GONORTE
Grupo Oncológico

Presentaciones más destacadas en cáncer urotelial

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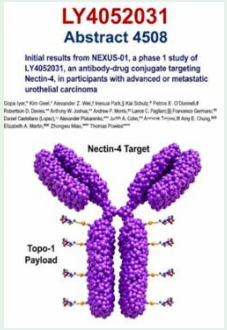
Índice de contenidos

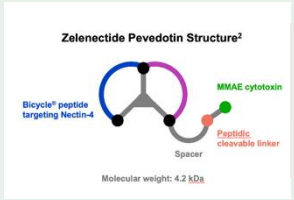
1. Carcinoma urotelial metastásico 1ª línea
EV-302: actualización 3,5 años

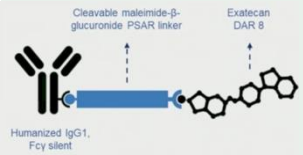
2. MIBC perioperatorio — rBCG + chemo-IO
SAKK 06/19

3. MIBC — Preservación vesical con CRT-IO
RAD-IO + SHR-A2102

4. Nuevos ADCs anti-Nectin-4
NEXUS-01 · Zelenectide · EXCEED





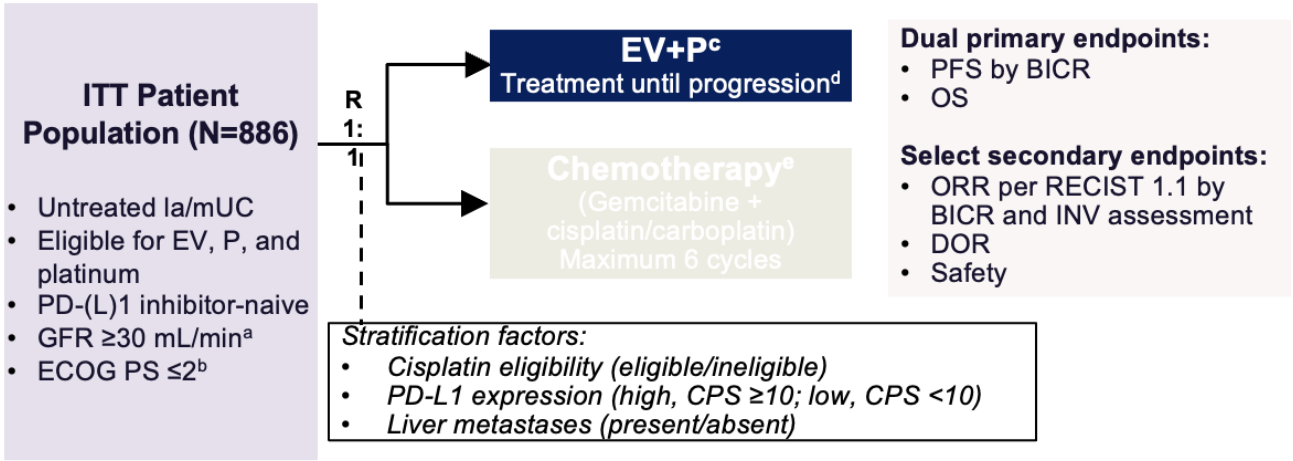


EV-302 / KEYNOTE-A39 — Actualización 3,5 años de seguimiento

Aim

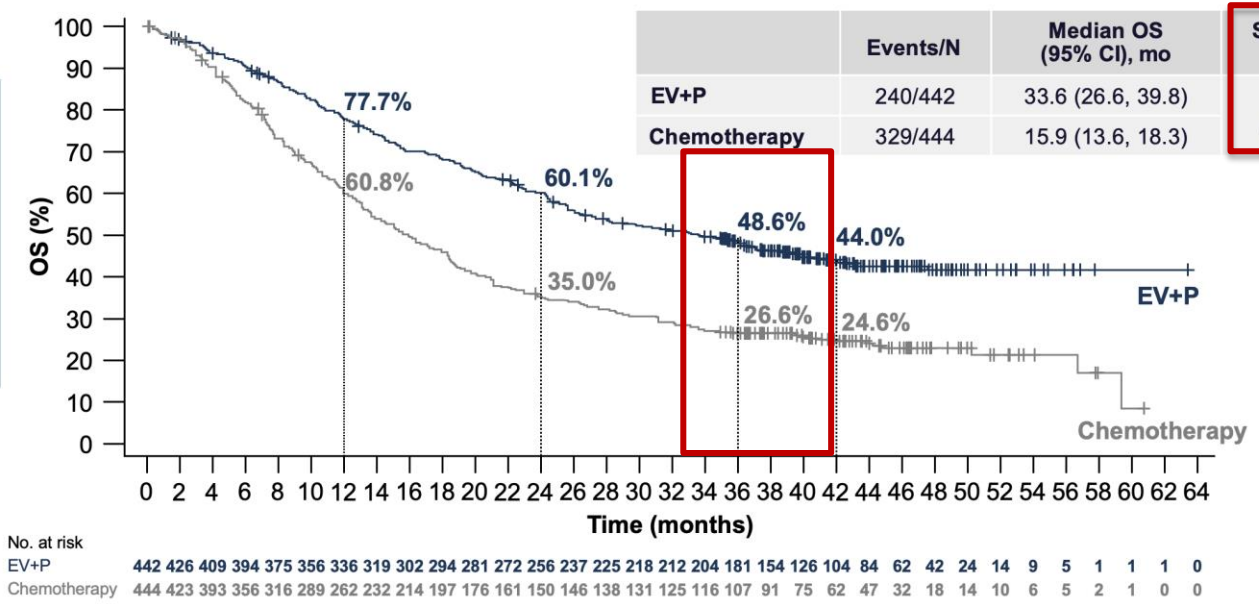
To present updated efficacy and safety after ~3.5 years of median follow-up, including exploratory subgroup analyses

Study Design



EV-302 / KEYNOTE-A39 — Actualización 3,5 años de seguimiento

At 3.5 years, an estimated 44.0% of patients in the EV+P arm were alive vs 24.6% in the chemotherapy arm[a]



	Events/N	Median OS (95% CI), mo	Stratified HR (95% CI)
EV+P	240/442	33.6 (26.6, 39.8)	0.53 (0.45, 0.63)
Chemotherapy	329/444	15.9 (13.6, 18.3)	

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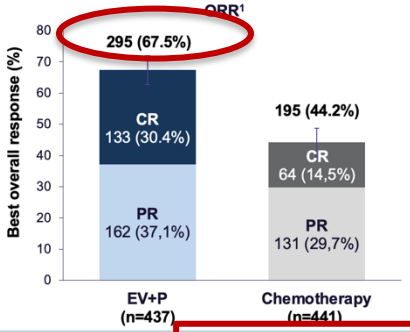
Objective Response and CR Rates in EV-302



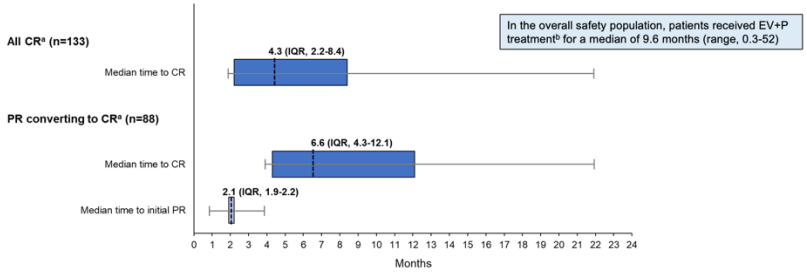
Complete response evolution²

	Response-evaluable patients	
	EV+P (n=437)	**Chemotherapy (n=441)**
Patients achieving CR, n (%)	**133 (30.4)**	**64 (14.5)**
Patients achieving CR directly	45 (10.3)	26 (5.9)
Patients achieving CR after PR	88 (20.1)	38 (8.6)

- Among patients with confirmed CR in the EV+P arm (n=133), 66.2% achieved PR initially, then converted from PR to CR (n=88)²

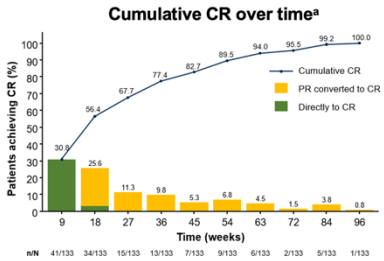
The CR rate was approximately doubled in the EV+P vs chemotherapy arm

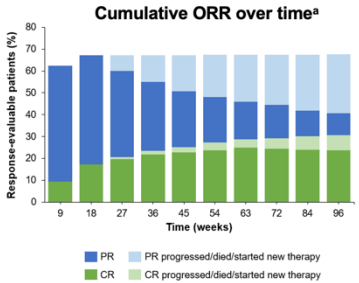
Median Time to CR[a] in the EV+P Arm



Patients with a PR converting to CR achieved CR after a median of 6.6 months from randomization

Cumulative Response Rates in the EV+P Arm



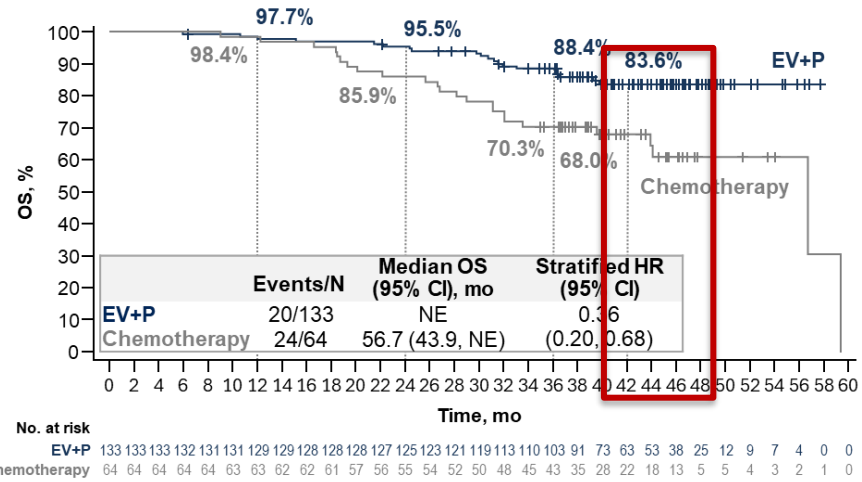


Patients continue to achieve CRs over time, and CRs show long-term durability

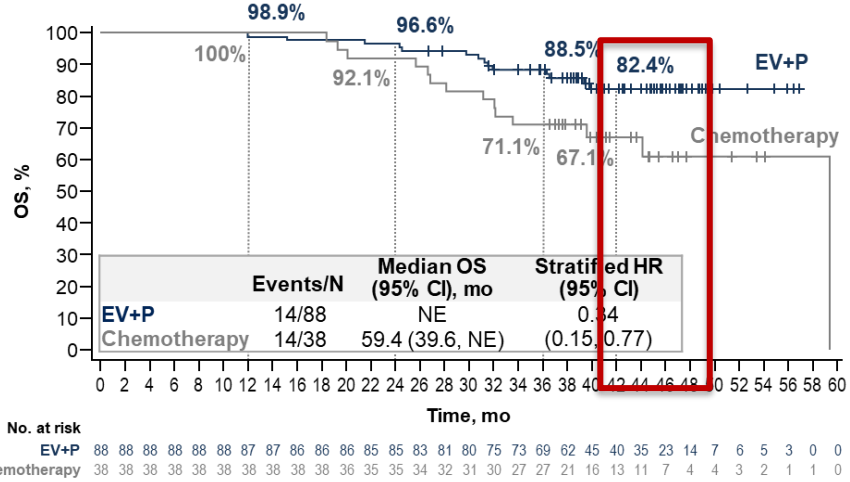
EV-302 / KEYNOTE-A39 — Actualización 3,5 años de seguimiento

OS benefit in patients with CR

All patients with CR[f]



PR converting to CR[f]



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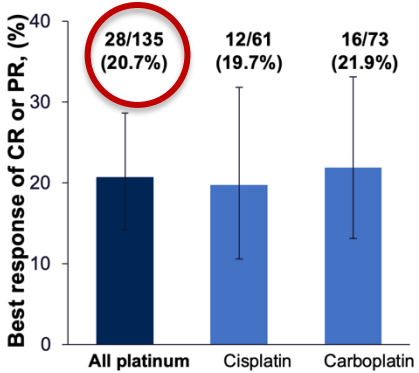
EV-302 / KEYNOTE-A39 — Actualización 3,5 años de seguimiento

Subsequent Therapy (ITT population)

	EV+P (n=442)
Patients who received subsequent anticancer therapies, n (%)	192 (43.4)
Systemic therapy	173 (39.1)
First subsequent systemic therapy, n (%)	
Platinum-containing chemotherapy[a]	135 (30.5)
Carboplatin-based therapy	73 (16.5)
Cisplatin-based therapy	61 (13.8)
PD-(L)1 inhibitor therapy[b]	17 (3.8)
Maintenance	0
EV+P-based therapy	2 (0.5)
Other PD-(L)1 inhibitor therapy	15 (3.4)
Atezolizumab	1 (0.2)
Pembrolizumab	14 (3.2)
Other	21 (4.8)

ORR in evaluable patients receiving subsequent platinum-based chemotherapy[a,c]



- Median OS from start of platinum-based chemotherapy was 10.9 months (95% CI 8.3, 12.8)

In the EV+P arm, the most common first subsequent treatment was platinum-based chemotherapy, which resulted in an ORR of 21% and a median OS of 10.9 months

La sensibilidad al platino se preserva tras EV-P

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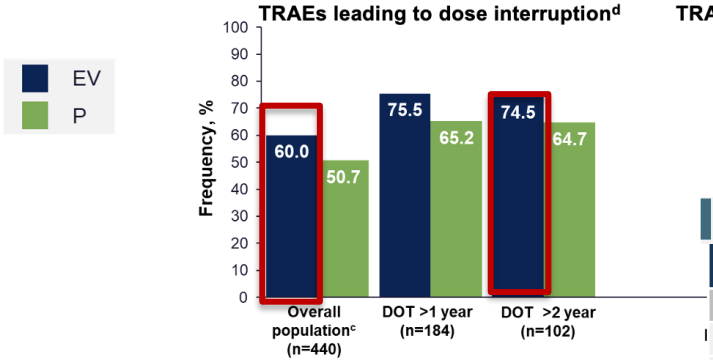
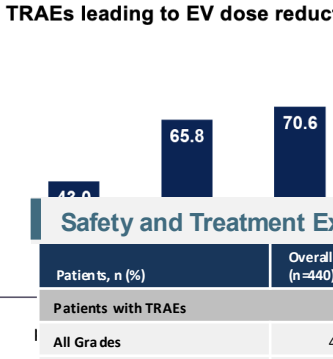
EV-302 / KEYNOTE-A39 — Actualización 3,5 años de seguimiento

Patients Remaining on Treatment and Dose Modifications (EV+P arm)[a]

Time Point	Patients on treatment[b]/ Overall population, n/n[c]	Percentage on treatment, %[b]
At 6 months	297/440	67.5%
At 12 months (1 years)	184/440	41.8%
At 18 months	139/440	31.6%
At 24 months (2 years)	102/440	23.2%





Manejo proactivo de dosis mantiene la eficacia

Safety and Treatment Exposure (EV+P arm)

Patients, n (%)	Overall population[g] (n=440)	DOT >1 year[h] (n=184)	DOT >2 year[h] (n=102)
Patients with TRAEs			
All Grades	428 (97.3)	183 (99.5)	102 (100)
Grade ≥3	251 (57.0)	108 (58.7)	59 (57.8)

At 2 years after treatment initiation, 23.2% of pati
Rate of TRAEs leading to dose modification remained similar regardless of treatment duration

Powles, T., et al. Presented at: ASCO Annual Meeting; May 28-June 2, 2026; Chicago, USA. Oral Presentation: Abstract 4507.

EV-302 / KEYNOTE-A39 — Actualización 3,5 años de seguimiento

Key takeaway points/conclusions

- EV + P continues to demonstrate superior overall survival benefit versus chemotherapy as 1L treatment for la/mUC
- After EV+P, subsequent platinum-based chemotherapy resulted in clinically meaningful response rates
- Cumulative responses to EV+P deepened over time, with particularly favorable outcomes in patients who achieved a CR
- Dose interruptions and reductions are important to manage AEs and continue EV+P therapy

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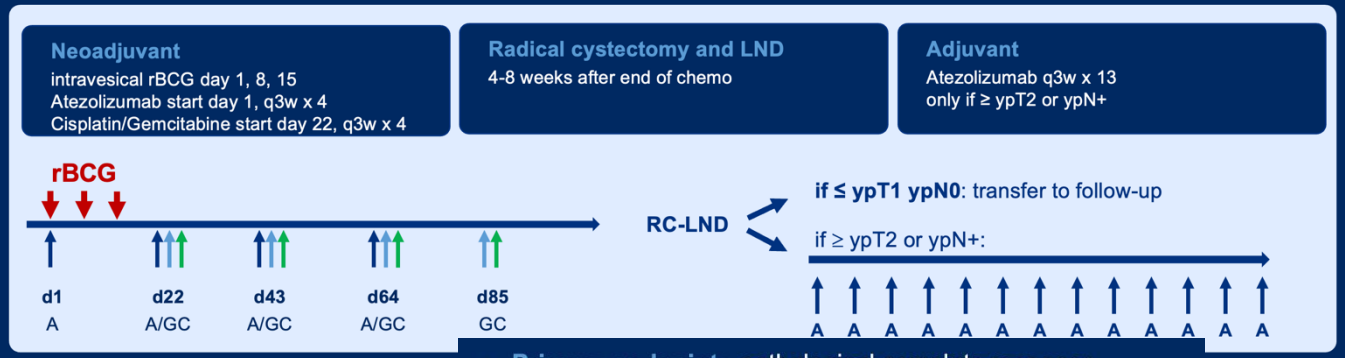
SAKK 06/19 — BCG recombinante intravesical + chemo-IO neoadyuvante en MIBC

Study design

- SAKK 06/19 is a prospective single arm, open-label multicenter phase II trial N:47
- **Inclusion:** cT2- T4a cN0/N1; WHO PS 0-1; cisplatin fit (GFR >50); UC, subtypes allowed*
- **Exclusion:** prior intravesical BCG; small cell component

* subtypes: no percentage threshold but no pure squamous/glandular



- **Primary endpoint:** pathological complete response (pCR, ypT0 ypN0) at cystectomy (central review)
- **Secondary endpoints:** pathological response (PaR) ≤ ypT1ypN0, EFS*, OS**, feasibility, safety

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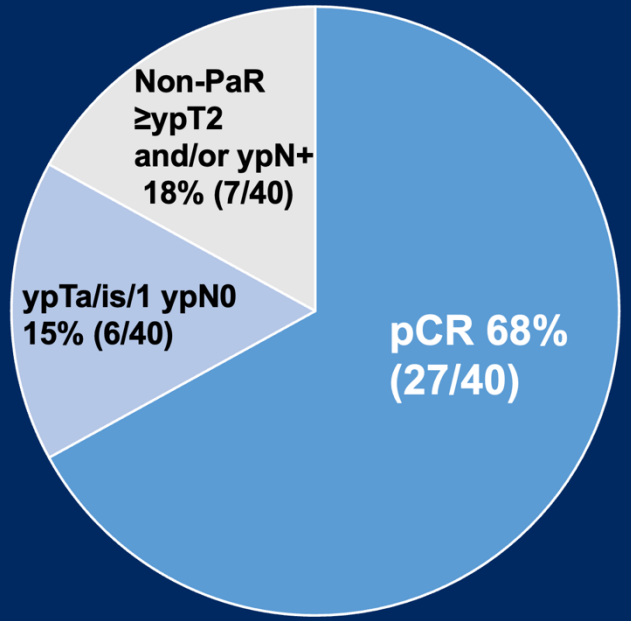
Baseline characteristics

	Full analysis set, N=47	Cystectomy set, n=40	Unresected set, n=7
Median age, years (range)	67 (24 – 78)	66 (24 – 78)	68 (48 – 73)
Female Male	9 (19%) 38 (81%)	8 (20%) 32 (80%)	1 (14%) 6 (86%)
WHO performance status 0 1	 37 (79%) 10 (21%)	 33 (82.5%) 7 (17.5%)	 4 (57%) 3 (43%)
Clinical T stage at presentation cT2 cT3 cT4a	 28 (60%) 15 (32%) 4 (8%)	 21 (52.5%) 15 (37.5%) 4 (10%)	 7 (100%) 0 (0%) 0 (0%)
Clinical N stage at presentation cN0 cN1	 42 (89%) 5 (11%)	 35 (87.5%) 5 (12.5%)	 7 (100%) 0 (0%)
Resection Status TURBT Macroscopically complete Macroscopically incomplete	 17 (36%) 30 (64%)	 15 (37.5%) 25 (62.5%)	 2 (29%) 5 (71%)
Histology Pure UC UC with subtype	 36 (77%) 11 (23%)	 30 (75%) 10 (25%)	 6 (86%) 1 (14%)

SAKK 06/19 — rBCG intravesical + chemo-IO neoadyuvante en MIBC

Primary endpoint: pCR at cystectomy

(centrally reviewed; N=40)



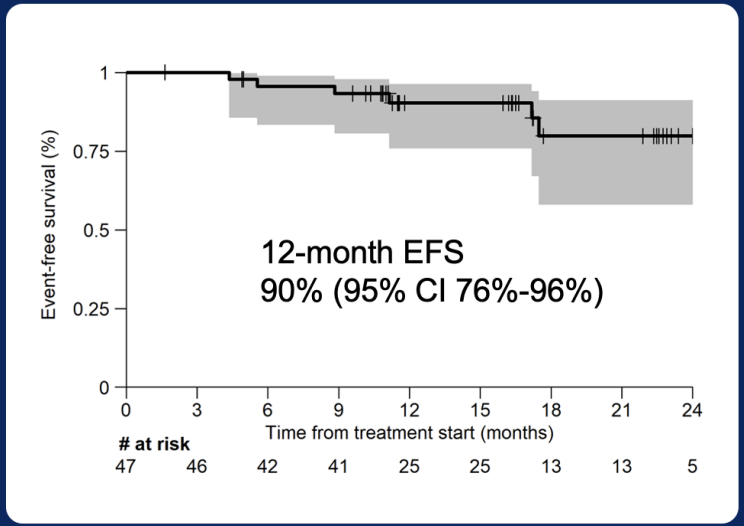
	N (%)
pCR (ypT0 ypN0)*	27 (68%)
PaR (≤ypT1 ypN0)	33 (83%)
non-pCR includes:	
- ypTa	1 (3%)
- ypTis	3 (8%)
- ypT1	2 (5%)
non-PaR ≥ypT2 and/or ypN+:	7 (18%)
- ≥ypT2 ypN0	2 (5%)
- ≥ypT2 ypN+	4 (10%)
- ypT0 ypN+	1 (3%)

*pCR one-sided 95%CI 53%: null hypothesis rejected (p<0.0001)

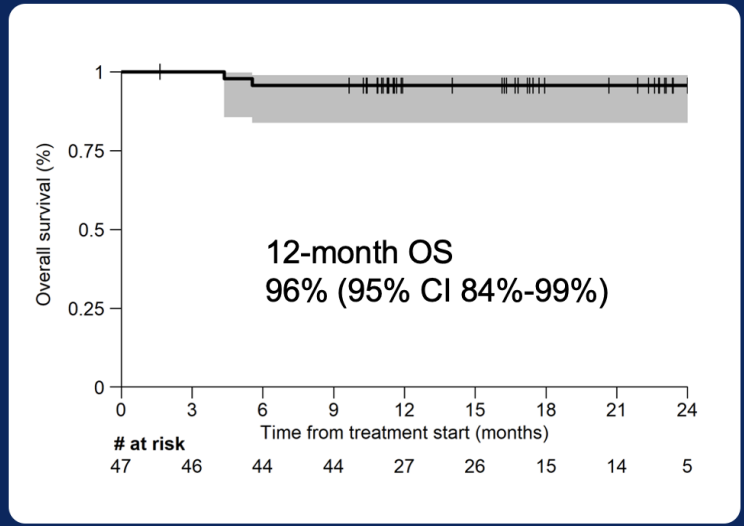
Resultados prometedores a los 12 meses (mFU 16.7 : inmaduros)

Secondary endpoints: EFS and OS

Median follow-up 16.7 months



Event-free survival



Overall survival

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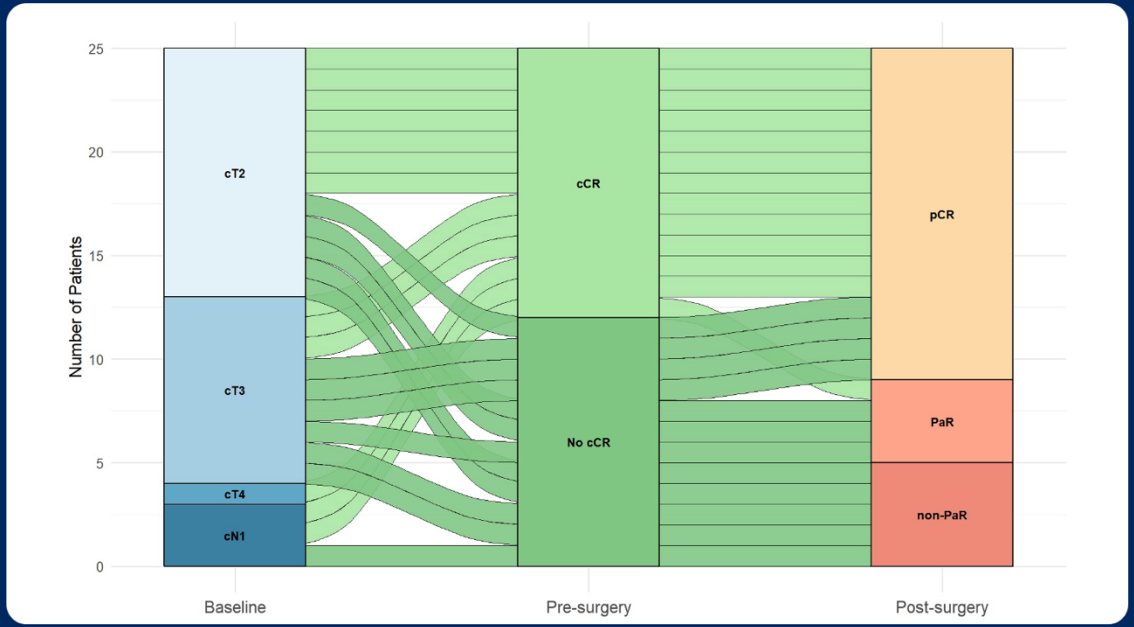
SAKK 06/19 —Valor predictivo de la CCR

Sankey plot: cT cN - clinical CR - pathological CR

Definition of clinical CR (cCR) based on: CT thorax/abdomen/pelvis, MRI bladder, cystoscopy, urine cytology



cCR:

PPV 92%

NPV 69%

N=25

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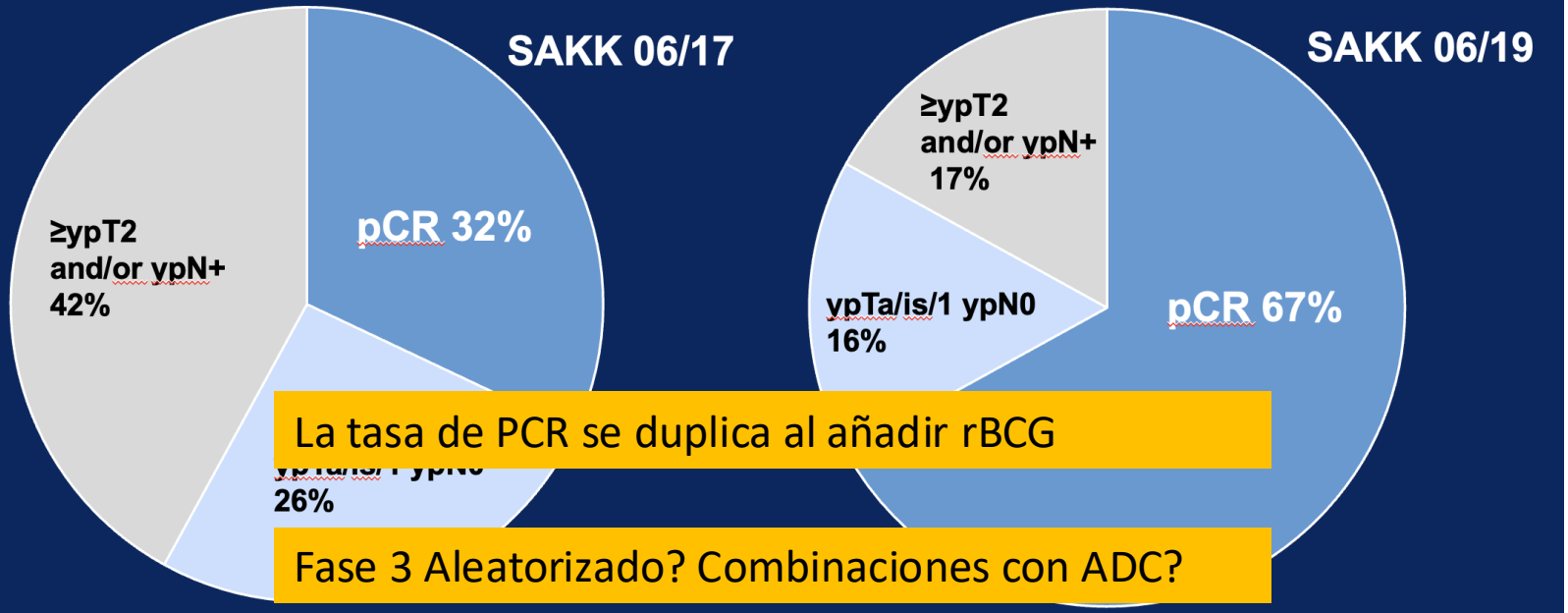
SAKK 06/19 — rBCG intravesical + chemo-IO neoadyuvante en MIBC

Comparison SAKK 06/17 vs SAKK 06/19 (PSW analysis)

pCR: odds ratio in multivariate analysis 5.13 (2.63 - 10.02; p<0.001)



La tasa de PCR se duplica al añadir rBCG

Fase 3 Aleatorizado? Combinaciones con ADC?

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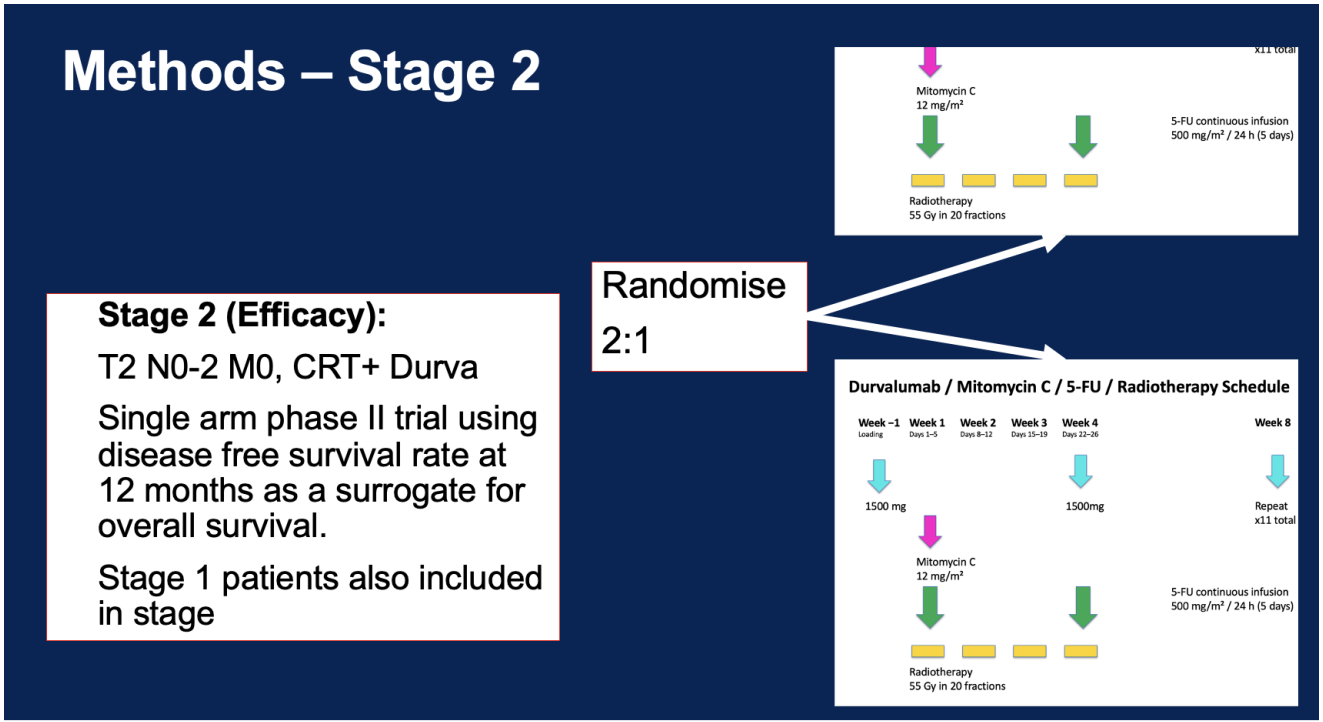
RAD-IO — Durvalumab + CRT (5-FU/Mitomicina C) en MIBC — Preservación vesical

CRT (RT + 5-FU/MMC) con durvalumab neoadyuvante, concurrente y 12 meses post-CRT



BC2011: QTRT vs RT; HR 0.78

+ Durvalumab

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RAD-IO — Durvalumab + CRT (5-FU/Mitomicina C) en MIBC — Preservación vesical

CRT (RT + 5-FU/MMC) con durvalumab neoadyuvante, concurrente y 12 meses post-CRT

Results – Baseline characteristics

Baseline Characteristics		Number (%)
Chemo-RT + durvalumab		55
Age (years)	Mean (IQR)	69 (62–76)
Sex,	Female	10 (18)
	Male	45 (82)
Previous neoadjuvant chemotherapy,	No	14 (25)
	Yes	41 (75)
Clinical stage,	T2	44 (80)
	T3	11 (20)
	N+	7 (13)
	N1	4
	N2	3

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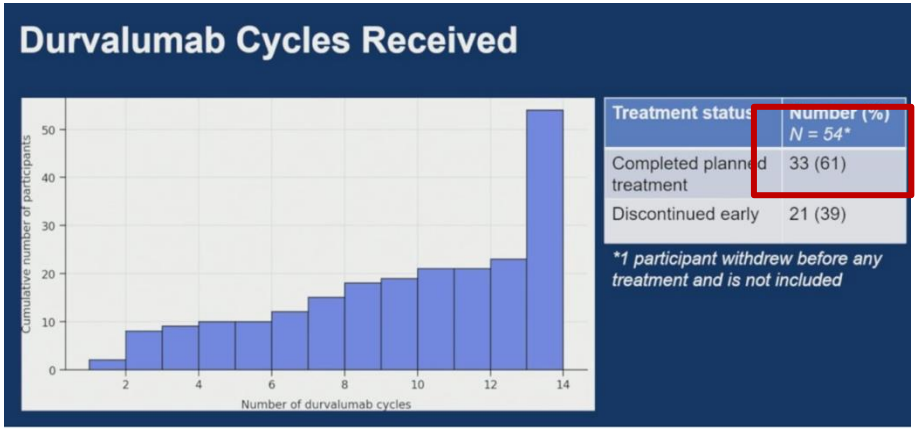
RAD-IO — Durvalumab + CRT (5-FU/Mitomicina C) en MIBC — Preservación vesical

CRT (RT + 5-FU/MMC) con durvalumab neoadyuvante, concurrente y 12 meses post-CRT | Abstract #4504 · Clinical Science Symposium

Radiotherapy Parameter	Number (%) *N = 54**
Received full 55 Gy in 20 fractions	54 (100)
Stopped treatment early	0
Treatment extended or delayed	7 (13)
No extension or delay	47 (87)

**1 participant withdrew before any treatment and is not included*



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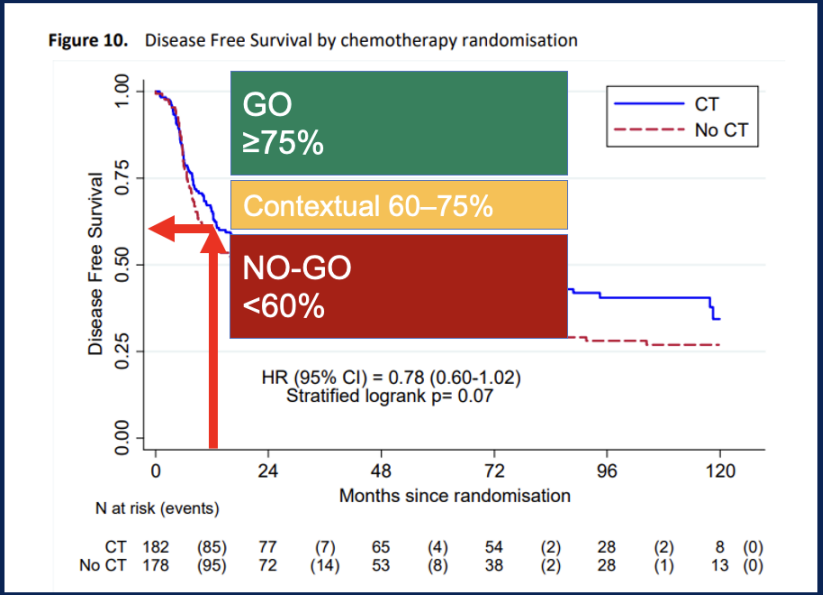
Primary Outcome: Disease-Free Survival rate (12 Months post chemoRT)

GO / NO-GO Decision Framework (12-Month DFS)



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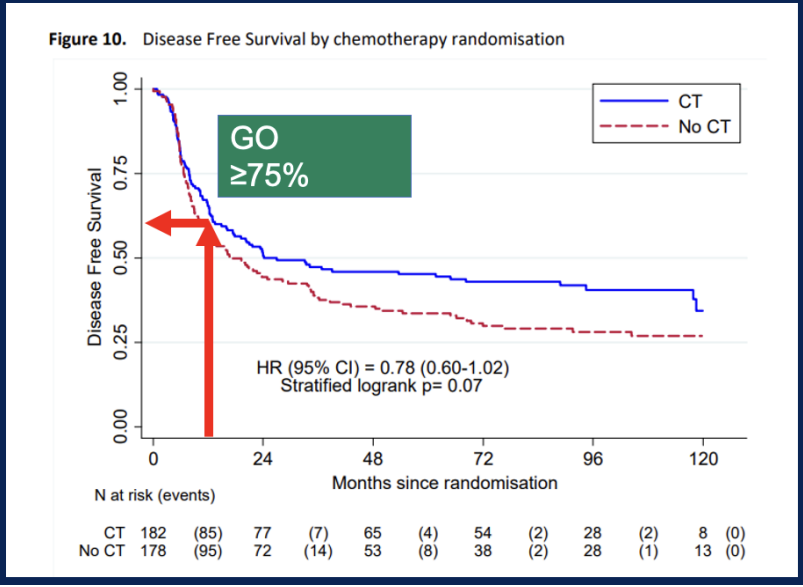
RAD-IO — Durvalumab + CRT (5-FU/Mitomicina C) en MIBC — Preservación vesical

Primary outcome – DFS Rate (12 Months post CRT)



DFS Rate at 12 months post CRT	
Disease Free Proportion	**40/50 (80%)**
95% CI	**0.67, 0.89**
Pending	*2*
Not Evaluable	*3*

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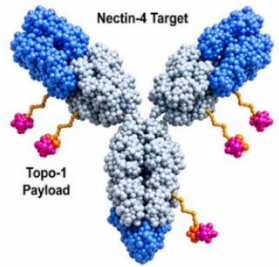
Secondary outcome – Cystectomy rate at 12 months

Status	Number (%)
Cystectomy Rate	0/52 (0.0%)
Pending	*1*
Not Evaluable	*2*

SHR-A2102 + adebrelimab — Nuevo ADC anti-Nectin-4 perioperatorio en MIBC

SHR-A2102
Abstract 4506

Perioperative SHR-A2102, a novel nectin-4-targeted antibody-drug conjugate, in combination with akebrelimab for patients with muscle-invasive bladder cancer: results from a phase 2/3 study



Payload: inh Top I

Trial design N:37

Open-label, Multicenter Phase 2 Study:
To evaluate the efficacy of SHR-A2102 combined with adebrelimab in the perioperative treatment of MIBC

Key Eligible Criteria:

- Pathologically and radiographically confirmed T2-4aN0M0 or T1-4aN1M0 MIBC
- Eligible for RC + PLND
- ECOG: 0-1
- Adequate organ function, CrCl ≥30 mL/min

pacientes INELEGIBLES

Neoadjuvant

SHR-A2102
8 mg/kg
+
Adebrelimab
1200 mg
Q3W×4 cycles

Within 6 weeks*

Radical Cystectomy

Adjuvant

SHR-A2102 8 mg/kg
Q3W×5 cycles
+
Adebrelimab
1200 mg
Q3W×13 cycles

Survival follow-up

Primary endpoints:

- Recommended phase 3 dose (RP3D)#
- Investigator-assessed pathological complete response (pCR, defined as pT0N0)

Secondary endpoints&:

- EFS, DFS, OS
- Preoperative ORR, DCR
- Safety

*Surgery was performed within six weeks after the last neoadjuvant therapy.
#Per protocol, the decision to proceed with exploration of additional combination doses of SHR-A2102 would be made based on study data.
&Other secondary endpoints include R0 resection rate and PK.

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SHR-A2102 + adebrelimab — Nuevo ADC anti-Nectin-4 perioperatorio en MIBC

Baseline characteristics

	Total (N=37)
Median age (range), years	66.0 (44.0-81.0)
Male, n (%)	34 (91.9)
ECOG performance-status score, n (%)	
0	9 (24.3)
1	28 (75.7)
Histology, n (%)	
Pure urothelial carcinoma	32 (86.5)
UC with other differentiation or variants*	5 (13.5)
Baseline cTNM stage, n (%)	
T2N0	11 (29.7)
T3-4aN0	19 (51.4)
T1-4aN1	7 (18.9)
Creatinine Clearance, n (%)	
≥60 mL/min	23 (62.2)
≥30 and <60 mL/min	14 (37.8)
Baseline PD-L1 CPS#, n (%)	
≥10	9 (24.3)
<10	26 (70.3)
Unknown&	2 (5.4)

* Include 2 with squamous differentiation, 2 with glandular differentiation, and 1 with sarcomatoid differentiation. # PD-L1 (E1L3N) IHC assay (Amoy Diagnostics Co., Ltd. China); CPS = the number of surviving tumor cells with varying degree of staining and tumor-associated immune cells (lymphocytes, macrophages) ÷ the total number of surviving invasive tumor cells in the entire slide × 100. & No qualified tissue sample was available for testing.

Alto riesgo

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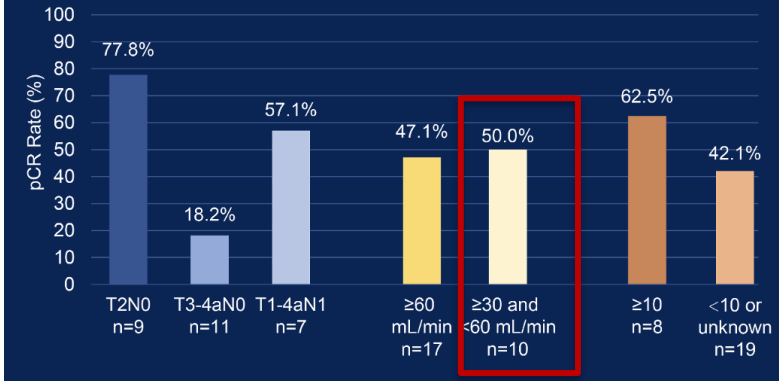
SHR-A2102 + adebrelimab — Nuevo ADC anti-Nectin-4 perioperatorio en MIBC

Efficacy

Pathologic Response	Evaluable Patients (N=27)
pCR (ypT0N0), n (%)	13 (48.1)
95% CI	28.7, 68.1
pDS (<ypT2N0), n (%)	16 (59.3)
95% CI	38.8, 77.6

Of the 9 patients who completed neoadjuvant treatment but didn't accept radical cystectomy:

- 5 underwent TURBT with 3 (60%) showed no evidence of residual tumor.



- pCR benefits were observed across all predefined subgroups;
- With the median follow-up of 4.7 months (IQR 2.1-6.6), 3 event-free survival events were reported, the median EFS not yet mature.

Opción para CDDP inelegibles

Datos preliminares(n:37, mFU 4,7m)

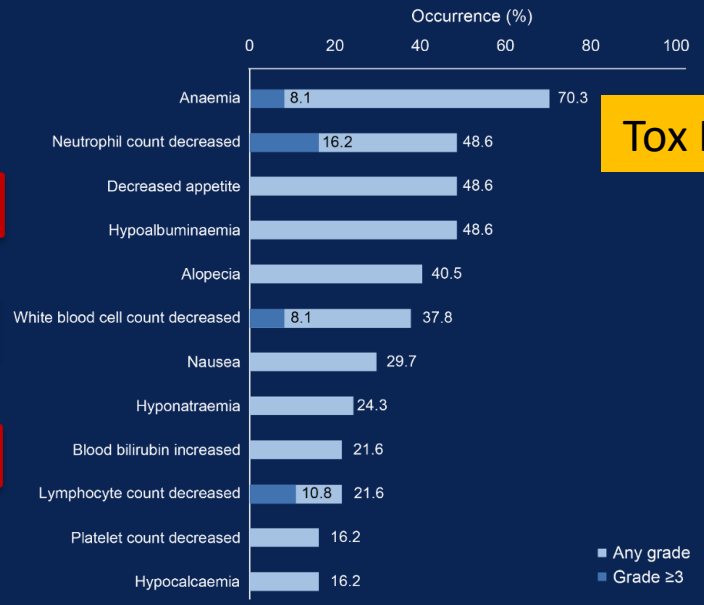
SHR-A2102 + adebrelimab — Nuevo ADC anti-Nectin-4 perioperatorio en MIBC

Safety

	Total (N=37)
Number of treatment cycles, median (range)	4.0 (3-7)
TRAE, n (%)	37 (100.0)
Grade ≥3 TRAE, n (%)	10 (27.0)
TRSAE, n (%)	4 (10.8)
TRAE leading to death, n	0
Neoadjuvant phase TRAE leading to any drug discontinuation, n (%)	1* (2.7)
TRAE leading patient ineligible for RC, n	0
TRAE leading to RC delay[a], n /N (%)	1#/27 (3.7)

*Grade 2 Immune-mediated myocarditis related to adebrelimab;
#Grade 2 Ventricular extrasystoles related to SHR-A2102 and adebrelimab.

TRAEs defined as adverse events considered related to SHR-A2102 or adebrelimab.
a. RC delay defined as >6 weeks from last perioperative dose to RC in the patients accepted RC



The most common TRAEs (>15% overall occurrence)

Tox Hematologica

Prof. Yijun Shen, ASCO 2026

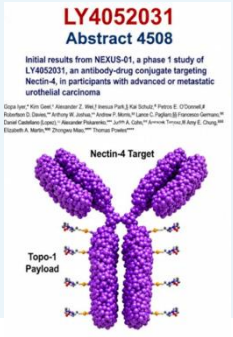
Nuevos agentes anti-Nectin-4 — ¿Qué hay después de EV?

LY4052031 (NEXUS-01)

ADC TopoI (Camp98) | DAR=8 fase 1 escalada de dosis

ORR en mUC (AS≥0,5): 42%
ORR en post-EV: 33%

Genotipado CYP2D6 obligatorio (actividad del metabolizador afecta toxicidad payload)

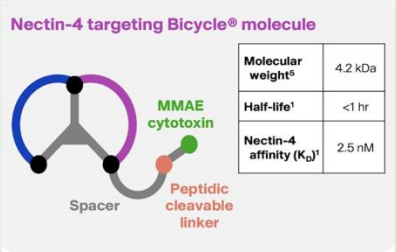


Zelenectide (BDC Nectin-4)

Bicycle Drug Conjugate (no ADC) MM<4,2 kDa · t½ <1h · Duravelo-2

ORR 1L (6mg/m²+pembro): 58%
Sin reacciones cut. graves: ✓
Neuropatía Gr≥3: 3%

Perfil de toxicidad diferenciado: neuropatía leve, sin reacciones cutáneas severas. Fase 3 en marcha.

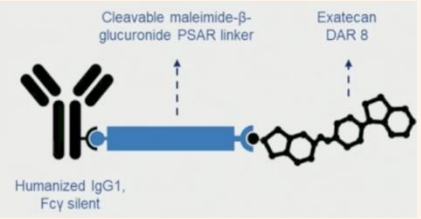


LY4101174 (EXCEED)

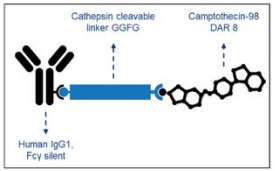
ADC exatecan | DAR=8 fase 1; 92% post-EV

ORR en mUC Q3W: 36%
DCR: 70%
Anemia Gr≥3: 47%

Actividad en post-EV pero toxicidad hematológica relevante. Requiere G-CSF profiláctico.



Nuevos agentes anti-Nectin-4 — NEXUS-01: mUC Lineas Subsecuentes



- LY4052031 is a next generation anti-Nectin-4 ADC, composed of a humanized IgG1 antibody linked to a novel Topo-I inhibitor, camp98, via a cleavable peptide linker at a homogeneous drug antibody ratio (DAR) of 8
- Clearance of camp98 is predominantly mediated by hepatic CYP2D6

Payload camp98, topo-I

Phase 1a Dose Escalation and Optimization (Q3W Dosing)

Cohort A1: Dose Escalation (n=105)
mUC and select solid tumors[a]

- DL5.5 5.4 mg/kg
- DL5 4.8 mg/kg
- DL4.5[b] 4.2 mg/kg
- DL4[b] 3.6 mg/kg
- DL3 2.4 mg/kg
- DL2 1.2 mg/kg
- DL1 0.6 mg/kg

Renal Insufficiency Sub-study (CrCl 30-49 mL/min)[b]

Cohort A2: Randomized Dose Optimization (n=32)
mUC

R
AS ≥ 0.5

- DL-A 2.4 mg/kg
- DL-B 3.6 mg/kg
- DL-C 4.2 mg/kg
- DL-D 4.8 mg/kg

CYP2D6 Sub-study
- AS 0.0 → 1.2 mg/kg
- AS 0.25 → 2.4 mg/kg

- CYP2D6 AS 0.0/0.25 associated with increased risk of severe toxicity
- Prospective CYP2D6 genotyping introduced to mitigate risk

Study Design
- BOIN design with backfilling
- 21-day cycle (DLT evaluation period)

Key Eligibility Criteria
- ECOG PS 0-1
- Advanced/metastatic select tumors known to express Nectin-4
- Measurable or non-measurable (cohort A1 only) disease per RECIST v1.1
- Prior EV permitted
- CYP2D6 Activity Score (AS)

Key Objectives
- Determine optimal dose
- Safety and tolerability
- Pharmacokinetics
- Preliminary efficacy per RECIST v1.1

Data cutoff date of 29 April 2026. [a]Eligible tumor types include cervical cancer, esophageal cancer, head and neck squamous cell carcinoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, and triple-negative breast cancer. [b]Moderate renal insufficiency sub-study enrolled at 3.6 (n=11) and 4.2 mg/kg (n=8). BOIN, Bayesian Optimal Interval Design; EV, enfortumab vedotin; R, randomization. NCT06465069

Dr. Gopa Iyer, ASCO 2026

Nuevos agentes anti-Nectin-4 — ¿Superar resistencias?

	All Participants (N=137)	mUC (n=107)
Median age, years (range)	67 (31 – 86)	67 (36 – 86)
Race, n (%)		
White	99 (72)	73 (68)
Asian	25 (18)	23 (22)
Black or African American	4 (3)	3 (3)
Not Reported	9 (7)	8 (8)
ECOG PS[a], n (%)		
0	54 (39)	44 (41)
1	82 (60)	62 (58)
Tumor type[b], n (%)		
mUC	107 (79)	107 (100)
non-mUC[c]	28 (21)	-
CYP2D6 AS, n (%)		
0	4 (3)	3 (3)
0.25	6 (4)	5 (5)
≥0.5	122 (89)	98 (92)
Unknown	5 (4)	1 (1)

Disease Characteristics of Special Interest in mUC (n=107)	
CrCl mL/min[b], n (%)	
30-49	20 (19)
50-59	17 (16)
≥60	68 (65)
Visceral metastases, n (%)	63 (59)
Liver metastases, n (%)	33 (31)
Median prior systemic regimens (range)	3 (1-9)
Prior Therapy, n (%)	
Platinum chemotherapy	94 (88)
EV with or without pembrolizumab	72 (67)
EVP	42 (39)
ICI[d]	99 (94)
ADC – Topo-I	25 (23)
Reason for EV discontinuation, n (%)	
Toxicity	6 (9)

Mismo target (Nectin-4, distinto payload)

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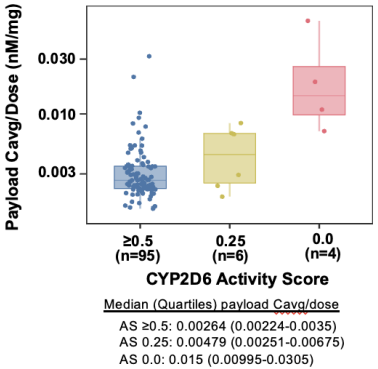
Payload Exposure (C_{avg}) and AEs of Interest by CYP2D6 Function



Treatment-Emergent AEs, known CYP2D6[a]						
TEAEs, %	AS 0.0 (n=4)		AS 0.25 (n=6)		AS ≥0.50 (n=122)	
	Any G, %	≥G3, %	Any G, %	≥G3, %	Any G, %	≥G3, %
Mucositis[b]	75	50	50	17	17	3
Neutropenia[c]	50	50	17	-	12	5
Febrile neutropenia	50	50	17	17	<1	<1
Sepsis[d]	25	25	-	-	2	2
Dose Modifications due to TEAEs, %						
Dose reductions	-		33		13	
Discontinuations	75		17		3	

- Participants with poor or minimal CYP2D6 function (AS 0.0/0.25) demonstrated higher payload exposure and increased risk of severe toxicity
- Prolonged neutropenia, complicated by febrile neutropenia and sepsis were observed
- There were 3 treatment related deaths – aspiration pneumonia (AS 0.25 at 4.8 mg/kg) and sepsis (AS 0.0 at 1.2 mg/kg and AS unknown at 3.6 mg/kg)[a,d]
- Prospective CYP2D6 genotyping enables a precision medicine approach to dose optimization; pharmacogenomic-guided dosing is ongoing for participants with AS 0.25; participants with AS 0.0 are not currently being enrolled

Genotipado CYP2D6 obligatorio (actividad del metabolizador afecta toxicidad payload)

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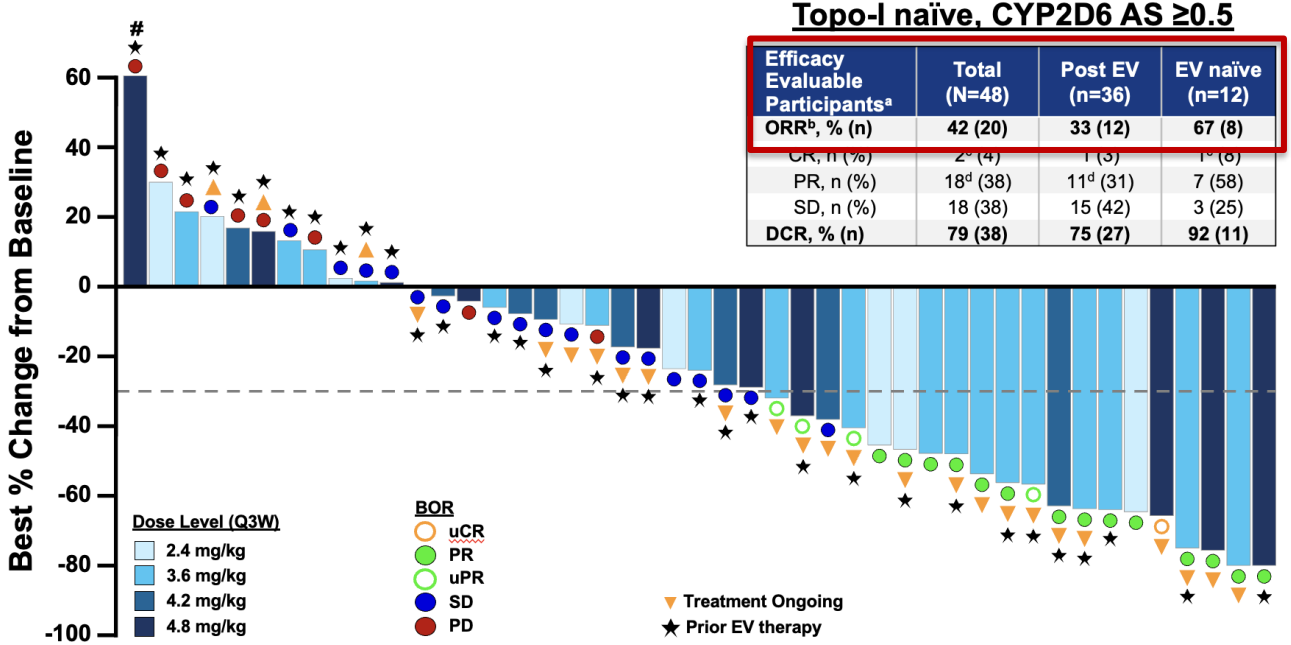
Nuevos agentes anti-Nectin-4 — NEXUS-01

Antitumor Activity in mUC



Topo-I naïve, CYP2D6 AS ≥0.5

Efficacy Evaluable Participants[a]	Total (N=48)	Post EV (n=36)	EV naïve (n=12)
ORR[b], % (n)	**42 (20)**	**33 (12)**	**67 (8)**
CR, n (%)	2[c] (4)	1 (3)	1[c] (8)
PR, n (%)	18[d] (38)	11[d] (31)	7 (58)
SD, n (%)	18 (38)	15 (42)	3 (25)
DCR, % (n)	**79 (38)**	**75 (27)**	**92 (11)**

- No confirmed responses were observed in Topo-I ADC pretreated participants (n=18)

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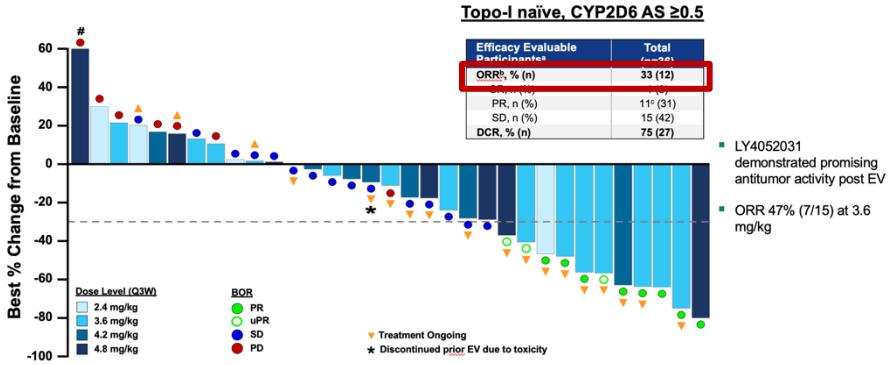
Nuevos agentes anti-Nectin-4 — NEXUS -01

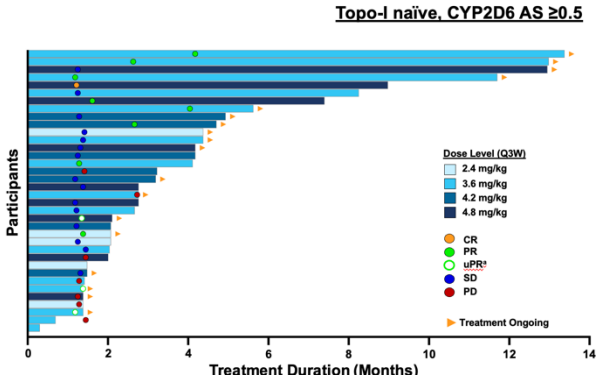
LY4052031 (NEXUS-01)

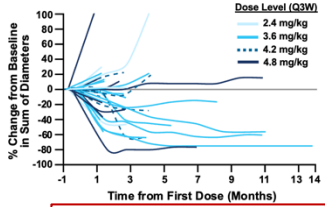
Antitumor Activity in mUC Post EV



- LY4052031 demonstrated promising antitumor activity post EV
- ORR 47% (7/15) at 3.6 mg/kg

Treatment Duration: mUC Post EV





- Median duration of response was 7.4 months (95% CI, 2.7-NE) among 9 confirmed responders
- 67% of responders are ongoing

- LY4052031 demonstrated promising clinical activity across multiple dose levels, suggesting Nectin-4 remains an important therapeutic target following progression on EV-based therapy
  - 42% (20/48) ORR and 79% DCR in EV-naïve and pretreated mUC
  - 33% (12/36) ORR, 75% (27/36) DCR and median DoR of 7.4 months in EV-pretreated mUC

CONCLUSIONES— NEXUS -01

- ORR 42% en mUC Topo-I ADC naïve con AS ≥0,5 — incluyendo 33% en pretratados con EV
- Nectin-4 sigue siendo diana válida tras progresión a EV gracias al payload alternativo (camp98, topo-I)
- Sin resistencia cruzada con EV (MMAE/P-glicoproteína), pero SÍ con otros Topo-I ADC — selección de pacientes crítica
- Farmacogenómica CYP2D6 obligatoria: el 7% de pacientes (AS 0,0–0,25) tiene riesgo de toxicidad grave — genotipado previo es requisito de seguridad
- Perfil de toxicidad cualitativamente diferente al de EV: sin neuropatía, sin ocular, sin cutáneo
- Estudio en fase 1 — pendiente confirmación en cohortes de expansión con optimización de dosis por CYP2D6

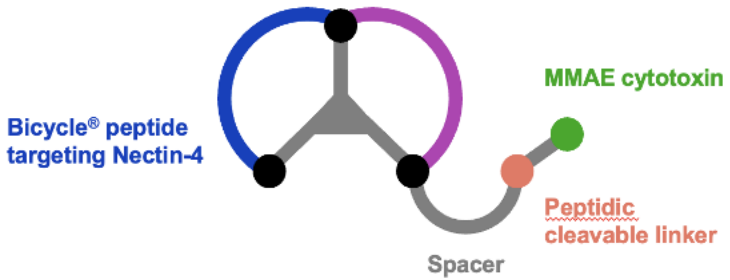
LY4052031 abre la puerta a un nuevo estándar en UC post-EV. La integración obligatoria del genotipado CYP2D6 representa un paradigma nuevo en oncología — es el primer ADC que requiere farmacogenómica para su desarrollo seguro y eficaz.

Dr. Gopa Iyer, ASCO 2026

Nuevos agentes anti-Nectin-4 — ¿Qué hay después de EV?

Zelenectide pevedotin (Duravelo-2)

- Zelenectide pevedotin (zele; BT8009) is a highly selective Bicycle® Drug Conjugate (BDC®) targeting Nectin-4, a protein overexpressed in la/mUC[2]
- In an expansion cohort of the Phase 1 Duravelo-1 study in cisplatin-ineligible patients, many with poor performance status, zele + pembro showed promising preliminary anti-tumor activity (50% cORR) and a potentially differentiating safety profile from currently available ADCs[3]
- Here, we report an interim analysis for zele + pembro (Cohort 1) dosage selection from the randomized Phase 2 Duravelo-2 study (NCT06225596/BT8009-230) in previously untreated patients with la/mUC



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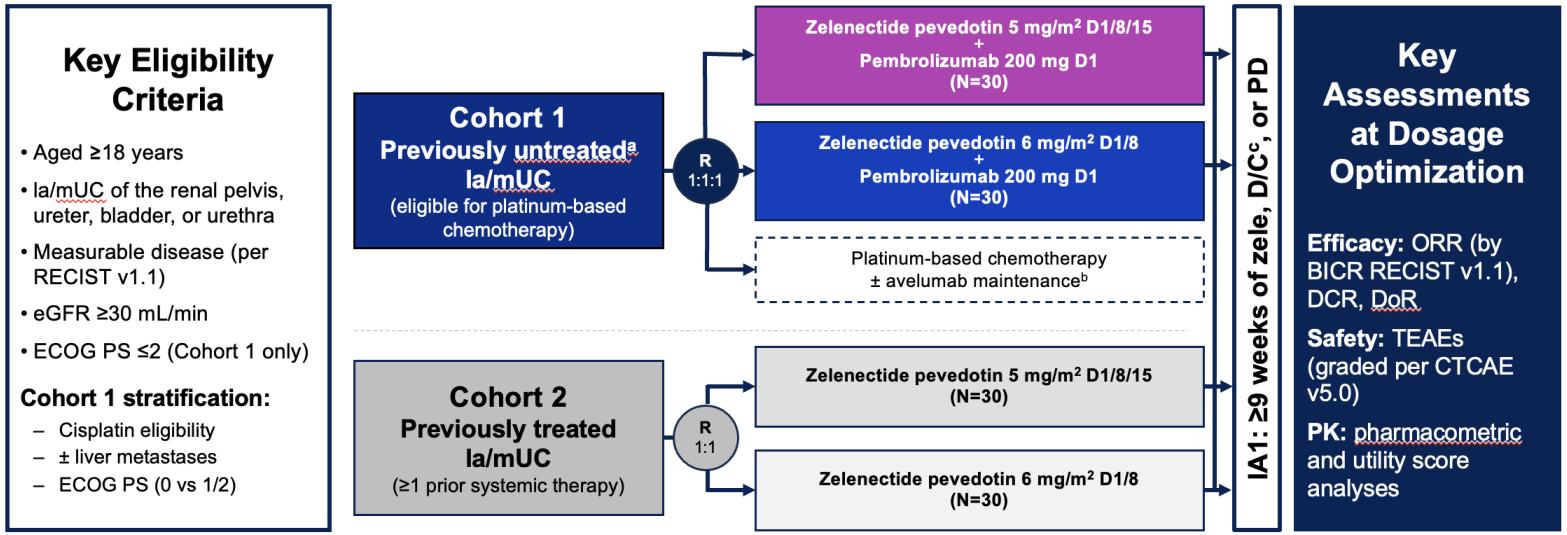
¿puede un BDC anti-nectin-4 ofrecer eficacia similar a EV+P?

Duravelo-2: Study Design for Dosage Optimization

Cohort 1: Previously Untreated la/mUC



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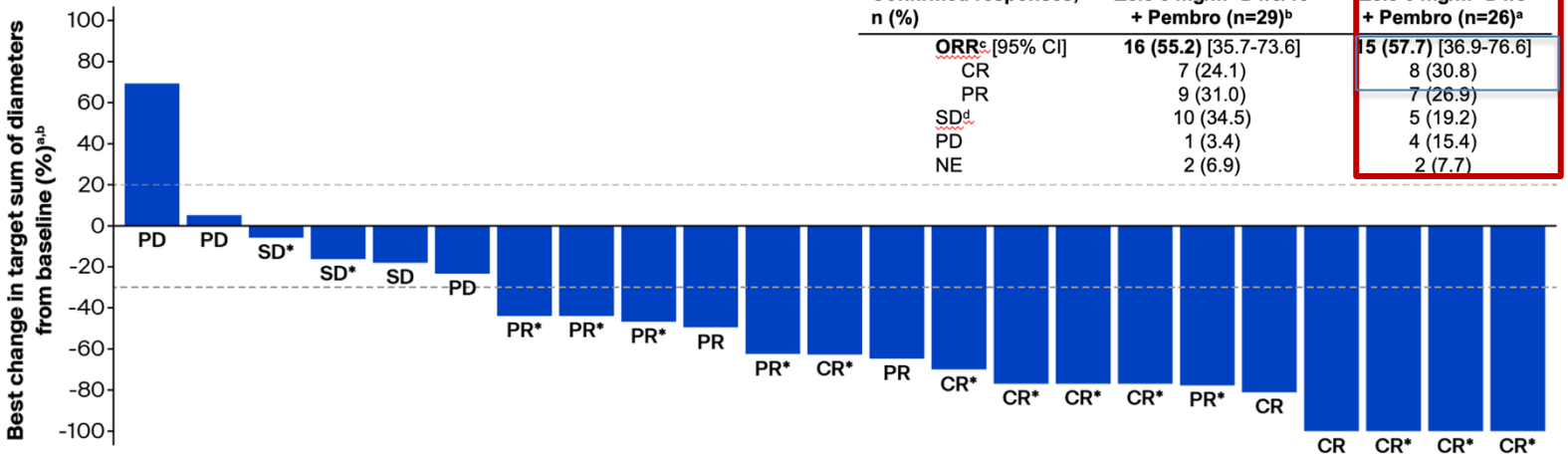
Responses to Zelenectide Pevedotin 6 mg/m² D1/8 + Pembrolizumab in Evaluable Patients (n=23)[a]



Confirmed responses, n (%)	Zele 5 mg/m² D1/8/15 + Pembro (n=29)[b]	Zele 6 mg/m² D1/8 + Pembro (n=26)[a]
ORR[c] [95% CI]	**16 (55.2)** [35.7-73.6]	**15 (57.7)** [36.9-76.6]
CR	7 (24.1)	8 (30.8)
PR	9 (31.0)	7 (26.9)
SD[d]	10 (34.5)	5 (19.2)
PD	1 (3.4)	4 (15.4)
NE	2 (6.9)	2 (7.7)

- Median duration of zele treatment at 6 mg/m² was 6.3 months (range, 0.7-10.6)

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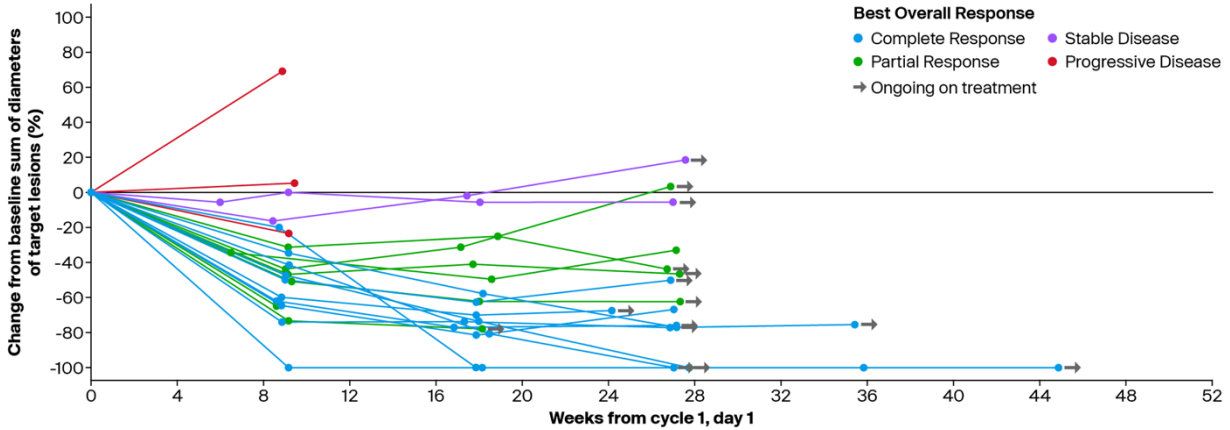
Nuevos agentes anti-Nectin-4

Duration of Response and Change from Baseline in Tumor Size With Zelenectide Pevedotin 6 mg/m² D1/8 + Pembrolizumab



- 15/23 (65.2%) efficacy evaluable patients receiving the 6 mg/m² dosage remained on treatment at data extraction[a]

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mF/U 27s

Zele-Related AEs of Clinical Interest With Zelenectide Pevedotin 6 mg/m² D1/8 + Pembrolizumab

argumento diferenciador

Category, n (%)[a,b]	Zele 6 mg/m² D1/8 + Pembro (N=30)					
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Peripheral neuropathy[c]	11 (36.7)	6 (20.0)	4 (13.3)	1 (3.3)	0	0
Sensory events	10 (33.3)	6 (20.0)	3 (10.0)	1 (3.3)	0	0
Motor events	1 (3.3)	0	1 (3.3)	0	0	0
Skin reactions[d]	5 (16.7)	3 (10.0)	2 (6.7)	0	0	0
Eye disorders[e]	3 (10.0)	3 (10.0)	0	0	0	0
Hyperglycemia[f]	0	0	0	0	0	0

- No zele-related severe skin reactions of any grade were reported at the 6 mg/m² D1/8 dosage
  - No events of Stevens-Johnson syndrome or toxic epidermal necrolysis occurred
- One patient had Grade 3 peripheral neuropathy that resolved to Grade ≤1 in 8.4 weeks
- The occurrence of zele-related AECIs was similar between arms, though any-grade peripheral neuropathy events occurred less frequently with the 6 mg/m² dosage

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CONCLUSIONES— DURAVELO-2

- Dosis optimizada seleccionada: 6 mg/m² D1/8 — mejor perfil beneficio-riesgo frente a 5 mg/m² D1/8/15
- Eficacia comparable a EV+P: ORR 58%, alta tasa de RC, 65% de pacientes aún en tratamiento
- Perfil de toxicidad cualitativamente diferente: sin toxicidad cutánea grave, sin SJS/NET en 595 pacientes
- Limitaciones importantes: análisis intermedio con n pequeño (30/brazo), 27 semanas de seguimiento, datos de SLP y SG inmaduros — fase 3 en marcha

Zelenectide pevedotin + pembrolizumab emerge como potencial alternativa a EV+P en 1.ª línea de UC avanzado, con eficacia similar y un perfil de seguridad cutánea y de combinabilidad potencialmente superior. El fase 3 definirá su lugar.

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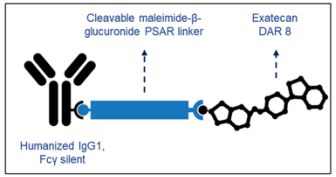
Nuevos agentes anti-Nectin-4:EXCEED

- Preclinical data suggest EV resistance may be mediated by P-gp-mediated payload efflux, supporting the continued investigation of Nectin-4 targeting with alternative ADC payloads



- LY4101174 is a next generation anti-Nectin-4 ADC composed of a humanized IgG1 antibody linked to the Topo-I inhibitor, exatecan, via a maleimide-β-glucuronide poly-sarcosine linker at a homogeneous DAR of 8

Phase 1a (N=143)

Cohort A1: Dose Escalation
mUC and select solid tumors[a]

Q2W Dose Levels

- DL6 8.0 mg/kg
- DL5 6.4 mg/kg
- DL4 4.8 mg/kg
- DL3 3.2 mg/kg
- DL2 1.6 mg/kg
- DL1 0.8 mg/kg

At 3.2 mg/kg Q2W, 3 participants had DLTs requiring a schedule change to Q3W

Q3W Dose Levels

- DL3.5* 4 mg/kg GCSF PPX Required
- DL3[b] 3.2 mg/kg
- DL2.5* 2.4 mg/kg

Study Design

- BOIN design with backfilling
- 14-day or 21-day cycle (DLT evaluation period)

Key Eligibility Criteria

- ECOG PS 0-1
- Advanced/metastatic solid tumors known to express Nectin-4
- Measurable or non-measurable (cohort A1 only) disease per RECIST v1.1
- Prior EV permitted

Key Objectives

- Determine optimal dose
- Safety and tolerability
- Pharmacokinetics
- Preliminary efficacy per RECIST v1.1

Xin Gao, ASCO 2026

Nuevos agentes anti-Nectin-4_EXCEED

	All Participants (n=143)	mUC (n=86)
Median age, years (range)	68 (30-85)	70 (35-85)
Race, n (%)		
White	94 (66)	57 (66)
Asian	19 (13)	9 (11)
Black or African American	6 (4)	4 (5)
Other	24 (17)[c]	16 (19)[d]
ECOG PS, n (%)		
0	56 (39)	33 (38)
1[a]	87 (61)	53 (62)
Tumor type, n (%)		
mUC	86 (60)	86 (100)
non-mUC[b]	57 (40)	-
CrCl mL/min, n (%)		
30-49	9 (6)	8 (9)
50-59	24 (17)	16 (19)
≥60	110 (77)	62 (72)

Disease Characteristics of Special Interest in mUC (n=86)	
Metastatic disease site[e], n (%)	
Visceral metastases	76 (88)
Liver metastases	27 (31)
Lymph node only	8 (9)
Median prior regimens for mUC (range)	3 (1-8)
Prior Therapy, n (%)	
Platinum chemotherapy	76 (88)
EV with or without pembrolizumab	79 (92)
EVP	26 (30)
ICI[f]	86 (100)
ADC – Topo-I	18 (21)
Reason for EV discontinuation	
Toxicity	15 (19)

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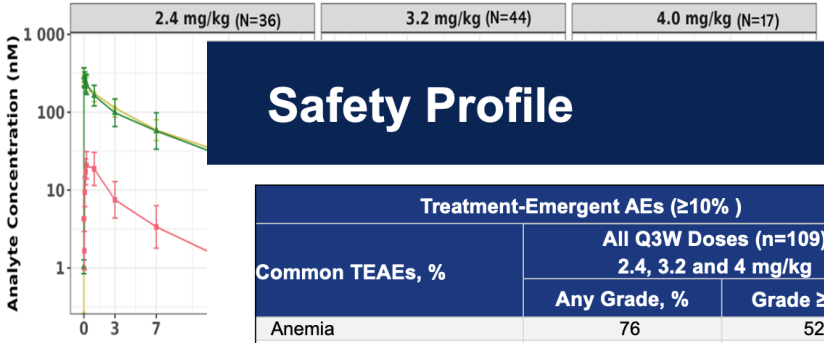
Pharmacokinetics

Concentration of LY4101174, total antibody, and total unconjugated exatecan in plasma (cycle 1)



Safety Profile

Treatment-Emergent AEs (≥10%)		
Common TEAEs, %	All Q3W Doses (n=109) 2.4, 3.2 and 4 mg/kg	
	Any Grade, %	Grade ≥3[g], %
Anemia	76	52
Fatigue[a]	56	9
Nausea	49	1
Neutropenia[b]	39	31
Thrombocytopenia[c]	36	24
Decreased appetite	28	2
Diarrhea	26	4
Vomiting	28	3
Leukopenia[d]	20	13
Stomatitis[e]	17	<1
Constipation	17	-
Cough	16	-
Back pain	15	3
Dysgeusia	14	-
Pyrexia	14	2
Hematuria	13	4
Abdominal pain	12	<1
Dyspnea	12	2
Urinary tract infection	12	7
Weight decreased	12	-
Blood creatinine increased	11	3
Febrile neutropenia[f]	10	10

Grade ≥3 Hematologic TEAEs by DL, (All Q3W Doses)			
Hematologic TEAEs, %	2.4 mg/kg (n=37)	3.2 mg/kg (n=47)	4 mg/kg (n=25)
Anemia	41	53	68
Neutropenia[b]	14	43	36
Thrombocytopenia[c]	5	26	48
Febrile neutropenia[f]	3	13	16
Dose reductions due to AEs[h], %	14	40	48

- 29 (27%) remained on treatment at the time of data cutoff
- Non-hematologic AEs were predominantly low grade and manageable
- Gr… im…
  - …mbocytopenia was observed in 32% at 4 mg/kg including …nically significant bleeding
- EV associated AEs (e.g. skin toxicities, peripheral neuropathy, ocular toxicity and hyperglycemia) were minimal

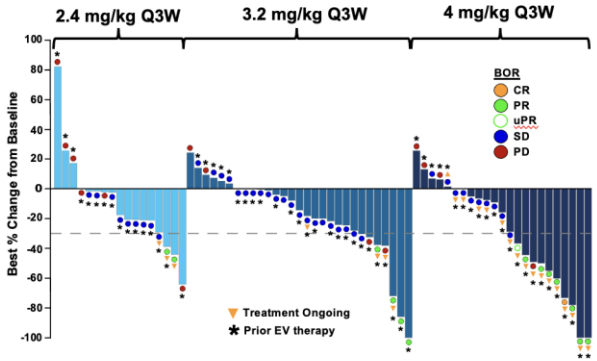
Mielosupresión severa por alta liberación plasmática del payload (~8%)

Data cutoff date of 9 March 2026. [a]Includes asthenia. [b]Includes neutrophil count decreased. [c]Includes platelet count decreased. [d]Includes white blood cell count decreased. [e]Includes aphthous ulcer, mouth ulceration, and mucosal inflammation. [f]Includes neutropenic sepsis. [g]27 participants had grade 4 events – anemia,

DISCONTINUACIÓN DEL DESARROLLO

Efficacy: mUC

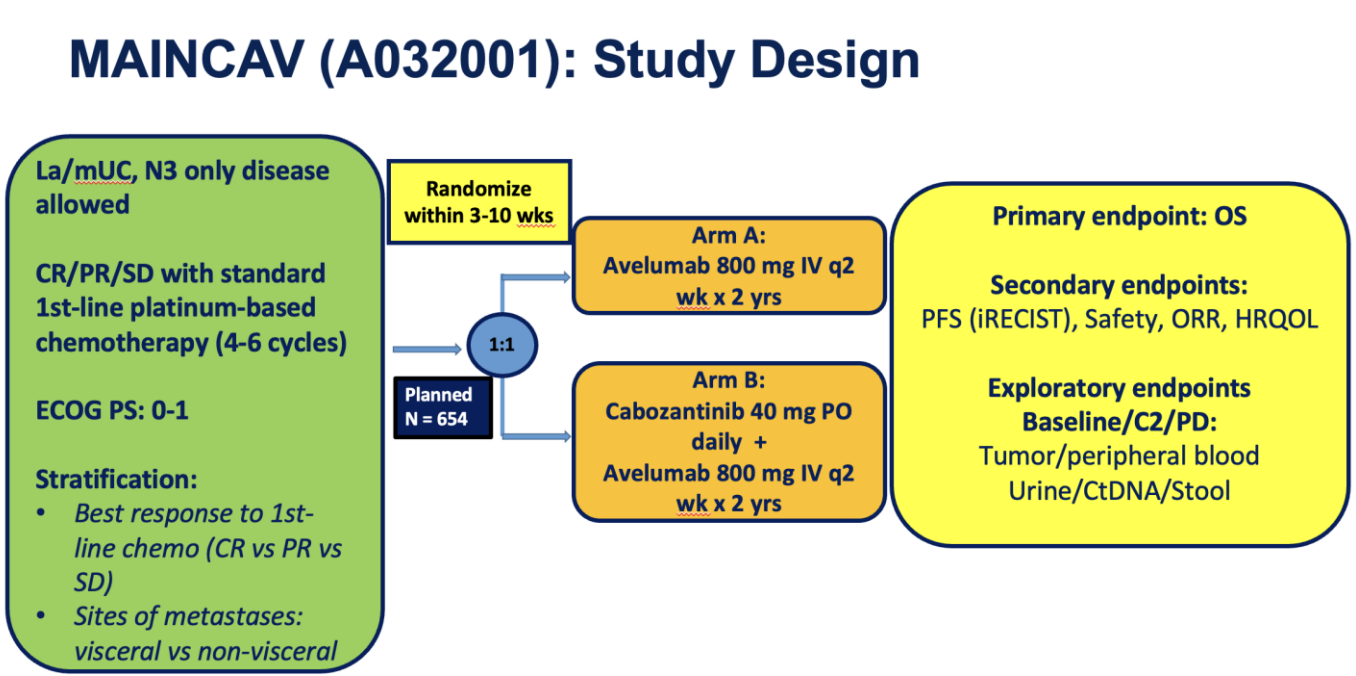
Efficacy Evaluable Participants[a]	Total Q3W (n=76)	2.4 mg/kg Q3W (n=19)	3.2 mg/kg Q3W (n=32)	4 mg/kg Q3W (n=25)
ORR, % (n)	**20 (15)**	**11 (2)**	**13 (4)**	**36 (9)**
CR, n (%)	1 (1)	-	-	1 (4)
PR, n (%)	14[b] (18)	2 (11)	4 (13)	8[b] (32)
SD, n (%)	40 (53)	9 (47)	21 (66)	10 (40)
DCR, % (n)	**72 (55)**	**58 (11)**	**78 (25)**	**76 (19)**



- In a heavily pretreated population (93% prior EV), preliminary efficacy suggests Nectin-4 remains an actionable target
- While 4 mg/kg demonstrated promising antitumor activity (ORR 36%), grade ≥3 hematologic toxicities compromised dose intensity and precluded further dose escalation

La premisa biológica es correcta — nectin-4 funciona como diana post-EV. El problema fue la instabilidad plasmática del linker, no la diana ni el payload.

MAIN-CAV — MANTENIMIENTO POST-PLATINO: contexto para futuras estrategias



N: 68
ESTUDIO INFRAPOTENCIADO

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MAIN-CAV— contexto para futuras estrategias

Adverse Events

Adverse Events (AEs)	Avelumab (N=33)	Cabozantinib + Avelumab (N=33)
Grade 3 TRAEs	8 (24.2%)	13 (39.4%)
Grade 3 Hypertension*	1 (3.0%)	6 (18.2%)
Grade ≥3 Hematologic TRAEs	0	3 (9.1%)
All-cause Grade 4 AEs	2 (6.1%)	0
All-cause Grade 5 AEs**	1 (3.0%)	2 (6.1%)
Grade 5 TRAEs **	0	1 (3.0%)

*Most common grade ≥3 AE occurring in ≥10% overall
**All-cause grade 5 AEs included dyspnea in the avelumab arm and 2 deaths, not otherwise specified, in the cabozantinib + avelumab arm, 1 of which was treatment-related.
No new safety signals beyond the known safety profiles of avelumab and cabozantinib

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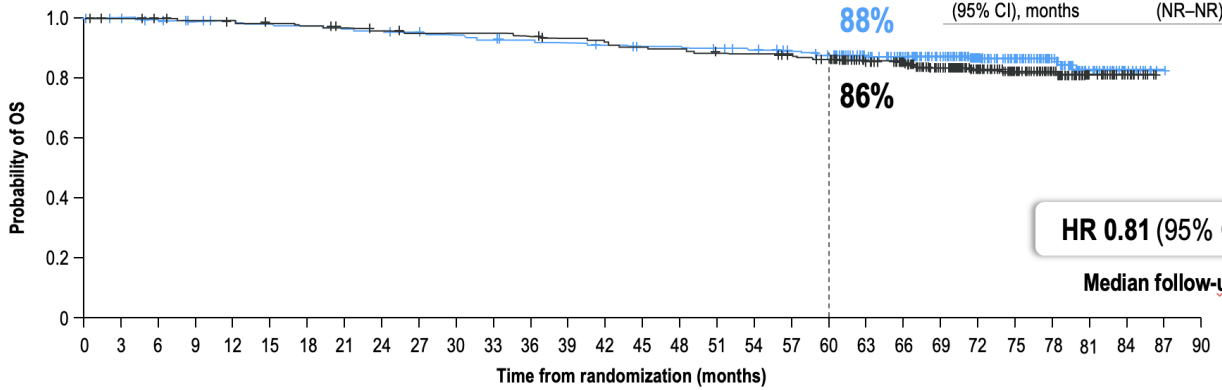
SIN DETRIMENTO EN SG

POTOMAC: 5-Year Overall Survival – ITT

No detriment at the 5-year OS analysis was observed with the addition of durvalumab to BCG (I+M) therapy

	D+BCG (I+M) N=339	BCG (I+M) N=340
Deaths, n (%)	45 (13)	56 (16)
Median OS (95% CI), months	NR (NR–NR)	NR (NR–NR)



HR 0.81 (95% CI, 0.54–1.19)

Median follow-up[a]: 72 months

No. of patients at risk

D+BCG (I+M)	339	336	329	326	324	320	319	315	314	311	306	303	298	296	293	290	290	286	283	277	270	236	217	182	141	115	73	30	11	1	0
BCG (I+M)	340	338	336	333	330	328	326	322	317	313	313	313	309	305	301	295	292	288	284	281	275	239	220	185	140	108	70	32	12	0	0

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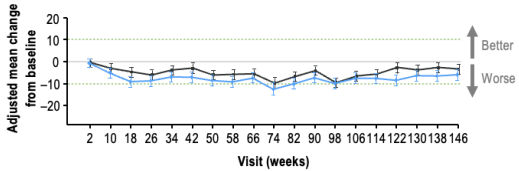
DURVALUMAB NO DETERIORA LA QOL (FATIGA)

POTOMAC: EORTC QLQ-C30 Change From Baseline

Adjusted mean changes from baseline showed modest deterioration in GHS/QoL and physical functioning and increased fatigue in both treatment arms, with generally similar changes between treatment arms

GHS/QoL[1]

Difference between arms: –2.7 (95% CI, –4.85 to –0.54)

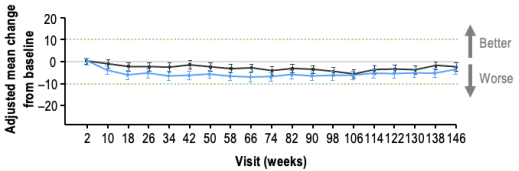


No. of patients in analysis

D+BCG (I+M)	214	202	189	180	177	174	171	156	149	142	148	138	138	130	126	122	117	104	105
BCG (I+M)	232	219	213	192	193	178	183	158	165	165	158	149	152	138	139	133	120	124	123

Physical Functioning

Difference between arms: –2.6 (95% CI, –4.43 to –0.81)

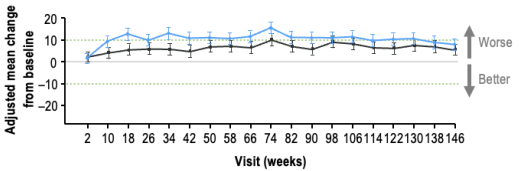


No. of patients in analysis

D+BCG (I+M)	214	202	189	180	177	174	171	156	149	142	148	138	138	130	126	122	117	104	105
BCG (I+M)	232	219	213	192	193	178	183	158	165	165	158	149	152	138	139	133	120	124	123

Fatigue

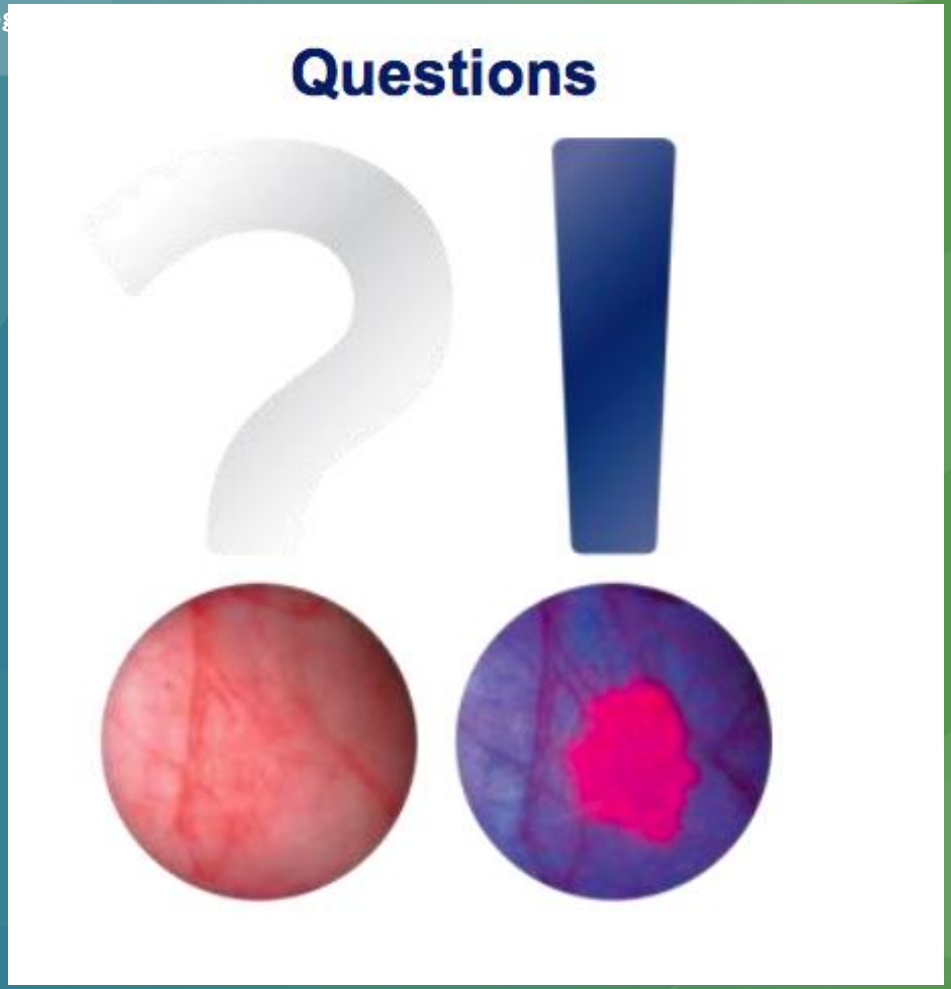
Difference between arms: 4.0 (95% CI, 1.50 to 6.46)



No. of patients in analysis

D+BCG (I+M)	214	202	189	180	177	174	171	156	149	142	148	138	138	130	126	122	117	104	105
BCG (I+M)	232	219	213	192	193	178	183	158	165	165	158	149	152	138	139	133	120	124	123

These data further support 1 year of durvalumab in combination with BCG induction and maintenance as a new treatment for patients with BCG-naïve, high-risk NMIBC


Questions