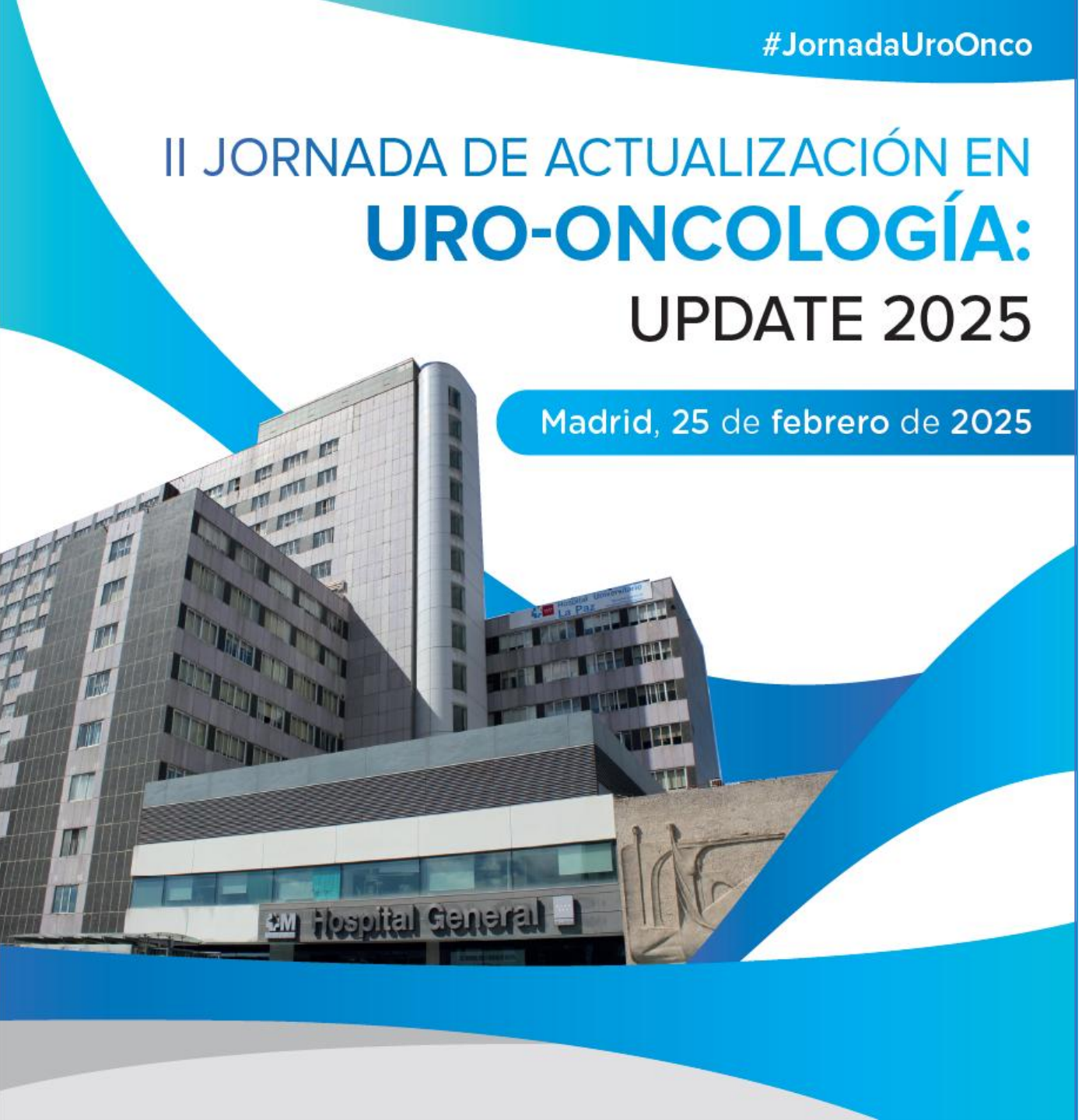

Adyuvancia en Cáncer Renal

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Disclosures

- **Industry Relationships**
  - **Consulting or advisory role / speaker honoraria** : GSK, Astellas, MSD, AstraZeneca, BMS, Ipsen, Jannsen, Merck, Pfizer, Roche
  - **Support for congress attendance (registration, travel, accommodation, etc.)**: Astellas, MSD, AstraZeneca, BMS, Ipsen, Jannsen, Merck, Pfizer, Roche, AstraZeneca, GSK

- *The data and opinions presented are independent and based on the best available scientific evidence.*

Mensajes clave

- **Pembrolizumab** es el **estándar** de tratamiento **adyuvante** para pacientes **riesgo intermedio/alto, alto riesgo** y **M1NED con cáncer renal de cél. claras.**
- **Pembrolizumab** ha demostrado **beneficio** en **SLE** y **SG** (1º fármaco en conseguirlo)

FDA APPROVED

EMA APPROVED

agencia española de medicamentos y productos sanitarios

✓

Adyuvancia ... ¿Para quién?

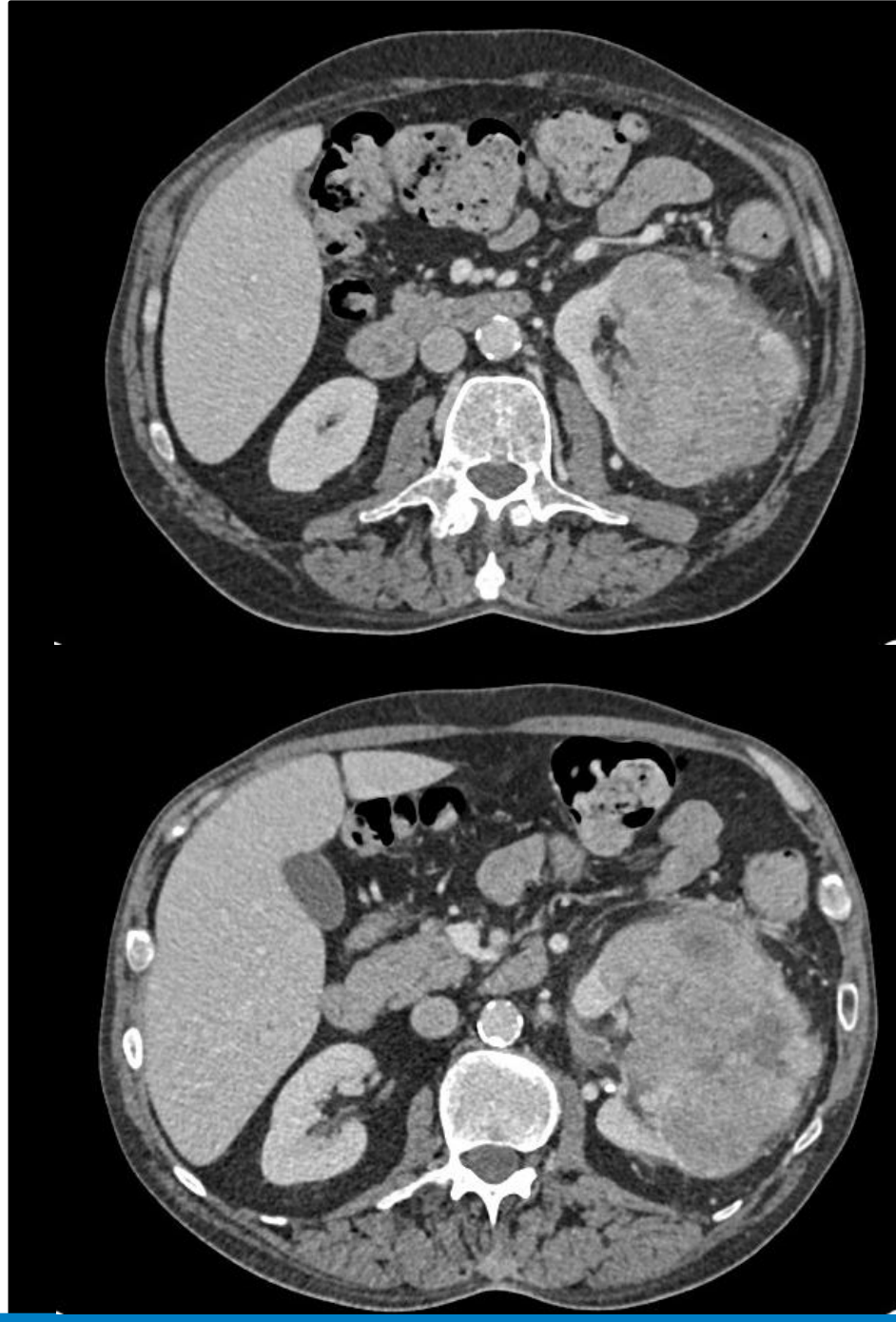
Antecedentes:

- ♂ 59 años
- Dolor lumbar - Diagnóstico masa renal izq, M0

Nefrectomía radical izq laparoscópica

AP:

- **Ca renal de Células Claras**
- 12,2 cm
- **ISUP Grado 4**
- No diferenciación sarcomatoide ni rabdoide, no necrosis tumoral
- Trombosis tumoral en ramas segmentarias vena renal
- Márgenes libres
- No ILV
- **pT3a N0 M0, R0**.
- *Pérdida de expresión de BAP1. CA IX+, PAX8+*
- *Estudio de traslocación para TFE3, TFEB, deleción en SMARCB1/CEP22: NEGATIVOS*



¿Qué dicen las guías clínicas?

Pembrolizumab adyuvante

European Association of Urology

European kidney cancer clinical guidelines updated

Recommendations	Strength rating
Do not use neoadjuvant therapy outside a clinical trial setting.	Weak
Discuss the contradictory results of the available adjuvant ICI trials with patients to facilitate shared decision making.	Strong
Inform patients about the potential risk of overtreatment and immune related side effects if adjuvant therapy is considered.	Strong
Do not offer adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab, or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma (ccRCC).	Weak
Offer adjuvant pembrolizumab to ccRCC patients, preferably within 12-16 weeks post-nephrectomy, with a recurrence risk as defined in the Keynote-564 trial: • Intermediate-high risk: - pT2, grade 4 or sarcomatoid, N0 M0 - pT3, any grade, N0, M0 • High risk: - pT4, any grade, N0, M0 - any pT, any grade, N+, M0 • M1 no evidence of disease (NED): - NED after resection of oligometastatic sites ≤ 1 year from nephrectomy	Weak *

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Kidney Cancer

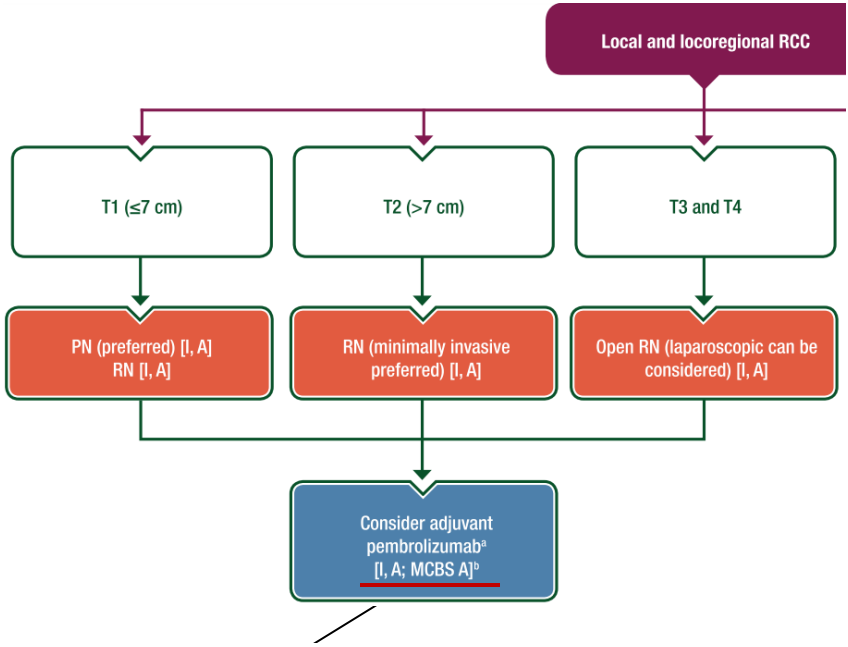
STAGE	PRIMARY TREATMENT[c,d]	ADJUVANT TREATMENT
Stage II	Partial nephrectomy or Radical nephrectomy	Clear cell histology: Surveillance[e] or Adjuvant pembrolizumab (category 1) (Grade 4 tumors with clear cell histology ± sarcomatoid features) Non-clear cell histology: Surveillance[e]
Stage III	Radical nephrectomy or Partial nephrectomy, if clinically indicated	Clear cell histology: Adjuvant pembrolizumab (category 1) or Surveillance[e] Non-clear cell histology: Surveillance[e] or clinical trial

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆



a) If appropriate at final histology (e.g. T2 with nuclear grade 4 or sarcomatoid differentiation, T3 or regional lymph node metastasis)

(*) Datos **NO actualizados** con resultados **+ de SG**

***Máximo nivel de evidencia* (IA)**

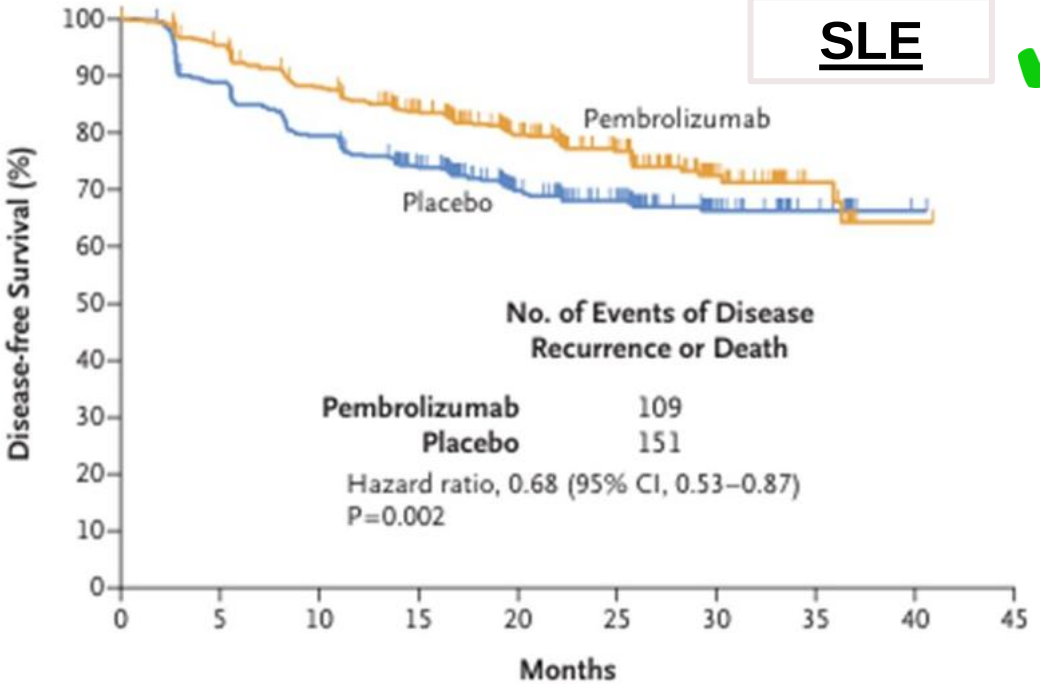
EAU Guidelines Renal Cancer 2024, NCCN Guidelines Kidney cancer 2025, ESMO Renal Cancer Guidelines 2024

Razones para el cambio

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 19, 2021 VOL. 385 NO. 8

Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma

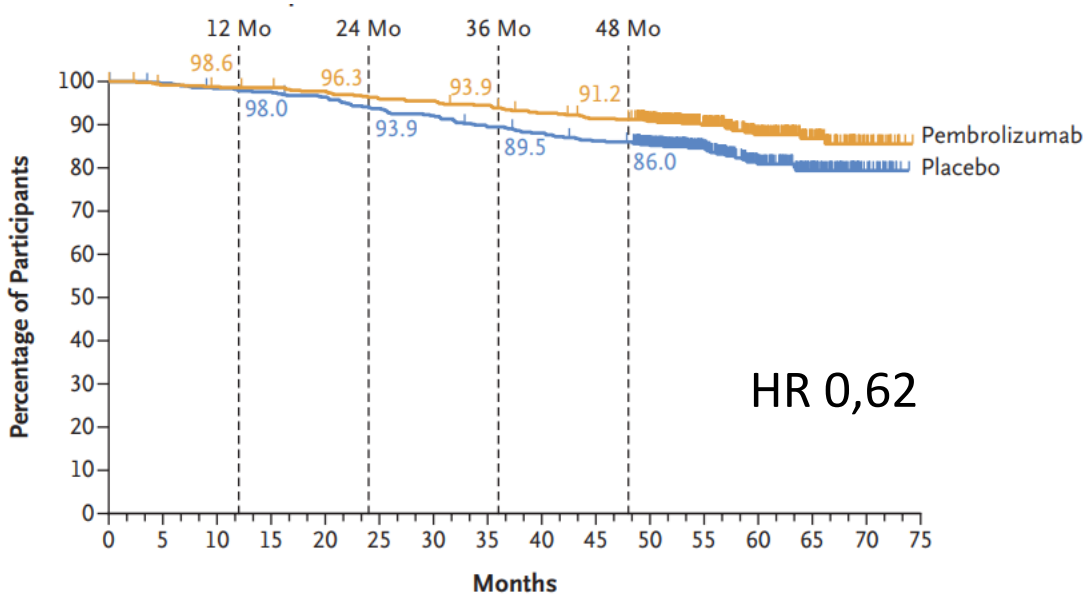
SLE ✓



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 18, 2024 VOL. 390 NO. 15

Overall Survival with Adjuvant Pembrolizumab in Renal-Cell Carcinoma

SG ✓



HR 0,62

Choueiri TK et al NEJM 2021; Choueiri TK et al NEJM 2024

¿Qué pacientes?

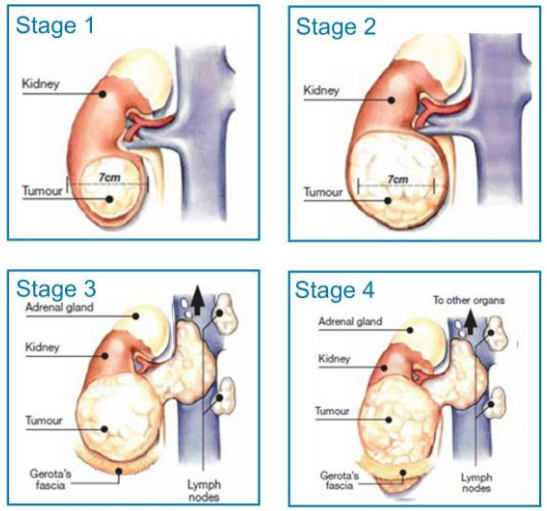
TODOS los incluidos en el KN-564

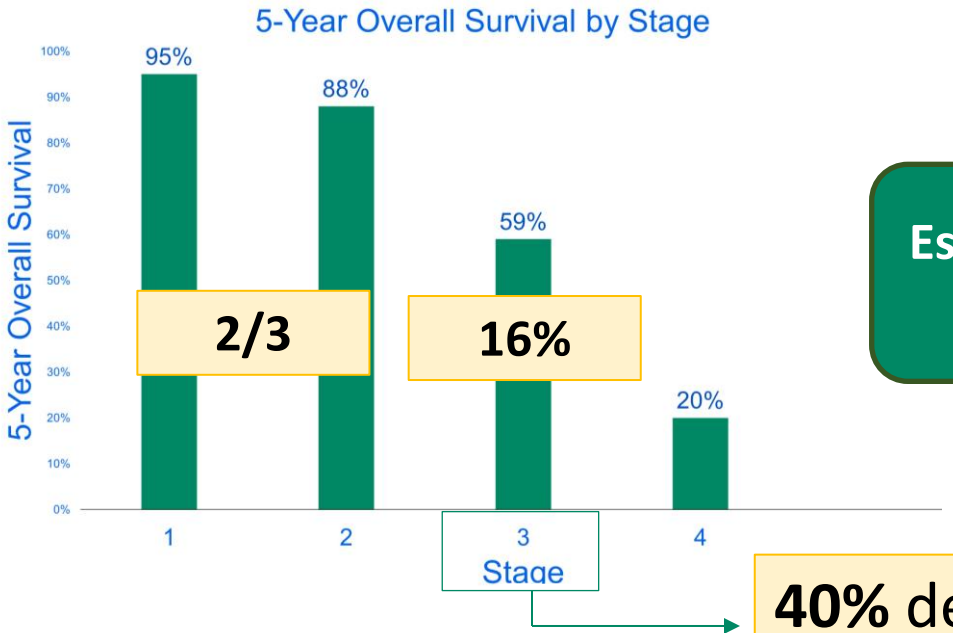
Cá renal células claras

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

Riesgo de recurrencia cáncer renal

TNM





Estadios avanzados, peor pronóstico

40% de estadios **III recaerán**

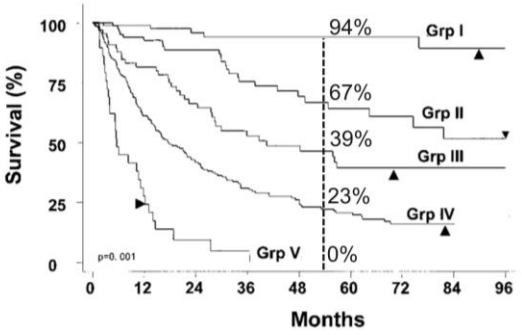
Nomogramas pronósticos

- **Estimar riesgo** de recaída
- Su uso **no estandarizado** por las guías

Model	Parameters	Outcome	Type
UISS	TNM, grade, ECOG PS	OS	KM Analysis
SSIGN	TNM, pN+, pM+, tumor size, grade, tumor necrosis	CSS	Algorithm
Leibovich	TNM, pN+, tumor size, grade, tumor necrosis	MFS	Algorithm
MSKCC	TNM, tumor size, grade, tumor necrosis, symptoms	RFS	Nomogram
Kattan	TNM, tumor size, histology, symptoms	RFS	Nomogram
Yaycioglu	Tumor size, symptoms	RFS	Formula
Karakiewic	TNM, age, sex, + margin, tumor size, symptoms	CSS	Nomogram
Cindolo	Tumor size, symptoms	RFS	Formula

UCLA Integrated Staging System

pTNM Stage, Grade, Performance status



Adaptado de presentación RR McKey en ASCO 2021

Riesgo de recurrencia cáncer renal

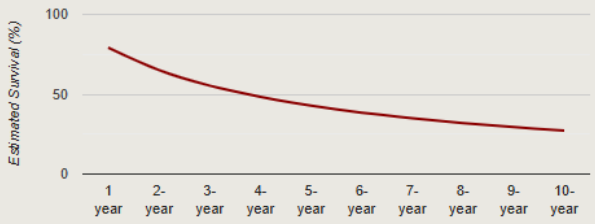
FOX CHASE CANCER CENTER
TEMPLE HEALTH

Assure RCC Prognostic Nomogram

A post-operative prediction model which provides a comprehensive review of expected oncological outcomes in patients with renal cell carcinoma.

Disease Free Survival (DFS) Probability

1 year	2- year	3- year	4- year	5- year	6- year	7- year	8- year	9- year	10- year
79.2%	65.1%	55.4%	48.4%	42.9%	38.5%	35.0%	32.0%	29.4%	27.2%



Memorial Sloan Kettering Cancer Center

Risk of Recurrence Following Surgery

RENAL CELL CARCINOMA
RECURRENCE-FREE PROBABILITY

5 YEAR

73%

UCLA Integrated Staging System (UISS) for Renal Cell Carcinoma (RCC)

Provides 5-year disease-free prognosis for localized and metastatic RCC.

Estimated 5-year Survival from Renal Cell Carcinoma Post-Nephrectomy

67 %

Gran variabilidad

Adaptado de presentación Albiges L en ASCO GU 2025

¿Evidencia previa?

Adyuvancia con citoquinas: NO impacto en SLE ni SG

Trial	Population	Arms	N	Primary	Outcome
Porzsolt et al (1992)	pT3-4N0 or pTxN1-3	IFN-α vs. Observation	270	TTF/Survival	No Difference
Trump et al (1996)	pT3-4aN0 or pTxN1-3	L-IFN vs. Observation	294	Recurrence	No Difference
Pizzocaro et al (2001)	pT3-4aN0 or pTxN1-3	IFN-α vs. Observation	247	5-year DFS	No Difference
Messing et al (2003)	pT3-4aN0 or pTxN1-3	IFN-α vs. Observation	283	5-year OS	No Difference
Clark et al (2003)	pT3b-4Nx or pTxN1-3	IL-2 vs. Observation	138	2-year DFS	No Difference
Atzpodien et al (2005)	pT3b-4Nx or pTxN1-3	IL-2/IFN-α/5-FU vs. Observation	203	2-year DFS	No Difference
Aitchison et al (2014)	pT3b-4Nx or pTxNa-2 or +margin/vascular invasion	IL-2/IFN-α/5-FU vs. Observation	309	3-year DFS	No Difference

IFN-α=Interferon alpha; L-IFN=Lymphoblastoid interferon; IL-2=Interleukin 2; 5-FU=5-Fluorouracil; TTF= Time to treatment failure; DFS=Disease-free survival; OS=Overall survival.

Porzsolt et al, Proceedings of ASCO, 1992; Trump et a;, Proceedings of ASCO, 1996; Pizzacaro et al, JCO, 2001; Messing et al, NEJM, 2003; Clark et al, JCO, 2003; Atzpodien et al Br J Cancer, 2005; Aitchizon et al, EJC, 2014

Adyuvancia con TKIs: NO impacto en SLE ni SG

	≠		≠	≠	≠		
Trial	**Exp arm**	**Control Arm**	**Duration**	**Inclusion criteria**	**Histology**	**N**	**DFS**
ASSURE	Sunitinib Sorafenib	Placebo	1	≥T1b	Any	1943	1.02, 0.85-1.23 0.97, 0.89-1.17
S-TRACT	Sunitinib	Placebo	1	≥Stage III	Clear cell	615	0.76, 0.59- 0.98
SORCE	Sorafenib	Placebo	1-3	Leibovich 3-11	Any	1711	1.01, 0.83-1.23
PROTECT	Pazo 600 Pazo 800	Placebo	1	pT2, pT3-4N0, N+	Clear cell	1538	0.94, 0.77-1.14 0.69, 0.51-0.94
ATLAS	Axitinib	Placebo	1-3	pT2, pT3-4N0, N+	Clear cell	724	0.87, 0.66-1.14
EVEREST	Everolimus	Placebo	1	≥pT1 G3-4	Any	1545	0.85, 0.72-1.00* 0.79, 0.65-0.97

*RFS: relapse free survival, exp:experimental, pazo:pazopanib

1. Ryan, C. W. et al. The Lancet 402, 1043–1051 (2023). 2. Motzer, R. J. et al. Eur Urol 79, 334–338 (2021). 3. Eisen, T. et al. J Clin Oncol 38, 4064–4075 (2020).
4. Ravaud, A. et al. NEJM 375, 2246–2254 (2016). 5. Gross-Goupil, M. et al. Ann Oncol 29, 2371–2378 (2018). 6. Motzer, R. J. et al. J Clin Oncol 35, 3916–3923 (2017).

Adyuvancia con TKIs:

Trial	Exp arm	Control Arm	Duration	Inclusion criteria	Histology	N	DFS
ASSURE	Sunitinib Sorafenib	Placebo	1	≥T1b	Any	1943	1.02, 0.85-1.23 0.97, 0.89-1.17
S-TRACT	Sunitinib	Placebo	1	≥Stage III	Clear cell	615	0.76, 0.59- 0.98
SORCE							-1.23
PROTECT							-1.14 -0.94
ATLAS	Axitinib	Placebo	1-3	pT2, pT3-4N0, N+	Clear cell	724	0.87, 0.66-1.14
EVEREST	Everolimus	Placebo	1	≥pT1 G3-4	Any	1545	0.85, 0.72-1.00* 0.79, 0.65-0.97

Only 1 POSITIVE TRIAL

*RFS: relapse free survival, exp:experimental, pazo:pazopanib

1. Ryan, C. W. et al. The Lancet 402, 1043–1051 (2023). 2. Motzer, R. J. et al. Eur Urol 79, 334–338 (2021). 3. Eisen, T. et al. J Clin Oncol 38, 4064–4075 (2020).
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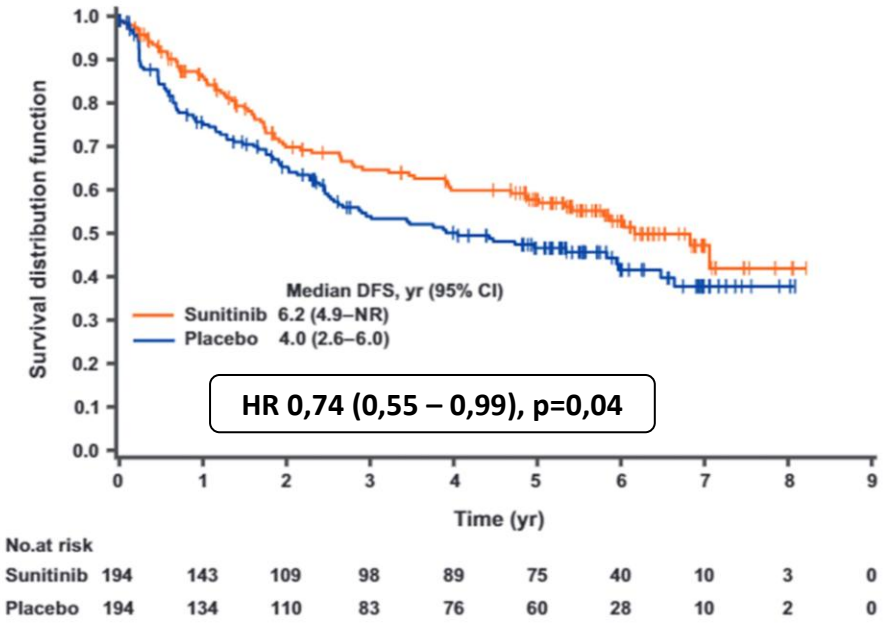
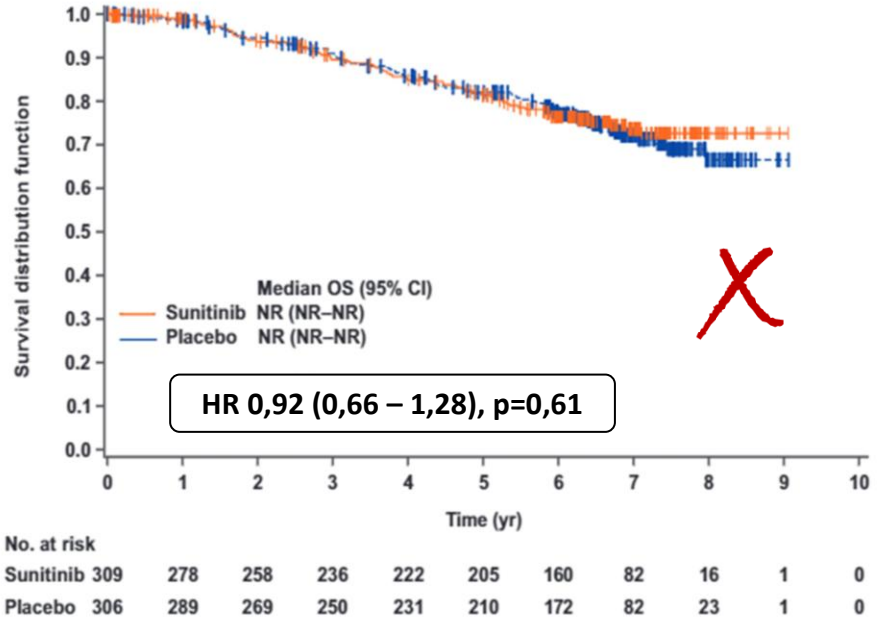
Adyuvancia con TKIs:

S-TRAC beneficio **SOLO** en **SLE para Sunitinib** adyuvante **(6,2 m vs 4 m)** – **NO en SG**

Disease-Free Survival



Overall Survival



Median follow-up 6.6 years in the sunitinib arm and 6.7 years in the placebo arm

Motzer et al, NEJM, 2016
Motzer et al, Eur Urol, 2018

En 2017 para pacientes de alto riesgo, pero **NO aprobado** por la **EMA**

Adyuvancia con TKIs: lecciones

Importancia de la toxicidad

- **Toxicidad > de la esperada**, > discontinuaciones
- Importancia perfil seguridad (pacientes curados)

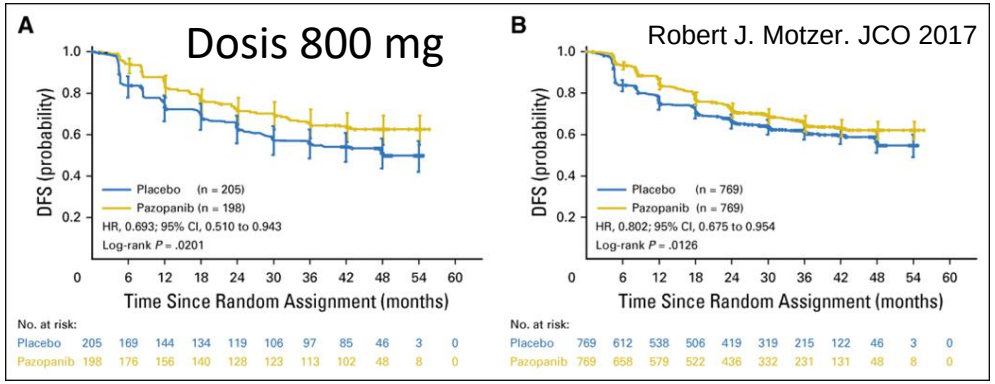
Toxicity Parameter	Sunitinib Arm
Any Attribution Grade 3 AE	48%
Any Attribution Grade 4 AE	12%
Dose Reduction	34%
Dose Interruption	46%
Completed 1-year of Therapy	56%
Treatment DC due to AE	28%

Pacientes alto riesgo – mayor beneficio

- **Importancia** de **estratificación** por grupo de riesgo **previo** al tratamiento adyuvante

Importancia de la dosis

Dosis **relacionada** con eficacia



Trial	Exp arm	Control Arm	Duration	Inclusion criteria	Histology	N	DFS	POSITIVE
ASSURE	Sunitinib Sorafenib	Placebo	1	≥T1b	Any	1943	1.02, 0.85-1.23 0.97, 0.89-1.17	
S-TRACT	Sunitinib	Placebo	1	≥Stage III		15	0.76, 0.59-0.98 0.74, 0.55-0.99	←
SORCE	Sorafenib	Placebo					1.01, 0.83-1.23	
PROTECT	Pazo 600 Pazo 8					1538	0.94, 0.77-1.14 0.69, 0.51-0.94	
ATLAS	Axitinib			pT2, pT3-4N0, N+	Clear cell	724	0.87, 0.66-1.14 0.73, 0.52-1.02	←
EVEREST	Everolimus	Placebo	1	≥pT1 G3-4	Any	1545	0.85, 0.72-1.00* 0.79, 0.65-0.97	←

Importante la selección de pacientes

1. Ryan, C. W. et al. The Lancet 402, 1043–1051 (2023). 2. Motzer, R. J. et al. Eur Urol 79, 334–338 (2021). 3. Eisen, T. et al. J Clin Oncol 38, 4064–4075 (2020).
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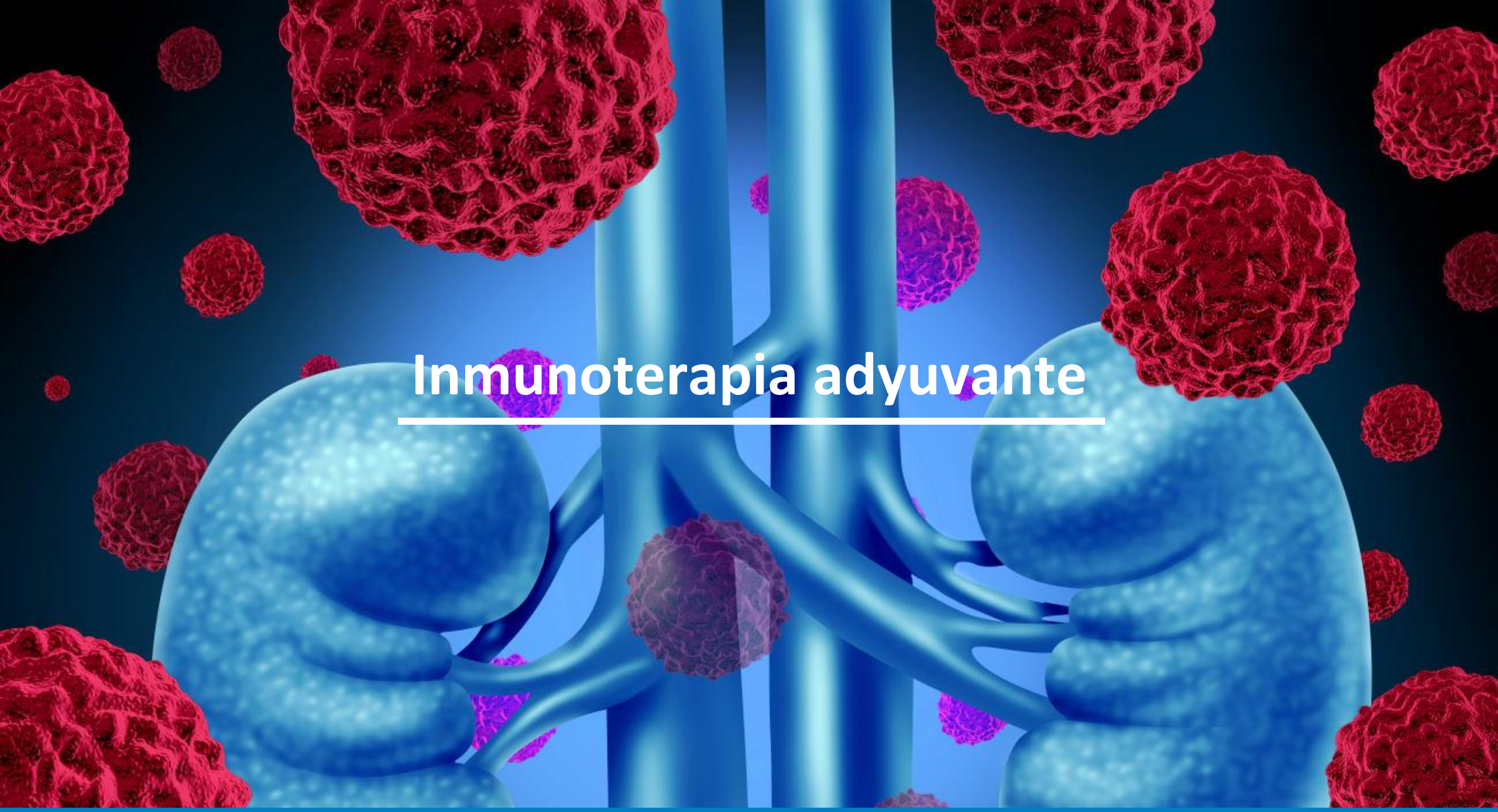
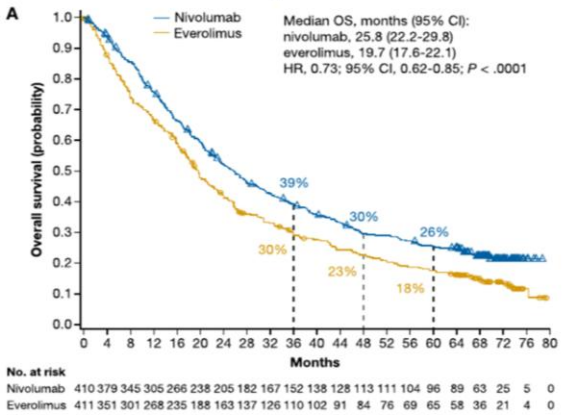


Inmunoterapia adyuvante

IO monoterapia como adyuvancia en cáncer renal

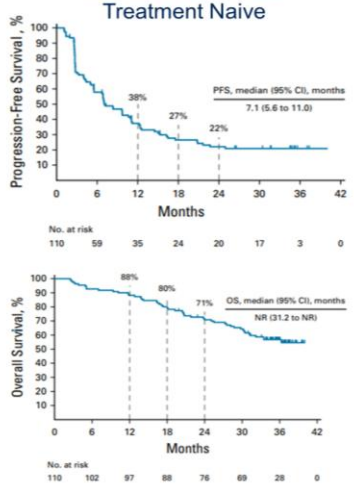
Eficacia conocida en **monoterapia** en etapas **avanzadas**

Randomized Phase 3 CheckMate 025
Nivolumab vs. Everolimus
VEGFi pretreated

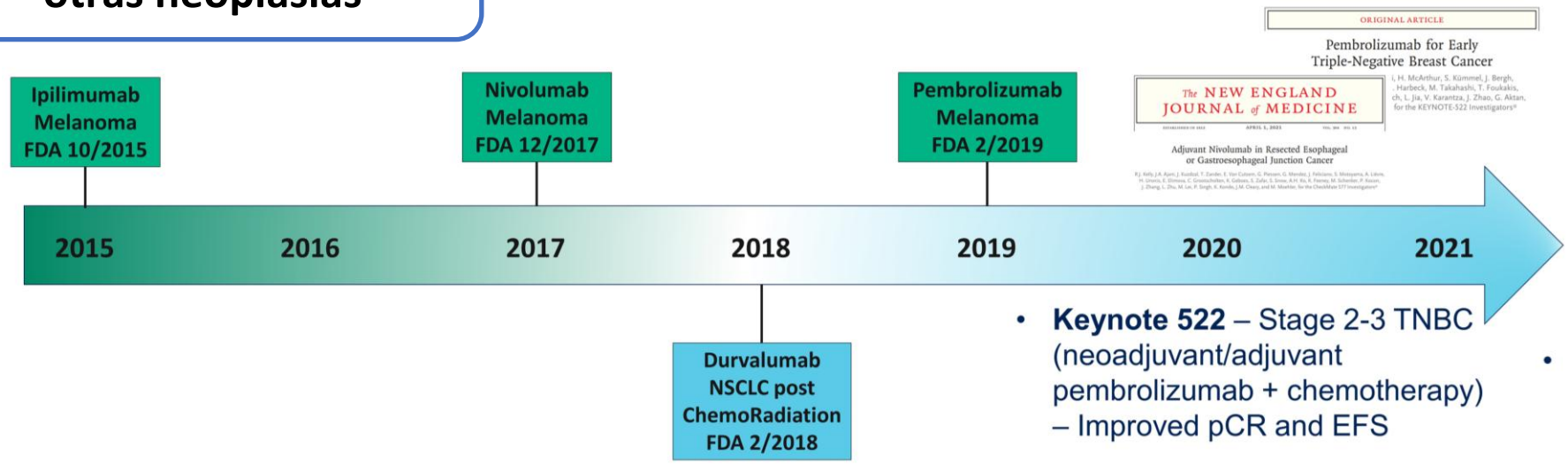


Median Follow Up 72 months

Single-Arm Phase 2 Keynote 427
Pembrolizumab
Treatment Naive



Eficacia conocida en **otras neoplasias**



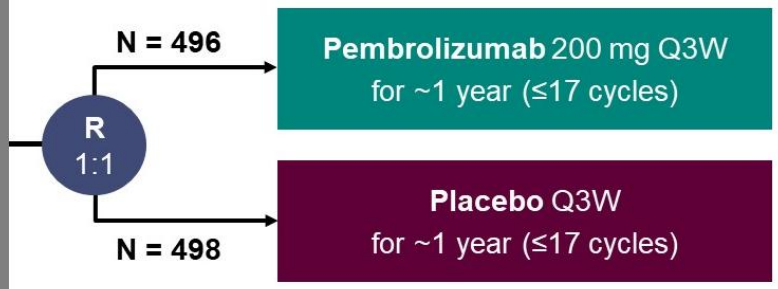
- **Keynote 522** – Stage 2-3 TNBC (neoadjuvant/adjuvant pembrolizumab + chemotherapy) – Improved pCR and EFS
- **CheckMate 577** – Stage 2-3 Esophageal/GEJ (adjuvant nivolumab) – Improved DFS

Adaptado de presentación RR McKey en ASCO 2021

F.III KN-564 Pembrolizumab adyuvante

Key Eligibility Criteria

- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1



O.1º: SLE por investigador
O.2º: SG y seguridad.

* **Stratification Factors**
- M stage (M0 vs. M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs. 1
  - US vs. non-US

No estratificación por grupos de riesgo

Intermediate-High Risk		High Risk		M1 NED
pT2 Grade 4 or sarcomatoid N0 M0	pT3 Any grade N0 M0	pT4 Any grade N0 M0	Any pT Any grade N+ M0	NED after resection of oligometastatic sites ≤1 year from nephrectomy
80% 5-year DFS UISS	55-80% 5-year DFS UISS	55% 5-year DFS UISS	32% 5-year DFS UISS	20% 3-year DFS E2810

Riesgo de recurrencia y SLE heterogéneo

KN-564 Pembrolizumab adyuvante

- **Características de la población**

	Pembro Arm (N = 496)	Placebo Arm (N = 498)
Age, median (range)	60 (27–81)	60 (25–84)
Male	347 (70.0%)	359 (72.1%)
ECOG PS 1	75 (15.1%)	72 (14.5%)
Geographic location		
North America	133 (26.8%)	125 (25.1%)
European Union	188 (37.9%)	187 (37.6%)
Rest of world	175 (35.3%)	186 (37.3%)
Disease risk category		
* M0 intermediate-high	427 (86.1%)[a]	433 (86.9%)
M0 high risk	40 (8.1%)	36 (7.2%)
M1 NED	29 (5.8%)	29 (5.8%)
Sarcomatoid features[b]		
Present	52 (10.5%)	59 (11.8%)
Absent	414 (83.5%)	415 (83.3%)
PD-L1 CPS[c,d]		
<1	124 (25.0%)	113 (22.7%)
≥1	365 (73.6%)	383 (76.9%)

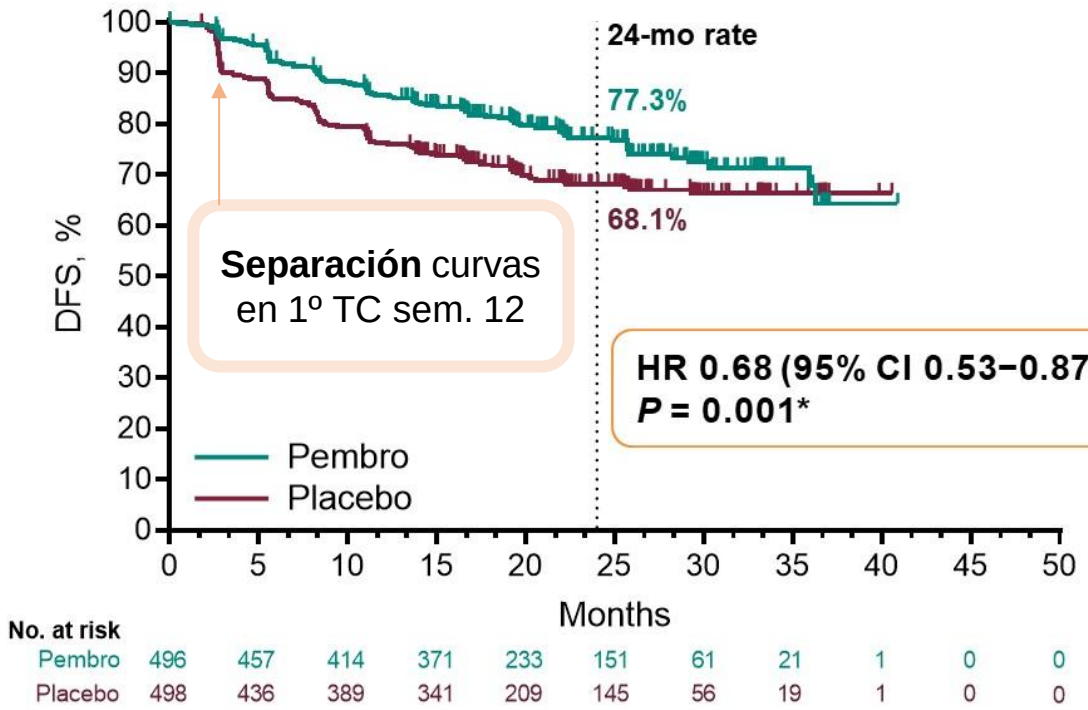
	Pembro Arm (N = 496)	Placebo Arm (N = 498)
Primary tumor stage		
T1	11 (2.2%)	15 (3.0%)
T2	27 (5.4%)	33 (6.6%)
T3	444 (89.5%)	437 (87.8%)
T4	14 (2.8%)	13 (2.6%)
Tumor nuclear grade[e]		
Grade 1	19 (3.8%)	16 (3.2%)
Grade 2	153 (30.8%)	150 (30.1%)
Grade 3	219 (44.2%)	213 (42.8%)
Grade 4	103 (20.8%)	119 (23.9%)
Lymph node stage		
N0	465 (93.8%)	467 (93.8%)
N1	31 (6.3%)	31 (6.2%)
Metastatic stage		
M0	467 (94.2%)	469 (94.2%)
M1 NED	29 (5.8%)	29 (5.8%)
Type of nephrectomy		
Partial	37 (7%)	38 (8%)
Radical	459 (93%)	460 (92%)

Adaptado de presentación Choueiri T en ASCO 2022. Powles T et al. Lancet Oncol. 2022

KN-564 Pembrolizumab adyuvante

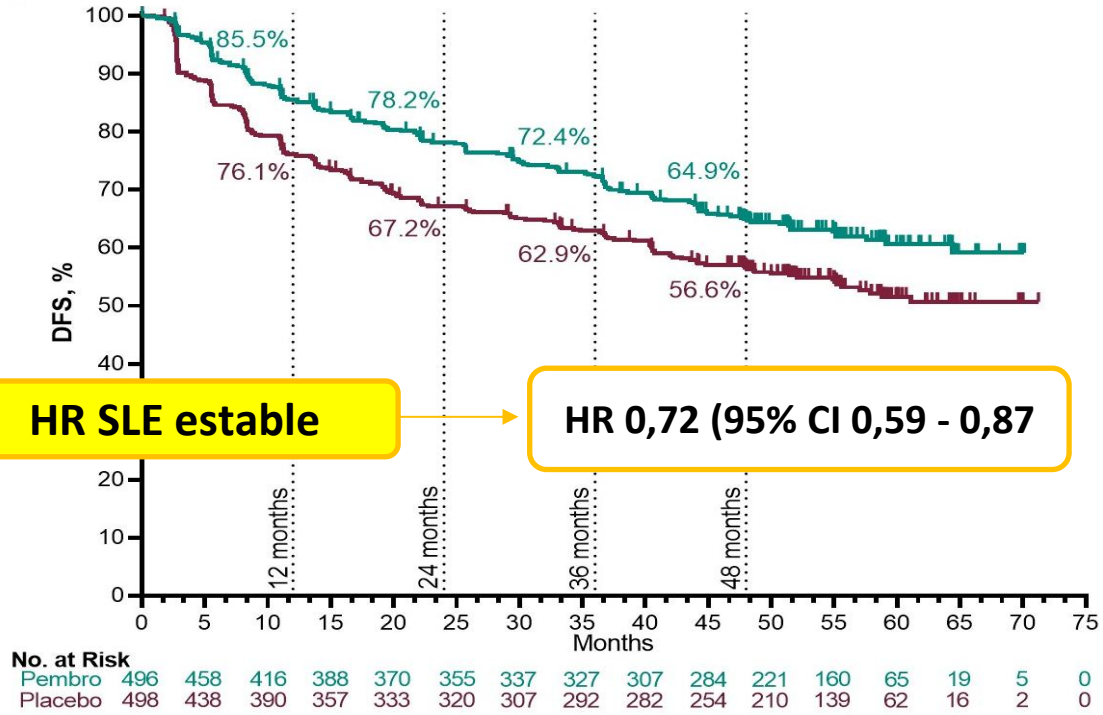
- **O.1º: SLE en ITT**

1º análisis: 24,1 m de seguimiento



	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)

Actualización tras 57,2 m (~5 años)



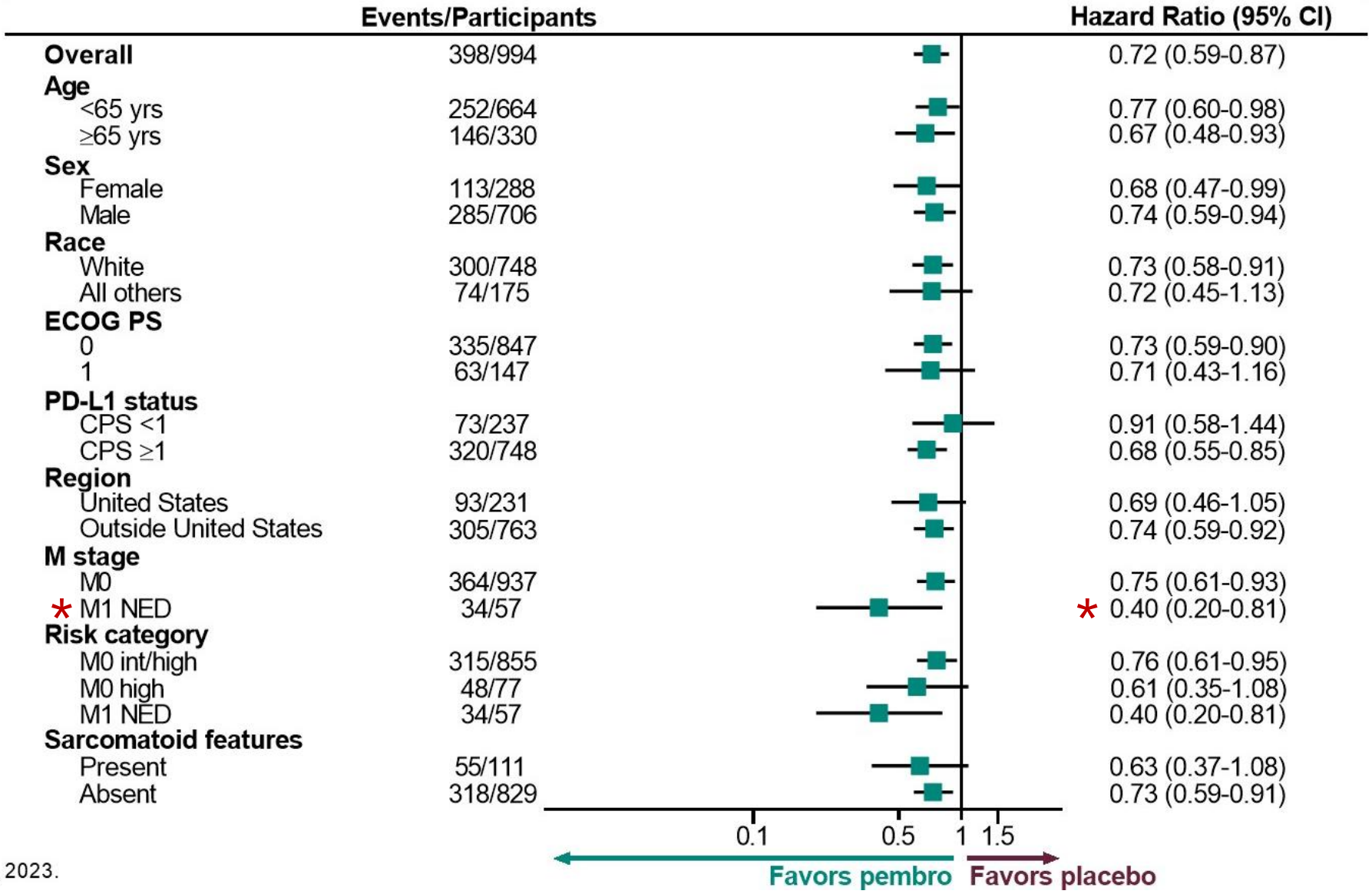
HR SLE estable

HR 0,72 (95% CI 0,59 - 0,87

	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)

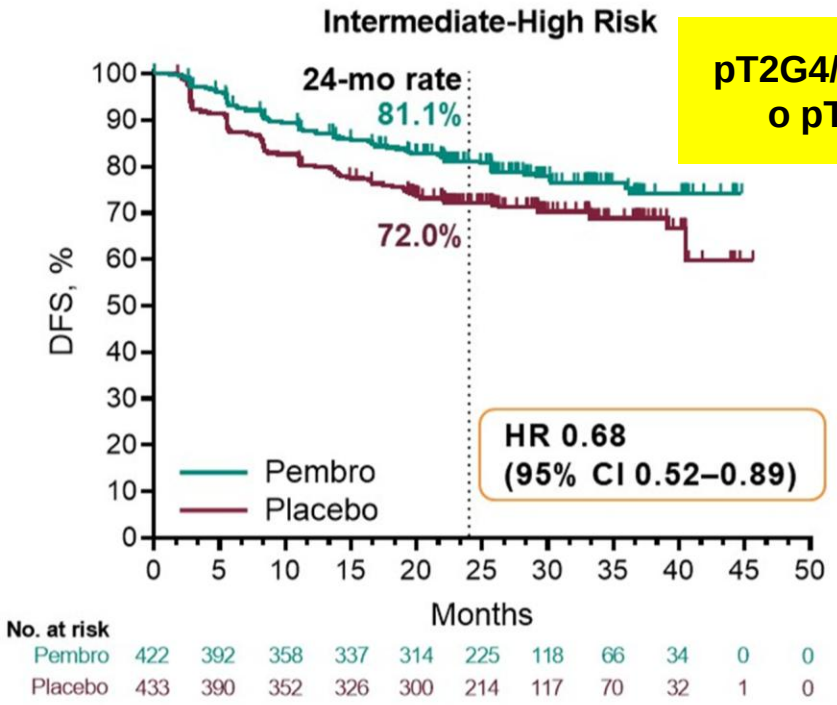
Adaptado de presentación Choueiri T en ASCO GU 2024, de Velasco G en ESMO 2023

- **Beneficio SLE consistente en todos los subgrupos**

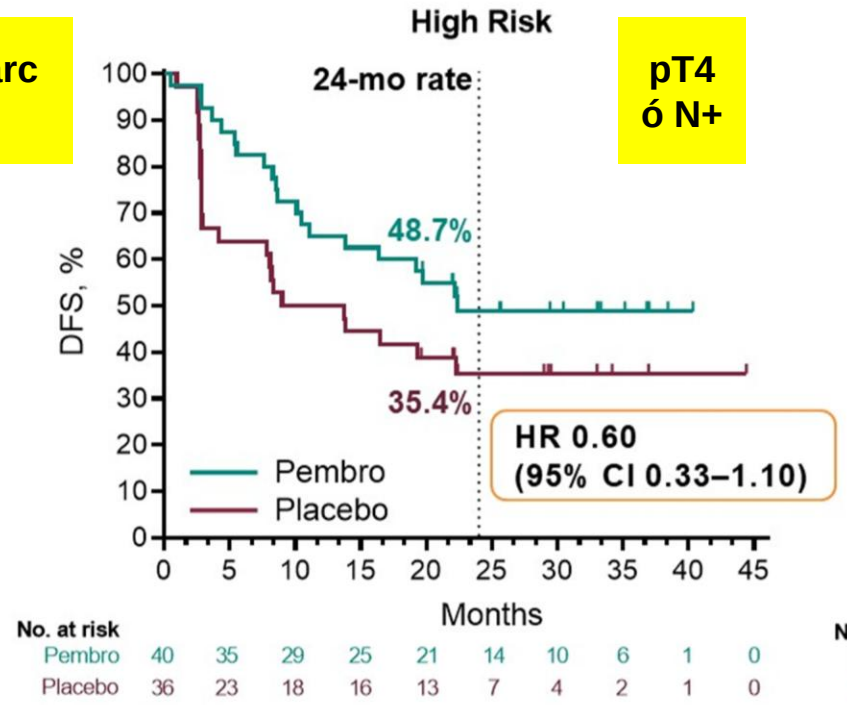


Data cutoff date: September 15, 2023.

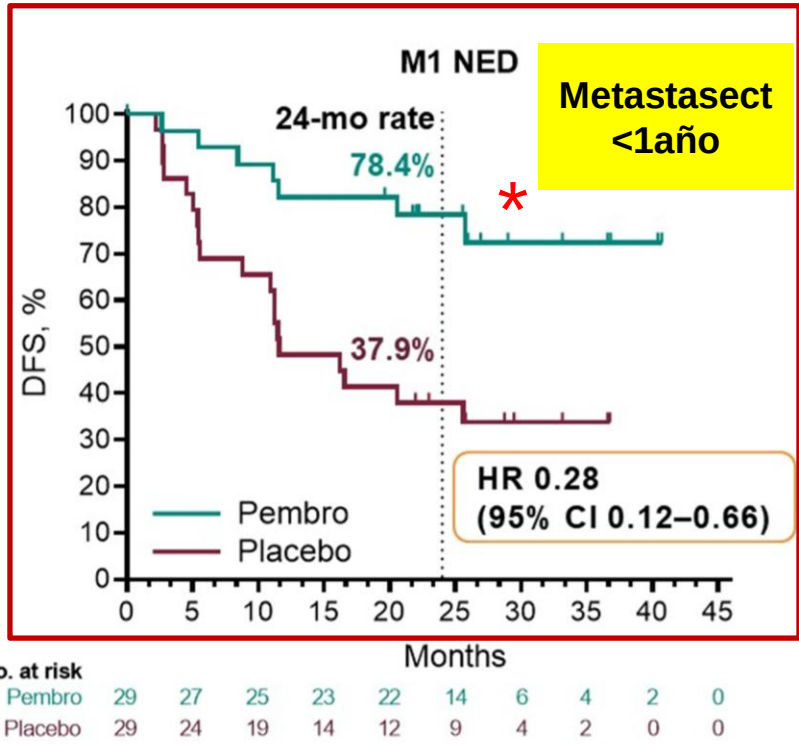
- **SLE por subgrupos de riesgo**



	Pts w/ Event	Median, mo (95% CI)
Pembro	87	NR (NR–NR)
Placebo	127	NR (40.5–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	20	22.4 (11.1–NR)
Placebo	23	11.4 (2.9–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

Adaptado de presentación Choueiri T en ASCO 2022 y ASCO GU 2023.

KN-564 Pembrolizumab adyuvante

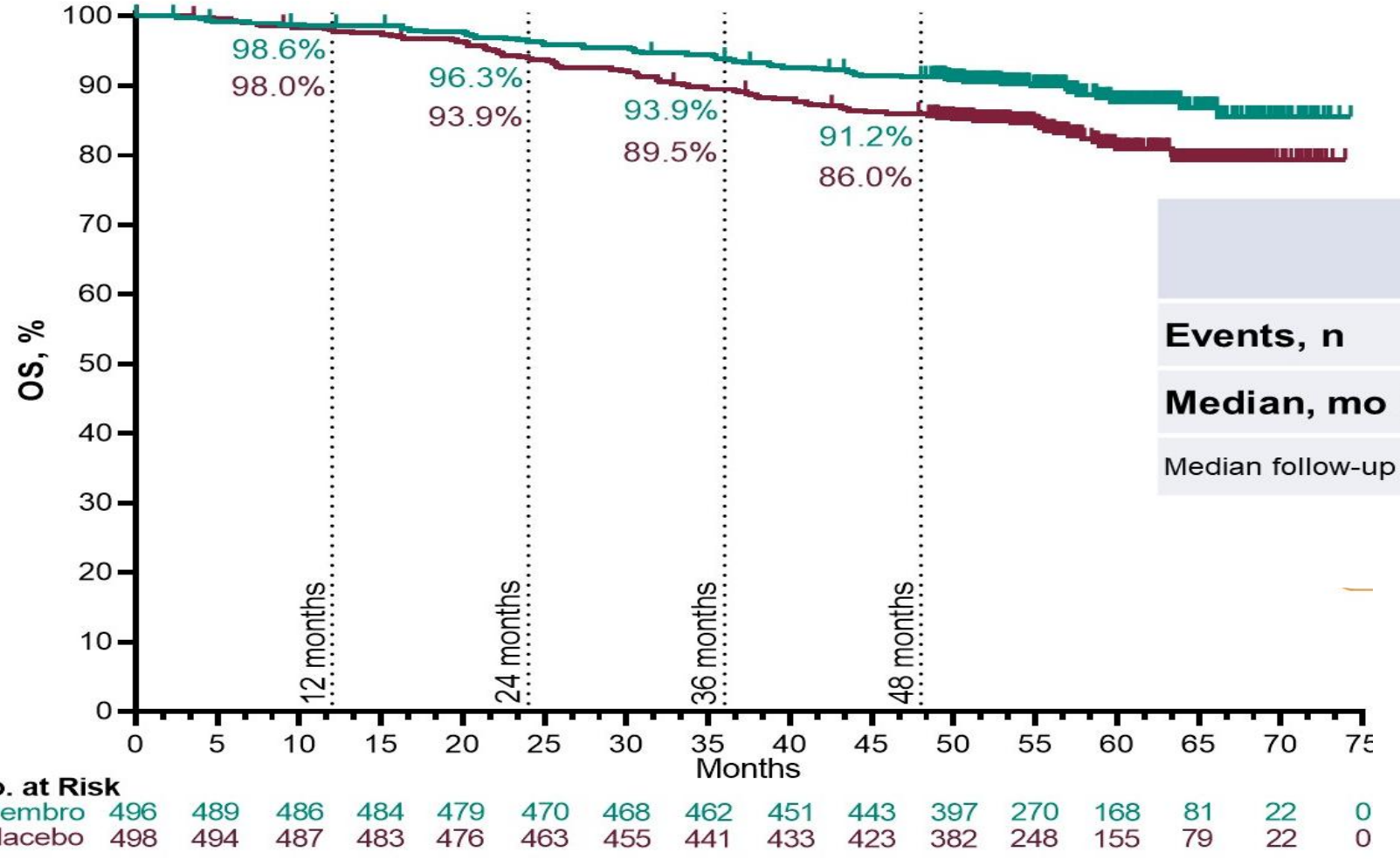
- **O.2º: SG**

STANDARD OF CARE

FDA APPROVED

EMA APPROVED

Actualización tras 57,2 m (~5 años)



	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

Median follow-up was 57.2 months (range, 47.9–74.5)

HR 0,62 (95% CI 0,44 - 0,87)
P= 0,02

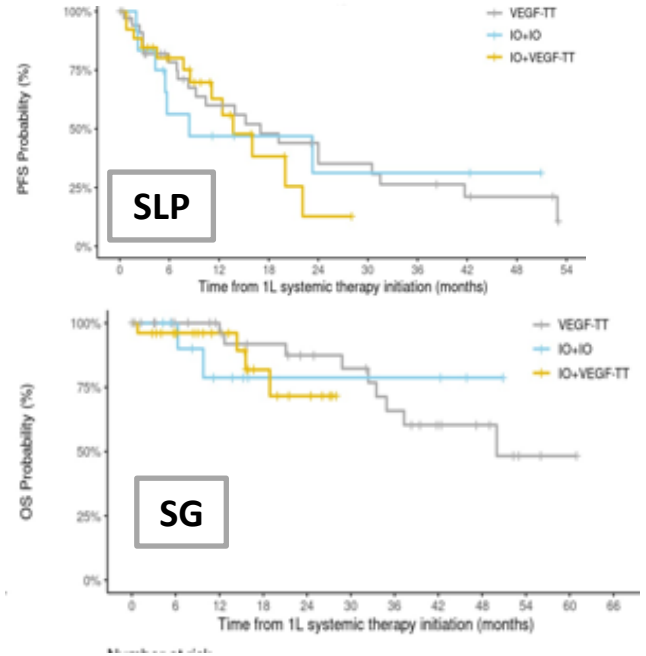
Adaptado de presentación Choueiri T en ASCO GU 2024

- **Datos de recaída y terapias subsiguientes**

	Pembrolizumab N = 496	Placebo N = 498
Total disease-free survival events—no. (%)	174 (35.1)	224 (45.0)
Recurrence*	161 (32.5)	210 (42.2)
Local	25 (5.0)	43 (8.6)
Distant	143 (28.8)	179 (35.9)
Death without documented recurrence	13 (2.6)	14 (2.8)

	Participants with Documented Recurrence	
	Pembrolizumab (N = 161)	Placebo (N = 210)
Received any subsequent therapy[a,b]	128/161 (79.5%)	171/210 (81.4%)
Received systemic anticancer drug therapy	102/128 (79.7%)	145/171 (84.8%)
Anti–PD-(L)1 therapy[c]	42/102 (41.2%)	101/145 (69.7%)
VEGF/VEGFR inhibitor[d]	94/102 (92.2%)	123/145 (84.8%)
Other[e]	32/102 (31.4%)	60/145 (41.4%)
Received radiation therapy	31/128 (24.2%)	33/171 (19.3%)
Received surgery	35/128 (27.3%)	50/171 (29.2%)
No subsequent therapy	28/161 (17.4%)	28/210 (13.3%)
No subsequent therapy data available	5/161 (3.1%)	11/210 (5.2%)

PFS and OS by 1L systemic therapy regimen types

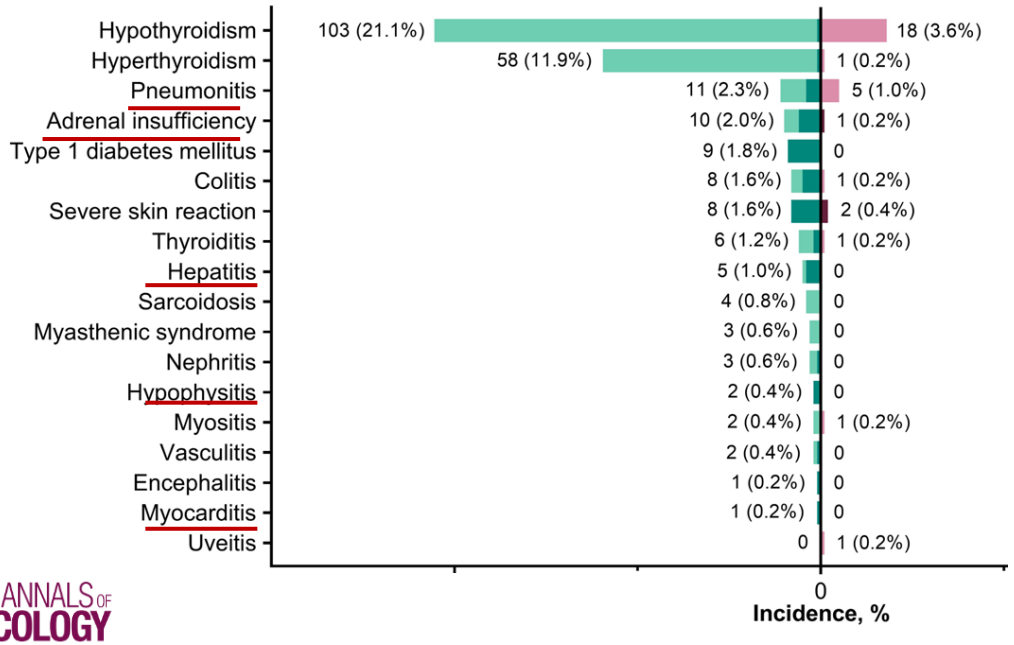


Choueiri T et al . NEJM 2024; El Zarif T presentado en ASCO 2024

- **Toxicidad**

	IA3 (57.2 mo follow-up)	
	Pembrolizumab (N = 488)	Placebo (N = 496)
Duration of therapy, median (range), months	11.1 (0.03–14.3)	11.1 (0.03–15.4)
Any-cause AEs[a]	470 (96.3%)	453 (91.3%)
Grade 3 to 5	156 (32.0%)	88 (17.7%)
Led to treatment discontinuation	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)
Serious AEs[a]	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)
Treatment-related AEs[a]	386 (79.1%)	263 (53.0%)
Grade 3 to 4	91 (18.6%)	6 (1.2%)
Led to treatment discontinuation	89 (18.2%)	4 (0.8%)
Led to death	0	0
Immune-mediated AEs and infusion reactions[b]	178 (36.5%)	36 (7.3%)
Grade 3 to 4	46 (9.4%)	3 (0.6%)
Led to death	0	0
Required high-dose (≥40 mg/day) systemic corticosteroids	37 (7.6%)	3 (0.6%)

- En su mayoría **leves**
- **PERO! 18 % EA G3/4**
- Importante **repercusión** de los EA graves:
  - Algunos **potencialmente mortal/ secuelas de por vida** → fundamental dx y tto **PRECOZ** por equipo entrenado



Manejo EA inmunomediados →

SPECIAL ARTICLE

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up ☆

Adaptado de presentación Choueiri T en ASCO GU 2024; Haanen J et al. Ann Oncol 2022.

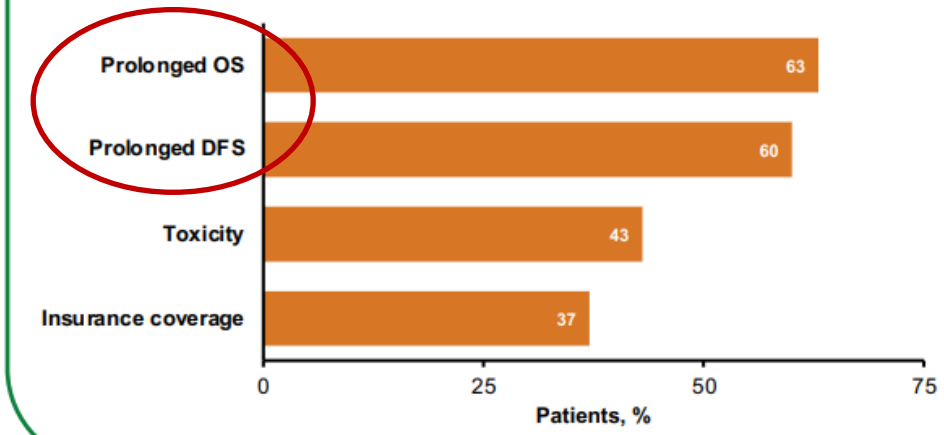
Beneficio/riesgo

- SLE (buen subgrogado?)
- **SG**

- Toxicidad – EA largo plazo
- Riesgo de sobre-tratamiento
- Calidad de vida
- Impacto económico

Preferencias del paciente respecto a adyuvancia

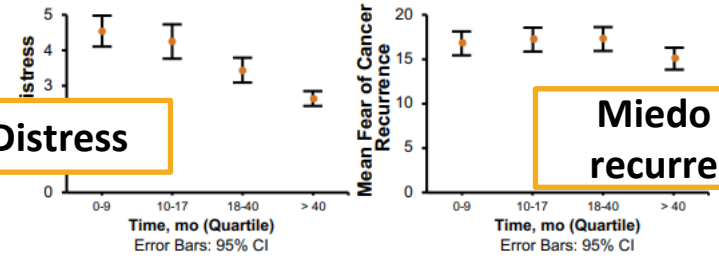
Q. If you were able to get treatment to prevent recurrence of your kidney cancer, what would be important for you?[1,2,a]



- Patient surveys indicate that patients are willing to use adjuvant therapy if the treatment prolongs OS or DFS
- Toxicity of treatment is less important to patients than efficacy endpoints

[a] N = 450 patients with RCC.
1. Battle D et al. *J Clin Oncol.* 2018;36(6_suppl):644. 2. Battle D et al. *J Clin Oncol.* 2018;36(15_suppl):4571.

Emotional Well-Being and Time Since Diagnosis[1,a]



Whereas rates of distress lessened as patients moved further from treatment, fear of cancer recurrence did not seem to dissipate over time

[a] N = 412 patients with localized RCC.
1. Bergerot CD et al. *JCO Oncol Pract.* 2020;16:e1264-e1271.

PeerView.com

Fig.1: Reasons for patients willing to take an adjuvant drug

Importancia comunicación médico - paciente

Encuesta a pacientes con Ca renal: percepción de beneficio/riesgo de la adyuvancia

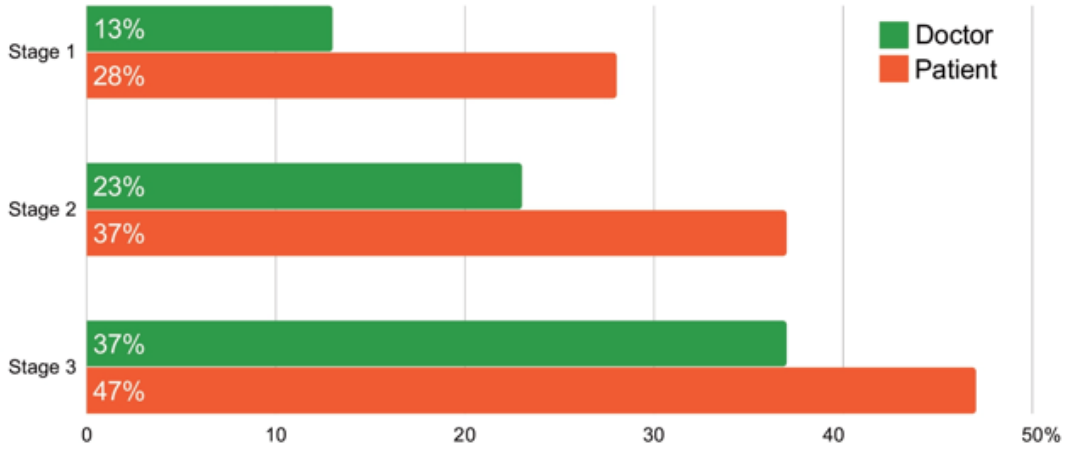


Figure 2: Risk assessment estimation according to stage

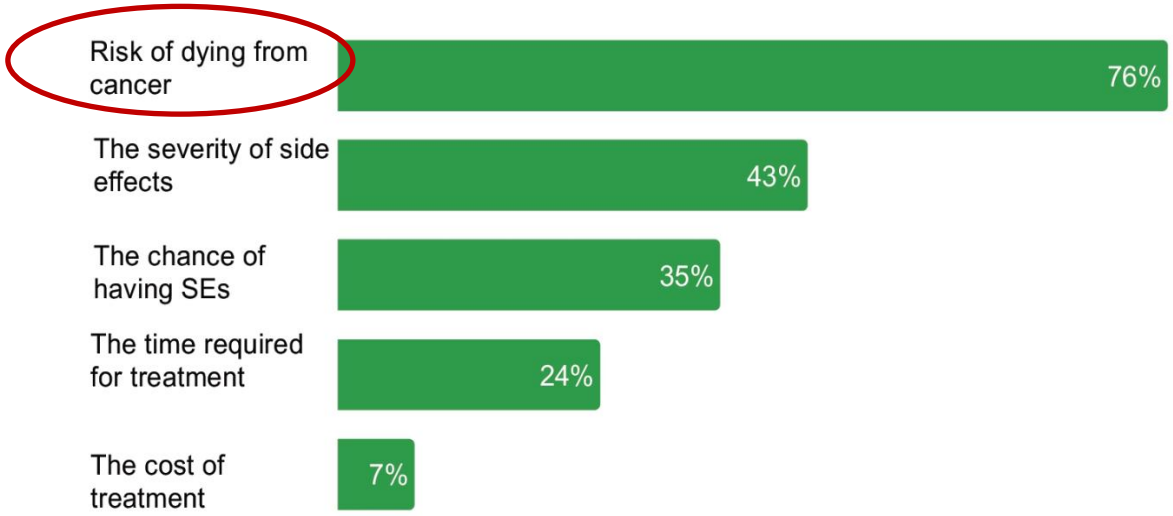


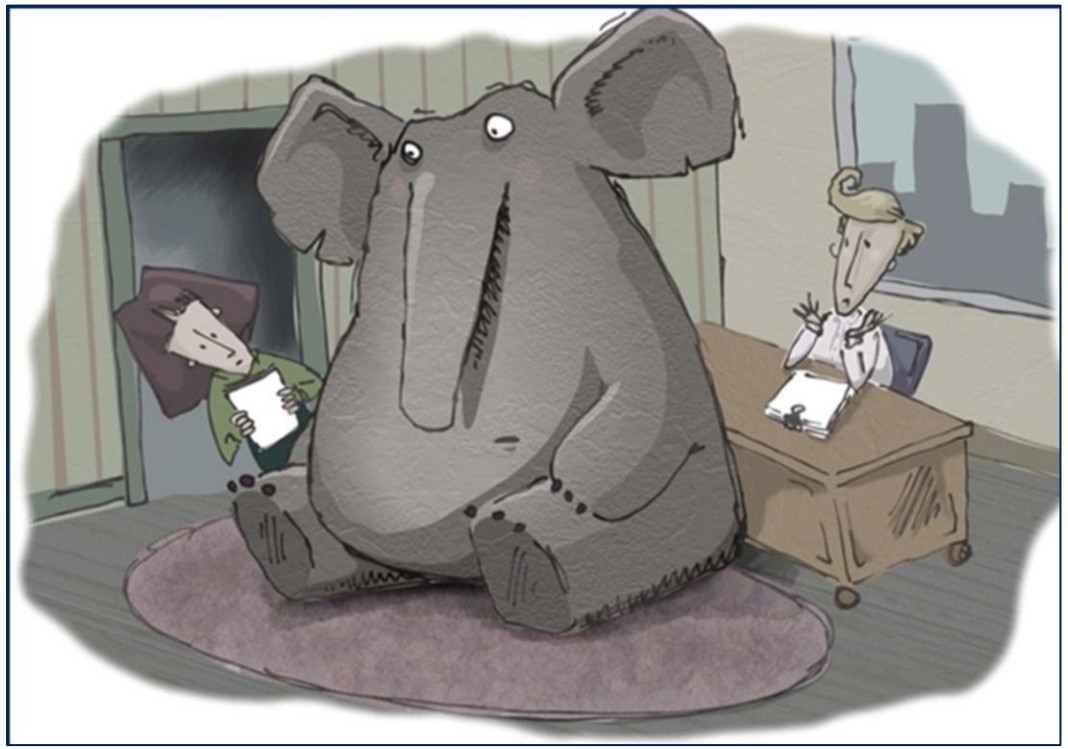
Figure 3: Factors impacting patients' decision on adjuvant therapy

Pacientes con enfermedad localizada de **alto riesgo** **sobreestiman** su **riesgo** de **recurrencia** respecto al riesgo calculado por sus médicos.

Pacientes **priorizan** el **riesgo de muerte** por cáncer por encima de los riesgos relacionados con la toxicidad

Sobreestimación del **beneficio** de la terapia adyuvante
- 49% cree reducirá riesgo recaída >30%
- **25% cree reducirá riesgo** recaída **>50%**

Adaptado de póster de Battle D en ASCO GU 2023



¿ Y el resto de estudios con inmunoterapia...?

Estudios de IO en adyuvancia Ca. Renal

Review

Adjuvant Therapy for Renal Cell Carcinoma: Hype or Hope?

Table 2. Clinical trials on immune checkpoint inhibitors in RCC adjuvant treatment.

Clinical Trial [Ref.]	No. of Patients	Tumor Features	Treatment Arms	Duration of Treatment	DFS	RFS	OS	Grade 3 or Worse AEs
KEYNOTE-564 [34]	994	Intermediate–high-risk M0-M1 NED Clear-cell RCC/sarcomatoid	Pembrolizumab Placebo	1 year	HR 0.63 (95% CI: 0.50–0.80 $p < 0.0001$)	75.2% (95% CI: 70.8–79.1) 65·5% (60.9–69.7)	HR 0.52 (95% CI 0.31–0.86, $p = 0.0048$)	32% 18%
IMmotion010 [36]	778	Intermediate–high-risk M0-M1 NED Clear-cell RCC/sarcomatoid	Atezolizumab Placebo	1 year	HR 0.93 (95% CI 0.75–1.15, $p = 0.50$)	NA	HR 0.97 (95% CI 0.67–1.42)	28% 24%
Checkmate-914 [38]	816	In M Cl RC					NA	28.5% 2%
PROSPER [39]	819	In M RC					HR: 1.48; (95% CI: 0.89–2.48; P1-sided = 0.93).	20% 6%
LITESPARK 002 [41]	1600	Cl gr N grade, N0, M0 or pT, any stage/grade, N+, M0) or M1 NED	Placebo + pembrolizumab				NA	NA
RAMPART [40]	1750	Clear-cell and non-clear-cell histological RCC subtypes with high or intermediate risk of relapse (Leibovich score 3–11).	Durvaumab + tremelimumab Placebo	1 year	DFS and OS	NA	NA	NA

NED, no evidence of disease; RCC, renal cell carcinoma; DFS, disease-free survival; RFS, relapse-free survival; CI, confidence interval; AEs, adverse events; OS, overall survival; NA, not available.

Heterogéneos

Cosso F et al. Int. J. Mol. Sci. 2023,

Estudios de IO en adyuvancia Ca. Renal

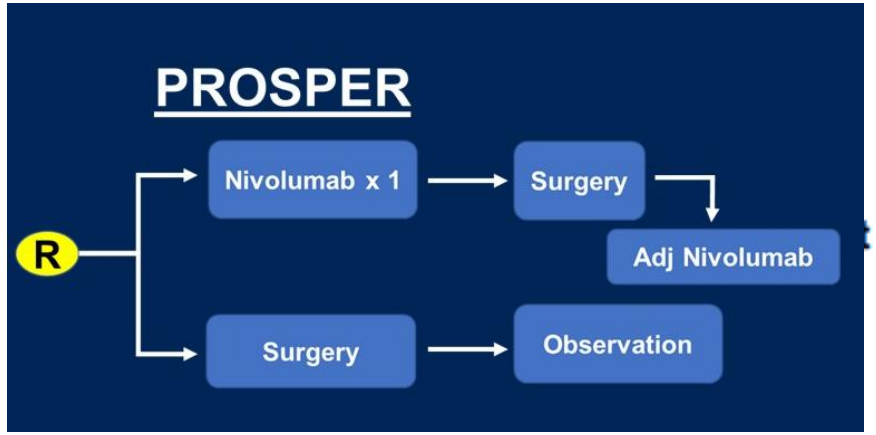
¿Por qué solo KN 564 ha conseguido demostrar beneficio en supervivencia?

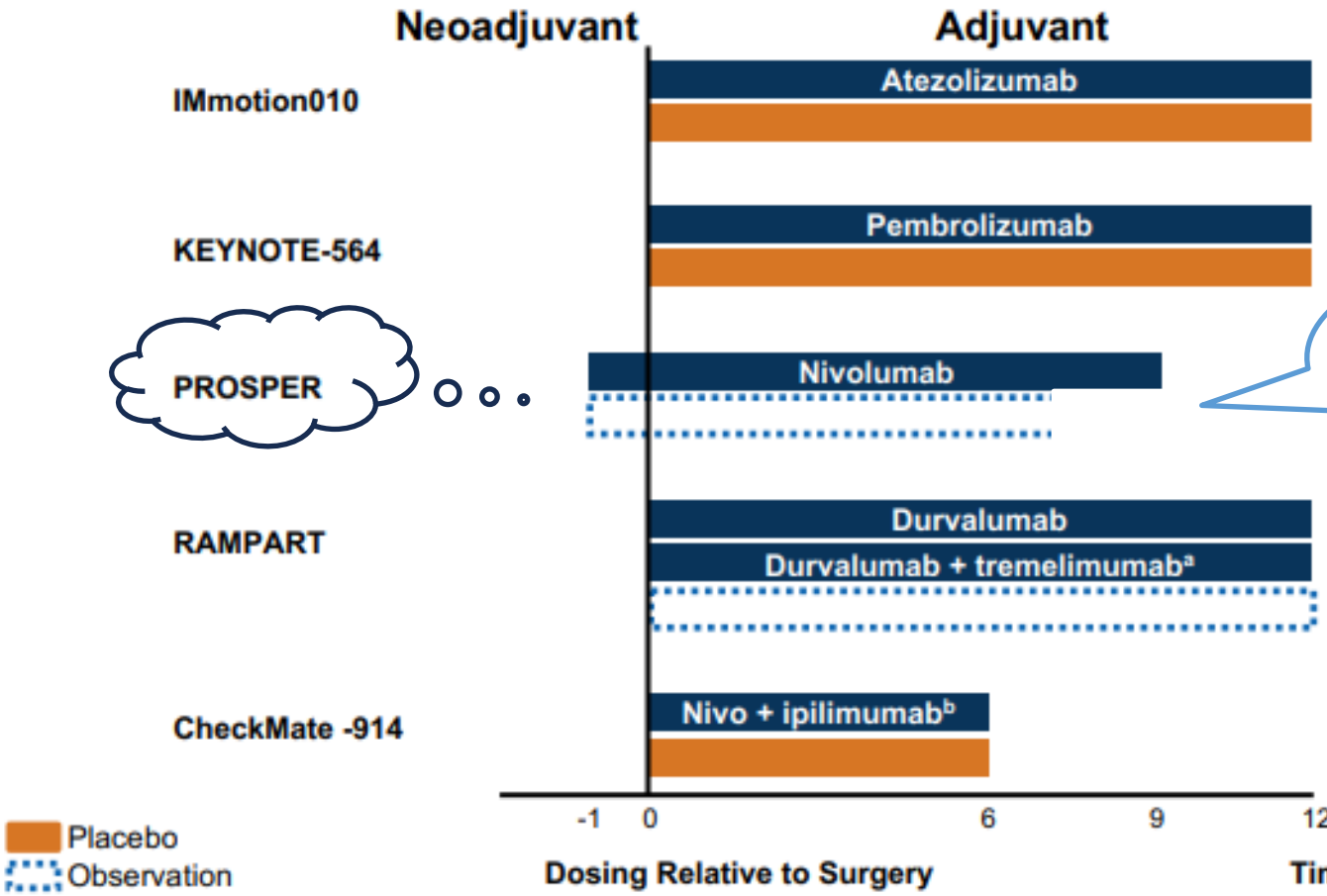
Trial	Experimental Arm	Control Arm	Duration	Inclusion Criteria	Histology	pT3/T4	pN1+	Sarcomatoid	M1	N	DFS/RFS
	≠		≠	≠	≠	≠			≠		
CM914 **part A**	IpiQ6W + Nivo Q2W	Placebo	6m	≥pT2aG3 N+	Clear cell	85%	N/A	5%	0%	816	0.92, 0.71-1.19
IMMOTION	AtezoQ3W	Placebo	12m	≥pT2aG4 M1NED	Clear cell	N/A*	N/A	9%	14%	778	0.93, 0.75-1.15
PROSPER	NivoQ4W	Observation	9m	cT1 OligoM1	Any	66%	10%	8%	3%	819	0.97, 0.74-1.28
KN 564	PemQ3W	Placebo	12m	≥pT2 G4 M1NED	Clear cell	93%	6%	10%	6%	984	0.63, 0.50-0.80
RAMPART	Durva/Treme Durva	Placebo	12m	Leibovich score 3-11	Any					1750	
LITESPARK 002	Belzutifan + Pembrolizumab	Placebo + Pembro	12m	≥pT2G4 M1 NED	Clear-cell						
CM 914 part B	NivoQ2w	Placebo	6m	≥pT2aG3 N+	Clear-cell	88%	N/A	7.8%	0%		**0,87 (0,62-1,21)**

1. Motzer, R. J. et al. Lancet 401, 821–832 (2023); 2. Pal, S. K. et al. The Lancet 400, 1103–1116 (2022
3. Allaf, M. et al. Annals of Oncology 33, S1432–S1433 (2022); 4. Choueiri, T. K. et al. NEJM 385, 683–
5. Powles, T. et al. Lancet Oncol 23, 1133–1144 (2022); 6. Oza, B. et al. Contemp Clin Trials 108, 1064

Adaptado de presentación de Velasco G en ESMO 2023 y Zibelman M en ASCO GU23; Motzer et al JCO 2025

≠ Diseño





1 dosis neo es suficiente???

		DFS	994 (actual)
PROSPER		EFS	766 (estimated)
RAMPART	ccRCC, nccRCC	DFS, OS	1,750 (estimated)
CheckMate -914	ccRCC	DFS	1,600 (estimated)

[a] Tremelimumab: two doses at the beginning of adjuvant treatment. [b] Ipilimumab: four doses at the beginning of adjuvant treatment.
1. https://clinicaltrials.gov. 2. Martinez Chanza N et al. *Curr Treat Options Oncol.* 2019;20:44.

Adaptado de presentación de Zibelman M en ASCO GU23; Zhang T - PeerView Live ASCO GU 2022

≠ Selección

Trial	Experimental Arm	Control Arm	Duration	Inclusion Criteria ≠	Histology ≠	pT3/T4 ≠	pN1+	Sarcomatoid	M1 ≠	N	DFS/RFS
CM914 **part A**	IpiQ6W + Nivo Q2W	Placebo	6m	≥pT2aG3 N+	Clear cell	85%	N/A	5%	0%	816	0.92, 0.71-1.19
IMMOTION	AtezoQ3W	Placebo	12m	≥pT2aG4 M1NED	Clear cell	N/A*	N/A	9%	14%	778	0.93, 0.75-1.15
PROSPER	NivoQ4W	Observation	9m	cT1 OligoM1	Any	66%	10%	8%	3%	819	0.97, 0.74-1.28
KN 564	PemQ3W	Placebo	12m	≥pT2 G4 M1NED	Clear cell	93%*	6%	10%*	6%	984	0.63, 0.50-0.80
RAMPART	Durva/Treme Durva	Placebo	12m	Leibovich score 3-11	Any					1750	
LITESPARK 002	Belzutifan + Pembrolizumab	Placebo + Pembro	12m	≥pT2G4 M1 NED	Clear-cell						
CM 914 part B	NivoQ2w	Placebo	6m	≥pT2aG3 N+	Clear-cell	88%	N/A	7.8%	0%		**0,87 (0,62-1,21)**

1. Motzer, R. J. et al. Lancet 401, 821–832 (2023); 2. Pal, S. K. et al. The Lancet 400, 1103–1116 (2022
3. Allaf, M. et al. Annals of Oncology 33, S1432–S1433 (2022); 4. Choueiri, T. K. et al. NEJM 385, 683–
5. Powles, T. et al. Lancet Oncol 23, 1133–1144 (2022); 6. Oza, B. et al. Contemp Clin Trials 108, 1064

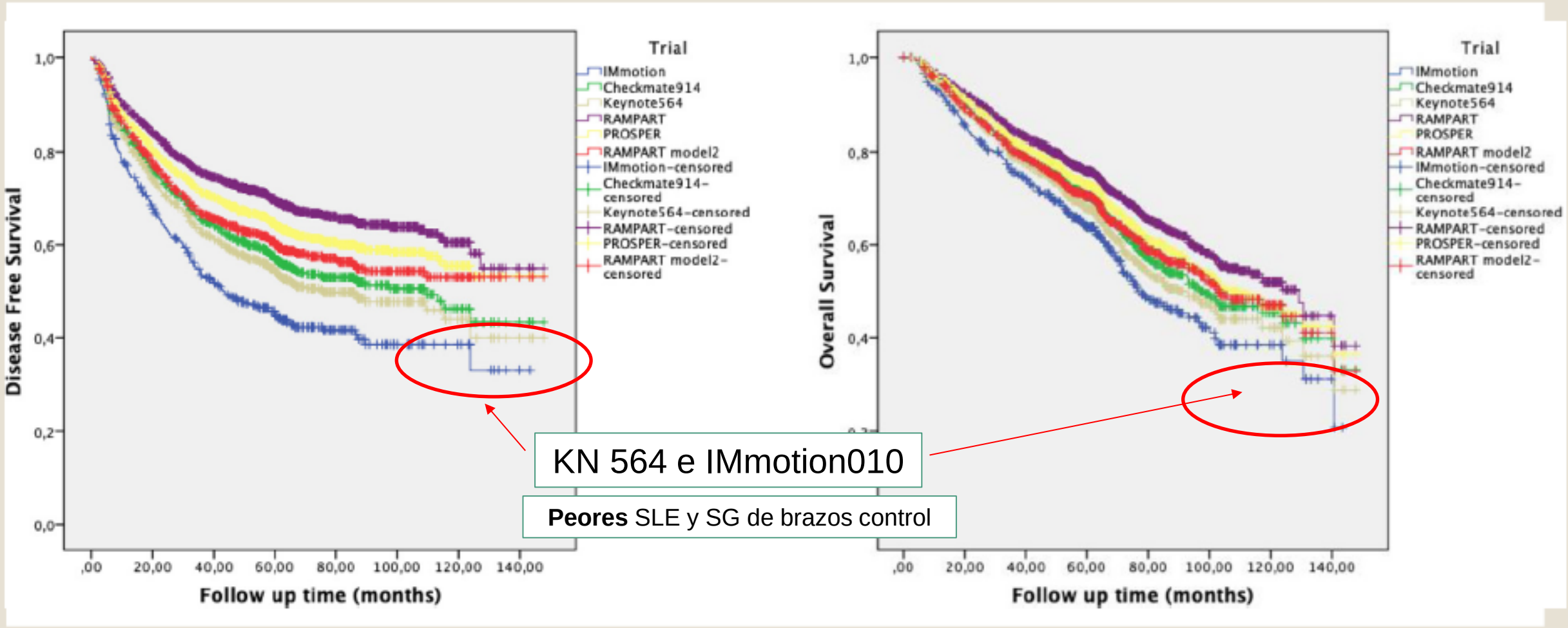
*IMmotion010 separa a los pacientes en T2/T3a y T3b-c/T4/N1 (21%)

Adaptado de presentación de Velasco G en ESMO 2023 y Zibelman M en ASCO GU23; Motzer et al JCO 2025

Brazo control ≠ pronóstico

Prevalence, Disease-free, and Overall Survival of Contemporary Patients With Renal Cell Carcinoma Eligible for Adjuvant Checkpoint Inhibitor Trials

Figure 3 A, Disease-free Survival. B, Overall Survival; Log Rank $P < .001$ (En brazos control)



KN 564 e IMmotion010

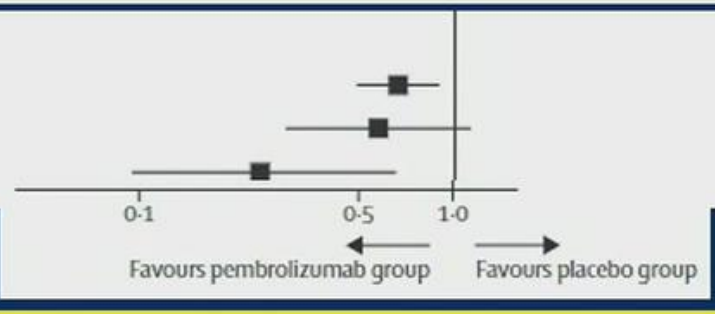
Peores SLE y SG de brazos control

≠ Definición de M1 NED → ≠ beneficio

-KN564 <12m
-Immotion 010 >12m

KN-564

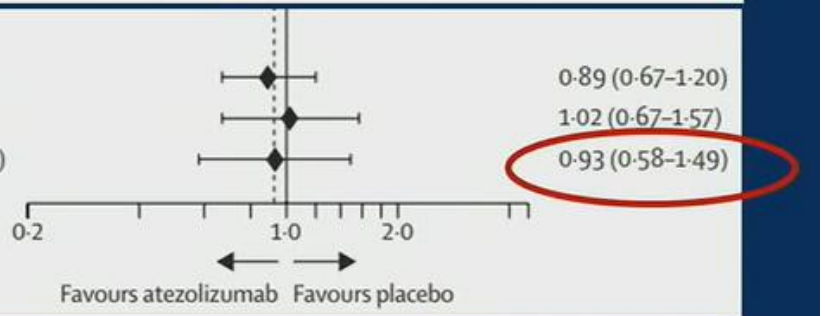
	Events/participants (n/N)		Hazard ratio (95% CI)
	Pembrolizumab	Placebo	
Disease risk category			
M0 intermediate-high	87/422	127/433	0·68 (0·52–0·89)
M0 high	20/40	23/36	0·60 (0·32–1·10)
M1 no evidence of disease	7/29	19/29	0·28 (0·12–0·66)



Powles et al. *Lancet*.2022

IMmotion 010

	Events (n)/patients (N)		Median disease-free survival, months (95% CI)		HR (95% CI)
	Atezolizumab	Placebo	Atezolizumab	Placebo	
UISS risk score‡					
Intermediate to high risk	90/240	88/221	NE (NE to NE)	52·9 (49·1 to NE)	0·89 (0·67–1·20)
High risk	39/94	46/115	NE (33·0 to NE)	NE (37·9 to NE)	1·02 (0·67–1·57)
M1 NED	35/56	34/52	24·8 (14·0 to 47·1)	30·0 (15·9 to 45·4)	0·93 (0·58–1·49)



Pal et al. *Lancet*. 2022

≠ Toxicidad

"Más" no siempre es mejor

	KN-564 (Pembro)	CM-914 (Ipi/Nivo)	IMmotion010 (Atezo)	PROSPER (Periop Nivo)
Gr 3+ AEs	32%	38%	27%	33%
Tx-related Gr 3+ AEs	19%	28%	14%	15%
Discontinuation due to AE	21%	33%	12%	13%
Received steroids for an irAE	8%	23%	10%	N/A

→ In CM-914, only 57% of patients completed all 4 doses of both drugs

Choueiri et al. *NEJM*. 2021; Powles et al. *Lancet*.2022; Motzer et al. ESMO 2022; Pal et al. *Lancet*. 2022; Allaf et al. ESMO 2022

Perspectivas futuras

Biomarcadores – mejor selección de pacientes

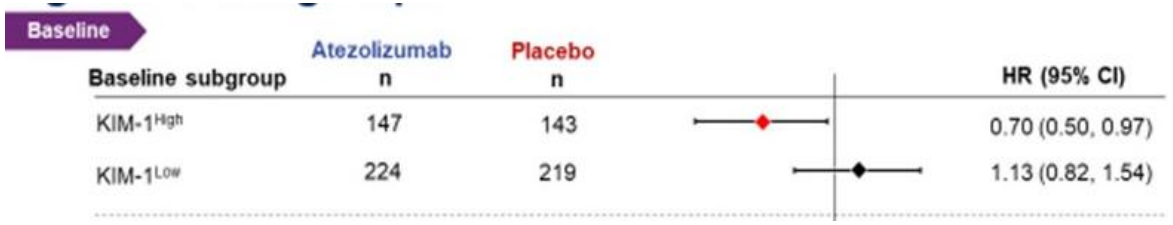
→ ***Ensayos basados en cohortes históricas de riesgo...***

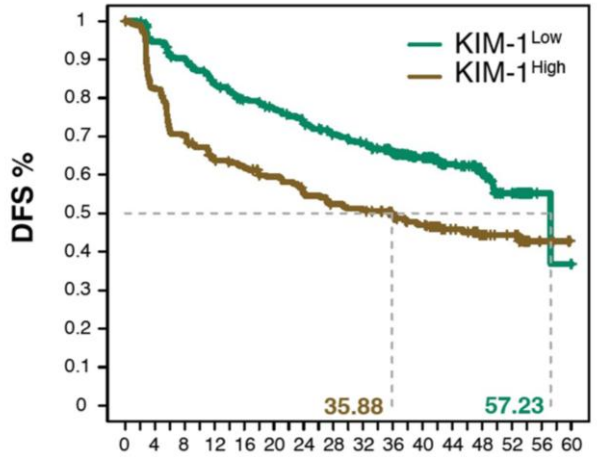
KIM-1

Como biomarcador pronóstico y predictivo

IMmotion010 – Atezolizumab:

- ↑ KIM-1 – peor SLE
- >beneficio Atezolizumab en aquellos ↑KIM-1



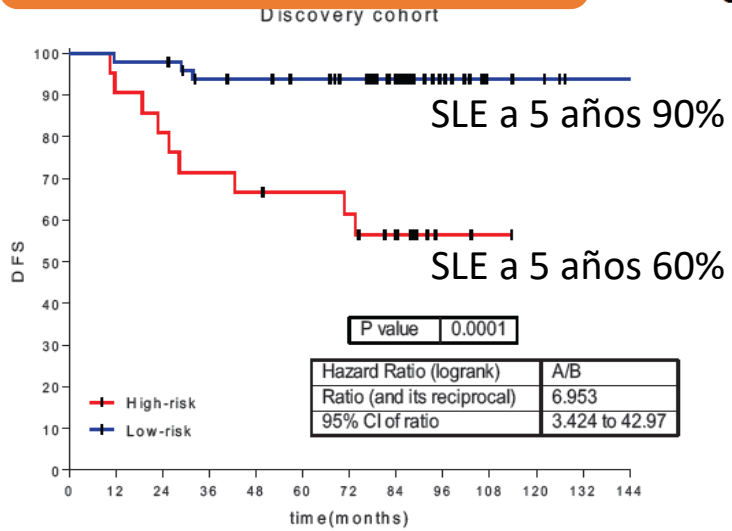


CM 914 – Ipi Nivo y Nivo adyuv:

- ↑ KIM-1 – peor SLE

Firma micro RNA

1473P - A prognostic microRNA-based signature for localized clear cell renal cell carcinoma and definition of therapeutic targets in high-risk patients



SLE a 5 años 90%

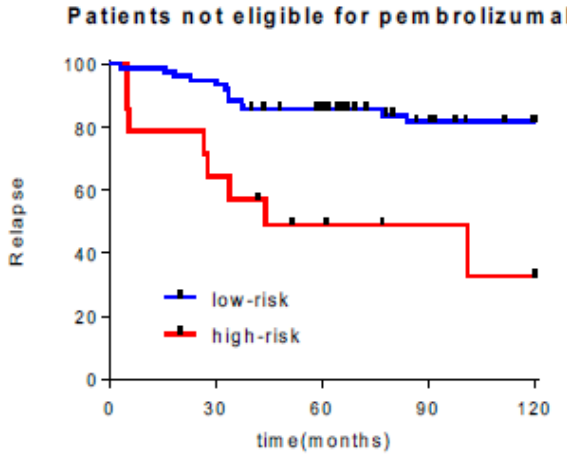
SLE a 5 años 60%

Pacientes de bajo riesgo, no incluidos en KN 564:

Amongst patients **excluded from the KEYNOTE-564 due to low-risk features**, Bio-miR defines a **high-risk population** who should be prioritized for adjuvant therapy.

P value	0.0002

Hazard Ratio (logrank)	A/B	B/A
Ratio (and its reciprocal)	0.2161	4.626
95% CI of ratio	0.02047 to 0.2919	3.426 to 48.85



Adaptado de presentación Albiges L en ASCO GU 2025; Adaptado de póster Pinto A en ESMO 2022

¿Cómo mejorar resultados? – Ensayos en curso perioperatorio

Ensayos de combinación

- ICI + inhibidores HIF 2α (belzutifan)
- ICI + TKI
- ICI + TKI +/- inhibidores HIF 2α (belzutifan)
- ICI + vacunas
- ICI + RT
- Vacuna neoadyuvante autóloga de DC1/péptido + TKI
- Ensayos en NO cél claras

Modular S.I + tasa de respuesta patológica

Study	NCT ID	# pts	Drugs
Nescio	NCT05148546	69	6 wks of Neoadj Nivolumab or neoadj ipi/nivo or neoadj relatlimab/nivo
Spartalizumab + Canakinumab in Pts With ccRCC (SPARC-1)	NCT04028245	14	Neoadj CTLA-4, neoadj PD-1
NeoAdj Pembrolizumab and STEreotactic Radiotherapy Prior to Nephrectomy for Renal Cell Carcinoma (NAPSTER)	NCT05024318	20	1 dose neoadj pembro , then SABR (42Gy x 3 fractions), then 2 doses pembro (12 wks) vs SABR (42Gy x 3 fractions)

Study	ID	Duration of therapy	Results	Ref
Neoadjuvant axitinib + avelumab in Pts with ccRCC	NCT03341845	12 weeks	40 pts enrolled 12/40 PR by RECIST	ASCO 2023
Neoadjuvant sitravatinib +nivolumab in Pts with ccRCC	NCT03680521	2 wks sitra 4-6 wks sitra + nivo	25 enrolled 17 for efficacy. ORR 11.8% by RECIST	Nature Comm 2023
Neoadjuvant durvalumab +/- tremelimumab in pts with any histology RCC	NCT02762006	1 dose durva or combination	29 pts enrolled Safety primary endpt	ASCO 2020
Neoadjuvant nivolumab in Pts with ccRCC	NCT02595918	4- 2 wk doses (8 wks)	18 pts enrolled 16/18 patients completed all four doses. 18/18 SD by RECIST	Eur Urol. 2022
Neoadjuvant nivolumab in Pts with ccRCC	NCT02575222	3- 2wk doses (6 wks)	17/17 SD 6.7% (1) IR PR	Eur Urol Oncol. 2022

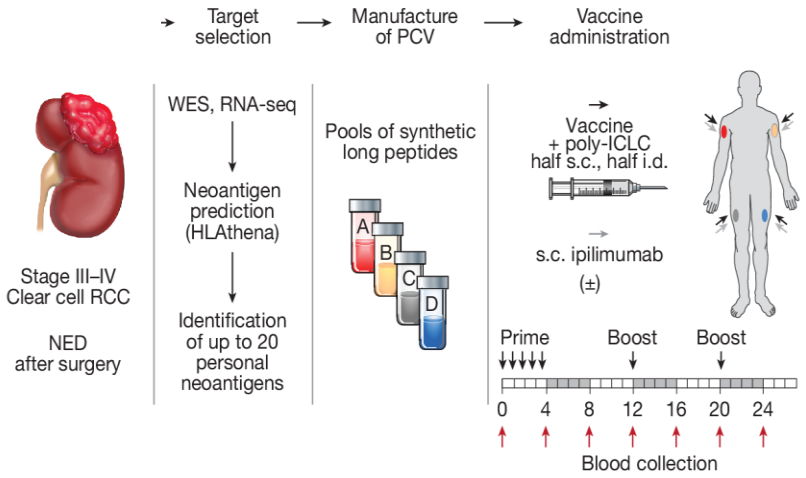
ICI + VEGFR-TKI Studies	NCT ID	# pts	Drugs
Neoadjuvant Lenvatinib and Pembrolizumab for IVC Tumor Thrombus	NCT05319015	30	12 weeks of Neoadj pembrolizumab Neoadj lenvantinib Adj pembro
Neoadjuvant Pembrolizumab and Lenvatinib for Renal Cell Carcinoma	NCT05733715	30	3 weeks Neoadj pembrolizumab +/- Neoadj lenvantinib Then Adj pembro
Perioperative Lenvatinib With Pembrolizumab in Patients With Locally Advanced Nonmetastatic Clear Cell Renal Cell Carcinoma	NCT04393350	20	12 wks neoadj Pembro + lenvantinib
Neoadjuvant AXITINIB and AVELUMAB for Patients With Localized Clear-cell RCC and a Moderate to High Risk	NCT03341845	40	Neoadj axitinib Neoadj Avelumab (PDL-1)
Neoadjuvant Pembrolizumab and Axitinib in Renal Cell Carcinoma with Inferior Vena Cava Tumor Thrombus (NEOPAX)	NCT05969496	17	12 weeks neoadj axitinib +pembro

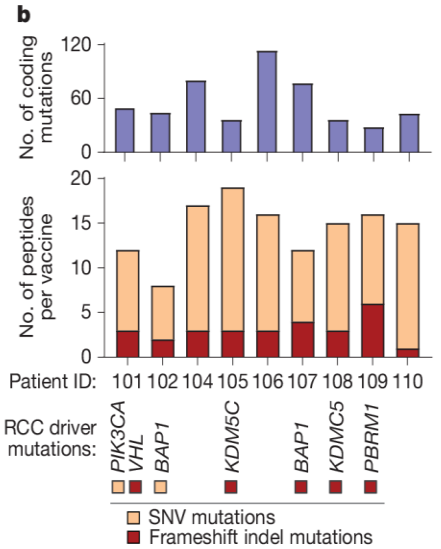
nature

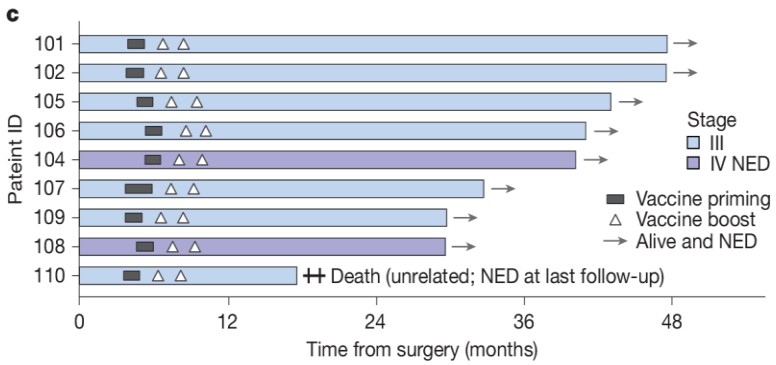
Article

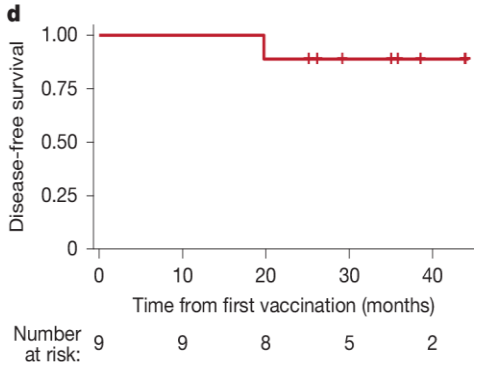
A neoantigen vaccine generates antitumour immunity in renal cell carcinoma

- **Ensayo Fase I**
- N=9 pacientes (7 estadio III, 2 estadio IV)
- Desarrollo vacuna personalizada basada en neoantígenos +/- 1 dosis Ipilimumab sc
- **Resultados**
  - Rpta inmune **fuerte** y **duradera**
  - **No recurrencias** durante seguimiento (**40,2 m**)
  - Bien tolerado. **No EA ≥G3**
- Precisa validación estudios más grandes y prospectivos







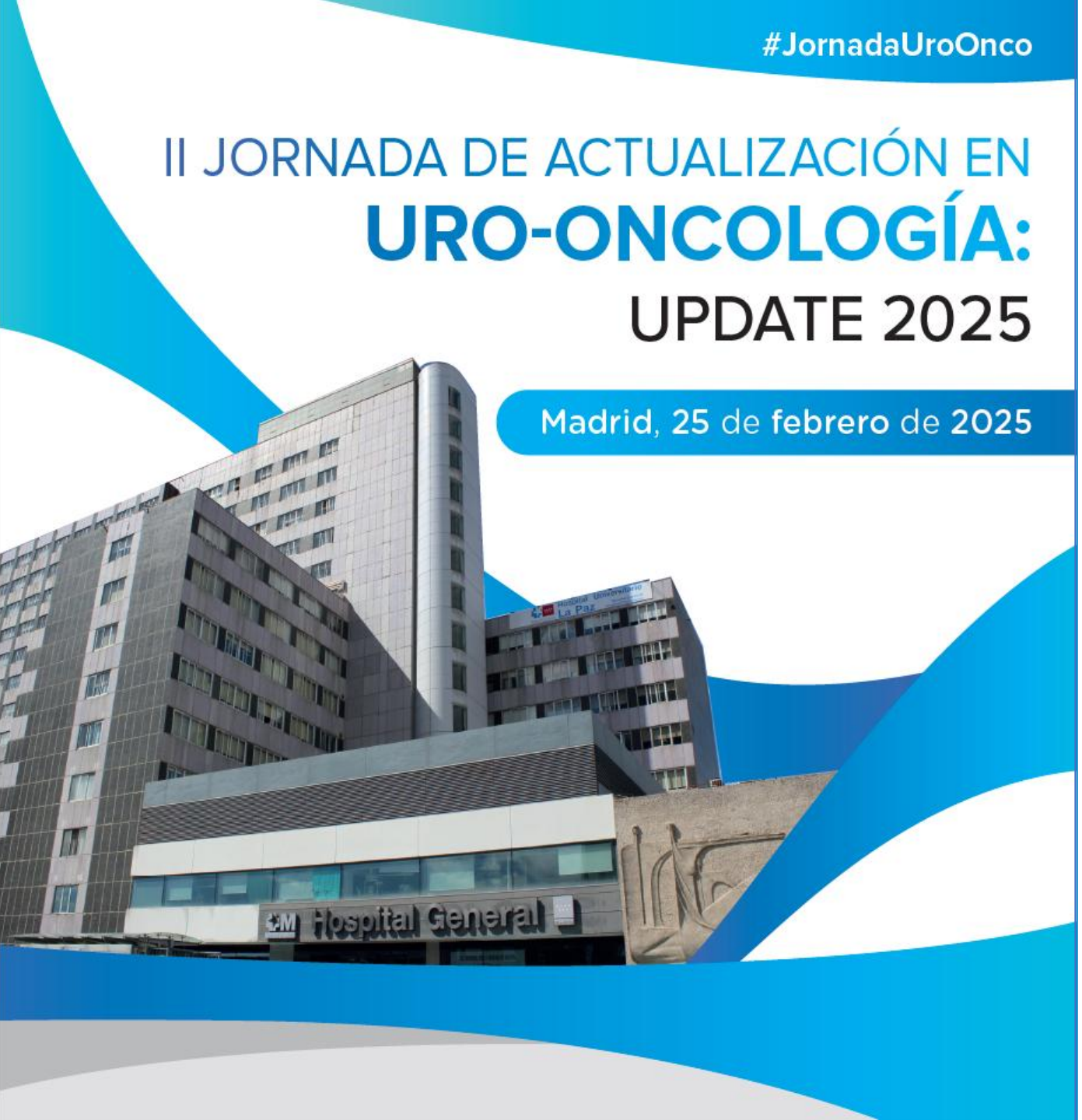


Conclusiones

- **Pembrolizumab** es el **estándar** de tratamiento en **adyuvancia de Cá renal de Cél. Claras riesgo intermedio/alto – alto – M1NED.**

  - Beneficio en **SLE** y **SG**
  - **Buen perfil de seguridad**, PERO, posibles EA inmunomediados – poco frec, pero potencialmente graves → fundamental diagnóstico y tratamiento **precoz**
  - Importancia **comunicación médico-paciente**

- **Importancia** de **SELECCIÓN DE PACIENTES y ESTRATIFICACIÓN del riesgo** en los ensayos clínicos
  - Necesitamos grupos de riesgo ACTUALIZADOS
  - Necesitamos BIOMARCADORES → elegir pacientes con mayor RIESGO
- **Cuestiones pendientes:**
  - Cómo mejorar resultados obtenidos Pembrolizumab? Ensayos perioperatorios en marcha...
  - Secuencia óptima de tratamientos a la progresión?
  - Histología no célula clara?



Muchas gracias

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