3ª Jornada de Actualización EN CÁNCER GINECOLÓGICO

Bilbao
12-13 junio 2025

ADCs EN TUMORES GINECOLÓGICOS. INDICACIONES, MANEJO Y TOXICIDADES

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Conflictos de interés

- Soporte para asistencia a congresos por Astra Zeneca, MSD, GSK, Pierre Fabre
- Advisory: Eisai, Astra Zeneca
- Speaker: Astra Zeneca, MSD, Bristol, Merck

AGENDA

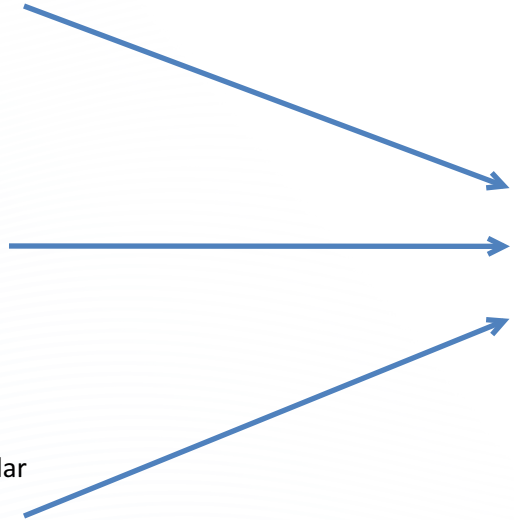
- Características de los ADCs
- Componentes
- Glosario
- Targets
- Desarrollo en ovario
- Desarrollo en cérvix
- Desarrollo en endometrio
- Efectos adversos
- Conclusiones y retos pendientes

Contribuciones recientes en cáncer ginecológico

OVARIO
- ✓Bevacizumab
- ✓PARPi
- ✓Biomarcadores (BRCA, HRD)

CERVIX
- ✓Bevacizumab
- ✓Mejoras en RXT
- ✓Inmuno en metastásica
- ✓Inmuno en LACC
- ✓Biomarcadores (PDL1)

ENDOMETRIO
- ✓FIGO 2023 y clasificación molecular
- ✓Ganglio centinela
- ✓Inmunoterapia
- ✓Pembro-lenva
- ✓Biomarcadores (IMS-MMR, RE, HER2, p53)



ADCs: inicialmente para situaciones con escasas opciones
Nuevos biomarcadores

¿Porqué ADCs?

- Buscar especificidad en células tumorales dirigiendo el fármaco a través de sus antígenos
- Incrementar concentración de citostático liberado directamente a la célula tumoral
- Combinar ventajas antitumorales de Ac+citostáticos
- MEJORAR ÍNDICE TERAPÉUTICO
- Testados con éxito en múltiples neoplasisa: mama, linfoma, mileloma, estómago , ovario
- Desarrollo más rápido

Requisitos y componentes de los ADCs

- Un Ac. altamente selectivo frente a un Ag. Presente en el tumor
- Un citotóxico potente que actúe internamente en la célula
- Un linker que una el citotóxico (payload) con el Ac. y que sea estable en la circulación y libere la quimio en las células diana
- La eficacia y los EA dependen del citotóxico y de la actividad del Ac.
- Solamente un 0,1% alcanza la célula tumoral
- Necesidad de utilizar citotóxicos potentes que no podrían utilizarse fuera de los conjugados

Glosario

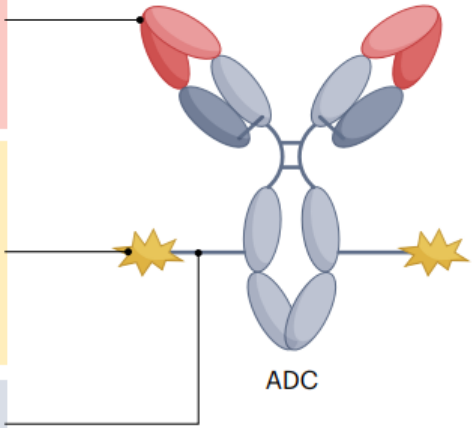
- Payload: citotóxico que debe liberarse en la célula tumoral
- Linker: molécula que mantiene adherido el Ac al citotóxico. Degradable o no degradable
- Effect “by stander”: capacidad de los payloads hidrofóbicos de difundir de nuevo al exterior de la célula diana pudiendo actuar en población celular Ag -, capaces de aumentar la eficacia en tumores heterogéneos pero también la toxicidad off-target
- EA on target: efectos fuera del tumor relacionados con la unión del Ac a Ag diana en celulas no tumorales.
- EA off target: efectos fuera del tumor, no relacionados con el Ag. ni con el Ac.
- DAR: Drug/antibody ratio

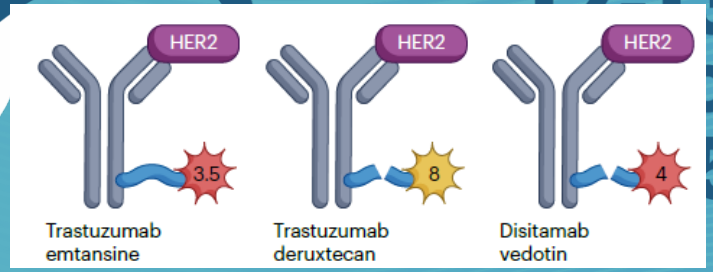
ADC: anatomía de un “silver bullet”

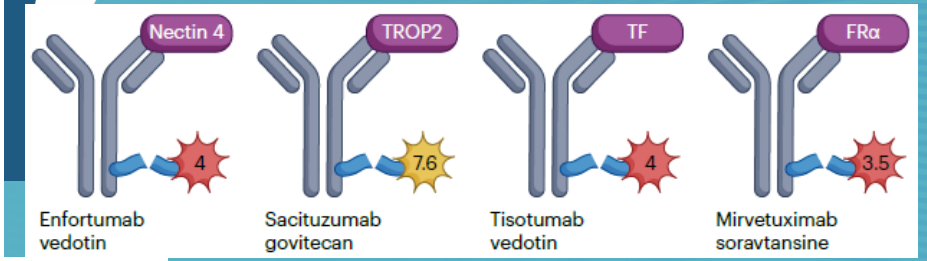
Antibody (human IgG1 in general)
- High tumour specificity
- Long circulation life
- Rapid internalization
- With or w/o immune activation
- Minimal immunogenicity

Payload
- Highly toxic compound
- Various mechanisms of action (such as microtubule inhibition and direct DNA damage)
- Bystander effect if hydrophobic
- Optimal DAR

Linker and conjugation chemistries
- Links the monoclonal antibody and the payload
- Homogeneity
- Non-cleavable or cleavable
- Affects physicochemical properties, stability in circulation and potency





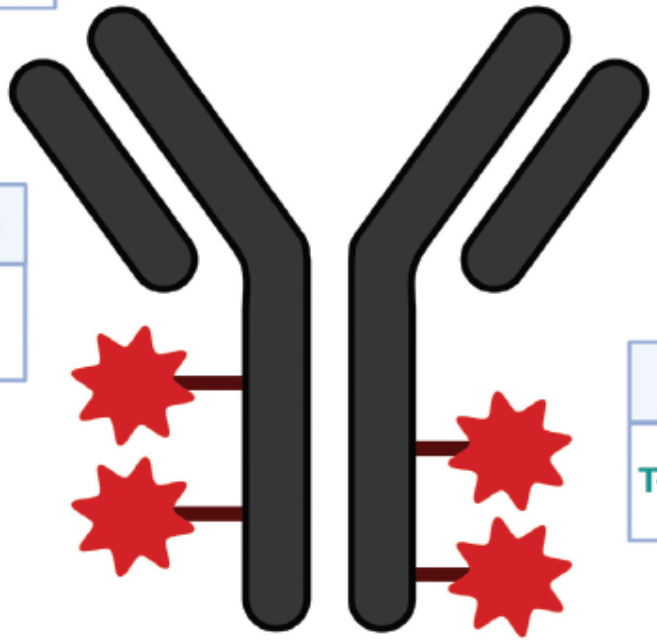


Tsuchikama K et al. Nature Reviews Clinical Oncology, 2024.

Mirvetuximab-soravtansine (MIRV)
Trastuzumab-deruxtecan (T-Dxd)
Tisotumab Vedotin (TV)

Approved ADCs in Gynecologic Malignancies

FDA



Target Antigen
MIRV: FRα
T-Dxd: HER-2
TV: TF

Payload
MIRV: DM4 (MTi)
T-Dxd: Deruxtecan (Ti)
TV: MMAE (MTi)

DAR
MIRV: 4
T-Dxd: 8
TV: 4

MTi: inhibidor microtúbulos
TI: inhibidor topoisomerasa
MMAE: Monometil auristatin E

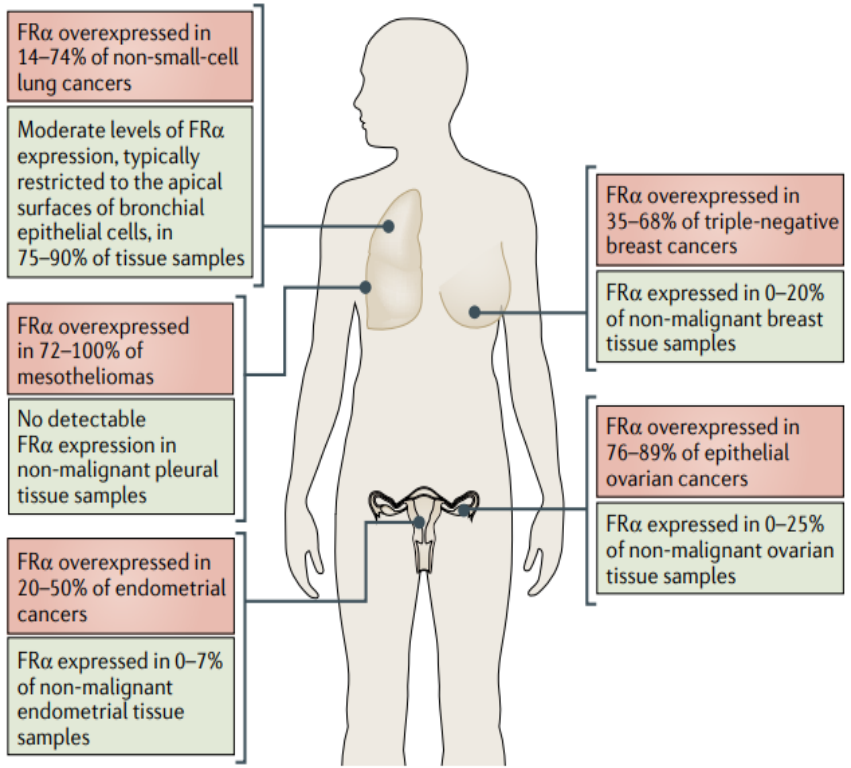
ADCs CÁNCER DE OVARIO

Reported expression in OC	60–100%	70%	5–60%	55–100%	80–90%	95%	25–100%	70–90%

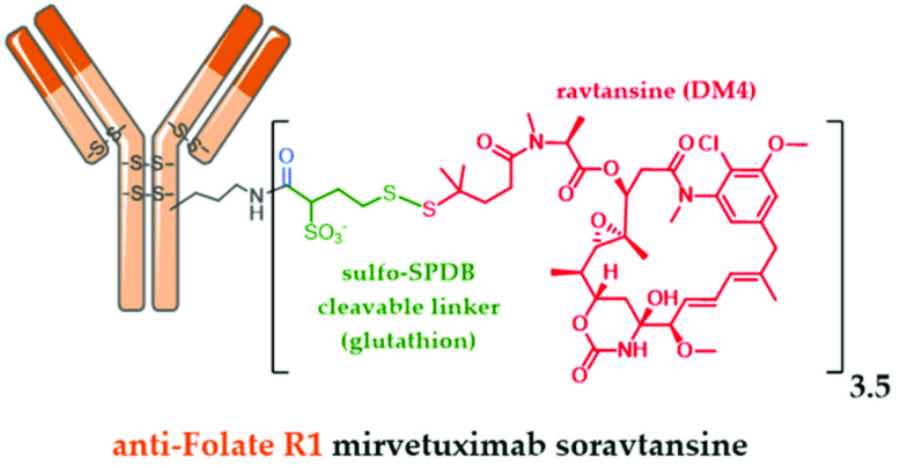
Chelariu-Raicu A, et al. Int J Gynecol Cancer. 2023

Receptor de folato α

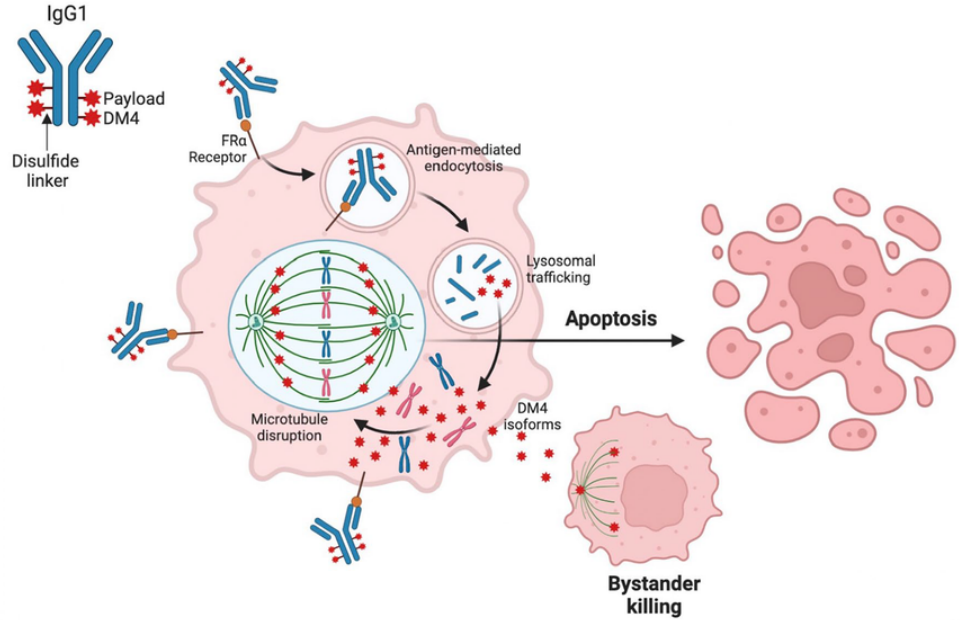
- Se expresa ampliamente en **tejidos muy proliferativos** y tejidos embrionarios.
- La expresión en tejidos sanos es muy limitada.
- FRα se sobreexpresa de forma variable en tumores sólidos **(>90% en cáncer de ovario)** y se asocia con mal pronóstico**.**
- Se valora mediante **IHQ** (PS2+ / 10X en >75% de las células tumorales).
- Su **expresión permanece estable** en el tiempo



Mirvetuximab soravtansina



anti-Folate R1 mirvetuximab soravtansine



Oza A et al. Clinical Medicine Insights: Oncology. 2023

Desarrollo del Mirvetuximab-sv

FORWARD I → Fase III en ovario PR
Negativo por mala definición del punto de corte de FRα (>50% cualquier tinción)

SORAYA → Fase II en PR
Aprobación acelerada FDA

MIRASOL → Fase III en PR
Aprobación completa

≥75% 2+

Mirvetuximab soravtansina (SORAYA)

SORAYA

A phase II single arm trial with Mirvetuximab soravtansine

Key eligibility criteria

- Platinum-resistant ovarian cancer
- Prior bevacizumab required, prior PARPi allowed
- 1–3 prior lines of therapy
- Patients with *BRCA* mutations allowed
- FRα-positive (≥75% of cells staining positive with ≥2+ staining intensity)

Mirvetuximab soravtansine (N=106)

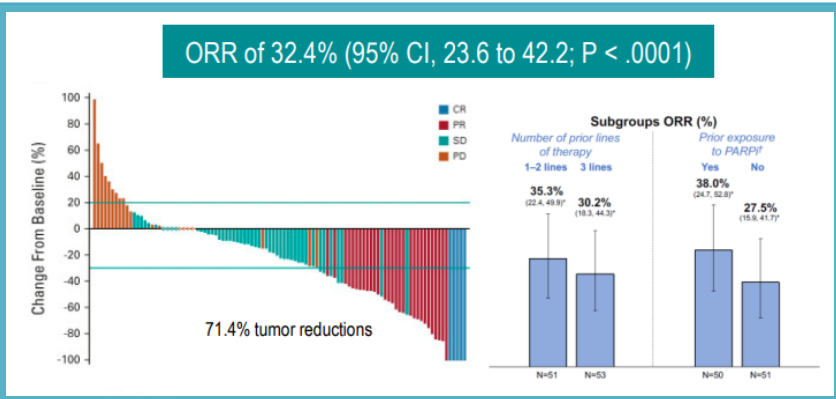
6.0 mg/kg adjusted ideal body weight (AIBW) q3w

Primary endpoint
- ORR per Investigator

Secondary endpoints
- DOR, PFS, OS, CA-125 response by GCIG criteria, safety

106 pacientes

Matulonis U et al. J Clin Oncol 2023



Resultados eficacia:

- ORR: 32,4% (5 pacientes RC).
- DOR: 6,9 meses.
- PFS: 4,3 meses.
- OS: 13,8 meses.

Resultados seguridad:

- EAs ≥ grado 3: 30% (visión borrosa, queratitis).
- EAs discontinuación: 9%.

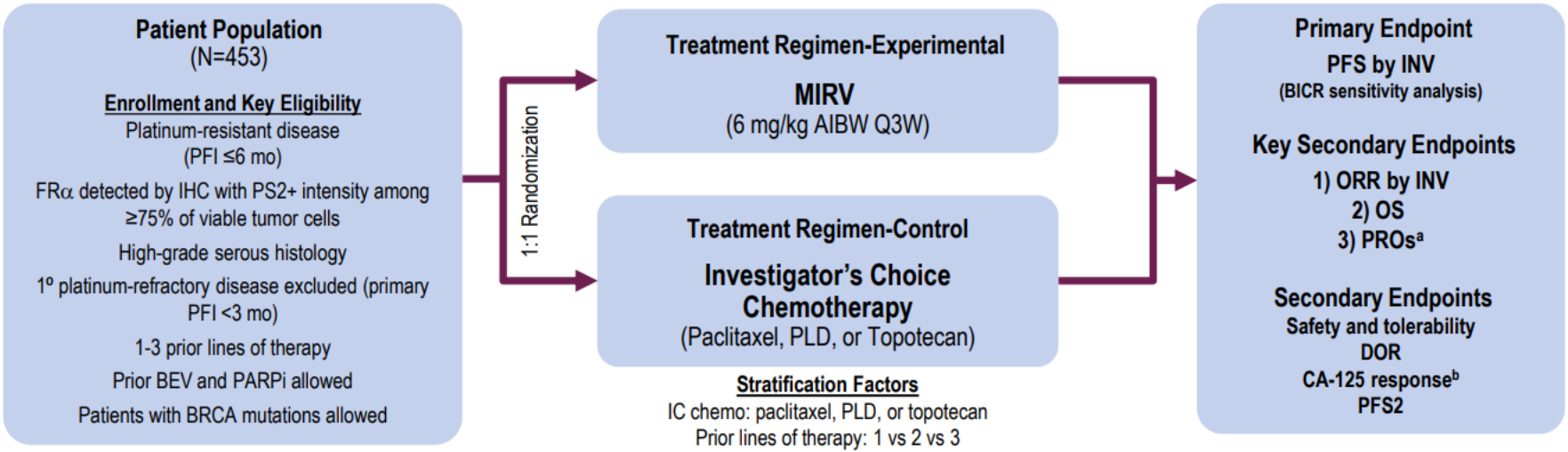
Mirvetuximab soravtansina (MIRASOL)

ORIGINAL ARTICLE

Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer

MIRASOL

An open-label, phase III randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer



Moore KL, et al. NEJM 2023

Baseline Demographics (N=453; ITT[a])

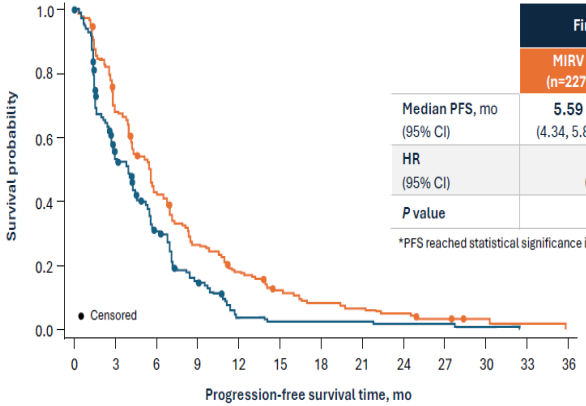
Characteristics[b]		MIRV (n=227)	ICC (n=226)
Age, mean (range)	Age in years	63 (32-88)	62 (29-87)
Stage at initial diagnosis, n (%)[c]	I-II	9 (4)	9 (4)
	III	137 (60)	147 (65)
	IV	76 (33)	65 (29)
BRCA mutation, n (%)	Yes	29 (13)	36 (16)
	No/unknown	198 (87)	190 (84)
Prior exposure, n (%)	Bevacizumab	138 (61)	143 (63)
	PARPi[d]	124 (55)	128 (57)
	Taxanes	227 (100)	224 (99)
Primary platinum-free interval, n (%)[e]	≤12 mo	145 (64)	142 (63)
	>12 mo	81 (36)	84 (37)
Platinum-free interval, n (%)[f]	≤3 mo	88 (39)	99 (44)
	>3 to ≤6 mo	138 (61)	124 (55)
Stratification factor: No. of prior systemic therapies, n (%)	1	29 (13)	34 (15)
	2	90 (40)	88 (39)
	3	108 (48)	104 (46)
Stratification factor: ICC	Paclitaxel	93 (41)	92 (41)
	PLD	82 (36)	81 (36)
	Topotecan	52 (23)	53 (23)

BRCA, BReast CAncer gene; ICC, investigator's choice chemotherapy; ITT, intent-to-treat; MIRV, mirvetuximab soravtansine-gynx; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; PLD, pegylated liposomal doxorubicin.

[a]The ITT population was defined as all patients who underwent randomization, regardless of receipt of assigned treatment. [b]Percentages may not add up to 100 due to rounding. [c]Five patients (2%) in the MIRV arm and 5 patients (2%) in the ICC arm were missing information for stage at initial diagnosis. [d]Prior exposure to PARPi in IC chemotherapy arm changed from 127 in primary analysis to 128 in final analysis due to an additional prior PARPi medication in 1 patient. [e]One patient (<1%) in the MIRV arm was missing information on primary platinum-free interval. Primary platinum-free interval ≤12 month in MIRV arm changed from 146 in primary analysis to 145 in final analysis due to the change in the dose date of 1 patient. [f]One patient (<1%) in the MIRV arm and 3 patients (1%) in the ICC arm enrolled with platinum-free interval of >6 months.

Moore KN, et al. *N Engl J Med*. 2023;389(23):2162-2174.

Final Progression-Free Survival by Investigator



Number of patients at risk:

MIRV	227	151	89	54	36	23	15	12	9	5	2	1	0
ICC	226	98	49	22	5	3	3	3	2	2	1	0	

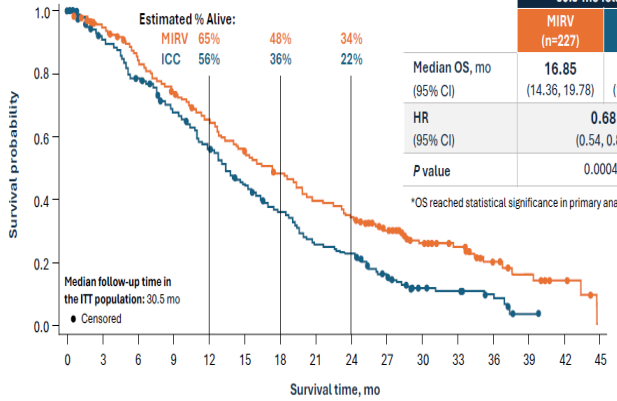
	Final analysis[a]		Primary analysis[b]	
	MIRV (n=227)	ICC (n=226)	MIRV (n=227)	ICC (n=226)
Median PFS, mo (95% CI)	**5.59** (4.34, 5.88)	**3.98** (2.86, 4.47)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
HR (95% CI)	**0.63** (0.51, 0.79)		0.65 (0.52, 0.81)	
P value	<0.0001*		<0.0001	

*PFS reached statistical significance in primary analysis. The *P* value at the final analysis is descriptive.

At the final analysis, the HR for PFS (0.63) **continued to favor MIRV** over ICC, with patients treated with MIRV exhibiting a **37% reduction in risk of progression**

HR, hazard ratio; ICC, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine-gynx; PFS, progression-free survival.
[a]Data cutoff: September 26, 2024. [b]Data cutoff: March 6, 2023.
Moore KN, et al. *N Engl J Med*. 2023;389(23):2162-2174.

Final Overall Survival



Number of patients at risk:

MIRV	227	204	178	156	135	114	98	80	70	50	33	25	12	8	4	0
ICC	226	186	159	134	110	85	67	48	42	25	13	11	7	1	0	

	Final analysis[a] 30.5-mo follow-up		Primary analysis[b] 13.1-mo follow-up	
	MIRV (n=227)	ICC (n=226)	MIRV (n=227)	ICC (n=226)
Median OS, mo (95% CI)	**16.85** (14.36, 19.78)	**13.34** (11.37, 15.15)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
HR (95% CI)	**0.68** (0.54, 0.84)		0.67 (0.50, 0.89)	
P value	0.0004*		0.0046	

*OS reached statistical significance in primary analysis. The *P* value at the final analysis is descriptive.

At the final analysis, the HR for OS (0.68) **continued to favor MIRV** over ICC, with patients treated with MIRV exhibiting a **32% reduction in risk of death**

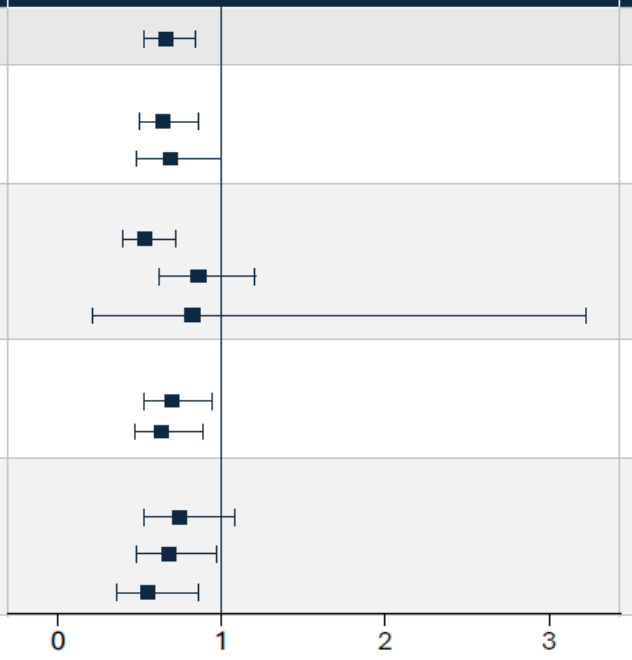
HR, hazard ratio; ICC, investigator's choice chemotherapy; ITT, intent-to-treat; MIRV, mirvetuximab soravtansine-gynx; OS, overall survival; PFS, progression-free survival.
[a]Data cutoff: September 26, 2024. [b]Data cutoff: March 6, 2023.
Moore KN, et al. *N Engl J Med*. 2023;389(23):2162-2174.

MULTIPLY YOUR IMPACT

Final Overall Survival Subgroup Analysis[a]

- OS subgroup analysis showed a **trend of improved OS for MIRV** vs IC chemotherapy across patient subgroups

	No. of patients	No. of events	Hazard ratio (95% CI)	Hazard ratio (95% CI)	*P* value[b]
All	453	339	0.68 (0.54, 0.84)		0.0004
Prior exposure to bevacizumab					
Yes	281	214	0.65 (0.50, 0.86)		0.0021
No	172	125	0.70 (0.49, 0.99)		0.0450
Prior exposure to PARPi maintenance					
Yes	252	186	0.54 (0.40, 0.73)		<0.0001
No	190	143	0.87 (0.62, 1.21)		0.4065
Uncertain	11	10	0.83 (0.22, 3.23)		0.7919
Number of prior lines of therapy					
1 or 2	245	180	0.70 (0.53, 0.95)		0.0190
3	208	159	0.65 (0.47, 0.89)		0.0062
Type of ICC					
Pegylated liposomal doxorubicin	163	119	0.75 (0.52, 1.08)		0.1242
Paclitaxel	185	132	0.68 (0.48, 0.97)		0.0313
Topotecan	105	88	0.56 (0.37, 0.86)		0.0073



ICC, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine-gynx; OS, overall survival; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor.

[a]Subgroups displayed include those based on prior therapy and stratification factors in MIRASOL. [b]*P* values were nominal.

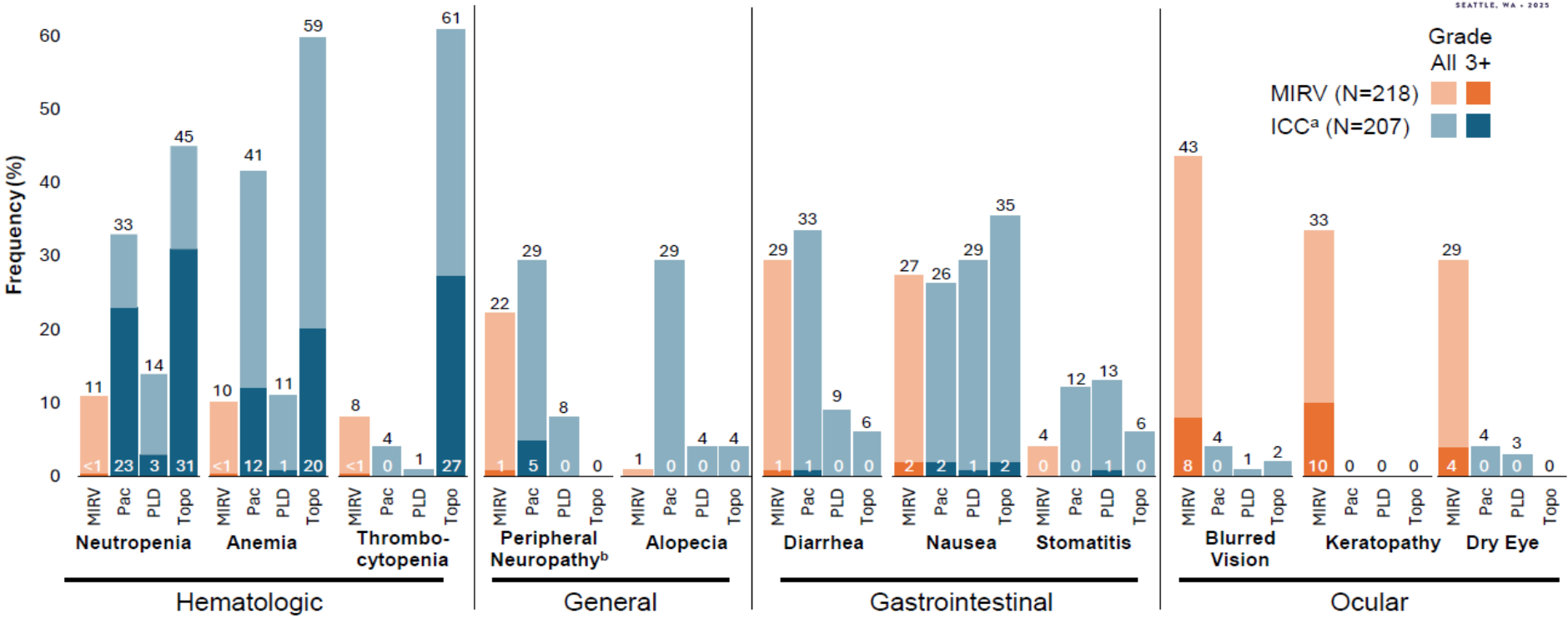
Efficacy Summary

Endpoints	Final analysis[a] MIRV (n=227)	ICC (n=226)
ORR by INV, n (%) (95% CI)	**95 (41.9)**[c] (35.4, 48.6)	**36 (15.9)** (11.4, 21.4)
Odds ratio (95% CI)	**3.75** (2.4, 5.85)	
Best overall response, n (%)		
Complete response	**13 (5.7)**	**0**
Partial response	**82 (36.1)**	**36 (15.9)**
Stable disease	87 (38.3)	91 (40.3)
Progressive disease	31 (13.7)	63 (27.9)
Not evaluable	14 (6.2)	36 (15.9)
Median DOR, mo (95% CI)	**6.93** (5.78, 8.84)	**4.44** (4.17, 5.75)
Median PFS2, mo (95% CI)	**11.01** (9.30, 12.02)	**7.59** (6.60, 8.84)
HR (95% CI)	**0.59** (0.480, 0.728)	

- At final analysis, MIRV maintained a **higher ORR (13 CRs vs none)** and **longer DOR** compared to ICC
- **PFS benefit for MIRV** over ICC was maintained **beyond the first progression** (PFS2 analysis) with an HR of 0.59

Efecto secundario "off-target": no existe expresión de FRα en el epitelio corneal.

Treatment-Emergent Adverse Events: No New Safety Signals at Final Analysis



Data cutoff: September 26, 2024

ICC, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine-gynx; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

[a]Pac, n=82 (40%); PLD, n=76 (37%); Topo, n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12%, 16%, and 3% of patients that received MIRV, PAC, or PLD, respectively.

Mirvetuximab soravtansina (otros estudios)

ESTUDIO FORWARD II

Phase Ib trial, MIRV in combination with bevacizumab in platinum agnostic OC

- Histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube cancer
- Recurrent disease with up to 3 prior regimens
- FRα-positive tumor expression
  - Medium (≥ 50%, <75% TC at ≥2+ intensity)
  - High (≥75% TC at ≥2+ intensity)

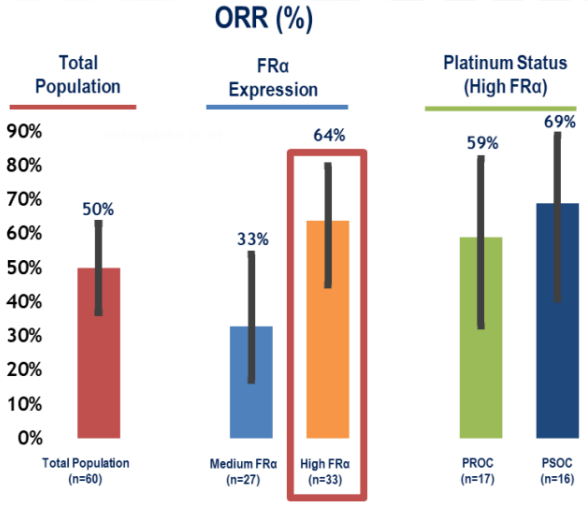
MIRV + Bev (N=94)

Primary Endpoint

Objective Response Rate

Secondary Endpoints included

DOR
PFS
Safety



- **50% ORR** (30/60) for overall cohort
- **64% ORR** (21/33) in high FRα tumors
  - **59% ORR** (10/17) in PROC subset
  - **69% ORR** (11/16) in PSOC subset

¿Deberíamos usar mirvetuximab en combinación con bevacizumab en enfermedad recurrente?

Gilbert L et al. Gynecologic Oncology 2023

Mirvetuximab soravtansina (otros estudios)

ESTUDIO PICCOLO

Single-arm Trial For Mirvetuximab In High Frα Patients With Platinum-sensitive OC

PICCOLO Patient Population (N=79)

Enrollment and Key Eligibility

- Platinum-sensitive disease (defined as radiographic progression >6 months from last dose of most recent platinum therapy)
- FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells
- At least 2 prior platinum-containing regimens
- Prior PARPi required if *BRCA*+
- Prior BEV not required
- Appropriate for single-agent therapy

Treatment Regimen

MIRV
(6 mg/kg AIBW Q3W)

Primary Endpoint

ORR by INV

Key Secondary Endpoint

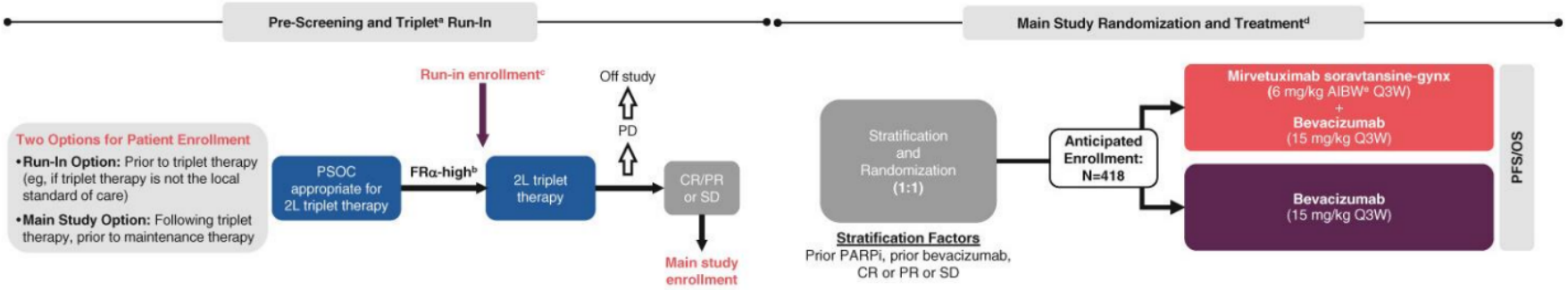
DOR by INV

Other Secondary Endpoints

- Safety and tolerability
- CA-125 response (GCIG criteria)
- PFS
- OS
- Sensitivity analyses

ESTUDIO GLORIOSA

Phase III trial for mirvetuximab + bevacizumab maintenance in FRα-high platinum-sensitive OC



Mirvetuximab soravtansina

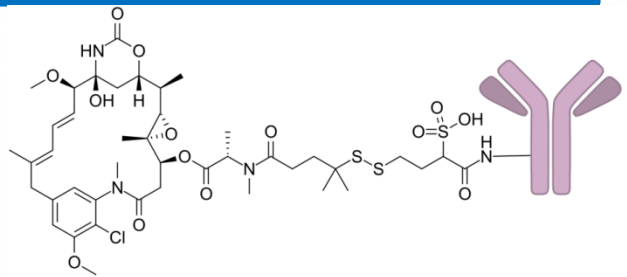
MIRVETUXIMAB SORAVTANSINA: INDICACIONES FICHA TÉCNICA

MINISTERIO DE SANIDAD

EN ESTUDIO

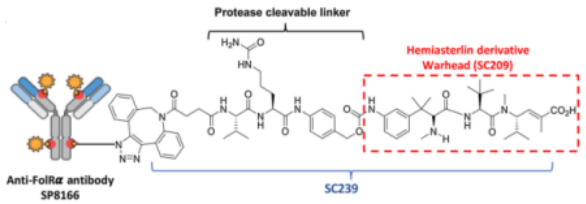
ELAHERE (mirvetuximab soravtansina) en monoterapia está indicado para el tratamiento de pacientes adultas con cáncer de ovario epitelial seroso de alto grado, trompas de Falopio o peritoneal primario con **positividad para el receptor de folato alfa (FRα)** y **resistente a platino** que han recibido **entre uno y tres esquemas de tratamiento sistémico previos**.

FDA approves mirvetuximab soravtansine-gynx for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer



Luveltamab tazevibulina

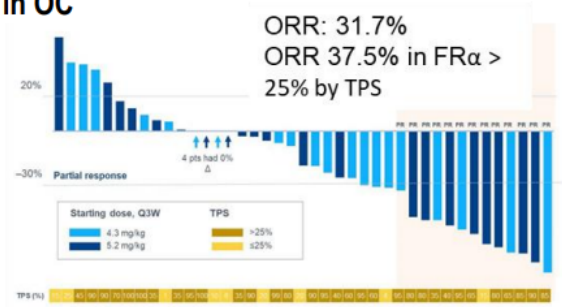
Luveltamab tazevibulin



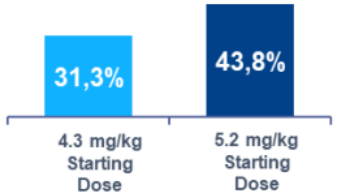
- Luvelta (STRO-002) is a homogenous ADC targeting FRα
- Cathepsin B linker, which is a stable protease-cleavable linker
- **Hemiasterlin-derivative**[a] cytotoxic payload
- DAR=4

Efficacy

Phase 1 dose-expansion study (NCT03748186) in OC



FRα >25% by TPS



Safety

Phase 1 dose-expansion study

TRAEs leading to dose reduction in 61.4%

- Neutropenia[a] in 17 patients (39%)
  - Primarily G3/4 uncomplicated (abnormal lab value only)
  - Febrile neutropenia in 2 patients (4.5%)
  - Resolved without growth factor support in most patients
  - Median duration of G3+ AEs, 8 days
- Arthralgia in 8 patients (18%)
- Peripheral neuropathy in 3 patients (6.8%)
  - Most G1/2

TEAEs leading to dose discontinuation in 3 patients (6.8%)

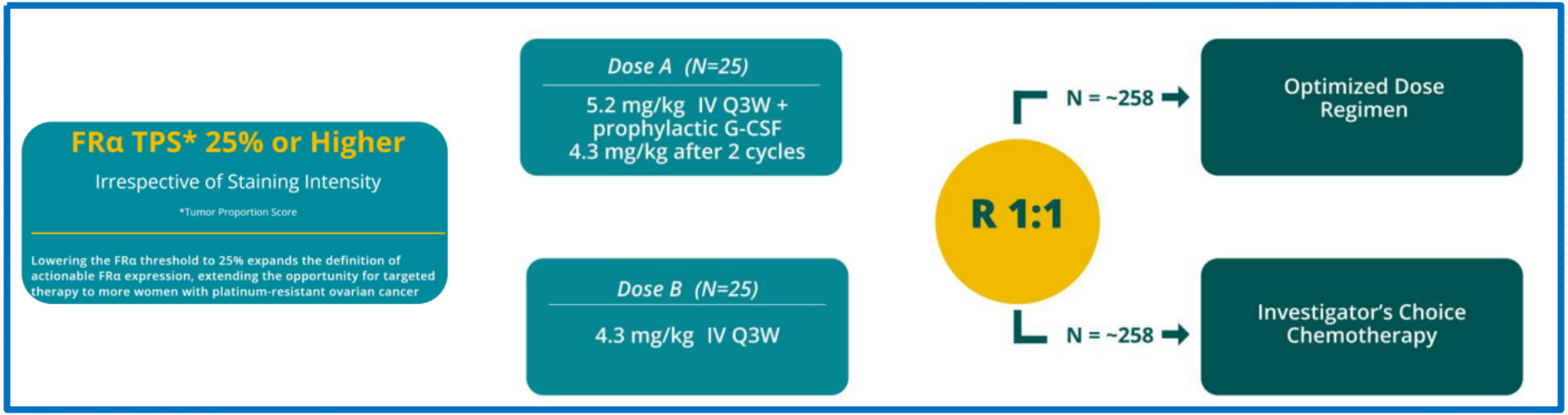
- G3 fatigue
- G2 neuropathy
- G5 Sepsis

1. Oaknin et al. Poster presented at ASCO 2023; Abstract 5508. 2. Sutro Biopharma. Accessed March 2, 2023

Luveltamab tazevibulina

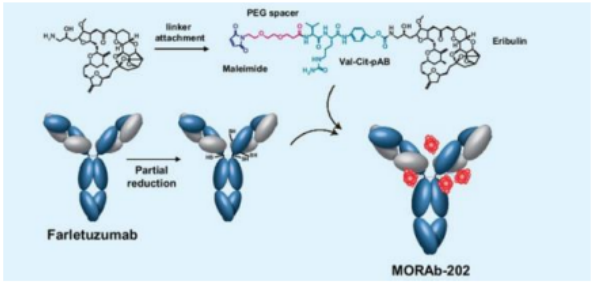
ESTUDIO REFRaME01

A Phase III Study to Investigate the Efficacy and Safety of Luveltamab Tazevibulin Versus Investigator's Choice (IC) Chemotherapy in Women With Ovarian Cancer (Including Fallopian Tube or Primary Peritoneal Cancers) Expressing FOLR1



Farletuzumab ecteribulina

MORAb-202[1,2]

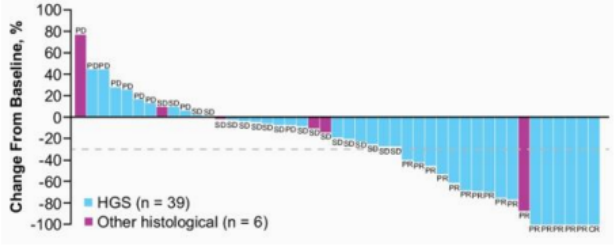


MORAb-202 is an ADC consisting of:

- Antibody: farletuzumab FRα
- Linker: cathepsin B cleavable linker
- Payload: **eribulin**, microtubule inhibitor
- DAR=4

Efficacy[1,2]

Phase 1 dose-expansion study in OC (NCT03386942)



Data cutoff date: October 31, 2021.

Parameter	Cohort 1: MORAb-202 0.9 mg/kg (n=24)	Cohort 2: MORAb-202 1.2 mg/kg (n=21)
ORR,	6 (25.0)	11 (52.4)
DCR,	16 (66.7)	20 (95.2)
mPFS,	6.7	8.2
mOS,	10.5	NE
ORR by FRα status		
FRα <50%	2/6 (33.3)	1/2 (50.0)
FRα ≥50%	4/18 (22.2)	10/19 (52.6)

Safety[1]

Phase 1 dose-expansion study

- The most common TEAE was **interstitial lung disease (ILD)/pneumonitis at both dose levels**
  - Cohort 1: 37.5% (n=9; 8 with Gr 1; 1 with Gr 2)
  - Cohort 2: 66.7% (n=14; 6 with Gr 1; 7 with Gr 2, 1 with Gr 3)
- Other common TEAEs of any grade, in Cohorts 1 and 2, respectively, were:
  - Nausea (25.0%; 33.3%)
  - Pyrexia (33.3%; 42.9%)
  - Malaise (16.7%; 28.6%)
  - Headache (12.5%; 47.6%)

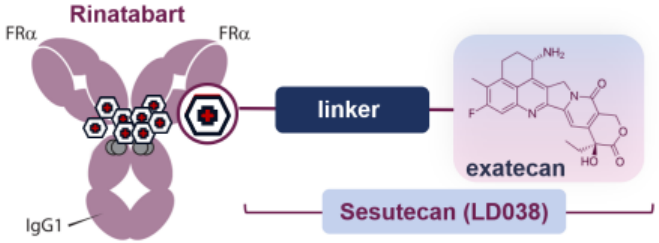
1. Nishio S et al. Poster presented at ASCO 2022; Abstract 5513. 2. Shimizu T et al. Poster presented at ASCO 2019; Abstract 5544.

Rinatabart sesutecan

Rinatabart sesutecan (Rina-S) is an investigational, novel ADC composed of[11]:

- A human monoclonal antibody directed at FRα
- A novel hydrophilic protease-cleavable linker
- Exatecan, a topoisomerase I inhibitor

Rina-S features a high, homogenous drug-to-antibody ratio of 8[10]



Study Design

Part A – Dose Escalation

- Solid tumors[a] dose escalation (n = 53) included patients regardless of FRα expression with previously treated OC (n = 32; 23 received Rina-S 100-120 mg/m² Q3W) and EC (n = 11; 5 received Rina-S 100-120 mg/m² Q3W)

Part B – Dose Expansion

- Planned tumor-specific dose expansion includes OC, EC, and *EGFR*-mutant NSCLC regardless of FRα expression[b]
- **Cohort B1 - OC Dose Expansion**
  - Inclusion criteria
    - Histologically or cytologically confirmed OC (must have epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer)
    - Prior treatment (1-3 prior lines for PROC or 4 prior lines regardless of platinum-sensitivity status)
    - ECOG PS 0-1
    - Measurable disease per RECIST v1.1
    - Adequate hematologic, hepatic, renal, and cardiac function
  - Randomized 1:1 to receive Rina-S 100 mg/m² or Rina-S 120 mg/m² Q3W

Patient Demographics and Disease Characteristics in OC Dose Expansion

OC Dose Expansion	Rina-S 100 mg/m² n = 22	Rina-S 120 mg/m² n = 20
Age, median (range), years	62.5 (42-82)	64.5 (37-83)
Prior lines of therapy, median (range)	3 (1-5)	3 (1-4)
Bevacizumab, n (%)	20 (90.9)	18 (90.0)
PARPi, n (%)	15 (68.2)	13 (65.0)
Mirvetuximab soravtansine, n (%)	4 (18.2)	4 (20.0)
Platinum sensitivity status, n (%)		
Resistant	20 (90.9)	19 (95.0)
Sensitive	2 (9.1)	1 (5.0)

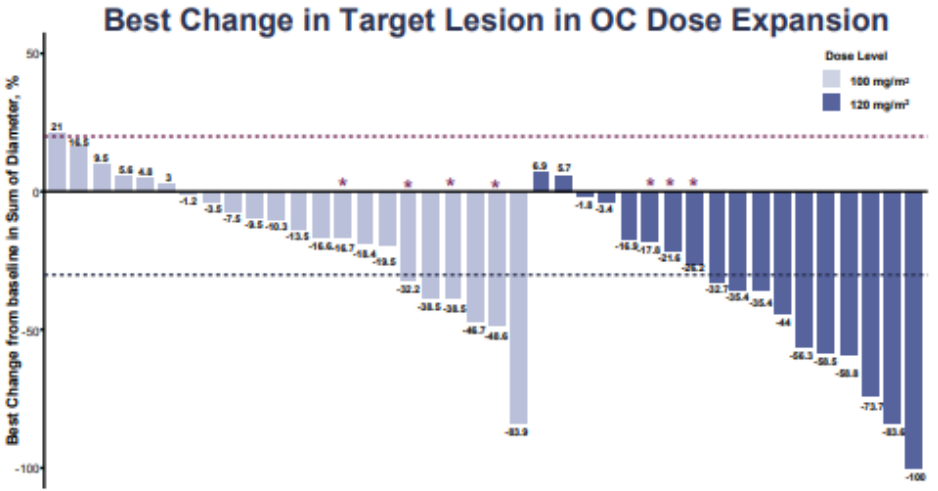
DCO: July 28, 2024

Rinatabart sesutecan

Rina-S demostró una actividad antitumoral prometedora a dosis de 120 mg/m2 cada 3 semanas (incluida una respuesta completa) en pacientes altamente pretratadas CO platino-resistente.

OC Dose Expansion	Rina-S 100 mg/m² n = 22[b]	Rina-S 120 mg/m² n = 18[b]
Confirmed ORR,[a,b] % (95% CI)	18.2 (5.2-40.3)	50.0 (26.0-74.0)
Best overall response,[b] n (%)		
CR	0	1 (5.6)
PR	4 (18.2)	8 (44.4)
SD	15 (68.2)	7 (38.9)
PD	3 (13.6)	1 (5.6)
Not evaluable	0	1 (5.6)
DCR, % (95% CI)	86.4 (65.1-97.1)	88.9 (65.3-98.6)
Median DOR (95% CI)	NR (NR-NR)	

Treatment duration, range: 3.0-42.0+ weeks
Median on-study follow-up: 24 weeks

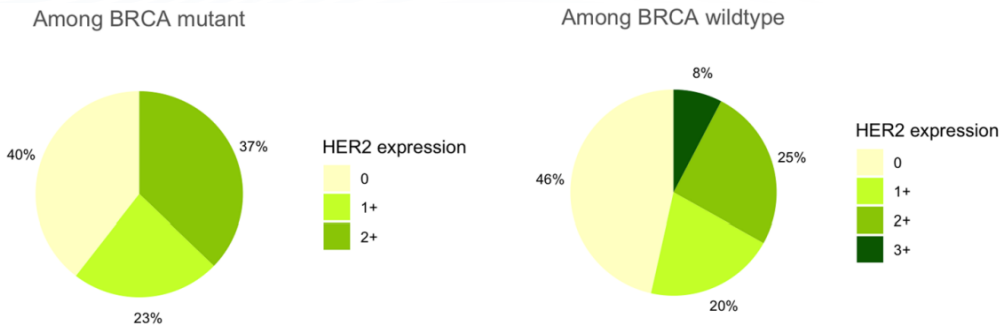


Median no. of cycles: 6.5 (100 mg/m²) and 7.0+ (120 mg/m²)

ADCs EN CÁNCER DE ENDOMETRIO

HER2 en cáncer ginecológico

Score	Gastric cancer[16,25]	Breast cancer[22]
IHC 0	No immunoreactivity or membranous reactivity in <10% tumor cells	No immunoreactivity
IHC 1+	Faint/barely perceptible membranous reactivity in >10% tumor cells; only partial membrane reactivity	Weak, incomplete membrane reactivity in any proportion of tumor cells
IHC 2+	Weak to moderate complete/basolateral/lateral membranous reactivity in >10% of tumor cells	Nonuniform or weak but otherwise circumferential reactivity in >10% of cells Intense, complete membrane staining in <30% of cells
IHC 3+	Strong complete/basolateral/lateral membrane reactivity in >10% tumor cells	Uniform, intense membrane staining in >30% tumor cells
FISH +	Her-2/CEP 17 > 2	>6 Her-2 gene copies/nucleus; Her-2/CEP 17 > 2.2
FISH equivocal	None	>4–<6 Her-2 gene copies/nucleus; Her-2/CEP 17 1.8–2.2
FISH−	Her-2/CEP 17 < 2	<4 Her-2; Her-2/CEP 17 < 1.8

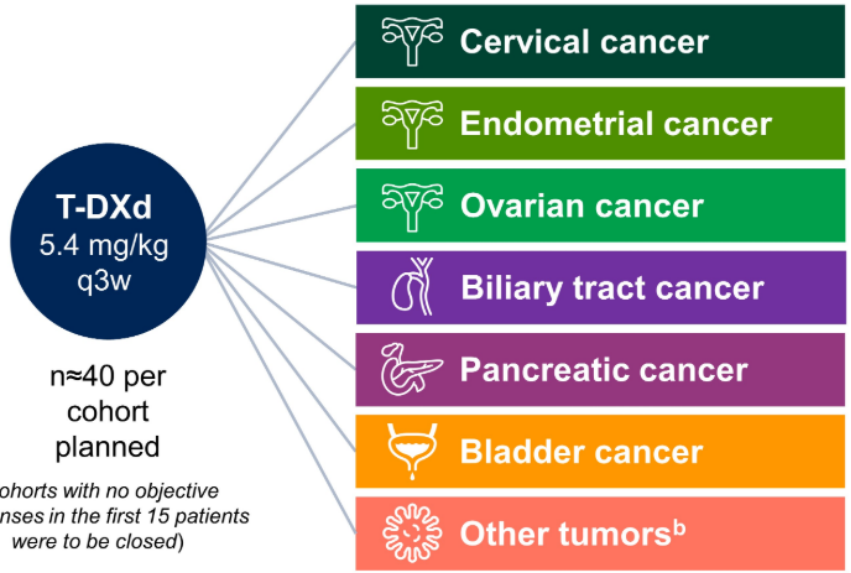


Baseline Characteristic	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)
Age, years, median (range)	67 (37-79)	49 (28-78)	56 (34-72)
HER2 IHC status (eligibility),[c] No. (%)			
IHC 3+	16 (40.0)	10 (25.0)	15 (37.5)
IHC 2+	24 (60.0)	25 (62.5)	25 (62.5)
IHC 1+[c]	0	5 (12.5)	0
Prior therapy lines			
Median (range)	2 (0-7)	2 (1-6)	3 (1-12)
0, No. (%)	1 (2.5)	0	0
1, No. (%)	8 (20.0)	6 (15.0)	8 (20.0)
2, No. (%)	18 (45.0)	15 (37.5)	8 (20.0)
3, No. (%)	6 (15.0)	9 (22.5)	5 (12.5)
4, No. (%)	3 (7.5)	6 (15.0)	5 (12.5)
≥5, No. (%)	4 (10.0)	4 (10.0)	14 (35.0)

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

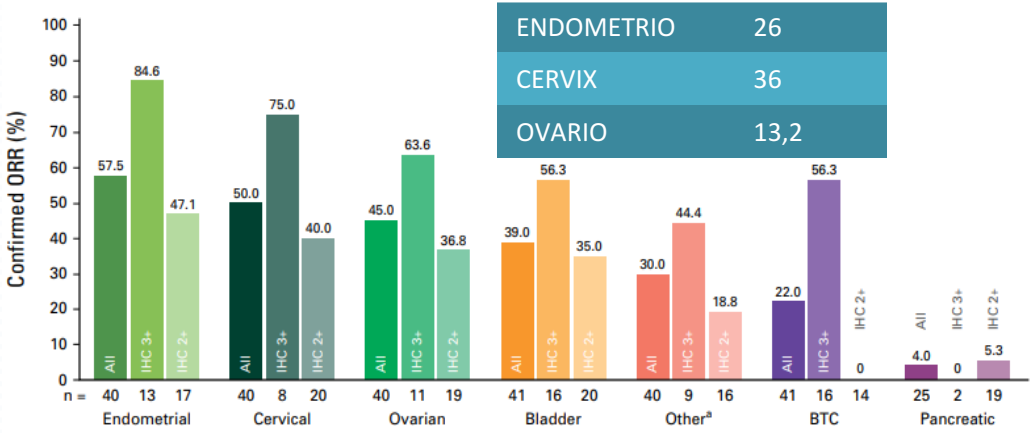
Data cut-off for analysis:

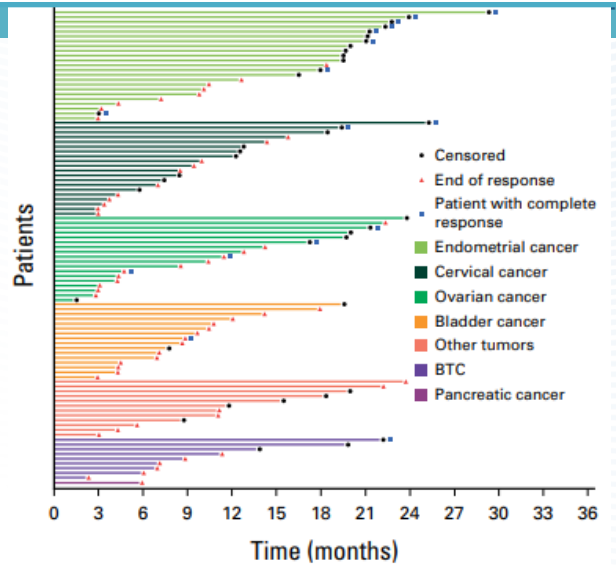
- Nov 16, 2022

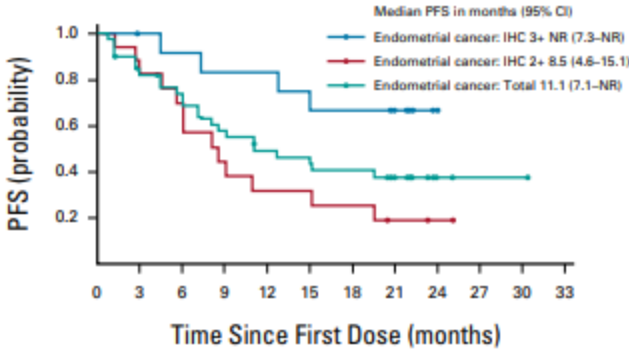
1. Meric-Bernstam F et al. Presented at: ASCO Annual Meeting; June 4-6, 2023; Chicago, IL. 2. Hofmann M, et al. Histopathology 2008;52(7):797–805.

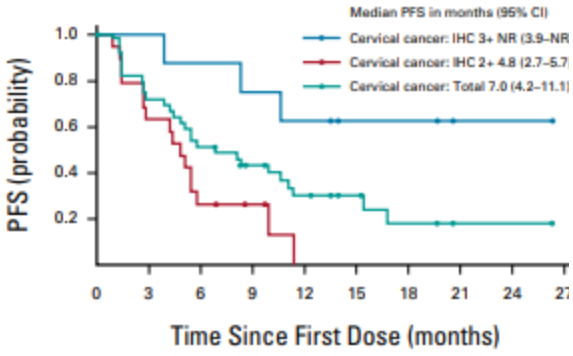
Trastuzumab deruxtecan (DESTINY-PanTumor02)

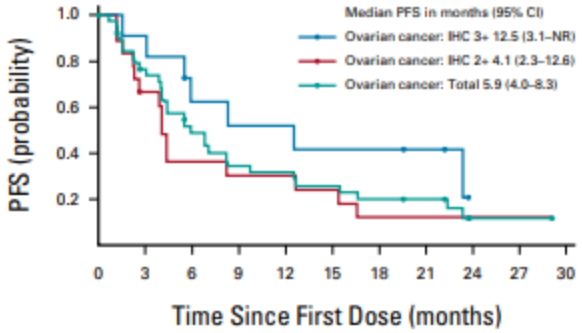
	OS mo
ENDOMETRIO	26
CERVIX	36
OVARIO	13,2











DESTINY-PanTumor02
Efectos Adversos

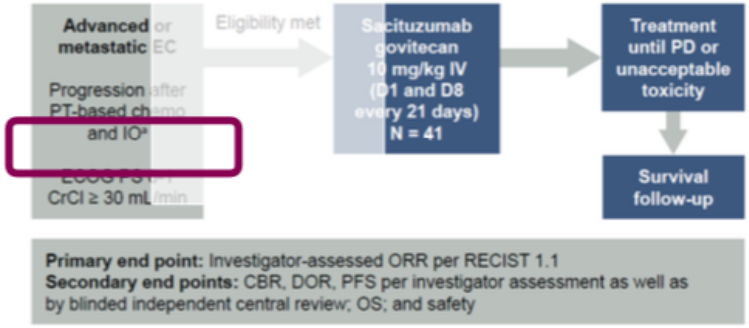
- **NEUMONITIS 10,5% (24 pts.)**
- **Fatal 1,1% (3 pts.)**

Adverse Event	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)
Drug-related adverse events, No. (%)	36 (90.0)	36 (90.0)	34 (85.0)
Grade ≥3	14 (35.0)	19 (47.5)	21 (52.5)
Serious adverse events	4 (10.0)	3 (7.5)	11 (27.5)
Leading to discontinuation	3 (7.5)	3 (7.5)	1 (2.5)
Leading to dose modification[a]	13 (32.5)	13 (32.5)	18 (45.0)
Associated with death	2 (5.0)	0	0
Most common drug-related adverse events (>10% of total patients), No. (%)			
Nausea	29 (72.5)	26 (65.0)	22 (55.0)
Anemia	7 (17.5)	15 (37.5)	15 (37.5)
Diarrhea	16 (40.0)	15 (37.5)	8 (20.0)
Fatigue	10 (25.0)	9 (22.5)	11 (27.5)
Vomiting	16 (40.0)	10 (25.0)	7 (17.5)
Neutropenia	4 (10.0)	8 (20.0)	5 (12.5)
Decreased appetite	8 (20.0)	7 (17.5)	8 (20.0)
Asthenia	11 (27.5)	9 (22.5)	6 (15.0)
Alopecia	9 (22.5)	8 (20.0)	5 (12.5)
Thrombocytopenia	2 (5.0)	2 (5.0)	5 (12.5)

Alternative treatment options: TROP-2

TROPiCS-03 is a multicohort, open-label, **phase 2** basket study in adult patients with metastatic solid tumors (NCT03964727)

All participants had previously **received platinum-based chemotherapy and most had receiv**ed immunotherapy t**o treat their cancer**



	SG (N = 41)
Median age (range), years	68 (44-83)
Race, n (%)	
White	21 (51)
Asian	8 (20)
Other	6 (15)
Not reported	6 (15)
ECOG PS, n (%)	
0	18 (44)
1	23 (56)
MSI-H, n (%)	8 (20)
Histological diagnosis, n (%)	
Endometrioid	20 (49)
Serous	17 (42)
Other	4 (10)
Prior anticancer therapy type, n (%)	
Chemotherapy	41 (100)
Immunotherapy	35 (85)
Targeted agents	26 (63)
Hormonal therapy	5 (12)
Other	1 (2)
Median prior anticancer regimens, n (range)	3 (1-6)
Prior platinum-based chemotherapy and immunotherapy, n (%)	35 (85)

- ORR: 27%
- PFS: 5 months
- OS: 15 months

Based on the findings from this study, a larger, randomized phase 3 study has been initiated (ASCENT-GYN-01)

ADCs EN CÁNCER DE CÉRVIX

innovaTV 204/GOG-3023/ENGOT-cx6

Fase II
Cérvix recurrente o metastásico
≤2 regímenes previos
Medible
ECOG 1-2

Tisotumab vedotin 2mg/k (max 200 mg)/21 d

Objetivo primario: ORR
102 pacientes

Target:TS (factor tisular)
Payload MMAE, antimicrotubulo

Histology	
Squamous cell carcinoma	69 (68%)
Adenocarcinoma	27 (27%)
Adenosquamous carcinoma	5 (5%)
Extrapelvic metastatic disease at baseline	95 (94%)
Recurrent disease*	
Yes	61 (60%)
No	40 (40%)
Previous cisplatin plus radiotherapy	
Yes	55 (54%)
No	46 (46%)
Previous lines of systemic therapies for recurrent or metastatic disease†	
1	71 (70%)
2	30 (30%)
Previous bevacizumab plus doublet chemotherapy‡ as first-line therapy	64 (63%)
Any previous bevacizumab	70 (69%)
Response to last systemic regimen†	
Yes	38 (38%)
No	57 (56%)
Unknown	6 (6%)
Positive TF expression§	
Membrane	77/80 (96%)

Objective response rate (95% CI)†	24% (16–33)
Complete response	7 (7%)
Partial response	17 (17%)
Stable disease	49 (49%)
Progressive disease	24 (24%)
Not evaluable	4 (4%)
Disease control rate (95% CI)‡	72% (63–81)
Median (95% CI) duration of response, months	8·3 (4·2–not reached)
Median (95% CI) progression-free survival, months	4·2 (3·0–4·4)
Median (95% CI) overall survival, months	12·1 (9·6–13·9)
6-month overall survival rate (95% CI)	79% (69–86)
12-month overall survival rate (95% CI)	51% (41–61)

Coleman, Robert LRaspagliesi, Francesco et al.
The Lancet Oncology, Volume 22, Issue 5, 609 - 619

Approved ADCs	Target	Indications	Approved Year/ R&D Organization	Common Adverse Events (Any Grades)	Common Grade ≥ 3 Adverse Events
Gemtuzumab Ozogamicin (Mylotarg®)	CD-33	Acute myeloid leukemia	2001 Pfizer	Thrombocytopenia, fatigue, neutropenia, pyrexia, nausea, infection, chills, hemorrhage, vomiting, headache, stomatitis, diarrhea, and abdominal pain	Neutropenia, thrombocytopenia, increased AST/ALT levels, and sepsis
Inotuzumab Ozogamicin (Besponsa®)	CD-22	B-cell precursor acute lymphoblastic leukemia	2017 Pfizer	Neutropenia, thrombocytopenia, infection, anemia, leukopenia, febrile neutropenia, and nausea	Neutropenia, thrombocytopenia, leukopenia, febrile neutropenia, anemia, and lymphopenia
Brentuximab Vedotin (Adcetris®)	CD-30	Hodgkin lymphoma, systemic anaplastic large-cell lymphoma, T-cell lymphoma	2011 Seattle Genetics	Peripheral sensory neuropathy, nausea, fatigue, neutropenia, diarrhea, pyrexia, vomiting, arthralgia, pruritus, myalgia, peripheral motor neuropathy, and alopecia	Neutropenia, peripheral sensory neuropathy, thrombocytopenia, and anemia
Polatuzumab Vedotin (Polivy®)	CD-79b	Diffuse large B-cell lymphoma	2019 Genentech	Neutropenia, anemia, and peripheral neuropathy	Neutropenia, anemia, and peripheral sensory neuropathy
Enfortumab Vedotin (Padcev®)	Nectin-4	Urothelial cancer	2019 Astellas	Fatigue, alopecia, decreased appetite, dysgeusia, nausea, peripheral sensory neuropathy, pruritus, diarrhea, and maculopapular rash	Rash, neutropenia, anemia, and fatigue
Enfortumab Vedotin (Padcev®)	Nectin-4	Urothelial cancer	2019 Astellas	Fatigue, alopecia, decreased appetite, dysgeusia, nausea, peripheral sensory neuropathy, pruritus, diarrhea, and maculopapular rash	Rash, neutropenia, anemia, and fatigue
Tisotumab Vedotin (Tivdak®)	Tissue factor	Cervical cancer	2021 Genmab	Epistaxis, fatigue, nausea, alopecia, conjunctivitis, decreased appetite, constipation, diarrhea, vomiting, peripheral neuropathy, dry eye, and abdominal pain	Fatigue, anemia, abdominal pain, hypokalemia, conjunctivitis, hyponatremia, peripheral neuropathy, and vomiting
Belantamab Mafodotin (Blenrep®)	B-cell maturation antigen	Multiple myeloma	2020 GSK	Keratopathy, thrombocytopenia, anemia, nausea, pyrexia, blurred vision, increased aspartate aminotransferase	Keratopathy, thrombocytopenia, anemia
Trastuzumab Emtansine (Kadcyla®)	HER-2	Breast cancer	2013 Genentech	Thrombocytopenia, elevated transaminases, fatigue, anemia, and nausea	Thrombocytopenia, increased aspartate aminotransferase levels, and anemia
Mirvetuximab Soravtansine (Elahere®)	Folate receptor α	Ovarian cancer	2022 Immunogen	Nausea, blurred vision, keratopathy, diarrhea, fatigue, peripheral neuropathy, dry eye, and decreased visual acuity	Blurred vision, peripheral neuropathy, and diarrhea
Trastuzumab Deruxtecan (Enhertu®)	HER-2	Breast cancer	2019 Daiichi Sankyo	Nausea, fatigue, alopecia, vomiting, neutropenia, constipation, anemia, decreased appetite, diarrhea, leukopenia, and thrombocytopenia	Neutropenia, anemia, nausea, leukopenia, lymphopenia, and fatigue
Sacituzumab Govitecan (Trodelvy®)	Trop-2	Breast cancer, urothelial cancer	2020 Gilead Sciences	Nausea, diarrhea, neutropenia, fatigue, vomiting, anemia, alopecia, and constipation	Neutropenia, anemia, diarrhea, and leukopenia

TOXICIDAD
Condicionantes de los EA y manejo

Toxicidad ADCs

- Metanálisis de 169 ensayos con ADCs, mostraron >90% de EA y 40% grado≥3
- Variable en función de la composición
- Predomina la del payload y son off-target off-tumor, también por désconjugación prematura en la circulación.
- Dependen también de la estabilidad del linker
- Muchos abandonos del desarrollo clínico

Condicionantes de la toxicidad de los ADCs

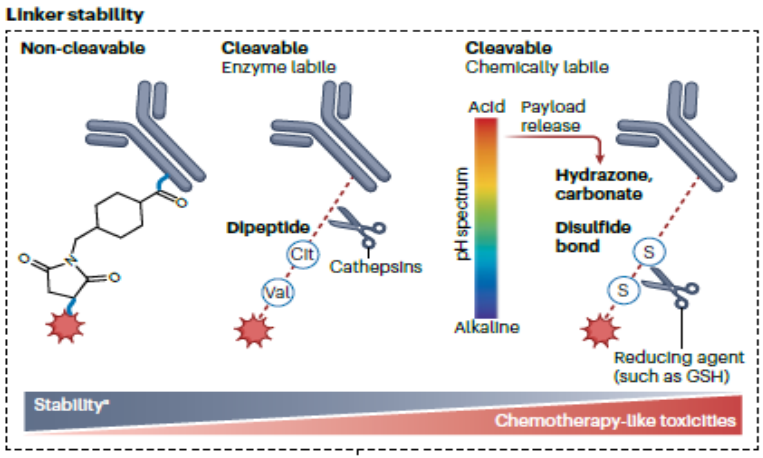
- Sólo el 0,1% del ADC se libera en la célula diana
- La farmacocinética de estos medicamentos es muy compleja e incluye aspectos químicos y físicos.
- La mayor parte se cataboliza “off site” en el interior de las células sanas
- Esta toxicidad “off site” puede ser:
  - “On target off site”: por existencia del Ag. en células sanas. No suele se la causa de la toxicidad limitante y se identifica fácilmente en los estudios precoces
  - “Off target off site”, suele el factor mas relevante y responsable de la DLT

Condicionantes de la toxicidad de los ADCs

- Los 3 componentes del ADC pueden causar EA
- Los ADCs que comparten "linker/payload" suelen compartir las mismas toxicidades
- Los "linker" **degradables** tienen mas facilidad para liberar el citotóxico en la circulación, fuera de las células diana, y los lipofílicos mas facilidad para atravesar la membrana de cualquier célula (diana y no diana), responsables de mayor toxicidad, y también de mayor eficacia por el efecto by stander
- Son los favoritos para el tratamiento de tumores con población Ag-mente hetrogénea
- Los "linker" **no degradables** suelen tener menos EA por reducción de la toxicidad "off target"

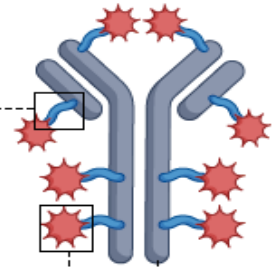
Condicionantes de la toxicidad de los ADCs

- El componente Ac. de los ADCs puede ser responsable de EA que no son típicos del payload, efecto "on target off site" (ILD o cardiotoxicidad de ADC her2-trastuzumab-)
- La toxicidad puede también variar en función del tumor a tratar con el mismo ADC



Patient-related factors

- Baseline organ function
- Comorbidities
- Pharmacogenomic polymorphisms
- Body composition
- Ethnicity



Payload

Mechanism of action

Microtubule inhibitors

- DM1: ↑ Thrombocytopenia, hepatotoxicity
- DM4: ↑ Ocular toxicity
- MMAE: ↑ Peripheral neuropathy, myelotoxicity
- MMAF: ↑ Ocular toxicity

Topoisomerase I inhibitors

- ↑ Diarrhoea
- ↑ Neutropenia

Calicheamicins
Duocarmycins
Pyrrolobenzodiazepines

- ↑ Neutropenia

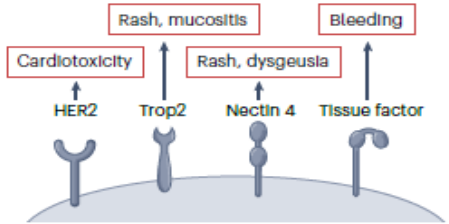
Payload potency

Drug-to-antibody ratio

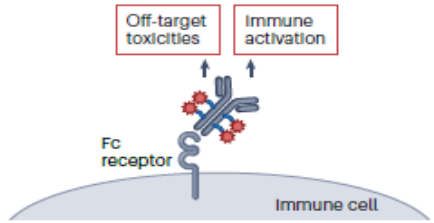
Toxicity

Antibody

On-target toxicities



Binding to Fc receptors on immune cells



Características de los EA de los ADCs

- Mielotoxicidad, hepatotoxicidad y efectos GI se deben a la liberación prematura del "payload" a la circulación
- Los efectos inmunomediados se deben a los Ac
- Metanálisis de 109 estudios (16.000 p): 91% de pacientes con EA, 46%≥G3, 1,3% muertes

	EA cualquier Grado %
LINFOPENIA	53
NEUTROPENIA	44
NAUSEA	44
VISIÓN BORROSA	40
NEUROPATÍA PERIFÉRICA	39

	EA ≥G3 %
NEUTROPENIA	31
HIPOESTESIA	23
TROMBOPENIA	22
NEUTROPENIA FEBRIL	21
LINFOPENIA	21

	CAUSAS DISC. %
NEUROPATÍA PERIFÉRICA	25,5
TROMBOPENIA	11

	MUERTE CAUSAS %
NEUMONITIS	12,4
NEUMONÍA	10
SEPSIS	7,7
FALLO RESPIR	6,5

Youhen Zu et al. Cancer. 2023;129:283–295.

EA de especial interés de los ADCs: ILD

- Instruir a pacientes de los síntomas precoces: tos, disnea, fiebre o emperamiento de cualquier clínica respiratoria y contactar
- Recomendamos DLO basal y cada 12 semanas
- Monitorizar con TC torácico de alta resolución basal y cada 9-12 semanas y cada 2 semanas en caso de neumonitis de cualquier grado
- Inicio de esteroides precozmente si neumonitis ≥2, y valorar en G1 en pacientes de mayor riesgo (afectación pulmonar previa)
- Actualmente se recomienda discontinuar definitivamente en G≥2

Monitor for suspected ILD/P

- Interrupt T-DXd if ILD/P is suspected
- Rule out ILD/P if radiographic changes consistent with ILD/P or if acute onset of new or worsening pulmonary symptoms develop

Confirm ILD/P by evaluation

- High-resolution CT, pulmonologist consultation, blood culture and CBC, bronchoscopy or BAL, PFTs and pulse oximetry, arterial blood gases, PK analysis of blood sample (as clinically indicated and feasible)[a]
- **All ILD/P events regardless of severity or seriousness should be followed until resolution including after drug discontinuation**

Manage ILD/P

Grade 1

- **Interrupt T-DXd**
- T-DXd can be resumed if the ILD/P resolves to grade 0
  - If resolved in ≤28 days from onset, maintain dose
  - If resolved in >28 days from onset, reduce dose by 1 level[b]

- **Discontinue T-DXd** if ILD/P occurs beyond day 22 and has not resolved within 49 days from the last infusion

- Monitor and closely follow-up in 2-7 days for onset of clinical symptoms and pulse oximetry
- Consider:
  - Follow-up imaging in 1-2 weeks, or as clinically indicated
  - Starting systemic glucocorticoids (e.g. ≥0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks

If diagnostic observations worsen despite initiation of corticosteroids, then follow grade 2 guidelines.

We suggest considering steroids for selected grade 1 cases that show extensive lung involvement or in patients at increased risk for progression of ILD/P

Grade 2 (symptomatic)

Permanently discontinue T-DXd

- Promptly start systemic glucocorticoids (e.g. ≥1 mg/kg/day prednisone or equivalent) for ≥14 days until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks
- Monitor symptoms closely
- Re-image as clinically indicated
- If worsening or no improvement in clinical or diagnostic observations in 5 days:
  - Consider increasing dose of glucocorticoids (e.g. 2 mg/kg/day prednisone or equivalent), and administration may be switched to i.v. (e.g. methylprednisolone)
  - Reconsider additional workup for alternative etiologies as described above
  - Escalate care as clinically indicated

Grade 3 or 4

Permanently discontinue T-DXd

- Hospitalization required
- Promptly start empirical high-dose methylprednisolone i.v. treatment (e.g. 500-1000 mg/day for 3 days), followed by ≥1.0 mg/kg/day of prednisone (or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks
- Re-image as clinically indicated
- If still no improvement within 3-5 days:
  - Reconsider additional workup for alternative etiologies as described above
  - Consider other immunosuppressants (e.g. infliximab or mycophenolate mofetil) and/or treat per local practice

Otros EA de los ADCs: prevención

- Tratamiento antiemético
- Premedicación para minimizar reacciones infusionales
- Seguimiento analítico estrecho: hematología y pruebas hepáticas
- Seleccionar cuidadosamente los ADCs en casos de neuropatía preexistente
- Cuidado ocular con chequeo oftalmológico, uso de lágrimas y esteroides tópicos
- Anti-HER2: valoración cardíaca previa y periódica, TAC torácico basal y cada
- 12 semanas, DLO basal y cada 3 ciclos, interrumpir tratamiento en caso de toxicidad pulmonar G2 (tos)

CONCLUSIONES

- Actualmente, no existe ningún ADC con financiación aprobada en España para cáncer ginecológico
- El único con indicación en ficha técnica es el mirvetuximab soramtansina vía uso compasivo y facturable, para tumores de ovario resistentes a platino y sobreexpresión de RF
- Trastuzumab deruxtecán es una buena opción para tumores de endometrio y ovario HER2++/+++
- Tisotumab vedotin es ADC mas desarrollado en cáncer de cérvix en 2ª línea, aunque los resultados hasta ahora son alentadores pero modestos
- Los ensayos clínicos son, en este momento, el mejor recurso

- Necesidad de nuevos equipos multidisciplinares y nuevos entrenamientos, en este caso, para el manejo de los EA
- A pesar del objetivo inicial de mejorar el índice terapéutico aún no se ha conseguido minimizar los EA a las dosis terapéuticas del citotóxico
- Más tiempo por paciente, más pruebas de imagen, mas dinero
- Queda mucho por hacer en identificar biomarcadores y EA potencialmente serios de forma precoz
- Cómo vamos a poder secuenciar los distintos ADCs en una misma paciente: alteración de los Ag target, resistencias utilizando similares payloads
- Naturaleza dinámica de algunos Ag target (muestra al diagnóstico o necesidad de nueva muestra a la recurrencia)
- Técnicas de procesamiento de las muestras

3ª Jornada de Actualización EN CÁNCER GINECOLÓGICO

Bilbao
12-13 junio 2025

GRACIAS
ESKERRIK ASKO