

XVII SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

Inmunoterapia en el carcinoma escamoso de cabeza y cuello localmente avanzado. **La vuelta a los tratamientos de inducción**

Dr. Santiago Cabezas, Hospital Universitario Clínico San Carlos, Madrid

CONFLICTOS DE INTERÉS

- **Conferencias:** BMS, Merck KGaA, MSD, J&J IM, Novocure
- **Asesoramiento experto:** BMS, Merck KGaA
- **Asistencia a congresos:** Merck KGaA, BMS, MSD, J&J IM
- **Apoyo a la investigación (institucional):** Merck KGaA, Sysmex Inostics, Inc., ThermoFisher

Scientific

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RACIONAL PARA LA IO EN LA ENFERMEDAD LOCALIZADA

IO + RT radical

Pacientes FIT & UNFIT: MK3475-412, JAVELIN H&N100, REACH, PembroRad

IO adyuvante

IMVOKE-010, JADE, eVOLVE, ADJORL, NIVO POST-OP

IO neoadyuvante

Racional

IO neoadyuvante & KN-689

IO + QT neoadyuvante

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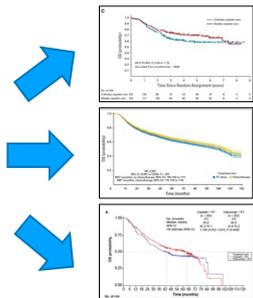
IO neoadyuvante & KN-689

IO + QT neoadyuvante

RACIONAL PARA LA IO EN LA ENFERMEDAD LOCALIZADA

Alta tasa de recaída y baja supervivencia

	RFS	5y-OS
Enfermedad RESECADA CON FR	54-75%	50-70%
Enfermedad LA RESECADA SIN FR	70-80%	70-75%
Enfermedad LA NO RESECADA	45%	40-70%



Melanoma



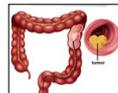
cSCC



Mama TN



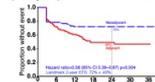
CNCP



CCR dMMR

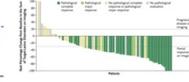
Neoadjuvant versus adjuvant pembrolizumab for resectable stage II-IV melanoma (SWOG S1801)

S1801 primary endpoint: Event-free survival



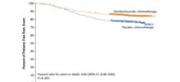
Pant. Annals of Oncology (2022) 33 (suppl_7): S808-S809

ORIGINAL ARTICLE
Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma



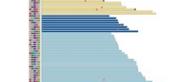
Gross. N Engl J Med 2022;387:1557-68.

ORIGINAL ARTICLE
Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer



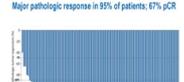
Schmid. N Engl J Med 2022;386:556-67

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (IMPOWER13): an open-label, multicentre, single-arm, phase 2 trial



Pronetto. Lancet Oncol 2020; 21(11):1413-1422.

Neoadjuvant immune checkpoint inhibition in locally advanced dMMR-deficient colon cancer: the NICHE-2 study

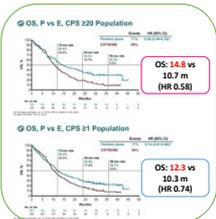


Chalabi. ESMO Congress 2022

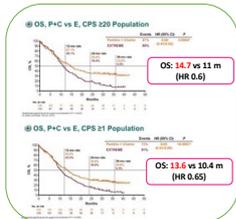
Impacto de la inmunoterapia en la enfermedad R/M

1ª LÍNEA: KN-048: PEMBRO +/- PLATINUM-5FU vs EXTREME

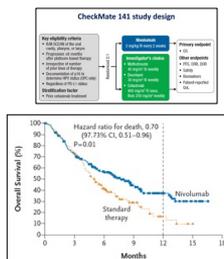
1ª LÍNEA: PEMBRO vs EXTREME



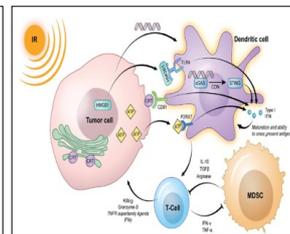
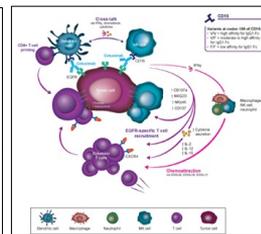
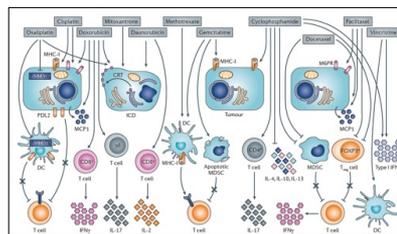
1ª LÍNEA: PEMBRO + PF vs EXTREME



2ª LÍNEA: CM-141: NIVO vs SOC



Efectos inmunológicos del tratamiento sistémico y de la radioterapia



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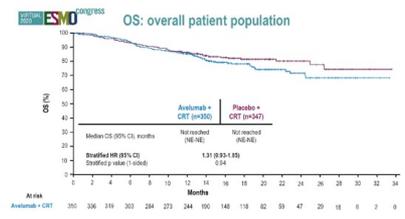
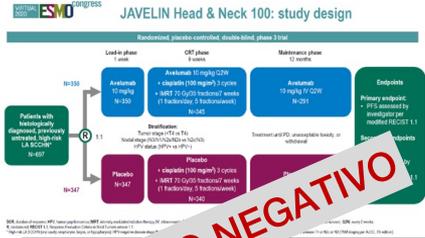
Racional

IO neoadyuvante & KN-689

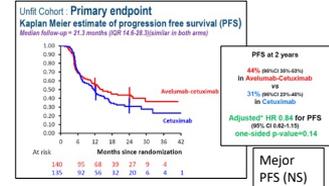
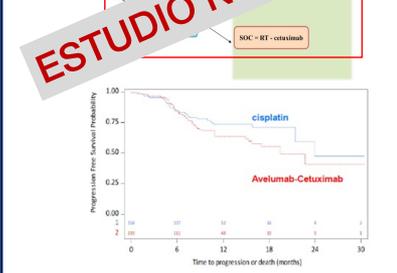
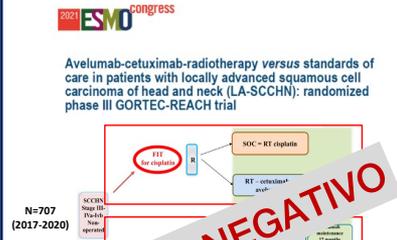
IO + QT neoadyuvante

IO + RT CONCOMITANTE

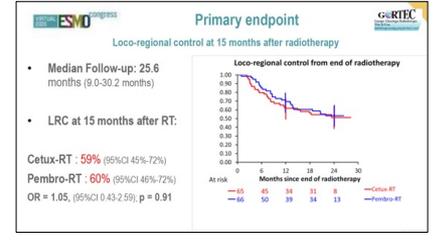
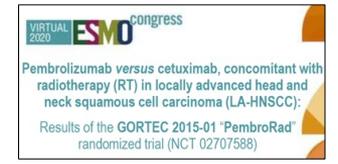
JAVELIN H&N 100



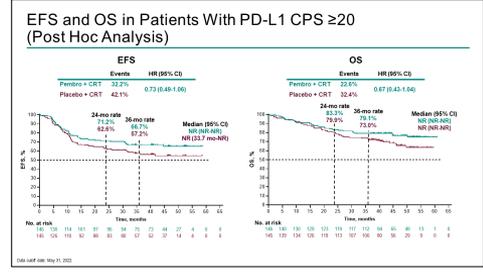
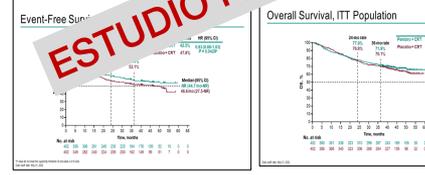
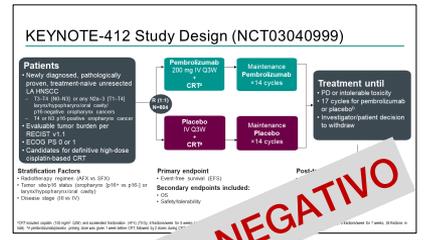
REACH



PEMBRORAD



KEYNOTE-412



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IO neoadyuvante

Racional

IO neoadyuvante & KN-689

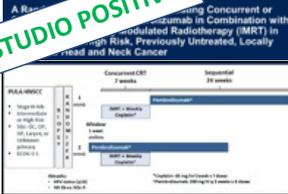
IO + QT neoadyuvante

IO ADYUVANTE

UPCI 15-132

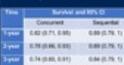
2022 ASCO ANNUAL MEETING

ESTUDIO POSITIVO



HN5CC: 15-132

Progression Free Survival



PFS

HN5CC: 15-132

Overall Survival



OS

N=80 Pembro *concomitante* vs *secuencial* en HPV- y HPV+ riesgo-intermedio (> 10 paq-año, T4 ó N3):

Pembro + RT + wkCDDP (40 mg/m²)

vs RT + wkCDDP (40 mg/m²) → Pembro *adyuvante*

• Mejor 1-y & 2-y PFS con *pembro secuencial*

Clump, DA, et al. ASCO 2022. Abstract 6007

A randomized, double-blind placebo-controlled **phase II** study of **adjuvant pembrolizumab versus placebo** in patients with head and neck squamous cell cancers at **high risk** for recurrence: the **PATHWay Study**

Alexander T. Pearson¹

Inclusion Classes

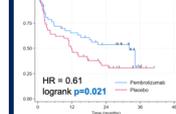
- A. High risk nodal disease or intermediate risk disease requiring treatment (n=10)
- B. Salvage surgery including resection of recurrent disease (n=37)
- C. Indeterminate disease requiring treatment for metastasis (n=0)
- D. Oligometastatic disease requiring treatment for metastasis (n=10)
- E. Multiple recurrences or relapse after surgery (n=4)
- F. Multiple recurrences or multiple treated primaries who have undergone surgery (n=37)

Results

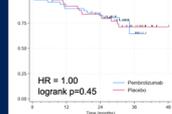
PFS and OS for Full Study Population

- Statistically significant difference in PFS (one-sided logrank p=0.021) with a Cox HR of 0.61 (80% CI: 0.43-88).
- OS curves were very similar (one-sided logrank p=0.45) with Cox HR=1.00 (80% CI: 0.60-1.68).
- Median PFS post-cross over = 12 months (n=19).

Total Population: PFS (N=100)



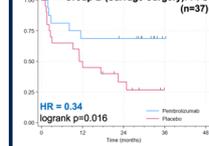
Total Population: OS (N=100)



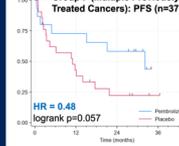
Primary PFS Endpoints Also Evaluated in 2 Large Sub-Cohorts

• Post-hoc analysis

Group B (Salvage Surgery): PFS (n=37)



Group F (Multiple Previously Treated Cancers): PFS (n=37)

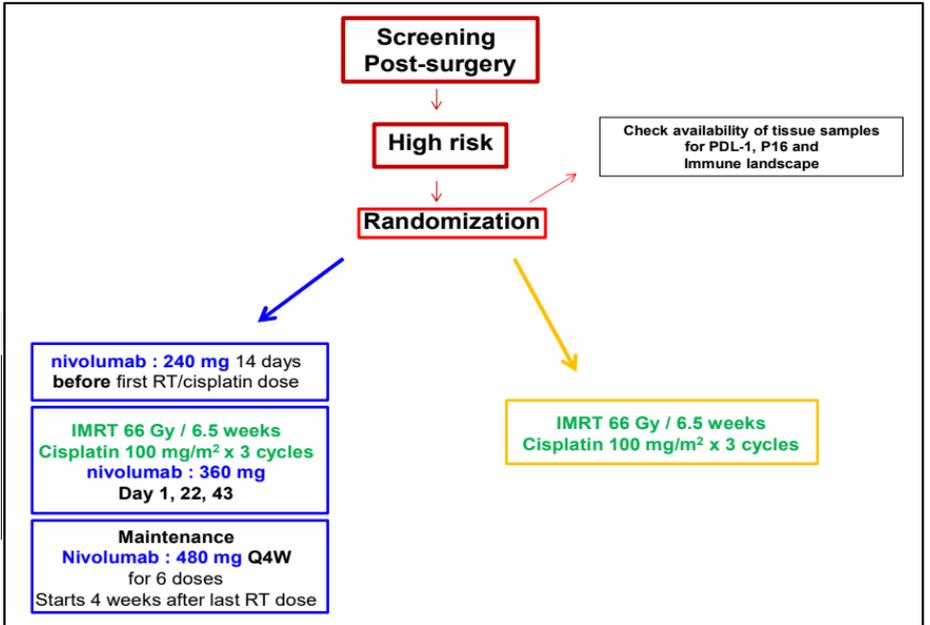


Pearson, et al. Presented at ASCO 2024

NIVO POST-OP

Post-Operative Nivolumab Significantly Improves DFS in Head and Neck Cancer

January 10, 2025



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IMVOKE-010, JADE, eVOLVE, ADJORL, NIVO POST-OP

IO neoadyuvante

Racional

IO neoadyuvante & KN-689

IO + QT neoadyuvante

Racional Clínico: Lecciones aprendidas de otras entidades

Current Perspective

Neoadjuvant immunotherapy is reshaping cancer management across multiple tumour types: The future is now!



Maio. Eur J Cancer 2021;152:155-164.



Journal for
ImmunoTherapy of Cancer

Neoadjuvant immunotherapy of locoregionally advanced solid tumors

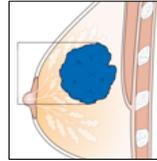
Tarhini, et al. JTC 2022 Aug;10(8):e005036.



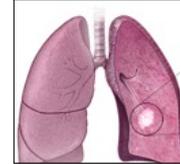
Melanoma



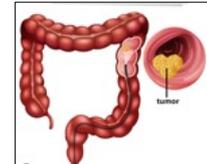
cSCC



Mama TN



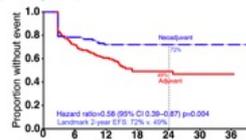
CPNCP



CCR dMMR

Neoadjuvant versus adjuvant pembrolizumab for resectable stage III-IV melanoma (SWOG S1801)

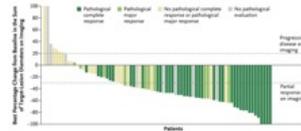
S1801 primary endpoint: Event-free survival



Patel. Annals of Oncology (2022) 33 (suppl_7): S808-S869

ORIGINAL ARTICLE

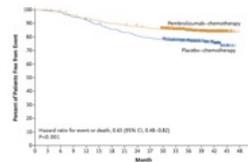
Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma



Gross. N Engl J Med 2022;387:1557-68.

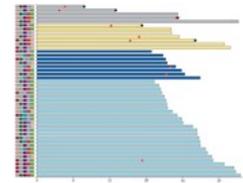
ORIGINAL ARTICLE

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer



Schmid. N Engl J Med 2022;386:556-67

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial



Provencio. Lancet Oncol 2020; 21(11):1413-1422.

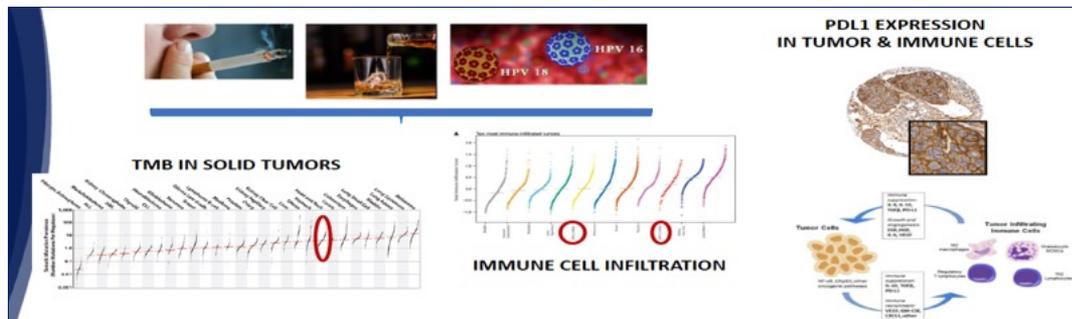
Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: the NICHE-2 study

Major pathologic response in 95% of patients; 67% pCR



Chalabi. ESMO Congress 2022

Racional: Pros y Contras para el desarrollo de la IO neoadyuvante en el CECC



Ventajas

Mayor antigenicidad

Mejor estatus inmunitario

Adelantar control sistémico

Respuesta patológica como endpoint subrogado

Ventana de oportunidad para estudios traslacionales

Oportunidad para estudios de combinación

Limitaciones

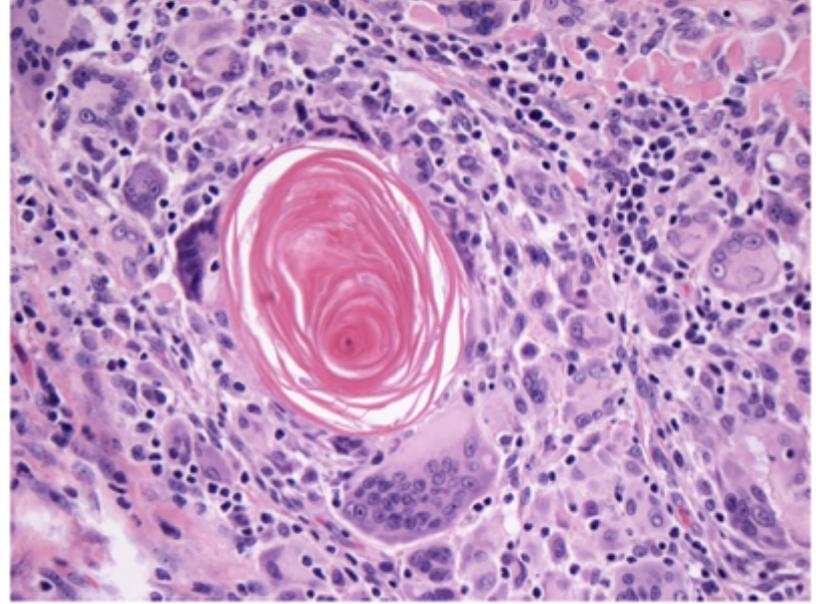
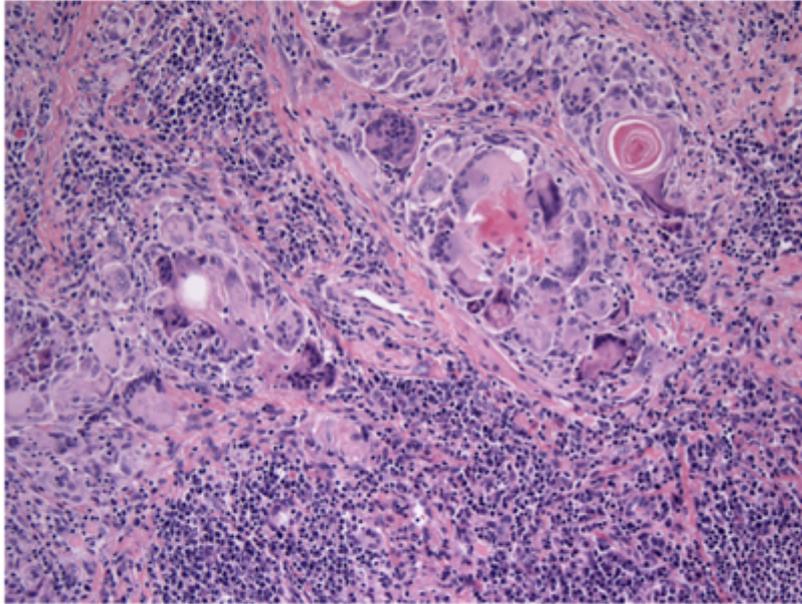
Baja ORR con anti-PD1 en monoterapia en SCCHN

Falta de buenos biomarcadores para selección de pacientes

Falta herramientas estandarizadas para evaluar respuesta (pTR, RECIST, Irecist..)

Riesgo de retraso de terapia definitiva (Cirugía, RT)

Significant Pathologic Response : “Regressed” tumor, inflammation, giant cell reaction, acellular keratin



Courtesy of Vickie Jo, Head and Neck Pathology Service

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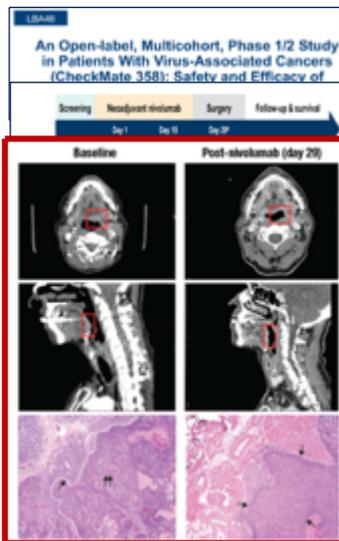
Racional

IO neoadyuvante & KN-689

IO + QT neoadyuvante

IO neoadyuvante en CECC: neoadyuvancia exclusiva

NIVO X 2 (N=29)

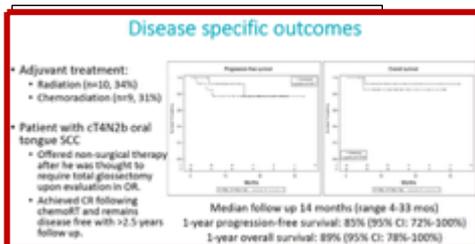


N=29
Safety: No surgical delays / G3/4 AEs: 13.8%
Efficacy:

- RR: 48% (50% HPV+, 46% HPV-)
- RR >40%: 3 pts
- RR 75%: 1 pt (HPV+)

Ferris RL, et al. ESMO Congress 2017
Ferris RL, et al. JTO 2021;9:E02568

NIVO X 2 +/- IPI (N=30)



N=30
Safety:

- No surgical delays.
- G3/4 TRAEs: Nivo (2/15), Nivo-Ipi (4/15)

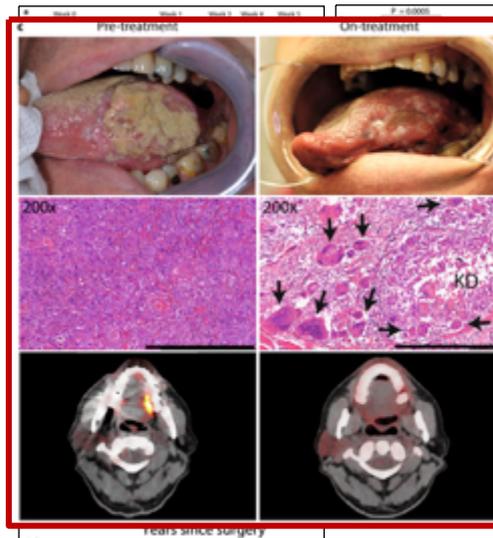
Efficacy:

- ORR: 13-38%
- VOL RR: 50-53%
- pTR (>50%): 15-33%
- pTR (>90%): 8-20%
- 1y-PFS: 85%
- 1y-OS: 89%

Presented By Jonathan Schoenfeld at 2020 Head & Neck Cancer Symposium, Scottsdale, AZ

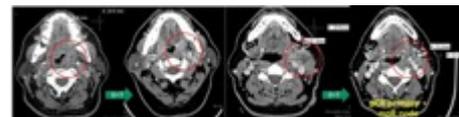
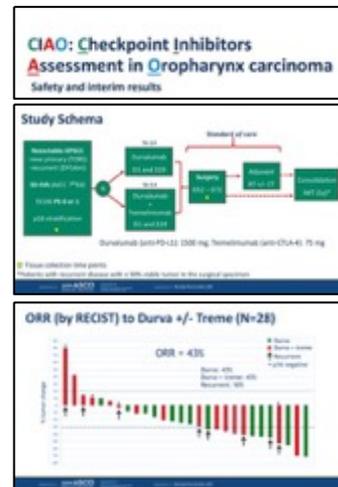
NIVO X 2 +/- IPI (N=29)

Neoadjuvant immunotherapy with nivolumab and ipilimumab induces major pathological responses in patients with head and neck squamous cell carcinoma



Vos JL, et al. Nature Comms 2021;12:7348

DURVA X 2 +/- TREME (N=28)



N=29 (86% HPV+)
Safety: No surgical delays / G3/4 AEs: 13.7%
Efficacy:

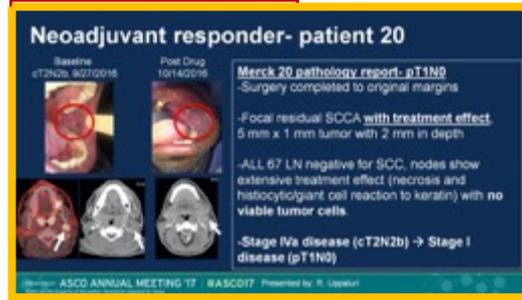
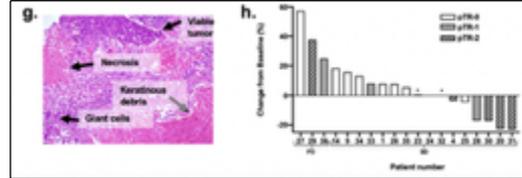
- ORR: 43% (D: 43%, D+T: 43%)
- mpRR: 32% (IO → SX)
- ALL Alive & NED (11m FU)

Presented By Renata Ferrarotto at 2019 ASCO Annual Meeting

IO neoadyuvante en CECC: *IO perioperatoria*

Pembro x1 → Cx → PORT + Pembro x 6

N=36



Pembro x2 → Cx → PORT + Pembro x 6

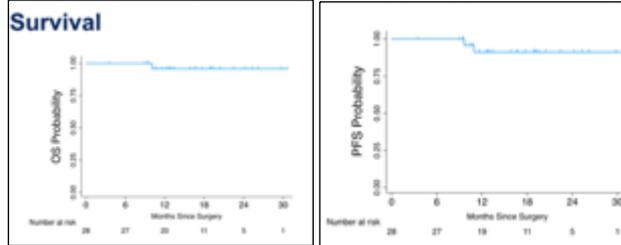
N=29

Neoadjuvant/ adjuvant checkpoint immunotherapy in surgically resectable HNSCC



Schema for Cohort 2

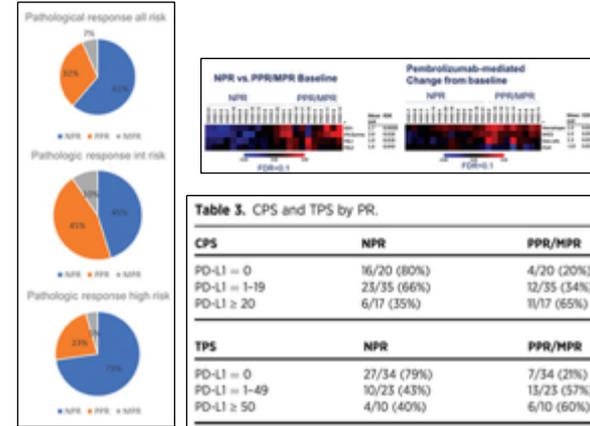
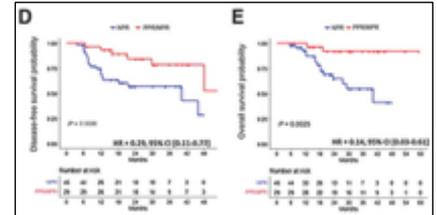
Characteristic	Cohort 2 (N=26)	Cohort 1 (N=36)	p-value	OR (95% CI)
pTR Category				
pTR=0	14 (53.8%)	26 (72.2%)	0.01	4.1 (1.0-16.5)
pTR=1	7 (26.9%)	8 (22.2%)		16.1 (1.0-263.5)
pTR=2	5 (19.2%)	2 (5.6%)		26.1 (1.1-74.0)
Overall survival (months)	20 (76.9%)	26 (72.2%)		32.1 (23.0-45.0)
High-risk	5 (19.2%)	16 (44.4%)	0.004	
Neoadjuvant pembrolizumab	20 (76.9%)	16 (44.4%)	0.004	12.1 (3.0-47.0)
Adjuvant pembrolizumab	16 (61.5%)	27 (75.0%)	0.001	20.0 (6.0-65.0)



Pembro x1 → Cx → PORT + Pembro x 6

N=92

Phase II Clinical Trial of Neoadjuvant and Adjuvant Pembrolizumab in Resectable Local-Regionally Advanced Head and Neck Squamous Cell Carcinoma



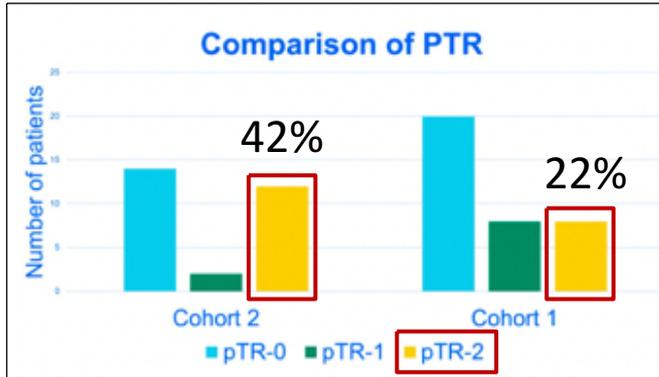
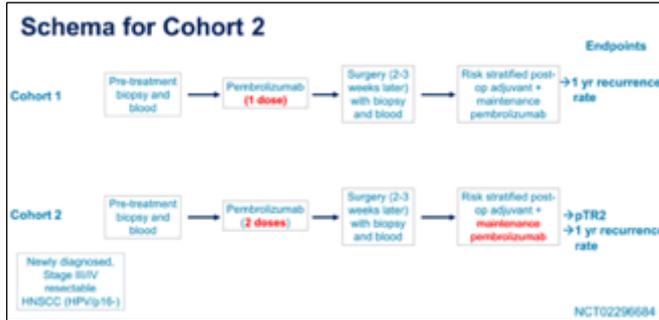
IO neoadyuvante en CECC: Otras lecciones e hipótesis

¿A mayor tiempo de tto. mayor respuesta?

¿Respuesta discordante 1º vs Cuello?

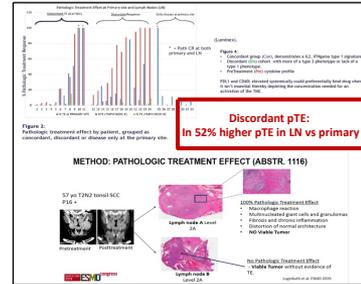
¿Potencial en el escenario Recurrente-Resecable?

Neoadjuvant/ adjuvant checkpoint immunotherapy in surgically resectable HNSCC

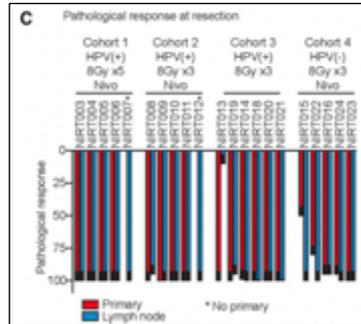


Uppaluri R, et al. ASCO 2021
Cabezas-Camareró S, et al. Crit Rev Oncol Hematol 2022; 169:103559

A WINDOW OF OPPORTUNITY TRIAL OF PREOPERATIVE NIVOLUMAB WITH OR WITHOUT TAGALAFIL IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN): SAFETY, CLINICAL, AND CORRELATIVE OUTCOMES



N=21 (N=16 HPV+ / N=5 HPV-)
Nivo + SBRT (tumor 1º) → Nivo x 2 → CIRUGÍA (wk6) → Nivo x 2-3 dosis



Nivolumab + Tadalafilo

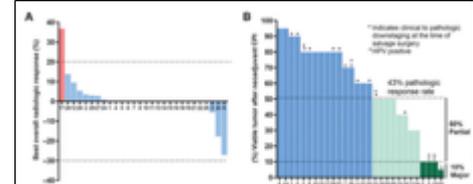
Discordancia pTE (1º-Cuello):
52% (> pTE en cuello)

SBRT sobre 1º + Nivolumab:

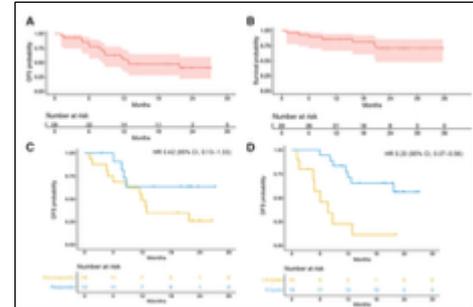
Concordancia pTE (1º-Cuello):
84%

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Neoadjuvant and Adjuvant Nivolumab and Lirilumab in Patients with Recurrent, Resectable Squamous Cell Carcinoma of the Head and Neck



pTR1:
43%



Hanna, et al. Clin Cancer Res 2022;28:468-78

Luginbuhl AJ, et al. Annals of Oncology (2019) 30 (suppl_5): v449-v474.
10.1093/annonc/mdz252
Leidner. JTC 2021;9:e002485

IO neoadyuvante en Enfermedad LA Resecable: **EC KEYNOTE-689**



Neoadjuvant and Adjuvant Pembrolizumab Plus Standard of Care in Resectable Locally Advanced Head and Neck Squamous Cell Carcinoma: Phase 3 KEYNOTE-689 Study

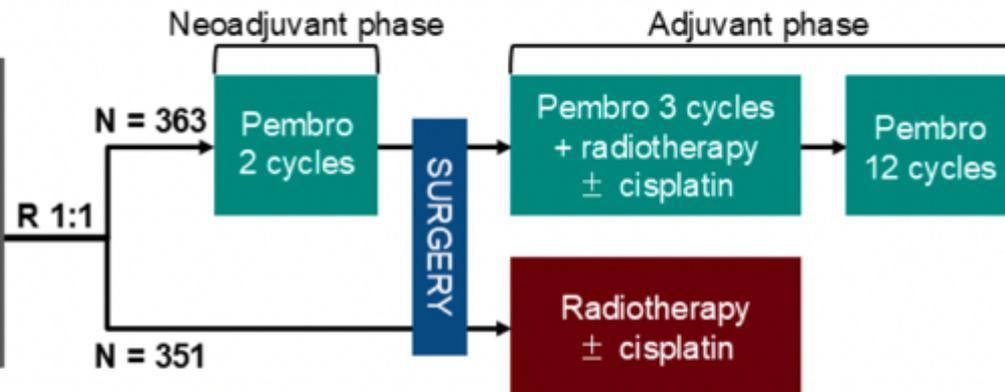
Ravindra Uppaluri MD/PhD, Robert I. Haddad MD, Yungan Tao MD/PhD, Christophe Le Toumeau MD, Nancy Y. Lee MD/FASTRO, William Westra MD, Rebecca Chernock MD, Makoto Tahara MD/PhD, Kevin Harrington MBBS/PhD, Arkadiy L. Klochikhin MD, Irene Braña MD/PhD, Gustavo V. Alves MD, Brett G. M. Hughes MD, Marc Oliva MD/PhD, Iane P. F. Lima MD, Tsutomu Ueda MD/PhD, Tomasz Rutkowski MD/PhD, Ursula Schroeder MD, Paul-Stefan Mauz MD, Thorsten Fuereder MD, Simon Laban MD, Nobuhiko Oridate MD/PhD, Aron Popovtzer MD, Nicolas Mach MD, Yevhen Korobko MD/PhD, Diogo Alpuim Costa MD/MSc, Anupama Hooda-Nehra MD, Cristina P. Rodriguez MD, R. Bryan Bell MD, Cole Manschot PhD, Kimberly Benjamin MD/MSc, Burak Gumuscu MD/PhD, Douglas Adkins MD

KEYNOTE-689 Study

NCT03765918

Key Eligibility Criteria

- Adults with resectable LA HNSCC
 - Larynx/hypopharynx/oral cavity stage III/IVA
 - Oropharyngeal stage III/IVA p16-
 - Oropharyngeal stage III T4 N0-2 p16+
- ECOG PS 0 or 1
- Tumor tissue for PD-L1 testing^a



Stratification factors

- Primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx)
- Tumor stage (III vs IVA)
- PD-L1 TPS^a (≥50% vs <50%)

Primary endpoint: EFS per RECIST 1.1 by BICR

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

Other secondary endpoints include: Safety

BICR, blinded independent central review; BIPR, blinded independent pathologist review; EFS, event-free survival; OS, overall survival.

^aAssessed by PD-L1 IHC 22C3 pharmDx; TPS=% tumor cells with membranous PD-L1 staining; CPS=number of PD-L1-staining cells + total # viable tumor cells × 100.

Statistical Considerations

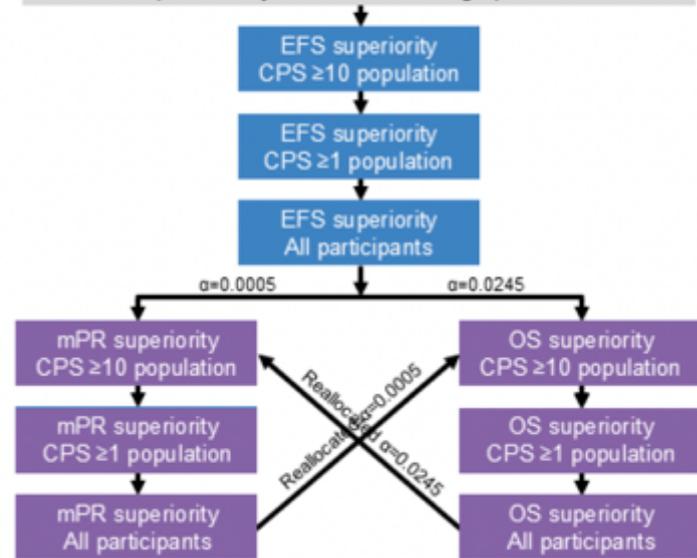
Sequential testing strategy

- EFS by stratified log-rank test at $\alpha=0.025$ (1-sided)
- mPR by stratified Miettinen and Numminen method at $\alpha=0.0005$ (1-sided)
- OS by stratified log-rank test at $\alpha=0.0245$ (1-sided)

Analysis populations

- Efficacy was assessed in all randomized participants (ITT population)
- Safety was assessed in all participants with ≥ 1 dose of study treatment, including surgery only (as-treated population)

Type I error rate strongly controlled at $\alpha=2.5\%$ (1-sided) across all comparisons by Maurer and Bretz graphical method



1^o
EFS

2^o
mPR
& OS

First Interim Analysis (IA1)

- Planned after ~207 EFS events in CPS ≥ 10 population and ~9 months after last participant randomized
- Final analysis for mPR; interim analysis for EFS and OS
- Data cutoff date: 25 July 2024
- Median (range) follow-up^a: 38.3 months (9.0–66.5)

Baseline Characteristics

Characteristic	Pembro + SOC (N = 363)	SOC (N = 351)
Median age (range), years	60.0 (29-82)	61.0 (22-87)
Male, n (%)	286 (78.8)	277 (78.9)
Current/former smoker, n (%) ^a	293 (80.7)	267 (76.1)
Alcohol use—yes, n (%) ^a	250 (68.9)	238 (67.8)
Primary tumor site, n (%)		
Oral cavity	219 (60.3)	213 (60.7)
Larynx	81 (22.3)	73 (20.8)
Hypopharynx	28 (7.7)	26 (7.4)
Oropharynx	35 (9.6)	38 (10.8)
Missing	0	1 (0.3)
Positive HPV status, n (%) ^b	12 (3.3)	15 (4.3)
PD-L1 CPS ≥10, n (%)	234 (64.5)	231 (65.8)
PD-L1 CPS ≥1, n (%)	347 (95.6)	335 (95.4)

CECO: 60%

CPS ≥ 10: 65%
CPS 1-9: 30%
CPS < 1: 5%

^a6 pts in the pembro + SOC group and 3 pts in the SOC group had unknown smoking and alcohol use status. ^bHPV (human papillomavirus) status was determined by local testing for pts with oropharyngeal cancer per p16 IHC. 1 pt in the SOC group had unknown HPV status.

Treatment Disposition

ITT Population

		Pembro + SOC	SOC
Study start	Participants randomized (Dec 2018-Oct 2023), N	363	351
Neoadjuvant therapy	Received ≥1 dose of neoadjuvant pembrolizumab, n (%)	360 (99.2)	2 ^a (0.6)
	Completed 2 cycles of pembrolizumab, n (%)	341 (93.9)	1 (0.3)
	Permanently discontinued all study therapy at this phase, n (%)	30 (8.3)	0
In-study surgery	Underwent surgery, n (%)	322 (88.7)	308 (87.7)
	Completed surgery	321 (88.4)	308 (87.7)
	Tumor found to be surgically unresectable	1 (0.3)	0
	Permanently discontinued all study therapy at this phase, n (%)	55 (15.2)	41 (11.7)
	Postoperative risk assessment by BIPR, n (%)		
	High-risk features present	118 (32.5)	156 (44.4)
Low risk (no high-risk features present)	196 (54.0)	148 (42.2)	
	Missing	49 (13.5)	47 (13.4)
Adjuvant therapy	Received ≥1 dose of adjuvant therapy after surgery, n (%)	267 (73.6) ^b	267 (76.1) ^b
	Started radiotherapy	266 (73.3)	267 (76.1)
	Started pembrolizumab	248 (68.3)	0
	Started cisplatin	100 (27.5)	132 (37.6)
	Permanently discontinued all study therapy at this phase, n (%)	109 (30.0)	14 (4.0)
All study treatment	Completed all study treatment, n (%)	155 (42.7)	261 (74.4)
	Treatment ongoing, n (%)	11 (3.0)	0

^a2 pts in the SOC group received neoadjuvant pembro in error (protocol deviations). ^b8 additional pts in each group received definitive therapy without surgery.

Data cutoff date

Cirugía:
88%

A-P alto riesgo:
↓ 27%

Inicio de la RT:
75%

Completó Todo el tratamiento en brazo de Pembro:
42.7%

Treatment Exposure

As-Treated Population

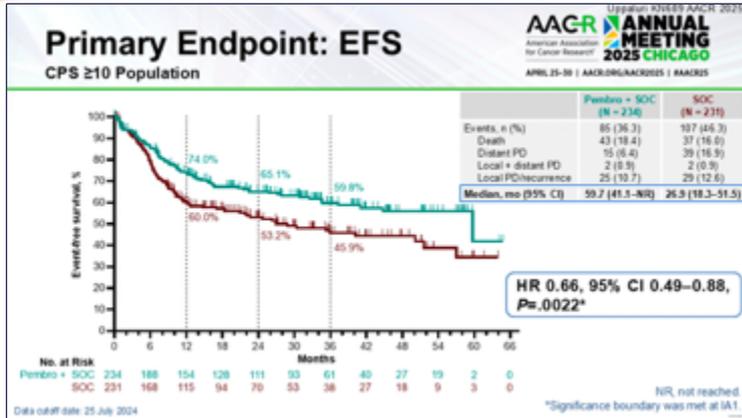
	Pembro + SOC	SOC
Total duration on study therapy, including study drugs and in-study surgery/radiotherapy		
N	361	315
Median duration (range), months	9.1 (0.03–22.3)	2.9 (0.03–7.2)
Duration of neoadjuvant pembrolizumab		
N	361^a	1^a
Median duration (range), months	0.7 (0.03–1.1)	0.03 (0.03–0.03)
Median cycles (range), n	2.0 (1.0–2.0)	1.0 (1.0–1.0)
Surgery, N	323	307
Duration of adjuvant therapy		
Pembrolizumab, N	255	0
Median duration (range), months	9.7 (0.03–18.9)	0
Median cycles (range), n	15.0 (1.0–16.0)	0
Radiotherapy, N	274	275
Median duration (range), days	44.0 (1.0–90.0)	45.0 (3.0–73.0)
Median dose (range), Gy	60.0 (2.0–70.0)	66.0 (6.0–72.0)
Cisplatin, N	107	139
Median duration (range), months	1.4 (0.0–1.8)	1.4 (0.0–1.7)
Median cycles (range), n	3.0 (1.0–3.0)	3.0 (1.0–3.0)
Total dose ≥200 mg, n (%)	95 (88.8)	126 (90.6)

Tpo Pembro: 9.7 m
Nº ciclos: 15 ciclos

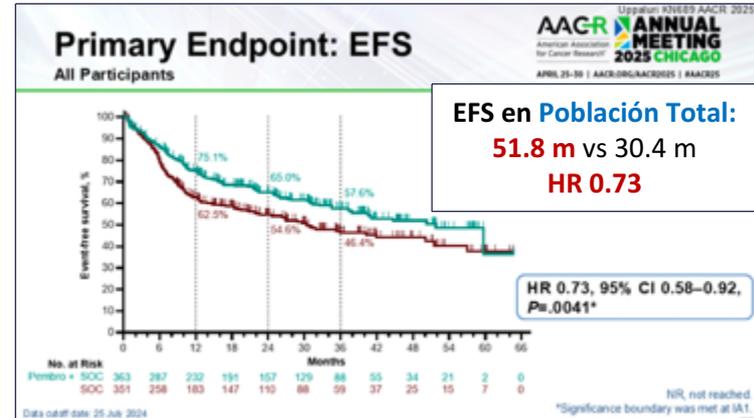
Dosis media RT:
60 vs 66 Gy

^a2 pts in SOC group received neoadjuvant pembro in error (protocol deviations); 1 is included in the pembro + SOC as-treated population.

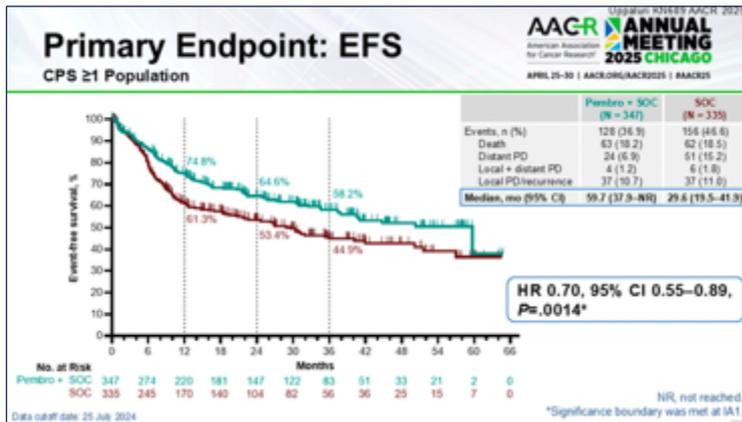
Resultados Objetivo 1º: EFS



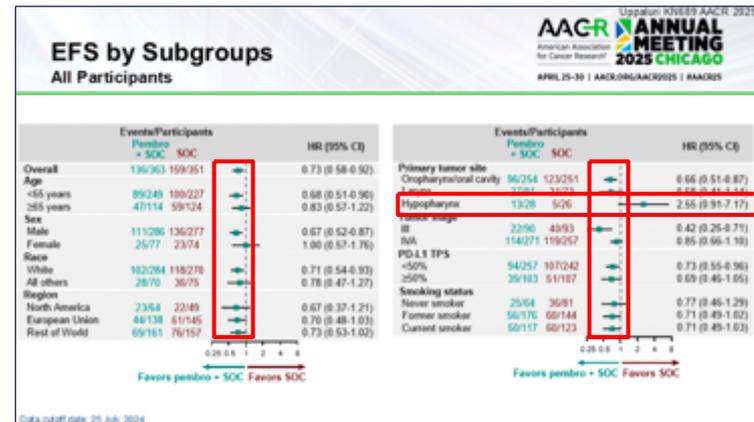
EFS en CPS ≥ 10:
59.7 m vs 26.9 m
HR 0.66



EFS en Población Total:
51.8 m vs 30.4 m
HR 0.73



EFS en CPS ≥ 1:
59.7 m vs 29.6 m
HR 0.70



Resultados Objetivos 2º: mPR y OS

Key Secondary Endpoint: mPR

Uppaluri KRB05 AACR 2025
AACR ANNUAL MEETING 2025 CHICAGO
 American Association for Cancer Research
 APRIL 25-30 | AACR.ORG/AACR2025 | #AACR25

	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	0	34	0	34	0
mPR rate, % (95% CI)	13.7 (9.5–18.8)	0.0 (0.0–1.6)	9.8 (6.9–13.4)	0.0 (0.0–1.1)	9.4 (6.6–12.8)	0.0 (0.0–1.0)
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*	

Major pathological response (mPR; ≤10% residual invasive SCC) by blinded independent pathologist review.

Data cutoff date: 25 July 2024

*Significance boundary was met at IA1.

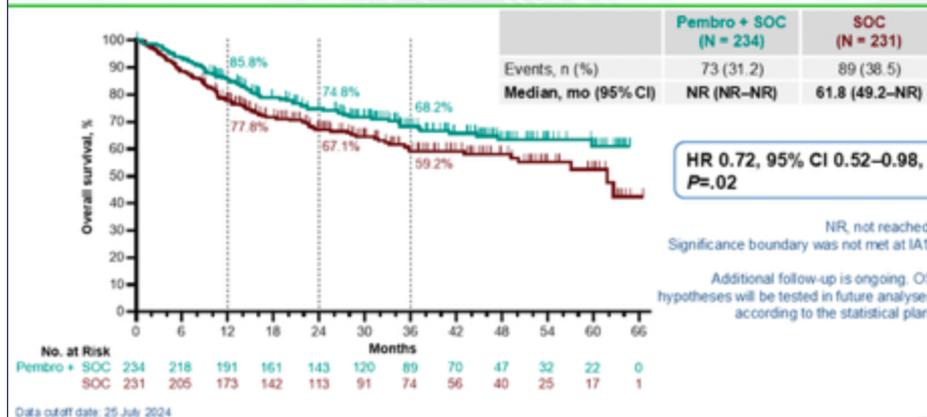
mPR en
CPS ≥ 10:
13.7%

mPR en
CPS ≥ 1:
9.8%

mPR en
Poblacion Total:
9.3%

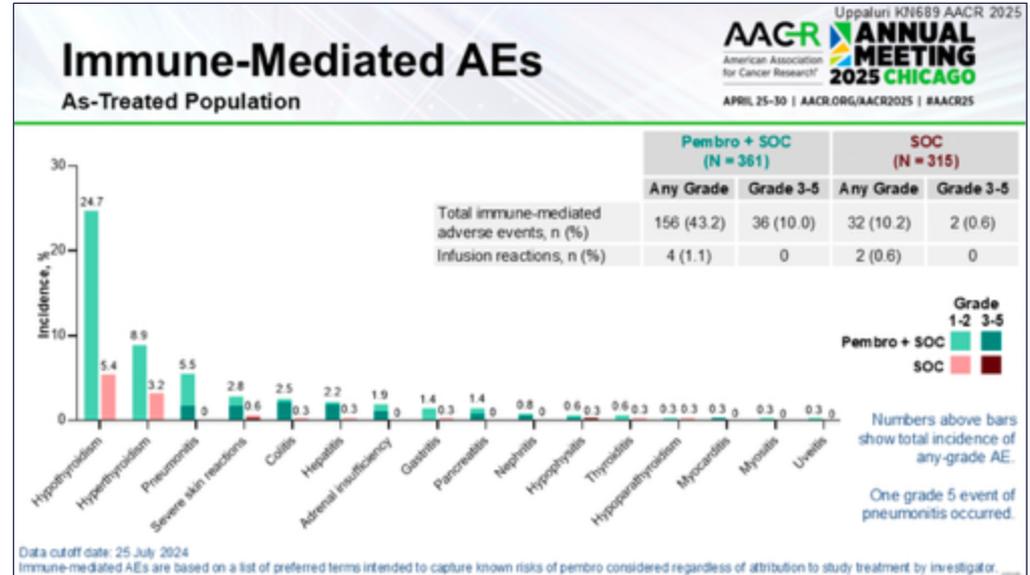
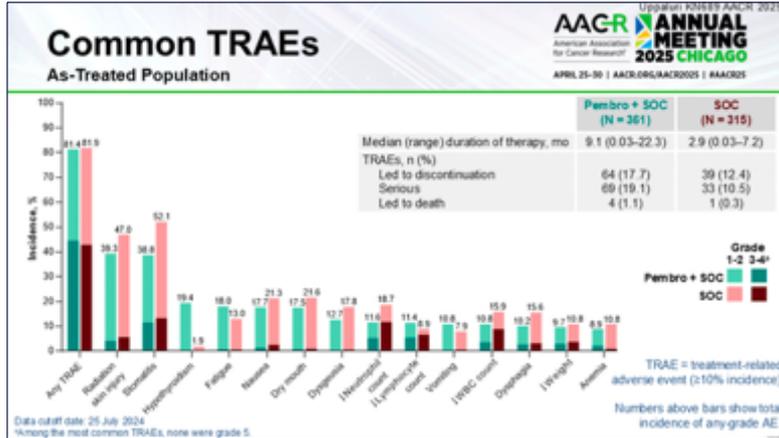
Key Secondary Endpoint: OS CPS ≥10 Population

Uppaluri KRB05 AACR 2025
AACR ANNUAL MEETING 2025 CHICAGO
 American Association for Cancer Research
 APRIL 25-30 | AACR.ORG/AACR2025 | #AACR25



OS: NR vs 61.8 m,
HR 0.72
(Resultados aún inmaduros)

Resultados Objetivos 2º: Seguridad



irTRAES: 43.2%

irTRAES G3-5: 10%

¿Pembro perioperatorio nuevo estándar en enfermedad LA reseccable?

Conclusion



Neoadjuvant pembrolizumab followed by surgery and adjuvant pembrolizumab concurrent with and after postoperative (chemo)radiotherapy represents a new standard of care in the treatment of patients with resectable locally advanced head and neck cancer

Sí pero aún varios aspectos que aclarar resolver...

- **Falta demostrar impacto en OS** (datos inmaduros)
- **Resultados en alto vs bajo riesgo?**
- **Estratificación por CPS sin agregar:** CPS 1-9 (30%) y CPS < 1 (5%)
- **Subestratificar CPS ≥ 10 :** CPS 20, CPS 50...
- **Resultados aplicables a cualquier sublocalización?**
- **Cirugía:**
 - 12-13% en ambos brazos no se operaron: por qué?
 - Hubo RC con Pembro que no se operaron?
- **Tratamiento completado en brazo de Pembro en 42.7%:** en qué momento abandonaron el resto y por qué?
- **Toxicidades:** en qué momento se produjeron? (Neoady, RT, Ady?)

ÍNDICE

RACIONAL PARA LA IO EN LA ENFERMEDAD LOCALIZADA

IO + RT radical

Pacientes FIT & UNFIT: MK3475-412, JAVELIN H&N100, REACH, PembroRad

IO adyuvante

IMVOKE-010, JADE, eVOLVE, ADJORL, NIVO POST-OP

IO neoadyuvante

Racional

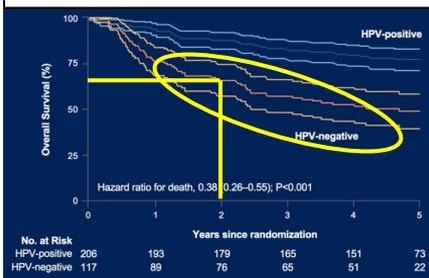
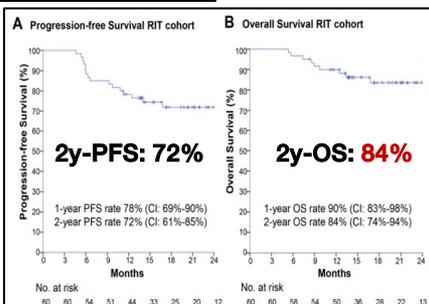
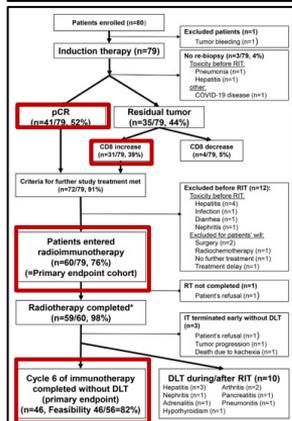
IO neoadyuvante & KN-689

IO + QT neoadyuvante

IO + QT neoadyuvante en VPH no-relacionado

DURVA + TREME + 3wkCarbo-Pacl

Journal for Immunotherapy of Cancer
Induction chemoimmunotherapy followed by CD8+ immune cell-based patient selection for chemotherapy-free radioimmunotherapy in locally advanced head and neck cancer

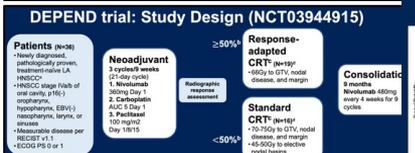


HISTÓRICO:
2y-OS: 67%

Hecht, et al. JTC 2020;8(2):1-10.
 Hecht, et al. JCO 2021;39(15_suppl)(May 20, 2021), 6007.
 Hecht, et al. JTC 2022;10:e003747.

DEPEND: NIVO + 3wkCarbo-Pacl

Neoadjuvant nivolumab, paclitaxel, and carboplatin followed by response-stratified chemoradiation in locoregionally advanced HPV negative head and neck squamous cell carcinoma (HNSCC): The DEPEND trial



Neoadjuvant nivolumab with chemotherapy Response Rate (RECIST v1.1)



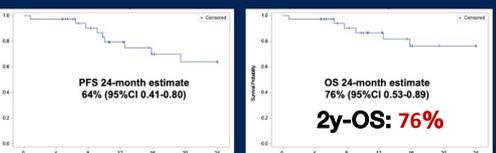
PD-L1 expression and neoadjuvant therapy Response rate and PD-L1 expression

PD-L1 Combined Positive Score (CPS)	Deep Response* n=19	Suboptimal Response* n=16	Total n=35	p-value
CPS < 1, n (%)	4 (21.1)	11 (68.8)	15 (42.9)	0.006
CPS ≥ 1, n (%)	15 (78.9)	5 (31.3)	20 (57.1)	

PD-L1 Combined Positive Score (CPS)	Deep Response* n=19	Suboptimal Response* n=16	Total n=35	p-value
CPS < 20, n (%)	14 (73.7)	13 (81.3)	27 (77.1)	0.77
CPS ≥ 20, n (%)	5 (26.3)	3 (18.8)	8 (22.9)	

*Deep Response (≥50% tumor shrinkage per RECIST v1.1)
 *Suboptimal Response (<50% tumor shrinkage per RECIST v1.1)

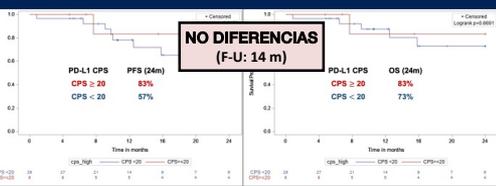
Full cohort (N=36)
 Progression Free Survival (PFS) and Overall Survival (OS)



Response-stratified survival Progression Free Survival (PFS) and Overall Survival (OS)



PD-L1 Expression and Survival Progression free survival (PFS) and Overall Survival (OS)

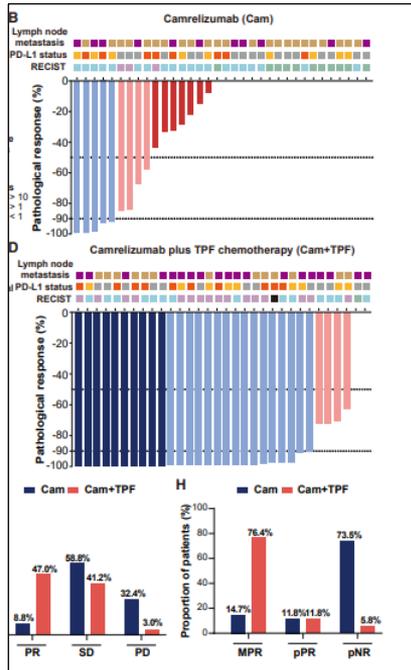


Rosenberg, et al. ASCO 2023
 Rosenberg, et al. JAMA Oncol 2025

IO + QT neoadyuvante en VPH no-relacionado

Article

Neoadjuvant immunotherapy with or without chemotherapy in locally advanced oral squamous cell carcinoma: Randomized, two-arm, phase 2 trial

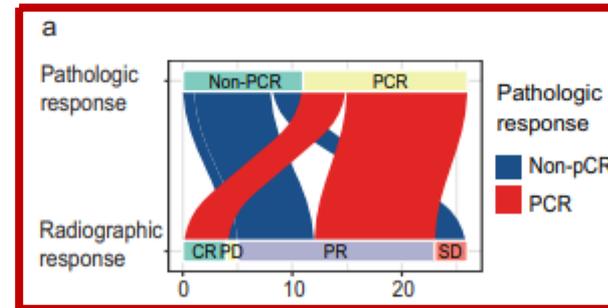
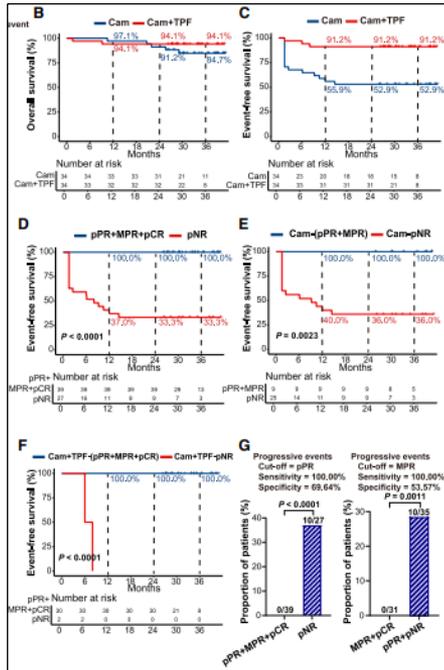
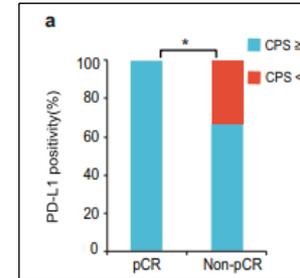
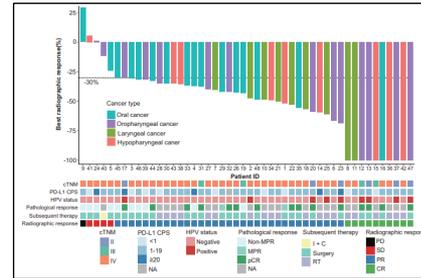


Liu, et al. Cell Reports Medicine 2025; e 6, 101930

Article

<https://doi.org/10.1038/s41467-024-46444-z>

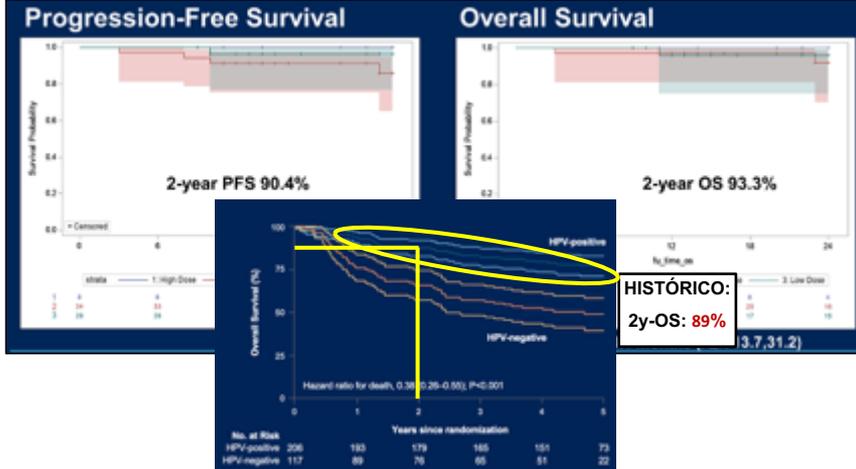
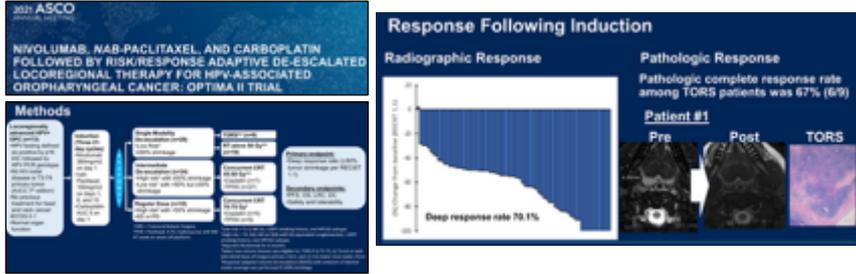
Neoadjuvant chemo-immunotherapy with camrelizumab plus nab-paclitaxel and cisplatin in resectable locally advanced squamous cell carcinoma of the head and neck: a pilot phase II trial



Wu, et al. Nature Comms 2024;15:2177

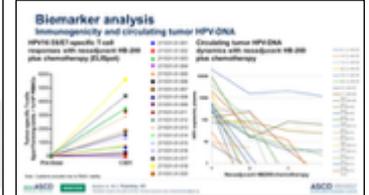
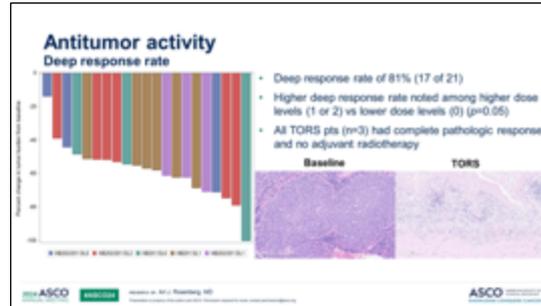
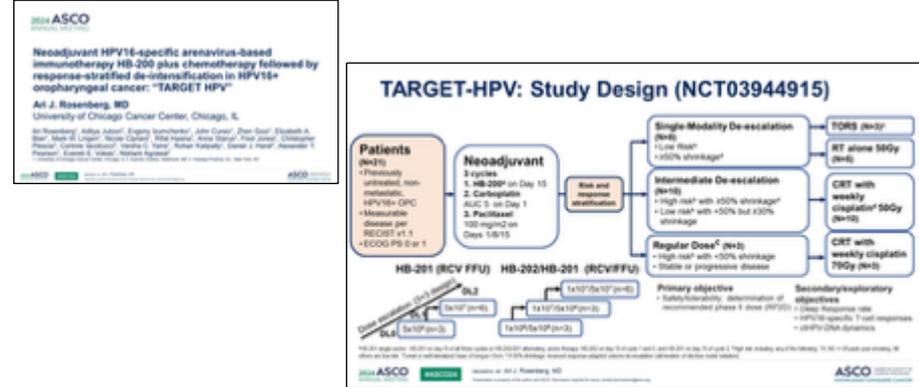
IO + QT neoadyuvante en orofaringe **VPH-positivo**

NIVO + QT neoadyuvante



Rosenberg, et al. ASCO 2021

HB200 + QT neoadyuvante

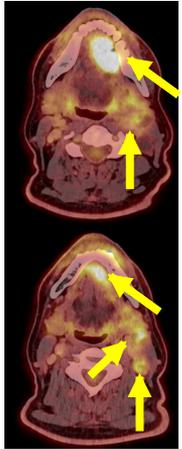


Rosenberg, et al. ASCO 2024

IO + QT neoadyuvante:

Varón 62 años. IPA 60. CECO cT4b N2 M0 (IVB). CPS=10

Basal



Pembro + wkCarbo-Taxol d1,8,15 x 3 ciclos

+ 4 meses



CIRUGÍA
(hemiglossectomía
parcial izqda + VRI)

pCR
ypT0ypN0

Pembro
(mantenimien-
to)



Desvitalización completa 1º y
parcial en cuello

IO neoadyuvante : Estudios más relevantes con resultados

	Autor	Fase, población	N	Agente NEOADYUVANTE	Agente ADYUVANTE	Toxicidad G3/4	Tasa de retraso quirúrgico	Respuesta patológica	Supervivencia
Pembro	Uppaluri (2020) Cohort 1	II, CECC LA reseccable, HPV(-)	36	Pembro x 1	Pembro x 6	0%	0%	pTR2: 22%	1y-RFS: 91%
	Uppaluri (2022) Cohort 2	II, CECC LA reseccable, HPV(-)	28	Pembro x 2	Pembro x 6	-	0%	pTR2: 45%	3y-RFS: 85% 3y-OS: 90%
	Uppaluri (2025) KN-689	III, CECC LA reseccable, HPV(-)	714	Pembro x 2	Pembro x 17	irAEs: 10%	0%	MPR (<= 10%): 9.6% - 13.6%	EFS: 51.8 – 59.7 meses
	Wise-Draper (2022)	II, CECC LA reseccable, HPV(-)	90	Pembro x 1	Pembro x 6	-	0%	MPR + PPR: 39%	1y-DFS: 80%
Nivo +/- Ipi	Ferris (2017)	II, CECC LA reseccable, HPV+/-	29	Nivo x 2	-	HPV+: 19%; HPV-: 11.5%	0%	MPR + PPR: HPV+ 23.5%; HPV- 5.9%	2y-RFS: 88% vs 54%
	Schoenfeld (2020)	II, CECC LA reseccable, HPV(-)	30	Nivo vs Nivo + Ipi	-	14% vs 30%	-	pTR2: 15 vs 23% MPR: 8 vs 20%	1y-RFS: 85%
	Vos (2021) IMCISION	II, CECC LA reseccable, HPV(-)	29	Nivo vs Nivo + Ipi	-	33% vs 38%	0%	MPR: 17 vs 35%	1y-RFS: 76%
Anti-PD(L)1 + QT	Ziinner (2020)	II, CECC LA, HPV+/-	27	Nivo + QT (TP)	-	37%	-	MPR: 69%	1y-RFS: 96%
	Hecht (2020)	II, CECC LA, HPV+/-	57	Durva + Treme + QT (TP)	-	68%	-	pCR: 48%	-
	Rosenberg (2023) DEPEND	II, CECC LA, HPV-	36	Nivo + QT (TP)	-	47%	-	DRR: 54% ORR: 89%	2y-PFS: 64%
	Even (2020) MEDINDUCTION	II, CECC LA, HPV+/-	14	Durva + TPF	-	79%	-	-	12m-RFS: 64%
HPV+	Ferrarotto (2020) CIAO	II, CECC LA reseccable, HPV+	29	Durva +/- Treme	-	20% vs 7%	10%	MPR: 8% vs 8%	15.7m-RFS: 93%
	Rosenberg (2021) OPTIMA II	II, CECC LA reseccable, HPV+	73	Nivo + QT (nabpac-carbop)	-	-	-	pCR: 67%	2y-RFS: 90% 2y-OS: 91.4%
Nivo + SBRT	Leidner (2021)	IB, CECC LA reseccable, HPV+/-	21	Pembro + SBRT	-	20%	0%	MPR: 86% cPR: 67%	-
Nivo en R-R	Hanna (2022)	II, CECC recurrente-reseccable, HPV+/-	28	Nivo + Lirilumab	-	11%	0%	MPR + PPR: 43%	1y-RFS: 55.2%

IO neoadyuvante : Estudios en curso

Smussi, et al Cancer Treat Rev 2023;121:102644;
Cabezas-Camarero, et al. Crit Rev Oncol Hematol 2022;169:103569
ClinicalTrials.gov (acceso 22/5/25)

ClinicalTrials.gov	Población	N	Diseño y Agente	Endpoint primario
NCT06647563 (NEO-ICT)	CECC LA resecable (III-IVB)	355	Fase III, Toripalimab + Nab-paclitaxel + Carboplatino +/- Cetuximab	2y-EFS
NCT05578170 (PROBES)	CECO LA resecable	47	Fase II, Pembrolizumab	pTR-2
NCT03708224	CECC LA resecable	55	Fase II, Atezolizumab + Tocilizumab ± Tiragolumab	Tasa resección R0, cambio en TILs CD3+
NCT03854032	CECC LA resecable, HPV+/-	48	Fase II, Nivolumab ± BMS-986205	ORR
NCT04988074 (MINIMA)	CECC LA resecable, HPV+	32	Fase II, Cemiplimab ± Carboplatin + Paclitaxel (→TORS vs de-escalated RT)	2y-PFS, cambio en QoL y función deglutoria
NCT03174275	CECC resecable, HPV+/-, neoady y ady	39	Fase II, Durvalumab + Carboplatin + Nabpaclitaxel	pCR
NCT04080804	CECC LA resecable, HPV+/-	60	Fase II, Nivolumab vs Nivolumab + Ipilimumab vs Nivolumab + Relatlimab	Seguridad
NCT04807140	CECC LA resecable, HPV+/-	57	Fase II, Toripalimab + Carboplatin + Nabpaclitaxel	pTR, seguridad
NCT05459415 (REMATCH)	CECC LA resecable, HPV(-)	54	Fase II, Quimio-inmunoterapia	DFS
NCT05483400 (TIRACAN -Basket trial)	Resectable LAHNSCC	97	Fase II, Atezolizumab + Tiragolumab	pTR
NCT04681469 (PRIME)	Niraparib + Dostarlimab	49	Fase II, Niraparib + Dostarlimab	MPR, seguridad
NCT05098119 (OOC-002)	Carboplatin + Nabpaclitaxel + Sintilimab	43	Fase II, Carboplatin + Nabpaclitaxel + Sintilimab	pTR2



Conclusiones

- **La inmunoterapia (IO) en la enfermedad LA supone el mayor avance terapéutico en el CECC desde 2019:**
 - Sólido racional biológico y clínico para el empleo de la IO en el CECC LA
 - La IO en el CECC LA consigue un **notable efecto patológico e incrementa EFS (KN-689) y DFS (Nivo Post-OP)**
- **Temas a debatir:**
 - **KN-689 vs NIVO POSTOP: Definir estrategia en CECC LA con A-P de alto riesgo: Neo(adyuvancia) vs Adyuvancia**
 - KN-689 vs NIVO POSTOP: IO durante 8 vs 12 meses
 - **KN-689: aprobación en población total o en CPS-seleccionado?**
 - **KN-689: EFS y OS en alto vs bajo riesgo?**
 - **KN-689: Falta demostrar impacto en OS (datos inmaduros)**
- **Estrategias a estudiar:**
 - **Combinación de IO + QT** neoadyuvante/inducción?
 - **Desescalar la terapia local** (cirugía, RT)



¡Muchas Gracias!