o mayor a 70.

3 ciclos de inducción:

- **TPF:** docetaxel 75 mg/m² día 1 + cisplatino 75 mg/m² día 1 + 5-fluorouracilo 750 mg/m²/día días 1 a 5
- **PF:** cisplatino 100 mg/m² día 1 + 5-fluorouracilo 1000 mg/m²/día días 1 a 5

Los respondedores fueron tratados con radioterapia concurrente ± quimioterapia.

Los no respondedores se derivaron a cirugía.

RESULTADOS PRINCIPALES

Tasa de preservación laríngea a los 5 y 10 años: **74%** vs **58,1%** y **70,3%** vs **46,5%** (p = 0,01) respectivamente a favor de TPF.

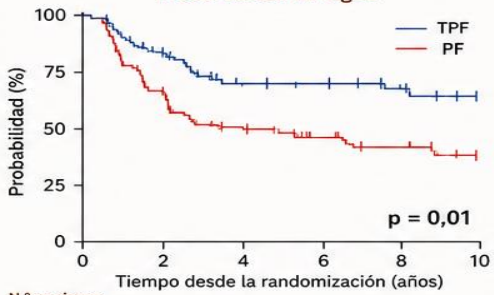
Tasa de LDF (libre de disfunción laríngea) a los 5 y 10 años: **67,2%** vs **46,5%** y **63,7%** vs **37,2%** (p = 0,001) respectivamente a favor de TPF.

No hubo diferencias en supervivencia global (SG), supervivencia libre de enfermedad (SLE) ni control locorregional.

El perfil de toxicidad fue comparable entre los grupos.

RESULTADOS

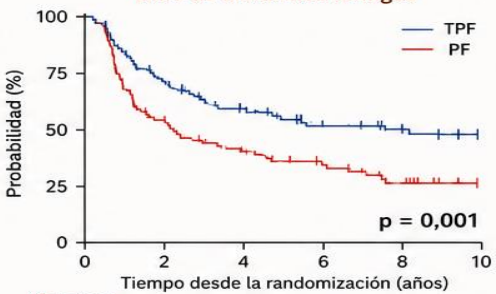
Preservación laríngea



N.° en riesgo

TPF	176	123	87	67	50	33
PF	173	108	71	47	31	17

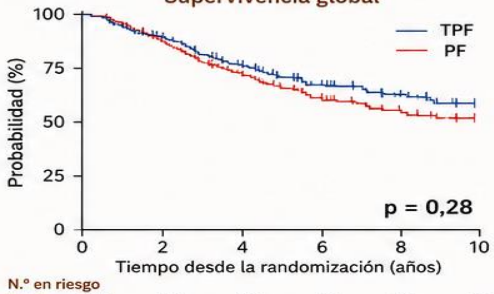
Libre de disfunción laríngea



N.° en riesgo

TPF	176	113	78	58	44	28
PF	173	92	57	36	24	13

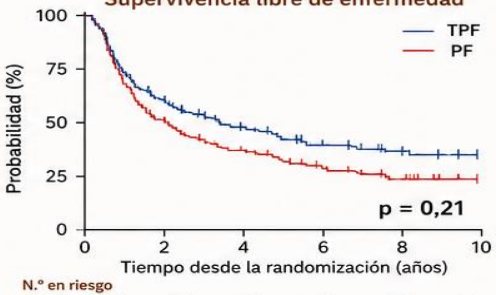
Supervivencia global



N.° en riesgo

TPF	176	150	113	84	63	40
PF	173	138	96	66	47	25

Supervivencia libre de enfermedad



N.° en riesgo

TPF	176	105	67	48	34	23
PF	173	90	54	34	22	13

TPF: docetaxel, cisplatino y 5-fluorouracilo; PF: cisplatino y 5-fluorouracilo;
LDF: libre de disfunción laríngea; SG: supervivencia global; SLE: supervivencia libre de enfermedad.

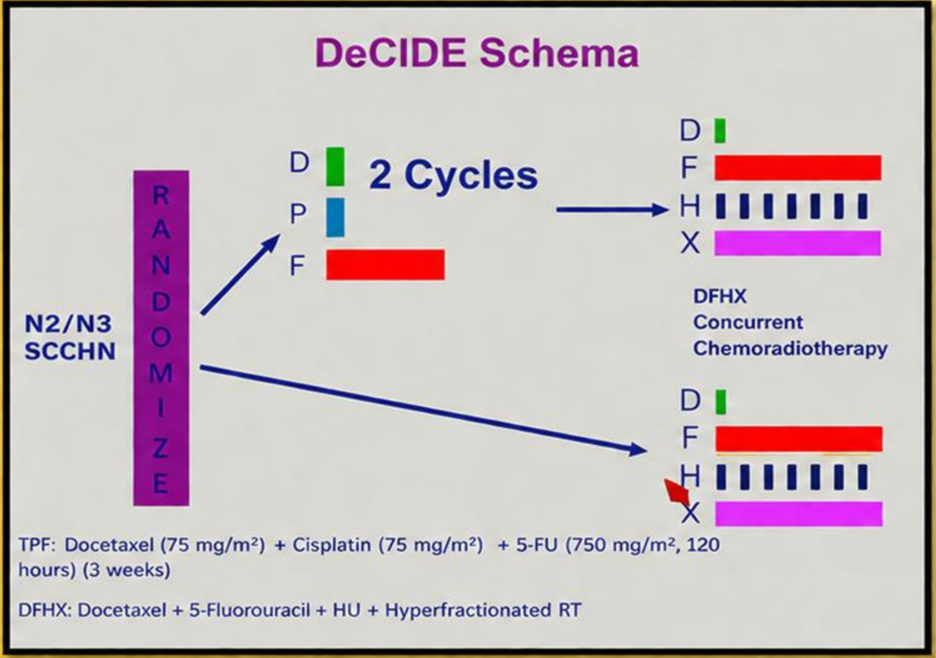
ENTONCES…

VOLUME 32 NUMBER 19 SEPTEMBER 1 2014
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Randomized Trial of Induction Chemotherapy in Patients With N2 or N3 Locally Advanced Head and Neck Cancer

Daniel P. Docetasel, Jossha. Josuha . Smith, Mohammed Kapur, Maries, Robles, Ramesh C. Wong, Russell J. Salosca, Bhagwan R. Rinn, Sduet, Cordes, Andrew Trnnt, Carolyn R Caron, Pessell J. Saltman, Bhagser, Conumgi Eiis, Sreian, Greopk, Congew, Gregye Ridge, E Cohen, Peter Wortman, H. Thomas Johung, Stephen E. Cohen

No diferencia en SG ni SLR



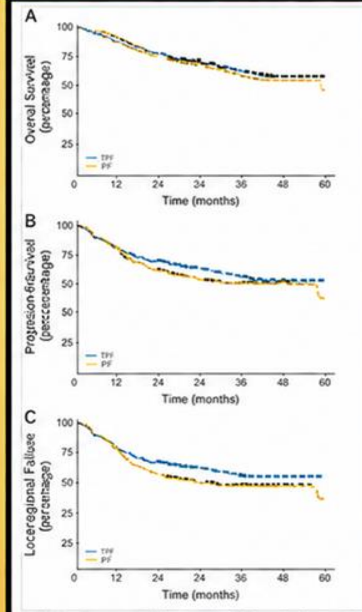


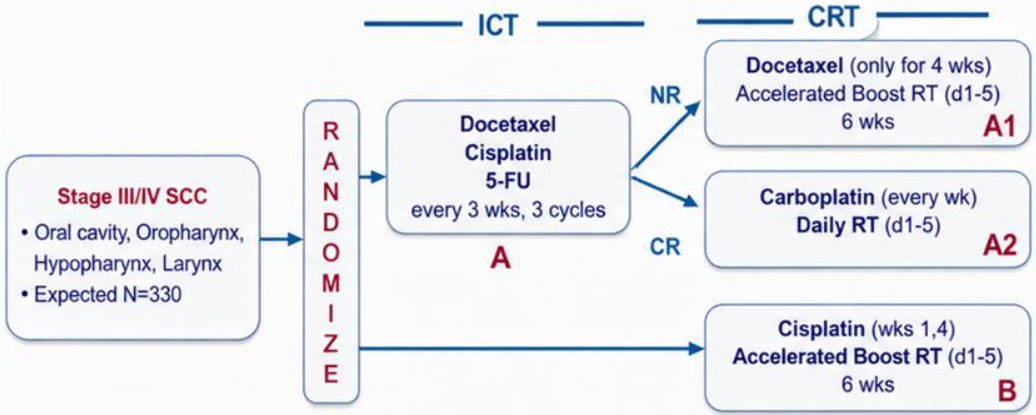
Fig 2. Survival outcomes. (A) Overall survival. (B) Progression-free survival. (C) Locoregional failure. PF, cisplatin (75 mg mg/m²/day on days 1, 22, and 43) + 5-fluorouracil (1,000 mg/m²/day on days 1–4 and 22–25, induction chemotherapy); TPF, docetaxel + cisplatin + 5-fluorouracil (induction chemotherapy).

Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial

Robert Haddad, Anne O'Neil, Guillaume Rebamev, Ray Taten, Fazi Qut Akman, Douglas Adkins, Joseph Clark, Nicholas Sorils, Jochin Lorch, Jonathan Irish, Sean Ridge, Marshall Posner

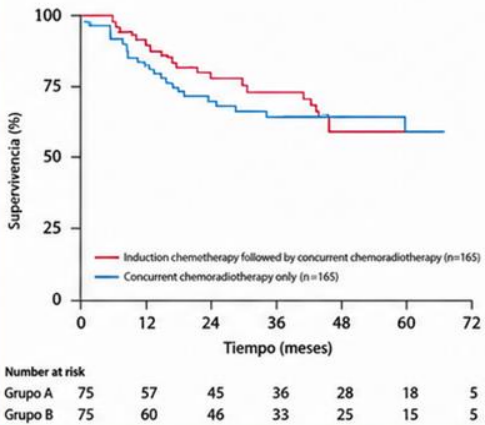
No diferencias en SG ni SLP

PARADIGM Study Design

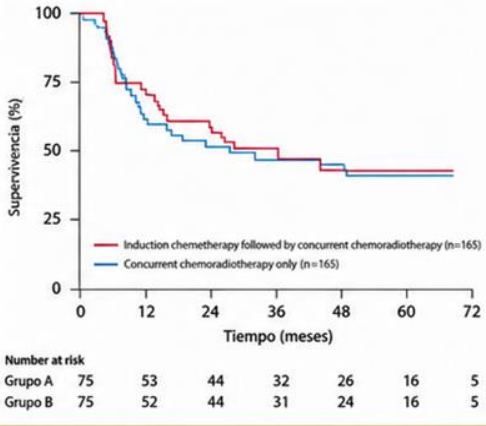


Haddad et al. Lancet Oncology. 2013 Mar;14(3):257-64.

SUPERVIVENCIA GLOBAL (SG)



SUPERVIVENCIA LIBRE DE PROGRESIÓN (SLP)



ANÁLISIS CRÍTICO

DECIDE y PARADIGM: ¿Por qué fracasó la quimioterapia de inducción?

1 ESTUDIOS SUB POTENCIADOS

- **Cierre prematuro:**
  Detención temprana por bajo reclutamiento.
  - **DECIDE:** 280/400 pacientes
  - **PARADIGM:** 145/330 pacientes
- **Falla estadística:**
  No se alcanzó el tamaño muestral. Estudios sin el poder estadístico necesario para detectar diferencias reales (alto riesgo de *Error Tipo II*).

2 EL "EFECTO VPH"

- **Inclusión desproporcionada:**
  Alta tasa de tumores de orofaringe VPH positivos (excelente pronóstico basal).
- **Caída de eventos:**
  La alta sensibilidad del VPH al tratamiento concurrente directo redujo drásticamente las recaídas y muertes esperadas en el brazo control, diluyendo el posible impacto del TPF.

3 TOXICIDAD SECUENCIAL Y PÉRDIDA DE INTENSIDAD DE DOSIS

- **El límite fisiológico:**
  El daño agudo generado por los 3 ciclos de TPF impidió administrar la consolidación concurrente a dosis plenas, comprometiendo la viabilidad del tratamiento definitivo.

MENSAJE CLAVE

La **ausencia** de beneficio de la quimioterapia de inducción probablemente refleja la combinación de **limitaciones metodológicas, cambios epidemiológicos (VPH) y toxicidad acumulada,** más que la **ineficacia intrínseca** del esquema TPF.

VOLUME 28 • NUMBER 21 • NOVEMBER 1, 2010

JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Induction Chemotherapy Followed by Cetuximab Radiotherapy Is Not Superior to Concurrent Chemoradiotherapy for Head and Neck Carcinomas: Results of the GORTEC 2007-02 Phase III Randomized Trial

Lucien Geoffrois, James Blanchard, Dominique Bourhis, Xavier Baujat, Eric Lartigau, Philippe Maingon, Joël Castelli, Sylvain Morvan, Olivier H. Chinot, Gilles Calais, Frédéric Peyrade, Axel Le Cesne, Jean-Paul Pignon, Didier Peiffert, Emmanuel Babin, Vincent Grégoire, Charles-Henri Armand, Remi H. Nakhle, Eric Chatoveau, Catherine Cremerius, Valérie Bruno, Alain G. Skladowski, Pierre Boulanger, Jean Bourhis, Isabelle Loubinoux, Christophe Hennequin, Michel Lacaurreye, Joël M. Mallet, Yves Pointreau, and Jean Bourhis; for the French Head and Neck Cancer Group and the Lyon Saint-Etienne Oncology Center Head and Neck Group

No diferencia en SLP ni en SG

Study design

n=1,174
2007-02

Carboplatin 70mg/m² +
5-FU 600mg/m²/d D1-D5, Weeks 1, 4 and 7

No induction → RT
70 Gy, 35 fractions,
5 fractions/week

R

T
P
F
x 3 cycles
I.C.R. 28 days ± 5D

Docetaxel 75mg/m² D1 (T)
+ cisplatin 75mg/m² D1 (P)
+ 5-FU 750mg/m² D1-5 (F)

Cetuximab
400mg/m² D1 then 250mg/m²/wk x 7 weeks

RT
70 Gy, 35 fractions,
5 fractions/week

Supportive therapy:
lansoprazole and ciprofloxacin

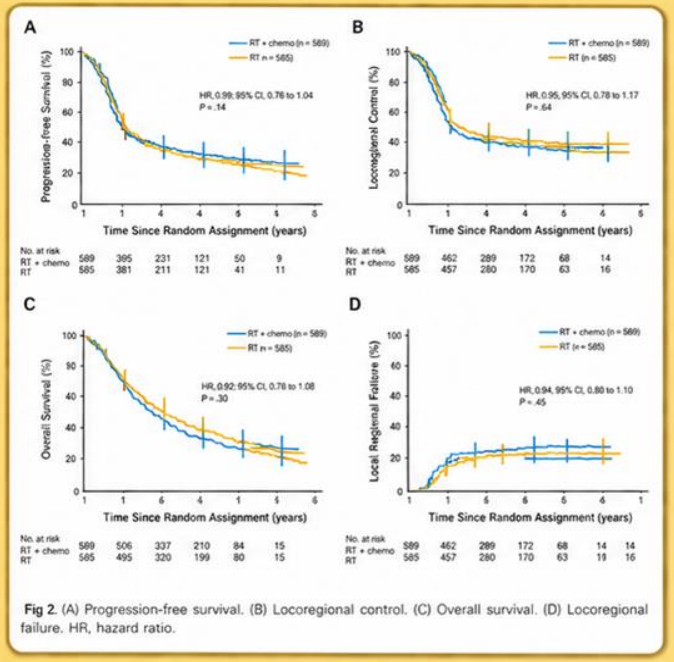


Fig 2. (A) Progression-free survival. (B) Locoregional control. (C) Overall survival. (D) Locoregional failure. HR, hazard ratio.

ANÁLISIS CRÍTICO

El fracaso del GORTEC 2007-02 se explica por una **limitación conceptual** que la evidencia posterior permitió esclarecer.

1 INFERIORIDAD DEL CETUXIMAB FRENTE AL CISPLATINO

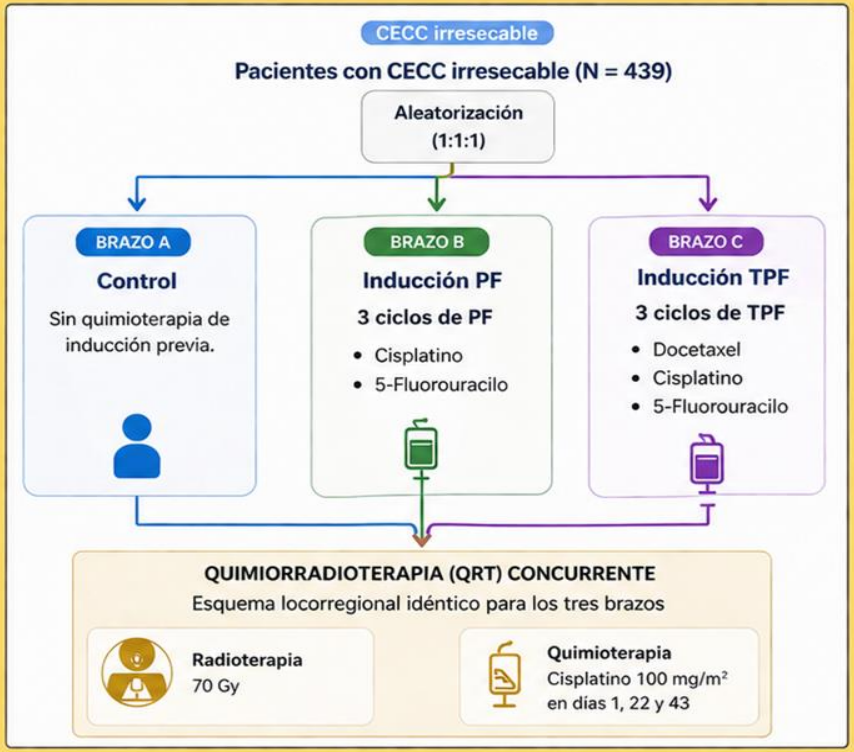
- El reemplazo del cisplatino por cetuximab durante la radioterapia buscó reducir la toxicidad, pero se asoció con una **menor eficacia locorregional**.
- Ensayos posteriores (**RTOG 1016** y **De-ESCALaTE HPV**) demostraron que el cetuximab es **inferior al cisplatino** como radiosensibilizador, con **peores resultados en control locorregional y supervivencia global**.
- En este contexto, la **menor eficacia locorregional** probablemente limitó el potencial beneficio de la quimioterapia de inducción, dificultando demostrar una ventaja clínica del esquema evaluado.

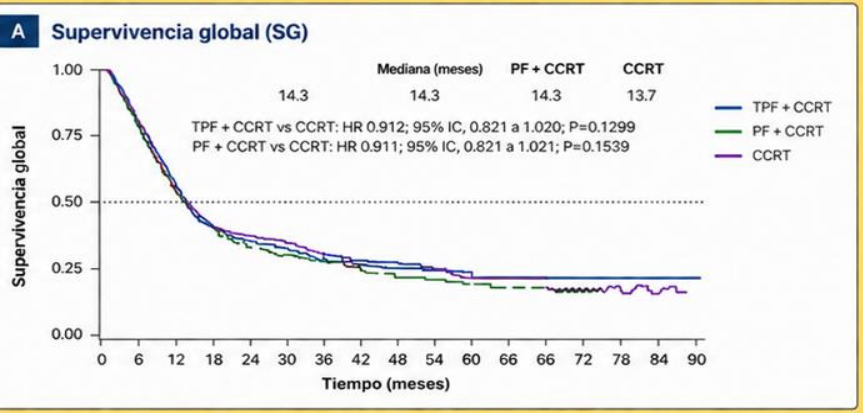
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

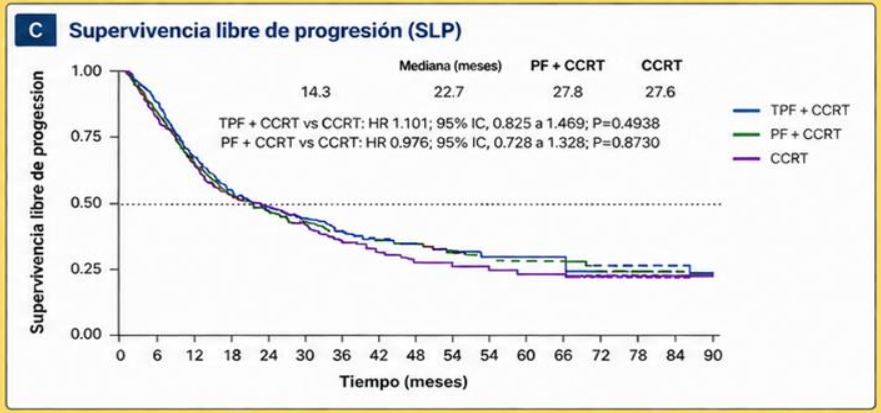
A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer

R. Hitt[1*], J.-J. Grau[2], A. López-Pousa[3], A. Berrocal[4], C. García-Girón[5], A. Irigoyen[6], J. Sastre[7], J. Martínez-Trufero[8], J. A. Brandiarz Castelo[9], E. Verge[10], J. J. Cruz-Hernández[11] & on behalf of the Spanish Head and Neck Cancer Cooperative Group (TTCC)[7]

No diferencias en SG ni en SLP







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Original article

Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials

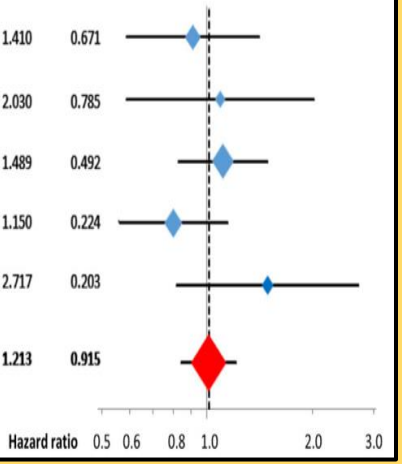
Wilfried Budach [a], Edwin Bölke [a], Kai Kammers [b], Peter Arne Gerber [d], Klaus Orth [c], Stephan Gripp [a], Christiane Matuschek [a,*]

[a] Medical Faculty, Department of Radiation Oncology, Heinrich Heine University, Dusseldorf, Germany; [b] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; [c] Medical Faculty, Department of General, Visceral, and Thoracic Surgery, Asklepios Harz Hospitals, Goslar; and [d] Medical Faculty, Department of Dermatology, Heinrich Heine University, Dusseldorf, Germany

TPF→RT-CHX vs. RT-CHX in locally advanced head and neck cancer

Meta-analysis of randomized controlled trials: **Overall Survival**

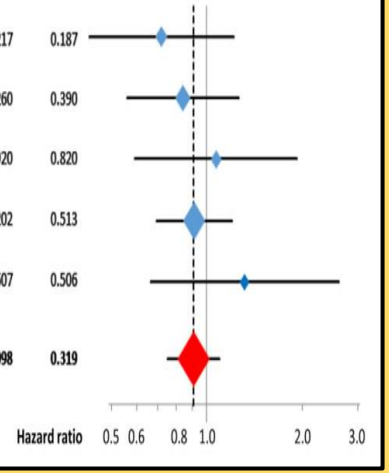
Reference	n *	HR	95% CL-	95% CL+	p
Cohen et al.[19]	273	0.910	0.590	1.410	0.671
Haddad et al.[14]	145	1.090	0.590	2.030	0.785
Hitt et al.[15]	283	1.109	0.825	1.489	0.492
Paccagnella et al. Ghi et al.[20]	258	0.800	0.560	1.150	0.224
Takácsi-Nagy et al.[18]	63	1.490	0.817	2.717	0.203
Total	**1022**	**1.010**	**0.841**	**1.213**	**0.915**

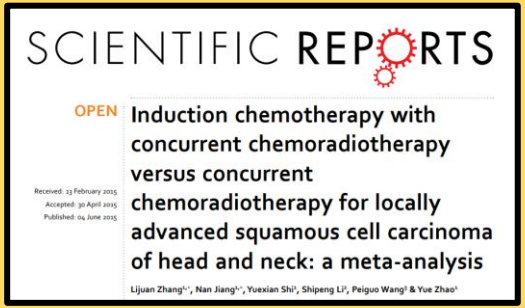


TPF→RT-CHX vs. RT-CHX in locally advanced head and neck cancer

Meta-analysis of randomized controlled trials: **PFS**

Reference	n *	HR	95% CL-	95% CL+	p
Paccagnella et al.[16]	101	0.718	0.424	1.217	0.187
Cohen et al.[19]	273	0.840	0.560	1.260	0.390
Haddad et al.[14]	145	1.070	0.590	1.920	0.820
Hitt et al.[15]	283	0.912	0.692	1.202	0.513
Takácsi-Nagy et al.[18]	60	1.315	0.663	2.607	0.506
Total	**862**	**0.908**	**0.751**	**1.098**	**0.319**





SCIENTIFIC REPORTS

OPEN

Induction chemotherapy with concurrent chemoradiotherapy versus concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of head and neck: a meta-analysis

Received: 13 February 2015
Accepted: 30 April 2015
Published: 04 June 2015

Lijuan Zhang[1,*], Nan Jiang[1,*], Yuexian Shi[1], Shipeng Li[2], Peiguo Wang[1] & Yue Zhao[1]

En comparación con QT-RT concomitante, quimioterapia de inducción no mostró diferencias estadísticamente significativas en SG, SLP, tasa de respuesta global ni tasa de recurrencia locorregional.

La tasa de metástasis a distancia disminuyó (p: 0,006) y la tasa de respuesta completa mejoró (p: 0,010) con quimioterapia de inducción.

CONCLUSIONES

Ventajas: reducción de la carga tumoral y órgano preservación.

Desventaja: incremento de la toxicidad, costo y duración del tratamiento y retraso del tratamiento estándar en los no respondedores.

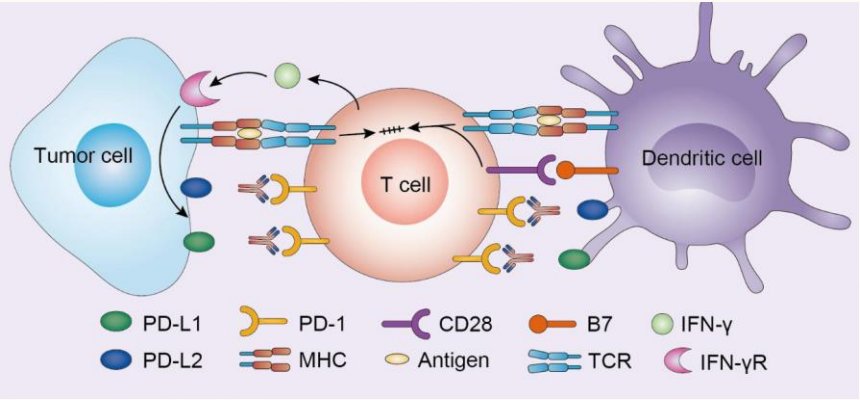
Inducción con taxano platino y 5 fu demostró tasas de respuesta del 70 %.

No se observó diferencia en sobrevida o control local comparada con el tratamiento estándar en la mayoría de los ensayos y metaanálisis.

En todos los casos debe haber una evaluación multidisciplinaria para decidir la mejor opción de tratamiento para cada paciente.

NEW

INMUNOTERAPIA



EXPRESIÓN DE PD-L1 EN CÁNCER EPIDERMOIDE DE CABEZA Y CUELLO (CECC)

En la actualidad, la cuantificación de la expresión de PD-L1 determina la **elegibilidad de los pacientes** para recibir inmunoterapia, dicta la **selección de terapias combinadas** frente a monoterapias en el escenario de enfermedad recurrente o metastásica y moldea el **diseño de las estrategias** de inducción y neoadyuvancia en etapas localmente avanzadas.

La evaluación de la expresión de PD-L1 en el CECC se realiza mediante **técnicas de inmunohistoquímica** aplicadas sobre muestras de tejido fijado en formalina e incluido en parafina.

COMBINED POSITIVE SCORE (CPS)

$$CPS = \frac{\text{Células tumorales PD-L1+} + \text{Linfocitos PD-L1+} + \text{Macrófagos PD-L1+}}{\text{Células tumorales viables (PD-L1+ o PD-L1–)}} \times 100$$

NÚMERO DE CÉLULAS PD-L1 POSITIVAS

NÚMERO TOTAL DE CÉLULAS TUMORALES VIABLES

FÓRMULA

$$CPS = \frac{(PTC + PIC)}{TC} \times 100$$

¿QUÉ SE CUENTA?

- **PTC (Positive Tumor Cells):** células tumorales con tinción membranosa de PD-L1 (parcial o completa)
- **PIC (Positive Immune Cells):** linfocitos y macrófagos con tinción de PD-L1 (membranosa o citoplasmática)
- **TC (Tumor Cells):** células tumorales viables totales (positivas o negativas)

El CPS integra la expresión de PD-L1 en células tumorales y células inmunes del microambiente tumoral, constituyendo un **biomarcador clave** en la toma de decisiones terapéuticas.

CECC: cáncer epidermoide de cabeza y cuello | PD-L1: programmed death-ligand 1 | CPS: combined positive score
PTC: positive tumor cells | PIC: positive immune cells | TC: tumor cells

ENFERMEDAD LOCALMENTE AVANZADA

Four negative phase 3 trials

- Immunotherapy before, during and after **CRT** versus CRT (with placebo or alone)
  - Avelumab (**Javelin HN 100**)
  - Pembrolizumab (**KEYNOTE-412**)
  - Durvalumab (**CompARE**)
- Avelumab (**REACH**) before, during and after **cetuximab RT** versus
  - Cetuximab RT (cisplatin unfit)
  - CRT (cisplatin fit)

Potential explanations for immunotherapy failure

- Biomarker unselected patient populations
- RT to lymph nodes abrogates T cell response
- RT destroys circulating T cells
- PD-L1 inhibitors are less effective than PD1 inhibitors

La administración de inmunoterapia en el período neoadyuvante aprovecha un microambiente tumoral intacto, favoreciendo la activación y expansión sistémica de linfocitos T específicos contra el tumor. Esto promueve una memoria inmunológica duradera y podría contribuir a la erradicación de la enfermedad micro metastásica residual.

Open access Original research

Journal for ImmunoTherapy of Cancer

Neoadjuvant nivolumab for patients with resectable HPV-positive and HPV-negative squamous cell carcinomas of the head and neck in the CheckMate 358 trial

Se administraron 2 dosis de **Nivolumab** (240 mg IV) los días 1 y 15.

Intervención Quirúrgica: Programada para el día 29.

Estado del VPH	Respuestas Patológicas (pPR + MPR)	Respuesta Patológica Completa (pCR)
VPH Positivo	23.5%	0%
VPH Negativo	5.9%	0%

Artículo original

Pembrolizumab neoadyuvante en cáncer de cabeza y cuello resecable, no relacionado con VPH: ensayo multicéntrico, fase 2

POBLACIÓN

36 pacientes
con CCECC resecable, estadios III–IVB, no relacionado con VPH.

*38 pacientes fueron reclutados; 36 fueron evaluables para eficacia.

FASE NEOADYUVANTE

1 dosis única de pembrolizumab (200 mg) administrada 13 a 22 días antes de la cirugía.

FASE ADYUVANTE (guiada por patología)

- **Alto riesgo** (márgenes positivos o extensión extranodal): QRT seguida de pembrolizumab adyuvante (8 dosis).
- **Riesgo bajo/intermedio:** RT u observación (sin pembrolizumab adyuvante).

RESPUESTA PATOLÓGICA TUMORAL (pTR) – n = 36 pacientes

pTR-0 (≥50% tumor viable residual)	pTR-1 (10–49% tumor viable residual)	pTR-2 (≤10% tumor viable residual) (respuesta patológica mayor, MPR)	Respuesta completa (pCR)
56%	22%	22%	0%
20 pacientes	8 pacientes	8 pacientes	0 pacientes

MENSAJE PRINCIPAL

Una única dosis preoperatoria de pembrolizumab fue segura, no retrasó la cirugía y produjo respuesta patológica en el 44% de los pacientes (22% pTR-2). Constituye la primera evidencia clínica que impulsó el desarrollo de los estudios fase III perioperatorios (KEYNOTE-689).

Estudio fase 2, exploratorio. No diseñado para evaluar supervivencia.

Uppaluri R et al. *J Immunother Cancer.* 2020;8(1):e000734.
doi: 10.1136/jitc-2020-000734

JITC Journal for ImmunoTherapy of Cancer

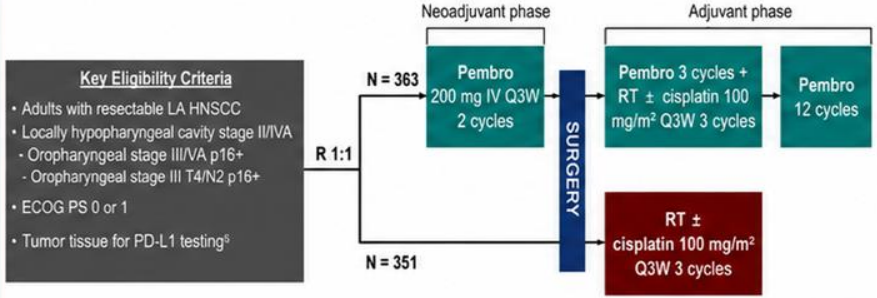
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant and Adjuvant Pembrolizumab in Locally Advanced Head and Neck Cancer

R. Uppaluri, V. R. Haddad, Y. Wu, J. C. E. Ferreira, M. V. Lou, W. Ma, G. Yoe,Coccoe, G. M. Tsai, S. D. Huanges, M. Mesinnum, J. E. Mierz. J. C. Sacca, C. T. Johnson, S. S. Hong, T. K. Tanaka, R. Ferriu, J. Hi. Y. Cao,' T. Urban, S. Talukder, U. Schinming:, P. S. Mago, T. Brunner, Z. Salmat, * M. Okafuji, C. P. Patelt, J. M. Bat, B. BurtnessM. D.C. Valero, H. Wirth, D. Ind. P. P. Porceddu, J. M. Zafereo, C. Montalvo, J. Estrada-' Hernandez, and J. P. Merck, for the KEYNOTE-689 Investigators*

KEYNOTE-689 Study (NCT03765918)



Stratification factors

- Primary tumor site (oropharyngeal cavity vs larynx vs hypopharynx)
- Tumor stage (III vs IVA)
- PD-L1 TPS§ (≥50% vs <50%)

Primary endpoint: EFS per RECIST 1.1 by BICR

Key secondary endpoints: Major pathological responses by BIPR (mPR: ≤10% residual invasive SCC in resected primary tumor + all sampled regional lymph nodes), OS

Other secondary endpoints include: Safety

Exploratory endpoints include: Locoregional failure rate, DMFS, second cancers

BICR, blinded independent central review; BIPR, blinded independent pathology review; DMFS, distant metastasis-free survival; EFS, event-free survival; OS, overall survival; RT, radiation therapy.

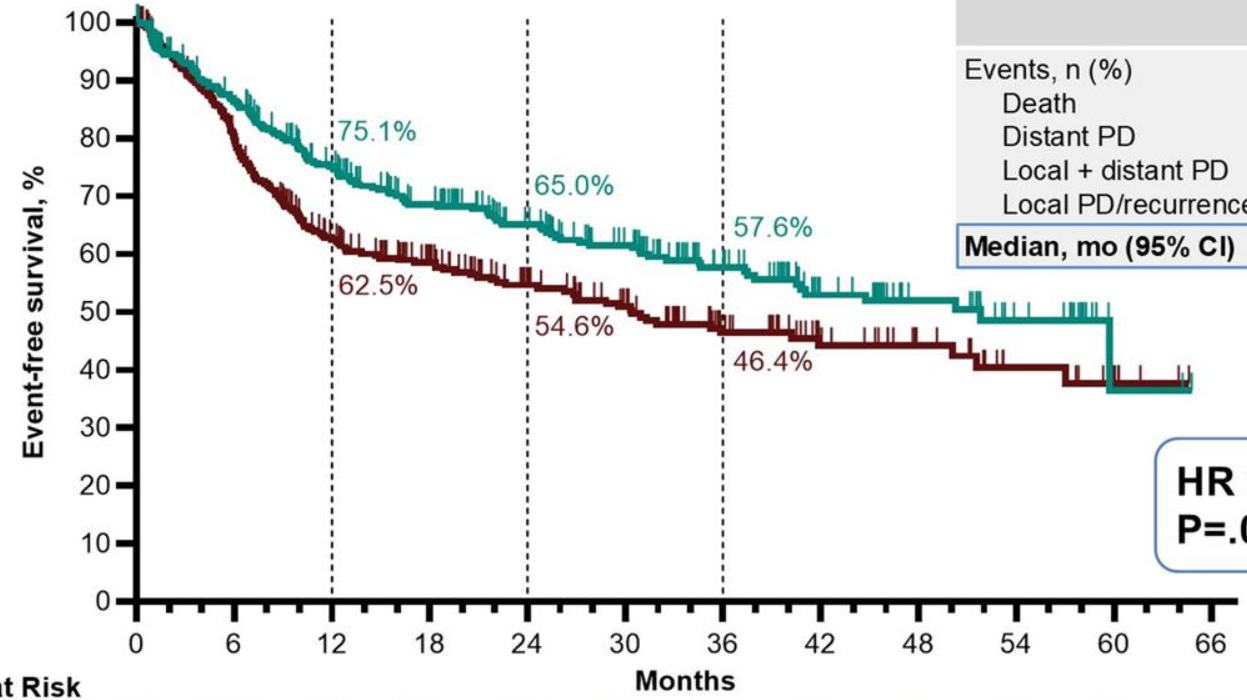
§Assessed by PD-L1 IHC 22C3 pharmDx. *TPS≥§ tumor cells with membranous PD-L1 staining.

Tabla. Características basales de la población del estudio

Característica	Pembrolizumab (N=363)	Control (N=351)	Característica	Pembrolizumab (N=363)	Control (N=351)
Edad mediana, años (rango)	60.0 (29–82)	61.0 (22–87)	Estado HPV, n (%)		
Sexo masculino, n (%)	286 (78.8)	277 (78.9)	• Positivo	12 (3.3)	15 (4.3)
ECOG 0, n (%)	199 (54.8)	209 (95.5)	• Negativo	351 (96.7)	335 (95.4)
Región geográfica, n (%)			Estado PD-L1, n (%)		
• Norteamérica	64 (17.6)	49 (14.0)	• TPS ≥50%	103 (28.4)	107 (30.5)
• Unión Europea	138 (38.0)	145 (41.3)	• CPS ≥10	234 (64.5)	231 (65.8)
• Resto del mundo	161 (44.4)	157 (44.7)	• CPS ≥1	347 (95.6)	335 (95.4)
Sitio tumoral primario, n (%)			• CPS <1	13 (3.6)	14 (4.0)
• Hipofaringe	28 (7.7)	26 (7.4)	Fumador actual o exfumador, n (%)	293 (80.7)	267 (76.1)
• Laringe	81 (22.3)	73 (20.8)	Consumo de alcohol, n (%)	250 (68.9)	238 (67.8)
• Cavidad oral	219 (60.3)	213 (60.7)			
• Orofaringe	35 (9.6)	38 (10.8)			

ECOG, Eastern Cooperative Oncology Group; HPV, virus del papiloma humano; PD-L1, ligando de muerte programada 1; TPS, Tumor Proportion Score; CPS, Combined Positive Score.

EFS by BICR,[a] All Participants



	Pembro + SOC (N = 363)	SOC (N = 351)
Events, n (%)	136 (37.5)	159 (45.3)
Death	67 (18.5)	64 (18.2)
Distant PD	26 (7.2)	51 (14.5)
Local + distant PD	4 (1.1)	7 (2.0)
Local PD/recurrence	39 (10.7)	37 (10.5)
Median, mo (95% CI)	**51.8 (37.5–NR)**	**30.4 (21.8–50.1)**

HR 0.73, 95% CI 0.58–0.92, P=.0041*

No. at Risk

Pembro + SOC	363	287	232	191	157	129	88	55	34	21	2	0
SOC	351	258	183	147	110	88	59	37	25	15	7	0

NR, not reached. *Significance boundary was met at IA1.

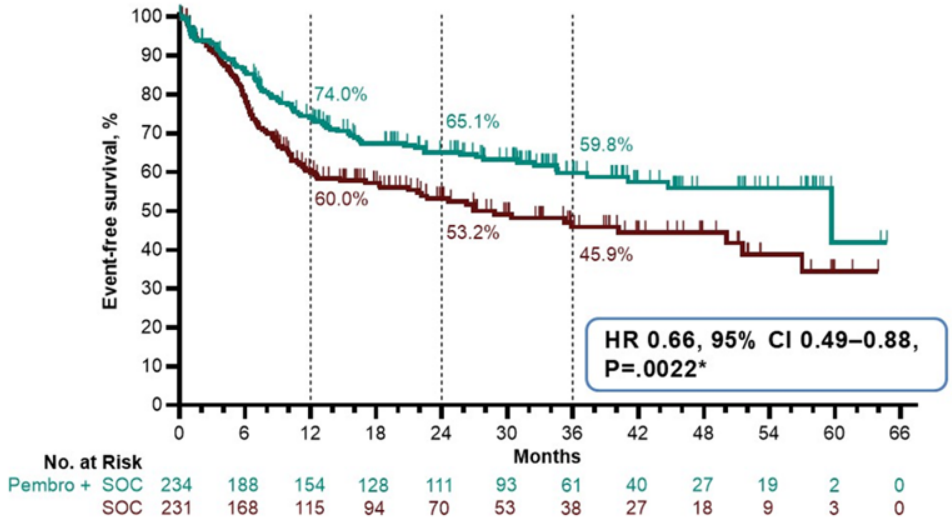
[a]Defined as time from randomization to first radiographic PD (including during neoadjuvant phase that precludes surgery, local or distant PD/recurrence by imaging/biopsy) or death due to any cause

Data cutoff date: 25 July 2024

Median follow-up (time from randomization to data cutoff date): 38.3 months (9.0–66.5).

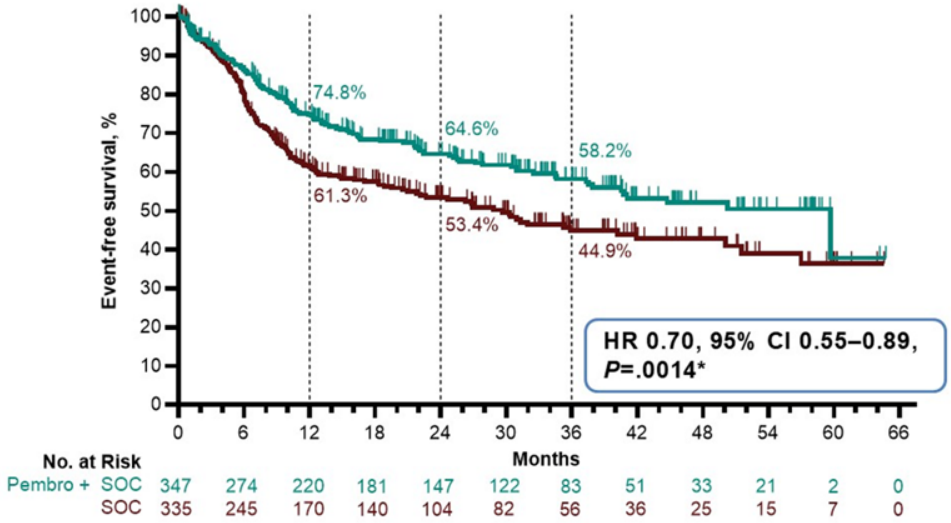
EFS by BICR, CPS ≥10 and CPS ≥1 Populations

CPS ≥10 Population



	Pembro + SOC N = 234	SOC N = 231
Events, n (%)	85 (36.3)	107 (46.3)
Median, mo (95% CI)	**59.7 (41.1–NR)**	**26.9 (18.3–51.5)**

CPS ≥1 Population



	Pembro + SOC N = 347	SOC N = 335
Events, n (%)	128 (36.9)	156 (46.6)
Median, mo (95% CI)	**59.7 (37.9–NR)**	**29.6 (19.5–41.9)**

NR, not reached. *Significance boundary was met at IA1.

Data cutoff date: 25 July 2024
Median follow-up: 38.3 months (9.0–66.5).

Pathological Response

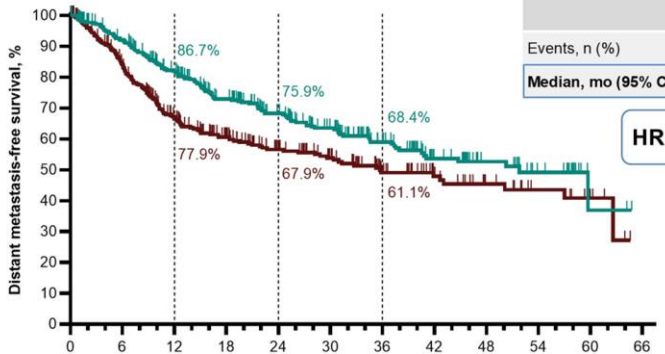
	CPS ≥10 Population		CPS ≥1 Population		All Participants	
	Pembro + SOC n = 234	SOC n = 231	Pembro + SOC n = 347	SOC n = 335	Pembro + SOC N = 363	SOC N = 351
mPR, n (%)	32 (13.7)	0	34 (9.8)	0	34 (9.4)	0
Estimated difference (95% CI)	13.7 (9.7–18.7)		9.8 (7.0–13.3)		9.3 (6.7–12.8)	
P value	<0.00001*		<0.00001*		<0.00001*	
pCR, n (%)	10 (4.3)	0	11 (3.2)	0	11 (3.0)	0
Estimated difference (95% CI)	4.2 (2.1–7.6)		3.1 (1.6–5.6)		3.0 (1.5–5.3)	

mPR (≤10% residual invasive SCC) and pCR evaluated by **blinded** independent pathologist review.

mPR, major pathological response; pCR, pathological complete response.
*Significance boundary was met at IA1.

Data cutoff date: 25 July 2024
Median follow-up: 38.3 months (9.0–66.5).

DMFS,[a] All Participants



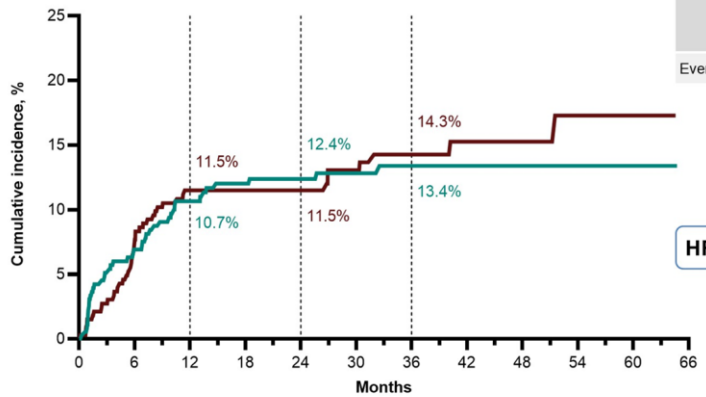
	Pembro + SOC N = 363	SOC N = 351
Events, n (%)	127 (35.0)	148 (42.2)
Median, mo (95% CI)	**51.8 (37.9–NR)**	**35.7 (26.3–57.0)**

HR 0.71, 95% CI 0.56–0.90

No. at Risk												
Pembro + SOC	363	303	251	203	166	134	90	55	34	21	2	0
SOC	351	266	190	149	112	90	61	40	26	16	8	0

NR, not reached. [a]Defined as time from randomization to date of first record of appearance of distant metastasis or death due to any cause.

Time to Locoregional Failure,[a] All Participants



	Pembro + SOC N = 363	SOC N = 351
Events, n (%)	136 (37.5)	159 (45.3)

HR 0.92, 95% CI 0.61–1.41

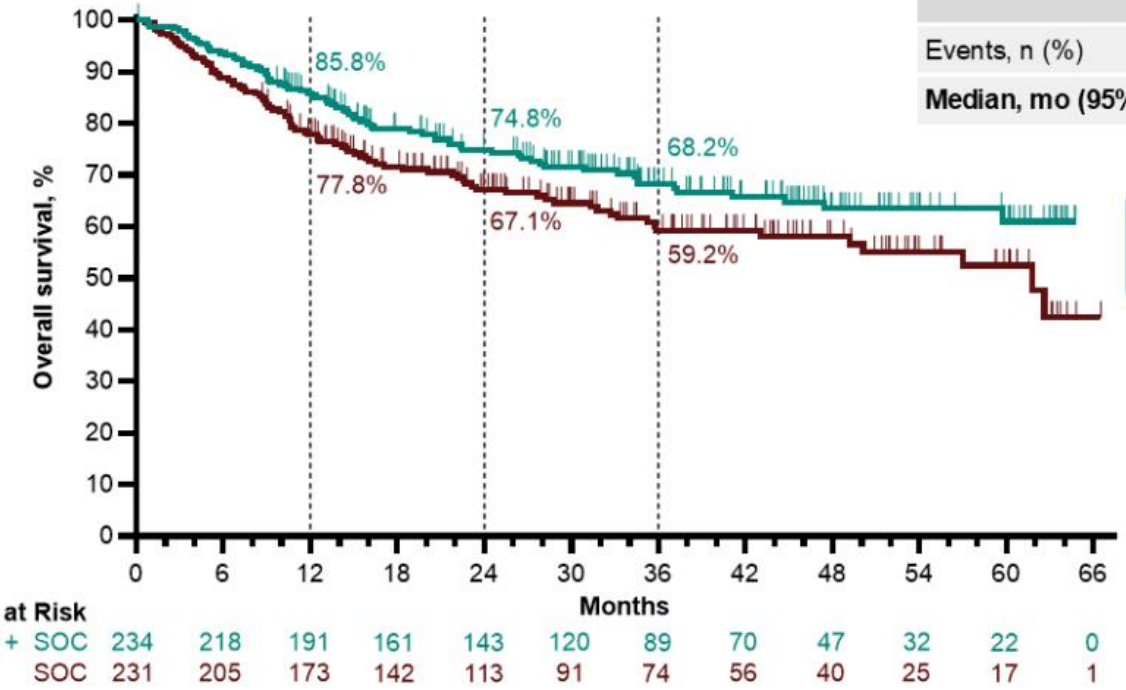
[a]Defined as time from randomization to date of first recorded radiographic PD (local recurrence by imaging or biopsy).

Data cutoff date: 25 July 2024
Median follow-up: 38.3 months (9.0–66.5).

Key Secondary Endpoint: OS

CPS ≥10 Population

	Pembro + SOC (N = 234)	SOC (N = 231)
Events, n (%)	73 (31.2)	89 (38.5)
Median, mo (95% CI)	**NR (NR–NR)**	**61.8 (49.2–NR)**



HR 0.72, 95% CI 0.52–0.98, P=.02

NR, not reached.
Significance boundary was not met at IA1.

Additional follow-up is ongoing. OS hypotheses will be tested in future analyses according to the statistical plan.

Data cutoff date: 25 July 2024

Summary of Safety, As-Treated Population

	Pembro + SOC N = 361	SOC N = 315
Median (range) duration of therapy, mo	9.1 (0.03–22.3)	2.9 (0.03–7.2)
Treatment-related adverse events, n (%)		
Any grade	294 (81.4)	258 (81.9)
Grade ≥3	161 (44.6)	135 (42.9)
Serious	69 (19.1)	33 (10.5)
Led to discontinuation	64 (17.7)	39 (12.4)
Led to death	4 (1.1)[a]	1 (0.3)[b]
Immune-mediated adverse events, n (%)		
Any grade	156 (43.2)	32 (10.2)
Grade ≥3	36 (10.0)	2 (0.6)

[a]Renal failure, COVID-19 pneumonia, death, and pneumonitis (n=1 each). [b]Acute kidney injury.
As-treated population included all pts with ≥1 dose study treatment (including surgery only).

Data cutoff date: 25 July 2024

El evento adverso más frecuente grado 3 o superior fue la estomatitis (11,6 % en el grupo de pembrolizumab y 13,3 % en el grupo de control)

El evento inmunomediado más frecuente fue el hipotiroidismo (24,7 % en el grupo de pembrolizumab y 5,4 % en el grupo de control).

La toxicidad fue manejable y no se detectaron nuevas señales de alarma en comparación con perfiles conocidos del fármaco.

La incidencia general de eventos adversos (EA) relacionados con el tratamiento fue similar en ambos brazos (aproximadamente 81%).

Los EA inmunomediados de grado 3 o superior ocurrieron en el 10% de los pacientes tratados con pembrolizumab.

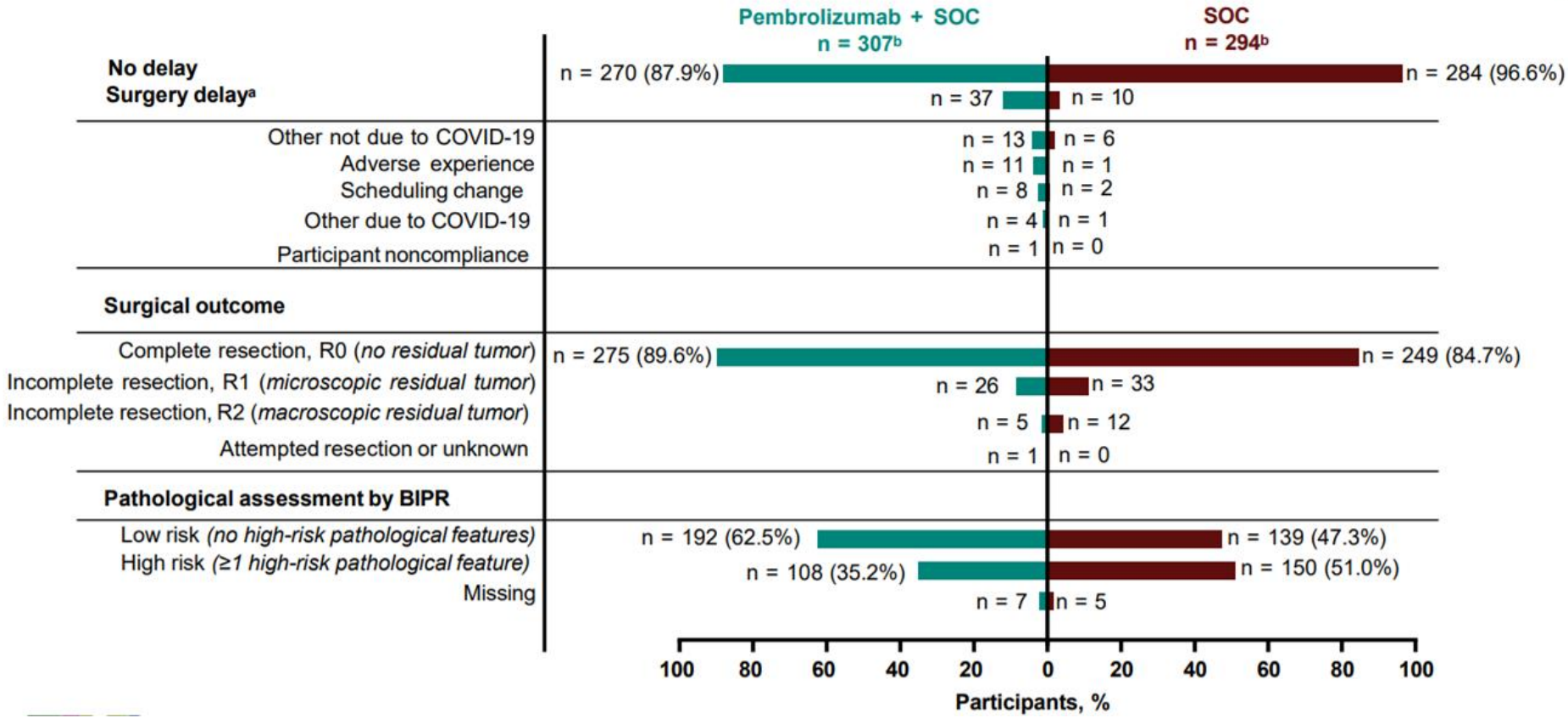
ICHNO 2026

19 -21 March 2026 Seville, Spain

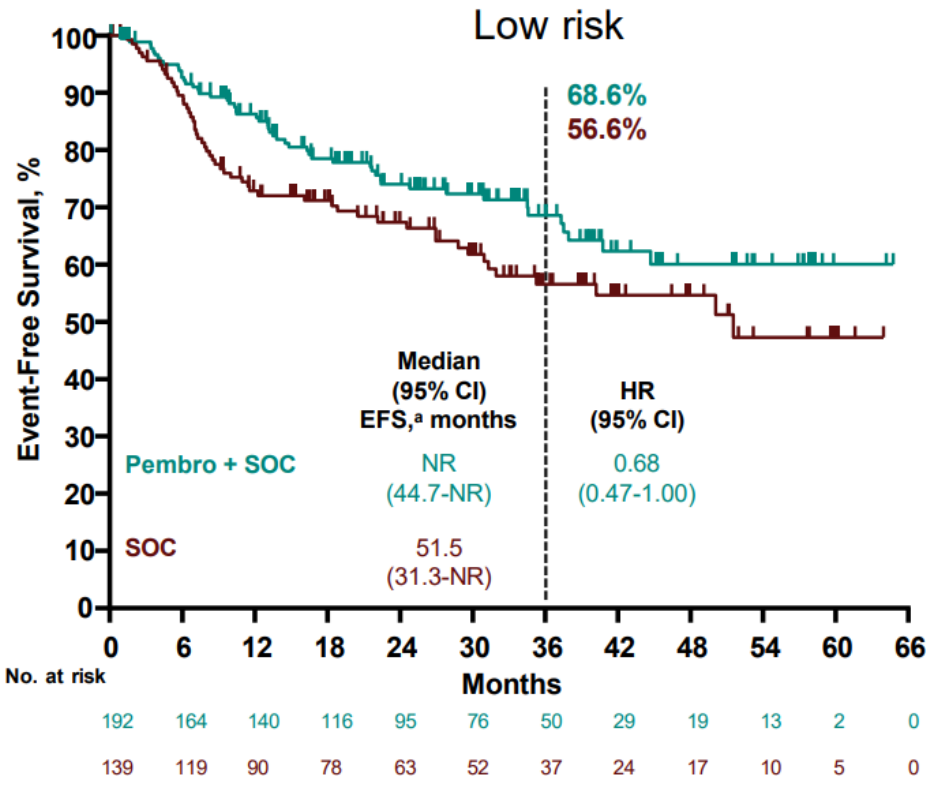
10th International Congress on Innovative Approaches in Head & Neck Oncology

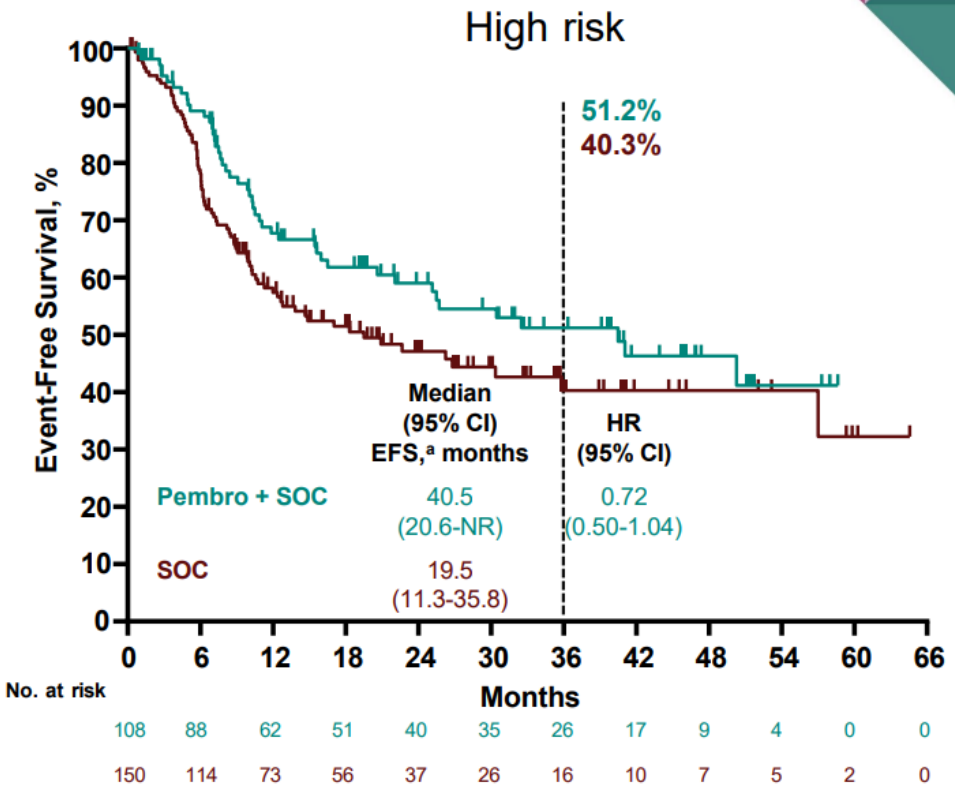
Neoadjuvant and Adjuvant Pembrolizumab Plus Standard of Care in LA HNSCC: Outcomes by Postoperative Risk in the PD-L1 CPS ≥1 Population of KEYNOTE-689

Surgical Outcomes, PD-L1 CPS ≥1



Event-Free Survival, PD-L1 CPS ≥1

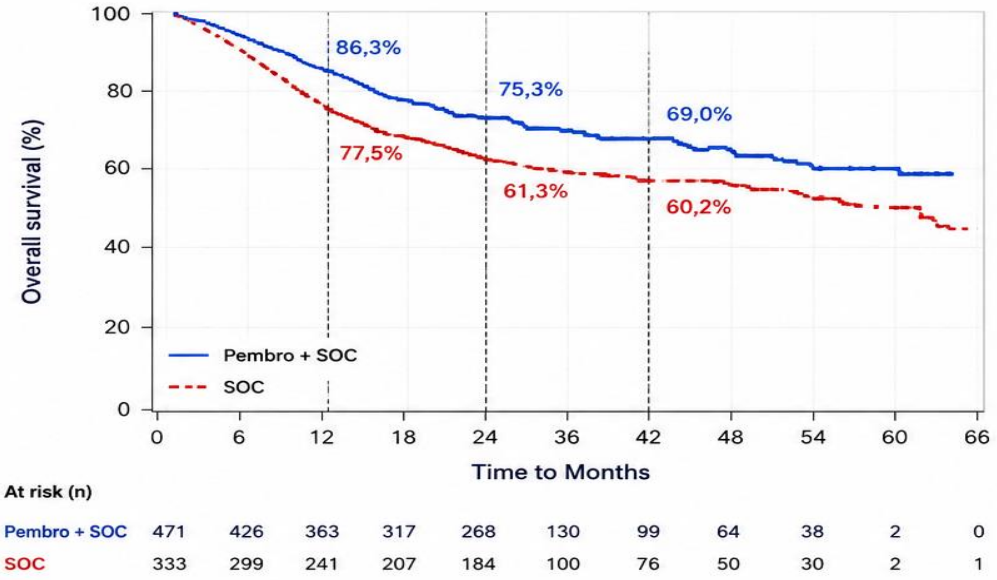




Key secondary endpoint: OS

Data cut-off: 11 September 2025
ITT Population N=804

CPS ≥1 Population



At risk (n)

Pembro + SOC	471	426	363	317	268	130	99	64	38	2	0
SOC	333	299	241	207	184	100	76	50	30	2	1

	Pembro + SOC (n = 471)	SOC (n = 333)
Events, n (%)	106 (22,5)	128 (38,4)
Median, mo (95% CI)	NR (NR, NR)	61,8 (49,2, NR)

HR 0,72
95% CI 0,56–0,94
p = 0,00666

NR, not reached.

OS was not formally tested in CPS ≥1 population.

Additional follow-up is ongoing. OS hypotheses will be tested in future analysis according to statistical plan.

En los pacientes con CPS ≥1, pembrolizumab perioperatorio mostró una **reducción del 28%** del riesgo de muerte (HR 0,72).

A los 3 años, la supervivencia estimada fue del **69%** frente al **60,2%** con el tratamiento estándar.

No obstante, este análisis corresponde a un análisis interno, por lo que el beneficio deberá confirmarse con un **seguimiento más prolongado.**

VIABILIDAD Y CALIDAD QUIRÚRGICA CON PEMBROLIZUMAB PERIOPERATORIO

Viabilidad Quirúrgica: La inmunoterapia neoadyuvante no comprometió el acto quirúrgico. El **88%** de la cohorte total completó la cirugía sin retrasos significativos.

La resección completa con márgenes negativos (**R0**) ocurrió en **89,6%** (pembro) y **84,7%** (control).

Un menor número de pacientes en el grupo de pembrolizumab presentó características patológicas de **alto riesgo** y recibió **cisplatino** después de la cirugía.

El pembrolizumab perioperatorio mejoró la calidad de la cirugía, aumentando la tasa de resección R0 y reduciendo los factores patológicos de alto riesgo, sin comprometer la factibilidad quirúrgica.

Treatment of Locally Advanced Disease

SEOM Sociedad Española de Oncología Médica

Surgery-based Treatment

Neoadjuvant Therapy	LE, GoR
There is no evidence to support the use of induction chemotherapy (ICT) before surgery for resectable locally advanced HNC[1]	I, A
Neoadjuvant and adjuvant pembrolizumab was approved by the FDA (June 2025) and EMA (October 2025) for patients with resectable locally advanced HNC whose tumors express PD-L1 by CPS (>1), and is currently awaiting approval from the Spanish Agency of Medicines and Medical Devices (AEMPS) for standard clinical use in Spain[2]: ▪ Pembrolizumab as monotherapy is INDICATED for the treatment of resectable locally advanced SCCHN as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin, and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1[3,4]	I, A
Adjuvant Therapy	**LE, GoR**
RT alone MAY BE CONSIDERED in multiple positive neck nodes (without ENE), perineural, vascular, or lymphatic invasion, a pT3 or pT4 primary, or oral cavity or oropharyngeal primary cancers with positive level IV or V nodes.	I, A
Concurrent chemoradiotherapy (CCRT) is RECOMMENDED for tumors with high risk pathological features such as affected margins and/or ENE extension[5]: ▪ 3-weekly intravenous cisplatin 100 mg/m2 on days 1, 22, and 43[5] ▪ Weekly 40 mg/m2 cisplatin can be a non-inferior alternative with better safety profile[6]	I, A I, A I, B
Adjuvant nivolumab plus chemoradiotheray shown improved DFS in patients with high-risk HNC, though approval is pending[7]	-

PRINCIPLES OF SYSTEMIC THERAPY FOR NON-NASOPHARYNGEAL CANCERS
(Oral Cavity [including mucosal lip], Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, and Occult Primary)[a]

Primary Systemic Therapy + Concurrent RT

Preferred
- High-dose Cisplatin (category 1)[3,4]
- Carboplatin/infusional Fluorouracil (category 1)[5,6]

Other Recommended
- Weekly Cisplatin (40 mg/m^2)[7,8,9,10,11]
- Carboplatin/Paclitaxel (category 2B)[12,13]

Useful in Certain Circumstances
- Docetaxel (if Cisplatin ineligible)[14]
- Cetuximab (category 2B)[15]
- Cisplatin/infusional Fluorouracil (category 2B)[16]
- Cisplatin/Paclitaxel (category 2B)[17]
- Infusional Fluorouracil/Hydroxyurea (category 2B)[17]

Select ethmoid/maxillary sinus cancers (ie, small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features):
- Carboplatin/Etoposide ± concurrent RT[18]
- Cisplatin/Etoposide ± concurrent RT[18,19]

Induction[b]/Sequential Systemic Therapy and Neoadjuvant immunotherapy

Preferred
- Cisplatin/Docetaxel/Infusional Fluorouracil[20-23] (category 1 if induction is chosen)

Other Recommended
- Cisplatin/infusional Fluorouracil/Paclitaxel[24]
- Stage III–IVA cancer of the oral cavity (with PD-L1 positive [CPS ≥1]):
  - Neoadjuvant Pembrolizumab followed by adjuvant Pembrolizumab/RT (with Cisplatin if extranodal extension and/or positive margin) followed by adjuvant Pembrolizumab[25,26]

Useful in Certain Circumstances
- Stage III-IVA cancer of p16-negative oropharynx, hypopharynx, and larynx (with PD-L1 positive (CPS ≥1)):
  - Neoadjuvant Pembrolizumab followed by adjuvant Pembrolizumab/RT (with Cisplatin if extranodal extension and/or positive margin) followed by adjuvant Pembrolizumab[25,26]
- Carboplatin/Paclitaxel (category 2B)[27,28]
- Carboplatin/Paclitaxel + Cetuximab[29] (induction only) (category 2B)

For Newly Diagnosed T3, T4a Ethmoid Sinus Tumor

Other Recommended
- Cisplatin/Docetaxel/Infusional Fluorouracil

Useful in Certain Circumstances
- Cisplatin/Etoposide

Select ethmoid/maxillary sinus cancers (ie, small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features):
- Cyclophosphamide/Doxorubicin/Vincristine[30] (followed by RT-based treatment)

BERLIN 2025 ESMO congress

Perioperative camrelizumab plus chemotherapy in locally advanced squamous cell carcinoma of the head and neck, a multicenter, open-label, randomized, phase II Study (CAMORAL)

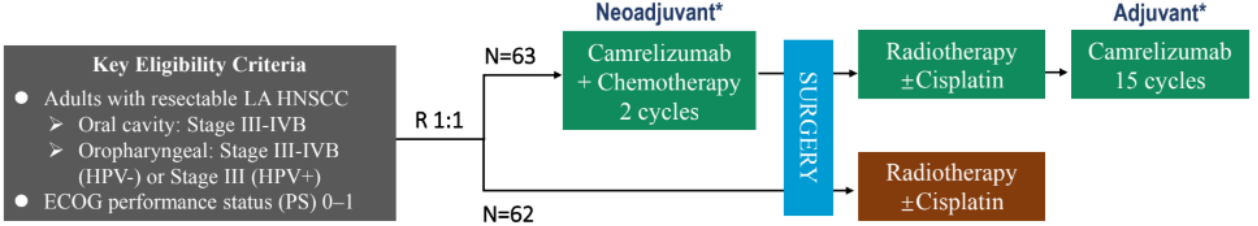
Yue He
Shanghai Ninth People's Hospital, Shanghai jiao Tong University School of Medicine; College of Stomatology, Shanghai jiao Tong University; National Center for Stomatology

18 October, 2025

CAMORAL Study ChiCTR2000037980

Key Eligibility Criteria

- Adults with resectable LA HNSCC
  - Oral cavity: Stage III-IVB
  - Oropharyngeal: Stage III-IVB (HPV-) or Stage III (HPV+)
- ECOG performance status (PS) 0–1



* Neoadjuvant (q3w × 2 cycles)
Albumin-bound paclitaxel: 100 mg/m² on (Days 1, 8, 15)
Carboplatin: area under the curve (AUC) 5 (Day 1)
Camrelizumab: 200 mg (Day 1)

*Adjuvant (q3w, up to 15 cycles)
Camrelizumab: 200 mg (Day 1)

Stratification factors

- ECOG PS (0 vs 1)
- Tumor stage (III vs IV)

Data cutoff: April 11, 2025
Median follow-up: 24.6 months

Endpoints

Primary endpoint: 2-year event-free survival (EFS, per RECIST 1.1, investigator-assessed)

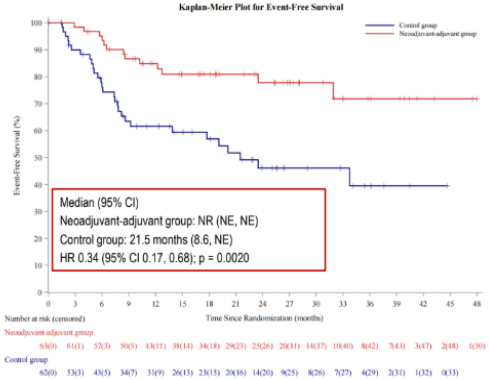
Secondary endpoints: 2-year overall survival (OS), major pathological response (mPR), pathological complete response (pCR), 2-year distant metastasis-free survival (DMFS)、2-year local recurrence-free survival (LRFS)、safety

mPR: ≤10% residual invasive SCC in resected tumor and all sampled lymph nodes
pCR: No residual invasive SCC in resected tumor and all sampled lymph nodes

BERLIN 2025 ESMO congress

Primary Endpoint: EFS

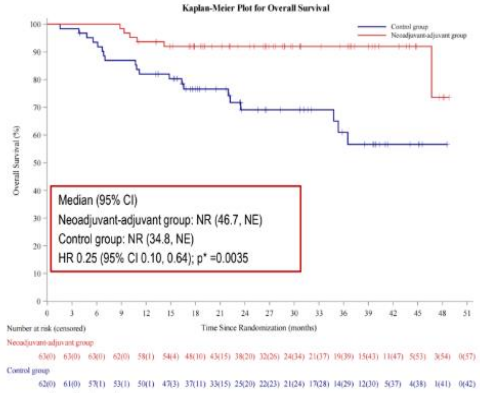
Intent-to-Treat (ITT) population



	neoadjuvant-adjuvant group (n=63)	control group (n=62)
EFS Events, n (%)	13 (20.6)	29 (46.8)
Censored, n (%)	50 (79.4)	33 (53.2)
EFS Rates (95% CI)		
6-month EFS Rate	95.11 (85.58, 98.40)	76.08 (62.95, 85.09)
12-month EFS Rate	84.86 (72.90, 91.83)	61.59 (47.68, 72.83)
24-month EFS Rate	77.80 (63.62, 87.00)	46.09 (31.34, 59.61)

Secondary Endpoint: OS

ITT population



* nominal p value

	neoadjuvant-adjuvant group (n=63)	control group (n=62)
death, n (%)	6 (9.5)	20 (32.3)
Censored, n (%)	57 (90.5)	42 (67.7)
OS Rates (95% CI)		
6-month OS Rate	100.00 (100.00, 100.00)	93.49 (83.58, 97.51)
12-month OS Rate	93.65 (83.96, 97.57)	82.01 (69.87, 89.61)
24-month OS Rate	91.98 (81.79, 96.58)	69.08 (54.52, 79.82)
Median Follow-up Time (months)	27.47	22.06

Pathological Response

	neoadjuvant-adjuvant group (n=63)	control group (n=62)
Surgical Cases, n (%)	58 (92.1)	56 (90.3)
pCR, n (%)	**16 (25.4)**	0
pCR rate (95%CI)	25.40 (15.27, 37.94)	0.00 (0.00, 5.78)
Between-Group Difference in pCR Rate	25.42 (14.65, 36.18)	
*P** value	<0.0001	
MPR, n (%)	**30 (47.6)**	0
MPR rate (95%CI)	47.62 (34.88, 60.59)	0.00 (0.00, 5.78)
Between-Group Difference in MPR Rate	47.97 (35.65, 60.28)	
*P** value	<0.0001	

* nominal p value

• mPR (≤10% residual invasive SCC) and pCR evaluated by blinded independent pathologist review.

Yue He, Shanghai Ninth People's Hospital

2025 ASCO ANNUAL MEETING

GORTEC

NIVOPOSTOP (GORTEC 2018-01)

A phase III randomized trial of adjuvant nivolumab added to radio-chemotherapy in patients with resected head and neck squamous cell carcinoma at high risk of relapse

Jean Bourhis, Anne Aupérin, Christian Borel, Gautier Lefebvre, Severine Racadot, Lionnel Geoffrois, Xu Shan Sun, Esma Saada, Beatriz Cirauqui, Tomasz Rutkowski, Stephanie Henry, Anouchka Modesto, Alison Johnson, Benoit Calderon, Yoann Pointreau, Elisabeth Perez Ruiz, Joanna Kazmierska, Amanda Psyrri, Ricard Mesia, Yungan Tao

on behalf of GORTEC

PRESENTED BY: Prof Jean Bourhis

Nivolumab added to cisplatin and radiotherapy versus cisplatin and radiotherapy alone after surgery for people with squamous cell carcinoma of the head and neck at a high risk of relapse (GORTEC 2018-01 NIVOPOST-OP): a randomised, open-label, phase 3 trial

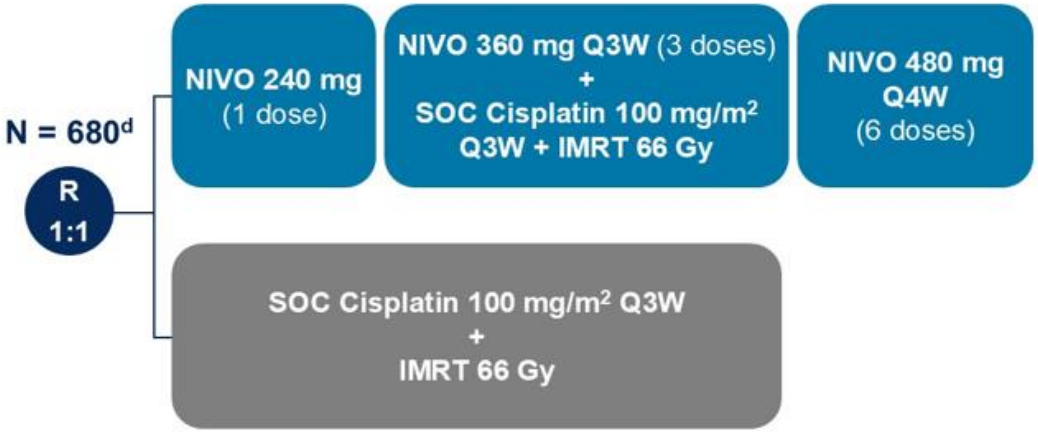
Jean Bourhis, Anne Aupérin*, Christian Borel, Gautier Lefebvre, Severine Racadot, Lionnel Geoffrois, Xu Shan Sun, Esma Saada, Beatriz Cirauqui, Tomasz Rutkowski, Stephanie Henry, Anouchka Modesto, Alison Johnson, Sophie Chapet, Benoit Calderon, Christian Sire, Olivier Malard, Matthieu Bainaud, Antonio Da Silva Motta, Sebastien Thureau, Yoann Pointreau, Pierre Blanchard, Guillaume Buiret, Laurence Bozec, Stephane Lopez, Julie Vanbockstael, Matthieu Bosset, Charlotte Greilsamer, Amaury Daste, Antoine Bruna, France N'Guyen, Maria Plana, Eluska Iruarrizaga, Stephane Temam, Caroline Even, Elisabeth Perez Ruiz, Mahasti Bert, Eleni Karamouza, Juliette Thariat, Joanna Kazmierska, Amanda Psyrri, Ricard Mesia†, Yungan Tao†*

NIVOPOSTOP study design

GORTEC

Key inclusion criteria:

- Adult patients <75 y/o
- ECOG PS 0-1
- SCC of the oral cavity, oropharynx, larynx, or hypopharynx with :
  - Complete macroscopic surgical resection
  - pStage III or IV[b] (AJCC 8th edition)
  - High-risk pathological features of relapse[c]



Obj primario: SLE

Obj secundarios: SG y Seguridad

[a]Minimization factors : p16 (OPC p16+ versus OPC p16- and non-OPC) and centers . [b]pStage II p16+ oropharynx if pT3/T4 and tobacco ≥20 packs/year; [c]extra capsular extension (ECE) of lymph node, microscopically positive tumor margins (R1 or close margin ≤ 1 mm), ≥ 4 cervical nodal involvements without ECE, multiple peri-neural invasions; [d]total number of randomized patients between October 2018 and July 2024.

N (%)	NIVO + CRT (n = 332[a])	CRT (n = 334[a])
Median age (IQR), y	59 (53–65)	59 (53–64)
Sex		
Male	250 (75)	257 (77)
Female	82 (25)	77 (23)
ECOG PS		
0	169 (51)	168 (50)
1	163 (49)	166 (50)
Smoking status		
Current	179 (54)	161 (48)
Former	108 (33)	109 (33)
Never	45 (14)	64 (19)
Median no. packs-years (IQR)	40 (25–50)	40 (25–45)
Tumor site and p16 status		
Oral cavity	192 (58)	193 (58)
Hypopharynx	43 (13)	40 (12)
Larynx	40 (12)	41 (12)
OPC p16-	41 (12)	43 (13)
OPC p16+	16 (5)	17 (5)

N (%)	NIVO + CRT (n = 332)	CRT (n = 334)
pStage		
I-II	12 (4)	11 (3)
III	44 (14)	46 (14)
IVA	128 (38)	117 (35)
IVB	148 (45)	160 (48)
High-risk pathological features[a]		
ECE or positive margins	190 (57)	196 (59)
ECE and positive margins	109 (33)	100 (30)
Multiple PNIs or ≥4 involved LNs	32 (10)	38 (11)
PD-L1 CPS		
<1	44 (13)	34 (10)
1-19	157 (47)	141 (42)
≥20	113 (34)	133 (40)
Not evaluable	18 (5)	26 (8)

Treatment exposure

GORTEC

	NIVO + CRT (n = 323)	CRT (n = 327)
Patients who received cisplatin, N	301	304
Cumulative dose ≥ 200 mg/m^2, n (%)	248 (82)	263 (87)
3 cycles, n (%)	186 (62)	207 (68)
Patients who received RT, N	303	306
Duration ≤ 55 days, n (%)	289 (95)	297 (97)
Dose 66 Gy, n (%)	275 (91)	291 (95)
Patients who received NIVO before/during RT, N	310	N/A
4 cycles, n (%)	232 (75)	
Patients who started NIVO maintenance, N	260	N/A
Median number of maintenance cycles (IQR)	6 (5–6)[a]	
Median total number of NIVO cycles (IQR)	10 (7–10)	N/A

[a]Among 258 patients who had stopped NIVO maintenance as of data cutoff., April 30, 2024.

Disease-free survival: (primary endpoint ; ITT)

GORTEC

Analysis based on **252 DFS events**
at the data cutoff of April 30th 2024

Median follow-up: 30.3 months (IQR 16-44.9)

3-years DFS

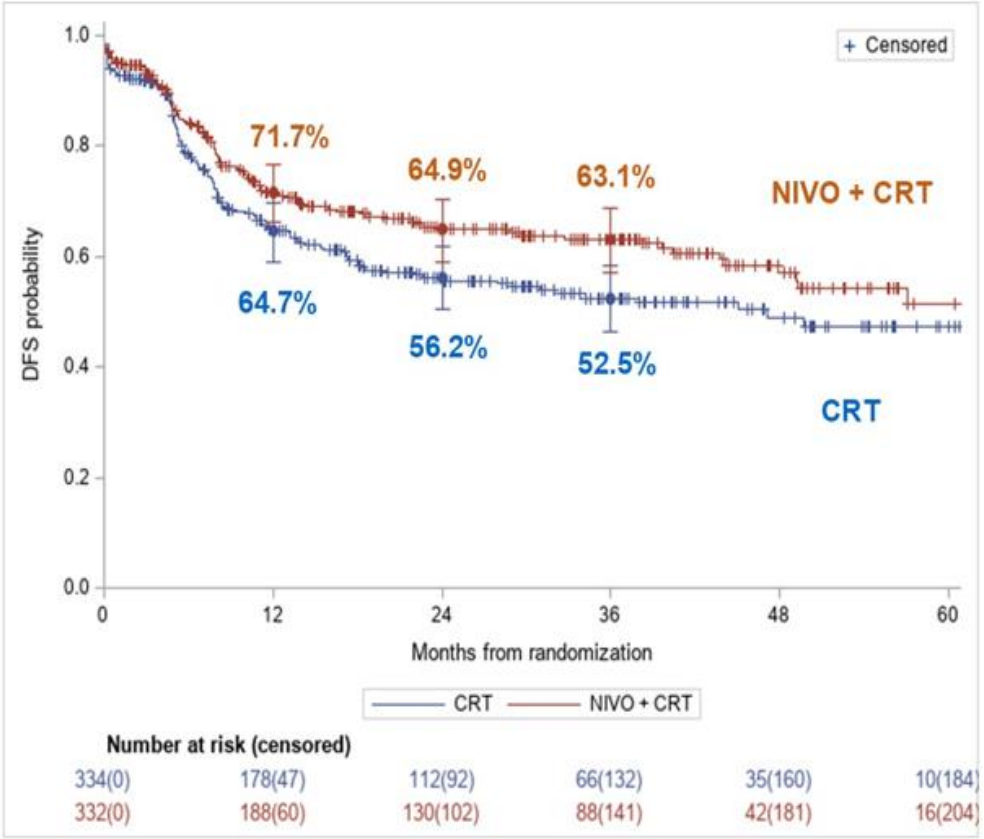
63.1% (95%CI 57.0%; 68.7%)
with NIVO + CRT

versus

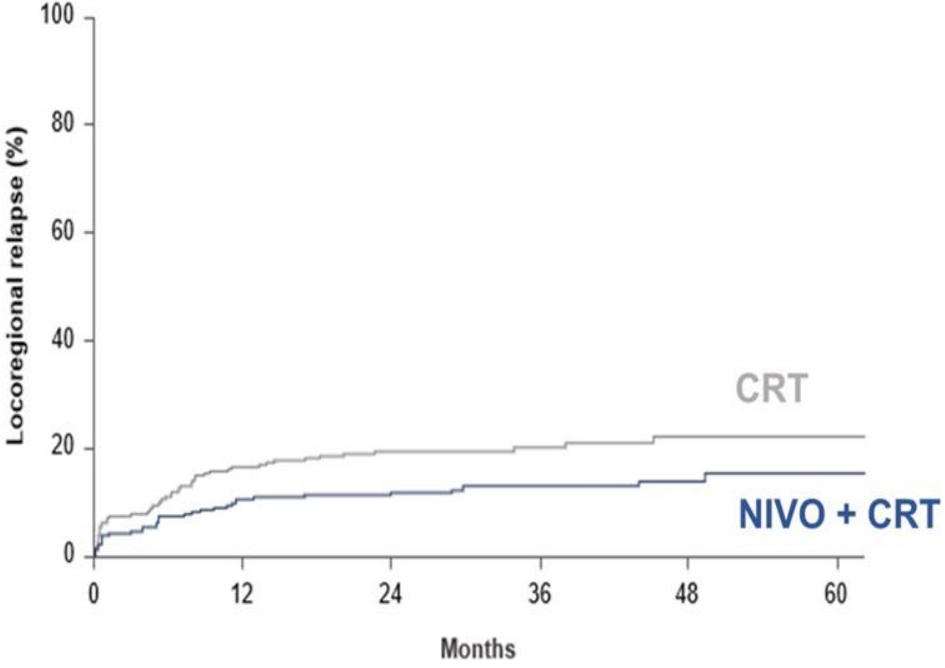
52.5% (95%CI 46.2%; 58.4%)
with CRT

Stratified* HR (95%CI) = 0.76 (0.60; 0.98)
Stratified log-rank p-value=0.034

*HR stratified for p16 status (OPC p16 positive *versus* OPC p16 negative and non-OPC) in Cox model



Cumulative incidence of loco-regional relapses alone



	NIVO + CRT (n = 332)	CRT (n = 334)
Number of events	39	61
Cumulative incidence, %		
1-year	11	16
2-year	12	19
3-year	13	20
Stratified sub-HR (95% CI)	**0.63 (0.42–0.94)**	

Sub-distribution HR stratified for p16 status (OPC p16 positive *versus* OPC p16 negative and non-OPC) in Fine-Gray model

DFS in subgroups : PDL-1/CPS

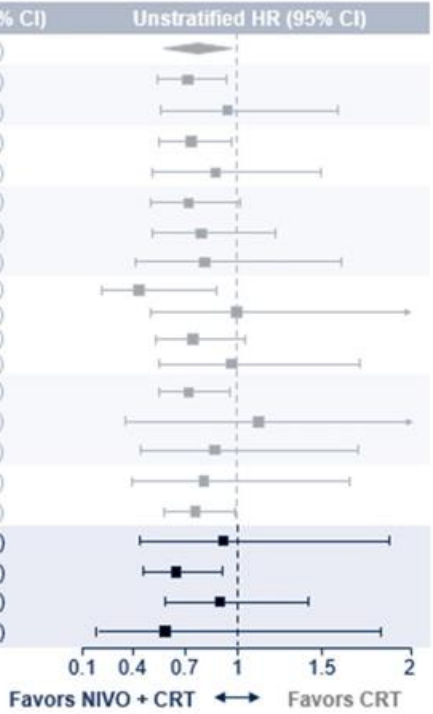
GORTEC

1) No selection based on CPS/PDL1

2) Benefit of nivolumab observed in all comers

3) CPS not strongly correlated with DFS

Subgroup		No. events/N	Unstratified HR (95% CI)
All patients		252/666	0.77 (0.60–0.98)
Age	< 65 years	195/515	0.71 (0.54–0.95)
	≥ 65 years	57/151	0.95 (0.56–1.59)
Sex	Male	196/507	0.74 (0.56–0.98)
	Female	56/159	0.88 (0.52–1.49)
Smoking status	Current smoker	131/340	0.72 (0.51–1.02)
	Former smoker	85/217	0.80 (0.52–1.22)
	Never smoker	36/109	0.82 (0.41–1.61)
Tumor site	Hypopharynx	37/83	0.44 (0.22–0.88)
	Larynx	32/81	1.00 (0.50–2.00)
	Oral cavity	135/385	0.75 (0.54–1.06)
	Oropharynx	48/117	0.97 (0.55–1.71)
p16 status	Non-OPC	204/549	0.73 (0.55–0.96)
	p16-positive OPC	12/33	1.13 (0.36–3.51)
	p16-negative OPC	36/84	0.87 (0.45–1.70)
pStage	I-III	31/113	0.81 (0.40–1.64)
	IV	221/553	0.76 (0.58–0.99)
PD-L1 CPS	**< 1**	**30/78**	**0.92 (0.45–1.88)**
	1-19	**126/298**	**0.65 (0.46–0.92)**
	≥ 20	**80/246**	**0.91 (0.58–1.41)**
	Unknown	**16/44**	**0.59 (0.19–1.83)**



Centrally assessed
PD-L1 IHC
28–8 pharmDx assay
(Labcorp)

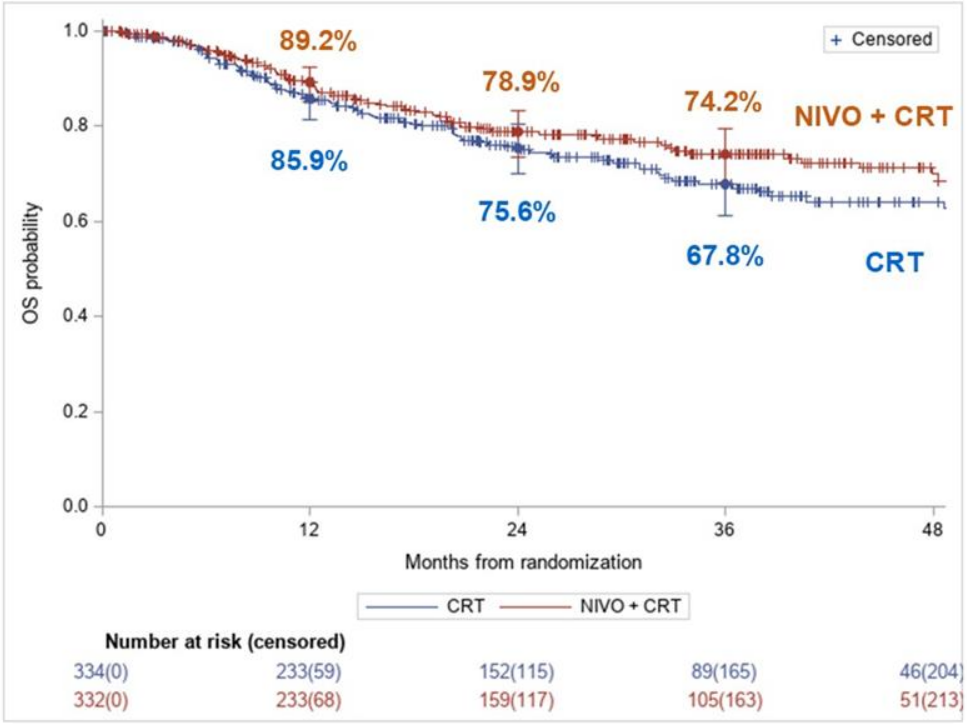
Overall survival (descriptive)

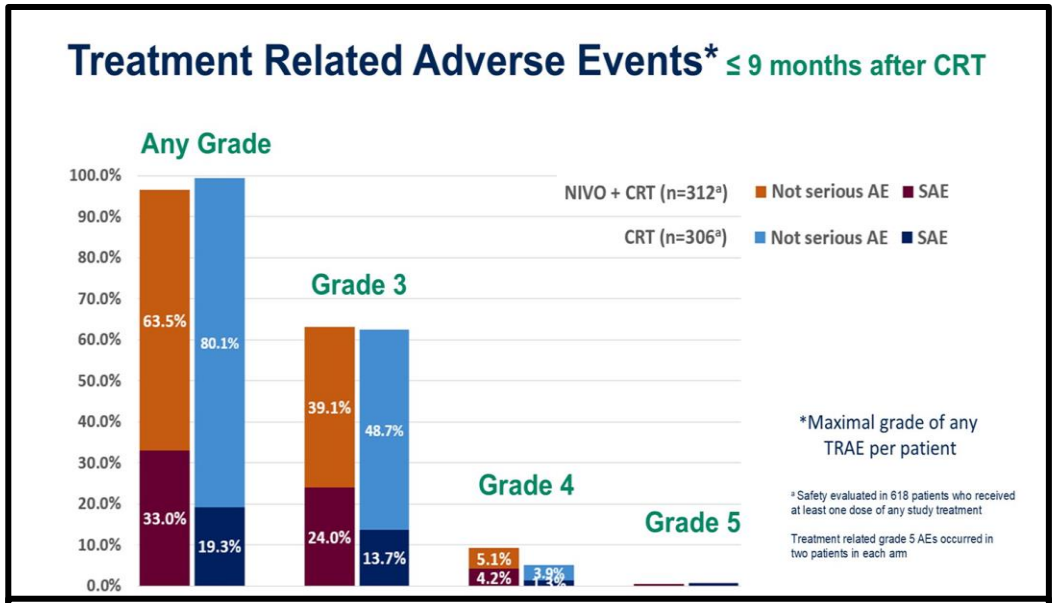
GORTEC

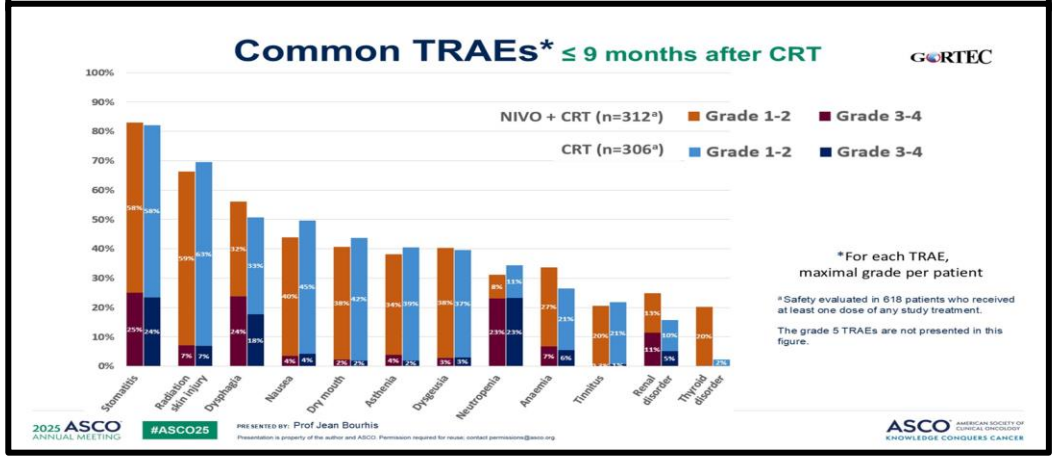
At the data cutoff, 158 patients died.

Results are in favor of NIVO + CRT but **OS could not be formally tested** since the pre-specified number of deaths was not reached.

The statistical analysis of OS requires more mature data according to the statistical plan.







Se observó un aumento en la tasa de eventos adversos grado 4 relacionados con el tratamiento con nivolumab, cisplatino y radioterapia en comparación con cisplatino y radioterapia (30 [10%] de 312 frente a 16 [5%] de 306).

Sin impacto clínico relevante sobre el tratamiento:

- Misma finalización de RT y cisplatino.
- Sin aumento de muertes relacionadas al tratamiento (0,6% vs. 0,7%).

Toxicidad inmunológica manejable:

- Principalmente alteraciones tiroideas.
- Sin incremento importante de neumonitis, hepatitis o colitis graves.

Mensajes clave

Es el primer estudio positivo que supera al **estándar histórico** de cisplatino + **radioterapia adyuvante** desde los ensayos **RTOG 9501** y **EORTC 22931**.

Probablemente **modifique las futuras guías internacionales** (NCCN, ESMO y ASCO), aunque aún se espera la **maduración** de los datos **de supervivencia global** y las **aprobaciones regulatorias**.

¡IMPORTANTE!

Este estudio representa un cambio de paradigma en el manejo **posoperatorio** del cáncer de cabeza y cuello.

2026 ASCO ANNUAL MEETING

Impact of lymph node dissection extent on disease-free survival with postoperative nivolumab plus concurrent chemoradiotherapy in head and neck squamous cell carcinoma: A post-hoc analysis of the NIVOPOSTOP trial

Ariane Lapierre, Anne Auperin, Juliette Thariat, Christian Borel, Gautier Lefebvre, Severine Racadot, Lionnel Geoffrois, Xu Shan Sun, Esma Saada, Joanna Kazmierska, Amanda Psyrri, Ricard Mesia, Samia Bouhir, Philippe Gorphe, Jean Bourhis, Yungan Tao

Results

- **Bilateral dissection** indicates higher disease burden

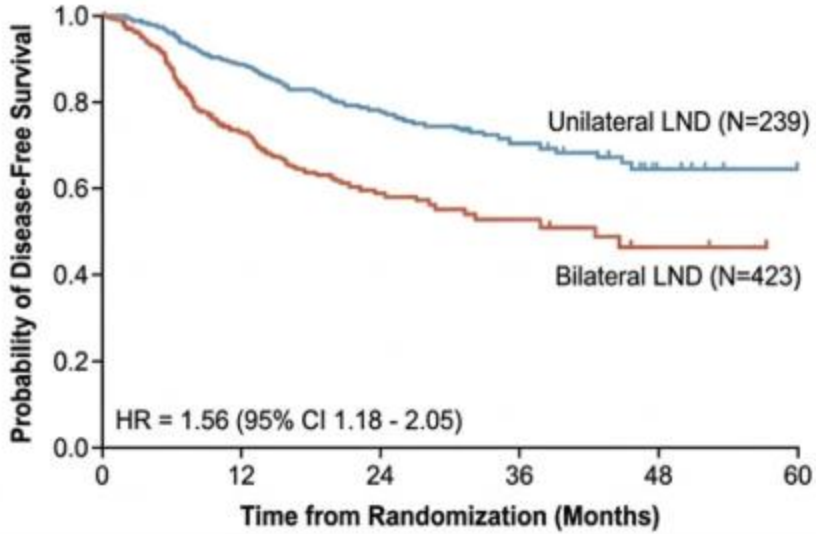
Unilateral LND (36%)

- **Median Nodes Removed:** 25 right / 24 left
- **Stage IV Disease:** 61%
- **Laryngeal / Hypopharyngeal Tumors:** 3% / 7%

Bilateral LND (64%)

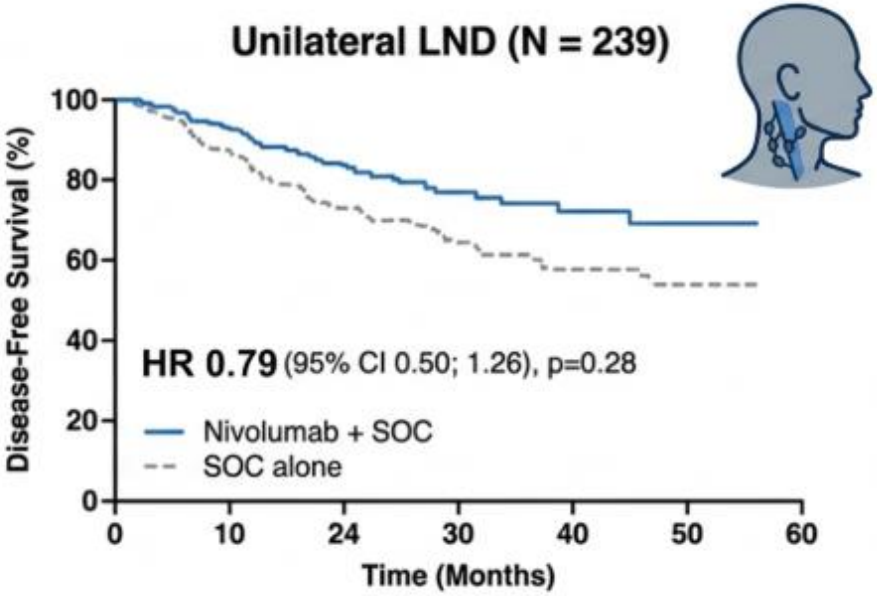
- **Median Nodes Removed:** 39 overall
- **Stage IV Disease:** 76% (Statistically higher, p=0.0002)
- **Laryngeal / Hypopharyngeal Tumors:** 17% / 16% (Statistically higher)

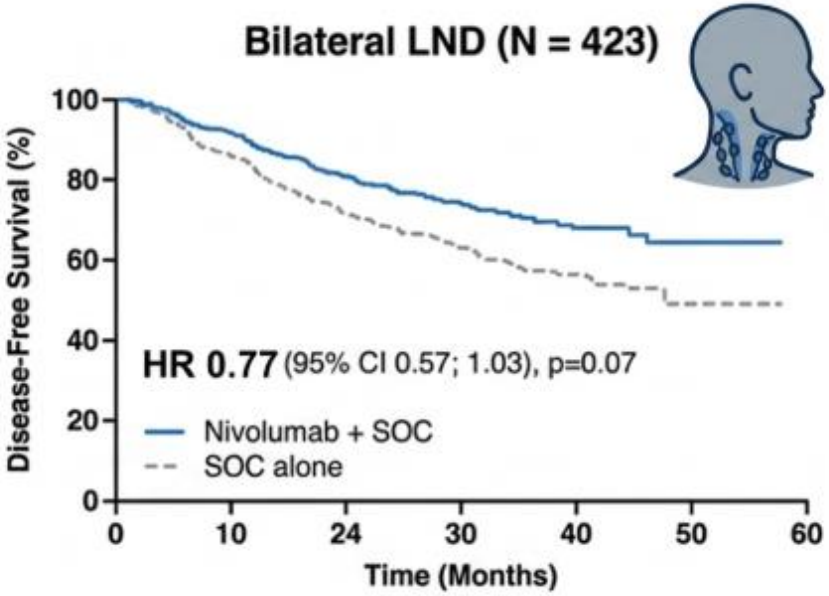
Disease-Free Survival by Surgical Laterality (All Arms)



Results

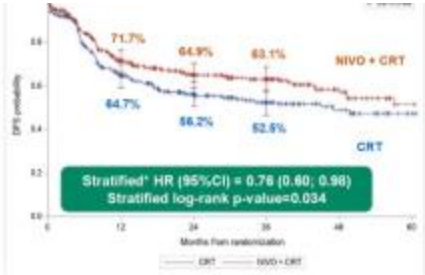
- Nivolumab efficacy is preserved **regardless** of dissection **laterality**





Results

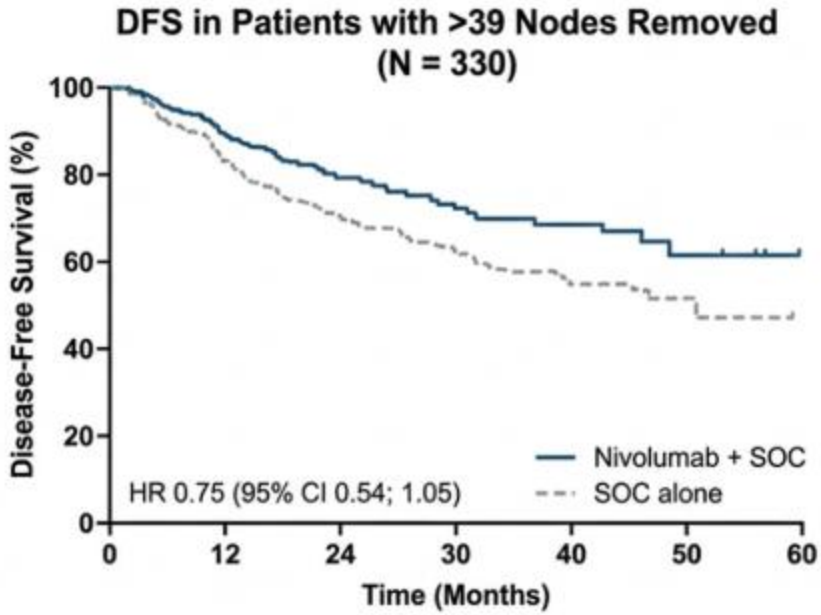
- **Extensive nodal dissection** does not hinder immunotherapy benefit



Total Cervical Nodes Removed: >39
(One or both sides, N = 330 patients)

DFS Benefit of Nivolumab + SOC vs SOC alone
HR 0.75
(95% CI 0.54; 1.05)

For patients with >18 nodes removed per side (N=233), the benefit also remained entirely intact:
HR 0.77



Conclusions

DFS benefit is preserved across surgical extents

The DFS benefit of adding adjuvant nivolumab is robust and identical regardless of whether the neck lymph node dissection was unilateral or bilateral

Extensive nodal clearance does not hinder immunotherapy

Removing a large number of lymph nodes (>39) does not abrogate the response to adjuvant nivolumab

Surgical standards must be maintained

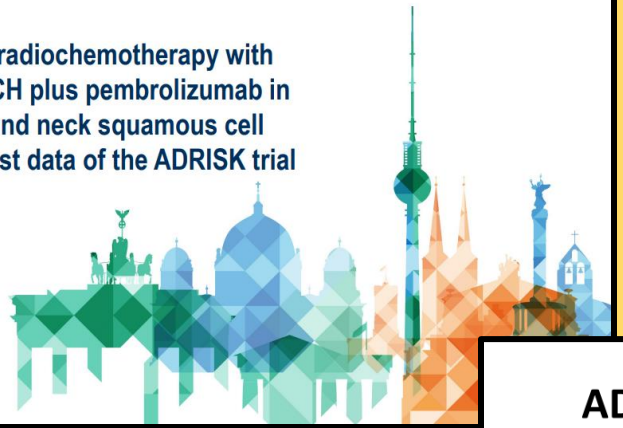
There is no evidence to support downgrading or reducing oncologic surgical resection when immunotherapy is planned as an adjuvant therapy in HNSCC

BERLIN 2025 ESMO congress

Postoperative adjuvant radiochemotherapy with cisplatin (aRCH) vs. aRCH plus pembrolizumab in locally advanced head and neck squamous cell carcinoma (HNSCC): First data of the ADRISK trial

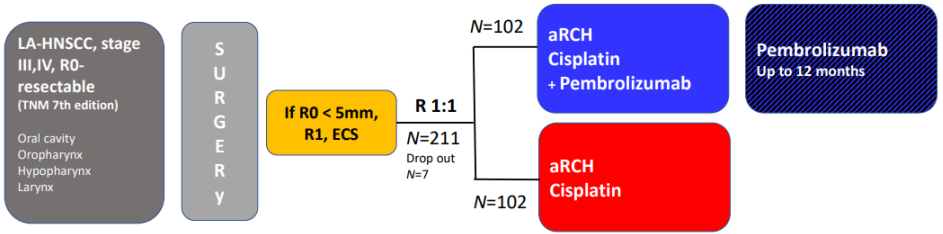
Andreas Dietz et al.

18th October 2025



ADRISK trial (EudraCT-No.: 2017-002546-74; NCT03480672)

first patient in: 06.08.2018; last patient in: 30.11.2023; last patient out: 30.01.2025



Stratification factors:
- Localization & p16
- Mode of Cisplatin: q1w/q3w regime

Primary endpoint:
- Event free survival (EFS)

Secondary Endpoints:
- Overall survival (OS)
- Safety

EFS is defined from R to first event:
- Loco-regional or distant recurrence (relapse),
- Occurrence of further malignant tumor (independent from localization and type),
- Death from any cause and
- Initiation of a new anti-cancer treatment without a previous endpoint (EP-) event (in case of safety concerns/toxicities observed)

Baseline Characteristics

FAS Population	Pembro + aRCH (N=102)	aRCH (N=102)
Median age (range), years	61.5 (36-84)	59.8 (33-80)
Male, n (%)	81 (79.4)	85 (83.3)
Current/former smoker, n (%)	80 (78.4)	78 (76.5)
Median drinks of alcohol (n=94/97)	1.0 (0-84)	2 (0-77)
Primary tumor site, n (%)		
Oral Cavity	24 (23.5)	19 (18.6)
Oropharynx	67 (65.7)	67 (65.7)
Larynx	7 (6.9)	10 (9.8)
Hypopharynx	4 (3.9)	6 (5.9)
Positive HPV status, n (%)	46 (68.7)	47 (70.1)
High risk	65 (63.7)	65 (63.7)
Intermediate risk	37 (36.3)	37 (36.3)
PD-L1 CPS >=10, n (%)	74 (72.5)	85 (83.3)
PD-L1 CPS >=1, n (%)	95 (93.1)	96 (94.1)

No relevant disbalances between arms were observed

Dietz A. et al.: ADRISK; ESMO 2025

ESMO FPN: 13200

Summary

- Pembrolizumab added to aRCH (SOC) after resection of high or intermediate risk LA-HNSCC was feasible and safe.
- Pembrolizumab added to aRCH (SOC) after resection of high or intermediate risk LA-HNSCC ***did not improve EFS and OS***.
- No new safety signals observed in the Pembrolizumab + aRCH arm
- Immune-mediated AEs were less than expected with Pembrolizumab + aRCH

- In resected intermediate and high risk p16+ LA-OPSCC, current aRCH is efficient with no unmet clinical need for further escalation.
- There is no evidence for substantial improvements by Pembrolizumab + aRCH after surgery without preoperative neoadjuvant treatment.

Dietz A. et al.: ADRISK; ESMO 2025

ESMO FPN: 13200

EVIDENCIA ACTUAL EN INMUNOTERAPIA EN CÁNCER DE CABEZA Y CUELLO RESECABLE

KEYNOTE-689 demostró que la incorporación de **pembrolizumab** perioperatorio mejora significativamente la supervivencia libre de eventos (EFS), estableciendo un nuevo paradigma en el tratamiento multimodal del paciente resecable.

NIVOPOSTOP confirmó que la intensificación del tratamiento adyuvante con **nivolumab asociado a quimio radioterapia** reduce el riesgo de recaída en pacientes con factores patológicos de alto riesgo, consolidando el papel de la inmunoterapia con intención curativa.

Persisten interrogantes relevantes sobre:

- EL IMPACTO EN LA SUPERVIVENCIA GLOBAL.
- LA IDENTIFICACIÓN DE BIOMARCADORES PREDICTIVOS.
- LA DESINTENSIFICACIÓN DEL TRATAMIENTO.
- Y LA MEJOR SECUENCIA TERAPÉUTICA.

GRACIAS